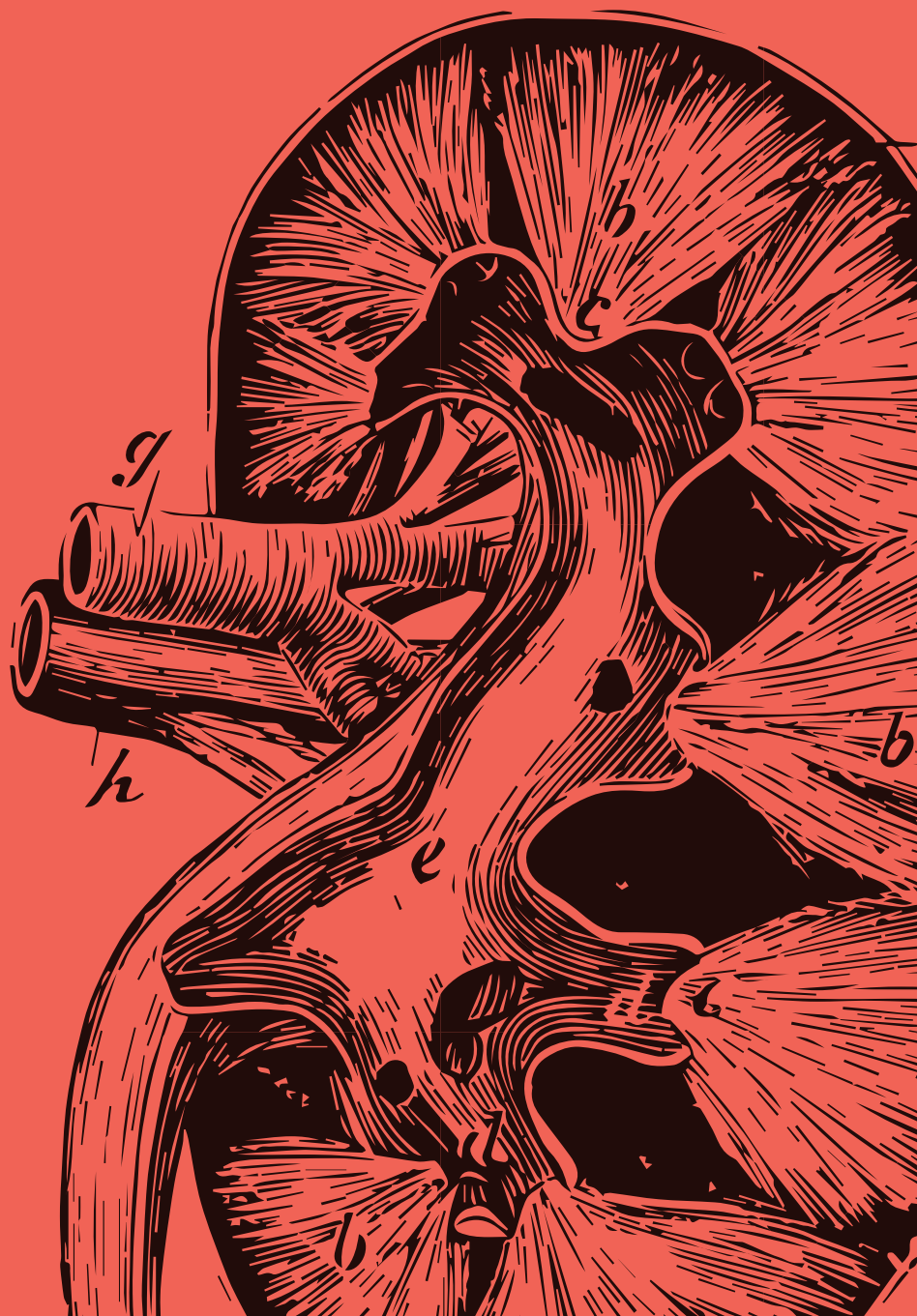
EISSN 2667-4440

Turkish Journal of Nephrology

Volume 29
Issue 1
January 2020



AVES turkjnephrol.org

Turkish Journal of Nephrology

TURKISH SOCIETY of NEPHROLOGY 1970

AVES

Publisher
İbrahim KARA

Publication Director
Ali ŞAHİN

Editorial Development
Gizem KAYAN

Finance and Administration
Zeynep YAKIŞIRER ÜREN

Deputy Publication Director
Gökhan ÇİMEN

Publication Coordinators
Betül ÇİMEN
Özlem ÇAKMAK
İrem SOYSAL
Arzu YILDIRIM

Project Coordinators
Sinem KOZ
Doğan ORUÇ

Graphics Department
Ünal ÖZER
Deniz DURAN
Beyzanur KARABULUT

Contact
Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com

Turkish Journal of Nephrology

Aims and Scope

Turkish Journal of Nephrology (Turk J Nephrol) is a double-blind peer-reviewed, open access, an international online-only publication of the Turkish Society of Nephrology. The journal is a quarterly publication, published in January, April, July and October. The publication language of the journal is English.

Turkish Journal of Nephrology aims to contribute to the literature by publishing manuscripts at the highest scientific level in the fields of nephrology, dialysis and transplantation. The journal publishes original articles, rare case reports, reviews, and letters to the editor that are prepared in accordance with the ethical guidelines.

The scope of the journal includes but not limited to; remarkable clinical and experimental investigations conducted in all fields of nephrology. The target audience of the journal includes specialists and professionals working and interested in all disciplines of nephrology and kidney care.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Turkish Journal of Nephrology is currently indexed in Web of Science-Emerging Sources Citation Index, Scopus, EBSCO, and TUBITAK ULAKBIM TR Index.

Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.turkjnephrol.org.

The journal guidelines, technical information, and the required forms are available on the journal's web page.

All expenses of the journal are covered by the Turkish Society of Nephrology. Potential advertisers should contact the Editorial Office. Advertisement images are published only upon the Editor-in-Chief's approval.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Turkish Society of Nephrology, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

Editor in Chief: Bülent Tokgöz
Address: Deparment of Nephrology, Erciyes University School of Medicine, 38039 Kayseri, Turkey
Phone: +90 212 219 48 82
Fax: +90 212 219 48 82
E-mail: bulentto@gmail.com

Publisher: AVES
Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
Web page: avesyayincilik.com

Turkish Journal of Nephrology

Instruction to Authors

Turkish Journal of Nephrology (Turk J Nephrol) is the double-blind peer reviewed, open access, international online-only publication of Turkish Society of Nephrology. The journal is a quarterly publication, published in January, April, July and October. The publication language of the journal is English.

Turkish Journal of Nephrology aims to contribute to the literature by publishing manuscripts at the highest scientific level in the fields of nephrology, dialysis and transplantation. The journal publishes original articles, rare case reports, reviews, and letters to the editor that are prepared in accordance with the ethical guidelines.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

Manuscripts submitted to Turkish Journal of Nephrology will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects,” amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors’ responsibility to carefully protect the patients’ anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed and the publication approval must be provided in the Materials and Methods section.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1 Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2 Drafting the work or revising it critically for important intellectual content; AND

3 Final approval of the version to be published; AND

4 Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are re-

sponsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

Turkish Journal of Nephrology requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through turkjnephrol.org) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

Turkish Journal of Nephrology requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

Turkish Journal of Nephrology requires each submission to be accompanied by a Copyright License Agreement (available for download turkjnephrol.org). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s). By signing the Copyright License Agreement, authors agree that the article, if accepted for publication by the Turkish Journal of Nephrology, will be licensed under a Creative Commons Attribution 4.0 International License (CC BY 4.0).

Statements or opinions expressed in the manuscripts published in Turkish Journal of Nephrology reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2018 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at turkjnephrol.org. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

- Copyright Agreement Form,
- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at turkjnephrol.org).

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, highest academic degree(s), and ORCID IDs of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Materials and Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analyses are essential features of medical studies, in order to answer the research questions with hypothesis testing. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading, as 'Statistical Analysis', under the Materials and Methods section. This section should detail the following:

(i) how the statistical assumptions are tested (e.g. Histogram and q-q plots were examined, Shapiro-Wilk's test was used to assess the data normality.);

(ii) which statistical methods are used for which purposes (e.g. To compare the miRNA levels of patients with and without CKD, a two-sided independent samples t test was applied.);

(ii) how the data values are expressed (e.g. Values are expressed as mean±SD or median(1st-3rd quartiles.);

(iv) which statistical software was used to analyze the data (e.g. Analyses were conducted using TURCOSA (Turcosa Analytics, Turkey) statistical software.).

Additionally, the study design (e.g. retrospective case-control, cross-sectional, cohort, etc.) and the sample size calculation procedure (power analysis) should also be detailed in the Materials and Methods section.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should in-

clude Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. The authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Altun B, Soylemezoglu O, Tokgoz B, Yilmaz MI, Odabas AR, Koc M. Hemodialysis complications. Turk Neph Dial Transpl 2010; 70: 1-4.

Book Section: Sagawa K. Analysis of the CNS ischemic feedback regulation of the circulation. Reeve EB, Guyton AC (eds). Physical Basis of Circulation Transport. Philadelphia: WB Saunders, 1967; p.129-139.

Books with a Single Author: West JB. Respiratory Physiology. 2nd ed. Baltimore: Williams and Wilkins; 1974.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs (serial online). 2002 Jun (cited 2002 Aug 12): 02(6). Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Revisions

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

Editor in Chief: Bülent Tokgöz
Address: Department of Nephrology, Erciyes University School of Medicine, 38039 Kayseri ,Turkey
Phone: +90 212 219 48 82
Fax: +90 212 219 48 82
E-mail: bulentto@gmail.com

Publisher: AVES
Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
www.avesyayincilik.com

Turkish Journal of Nephrology

Contents

Turkish Journal of Nephrology

Contents

Case Reports

10.5152/turkjnephrol.2020.140120

Turkish Journal of Nephrology

The Turkish Society of Nephrology from 1970 to 2020: A 50-Year History

Kenan Ateş

1 Department of Internal Medicine, Division of Nephrology, Ankara University School of Medicine, Ankara, Turkey

Corresponding Author: Kenan Ateş ✉ ates@medicine.ankara.edu.tr

Cite this article as: Ateş K. The Turkish Society of Nephrology from 1970 to 2020: A 50-Year History. Turk J Nephrol 2020; 29(1): 1-5.

INTRODUCTION

Turkish Society of Nephrology (TSN) celebrates its 50th anniversary in 2020. Since its establishment, the TSN intended to operate by following its core purposes which are raising the level of education, scientific studies, and research, preventive and therapeutic health services in the fields of nephrology, hypertension, dialysis, and transplantation throughout Turkey, developing professional, scientific and social relations among its members, protecting the rights of its field and its members and carrying out studies to ensure the best representation of Turkish nephrology at the national and international levels. In this article, the readers will find a summary of the 50-year success story of TSN.

Establishment

The TSN was founded on March 3, 1970, at Istanbul University Haseki Hospital Pharmacology and Treatment Clinic by Ord. Prof. Ekrem Şerif Egeli, Ord. Prof. Sedat Tavat, Prof. Reşat Garan, Prof. Kemal Önen, Prof. Osman Barlas, Prof. Ferhan Berker, Prof. Gıyas Korkut, and Assoc. Prof. Necdet Koçak. At the inaugural meeting of the founding members, Ord. Prof. Ekrem Şerif Egeli was elected president of the association, Prof. Kemal Önen, as the secretary-general and Prof. Osman Barlas, Prof. Reşat Garan and Prof. Ferhan Berker as board members. Ord. Prof. Ekrem Şerif Egeli held the position of president until 1978, at which point Prof. Kemal Önen took over, serving until 1996 to make him the longest-serving chairman of TSN. Prof. Ekrem Erek was the president of the association between 1996 and 2000, Prof. Kamil Serdengeçti between 2000 and 2008, Prof. Gültekin Süleymanlar between 2008 and 2014 and Prof. Turgay Arınsoy between 2014 and 2017. From November 2017 to the present day, the position has been held by Prof. Kenan Ateş.

As of the last election, the board of directors has been composed of the following members: Prof. Kenan Ateş (president), Prof. Alaattin Yıldız (vice president), Prof. Mustafa Arıcı (secretary-general), Prof. Ali Rıza Odabaş (treasurer), Prof. Siren Sezer, Prof. Halil Zeki Tonbul and Prof. Bülent Tokgöz.

Society Membership

As per the statute of the society, nephrology and pediatric nephrology specialists and assistants can become full members of TSN. The number of society members, which was eight at the time of its establishment and 23 at the beginning of 1971, has gradually increased over the years, reaching a total of 590 today. Currently, 96% of the members are nephrologists or nephrology assistants (84% are adult nephrologists, and 16% are pediatric nephrologists). Besides, seven foreign scientists, who have made significant contributions to Turkish nephrology, were granted honorary membership.

Branches of the Society

In order to expand the activities of the society throughout Turkey and to ensure broader participation, the first branch was established in Antalya in 1997, followed by new branches in Izmir, Kayseri, and Istanbul in 2000, Bursa in 2004, Konya in 2005, Adana in 2006, and Anka-

ra in 2007. The Konya branch subsequently dissolved itself. The branches organize regional activities in line with the aims and working areas of the society.

Permanent Committees

The Registry and Statistics Committee: This committee was established with the aim of collecting, analyzing, and publishing data related to nephrology, hypertension, dialysis, and transplantation across Turkey, planning and implementing epidemiological research, and cooperating with international organizations in data sharing and the facilitation of collaborative studies. Prof. Ekrem Erek, Prof. Kamil Serdengeçti, and Prof. Gültekin Süleymanlar served as presidents of this committee, respectively. Since 1990, the committee has focused on collecting data related to nephrology, dialysis, and transplantation in a center-based manner, and, following the subsequent analyses, publishing the results in a series of books entitled Registry of the Nephrology, Dialysis, and Transplantation in Turkey. In 2019, the 29th book in the series was published. This series of books, which are unprecedented in any other national association, remains an essential source of reference for researchers, both in Turkey and the World seeking to obtain Turkish data on these topics. Besides, these books are also used by the health authorities and other institutions for the planning of dialysis and transplantation services. The books have been published in Turkish and English since 2000. The data related to Turkey has been present in the section B of the European Dialysis and Transplant Association–The European Renal Association (EDTA–ERA) Registry since 2001 and in the section of international comparisons of the United States Renal Data System since 2003, which allows for the comparison of the dialysis and transplantation results of the country with other data from the United States and Europe.

The Journal and the Editorial Board: The primary purpose of this editorial board is to regularly publish the Turkish Journal of Nephrology, Dialysis, and Transplantation, and its supplementary issues. The Turkish Journal of Nephrology, Dialysis, and Transplantation was first published under Prof. Ekrem Erek editorship. Following this, Prof. Emel Akoğlu, Prof. Cengiz Utaş, Prof. Bülent Altun and Prof. Bülent Tokgöz have all served as editors. As of 2019, the journal is being published in English with its new title, the Turkish Journal of Nephrology. The journal, which is currently indexed by the Web of Science-Emerging Sources Citation Index, Scopus, EBSCO, and the TUBITAK ULAKBIM TR index, is expected to become available in PubMed in the near future.

The Renal Disaster Task Force: This committee was established under the presidency of Prof. Ekrem Erek and under the coordination of Prof. Mehmet Şükrü Sever following the earthquake of August 17, 1999, which hit the Marmara region of Turkey and led to the loss of 17,000 citizens. Prof. Mehmet Şükrü Sever held the position of chairman of the committee for many years, while today, this position is held by Prof. Serhan Tuğlular. The committee provided essential services in the organization of domestic and international aid activities, conducting chronic dialysis services, and arranging the treatment of patients with crush syndrome following the Marmara earthquake. The task force collected and analyzed the data of 639 cases with crush syndrome from the Marmara Earthquake, and later published 27 related articles in international journals. In addition, the book entitled Crush Syndrome and Lessons Learned from the Marmara Earthquake was written by Prof. Mehmet Şükrü Sever, which was subsequently published in English by Karger Publishing. Meanwhile, more than 30 training meetings were organized in Turkey under the leadership of Prof. Mehmet Şükrü Sever, while numerous national guidelines were created, and the task force contributed to various international guidelines. In addition, the task force actively contributed to the relief efforts following the Bingöl (2003) and Van (2011) earthquakes in Turkey, as well as Iran, Pakistan, and Haiti earthquakes.

Turkish Board of Nephrology: This committee was established in 2004 with the aim of establishing, maintaining and raising the standards of nephrology specialty education, providing quality control, performing accreditation studies, conducting standard exams after the specialty education, providing a nephrology proficiency certificate, and encouraging and supervising the participation in continuous medical education activities. Prof. Kenan Ateş has been the president of the committee since its establishment. The committee has prepared the Nephrology Specialist Training Principles and the Nephrology Core Curriculum and conducts proficiency exams since 2008. A total of 75 nephrologists have been awarded the competency certificate as a result of the 12 examinations conducted thus far. In addition, a significant contribution was made to the preparation of the Nephrology Core Curriculum of the Medical Specialization Committee. Quality and accreditation studies are planned to begin in the near future. The committee is represented at the Union Européenne des Médecins Spécialistes and the European Board of Nephrology, formerly by Prof. Oğuz Söylemezoğlu, Prof. Cem Sungur and Prof. Tevfik Ecder and currently by Prof. Mustafa Arıcı.

Term Committee: This committee was founded in 2003 with the aim of protecting the Turkish language as the language of science and using it properly. Prof. Taner Çamsarı has been the president of the committee since its establishment. The committee, which regularly publishes the Term Committee Bulletin, organized the 1st Turkish Language of Medicine Symposium in May 2019.

Working Groups: Working groups were established in 2002 to conduct regional and international epidemiological, clinical, and experimental studies on issues related to basic and clinical nephrology, hypertension, dialysis, and transplantation, to produce and disseminate information, to determine the scientific and clinical practice standards and prepare guidelines of Turkey on related issues, to consult TSN's executive board and other

committees, and to establish health policies. The society currently has 10 working groups focusing on the following areas: acute kidney injury and intensive care nephrology; nutrition and metabolism; diabetic kidney disease; glomerular diseases; hypertension; cystic kidney diseases; mineral and bone disorders; peritoneal dialysis; renal anemia; and transplantation. The groups organize scientific meetings both during national meetings and on an independent basis, as well as conduct scientific research and prepare guidelines on related topics. Finally, the Diagnosis and Treatment of Primary Glomerular Diseases: National Consensus Report was prepared by the Glomerular Diseases Working Group, and the Hypertension Working Group contributed to the Turkish Hypertension Consensus Report. The national consensus report on diabetic kidney disease is currently under preparation.

The Turkish Society of Nephrology Website

The website of the TSN was built in 2000 at www.tsn.org.tr. Information on events organized by the society, as well as other general useful information and current announcements, are available through this website. In 2018, the Website and Social Media Group was established within the society, and a new website was launched with a new domain name at www.nefroloji.org.tr. In addition, the society is represented through social media channels, including Twitter, Instagram, and Facebook.

National Scientific Meetings

One of the most important activities of the TSN is to organize scientific meetings to contribute to the education of physicians and nurses working in the field of nephrology. The first national congress was held in 1980 in Bursa under the supervision of Prof. Aydoğan Öbek. However, after the military coup of 1980, the activities of TSN, much like those of all other associations, were halted, and the scientific meetings had to be suspended. In 1985, the Innovations in Nephrology Congress was held in Erzurum under Prof. Ayla San's chairmanship, and, since then, a total of 36 congresses were held at regular intervals under the name of National Kidney Disease, Hypertension, Dialysis and Transplantation Congress. The name of the annual congress was changed to National Nephrology Congress in 2019. Each year, some 1,100–1,300 people attend the national congresses, making them the most successful meetings in Turkey for the covered topics.

Winter School of Nephrology is another regular national scientific activity of the society. These meetings, initiated under the leadership of Prof. Cengiz Utaş, make a significant contribution, especially to the continuous training of physicians dealing with dialysis. A total of 18 winter schools was organized, the first of which was in 2002. The winter schools are generally attended by 350 to 500 participants.

In addition to these, nephrology subspecialty education meetings, dialysis schools, transplantation intensive training programs, and various regional activities are organized in order to contribute to the continuous training of young nephrologists and nephrology specialty students.

International Scientific Meetings

Through the close relations established with associations such as the International Society of Nephrology (ISN), EDTA–ERA, and the International Society for Peritoneal Dialysis (ISPD), Turkey hosted many international congresses, and several joint meetings held with the participation of these associations.

• The 15th EDTA Congress was organized under the chairmanship of Prof. Kemal Önen in Istanbul between 4-7 June 1978. The congress, attended by approximately 1,500 people, went on record as the biggest and most successful congress of the EDTA at the time.

• The 42nd ERA-EDTA Congress was held between 4-7 June 2005 in Istanbul under the chairmanship of Prof. Kamil Serdengeçti. This was the most successful congress of ERA-EDTA up until then in terms of participants (6,135 people from 100 countries) and the number of abstracts (1,959).

• The 50th ERA-EDTA Congress was held with a total of 7,634 participants between 18-21 May 2013 in Istanbul under the chairmanship of Prof. Gültekin Süleymanlar. Organizing ERA-EDTA's 50th congress in Turkey was a great honor for the Turkish nephrology community.

• The 12th ISPD Congress was held between 20-24 June 2008 in Istanbul under the chairmanship of Prof. Cengiz Utaş. Some 2,169 people from 73 countries participated in the congress.

• The 4th BANTAO Congress was held in İzmir in 1999, and the 9th BANTAO Congress was held in Antalya in 2009.

• The 9th International Geriatric Nephrology and Urology Conference was held in 2007 in Antalya under the chairmanship of Prof. Fevzi Ersoy.

• In addition, approximately 50 joint meetings were held during national congresses or independently, in cooperation with international associations. One of the most important of these is the Giants of Nephrology in Istanbul meeting held on June 5, 2000, on the occasion of the 30th anniversary of TSN and the 40th anniversary of the ISN. A similar meeting will be held in Istanbul under the name KidneyIST between 5-6 March 2020 within the scope of the 50th anniversary of TSN.

Duties in International Associations

As a result of the efforts of the TSN to expand internationally and to develop relations, many of our members have held important positions in international associations. For example, Prof. Ali Başçı (2002-2005), Prof. Cengiz Utaş (2005-2008), Prof. Gültekin Süleymanlar (2008-2011), Prof. Mehmet Şükrü Sever (2012-2015) and Prof. Mustafa Arıcı (2015-2018) served as Coun-

cil Members of the ERA–EDTA, while Prof. Kamil Serdengecti was elected as a member of the ISN Council from 2005–2011. Presently, Prof. Rümeyza Kazancıoğlu is a member of the ISN Council, while Prof. Mustafa Arıcı is a member of KDIGO. In addition, Prof. Mehmet Şükrü Sever, Prof. Kültigin Türkmen, Prof. Sevcan Bakkaloğlu, and Prof. Mehmet Kanbay currently serve on various committees of ERA-EDTA.

Books Published by the Turkish Society of Nephrology

The TSN has published 36 books, 23 of which were licensed and 13 of which were translations for the benefit of the readers, in line with its mission to raise the level of education in the areas of nephrology, hypertension, dialysis, and transplantation in Turkey. Currently, two licensed books are being prepared for publication. In addition, TSN's Website and Social Media Group has been publishing summaries and reviews of several articles published in high impact journals since 2018 under the name Nefroblog.

Scholarships to Study Abroad and Other Supports

Since 2000, the TSN has been awarding scholarships to young nephrologists and nephropathologists for studying abroad. The first fellowship was awarded to Dr. Ercan Ok from the Nephrology Department of Ege University School of Medicine, who traveled to the USA. Since then, a total of 60 young researchers, including 48 nephrologists and 12 nephropathologists, benefited from the TSN training scholarship for periods of between 3 and 12 months. TSN also provides financial support to its members when participating in national and international congresses and for article publication bonuses.

Epidemiological Studies

Chronic kidney disease is a significant public health problem, affecting approximately 10% of adults worldwide. In order to define the prevalence and distribution of chronic kidney disease and the related risk factors in Turkey, between 2006 and 2008, TSN conducted the Chronic Kidney Disease Prevalence in Turkey Study (CREDIT) in 23 provinces across the country, with the participation of 10,750 adults and 5,000 children. In this study, the prevalence of chronic kidney disease in our country was found to be 15.7%. The results of the study were presented at multiple national and international meetings and were subsequently published in four separate articles in international journals.

The second stage of the CREDIT study (CREDIT-Incidence), which aimed to determine the incidence and course of chronic kidney disease, was performed with the participation of a total of 4,243 individuals between 2011 and 2013. This study found that the prevalence of chronic kidney disease in Turkey had decreased slightly from that recorded in the previous study.

The preparations for a new epidemiological study aimed at determining the prevalence, distribution according to the stages, and risk factors of diabetic kidney disease, have been completed. The plan is now to execute the study in the first half of 2020.

Kidney Diseases Prevention and Control Program in Turkey

After the serious dimensions of the problem of chronic kidney disease in Turkey were revealed through the CREDIT study, with the initiatives of TSN, the Turkish Kidney Diseases Prevention and Control Program was prepared under the leadership of the Ministry of Health's Public Health Institute alongside an action plan covering the years 2014-2017. Currently, an action plan covering the years 2018-2022 is being implemented, with significant contributions from TSN.

Activities Directed to Public

TSN, which has continued its educational and scientific work for the development of kidney science in Turkey without interruption for 50 years, organizes various activities to increase public consciousness and awareness of kidney health and disease and to emphasize the importance of early diagnosis per its social responsibility. These activities are summarized below:

World Kidney Day: Starting from 2006, every year, the second Thursday of March is celebrated as World Kidney Day by the ISN and the International Federation of Kidney Foundations. Every year since 2006, TSN and its branches have organized numerous activities on World Kidney Day to raise public awareness of kidney health and disease, emphasizing the importance of early diagnosis and informing the public about the heavy burden of kidney disease on both human health and the national economy. Details of these studies can be found on the World Kidney Day website (www.worldkidneyday.org) and the TSN website (www.nefroloji.org.tr).

Kidney Health Bus: TSN, which is committed to taking an active role in social responsibility projects concerning the community, realized the Kidney Health Bus project during its 40th anniversary. During the 75-day project, which started in Antalya on September 23, 2010, and ended in İzmir on December 5, 2010, a total of 21 cities were visited, and approximately 50,000 people who visited the bus were informed about kidney health and disease through brochure distribution, video screening, and information-based meetings. In addition, 6,483 people were screened for kidney disease and the attendant risk factors.

Attention Health Contest: In order to inform the public about healthy living and kidney disease, TSN organized a competition program entitled "Attention Health" on TRT Ankara Radio between January 2010 and December 2010, lasting for a total of 50 weeks. In this program, a separate topic was discussed every week, and the audience was first asked three "right or wrong?" questions before the relevant information was conveyed by the board members of TSN (Prof. Kenan Ateş, Prof. Bülent Altun and Prof. Gültekin Süleymanlar), who were contacted by telephone.

Organ Donation Cartoon Contest: A cartoon contest was organized in 2010 to encourage organ donation. The resulting works of art were collected in a book, exhibited during the national congress, and used in various community-oriented activities.

The TSN plans to give a start to various social responsibility projects in its 50th anniversary year, 2020.

CONCLUSION

The TSN has taken essential steps in the name of institutionalization, opening itself up to the international arena and achieving the objectives stated in its original statute, created some 50 years ago. The society will continue its activities with increasing momentum in 2020 and the following years, and it will continue to carry out successful works.

Prof. Dr. Kenan ATEŞ
President of the Turkish Society of Nephrology

10.5152/turkjnephrol.2020.4249

Original Article

Turkish Journal of Nephrology

Current Status of Renal Replacement Therapy in Turkey: A Summary of the Turkish Society of Nephrology Registry Report

Nurhan Seyahi[1], Kenan Ateş[2], Gültekin Süleymanlar[3]

[1]Division of Nephrology, Department of Internal Medicine, İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, İstanbul, Turkey
[2]Division of Nephrology, Department of Internal Medicine, Ankara University School of Medicine, Ankara, Turkey
[3]Division of Nephrology, Department of Internal Medicine, Akdeniz University School of Medicine, Antalya, Turkey

Abstract

Objective: Every year, the registry of the Turkish Society of Nephrology conducts data collection on hemodialysis, peritoneal dialysis, and transplantation. Registry reports are printed annually as a booklet, thus making 2019 the 29th year of registry reports. The registry is in close collaboration with international registries.
Materials and Methods: This paper summarizes the data from the 2018 registry report. Additionally, this paper provides the yearly trends in the management of end-stage renal disease.
Results: There is an alarming increase in the number of patients undergoing renal replacement therapy (RRT). At the end of 2018, 81,055 patients had undergone RRT. The prevalence and incidence of end-stage renal disease were 988 and 149 per million populations, respectively. Diabetes was termed as the most widespread cause of end-stage renal disease. Hemodialysis (74.8%) serves as the most common type of treatment modality, followed by transplantation (21.2%) and peritoneal dialysis (3.9%).
Conclusion: End-stage renal disease is a critical and growing health concern in our country. The Turkish Renal Registry of the Turkish Society of Nephrology continues to be one of the leading tools for providing the current and sound data on this public health problem.
Keywords: Kidney failure, renal replacement therapy, hemodialysis, peritoneal dialysis, renal transplantation, registry

Corresponding Author: Nurhan Seyahi ✉ nseyahi@yahoo.com
Received: 25.12.2019 **Accepted:** 25.12.2019

Cite this article as: Seyahi N, Ateş K, Süleymanlar G. Current Status of Renal Replacement Therapy in Turkey: A Summary of the Turkish Society of Nephrology Registry Report. Turk J Nephrol 2020; 29(1): 6-11.

INTRODUCTION

In 1990, Professor Ekrem Erek founded the registry of the Turkish Society of Nephrology (Turkish Renal Registry), and 2019 marks its 29th anniversary. Since its inception, paper forms were employed to collect center-based data. However, the data were collected using electronic forms accessed via the internet since 2007. Every year, data regarding renal replacement therapies (RRT), such as hemodialysis, peritoneal dialysis, and transplantation, are collected. Moreover, in selected years, data on specialized topics, such as clinical nephrology (predialysis care), acute kidney injury, and renal pathology, are collected. Data from the Turkish Renal Registry are published and shared with the United States Renal Data System and European Renal Association-European Dialysis and Transplantation Association registry.

This manuscript provides a summary of the 2018 registry report (1). The booklet "Registry of the nephrology, dialysis, and transplantation in Turkey, Registry 2018" published by the Turkish Society of Nephrology provides more comprehensive and detailed data. The website of the Turkish Society of Nephrology (www.tsn.org.tr or www.nefroloji.org.tr) provides complete access to current and previous reports.

Data were collected from the selected RRT centers; moreover, a database of the Ministry of Health was extensively used to obtain the complete data. This approach has been used since 2012.

Incidence and Prevalence

A total of 81,055 patients had undergone RRT till the end of year 2018. The number of patients on RRT continues to

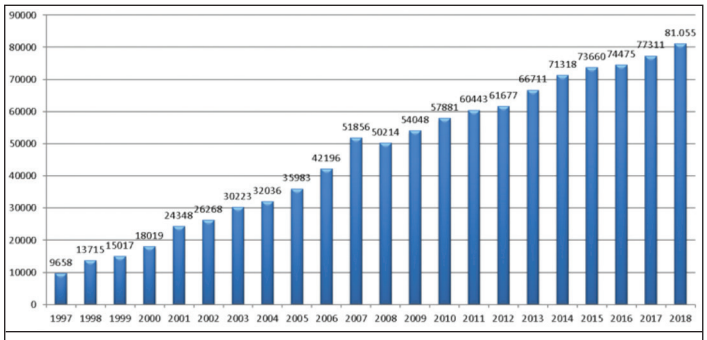


Figure 1. Number of patients receiving renal replacement therapy in Turkey by years.

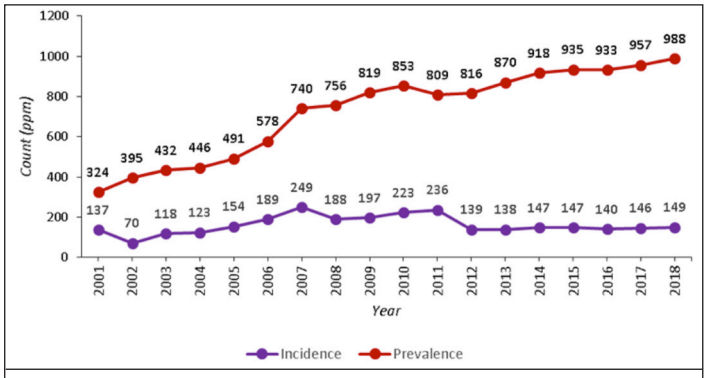


Figure 2. Prevalence and incidence of patients on renal replacement therapy by years. The incidence number for 2002 was corrected to 70. Since 2012, patient-based data provided by the Ministry of Health is used for the calculations.

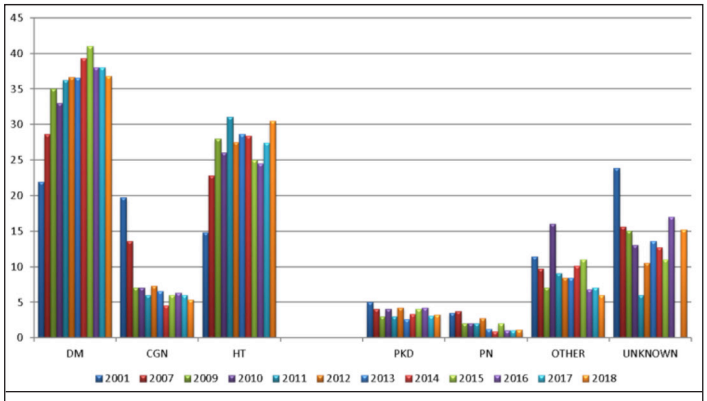


Figure 3. Primary etiology of kidney failure by years.
DM: Diabetes mellitus; CGI: Chronic glomerulonephritis; HT: Hypertension; PKD: Polycystic kidney disease; PN: Pyelonephritis.

increase at an alarming rate (Figure 1). The most common type of RRT is hemodialysis (74.8%), followed by transplantation (21.2%) and peritoneal dialysis (3.9%). The prevalence and incidence of end-stage renal disease were 988 and 149 per million populations, respectively. Yearly changes in prevalence and incidence are presented in Figure 2. During the data checks, the incidence data of 2002 was corrected: incidence was updated as 70 instead of 93.

Hemodialysis

The number of patients on hemodialysis continues to increase at a worrying rate. There were 60,643 (57.1% male) patients on hemodialysis at the end of 2018. The age distribution of the patients is presented in Table 1. It should be noted that >45% of the population on hemodialysis comprises old patients. The number of incident patients on hemodialysis was 9645. The most common cause of kidney failure was diabetes mellitus (36.8%) followed by hypertension (30.5%), glomerulonephritis (5.34%), polycystic kidney disease (3.2%), and other causes 9.0%in these patients. The primary etiology was unknown in 15.2% of the patients. The frequency of diabetes started to consolidate in the last few years (Figure 3). It is not possible to clarify whether the high rate of hypertension is the primary or secondary reason due to an underlying kidney disease. The incidence of diabetes increased with age.

Table 1. Age distribution of patients undertaking hemodialysis, peritoneal dialysis, and transplantation

Age	0-19	20-44	45-64	65-74	75+
Hemodialysis (%)	0.7	12.5	40.7	28	18.2
Peritoneal dialysis (%)	12.2	22.8	42.3	16.5	6.2
Transplantation (%)	8.6	45.0	42.6	3.7	0.2

The presented data are for the prevalent patients on dialysis and for incident patients undergoing transplantation

The initiation of hemodialysis was urgent in 57.5% and scheduled in 42.5% of the patients. The most common type of vascular access at the initiation of hemodialysis was permanent catheters in 42.5%, followed by arteriovenous fistulae in 38%, temporary catheters in 19%, and arteriovenous grafts in 0.5%. Longitudinal data regarding arteriovenous access is shown in Table 2. Arteriovenous fistula was the most common type of access (77.4%); however, a trend of increasing use of catheters should be noted. The most common access site for temporary catheter placement was the internal jugular vein (66.5%), followed by the femoral vein (27.8%) and subclavian (4.1%) vein. Subclavian catheterization is associated with venous thrombosis; therefore, the use of this vein is contraindicated in patients with chronic kidney disease (CKD).

Technical changes regarding hemodialysis treatment are presented in Table 2. The increased use of high-flux membranes should be noted. The frequency of hemodialysis was three times a week in most of the patients (Table 2). In line with the previous findings, an increasing trend in the Kt/V values is observed (Table 2). As of the end of 2018, the Kt/V value was >1.4 in most of the patients (74.0%).

A blood pressure target of <140/90 mmHg was achieved in 79.4% of patients on hemodialysis with or without antihypertensive treatment. Yearly changes of several parameters with respect to hemodialysis treatment are listed in Table 3. The decreasing frequency of hypoalbuminemia was observed until 2016. As of 2018, the albumin level was >4.0 g/dL in 47.2% patients. In total, 49.3% of the patients were current users of erythropoiesis-stim-

Table 2. Variation of the technical characteristics of hemodialysis treatment over the years (data represent percentage of patients) *

Years	2005	2006	2007	2008	2009	2013	2014	2015	2016	2017	2018
Vascular access											
AV fistulae	88.7	85.7	86.0	85.4	84.0	82.9	81.1	80.4	79.1	78.7	77.4
Permanent catheter	3.6	6.9	7.0	7.7	9.3	11.7	13.4	14.4	15.6	18.0	19.1
AV graft	2.7	3.2	2.9	2.9	2.7	1.8	1.6	1.5	1.4	1.3	1.2
Other	5.0	4.2	4.1	4.0	4.0	3.6	3.9	3.8	3.9	2.1	2.3
Dialyzer type											
Synthetic	43.0	62.8	67.2	60.3	65.0	58.9	-	-	-	-	-
Semi-synthetic	47.8	22.1	19.1	17.6	14.0	7.0	-	-	-	-	-
High-flux	9.0	15.0	13.7	21.8	21.0	34.1	33.3	36.3	45.6	46.2	46.3
Kuprophan	0.2	0.1	0.0	0.3	0.0	0	-	-	-	-	-
Dialysis frequency											
Once per week	1.7	1.5	0.9	0.9	0.9	0.6	0.6	0.5	0.5	0.6	0.7
Twice per week	10.2	9.3	7.8	7.5	7.0	7.7	7.9	8.0	8.7	10.0	10.3
Tree times per week	88.1	89.2	89.9	90.2	90.1	90.1	90.8	90.7	89.7	88.3	88.0
More than three times per week or night HD	-	-	1.4	1.4	2.0	0.7	0.8	0.8	1.1	1.1	1.0
Kt/V value											
<1,20	27.8	14.5	12.7	11.3	10.2	11.0	11.3	9.8	8.3	8.4	7.4
≥1,20	72.2	85.5	87.3	88.8	89.8	89.0	88.7	90.2	91.7	91.6	92.6

* Years that are not available or incompatible with other reports due to differences in data collection are left blank.
AV: Arteriovenous; HD: hemodialysis

Table 3. Hypoalbuminemia rate and treatment characteristics in patients on dialysis

Year	2005	2006	2007	2008	2009	2013	2014	2015	2016	2017	2018
Hemodialysis											
Hypoalbuminemia (<3.5 gr/dL)	13.5	12.7	12.0	11.7	11.1	13.0	15.2	13.4	10.1	12.9	10.5
ESA use (%)	60.4	59.8	61.8	62.7	62.4	70.6	55.3	55.3	54.0	54.6	49.3
Iron treatment (%)	57.2	73.0	54.7	54.8	55.0	59.0	55.8	53.5	51.4	55.9	57.2
Active vitamin D use*	42.3	38.4	36.9	41.1	45	43.6	43.0	58.2	58.2	57.5	58.6
Peritoneal dialysis											
Hypoalbuminemia (<3.5 gr/dL)	30.6	24.3	28.1	25.1	30.8	28.8	24.9	24.6	30.1	26.2	26.1
ESA use (%)	52.7	55.4	54.1	51.8	53.5	59.7	44.9	43.3	48.5	46.6	52.2
Iron treatment (%)	53.8	55.1	60.0	47.9	51.0	52.1	47.7	55.3	43.6	44.0	50.4
Active D use*	41.5	41.4	37.6	37.6	56.8	55.9	59.1	67.5	68.3	66.2	68.7

*Following 2015; use of drugs for the treatment of secondary hyperparathyroidism

ulating agents, with 22.1% of them being previous users. In all, 57.2% of the patients were taking iron treatment. Drug treatment for secondary hyperparathyroidism was used by 58.6% of the patients (intravenous vitamin D, 34.8%; vitamin D analogs, 27.3%; calcimimetics, 12.4%; oral vitamin D, 11.7%; and different combinations, 13.9%). The mostly used phosphate binder agent was calcium acetate (43.4 %), followed by sevelamer (27.3%) and calcium carbonate 13.9%. Data on Lanthanum use were not collected. In total, 19.2% of the patients did not use phosphate binders.

Hepatitis B virus (HBV) surface antigen (HBsAg) was positive in 2.6% of the patients, and anti-hepatitis C virus (HCV) antibody was positive in 3.5% of the patients. In addition, double posi-

Table 4. Duration of renal replacement therapy

Time (years)	0-5	6-10	11-15	16-20	>20
Hemodialysis (%)	64.8	21.7	8.3	3.5	1.9
Peritoneal dialysis (%)	69.2	21.2	7.5	1.0	0.0

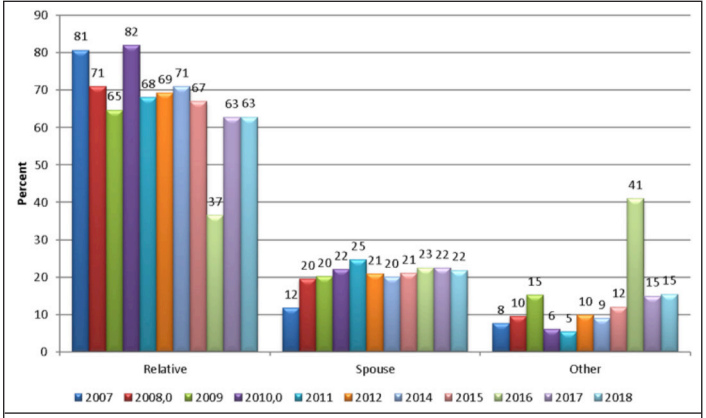


Figure 4. Relationship of the living donor with the recipient.

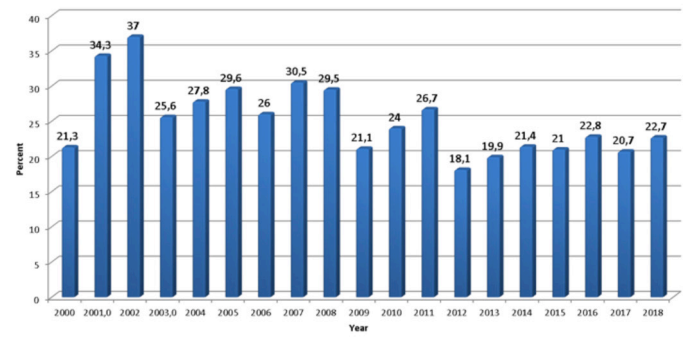


Figure 5. Cadaveric kidney transplantation rate by years.

tivity was observed in 0.2% of the patients. There was a noticed decrease in the prevalence of both HBV and HCV.

The distribution of patients with respect to hemodialysis treatment duration is presented in Table 4. In all, 35.2% of the patients were taking hemodialysis treatment for >5 years. During 2018, 8980 patients on hemodialysis died. Cardiovascular diseases (48%) were the most common causes of death, followed by cerebrovascular causes and malignancy.

Peritoneal Dialysis

As of the end of 2018, the total number of patients on peritoneal dialysis was 3192. There was a continued decrease in the number of patients on peritoneal dialysis during the last decade. The lack of recruitment of new patients is an essential factor that can be partially related to the increased transplantation activity. The male patients were 49.2%, whose age distribution is shown in Table 1. The total number of incident patients for 2018 was 886. The most common cause of kidney failure was hypertension in 29.1% of the patients, followed by diabetes mellitus in 27.5%, glomerulonephritis in 7.4%, polycystic kidney disease in 6.9%, and other causes 15.9%. The etiology was unknown in 13.2% of the patients. The frequency of hypertension was high; however, it is not possible to differentiate between primary and secondary hypertension due to renal disease.

The blood pressure in 26.4% of patients was above the threshold limit of 140/90 mmHg. The changes in treatment-related parameters are summarized in Table 3. Albumin, which is an essential nutritional marker, was <3.5 g/dL in 26.1% of patients, whereas it was above 4 g/dL in 21.1% of the patients. During the last decade, the frequency of hypoalbuminemia was in the range of 25%-30%. In total, 52.2% of the patients were current users of erythropoiesis-stimulating agents, with 18.3% of them being previous users. In total, 50.4% of the patients were taking iron treatment. In fact, most of the patients on peritoneal dialysis were administered iron via the oral route (84.8%). Drug treatment for secondary hyperparathyroidism was used by 68.7% of the patients (oral vitamin D, 55.8%; calcimimetics, 14.9%; vitamin D analogs, 14.7%; and intravenous vitamin D, 0.2%). The most used phosphate binders were calcium acetate (42.5%), followed by sevelamer (22.3%) and calcium carbonate (15.3%).

Obesity (8.4%) was the common complication followed by peritonitis and hernia (6.1%), inadequate dialysis (4.6%), dialysate leakage (4.4%), ultrafiltration failure (3.6%), and drainage problems (3.1%).

The positivity of HbsAg and anti-HCV was present in 2.0% and 1.2% of the patients, respectively. In some patients, there was double positivity of HbsAg and anti-HCV (0.2%). There was a decrease in the prevalence of HBV and HCV. Human immunodeficiency virus was positive in one patient.

The distribution of patients with respect to the duration of peritoneal dialysis is presented in Table 4. In all, 30.8% of the patients were on peritoneal dialysis for >5 years. The most common cause of death was cardiovascular disease (54.3%), followed by cerebrovascular disease (12.9%) and infection (12.9%).

Transplantation

Over the years, there has been a gradual increase in kidney transplantation procedures in Turkey. According to the data provided by the Ministry of Health during 2018, 3871 kidney transplantation procedures were performed. In total, 64.3% of the recipients were male, and the age distribution is shown in Table 1. Most of the patients were aged between 20 and 44 years. Most of the patients were living donors (77.9%). First-degree relatives were the most common source of living donors (35.2%), followed by spouses (21.8%). The incidence of non-related donors was 9.4%.

Longitudinal data regarding living donor types is presented in Figure 4. The rate of cadaveric transplantation was 22.2%, and the longitudinal data regarding the donor type is shown in Figure 5.

The most common cause of kidney failure was hypertension (16.6%), followed by diabetes (16.1%), glomerulonephritis (15.3%), and polycystic kidney disease (5.6%). Primary etiology is not known in 24.6% of the patients. It should be noted that hypertension might be a secondary cause, at least in some patients. Previous RRT type was hemodialysis in 52.0% of the patients and peritoneal dialysis in 4.1%. The high rate of pre-emptive transplantation should be noted.

The prognosis of the new transplantations was evaluated according to the data of 3871 patients. In all, 167 deaths were reported due to new transplantations in the same year, with a mortality rate of 2.5% for live donors and 10.8% for cadaveric donors. Besides, while evaluating these figures, it should be noted that the number of live donors in our country is high. Death occurs mainly due to infection (41.3%) and cardiovascular (27.5%) reasons.

DISCUSSION

It may be more accurate to consider the trend-forming changes while examining the change in the registry data over the years. Annual volatilities not associated with actual change can be caused by several reasons such as data collection methods, center features, and dataset properties. Epidemiological studies such as CREDIT and TURDEP have shown that the rate of diabetes mellitus has witnessed an approximate two-fold increase in our country in the last decade (2, 3). When we look at the etiologic distribution of the incidence of incidental hemodialysis in our registry, we observed that the rate of patients with diabetes increased to approximately 40%. These data prove that diabetes mellitus and diabetic nephropathy have become the first major points of the nephrology agenda. The mean age of patients with diabetes is higher than that of the other patients, and the prevalence of vascular access and cardiovascular disease for hemodialysis in these patients is much higher than that in patients without diabetes due to widespread and severe vascular diseases. In our country, hemodialysis is the most common type of RRT. There is a continuous development of significant qualitative improvements in this treatment method. The number of patients undergoing peritoneal dialysis had witnessed a continued decrease since 2006. This trend has seemingly come into existence especially due to the lack of new patient recruitment and an increase in pre-emptive transplantation activity.

The incidence of transplantation has witnessed a continued increase. In terms of the number of living transplantation, our country has reached the top rankings according to many metrics in the world. Choosing the appropriate live donor is extremely essential. The pre-emptive transplantation rate, which was 38.4% in the previous year, increased to 43.9% this year. This high rate is remarkable and raises some concerns about the timing of the transplantation. In 2018, 9.4% of living donor transplantation was made from the unrelated donors. There is a need to carefully monitor the ethical compliance of those patients.

Despite the increase in transplantation, the lack of the desired increase in the rate of cadaver-derived kidney transplantation is a growing concern of organ donation process from the cadaver. Besides, especially in cadaveric donor transplantations, mortality and graft loss rates are viewed as essential challenges in the first year, furthering the need to be closely monitored.

To increase renal transplantation, which is the most appropriate treatment in terms of mortality, patient's well-being, and cost-effectiveness, establishing an active organization among university, Ministry of Health, and community is essential for the health of our patients and the national economy. The state can provide various advantages to the family of cadaveric donors.

Registry data provide information about the patients receiving RRT for CKD. We want to emphasize that these patients are like the visible part of the iceberg, and the number of patients who are in the earlier stages of CKD is much higher. The CREDIT study revealed that CKD is a significant public health concern of our country (2). It also showed that the prevalence of CKD in adult population (aged >18 years) in Turkey was 15.7% and that of stage 5.2 CKD was 5.2%. The prevalence of hypertension, diabetes mellitus, obesity, and metabolic syndrome in our population is a major risk factor for both CKD and cardiovascular disease.

Registry studies and the CREDIT study have shown that CKD and end-stage renal disease are one of the most critical health problems of our country. The quality of RRT is improving each year, and it is nearly universally accessible in our country. The Ministry of Health initiated the National Kidney Disease Prevention Program with the objectives of preventing CKD, early diagnosis and treatment of CKD, and slowing the progression of CKD.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.S., K.A., G.S.; Design - N.S., K.A., G.S.; Supervision - K.A., G.S.; Materials - Data Collection and/or Processing - K.A., G.S.; Analysis and/or Interpretation - N.S., K.A.; Literature Search - N.S.; Writing - N.S., K.A., G.S.; Critical Reviews - K.A.,G.S.

Acknowledgements: The authors would like to thank the following;

- 2018 registry board members: Siren Sezer, Mehmet Rıza Altıparmak, Zeki Tonbul, Soner Duman and İsmail Koçyiğit.
- Staff of dialysis and transplantation centers that have been providing regular information to the board for years.
- Şeyda Gül Özcan for her help in the editing of the manuscript.
- The following physicians (listed alphabetically) for their contributions in the data collection process

Abdullah Şumnu, Abdullah Uyanık, Adem Ergin, Ahmet Saygılı, Alaattin Kalı, Ali Değirmenci, Ali Delibaş, Ali Kemal Kadiroğlu, Alper Azak, Alper Soylu, Aydın Güçlü, Aydın Türkmen, Aykut Sifil, Aysel Kıyak, Aysun Karabay Bayazıt, Barış Seloğlu, Belda Dursun, Beltinge D. Kılıç, Beril Akman, Bülent Ataş, Celalettin Usalan, Cengiz Keleş, Dilek Güven

Taymez, Dilek Torun, Dilek Yılmaz, Ebru Sevinç Ok, Ercan Balcı, Ergün Parmaksız, Erhan Tatar, Esra Baskın, F. Fevzi Ersoy, Fatma Ülkü Adam, Fuad Karslı, Garip Bekfilavioğlu, Garip Şahin, Gökhan Temiz, Gül Özensel Duman, Gülçin Kantarcı, Gülperi Çelik, Gülseren Pehlivan, Halim Tuncez, Harika Alpay, Harun Aktaş, Hasan Yıkar, Hülya Çolak, Hüseyin Seren, İbrahim Ortagedik, İhsan Ergün, İsmail Dursun, Kamil Dilek, Kenan Bahadırlı, Kenan Bek, M. Deniz Aylı, Medine Gülşen Serin, Mehmet Erol, Mehmet İşcan, Mehmet Karakaya, Mehmet Polat, Meltem Gürsu, Mesiha Ekim, Murat Duranay, Murat Karakaş, Murat Tıkıç, Murathan Uyar, Mustafa Başgümüş, Mustafa Sevinç, N. Yılmaz Selçuk, Neşe Özkayın, Neval Duman, Nevzat Yurdakul, Osman Akpınar, Osman Dönmez, Rezan Topaloğlu, Sebahat Tülpar, Selçuk Yüksel, Sema Akman, Serhan Tuğlular, Serhan Vahit Pişkinpaşa, Serpil Göksu, Sevcan Bakkaloğlu, Seyhun Kürşat, Sümeyra Koyuncu, Şeref Rahmi Yılmaz, Tahsin Güzelyurt, Tamer Arıkan, Tansu Sav, Turgay Arınsoy, Tülay Aksoy, Yakup Ekmekçi, Yavuz Yeniçerioğlu, Zeki Aydın, Zekiye Aytül Noyan

Conflict of Interest: Nurhan Seyahi is a member of the Turkish Society of Nephrology. Kenan Ateş is the current President of the Turkish Society of Nephrology, and Gültekin Süleymanlar is the Former President of the Turkish Society of Nephrology (2008-2011).

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Türkiye'de, Nefroloji-Diyaliz ve Transplantasyon. Registry 2018: Türk Nefroloji Derneği Yayınları; Miki Matbaacılık San. Ve Tic. Ltd. Şti. Ankara, 2019
2. Süleymanlar G, Utaş C, Arinsoy T, Ateş K, Altun B, Altiparmak MR, et al. A population-based survey of Chronic REnal Disease in Turkey - the CREDIT study. Nephrol Dial Transplant 2011; 26: 1862-71. [CrossRef]
3. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, et al. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol 2013; 28: 169-80. [CrossRef]

10.5152/turkjnephrol.2020.3580

Original Article

Turkish Journal of Nephrology

BK Virus Nephropathy in Renal Transplantation: Case Series and Review of the Literature

İsmail Baloğlu[1], Kültigin Türkmen[1], Hacı Hasan Esen[2], Nedim Yılmaz Selçuk[1], Halil Zeki Tonbul[1]

[1]Division of Nephrology, Necmettin Erbakan University School of Medicine, Konya, Turkey
[2]Department of Pathology, Necmettin Erbakan University Meram School of Medicine, Konya, Turkey

Abstract

Objective: BK virus nephropathy (BKVN) is an important cause of kidney transplant failure. In this study, we aimed to evaluate our center's experience with BKVN in patients who had undergone renal transplantation and also discussed important aspects of the disease in this patient population.
Materials and Methods: In this study, 8 patients with BKVN were evaluated retrospectively, having been selected from a group of 330 patients (178 females, 152 males; mean age: 48.37±13.25 years) who had undergone renal transplantation between 2007 and 2017 and were followed up at our center.
Results: BKVN was detected in 8 of 330 renal transplantation patients (4 females, 4 males; mean age: 51.25±11.14 years). Their immunosuppressive regimen consisted of tacrolimus (FK), mycophenolate mofetil (MMF), and methylprednisolone. To reduce immunosuppressive dose, FK was discontinued in 3 patients, and they were switched to everolimus. In 2 of 7 patients, MMF was discontinued, and they were switched to azathioprine. FK or MMF doses were reduced in the8 patients with BKVN. Out of the 8 patients, cidofovir was administered to 1 patient, whereas intravenous immunoglobulins were administered to 3 patients. Additionally, pulse steroid treatment was administered to 1 patient who was diagnosed with acute rejection based on allograft biopsy findings. Among the 8 patients with BKVN, 1 (12.5%) experienced graft loss and was returned to hemodialysis treatment.
Conclusion: Although new alternative treatments are available, immunosuppressive dose reduction is still considered the most effective treatment. Therefore, we believe that effective screening and preemptive strategies should be defined more clearly instead of focusing on treatment strategies.
Keywords: Renal transplantation, BK virus, BK virus nephropathy

Corresponding Author: İsmail Baloğlu ✉ i_baloglu@hotmail.com
Received: 17.09.2018 **Accepted:** 15.10.2018

Presented in: This study was presented at the 35th National Congress of Nephrology, Hypertension, Dialysis and Transplantation, 3-7 October 2018, Antalya, Turkey.

Cite this article as: Baloğlu İ, Türkmen K, Esen HH, Selçuk NY, Tonbul HZ. BK Virus Nephropathy in Renal Transplantation: Case Series and Review of the Literature. Turk J Nephrol 2020; 29(1): 12-7.

INTRODUCTION

In organ transplant recipients, viral infections have become more important and prevalent due to iatrogenic immunosuppression. One of the causes of such viral infections is the BK virus, which was isolated in 1971 by Gardner et al. (1) from the urine of a patient with a ureteral stricture. BK virus (Polyomahominis 1) is a non-enveloped DNA virus belonging to the papovavirus family (2). Primary infections typically occur without specific signs or symptoms in approximately 60%-90% of the population. The virus persists in the urinary tract epithelium and may get reactivated under immunosuppressive conditions (3, 4).

Although BK virus nephropathy (BKVN) rarely occurs in renal allograft recipients after kidney transplantation, when it does occur, it causes various complications, such as ureteric stenosis, transient renal function deterioration, widespread viral nephropathy, and irreversible graft failure (5, 6). In addition, the prevalence of BKVN, which

is a major cause of graft loss, is between 1% and 10% in renal transplant recipients (3, 7). Although multiple factors related to the patient, graft, or extreme immunosuppression are implicated in BKVN, the factors that are truly responsible are not well known (8, 9). At the same time, although not an established protocol for treatment, reducing the dose of immunosuppressive drugs and facilitating the administration of immunoglobulins and various antiviral drugs are the usual methods of therapy (10).

In the present study, we aimed to investigate the incidence of BKVN in our center and to evaluate the diagnostic and therapeutic methods for BKVN in the light of current literature.

MATERIALS AND METHODS

The study protocol was approved by the Medical Ethics Committee of the Necmettin Erbakan University (School of Medicine, Konya, Turkey). Written informed consent was obtained from all subjects included in the study. This was a cross-sectional study comprising 330 patients (178 females, 152 males; mean age: 48.37±13.25 years) who underwent renal transplantation between January 2007 and December 2017 and followed up at our center. A review of medical records (including information on age, sex, transplantation dates, posttransplantation follow-up duration, time to BKVN diagnosis after transplantation, time between BKVN diagnosis and the last visit to transplantation outpatient clinic, immunosuppressive treatment regimens during and after BKVN, and serum creatinine levels at BKVN diagnosis and at the last visit) of BKVN patients was performed.

Screening for BKVN was performed using polymerase chain reaction (PCR) for BK virus DNA in the blood. The final diagnosis was established by detecting characteristic cytopathic changes associated with BK virus on renal biopsy and performing an immunohistopathological examination (11).

Statistical Analysis

Clinical and experimental data were analyzed using The Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 software (IBM Corp.; Armonk, NY, USA). Descriptive statistics for each variable were determined. Data were expressed as mean±standard deviation.

RESULTS

The evaluated patients had received renal transplantation from 40% of live donors and 60% of cadaveric donors. Their immunosuppressive regimen consisted of tacrolimus (FK), mycophenolatemofetil (MMF), and methylprednisolone (PRD).

BKVN was detected in 8 of the 330 renal transplantation patients (4 females, 4 males; mean age: 51.25±11.14 years). Thus, the incidence of BKVN was 2.4% in our center. Patients had received renal transplantation from living (2 patients) and cadaveric (6 patients) donors. Their mean follow-up duration was 58±13 months, and the mean time to BKVN diagnosis after transplantation was 25±20 months. The mean creatinine level at diagnosis was 1.68±0.35 mg/dL. The clinical and laboratory characteristics of the patients are shown in Table 1.

PCR was used to screen for the presence of BK virus DNA in the patients' blood. BKVN diagnosis was confirmed on the basis of the results of transplanted kidney biopsies that were all performed at our center. In addition, while acute rejection findings were observed in 1 patient's biopsy results, suspicious rejection findings were observed in 2 patients' biopsy results.

After the diagnosis of BKVN, to reduce the immunosuppressive dose, FK was discontinued in 3 patients, and they were switched to everolimus. In 2 of 7 patients, MMF was discontin-

Table 1. Clinical and laboratory characteristics of BKVN patients

Patient	Age	Sex	Donor type	Induction regimens for Tx	Immunosuppressive regimens before BKVN	Creatinin levels at BKVN diagnosis (mg/dL)	Post-transplantation follow-up duration (month)	Tx-BKVN Duration (month)
1	62	Female	Cadaveric	Basiliximab	FK+MMF+PRD	1.35	33	7
2	62	Male	Cadaveric	Basiliximab	FK+MMF+PRD	1.29	76	28
3	32	Female	Living	ATG	FK+MMF+PRD	2.10	71	35
4	45	Male	Living	ATG	FK+MMF+PRD	1.43	15	4
5	62	Female	Cadaveric	Basiliximab	FK+MMF+PRD	2.29	54	22
6	54	Male	Cadaveric	Basiliximab	FK+MMF+PRD	1.78	121	68
7	41	Male	Cadaveric	Basiliximab	FK+MMF+PRD	1.54	84	29
8	52	Female	Cadaveric	ATG	FK+MMF+PRD	1.72	13	10

FK: tacrolimus; MMF: mycophenolate mofetil; PRD: methylprednisolone; BKVN: BK virus-associated nephropathy

Table 2. Clinical outcomes of patients with BKVN

Patient	Post-BKVN follow-up Duration (month)	BKV-DNA levels at BKVN diagnosis (copy/mL)	BKV-DNA levels at lastevaluation (copy/mL)	Creatinin levels at BKVN diagnosis (mg/dL)	Creatinin levels at last evaluation (mg/dL)	Immunosuppressive regimens after BKVN	Additional treatment for BKVN
1	26	28760	0	1.35	1.02	Everolimus+ MMF + PRD	
2	48	11360	110	1.29	1.34	FK + MMF + PRD	
3	36	720	0	2.10	1.48	FK + MMF + PRD	
4	11	23400	993	1.43	2.56	Everolimus + Azathio-prine + PRD	Cidofovir + IVIg
5	15	8910	HD	2.29	HD	Everolimus + MMF + PRD	IVIg + Pulse PRD
6	53	3680	0	1.78	1.63	FK + MMF + PRD	
7	55	456	0	1.54	1.42	FK + MMF + PRD	
8	3	2957114	1819	1.72	1.43	FK + Azathioprine	IVIg

BKVN: BK virus-associated nephropathy

Table 3. Clinical outcomes of patients with BKVN

Patient	Post-BKVN follow-up Duration (month)	BKV-DNA levels at BKVN diagnosis (copy/mL)	BKV-DNA at last levels evaluation (copy/mL)	Creatinin levels at BKVN diagnosis (mg/dL)	Creatinin levels at last evaluation (mg/dL)	Treatment for BKVN
1	26	28760	0	1.35	1.02	RID
2	48	11360	110	1.29	1.34	RID
3	36	720	0	2.10	1.48	RID
4	11	23400	993	1.43	2.56	RID+Cidofovir + IVIg
5	15	8910	HD	2.29	HD	RID+IVIg+pulsePRD
6	53	3680	0	1.78	1.63	RID
7	55	456	0	1.54	1.42	RID
8	3	2957114	1819	1.72	1.43	RID+IVIg

BKVN: BK virus-associated nephropathy

ued, and they were switched to azathioprine. FK or MMF doses were reduced in all the 8 patients. Of these 8 patients, cidofovir was administered to 1 patient, whereas intravenous immunoglobuline (IVIgs) were administered to 3 patients. Additionally, pulse steroid treatment was administered to 1 patient who was diagnosed with acute rejection based on allograft biopsy results (Table 2).

Patients were followedup for BKVN manifestations for a mean duration of 30±20 months (3-55 months). Among the 8 patients with BKVN, 1 (12.5%) experienced graft loss and was returned to hemodialysis treatment. The finalmean creatinine level in the other 7 patients was 1.66±0.48 mg/dL. In the evaluation of the last PCR performed for the 7 patients, the mean BK virus DNA load was 417±717 copy/mL (0-1819 copy/mL) (Table 3). A control biopsy was performed in a patient with increased creatinine levels, and it was observed that the viral cytopathic effect persisted despite the decrease in the plasma BK virus DNA load (Figure 1).

DISCUSSION

Our study results showed numerous major findings regarding BKVN. First, the incidence of BKVN in our center was 2.4%. Second, a reduction in immunesuppressive dose was sufficient to treat BKVN in most patients. Third, the viral cytopathic effect can persist despite a decrease in the plasma BK virus DNA load. Fourth, we concluded that effective screening and preemptive strategies for BKVN need to be identified.

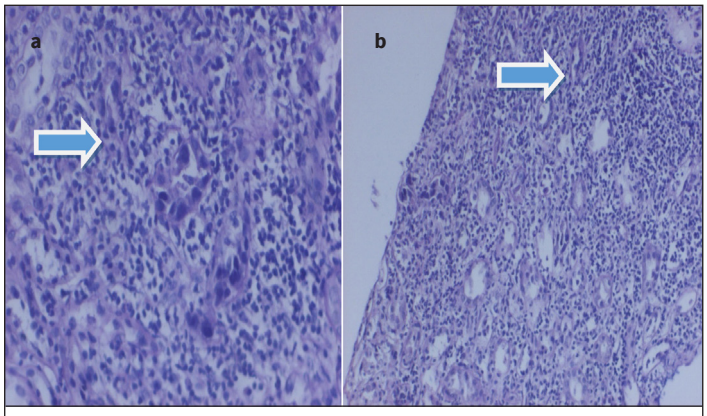


Figure 1. a, b. a) Image of BKVN in transplanted kidney biopsy at diagnosis time. b) The viral cytopathic effect was found to be continued at the control biopsy.

Recently, there has been a cumulative increase in the incidence of BKVN in renal transplant recipients. The etiology of this increase probably involves the interaction of multiple risk factors, including immunosuppression, patient determinants, the transplanted organ, and the virus itself. The incidence of BKVN in transplantation centers worldwide is between 2% and 9.3% (12-14), and the incidence (2.4%) observed in our center was consistent with that reported previously. Although an increase in the incidence of BKVN has been reported, there is no optimal method for diagnosis and screening of the same (15). BK viremia is usually detected within the first 3-4 months of transplantation. Therefore, based on the available literature, the suggested reasonable approach is that all transplantation patients be screened monthly for the first 6months. In addition, screening should be performed whenever kidney allograft dysfunction occurs (16). BKVN diagnosis can be presumed by observing an increase in the plasma BK virus DNA load or by the characteristic histological findings observed on renal biopsy.

BKVN is a major cause of graft loss in transplant recipients (15). Overall, the incidence of allograft failure ranges from 15% to 50% in the affected individuals (4, 17, 18). In 2006, Wadei et al. (19) analyzed data from 55 patients with biopsy-proven polyomavirus-associated nephropathy and found the frequency of graft loss to be 15%. Similarly, Ramos et al. (8) found the frequency of graft loss to be 16.4%. In our center, the rate of graft loss among patients with BKVN was 12.5%. Male gender, advanced age, HLA incompatibility, and early graft rejection have been reported as major risk factors for the development of BKVN (20, 21). However, female to male patient ratio was equal in our subjects, none of whom were of advanced age. Additionally, early rejection and HLA incompatibility were not detected in any patient. Concurrent acute rejection associated with BKVN is a common problem (22). On the other hand, it is well known that pulse steroid treatment for acute rejection increases the risk for BKVN, whereas reducing immunosuppressive dose to treat BKVN increases the risk for acute rejection (23). In our center, only 1 patient—in whom concurrent BKVN and acute rejection were confirmed via biopsy—was administered pulse PRD and IVIg treatment, followed by immunosuppressive dose reduction. However, graft loss occurred in this patient despite treatment, and he was returned to hemodialysis support.

Intense immunosuppression is perceived as a major risk factor for BKVN (24, 25). In recent years, a majority of patients with renal transplantation have been receiving a combination of FK and MMF. The prevalence of BKVN has increased after the use of these powerful immunosuppressant drugs (24). A prospective study conducted by Brennan et al. (26) has demonstrated that the use of FK-MMF-corticosteroid combinations is associated with an increased risk of BK virus replication and thus BKVN. In 2003, Mengel et al. (14) reported that there is a 13-fold greater risk of BKVN development in patients receiving a FK+MMF+PRD regimen. Therefore, the most common approach in BKVN treatment is reducing immunosuppression (27). Similarly, in our center, in accordance with previous data, all the patients with BKVN were receiving a FK+MMF+PRD regimen at the time of BKVN diagnosis. We also reduced the immunosuppressive doses of all patients with BKVN. However, it should be noticed that BKVN has been observed in patients exposed to drugs other than FK or MMF (28). Hence, no specific immunosuppressive drug can be exclusively associated with BKVN.

Cidofovir is a nucleotide analog that has recently been shown to be beneficial in the treatment of BKVN (10, 29). However, the underlying mechanism of inhibition of BKV replication by cidofovir is uncertain because the primary target for cidofovir inhibition is viral DNA polymerase, whereas BK virus does not specifically encode DNA polymerase (30). In addition, this agent is potentially highly nephrotoxic, causing proteinuria and renal failure (31). We used cidofovir (0.5 mg/kg, once in 2 weeks) in one patient at our center, in addition to immunosuppressive dose reduction and IVIg treatment. However, because of the increase in creatinine levels in this patient, the drug was discontinued.

Ig therapy is used as an alternative treatment for BKVN because it comprises BKV-neutralizing antibodies against all major genotypes (32). On the other hand, a study has shown that these antibodies may not exert neutralizing effects (33). Hence, immunoglobulin treatment may be a valuable option for treating BKVN, particularly in cases with both BK infection and graft rejection (34). We used IVIg treatment in 3patients with acute or concurrent suspicious rejection findings. A decline in the plasma BK virus DNA load was detected in 2 patients. However, a decline in creatinine levels was observed in only one patient.

Leflunomide is another treatment option that exerts both immunosuppressive and antiviral effects (35). Although its mechanism of action against BK virus is unknown, improvement or stabilization of the condition has been observed in patients with BKVN in a previous case series (36). However, the availability of limited number of studies and the potential for hematologic and hepatic toxicity preclude the routine use of leflunomide for the treatment of BKVN.

Comoli et al. (37) have shown that CD-3T cells play a critical role in the initiation and progression of BKVN. In another study, Comoli et al. (38) have reported that both CD8 and CD4T cells are involved in the recognition and elimination of BK virus (39, 40). It has also been verified that CD4T cells exhibit a specific multifunctional antiviral activity in BK virus infections (41, 42). The virion protein 1 of BKV stimulates the CD-4T-cells via the major histocompatibility complexI (43). CD-4T-cells may control BKV infection via the secretion of tumor necrosis factor-alpha, interferon-γ, and interleukin-2 (44). In patients with BKVN, the number of CD-4T-cells in the transplanted kidney also increase. Taking these reports into consideration, we speculate that Tlymphocyte-mediated immune responses can play an important role in the pathogenesis of BKVN.

In recent years, a study has shown that the percentage of Blymphocytes in kidneys transplanted to patients with BKVN is significantly increased (45). In addition, in another study, it was also found that BKVN progression is significantly associated with an increase in CD-20 cells and plasma cells (CD138-positive) (46). Therefore, humoral immunity was thought to be related to the pathogenesis of BKVN, but the exact immunopathological mechanisms remain uncertain. Part of the virus may increase the production of B-cell activating factor, thereby increasing the Blymphocyte count, which may in turn activate the Nuclear Factor kappa B (NF-κB) signaling pathway after the initiation of infection (47). However, whether BKV causes damage to the allograft via this mechanism has not been proven. Our study has some limitations. First, all the patients enrolled in the study were of Turkish ethnicity. Second, our study had a single-center design and a relatively small sample size.

CONCLUSION

Immunosuppressive dose reduction is still considered to be the most important treatment for BKVN. In addition, the viral cytopathic effect can persist independent of the plasma BK virus DNA load. Therefore, BKVN should be closely monitored, and effective screening and preemptive strategies should be defined for it in future studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Necmettin Erbakan University (School of Medicine, Konya, Turkey).

Informed Consent: Written informed consent was obtained from the patients who were included in this study.

Peer-review: Externally peer-reviewed

Author Contributions: Concept – K.T., İ.B.; Design - K.T., İ.B.; Supervision - K.T., N.Y.S., H.Z.T.; Resource - K.T., İ.B.; Materials - İ.B., H.H.E.; Data Collection and/or Processing - İ.B., H.H.E.; Analysis and/or Interpretation - İ.B., H.H.E., K.T.; Literature Search - K.T., İ.B.; Writing - K.T., İ.B., N.Y.S., H.Z.T.; Critical Reviews - K.T., N.Y.S., H.Z.T.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declare that they have received no financial support for this study.

REFERENCES

1. Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet 1971; 1: 1253-7. [CrossRef]
2. Hirsch HH, Steiger J. Polyomavirus BK. Lancet Infect Dis 2003; 3: 611-23.[CrossRef]
3. Shah KV. Polyomaviruses. In: Fields, BN, Knipe, DM, Howley, PM et al., eds. Fields Virology, 3rd edn. Philadelphia: Lippincott-Raven Publishers; 1996, p. 2027-43.
4. Trofe J, Gaber LW, Stratta RJ, Shokouh-Amiri MH, Vera SR, Alloway RR, et al. Polyomavirus in kidney and kidney-pancreas transplant recipients. Transpl Infect Dis 2003; 5: 21-8. [CrossRef]
5. Andrews CA, Shah KV, Daniel RW, Hirsch MS, Rubin RH. A serological investigation of BK virus and JC virus infections in recipients of renal allografts. J InfectDis 1988; 158: 176-81. [CrossRef]
6. Binet I, Nickeleit V, Hirsch HH. Polyomavirus infections in transplant recipients. Curr Opin Organ Transplant 2000; 5: 210-6. [CrossRef]
7. Shah KV, Daniel R, Warszawski R. High prevalence of antibodiesto BK virus, an SV40-related papovavirus, in residents of Maryland. J Infect Dis 1973; 128: 784-7. [CrossRef]
8. Ramos E, Drachenberg CB, Papadimitriou JC, Hamze O, Fink JC, Klassen DK, et al. Clinical course of polyomavirus nephropathy in 67 renal transplant patients. J Am Soc Nephrol 2002; 13: 2145-51. [CrossRef]
9. Randhawa PS, Khaleel-Ur-Rehman K, Swalsky PA, Vats A, Scantlebury V, Shapiro R, et al. DNA sequencing of viral capsid protein VP-1 region in patients with BK virus interstitial nephritis. Transplantation 2002; 73: 1090-4. [CrossRef]
10. Kadambi PV, Josephson MA, Williams J, Corey L, Jerome KR, Meehan SM, et al. Treatment of refractory BK virus-associated nephropathy with cidofovir. Am J Transplant 2003; 3: 186-9. [CrossRef]
11. Nickeleit V, Hirsch HH, Zeiler M, Gudat F, Prince O, Thiel G, et al. BK-virus nephropathy in renal transplants-tubular necrosis, MHC-class II expression and rejection in a puzzling game. Nephrol Dial Transplant 2000; 15: 324-32. [CrossRef]
12. Hirsch HH. Polyomavirus BK nephropathy: A (re-) emerging complication in renal transplantation. Am J Transplant 2002; 2: 25-30. [CrossRef]
13. Randhawa PS, Demetris AJ. Nephropathy due to polyomavirus type BK. N Engl J Med 2000; 342: 1361-3. [CrossRef]
14. Mengel M, Marwedel M, Radermacher J, Eden G, Schwarz A, Haller H, et al. Incidence of polyomavirus-nephropathy in renal allografts: influence of modern immunosuppressive drugs. Nephro Dial Transplant 2003; 18: 1190-6. [CrossRef]
15. Hirsch HH, Brennan DC, Drachenberg CB, Ginevri F, Gordon J, Limaye AP, et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. Transplantation 2005; 79: 1277-86. [CrossRef]
16. Randhawa PS, Brennnan DC. BK virus infection in transplant recipients: an overview and update. Am J Transplant 2006; 6: 2000-5. [CrossRef]
17. Drachenberg CB, Beskow CO, Cangro CB, Bourquin PM, Simsir A, Fink J, et al. Human polyoma virus in renal allograft biopsies: morphological findings and correlation with urine cytology. Hum Pathol 1999; 30: 970-7. [CrossRef]
18. Howell DN, Smith SR, Butterly DW, Klassen PS, Krigman HR, Burchette JL Jr, et al. Diagnosis and management of BK polyomavirus

interstitial nephritis in renal transplant recipients. Transplantation 1999; 68: 1279-88. [CrossRef]
19. Wadei HM, Rule AD, Lewin M, Mahale AS, Khamash HA, Schwab TR, et al. Kidney transplant function and histological clearance of virus following diagnosis of polyomavirus-associated nephropathy (PVAN). Am J Transplant 2006; 6: 1025-32. [CrossRef]
20. Bartlett S. Laparoscopic donor nephrectomy after seven years. Am J Transplant 2002; 2: 896-7. [CrossRef]
21. Hamze O, Ramos E, Papadimitriou JC, et al. Prospective incidence of polyomavirus in the early transplantation period. Am J Transplant 2002; 2: 261.
22. Drachenberg CB, Papadimitriou JC, Hirsch HH, Wali R, Crowder C, Nogueira J, et al. Histological patterns of polyomavirus nephropathy: correlation with graft outcome and viral load. Am J Transplant 2004; 4: 2082-92. [CrossRef]
23. Trofe J, Roy-Chaudhury P, Gordon J, Wadih G, Maru D, Cardi MA, et al. Outcomes of patients with rejection post-polyomavirus nephropathy. Transplant Proc 2005; 37: 942-4. [CrossRef]
24. Binet I, Nickeleit V, HirschH H, Prince O, Dalquen P, Gudat F, et al. Polyomavirus disease under new immunosuppressive drugs: a cause of renal graft dysfunction and graft loss. Transplantation 1999; 67: 918-22. [CrossRef]
25. Hodur DM, Mandelbrot D. Immunosuppression and BKV Nephropathy. N Engl J Med 2002; 347: 2079-80. [CrossRef]
26. Trofe J, Cavello T, First MR, Weiskittel P, Peddi VR, Roy-Chaudhury P, et al. Polyomavirus in kidney and kidney-pancreas transplantation: A defined protocol for immunosuppression reduction and histologic monitoring. Am J Transplant 2002; 34: 1788-9. [CrossRef]
27. Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. Am J Transplant 2005; 5: 582-94. [CrossRef]
28. Sachdeva MS, Nada R, Jha V, Sakhuja V, Joshi K. The high incidence of BK polyoma virus infection among renal transplant recipients in India. Transplantation 2004; 77: 429-31. [CrossRef]
29. Limaye AP, Jerome KR, Kuhr CS, Ferrenberg J, Huang ML, Davis CL, et al. Quantitation of BK virus load in serum for the diagnosis of BK virus-associated nephropathy in renal transplant recipients. J Infect Dis 2001: 183: 1669-72. [CrossRef]
30. Farasati NA, Shapiro R, Vats A, Randhawa P. Effect of leflunomide and cidofovir on replication of BK virus in an in vitro culture system. Transplantation 2005; 79: 116-8. [CrossRef]
31. Bagnis C, Izzdine H, Deray G. Renal tolerance of cidofovir. Therapie 1999; 54: 689-91.
32. Randhawa P, Pastrana DV, Zeng G, Huang Y, Shapiro R, Sood P, et al. Commercially available immunoglobulins contain virus neutralizing antibodies against all major genotypes of polyomavirus BK. Am J Transplant 2015; 15: 1014-20. [CrossRef]
33. Bohl DL, Brennan DC, Rkschkewitsch C, Gaudreault-Keener M, Major EO, Storch GA. BK virus antibody titers and intensity of infections after renal transplantation. J ClinVirol 2008; 43: 184-9. [CrossRef]
34. Casadei DH, del C Rial M, Opelz G, Golberg JC, Argento JA, Greco G, et al. A randomized and prospective study comparing treatment with high-dose intravenous immunoglobulin with monoclonal antibodies for rescue of kidney grafts with steroid-resistant rejection. Transplantation 2001; 71: 53-8. [CrossRef]
35. Chong AS, Zeng H, Knight DA, Shen J, Meister GT, Williams JW, et al. Concurrent antiviral and immunosuppressive activities of leflunomide in vivo. Am J Transplant 2006; 6: 69-75. [CrossRef]
36. Josephson MA, Gillen D, Javaid B, Kadambi P, Meehan S, Foster P, et al. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplantation 2006; 81: 704-10. [CrossRef]
37. Comoli P, Cioni M, Basso S, Gagliardone C, Potenza L, Verrina E, et al. Immunity to polyomavirus BK infection: immune monitoring to regulate the balance between risk of BKV nephropathy and induction of alloimmunity. Clin Dev Immunol 2013: 256923. [CrossRef]
38. Comoli P, Hirsch HH, Ginevri F. Cellular immune responses to BK virus. Curr Opin Organ Transplant 2008; 13: 569-74. [CrossRef]
39. Lamarche C, Orio J, Collette S, Senécal L, Hébert MJ, Renoult É, et al. BK polyoma virus and the transplanted kidney: immunopathology and therapeutic approaches. Transplantation 2016; 100: 2276-87. [CrossRef]
40. Dekeyser M, François H, Beaudreuil S, Durrbach A. Polyomavirus-specific cellular immunity: from BK-virus-specific cellular immunity to BK-virus-associated nephropathy. Front Immunol 2015; 6: 307. [CrossRef]
41. Binggeli S, Egli A, Schaub S, Binet I, Mayr M, Steiger J, et al. Polyomavirus BK-specific cellular immune response to VP1 and large T-antigen in kidney transplant recipients. Am J Transplant 2007; 7: 1131-9. [CrossRef]
42. Schmidt T, Adam C, Hirsch HH, Janssen MW, Wolf M, Dirks J, et al. BK polyomavirus-specific cellular immune responses are age-dependent and strongly correlate with phases of virus replication. Am J Transplant 2014; 14: 1334-45. [CrossRef]
43. Li X, Sun Q, Chen J, Ji S, Wen J, Cheng D, et al. Immunophenotyping in BK virus allograft nephropathy distinct from acute rejection. Clin Dev Immunol 2013: 412902. [CrossRef]
44. Buettner M, Xu H, Böhme R, Seliger B, Jacobi J, Wiesener M, et al. Predominance of TH2 cells and plasma cells in polyomavirus nephropathy: a role for humoral immunity. Hum Pathol 2012; 43: 1453-62. [CrossRef]
45. Lu B, Zhang B, Wang L, Ma C, Liu X, Zhao Y, et al. Hepatitis B virus e antigen regulates monocyte function and promotes b lymphocyte activation. Viral Immunol 2017; 30: 35-44. [CrossRef]

10.5152/turkjnephrol.2020.3585

Original Article

Turkish Journal of Nephrology

Evaluation of Long-Term Thirst due to Ramadan Fasting in Terms of Acute Kidney Injury

İsmail Baloğlu, Fatih Pektaş, Halil Zeki Tonbul, Nedim Yılmaz Selçuk, Kültigin Türkmen

Division of Nephrology, Necmettin Erbakan University School of Medicine, Konya, Turkey

Abstract

Objective: Acute kidney injury (AKI) is characterized by a rapid decline (i.e., within hours and days) of renal function. Long-term thirst due to fasting may cause a decrease in both the intravascular volume and kidney perfusion. The aim of this study was to investigate the relationship between long-term thirst due to fasting and AKI.

Materials and Methods: Forty-five individuals (24 females, 21 males; mean age, 75±12 years) whose kidney function was normal and who were fasting during the month of Ramadan in 2014 participated in the study. The participants were divided into three groups: the first group was aged >60 years and using angiotensin-converting enzyme inhibitors for hypertension, the second group was aged >60 years and did not use drugs, and the third group was aged <40 years. The thirst period was 18 hours. The Acute Kidney Injury Network (AKIN) criteria were used for AKI diagnosis.

Results: When all groups were evaluated according to the AKIN-urinary output criteria, the first 6-hour period was the AKI stage1, and the final 12-hour period was the AKI stage 2. There was a small (0.06 mg/dL) but significant increase in the mean serum creatinine level in all groups (p=0.001). Cases could not be evaluated in terms of the AKIN creatinine criteria because the thirst period was not 48 hours long and the increase in creatinine levels was not >0.3 mg/dL.

Conclusion: The thirst due to fasting did not increase the risk of AKI in the population with a normal kidney function, and the AKIN-urinary output criteria alone were not adequate to evaluate AKI in patients who were fasting during the month of Ramadan.

Keywords: Acute kidney injury, Ramadan fasting, thirst

Corresponding Author: İsmail Baloğlu ✉ i_baloglu@hotmail.com

Received: 19.09.2018 **Accepted:** 28.11.2018

Presented in: This study was presented at the ERA-EDTA 54th Congress, June 3-6, 2017, Madrid, Spain.

Cite this article as: Baloğlu İ, Pektaş F, Tonbul HZ, Selçuk NY, Türkmen K. Evaluation of Long-Term Thirst due to Ramadan Fasting in Terms of Acute Kidney Injury. Turk J Nephrol 2020; 29(1): 18-22.

INTRODUCTION

Acute kidney injury is a clinical syndrome characterized by a rapid loss of kidney function as a result of decreased glomerular filtration rate (GFR), which develops within hours, days, or weeks (1). Risk factors for acute renal failure include advanced age, gender, concomitant diseases, sepsis, history of major surgery, cardiogenic shock, use of nephrotoxic drugs, and substance abuse (2). The diagnosis of acute kidney injury (AKI) is still based on an increase in serum creatinine levels and a decrease in the urine volume. Acute renal failure is defined as anincrease in serum creatinine levels by >0.3 mg/dL within 48 hours or a urine volume <0.5 mL/kg/h for 6 hours (3).

A long life spanleads to an increase in the number of elderly patients. Although the proportion of elderly population is determined to be 12% at present, the estimated elderly population expected after 25 years is 21%. In addition, life expectancy is increasing rapidly among elderly individuals aged >65 years in developed countries. Acute renal failure in elderly individuals is associated with a decreased metabolic capacity of the kidneys, certain aging-related anatomic or physiological changes in the kidneys, and more frequent occurrence of systemic diseases such as diabetes or hypertension (4).

Prolonged thirst due to fasting may result in a decreased intravascular volume and renal perfusion. Acute renal

failure is more common in elderly patients with a decreased renal reserve because they are more susceptible to ischemia (5-7). The use of a renin-angiotensin system (RAS) blocker is one of the important causes of prerenal AKI. The use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers in patients with hypotension or reduced blood volume (especially in those with heart failure) may contribute to the development of AKI (8). In this study, we aimed to determine whether long-term thirst due to Ramadan fasting leads to acute renal failure according to the AKIN criteria in patients who are elderly and/or are using RAS blockers.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of the Necmettin Erbakan University School of Medicine. Written informed consent was obtained from study participants.

In this study, 45 (F/M:24/21) individuals who had applied to internal medicine clinics and were fasting were evaluated. The month of Ramadan coincided with July, a hot summer month, and the fasting period was too long (approximately 18 hours). The study was conducted on the 3rd and 4th weeks of Ramadan.

In the first group of patients, 15 patients aged >60 years who used an ACE inhibitor as an antihypertensive agent were evaluated. In the second group, 15 patients aged >60 years who received no medication were evaluated. In the last group, 15 healthy people aged <40 years were included. The fasting period was 18 hours. The AKIN criteria were used in the diagnosis and staging of AKI.

The body weight and blood pressure values measured in the morning and before the fasting break were recorded. Blood and urine samples were analyzed at 09.00 am and in the evening before the fasting break. Urea, creatinine, and urine densities were measured. Urine secreted during the 18-hour period of thirst/fasting was collected separately every 6 hours.

Statistical Analysis

Clinical data were analyzed using The Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 (IBM Corp.; Armonk, NY, USA). Descriptive statistics for each variable were presented. Continuous data were expressed as the mean±standard deviation. Categorical data were expressed as frequencies and percentages. Mixed analysis of variance (ANOVA) models were used to assess between-group differences in terms of continuous variables. Group and time main effects and their interaction were examined in these mixed ANOVA models. Tests of simple effects were performed when a significant main effect was reached. Baseline eGFR values were compared using ANOVA. A difference was considered significant when p-value was <0.05.

RESULTS

The mean age of the patients was 75±12 (25-78) years, and the mean body weight was 75±12 kilograms GFR of the groups was calculated according to the modification of diet in the renal diseases study. On examining the group averages, GFR was higher in younger patients as expected (p<0.001) (Table 1).

The average volume of urine collected during the thirst period was 900±166 mL. It was observed that 70% of the total urine output occurred in the first 6-hour period. The average volume of urine collected during the second 6-hour period was 174±61 mL and during the third 6-hour period was 78±29 mL. When urine output was calculated in terms of mL/kg/h according to the AKIN-urinary output criteria, all the groups were found to have AKI stage 1 in the second 6-hour period and AKI stage 2 in the last 12-hour period (Table 2).

Table 1. Mean GFR values in patient groups according to MDRD

	GFR (min-max)	p
Age <40	114.17+19.24 (85-150.6)	<0.001
Age >60	81.94+11.62 (55.2-98.1)	
Age >60+ACE-I	87.34+19.58 (61-129)	

Table 2. Hourly mean urine volumes duringthe period of thirst

	Second 6 Hours	Third 6 Hours	Last 12 Hours
Age <40	0.42±0.14 mL/kg/h	0.17±0.07 mL/kg/h	0.29±0.1 mL/kg/h
Age >60	0.40±0.12 mL/kg/h	0.18±0.07 mL/kg/h	0.28±0.08 mL/kg/h
Age >60+ACE-I	0.35±0.11 mL/kg/h	0.16±0.06 mL/kg/h	0.25±0.09 mL/kg/h

Table 3. Systolic and diastolic blood pressure

	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)	
	Morning	Before Fasting Break	Morning	Before Fasting Break
Age <40	115.00±12.00	113.00±13.00	76.00±5.00	78.00±4.00
Age >60	126.00±9.00	124.00±10.00	88.00±3.00	85.00±6.00
Age >60+ACE-I	138.00±10.00	135.00±8.00	110.6±6.00	108.00±7.00

Table 4. Differences between groups (mixed analysis of variance models)

	Group	Time	Group/Time Interaction
eGFR	<0.001	<0.001	0.285
Urine densities	0.98	<0.001	0.98
Systolic blood pressure	<0.001	0.09	0.31
Diastolic blood pressure	0.08	0.80	0.91
Weight	0.019	<0.001	0.98

Table 5. Serum creatinine level during the period of thirst

	Morning	Evening (before fasting break)	p
Age <40	0.78±0.15 mg/dL	0.85±0.13 mg/dL	p=0.001
Age >60	0.88±0.12 mg/dL	0.94±0.13 mg/dL	p=0.001
Age >60+ACE-I	0.77±0.14 mg/dL	0.82±0.13 mg/dL	p=0.001

Table 6. Results of between-subjects effects according to mixed analysis of variance

Source	df	Mean Square	F	p
Weight				
Group	2	1084.837	4.381	0.019
Error	42	247.605		
Systolic blood pressure				
Group	2	6915.833	25.328	<0.001
Error	42	273.056		
Diastolic blood pressure				
Group	2	1123.333	5.962	0.005
Error	42	188.413		
eGFR				
Group	2	7537.408	16.210	<0.001
Error	42	464.980		
Urine densities				
Group	2	138.100	3.481	0.040
Error	42	39.671		
Urine volume				
Group	2	573.889	0.020	0.980
Error	42	28036.032		
Hourly mean urine volume				
Group	2	0.017	1.070	0.352
Error	42	0.016		

The patients' body weight was examined in the morning and before the fasting break. The average body weight of the group that did not use drugs and was aged >60 years was the highest among the three groups. There was a significant decrease in body weight due to 18 hours of hunger and thirst. While the average body weight of the three groups was 75±12 kg, the body weight decreased by 1.2 kg to 73.8±12 kg before the fasting break

Table 7. Results of within-subjects effects according to mixed analysis of variance

Source	df	Mean Square	F	p
Weight				
Time	1	35.469	928.751	<0.001
Group x Time	2	0.001	0.020	0.980
Error	42	0.038		
Systolic blood pressure				
Time	1	146.944	2.946	0.093
Group x Time	2	60.278	1.208	0.309
Error	42	49.881		
Diastolic blood pressure				
Time	1	17.778	.439	0.511
Group x Time	2	41.111	1.016	0.371
Error	42	40.476		
eGFR				
Time	1	1373.193	29.780	<0.001
Group x Time	2	59.639	1.293	0.285
Error	42	46.112		
Urine densities				
Time	1	3385.600	332.077	<0.001
Group x Time	2	93.100	9.132	0.001
Error	42	10.195		
Urine volume				
Time	3	6808872.037	865.011	<0.001
Group x Time	6	426.481	0.054	0.999
Error	126	7871.429		
Hourly mean urine volume				
Time	1	1.100	229.963	<0.001
Group x Time	2	0.006	1.319	0.278
Error	42	0.005		

(p<0.001).In addition, urinalysis was performed in the morning and before the fasting break. It was observed that urine densities were increased in all three groups (p<0.001). Systolic and diastolic blood pressures were measured in the morning and before the fasting break. The systolic blood pressure was the highest among the patients who were aged >60 years and used ACE inhibitors (Tables 3, 4). There were no significant changes in blood pressure. There was a small (0.06 mg/dL) but significant increase in the mean serum creatinine level in all the groups (p<0.001) (Table 5). Cases could not be evaluated in terms of the AKIN creatinine criteria because the thirst period was not 48 hours long and the increase in creatinine levels was not >0.3 mg/dL. Between-group differences in terms of continuous variables were examined using mixed ANOVA models (Tables 6, 7).

DISCUSSION

Our study results showed numerous findings. First, although fasting caused a small but significant increase in creatinine levels, it did not cause an increase in AKI. Second, when there is limited fluid intake (such as the month of Ramadan), the kidneys may produce less urine. Therefore, it may be misleading to consider AKI on the basis of urine volume only. These findings have been presented in a less detailed form as a poster at the 54th ERA-EDTA Congress (9).

Various studies have shown that fasting during the month of Ramadan does not cause any adverse effects on healthy adults (10). However, in patients aged >60 years and in those taking ACE inhibitors, the effect of fasting on renal damage has not been studied. Elderly patients with a decreased renal reserve are more susceptible to ischemia, and therefore, AKI develops more frequently in them. In case of hypovolemia, angiotensin II plays an important role in maintaining intraglomerular pressure and GFR within the normal limits. The use of ACE inhibitors may impair this autoregulation and lead to a reduction in GFR in hypovolemia, especially in patients undergoing coronary bypass grafting (11). In our study, serum creatinine levels increased in all three groups but did not exceed the 0.3 mg/dL limit set by AKIN. In addition, because the thirst period was not 48 hours, no evaluation was made in this respect. In terms of increase in creatinine levels, there was no significant difference between the groups of patients aged <40 years and those aged >60 years as well as between the groups that did and did not use ACE inhibitors (p>0.05).

Cheah et al. (12) showed that during the month of Ramadan, the body is well adapted to hunger/thirst, and the renal function is not adversely affected. While the daytime urine output was significantly decreased, the night time urine output was increased, and the total urine volume remain unchanged. Under normal conditions, even a 2% decrease in the extracellular fluid volume increases osmolarity, stimulates antidiuretic hormone secretion, and prevents diuresis. In our study, the participants' body weight in the evening decreased by an average of 1.2 kg compared with that in the morning. The average urine output in the last 12 hours of the fasting period was approximately 250 mL, indicating the oliguria level. There was no difference between the groups in terms of urine volume (p>0.05).

The number of cases in studies on kidney function among patients with advanced-stage chronic kidney disease (CKD) are generally insufficient and have reported contradictory results. Especially in patients with sodium-losing nephropathy, fasting can lead to dehydration and impaired renal function (13). In 2014, Al Wakeel et al. (14) examined the effect of fasting during 14 hours in Ramadan on blood levels of certain parameters in 39 patients with stage 3-4 CKD and 32 patients on hemodialysis (HD). They showed that blood urea, creatinine, uric acid, and phosphorus levels were increased after the fasting period in patients on HD, and 25% of these patients developed hyperkalemia, although there was no significant effect on patients with stage 3-4 CKD (14).

It has been shown in various studies that there is no harmful effect of fasting on renal function in transplant patients with normal graft function. Similarly, Boobes et al. (15) found that there was no significant change in eGFR before and after the month of Ramadan. Our study has some limitations. First, all the patients enrolled in the study were Turkish. Second, our study had a single-center design, and the sample size was relatively small. Third, the patients were not evaluated in terms of the AKIN creatinine criteria.

CONCLUSION

We found that long-term thirst due to Ramadan fasting caused a small but significant increase in creatinine levels in all the three groups, but this increase was not sufficient enough to be evaluated as per the AKIN creatinine criteria. When evaluating urinary output according to the AKIN criteria, it was observed that AKI stage 2 developed in all the three groups. After the fasting break, the urine volume returned to normal in a couple of hours. Therefore, the thirst caused by fasting did not increase the risk of AKI in the population with a normal renal function, and the AKIN-urinary output criteria alone were not enough to assess renal damage in patients who were fasting.

Ethics Committee Approval: Ethics Committee approval was received for this study from the Ethics Committee of the Necmettin Erbakan University (School of Medicine, Konya, Turkey).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.Z.T., F.P., N.Y.S.; Design – H.Z.T., F.P., N.Y.S.; Supervision – H.Z.T., N.Y.S., K.T.; Resource – F.P., İ.B.; Materials – F.P., İ.B.; Data Collection and/or Processing – F.P., İ.B.; Analysis and/or Interpretation – H.Z.T., F.P., K.T.; Literature Search – F.P., İ.B., H.Z.T.; Writing – İ.B., K.T., H.Z.T.; Critical Reviews – N.Y.S., H.Z.T., K.T.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declare that they have received no financial support for this study.

REFERENCES

1. Van Biesen W, Lameire N, Vanholder R, Mehta R. Relation between acute kidney injury and multiple-organ failure: the chicken and the egg question. Crit Care Med 2007; 35: 316-7. [CrossRef]
2. Bagshaw SM, Bellomo R. Early diagnosis of acute kidney injury. Curr Opin Crit Care 2007; 13: 638-44. [CrossRef]
3. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11: R31. [CrossRef]
4. Rosner M, Abdel-Rahman E, Williams ME, ASN Advisory Group on Geriatric Nephrology. Geriatric nephrology: responding to a growing challenge. Clin J Am Soc Nephrol 2010; 5: 936-42. [CrossRef]
5. Mustafa KY, Mahmoud NA, Gumaa KA, Gader AM. The effects of fasting in Ramadan. 2. Fluid and electrolyte balance. Br J Nutr 1978; 40: 583-9. [CrossRef]
6. Akcay A, Turkmen K, Lee D, Edelstein CL. Update on the diagnosis and management of acute kidney injury. Int J Nephrol Renovasc Dis 2010; 3: 129-40. [CrossRef]
7. Akcay A, Nguyen Q, He Z, Turkmen K, Won Lee D, Hernando AA, et al. IL-33 exacerbates acute kidney injury. J Am Soc Nephrol 2011; 22: 2057-67. [CrossRef]
8. Tonelli M, Gill J, Pandeya S, Bohm C, Levin A, Kiberd BA. Barriers to blood pressure control and angiotensin enzyme inhibitor use in Canadian patients with chronic renal insufficiency. Nephrol Dial Transplant 2002; 17: 1426-33. [CrossRef]
9. Nephrology Dialysis Transplantation; Suppl 3: 175. 54th ERA-EDTA Congress, Madrid Spain, June 3th-6th, 2017.
10. Berbari AE, Daouk NA, Mallat SG, Jurjus AR. Ramadan fasting in health anddisease. In: Berbari AE, Mancia G, editors. Special Issues in Hypertension. Milan, Italy: Springer-Verlag; 2012. [CrossRef]
11. Onk OA, Onk D, Ozcelik F, Gunay M, Turkmen K. Risk factors for acute kidney injury after coronary artery bypass surgery and its detection using neutrophil gelatinase-associated lipocalin. Cardiorenal Med 2016; 6: 216-29. [CrossRef]
12. Cheah SH, Ch'ng SL, Hussain R, Duncan MT. Effects of fasting during Ramadan on urinary excretion in Malaysian Muslims. Br J Nutr 1990; 63: 329-37. [CrossRef]
13. Bernieh B, Al Hakim MR, Boobes Y, Abu Zidan FM. Fasting Ramadan in chronic kidney disease patients: clinical and biochemical effects. Saudi J Kidney Dis Transpl 2010; 21: 898-902.
14. Al Wakeel J. Kidney function and metabolic profile of chronic kidney disease and hemodialysis patients during Ramadan fasting. Iran J Kidney Dis 2014; 8: 321-8.
15. Boobes Y, Bernieh B, Al Hakim MR. Fasting Ramadan in kidney transplant patients is safe. Saudi J Kidney Dis Transpl 2009; 20: 198-200.

10.5152/turkjnephrol.2020.3631

Original Article

Turkish Journal of Nephrology

Effects of Keto-Analogs in the Pathologic Findings of Diabetic Nephropathic Rats

Yelda Deligöz Bildaci[1], Ganime Çoban[2], Huri Bulut[3], Meltem Gürsu[1], Ömer Celal Elçioğlu[1], Rümeyza Kazancıoğlu[1]

[1]Division of Nephrology, Bezmialem University School of Medicine, İstanbul, Turkey
[2]Department of Pathology, Bezmialem University School of Medicine, İstanbul, Turkey
[3]Department of Biochemistry, Bezmialem University School of Medicine, İstanbul, Turkey

Abstract

Objective: Some studies have shown that keto amino acids (KA) reduce proteinuria and improve renal function as well as nutritional status in patients with diabetic nephropathy. We aimed to compare the pathologic findings of kidneys of rats that were given protein-restricted diets enriched with KA with those of rats given protein-restricted diet alone.
Materials and Methods: The study included 22 16-week-old Sprague–Dawley rats and was conducted at the research center. The rats were randomly divided into two equal groups. Group I (study) received KA (35-70 mg/kg) with gavage along with low-protein diet (10% protein), and Group II (control group) received low-protein diet alone. The treatment was continued for 2 weeks, after which the study ended. Blood samples were obtained in the 5th and 7th weeks of treatment for measuring albumin and creatinine levels; bilateral nephrectomy was performed at the end of the study.
Results: All rats had minimal thickness of the basement membrane. The serum albumin levels were significantly higher in the study group ($p<0.05$). The study group rats had greater thickness of the basement membranes.
Conclusion: Our study may inspire further studies in this particular field with the question whether KA can slow the progression of diabetic nephropathy.
Keywords: Diabetic nephropathy, keto amino acids, kidney failure

Corresponding Author: Yelda Deligöz Bildaci ✉ yeldadeligoz@gmail.com
Received: 20.10.2018 **Accepted:** 20.11.2018

Presented in: This study was presented at the 34th National Neprology Congress, 10/2017, Antalya, Turkey.

Cite this article as: Deligöz Bildaci Y, Çoban G, Bulut H, Gürsu M, Elçioğlu ÖC, Kazancıoğlu R. Effects of Keto-analogs in the Pathologic Findings of Diabetic Nephropathic Rats. Turk J Nephrol 2020; 29(1): 23-7.

INTRODUCTION

End-stage renal failure (ESRD) represents an important health concern due to its increasing incidence and prevalence (1, 2). One of the leading causes of ESRD globally is diabetic nephropathy (DNP), which is also the most common cause of ESRD in Turkey (3, 4). Therefore, preventing this complication of diabetes, the mechanism of which is not fully understood, will be an important step in preventing ESRD development.

DNP is a clinical condition characterized by proteinuria or albuminuria (300 mg/day or 200 mcg/min, respectively), decreased glomerular filtration rate, and increased arterial blood pressure, demonstrated in two different urine assays for 3-6 months (5). Genetic factors may be present in the pathophysiology of DNP; however, environmental factors play a role in the progression of the disease (2).

The amount of protein in the diet is important in all patients with chronic kidney disease (CKD) (6). It has been shown that a low-protein (0.6 mg/kg/day) diet in patients with CKD, including DNP, has been shown to slow the progression to ESRD (7). Low-protein dietary intake causes a decrease in uremic symptoms and levels of phosphate, sulfate, organic acid, and amine, which occurs as a result of protein catabolism in patients (8). However, the fact that patients cannot receive essential amino acids, while they are limited from taking protein causes nutritional deficiency (8, 9). Malnutrition develops in these patients due to protein-restricted diet. In

addition, a very low-protein diet has been associated with increased mortality in CKD (9).

Keto amino acids (KA) are composed of nitrogen-poor analogs of essential amino acids. KA neutralize the excess nitrogen load by inhibiting the urea cycle and preventing urea production. In addition, it helps in maintaining the nutritional status (10).

In this study, the effects of protein-poor diet and KA given in addition to the protein-poor diet on the kidney of rats with DNP were examined comparatively under light microscopy.

MATERIALS AND METHODS

The study included 22 16-week-old Sprague–Dawley rats and was conducted at the research center. The rats were kept on a 12-hour day/night cycle with a controlled temperature of 23°C±2°C and free access to water and food. At the beginning of the study, 65 mg/kg intraperitoneal streptozocin injection was administered to the rats. At 48 hours, venous blood glucose was measured with glucostrip (Abbott Medical, IL, USA), and rats with blood glucose levels of ≥300 mg/dL were considered diabetic. Rats were fed with a standard rat feed containing 20% protein up to the 5th week. The rats were placed in metabolic cabinets in the 5th week, and 24-hour urine was collected. On the day of collection, anesthesia was performed with propofol and ketamine, and 1 cc of blood was collected from the subclavian artery. It was centrifuged, and the serum was stored at −80°C. The amount of protein in the 24-hour urine was measured using the rat kit (Vettest UPC Urine Protein/Creatinine 24 test).

Eighteen rats with DNP diagnosis were randomly divided into two equal groups. Group 1 (study group) received a low-protein diet (10% protein) and 35-70 mg/kg KA with gavage (11), and Group 2 (control group) was given a low-protein diet alone. The rats received subcutaneous long-acting insulin (insulin glargine-Sanofi) three times a week. This treatment was continued for 2 weeks. At the end of these 2 weeks, the animals were anesthetized with propofol and ketamine, and their blood was collected, centrifuged, and stored at −80°C. The rats were weighed at the beginning and at the end of the experiment, and their weights were recorded. Then, nephrectomy was performed, and all animals were sacrificed. Nephrectomy content was put into formol and sent to pathology laboratory. During the study, the care and evaluation of the data of the animals were conducted in accordance with the principles of the Guide for the Care and Use of Laboratory Animals. This study was approved by the University Ethics Committee for Experimental Animals and supported by the University Scientific Research Projects Unit.

Biochemical Method

Rat albumin Enzyme Linked Immunosorbent Assay (ELISA)

Following the thawing of the serum and urine samples, an albumin ELISA kit (elabscience, USA, lot no: E-EL-R0362) was used to measure the albumin beta value. Samples and standards were added to the plates coated with antihuman monoclonal antibodies prior to incubation. After incubation, the plate was washed to remove the unbound enzyme. Then, the 3,3′,5,5′-Tetramethylbenzidine (TMB) solution was added to change the color of the liquid to blue. With the effect of the acid, the final color was yellow. The optical density was evaluated at 450 nm with a standard plate reader (Thermo Scientific Microplate Reader). The detection limits of the kit used were between 1.25 and 80 µg/mL.

Rat serum creatinine ELISA

Following the thawing of the serum and urine samples, a serum creatinine ELISA kit (elabscience, USA, lot no: E-EL-R0058) was used to measure the serum creatinine beta value. Samples and standards were added to the plates coated with antihuman monoclonal antibodies prior to incubation. After the incubation, the plate was washed to remove the unbound enzyme. Then, the TMB solution was added to change the color of the liquid to blue. With the effect of the acid, the final color was yellow. The optical density was evaluated at 450 nm with a standard layer reader (Thermo Scientific Microplate Reader). The detection limits of the kit were between 3.13 and 200 µg/mL.

Evaluation of urine protein

The protein amounts in the samples were evaluated using the Bradford assay kit (Thermo scientific Pierce BCA) and were monitored with a microplate Reader at a wavelength of 595 nm (Thermo Scientific Multiskan FC, 2011-06, USA).

Pathological evaluation

For histological evaluation, bilateral nephrectomy materials were fixed with 10% formol. These tissues were recorded and transferred to a Thermo closed system, a fully automatic tissue tracking device. The tissue was embedded in paraffin blocks after the tissue follow-up was completed; 3-µm-thick sections were taken with microtome. All sections were stained with hematoxylin–eosin and periodic acid Schiff stains. The histopathological examination was evaluated by light microscopy. The pathological classification was performed according to the criteria published by Tervaert et al. in 2010 (12). Glomerular lesions (thickening of basement membranes, mesangial enlargement, nodular sclerosis, and advanced diabetic glomerulosclerosis) and tubulointerstitial lesions (tubular atrophy and interstitial fibrosis) were evaluated as none: 0, <25%: 1, 25%-50%: 2, and >50%: 3; interstitial inflammation was evaluated as none: 0, if around fibrotic interstitium and atrophic tubule: 1, and if in other areas: 2; arteriolar hyalinosis was evaluated as none: 0, one arteriole: 1, and multiple arterioles: 2.

Statistical Analysis

Data are presented as average±standard deviation. The comparison of the averages of variables that do not show normal distribution was performed using the variance analysis and Mann–Whitney U tests. Two-tailed $p<0.05$ were considered sta-

tistically significant. Statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS) version 19.0 (IBM Corp.; Armonk, NY, USA).

RESULTS

The characteristics of the rats at the beginning of the experiment are shown in Table 1. There was no significant difference between their weights and blood sugar levels on the 1st day of the study (p=0.161). In all rats, the blood glucose level was >300 mg/dL 48 h after streptozocin injection. Polyuria and weight loss in the animals continued throughout the experiment. The average proteinuria in the 5th week was 19.67±9.31 µg/mL. When the rats were divided into two groups, this value was found to be 19.38 µg/mL in the study group and 19.96 µg/mL in the control group. There was no significant difference between the groups (p=1.00).

In the biochemical analysis performed, the average serum creatinine level in the study group was 45.26±29.87 µg/mL in the 5th week and 86.20±19.36 µg/mL in the 7th week (p=0.79). In the control group, the average serum creatinine level was 51.27±14.98 µg/mL in the 5th week and 92.26±23.04 µg/mL in the 7th week (p=0.79).

The average serum albumin level of the rats was 16.03±3.89 µg/mL in the 5th week and 10.12±4.58 µg/mL in the 7th week. The average serum albumin level in the 5th week was 16.11±3.49 µg/mL in the study group and 15.95±4.45 µg/mL in the control group. The average serum albumin level in the 7th week was 13.15±4.53 mg/dL in the study group and 7.09±1.83mg/dL in the control group. In both groups, the serum albumin levels in the 7th week were lower than those in the 5th week. The decrease in serum albumin level was significantly lower in the study group than in the control group (p=0.008).

Table 1. Evaluation of Study Variables Using the Mann–Whitney U test

	Study Group (n=9)	Control Group (n=9)	p
First weight, gr	339.11±54.92	317.00±29.82	0.387
Weight in the 7th week, gr	225.44±50.46	232.44±22.24	0.931
Blood glucose level in the 5th week, mg/dL	95.88±14.49	103.00±13.78	0.161
Serum creatinine in the 5th week, µg/mL	45.26±29.87	51.27±14.98	0.796
Serum creatinine in the 7th week, µg/mL	86.21±19.37	92.26±23.04	0.546
Proteinuria in the 5th week, µg/mL	19.38±8.01	19.96±10.93	1.00
Albumin in the 5th week, µg/mL	16.11±3.49	15.95±4.45	0.863
Albumin in the 7th week, µg/mL	13.15±4.53	7.09±1.83	0.008

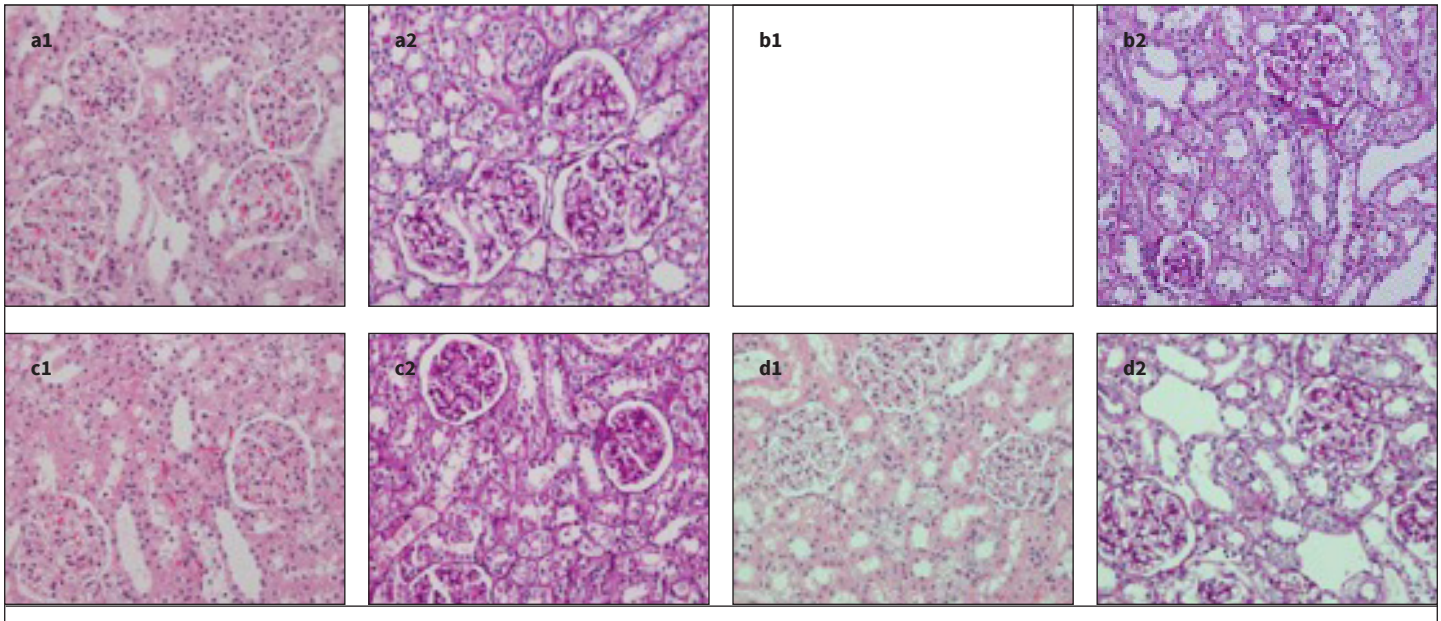


Figure 1. a-d. Pathological samples from rats; Groups a and b: study groups, Groups c and d: not receiving keto-amino acid. In Groups a) and b), HEX200 and PASX200 dyes show segmental thickening of the basement membranes and regular tubulus structures. In Groups c) and d), normal tubulus cells draw attention in HEX200 and PASX200 dyes.

In the pathological examination of the kidneys of the rats, a minimal thickness increase in the basement membranes was detected. It was observed that the basement membrane was thicker in two rats when compared to others, and atrophic tubules with minimal mononuclear infiltration were seen in one rat (Figure 1).

DISCUSSION

In the diabetic rat model, the use of KA in the diet along with a low-protein diet did not lead to an increase in nitrogenemia while maintaining albumin levels. In the study, no significant difference was found between the serum creatinine levels at the end of 7 weeks. In both groups, the serum albumin levels in the 7th week were found to be lower than those in the 5th week in accordance with the progression of DNP. However, when the albumin levels of both groups were analyzed separately, the albumin levels were significantly higher in the group receiving KA. Although the mechanism of this anabolic effect caused by KA has not been fully resolved, in a rat model of CKD, it was shown that apoptosis was suppressed in rats fed very low-protein diet in which KA were given, protein synthesis was increased, and protein degradation was observed (13).

In a prospective, randomized controlled study, 23 patients with Stage IV DNP were given KA with low-protein diet for 1 year, and the other group received diabetic diet only. At the end of the study, proteinuria was found to be significantly lower in the group receiving KA, and the decrease in glomerular filtration rate was found to be slower (14). In our study, our aim was to determine the amount of final proteinuria in rats fed according to our protocol. However, due to the deterioration of the general condition of the rats and the rapid progression of the catabolic process, the study was terminated early, and the control proteinuria could not be evaluated. However, if we consider that the albumin level is significantly higher in the study group than in the control group, we believe that proteinuria is lower in the study group than in the control group. There was no significant difference in the serum creatinine levels between the study and control groups. Because the study was terminated earlier than planned, the positive effect on the serum albumin levels of the study group could possibly not be detected in the serum creatinine levels.

The relationship between structural abnormalities and renal function in DNP is better explained using light and electron microscopies (15). Mesangial dilatation, which can be detected by electron microscopy in Type I diabetes mellitus, is the best demonstrated parameter in relation to renal function (16).

Glomerular basement membrane thickening detected in pathological examination manifests itself more clinically with proteinuria (17). In our study, the prominent pathology detected in the nephrectomy content was also the glomerular basement membrane thickening (Figure 1). Other findings that may be seen in DNP are structural changes that occur in podocytes, renal tubules, interstitium, and arterioles (18). These pathologies could not be detected in the samples obtained in our study. The failure to show mesangial expansion may be attributed to the lack of electron microscopic examination. In a study by Fioretti et al. (15), it was found that over 15% of overt proteinuria was detected in biopsy materials with normal or near-normal renal structure, and 50% proteinuria developed in cases with DNP. Because the 24-hour proteinuria of the rats in our study is >10 g/day, it can be said that there is severe nephrotic proteinuria in the rats and that DNP is severe when the amount of proteinuria is examined.

We consider that the detection of only glomerular basement membrane thickening in our samples could be correlated with the fact that we could not perform the electron microscope examination and the shortness of the follow-up period. In addition, low-protein diet given after grouping of animals may have a positive effect on the pathological findings. The short follow-up period after rats were divided into two groups may be the reason why we could not see the positive effect of KA on pathology. Also, in another study, it would be possible to form a group of rats receiving a normal protein diet to rule out the likelihood that the present positive effect results from the low-protein diet.

CONCLUSION

DNP is an important renal disease in terms of causing ESRD. Low-protein intake plays an important role in the prevention of this disease. Although KA given in addition to a low-protein diet have been shown to affect serum albumin levels positively, in our study, to determine their effects on renal pathology, there is a need for electron microscopy studies using animal models that may also have long-term life expectancy.

REFERENCES

1. Jha V, Wang AY, Wang H. The impact of CKD identification in large countries: the burden of illness. Nephrol Dial Transplant 2012; 27 Suppl 3: iii32-8. [CrossRef]
2. Ayodele OE, Alebiosu CO, Salako BL. Diabetic nephropathy--a review of the natural history, burden, risk factors and treatment. J Natl Med Assoc 2004; 96: 1445-54.
3. Süleymanlar G. AK, Seyhani N. T.C. Sağlık Bakanlığı Ve Türk Nefroloji Derneği Ortak Raporu. 2016.
4. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int 2012.
5. Reutens AT PL, Atkins R. The epidemiology of diabetic kidney disease.: In: Ekoe J, ed. The Epidemiology of Diabetes Mellitus. 2nd ed. Chichester: John Wiley & Sons Ltd.; 2008. [CrossRef]
6. Levey AS, Adler S, Caggiula AW, England BK, Greene T, Hunsicker LG, et al. Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. Am J Kidney Dis 1996; 27: 652-63. [CrossRef]
7. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med 1991; 324: 78-84. [CrossRef]
8. Chang JH, Kim DK, Park JT, Kang EW, Yoo TH, Kim BS, et al. Influence of ketoanalogs supplementation on the progression in

chronic kidney disease patients who had training on low-protein diet. Nephrology (Carlton) 2009; 14: 750-7. [CrossRef]
9. Menon V, Kopple JD, Wang X, Beck GJ, Collins AJ, Kusek JW, et al. Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. Am J Kidney Dis 2009; 53: 208-17. [CrossRef]
10. Mitch WE. Dietary protein restriction in chronic renal failure: nutritional efficacy, compliance, and progression of renal insufficiency. J Am Soc Nephrol 1991; 2: 823-31. [CrossRef]
11. de Almeida RD, Prado ES, Llosa CD, Magalhaes-Neto A, Cameron LC. Acute supplementation with keto analogues and amino acids in rats during resistance exercise. Br J Nutr 2010; 104: 1438-42. [CrossRef]
12. Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol 2010; 21: 556-63. [CrossRef]
13. Wang DT, Lu L, Shi Y, Geng ZB, Yin Y, Wang M, et al. Supplementation of ketoacids contributes to the up-regulation of the Wnt7a/Akt/p70S6K pathway and the down-regulation of apoptotic and ubiquitin-proteasome systems in the muscle of 5/6 nephrectomised rats. Br J Nutr 2014; 111: 1536-48. [CrossRef]
14. Qiu HY, Liu F, Zhao LJ, Huang SM, Zuo C, Zhong H, et al. [Comparison of the effects of alpha-keto/ amino acid supplemented low protein diet and diabetes diet in patients with diabetic nephropathy]. Sichuan Da Xue Xue Bao Yi Xue Ban 2012; 43: 425-8.
15. Fioretto P, Mauer M. Histopathology of diabetic nephropathy. Semin Nephrol 2007; 27: 195-207. [CrossRef]
16. Caramori ML, Kim Y, Huang C, Fish AJ, Rich SS, Miller ME, et al. Cellular basis of diabetic nephropathy: 1. Study design and renal structural-functional relationships in patients with long-standing type 1 diabetes. Diabetes 2002; 51: 506-13. [CrossRef]
17. Fioretto P, Steffes MW, Mauer M. Glomerular structure in nonproteinuric IDDM patients with various levels of albuminuria. Diabetes 1994; 43: 1358-64. [CrossRef]
18. Mauer MF, Woredekal Y, et al. Diabetic nephropathy. Schrier R, Editor 2001.

10.5152/turkjnephrol.2020.3633

Original Article

Turkish Journal of Nephrology

Subclinical Cardiovascular Risk Factors in Chronic Kidney Disease: Abnormal Heart Rate Recovery

Didem Turgut[1], Ezgi Coşkun Yenigün[2], Harun Kundi[3], Nihal Özkayar[4], Fatih Dede[2]

[1]Clinic of Nephrology, Amasya State Hospital, Amasya, Turkey
[2]Division of Nephrology, Ankara Numune Training and Research Hospital, Ankara, Turkey
[3]Department of Cardiology, Ankara Numune Training and Research Hospital, Ankara, Turkey
[4]Division of Nephrology, Çorum Hitit University School of Medicine, Çorum, Turkey

Abstract

Objective: Chronic kidney disease (CKD) is associated with increased mortality and high cardiovascular (CV) risk. Slow heart rate recovery (HRR) is an index of cardiac autonomic dysfunction and also a prognostic tool for cardiac and all-cause mortality in high-risk groups. In this study, we aimed to investigate the subclinical CV risk factor in different stages of CKD.
Materials and Methods: Fifty-one patients with stage 1–5 CKD (mean age, 42.5±8.1 years) and 42 healthy individuals (mean age, 36.0±7.9 years) were included in the study. The HRR was calculated by subtracting the heart rates in the 1st, 2nd, and 3rd minute of the recovery period from the maximum heart rate attained during the exercise stress test.
Results: The HRR in the 1st minute was significantly slower in the CKD group compared with that in the control group (22.4±11.3 and 32.4±11.1, respectively; p<0.001). The HRR in the 2nd and 3rd minute was also slower in the patient group, but the difference was not statistically significant. Seventeen patients with the 1st minute HRR ≤18 beats/min were mainly distributed in CKD stages 4 and 5.
Conclusion: Patients with CKD with no known cardiac disease and no structural cardiac changes were at risk of CV events with a slow HRR in the exercise test. Clinicians should be careful not to underestimate CV events in this group of patients.
Keywords: Cardiovascular risk, chronic kidney disease, heart rate recovery

Corresponding Author: Didem Turgut ✉ didemturgut@yahoo.com
Received: 25.10.2018 **Accepted:** 27.01.2019

Cite this article as: Turgut D, Coşkun Yenigün E, Kundi H, Özkayar N, Dede F. Subclinical Cardiovascular Risk Factors in Chronic Kidney Disease: Abnormal Heart Rate Recovery. Turk J Nephrol 2020; 29(1): 28-32.

INTRODUCTION

Chronic kidney disease (CKD) is strongly associated with increased all-cause mortality and is mainly related to cardiovascular (CV) causes. Early estimation of CV risks in this group is vital. There is a combination of conventional CV risk factors, kidney-specific risk factors, and heart problems related to structural changes (1). In addition, cardiac autonomic dysfunction (CAnD) is a major complication of CKD that likely contributes to the high incidence of CV mortality in this patient population (2). New variables such as exercise capacity and heart rate recovery (HRR) provide an easy method to analyze CAnD (3).

The decrease in heart rate after exercise is known as HRR. HRR is associated with the balance between sympathetic withdrawal and parasympathetic reactivation after a graded exercise and is a good predictor of cardiac autonomic activity (2). It is evident that a slower HRR is not just an index of autonomic dysfunction but also a powerful prognostic tool for cardiac and all-cause mortality in high-risk groups (3). The HRR at 1 to 5 min detected during the treadmill stress test exercise has been established as a valid method (4). The 1st minute of recovery (HRR1) (fast phase) characterizes a period in which there is an abrupt and rapid decrease in HR. After the 1st minute (slow phase), it takes 2 to 5 min for HR to return to its resting values (5).

In patients with CKD, reduced exercise capacity is associated with poor survival (6). All CV risks and CAnD increase the mortality risk not only in symptomatic pa-

tients but also in asymptomatic patients. An abnormal HRR after a graded exercise is also used to estimate subclinical CV risks in patients with CKD (7). In this study, we aimed to estimate HRR abnormalities in different stages of CKD with respect to the normal population.

MATERIALS AND METHODS

Study Population

The study population comprised 51 patients with CKD (29 men and 22 women; mean age, 42.5±8.1 years) and 42 healthy individuals (21 men and 21 women; mean age, 36.0±7.9 years). Patients with CKD were between stages 1 to 5 and without any renal replacement treatment (RRT). Regarding the primary kidney diseases in patients, 29 (56.8%) were of unknown origin, 13 (25.4%) had diabetic nephropathy, and 9 (17.8%) had cystic kidney diseases. CKD and stages were defined based on eGFR according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of CKD. No patient had known heart failure, and none of the treated coronary artery diseases (CAD) were accepted. Patients with symptoms of heart failure (NYHA III-IV) as well as patients with electrocardiogram (ECG) abnormalities, atrial fibrillation, or uncontrolled hypertension were excluded. Hypertension, diabetes mellitus, and dyslipidemia (recent total cholesterol value ≥250 mg/dL, triglyceride ≥150 mg/dL, and HDL <40 mg/dL) were defined by history and/or medication use. All included patients were able to perform exercise testing. The patients were advised to remain on a low sodium diet (100 mmol/day) and protein reduction to 0.6-0.8 g/kg/day, and they were encouraged to cease smoking and exercise regularly. The control group was selected from healthy volunteers with no known drug use and disease whose GFR was >90 mL/min/1.73 m^2 with normal urine protein excretion (<150 mg/day).

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ankara Numune Education and Research Ethics Committee. All subjects provided written informed consent prior to participating in the study.

Table 1. Demographic properties of patient and control groups

	CKD Group (n=51)	Control Group (n=42)	p
Age (year) (±SD)	42.5±8.1	36.0±7.9	0.071
Female / Male n (%)	22/29 (43%/57%)	21 /21 (50%/50%)	
Body Mass Index (kg/m^2) (±SD)	28.36±1.3	25.4±2.2	0.063
Diabetes n (%)	17 (33%)	-	
Hypertension n (%)	40 (78%)	-	
Dyslipidemia n (%)	18 (35%)	-	

bpm: beats per minute; HRR1: 1st minute heart rate recovery; HRR2: 2nd minute heart rate recovery; HRR3: 3rd minute heart rate recovery

Protocol for Exercise Stress Test

The patients underwent a standard maximal graded exercise treadmill test according to the standard Bruce protocol. Continuous 12-lead ECG monitoring was performed throughout testing. The participants exercised until the HR was >95% of the estimated maximal HR (220-age). The patients underwent the stress test without a cool-down period. HRR values were calculated by subtracting the HR at the 1st, 2nd, and 3rd minute of the recovery period from the HR attained at peak exercise. A HRR of ≤18 beats/min was considered abnormal (8). The exercise capacity was calculated as total metabolic equivalent units (METs) achieved at peak exercise.

Statistical Analysis

Continuous variables were expressed as the mean±standard deviation, and categorical variables were expressed as percentages. Comparisons of categorical and continuous variables between the two groups were performed by using the x2 test and unpaired t-test, respectively. The correlation between various parameters was evaluated using the Pearson correlation test. p<0.05 was considered statistically significant. The Statistical Package for the Social Sciences (SPSS) (IBM Corp.; Armonk, NY, USA) version 23.0 statistical package was used for all analyses.

RESULTS

Our patient population comprised 51 patients with CKD stage 1-5 and 42 healthy controls. CKD stages were as follows: stages 1-2, 5 (9%) patients; stage 3, 29 (56%) patients; and stage 4-5, 17 (33%) patients. None of the patients were on RRT. There was no difference in terms of age, gender, and body mass index between the groups. Eleven (21%) patients were on Angiotensin converting enzyme inhibitor (ACEI) medication, and 26 (50%) patients were using Anjiotensin receptor blocker (ARB). Only one patient was administered erythropoietin, and only one patient was a smoker. The baseline characteristics of patients and the controls are shown in Table 1.

The pre-exercise stress test (EST) and cardiac autonomous function-related findings for the patient and control groups are summarized in Table 2. Although mean ejection fractions of the patients were lower in the patient group (62±2 and 65±3, p<0.001), maximum left ventricular wall thickness, basal systolic blood pressure (SBP), maximum SBP, basal diastolic blood pressure (DBP), maximum DBP, and basal heart rate (HR) were similar in both groups. However, maximum HR was significantly lower in patients with CKD (p<0.001). In an analysis of exercise capacity, all study groups achieved a MET score >10. However, the patient group had a statistically lower MET score than the control group (11.2±2.5 and 14.2±3, respectively; p<0.001).

When the HRR results were analyzed, in the 1st minute, the HRR was significantly slower in the CKD group than in the control group (22.4±11.3 and 32.4±11.1, respectively; p<0.005). Although the HRR in the 2nd and 3rd minutes was faster in the control group than in the patient group, the difference was not statistically significant (p=0.122 and p=0.22, respectively) (Figure 1). When we analyzed 17 patients with HRR1≤18 beats/min, it was demonstrated that patients were mainly distributed in CKD stages 4 and 5. These results are summarized in Table 3.

Table 2. Analysis of pre-exercise stress test and cardiac autonomous function related findings

	CKD Group (n=51)	Control Group (n=42)	p
LVEF (%) (±SD)	62±2	65±3	<0.001
LV wall thickness (mm) (± SD)	4.9±0.4	4.6±0.5	0.112
Basal SBP (mmHg) (min-max)	130 (100-180)	120 (90-130)	0.208
Max. SBP (mmHg) (min-max)	150 (125-220)	140 (100-200)	0.068
Basal DBP (mmHg) (min-max)	80 (55-119)	80 (60-90)	0.131
Max. DBP (mmHg) (min-max)	70 (40-120)	80 (60-100)	0.421
METs (mL/kg/min) (±SD)	11.2±2.5	14.2±3	<0.001
Basal HR (bpm) (±SD)	93.4±15.5	92.7±15.7	0.084
Max. HR (bpm) (±SD)	148.2±14.3	167.7±14.2	<0.001
HRR1 (bpm) (±SD)	22.4±11.3	32.4±11.1	<0.001
HRR2 (bpm) (±SD)	47.2±13.6	52.2±12.6	0.122
HRR3 (bpm) (±SD)	51.8±14.2	58.7±15.1	0.22

bpm: beats per minute; DP: diastolic blood pressure; HR: heart rate; HRR1: 1st minute heart rate recovery; HRR2: 2nd minute heart rate recovery; HRR3: 3rd minute heart rate recovery; LVEF: left ventricular ejection fraction; LV: left ventricule; METs: metabolic equivalents; SBP: systolic blood pressure.

Table 3. Abnormal heart rate recovery in patient group

	CKD Group (n=51)	Control Group (n=42)
HRR≤18/min; n (%)	17 (33 %)	1 (2%)
	CKD Stage 1-2: 0 (0%)	
	CKD Stage 3: 2 (3%)	
	CKD Stage 4-5: 15 (87%)	
HRR>18/min; n (%)	34 (69 %)	41 (98%)

CKD: Chronic kidney disease

DISCUSSION

Our study showed that patients with CKD had a slower HRR after EST, especially in the 1st minute of recovery. An abnormal HRR1 (≤18 beats/min) is mainly observed in progressive kidney disease.

Many studies have reported an increase in HR during EST and a decrease in HR during the recovery period mainly due to changes in the tone balance between the sympathetic and the parasympathetic nervous systems (9). Any alteration in this system mainly favoring increased activity of sympathetic system and decreased parasympathetic system refers to CAnD (10). It is documented that CAnD is a result of inflammation, endothelial dysfunction, atherosclerosis, and arrhythmia (11). The exact mechanisms contributing to CAnD in CKD are unclear, but many studies have shown that there is an increased risk of premature death and direct detrimental effects on the clinical prognosis of renal failure (12-14). Sympathetic overactivity and abnormalities in CV reflexes are some of the causes of CAnD in CKD (2, 15).

Dysfunctional vagal control of HR, known as slow HRR, is a new non-ECG measure that helps to assess and define CAnD (16). Decreased HRR has been associated with a higher incidence of all-cause mortality, sudden cardiac death, and CV events (7, 16, 17). The HRR has been calculated at the 1st, 2nd, 3rd, and 5th minute in different studies, but mainly at the 1st min. In the literature, there are various cut-off HRR values. In some studies, an HRR ≤12 beats/min is directly associated with mortality (8, 18, 19). However, in a study by Watanabe et al. (20), a total of 5438 patients were enrolled for 3 years, and HRR was defined as the difference in HR between the peak exercise and that after 1 min; a value ≤18 beats/min was considered abnormal. Furthermore, after adjusting for all confounding factors, an HRR ≤18 beats/min was found to be a powerful and independent predictor of death (20). In our study, we found that patients in stages 4 and 5 with the 1st minute HRR ≤18 beats/min were a majority,

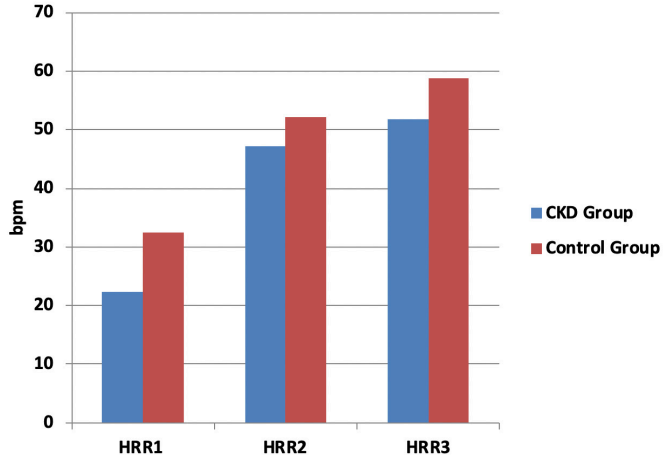


Figure 1. Heart rate recovery results in the 1st, 2nd, and 3rd minutes in patient and control groups.

although it was not statistically significant. With studies composed of large groups at different CKD stages, the HRR would be analyzed as an early predictor of CV risks in these vulnerable patients.

Lipinski et al. (21) retrospectively analyzed exercise treadmill and coronary angiographic data of 2193 men and found that the first 2 min of HRR predicted mortality and that the HR decrease during the 2nd minute of recovery predicted the presence of CAnD. In our study, we analyzed the 1st, 2nd, and 3rd minutes of HRR and found that the 1st minute HRR in patients with CKD was significantly slower. The 2nd and 3rd minute HRR were also slower in the CKD group, but it was not statistically significant. The correlation with HRR should be analyzed with large patient groups composed of homogenous stages 1-5 CKD in future studies.

CKD is a known risk factor for increasing the progression of CV problems. However, without any known cardiac illness, it is not certain whether CKD is associated with functional or structural cardiac changes. Nelson et al. (22) analyzed 840 patients with a GFR >60 mL/min and 93 patients with stage 3 CKD. Patients were assessed for their cardiopulmonary exercise as a marker of autonomic function. It was concluded that maladaptive CV/autonomic dysfunction in stage 3 CKD may suggest subclinical cardiopulmonary dysfunction preceding end-stage kidney disease (ESKD)-related cardiac problems. In our study, all patients were without any known cardiac disease with a preserved LVEF. Although our patients mainly had stage 3-5 CKD, our findings provide functional and physiological data. Without any known cardiac disease and no structural cardiac changes, patients with CKD are under risk of CV events with a slow HRR in the exercise test.

CONCLUSION

The most important limitation of our study is that it was a cross-sectional study with a small population, and we could not analyze the mortality. Also, patients were not homogenous considering the CKD stages. However, it is evident that patients with CKD without a diminished cardiac function should be carefully followed to prevent cardiac related deaths.

Ethics Committee Approval: Ethics Committee approval was received for this study from the Ethics Committee of Ankara Numune Training and Research Hospital.

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.T., E.Y, F.D.; Design – D.T., E.Y., F.D.; Supervision – F.D., N.Ö., E.Y; Resource – E.Y., D.T., F.D.; Materials – H.K., E.Y., D.T; Data Collection and/or Processing – D.T., H.K., E.Y.; Analysis and/or Interpretation – D.T., E.Y, N.Ö.; Literature Search – D.T., E.Y.; Writing – D.T., E.Y.; Critical Reviews – F.D, H, K, N.Ö.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

REFERENCES

1. McCullough PA, Roberts WC. Influence of chronic renal failure on cardiac structure. J Am Coll Cardiol 2016; 67: 1183-5. [CrossRef]
2. Salman IM. Cardiovascular autonomic dysfunction in chronic kidney disease: a comprehensive review. Curr Hypertens Rep 2015; 17: 59. [CrossRef]
3. Peçanha T, Silva-Júnior ND, Forjaz CL. Heart rate recovery: autonomic determinants, methods of assessment and association with mortality and cardiovascular diseases. Clin Physiol Funct Imaging 2014; 34; 327-39. [CrossRef]
4. Shetler K, Marcus R, Froelicher VF, Vora S, Kalisetti D, Prakash M, et al. Heart rate recovery: validation and methodologic issues. J Am Coll Cardiol 2001; 38: 1980-7. [CrossRef]
5. Qiu S, Cai X, Sun Z, Li L, Zuegel M, Steinacker JM, et al. Heart rate recovery and risk of cardiovascular events and all-cause mortality: A meta-analysis of prospective cohort studies. J Am Heart Assoc 2017; 6: e005505. [CrossRef]
6. Sietsema KE, Amato A, Adler SG, Brass EP. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. Kidney Int 2004; 65: 719-24. [CrossRef]
7. Késoi I, Sági B, Vas T, Kovács T, Wittmann I, Nagy J. Heart rate recovery after exercise is associated with renal function in patients with a homogenous chronic renal disease. Nephrol Dial Transplant 2010; 25: 509-13. [CrossRef]
8. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. Ann Intern Med 2000; 132: 552-5. [CrossRef]
9. Arai Y, Saul JP, Albrecht P, Hartley LH, Lilly LS, Cohen RJ, et al. Modulation of cardiac autonomic activity during and immediately after exercise. Am J Physiol 1989; 256: 132-41. [CrossRef]
10. Pa GK, Pal P, Nanda N, Amudharaj D, Adithan C. Cardiovascular dysfunctions and sympathovagal imbalance in hypertension and prehypertension: physiological perspectives. Futur Cardiol 2013; 9: 53-69. [CrossRef]
11. Qiu S, Cai X, Sun Z, Li L, Zuegel M, Steinacker JM, et al. Heart rate recovery and risk of cardiovascular events and all-cause mortality: A meta-analysis of prospective cohort studies. J Am Heart Assoc 2017; 6: e005505. [CrossRef]
12. Dursun B, Demircioglu F, Varan HI, Basarici I, Kabukcu M, Ersoy F. Effects of different dialysis modalities on cardiac autonomic dysfunctions in end-stage renal disease patients: one year prospective study. Ren Fail 2004; 26: 35-8. [CrossRef]
13. Ranpuria R, Hall M, Chan CT, Unruh M. Heart rate variability (HRV) in kidney failure: measurement and consequences of reduced HRV. Nephrol Dial Transplant 2008; 23: 444-9. [CrossRef]
14. Shamseddin MK, Parfrey PS. Sudden cardiac death in chronic kidney disease: epidemiology and prevention. Nat Rev Nephrol 2011; 7: 145-54. [CrossRef]
15. Koomans HA, Blankestijn PJ, Joles JA. Sympathetic hyperactivity in chronic renal failure: a wake-upcall. J Am Soc Nephrol 2004; 15: 524-37. [CrossRef]
16. Ghaffari S, Kazemi B, Aliakbarzadeh P. Abnormal heart rate recovery after exercise predicts coronary artery disease severity. Cardiol J 2011; 18: 47-54.

17. Converse RL Jr, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, et al. Sympathetic over activity in patients with chronic renal failure. N Engl J Med 1992; 327: 1912-8. [CrossRef]
18. Morshedi-Meibodi A, Larson MG, Levy D, O'Donnell CJ, Vasan RS. Heart rate recovery after treadmill exercise testing and risk of cardiovascular disease events(The Framingham Heart Study). Am J Cardiol 2002; 90: 848-52. [CrossRef]
19. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. JAMA 2000; 284: 1392-8. [CrossRef]
20. Watanabe J, Thamilarasan M, Blackstone EH, Thomas JD, Lauer MS. Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality: The case of stress echocardiography. Circulation 2001; 104: 1911-6. [CrossRef]
21. Lipinski MJ, Vetrovec GW, Froelicher VF. Importance of the first two minutes of heart rate recovery after exercise treadmill testing in predicting mortality and the presence of coronary artery disease in men. Am J Cardiol 2004; 93: 445-9. [CrossRef]
22. Nelson A, Otto J, Whittle J, Stephens RC, Martin DS, Prowle JR, et al. Sub clinical cardiopulmonary dysfunction in stage 3 chronic kidney disease. Open Heart 2016; 3: e000370. [CrossRef]

10.5152/turkjnephrol.2020.3643

Original Article

Turkish Journal of Nephrology

Examination of the Effects of Nursing Interventions on Intradialytic Hypotension

Gülşah Kesik, Leyla Özdemir

Hacettepe University School of Nursing, Ankara, Turkey

Abstract

Objective: This study will contribute to the understanding and management of hemodialysis-related complications, increase hemodialysis nurses' awareness and skills related to intradialytic hypotension management, help establish evidence-based clinical practice, and help develop clinical guidelines for the management of hemodialysis-related complications.

Materials and Methods: This descriptive study involved 57 patients whose blood pressures and interventions for intradialytic hypotension were recorded for six hemodialysis sessions, for a total of 342 follow-ups.

Results: Intradialytic hypotension developed at significantly high rates in cases in which the first hemodialysis session was performed after a 2-day break and in cases of high target ultrafiltration and pump rate values. Intradialytic hypotension developed during 219 of the 342 follow-ups. The Trendelenburg position alone was used in 195 follow-ups (89%) in which intradialytic hypotension developed, and the Trendelenburg position and pump rate reduction were used in 24 follow-ups (11%). Pump rate reduction alone was used in 151 follow-ups (68.9%).

Conclusion: Using the Trendelenburg position alone and reducing the pump rate along with using the Trendelenburg position significantly increased the blood pressure in cases of intradialytic hypotension. Excessive use of the Trendelenburg position and reduction of the pump rate by 20-60 mL/min compared with the onset rate of hemodialysis were more effective in increasing the blood pressure.

Keywords: Hemodialysis, blood pressure, nursing interventions, nursing

Corresponding Author: Gülşah Kesik ✉ gulsah_dogann@outlook.com

Received: 26.10.2018 **Accepted:** 29.12.2018

Presented in: This study was presented at the 2. Internatıonal Congress of Nursing (ICON)-2018, 13-15 April 2018, İstanbul, Turkey.

Cite this article as: Kesik G, Özdemir L. Examination of the Effects of Nursing Interventions used for Intradialytic Hypotension. Turk J Nephrol 2020; 29(1): 33-8.

INTRODUCTION

Approximately 15% of the world's population suffers from chronic renal failure disease, and nearly 56% of patients are treated with dialysis (19). Hemodialysis is one of the treatment options frequently used in end-stage renal failure. In hemodialysis, the patient's blood is filtered through a hemodialysis device and subsequently re-administered. For this procedure, a water system, a hemodialysis device, arteriovenous sets and needles, a hemodialysate, and acid and bicarbonate solutions are needed.

Although treatment with hemodialysis is life-saving for these patients, it may cause many acute and chronic complications (1, 6, 9, 17). Intradialytic complications refer to acute complications observed during hemodialysis; common intradialytic complications include hypotension (30%-35%), cramps (5%-20%), nausea/vomiting (5%-15%), headache (5%), chest pain (2%-5%), back pain (2%-5%), itching (5%), and fever/shivering (<1%) (2, 12, 17). Intradialytic hypotension (IDH) is defined as a reduction of ≥20 mmHg in the systolic blood pressure or a reduction of ≥10 mmHg in the mean blood pressure during

hemodialysis (2, 11, 12). IDH may result because of decrease in the fluid volume, failure to provide vasoconstriction, or cardiac factors. Many studies have identified a close association between the quantity of ultrafiltration and IDH (12, 17). The target ultrafiltration value is determined by the difference between the patient's weight at admission and the dry weight. The pump rate, another parameter for hemodialysis, is calculated by considering the target ultrafiltration and hemodialysis treatment period. By increasing the target ultrafiltration value, a higher quantity of water is drawn within a shorter time, and this is associated with a higher risk of IDH by causing imbalance in the fluid volume.

In addition to being the most common complication during hemodialysis, IDH is an etiological factor for other intradialytic complications such as nausea, vomiting, and cramps (2, 4, 19). Patients with IDH commonly present with symptoms such as tiredness, restlessness, and dizziness. Thus, IDH may affect the treatment progression and may result in an earlier termination of hemodialysis if the blood pressure cannot be normalized (6, 11, 12).

Furthermore, because IDH requires close monitoring and interventions, this complication increases the workload for the nurses (17).

The interventions for IDH should be evidence based, as with the other aspects of nursing practice. However, a thorough literature search found no study on the efficiency or standards of the interventions for IDH, and studies assessing the correlations of the interventions for IDH with blood pressure are needed.

MATERIALS AND METHODS

The present study aimed to examine the interventions used for IDH and their effects on the blood pressure of the patients.

This descriptive study was performed in the hemodialysis units of a university hospital and a public hospital between January and June 2016. A flow diagram of the progression of patients through the phases of the study is shown in Figure 1.

The sample size was determined with a power of 93% and an α-value of 0.05; a power analysis was conducted using the G*Power program, version 3.1.735, and it was based on the rate of the development of IDH.

Patients aged >18 years, those who received hemodialysis treatment because of end-stage kidney failure, and those who received hemodialysis during 4-h sessions were included in the study. Patients who did not have IDH in the preliminary follow-up for six sessions were excluded. In the preliminary evaluation of 180 patients, 123 patients were excluded from the study (121 patients because of not developing IDH during the preliminary monitoring for six sessions and 2 patients because of agitated behaviors that made communication impossible). Finally, 57 patients who developed IDH at least once during the preliminary monitoring for six sessions and who met inclusion criteria were included in the study. The blood pressure of the 57 patients and interventions for IDH during the six sessions were followed; in total, 342 follow-ups were conducted.

Data Collection

The study data were gathered by the primary investigator (PI) from the Patient Description Form, Patient Information for Hemodialysis Sessions and Blood Pressure Monitoring Chart, and Blood Pressure Monitoring and Interventions Chart for Patients with Intradialytic Hypotension. All data collection tools were prepared by the PI following a review of the relevant literature (5-7, 13-15).

In this study, IDH was defined as a decrease of ≥20 mmHg in systolic blood pressure (11, 12, 15). All study data were collected by the PI. The Patient Description Form was used to determine the descriptive characteristics of the patients, such as age, gender, and duration of hemodialysis treatment. The Patient Information for Hemodialysis Sessions and Blood Pressure Monitoring Chart was used to record the vascular access type (permanent catheter, arteriovenous fistula, arteriovenous graft), dry weight, weight at admission, target ultrafiltration value, and pump rate and monitor the blood pressure every 30 min during each hemodialysis session for the detection of IDH. The Blood Pressure Monitoring and Interventions Chart for Patients with Intradialytic Hypotension was used to record the degree of Trendelenburg position, which was classified as minimum Trendelenburg (15–30°) and maximum Trendelenburg (45°), based on the literature; the degree of pump rate reduction (mL/min); and characteristics of the intravenously administrated fluid (1, 3).

After the interventions were performed for the patients with IDH by hemodialysis nurses, the blood pressure was monitored every 15 min by the PI and recorded in their charts.

The project was approved by the Hacettepe University Non-invasive Studies Ethics Committee.

Statistical Analysis

Data analyses were conducted using The Statistical Package for the Social Sciences, version 22.00 (IBM Corp.; Armonk, NY, USA). Frequency and percentage distributions were used for evaluating categorical variables. The chi-square test was used to examine the association between two categorical variables. Differences between two independent groups were evaluated using the independent samples t-test.

RESULTS

Of the patients included in the study, 50.9% were female and 52.6% were aged >60 years. Of all patients, 64.9% were married. A history of familial kidney failure was identified in 71.9% of the patients. In terms of the relatives of the patients diagnosed with kidney failure, 90.9% were first-degree relatives and 38.6% received dialysis treatment. In addition to kidney failure, 52.6%

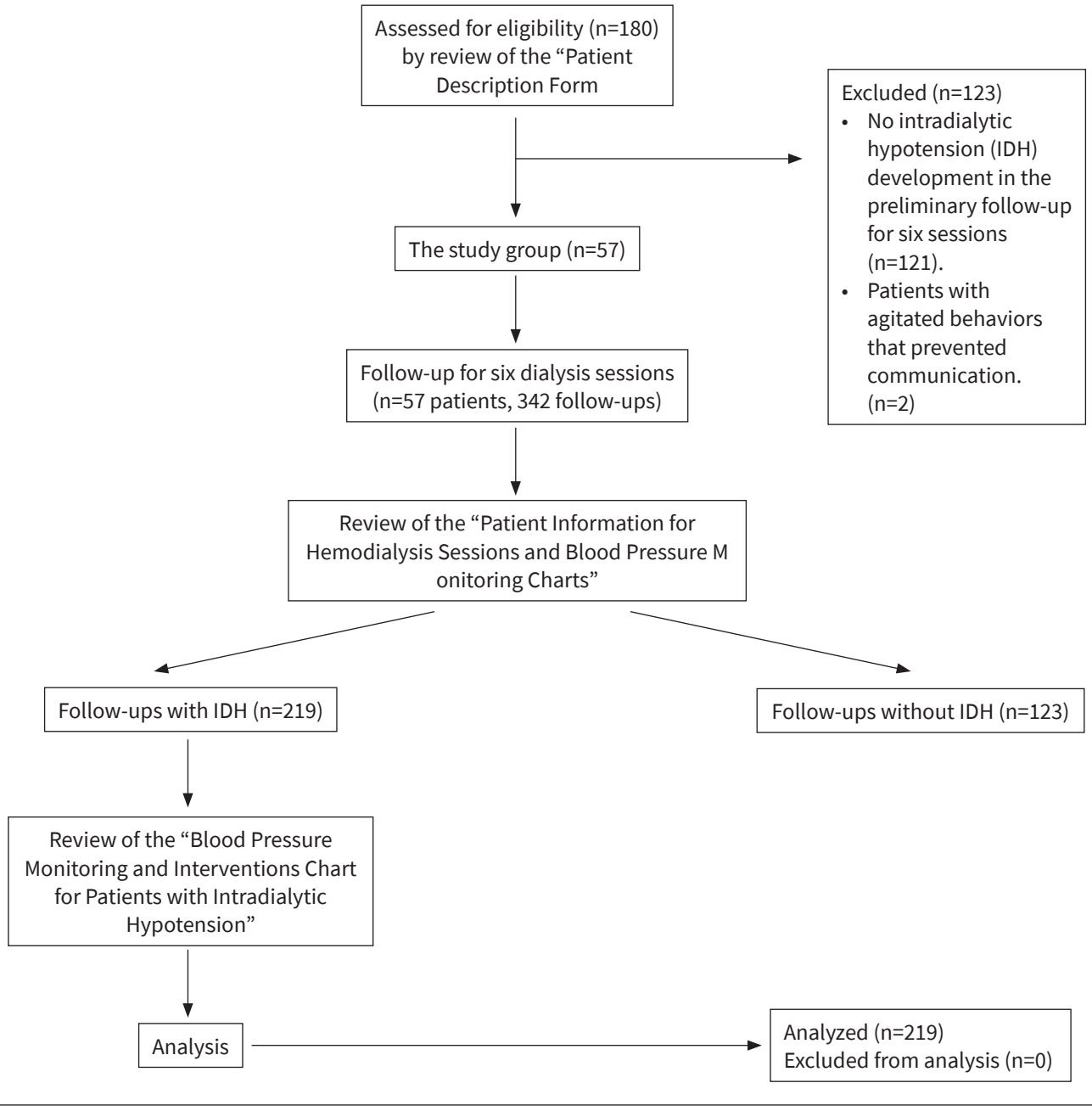


Figure 1. Flow diagram of the subject enrollment through the phases of the study.

of the patients had a concomitant chronic disease (40% hypertension, 33.3% diabetes, 20% cerebrovascular event history, 6.7% coronary heart disease). Hemodialysis treatment was administered to 40.4% of the patients for 91–180 months. All patients had an arteriovenous fistula as vascular access. The most common symptom accompanying IDH was exhaustion, which occurred in 75.4% of the cases. Furthermore, 57.9% of the patients experienced muscle cramps, and 38.6% presented with dizziness. The patients received hemodialysis on Mondays, Wednesdays, and Fridays or on Tuesdays, Thursdays, and Saturdays. The dry weights of the patients ranged between 72.1 and 98.0 kg in 35.1% of patients. The body weight of the patients at admission ranged between 72.1 kg and 101.0 kg in 35.6% of patients. The body weight after hemodialysis was not below the dry weight in the vast majority (99.2%) of patients. When the hemodialysis treatment characteristics were investigated, the target ultrafiltration quantities ranged between 1500 and 2750 in 51.5% of cases and the pump rate was between 341 and 380 ml/min in 68.1% of cases (Table 1).

Significant associations were identified among target ultrafiltration, pump rate values, and development of IDH. The mean target ultrafiltration and pump rate values of the patients with IDH were significantly higher than those in patients without

IDH (t=5.311, p<0.001). A significant association was found between the IDH development state and the days of hemodialysis (t=5.293, p<0.001). The IDH development rates on Mondays and Tuesdays were significantly higher than those on Thursdays, Fridays, and Saturdays.

Table 1. Distribution of the Descriptive Data Related to the Patients and Treatment (n=57)

	n	%
Gender		
Female	29	50.9
Male	28	49.1
Age (years)		
(Mean=60.7, SD=11.4, Min=44.0, Max=98.0)		
<60 years	27	47.4
>60 years	30	52.6
Duration of hemodialysis treatment (months)		
(Mean=162.6, SD=101.6, Min=30, Max=420)		
0-90 months	20	35.1
91-180 months	23	40.4
>180 months	14	24.5
Dry weight (kg)		
(Mean=67.7, SD=13.6, Min=43, Max=98)		
43.0-61.0 kg	114	33.3
61.1-72.0 kg	108	31.6
72.1-98.0 kg	120	35.1
Body weight at admission (kg)		
(Mean=69.9, SD=13.8, Min=43.75, Max=101)		
43.0-61.0 kg	112	32.8
61.1-72.0 kg	108	31.6
72.1-101.0 kg	122	35.6
Target ultrafiltration quantity		
(Mean=2795.9, SD=624.9, Min=1500, Max=3800)		
1500-2750	176	51.5
2751-3800	166	48.5
Pump rate (ml/min)		
(Mean=348.3, SD=26.9, Min=300, Max=380)		
300-340 mL/min	109	31.9
341-380 mL/min	233	68.1
Body weight at discharge (kg)		
(Mean=67.7, SD=13.7, Min=43, Max=98)		
43.0-61.0 kg	113	33
61.1-72.0 kg	106	31
72.1-98.0 kg	123	36
Difference between the discharge weight and dry weight		
Decreased below the dry weight	3	0.8
Did not decrease below the dry weight	339	99.2

IDH was identified in 219 of the 342 follow-ups. Nurses intervened in all IDH cases. The Trendelenburg position was used in all 219 follow-ups. In 195 of the 219 follow-ups with IDH, the Trendelenburg position was used alone (89%), whereas the Trendelenburg position and pump rate reduction were used in combination in 24 follow-ups as the first intervention (11%). Pump rate reduction alone was used in 151 of 219 follow-ups as the second intervention (68.9%). The isotonic fluid replacement was used alone in 53 follow-ups as the second or third intervention (24.2%). The Trendelenburg positioning alone and pump rate reduction along with the Trendelenburg position increased the blood pressure significantly (p<0.001 for both). No significant association was found between pump rate reduction and isotonic fluid replacement and blood pressure (p>0.05 for both) (Table 2). The increase in blood pressure was found to be significantly higher in cases with maximum Trendelenburg position than in cases with minimum Trendelenburg position. When comparing the amounts of pump rate reduction, reducing the pump rate by >20 mL/min compared with that at the onset of hemodialysis was found to be more effective in increasing the blood pressure than reducing it by ≤20 mL/min (p<0.001). The differences in the effect of using different amounts of isotonic fluid replacement (mL) on the blood pressure increase were not significant (p>0.05) (Table 3).

DISCUSSION

The present study revealed that higher ultrafiltration and pump rate values were associated with increased rates of IDH development. Prolongation of the dialysis session and reduction of the pump rate were effective in preventing IDH in patients with a high target ultrafiltration value. Because the pump rate is adjusted according to the target ultrafiltration value, during sessions in which the target ultrafiltration value is high, the pump rate is also adjusted to be high. Patients with higher pump rates have a higher decrease in the intravascular volume; however, a high decrease in the intravascular volume within a short period may cause IDH in these patients (4). In the present study, the rate of IDH development was found to be significantly higher on Mondays and Tuesdays, i.e., on days when the patients received the first hemodialysis of the week, compared with that on the other days. Because the patients did not receive hemodialysis for 2 days before Monday or Tuesday, the target ultrafiltration rate was increased on these days. Consequently, IDH developed significantly more frequently on these 2 days, as reported previously (9, 16).

The Trendelenburg position was used in all 129 follow-ups with IDH, including Trendelenburg alone in 195 cases and in combination with pump rate reduction in 24 cases. The Trendelenburg position is a common practice because it is both practical and influential and does not lead to any interruption in the treatment process. According to the statistical analysis of the data obtained in the present study, the use of the Trendelenburg position significantly increased the blood pressure in patients with IDH. Furthermore, when the Trendelenburg position grade

Table 2. Effects of the Different Interventions for Intradialytic Hypotension on Blood Pressure (n=423)

Intervention		Effect on Blood Pressure: Increased	No Change	Continued to Decrease	χ2	p
Trendelenburg (n=195)	n	67	115	13	26.509	<0.001
	%	34.4	58.9	6.7		
Pump rate reduction (n=151)	n	66	75	10	2.489	0.968
	%	43.7	49.7	6.6		
Isotonic fluid replacement (n=53)	n	29	24	0	0.848	0.087
	%	54.7	45.3	0.0		
Trendelenburg plus pump rate reduction (n=24)	n	24	0	0	24.200	<0.001
	%	100	0.0	0.0		

Table 3. Effects of the Intervention Characteristics on Blood Pressure

Intervention Characteristics			Effect on Blood Pressure: Increased	No Change	Continued to Decrease	χ2	p	Difference
Trendelenburg Grade (n=219)	Minimum	n	28	33	12	24.290	<0.001	1-2
		%	30.8	28.7	92.3			
	Excessive	n	63	82	1			
		%	69.2	71.3	7.7			
Pump rate reduction (mL/min) (n=175)	20	n	10	14	1	28.410	<0.001	1-2,3
		%	11.0	18.4	12.5			
	20-40	n	50	62	7			
		%	54.9	81.6	87.5			
	40-60	n	31	0	0			
		%	34.1	0.0	0.0			
			Increased	**No Change**				
Isotonic replacement (mL) (n=53)	100	n	29	21	0.960		0.086	-
		%	100.0	87.5				
	200	n	0	3				
		%	0.0	12.5				

was analyzed, the maximum Trendelenburg position was found to be significantly superior to the minimum Trendelenburg position for increasing the blood pressure. The Trendelenburg position enables the transfer of blood from the lower extremities to the vital organs and upper extremities. Thus, the decreased blood volume in the vital organs and upper extremities is replenished. In this case, applying the Trendelenburg position to patients with IDH may help to increase blood pressure, and the use of maximum Trendelenburg positioning should be applied if possible (10).

The literature suggests reducing the pump rate for the management of IDH (1). This intervention may provide a blood pressure increasing effect via reductions of the volume rate drawn from the patient. However, in the present study, the statistical analysis showed that reducing the pump rate alone did not have a significant effect on the blood pressure increase, whereas reducing the pump rate in addition to using the Trendelenburg position increased the blood pressure significantly. Furthermore, when the blood pressure increase was compared in accordance with different pump rate reduction values, reducing the pump rate by >20 mL/min was found to be more effective. Hence, in cases of IDH, higher reduction of the pump rate and/or Trendelenburg positioning may effectively increase the blood pressure.

Theoretically, intravenous fluid replacement in the treatment of IDH resulting from hypovolemia can be useful (5). Hypovolemia is one of the etiological factors of IDH and results when the weight decreases below the dry weight in hemodialysis. In the present study, the effect of isotonic fluid replacement on the increase in blood pressure was not found to be significant. The discharge weights were not below the dry weights in most

patients (99.2%) in this study. Thus, because hypovolemia did not appear to influence the etiology of IDH in our study, isotonic fluid replacement may not be effective in the treatment of IDH.

Limitations

The present study was limited to hemodialysis patients with IDH; therefore, our results cannot be generalized to other populations. The small sample size was another limitation of the study.

CONCLUSION

According to the findings obtained in the present study, the rate of IDH development was the highest on Mondays and Tuesdays, when the first hemodialysis treatment of the week was applied, compared with that on Wednesdays, Thursdays, Fridays, and Saturdays. The rate of IDH development was significantly high in patients with higher target ultrafiltration and pump rate values. The Trendelenburg position was found to be effective for increasing the blood pressure in cases of IDH. In the follow-up where the maximum Trendelenburg position was applied, the increase rate in blood pressure was found to be significantly higher than that in cases of minimum Trendelenburg positioning. The effect of pump rate reduction alone was insignificant, whereas a combination of this method with the Trendelenburg position increased the blood pressure significantly. Analyses of the use of different reduction rates of the pump revealed that reducing the pump rate by 20-60 mL/min increased the blood pressure significantly compared with reducing it by ≤20 mL/min. Furthermore, the effect of isotonic fluid replacement on the blood pressure increase was not significant. Based on the findings of the present study, we conclude that in cases of IDH, using the Trendelenburg position, preferably the maximum Trendelenburg position; reducing the pump rate by 20-60 mL/min; and/or reducing the pump rate together with using the Trendelenburg positioning appear to be most effective. Furthermore, to prevent IDH, patient education regarding reducing the target ultrafiltration rates, such as prevention of maximum weight gain between two sessions and restrictions of salt and fluids, may also be helpful.

Ethics Committee Approval: Ethics Committee approval was received for this study from the Hacettepe University Non Invasive Studies Ethics Committee (Decision No: GO-15/613-17).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.K., L.Ö.; Design – G.K., L.Ö.; Supervision – G.K., L.Ö.; Resources – G.K., L.Ö.; Materials – G.K., L.Ö.; Data Collection and/or Processing – G.K., L.Ö.; Analysis and/or Interpretation – G.K., L.Ö.; Literature Search – G.K., L.Ö.; Writing – G.K., L.Ö.; Critical Reviews – G.K., L.Ö.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

REFERENCES

1. Ahmad S. Complications of hemodialysis (2009) In: Ahmad S, ed. Manual of clinical dialysis. New York, NY: Springer; 59-68. [CrossRef]
2. Chesterton LJ, Selby NM, Burton JO. Cool dialysate reduces asymptomatic intradialytic hypotension and increases baroreflex variability. Hemodial Int 2009; 13; 189-96. [CrossRef]
3. Dasselaar JJ, van der Sande FM, Franssen CF. Critical evaluation of blood volume measurements during hemodialysis. Blood Purif 2012; 33: 177-82. [CrossRef]
4. Daugirdas J. Measuring intradialytic hypotension to improve quality of care. J Am Soc Nephrol 2015; 26: 512-4. [CrossRef]
5. Davenport A. Can advances in hemodialysis machine technology prevent intradialytic hypotension? Semin Dial 2009; 22: 231-6. [CrossRef]
6. Flythe JE, Kunaparaju S, Dinesh K, Cape K, Feldman HI, Brunelli SM. Factors associated with intradialytic systolic blood pressure variability. Am J Kidney Dis 2012; 59: 409-18. [CrossRef]
7. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM (2014) Association of mortality risk with various definitions of intradialytic hypotension. J Am Soc Nephrol 2014; 26: 724-34. [CrossRef]
8. Franssen CF, Dasselaar JJ, Sytsma P (2005) Automatic feedback control of relative blood volume changes during hemodialysis improves blood pressure stability during and after dialysis. Hemodial Int 2005; 9: 383-92. [CrossRef]
9. Jennifer E, Flythe J, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. J Am Soc Nephrol 2015; 26: 724-34. [CrossRef]
10. Leunissen KM, Kooman JP, van der Sande FM, van Kuijk WH. Hypotension and ultrafiltration physiology in dialysis. Blood Purif 2000; 18: 251-4. [CrossRef]
11. Lin YF, Huang JW, Wu MS. Comparison of residual renal function in patients undergoing twice-weekly versus three-times-weekly haemodialysis. Nephrology 2010; 14: 59-64. [CrossRef]
12. Locatelli F, Altieri P, Andrulli S, Bolasco P, Sau G, Pedrini LA, et al. Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. J Am Soc Nephrol 2010; 21: 1798-807. [CrossRef]
13. Mousavi S, Tamadon M. Vasopressin and prevention of hypotension during hemodialysis. Iran Red Crescent Med J 2014; 16: e20219. [CrossRef]
14. Nasri H. Correlation of serum magnesium with serum levels of 25-hydroxyvitamin D in hemodialysis patients. J Parathyr Dis 2014; 2: 11-3.
15. Owen PJ, Priestman WS, Sigrist MK. Myocardial contractile function and intradialytic hypotension. Hemodial Int 2009; 13: 293-300. [CrossRef]
16. Raimann J, Liu L, Tyagi S, Levin NW, Kotanko P. A fresh look at dry weight. Hemodial Int 2008; 12: 395-405. [CrossRef]
17. Tai D, Ahmed S, Derflinger L, Hemmelgarn B, MacRae J. Pneumatic compression devices during hemodialysis: A randomized crossover trial. Nephrol Dial Transplant 2013; 28: 982-90. [CrossRef]
18. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative 2015 https://www.kidney.org/professionals/guidelines/hemodialysis (accessed 6 June 2016)
19. U.S. Renal Data System (2013) Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States.

10.5152/turkjnephrol.2020.3662

Original Article

Turkish Journal of Nephrology

Challenges in Kidney Donation Faced by Relatives in Iran: A Qualitative Study

Ziba Borzabadi Farahani[1], Maryam Esmaeili[2], Nahid Dehghan-Nayeri[2], Mahvash Salsali[3]

[1]School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]School of Nursing and Midwifery, Nursing and Midwifery Care Research Center, Tehran University of Medical Sciences, Tehran, Iran
[3]School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Objective: Kidney donation from a relative is an ideal option for transplantation that would improve the recipients' quality of life. The aim of the present study was to evaluate the challenges in the donation process faced by kidney donors related to patients.

Materials and Methods: This is a descriptive qualitative study that uses a content analysis approach. In this study, 16 relative donors from kidney transplant centers of all the educational hospitals affiliated with Tehran University of Medical Sciences were selected through purposive sampling. Data were collected using face-to-face, in-depth, semi-structured interviews.

Results: The data analysis results led to the extraction of three main themes: initial confrontation, hospitalization, and endless concerns. The second theme of the study had two sub-themes: being ignored and the rights of the donor.

Conclusion: The challenges faced during the donation process were difficulties in performing tests, difficulties during hospitalization, and endless concerns. These challenges eventually become bearable for the donors because of their love for the recipient and because they totally forget themselves and their needs during the donation process.

Keywords: Donation, kidney, challenge, relative, qualitative

Corresponding Author: Maryam Esmaeili ✉ esmaeiliem@yahoo.com; esmaeili_m@ tums.ac.ir **Received:** 08.11.2018 **Accepted:** 05.02.2019

Cite this article as: Farahani FB, Esmaeili M, Dehghan-Nayeri N, Salsali M. Challenges in Kidney Donation Faced by Relatives in Iran: A Qualitative Study. Turk J Nephrol 2020; 29(1): 39-44.

INTRODUCTION

Kidney transplantation is more affordable than dialysis and is associated with a better quality of life and prolonged lifespan for the patients (1, 2). The need for dialysis would be resolved following a successful kidney transplant, which would improve the patients' quality of life (3). There are three main known sources for kidney transplant, including a related living donor (related by blood and by marriage), an unrelated living donor (financial compensation or humanitarian), and brain-dead donor (4). In recent years, the mean interval between being placed on the waiting list and receiving a kidney from a brain-dead donor has significantly increased; this interval is approximately 3-7 years for kidney transplant patients (2, 5). In Iran, because the number of brain-dead donors is much lower than the number of patients requiring a kidney transplant, the need for living donors is very high (6).

During the past decades, the number of unrelated kidney donors with humanitarian intent has increased in developed countries, but the supply has been lower than the demand, which has led to a severe shortage of kidneys along with an increased mortality rate and increased business incentives for donation and transplant tourism (7). The increased number of unrelated donors with financial compensation has decreased the number of donations from relatives in Iran. However, unrelated donors seeking financial compensation usually have a lower quality of life than related donors, and they mostly regret donation (8). In fact, their main motivation for donation is solving their financial problems (2).

Receiving a kidney from a relative would increase the survival rate of the kidney recipient. In addition, the need for receiving an immunosuppressive regimen after transplant would be decreased in the recipient (9, 10). Therefore, kidney donation from a relative is an ideal option in transplantation that would improve the recipients' quality of life after transplant (11). Although the number of donors is increasing in Iran, few relatives make the decision to donate (12). Furthermore, their manner of encountering donation and also the challenges they face are ambiguous. Theoretical knowledge and information about the process of donation, the steps involved in completing the donation process, and the challenges faced by relative donors, especially first-degree relative donors, are limited. Evaluation of the experience of donors 1 week after donation revealed that the related donors experienced more stress after donation compared with that faced unrelated donors because of their dual roles (being a donor and a relative to the recipient) (13). Because few studies exist on the challenges faced by related donors, the aim of the present study was to evaluate the challenges for related kidney donors in the process of donation.

MATERIALS AND METHODS

The present study was a qualitative study with a conventional content analysis approach for collecting and analyzing data to determine the challenges faced by kidney donors in the process of donation.

Participants

A total of 16 related donors (10 women and 6 men) were selected from kidney transplantation centers of educational hospitals affiliated with Tehran University of Medical Sciences using a purposive sampling method. The inclusion criteria were being >18 years, being related to the recipient, having a favorable physical and mental condition for participating in the study, being willing to participate, and signing the informed consent form. In this study, the age range, gender, family relationship, and duration passed after donation were factors that could be considered to achieve maximum variability.

Data Collection

Data were collected using in-depth semi-structured face-to-face and phone interviews. Data collection lasted for 8 months (May 2015 to October 2015). The duration of the interviews varied from 45 to 90 min. Interviews were recorded using a voice recording device, and the answers were written down verbatim after each session. The main questions in the interview were, "What steps have you completed during the donation process?" and "What challenges did you face during the process of donation?" Furthermore, investigative questions were used during the interviews to clarify the answers of the participants.

This s was adopted from a Ph.D. thesis in nursing. The proposal for this study was approved by the ethics committee of the research council of Tehran University of Medical Sciences (IR.TUMS.REC.1395.2593). The goals and methods of the study were explained to the participants. Additionally, during the study, participants were allowed to leave without any penalties or losses. Written informed consent was obtained from all the participants. Their permission was obtained for recording of the interviews. Participants were assured that their information would remain confidential.

Statistical Analysis

We analyzed the study data using the qualitative content analysis approach. Content analysis is a scientific data analysis approach in which a researcher reduces and organizes data to explore the symbolic meaning of experiences (14). In the present study, immediately after each interview, we transcribed the interview verbatim and read the transcript several times to gain familiarity with the main ideas of the interview. Next, we divided the text into meaningful units. Subsequently, we condensed the meaningful units for the sake of abstraction and accordingly coded the condensed meaningful units. Finally, we compared the codes with each other and categorized the codes into themes and sub-themes according to their similarities and differences.

Trustworthiness

The study accuracy is one of the important aspects during the process of any qualitative study, which would lead to reader's audit of the facts, effects, and researchers' actions (15). In this study, peer review was used to achieve trustworthiness. Data were coded and categorized by the researchers separately. Then, the obtained themes from the analysis were compared with each other. In case of disagreement about a theme, researchers discussed the issue until achieving a common decision. A member check was also used so that a summary of extracted themes was given to some of the participants to approve them based on their own experiences. Accurate auditing from the very first steps of the study and during data gathering was used to achieve the trustworthiness of the study.

RESULTS

The results of the present study were obtained after analyzing interviews of 16 relative kidney donors; interviews were continued until data saturation. The mean age of the participants was 41 years, and the mean time passed after the donation was 5 years. Other demographic characteristics of the participants are presented in Table 1. Results of data analysis led to the extraction of three main themes: initial confrontation, hospitalization, and endless concerns. The second theme of the study had two sub-themes: being ignored and the rights of the donor. What follows is the meaning of each theme and sub-theme and the direct quotations from the participants.

Initial Confrontation

Initial confrontation means starting the process of donation after making the decision. During the initial confrontation, the donor needed to pass preliminary tests to approve the appropriateness of donation to the relative. Performing the tests was

Table 1. Donors' Demographic Characteristics	
Characteristics	**N (%)**
Gender	
Female	6 (37.5)
Male	10 (63.5)
Educational Level	
Elementary	2 (13)
High School Diploma	10 (62)
Bachelor's	4 (25)
Age	
mean±standard deviation	40±3.45
Time after donation	
<1 year	4 (25)
1-5 years	6 (37.5)
>5years	6 (37.5)

one of the longest and most stressful parts of the donation process, and according to the participants, lasted at least 6 months. Most participants complained about the delayed duration of this period. Some of the donors got exhausted during this period and sometimes even regretted their decision to donate. Some participants complained about the lack of a comprehensive systematic program and some about the lack of a supportive system during this period; most participants tolerated significant mental and psychological pressures during this period. Some participants had traveled to Tehran from smaller cities to undergo the preliminary test because of the equipped laboratories in Tehran. They mentioned feelings of loneliness and homesickness, lack of support, and lack of a place of residence. During the first confrontation with donation, most donors believed that the worst and toughest part was performing preliminary tests.

Although donating parents, especially mothers, had patience and provided unconditional love throughout the entire donation process, they experienced restlessness and intolerance during the tests owing to their difficulty and lengthy durations. A mother who donated a kidney to her daughter provided the following statement:

"There was a heart test too, during which I got really tired and confused. I was saying why don't these end? I never thought that it could be so long and tough. I used to think that matching blood types is enough. I was whispering 'Oh God, please let this stop.'" (Second donor, mother's donation to her daughter)

Some participants also believed that the lengthy period of the tests was threatening their job because they had to take repeated leave of absences for undergoing the tests.

"The time that we spent performing the tests was too long. They delayed the work so much. I was employed, so I had to take repeated leaves and pay cuts from my work. I was so worried sometimes that I couldn't take it anymore." (First donor, daughter's donation to her father)

Lengthy test periods, their high cost, repeating various tests, and the ambiguity of the results of the match between the donor and the recipient were some of the challenges and difficulties that donors faced during the donation process, such that some of the participants mentioned considering withdrawal and regretted the decision to donate.

Hospitalization

After passing the long and difficult period of testing, donors would be hospitalized for donations. Participants reported various experiences during this period from their confrontations with physicians and nurses at hospitals. Most participants' interactions during hospitalization and nephrectomy were with nurses, and they experienced little interaction with their physicians. This theme had two sub-themes: being ignored and the rights of the donor.

Being ignored

Most participants in the present study stated that most of their interactions with the physicians were at the early stages while they were being instructed about the preferability of donation from a relative. They believed that they were ignored by the transplantation team after the surgery and kidney donation. Some of the participants mentioned lack of attention and support. Participants believed that nurses mostly paid attention to the recipients, and the donors had not received any special attention before and after the surgery. One of the donors stated as follows:

"Not before the surgery and not even after the surgery the nurses spoke to us about what was going to happen or did anything for us or pay any attention to us; instead, they were mostly focused on the recipients." (Sixth donor, spouse's donation to the spouse)

While interviewing some of the nurses from the transplant ward, they mentioned that numerous and sensitive care procedures and follow-ups of the recipients were one of the reasons for not paying sufficient attention to the donors. They also mentioned the lack of a standard protective and educational plan and protocol for donors at the hospital environment. Nurses believed that the reasons for not paying sufficient attention and support to the donors were physicians' ignorance toward the donors after donation, lack of a specific position for nurses among the transplantation team, lack of a referring center for donors to perform donation follow-ups, and the health system not paying the donors.

The rights of the donors

In the present study, some of the participants complained about disrespecting the patients and their rights at the time

of their need for attention and emotional and mental support. Most participants were eager to receive information and respect during the process of donation. They expected to receive the minimum rights of the patients; they did not have high expectations from the treatment team. Their expectations following hospitalization were being met, and they were interacted with humanly and obtained correct information from an experienced and aware team.

One of the greatest expectations of the donors during hospitalization was receiving an educational program for improving the quality of life after donation. The participants stated that after the surgery, they had many questions about their health condition, required follow-ups, and consequences of transplantation, but they had not received sufficient answers from the treatment team. According to the donors, prepping the patients before the donation is the duty of the transplant team. They believed that the presence of a counselor and a psychologist before the surgery was one of their rights that was neglected. Regarding psychological counseling, one of the participants stated as follows:

"I wanted to donate my kidney with love and interest, but I was so nervous and stressed. I wanted someone to be there so that I could talk to them and remain calm." (Tenth donor, sister's donation to a sibling)

Participants in the present study had very little information before the surgery regarding the possible physical consequences of donation, such as severe pain or nausea and vomiting. They mentioned that they encountered an unbearable pain without being prepared, which caused excessive tension and discomfort for the donors. Furthermore, they had not received an educational program for self-care and postoperative follow-ups.

Endless concerns

Although the donors who were relatives in the present study had willingly decided to donate their kidney, they were worried during the entire process of donation. They believed that only the condition of their worry was changed at different stages of the donation. They also believed that even transplantation could not completely resolve their concerns about the health of their recipient, and it only decreased their concerns. Concerns about blood type incompatibility at the stage of performing the tests, concerns about anesthesia and surgery, and concerns about rejection of the donated kidney were some of the concerns expressed by relative donors. One of the participants stated as follows:

"At the hospital, I was in so much pain, but I wasn't thinking of myself, I was thinking of my sister. I was worried that her body might reject the kidney or that she might have not come out of anesthesia; I had completely forgotten about myself." (Eighth donor, sister's donation to a sibling)

The fear of the rejection of the donated kidney was one of the fears of most of the donors, even years after the donation. This concern was specifically significant among donating parents. Some of the donors even found another relative for donation because of their fear of rejection of the donated kidney.

Another concern of the donors, especially among donating parents, was the side effects of the drugs taken by the patient after transplantation. They believed that because of the administration of immunosuppressive drugs, the patient would be prone to various diseases, and this made them concerned.

A mother, after donating a kidney to her child, expressed the endless difficulties and concerns regarding the donation. She stated that not only are her concerns over but her life is now entangled with concern and anxiety:

"I didn't think that I still would be so concerned after the transplant, but I notice that I'm always worried and anxious. I fear that my child could get sick more than others, and that's because of the drugs she is taking. On the other hand, I constantly think what if her body rejects the kidney, then what should I do? I don't forget even for a second. It is like a concern, and anxiety has become a part of me." (Second donor, mother's donation to her daughter)

DISCUSSION

Participants in the present study stated that the challenges that they faced during the donation process were difficulties in performing tests, difficulties during hospitalization, and endless concerns. To obtain the final approval and confirmation of being a suitable candidate for donation, the donors should pass all the necessary tests. In the present study, the testing stage was one of the longest and most stressful stages during the donation process. The results of a previous study showed that the donors reported the stage of performing the tests as the toughest, longest, and worst part of the donation process (16). They had experienced a significant amount of stress and anxiety about the results of the tests, which even made some of them reconsider their decision about the donation (1). Results of the study also revealed that performing the tests causes stress and anxiety for the donors, and referring to the laboratory and performing the tests before the donation is an uncomfortable experience for them. Because of the lack of coordination, delay, and wasting of time on testing, the testing stage was reported as stressful for donors (17). Some participants in the present study reported exhaustion at this stage and even reconsidered their decision to donate, but eventually, despite all the difficulties and lengthiness of the testing stage, they completed this process and donated their kidney because of their feelings of responsibility, along with love and motivation.

Some participants in the present reported feelings of being left out, ignored, and not supported by the nurses and physicians. They believed that the nurses' attention was mostly focused

on the recipients and that they were treated with impatience and inattention. The study by Sanner (2005) showed that some of the donors reported feelings of being abandoned, left out, and neglected by the personnel of the ward (18). In this regard, Elciego and Doman (2011) recommended and emphasized that the control, follow-up, and accurate observation by the transplantation team of the donors should be the same as for those of the recipients (17). Although donors in the study by Delanaye (2012) had positive experiences from the received cares in the hospital, most of them experienced a lack of follow-up care after being discharged (19). Some felt neglected by and insignificant to the treatment team, and some even felt that the treatment team has treated them as a tool to end the recipient's treatment. Donors in the study by Lima et al. (2) in 2006 were also dissatisfied with the received medical services during their hospitalization.

Some of the participants in the present study stated that they had not received any educational program for preparation for the surgery or for taking care of themselves after discharge and performing routine follow-up visits to the physician or the nurse from the transplantation team. Lack of sufficient information after donation is one of the disadvantages of the donation process. Therefore, it is necessary for the health personnel to have appropriate understanding of the nature of the donation process and the needs of the donors (6). Focusing on physical, mental, psychological, and interpersonal factors during counseling and educating the donors is essential (19, 20). In the study by Mazaris et al. (21) in 2012, the greatest sources of information for the donors were the transplantation team, journals, and electronic media. Results of another study showed how the lack of knowledge and awareness could affect different aspects of donation (22). The lack of knowledge and awareness might cause the donor to avoid donation. The need for educating the donors is the content of most of the conducted studies (1, 2).

Endless concern was another challenge faced by the relative donors in the present study. The most important concern of the donors after donation was that the recipient's body would reject the kidney (13, 22). In the process of donation, the donors' priority is always attending to the needs of the recipient, and they mostly felt concerned about the results of the transplant and failure in transplant (1). Donors in the study by Lennerling et al. (23) in 2004 were also concerned about the health of and prognosis of donation in the recipient during the entire donation process. Sacrifice, dedication, forgiveness, and self-devotion in donation are some of the features of the donors in the present study. In general, the experience of surgery by the donors has been reported to be somewhat unfamiliar and dissimilar to anything else. Usually, the recipient and the donor would both feel much fear and anxiety during the process of donation. They usually fear death and are anxious about the consequences that might happen after donation. Their fear usually increases at the day of the procedure, and it includes the fear of risking their lives, fear of pain, fear of the unknown, fear of the postoperative consequences, fear of opioids, fear of the operating room, and fear of being away from the family (24). In a thematic synthesis conducted by Tong et al. (25) in 2012, most donors stated that after the donation, they were particularly concerned about the recipient and the possibility of failure in the function of the donated kidney. Most of the concerns of the donors were regarding postoperative pain, duration of recovery, recipient's health, occupational issues, possible risks, and limitations in the new lifestyle.

The findings of this study showed that relative kidney donors face numerous challenges in the donation process. Focusing on the concerns of donors at the initial consultation and trying to shorten the test duration will be helpful. Nurses can provide more favorable conditions with more support from family donors seeking hospitalization and respect for their rights. Establishment of the Donor Support Association to address the problems and needs of these individuals will be effective in improving the quality of life and addressing their concerns.

CONCLUSION

The present study aimed to discuss some of the challenges faced by relative donors. The duration of testing, not respecting the rights of the donors during the period of hospitalization, and various concerns by the donors were some of the challenges faced during the donation process. According to the results of the present study, the presence of a counselor or a psychologist, especially during the hospitalization period, could be helpful in decreasing the concerns of the donors. Because there are few relative kidney donors in Iran, finding participants for the present study was difficult. In addition, similar to other qualitative studies, the generalizability of the present study is low.

Ethics Committee Approval: Ethics committee approval for this study was received from the research ethics committee of the Tehran University of Medical Sciences.

Informed Consent: All participants gave informed consent for the research, and their anonymity was preserved.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.E., Z.F., M.S.; Design – M.E., Z.F., M.S.; Supervision – M.E., M.S., N.D.N.; Resources – M.E., Z.F.; Materials – M.E., Z.F.; Data Collection and/or Processing – Z.F.; Analysis and/or Interpretation – M.E., M.S., N.D.N.; Literature Search – M.E., Z.F.; Writing – M.E., Z.F.; Critical Reviews – M.E., Z.F.

Acknowledgements: The authors would like to thank all the participants during the different stages of this study. This study was one part of a PhD dissertation of the first author, which was financially supported by Tehran University of Medical Sciences.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This research received funding from Tehran University of Medical Sciences.

REFERENCES

1. Ummel D, Achille M, Mekkelholt J. Donors and recipients of living kidney donation: A qualitative metasummary of their experiences. J Trans 2011; 21: 1-11. [CrossRef]
2. Lima DX, Petroianu A, Hauter HL. Quality of life and surgical complications of kidney donors in the late post-operative period in Brazil. Neph Dial Transplant 2006; 21: 3238-42. [CrossRef]
3. Suzanne C, Smeltzer O. Brunner & Suddarth's Textbook of Medical Surgical Nursing (12th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2014, 642-51.
4. Timmerman L, Laging M, Westerhof GJ, Timman R, Zuidema WC, Beck DK, et al. Mental health among living kidney donors: A prospective comparison with matched controls from the general population. Am J Transplant 2015; 15: 508-17. [CrossRef]
5. Mathur AK, Ashby VB, Sands RL, Wolfe RA. Geographic variation in end-stage renal disease incidence and access to deceased donor kidney transplantation. Am J Transplan 2010; 10: 1069-80. [CrossRef]
6. Farahani ZB, Esmaeili M, Salsali M, Nayeri N. Living related transplantation: the outcomes of kidney donation in Iran. Acta Medica Mediterranea 2016; 32: 1071.
7. Fallahzadeh MK, Jafari L, Roozbeh J. Comparison of health status and quality of life of related versus paid unrelated living kidney donors. Am J Transplant 2013; 13: 3210-4. [CrossRef]
8. Zheng XY, Han S, Wang LM, Zhu YH, Zeng L, Zhou MS. Quality of life and psychology after living-related kidney transplantation from donors and recipients in China. Transplant Proc 2014; 46: 3426-30. [CrossRef]
9. Santori G, Barocci S, Fontana I, Bertocchi M, Tagliamacco A, Biticchi R, et al. Kidney transplantation from living donors genetically related or unrelated to the recipients: a single-center analysis. Transplant Proc 2012; 44: 1892-6. [CrossRef]
10. Garcia MFFM, Andrade LGM, Carvalho MFC. Living kidney donors--a prospective study of quality of life before and after kidney donation. Clin Transplant 2013; 27: 9-14. [CrossRef]
11. Vemuru Reddy SK, Guleria S, Okechukwu O, Sagar R, Bhowmik D, Mahajan S. Live related donors in India: Their quality of life using world health organization quality of life brief questionnaire. Indian J Urol 2011; 27: 25-9. [CrossRef]
12. Simforoosh N, Soltani MH, Basiri A, Tabibi A, Gooran S, Sharifi SH, et al. Evolution of laparoscopic live donor nephrectomy: A single-center experience with 1510 cases over 14 years. J Endourol 2014; 28: 34-9. [CrossRef]
13. Anderson MH, Mathisen L, Oyen O, Wahi A, Hanestad BR. Living donors experiences 1 week after donating a kidney. Clin Transplant 2005; 19: 90-6. [CrossRef]
14. Streubert HJ, Carpenter DR. Qualitative Research in Nursing. Philadelphia: Lippincott, Williams &Willkins. 2011.
15. Holloway I, Wheeler S. Qualitative Research for Nurses. Blackwell Science Publishing, 2010.
16. Stothers L, Gourlay WA, Liu L. Attitudes and predictive factors for live kidney donation: A comparison of live kidney donors versus non-donors. Kidney Int 2005; 67: 1105-11. [CrossRef]
17. Elcioglu O, Duman S. Concept of the voluntariness in kidney transplantation from the position of donors and recipients. Glob Bioeth - Perspect Hum Surviv 2011; 1: 31-7. [CrossRef]
18. Sanner MA. The donation process of living kidney donors. Nephrol Dial Transplant 2005; 20: 1707-13. [CrossRef]
19. Delanaye P, Weekers L, Dubois BE, Cavalier E, Detry O, Squifflet JP, et al. Outcome of the living kidney donor. Nephrol Dial Transplant 2011; 27: 41-50. [CrossRef]
20. Gill P. Stressors and coping mechanisms in live-related renal transplantation. J Clin Nurs 2012; 21: 1622-31. [CrossRef]
21. Mazaris EM, Warrens AN, Smith G, Tekkis P, Papalois VE. Live kidney donation: attitudes towards donor approach, motives and factors promoting donation. Nephrol Dial Transplant 2012; 27: 2517-25. [CrossRef]
22. Siegel JT, O'Brien EK, Alvaro EM, Poulsen JA. Barriers to living donation among low-resource Hispanics. Qual Health Res 2014; 24: 1360-7. [CrossRef]
23. Lennerling A, Forsberg A, Meyer K, Nyberg G. Motives for becoming a living kidney donor. Nephrol Dial Transplant 2004; 19(6):1600-5. [CrossRef]
24. Ghahramani N, Karparvar Z, Ghahramani M, Shadrou S. International survey of nephrologists' perceptions and attitudes about rewards and compensations for kidney donation. Nephrol Dial Transplant 2013; 28: 1610-21. [CrossRef]
25. Tong A, Chapman JR, Wong G, Kanellis J, McCarthy G, Craig JC. The motivations and experiences of living kidney donors: A thematic synthesis. Am J Kid Dis 2012; 60: 15-26. [CrossRef]

10.5152/turkjnephrol.2020.3859

Original Article

Turkish Journal of Nephrology

Evaluation of the Parathyroid Gland using Ultrasound Elastography in Children with Mineral Bone Disorder Due to Chronic Kidney Disease

İlknur Girişgen[1], Gülay Güngör[2], Selçuk Yüksel[1]

[1]Division of Pediatric Nephrology, Pamukkale University School of Medicine, Denizli, Turkey
[2]Department of Radiology, Pamukkale University School of Medicine, Denizli, Turkey

Abstract

Objective: Mineral bone disorders due to chronic kidney disease (CKD-MBD) in children occur as a result of decreased glomerular filtration rate and abnormalities in phosphorus, calcium, parathyroid hormone, and vitamin D metabolism rates. Increased parathormone synthesis may result in the development of adenomas in the parathyroid gland. The aim of this study was to evaluate parathyroid lesions in children with CKD-MBD using ultrasound (US) elastography.
Materials and Methods: Fifteen patients with a diagnosis of CKD-MBD (average age, 15.5±2.4 years; seven girls) and 15 healthy children (average age, 13.8±2.5 years; six girls) were included in the study. The patients were evaluated clinically and in terms of laboratory findings (calcium, phosphorus, alkaline phosphatase, vitamin D, and parathormone levels), and all patients were evaluated using strain US elastography. The parathyroid strain ratio indices of the study group were compared with the thyroid strain ratio indices of the control group.
Results: Among 11 patients with stage 5 CKD who underwent parathyroid US, nodules were observed in 8 patients, whereas parathyroid nodules were not observed in 3 patients with stage 3-4 CKD. The parathyroid lesions average strain ratio index (1.1±0.5) was significantly higher than that of the control group (0.46±0.16).
Conclusion: The stiffness of parathyroid lesions in children with US elastography was evaluated for the first time in this study to the best of our knowledge, and it is believed that a high strain ratio index could be a useful indicator of the presence of adenomas. We propose that the findings be supported by future larger studies.
Keywords: Elastography, children, parathyroid gland

Corresponding Author: Selçuk Yüksel ✉ selcukyuksel.nephrology@gmail.com
Received: 21.03.2019 **Accepted:** 18.11.2019

Presented in: This study was presented at the "10th Turkısh Pediatric Nephrology Congress," 1-4 May 2019, Muğla, Turkey.

Cite this article as: Girişgen İ, Güngör G, Yüksel S. Evaluation of the Parathyroid Gland using Ultrasound Elastography in Children with Mineral Bone Disorder Due to Chronic Kidney Disease. Turk J Nephrol 2020; 29(1): 45-51.

INTRODUCTION

Mineral bone disorders in children with chronic kidney disease (CKD-MBD) are caused by abnormal interactions between the kidney, bone, and parathyroid gland, and they are closely associated with cardiovascular morbidity and mortality (1). As the glomerular filtration rate (GFR) decreases, phosphorus excretion in the urine in the early stages and active vitamin D synthesis in the kidney decrease, leading to a decrease in calcium, and the synthesis of secondary FGF-23 and parathormone (PTH) begins to increase. Secondary hyperparathyroidism is clinically called renal osteodystrophy (RO) and is classified into three types according to bone transformation/mineralization. In high bone turnover RO, the osteoblastic and osteoclastic number and cycle increase, the PTH level is high, osteitis fibrosa cystica can be observed, and bone mineralization is normal. In low bone turnover RO (adynamic bone disease, osteomalacia), bone formation is decreased, mineral-free bone tissue is increased, and the PTH level is low. In mixed bone disease, the bone turnover is increased and mineralization is decreased (1, 2). CKD-MBD in children results in bone fractures, skeletal deformities, growth disorders, bone pain, and vascular, metastatic, and soft tissue calcifications (1). Increased

PTH synthesis may result in diffuse or nodular cell growth and development of adenomas in the parathyroid gland. If the hyperplasia of the parathyroid gland is particularly nodular, the development of adenomas is more likely. As a result of the decrease in calcium and vitamin D receptors in the parathyroid gland, the adenoma can become autonomous, and resistance to active vitamin D treatment may develop (3). Tertiary hyperparathyroidism may develop in patients with secondary hyperparathyroidism in whom the parathyriod gland works autonomously which cannot be suppressed by treatment.

Ultrasonography (USG) and ^{99m}Tc Sestamibi (MIBI) scintigraphy are currently the most widely used imaging techniques to detect the location of parathyroid adenomas. The sensitivity of these techniques in identifying parathyroid adenomas is 70%-90%. Although magnetic resonance imaging and 4-D computed tomography have the potential to increase the accuracy of identification, they are expensive (4-7). USG is an inexpensive, noninvasive, and widely used imaging modality to evaluate the parathyroid gland in patients with hyperparathyroidism. However, it may be difficult to differentiate a parathyroid lesion from thyroid nodules or cervical lymph nodes (8, 9).

Currently, elastography, which is a relatively new technique developed by adding software, is based on the general principle that stress applied to the tissues with the help of USG, similar to the palpation technique in physical examination, causes changes in the tissue depending on the elastic properties of the tissue (10). Strain elastography (SE), which is one of the elastography techniques, provides semi-quantitative values of the stiffness of the tissue and the strain ratio (SR) value calculated with the help of software and thus helps to differentiate between tissues and accurately evaluate superficial tissues such as the breasts, prostate, scrotum, neck, and thyroid. If adequate external pressure is applied, adjacent organs such as the parathyroid gland can also be evaluated using this technique (11, 12).

It is well known that the parathyroid gland is normally composed of 40%-70% adipose tissue and that there is a significant decrease in fat content in parathyroid adenomas. In addition, parathyroid adenomas have been shown to have thickened capsules (13, 14). Therefore, parathyroid adenomas are expected to be relatively hard lesions. In recent years, parathyroid lesions have been evaluated using various elastography methods in adults in a limited number of studies. In addition, to the best of our knowledge, although there is a publication evaluating the images of parathyroid lesions using the SE technique in adult patients, no study has been performed using this method in pediatric patients (11).

The aim of this study was to evaluate the appearance of parathyroid lesions in children with secondary hyperparathyroidism caused by CKD by USG and to prospectively determine whether SE can be a valuable additional tool in the diagnosis of parathyroid adenoma.

MATERIALS AND METHODS

The study was prospectively designed to evaluate the parathyroid lesions of 15 children with CKD-MBD using USG elastography. The control group comprised 15 age- and sex-matched healthy children.

Calcium, phosphorus, alkaline phosphatase, vitamin D, and PTH were evaluated in serum samples taken in the morning in routine laboratory tests for BMD. Analyses of biochemical laboratory tests were performed using routine Cobas 8000 series modular autoanalyzers (Roche Diagnostics, Mannheim, Germany). Serum calcium, phosphorus, and alkaline phosphatase levels were measured using the photometric method with a c702 autoanalyzer, and vitamin D and PTH levels were measured using the electrochemiluminescence immunological method with an e601 autoanalyzer.

Radiologically, all patients were evaluated using a conventional B-mode and SE. Axial B-mode and SE images were obtained using a digital sonography device (LOGIQ E9, GE Healthcare, Milwaukee, WI) supported by SE software using 11-15 MHz linear probes to parathyroid glands. All measurements were performed by the same radiologist who had 10 years of experience with USG and 7 years with SE. An USG evaluation was performed using an adequate amount of USG gel. For the measurement of the parathyroid lesion, subjects were laid supine on the examination table in a position with the neck slightly extended. First, B-mode USG was performed, and morphological characteristics (echo pattern, shape, presence of halo sign, and presence of calcification), size, and localization of each lesion were evaluated.

In the second stage, SE was performed immediately after B-mode USG. While the parathyroid images were captured, the SE mode was turned on, and another B-mode image was opened next to the original B-mode image. The local strain was achieved by applying light repetitive compression (rhythmic compression-relaxation cycle) with a free-hand technique while the probe was in the scanning position (15, 16). The SE image was observed as a translucent, color-coded, and real-time image superimposed with the B-mode image. Repetitive compression was continued until more than three SE images were obtained. The hardness of tissues was shown in a color-coded map in which soft tissues were red, hard tissues were blue, and moderately elastic tissues were green (17). Strain elastograms were classified into elastographic patterns according to tissue stiffness (17-20). Figure 1 gives an example of cases with various elastographic patterns. After screening, three SE images were selected randomly during each measurement. In each of the three images, a circular region of interest (ROI) was placed separately into the parathyroid and adjacent thyroid gland. The SR value (B/A) in each ROI was automatically calculated using the USG device by comparing parathyroid (A) to adjacent thyroid (B) for each patient, and the average values were obtained (Figure 2). An SR value was calculated for each of the three images. The average value of the three trials was considered as the SR value

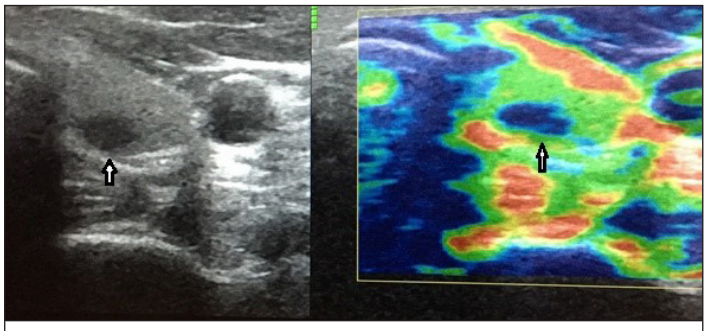


Figure 1. Example of parathyroid adenoma image in conventional ultrasonography (US) and strain elastography (SE). The image on the right shows an oval hypoechoic parathyroid adenoma (arrow) in the inferior neighborhood of the left lobe of the thyroid gland on the gray-scale axial US image. In the picture on the left, Pattern 4 images are seen in SE.

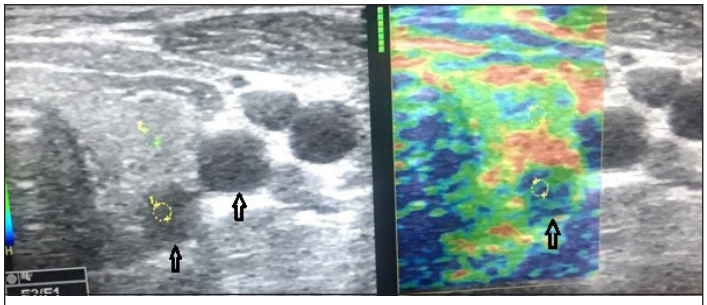


Figure 2. Image of two nodules in the left parathyroid. In the picture on the right, the gray-scale USG shows two well-circumscribed hypoechoic nodules (arrows). The picture on the left shows that the elasticity score of one of the nodules in the SE is consistent with Pattern 4 (arrow). The strain ratio is 0.5.

of each measurement time. The measurements were obtained from only the solid part and noncalcified part of each lesion.

Because normal parathyroid glands are very small, they cannot be evaluated using USG. Therefore, the SR values of the parathyroid gland lesions were compared with the adjacent normal thyroid parenchyma. In the control group, similar measurements were performed for the thyroid gland and compared with the adjacent subcutaneous adipose tissue.

Informed consent was obtained from the families of the patients, and ethics committee approval (19.03.2019/06) was obtained from Pamukkale University medical ethics committee.

Statistical Analysis

Data were analyzed using the The Statistical Package for the Social Sciences (SPSS) version 24.0 package program (IBM Corp.; Armonk, NY, USA). Continuous variables were expressed as the average±standard deviation, and categorical variables were expressed as numbers and percentages. The suitability of the data for normal distribution was examined using the Shapiro-Wilk test. Independent group t-test was used for the analysis of independent group differences, and chi-square analysis was used for the differences between categorical variables. Spearman correlation analysis was used to examine the relationships between continuous variables. In all analyses, $p<0.05$ was considered statistically significant.

RESULTS

The study group comprised 15 laboratory-confirmed patients with CKD-related BMD. The average age of the study group was 15.5±2.4 (12-19) years, and the female-to-male ratio was 7:8. The control group comprised healthy children. The average age was 13.8±2.5 (10-18) years, the female-to-male ratio was 6:9, and there was no significant difference in terms of age and sex between the groups. Demographic and laboratory data and patient treatments are given in Table 1.

The etiologies of patients with CKD were varied, and chronic glomerulonephritis was the most frequently observed etiology (Table 1). Among 15 children with CKD in the study group, 11 had stage 5, 3 had stage 4, and 1 had stage 3 CKD. The dialysis modality of 10 patients with stage 5 CKD was peritoneal dialysis, and one patient was receiving hemodialysis treatment. One patient had a low calcium level, and three had levels >10.2 mg/dL, the target level for that age. The phosphorus level of 13 patients was above the normal limit for that age (>12 years target P level 2.3-4.5 mg/dL [1.21]). Eleven of the 13 patients using active vitamin D had PTH levels more than the target level (PTH target level, 100-300 pg/mL for stage 5 CKD; PTH level, 70-110 pg/mL for stage 3-4 CKD [1.21]). All patients were using calcium-based phosphate binders; 5 were using additional calcium-free phosphate binders (sevelamer), and 13 were on active vitamin D therapy (Table 1).

In the parathyroid USG, nodular lesions (parathyroid adenoma/hyperplasia) were detected in eight patients with stage 5 CKD, whereas three patients had no lesions. No lesions were detected in the patients with stage 3-4 CKD. Table 2 shows the nodule size and SR of the patients with parathyroid nodules. In addition, thyroid nodules were detected using USG in two patients (Table 2). Parathyroid elastography was performed in eight patients with parathyroid lesions in the study group; two patients had pattern 2, one patient had pattern 3, four patients had pattern 4, and one patient with two parathyroid lesions had elastographic patterns 3 and 4. The average parathyroid elastography SR value of the patients with parathyroid lesions in the study group was 1.1±0.5, the average thyroid elastography SR value of the control group was 0.46±0.16, and the average SR value of the study group was significantly high (Table 3).

The presence, size, and SR values of the parathyroid lesion were not correlated with PTH levels.

DISCUSSION

In our study, the parathyroid glands of patients with CKD-BMD were evaluated using USG and elastography. In cases with parathyroid lesions, elastographic features and SR indices were evaluated according to the color score. When compared with the thyroid SR index of the control group, the SR index of para-

Table 1. Demographic, laboratory findings, and treatments of children with bone mineral

Patient Number	Age	Sex	CKD Stage	Primary Disease	Dialysis Modality	Ca	P	ALP	PTH	Vit. D	Ca-based P Binder	Sevalemer	Calcitriol
1	15	M	5	FSGS	PD	9.7	5.1	372	1191	28	+	+	+
2	19	F	5	FSGS	PD	11.3	5.1	56	274	36	+	+	+
3	18	F	5	VUR	PD	9.4	5.7	70	308	46	+	-	+
4	13	F	5	CGN	PD	7.9	5	589	1958	25	+	-	+
5	19	M	5	SLE	PD	8.8	4	142	107	22	+	-	-
6	19	M	5	VUR	PD	9.5	7	68	283	46	+	-	+
7	14	M	5	CGN	PD	7.8	5.5	662	1062	11	+	+	+
8	12	F	5	Neurogenic bladder	PD	10.5	4.4	88	193	29	+	-	-
9	12	F	5	Nephronophthisis	PD	10.8	5.8	188	425	25	+	+	+
10	15	F	5	VUR	PD	9	6.1	283	1738	23	+	-	+
11	14	M	5	VUR	HD	10.1	6.9	819	1500	77	+	+	+
12	14	M	4	FSGS	-	7.6	7.6	129	266	9	+	-	+
13	15	M	3	Nephronophthisis	-	9.7	4.7	246	237	18	+	-	+
14	15	M	4	VUR	-	9.06	4.8	91	217	33	+	-	+
15	19	F	4	IgA nephropathy	-	9.06	5.1	61	242	12	+	-	+

PD: Peritoneal dialysis; HD: Hemodialysis; CKD: Chronic kidney disease; FSGS: Focal segmental glomerulosclerosis; VUR: Vesicoureteral reflux; CGN: Crescentic glomeru- lonephritis; SLE: Systemic lupus erythematosus

Table 2. Ultrasonography and strain elastography results of chil- dren with bone mineral metabolism disorder due to chronic kidney disease

Patient Number	Parathyroid Nodule (mm)	Parathyroid Elastography Strain Ratio	Thyroid Nodule (mm)
1	4x2.5	1.6	-
2	11x10	2.1	-
3	3x3	0.9	-
4	4.5x2.5	0.8	-
5	Absent	-	-
6	Absent	-	-
7	4.7x2.4	1.2	3x2
8	Absent	-	-
9	4.8x2.1	0.8	-
10	5.7x3.6	1	-
11	10.6x10.2	0.5	-
12	Absent	-	8.5x4
13	Absent	-	-
14	Absent	-	-
15	Absent	-	-

thyroid lesions was found to be higher. One of the main findings of this study was that the parathyroid lesions (adenoma/hyperplasia) were very hard masses. It was also thought that SR index elevation may be an indicator of adenoma in patients with parathyroid lesions.

K-DIGO defined CKD-BMD as the presence of one or more of the following findings (21, 22):

Impairment in Ca, P, vitamin D, and PTH metabolism rates

Abnormalities in bone turnover and mineralization and linear bone growth

Calcification in vascular or other soft tissues

Generally, at stage 2 CKD, i.e., a GFR of <90 mL/min/1.73 m^2, laboratory findings of BMD start to emerge (21). Clinically, bone pain, skeletal deformities such as genu valgum, genu varum, fractures, growth retardation, and non-bone vascular and soft tissue calcifications, and myopathy can be observed (21). In addition to laboratory findings, bone marrow biopsy is used to evaluate bone turnover (osteoblastic-osteoclast activity), and bone densitometry is used to evaluate bone mineralization in some cases (22).

In the treatment, phosphorus restriction is made by maintaining phosphorus within normal limits according to age (1-23). Calcium is maintained within normal limits according to age. Phosphorus-binding agents (calcium-containing and non-calcium-containing sevelamer) and active vitamin D-calcitriol to lower the PTH level are used. The target PTH level in children

Table 3. Comparison of the parathyroid elastography parameters of the study group and the thyroid elastography parameters of the control group

	Study Group n=14	Control Group n=15	p
Age (year)	15.2±2.4 (12-19)	13.8±2.5 (10-18)	0.14
Sex (F/M)	7/8	6/9	0.8
Parathyroid nodule elastography (strain ratio index)	1.1±0.5	0.46±0.16	0.009

with stage 5 CKD in the pediatric age group is recommended to be maintained between 100 and 300 pg/mL, and when this level is >500 pg/mL, growth is impaired and the incidence of osteitis fibrosa cystica increases, whereas the risk of hypercalcemia occurs when the level is <100 pg/mL (1,21). If the PTH level exceeds 1000 pg/mL, subtotal parathyroidectomy should be considered when there is no response to vitamin D treatment (vitamin D and Ca receptor levels of the nodular compartment developing in the hyperplastic gland in parathyroid are decreasing), and calcification and calciphylaxis in soft tissues occur. All our patients were receiving phosphorus-restricted diet and calcium-containing phosphorus-binding and active vitamin D therapy, and five patients were receiving additional sevelamer therapy. Despite these treatments, five patients had a PTH level of 1000 pg/mL and 11 had a PTH level above the normal level.

USG is the modality of choice for imaging the parathyroid gland in children. The presence of nodules can be demonstrated using USG. Studies have shown that other lesions in the cervical region (thyroid nodules and lymph nodes) can be confused with parathyroid adenomas in terms of location and structure (8, 9, 24). The indications for MIBI scintigraphy are disputable, and this modality is usually not considered for the diagnosis and for determining the location of the lesion. If parathyroidectomy is indicated, it should be performed to show localization of adenoma or if there is suspicion of ectopic adenoma (21, 25). In addition, if thyroid nodules, lymph nodes, and metastatic masses are present, MIBI scintigraphy specificity decreases, and it has disadvantages such as radiation exposure (25). Studies have shown that the sensitivity of MIBI in hyperparathyroidism is 50%-85%, and at the same time, its sensitivity for the detection of nodules <1 cm decreases further (6, 26).

USG elastography deals with the mechanical properties of the tissue. The hardness of the measured tissue relative to that of neighboring tissues provides information about its consistency. By applying external force, the positional change of the tissue can be examined. The lesser the displacement of a tissue, the greater is the hardness of that tissue. Strain index is obtained by dividing the elasticity ratio of the mass by the elasticity ratio of the healthy adjacent tissue. The first evaluation of the parathyroid gland using the SE method was performed by Ünlütürk et al. (11). It was observed that parathyroid adenomas were hard in SE, and the parathyroid hyperplasias were soft in almost half the cases. The authors found higher SR values and higher elasticity scores (scores 3 and 4) in patients with parathyroid adenoma compared with those with hyperplasia. Similarly, in our study, high elasticity scores and SR values were found in parathyroid lesions. Although the prospective characteristics of the study by Ünlütürk et al. (11) and evaluation in accordance with pathological correlations made positive contributions to the literature, we think that the over-dependency of SE on users is the drawback of the study. There are a considerably fewer number of studies evaluating parathyroid adenomas using elastography. On review of the literature and to the best of our knowledge, there are no studies on this subject in children. After parathyroid adenoma is detected using USG, the SR values calculated when elastography is performed cannot be compared with those of a normal parathyroid gland because normal-sized parathyroid glands are not identified by most imaging methods. Therefore, if the parathyroid gland can be observed on USG, it should be considered a pathological lesion. In our study, parathyroid adenoma SR values were compared with SR values of adjacent tissues, such as the thyroid tissue. In the study by Ioana et al., the parathyroid adenoma SR rates were lower than the thyroid tissue SR rates. However, different results were obtained in different studies. Chandramohan et al. (5) showed that parathyroid adenomas were softer than benign and malignant thyroid nodules, and Batur et al. (27) showed that parathyroid adenomas were more rigid than benign thyroid nodules and less rigid than malignant lesions. In our study, we calculated that the SR values of patients with parathyroid nodules were significantly higher than those of the control group. All patients with parathyroid nodules were stage 5 CKD, and no adenoma was detected in patients with stage 3-4 CKD. In addition, a thyroid nodule was found incidentally on USG in two patients in the study group. Parathyroid adenoma was detected in one of the two patients with thyroid nodules, and reference values in the SR measurements were obtained from localization of normal thyroid parenchyma without thyroid nodules. In other words, lesions observed in the thyroid that could change the reference value did not prevent the evaluation of the parathyroid gland.

The indication for parathyroid scintigraphy is to show the exact localization of adenoma in patients who are considered to require parathyroidectomy because they do not respond to active vitamin D therapy. In our study, parathyroid scintigraphy was performed in one of the patients with secondary hyperparathyroidism (patient 4), whose PTH levels (1958 pg/mL) could not be decreased despite active vitamin D and phosphorus-binding treatments. This patient had suspicious adenoma on USG, and the SR index was 0.8. Parathyroid scintigraphy did not reveal adenoma.

In another patient (patient 2), an adenoma of >1 cm was detected using USG, and the SR index was 2.1, which was considerably high. The PTH level was 274 pg/mL, and parathyroid scintigra-

phy revealed the presence of the adenoma. In the patient (patient 11) with vascular calcification and PTH level of 1500 pg/mL, despite active vitamin D treatment and a 1-cm parathyroid nodule detected on USG, but who had a low SR index (0.5), adenoma was not detected in the scintigraphy performed with the indication of parathyroidectomy. In conclusion, adenoma was not detected in parathyroid scintigraphy in the patient who was resistant to vitamin D therapy, had a PTH level >1000 pg/mL, and a parathyroid nodule >1 cm, but had a low SR index. However, scintigraphy showed an adenoma in the patient whose USG elastography did not show a very high PTH level but had a high SR index.

The data obtained from these three cases suggest that SR, i.e., the elasticity index, in elastography, may be more useful than the increased level of PTH and the size of the adenoma on USG to demonstrate the presence of an adenoma. However, the results from such a small number of patients are insufficient for such a prediction. This finding may serve as a base for larger studies in the future.

CONCLUSION

When we searched the literature, and to the best of our knowledge, there were no similar studies in patients with secondary hyperparathyroidism caused by CKD-BMD, nor was there any study in which the parathyroid gland was evaluated using elastography in children. The first result of our study was that the parathyroid adenomas had higher SR indexes than the thyroid tissue; in other words, they were very hard masses. The second result was that a high SR index may be a good indicator of the presence of adenomas. The limitations of the study are the small number of patients and the inability to detect parathyroid adenomas using parathyroid scintigraphy or parathyroidectomy in all patients. This method was not preferred due to ethical problems. There is a need for studies with more cases and studies compared with parathyroid scintigraphy within the indication.

Ethics Committee Approval: The ethics committee approval was received for this study from the ethics committee of Pamukkale University (19.03.2019/06).

Informed Consent: Written informed consent was obtained from the patients' families who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.G.; Design - İ.G.; Supervision - S.Y.; Resources - G.G.; Materials - İ.G., G.G.; Data Collection and/or Processing - İ.G., G.G.; Analysis and/or Interpretation - İ.G., S.Y.; Literature Search - İ.G., G.G.; Writing - İ.G., G.G., S.Y.; Critical Reviews - S.Y.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

REFERENCES

1. Hanudel MR, Salusky IB. Treatment of pediatric chronic kidney disease-mineral and bone disorder. Curr Osteoporos Rep 2017; 15: 198-206. [CrossRef]
2. Kültür T, Çifci A, İnanır A. Bone-minerale metabolism disorders (renal osteodystrophy) in chronic kidney disease and treatment approach. Ortadogu Medical Journal 2016; 8: 214-7.
3. Öncel L. Kronik renal yetmezlikli hastalarda hiperparatiroidizm, tedavi yaklaşımları ve kalsiyum reseptörü allel tiplendirmesi. Haydarpaşa Numune Eğitim ve Araştırma Hastanesi, Doktora tezi. 2017.
4. Johnson NA, Tublin ME, Ogilvie JB. Parathyroid imaging: technique and role in the preoperative evaluation of primary hyperparathyroidism. Am J Roentgenol 2007; 188: 1706-15. [CrossRef]
5. Chandramohan A, Therese M, Abhraham D, Paul TV, Mazhuvanchary PJ. Can ARFI elastography be used to differentiate parathyroid from thyroid lesions? J Endocrinol Invest 2018; 41: 111-9. [CrossRef]
6. Azizi G, Piper K, Keller JM, Mayo ML, Puett D, Earp KM, et al. Shear wave elastography and parathyroid adenoma: A new tool for diagnosing parathyroid adenomas. Eur J Radiol 2016; 85: 1586-93. [CrossRef]
7. Huppert BJ, Reading CC. The parathyroid glands. In:Rumack CM, Wilson SR, Charboneau JW, Levine D eds. Diagnostic Ultrasound, 4th edn, Elsevier Mosby, 2011; pp. 750-69.
8. Polat AV, Ozturk M, Akyuz B, Celenk C, Kefeli M, Polat C. The diagnostic value of shear wave elastography for parathyroid lesions and comparison with cervical lymph nodes. Med Ultrason 2017; 29: 386-91. [CrossRef]
9. Barbaros U, Erbil Y, Salmashoglu A, Işsever H, Aral F, Tunaci M, et al. The characteristics of concomitant thyroid nodules cause false-positive ultrasonography results in primary hyperparathyroidism. Am J Otolaryngol 2009; 30: 239-43. [CrossRef]
10. Menzilcioglu MS, Duymus M, Avcu S. Sonographic elastography of the thyroid gland. Pol J Radiol 2016; 81: 152-6. [CrossRef]
11. Ünlütürk U, Erdoğan MF, Demir O, Culha C, Güllü S, Baskal S. The role of ultrasound elastography in preoperative localization of parathyroid lesions: a new assisting method to preoperative parathyroid ultrasonography. Clin Endocrinol 2012; 76: 492-8. [CrossRef]
12. Garra BS. Imaging and estimation of tissue elasticity by ultrasound. Ultrasound Quarterly 2007; 23: 255-68. [CrossRef]
13. Isidori AM, Cantisani V, Giannetta E, Diacinti D, David E, Forte V, et al. Multiparametric ultrasonography and ultrasound elastography in the differentiation of parathyroid lesions from ectopic thyroid lesions or lymphadenopathies. Endocrine 2017; 57: 335-43. [CrossRef]
14. Herrera MF. Parathyroid embryology, anatomy, and pathology. In: O.H. Clark, Q.Y. Duh, E. Kebebew eds. Textbook of Endocrine Surgery, 2nd edn, Elsevier Saunders, Philadelphia, PA, 2005; pp. 365-71. [CrossRef]
15. Herek D, Herek O, Akbulut M, Ufuk F. Role of strain elastography in the evaluation of testicular torsion: An experimental study. J Ultrasound Med 2016; 35: 2149-58. [CrossRef]
16. Ophir J, Alam SK, Garra B, Kallel F, Konofagou E, Krouskop T, et al. Elastography: ultrasonic estimation and imaging of the elastic properties of tissues. Proc Inst Mech Eng H 1999; 213: 203-33. [CrossRef]
17. Dowell B. Real-time tissue elastography. Ultrasound 2008; 16: 123-7. [CrossRef]
18. Dumitriu D, Dudea S, Botar-Jid C, Baciut M, Baciut G. Real-time sonoelastography of major salivary gland tumors. Am J Roentgenol 2011; 197: 924-30. [CrossRef]

19. Itoh A, Ueno E, Tohno E, Kamma H, Takahashi H, Shiina T, et al. Breast disease: clinical application of US elastography for diagnosis. Radiology 2006; 239: 341-50. [CrossRef]
20. Choi YJ, Lee JH, Baek JH. Ultrasound elastography for evaluation of cervical lymph nodes. Ultrasonography 2015; 34: 157-64. [CrossRef]
21. Schmitt CP, Shroff R. Disorder of bone mineral metabolism in chronic kidney disease. Geary DF, Schaefer F eds. Pediatric Kidney Disease. 2nd edn. Springer-Verlag Berlin Heidelberg. 2008; pp. 1533-66. [CrossRef]
22. Bakkaloglu SA, Wesseling-Perry K, Pereira RC, Gales B, Wang HJ, Elashoff RM, et al. Value of the new bone classification system in pediatric renal osteodystrophy. Clin J Am Soc Nephrol 2010; 5: 1860-6. [CrossRef]
23. K-DIGO Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2009; 113: 1-130.
24. Golu I, Sporea I, Moleriu L, Tudor A, Cornianu M, Vlad A, et al. 2D-shear wave elastography in the evaluation of parathyroid lesions in patients with hyperparathyroidism. Int J Endocrinol 2017; 2017: 9092120. [CrossRef]
25. Kiratli PO, Ceylan E, Naldöken S, Beylergil V. Impaired Tc-99 m MIBI uptake in the thyroid and parathyroid glands during early phase imaging in hemodialysis patients. Rev Esp Med Nucl 2004; 23: 347-51. [CrossRef]
26. Chapuis Y, Fulla Y, Bonnichon P, Tarla E, Abboud B, Pitre J, et al. Values of ultrasonography, sestamibi scintigraphy, and intraoperative measurement of 1-84 PTH for unilateral neck exploration of primary hyperparathyroidism. World J Surg 1996; 20: 835-9. [CrossRef]
27. Batur A, Atmaca M, Yavuz A, Ozgökce M, Bora A, Bulut MD, et al. Ultrasound elastography for distinction between parathyroid adenomas and thyroid nodules. J Ultrasound Med 2016; 35: 1277-82. [CrossRef]

10.5152/turkjnephrol.2020.3682

Original Article

Turkish Journal of Nephrology

Effect of Conductance and Sodium Balance on Inter/Intra-Dialytic Symptoms

Prasanna Kumar[1], Aviral Dube[1], Beegum Sheena Karim[1], Tarun Rache[1], Ravindra Prabhu Attur[2], Sreedhran Nair[1], Anna Suresh[1]

[1]Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Karnataka, India
[2]Department of Nephrology, Kasturba Medical College, Kasturba Hospital, Manipal Academy of Higher Education, Karnataka, India

Abstract

Objective: To evaluate Patient Reported Outcomes of intra/interdialytic symptoms and to optimize the ideal conductivity settings maintained for minimal symptom expressions.
Materials and Methods: A prospective observational study, carried out in a south Indian tertiary care teaching hospital. Patient Reported Outcomes Kidney Disease Quality of Life (KDQOLTM) 35 Symptom List Questionnaire was administered to each patient to determine inter/intradialytic symptoms coupled with sodium conductivity measurement during hemodialysis.
Results: Of the 126 study populations, 97 consented were involved, the mean age was 50±11 years, with male predominance of 79%. Of the 31 parameters studied, 9 correlated significantly to conductivity showing some relationship ($p<0.05$). Muscle cramps, muscle soreness, fatigue, trouble sleeping and nausea were least at population conductivity mean of 14.4 mS/m and peaked at the extremes of mean conductivity range of 13.2 and 15.1 mS/m. Whereas hypotensive symptoms and hot & cold spells were lowest at higher extreme of mean conductivity and peaks at lower end due to sodium removal & hyponatremia.
Conclusion: The change in sodium conductivity with response to sodium gradient was associated with significant increases in inter/intra-dialytic symptom rates associated with symptoms like cramps, soreness, fatigue, nausea and trouble sleeping are least severe around a conductivity of 14.5 mS/m.
Keywords: Conductance, intra/interdialytic symptoms, sodium gradient, kidney disease quality of life

Corresponding Author: Prasanna Kumar ✉ shetty.prasannakumar@gmail.com
Received: 30.10.2018 **Accepted:** 04.02.2019

Presented in: This study was presented at the Renal Pharmacy Group Conference, from 26th – 27th September 2014, Manchester, United Kingdom.

Cite this article as: Kumar P, Dube A, Sheena Karim B, Rache T, Prabhu Attur R, Nair S, et al. Effect of Conductance and Sodium Balance on Inter/Intra-Dialytic Symptoms. Turk J Nephrol 2020; 29(1): 52-8.

INTRODUCTION

Dialysis is a treatment used for individuals in their late stage kidney failure (chronic kidney disease, CKD) which involves the removal of waste and excess water from the blood (1). A damaged kidney cannot remove excess sodium and fluid from the body that will lead to hypertension and fluid overload. An efficient sodium balance and a controlled rate of volume contraction are prerequisites for maintaining euvolemia throughout the intra and interdialytic periods and preventing complications (2). Positive sodium gradient (dialysate minus pre-dialysis serum sodium) is characterized by diffusive transport of sodium from the dialysate to the blood compartment, reduced intradialytic sodium removal, and hypernatremia, thus resulting in interdialytic symptoms, such as thirst, subsequent increase in interdialytic weight gain (IDWG), and hypertension. Conversely, a negative sodium gradient results in diffusive transport of sodium from the blood to the dialysate, hyponatremia, and intradialytic symptoms, such as muscle cramps, hypotensive episodes, hot and cold spells, and sleep disturbances (2).

Despite the improvement in the techniques of hemodialysis (HD), treatment continues to be complicated by hypotension, muscle cramps, headache, nausea, vomiting, fatigue, hypertension, and excessive thirst. Muscle cramps are a common complication occurring in 33%-86% of patients leading to the early termina-

tion of an HD session and under-dialyzed (3). Volume contraction and hyponatremia are the most likely underlying causative factors; this hypothesis is supported in part by the reduction in the frequency of cramping in association with sodium modeling or ramping (4). Moreover, a change in extracellular volume (due to increased osmolarity and hence increased volume) may have a pressor effect. The associated increase/decrease in plasma sodium itself may also cause the blood pressure (BP) to increase/decrease. In addition, small changes in plasma sodium may directly affect the hypothalamus control of BP through the local renin–angiotensin system (5). Intradialytic hypotension results in dizziness and possibly cessation of dialysis if hypotension progressively worsens. The incidence is approximately 40%. Headache is another common finding, and the incidence is approximately 20% mostly due to BP changes (6). Thirst increases the risk of IDWG which further necessitates a long and extensive duration of dialysis to re-render euvolemia, reducing patient compliance and increasing morbidity (7-9).

Currently, dialysate conductivity is used as surrogate for sodium concentration based on the fact that electrical conductivity of solutions reflects the concentration of solute. In addition, sodium is the major electrolyte present in dialysate, and ion exchange resin traps other cations, except sodium, thus providing an easy, accurate and real-time estimation of dialysate sodium concentration (1 mS/m (unit of conductivity)=10 Na mEq/L) (2, 4, 6). Hence, there is a need for study to identify the relationship between dialysate conductivity, which is reflected by dialysate Na^+ concentration, with that of the various intra/interdialytic symptoms experienced related to HD

The aim of the present study was to (1) identify and study the various intra/interdialytic symptoms experienced by patients with CKD as a complication of HD and (2) establish a relationship between dialysate conductivity with the symptoms experienced and derive an optimal dialysate conductivity rendering lesser intra/interdialytic symptoms.

MATERIALS AND METHODS

A cross-sectional study for a period of 6 months was conducted in a dialysis center at a south Indian tertiary care teaching hospital. The study was approved by the Institutional Ethics Committee (IEC 485/2013). Of the 129 patients with end-stage renal disease (ESRD) actively undergoing HD reviewed, 97 consented and were enrolled in the study. Each patient was followed up for two consecutive dialysis sessions. Inclusion criteria were as follows: (1) patients (age ≥18 years) with CKD and ESRD (estimated glomerular filtration rate <15 mL/min/1.73 m^2) who were anuric (urine output <100 mL/day) as per the NKF KDOQI guidelines and (2) patients undergoing maintenance HD >3 months and at least twice per week. Exclusion criteria were as follows: (1) patients with polycystic kidney disease, human immunodeficiency virus infection, cirrhosis, active cancer, or cancer treatment within the past 2 years, (2) pregnant women, (3) hemodynamically unstable/critically ill patients, and (4) individuals who refuse to provide informed consent.

Assessing the inter/intradialytic symptoms

The occurrence of inter/intradialytic symptoms was determined by employing the well-validated, self-completed *Patient Reported Outcomes Instrument KDQOL 35 Symptom List Questionnaire* (31 out of 35 questions were relevant to the study and were included in the questionnaire). The questions included were about inter/intradialytic symptoms which the patients were bothered off during the past 4 weeks (10-12). The questionnaire was directly addressed to the patient during or soon after his/her dialysis session. The converted Kannada *questionnaire* (local language) was dually evaluated by the Institutional Ethical Committee team and healthcare team (nephrologist and pharmacist) and was made duly available to the patient at the time of performing the study. They were instructed to mark the box with a score of 1 (not at all bothered), 2 (somewhat bothered), 3 (moderately bothered), 4 (very much bothered), and 5 (extremely bothered). Study subjects with symptom scores of 1 and 2 were allocated to group 1, and those with symptom scores of 3, 4, and 5 were assigned to group 2.

Determining the dialysate conductance and volume of fluid removed

Dialysate conductance, transmembrane pressure (TMP), and volume of fluid removed were recorded from the dialysis machine. The values displayed in the dialysis machine were recorded 5 min (to avoid interference from the filter rinsing saline solution) after the start of each dialysis session. Patient demographic details, medical and medication histories, clinical investigations, and laboratory reports were noted from the patient's record file and recorded in pre-designed Case Record Form (CRF) during the dialysis sessions.

Determining IDWG

The patient's weight, both after a session of dialysis and before the next dialysis, were recorded, and the difference between these gives the delta weight or the total weight gain between the consecutive dialysis sessions.

Data collection

Patients with ESRD undergoing maintenance HD during 2014-2015 were identified from patient records available in the dialysis center. Patients with ESRD who have fulfilled the inclusion criteria were selected, and their demographic details, such as age, sex, and weight; medical and medication histories; reports of laboratory investigations; and other details, such as pre- and post-HD weight, delta weight, pre- and post-HD BP, intradialytic weight loss (IDWL), total volume of fluid removed, TMP, and conductivity, were recorded in the CRF. Symptom List Questionnaire was administered in their local language to each patient during the first day of data collection. Questions on trouble sleeping, excessive thirst, cramps after dialysis, and fatigue were asked during their next visit to the dialysis center.

Table 1. Patient demographics of HD patients

Demographic characteristics	Mean±SD/frequency
Age	50.86±11.24 years
Sex	Males 79% (n=77)
Females 21% (n=20)	
Clinical characteristics	Mean/frequency
Hemoglobin level	8.74±1.49 g/dL
Mean pre-dialysis blood pressure	
Systolic	157±22 mm Hg
Diastolic	89±9 mm Hg
Mean post-dialysis blood pressure	
Systolic	162±28 mm Hg
Diastolic	89±12 mm Hg
Mean conductivity	14.47±0.28 mS/m
Mean fluid removed (UF volume)	4.41±1.04 L
Mean dry weight	58.48±10.61 kg
Mean intradialytic weight loss	3.995±1.06 kg
Median transmembrane pressure	100 (73, 119)
Duration of time since on dialysis	1.2±0.8 years
Relevant comorbidities	n (%)
Hypertension	97 (100)
Diabetes mellitus	47 (48.5)
Other kidney diseases, such as PCKD, Alport syndrome, IgA nephropathy, SLE, post-infectious and chronic glomerulonephritis	18 (18.5)

Table 2. Significance of relationships using t-test

SI no.	Symptom	Means		Significance
		Group 1	Group 2	
1	Cramps during dialysis	14.61±0.42	14.41±0.18	0.002
2	Muscle soreness	14.57±0.33	14.43±0.97	0.037
3	Fatigue	14.66±0.43	14.41±0.19	0.001
4	Excessive thirst	14.82±0.17	14.40±0.25	0.001
5	Dry mouth	14.67±0.18	14.38±0.27	0.001
6	Low BP	13.8±0.37	14.51±0.23	0.001
7	Hot and cold spells	14.33±0.39	14.50±0.24	0.014
8	Trouble sleeping	14.58±0.33	14.48±0.22	0.049
9	Nausea	14.54±0.39	14.42±0.22	0.043
10	Headaches	14.5±0.22	14.46±0.30	0.705
11	Dry skin	14.5±0.24	14.46±0.29	0.683
12	Itchy skin	14.50±0.23	14.46±0.29	0.643
13	Lack of strength	14.47±0.28	14.47±0.29	0.984
14	Washed out/drained	14.37±0.35	14.47±0.28	0.48
15	Joint pain	14.41±0.36	14.48±0.26	0.318
16	Easy bruise	14.39±0.28	14.47±0.29	0.416
17	Sleepiness during the day	14.40±0.25	14.47±0.29	0.552
18	Joint stiffness	14.60±0.19	14.46±0.29	0.194
19	Back pain	14.41±0.27	14.48±0.29	0.345
20	Numbness in the hand or feet	14.48±0.12	14.47±0.29	0.936
21	Bone aches	14.52±0.25	14.47±0.29	0.718
22	Lack of appetite	14.50±0.30	14.46±0.28	0.694
23	Trouble with memory	14.22±0.19	14.48±0.28	0.074
24	Shortness of breath	14.45±0.46	14.47±0.26	0.838
25	Cramps after dialysis	14.46±0.24	14.47±0.29	0.912
26	Dizziness	14.44±0.18	14.47±0.29	0.764
27	Trouble concentrating	14.8±0.1	14.47±0.26	0.252
28	Blurred vision	14.46±0.26	14.47±0.29	0.897
29	Chest pain	14.47±0.19	14.47±0.29	0.996
30	Swelling of the ankles	14.48±0.19	14.47±0.30	0.866
31	Loss of taste	14.43±0.26	14.47±0.29	0.629

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Demographic characteristics were analyzed using descriptive statistics, mean (±standard deviation), and frequency (%), as appropriate. Independent samples t-test was used to establish the relationship between each inter- and intradialytic symptom and conductivity. Each symptom severity listed in the questionnaire was divided into two groups (requisite of t-test). The relationship between conductance and each symptom studied was positive if significant ($p \leq 0.05$) and negative if significant ($p > 0.05$). The relationship was confirmed, and the type of correlation between symptom and conductivity was established using ANOVA and obtaining the means plot post ANOVA. The means of severity were plotted against the means of conductivity (corrected by ANOVA), and the trend was observed to establish the type of relationship.

RESULTS

A total of 97 patients were enrolled in the study. There were 77 (79%) male patients. Baseline characteristics of the study population are shown in Table 1. The mean age of the patients was 62.2 years, and the mean dialysis vintage was 1.2±0.8 years. The mean hemoglobin level was 8.72±0.17 g/dL in males, whereas it was 8.83±0.31 g/dL in females. During the study, the mean conductivity was determined to be 14.47±0.28 mS/m; approximately 60% (n=59) of the study population was maintained on a conductivity ranging from 14.2 to 14.6 mS/m. The mean ultrafiltration volume and mean IDWL were determined to be 4.41±1.04 L and 3.995±1.06 kg, respectively.

Relationship between conductivity and symptoms

The mean conductivity across the population was found to be 14.47±0.28 mS/m. The results of the t-test used in determining the presence or absence of a relationship are given in Table 2. Of the 31 parameters studied, the first 9 symptoms listed correlated significantly to conductivity showing some relationship.

The relationship between conductivity and symptoms was established by using ANOVA and deriving the means plots of each

Table 3. One-way analysis of variance between symptoms and conductivity

SI no.	Symptom	ANOVA	
		F value	Significance
1	Muscle cramps during HD	8.431	0.0001
2	Muscle soreness	4.83	0.0001
3	Fatigue	6.895	0.0001
4	Excessive thirst	7.529	0.0001
5	Dry mouth	2.274	0.003
6	Symptoms of low BP	10.365	0.0001
7	Hot and cold spells	1.535	0.012
8	Trouble sleeping	1.526	0.012
9	Nausea	1.57	0.011

Table 4. Conductivity corresponding to least severity of symptoms

SI no.	Symptom	ROC curve		
		Lower limit	Upper limit	Asymptotic sig.
1	Muscle cramps during HD	14.45	14.55	0.005
2	Muscle soreness	14.45	14.55	0.0001
3	Fatigue	14.45	14.55	0.002
4	Nausea	14.45	14.55	0.453
5	Dry mouth	14.35	14.45	0.0001
6	Excessive thirst	14.45	14.55	0.0001
7	Symptoms of low BP	13.85	14.45	0.005
8	Hot and cold spells	14.25	14.55	0.130
9	Trouble sleeping	14.35	14.45	0.404

studied symptom. The results of the same are given in Table 3. A mean plot post ANOVA was also obtained to verify the trends and correlation between symptoms and conductivity (Figures 1-4). Symptoms, such as muscle cramps, muscle soreness, fatigue, trouble sleeping, and nausea, were lowest around the population mean conductivity (14.4 mS/m) and highest at the extremes (13.2 and 15.1 mS/m) (Figures 1 and 2). Excessive thirst and dry mouth follow a similar trend (Figure 3). Both are lowest at the lower end of the population mean conductivity (13.2 mS/m) and increase across the mean to peak at the higher extreme of the mean (15.1 mS/m) as they are mutually inclusive. Figure 4 shows that both symptoms of hypotensive symptoms and hot and cold spells are lowest at the higher extreme of the mean conductivity (15.1 mS/m) and increase across the mean to peak at the lower end of the population mean conductivity

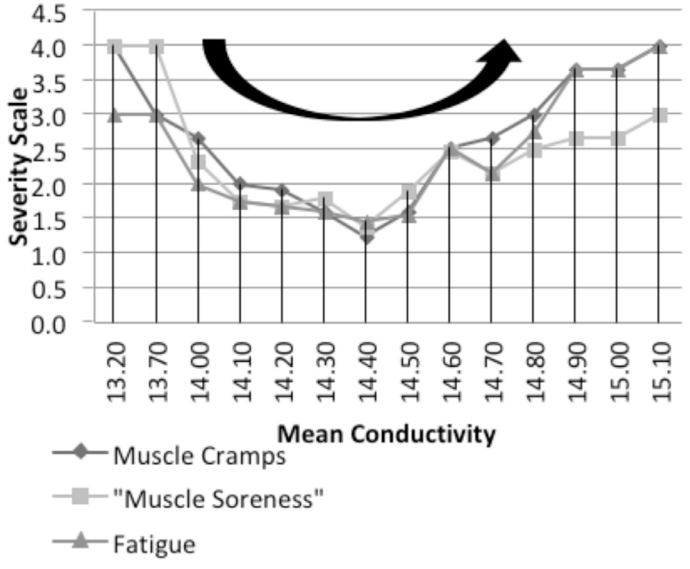


Figure 1. Trends in symptom severity of muscle cramps, muscle soreness, and fatigue.

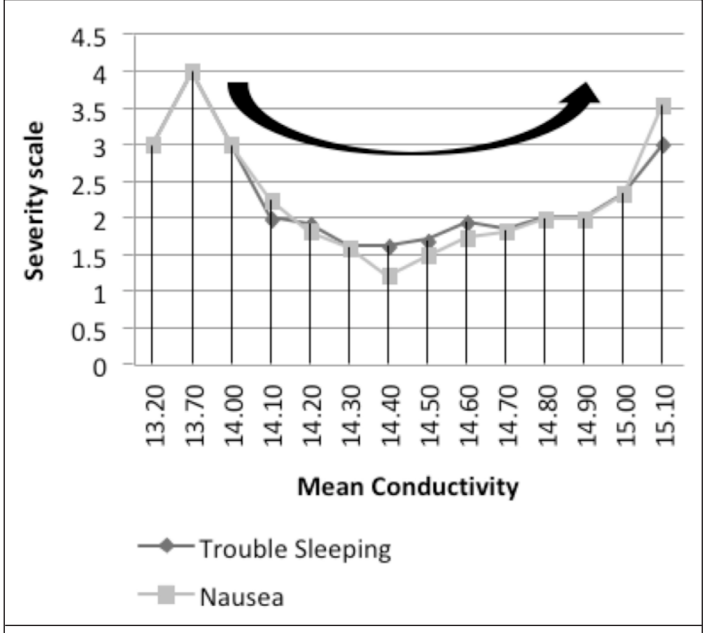


Figure 2. Trends in symptom severity of trouble sleeping and nausea.

(13.2 mS/m). Each of the nine symptoms with an established relationship to conductivity was subjected to an ROC performance (receiver operating characteristic) to derive the optimal range where patients report least discomfort (Table 4). Based on the aforementioned derived limits, the optimal conductivity for minimizing the severity of symptoms was determined to be 14.45-14.55.

DISCUSSION

Despite improvement in dialysis technology, dialysis treatment itself has a number of minor and major complications, mainly

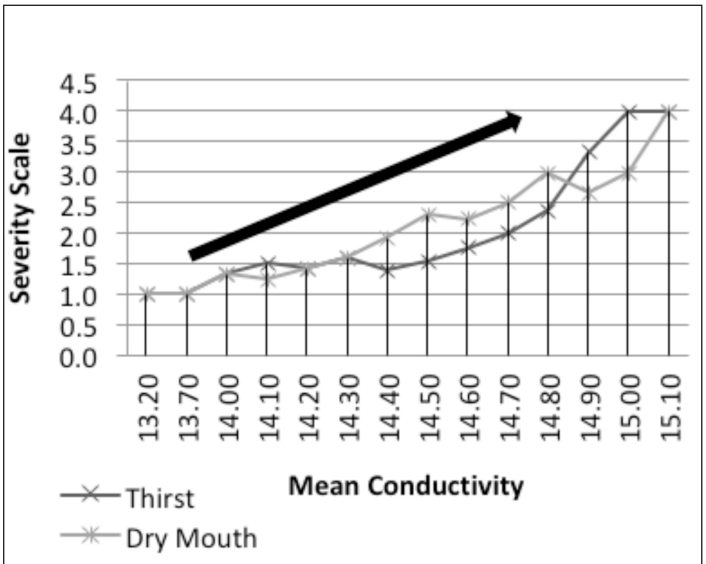


Figure 3. Trends in symptom severity of thirst and dry mouth.

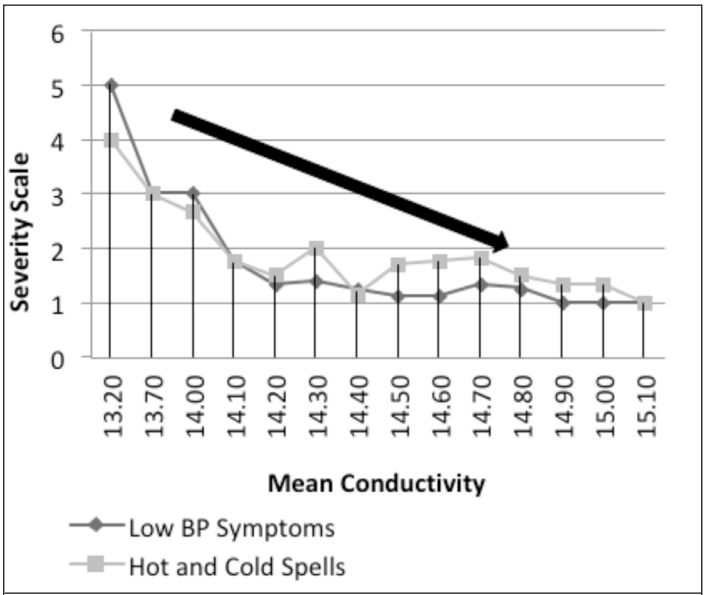


Figure 4. Trends in symptom severity of low BP symptoms and hot and cold spells.

resulting from disturbance in the body's homeostasis. Sodium pooling in the body with dialysis treatment has very important clinical implications, mainly with respect to inter- and intradialytic symptoms depending on the maintenance of constant dialysate sodium concentration (13). To the best of our knowledge, this is the first study attempting to answer the question as to whether a low or high dialysate sodium maintenance is to be advocated in chronic HD for reduced symptoms, reviewed via a Patient Reported Outcomes questionnaire. This study attempted to answer the commonly reported intra/interdialytic symptoms by means of the Patient *Reported Outcomes* using the *KDQOL 35 Symptom List Questionnaire* and tried to establish the relationship between the symptom's severities with dialysate conductivity and also to derive an optimal dialysate conductivity range to be maintained for minimal symptoms expression. The study showed that there was a change in trends of symptoms severity with the changes of the trough and peak value of the sodium conductivity maintained during HD. Sodium homeostasis during HD treatment is important to preserve the patient from clinical events related to hypo- or hypernatremia (4). Our study showed a positive correlation of the symptoms expressed as muscle cramps, muscle soreness, fatigue, trouble sleeping, and nausea with the sodium gradient bothering the patients during inter/intrahemodialytic phases when compared with the value of dialysate conductivity displayed in the dialysis machine. Our study (Figures 1, 2) showed that symptoms are lowest around the study population mean conductivity (14.4 mS/m) and highest at the extremes (13.2 and 15.1 mS/m) consistent with the current literature (14-16). In the DOPPS study, it was observed that lower serum sodium levels are associated with certain HD symptoms and higher adjusted risk of death with serum sodium <137 mEq/L and lower mortality risk in patients with dialysate sodium prescriptions >140 mEq/L. These observations found were to be clinically meaningful because serum sodium measured routinely is rarely interpreted for sodium balancing in HD patients. Thus, dialysate sodium prescriptions are essential for ideal maintenance of sodium conductivity for reduced symptoms in pre- and post-HD of the patients (17). The associations of a high sodium gradient with fluid overload are likely explained by a high dialysate sodium concentration leading to an elevated post-dialysis serum sodium level with the consequence of increased thirst and fluid intake (18). Basile et al. (19) also expressed that the range of 138-140 mmol/L dialysate sodium concentration maintenance is a comfortable target to reduce the impact of mortality or other cardiovascular outcomes in the study. Increased severity of muscle cramps and soreness at the extremes of the study populations mean conductivity range in our study was most likely due to temporary hyponatremic and hypernatremic situations caused by high and low conductivity levels during dialysis. This finding was also observed by Albalate et al. (20) Fatigue has multiple etiologies, but none the less does show a dependence on dialysate conductivity and follows a similar trend as muscle cramps albeit with less severity (21). Fatigue could also be due to mild cerebral edema developed because of rapid urea clearance creating osmotic gradient during dialysis, as cited by Caplin et al. (22) Sleeping problems and nausea severity are also both highest at the extremes and lowest around the population mean conductivity. The prevalence of sleep apnea is >50% in dialysis patients. Resulting fluid overload due to higher dialysate conductivity and overnight shift of fluids from legs to neck soft tissue is considered as the most possible causative factor as mentioned in Murray and Nadel's textbook of respiratory medicine (23). Excessive thirst and dry mouth follow a trend of both lowest at the lower end of the population mean conductivity (13.2 mS/m) and increase across the mean to peak at the higher extreme of the mean (15.1 mS/m) (Figure 3). Thirst is largely dependent on serum osmolality, which increases during hypernatremia and/or rapid and excessive volume contraction.

Figure 4 shows that both symptoms of hypotensive symptoms and hot and cold spells are lowest at the higher extreme of the mean conductivity (15.1 mS/m) and increase across the mean to peak at the lower end of the population mean conductivity (13.2 mS/m). Irrespective of the smallest IDWG, with the lowest ultrafiltration requirements and use of very less number of antihypertensive medications in the study population by Davenport et al. (24), there were more reports of lowest pre- and post-dialysis systolic blood those dialyzing with a median dialysate sodium of <140 mmol/L, but reduced the complaint of low BP with a median dialysate sodium of >140 mmol/L. The similar outcome expressed in our study showed that there were higher complaints with reduced symptoms severity with mean conductance rising near 15.1 mS/m. Hypotensive symptoms and hot and cold spells are lowest at the higher extreme of the mean and increase across the mean to peak at the lower end of the study populations mean conductivity due to hyponatremia as a result of negative sodium gradient between dialysate and plasma as previously shown by Agarwal et al. (25) and Nesrallah et al. (26). However, there was no significant reduction of BP post-dialysis neither were there any correlations to conductivity or volume of fluid lost during HD. The present research demonstrated that of a total of 31 symptoms assessed, nearly 9 correlated significantly to conductivity showing some relationship. These included cramps during HD, muscle soreness, symptoms of low BP, hot and cold spells, thirst, dry mouth, fatigue, nausea, and trouble sleeping. Cramps, muscle soreness, fatigue, nausea, and trouble sleeping showed a similar trend of being least severe around a conductivity of 14.5 mS/m. Thirst and dry mouth severity increased as conductivity increased, whereas hypotensive symptoms and hot and cold spells decreased as conductivity increased. Based on the correlations, an optimal range for conductivity was derived as 14.45-14.55 mS/m for minimizing the sodium gap that may lead to less symptom rates in conventional HD patients.

Ethics Committee Approval: The ethics committee approval was received for this study from the Institutional Ethics Committee, Kasturba Hospital, IEC 485/2013.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.K.; Design – P.K., A.D.; Supervision – P.K., R.P.A.; Data Collection and/or Processing - B.S.K., A.D., T.R.; Analysis and/or Interpretation - B.S.K., A.D., T.R.; Literature Search – B.S.K., A.D., T.R.; Writing – B.S.K., A.D., T.R., P.K., A.S., S.N. Critical Reviews – R.P.A.

Acknowledgements: The authors would like to thank all the patients who actively participated in the present study. The authors are also thankful to the hospital hemodialysis center for giving permission to conduct this study. Finally, special thanks to the Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education for providing the research facilities. The authors acknowledge RAND for RAND-36 questionnaire and Mapi Research.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Sowinski K, Churchell M. Hemodialysis and Peritoneal Dialysis. In: Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM Dipiro JT, editors. Pharmacotherapy: A Pathophysiologic Approach. New York: McGraw-Hill; 2011. pp. 817.
2. Gembala M, Kumar S. Sodium and Hemodialysis. In: Angelo Carpi, editor. Progress in Hemodialysis - From Emergent Biotechnology to Clinical Practice. InTech; 2011. 47-59. [CrossRef]
3. Cox KJ, Parshall MB, Hernandez SH, Parvez SZ, Unruh ML. Symptoms among patients receiving in-center hemodialysis: A qualitative study. Hemodial Int 2017; 21: 524-33. [CrossRef]
4. Tura A, Sbrignadello S, Mambelli E, Ravazzani P, Santoro A, Pacini G. Sodium concentration measurement during hemodialysis through ion-exchange resin and conductivity measure approach: in vitro experiments. Plos One. 2013 Jul 2; 8 (7): e69227. [CrossRef]
5. De Wardener HE, He FJ, MacGregor GA. Plasma sodium and hypertension. Kidney Int 2004; 66: 2454-66. [CrossRef]
6. Locatelli F, Di Filippo S, Manzoni C. Relevance of the conductivity kinetic model in the control of sodium pool. Kidney Int Suppl 2000 Aug; 76: S89-95. [CrossRef]
7. McGee SR. Muscle cramps. Arch Intern Med 1990; 150: 511-8. [CrossRef]
8. Ateş K, Nergizoğlu G, Keven K, Sen A, Kutlay S, Ertürk S, et al. Effect of fluid and sodium removal on mortality in peritoneal dialysis patients. Kidney Int 2001; 60: 767-76. [CrossRef]
9. Kimmel PL, Varela MP, Peterson RA, Weihs KL, Simmens SJ, Alleyne S, et al. Interdialytic weight gain and survival in hemodialysis patients: effects of duration of ESRD and diabetes mellitus. Kidney Int 2000; 57: 1141-51. [CrossRef]
10. Weisbord SD, Fried LF, Arnold RM, Rotondi AJ, Fine MJ, Levenson DJ, et al. Development of a symptom assessment instrument for chronic hemodialysis patients: The Dialysis Symptom Index. J Pain Symptom Manage 2004; 27: 226-40. [CrossRef]
11. Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the Kidney Disease Quality of Life (KDQOL) instrument. Qual Life Res 1994; 3: 329-38. [CrossRef]
12. Danquah FVN, Zimmerman L, Diamond PM, Meininger J, Bergstrom N. Frequency, severity, and distress of dialysis-related symptoms reported by patients on hemodialysis. Nephrol Nurs J 2010; 37: 627-38.
13. van der Sande FM, Kooman JP, Leunissen KM. Intradialytic hypotension--new concepts on an old problem. Nephrol Dial Transplant 2000; 15: 1746-8. [CrossRef]
14. Munoz Mendoza J, Sun S, Chertow GM, Moran J, Doss S, Schiller B. Dialysate sodium and sodium gradient in maintenance hemodialysis: a neglected sodium restriction approach? Nephrol Dial Transplant 2011; 26: 1281-87. [CrossRef]
15. Santos SF, Peixoto AJ. Sodium balance in maintenance hemodialysis. Semin Dial 2010; 23: 549-55. [CrossRef]
16. Kumar S, Khosravi M, Massart A, Potluri M, Davenport A. Are serum to dialysate sodium gradient and segmental bioimpedance volumes associated with the fall in blood pressure with hemodialysis? Int J Artif Organs 2014; 37: 21-8. [CrossRef]
17. Hecking M, Karaboyas A, Saran R, Sen A, Hörl WH, Pisoni RL, et al. Predialysis serum sodium level, dialysate sodium, and mortality in maintenance hemodialysis patients: the Dialysis Outcomes and

Practice Patterns Study (DOPPS). Am J Kidney Dis 2012; 59: 238-48. [CrossRef]
18. Trinh E, Weber C. The Dialysis Sodium Gradient: A Modifiable Risk Factor for Fluid Overload. Nephron Extra 2017; 7: 10-17. [CrossRef]
19. Basile C, Lomonte C. A neglected issue in dialysis practice: haemodialysate. Clin Kidney J. 2015; 8: 393-9. [CrossRef]
20. Albalate Ramón M, de Sequera Ortiz P, Pérez-García R, Ruiz-Álvarez MJ, Corchete Prats E, Talaván T, et al. Sodium set-point in haemodialysis: is it what we see clinically? Nefrologia 2013; 33: 808-15.
21. Hecking M, Karaboyas A, Rayner H, Saran R, Sen A, Inaba M, et al. Dialysate sodium prescription and blood pressure in hemodialysis patients. Am J Hypertens 2014; 27: 1160-9. [CrossRef]
22. Caplin B, Kumar S, Davenport A. Patients' perspective of haemodialysis-associated symptoms. Nephrol Dial Transplant 2011; 26: 2656-63. [CrossRef]
23. Roberto Rodriguez-Rosin, Gerard Huchon. Pulmonary Complications of abdominal diseases. In: V. Courtney Broaddus, Robert C Mason, Joel D Ernst, editors. Murray & Nadel's Textbook of Respiratory Medicine. 6th Edition. Canada: Elsevier; 2016:1639-51. [CrossRef]
24. Davenport A. Audit of the effect of dialysate sodium concentration on inter-dialytic weight gains and blood pressure control in chronic haemodialysis patients. Nephron Clin Pract. 2006; 104: c120-5. [CrossRef]
25. Agarwal R. How can we prevent intradialytic hypotension? Curr Opin Nephrol Hypertens 2012; 21: 593-9. [CrossRef]
26. Nesrallah GE, Suri RS, Guyatt G, Mustafa RA, Walter SD, Lindsay RM, et al. Biofeedback dialysis for hypotension and hypervolemia: a systematic review and meta-analysis. Nephrol Dial Transplant 2013; 28: 182-91. [CrossRef]

10.5152/turkjnephrol.2020.4227

Review

Turkish Journal of Nephrology

Proteolytic Activation of the Epithelial Sodium Channel in Nephrotic Syndrome by Proteasuria: Concept and Therapeutic Potential

Ferruh Artunç

Division of Nephrology and Hypertension, Department of Internal Medicine, University of Tübingen, Tübingen, Germany

Abstract

The epithelial sodium channel (ENaC) is expressed in the aldosterone-sensitive distal nephron, and it determines the final urinary sodium concentration. To ensure sodium preservation, ENaC-mediated sodium transport is redundantly regulated by several mechanisms. Among them, activation by proteases is a special feature that leads to the removal of inhibitory tracts from the α- and γ-subunits, thus maximizing the channel open probability. Proteolytic ENaC activation by aberrantly filtered proteases or proteasuria has been implicated in the pathogenesis of edema formation and sodium retention in nephrotic syndrome. This concept was strongly supported by the finding that sodium retention in nephrotic mice could be prevented by treatment with either the ENaC blocker amiloride or the serine protease inhibitor aprotinin. In clinical practice, loop diuretics such as furosemide are most commonly used for the antiedematous treatment of patients with nephrotic syndrome. ENaC blockade using amiloride or triamterene could serve as an alternative with better efficacy; however, clinical data are scarce, and ENaC blockade poses the threat of hyperkalemia. This review starts with a case vignette that highlights the therapeutic potential of pharmacological ENaC blockade in treatment-resistant nephrotic edema and continues with discussing the concept of proteolytic ENaC activation in nephrotic syndrome and its therapeutic potential.

Keywords: ENaC, nephrotic syndrome, proteasuria, amiloride

Corresponding Author: Ferruh Artunç ✉ ferruh.artunc@med.uni-tuebingen.de

Received: 03.12.2019 **Accepted:** 19.12.2019

Cite this article as: Artunç F. Proteolytic Activation of the Epithelial Sodium Channel in Nephrotic Syndrome by Proteasuria: Concept and Therapeutic Potential. Turk J Nephrol 2020; 29(1): 59-65.

Case Vignette

A 56-year-old male patient presented to our international unit at the University Hospital Tübingen, Germany, for severe treatment-refractory nephrotic syndrome due to primary membranous glomerulonephritis. The disease was diagnosed 2 years ago after manifestation of edema. Biopsy was performed, and he was treated with 4×375 mg/m^2 of rituximab, which showed no effect on proteinuria. Then, he was transiently treated with tacrolimus, which had to be discontinued due to worsening of kidney function. For the treatment of edema, he was prescribed with 1×40 mg furosemide per day. In addition, he was administered valsartan 1x160 mg. On examination, he had massive peripheral edema, and his blood pressure was elevated to 170/98 mm Hg. Bioimpedance spectroscopy revealed an overhydration of 13 L. Laboratory analyses revealed that the plasma creatinine concentration was 2.5 mg/dL, the estimated glomerular filtration rate (GFR) was 27 mL/min/1.73 m^2, the plasma Na+ concentration was 139 mM, and the plasma K + concentration was 4.5 mM. Proteinuria was very high at 15.4 g/g creatinine, of which albuminuria accounted for 10.0 g/g creatinine and was accompanied by protein and albumin depletion in the plasma (total protein level, 4.6 g/dL and plasma albumin level, 1.6 g/dL). The antibody titer against PLA2-receptor was 1:640, which indicated active primary membranous glomerulonephritis.

Assuming that the overhydration was presumably mediated by proteolytic activation of the epithelial sodium channel (ENaC), the diuretic treatment regimen was switched to a fixed-dose combination of the ENaC

blocker amiloride (5 mg) with 50 mg hydrochlorothiazide (Amiloretik® 5/50), while discontinuing furosemide. Within the subsequent 4 weeks, the patient lost 16 kg of body weight, and edema was almost completely resolved. This was accompanied by a reduction in blood pressure to values of <120/80 mm Hg. After reducing the dose of Amiloretik® by 50%, the body weight increased again; so, the dose was adjusted again to one tablet. Under Amiloretik® treatment, the kidney function was stable (plasma creatinine concentration, 1.9 mg/dL: estimated GFR, 37 mL/min/1.73 m^2) and proteinuria decreased to 9 g/g creatinine, which allowed mild recovery of total plasma protein and plasma albumin levels (increased to 4.8 and 1.8 g/dL, respectively). The plasma Na+ concentration was 144 mM, and the plasma K + concentration was 4.0 mM. In addition to diuretic treatment, the patient received another course of 2×1 g of rituximab. After 3 months of treatment, the patient returned to his home country for further follow-up. He was advised to continue Amiloretik® to maintain his current weight and prevent sodium retention due to persisting proteinuria.

Pathophysiology of Sodium Retention in Nephrotic Syndrome

Nephrotic syndrome is the most extreme manifestation of proteinuric kidney disease and is characterized by high proteinuria and expansion of the extracellular volume due to renal sodium retention. Clinically, patients develop edema in the lower extremities and typically in the eyelids after overnight rest. In addition, fluid may accumulate in the pleura, peritoneum, and rarely, the pericardium. Two opposing mechanisms, namely, the underfill and the overfill theories have been put forward to explain sodium retention (1, 2). According to the underfill theory formulated by Epstein about 100 years ago (3), hypoalbuminemia due to urinary protein losses leads to intravascular volume depletion or underfilling that provokes secondary sodium retention by the kidneys to restore the intravascular volume. This is mainly mediated by a stimulated renin–angiotensin–aldosterone-system (RAAS) that involves the stimulation of ENaC by aldosterone (1, 4). In contrast, the overfill theory, first formulated by Meltzer et al. (5) in 1979, states that sodium retention is primarily caused by the diseased kidney due to tubular defect that leads to sodium avidity without any signs of volume depletion or a stimulated RAAS (6-8).

So far, the exact mechanisms that explain sodium retention by nephrotic kidneys remain unclear. Over the last few years, proteolytic activation of the ENaC by aberrantly filtered active serine proteases or proteasuria has been put forward as a mechanism that could explain sodium retention (9). There is strong evidence that proteasuria can be considered as a key mechanism of sodium retention in patients with nephrotic syndrome.

In an attempt to reconcile the apparent discrepancy between the underfill and overfill theories, we developed a scheme that integrates both theories (Figure 1). According to this scheme, underfill and overfill represent the two ends of a continuous spectrum of ENaC-mediated sodium retention. This implies that these theories are not mutually exclusive and can coexist in the same patient (9). According to the reconciled scheme, proteasuria as a part of nephrotic proteinuria leads to sodium retention by direct endoluminal ENaC activation in agreement with the overfill theory. When proteinuria is sufficient to induce hypoalbuminemia and underfill, ENaC is additionally activated by RAAS. Therefore, underfill can superimpose on any patient with nephrotic syndrome and edema primarily due to proteasuria and overfill. Clinically, patients with nephrotic syndrome due to minimal change disease often have superimposed underfill, particularly pediatric patients.

It seems reasonable to assume that the quality and quantity of excreted serine proteases can make a difference with regard to proteolytic ENaC activation and sodium retention. Urinary composition can vary according to the underlying glomerular disease (diabetic nephropathy or immunological disease or others) and the extent of podocyte damage (podocytopathy). Although proteasuria follows overall proteinuria and albuminuria, variations in the excretion of serine proteases could explain the occurrence of high proteinuria without sodium retention.

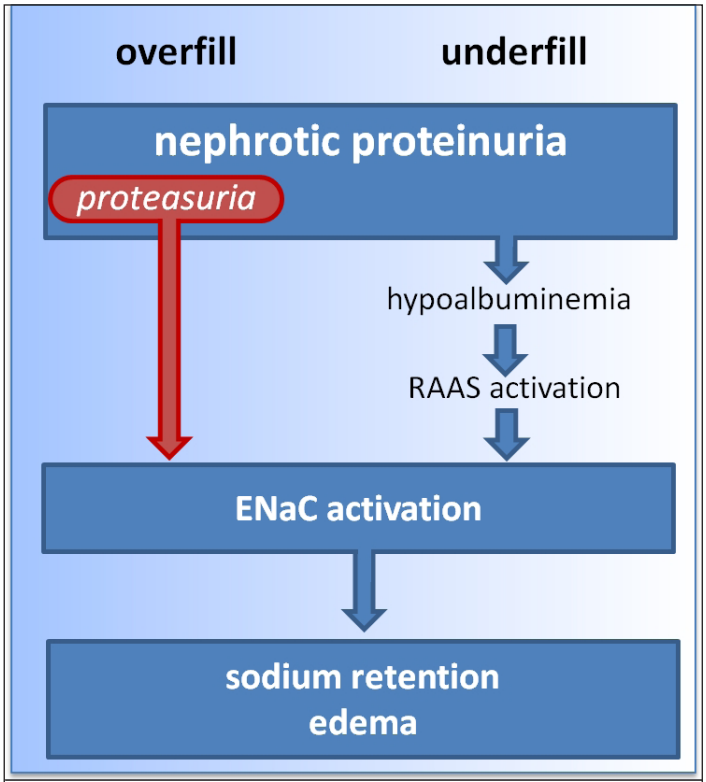


Figure 1. Sodium retention in nephrotic syndrome. Under- and overfill theories represent two ends of a continuous spectrum and some patients may be situated in between. Proteasuria as part of nephrotic proteinuria leads to sodium retention by direct endoluminal ENaC activation in agreement with the overfill theory. When proteinuria is sufficient to induce hypoalbuminemia and underfill, ENaC is additionally activated by the RAAS. There is a continuous relationship between both, and underfill can superimpose on any nephrotic patient with edema primarily due to proteasuria and overfill. Analogous to (9).

Proteolytic ENaC Activation in Nephrotic Syndrome

Animal experiments have indicated that the distal tubule expressing ENaC is the site of sodium retention in nephrotic syndrome (10, 11). This is supported by the finding that treatment with the ENaC blocker amiloride prevented volume retention in both nephrotic rats and mice (10, 12, 13). Further data demonstrated that ENaC activation in experimental nephrotic syndrome is not dependent on the action of mineralocorticoid receptor (13-15). Among the complex and abundant regulatory mechanisms for ENaC including aldosterone (16, 17), a special feature of ENaC is its complex posttranslational regulation by serine proteases. This leads to endoluminal channel activation by the cleavage of specific sites in the extracellular domains of the α and γ-subunits (18-20). Proteolytic cleavage at three sites (two in α-ENaC and one in γ-ENaC) occurs by the intracellular serine protease furin during maturation before the channel reaches the plasma membrane (21). A second cleavage event in γ-ENaC is mediated by extracellular serine proteases distal to the furin site at specific cleavage sites, thereby leading to the release of a peptide (43 amino acids) in length and maximizes the channel open probability (Figure 2). Serine proteases involved in the physiological regulation of ENaC, are the membrane-anchored prostasin (22), and soluble tissue kallikreins (23).

Under the pathophysiological conditions of nephrotic syndrome, serine proteases with large molecular weight are aberrantly filtered from the plasma and can mediate the second cleavage event in γ-ENaC, thereby leading to full channel activation. The relevance of this mechanism has been recently shown in wild-type mice with experimental nephrotic syndrome that were protected from proteolytic ENaC activation and sodium retention by treatment with the broad-spectrum serine protease inhibitor aprotinin (13). So far, the exact identity of the essential serine protease(s) is unknown, and it continues to be the focus of current research of the authors' group. Previously, Svenningsen et al. (24) proposed that in nephrotic syndrome, ENaC might be proteolytically activated by the serine protease plasmin after the aberrant filtration of plasminogen (Plg) from damaged glomeruli and its conversion to plasmin by the tubular urokinase-type plasminogen activator (uPA). Since then, the concept of proteolytic ENaC activation by aberrantly filtered plasminogen has been embraced as an attractive explanation for sodium retention in nephrotic syndrome (25-27); however, there was a lack of definitive proof from a knockout model (28). This gap of knowledge was recently closed by the authors' group using mice deficient in either uPA (uPA−/−) or plasminogen (plg−/−) that were studied for sodium retention after the induction of experimental nephrotic syndrome (12, 29). Contrary to the above-mentioned concept of uPA/Plg-activating ENaC in nephrotic syndrome, nephrotic uPA−/− and plg−/− mice were not protected from sodium retention compared with wild-type mice; however, both had almost no or absent urinary plasmin activity. The results of these studies strongly argued against the essential role of uPA/plg in mediating the proteolytic ENaC activation in experimental nephrotic syndrome. Currently, there is an ongoing research on this topic, and the exact identity of the essential serine protease(s) or cascade remains to be elucidated.

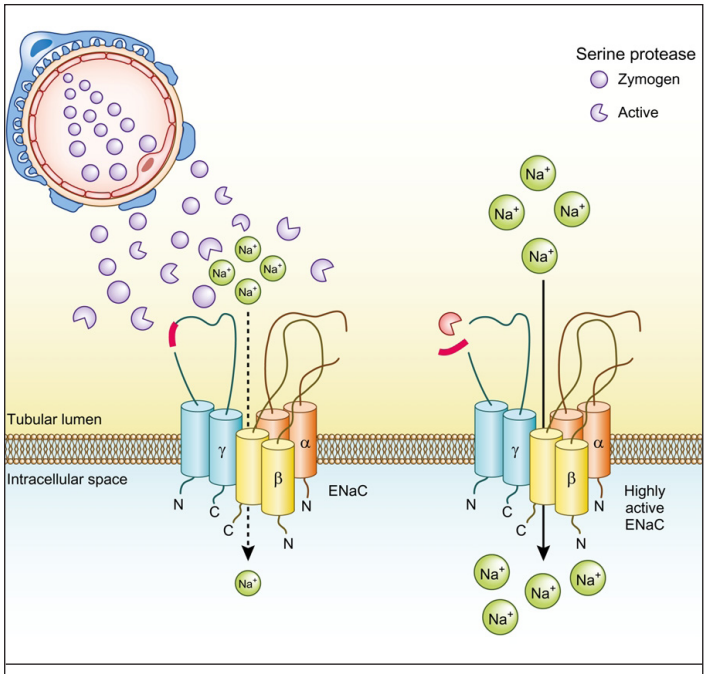


Figure 2. Model of ENaC-mediated sodium retention in nephrotic syndrome. In glomerular disease, increased permeability for proteins larger than albumin leads to the excretion of aprotinin-sensitive serine proteases that, once active, may activate ENaC by cleavage at its γ-subunit, thereby releasing an inhibitory peptide (red) and stimulating Na+ resorption.
Analogous to (9).

Proteasuria in nephrotic syndrome reflects the translocation and excretion of proteases from the plasma compartment into the urine. Since plasma proteases are very similar, if not identical, in rodents and humans, there is no reason to assume that there are fundamental differences in the role of proteasuria in promoting proteolytic ENaC activation between these species. Therefore, the results from the rodent models of nephrotic syndrome should also be valid for humans. For instance, patients with acute nephrotic syndrome exhibited an increased urinary excretion of aprotinin-sensitive proteases as those observed in the nephrotic mice (13). However, it must be underscored that there is only weak evidence from human studies to support a role for proteolytic activation of ENaC in nephrotic syndrome. The most specific evidence in favor of proteolytic ENaC activation in humans originates from a study that involved proteinuric patients who underwent nephrectomy for kidney cancer (30). Using antibodies specific for differentially cleaved γ-ENaC, the authors demonstrated staining for furin-mediated cleavage under physiologic conditions and positive staining for a second-hit processing of γ-ENaC in histological nephrectomy specimens.

Therapeutic Potential of ENaC Blockade in Nephrotic Syndrome

In nephrotic syndrome, ENaC inhibition might be a good choice as highlighted in the case vignette above. Remarkably, the

presented patient had persistent edema despite ongoing diuretic treatment with furosemide. Earlier reports have shown a reduced efficacy of furosemide in patients with nephrotic syndrome, which is indicated by a lower urinary sodium-to-urinary furosemide ratio and a shift of the dose—response curve to the right with a lower maximum value in patients with nephrotic syndrome (31, 32). Importantly, the blunted effect of furosemide was not related to the binding to tubular proteins or altered pharmacokinetics. Proteolytic ENaC activation in nephrotic syndrome predicts that the dose–response curve would be shifted to the left. In accordance with this observation, the response to a single dose of amiloride is enhanced in nephrotic mice compared with healthy mice (Figure 3) (12, 33). Moreover, daily treatment of nephrotic mice with amiloride prevents sodium retention after the onset of proteinuria (Figure 3) (12, 13). This effect was achieved by a single dose per day by inducing natriuresis for several hours due the relatively long half-live of amiloride that ranges between 6 and 9 hours (12, 34). Triamterene is another ENaC pore blocker, which is very similar to amiloride, and can be used at an equivalent dose (mg) that is tenfold higher (35). As with amiloride, it is marketed only as a fixed-dose combination with hydrochlorothiazide (50 mg/50 mg).

In addition to the regulation of activity, ENaC membrane expression can be suppressed using the mineralocorticoid antagonists (MRAs) spironolactone or eplerenone. In addition, newer drugs of this class are being tested in trials (36). MRAs prevent the genomic upregulation of ENaC in high aldosterone or low-salt intake conditions (37). However, ENaC that is present in the membrane may be activated by proteasuria; therefore, MRAs are expected to be less efficient in the prevention of ENaC-mediated sodium retention compared with direct ENaC inhibition by amiloride or triamterene. In keeping with this observation, nephrotic animals with lack of aldosterone after adrenalectomy (14) or aldosterone-resistance [deficiency of the serum-and-glucocorticoid kinase 1, (15)] developed sodium retention; however, there was one-third reduction in the maximal body weight of SGK1 knockout mice.

The animal data clearly suggest that ENaC blockade has a high therapeutic potential to treat sodium retention in patients with nephrotic syndrome. However, one must bear in mind that ENaC activity is essential for potassium secretion and kaliuresis. This was most impressively illustrated in mice with an inducible deletion of γENaC in adulthood that led to the development of fatal hyperkalemia and acidosis within a few days after the induction of ENaC deletion and could only be rescued by a potassium-free diet (38). The fear of inducing life-threatening hyperkalemia certainly limits amiloride treatment in clinical practice, particularly in patients with kidney failure (39-42). Therefore, ENaC inhibition (or MRAs) cannot be recommended in patients with a reduced GFR and/or hyperkalemia.

Clinical Evidence of ENaC Blockade

Although available since the 1960s, ENaC blockers such as amiloride or triamterene are underutilized in clinical nephrology. One reason is the fact that there is a lack of controlled clinical studies that show an improved efficacy of amiloride over other diuretic regimens such as the most commonly used loop diuret-

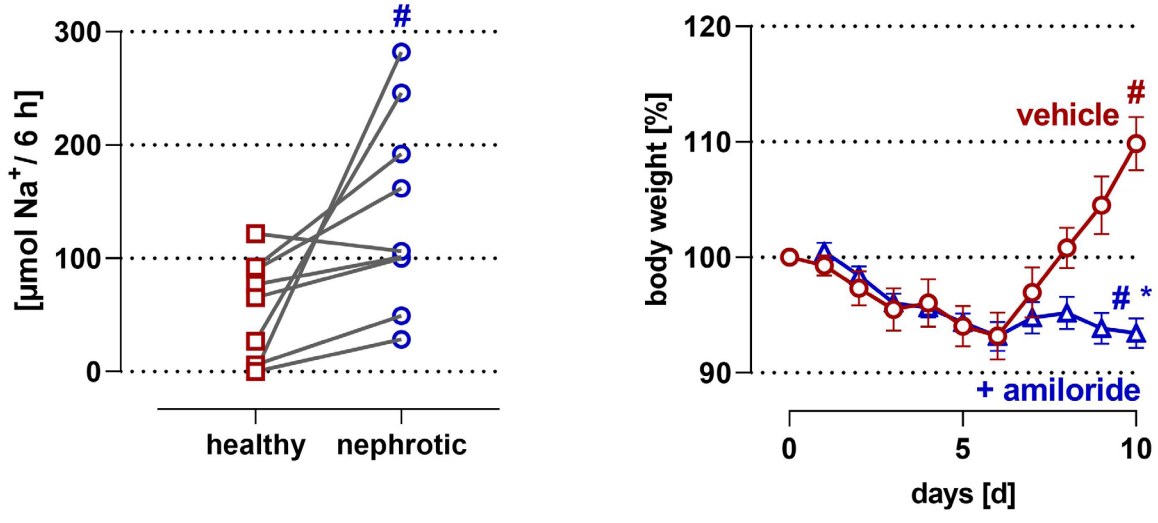


Figure 3. Stimulation of ENaC-mediated sodium transport and prevention of sodium retention by the ENaC blocker amiloride in nephrotic mice. Left: In a sequential experimental design, amiloride-sensitive natriuresis was studied in the wild-type mice before and after the induction of experimental nephrotic syndrome by injecting the ENaC blocker amiloride. Compared to the healthy state, amiloride induced significantly higher natriuresis during six hours in the nephrotic state. Values were corrected for natriuresis after vehicle injection.
Right: After the induction of experimental nephrotic syndrome on day 0 by doxorubicin, daily doses of amiloride prevented the body weight (bw) gain in nephrotic mice as compared to the vehicle-treated mice. Data are adopted from (12, 33).

ics (furosemide). Similar to the case presented above, Hinrichs et al. (43) reported a case of a patient with severe hypertension in whom the addition of amiloride to a regimen containing RAAS blockade and a loop diuretic disrupted the refractory edematous state. Two other recent case reports describe the efficacy of the ENaC blocker triamterene in resolving nephrotic edema (44, 45). In diabetic patients with nephropathy and proteinuria, a single oral amiloride dose failed to induce an enhanced natriuresis compared with that in diabetic patients without nephropathy (46). However, proteinuria was not in the nephrotic range (1.1 g vs. 0.1 g per day). In a double-blind randomized trial with a crossover design, amiloride was compared to hydrochlorothiazide in nine patients with proteinuria and type 2 diabetes (47). Both diuretics were equally effective in lowering the blood pressure. However, two patients treated with amiloride developed hyperkalemia and acute kidney injury. It must be added that the amiloride was administered at a high dose of 20 mg per day. Like with any diuretic, potent saluresis can impose acute prerenal failure, particularly in the presence of nephrotic syndrome with underfill. Currently, more controlled studies are needed to support the use of amiloride in the treatment of nephrotic edema.

Pediatric patients with nephrotic syndrome are often treated with a combination of spironolactone with furosemide (48). In adult patients with chronic kidney disease, a meta-analysis found that low-dose spironolactone treatment (mostly 25 mg) reduced proteinuria by 30%-40% and also lowered blood pressure (49). It is noteworthy that these effects were achieved on top of a renin-angiotensin blockade. The incidence of severe hyperkalemia of >6.0 mM was not significantly increased, whereas GFR was reduced in some patients (49). It is likely that reduction of ENaC-mediated sodium retention by spironolactone might have accounted for these effects.

Targeting Proteasuria as a New Therapeutic Strategy in Nephrotic Syndrome

The prevention of sodium retention in experimental nephrotic syndrome by the serine protease inhibitor aprotinin is a proof of the principle that the inhibition of proteasuria could be a new therapeutic approach in patients with nephrotic syndrome (13). In comparison to ENaC blockade with amiloride, the inhibition of excessive urinary serine protease activity could protect from ENaC overactivation without interfering with basal ENaC function. However, before the translation of inhibition of proteasuria to clinical medicine, more research must be conducted to reveal the exact identity of the pathophysiologically relevant proteases. This would enable the improved targeting of those and would avoid the use of broad-spectrum protease inhibitors such as aprotinin or camostat (50, 51). These drugs have the potential to exert negative effects on the other proteases of the plasma compartment that serve important physiological functions. Currently, aprotinin is not available since it has been withdrawn from the market in 2008 owing to side effects, wherein kidney events have been described (52).

CONCLUSION

The activation of ENaC by aberrantly filtered active plasma proteases or proteasuria seems to be a key mechanism of sodium retention in nephrotic syndrome. The pharmacological inhibition of ENaC by diuretics such as amiloride or triamterene promises to be a potent approach to treat nephrotic edema, particularly in case of a treatment-refractory state. However, there is a lack of high-quality evidence from controlled trials for supporting the ENaC inhibition in nephrotic syndrome. One must be cautious to avoid hyperkalemia and acute prerenal failure during ENaC inhibition that needs a close follow-up of the patient and titration of the dose. Future research will possibly identify the essential components of proteasuria that could be inhibited specifically without interfering with basal ENaC function.

Peer-review: EExternally peer-reviewed.

Acknowledgements: We thank Marina Corral Spence for the artwork in Figure 2.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This study was supported by a grant from the German Research Foundation (DFG, AR 1092/2-1).

REFERENCES

1. Bockenhauer D. Over- or underfill: not all nephrotic states are created equal. Pediatr Nephrol 2013; 28: 1153-6. [CrossRef]
2. Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (2). N Engl J Med 1988; 319: 1127-34. [CrossRef]
3. Epstein A. Concerning the causation of edema in chronic parenchymatous nephritis: methods for its alteration. Am J Med Sci 1917; 154: 638-47. [CrossRef]
4. Schrier RW. Decreased Effective Blood Volume in Edematous Disorders: What Does This Mean? J Am Soc Nephrol 2007; 18: 2028-31. [CrossRef]
5. Meltzer JI, Keim HJ, Laragh JH, Sealey JE, Jan KM, Chien S. Nephrotic syndrome: vasoconstriction and hypervolemic types indicated by renin-sodium profiling. Ann Intern Med 1979; 91: 688-96. [CrossRef]
6. Hammond TG, Whitworth JA, Saines D, Thatcher R, Andrews J, Kincaid-Smith P. Renin-angiotensin-aldosterone system in nephrotic syndrome. Am J Kidney Dis 1984; 4: 18-23. [CrossRef]
7. Dorhout EJ, Roos JC, Boer P, Yoe OH, Simatupang TA. Observations on edema formation in the nephrotic syndrome in adults with minimal lesions. Am J Med 1979; 67: 378-84. [CrossRef]
8. Brown EA, Markandu ND, Roulston JE, Jones BE, Squires M, MacGregor GA. Is the renin-angiotensin-aldosterone system involved in the sodium retention in the nephrotic syndrome? Nephron 1982; 32: 102-7. [CrossRef]
9. Artunc F, Worn M, Schork A, Bohnert BN. Proteasuria-The impact of active urinary proteases on sodium retention in nephrotic syndrome. Acta Physiol (Oxf) 2019; 225: e13249. [CrossRef]
10. Deschenes G, Wittner M, Stefano A, Jounier S, Doucet A. Collecting duct is a site of sodium retention in PAN nephrosis: a rationale for amiloride therapy. J Am Soc Nephrol 2001; 12: 598-601.

11. Ichikawa I, Rennke HG, Hoyer JR, Badr KF, Schor N, Troy JL, et al. Role for intrarenal mechanisms in the impaired salt excretion of experimental nephrotic syndrome. J Clin Invest 1983; 71: 91-103. [CrossRef]
12. Bohnert BN, Daiminger S, Worn M, Sure F, Staudner T, Ilyaskin AV, et al. Urokinase-type plasminogen activator (uPA) is not essential for epithelial sodium channel (ENaC)-mediated sodium retention in experimental nephrotic syndrome. Acta Physiol (Oxf) 2019; e13286. [CrossRef]
13. Bohnert BN, Menacher M, Janessa A, Worn M, Schork A, Daiminger S, et al. Aprotinin prevents proteolytic epithelial sodium channel (ENaC) activation and volume retention in nephrotic syndrome. Kidney Int 2018; 93: 159-72. [CrossRef]
14. de Seigneux S, Kim SW, Hemmingsen SC, Frokiaer J, Nielsen S. Increased expression but not targeting of ENaC in adrenalectomized rats with PAN-induced nephrotic syndrome. Am J Physiol Renal Physiol 2006; 291: F208-17. [CrossRef]
15. Artunc F, Nasir O, Amann K, Boini KM, Haring HU, Risler T, et al. Serum- and glucocorticoid-inducible kinase 1 in doxorubicin-induced nephrotic syndrome. Am J Physiol Renal Physiol 2008; 295: F1624-34. [CrossRef]
16. Palmer LG, Frindt G. Regulation of epithelial Na channels by aldosterone. Kitasato Med J 2016; 46: 1-7.
17. Kleyman TR, Kashlan OB, Hughey RP. Epithelial Na(+) Channel Regulation by Extracellular and Intracellular Factors. Annu Rev Physiol 2018; 80: 263-81. [CrossRef]
18. Rossier BC, Stutts MJ. Activation of the epithelial sodium channel (ENaC) by serine proteases. Annu Rev Physiol 2009; 71: 361-79. [CrossRef]
19. Kleyman TR, Carattino MD, Hughey RP. ENaC at the cutting edge: regulation of epithelial sodium channels by proteases. J Biol Chem 2009; 284: 20447-51. [CrossRef]
20. Warnock DG, Kusche-Vihrog K, Tarjus A, Sheng S, Oberleithner H, Kleyman TR, et al. Blood pressure and amiloride-sensitive sodium channels in vascular and renal cells. Nat Rev Nephrol 2014; 10: 146-57. [CrossRef]
21. Hughey RP, Bruns JB, Kinlough CL, Harkleroad KL, Tong Q, Carattino MD, et al. Epithelial sodium channels are activated by furin-dependent proteolysis. J Biol Chem 2004; 279: 18111-4. [CrossRef]
22. Carattino MD, Mueller GM, Palmer LG, Frindt G, Rued AC, Hughey RP, et al. Prostasin interacts with the epithelial Na+ channel and facilitates cleavage of the γ-subunit by a second protease. Am J Physiol Renal Physiol 2014; 307: F1080-7. [CrossRef]
23. Patel AB, Chao J, Palmer LG. Tissue kallikrein activation of the epithelial Na channel. Am J Physiol Renal Physiol 2012; 303: F540-50. [CrossRef]
24. Svenningsen P, Bistrup C, Friis UG, Bertog M, Haerteis S, Krueger B, et al. Plasmin in nephrotic urine activates the epithelial sodium channel. J Am Soc Nephrol 2009; 20: 299-310. [CrossRef]
25. Passero CJ, Hughey RP, Kleyman TR. New role for plasmin in sodium homeostasis. Curr Opin Nephrol Hypertens 2010; 19: 13-9. [CrossRef]
26. Siddall EC, Radhakrishnan J. The pathophysiology of edema formation in the nephrotic syndrome. Kidney Int 2012; 82: 635-42. [CrossRef]
27. Schork A, Woern M, Kalbacher H, Voelter W, Nacken R, Bertog M, et al. Association of Plasminuria with Overhydration in Patients with CKD. Clin J Am Soc Nephrol 2016; 11: 761-9. [CrossRef]
28. Kleyman TR, Hughey RP. Plasmin and Sodium Retention in Nephrotic Syndrome. J Am Soc Nephrol 2009; 20: 233-4. [CrossRef]
29. Xiao M, Bohnert BN, Wörn M, Mollet GR, Plow EF, Huber TB, et al. Plasminogen defiency does not protect from sodium retention in nephrotic mice with inducible podocin deficiency. 11th Annual Meeting of the German Society of Nephrology, Düsseldorf, 2019; https://nephro2019.psdisc-documedias.com/abstracts.html#/abstract/DA7AD0C0-3ED1-4500-1146-0A0000001023:
30. Zachar RM, Skjodt K, Marcussen N, Walter S, Toft A, Nielsen MR, et al. The epithelial sodium channel gamma-subunit is processed proteolytically in human kidney. J Am Soc Nephrol 2015; 26: 95-106. [CrossRef]
31. Keller E, Hoppe-Seyler G, Schollmeyer P. Disposition and diuretic effect of furosemide in the nephrotic syndrome. Clin Pharmacol Ther 1982; 32: 442-9. [CrossRef]
32. Smith DE, Hyneck ML, Berardi RR, Port FK. Urinary protein binding, kinetics, and dynamics of furosemide in nephrotic patients. J Pharm Sci 1985; 74: 603-7. [CrossRef]
33. Haerteis S, Schork A, Dörffel T, Bohnert BN, Nacken R, Wörn M, et al. Plasma kallikrein activates the epithelial sodium channel (ENaC) in vitro but is not essential for volume retention in nephrotic mice. Acta Physiol (Oxf) 2018; 224(1): e13060. [CrossRef]
34. Vidt DG. Mechanism of action, pharmacokinetics, adverse effects, and therapeutic uses of amiloride hydrochloride, a new potassium-sparing diuretic. Pharmacotherapy 1981; 1: 179-87. [CrossRef]
35. Jackson PR, Ramsay LE, Wakefield V. Relative potency of spironolactone, triamterene and potassium chloride in thiazide-induced hypokalaemia. Br J Clin Pharm 1982; 14: 257-63. [CrossRef]
36. Capelli I, Gasperoni L, Ruggeri M, Donati G, Baraldi O, Sorrenti G, et al. New mineralocorticoid receptor antagonists: update on their use in chronic kidney disease and heart failure. J Nephrol 2019; Apr 15. doi: 10.1007/s40620-019-00600-7. [Epub ahead of print] [CrossRef]
37. Nielsen J, Kwon TH, Masilamani S, Beutler K, Hager H, Nielsen S, et al. Sodium transporter abundance profiling in kidney: effect of spironolactone. Am J Physiol Renal Physiol 2002; 283: F923-33. [CrossRef]
38. Boscardin E, Perrier R, Sergi C, Maillard MP, Loffing J, Loffing-Cueni D, et al. Plasma Potassium Determines NCC Abundance in Adult Kidney-Specific gammaENaC Knockout. J Am Soc Nephrol 2018; 29: 97-90. [CrossRef]
39. Levy Yeyati N, Fellet A, Arranz C, Balaszczuk AM, Adrogue HJ. Amiloride-sensitive and amiloride-insensitive kaliuresis in advanced chronic kidney disease. J Nephrol 2008; 21: 93-8.
40. Chiu TF, Bullard MJ, Chen JC, Liaw SJ, Ng CJ. Rapid life-threatening hyperkalemia after addition of amiloride HCl/hydrochlorothiazide to angiotensin-converting enzyme inhibitor therapy. Ann Emerg Med 1997; 30: 612-5. [CrossRef]
41. Whiting GF, McLaran CJ, Bochner F. Severe hyperkalaemia with Moduretic. Med J Aust 1979; 1: 409. [CrossRef]
42. Jaffey L, Martin A. Malignant hyperkalaemia after amiloride/hydrochlorothiazide treatment. Lancet 1981; 1: 1272. [CrossRef]
43. Hinrichs GR, Mortensen LA, Jensen BL, Bistrup C. Amiloride resolves resistant edema and hypertension in a patient with nephrotic syndrome; a case report. Physiol Rep 2018; 6: e13743. [CrossRef]
44. Hoorn EJ, Ellison DH. Diuretic Resistance. Am J Kidney Dis 2017; 69: 136-42. [CrossRef]
45. Yamaguchi E, Yoshikawa K, Nakaya I, Kato K, Miyasato Y, Nakagawa T, et al. Liddle's-like syndrome associated with nephrotic syndrome secondary to membranous nephropathy: the first case report. BMC Nephrol 2018; 19: 122. [CrossRef]

46. Andersen H, Hansen PB, Bistrup C, Nielsen F, Henriksen JE, Jensen BL. Significant natriuretic and antihypertensive action of the epithelial sodium channel blocker amiloride in diabetic patients with and without nephropathy. J Hypertens 2016; 34: 1621-9. [CrossRef]
47. Unruh ML, Pankratz VS, Demko JE, Ray EC, Hughey RP, Kleyman TR. Trial of Amiloride in Type 2 Diabetes with Proteinuria. Kidney Int Rep 2017; 2: 893-904. [CrossRef]
48. Kapur G, Valentini RP, Imam AA, Mattoo TK. Treatment of Severe Edema in Children with Nephrotic Syndrome with Diuretics Alone - A Prospective Study. Clin J Am Soc Nephrol 2009; 4: 907-13. [CrossRef]
49. Bomback AS, Kshirsagar AV, Amamoo MA, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. Am J Kidney Dis 2008; 51: 199-211. [CrossRef]
50. Makino H, Onbe T, Kumagai I, Murakami K, Ota Z. A proteinase inhibitor reduces proteinuria in nephrotic syndrome. Am J Nephrol 1991; 11: 164-5. [CrossRef]
51. Onbe T, Makino H, Kumagai I, Haramoto T, Murakami K, Ota Z. Effect of proteinase inhibitor camostat mesilate on nephrotic syndrome with diabetic nephropathy. J Diabet Complications 1991; 5: 167-8. [CrossRef]
52. Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006; 354: 353-65. [CrossRef]

10.5152/turkjnephrol.2020.3554

Review

Turkish Journal of Nephrology

Urinary Findings and Biomarkers in Autosomal Dominant Polycystic Kidney Disease

İsmail Koçyiğit[1], Eray Eroğlu[1], Tevfik Ecder[2]

[1]Division of Nephrology, Erciyes University School of Medicine, Kayseri, Turkey
[2]Division of Nephrology, İstanbul Bilim University School of Medicine, İstanbul, Turkey

Abstract

Autosomal dominant polycystic kidney disease (ADPKD), characterized by the development of multiple cysts in the kidneys and other organs, is the most common hereditary renal disorder and the fourth leading cause of end-stage renal disease. In adults with a positive family history, the diagnosis of ADPKD is made based on the radiologic evidence of bilateral, fluid-filled renal cysts. Furthermore, initial symptoms including pain, increased thirst, polyuria, nocturia, and increased urinary frequency may lead to the diagnosis of ADPKD. An easily accessible, applicable, and cost-effective biomarker is needed to predict the clinical course of ADPKD due to its progressive pattern. Urine is an easily obtainable and widely used test specimen for diagnosis and follow-up in several renal diseases. Thus, the aim of the present study was to review and assess new urinary biomarkers and urinary findings in ADPKD.

Keywords: Polycystic kidney disease, biomarkers, urine

Corresponding Author: İsmail Koçyiğit ✉ iikocyigit@gmail.com

Received: 04.09.2018 **Accepted:** 10.10.2018

Cite this article as: Koçyiğit İ, Eroğlu E, Ecder T. Urinary Findings and Biomarkers in Autosomal Dominant Polycystic Kidney Disease. Turk J Nephrol 2020; 29(1): 66-76

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is one of the common genetic causes of end-stage renal disease (ESRD) (1). It is also a systemic disorder that is characterized by renal and extrarenal involvement (2). ADPKD is caused by mutations in either of the two genes encoding the plasma membrane-spanning polycystin 1 (PKD1) and polycystin 2 (PKD2). Polycystin 1 is a membrane receptor and plays a role in maintaining intracellular responses active in several pathways. Polycystin 2 acts as a calcium-permeable channel. Moreover, polycystins regulate tubular and vascular development in the kidneys and other organs (liver, brain, heart, and pancreas) (3-5).

The two types of ADPKD have similar pathological and physiological features. However, type II ADPKD has a later onset of symptoms and a slower rate of progression to ESRD (6). Although the proposed gene PKD3 has not yet been determined, some patients with typical features of ADPKD have no mutations in PKD1 or PKD2, suggesting that there is a rare third form of the disease (7, 8).

The diagnosis of ADPKD is made based on the radiologic evidence of bilateral, fluid-filled renal cysts in adults with a positive family history. Ultrasonography findings have revealed cysts measuring ≥1 cm in diameter and that ADPKD is highly sensitive to be diagnosed in adults (9). Moreover, the presence of ≥3 (unilateral or bilateral) renal cysts is enough for establishing a diagnosis in individuals aged 15-39 years, ≥2 cysts in each kidney for subjects aged 40-59 years, and ≥4 cysts in each kidney for subjects aged ≥60 years belonging to families with unknown genotype (10).

Several clinical complaints might be related to ADPKD and lead to the diagnosis of the disease. In particular, increased thirst, polyuria, nocturia, urinary frequency, and urinary concentrating defects are the most common initial symptoms and functional abnormalities of

ADPKD (11). It is plausible to find a cheaper, applicable, and easily accessible biomarker to predict the clinical course of ADPKD due to its progressive pattern. Urine is one of the important materials for finding a noninvasive prognostic and therapeutic monitoring test for renal diseases. Here the aim of the present study was to review and discuss the urinary abnormalities in ADPKD as well as to assess new urinary biomarkers and urinary findings in ADPKD.

Urine Osmolality

The antidiuretic hormone arginine vasopressin (AVP) plays an important role in osmoregulation. AVP is secreted by the pituitary gland and activates the V2 receptors of renal collecting duct cells when the plasma osmolality increases (12); in turn, this activation induces the translocation of aquaporin 2 to the luminal surface of these cells, making them permeable to water (13). AVP is needed in the physiological stimulation of water reabsorption, and it also plays an important role in the pathophysiology of ADPKD (14). A large-scale trial showed that blocking the AVP V2 receptor with a V2 receptor antagonist leads to a reduced rate of cyst growth and renal function decline in patients with ADPKD (15, 16). It is widely established that a urine osmolality of <285 mosM/kg H_2O, or lower than plasma osmolality, reflects adequate suppression of AVP (17, 18).

Similar to other causes of chronic kidney disease (CKD), a defect in the kidney's capacity to conserve water has been described in patients with ADPKD (11, 19). Vasopressin-resistant renal concentrating defect has been shown in ADPKD prior to the deterioration of kidney function (20). Urine concentrating defect is one of the common clinical findings in patients with ADPKD (21). Decreased urinary osmolality, which may be caused by the disruption of the renal architecture by the cysts, is thought to interfere with the countercurrent exchange and multiple mechanisms in the kidney regardless of age, glomerular filtration rate, and solute excretion in patients with ADPKD (22, 23).

Gabow et al. (11) suggested that a defect in the extracellular matrix in ADPKD affects renal epithelial transport or vasopressin responsiveness, thus producing a concentrating defect. Moreover, structural abnormalities in the polycystic kidneys might affect the physics of the concentrating mechanism and produce a concentrating defect. The urinary concentration defect that develops as the disease progresses is thought to be due to impaired renal medullar osmolar gradient by cyst formation in patients with ADPKD. This lack of renal concentrating capacity is expected to lead to a lower urine osmolality, a higher plasma osmolality, and a compensatory high level of AVP. Clinically, it has been observed that in the later stages of the disease, urine osmolality can indeed be low, whereas AVP is high (11-14). Interestingly, Ho et al. (24) reported that patients with ADPKD show both a central and peripheral defect in osmoregulation early in the course of the disease. They identified a central defect, which parallels the expression of polycystic kidney disease genes in hypothalamic neurons that synthesize and release AVP as a novel extrarenal manifestation of ADPKD (24). The results of this study provided insights into the role of polycystins in the brain and are relevant when considering treatments targeting AVP in ADPKD.

Hematuria

Hematuria is the most common presenting symptom of ADPKD, usually occurring before the loss of kidney function and is frequently associated with cyst wall calcifications on renal imaging (1, 25). It develops in 35%-50% of patients with ADPKD throughout their life and can be acute. It is commonly associated with infection or severe physical activity and acute cyst expansion. It generally presents with local pain, fever, and dysuria without infection (1, 2, 25). When these symptoms occur, it is important to eliminate pyelonephritis, nephrolithiasis, and lower urinary tract infections (UTIs), particularly in women.

Rupture of a cyst into the collecting system is the most common cause of macroscopic and microscopic hematuria in ADPKD. Hematuria due to cyst rupture tends to improve within approximately 1 week with conservative therapy. Rarely, hematuria can persist for several weeks and can be more severe requiring interventional therapy modalities including transcatheter renal arterial embolization, transfusion, or nephrectomy (26).

Patients with ADPKD and gross hematuria have increased total kidney volume (TKV). Hematuria is also closely associated with rapid disease progression and hypertension. Gross hematuria may have an unfavorable effect on long-term renal function, possibly reflecting accelerated cyst expansion (25, 27). Moreover, frequent episodes of gross hematuria may accelerate renal function decline, by causing acute kidney injury (AKI) and/or chronic iron toxicity. Cyst ruptures with gross hematuria may lead to the release and deposition of free iron and heme, promoting the generation of reactive oxygen species and proinflammatory cytokines (25, 28).

Although most patients report trauma or strict exercise as possible triggers, a precise association has not been identified between such triggering mechanisms and the condition. Although polycystic kidneys are quite resistant to traumatic damage, mild trauma may lead to intrarenal or retroperitoneal bleeding, which may present with intense pain and require administration of aggressive medical therapy, especially narcotics (29-31).

When gross hematuria first occurs after the age of 50 years, malignancy should be screened. However, gross hematuria can be associated with renal or extrarenal hemorrhage or bleeding into the urinary collecting system, which may be detected via computerized tomography (CT) or magnetic resonance imaging. Acute clots in the collecting system may result in severe renal pain. In such a situation, hydration to increase the urinary flow rate to 2-3 L/day, rest, and analgesics are recommended. Patients should be informed regarding self-treatment options for repeated episodes. Hematuria generally decreases to micro-

scopic levels in a few days. The use of antiplatelet or anticoagulants should be avoided in the absence of a strong indication in patients with a history of gross hematuria (2, 32, 33). Gabow et al. (25) found that male athletes with ADPKD who participated in contact sports have more hematuria episodes and develop kidney failure faster than those who did not participate in such sports. Thus, all patients with ADPKD should be warned to avoid sports that may cause abdominal trauma.

Cysts are associated with excessive angiogenesis indicated by fragile vessels stretched across their distended walls. These vessels present an array of malformations, including aneurysms and spiral shapes. Hemorrhage may occur spontaneously in the cyst due to these vessels, and the cysts can enlarge rapidly resulting in severe pain (34, 35). Gabow et al. (25) investigated the clinical profiles of patients with ADPKD and showed that patients with ADPKD and visible hematuria have increased TKV and worse renal function. These results suggest that visible hematuria has an unfavorable effect on long-term renal function, which might reflect accelerated cyst expansion. In addition, it has been hypothesized that recurrent gross hematuria results in tubular obstruction and triggers the fibrotic process by disrupting the renal parenchyma. It appears that the relationship with hematuria and disease progression affects each other vice versa (21, 25). According to the current literature, there is no method (except urine microscopic evaluation of the characteristics of red blood cells) to differentiate the origin of the blood. Direct microscopic evaluation may help to distinguish the origin of red blood cells, that is, whether they are from the superior or inferior urinary system.

Additionally, the coincidence of hematuria, overt proteinuria, and rapid renal dysfunction in patients with ADPKD may be related to proliferative glomerulonephritis and rapidly progressive glomerulonephritis, including an antineutrophil cytoplasmic antibody-associated crescentic glomerulonephritis (36, 37).

Proteinuria

Proteinuria usually occurs at mild to moderate levels in approximately 25% of patients with ADPKD. The presence and severity of proteinuria is a negative prognostic risk factor and is associated with greater prevalence of increased TKV, hypertension, and renal deterioration (38, 39). Urinary albumin excretion (UAE) was positively correlated with TKV and negatively correlated with estimated glomerular filtration rate (eGFR) in the HALT Progression of Polycystic Kidney Disease study at baseline (40). Thus, it is proposed that increased levels of UAE are a valuable predictive marker of ADPKD severity before renal function decline. Higher levels of proteinuria were also associated with a faster decline in GFR among patients with ADPKD in the Modification of Diet in Renal Disease study (41).

Chapman et al. (38) reported that approximately 20% of 270 patients with ADPKD have overt proteinuria (>300 mg/day), which is associated with worse renal function, hypertension, and increased TKV. Patients with overt proteinuria reached a serum creatinine level of 1.5 mg/dL at a significantly younger age compared with those with mild proteinuria. Additionally, microalbuminuria was observed in 20 out of 49 patients with ADPKD, hypertension, and left ventricular hypertrophy. Blood pressure and TKV were significantly higher in patients with microalbuminuria. In addition, the degree of albuminuria was correlated with TKV and kidney volume growth rate in a study of 100 young patients with ADPKD and preserved renal function (42). Meijer et al. (43) showed a high prevalence of microalbuminuria in young adult patients with ADPKD.

If proteinuria exceeds 1 g/day, the possibility of another independent glomerular disease should be considered. The association of nephrotic syndrome (NS) with ADPKD is very rare (44, 45) and, if possible, needs to be investigated further to exclude coexisting glomerular disease. The determination of the exact reason of proteinuria in this subgroup of patients often requires kidney biopsy. Indeed, there are some cases of ADPKD associated with NS; focal segmental glomerulosclerosis is the most common presented type of NS in this population (45). In addition, proteinuria may not be specific to ADPKD; it may be the result of CKD.

Pyuria

Although it is quite common in patients with ADPKD, the etiology, incidence, and clinical implications of pyuria are not well identified. Asymptomatic pyuria often persists or relapses without treatment in ADPKD (46). The microorganisms in the urine cultures of these patients with asymptomatic pyuria are similar in UTIs (47). This suggests that asymptomatic pyuria is a type of subclinical bacterial infection in patients with ADPKD. Chronic asymptomatic pyuria may also increase the risk of developing overt UTI and may contribute to the deterioration of kidney function in ADPKD. It has been well established that chronic UTI is an important risk factor for renal function decline (47). In addition, women are more susceptible to UTI than men as with the general population, and they also have a higher incidence of parenchymal and cyst infections in the ADPKD population (48). Radiologic and urologic evaluation is needed in male patients with ADPKD. Acute pyelonephritis and symptomatic cyst infection indicate hospitalization, with positive blood or urine cultures. Coliforms are the most common detected pathogens. Antibiotics are administered intravenously until fever and renal pain cease for these infections in both sexes (2, 49).

The diagnosis of cystic infections may be difficult in the presence of hemorrhage. Positron emission tomography-CT allows us to distinguish hemorrhages from cystic infections (50, 51). Evidence from CT scans suggests that intracystic hemorrhage, shown as hyperdense subcapsular cysts, is present in 90% of patients with ADPKD (1, 52).

UTI is a risk factor for renal progression in patients with ADPKD (53). A recent study showed that asymptomatic pyuria and overt UTI were associated with rapid decline in renal function, but it is unclear whether this result was independent of other factors, such as baseline GFR and TKV (53).

Urinary Calculi

The prevalence of urinary calculi is greater in patients with ADPKD than in the general population (54). Kidney stone formation has been reported in 20%-36% of patients with ADPKD (54, 55). Uric acid is the major constituent of stones in patients with ADPKD, with an incidence of approximately 60% among patients with ADPKD and urinary calculi (54, 56). Calcium oxalate-containing stones occur less frequently, with an incidence that is lower than that in the general population (56). Risk factors for stone formation in ADPKD include metabolic abnormalities and anatomic obstruction with resultant urinary stasis (57, 58). There is also a relationship between nephrolithiasis and an increased number and size of renal cysts in patients with ADPKD, suggesting that compression associated with distortion of the medullary architecture results in urinary stasis (57). Urinary citrate excretion, which is decreased in patients with ADPKD before the loss of kidney function, may be an important contributing factor (57-59). A crucial risk factor for uric acid stone formation in patients with ADPKD is a low urinary pH. Urinary pH has been shown to be <5.5 in >50% of patients with ADPKD and is independently associated with urinary calculi (59). The ionization constant (pKa) for uric acid is 5.5 (60); therefore, when the urine pH is <5.5, urine becomes supersaturated with undissociated uric acid that precipitates, forming uric acid stones (61). The low urine pH in ADPKD may be attributed to a defective ammonium excretion (20, 62). Other important risk factors for increased urinary calculi in patients with ADPKD include low urine flow states or low fluid intake, hypercalciuria, and hyperuricosuria similar to non-ADPKD population (54, 63).

Nishiura et al. (59) reported that hyperuricosuria is less prevalent in ADPKD, with an incidence similar to normal subjects. Moreover, they found that hyperoxaluria is significantly higher in patients with ADPKD, particularly those with urinary calculi. The higher percentage of hyperoxaluria and hypocitraturia in ADPKD is reported by other studies (54, 57). These findings remain to be explained. In addition, most patients with ADPKD and urine calculi had a urinary pH of <5.5, either spontaneously (62% of them) or after NH4Cl load (30% of them), indicating that a low rather than a high urine pH has been commonly observed in these patients, which is consistent with previous reports (20, 54, 56, 64, 65). Indeed, patients with ADPKD and urine calculi exhibited lower ammonium excretion after NH4Cl load than healthy subjects, suggesting that there is a possible defect in ammonium excretion (61, 62), similar to the one observed in uric acid stone formers (61). It has been suggested that ammonium excretion defect predisposes the formation of uric acid stones (56). However, hyperuricosuria was only found in three out of 28 patients with ADPKD and renal calculi (59).

In addition to hypocitraturia and aciduria, some urinary metabolic abnormalities including hypomagnesuria and low urine volume also predispose stone formation in ADPKD (54, 57). Eventually, the targets should be placed on not only treating nephrolithiasis but also predisposing metabolic and structural factors.

Urine Biomarkers

Although there is ongoing research, specific therapies for ADPKD are still lacking, and one of the challenges is the absence of appropriate biomarkers to predict and monitor disease progression before significant impairment occurs (21). Currently, TKV is a widely accepted marker for disease progression; however, it is expensive and unavailable worldwide (66). Therefore, it is plausible to find cheaper, applicable, and easily accessible biomarkers to predict the clinical course of ADPKD due to its progressive pattern.

Urine, as a well-accessible compartment, appears to be an ideal material for finding a noninvasive prognostic and therapy monitoring test for renal diseases. Cystogenesis in ADPKD is a unique process characterized by abnormalities in fluid secretion, tubular cell proliferation, extracellular matrix formation, apoptosis, and cell polarity (67, 68). The process results in an impaired filtration barrier, diminished tubular reabsorption, upregulation of tubular proteins, and release of markers by recruited cells, which can be detected in the urine of patients with ADPKD (69). Therefore, the application of a noninvasive urine biomarker is needed to understand the pathophysiological processes and potential therapeutic options for these patients (70). Moreover, the recent focus of interest has shifted toward urine biomarkers in patients with ADPKD (Table 1).

Urinary angiotensinogen (UAGT), a marker of intrarenal renin angiotensin system (RAS), has been shown to be associated with hypertension in patients with ADPKD (71). This finding suggests that UAGT is a potential novel biomarker of intrarenal RAS status in patients with hypertension with ADPKD. Moreover, UAGT levels may be an applicable and useful index to predict future cardiovascular complications and progressive kidney disease in patients with ADPKD. In addition, Park et al. (72) reported that UAGT is positively correlated with TKV and negatively correlated with eGFR.

Neutrophil gelatinase-associated lipocalin (NGAL) is a member of superfamily of lipocalin proteins, which is expressed in the lung, kidney, and gastrointestinal system. It plays a role in iron transport, epithelial differentiation pathways, inflammation, and cell proliferation in the kidneys (73). NGAL expression increases in kidney epithelial cells in response to injury. In addition, the predictive value of urinary NGAL levels has been shown for AKI occurrence in several studies in many populations rather than ADPKD (74, 75). NGAL levels are thought to increase in urine as ADPKD kidneys show inflammation, cyst proliferation, and kidney enlargement. More recently, it has been reported in two different studies that urinary NGAL excretion is mildly and stably elevated in ADPKD, but does not correlate with changes in TKV or kidney function (70, 76). However, Vareesangthip et al. (77) demonstrated a negative correlation between urinary NGAL and eGFR in patients with ADPKD. Similarly, Bolignano et al. (78) reported markedly higher urinary NGAL levels in patients with ADPKD at the late stage than in healthy volunteers. Meijer et al. (79) found a correlation between urinary NGAL lev-

Table 1. Urine parameters and biomarkers in autosomal dominant polycystic kidney disease

Biomarker	Association/Change
Urine osmolality	Urine osmolality reduced in ADPKD (680±14 mOsm/kg) compared to non-ADPKD subjects (812±13 mosm/kg).
Hematuria	The incidence of gross hematuria is increased in ADPKD patients and it is associated with rapid renal disease progression.
Proteinuria	Microalbuminuria and mild proteinuria is associated with cardiovas- cular disease and renal function decline and increased total kidney volume.
Pyuria	Asymptomatic pyuria is associated with urinary tract infection and precedes kidney function deterioration.
Urine pH	Urinary pH <5.5 occurs in >50% of patients with ADPKD and it is inde- pendently associated with urinary calculi, particularly uric acid stones.
Hypocitraturia, hyperoxaluria, hypercalciuria	Hypocitraturia, hyperoxaluria, and hypercalciuria were observed in ADPKD patients.
Urinary angiotensinogen	Increased urinary angiotensinogen levels in patients with ADPKD, par- ticularly hypertensive ones and correlated with total kidney volume.
Urinary neutrophil gelatinase-associated lipo- calin	Urinary NGAL is mildly elevated ADPKD patients compared to healthy controls and some studies found correlation with total kidney volume and decreased eGFR.
Urinary interleukin-18	Urinary IL-18 is mildly elevated in ADPKD patients.
Urinary complement proteins	Urinary complement changes: Increased levels of factor B (CFB), SERP- ING1 and C9 and decreased levels of complement component1, C1RL, CD55 and CD59 were correlated with the different stages of ADPKD.
Urinary proteomics	These marker proteins, most of which were collagen fragments, such as uromodulin were found at significantly different levels in ADPKD patients than controls.
Secreted Frizzled-related	
protein 4	sFRP4 was detected in the urine of both ADPKD patients and animals with PKD.
Hyperphosphaturia	The tubular maximum of phosphate reabsorption per glomerular filtration rate was found to be lowest in 100 ADPKD patients in compar- ison with 20 non-diabetic CKD patients, 26 diabetic patients and 20 healthy controls.
Urinary copeptin	Urinary copeptin/urinary creatinine is associated with the TKV and eGFR which is harbinger of disease severity in ADPKD
Urinary fetuin alpha	Urinary Fetuin-A levels were significantly higher in 66 ADPKD patients compared to 17 healthy volunteers and 50 control patients with renal diseases of other causes.
Urine micro-RNA	Primary cell cultures were obtained from urine specimens of 20 patients with ADPKD and 20 patients with CKD. The abundance of mir- 223; mir-199a and mir-199b in ADPKD urine cells have been reported.
Urinary heparin-binding EGF-like growth factor	Urinary HB-EGF excretion and plasma concentration were higher in 27 patients with ADPKD than in 27 controls and it is correlated with disease severity in ADPKD.

eGFR: Estimated glomerular filtration rate; mir: microRNA; ADPKD: Autosomal dominant polycystic kidney disease; NGAL: Neutrophil gelatinase-associated lipocalin; IL-18: Interleukin-18; CFB: Complement factor B; SERPING 1: Serpin Family G Member 1 (The human complement factor 1-inhibitor gene); C9: Complement factor 9; C1RL: Complement C1r subcomponent Like; sFRP4: Secreted frizzled-related protein 4; CKD: Chronic kidney disease; PKD: Polycystic kidney disease; TKV: Total kidney volume; HB-EGF: Heparin-binding epidermal growth factor-like growth factor

els with TKV in a cohort of 102 patients with ADPKD. Briefly, urinary NGAL levels may increase only in advanced disease, and data about the predictive role of NGAL in ADPKD are not enough in the current literature.

Interleukin-18 (IL-18), a member of the IL-1 family of cytokines, is synthesized as an inactive 23-kDa precursor by several tissues including monocytes, macrophages, and proximal tubular epithelial cells and is processed into an active 18.3 kDa cytokine by caspase-1 (80). It has been demonstrated that urinary IL-8 could be a biomarker of AKI (81). Several clinical trials have focused on the diagnostic accuracy of IL-18 level in predicting AKI in recent years (82-84). Urinary IL-18 is elevated during apoptosis and necrosis of renal tubular cells, which is associated with

AKI in animal and human studies. Parikh et al. (70) demonstrated that urine IL-18 levels are mildly elevated in patients with ADPKD, but do not correlate with changes in kidney function and TKV. They speculated that urine IL-18 levels are enriched in cyst fluid derived from patients with ADPKD, demonstrating the translation of the findings from murine and rat models to human disease (70).

Recently, the role of complement system activation has been thought to be related in ADPKD. Furthermore, it has been shown that substantial amounts of complement proteins are present in the renal cyst fluid of patients with ADPKD (85). In this regard, over a hundred different glycoproteins and glycopeptides in the urine were identified; however, significant expression changes were only observed in six complement components in the urine from patients with ADPKD by using a robust quantitative proteomics screen. In conclusion, it has been found that the increased levels of urinary complement components complement factor B, SERPING1, and C9, and the decreased levels of complement component 1, r subcomponent-like, CD55, and CD59 were correlated with the different stages of ADPKD (86).

Multidimensional nuclear magnetic resonance (NMR) spectroscopy was used to investigate the urine specimens of patients with ADPKD and compared with those of healthy controls (87). In the present study, the authors showed that the support vector machine-based classification of urinary NMR fingerprints yielded to discriminate patients with early-stage ADPKD from patients with ESRD and healthy subjects (87, 88). In addition to the NMR-based metabolomics approach pursued in the present study, urinary proteomics has been successfully applied to the prediction of ADPKD. There were many proteins with significantly altered urinary excretion, most of which were collagen fragments. Uromodulin peptides, previously implicated in tubular injury, were also found in urine specimens. These marker proteins were found to distinguish patients from controls with a high degree of accuracy (89). The coupling of capillary electrophoresis to mass spectrometry allowed the identification of a unique set of proteins serving as reliable biomarkers for the prediction of ADPKD. The use of NMR-based metabolomics offers the additional advantage of only minimal required sample pretreatment and easy sample handling, enabling fast and fully automatic data collection (88).

Secreted frizzled-related protein 4 (sFRP4) expression promotes cyst formation in ADPKD. sFRP4 is induced by a similar mechanism that antagonizes the Wnt signaling cascade as a differentially regulated gene in cystogenesis. Cyst fluid from ADPKD kidneys activates the production of sFRP4 protein in renal tubular epithelial cell lines (90, 91). Vasopressin 2 receptor antagonism resulted in a decrease of promoter activity and tubular sFRP4 expression. Moreover, sFRP4 was found in the urine of patients and animals with ADPKD, indicating that sFRP4 may be a potential biomarker for monitoring the progression of ADPKD (92).

Fibroblast growth factor 23 (FGF23) associated with increased phosphate levels in urine is substantially higher in patients with ADPKD than in other patients with CKD (93). Moreover, polycystin 1 is highly expressed in osteoblasts and osteocytes, which are the main sources for FGF23 production (94). It could be hypothesized that polycystin 1 is directly involved in the regulation of FGF23 production and that mutant polycystin 1 is responsible for the increased FGF23 secretion in ADPKD. The finding of elevated FGF23 levels in ADPKD with normal renal function, normal parathyroid hormone, and renal leak of phosphate represents an early manifestation of ADPKD (93).

It has been well established that patients with ADPKD already have decreased urinary concentration capacity (43) and that plasma osmolality is maintained within the normal range at higher plasma copeptin and AVP levels (23). Plasma copeptin is elevated in patients with ADPKD and predicts disease progression (95, 96). Nakajima et al. (97) showed that urinary copeptin/u-Cr is closely associated with the two important markers of disease severity in ADPKD (positively with TKV and negatively with eGFR). They suggested that U-copeptin/u-Cr is a preferable and easily measured surrogate marker to help predict disease progression in ADPKD.

Fetuin alpha (FETUA) expression is restricted to the liver in adults; however, it is expressed in many organs including the kidney, brain, liver, bone, lungs, and heart in the fetal period (98). Despite the absence of FETUA mRNA genetically, the FETUA protein has been detected in proximal tubule epithelial cells of rat kidneys in a previous study (99). Thus, it is speculated that FETUA may reach proximal tubule cells by reabsorption from the tubule lumen after passing from plasma through the glomerular filtration barrier (99, 100). Recently, Piazzon et al. (101) observed higher urinary FETUA levels in patients with ADPKD than in healthy controls.

MicroRNAs (miRs) are noncoding, small RNA molecules that modulate gene expressions by regulating many different intracellular pathways at the posttranscriptional level. There are many multiple putative targets for each miR, and they can also change between cell types and over time. It appears that they may play an important role in cell physiology (102). miRs play a role in both embryonic development and kidney disease processes. Their different blood or urine levels have been associated with several specific kidney diseases in animal models and human studies (103-105). miRs may play a crucial role in the regulation of profibrotic calcium signaling depending on some studies that have investigated their effect in ADPKD (106). Serum miR-3907 levels were recently demonstrated to be associated with disease progression of ADPKD (107). Indeed, urine has been widely used as a specimen to detect protein biomarkers in polycystic kidney disease (89). Ben-Dov et al. (108) evaluated the miRs in urine specimens and kidney epithelial cells of patients with ADPKD and without ADPKD. They demonstrated that miRNA previously implicated as kidney tumor suppressors

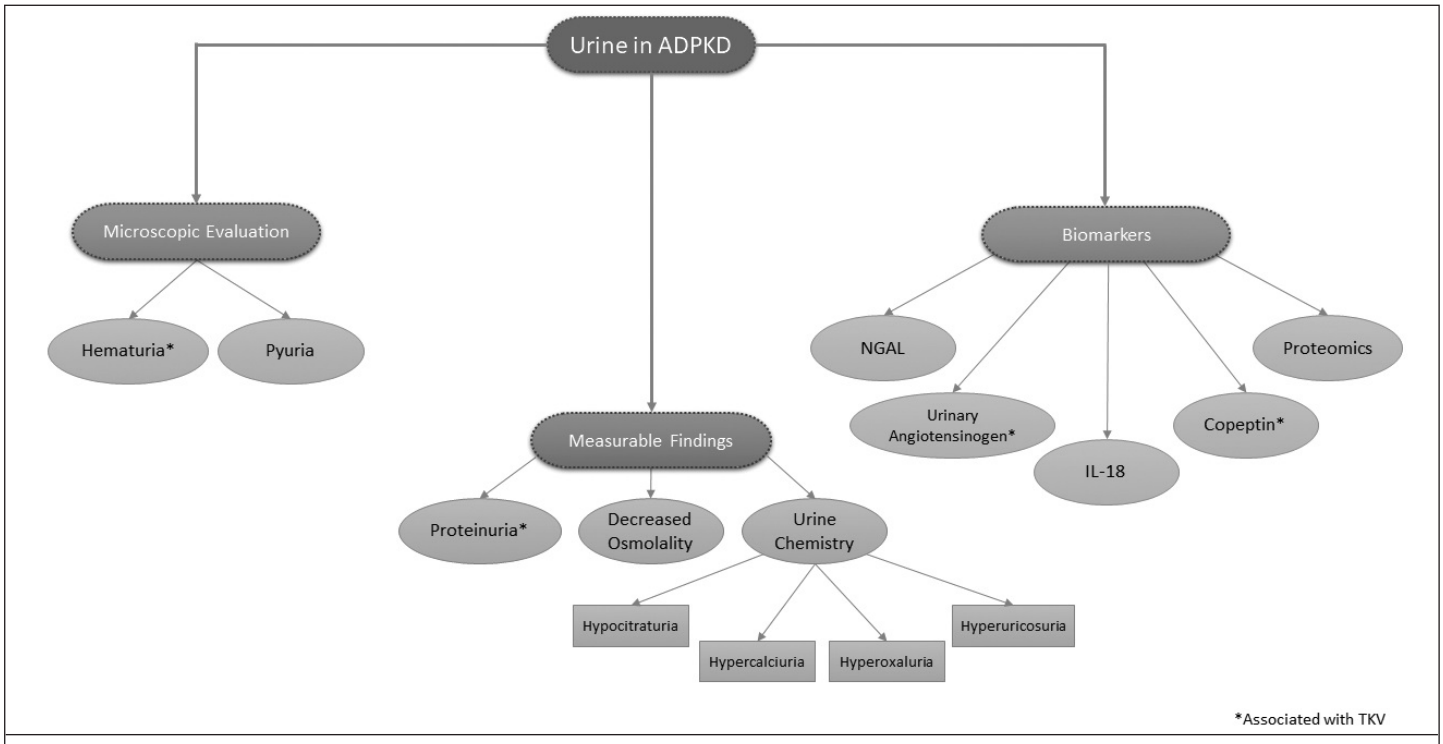


Figure 1. The evaluation of urinary specimen in autosomal dominant polycystic kidney disease.

(miR-1 and miR-133), as well as miRNA of presumed inflammatory and fibroblast cell origin (miR-223/miR-199), is dysregulated in ADPKD urine specimens compared with other patients with CKD (109).

Recently, urine proteome or peptidome markers have become clinically useful as urine biomarkers. Kistler et al. (89) defined the urinary biomarker profile of ADPKD and found a low molecular (<15 kDa) proteome fraction in the urine. Bakun et al. (109) studied the proteins of masses >10 kDa by using two-dimensional tryptic peptides separation. They showed that an ADPKD-characteristic footprint of 155 proteins significantly up- or down-regulated in the urine specimens of patients with ADPKD. There were significant differences in proteins of complement system, apolipoproteins, serpins, some growth factors, collagens, and extracellular matrix components in patients with ADPKD compared with those in healthy controls (109).

Epidermal growth factor (EGF) receptor pathway is shown to be involved with growth, migration, and proliferation of renal tubular cells (110). Dysregulation of this pathway has been suggested to play a role in the pathogenesis of ADPKD (64, 67). Heparin-binding EGF-like growth factor (HB-EGF) is known to be a more potent mitogen for renal tubular epithelia than EGF (111). Harskamp et al. (112) reported that EGF receptor ligands, such as HB-EGF, EGF, and transforming growth factor-α, are measured in blood and urine concentrations in patients with ADPKD at baseline and after treatment with a vasopressin V2 receptor antagonist (V2RA). Higher urinary HB-EGF excretion was found to be correlated with the severity of the disease in patients with ADPKD. Interestingly, HB-EGF excretion increased during V2RA treatment. In addition, further studies are needed to explain this result in patients with ADPKD.

Finally, Kawano et al. (113) analyzed many urine biomarkers in patients with ADPKD and compared them with those in healthy controls. There were significant differences between healthy subjects and patients with ADPKD with respect to several biomarkers including von Willebrand factor, IL-8, macrophage colony-stimulating factor, interferon receptor 2, perpetual flowering 1, trefoil factor family 3, hepatocyte growth factor, multicopper oxidase-1, 8-hydroxydeoxyguanosine, NGAL, liver-type fatty acid-binding protein (L-FABP), angiotensinogen, and ceruloplasmin. The levels of markers for multiple parts of the nephron are increased in patients with ADPKD. In addition to the measurement of UAE, the measurement of urinary β (2)-microglobulin, kidney injury molecule-1, heart-type-FABP, monocyte chemoattractant protein-1, N-acetyl-β-d-glucosaminidase, and endothelin-1 could be of value for determining the disease severity in patients with ADPKD (76, 79, 114-116).

CONCLUSION

Important new findings of the urine evaluation have improved our understanding with several pathogenic mechanisms including inflammation, cystogenesis, and disease progression in patients with ADPKD. Recent insights have highlighted the fact that urine concentration defect, hematuria, proteinuria, pyuria, urine calculi, and several urine biomarkers are not only pathological findings but also help clinicians with respect to disease progression during the follow-up of patients with ADPKD (Fig-

ure 1). In addition, several urine biomarkers in ADPKD were found to be associated with the severity of the disease and may be important in the near future to predict disease progression. Further studies are needed to clarify the mechanisms that lead to urine abnormalities of ADPKD from other kidney diseases.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.K.; Design - E.E., İ.K.; Supervision - İ.K.; Resource - E.E.; Materials - E.E.; Data Collection and/or Processing - E.E.; Analysis and/or Interpretation - E.E., İ.K.; Literature Search - E.E.; Writing - E.E., İ.K.; Critical Reviews - T.E.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Gabow PA. Autosomal dominant polycystic kidney disease. N Engl J Med 1993; 329: 332-42. [CrossRef]
2. Grantham JJ. Clinical practice. Autosomal dominant polycystic kidney disease. N Engl J Med 2008; 359: 1477-85. [CrossRef]
3. Igarashi P, Somlo S. Genetics and pathogenesis of polycystic kidney disease. J Am Soc Nephrol 2002; 13: 2384-98. [CrossRef]
4. The European Polycystic Kidney Disease Consortium. The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. Cell 1994; 17; 77: 881-94. [CrossRef]
5. Mochizuki T, Wu G, Hayashi T, Xenophontos SL, Veldhuisen B, Saris JJ, et al. PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. Science 1996; 272: 1339-42. [CrossRef]
6. Hateboer N, v Dijk MA, Bogdanova N, Coto E, Saggar-Malik AK, San Millan JL, et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. Lancet 1999; 353: 103-7. [CrossRef]
7. Ariza M, Alvarez V, Marín R, Aguado S, López-Larrea C, Alvarez J, et al. A family with a milder form of adult dominant polycystic kidney disease not linked to the PKD1 (16p) or PKD2 (4q) genes. J Med Genet 1997; 34: 587-9. [CrossRef]
8. Pei Y, Paterson AD, Wang KR, He N, Hefferton D, Watnick T, et al. Bilineal disease and trans-heterozygotes in autosomal dominant polycystic kidney disease. Am J Hum Genet 2001; 68: 355-63. [CrossRef]
9. Taylor M, Johnson AM, Tison M, Fain P, Schrier RW. Earlier diagnosis of autosomal dominant polycystic kidney disease: importance of family history and implications for cardiovascular and renal complications. Am J Kidney Dis 2005; 46: 415-23. [CrossRef]
10. Pei Y, Obaji J, Dupuis A, Paterson AD, Magistroni R, Dicks E, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol 2009; 20: 205-12. [CrossRef]
11. Gabow PA, Kaehny WD, Johnson AM, Duley IT, Manco-Johnson M, Lezotte DC, et al. The clinical utility of renal concentrating capacity in polycystic kidney disease. Kidney Int 1989; 35: 675-80. [CrossRef]
12. Dunn FL, Brennan TJ, Nelson AE, Robertson GL. The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 1973; 52: 3212-9. [CrossRef]
13. Gattone VH 2nd, Wang X, Harris PC, Torres VE. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. Nat Med 2003; 9: 1323-6. [CrossRef]
14. Devuyst O, Torres VE. Osmoregulation, vasopressin, and cAMP signaling in autosomal dominant polycystic kidney disease. Curr Opin Nephrol Hypertens 2013; 22: 459-70. [CrossRef]
15. Gattone VH 2nd, Grantham JJ. Understanding human cystic disease through experimental models. Semin Nephrol 1991; 11: 617-31.
16. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012; 367: 2407-18. [CrossRef]
17. Torres VE, Bankir L, Grantham JJ. A case for water in the treatment of polycystic kidney disease. Clin J Am Soc Nephrol 2009; 4: 1140-50. [CrossRef]
18. Wang CJ, Grantham JJ, Wetmore JB. The medicinal use of water in renal disease. Kidney Int 2013; 84: 45-53. [CrossRef]
19. Martinez-Maldonado M, Yium JJ, Eknoyan G, Suki WN. Adult polycystic kidney disease: studies of the defect in urine concentration. Kidney Int 1972; 2: 107-13. [CrossRef]
20. Preuss H, Geoly K, Johnson M, Chester A, Kliger A, Schreiner G. Tubular function in adult polycystic kidney disease. Nephron 1979; 24: 198-204. [CrossRef]
21. Schrier RW, Brosnahan G, CadnapaphornchaiMA, Chonchol M, Friend K, Gitomer B, et al. Predictors of autosomal dominant polycystic kidney disease progression. J Am Soc Nephrol 2014; 25: 2399-418. [CrossRef]
22. Casteleijn NF, Zittema D, Bakker SJ, Boertien WE, Gaillard CA, Meijer E, et al. Urine and plasma osmolality in patients with autosomal dominant polycystic kidney disease: reliable indicators of vasopressin activity and disease prognosis? Am J Nephrol 2015; 41: 248-56. [CrossRef]
23. Zittema D, Boertien WE, van Beek AP, Dullaart RP, Franssen CF, de Jong PE, et al. Vasopressin, copeptin, and renal concentrating capacity in patients with autosomal dominant polycystic kidney disease without renal impairment. Clin J Am Soc Nephrol 2012; 7: 906-13. [CrossRef]
24. Ho TA, Godefroid N, Gruzon D, Haymann JP, Maréchal C, Wang X, et al. Autosomal dominant polycystic kidney disease is associated with central and nephrogenic defects in osmoregulation. Kidney Int 2012; 82: 1121-9. [CrossRef]
25. Gabow PA, Duley I, Johnson AM. Clinical profiles of gross hematuria in autosomal dominant polycystic kidney disease. Am J Kidney Dis 1992; 20: 140-3. [CrossRef]
26. Ubara Y, Katori H, Tagami T, Tanaka S, Yokota M, Matsushita Y, et al.Transcatheter renal arterial embolization therapy on a patient with polycystic kidney disease on hemodialysis. Am J Kidney Dis 1999; 34: 926-31. [CrossRef]
27. Gabow PA, Johnson AM, Kaehny WD, Kimberling WJ, Lezotte DC, Duley IT, et al. Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease. Kidney Int 1992; 41: 1311-9. [CrossRef]
28. Tracz MJ, Alam J, Nath KA. Physiology and pathophysiology of heme: implications for kidney disease. J Am Soc Nephrol 2007; 18: 414-20. [CrossRef]
29. Leslie CL, Simon BJ, Lee KF, Emhoff TA, Munshi IA. Bilateral rupture of multicystic kidneys after blunt abdominal trauma. J Trauma 2000; 48: 336-7. [CrossRef]
30. Mufarrij AJ, Hitti E. Acute cystic rupture and hemorrhagic shock after a vigorous massage chair session in a patient with polycystic kidney disease. Am J Med Sci 2011; 342: 76-8. [CrossRef]
31. Bajwa ZH, Gupta S, Warfield CA, Steinman TI. Pain management in polycystic kidney disease. Kidney Int 2001; 60: 1631-44. [CrossRef]

32. Johnson AM, Gabow PA. Identification of patients with autosomal dominant polycystic kidney disease at highest risk for end-stage renal disease. J Am Soc Nephrol 1997; 8: 1560-7. [CrossRef]
33. Schrier RW, Brosnahan G, Cadnapaphornchai MA, Chonchol M, Friend K, Gitomer B, et al. Predictors of autosomal dominant polycystic kidney disease progression. J Am Soc Nephrol 2014; 25: 2399-418. [CrossRef]
34. Bello-Reuss E, Holubec K, Rajaraman S. Angiogenesis in autosomal-dominant polycystic kidney disease. Kidney Int 2001; 60: 37-45. [CrossRef]
35. Wei W, Popov V, Walocha JA, Wen J, Bello-Reuss E. Evidence of angiogenesis and microvascular regression in autosomal-dominant polycystic kidney disease kidneys: a corrosion cast study. Kidney Int 2006; 70: 1261-8. [CrossRef]
36. Licina MG, Adler S, Bruns FJ. Acute renal failure in a patient with polycystic kidney disease. JAMA 1981; 245: 1664-5. [CrossRef]
37. Sumida K, Ubara Y, Hoshino J, Hayami N, Suwabe T, Hiramatsu R, et al. Myeloperoxidase-antineutrophil cytoplasmic antibody-associated crescentic glomerulonephritis in autosomal dominant polycystic kidney disease. BMC Nephrol 2013; 14: 94. [CrossRef]
38. Chapman AB, Johnson AM, Gabow PA, Schrier RW. Overt proteinuria and microalbuminuria in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 1994; 5: 1349-54.
39. Bakker J, Olree M, Kaatee R, de Lange EE, Moons KG, Beutler JJ, et al. Renal volume measurements: accuracy and repeatability of US compared with that of MR imaging. Radiology 1999; 211: 623-8. [CrossRef]
40. Torres VE, Chapman AB, Perrone RD, Bae KT, Abebe KZ, Bost JE, et al.HALT PKD Study Group. Analysis of baseline parameters in the HALT polycystic kidney disease trials. Kidney Int 2012; 81: 577-85. [CrossRef]
41. Klahr S, Breyer JA, Beck GJ, Dennis VW, Hartman JA, Roth D, et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol 1995; 5: 2037-47.
42. Kistler AD, Poster D, KrauerFetal.Increases in kidney volume in autosomal dominant polycystic kidney disease can be detected within 6 months. Kidney Int 2009; 75: 235-41. [CrossRef]
43. Meijer E, Rook M, Tent H, Weishaupt D, Raina S, Senn O, et al. Early renal abnormalities in autosomal dominant polycystic kidney disease. Clin J Am SocNephrol 2010; 5: 1091-8. [CrossRef]
44. Visciano B, Di Pietro RA, Rossano R, Mancini A, Zamboli P, Ciancia-ruso B, et al. Nephrotic syndrome and autosomal dominant polycystic kidney disease. Clin Kidney J 2012; 5: 508-11. [CrossRef]
45. Contreras G, Mercado A, Pardo V, Vaamonde CA. Nephrotic syndrome in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 1995; 6: 1354-9.
46. Chow CL, Ong AC. Autosomal dominant polycystic kidney disease. Clin Med 2009; 9: 278-283. [CrossRef]
47. Hwang JH, Park HC, Jeong JC, Ha Baek S, Han MY, Bang K, et al. Chronic asymptomatic pyuria precedes overt urinary tract infection and deterioration of renal function in autosomal dominant polycystic kidney disease. BMC Nephrol 2013: 14; 1. [CrossRef]
48. Sklar AH, Caruana RJ, Lammers JE, Strauser GD. Renal infections in autosomal dominant polycystic kidney disease. Am J Kidney Dis 1987; 10: 81-8. [CrossRef]
49. Gibson P, Watson ML. Cyst infection in polycystic kidney disease: a clinical challenge. Nephrol Dial Transplant 1998; 13: 2455-7. [CrossRef]
50. Piccoli GB, Arena V, Consiglio V, Deagostini MC, Pelosi E, Dourou-kas A, et al.Positron emission tomography in the diagnostic pathway for intracystic infection in ADPKD and "cystic" kidneys. A case series. BMC Nephrol 2011; 12: 48. [CrossRef]
51. Jouret F, Lhommel R, Beguin C, Devuyst O, Pirson Y, Hassoun Z, et al. Positron-emission computed tomography in cyst infection diagnosis in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol 2011; 6: 1644-50. [CrossRef]
52. Levine E, Grantham JJ. High-density renal cysts in autosomal dominant polycystic kidney disease demonstrated by CT. Radiology 1985; 154: 477-82. [CrossRef]
53. Ahmed ER, Tashkandi MA, Nahrir S, Maulana A. Retrospective analysis of factors affecting the progression of chronic renal failure in adult polycystic kidney disease. Saudi J Kidney Dis Transpl 2006; 17: 511-5.
54. Torres VE, Erickson SB, Smith LH, Wilson DM, Hattery RR, Segura JW. The association of nephrolithiasis and autosomal dominant polycystic kidney disease. Am J Kidney Dis 1988; 11: 318-25. [CrossRef]
55. Levine E, Grantham JJ. Calcified renal stones and cyst calcifications in autosomal dominant polycystic kidney disease: clinical and CT study in 84 patients. AJR Am J Roentgenol 1992; 159: 77-81. [CrossRef]
56. Torres VE, Wilson DM, Hattery RR, Segura JW. Renal stone disease in autosomal dominant polycystic kidney disease. Am J Kidney Dis 1993; 22: 513-9. [CrossRef]
57. Grampsas SA, Chandhoke PS, Fan J, Glass MA, Townsend R, Johnson AM, et al. Anatomic and metabolic risk factors for nephrolithiasis in patients with autosomal dominant polycystic kidney disease. Am J Kidney Dis 2000; 36: 53-7. [CrossRef]
58. Gambaro G, Fabris A, Puliatta D, Lupo A. Lithiasis in cystic kidney disease and malformations of the urinary tract. Urol Res 2006; 34: 102-7. [CrossRef]
59. Nishiura JL, Neves RF, Eloi SR, Cintra SM, Ajzen SA, Heilberg IP. Evaluation of nephrolithiasis in autosomal dominant polycystic kidney disease patients. Clin J Am Soc Nephrol 2009; 4: 838-44. [CrossRef]
60. Riese RJ, Sakhaee K. Uric acid nephrolithiasis: pathogenesis and treatment. J Urol 1992; 148: 765-71. [CrossRef]
61. Sakhaee K, Adams-Huet B, Moe OW, Pak CY. Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. Kidney Int 2002; 62: 971-9. [CrossRef]
62. Torres VE, Keith DS, Offord KP, Kon SP, Wilson DM. Renal ammonia in autosomal dominant polycystic kidney disease. Kidney Int 1994; 45: 1745-53. [CrossRef]
63. Cheidde L, Ajzen SA, Tamer Langen CH, Christophalo D, Heilberg IP. A critical appraisal of the radiological evaluation of nephrocalcinosis. Nephron Clin Pract 2007; 106: c119-24. [CrossRef]
64. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet 2007; 369: 1287-301. [CrossRef]
65. Idrizi A, Barbullushi M, Petrela E, Kodra S, Koroshi A, Thereska N. The influence of renal manifestations to the progression of autosomal dominant polycystic kidney disease. Hippokratia 2009; 13: 161-4. [CrossRef]
66. Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King BF Jr, et al. Volume progression in polycystic kidney disease. N Engl J Med 2006; 354: 2122-30.[CrossRef]
67. Harris PC, Torres VE. Polycystic Kidney Disease. Annu Rev Med 2009; 60: 321-7. [CrossRef]
68. Ong AC, Harris PC. Molecular pathogenesis of ADPKD: the polycystin complex gets complex. Kidney Int 2005; 67: 1234-47. [CrossRef]

69. Briggs JP. The hunt for the perfect biomarker for acute kidney injury: back to gamma-trace? Kidney Int 2008; 74: 987-9. [CrossRef]
70. Parikh CR, Dahl NK, Chapman AB, Bost JE, Edelstein CL, Comer DM, et al. Evaluation of urine biomarkers of kidney injury in polycystic kidney disease. Kidney Int 2012; 81: 784-90. [CrossRef]
71. Kocyigit I, Yilmaz MI, Unal A, Ozturk F, Eroglu E, Yazici C, et al.A link between the intrarenal renin angiotensin system and hypertension in autosomal dominant polycystic kidney disease. Am J Nephrol 2013; 38: 218-25. [CrossRef]
72. Park HC, Kang AY, Jang JY, Kim H, Han M, Oh KH, et al.Increased urinary angiotensinogen/creatinine (AGT/Cr) ratio may be associated with reduced renal function in autosomal dominant polycystic kidney disease patients. BMC Nephrol 2015; 20; 16: 86. [CrossRef]
73. Kjeldsen L, Johnsen AH, Sengeløv H, Borregaard N. Isolation and primary structure of NGAL, a novel protein associated with human neutrophil gelatinase. J Biol Chem 1993; 268: 10425-32.
74. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, et al. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 2003; 14: 2534-43. [CrossRef]
75. Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney Int 2008; 73: 1008-16. [CrossRef]
76. Petzold K, Poster D, Krauer F, Spanaus K, Andreisek G, Nguyen-Kim TD, et al.Urinary biomarkers at early ADPKD disease stage. PLoS One 2015; 10: e0123555. [CrossRef]
77. Vareesangthip K, Vareesangthip K, Limwongse C, Reesukumal K. Role of urinary neutrophil gelatinase-associated lipocalin for predicting the severity of renal functions in patients with autosomal-dominant polycystic kidney disease. Transplant Proc 2017; 49: 950-4. [CrossRef]
78. Bolignano D, Lacquaniti A, Coppolino G, Donato V, Campo S, Fazio MR, et al. Neutrophilgelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. Clin J Am Soc Nephrol 2009; 4: 337-44. [CrossRef]
79. Meijer E, Boertien WE, Nauta FL, Bakker SJ, van Oeveren W, Rook M, et al. Association of urinary biomarkers with disease severity in patients with autosomal dominant polycystic kidney disease: a cross-sectional analysis. Am J Kidney Dis 2010; 56: 883-95. [CrossRef]
80. Dinarello CA. Interleukin-18 and the pathogenesis of inflammatory diseases. Semin Nephrol 2007; 27: 98-114. [CrossRef]
81. Lin X, Yuan J, Zhao Y, Zha Y. Urine interleukin-18 in prediction of acute kidney injury: a systemic review and meta-analysis. J Nephrol 2015; 28: 7-16. [CrossRef]
82. Parikh CR, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin-18 is a marker of human acute tubular necrosis. Am J Kidney Dis 2004; 43: 405-14. [CrossRef]
83. Parikh CR, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C, et al. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int 2006; 70: 199-203. [CrossRef]
84. Parikh CR, Jani A, Mishra J, Ma Q, Kelly C, Barasch J, et al.Urine NGAL and IL-18 are predictive biomarkers for delayed graft function following kidney transplantation. Am J Transplant 2006; 6: 1639-45. [CrossRef]
85. Lai X, Bacallao RL, Blazer-Yost BL, Hong D, Mason SB, Witzmann FA. Characterization of the renal cyst fluid proteome in autosomal dominant polycystic kidney disease (ADPKD) patients. Proteomics Clin Appl 2008; 2: 1140-52. [CrossRef]
86. Su Z, Wang X, Gao X, Liu Y, Pan C, Hu H, et al. Excessive activation of the alternative complement pathway in autosomal dominant polycystic kidney disease. J Intern Med 2014; 276: 470-85. [CrossRef]
87. Gronwald W, Klein MS, Kaspar H, Fagerer SR, Nürnberger N, Dettmer K, et al. Urinary metabolite quantification employing 2D NMR spectroscopy. Anal Chem 2008; 80: 9288-97. [CrossRef]
88. Gronwald W, Klein MS, Zeltner R, Schulze BD, Reinhold SW, Deutschmann M, et al. Detection of autosomal dominant polycystic kidney disease by NMR spectroscopic fingerprinting of urine. Kidney Int 2011; 79: 1244-53. [CrossRef]
89. Kistler AD, Mischak H, Poster D, Dakna M, Wüthrich RP, Serra AL. Identification of a unique urinary biomarker profile in patients with autosomal dominant polycystic kidney disease. Kidney Int 2009; 76: 89-96. [CrossRef]
90. Dennis S, Aikawa M, Szeto W, d'Amore PA, Papkoff J. A secreted frizzled related protein, FrzA, selectively associates with Wnt-1 protein and regulates wnt-1 signaling. J Cell Sci 1999; 112: 3815-20.
91. Benzing T, Simons M, Walz G. Wnt signaling in polycystic kidney disease. J Am Soc Nephrol 2007; 18: 1389-98. [CrossRef]
92. Romaker D, Puetz M, Teschner S, Donauer J, Geyer M, Gerke P, et al. Increased expression of secreted frizzled-related protein 4 in polycystic kidneys. J Am Soc Nephrol 2009; 20: 48-56. [CrossRef]
93. Pavik I, Jaeger P, Kistler AD, Poster D, Krauer F, Cavelti-Weder C, et al. Patients with autosomal dominant polycystic kidney disease have elevated fibroblast growth factor 23 levels and a renal leak of phosphate. Kidney Int 2011; 79: 234-40. [CrossRef]
94. Xiao Z, Zhang S, Mahlios J, Zhou G, Magenheimer BS, Guo D, et al. Cilia-like structures and polycystin-1 in osteoblasts/osteocytes and associated abnormalities in skeletogenesis and Runx2 expression. J Biol Chem 2006; 281: 30884-95. [CrossRef]
95. Boertien WE, Meijer E, Zittema D, van Dijk MA, Rabelink TJ, Breuning MH, et al. Copeptin, a surrogate marker for vasopressin, is associated with kidney function decline in subjects with autosomal dominant polycystic kidney disease. Nephrol Dial Transplant 2012; 27: 4131-7. [CrossRef]
96. Kocyigit I, Yilmaz MI, Gungor O, Eroglu E, Unal A, Orscelik O, et al. Vasopressin-related copeptin is a novel predictor of early endothelial dysfunction in patients with adult polycystic kidney disease. BMC Nephrol 2016; 17: 196. [CrossRef]
97. Nakajima A, Lu Y, Kawano H, Horie S, Muto S. Association of arginine vasopressin surrogate marker urinary copeptin with severity of autosomal dominant polycystic kidney disease (ADPKD). ClinExpNephrol 2015; 19: 1199-205. [CrossRef]
98. Denecke B, Gräber S, Schäfer C, Heiss A, Wöltje M, Jahnen-Dechent W. Tissue distribution and activity testing suggest a similar but not identical function of fetuin-B and fetuin-A. Biochem J 2003; 376: 135-45. [CrossRef]
99. Matsui I, Hamano T, Mikami S, Inoue K, Shimomura A, Nagasawa Y, et al. Retention of fetuin-A in renal tubular lumen protects the kidney from nephrocalcinosis in rats. Am J Physiol Renal Physiol 2013; 304: F751-60. [CrossRef]
100. Matsui I, Hamano T, Mikami S, Fujii N, Takabatake Y, Nagasawa Y, et al. Fully phosphorylated fetuin-A forms a mineral complex in the serum of rats with adenine-induced renal failure. Kidney Int 2009; 75: 915-28. [CrossRef]
101. Piazzon N, Bernet F, Guihard L, Leonhard WN, Urfer S, Firsov D, et al. UrineFetuin-A is a biomarker of autosomal dominant polycystic kidney disease progression. J Transl Med 2015; 13: 103. [CrossRef]

102. Wing MR, Ramezani A, Gill HS, Devaney JM, Raj DS. Epigenetics of progression of chronic kidney disease: fact or fantasy? Semin Nephrol 2013; 33: 363-74. [CrossRef]
103. Duan ZY, Cai GY, Bu R, Lu Y, Hou K, Chen XM. Selection of urinary sediment miRNAs as specific biomarkers of IgA nephropathy. Sci Rep 2016: 22; 23498 [CrossRef]
104. Liep J, Kilic E, Meyer HA, Busch J, Jung K, Rabien A. Cooperative Effect of miR-141-3p and miR-145-5p in the Regulation of Targets in Clear Cell Renal Cell Carcinoma. PLoS One 2016; 11: e0157801. [CrossRef]
105. Patel V, Williams D, Hajarnis S, Hunter R, Pontoglio M, Somlo S, et al. miR-17~92 miRNA cluster promotes kidney cyst growth in polycystic kidney disease. Proc Natl Acad Sci U S A 2013; 110: 10765-70. [CrossRef]
106. Pandey P, Qin S, Ho J, Zhou J, Kreidberg JA. Systems biology approach to identify transcriptome reprogramming and candidate microRNA targets during the progression of polycystic kidney disease. BMC Syst Biol 2011; 5: 56. [CrossRef]
107. Kocyigit I, Taheri S, Sener EF, Eroglu E, Ozturk F, Unal A, et al. Serum micro-rna profiles in patients with autosomal dominant polycystic kidney disease according to hypertension and renal function. BMC Nephrol 2017; 18: 179. [CrossRef]
108. Ben-Dov IZ, Tan YC, Morozov P, Wilson PD, Rennert H, Blumenfeld JD, et al. Urine microRNA as potential biomarkers of autosomal dominant polycystic kidney disease progression: description of miRNA profiles at baseline. PLoS One 2014; 9: e86856. [CrossRef]
109. Bakun M, Niemczyk M, Domanski D, Jazwiec R, Perzanowska A, Niemczyk S, et al. Urine proteome of autosomal dominant polycystic kidney disease patients. Clin Proteomics 2012; 9: 13. [CrossRef]
110. Melenhorst WB, Mulder GM, Xi Q, Hoenderop JG, Kimura K, Eguchi S, et al. Epidermal growth factor receptor signaling in the kidney: key roles in physiology and disease. Hypertension 2008; 52: 987-93. [CrossRef]
111. Horikoshi S, Kubota S, Martin GR, Yamada Y, Klotman PE. Epidermal growth factor (EGF) expression in the congenital polycystic mouse kidney. Kidney Int 1991; 39: 57-62. [CrossRef]
112. Harskamp LR, Gansevoort RT, Boertien WE, van Oeveren W, Engels GE, van Goor H, et al. Urinary EGF receptor ligand excretion in patients with autosomal dominant polycystic kidney disease and response to tolvaptan. Clin J Am SocNephrol 2015; 10: 1749-56. [CrossRef]
113. Kawano H, Muto S, Ohmoto Y, Iwata F, Fujiki H, Mori T, et al. Exploring urinary biomarkers in autosomal dominant polycystic kidney disease. Clin Exp Nephrol 2015; 19: 968-73. [CrossRef]
114. Birenboim N, Donoso VS, Huseman RA, Grantham JJ. Renal excretion and cyst accumulation of beta 2 microglobulin in polycystic kidney disease. Kidney Int 1987; 31: 85-92. [CrossRef]
115. Park HC, Hwang JH, Kang AY, Ro H, Kim MG, An JN, et al. Urinary N-acetyl-β-D glucosaminidase as a surrogate marker for renal function in autosomal dominant polycystic kidney disease: 1 year prospective cohort study. BMC Nephrol 2012; 13: 93. [CrossRef]
116. Raina R, Lou L, Berger B, Vogt B, Do AS, Cunningham R, et al. Relationship of urinary endothelin-1 with estimated glomerular filtration rate in autosomal dominant polycystic kidney disease: a pilot cross-sectional analysis. BMC Nephrol 2016; 17: 22. [CrossRef]

10.5152/turkjnephrol.2020.3900

Review

Turkish Journal of Nephrology

Why Crossmatch Tests are Very Important and What Do They Tell Us?

Mesut İzzet Titiz[1], Türker Bilgen[2]

[1]Tekirdağ Namık Kemal University School of Medicine, Tekirdağ, Turkey
[2]Tekirdağ Namık Kemal University School of Health, Tekirdağ, Turkey

Abstract

Organ transplantation is a very complex procedure that can save lives. It is a very useful procedure if the concepts of immunology, gained through bitter experience over the years, are kept in mind during practice. Allogeneic sensitization due to previous exposure(s) to alloantigens can hamper the procedure and remains the main obstacle to organ transplantation. Allosensitization and its level in a patient can be revealed before transplantation using the crossmatch test performed by incubating the patient's serum with the possible donor's lymphocytes in a laboratory environment. Crossmatch tests are routinely used prior to transplantation to prevent acute humoral reactions to the allograft tissue following reperfusion and also for long-term monitoring of the patient's humoral status during the pre- and post-transplantation periods.

Keywords: Transplantation, crossmatch test, sensitization

Corresponding Author: Mesut İzzet Titiz ✉ mititiz@nku.edu.tr

Received: 02.04.2019 **Accepted:** 09.07.2019

Cite this article as: Titiz Mİ, Bilgen T. Why Crossmatch Tests are Very Important and What Do They Tell Us? Turk J Nephrol 2020; 29(1): 77-81.

INTRODUCTION

Crossmatch tests are used in many areas of medicine. In the context of transplantation, crossmatch tests have widely been used for evaluating the immunological and anamnestic responses of the recipient to the graft antigens and vice versa as well as the response of the allograft to the recipient. Cell-to-cell crossmatch and serum-to-cell crossmatch have commonly been used to determine graft and patient compatibility. Crossmatch tests can be used for monitoring the patient's humoral status during and after transplantation. Practically, patients' possible humoral reactions against possible donor antigens are in focus. Positive crossmatch test results, even at a low positivity, indicate that the antigens have at least once been introduced in the body, that they have been processed and stored in the immune memory, and that they have the potential for inducing future humoral reactions and injuries. During the pre-transplantation period, crossmatch tests can be performed against a specific donor to detect possible sensitizations and presence of antibodies (Abs) specific to the donor and also the overall general population to generate the % panel-reactive antibodies (% PRA) that represents the allosensitization level of the recipient. Organ failure patients who require support for failing organ function are usually treated via very complex medical procedures, including artificial organ replacement systems, transplantation, and/or multiple transfusions to extend their survival; therefore, they usually become sensitized to many alloantigens in the population they live within. Sensitizing antigens when encountered and accepted as important by the host immune system are recorded as an immune memory in B cells, similar to what occurs in vaccination. Currently, sensitization is an ever increasing problem for the patients waiting for transplantation. In recent years, owing to the shortage of good matched donor organs, there has been an increasing interest in overcoming the problem of allosensitization through desensitization procedures that turn sensitized patients to transplantable cases. The level of desensitization is measured and monitored via crossmatch tests following particular desensitization procedures to save the graft from humoral injury (1-3).

Acquired immune reactions post transplantation are antigen-specific reactions to particular allograft antigens, which can lead to acute rejection. The most effective and active arm of acquired reactions is humoral, not cellular, through anti-human leukocyte antigen (HLA) Abs against particular graft antigens. To perform safe organ transplantation, collection of data that will explain the past and current immune status of the patient to accurately predict the fate of organ being transplanted is a prerequisite. The reaction against allogenic tissue is mostly immunogenic, i.e., overall inflammatory, in nature. Innate and acquired immune reactions begin to cooperate immediately post reperfusion and work synergistically to remove the foreign tissue rapidly, even though its function is life saving for the body. If immunosuppressive therapy is not orchestrated properly and remains ineffective and if immune cell functions are not suppressed to comply with the rules of tolerance, the end result is the loss of a great opportunity of survival (4, 5). Tolerance is survival of both the allograft and patient, without reacting against each other. This state is usually achieved with proper graft and patient histocompatibility matching as well as via pharmacological immunosuppression, which realizes silencing of the immune cells and their specific reactions against the graft alloantigens (5).

The immune system, evolved and organized with very painful experiences over hundreds of years, records important information in memory B cells and stores it as memory for the second set reaction. Upon encountering the same antigens again, memory B cells react directly, without T cell assistance, and begin to produce specific Abs spontaneously. When the antigen–antibody complexes are formed, the complement system is activated through the classical way, and the allograft is destroyed; this is the second set reaction (1, 2). Second set reaction is mediated mainly through antigen-specific immunoglobulin (Ig) G-type Abs, and they have a long half-life in the circulation. There are four main IgG Ab subgroups. IgG1 and IgG3 subgroup Abs set and accelerate the immune reactions up and can effectively activate the complement cascade. IgG2 and IgG4 subgroup Abs are rather tolerogenic and do not activate the complement system as effectively as do IgG1 and IgG3. These class differentiations are affected and routed mostly via influences of the local environmental cytokine-mediated factors present around the allograft region, depending on local effects of cytokines, including an inflammatory rejection reaction, a certain tolerogenic effect, and even deceleration of an immune reaction (6, 7). We have to keep in mind that Abs against specific foreign antigens are produced by the acquired immune system, and even though if they do not lead to significant complement activation for effective cytotoxicity, they can still induce opsonization as a low-intensity reaction or subclinical chronic immune reactions that can harm the graft in the long run (4, 5).

Ischemia/reperfusion injury following reperfusion, which is unavoidable during vascularized organ transplantation, leads to severe inflammation due to activation of components of the innate immune system, thus injuring the vascular endothelium of the graft. The inflamed endothelium becomes highly antigenic since endothelial cells are immune cells in nature. These cells are rich in major histocompatibility complex (MHC) antigens under inflammation and present those antigens to the host's acquired immune system (5, 8-11). When the patient is already sensitized, the circulating recipient blood is rich in allo-Abs against the alloantigens, which the graft already expresses; this leads to antibody–antigen binding and complement activation, which in turn activates the classical cascade leading to a series of harmful reactions. These reactions inflict serious additional injuries to the endothelial tissue of the graft as well as the functional parenchymal cells. Depending on the intensity and severity of this endothelial injury, immune activation triggers another innate system, and the coagulation cascades are activated; circulation in the graft stops, and the graft becomes gangrenous. If the immune reaction is less severe at the beginning as well as latter, the acquired immune reaction can be adequately suppressed via pharmacological means; this way, the reaction does not accelerate and remains slow and the slightly injured tissue may be repaired by live graft cells, leading to healing of the graft and its functioning as expected (5). In case of previous sensitization, the recipient will react to the recorded alloantigens immediately after reperfusion as a second set reaction, which is an accelerated response and cannot be halted. Modern powerful prophylactic immunosuppression techniques can prevent delayed type IV first set immune reactions; however, these are not effective against the type of immune cells with memory functions. Abs against the graft antigens, sooner or later, will destroy the allo-organ and return the patient to end-stage organ failure (11, 12).

Abs initiate all alloreactions against the allograft tissue in the recipient body according to the humoral theory. Sensitized patients show lower graft survival rates, as indicated in almost all multicenter studies, even if they are transplanted upon a negative crossmatch test result on a given date (13). Currently, crossmatch tests are widely used to evaluate humoral immunity rather than cellular immunity, and considering the humoral theory of rejection, cell-to-cell immunity tests are very rarely used (14-20). From this point of view, since sensitization and its level are the ultimate predictors during transplantation, crossmatch tests are performed at the beginning to offer an opportunity for correct matching of the allograft and patient as well as to provide information for the potential long-term fate of the allograft via humoral immune monitoring. Crossmatching is a highly strategic test with a particular meaning, and it can be repeated several times according to the indications and implications for future graft survival.

Pre-transplantation understanding of the true sensitization state is essential for achieving a good outcome in transplantation practice. Since importance of sensitizations has been historically demonstrated through bitter experiences, many effective and comprehensive crossmatch test have evolved and many re-

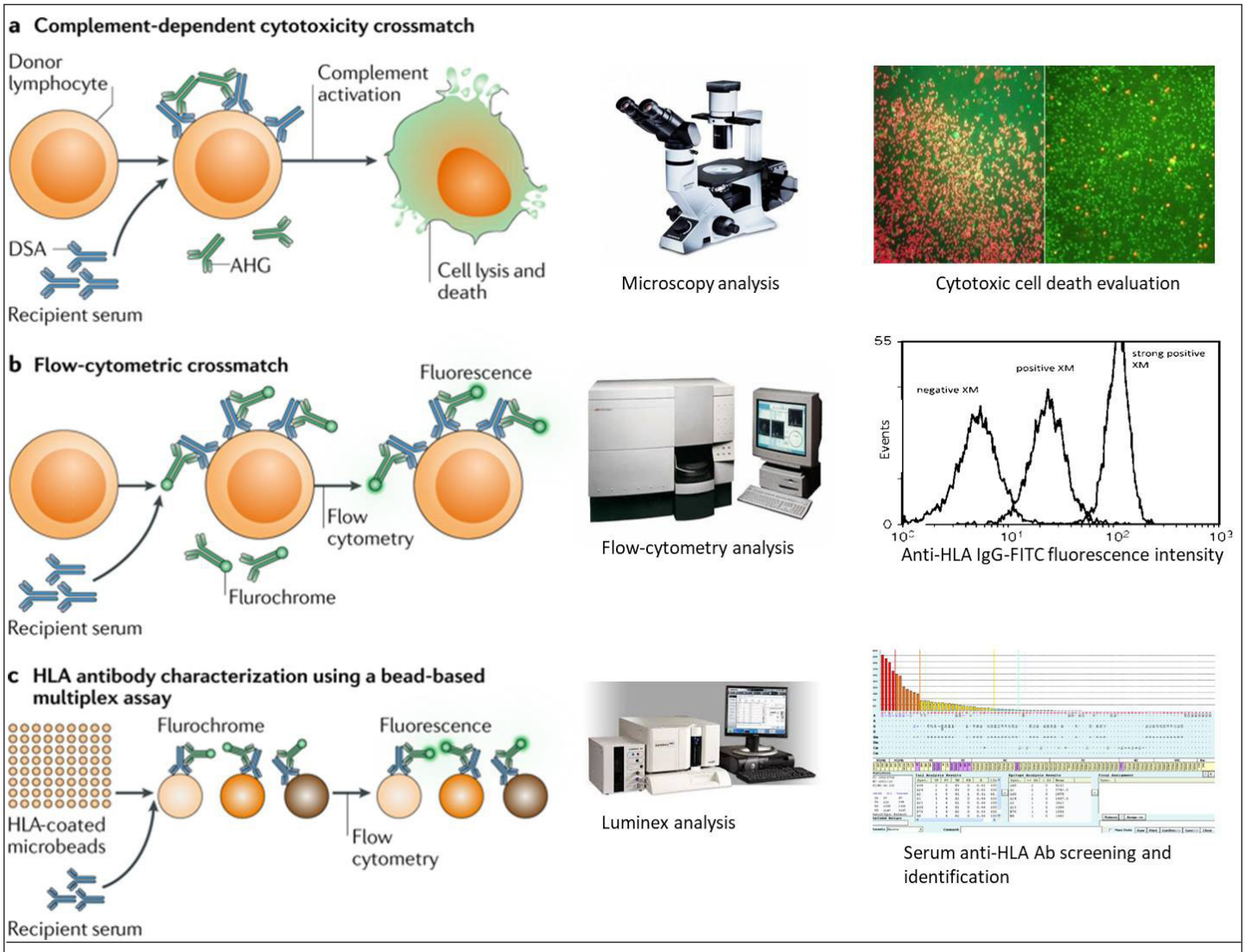


Figure 1. a-c. Schematic illustration on the basis of experimental stages, data collection, and results on the (a) CDCXM, (b) FCXM, and (c) Luminex assays. (Modified from Montgomery RA et al., Nature Reviews Nephrology 14, 558–570 (2018)).

searchers are still working on perfecting and increasing the reliability of these test (4, 6, 7, 12, 13). Theoretically, crossmatch tests have primarily been performed by two methods complementing each other using different antigen sources (Figure 1).

Patient serum in which the allo-Abs are searched for is crossmatched using either of the following assays:

1. Live donor lymphocytes as target antigens, called "cellular" or "cell-based" assays
2. A solid surface or ready-to-use microbeads, fitted with donor lymphocyte lysates or known MHC antigens, called "solid-phase" assays

Cell-based assays serologically demonstrate the complement-dependent donor lymphocyte lysis under the microscope (CDCXM) or using fluorescent-tagged anti-human IgG Abs, followed by the detection of allogeneic Abs in the patient serum (FCXM) using flow cytometry.

Solid-phase crossmatch test detect donor-specific allo-Abs in patient serum. It can be performed as a panel study-% PRA-using a set of possible HLA antigens in the population to demonstrate anti-HLA Abs present in the serum of a patient in the waiting list. Solid-phase assays are preferably performed for revealing the allogeneic sensitization level. During screening, a large number of patients' serum samples are tested and anti-HLA Abs are characterized (5, 16). Knowledge of patient characteristics, their sensitization status, and particular antigens they are sensitized to is very important before transplantation for proper matching while they are still in the national waiting list. This may increase their chance to find a donor who presents no HLA antigens the patient is sensitized to. Theoretically, with the aid of this information, the graft can be sent to the most matching remote patient in the waiting list without the need of performing the final actual pre-transplantation crossmatch test. The procedure, called "virtual crossmatch," saves time and allows for share and sending the allograft to remote areas and transplant it with a short cold ischemia time (3, 15, 18).

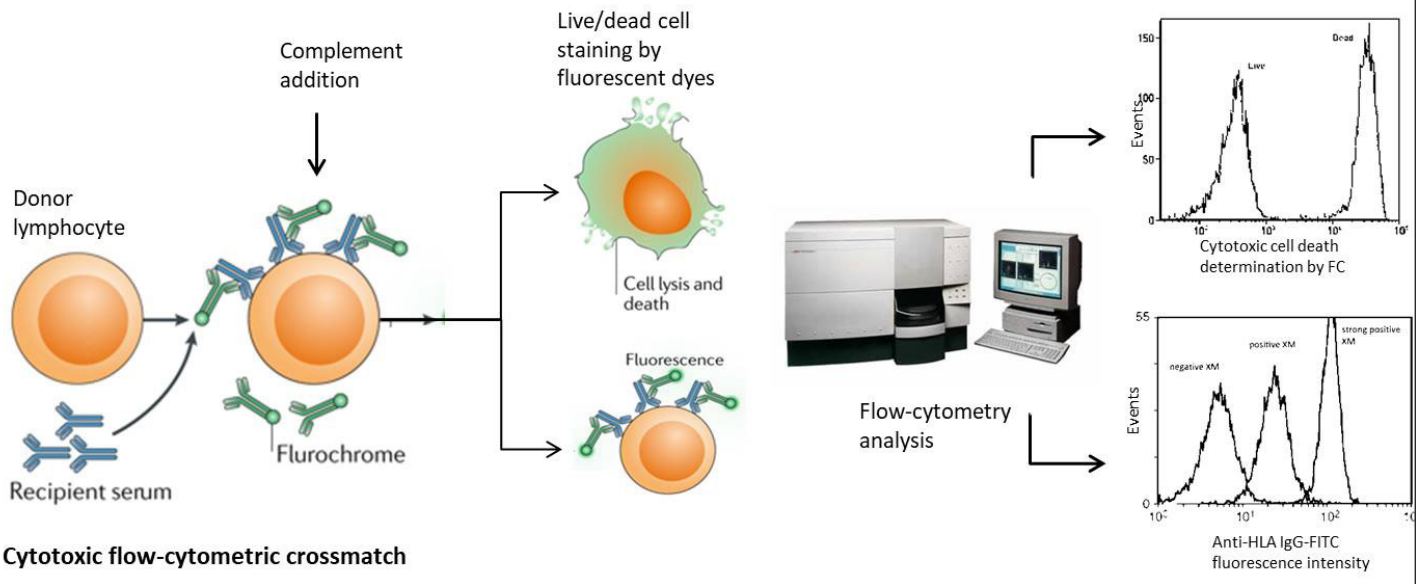


Figure 2. Schematic illustration on the basis of experimental stages, data collection, and results of the cFCXM assay. (Modified from Montgomery RA et al., Nature Reviews Nephrology 14, 558–570 (2018)).

In today's transplantation practice, most cell-based crossmatch tests are performed as CDCXM and provide visual evidence of sensitization and percent cytotoxicity. Serological crossmatch test, in which the complement is used, helps measure cytotoxicity visually. However, the decision is a subjective opinion since the result is read by a specialist in charge on that specific day, and the percentage of stained dead cells is calculated by counting them according to their morphology and color in the microscopic area being observed by the specialist. Another popular cell-based crossmatch test is performed using flow cytometry and fluorescent-tagged anti-human Abs. Flow cytometry is a computerized version of fluorescent microscopy in principle. It detects the presence and calculates the intensity of allo-Abs in the recipient's serum. However, since the complement is not used, it does not reveal cytotoxicity. Because the number of fluorescent-tagged lymphocytes is counted electronically, sensitivity of this assay is several times higher than that of the visual serological CDC method. Therefore, flow cytometric crossmatch is statistically more reliable. These two experiments take over 4 h in a laboratory to obtain reliable and detailed results. Flow cytometric crossmatch electronically measures the number of IgG-type allo-Abs attached to the surface of the flowed donor lymphocytes when the sample is passed under a laser beam using a computer program; therefore, it is highly objective. The cells with fluorescent Abs counted by the device are in thousands; thus, the results of this method are much more significant than those of the serological method. Since no complement is used in the flow crossmatch assay, although the Abs attached to the surface of the donor lymphocytes are detected, percent cytotoxicity and presence of complement-binding Abs cannot be determined. In routine practice, many tissue typing laboratories perform both serological and flow cytometric crossmatch tests together to obtain the most necessary information (7). A specialist clinician is aware of the existence of allo-Abs but cannot determine the cytotoxicity. Another flow cytometric test combining both methods (CDC+FCXM) was recently developed—cytotoxic flow cytometric crossmatch (cFCXM); this assay measures the level of allo-Abs and, with complement usage, determines their cytotoxicity in the same experiment (Figure 2). It is a functional test, resembling a serological cytotoxicity test performed using a flow cytometer. The advantage of this method is that it provides more information than both serological and flow cytometric crossmatch tests alone within a single experiment, saves time, and helps reduce the cold ischemia time. Moreover, since it is performed using flow cytometry, thousands of cells are counted and the data obtained are more reliable and significant (8).

These pre-transplant serological and flow cytometric cell-based crossmatch tests are designed to prevent hyperacute humoral injuries and/or possible second set anamnestic reactions against the graft. Availability of information on sensitization memory in advance may increase allograft survival through proper matching and immunosuppression. Studies on the humoral theory have revealed that second set reactions are not rare. Transplant patients with a history of alloimmunization and negative pre-transplant crossmatch test results may harbor sleeping memory B cells, which may become activated rapidly and become plasma cells upon antigen re-encounter after reperfusion (second set reaction); this cannot be prevented by crossmatch tests alone. In this case, the potential of the recipient's anamnestic reactions generated through their immune memory may lead to severe second set humoral rejection reactions following transplantation. It is almost the same reaction principle expected in vaccination reactions. Currently available methods to detect the presence and activity of recipient

HLA-specific memory B cells are scarce and insufficient in quantifying the complete donor-specific memory B cell response following transplantation. There have been an increasing number of articles on this topic over the recent years. Studies have shown that alloreactive memory B cell profiling provides more information on the recipient's allosensitization in addition to the information detected by the serum Ab screenings and crossmatch assays (21). Therefore, we need to gain information on the potential of memory B cells for better long-term graft survival. It is a very useful idea to uncover the possible immune memory status and potential of the recipient to prevent second set reactions (22).

CONCLUSION

Therefore, to gain a better understanding of the patient's immune memory status for extending graft survival, research to establish better pre-transplant crossmatch tests is an open-ended and ever-improving subject.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.I.T., T.B.; Design - M.I.T., T.B.; Supervision - M.I.T., T.B.; Data Collection and/or Processing - Analysis and/or Interpretation -; Literature Search - M.I.T., T.B.; Writing - M.I.T., T.B.; Critical Reviews - M.I.T., T.B.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Vaughan R, Shaw O. How much donor human leukocyte antigen-specific antibody is too much for a renal transplant? Transplantation 2008; 85: 1081-2. [CrossRef]
2. Schinstock CA, Gandhi MJ, Stegall MD. Interpreting anti-hla antibody testing data: a practical guide for physicians. Transplantation 2016; 100: 1619-28. [CrossRef]
3. Schlaf G, Apel S, Wahle A, Altermann WW. Solid phase-based cross-matching as solution for kidney allograft recipients pretreated with therapeutic antibodies. Biomed Res Int 2015; 2015: 587158. [CrossRef]
4. Gautreaux M, D. Histocompatibility Testing in the Transplant Setting in Kidney Transplantation, Bioengineering and Regeneration. 1st ed. Academic Press 2017. [CrossRef]
5. Ata P. Bağışıklık Sistemi ve Antikorlar. Titiz MI, editor. Laboratuvardan Kliniğe Transplantasyon Pratiği. 1st ed. Tekirdağ 2017.
6. Hönger G, Hopfer H, Arnold ML, Spriewald BM, Schaub S, Amico P. Pretransplant IgG subclasses of donor-specific human leukocyte antigen antibodies and development of antibody-mediated rejection. Transplantation 2011; 92: 41-7. [CrossRef]
7. Ata P, Canbakan M, Kara M, Özel L, Ünal E, Titiz M. Serum flow cytometric C1q binding antibody analysis of renal recipients with low levels of sensitization. Transplant Proc 2012; 44: 1652-5. [CrossRef]
8. Bilgen T, Ata P, Tozkir J, Tozkir H, Titiz MI. Cytotoxic Antibody detection by means of flow-cytometric cross-match. Transplant Proc 2017; 49: 440-4. [CrossRef]
9. Bonventre JV, Weinberg JM. Recent advances in the pathophysiology of ischemic acute renal failure. J Am Soc Nephrol 2003; 14: 2199-210. [CrossRef]
10. Requião-Moura LR, Durão MeS, Tonato EJ, Matos AC, Ozaki KS, Câmara NO, et al. Effects of ischemia and reperfusion injury on long-term graft function. Transplant Proc 2011; 43: 70-3. [CrossRef]
11. Kosieradzki M, Rowiński W. Ischemia/reperfusion injury in kidney transplantation: mechanisms and prevention. Transplant Proc 2008; 40: 3279-88. [CrossRef]
12. Terasaki PI, Cai J. Human leukocyte antigen antibodies and chronic rejection: from association to causation. Transplantation 2008; 86: 377-83. [CrossRef]
13. Terasaki PI. A personal perspective: 100-year history of the humoral theory of transplantation. Transplantation 2012; 93: 751-6. [CrossRef]
14. Platt JL, Cascalho M. B Cells in transplantation of rat, mouse, and man. Transplantation 2018; 102: 357-8. [CrossRef]
15. Piazza A, Ozzella G, Poggi E, Caputo D, Manfreda A, Adorno D. Virtual crossmatch in kidney transplantation. Transplant Proc 2014; 46: 2195-8. [CrossRef]
16. Koenig A, Mariat C, Mousson C, Wood KJ, Rifle G, Thaunat O. B Cells and Antibodies in Transplantation. Transplantation 2016; 100: 1460-4. [CrossRef]
17. Morath C, Opelz G, Zeier M, Süsal C. Prevention of antibody-mediated kidney transplant rejection. Transpl Int 2012; 25: 633-45. [CrossRef]
18. Roelen DL, Doxiadis II, Claas FH. Detection and clinical relevance of donor specific HLA antibodies: a matter of debate. Transpl Int 2012; 25: 604-10. [CrossRef]
19. Nascimento E, Fabreti de Oliveira RA, Maciel MD, Pereira AB, das Mercês de Lucas F, Salomão-Filho A, et al. Kidney transplantation: evaluation and clinical outcome of 237 recipients at low, medium, high, or strong immunological risk of rejection. Transplant Proc 2014; 46: 101-7. [CrossRef]
20. Mizutani K, Terasaki P, Hamdani E, Esquenazi V, Rosen A, Miller J, et al. The importance of anti-HLA-specific antibody strength in monitoring kidney transplant patients. Am J Transplant 2007; 7: 1027-31. [CrossRef]
21. Karahan GE, Eikmans M, Anholts JD, Claas FH, Heidt S. Polyclonal B cell activation for accurate analysis of pre-existing antigen-specific memory B cells. Clin Exp Immunol 2014; 177: 333-4. [CrossRef]
22. Karahan GE, Krop J, Wehmeier C, de Vaal Yvonne JH, Langerak-Langerak J, Roelen DL, et al. An Easy and Sensitive Method to Profile the Antibody Specificities of HLA-specific Memory B Cells. Transplantation 2019; 103: 716-23. [CrossRef]

10.5152/turkjnephrol.2020.3567

Case Report

Turkish Journal of Nephrology

Everolimus Toxicity in a Kidney Transplant Recipient Treated with Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir for Chronic Hepatitis C

Mete Akın[1], Osman Çağın Buldukoğlu[1], Haydar Adanır[1], Tolga Yalçınkaya[1], Vural Taner Yılmaz[2], Bülent Yıldırım[1], Yaşar Tuna[1], İnci Süleymanlar[1], Dinç Dinçer[1]

[1]Division of Gastroenterology, Akdeniz University School of Medicine, Antalya, Turkey
[2]Division of Nephrology, Akdeniz University School of Medicine, Antalya, Turkey

Abstract

The incidence of chronic hepatitis C virus (HCV) infection in kidney transplant recipients is 5%-15%, and HCV is an important risk factor for posttransplant kidney issues. Novel interferon-free regimens with direct-acting oral antiviral agents have extremely high response rates in solid organ transplant patients with HCV; however, drug–drug interactions, particularly with immunosuppressive agents, should be considered when deciding the treatment. Here we report a case of severe everolimus toxicity in a kidney transplant recipient receiving ombitasvir/paritaprevir/ritonavir and dasabuvir combination treatment.

Keywords: Everolimus, toxicity, chronic hepatitis C, ombitasvir/paritaprevir/ritonavir

Corresponding Author: Mete Akın ✉ drmeteakin@yahoo.com

Received: 12.09.2018 **Accepted:** 28.09.2018

Presented in: This study was presented at the 11th National Hepatology Congress, 17-21 May 2017, Antalya, Turkey.

Cite this article as: Akın M, Buldukoğlu OÇ, Adanır H, Yalçınkaya T, Yılmaz VT, Yıldırım B, et al. Everolimus Toxicity in a Kidney Transplant Recipient Treated with Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir for Chronic Hepatitis C. Turk J Nephrol 2020; 29(1): 82-3.

INTRODUCTION

The incidence of chronic hepatitis C virus (HCV) infection in kidney transplant recipients is 5%-15%; HCV is an important risk factor for posttransplant kidney issues such as glomerulopathy, chronic rejection, and graft loss in these patients (1). In the past years, interferon-based therapies could not be used for HCV treatment in posttransplant patients owing to the high risk of allograft dysfunction and rejection (2). Novel interferon-free regimens with direct-acting oral antiviral agents have extremely high response rates in solid organ transplant patients with HCV; however, drug-drug interactions, particularly with immunosuppressive agents, should be considered when deciding the treatment. Here, we report a case of severe everolimus toxicity in a kidney transplant recipient receiving ombitasvir/paritaprevir/ritonavir and dasabuvir (OBV/PTV/r+DSV) combination treatment.

CASE PRESENTATION

A 34-year-old male patient who underwent kidney transplantation from a live donor in 1996 was admitted to our clinic for chronic HCV treatment. His medical history included a diagnosis of chronic HCV in 1994, but he did not receive any treatment for the same. Although the patient was using tacrolimus following kidney transplantation, the treatment was changed to cyclosporine because of the creatinine elevation on tacrolimus therapy. Physical examination findings were normal. Following findings were detected on laboratory evaluation: alanine transaminase, 34 U/L; creatinine, 1.2 mg/dL; estimated glomerular filtration rate, 71 mL/min; total bilirubin, 1.1 mg/dL; albumin, 4.5 g/dL; international normalized ratio, 1.09; HCV-RNA, 3.740.000 IU/mL; and genotype 1b. Liver parenchyma and contours were normal, the portal vein diameter was 9 mm, the spleen was 82 mm in size on the longitudinal axis, and asci-

tes was absent on abdominal ultrasonography. The OBV/PTV/r+DSV regimen was initiated. The serum cyclosporine level was initially 54 ng/mL, and it increased to 457 ng/mL on follow-up. Despite cyclosporine dose reduction and intermittent discontinuation, the drug level remained 350-400 ng/mL for 4 weeks and could not be appropriately adjusted. The patient had a history of tacrolimus toxicity; hence, immunosuppressive therapy was changed to everolimus by the nephrology transplantation unit without our knowledge. The everolimus levels increased beyond the target level during the following week despite the dose reduction. The everolimus level was 30, 36, and 33 ng/mL on day 2, 5, and 7, respectively. At the end of the first week of everolimus therapy, the patient was admitted to the transplantation outpatient clinic owing to skin rashes and widespread ulcerations in the mouth and throat and was hospitalized with the diagnosis of everolimus toxicity. Moreover, the OBV/PTV/r+DSV regimen was discontinued during this hospitalization period along with everolimus, and the patient was re-initiated on cyclosporine therapy before being discharged. The patient was referred to our clinic 2 weeks after being discharged. Owing to the 2-week cessation period of the OBV/PTV/r+DSV regimen, the same treatment was not re-initiated. HCV-RNA was negative at this point. At 6 weeks after the cessation of the OBV/PTV/r+DSV regimen, the HCV-RNA level was detected to be 256,000 IU/mL. Thereafter, a combination of sofosbuvir (SOF)/ledipasvir (LDV) and ribavirin was administered to the patient for 12 weeks. HCV-RNA was negative at week 4, at the end of treatment, and at 12 weeks after the treatment. No side effects or changes in the cyclosporine drug levels were observed, and no dosage adjustments were required during the 12-week treatment period.

DISCUSSION

The calcineurin inhibitors tacrolimus and cyclosporine and the mammalian target of rapamycin inhibitors sirolimus and everolimus, which are used for immunosuppression following transplantation, are substrates for the cytochrome P450 (CYP) isoenzyme 3A4 and the drug transporter P-glycoprotein (P-gp), respectively. Therefore, the concomitant use of these drugs with agents that inhibit the aforementioned pathways may lead to increased drug levels, and dose modification might be required. SOF is not associated with drug-drug interaction with CYP3A4 and P-gp, whereas protease inhibitors (simeprevir and ritonavir-boosted paritaprevir) may cause serious drug-drug interactions with agents that use these pathways. A significant increase in the everolimus levels can be observed due to the inhibition of CYP3A4 enzyme, which is responsible for the metabolism of everolimus in the intestinal and liver cells by ritonavir. There is no recommended dose adjustment for everolimus administration in combination with the OBV/PTV/r+DSV regimen and is not recommended for concomitant use (3, 4). In the recent European Association for the Study of the Liver guidelines as well as in our national guidelines, a fixed dose combination of SOF/LDV (for genotypes 1, 4, 5, and 6) or SOF/daclatasvir or SOF/velpatasvir (for all genotypes) is the recommended regimen for HCV treatment in patients with solid organ transplantations, other than that of the liver, without the requirement for immunosuppressive drug dose adjustments (5, 6).

However, only two regimens (SOF/LDV and OBV/PTV/r+DSV combination) are available for the treatment of HCV in Turkey, and some centers may choose to administer the OBV/PTV/r+DSV combination to transplant patients.

In our patient, significant cyclosporine level increase during treatment and severe everolimus toxicity were observed owing to the drug switch performed without considering the potential drug-drug interactions.

CONCLUSION

The concomitant use of the OBV/PTV/r+DSV regimen and everolimus is contraindicated and must be avoided. Treatment process should be conducted in coordination with a nephrologist and gastroenterologist in kidney transplant recipients scheduled to receive the OBV/PTV/r+DSV regimen.

Informed Consent: Written informed consent was received from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.A., O.C.B, H.A.; Design - M.A, O.C.B., H.A., T.Y.; Supervision - M.A., V.T.Y., B.Y., Y.T., İ.S., D.D.; Resource - B.Y., İ.S., D.D.; Materials - T.Y., V.T.Y., Y.T.; Data Collection and/or Processing - M.A., O.C.B, H.A., T.Y.; Analysis and/or Interpretation - M.A., V.T.Y., Y.T., İ.S., D.D.; Literature Search - M.A., O.C.B., H.A., T.Y.; Writing - M.A., O.C.B.; Critical Reviews - M.A., V.T.Y., B.Y., Y.T., İ.S., D.D.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Morales JM, Fabrizi F. Hepatitis C and its impact on renal transplantation. Nat Rev Nephrol 2015; 11: 172-82. [CrossRef]
2. Fabrizi F, Penatti A, Messa P, Martin P. Treatment of hepatitis C after kidney transplant: a pooled analysis of observational studies. J Med Virol 2014; 86: 933-40. [CrossRef]
3. Burgess S, Partovi N, Yoshida EM, Erb SR, Azalgara VM, Hussaini T. Drug Interactions With Direct Acting Antivirals for Hepatitis C: Implications for HIV and Transplant Patients. Ann Pharmacother 2015; 49: 674-87. [CrossRef]
4. Kwo PY, Badshah MB. New hepatitis C virus therapies: drug classes and metabolism, drug interactions relevant in the transplant settings, drug options in decompensated cirrhosis, and drug options in end-stage renal disease. Curr Opin Organ Transplant 2015; 20: 235-41. [CrossRef]
5. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol 2018; 59: 461-511.
6. Kaymakoğlu S, Köksal İ, Tabak F, Akarca US, Akbulut A, Akyüz F, et al. Recommendation for treatment of hepatitis C virus infection. Turk J Gastroenterol 2017; 28: 94-100.[CrossRef]

10.5152/turkjnephrol.2020.3579

Case Report

Turkish Journal of Nephrology

Lupus Nephritis Presenting with Preeclampsia

Eray Eroğlu[1], Mustafa Çetin[2], İsmail Koçyiğit[1], Hülya Akgün[3], Murat Hayri Sipahioğlu[1], Bülent Tokgöz[1], Oktay Oymak[1]

[1]Division of Nephrology, Erciyes Üniversitesi School of Medicine, Kayseri, Turkey
[2]Department of Internal Medicine, Erciyes Üniversitesi School of Medicine, Kayseri, Turkey
[3]Department of Pathology, Erciyes Üniversitesi School of Medicine, Kayseri, Turkey

Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multisystem involvement. The renal involvement of SLE may present with hematuria , proteinuria or acute kidney dysfunction. It is well established that pregnancy may trigger the disease activation in patients with SLE. Lupus nephritis (LN) may be diagnosed during pregnancy in very few patients. Preeclampsia is a pregnancy-related disorder characterized by maternal hypertension, proteinuria, and edema and is sometimes complicated by renal dysfunction, which usually occurs in the last trimester of pregnancy. However preeclampsia rarely occurs within 48 h of postpartum. In this report, we present the case of a 20-year-old patient with oliguria, proteinuria, edema, and hypertension who was diagnosed with preeclampsia starting at the 35th week of her first pregnancy. Acute kidney failure developed in the postpartum period after emergency cesarian delivery. Crescentic and diffuse LN was revealed by renal biopsy. While SLE is a risk factor for preeclampsia, LN should be considered in kidney failure in the third trimester or postpartum period.
Keywords: Pregnancy, preeclampsia, lupus nephritis

Corresponding Author: Eray Eroğlu ✉ drerayeroglu@hotmail.com
Received: 16.09.2018 **Accepted:** 30.09.2018

Cite this article as: Eroğlu E, Çetin M, Koçyiğit İ, Akgün H, Sipahioğlu MH, Tokgöz B, et al. Lupus Nephritis Presenting with Preeclampsia. Turk J Nephrol 2020; 29(1): 84-8.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with multisystem involvement. Approximately 50% of patients with SLE may present with renal involvement. Renal involvement typically manifests as hematuria, proteinuria, or sudden onset renal dysfunction. In 1957, Muehrcke et al. (1) described lupus nephritis (LN) by kidney biopsy for the first time. LN is a serious but curable disease. Clinically, LN may also present with nephrotic syndrome, nephritic syndrome, or crescentic glomerulonephritis. Clinicopathologically, LN is classified into six types. The most frequent and the most severe prognosis is the form with diffuse proliferative glomerulonephritis (type IV) (2). Approximately 15%-25% of patients progress to end-stage renal disease within 10 years.

Several studies have demonstrated that pregnancy leads to the activation of this disease in women with SLE (3-6). Chronic LN, if activated during pregnancy, can lead to hypertension and renal failure, which can adversely affect the health of the mother and fetus. In rare cases, LN can be diagnosed during pregnancy. In particular, the clinical findings of patients who have not been previously diagnosed with LN may become apparent following activation during pregnancy. However, it is possible that the physiological changes related to pregnancy may mask some of the clinical presentations of LN including of proteinuria and edema. Otherwise, various diseases may cause renal dysfunction during pregnancy (4, 5). Among these, there are many possible causes of acute renal failure in pregnancy such as preeclampsia, hemolytic uremic syndrome, and perioperative complications (acute tubular necrosis) and rapidly progressive glomerulonephritis (2, 6). Preeclampsia is an important health problem that causes serious maternal and fetal complications in approximately 7%-10% of all pregnancies, mostly during the last trimester and rarely within 48 h postpartum. It is characterized by systemic vaso-

Table 1. Laboratory parameters of the patient at admission

Parameters	Value	Normal range
White blood cell (10^3/µL)	7.1	4.8-10.7
Hemoglobin (g/dL)	8.9	12-16
Platelets (10^3/µL)	204	130-400
Glucose (mg/dL)	110	74-106
BUN (mg/dL)	32	8-23
Creatinine (mg/dL)	1.82	0.7-1.20
Uric acid (mg/dL)	8.1	2.4-5.7
Calcium (mg/dL)	8.7	8.6-10.2
Phosphorus (mg/dL)	6.5	2.5-4.5
Magnesium (mmol/L)	1.2	0.66-1.77
Sodium (mmol/L)	136	136-145
Potassium (mmol/L)	6.03	3.5-5.1
Clor (mmol/L)	103	98-107
Total bilirubin (mg/dL)	0.15	0.2-1.2
Direct bilirubin (mg/dL)	0.09	0-0.3
GGT (U/L)	11	10-71
LDH (U/L)	411	135-225
AST (U/L)	39	0-40
ALT (U/L)	28	0-41
ALP (U/L)	151	40-130
Total protein (g/dL)	4.3	6.4-8.3
Albumin (g/dL)	2.1	3.5-5.2
PT (s)	10	10.1-14.9
APTT (s)	26	20-36
INR	0.89	0.8-1.2
UDT		
Protein (mg/dL)	100	0-10
Blood (ery/µL)	80	0-5
Leu (leu/µL)	29	0-10
Urine microscopy		
Erythrocyte (HPF)	80	0-3
Leukocyte (HPF)	29	0-5
Urine microprotein (mg/dL)	2950	28-217
Urine creatinine (mg/dL)	289	0-15

BUN: blood urea nitrogen; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; UDT: Urine dipstick test

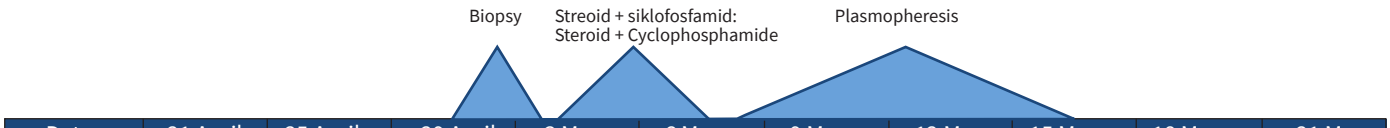
spasm, maternal hypertension, proteinuria, edema, increased platelet aggregation, and decreased uteroplacental blood flow and is observed in the presence of placental tissue and resolves within a short time after birth. The pathophysiology of the disease are still unclear (7-9).

In this case report, we describe the case of a 20-year-old patient without a history of any disease who developed proteinuria, edema, and hypertension at 35 weeks of her first pregnancy. She underwent emergency cesarean section (C/S) due to preeclampsia, developed oliguria and renal dysfunction in the postpartum period, and was directed to our clinic. Subsequently, she was diagnosed with crescentic LN with renal biopsy.

CASE PRESENTATION

A 20-year-old woman without a history of kidney disease presented to a private hospital with elevated blood pressure and swelling of the lower limbs during 35th week of her first pregnancy. Emergency C/S was performed due to the diagnosis of preeclampsia. Patient's postoperative urine output decreased (200 cc in 12 h) and serum creatinine level increased to 1.8 mg/dL; so urinary system ultrasound was performed and ectasia was not detected in the pelvicalyceal system. Kidney sizes were reported within normal range. In the postoperative period, 40 mg furosemide was administered intravenously (iv) due to oliguria. She was transferred to the nephrology department of our university hospital in April 2017 with the preliminary diagnosis of oliguric acute renal failure. There were no complications such as perioperative bleeding, hypovolemia, and hypotension. There was no history of nonsteroidal anti-inflammatory drug use. Complaints of fatigue and oliguria were noted in the systemic query. On physical examination, her body temperature was 37.0°C, pulse rate was 112 beats/min, blood pressure was 130/80 mmHg, and respiratory rate was 22 breaths/min; decreased breathing sounds in the lower lung fields at the bottom of the rib cage was detected byauscultation , and significant amount of ascites was detected in the abdomen and pretibial +++/+++ edema was detected in the examination of distal extremities. The laboratory test results are shown in Table 1.

Ten grams of proteinuria was detected in the spot urine microprotein/creatinine test. Microscopic examination of urinary sediment revealed dysmorphic erythrocytes, leukocyte casts , and granular casts. Urinary ultrasonography revealed that both kidney sizes were normal, parenchymal echoes increased to grade 1 in both kidneys without pelvicalyceal ectasia and stones, and intra-abdominal ascites was present. The patient's renal function tests deteriorated during the following days in the nephrology clinic. There were no abnormal results in the urine gram, and no bacteria were detected in urine culture. Diuretic treatment was initiated as the patient had increased pretibial edema, oliguric course, and hypervolemia. There was no response to diuretic treatment with furosemide. At the follow-up, the patient developed anuria and diuretic-resistant hypervolemia and was treated with intermittent hemodialysis (HD) and ultrafiltration



Date	21 April	25 April	29 April	3 May	6 May	9 May	12 May	15 May	18 May	21 May
BUN	32	17	13	22	48	47	34	39	53	47
Creatinine	1.89	2.34	2.6	5.2	5.2	5.2	3.2	3.2	2.6	2.4
Received (volum-cc)	1300	2500	2200	3350	1700	2600	3000	4250	1350	2100
Removed (volum-cc)	350	150	50	Yok	50	200	750	4850	3250	4250

Figure 1. Patient's clinical follow-up and treatment schedule.

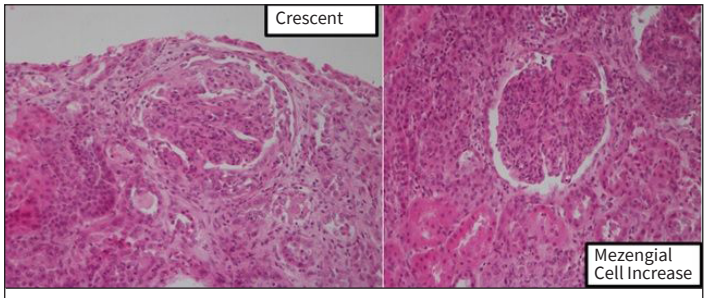


Figure 2. Presence of crescent formation and mesangial cell increase in glomeruli in renal biopsy specimen (H&E, ×40).

(UF). The patient received intermittent HD+UF treatment in the following days. After dialysis, regression was observed in hypervolemia findings. Urine output remained oliguric. An autoimmune panel was obtained from the patient, who showed signs of proteinuria, hypoalbuminemia, edema, oliguric renal failure, and active urine sediment. Renal biopsy was performed. After the pathological examination of the kidney biopsy revealed crescent formation, the patient was given pulse steroid treatment (1 g/day for 3 days), followed by cyclophosphamide + mesna iv (750 mg/day) immunosuppressive therapy. Based on the autoimmune panel findings, the patient was diagnosed with SLE with antinuclear antibody (ANA) positivity, anti-double stranded DNA antibody (anti-dsDNA) positivity, and lupus anticoagulant positivity, and low levels of complement factor 3 (C3) and complement factor 4 (C4) were noted. The patient was evaluated for other SLE findings. There was no history of oral aphthae or arthralgia. Mild hyperemia was noted on the face. However, typical malar rash was not detected. As a result of the pathology, type IV diffuse LN+crescentic glomerulonephritis was reported (Figure 1). Hydroxychloroquine treatment was initiated after the ophthalmology consultation. Simultaneous plasmapheresis treatment was planned. The patient underwent plasmapheresis for seven sessions. At the follow-up, her urine output increased after the 6th session of plasmapheresis (Figure 2). Intermittent dialysis was also administered during this period.

The patient's serum blood urea nitrogen (BUN)/creatinine (Cre) level decreased from 61/5.7 mg/dL to 47/2.43 mg/dL. She was discharged with a twice weekly intermittent HD program and monthly cyclophosphamide treatment plan. She received six cycles of cyclophosphamide treatment. Dialysis treatment was discontinued in July 2017 when her renal function improved. In November 2017, BUN/Cre level of 6.2/0.48 mg/dL and proteinuria of 6.7 g/day were noted. Maintenance therapy of mycophenolate mofetil was started, and out-patient clinic controls were continued in remission.

DISCUSSION

Systemic lupus erythematosus is the most common rheumatologic disease in pregnancy because it is usually observed in women in the reproductive age group. Fertility in women with SLE is similar to that in the normal population. The exacerbation of the disease during pregnancy and in the postpartum period is approximately 50%. In patients with lupus and pregnancy, the disease is usually exacerbated in the last trimester of pregnancy and within a few weeks after birth. Lupus exacerbations during pregnancy are frequently associated with renal and hematologic systems (1-4). Many complications in lupus can occur during pregnancy. These complications include exacerbation of the disease (leukomotor-hematologic-renal), abortion (especially in the presence of antiphospholipid antibodies), premature birth, intrauterine growth retardation, hypertension, increased risk of preeclampsia (especially in nephritis cases), risk of renal failure development, and maternal death. Therefore, the follow-up of pregnant women with SLE, which can cause significant maternal and fetal complications, should be performed with care. On the other hand, patients who become pregnant before the diagnosis of SLE may admit to the hospital with lupus complications. In the present report, we described a patient diagnosed with preeclampsia and LN due to oliguric acute renal failure after C/S.

Preeclampsia is defined as a combination of proteinuria , edema and increased blood pressure as >140/90 mmHg or increase in systolic blood pressure by 30 mmHg and increase in diastolic blood pressure by 15 mmHg in pregnant women at >20th week pregnancy, and the definitive treatment of preeclampsia is delivery of the fetus. Although preeclampsia and LN may coexist during pregnancy, it is very important to establish the differen-

tial diagnosis as their treatments are different. Steroids are used to treat LN, which worsens preeclampsia. Therefore, signs and symptoms that are more reliable in showing SLE exacerbation and diagnosis in pregnancy can be summarized as ANA positivity, increased anti-dsDNA autoantibody titer (if known before), lymphopenia, active urine sediment, erythrocyte casts, direct Coombs test positivity, hemolytic anemia, fever, lymphadenopathy, typical oral mucosal ulcers, inflammatory arthritis, and cutaneous vasculitis. However, findings such as hypertension, edema, proteinuria, impaired renal function, and thrombocytopenia are common factors in both preeclampsia and exacerbation of SLE. In addition, proteinuria that occurs during pregnancy may be at physiological limits or may be related to lupus. In this context, the presence of hematuria and examination of urine sediment may be suggestive of renal involvement due to SLE (2, 3, 8). Anti-dsDNA positivity with hypocomplementemia, even in the absence of clinical activity, may be a predictor of abortion or preterm birth, particularly in the second trimester of SLE pregnancies. C3 and C4 levels are typically reduced by 25% in LN. In contrast, their levels may increase by 10%-15% in pregnancy and preeclampsia.

Performing renal biopsy in LN is crucial in determining the treatment, identifying patients who need urgent treatment, evaluating the response to treatment, and predicting the prognosis (10).

The prognosis is better if SLE is in clinical remission for at least 6 months before pregnancy. The live birth rate is approximately 90%. However, the maternal mortality rate of patients with active disease in the last 6 months before the conception is approximately 15%. Approximately 60% of infants born from these mothers have morbidity or mortality. If SLE first appeared during pregnancy, maternal and fetal prognoses are similar to those patients with SLE who have active disease in the last 6 months before the conception. Only heart blocks have been reported as congenital problems in infants of mothers with SLE (11). Even in the case series with best results, some patients with LN develop renal failure that requires dialysis. Dialysis support may be discontinued in 10%-28% of these patients. These are usually patients with rapid renal dysfunction, suggesting acute and potentially reversible disease activation. Only 1%-4% of the chronic dialysis and transplant population are patients with lupus. The clinical and serological activities of lupus usually decrease after reaching end-stage renal failure. The majority of deaths in patients with lupus occurs during the first 3 months of dialysis and is usually caused by an infection. After three months mortality causes are cardiovascular disease and infection. The prognosis of patients surviving during the first 3 months of dialysis is not different from that of patients withoutlupus (12).

Our patient was admitted to the hospital with suddenly elevated blood pressure and swelling of the lower limbs when she was in the 35th week of pregnancy. . Emergency C/S was performed with a diagnosis of preeclampsia. Urinary system ultrasound were reported as normal after the patient's urine output decreased (200 mL in 12 h) and postoperative serum creatinine increased to 1.8 mg/dL. She was transferred to our nephrology clinic with a preliminary diagnosis of oliguric acute renal failure. She was diagnosed with LN after autoimmune serology and renal biopsy results. The patient underwent dialysis for approximately 1 month, and her renal function improved with immunosuppressive and plasmapheresis therapy.

CONCLUSION

SLE may be the underlying cause of preeclampsia during pregnancy with concomitant renal dysfunction. Physicians should be aware of SLE as an unusual cause of preeclampsia during pregnancy.

Informed Consent: Written informed consent was received from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.E.; Design - E.E.; Supervision - İ.K.; Resource - M.Ç.; Materials - M.Ç., H.A.; Data Collection and/or Processing - M.Ç., E.E., H.A.; Analysis and/or Interpretation - E.E., M.Ç.; Literature Search - M.Ç., E.E; Writing - M.Ç., E.E.; Critical Reviews-M.H.S., B.T., O.O.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

REFERENCES

1. Muehrcke RC, Kark RM, Pirani CL, Pollak VE. Lupus nephritis: a clinical and pathological study based on renal biopsies. Medicine (Baltimore) 1957; 36: 1-145. [CrossRef]
2. Murrah FA. Lupus erythematosus in pregnancy. J Obstet Gynaecol Br Emp 1958; 65: 401-8. [CrossRef]
3. Garsenstein M, PollakVE, Kark RM. Systemic lupus erythematosus and pregnancy. New Engl J Med 1962; 267: 165-9. [CrossRef]
4. Estes D, Larson DL. Systemic lupus erithematosus and pregnancy. Clin Obstet Gynecol 1965; 8: 307-21. [CrossRef]
5. Bear RA. Pregnancy in patients with renal disease: A study of 44 cases. Obstet Gynecol 1976; 48: 13-26.
6. Houser MT, Fish AJ, Tagats GE, Williams PP, Michael AF. Pregnancy and systemic lupus erythematosus. Am J Obstet Gynecol 1980; 138: 409-13. [CrossRef]
7. Mikhail MS, Anyaegbunam A, Garfinkel D, Palan PR, Basu J, Romney SL. Preeclampsia and antioxidant nutrients: Decreased plasma levels of reduced ascorbic acid, a-tocopherol, and beta-carotene in women with preeclampsia. Am J Obstet Gynecol 1994; 171: 150-7. [CrossRef]
8. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: An endothelial cell disorder. Am J Obstet Gynecol 1989; 161: 1200-4. [CrossRef]
9. Wang Y, Walsh SW, Guo J, Zhang J. The imbalance between thromboxane and prostacyclin in preeclampsia is associated with an imbalance between lipid peroxides and vitamin E in maternal blood. Am J Obstet Gynecol 1991; 165: 1695-700. [CrossRef]

10. Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008; 67: 195-205. [CrossRef]
11. Mills JA. Systemic lupus erythematosus. N Engl J Med 1994; 26: 1871-9. [CrossRef]
12. Magil AB, Puterman ML, Ballon HS, Chan V, Lirenman DS, Rae A, et al. Prognostic factors in diffuse proliferative lupus glomerulonephritis. Kidney Int 1988; 34: 511-7. [CrossRef]

10.5152/turkjnephrol.2020.3582

Case Report

Turkish Journal of Nephrology

A Rare Complication of Renal Transplantation: Spontaneous Allograft Rupture

Atilla Gemici, Gülşah Kaya Aksoy, Elif Çomak, Mustafa Koyun, Sema Akman

Division of Pediatric Nephrology, Akdeniz University School of Medicine, Antalya, Turkey

Abstract

Spontaneous allograft rupture (SAR) is very rare in the posttransplant period. It is a life-threatening complication that affects the survival of the graft. It is associated with high rates of graft loss. SAR is most commonly associated with immunological processes. Acute rejection is the most common cause of SAR. Here we report the case of a child who had SAR with life-threatening complications and his treatment and follow-up.

Keywords: Children, renal transplantation, spontaneous allograft rupture

Corresponding Author: Atilla Gemici ✉ dratillagemici@hotmail.com

Received: 18.09.2018 **Accepted:** 06.11.2018

Cite this article as: Gemici A, Kaya Aksoy G, Çomak E, Koyun M, Akman S. A Rare Complication of Renal Transplantation: Spontaneous Allograft Rupture. Turk J Nephrol 2020; 29(1): 89-92.

INTRODUCTION

Renal transplantation is the treatment of choice for end-stage renal failure. Spontaneous allograft rupture (SAR) is rare, and it typically occurs within the first few weeks after transplantation. It presents with allograft sensitivity, sudden onset pain, hematoma, shock-causing hypotension, and oliguria. It is a potentially life-threatening complication of renal transplantation. It is associated with high rates of graft loss. Surgically, the graft requires nephrectomy or surgical repair. The first renal graft rupture in Turkey was reported by Haberal et al. (1). According to the literature, its frequency is 0.8%-6% (1). At present, it is a rare complication. However, 53% of cases result in graft loss and 6% in death (2). SAR is most commonly accompanied by immunological reactions. Updated immunosuppressive treatments have led to a reduction in the incidence of SAR. Acute rejection is the most common cause. Advances in immunosuppressive treatments have led to a reduction in the incidence of SAR. Acute tubular necrosis, vascular thrombosis (3), hypertension (4), trauma, and infections are other causes of SAR. In this report, we present the case of a child with SAR, which is rarely observed in all age groups.

CASE PRESENTATION

A 14-year-old boy with neurogenic bladder due to congenital anomalies of the kidney and urinary system was diagnosed with initial chronic kidney disease at the age of 7 months and with end-stage renal disease (ESRD) at the age of 8 years. His parents were cousins. He had been on peritoneal dialysis for 5 years and hemodialysis program for the previous year.

The donor was a 10-year-old boy who was followed up in the intensive care unit owing to a fall from a height. Empirical piperacillin-tazobactam and teicoplanin were started without signs of infection. Although the donor in the intensive care unit received noradrenaline infusion for 2 days, his blood pressure was 47/37 mmHg and he had tachycardia; his serum creatinine level was 1.09 mg/dL.

On 12 December 2006, renal transplantation with a 5 HLA mismatch 1DR compliance and blood type-matched deceased donor with a cold ischemia time of 19 hours was performed. Panel reactive antibody (PRA) Classes 1 and 2, Complement-dependent cytotoxicity

(CDC) crossmatch, and flow-lymphocyte crossmatch were all negative. Donor-specific antibody (DSA) test, a flow cytometry method that detects HLA antibodies against the donor using microparticles coated with recombinant or soluble HLA antigens, was performed. DSA was found to be Class 1 negative and Class 2 positive (MFI: 122) (normal value<2000). Induction therapy was started with 270 mg methylprednisolone according to the protocol before surgery and was continued with 270 mg methylprednisolone and 3 mg/kg/dose antithymocyte globulin (ATG) after transplantation. Enoxaparin sodium was started at 1 mg/kg/dose.

The patient was taken to the pediatric intensive care unit and intubated postoperatively. His blood pressure was 127/84 mm/Hg, and although he received a total of 1000 mL intravenous (IV) fluids during the surgery, he had a urine output of 40 mL. Isotonic saline loading was performed intravenously, and he had a urine output of 20 mL. Based on these findings, acute tubular necrosis (ATN) causing delayed graft function was considered for the patient who did not have sufficient urine output. The fluids he received were adjusted to his urine output and daily needs. Renal Doppler ultrasonography (USG) findings were unremarkable. His urine output was 313, 220, and 210 mL and daily creatinine values were 5.2, 6.82, and 5.25 mg/dL, for the first 3 days of transplantation, respectively. The need for hemodialysis (HD) and ultrafiltration (UF) occurred on the 3rd day. Renal biopsy was planned on the 3rd posttransplant day but could not be performed because the clinical status was not appropriate. In addition to induction therapy, 30 mg/kg/dose with a total of 600 mg pulse methyl prednisolone was added to the treatment considering the development of cellular rejection. There was a need for intermittent UF and hemodialysis between the 4th and 8th day posttransplantation. PRA levels were negative for Class 1-2. His serum creatinine level was 4.4 mg/dL and urine output was 800 mL/day on the 8th day posttransplantation. He mobilized on the 9th day posttransplantation, and suddenly, 300 mL of bloody fluid was drained from his kidney came from his drain. He had experienced no previous abdominal pain and no sensitivity in the transplant kidney in his daily examination. Fluid was given for a possible development of rapid shock due to bleeding, and vital signs were followed up. Urgent renal Doppler USG showed that the left lower-quadrant transplant kidney size was 95 mm, the parenchymal echo increased to Grade 1, intrarenal systolic acceleration increased, renal arterial resistive indexes increased to above 1 (N: 0.7), parenchymal biphasic flow was present, with high-resistance findings (evaluation for rejection). Diffuse free liquid with a depth of 5 cm was noted in the deepest part of the pelvis. The patient was urgently explored. Graft rupture was detected, and primary repair was performed. Figure 1 shows the ruptured graft. On the 2nd day after primary repair, renal artery flow and velocity were measured at 65/15 cm/sec on renal Doppler USG, and its velocity and form were normal. The size of the transplanted kidney was 88 mm, the resistive index was 0.51-0.52, and no lymphocele was observed. There was a decrease in free fluid in the abdomen. During primary repair, a biopsy was taken from the ruptured margin of the transplant kidney. At the end of the biopsy, 65 glomeruli were noted; there were no glomeruli with global sclerosis, segmental sclerosis, and necrosis. There was brush border loss in the tubules, necrotic findings, and fibrinoid necrosis in the arteries; however, since the biopsy was taken from the rupture margin, it was reported that it could not be associated with acute humoral rejection due to the absence of endotheliitis and fibrin thrombi, and although C4D was found to be positive in the peritubular capillaries, immunohistochemical staining was reported to be unreliable due to tissue trauma.

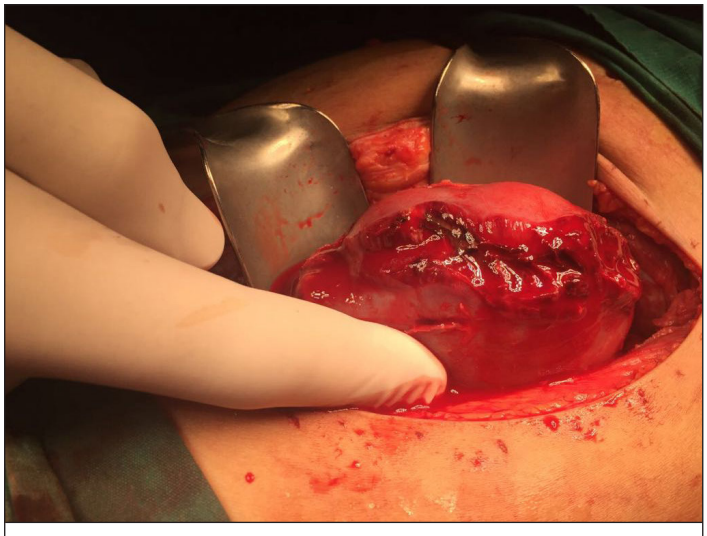


Figure 1. Appearance of a ruptured kidney during exploration (our case who developed SAR at posttransplant Day 9).

The patient's urine output was 863 mL on the 13th day posttransplantation and on the 4th day of primary repair. Immunosuppressive therapy comprising steroids, tacrolimus, and mycophenolate mofetil was administered. During the follow-up, his urine output gradually increased and renal function improved. He subsequently did not need hemodialysis. While his serum creatinine level was 1 mg/dL and cystatin C level was 1.98 mg/L in the first month posttransplantation, at the end of the 18th month, his serum creatinine level was 1.12 mg/dL and cystatin C level was 1.88 mg/L. His condition was stable.

DISCUSSION

Spontaneous allograft rupture is defined as the laceration of the renal capsule and parenchyma in the kidney without any injury before and during transplantation (5, 6). Although SAR typically occurs within the first 3 weeks after transplantation, late ruptures have also been described (7). Previously, SAR was reported to occur after the immunosuppressive treatment change at the 63rd month posttransplantation (8). It was first reported worldwide by Ray et al. (9). The prevalence of SAR varies between 0.3% and 9.6% (9). Among the causes of SAR, acute graft rejection has been reported most commonly, with an incidence of 60%-80% (10). Other etiological factors include ATN,

renal vein thrombosis, hydronephrosis due to ureteral obstruction, lymphocele, local ischemia, septic infarction, and tumors developing in the transplanted kidney (10). The condition may rarely develop after renal biopsy (11). Although its pathogenic mechanism is not fully understood, it is accepted that it results in the infiltration of inflammatory cells, ischemia, and rupture due to an increase in capsular tension in the transplanted kidney with interstitial edema during the immune-mediated rejection. However, high-dose intravenous immunoglobulin (IVIG) is used in the treatment of antibody-mediated rejection. The use of a high-dose IVIG results in platelet activation, which leads to thrombosis via increased plasma viscosity and the contamination of Factor 13. It has been reported in a single case that vascular thrombosis after IVIG treatment causes SAR (3). Spontaneous subcapsular hematomas in the renal allograft cause hypoperfused areas due to pressure on the kidney. Hypoperfusion and renal microvascular ischemia activate the renin–angiotensin–aldosterone (RAA) system. RAA activation causes hypertension, which in turn causes SAR (4). Articles have reported the spontaneous resolution of subcapsular hematoma (12, 13). In these articles, a conservative follow-up was performed in terms of spontaneous resolution by serial USG examinations. In one case, it was reported that subcapsular hematoma maturned into SAR during follow-up; which required surgical intervention (4). Similarly, lymphocele and urinomas developing after transplantation increase the risk of SAR with the same mechanism (14, 15). In particular, obstruction-induced hydronephrosis and lymphocele transplantation both prevent drainage of the kidney and increase ischemia on the kidney surface and cause hypertension, as well as associated subcapsular hematoma and SAR, by activating the RAA system (4). In our case, the graft was rescued via surgical repair. Because of its high morbidity and mortality, SAR requires an experienced pediatric nephrology and transplant team familiar with treatment management.

Ray et al. (9) reported that heparin used in hemodialysis during the posttransplant period is one of the possible factors of SAR. In our case, we demonstrated that the etiologic causes of SAR described above, i.e., lymphocele, hydronephrosis, renal vein thrombosis, and tumors, were absent, which was demonstrated using Doppler and renal USG findings. USG has a sensitivity of 87% and specificity of 100% in the diagnosis (9). In our case, lymphocele, hydronephrosis, and mass-forming cancer findings were also not observed during surgery. Considering the donor's condition in the present case, the patient being hospitalized in the intensive care unit, having a high serum creatinine level, and the kidney being transferred from a hypotensive cadaver despite receiving inotropic agent suggested a delayed graft function after transplantation. During the follow-up, while biopsy was planned, the transplanted kidney developed spontaneous rupture. The sample taken from the rupture area at the time of surgery was suspicious for antibody-mediated rejection, and endotheliitis and fibrin thrombi were not detected in the histopathological examination, although the C4D staining was positive for antibody-mediated rejection markers at biopsy. In the diagnosis of antibody-mediated rejection, DSA was planned as a serological compliance test. However, because the donor blood sample was insufficient, PRA screening was performed. Follow-up PRAs of the patient were Class 1 and 2 negative. The results did not support our diagnosis, although we considered the antibody-mediated rejection in our case.

Renal transplantation is still the best treatment option in patients with ESRD. Our patient had renal transplantation from a marginal donor. We attributed the lack of adequate urine output after renal transplantation and the lack of expected improvement in renal function to delayed graft function. ATN can cause both delayed graft function and SAR.

CONCLUSION

Spontaneous allograft rupture is a clinical entity that requires rapid intervention and can affect life and graft survival. Our patient was a 14-year-old boy who had a renal transplant. Because of the limited literature available on children with SAR, we aimed to present the case here. Delayed graft function is an expected situation in transplantation from marginal donors. However, rejection should be kept in mind as we did to determine the etiology in our case, and performing rapid laboratory investigations including biopsy for diagnosis is an important requirement for graft survival. Graft removal is the safest option. In particular, because of the long waiting lists for transplantation from cadaveric donors and low chance of second transplantation, repair is recommended if the patient can be stabilized and the damage of the graft can be ignored.

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.G., G.K.A., E.Ç.; Design – A.G., M.K., S.A.; Supervision – E.Ç., M.K., S.A.; Resource – A.G., G.K.A., E.Ç.; Materials – G.K.A., E.Ç.; Data Collection and/or Processing – A.G., G.K.A., M.K.; Analysis and/or Interpretation – A.G., E.Ç., S.A.; Literature Search – A.G., G.K.A.; Writing – A.G., G.K.A; Critical Reviews – A.G., G.K.A., M.K., E.Ç., S.A.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Haberal MA, Picache RS, Husberg BS, Bakshandeh K, Starzl TE. Late spontaneous rupture in a homografted kidney: a case report. Arch Surg 1974; 109: 824-6. [CrossRef]
2. van der Vliet JA, Kootstra G, Tegzess AM, Meijer S, Krom RA, Slooff MJ, et al. Management of rupture in allografted kidneys. Neth J Surg 1980; 32: 45-8. [CrossRef]
3. Yong HS, Yong JK, Joon SO, Jın HL, Seong MK, Joong KK. Graft rupture after high-dose intravenous immunoglobulin therapy in a renal transplant patient. Nephrology 2014; 19: Suppl 3: 35-6. [CrossRef]

4. Ay N, Beyazıt Ü, Alp V, Duymuş R, Sevük U, Anıl M, et al. Rupture of a subcapsular hematoma after kidney transplant: Case report. Exp Clin Transplant 2017; 3: 358-60.
5. Richardson AJ, Higgins RM, Jaskowski AJ, Murie JA, Dunnill MS, Ting A, et al. Spontaneous rupture of renal allografts: the importance of renal vein thrombosis in the cyclosporine era. Br J Surg 1991; 77: 558-60. [CrossRef]
6. Shahrokh H, Rasouli H, Zargar MA, Karimi K, Zargar K. Spontaneous kidney allograft rupture. Transplant Proc 2005; 37: 3079-80. [CrossRef]
7. Finley DS, Roberts JP. Frequent salvage of ruptured renal allografts: a large single center experience. Clin Transplant 2003; 17: 126-9. [CrossRef]
8. Askandarani S, Aloudah N, Al Enazi H, Alsaad KO, Altamimi A. Late renal allograft rupture associated with cessation of immunosuppression following graft failure. Case Rep Transplant 2011; 2011: 512893. [CrossRef]
9. Ray DS, Thukral SH. Spontaneous renal allograft rupture caused by acute tubular necrosis: A case report and review of the literature. Case Rep Transplant 2017; 2017: 9158237. [CrossRef]
10. Favi E, Lesari S, Cina A, Citterio F. Spontaneous renal allograft rupture complicated by urinary leakage: case report and review of the literature. BMC Urol 2015; 15: 114. [CrossRef]
11. Almarastani M, Aloudahb N, Hamshow M, Hegab B, Alsaad KO. Salvaging of severely ruptured living-related renal allograft secondary to acute antibody mediated rejection. Int J Surg Case Rep 2014; 5: 723-6. [CrossRef]
12. Salgado OJ, Vidal AM, Semprun P, Garcia R. Conservative management of an extensive renal graft subcapsular hematoma arising during living donor nephrectomy. Role of Doppler sonographic post-transplant follow-up. J Clin Ultrasound 2010; 38: 164-7. [CrossRef]
13. Butt FK, Seawright AH, Kokko KE, Hawxby AM. An unusual presentation of a Page kidney 24 days after transplantation: case report. Transplant Proc 2010; 42: 4291-4. [CrossRef]
14. Chung J, Caumartin Y, Warren J, Luke PP. Acute Page kidney following renal allograft biopsy: a complication requiring early recognition and treatment. Am J Transplant 2008; 8: 1323-8. [CrossRef]
15. Posadas MA, Yang V, Ho B, Omer M, Batlle D. Acute renal failure and severe hypertension from a Page kidney post-transplant biopsy. Sci World J 2010; 10: 1539-42. [CrossRef]

10.5152/turkjnephrol.2020.3603

Case Report

Turkish Journal of Nephrology

A Case of Chickenpox Developing 11 Years after Renal Transplantation

Deniz Akyol[1], Hüsnü Pullukçu[1], Aygül Çeltik[2], Gülşen Mermut[1], Meltem Taşbakan Işıkgöz[1]

[1]Department of Infectious Diseases and Clinical Microbiology, Ege University School of Medicine, İzmir, Turkey
[2]Department of Internal Medicine, Ege University School of Medicine, İzmir, Turkey

Abstract

In solid organ transplant recipients, it is recommended that the necessary vaccinations be completed at least 4 weeks before transplant. Chickenpox infection in adulthood can lead to serious clinical conditions such as pneumonia, hepatitis, and central nervous system infections. Herein, the case of chickenpox in a 36-year-old female patient with renal transplantation for end-stage renal disease due to vesicoureteral reflux 11 years previously and without a history of chickenpox or its vaccination before and after transplantation is reported. In this case, because of the development of thrombocytopenia associated with intravenous acyclovir, treatment was successfully concluded with oral valacyclovir.

Keywords: Chickenpox, renal transplant, vaccination

Corresponding Author: Deniz Akyol ✉ denizakyol416@gmail.com

Received: 02.10.2018 **Accepted:** 19.11.2018

Presented in: This study was presented at the 2nd International Vaccinology Congress, 24–26 May 2018, İzmir, Turkey.

Cite this article as: Akyol D, Pullukçu H, Çeltik A, Mermut G, Taşbakan Işıkgöz M. A Case of Chickenpox Developing 11 Years after Renal Transplantation. Turk J Nephrol 2020; 29(1): 93-5.

INTRODUCTION

Varicella zoster virus (VZV) is a human herpes virus known as human herpes virus-3 (HHV-3). The only known carriers of HHV-3 are humans, and it causes two clinical scenarios. Chickenpox is a primary disease that usually occurs in childhood and is characterized by vesicular eruptions on the erythematous base, starting with red papules. Herpes zoster is a recurrent viral infection, which remains latent in the dorsal root ganglia after primary infection, and it is common in advanced age (1). Although chickenpox usually occurs in children aged <15 years, it may cause severe clinical manifestations in adulthood, such as pneumonia, hepatitis, and central nerve system infections. Nowadays, in addition to routine childhood vaccination recommendations, it is suggested that all individuals who are not immune to chickenpox in adulthood should be vaccinated with two doses at 1-month intervals. In vaccination recommendations for special adult groups, primary immunization in solid organ recipients is suggested at least 4 weeks prior to transplantation. However, if vaccination cannot be performed before transplantation, it should be performed during the follow-up of post-transplant cases (2). Herein, a case of acquired chickenpox in an immunocompromised host who had undergone renal transplantation for end-stage renal disease due to vesicoureteral reflux 11 years before and who had no history of chickenpox or its vaccination before and after transplantation is presented.

CASE PRESENTATION

A 36-year-old female patient underwent live renal transplantation due to vesicoureteral reflux-induced end-stage renal disease in 2007 and received immunosuppressive therapy with tacrolimus 1 mg (2×1)/day, prednisolone 5 mg (1×1)/day, and azathioprine 50 mg (2×1)/day. She presented no history of rejection in the post-transplant follow-up. She worked as a primary school teacher. Eleven years after renal transplantation, the patient presented to the external center about

1 week before her admission to our clinic primarily because of itchy, vesicular-exanthematous rash and oral rash spreading throughout the body starting from the scalp. Two doses of cefazolin followed by ampicillin were administered with a preliminary diagnosis of urinary tract infection. However, her complaints did not improve, and she presented to our clinic due to chills and shivering and was followed up with a preliminary diagnosis of chickenpox. She presented no history of chickenpox or vaccination for it before and after renal transplantation. She reported that a child in her primary school has developed chickenpox a few weeks before the onset of her complaints. On routine hemogram, leukocyte count was 3.76×10^3/mL, neutrophil count was 40%, lymphocyte count was 48.2%, hemoglobin level was 10.2 g/dL, and platelet count was 170×10^3/mL; results of liver function tests were normal. Creatinine level was 0.99 mg/dL; eGFR was >60 mL/min/1.73 m^2; proteinuria was <150 mg/day; and C-reactive protein level was 2 mg/dL (N<0.5 mg/dL). Intravenous acyclovir 3×10 mg/kg was initiated, but chickenpox zoster immunoglobulin (VZIG) was not administered. Topical treatment was rearranged by a dermatology physician, and immunosuppressive treatment was rearranged by nephrology. Azathioprine treatment was discontinued and replaced with tacrolimus, and prednisolone was recommended. No growth was observed in three sets of blood cultures examined during the febrile (inflammatory) period. Varicella zoster Immunoglobulin M (IgM) was positive in the blood. Pneumonic infiltration was not detected on the chest radiography. After 4 days of acyclovir treatment, the platelet count became 20×10^3/mL. Since there was no evidence of active bleeding, platelet replacement was not performed. There was no decrease in leukocyte count and hemoglobin level.

DISCUSSION

It is essential to prevent the development of infections due to their rapid and severe progression following renal transplantation, high morbidity and mortality rates, and the fact that some infections (e.g., influenza) may trigger graft rejection (3). Pre-transplant serological screening and completion of all necessary vaccinations in the early post-transplant period are the primary recommended methods for preventing possible infections (4).

Intensive immunosuppressive treatments administered after transplantation increase the risk of infection in the post-transplant period and decrease the expected antibody response of the body to vaccination (2). When infections develop, as noted in our case, immunosuppressive therapy should be reviewed and its dose should be reduced during active infection (5). However, dose reduction during immunosuppressive therapy also increases the risk of graft rejection (6). Because our patient had undergone transplantation 11 years before and presented no history of rejection, the risk of graft rejection as a result of dose reduction of immunosuppressive therapy was low. Arrangement of immunosuppressive treatment during active infection should be evaluated according to the patient's clinical condition and the drugs administered (7, 8).

Solid organ transplant recipients are anticipated to benefit from vaccination; thus, vaccination should be performed in such patients. It is important that primary vaccination be performed early before transplantation. However, when vaccination is not performed before transplantation, immune response is insufficient within the first 6 months following transplantation. It is recommended that the vaccination scheme be completed after the 6th month and that the development of antibody response be followed. However, vaccination with live vaccines after solid organ transplantation remains a controversial issue (2). Chickenpox vaccination is recommended in all susceptible individuals in the adult population. However, it is recommended primarily for groups at a high risk of contamination or contact (teachers of small children, caregivers, medical staff, and family members of immunocompromised individuals, among others). Our case, who is a primary school teacher, likely contracted the virus via droplet infection from a student with chickenpox 11 years after transplantation. Our patient was not vaccinated before transplantation; no serological screening was performed; and no routine vaccination was recommended during the routine follow-up.

Bacterial infections are frequent following renal transplantation and are often followed by viral infections (9). VZV infections usually occur in the first 5 years following renal transplantation (10). However, since it is the most intense period of immunosuppression, between the 1st and 6th months after transplantation, majority of the patients develop cytomegalovirus, Epstein–Barr virus, VZV, and human herpes virus-6 infections (11). In patients with solid organ transplantation, primary VZV is less common than VZV reactivation (12). However, as seen in our case, it may occur in the very late post-transplant period and as a primary infection. In a study by Duchini et al. (3), 1139 patients who underwent renal transplantation were followed up for 38 years in terms of the development of VZV infection after transplantation and the average time to infection development after transplant was found to be 2.13 years (min, 9 days; max, 19 years). This indicates the importance of vaccination given the risk of severe life-threatening primary VZV infection that may develop in special patient groups, such as solid organ transplant receivers, as well as of early diagnosis and initiation of antiviral treatment as soon as possible when infections develops (14, 15).

For patients undergoing renal transplantation who develop primary VZV infection, intravenous acyclovir or oral valaciclovir is recommended until the lesions are completely crusted (16). In our case, due to the development of thrombocytopenia on the 4th day of intravenous acyclovir treatment introduced upon the recommendation, the treatment was switched to oral valaciclovir. Thrombocytopenia may also develop in the natural course of infection (17). However, no additional pathology in peripheral smear and improvement of platelet count after drug switching indicated the association with acyclovir. One should also be cautious of unforeseen side effects of drugs during treatment.

The latest recommendations of the Centers for Disease Control and Prevention in 2013, VZIG may be indicate up to 10 days after contact with people that have a proven diagnosis of chickenpox (18). Prophylaxis should be administered to individuals who have previously been shown to not be immune VZV and who are at an increased risk of possible complications of infection compared with the general population (immunocompromised individuals sensitive to chickenpox or pregnant women, among others). In our case, VZIG could not be administered because 10 days had elapsed since the contact and active infection was already present.

CONCLUSION

Since immunosuppressive therapy administered to renal transplantation patients may decrease their antibody response, chickenpox vaccination prior to transplantation is recommended. However, when vaccination is not performed, continued follow-up after transplantation and cooperation between the nephrology and infectious diseases units are important for preventing the clinical scenario in which the acquired infections in adulthood progress and result in high morbidity and mortality.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.T.; Design - H.P.; Supervision - M.T.; Resource - A.Ç., G.M.; Materials - A.Ç.; Data Collection and/or Processing - D.A.; Analysis and/or Interpretation - D.A.; Literature Search - D.A.; Writing - D.A.; Critical Reviews - H.P

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

REFERENCES

1. Azap A, Kurt H. Varisella Zoster Virüs İnfeksiyonları. Ankara Üniversitesi Tıp Fakültesi Mecmuası. 2001; 54: 357-70. [CrossRef]
2. Türkiye Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Uzmanlık Derneği. Erişkin Bağışıklama Rehberi 2.Güncelleme. Mayıs 2016.
3. Duchini A, Goss John A, Karpen S, Pockros Paul J. Vaccinations for Adult Solid-Organ Transplant Recipients: Current Recommendations and Protocols. Clin Microbiol Rev 2003; 16: 357-64. [CrossRef]
4. Danziger-Isakov L. Vaccination in Solid Organ Transplantation. Am J Transplant 2013; 13: 311-7. [CrossRef]
5. Mustapic Z, Basic-Jukic N, Kes P, Lovcic V, Bubic-Filipi Lj, Mokos I, et al. Varicella Zoster Infection in Renal Transplant Recipients: Prevalence, Complications and Outcome. Kidney Blood Press Res 2011; 34: 382-6. [CrossRef]
6. Kotton C.N, Fishman J.A. Viral Infection in the Renal Transplant Recipient. J Am Soc Nephrol 2005; 16: 1758-74. [CrossRef]
7. Rubin RH. Infectious Disease Complications of Renal Transplantation. Kidney Int 1993; 44: 221-36. [CrossRef]
8. Bradley JR, Wreghitt TG, Evans DB. Chickenpox in Adult Renal Transplant Recipients. Nephrol Dial Transplant 1987; 1: 245-5.
9. Özdemir D, Şencan İ, Karabay O, Kurt H. Solid Organ Transplant Alıcılarında Görülen İnfeksiyonlar ve Korunma. Flora 2006; 11: 70-82.
10. Netchiporouk E, Tchervenkov J, Paraskevas S, Sasseville D, Billick R. Evaluation of Varicella Zoster Virus Infection Morbidity and Mortality in Pancreas and Kidney-Pancreas Transplant Recipients. Transplant Proc 2013; 45: 701-4. [CrossRef]
11. Oğuz Y, Bulucu F, Çağlar K, Yenicesu M, Doğancı L, Vural A. Böbrek Nakli Sonrası İnfeksiyon Gelişimi. Hastane İnfeksiyonları Dergisi 2000; 4: 39-46.
12. Miller GG, Dummer JS: Herpes Simplex and Varicella Zoster Viruses: Forgotten but not Gone. Am J Transplant 2007; 7: 741-7. [CrossRef]
13. Rommelaere M, Maréchal C, Yombi JC, Goffin E, Kanaan N. Disseminated Varicella Zoster Virus Infection in Adult Renal Transplant Recipients: Outcome and Risk Factors. Transplant Proc 2012; 44: 2814-7. [CrossRef]
14. Guidelines for the Prevention and Management of Infectious Complications of Solid Organ Transplantation: HHV-6, HHV-7, HHV-8, HSV-1 and -2, VZV. Am J Transplant 2004; 4: 66-71.
15. Rodriguez-Moreno A, Sanchez-Fructuoso AI, Calvo N, Ridao N, Conesa J, Marques M, et al. Varicella Infection in Adult Renal Allograft Recipients: Experience at One Center. Transplant Proc 2006; 38: 2416-8. [CrossRef]
16. KDIGO. Clinical Practice Guideline fort the Care of Kidney Transplant Recipients. Am J Transplant 2009; 9: S44-58. [CrossRef]
17. Rand ML, Wright JF. Virus-associated Idiopathic Thrombocytopenic purpura. Transfus Sci 1998; 19: 253-9. [CrossRef]
18. Centers for Disease Control and Prevention (CDC). Updated Recommendations for Use of VariZIG--United States, 2013. MMWR Morb Mortal Wkly Rep 2013; 62: 574-6.

10.5152/turkjnephrol.2020.3658

Case Report

Turkish Journal of Nephrology

Iliac Bone Perforation in a Patient on Hemodialysis

Mustafa Sevinç[1]*, Elif Şahutoğlu[2], Tamer Sakacı[1], Tuncay Şahutoğlu[3]*

[1]Division of Nephrology, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey
[2]Department of Chest Diseases, Şanlıurfa Training and Research Hospital, Şanlıurfa, Turkey
[3]Division of Nephrology, SBÜ-Mehmet Akif İnan Training and Research Hospital, Şanlıurfa, Turkey
*Mustafa Sevinç and Tuncay Şahutoğlu are the co-primary authors of this report.

Abstract

We report severe bone resorption with iliac bone perforation and vascular calcification due to longstanding hyperparathyroidism in a 60-year-old male patient who had undergone hemodialysis for 16 years. Computed tomography images were obtained following a complicated hemodialysis catheterization of the femoral vein, and unprecedented bone findings were observed. Improper management of chronic kidney disease–mineral bone disorder can lead to severe consequences, as observed in the present patient.

Keywords: CKD-MBD, bone perforation, vascular calcification, chronic hemodialysis, computed tomography

Corresponding Author: Tuncay Şahutoğlu ✉ tu_cay83@yahoo.com

Received: 03.11.2018 **Accepted:** 08.12.2018

Presented in: This study was presented at the 11th International Society for Hemodialysis International Congress, 2-5 August 2017, Bangkok, Thailand.

Cite this article as: Sevinç M, Şahutoğlu E, Sakacı T, Şahutoğlu T. Iliac Bone Perforation in a Patient on Hemodialysis. Turk J Nephrol 2020; 29(1): 96-8.

INTRODUCTION

Chronic kidney disease–mineral bone disorder (CKD-MBD) is a complex syndrome that has both skeletal and extraskeletal manifestations. The gold standard for the diagnosis of renal osteodystrophy is bone biopsy, which reveals categorically high bone turnover (osteitis fibrosa cystica), low bone turnover (adynamic bone disease), abnormal mineralization (osteomalacia), or a mixture of these diseases (mixed uremic osteodystrophy) (1). However, the issue is not limited to bone disorders, and because the disease is invasive and patient follow-up using bone biopsy is expensive, detecting alterations in biochemical parameters (such as changes in serum phosphorus, calcium, parathyroid hormone, vitamin D, and fibroblast growth factor 23 levels) has become the cornerstone of the current management and diagnosis, although this has led to some compromises in the correct diagnosis and treatment (2). The risk of morbidity and mortality that is associated with CKD-MBD is conceivable; however, it may be difficult for an inexperienced eye to identify this risk (3). We herein report the case of a patient with exceptionally dramatic skeletal and vascular findings due to CKD-MBD.

CASE PRESENTATION

A 60-year-old man who had been undergoing a maintenance hemodialysis program for 16 years was admitted to the hospital for left arteriovenous fistula failure. The patient had a history of multiple arteriovenous fistulae, hemodialysis catheterizations, and a longstanding tertiary hyperparathyroidism (for which he refused any attempt for parathyroidectomy or calcimimetic therapy). A tunneled hemodialysis catheter was inserted via his left femoral vein without any apparent complication. However, painful distention developed on the left inguinal area 1 day later, and intravenous contrast-enhanced computed tomography (CT) revealed bleeding from the left common iliac vein. A three-dimensional reconstruction of the CT images showed widespread severe bone resorption, which was most prominent within the pelvic bones

and trabecular areas of the long bones; severe calcifications of the arteries; and perforation of both the iliac wings (Figure 1). The patient's predialysis laboratory test results were as follows: leukocytes, 4.640/µL; hemoglobin, 12.1 g/dL; platelets, 171.000/µL; urea, 67 mg/dL; creatinine, 5.1 mg/dL; Na, 135 mEq/L; K, 3.9 mEq/L; Ca, 9.6 mg/dL; P, 6.4 mg/dL; albumin, 4.2 g/dL; ALP, 620 U/L; and intact parathyroid hormone (iPTH), 4707 pg/mL.

DISCUSSION

The clinical presentation of CKD-MBD mainly depends on the prevailing metabolic abnormalities, and it is characterized by laboratory abnormalities, bone abnormalities, and vascular calcification (4). Cardiovascular disease, bone fractures, and mortality are the hard endpoints in the course of CKD-MBD, and unless they occur, explaining the complexity of this disease to a patient can be difficult. The findings of excessive bone resorption and vascular calcification observed in this patient may be exceptional in terms of demonstrating the consequences of this disease. One of our concerns is that some patients lose compliance to treatment over time, often mentioning that "we have been taking all the medications for years (or months), without any noticeable benefit." Although the term "risk" is an abstract concept, the images obtained are concrete findings; therefore, we speculated whether it would be more effective to discuss CKD-MBD with the patient (for example, the present case) using such illustrations. To date, CKD-MBD does not appear curable; therefore, the prevention of the harmful consequences is pivotal, and treatment goals for serum phosphate (3.5-5.5 mg/dL), calcium (<9.5 mg/dL), and parathyroid hormone (2-9 times the upper limit of normal) levels have been established for patients on dialysis (2, 5). The current armamentarium to achieve these goals is far from being ideal because of gastrointestinal intolerance, polypharmacy, adverse effects, insufficient potency, and patient reluctance to indefinitely ingest the medicines.

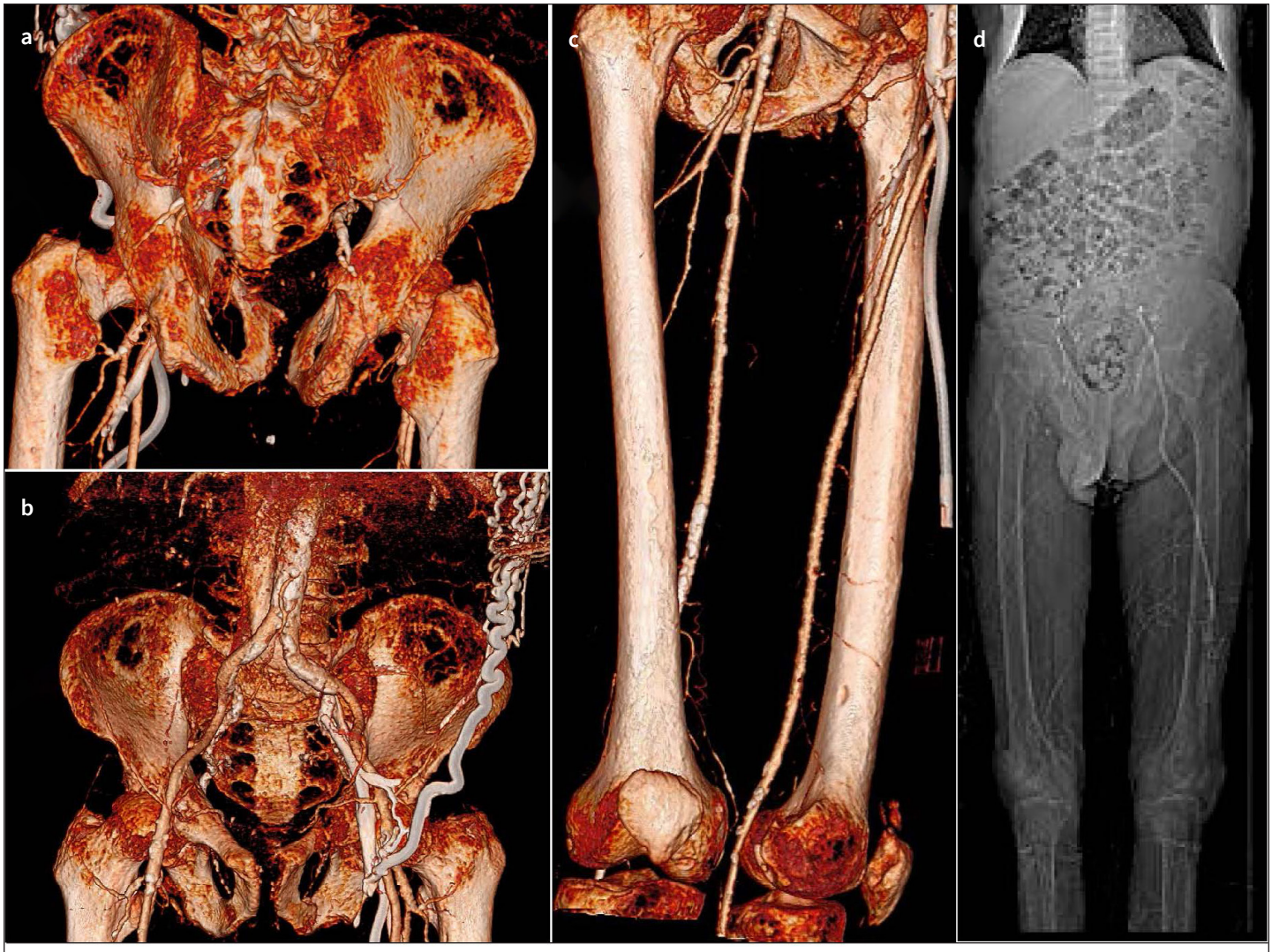


Figure 1. a-d. a) and b) Posterior and anterior views of the 3D reconstruction of computed tomography of the pelvic region shows severe bone resorption throughout the pelvic bones, vertebral processes, and femoral trochanters and necks; widening of the sacral foramina; perforation of the alae iliums; and excessive calcification of the abdominal aorta and its branches. c) 3D reconstruction of the leg area reveals severe bone resorption at the femoral and tibial condyles with an appearance similar to perforations and excessive calcification of the femoral arteries and their branches. d) An X-ray of the body shows diffuse low bone density and left femoral hemodialysis catheter.

Some patients may develop extremely high serum parathyroid hormone levels that are not suppressible with phosphate binders, vitamin D analogs, and calcimimetic agents; this condition is defined as refractory hyperparathyroidism. Hypercalcemia, refractory hyperphosphatemia, bone pain, pruritus, myopathy, and uremic calcific arteriolopathy may accompany refractory hyperparathyroidism. Parathyroidectomy is an effective treatment for refractory hyperparathyroidism, and currently, it is suggested for patients with symptomatic severe refractory hyperparathyroidism (iPTH>800 pg/mL) (5). Although randomized controlled trials to assess the outcomes of parathyroidectomy are lacking, several observational studies have shown improved survival, reduced bone fracture risk, and increased bone mineral density after parathyroidectomy (6-10). Nonetheless, immediate postoperative mortality and morbidity (2% mortality rate and 23.9% re-hospitalization rate within postoperative 30 days among 4435 Medicare patients following parathyroidectomy) are the trade-off of surgery; therefore, a thorough assessment and follow-up are the critical adjuncts to parathyroidectomy (11).

CONCLUSION

Patient refusal of treatment is an inconvenient truth of medical practice; therefore, in addition to the wealth and shortcomings of the current knowledge (12), we may have to consider strategies to share the results of sophisticated studies with the patients.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed

Author Contributions: Concept – T.Ş., M.S.; Design - T.Ş.; Supervision – T.S.; Resource - None; Data Collection and/or Processing – E.S., T.Ş.; Analysis and/or Interpretation - T.Ş.; Literature Search - T.Ş.; Writing – T.Ş.; Critical Review - T.Ş.

Acknowledgements: We would like to thank our principal hemodialysis nurse Ayse Tülü for her help in the management of the patient.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declare that they have received no financial support for this study.

REFERENCES

1. Moorthi RN, Moe SM. CKD-mineral and bone disorder: core curriculum 2011. Am J Kidney Dis 2011; 58: 1022-36. [CrossRef]
2. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. Kidney Int 2017; 92: 26-36. [CrossRef]
3. Floege J, Kim J, Ireland E, Chazot C, Drueke T, de Francisco A, et al. Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. Nephrol Dial Transplant 2011; 26: 1948-55. [CrossRef]
4. Bover J, Cozzolino M. Mineral and bone disorders in chronic kidney disease and end-stage renal disease patients: new insights into vitamin D receptor activation. Kidney Int Suppl 2011; 1: 122-9. [CrossRef]
5. Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003; 42: 1-201. [CrossRef]
6. Sharma J, Raggi P, Kutner N, Bailey J, Zhang R, Huang Y, et al. Improved long-term survival of dialysis patients after near-total parathyroidectomy. J Am Coll Surg 2012; 214: 400-7; discussion 407-8. [CrossRef]
7. Kestenbaum B, Andress DL, Schwartz SM, Gillen DL, Seliger SL, Jadav PR, et al. Survival following parathyroidectomy among United States dialysis patients. Kidney Int 2004; 66: 2010-6. [CrossRef]
8. Komaba H, Taniguchi M, Wada A, Iseki K, Tsubakihara Y, Fukagawa M. Parathyroidectomy and survival among Japanese hemodialysis patients with secondary hyperparathyroidism. Kidney Int 2015; 88: 350-9. [CrossRef]
9. Rudser KD, de Boer IH, Dooley A, Young B, Kestenbaum B. Fracture risk after parathyroidectomy among chronic hemodialysis patients. J Am Soc Nephrol 2007; 18: 2401-7. [CrossRef]
10. Abdelhadi M, Nordenström J. Bone mineral recovery after parathyroidectomy in patients with primary and renal hyperparathyroidism. J Clin Endocrinol Metab 1998; 83: 3845-51. [CrossRef]
11. Ishani A, Liu J, Wetmore JB, Lowe KA, Do T, Bradbury BD, et al. Clinical outcomes after parathyroidectomy in a nationwide cohort of patients on hemodialysis. Clin J Am Soc Nephrol 2015; 10: 90-7. [CrossRef]
12. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder: Synopsis of the Kidney Disease: Improving Global Outcomes 2017 Clinical Practice Guideline Update. Ann Intern Med 2018; 168: 422-30. [CrossRef]