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From Editors

Welcome to the April 2024 Issue of The Journal of European Internal Medicine Professionals (JEIMP);

We are pleased to present the latest issue of JEIMP, offering a diverse and comprehensive collection of articles that contribute significantly to the fields of medicine and pharmacology. Our April issue showcases a range of original research, reviews, case reports, and letters to the editor, reflecting the journal's commitment to advancing medical knowledge and clinical practice.

Our issue begins with a comparative study on the gastrointestinal side effects of selective COX-2 inhibitor celecoxib and indomethacin in patients with osteoarthritis. This investigation provides valuable insights into the safety profiles of these commonly used medications, aiming to guide clinicians in optimizing treatment strategies for osteoarthritis patients while minimizing adverse effects.

Next, we present a single-center experience from Türkiye on the outcomes of deceased donor kidney transplantation. This study highlights critical factors influencing transplant success and patient outcomes, contributing to the growing body of knowledge essential for improving transplantation practices and patient care in the field of nephrology.

Following this, we explore the evaluation of ocular parameters in patients undergoing hemodialysis treatment. This research emphasizes the importance of regular ocular assessments in hemodialysis patients, identifying potential risks and proposing measures to mitigate ocular complications associated with chronic kidney disease and its treatment.

In our review section, we delve into the genetic and epigenetic features of Familial Mediterranean Fever (FMF), presenting the latest advancements and discoveries in this area. This comprehensive review provides a detailed overview of the current understanding of FMF pathogenesis, offering new perspectives for future research and potential therapeutic approaches.

We include a compelling case report on the coexistence of Autosomal Dominant Polycystic Kidney Disease and Hereditary Distal Renal Tubular Acidosis in a child. This rare case, accompanied by a literature review, underscores the importance of recognizing and managing complex and uncommon renal conditions, contributing to the broader medical literature on pediatric nephrology.

Our issue also features a thought-provoking letter to the editor comparing FDG and Ga-68 PSMA PET/CT findings in a case of metastatic hepatocellular carcinoma. This correspondence provides critical insights and fosters discussion on the diagnostic imaging techniques used in oncology, particularly in the context of advanced liver cancer.

Finally, we are excited to include a special feature on cancer treatment with immune checkpoint inhibitors in kidney recipients. This emerging area of research is particularly relevant given the increasing use of immune checkpoint inhibitors in oncology and the unique challenges faced by kidney transplant recipients. This feature aims to inform and guide clinicians on the complexities and considerations involved in managing cancer in this special population.

We hope that you find this issue of JEIMP both informative and inspiring. Our editorial team remains dedicated to bringing you high-quality research and insightful discussions that advance the frontiers of medicine and pharmacology. We encourage you to engage with the content, share your thoughts, and contribute to the ongoing dialogue in our field.

Thank you for your continued support and readership.

Warm regards,

Tuncay Şahutoğlu, Alper Azak
Issue Editors/Editorial Board Members
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The Science

Original Article

Comparison of the Gastrointestinal Side Effects of Selective COX-2 Inhibitor Celecoxib and Indomethacin in Patients With Osteoarthritis

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Abstract

Background: Nonsteroidal anti-inflammatory drugs are commonly prescribed for osteoarthritis management but are associated with gastrointestinal (GI) adverse events. This study aimed to compare GI findings in patients receiving indomethacin and celecoxib for osteoarthritis.

Methods: A retrospective analysis was conducted on 50 patients (42 females, 8 males) with osteoarthritis, divided into indomethacin (n=25) and celecoxib (n=25) groups. Clinical data, including age, gender, disease duration, and *H. pylori* status, were collected. Baseline and post-treatment gastroduodenoscopy findings were compared between groups.

Results: No cases of GI bleeding were reported. Indomethacin use was associated with a higher risk of gastroduodenal lesions compared to celecoxib ($p<0.05$). Celecoxib combined with proton pump inhibitors (PPIs) showed a slight improvement in gastric lesions. *H. pylori* prevalence was 86% in the study population.

Conclusion: Despite the absence of GI adverse events, indomethacin use posed a higher risk of gastroduodenal lesions compared to celecoxib. The addition of PPIs appeared to mitigate GI adverse events, particularly in the celecoxib group. Individualized treatment approaches balancing therapeutic benefits and potential adverse effects are essential in osteoarthritis management. Further research with larger sample sizes and longer follow-up durations is warranted to validate these findings.

Keywords: Nonsteroidal anti-inflammatory drugs, gastroduodenal lesions, celecoxib, indomethacin, proton pump inhibitors

INTRODUCTION

Osteoarthritis (OA) is the most common manifestation of arthritis and leading contributor to persistent pain and disability among the elderly (1-3). Obesity and ageing population are the two main factors associated with increasing prevalence of OA (3). World Health Organization reports more than 528 million people worldwide are living with OA; an increase of more tha 100% since 1990 (4). The knee is the most frequently affected joint, followed by the hip and the hand (4).

The treatment of OA includes surgical and non-surgical interventions. It is suggested that pharmacologic treatment should begin with acetaminophen and switch to nonsteroidal anti-inflammatory drugs (NSAIDs) if not responder to acetaminophen in patients with pain (5,6). Exercise is useful to reduce pain and disability, in adjunct to pharmacotherapy (6). Supplements such as glucosamine, chondroitin, collagen hydrolysate, passion fruit peel extract, Curcuma longa extract, Boswellia serrata extract, curcumin, pycnogenol and L-carnitine provided moderate and clinically meaningful treatment effects on pain and function in patients with hand, hip or knee osteoarthritis at short term, although the quality of evidence was very low (7). Corticosteroid injections provide immediate, short-term (four to eight weeks) relief of OA flare-ups of the knee, whereas hyaluronic acid injections provide symptom improvement for longer periods but have a higher cost. Total joint replacement of the hip, knee, or shoulder is recommended for suitable patients with persistent pain and disability despite

maximal medical therapy.

In the realm of OA treatment, NSAIDs have traditionally held a central position. However, recent studies have controversies on the widespread utilization of oral NSAIDs, emphasizing the higher prevalence of upper gastrointestinal (GI) complications and cardiovascular adverse events (CAEs) (8,9). A recent meta-analysis reported that celecoxib was the only NSAID associated with long-term pain improvement, better long-term GI tolerability than nonselective NSAIDs and is not associated with higher risk of CAEs (10). Chan et al. demonstrated 44.0% lower GI bleeding risk with celecoxib compared to naproxen (11).

Although previous studies reported lower GI adverse events with celecoxib, the most used selective cyclooxygenase-2 inhibitor, celecoxib carries an additional FDA-boxed warning for GI effects, including bleeding, ulceration, and perforation of the stomach and intestines (12).

In this study, we aim to re-discuss "an old story" with updated literature by comparing the GI effects of celecoxib and indomethacin in patients with OA.

METHODS

This prospective study was conducted between 2001-2002 at the Istanbul Prof. Dr. Cemil Taşçıoğlu City Hospital, Departments of Rheumatology, Internal Medicine, and Orthopedics Clinics, where patients presented with knee osteoarthritis. This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for Human researches.

Inclusion: Patients had complaints for at least 6 months, receiving NSAIDs therapy, meeting the American College of Rheumatology clinical criteria for primary knee OA, including functional classes I, II, and III, and were suitable for inclusion if they were aged 50 or older. Patients meeting these criteria were informed about the study and their consent was obtained.

Exclusion: Patients with active duodenal, gastric, or esophageal ulcers, pyloric obstruction, or erosive esophagitis at baseline endoscopy were excluded from the study. Patients who had undergone upper gastrointestinal surgery, had inflammatory bowel disease, serum creatinine levels >2.0 mg/dL, calculated creatinine clearance <30 ml/min, positive occult blood in stool, congestive heart failure, chronic liver disease, a history of malignancy in the last 5 years, cerebral vascular events in the last 2 years, bleeding diathesis, or required anticoagulant therapy, corticosteroids, ticlopidine, or aspirin were also excluded.

Measurements: Detailed medical histories of patients were obtained at baseline, along with physical examinations, complete blood count, erythrocyte sedimentation rate, c-reactive protein (CRP), rheumatoid factor (RF), blood biochemistry, and occult blood in stool were studied before interventions (15 days and monthly for three months). Following baseline assessments, patients underwent physical examination, The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Likert index, and Visual Analog Scale (VAS) were performed. Participants were divided into two groups after a two-week drug "wash-out" period. A group received per os 3x25 mg/day indomethacin, and other group received per os 2x100 mg/day celecoxib. Participants were addressed to the groups according an age and gender matching method manually.

Gastroduedonoscopy: Gastroduedonoscopy was performed at baseline and at the end of treatment. Gastroduedonoscopy was not performed at the end of treatment for patients who discontinued the study due to side effects or inefficacy. The findings included gastric and duodenal ulcers, erosive gastritis, etc. Multiple biopsies were obtained. Pathology and the culture studies were performed. *H. Pylori* presence were noted. Patients with *H. Pylori* positivity were received a 2-3 weeks of treatment for eradication. All individuals received a standard proton pump inhibitor (PPI) regimen during the study.

STATISTICAL ANALYSIS

The data obtained were analyzed using the SPSS version 15 for Windows program. Numerical variables were expressed as mean and ± standard deviation. Independent Samples T-test was used to compare the parametric variables of the two groups. Kolmogorov-Smirnov test was used to determine the distribution types of the variables. Chi-square and Wilcoxon tests were used for comparisons of categorical parameters. $p<0.05$ was considered statistically significant.

RESULTS

Fifty patients were included in the study cohort, comprising 42 females (84%) and 8 males (16%). Twenty females (80%) and 5 males (20%) were assigned to the indomethacin group, while 22 females (88%) and 3 males (12%) were assigned to the celecoxib group. Statistical analysis revealed no significant difference in gender distribution between the two treatment groups ($p=0.782$). The clinical and demogrophical features of the participants were presented in **Table 1**. The mean duration of osteoarthritis was 4.52±2.29 years (range: 1-10) in the indomethacin group and 5.04±1.67 years (range: 2-9) in the celecoxib group, two groups exhibited a similar duration of illness ($p=0.625$).

Repeated gastroduedonoscopy was performed 3 months later in 19 cases of the indomethacin. In 13 (68.4%) cases, no change was observed in the findings of gastroduedonoscopy, while worsening was observed in

Table 1. The clinical and laboratory of th participants and the comparison of thw two groups

	Indomethacin, n=25	Celecoxib, n=25	P value
Age, years	52.92±4.68	55.48±4.82	0.055
Male, female, n	5/20	3/22	0.782
Disease duration, years	4.52±2.29	5.04±1.67	0.625
H. Pylori positivity, n	23	20	0.522
Cases stopped to receive medicine, n **Causes of stopping medicine, n**	6 Ineffective (2)* Refused to continue (3 cases refused the next gastroduedonoscopy) Adverse reactions (1 case of edema)	6 Ineffective (2)* Refused to continue (2 cases refused the next gastroduedonoscopy) Adverse reactions (1 case of allergy and 1 case of coronary bypass operation)	1.000

*Evaluations based on the VAS index, Likert index, and WOMAC scale were taken into account to determine medication ineffectiveness.

6 (30%). Number of cases with gastroduodenal erosion increased folowing indomethacin treatment (p=0.014).

In the celecoxib group, 19 out of 25 patients (76%) completed the treatment and underwent repeated gastroduedonoscopy. There was no change in 17 patients (84%), while finding got worsened in 2 individuals (16%). Pretreatment and posttreatment GI findings did not exhibit a significant change (p=0.157) in the celecoxib group (Table 2). The prevalence of *H. Pylori* was 86% (43 of 50 patients).

Following indomethacin treatment 3 of 4 patients with normal gastroduedonoscopy findings developed pangastritis, while in the celecoxib group 3 patient with pangastritis recoverd to normal gastrocopy findings (Table 3). However, in the celecoxib group one patient developed duodenal ulcer. Beside, celecoxib group had less tendency to develop duodeneal erosive lesions (1 case vs 4 cases and p=0.005).

DISCUSSION

This study demonstrates a comparison of gastrointestinal findings in indomethacin and celecoxib users. Despite there being no cases of GI bleeding with selective and nonselective NSAIDs in this study, indomethacin exhibited a significant risk increase for gastroduodenal lesion development compared to celecoxib use. Further, in the celecoxib users, a slight improvement in gastric lesions was observed under the PPI use.

Pain is the main symptom and indication in the treatment of OA. Guidelines recommend the use of NSAIDs, a group of medicines that inhibit the production of prostaglandins and thromboxane A by blocking cyclooxygenase (COX) (6,13,14). Traditional NSAIDs target the COX-1 and COX-2 isozymes to varying degrees and play a significant role in the symptomatic treatment of pain in musculoskeletal disorders (15,16). However, their prolonged use raises concerns regarding toxicity, especially cardiovascular, gastrointestinal, and renal issues. Furthermore, previous studies have indicated a lower risk of gastrointestinal bleeding or intolerance with selective COX-2 inhibitors, at least in the short term (6-12 months) (16-18). In this study, there was no cases of GI bleeding or dyspepsia, which the leading causes of premature discontinuation of the drug (19). This outcome is likely linked to the use of PPIs alongside NSAIDs, as suggested by Bakriansyah et al. Their study demonstrated that selective COX-2 inhibitors with PPIs, as well as selective COX-2 inhibitors and conventional NSAIDs with PPIs, were associated with a reduced risk of gastrointestinal adverse events compared

Table 2. Pre and posttreatment gastroduedonoscopy findings

	Indomethacin, n=19	Celecoxib, n=19	P value
Baseline; n •Pangastrit, •Nonerosive duodenitis •Antral erosvive lesions	 25 (6 were excluded) 5 0	 25 (6 were excluded) 1 0	1.00
Posttreatment; n •Pangastrit, •Nonerosive duodenitis •Antral erosive lesions •Normal	 13 5 7 1	 15 2 1 3	<0.05

Table 3. All cases are given with their gastroduedonoscopy findings

Cases and Groups	Gender	Age	Disease Duration	H.Pylori	Baseline Gastroduedonoscopy	Posttreatment Gastroduedonoscopy
1-Indomethacin	Female	60	4	-	PG	PG + NED
2-Indomethacin	Male	57	5	+	N	PG
3-Indomethacin	Female	72	9	-	PG	PG (ae)
4-Indomethacin	Female	56	5	-	PG	PG(ae)
5-Indomethacin	Male	63	3	+	PG	PG (ae) + NED
6-Indomethacin	Female	64	4	+	PG	PG (ae)
7-Indomethacin	Female	42	1	-	PG + NED	PG
8-Indomethacin	Male	66	5	+	N	PG
9-Indomethacin	Female	68	4	+	PG	PG
10-Indomethacin	Female	53	3	+	N	PG
11-Indomethacin	Female	50	5	+	PG + NED	PG
12-Indomethacin	Female	49	3	+	PG	PG (ae)
13-Indomethacin	Female	45	1	+	N	N
14-Indomethacin	Female	70	10	+	PG	PG
15-Indomethacin	Female	55	6	+	PG + NED	PG
16-Indomethacin	Female	62	5	+	PG	PG
17-Indomethacin	Female	53	4	+	PG +NED	PG (ae) + NED
18-Indomethacin	Female	46	1	+	PG	PG (ae) + NED
19-Indomethacin	Female	52	3	+	PG + NED	PG
20-Indomethacin	Female	71	9	+	PG	
21-Indomethacin	Male	66	5	+	PG	PG + NED
22-Indomethacin	Female	52	4	-	PG	
23-Indomethacin	Female	59	5	+	PG	
24-Indomethacin	Female	67	6	+	PG	
25-Indomethacin	Male	52	3	+	PG	
1-Celeocoxib	Female	48	2	+	PG	Duodenal Ulcer
2- Celeocoxib	Female	52	4	+	PG	PG
3- Celeocoxib	Female	66	3	+	PG	PG
4- Celeocoxib	Male	41	3	+	PG	N
5- Celeocoxib	Female	60	5	+	PG	PG
6- Celeocoxib	Female	55	6	+	PG	PG (ae)
7- Celeocoxib	Female	53	5	+	PG + NED	PG + NED
8- Celeocoxib	Female	56	5	+	PG	N
9- Celeocoxib	Female	47	5	+	PG	N
10- Celeocoxib	Male	59	6	+	PG	
11- Celeocoxib	Female	52	4	+	PG	PG + NED
12- Celeocoxib	Female	53	7	-	PG	PG
13- Celeocoxib	Female	63	7	-	PG	
14- Celeocoxib	Female	71	9	+	PG	
15- Celeocoxib	Female	61	6	+	PG	PG
16- Celeocoxib	Male	65	7	+	PG	PG
17- Celeocoxib	Female	52	3	+	PG	
18- Celeocoxib	Female	50	6	+	PG	PG
19- Celeocoxib	Female	62	5	+	PG	PG
20- Celeocoxib	Female	57	4	+	PG	
21- Celeocoxib	Female	67	7	+	PG	
22- Celeocoxib	Female	60	4	+	PG	PG
23- Celeocoxib	Female	53	3	+	PG	PG
24- Celeocoxib	Female	54	4	+	PG	PG
25- Celeocoxib	Female	67	6	+	PG	PG

PG; pangastritis, NED; nonerosive duodenitis, ae; antral erosive lesion

to conventional NSAIDs (17). However, celecoxib showed a lower incidence of nonerosive duodenitis and antral erosive lesions. Moreover, three cases exhibited a transition to normal gastric findings with celecoxib combined with PPI usage, whereas only one case showed a similar improvement with indomethacin combined with PPI. It's worth noting that most patients had a prolonged history of NSAID use before being enrolled in the study. Despite a short "drug wash-out" period, prior NSAID exposure might have influenced the outcomes.

A meta-analysis of 410.879 participants from 73 countries across six continents revealed an overall *H. Pylori* prevalence of 44.3% worldwide. This rate varied, with developing countries showing a higher prevalence of 50.8% compared to 34.7% in developed countries. Globally, the *H. pylori* infection rate was 42.7% in females and 46.3% in males. Furthermore, the prevalence in adults (≥18 years) was significantly higher than in children, with rates of 48.6% and 32.6%, respectively (20). The prevalence of *H. Pylori* in Turkey was found 82.5% according to the TURHEP study

(21). Our study reveals a high prevalence, with 86% of participants testing positive for *H. Pylori*, a figure close to the data presented in TURHEP. Despite NSAIDs and *H. Pylori* share a number of similar pathogenic mechanisms, there is no evidence to argue a significant synergistic action between these two risk factors for GI bleeding or dyspepsia. Lazzaroni et al. reported that neither short- nor long-term NSAID administration definitively poses a major risk of gastric and duodenal injury or, more importantly, ulcer-related complications such as bleeding or perforation in *H. Pylori*-positive patients (22). Similarly, despite the high prevalence of *H. Pylori* in this study population, no GI adverse events were observed.

COX-2 selective NSAIDs have been associated with electrolyte imbalance including hyponatremia and hyperkalemia (23,24). However, in this study we did not observe any case of electrolyte imbalance.

NSAIDs are effective agents in the treatment of osteoarthritis and a recent study revealed that topical NSAIDs can demonstrate comparable efficacy to oral NSAIDs in treating osteoarthritis, with both forms effectively reducing pain and enhancing physical function among OA patients (25). Therefore, topical treatment approaches may reduce GIS side effects at high risk patients.

Limitations of the Study

The relatively small sample size in this study may limit the generalizability of our findings to broader populations. A larger sample size would enhance the statistical power of the analysis and provide more robust conclusions. The brief period between cessation of prior NSAID use and study enrollment may not have adequately mitigated the lingering effects of previous NSAID exposure. This could influence the interpretation of outcomes, particularly regarding the comparison between indomethacin and celecoxib. The relatively short follow-up duration may have precluded the detection of long-term GI complications associated with NSAID use. Extended monitoring periods could provide a more comprehensive understanding of treatment-related adverse events. The recruitment of participants from a single center may introduce selection bias and limit the diversity of the study population. Including participants from multiple centers or employing a multicenter study design could mitigate this limitation. Detailed information regarding the duration, frequency, and types of prior NSAID use was not consistently available for all participants. This lack of comprehensive data may have influenced the analysis of treatment outcomes and adverse events. While efforts were made to control for potential confounding variables, such as concomitant medication use and comorbidities, the presence of unmeasured confounders could impact the validity of our results. Our study focused primarily on GI findings associated with indomethacin and celecoxib use, neglecting other potential adverse events and long-term outcomes. A broader assessment encompassing systemic effects and patient-reported outcomes would provide a more holistic understanding of treatment safety and efficacy.

CONCLUSION

Our findings underscore the importance of considering both the efficacy and safety profiles of NSAIDs in clinical decision-making for osteoarthritis treatment. While traditional NSAIDs like indomethacin remain effective in pain management, their use may necessitate careful monitoring for gastrointestinal complications. In contrast, celecoxib, a COX-2 selective inhibitor, offers a potentially safer alternative with a reduced risk of gastric lesions, particularly when combined with PPI therapy.

DECLERATIONS

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Original Article

Outcomes of Deceased Donor Kidney Transplantation: A Single-Center Experience from Turkiye

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Abstract

Background: In Turkey, approximately 90% of kidney transplants are conducted utilizing allografts from living donors. Due to the low incidence of cadaveric kidney transplants in the country, comprehensive data on the short-term and long-term outcomes of these procedures remain limited. We aim to present the outcomes of deceased donor-related kidney transplantations (DDKTs) performed in our center.

Methods: This retrospective single-center study was conducted at Atilim University School of Medicine-affiliated Medicana International Ankara Hospital. We analyzed DDKTs performed since 2010. Recipients' demographical features, one and five-year recipient and allograft survival rates, functions of surviving allografts, rates of primary non-functioning graft, and delayed graft function were noted.

Results: Among 1155 transplants performed between 2010 and 2023, 83 (7.2%) were DDKTs. Recipients were followed-up mean of 84 months. The one- and five-year survival rates for recipients were 94.0% and 81.2%, respectively, while the survival rates for allografts were 89.2% and 72.7%, respectively. Recipient and allograft survival rates were comparable between genders. The optimal allograft function is observed between one and five years post-transplantation; thereafter, a decline in allograft function is typically noted.

Conclusion: Our study demonstrates promising survival rates for recipients of DDKTs in our center, emphasizing the efficacy of this treatment modality for ESRD patients. DDKT can provide substantial dialysis-free survival for most patients with ESRD.

Keywords: Kidney transplantation, deceased donor, survival, ESRD, mortality, Turkiye

INTRODUCTION

Kidney transplantation is the optimal and preferable treatment option for improving survival and quality of life for patients with end-stage renal disease (ESRD), today (1,2). However, the shortage of allografts is the major obstacle that stands in front of providing more organs for ESRD patients (3).

Turkey is a leading country regarding organ transplantation with growing experiences since 1975 (4). It has become one of the world's leading transplant centers, performing 3,800 kidney transplants annually before the COVID-19 pandemic (5,6). Besides all efforts, however, deceased donor-related kidney transplantation (DDKT) numbers have been decreasing year-to-year in Turkiye and have fallen below 10% of all kidney transplantation (5-8). Since the number of DDKT is low, the outcomes and their implications on clinical practice are also less known.

Our hospital is a high-volume transplant center that has been performing kidney transplants for over 15 years. In this regard, we aim to present the basic outcomes of DDKT conducted in our center.

METHODS

This retrospective single-center study was conducted

at Atilim University School of Medicine-affiliated Medicana International Ankara Hospital. All DDKTs performed since 2010 were noted by investigating the hospital software system. The study was carried out in accordance with the Declaration of Helsinki. The consent form is not available since the study is retrospective. The study was approved by the ethics committee of scientific research at Medicana International Ankara Hospital.

The primary goal of the study is to reveal recipient and allograft survival rates. Rejection rates and immunosuppression protocols are not the subjects of the study. One, three, and five-year survival rates were analyzed.

The recipients' demographic features were noted. Allograft functions at one, three, and five years, delayed graft functions, and primary non-functioning allografts were also recorded.

Allograft functions were calculated using an online formula at www.mdrd.com (Chronic Kidney Disease – Epidemiology Collaboration 2009). Recipients who required dialysis within the first postoperative week (due to any cause) were assigned as having delayed allograft function (DGF), while allografts that never functioned were assigned as primary non-functioning allografts.

STATISTICAL ANALYSIS

Statistical analysis was conducted using SPSS (version 13.0 for Windows). Initially, all data underwent normality testing using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Parametric data are presented as mean ± standard deviation, while non-parametric data are presented as median (minimum-maximum). Categorical variables were compared using Pearson's or Fisher's exact test. The impact of factors on survival rates were investigated with regression analysis. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 1155 transplants were performed between 2010 and 2023 at our hospital. 83 of 1155 transplants (7.2%) were DDKT. The mean ages of recipients and donors were 43.85±31 (9-71) and 45.61±17.67 (6-83), respectively. 62.7% of recipients (n=52) were male. The clinical and laboratory features of the recipients and donors are given in **Table 1**. The recipient and allograft survival rates were similar between genders (p=0.867 and p=0.657).

The mean recipient and allograft survivals were 84(0-120) and 48(0-120) months, respectively. Recipient and allograft survivals according to posttransplant years were given in **Table 2**. **Figure 1** and **Figure 2** demonstrate recipient and allograft 5-year survival rates. **Figure 3** and **Figure 4** exhibits a similar 5-year allograft and recipient survival rates between males and females (p>0.05).

Despite a substantial increase in KT numbers in the last decade in our center, the DDKT ratio decreased (**Figure 5**). In univariate analysis, the recipient and donor age had an impact on the recipient's survival rates (**Table 3**).

Surviving allografts exhibited a stable function within 5 years of posttransplant period. However, receipients who received their allografts from older donors (≥65

Table 2. Recipient and allograft survival rates, one to ten years

	Recipient survivor/ nonsurvivor, n(%)	Allograft survivor/ nonsurvivor, n(%)
Year 1	78(94.0%)/5(6.0%)	74(89.2%)/9(10.8%)
Year 2	73(92.4%)/6(7.6%)	63(84.0%)/12(16.0%)
Year 3	70(92.1%)/6(7.9%)	57(82.6%)/12(17.4%)
Year 4	64(88.9%)/8(11.1%)	47(72.3%)/18(27.7%)
Year 5	56(81.2%)/13(18.8)	36(72.0%)/14(28.0%)
Year 6	50(79.4%)/13(20.6%)	32(72.7%)/12(27.3%)
Year 7	46(82.1)/10(17.9%)	24(60.0%)/16(40.0%)
Year 8	40(78.4%)/11(21.6%)	19(22.9%)/17(47.2%)
Year 9	35(76.1%)/11(23.9%)	13(40.6%)/19(59.4%)
Year 10	33(84.6%)/6(15.4%)	9(36.0%)/16(64.0%)

Table 1. The clinical and laboratory features of the recipients and donors

Age, years (recipient)	43.85±31
Gender, male/female, n(%)(recipient)	52(67.2%)/31(32.5%)
Recipient Survivor/nonsurvivor, n(%)	58(69.9%)/25(30.1%)
Allograft Survivor/nonsurvivor, n(%)	56(67.5%)/27(32.5%)
Age, years (donor)	45.61±17.67
Dialysis duration, month	96(2-144)
Delayed allograft function, n(%)	30(36.14%)
Primary-nonfunctioning allograft, n(%)	3(3.6%)
Hospital stay within postoperative 1 month, day	6.3 (4-30)
Discharge serum creatinine, mg/dl	1.7 (0.68-6.20)
Total ATG dose administered within postoperative 1 month, mg	600 (400-1000)
Surgical complications, lymphocele, wound infection, urinoma, vascular, n(%)	11 (13.2%)
Rejection, n(%) biopsy-proven or anti-rejection treatment applied under high clinical suspicion, n(%)	18(22.5%)

ATG; anti-thymocyte immunoglobulin

Table 3. The impact of donor and recipient age on recipient and allograft survival rates

		Univariate		Multivariate	
		P value	CI %95	P value	CI %95
Recipient Survival	Recipient age	<0.001	0.005 – 0.008	<0.001	0.005 – 0.005
	Donor age	0.002	0.001 – 0.004	0.004	0.682 – 0.861
Allograft Survival	Recipient age	0.048	0.011 – 0.054	0.098	0.020 – 0.102
	Donor age	<0.001	0.002 – 0.007	0.002	0.375 – 0.652

years old) had a worse allograft function compared to recipients who received their allografts from donors <65 years old (**Figure 6**) (p<0.05).

DISCUSSION

While kidney transplantation (KT) offers superior life expectancy and enhanced quality of life compared to current dialysis modalities, the scarcity of available allografts persists as a significant obstacle. Due to the low number of deceased-sourced donations, Turkey ranks first in living-related kidney transplantation. Therefore, little is known about the outcomes of deceased donor-related kidney transplantations (DDKTs) in Turkey. In our center, deceased donor-related kidney transplantation accounts for 7.2% of all KTs and provides a 5-year recipient and dialysis-free survival rates of 81.2% and 72.0%, respectively.

Previous studies demonstrated a correlation between the prevalence and incidence of KT and the income level of a country. However, variations in these patterns, such as Japan's low incidence of KT, indicate that cultural practices and considerations regarding deceased donation can constrain the adoption of KT even in high-income countries (9,10). The variable rates of prevalence and incidence of KT worldwide seem to be significantly influenced by government funding strategies for chronic diseases, the availability of donors, and the capacity of healthcare network organizations (10). On the other hand, to compensate for the gap between organ demand and delivery, there is an increasing trend to use low-quality

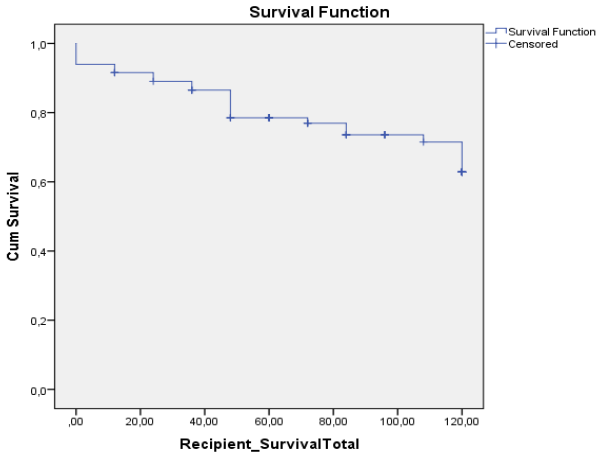

Figure 1. The five year recipients' survival rates

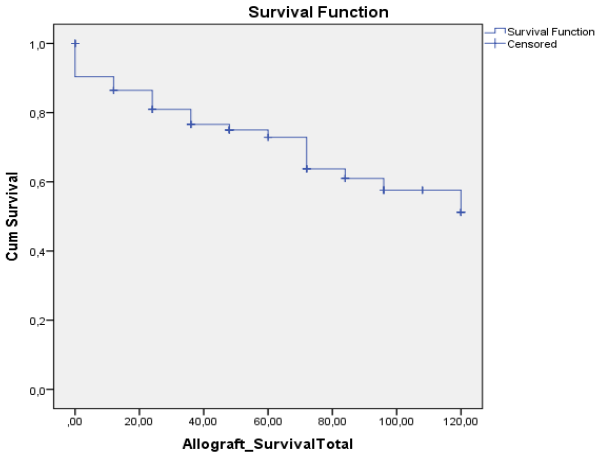

Figure 2. The five year allografts' survival rates

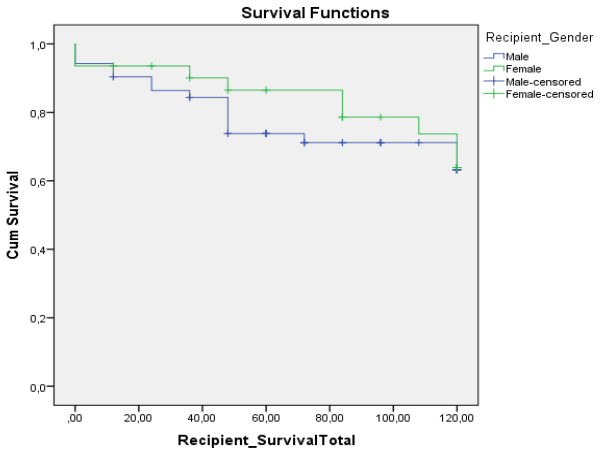

Figure 3. The five year recipients' survival rates according to genders

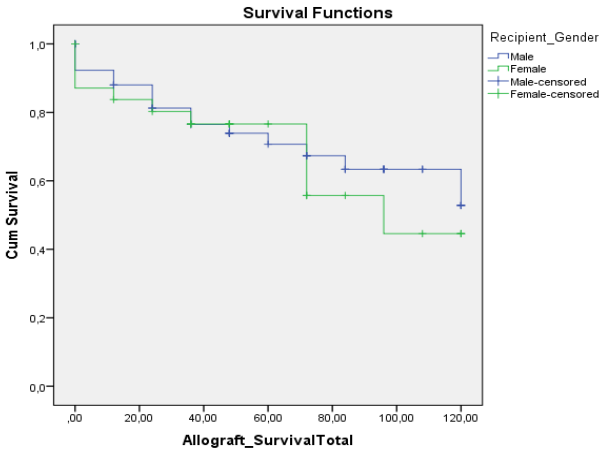

Figure 4. The five year allografts' survival rates according to genders

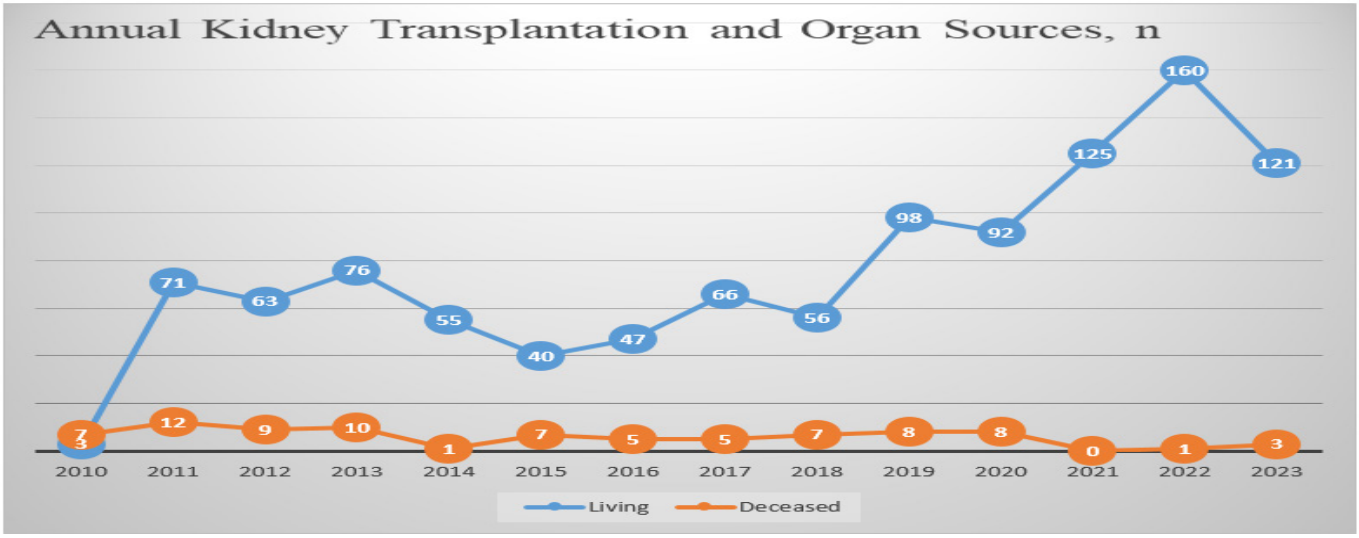

Figure 5. Deceased and living donor kidney transplantation trends between 2010 and 2023 in our center

allografts in KT (11). Nevertheless, despite the use of more low-quality allograft kidneys over the past 10 years, patient and graft survival have remained unchanged. Several factors may have contributed to improving both recipient and graft survival, potentially offsetting the effects of the decline in the quality of donor kidneys (11). This result may be, at least partially, associated with the decreased prevalence of cardiovascular co-morbidities at the commencement of KT as well as improved survival of the general population (13,14).

Turkey has exhibited an interesting trend regarding donor sources in the last decade. Despite being among countries with a high Human Development Index and a substantial increase in the development of its healthcare system, DDKT rates have reduced year by year (ranking 42nd among countries with a transplant program) in Turkey (15). Moreover, this reduction rate in DDKT has emerged despite a substantial increment in total annual kidney transplantations (5,6). Additionally, the COVID-19 pandemic has caused a sharp decline in DDKT rate, down to around 8% (5). In our center, 1155 kidney transplant performed since 2010 and the overall DDKT prevalence is 7.27%. However, similar to the national registries there is a sharp decline in DDKT numbers was observed following the COVID-19 pandemic. The overall DDKT rates of the last 3 years are around 1.0% in our center, which is not an acceptable and desirable result.

KT provides lower mortality and the risk of cardiovascular events compared to dialysis and the relative benefits of KT likely increase over time (16). In the United States, the 5-year survival rates for living- and DDKTs are 84.6% and 72.4%, respectively. Focusing on other countries, in Australia, New Zealand, Europe, Canada, and South Korea, these rates range from 81% to 90%. Our study holds significance as it provides long-term

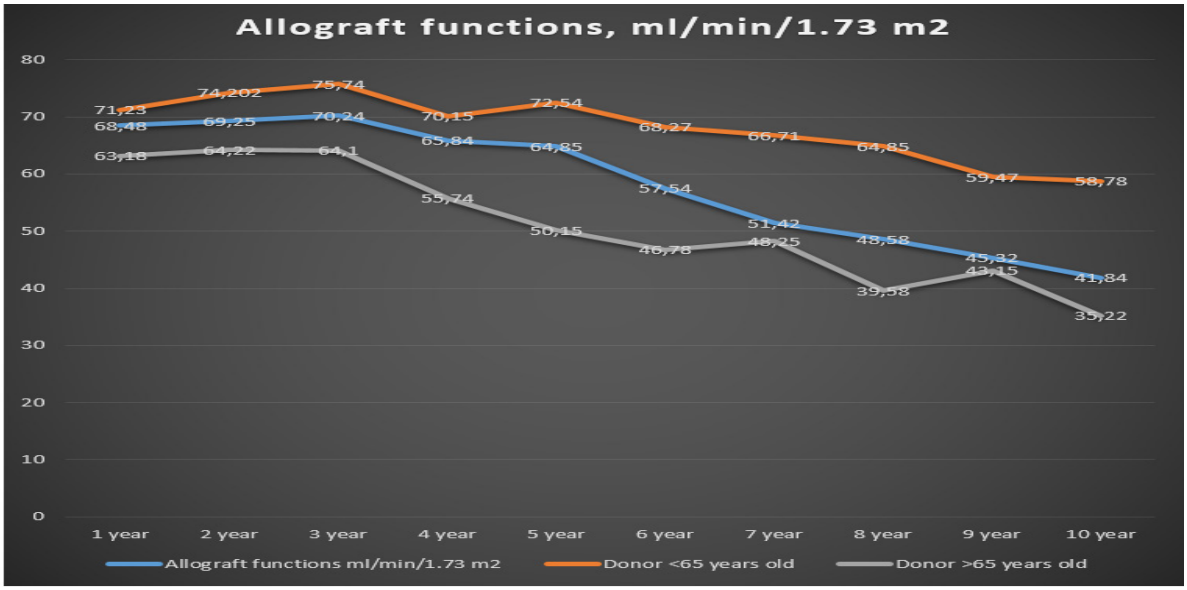

Figure 5. Allograft functions are given in a 10-year time interval

national KT outcomes, enabling valuable comparisons with global results (10,17,18). The survival rates for both living and deceased donor-related kidney transplants are approximately 94.0% and 86.0%, respectively, according to data from the Turkish Society of Nephrology (TSN) Registries (5,6). However, specific survival rates for individual centers remain unknown. Soylu et al. reported composite recipient survival rates for one and five years, combining both living and deceased donors, at 90.9% and 88.9%, respectively (19). Merhametsiz et al. demonstrated an average recipient and allograft survival rate of around 80% in their study, which included 268 deceased donor kidney transplants (20). In this study, one-year recipient and allograft survival rates were 94.0% and 89.2%, respectively, while five-year recipient and allograft survival rates were 81.2% and 72.0%, respectively. Considering that the 5-year mortality rate reaches 50% in dialysis patients, these results are favorable for individuals with ESRD (21). According to the TSN registry, the annual mortality rate is 10-12% (5).

Older donor age and recipient age are two well-known risk factors for the worse recipient and allograft survival longevity (22,23). In this study, similar outcomes were demonstrated with previous studies. However, younger donors (<65 years old) provided a better allograft functions in recipients.

This study aimed to demonstrate the crude survival rates of deceased donor kidney transplants (DDKTs) performed in a single center. As such, it raises several questions regarding the outcomes. However, the results appear to be superior to those of patients undergoing hemodialysis treatment and comparable to national and international reports.

Limitations of the Study

The study focuses on outcomes from a single center, which may not be representative of broader population trends or variations in transplant practices across different centers. The study has a relatively small sample size, which can affect the generalizability of the findings and limit the statistical power to detect differences or associations. The study does not account for external factors that may influence transplant outcomes, such as changes in medical practice, advancements in immunosuppressive therapies, or variations in healthcare infrastructure and policies over time. The study acknowledges the impact of the COVID-19 pandemic on transplant rates but does not delve deeply into how this may have influenced the observed outcomes or introduced biases due to changes in transplant practices during the pandemic. While the study compares outcomes with national and international reports, it does not include direct comparison groups, such as patients on dialysis or those receiving transplants from living donors, which could provide additional context for interpreting the findings.

CONCLUSION

In this single-center report, we observe recipient and allograft survival rates comparable to those reported nationally and internationally. Notably, our findings reveal one and five-year recipient survival rates of 94.0% and 81.2%, respectively, similar to previous reports on dialysis survival rates. Given the acknowledged benefits of kidney transplantation, particularly in comparison to dialysis, deceased donor kidney transplantation emerges as a favorable treatment option for patients with end-stage renal disease.

DECLARATIONS

Ethics Committee Approval: A local Ethics Committe Approval was obtained for this singe-center retrospective study (2023/12).

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Author contributions: All researchers equally contributed to data collection and analyzing the final version of the article. All authors read and approved the final manuscript.

Conflict of interest: None

Informed consent form: Not available

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Original Article

Evaluation Of Ocular Parameters In Patients Receiving Hemodialysis Treatment

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Abstract

Background: Changes in retrobulbar blood flow during hemodialysis (HD) may result in ocular changes. It may have effects especially on the choroid, which is the area with high blood flow, and therefore the retina. This study aims to compare choroidal and retinal changes before and after a single HD session.

Methods: In this prospective study, patients receiving HD treatment in the dialysis unit between October 2022 and February 2023 were included. The patients were divided into two groups: diabetes mellitus (DM) and non-DM. Measurements were made before and after dialysis treatment using optical coherence tomography. Using computerized segmentation, macular retinal layer volumes of the eye (total retinal volume and ganglion cell layer from outside to inside, inner plexiform layer) were measured. The enhanced depth imaging system of optical coherence tomography was used to measure choroidal thickness.

Results: A total of 28 patients (18 women and 10 men) participated the study. All patients underwent in-depth eye examination. After HD session, a statistically significant decrease in choroidal thickness was observed in the macula temporal, subfoveal region, macula nasal and optic disc nasal in both the DM and non-DM groups. According to the measurements made on the retinal layers before and after HD, it was observed that there was no change in the macular thickness of the ganglion cell layer and inner plexiform layer.

Conclusion: The lack of change in the macular thickness of the ganglion cell layer and inner plexiform layer suggested that HD did not have any effect on the neural tissue. Thinning was observed in the choroidal layer after hemodialysis. It was observed that HD affected choroidal blood flow and caused changes in the vascular layer of the eye. Changes in the choroidal tissue in the optic disc nasal and posterior pole regions also suggest that HD affects the vascular layer of the eye globally.

Keywords: Ganglion cell layer, hemodialysis, inner plexiform layer, choroid thickness

INTRODUCTION

The incidence of end-stage renal disease (ESRD) is progressively rising due to the demographic shift towards an aging population, making it a burgeoning global public health concern. Hemodialysis (HD) is a therapy modality that incurs significant costs and has been associated with a decline in quality of life (1). HD is a process utilized to eliminate metabolic wastes and excess fluid from extracorporeal blood. Simultaneously, renal replacement fluid therapy is employed to uphold electrolyte and acid-base balance (2).

Metabolic alterations manifest during hemodialysis, and scientific data suggests that these changes can impact ocular health, as well as various other human tissues and organs (3,4).

Hemodialysis can lead to alterations in retrobulbar blood flow, which can subsequently cause modifications in ocular physiology. The potential impact of this phenomenon is particularly notable in the choroid, a region characterized by its abundant blood supply, and consequently, the retina. Optical coherence tomography (OCT) is a non-invasive imaging modality utilized for the assessment of retinal tomography and retinal histopathology. This technique operates on the idea of analyzing the characteristics of reflections from tissues with distinct optical properties, achieved by directing

infrared light towards the retina (6).

The choroid supplies blood to both the retinal pigment epithelium (RPE) and the retina. The regulatory capacity of the choroidal arteries is limited, rendering them susceptible to systemic alterations (6,7). Additionally, it has been observed that this particular phenomenon can lead to RPE and retinal malfunction, ischemia, and potentially result in the demise of photoreceptor cells (6).

In addition to the immediate alterations observed in ophthalmological observations prior to and following a solitary hemodialysis session, this investigation seeks to assess the variations in peripapillary and macular regions, as well as choroidal and retinal regions. Furthermore, we hope to examine the associations between these alterations and systemic parameters.

The aim of this study was to evaluate changes in the thickness of the choroid, both within and outside the macula, in patients with ESRD who are having HD treatment.

METHODS

The present cross-sectional study was conducted at the Ophthalmology and Nephrology clinics of Gebze Fatih State Hospital from October 2022 to February 2023. For this study, ethics committee approval numbered 2022/83 was received from the Health Sciences University Ethics Committee on 13.10.2022 and study was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

Patients receiving hemodialysis treatment at Gebze Fatih State Hospital Nephrology Clinic were included in the study. The study population consisted of individuals diagnosed with ESRD, who were then categorized into two groups based on the presence or absence of diabetes mellitus (DM). The study comprised individuals who had a best-corrected visual acuity greater than 20/200 and eyes with an ocular axis length (AL) ranging from 22.1 to 25.9 mm. This study excluded patients who had a medical history of retinal vein occlusion, glaucoma, age-related macular degeneration (AMD), or uveitis, and who had experienced anterior or posterior segment disease that hindered the ability to conduct precise examination, ocular surgery, or retinal laser treatments within a period of 3 months prior to the commencement of the study. The study did not include patients who were undergoing active ophthalmological treatment for diabetic retinopathy.

In the present study, all participants had hemodialysis treatments three times per week, each session lasting four hours, for a minimum duration of three months. The study employed the usage of the Fresenius Medical Care 4008s (TR-TR 1A. 2014) and Gambro ak98 (program version2.xx, Gambro Lundia AB PO Box 10101 SE 22010 Lund Sweeden) dialysis machines in conjunction with the polynephron synthetic hollow fiber dialyzer and low molecular weight heparin as an anticoagulant. The patient was subjected to bicarbonate dialysis, utilizing a dialysate flow rate of 500 ml/min and a blood flow rate ranging from 300 to 350 ml/min. The body weight and blood pressure of each patient were assessed both prior to and following the dialysis procedure.

Each individual underwent a comprehensive ophthalmological evaluation, including dilated fundus ophthalmoscopy and structural spectral-domain optical coherence tomography (SD-OCT). The exclusion criteria encompassed glaucoma, vitreoretinal and retinal vascular illnesses, ocular media opacity, any prior laser photocoagulation therapy or ocular surgery in the study eye, as well as macular dystrophies and diseases.

The ophthalmologist obtained OCT readings both prior to and following the initial hemodialysis session of the week, which took place on either Monday or Tuesday. In order to mitigate the influence of circadian rhythm on choroidal thickness, measurements were conducted during the early morning hours, without the use of pupil dilation. Measurements using OCT were conducted both prior to and following the administration of dialysis treatment. Once the patient was positioned in the correct manner, measurements of the retinal layer of the eye were obtained.

The OCT scans were obtained by a single operator utilizing an eye-tracking device (Automated Real-Time system). The identical regions were scanned both prior to and subsequent to the HD.

The imaging procedure involves the utilization of a high-speed, high-resolution SD-OCT device (Spectralis® OCT, Heidelberg Engineering, Heidelberg, Germany) to focus on the macula and optic disc. The superluminescent diode (SLD) is utilized to generate an infrared beam with an average wavelength of 870 nm for the intended application. To mitigate the potential influence of movement artifacts caused by tiny eye movements during the examination, a advenced eye tracking system was integrated into the SD-OCT device.

The volumes of the macular retina layer in both eyes were quantified using digital segmentation. The aforementioned volumes encompassed the aggregate retinal volume, along with the volumes of the ganglion cell layer (GCL) and inner plexiform layers (IPL).

The measurement of choroidal thicknesses was conducted using the enhanced depth imaging (EDI) technology of OCT. An integrated device was used to measure the choroid-sclera border at the fovea and optic disc. The device was positioned vertically from the outer margin of the retinal pigment epithelium (Figure

Table 1. The clinical and laboratory of th participants and the comparison of thw two groups

	DM (n=13)	Non DM (n=15)
Age (years)	66.61 ± 9.69	58.50 ± 16.40
Dialysis duration (years)	3.22 ± 2.31	3.25 ±2.20
DM duration (years)	11.39 ± 5.54	-
Weight before HD (kg)	82.60 ± 17.85	73.70 ± 15.03
Weight after HD (kg)	79.86 ± 17.35	70.74 ± 14.99
Systolic Blood Pressure before HD (mmHg)	130.56 ± 27.96	135.63 ±21.28
Systolic Blood Pressure after HD (mmHg)	118.33 ± 26.62	125.00 ± 17.88

DM; diabetes mellitus; HD; hemodialysis

1). Retinal and choroidal thickness measurements were taken in both the macula region and areas outside of it. The measurement of retinal and choroidal thickness in the macula revealed a consistent value of 1.5 mm at the central region of the fovea, both towards the temporal and nasal directions leading to the center of the fovea. Measurements of the thickness of the retina and choroid were conducted in the nasal region, namely at a distance of 3.5 mm from the edge of the optic disc, excluding the macula.

STATISTICAL ANALYSIS

The statistical analysis was conducted using the SPSS Ver. 22.0 software (SPSS Chicago, Illinois, USA). A p value below 0.05 was deemed statistically significant. The Shapiro-Wilk test was employed to ascertain the presence of a normal distribution. The study assessed the disparities between pre- and post-hemodialysis measures using the dependent groups T test for variables that followed a normal distribution, and the Wilcoxon signed ranks test for variables that did not follow a normal distribution.

RESULTS

The demographic characteristics of each group are shown in **Table 1**. The DM group comprised 13 patients, while the non-DM had 15 patients. In the DM group (n=13), the estimated duration of DM was 11.39±5.54 years. Hemodialysis duration was 3.22±2.31 years in the DM group and 3.25±2.20 years in the non-DM group. The times did not differ significantly between the two groups (p=0.959). After hemodialysis, the mean body weight decreased from 82.60±17.85 kg to 79.86±17.35 kg (p<0.001) in the DM group and from 73.70±15.03 to 70.74±14.99 kg (p<0.001) in the Non-DM group.

After hemodialysis; it was observed that systolic blood pressure (SBP) decreased from 130.56±27.96 to 118.33±26.62 mmHg (p<0.054) in the DM group and from 135.63±21.28 to 125.00±17.88 mmHg (p<0.059) in the non-DM group.

The mean central macular thickness before the start of hemodialysis was 258.38±36.31µm and 253.46±22.35 µm (p=0.327) in the DM and non-DM groups, respectively. After completion of dialysis, the values were 250.69±40.35 µm and 247.60±25.79 µm (p= 0.114) in the DM and non-DM groups, respectively.

According to the measurements made in the retinal layers before and after HD, it was observed that there was no change in GCL and IPL macular thickness. **Table 2** shows GCL and IPL measurement details.

Table 2. GCL and IPL layer volume analysis in DM and non-DM groups before and after HD obtained by SD-OCT in end-stage renal disease patients.

	DM(n=13)				Non DM (n=15)			
	Before HD		After HD		Before HD		After HD	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
GCL								
Makula Temporal	29.31	6.52	30.15	7.04	29.47	7.10	32.33	6.01
Subfoveal	15.38	6.39	16.76	7.32	11.93	4.62	12.66	5.19
Macula Nasal	31.31	5.31	30.61	9.91	35.67	6.81	36.20	7.58
Optic Disc Nasal	21.15	5.85	23.30	3.27	22.73	5.70	30.13	2.99
IPL								
Makula Temporal	28.15	4.12	29.30	3.79	30.07	4.30	30.13	2.99
Subfoveal	20.38	5.05	19.76	6.15	17.40	3.75	17.73	4.14
Macula Nasal	25.00	4.63	25.46	4.19	27.73	4.59	29.20	4.91
Optic Disc Nasal	21.54	5.15	23.23	4.14	22.13	7.38	21.60	7.62

DM; diabetes mellitus; HD; hemodialysis; GCL; ganglion cell layer; IPL; inner plexus layer, SD-OCT; spectral domain optic cohorens tomography; SD; standart deviation

Table 3. The variations in choroidal layer thickness in both diabetic and non-diabetic groups prior to and following hemodialysis. These measurements were acquired using enhanced depth imaging optical coherence tomography (EDI-OCT) in patients with ESRD.

	DM			Non-DM		
Choroidal Thickness	**Before HD**	**After HD**	**p**	**Before HD**	**After HD**	**p**
Macula Temporal	259.23±48.67	212.92 ± 48.33	<0.001	259.23±48.67	224.92±48.32	<0.001
Subfoveal	296.15±62.71	230±62.83	<0.001	296.15±62.71	251.46±62.82	<0.001
Macula Nasal	214.38±90.35	187.92±78.11	<0.001	255.38±90.34	209.92±78.11	<0.001
Optic Disc Nasal	190.92±73.10	150.46±66.36	<0.001	202.92±73.10	166.46±66.36	<0.001

DM; diabetes mellitus; HD; hemodialysis;

In the DM group, choroidal thickness was 259.23± 48.67µm at the temporal macula before hemodialysis; subfoveal 296.15±62.71µm; 214.38±90.35µm at macula nasal; The optic disc was 190.92±73.10µm nasally. In the measurement made after HD, it was 212.92 ± 48.33µm at the temporal macula; subfoveal 230±62.83µm; 187.92±78.11µm at macula nasal; 150.46±66.36µm was measured nasal to the optic disc. An observable reduction in choroidal thickness was found to be statistically significant following HD (p value was <0.001, 0.003, 0.001, 0.002 for macula temporal, subfoveal, and macula nasal, respectively).

In the non-DM group, choroidal thickness was 259.23±48.67µm at the temporal macula before hemodialysis; subfoveal 296.15±62.71µm; 255.38±90.34µm at macula nasal; The optic disc was 202.92±73.10µm nasally. In the measurement made after HD, it was 224.92±48.32µm in the temporal macula; subfoveal 251.46±62.82µm; 209.92±78.11µm at macula nasal; 166.46 ±66.36 µm was measured nasal to the optic disc. According to the values given in the Table 3, a statistically significant decrease was detected in choroidal thickness after hemodialysis (p<0.001 for macula temporal, subfoveal, macula nasal) (p=0.008 for OD nasal) (**Table 3**).

The mean difference in choroidal thickness in the macular region, assessed at the foveal center and 1.5 mm to the right of the foveal center, was higher in the group of individuals with DM (44.69; 34.30 µm) compared to the group non-DM (35.73; 29.00 µm). The statistical significance of the results are indicated by a p-value of less than 0.001, as shown in **Table 4**. The mean difference in choroidal thickness outside the macula in the group of individuals with DM (macula nasal 45.46; optic disc nasal 36.46 µm) was likewise substantially distinct (p<0.001) from that in the group non-DM (macula nasal 34.13; optic disc nasal 18.56 µm). The information is presented in **Table 4**.

DISCUSSION

In the present study, it was shown that HD had no discernible impact on the ganglion cell layer and inner plexiform layer, both of which constitute the neuronal layers of the retina. However, noteworthy alterations were observed in the choroid tissue.

Patients with chronic renal disease who are receiving HD may have exacerbation of corneal and conjunctival ocular abnormalities, leading to the development and progression of dry eye and red eye symptoms [8]. Renal failure and renal immunity can lead to HD, which in turn may result in ocular alterations or exacerbation of pre-existing ocular conditions (9). The presence of a choroidal tissue that is both structurally and functionally intact is essential for the proper functioning of the retina. The presence of abnormal choroidal blood flow has been identified as a potential factor contributing to photoreceptor malfunction and subsequent cell death (6,10).

Two intradialytic pressures, ultrafiltration and solute clearance, have an impact on ocular structures. It is important to mention that a major element that causes changes in eye measurements during HD is the movement of fluids and molecules between the blood and the fluids inside the eye, such as the aqueous humor, vitreous, and choroidal interstitium (8). During HD, the process of ultrafiltration leads to a progressive reduction in the volume of fluid inside the extracellular fluid compartment. This finally results in an elevation of the oncotic pressure within the extracellular space, leading to the withdrawal of fluid from the adjacent tissues. Fluid transport from the eye to the plasma is facilitated by the elevation of plasma colloid osmotic pressure

Table 4. The comparison of thickness differences in the eye measurements before and after hemodialysis in the DM and non-DM groups (p values for the comparison of each parameter <0.05)

		Macular Temporal Choroidal Thickness Difference	Subfoveal Choroidal Thickness Difference	Macular Nasal Choroidal Thickness Difference	Optic Disc Nasal Choroidal Thickness Difference
DM	Median	12.0(-18.0 - 159.0)	19.0(-4.0 - 103.0)	33.0(-5.0 - 95.0)	10.0(-28.0 - 57.0)
Non-DM	Median	21.0(2.0 - 96.0)	38.0(0 - 159.0)	31.0(2.0 - 117.0)	33.0(-14.0 -126.0)

(11). The aforementioned modifications may potentially result in a reduction in choroidal thickness, as indicated by previous studies (11-13). Hence, it is postulated that the occurrence of choroidal thinning can be attributed to hypovolemia resulting from ultrafiltration and the subsequent elevation in plasma colloid osmotic pressure. Numerous investigations have demonstrated a reduction in choroidal thickness and retinal edema subsequent to HD, therefore aligning with this perspective (14-17.

A study was conducted to examine the impact of HD on peripapillary choroidal thickness in patients with ESRD. The study utilized swept source OCT and other ophthalmological parameters. The results revealed a notable association between changes in PCT and subfoveal choroidal thickness. In our study, we demonstrated the decrease in subfoveal choroidal thickness. Differently, we did not measure the peripapillary choroidal thickness, which may be a limitation of our study. We measured the choroidal thickness in the nasal region of the optic disc. HD can affect the optic nerve head and surrounding structures.

In a study conducted by Chang et al., it was found that patients undergoing HD saw a reduction in choroidal thickness, body weight, serum osmolarity, and SBP (18). In parallel with our study, mean choroidal thickness changes were greater in the DM group than in the non-DM group. In that study, overall changes in peripapillary retinal nerve fiber layer thickness were not statistically significant.

Following the process of HD, a notable reduction in choroidal layer thickness was noted in both the groups with DM and non-DM. However, no discernible alterations were detected in the layers of the neural retina. In this study, we aimed to assess the temporal macula, macula, nasal macula, and optic disc utilizing OCT within a comparatively expansive region in comparison to prior research efforts. The observed correlation in the nasal optic disc led us to consider the comprehensive impact of hemodialysis on the choroid layer, particularly in the DM group.

There are certain limitations inherent in our investigation. Initially, it is worth noting that the study sample size was rather limited. Consequently, it is imperative to conduct additional research using a larger sample in order to establish conclusive findings on alterations in choroidal thickness and GCL. Furthermore, all parameters were recorded 30 minutes prior to and 30 minutes subsequent to HD. Conducting additional OCT examinations over time intervals when the body has had sufficient opportunity to attain complete equilibrium and fluid balance may yield varied outcomes.

The fluctuations in body weight and blood pressure that occur during HD have the potential to impact the thickness of the choroid, both within and outside the macula. Additional research is required to assess the potential alterations that can arise in different ocular pathological states following hemodialysis in individuals with ESRD.

CONCLUSION

This study showed us that the lack of change in GCL and IPL macular thickness suggested that HD did not have any effect on neural tissue. Thinning was observed in the choroidal layer after hemodialysis. It was observed that HD affected choroidal blood flow and caused changes in the vascular layer of the eye. Changes in the choroidal tissue in the optic disc nasal and posterior pole regions also suggest that HD affects the vascular layer of the eye globally.

DECLERATIONS

Informed consent was obtained from all individual participants included in the study. Informed consent was obtained from patients regarding publishing their data and photographs. Ethics committee approval numbered 2022/83 was received from the Kocaeli Derince Training Hospital on 13.10.2022

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Conflict of interest: None

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

This study has not been published anywhere.

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Review

Genetic and Epigenetic Features of Familial Mediterranean Fever: What is New?

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Abstract

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent fever episodes and systemic inflammation, primarily attributed to mutations in the Mediterranean Fever (*MEFV*) gene.

Genetic studies have identified various mutations in the *MEFV* gene, with notable variants such as *V726A*, *M694V*, *M694I*, *M680I*, and *E148Q* predominating in affected populations. The *MEFV* gene encodes the pyrin protein, crucial for inflammasome assembly and subsequent inflammatory responses. While biallelic mutations are typical in FMF, monoallelic carriers also exhibit phenotypic variability, suggesting the involvement of additional genetic and environmental factors. Epigenetic mechanisms, particularly DNA methylation and histone modifications, play pivotal roles in regulating gene expression and inflammatory pathways in FMF. Studies investigating DNA methylation patterns of the *MEFV* gene have yielded conflicting results regarding their association with disease severity and colchicine responsiveness. Furthermore, histone modifications, including acetylation and methylation, have been implicated in inflammasome activation and FMF pathophysiology, offering potential therapeutic targets

MicroRNAs (miRNAs), crucial regulators of gene expression, have emerged as key players in FMF pathogenesis. Dysregulated miRNA expression profiles in FMF patients, particularly those homozygous for specific mutations, suggest their involvement in immune dysregulation and cytokine modulation. Moreover, miRNAs hold promise as diagnostic biomarkers and therapeutic targets, with potential implications for personalized treatment strategies.

Keywords: Familial Mediterranean Fever, FMF, MEFV gene, epigenetics, miRNAs

INTRODUCTION

Familial Mediterranean Fever (FMF) is an inherited autoinflammatory disease characterized by recurrent fever attacks, arthritis, serositis, and amyloidosis caused kidney involvement. FMF has a frequency of 100-200 per 100,000 people, predominantly affecting those of Eastern Mediterranean origin (1). Initially thought to primarily impact individuals living in the Mediterranean region (Arabs, Armenians, and Turks), it has now become increasingly diagnosed worldwide due to easier transportation and increased migration (2). Notably, individuals from Japan, North America, and Europe have also reported cases of FMF. Among the affected populations.

EPIDEMIOLOGY

FMF is common among communities around the Mediterranean (2). It is most commonly seen in individuals of Armenian, Turkish, North African, Middle Eastern Jewish, and Arab descent. The prevalence of FMF in Turkey is approximately 1/400 - 1/1000, making it likely the country with the highest rate of FMF patients worldwide (3,4). Among Armenian citizens, the carrier rate for FMF mutation is approximately 1/7, with a disease occurrence rate of 1/500 (5). In Israel, the carrier rate among Jewish populations varies, with 1/8 among Ashkenazi Jews, 1/6 among North African Jews, and 1/4 among Iraqi Jews (6). The disease is not limited to these ethnic backgrounds and is also observed in countries with lower rates such as China, Greece, Japan, and Italy (2,7,8). In the Balkans, as countries move away from Turkey, the number of FMF patients and the carrier rate of *MEFV* mutations decrease (9). This could reflect the expansion of the Ottoman Empire in this region. FMF is presumed to have originated more than 3000 years ago

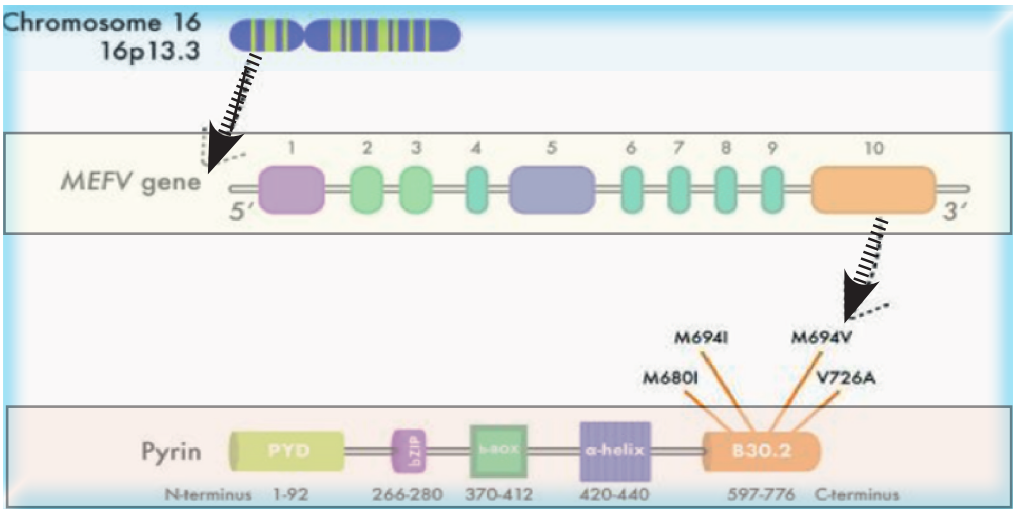

Figure 1. The MEFV gene, situated on chromosome 16's short arm at locus 16p13.3, comprises 10 exons and is responsible for encoding the pyrin protein. Pyrin, a crucial player in the innate immune system, consists of five distinct domains: PYD, bZIP transcription factor, B-box, α-helical coiled-coil, and B30.2. Among these, the C-terminal B30.2 domain holds particular significance, as it serves as the primary site where the most prevalent FMF mutations, including *M680I, M694I, M694V*, and *V726A*, are concentrated. These mutations within the *MEFV* gene lead to the activation of pyrin, triggering its assembly with pro-caspase-1 and ASC into a multiprotein complex known as the inflammasome. This molecular complex plays a pivotal role in initiating the inflammatory response, ultimately contributing to the characteristic symptoms observed in FMF patients. (Adopted from the Reference 16).

in Mesopotamia (10). In the modern world, the spread of the disease from the Mediterranean region to distant countries can be explained by overseas transportation and air travel.

GENETIC MUTATIONS

MEFV Gene Mutation

FMF is generally considered an autosomal recessive disease. Affected individuals carry biallelic pathogenic mutations in the Mediterranean Fever (*MEFV*) gene located on the short arm of chromosome 16 (16p13.3) (**Figure 1**) (11,12). The *MEFV* gene consists of 10 exons, with over 370 variants identified to date (13). The number of variants continues to increase with the use of genome sequencing. Mutations including *V726A, M694V, M694I, M680I,* and *E148Q* constitute approximately 75% of FMF chromosomes in typical cases among Armenian, Arab, Jewish, and Turkish populations (14). Among these mutations, *M694V* is the most common, occurring in 20%-65% of cases across all four populations. Additionally, approximately 10%-20% of individuals meeting the diagnostic criteria for FMF do not have *MEFV* mutations. It is debated whether this represents a FMF-like condition or true FMF with unidentified genetic variations (15).

In FMF endemic countries, approximately 30% of patients carry a single pathogenic variant (monoallelic disease) (16,17). This observation raises the question of whether the disease may also be transmitted as an autosomal dominant trait. Some reports suggest a dominant feature among patients with specific mutations such as the deletion mutation *M694V* and missense mutations *H478Y, T577N*, and *P373L* (18-20). The deletion mutation can lead to a severe defect in the encoded pyrin protein, resulting in the onset of clinical FMF. However, there is no clear explanation for the presence of FMF in individuals carrying other single missense mutations. It is thought that additional genetic and environmental (epigenetic) factors affect the phenotypic characteristics of asymptomatic disease in more than 95% of carriers (heterozygotes) of a single MEFV mutation. In a study aimed at estimating the contribution of heterozygosity to disease prevalence, a genotype comparison was conducted in 63 sibling pairs from familial types and a genotype study in 557 patients from four Mediterranean populations (21). This study demonstrated that heterozygosity alone is not responsible for classic Mendelian inherited FMF, but it constitutes a risk factor for developing FMF with a six- to eight-fold higher risk compared to individuals without *MEFV* mutations.

Although mutations in the entire *MEFV* gene are found in FMF patients, *M694V* and *M680I* are the mutations associated with the most severe forms of the disease, clustered in exon 10, encoding a motif known as the B30.2/SPRY domain at the C-terminal of the protein. Homozygotes for *M694V* exhibit a severe phenotype, with a higher likelihood of early disease onset, arthritis, erysipelas-like skin lesions, high fever, splenomegaly, more frequent attacks, and renal amyloidosis compared to individuals with other *MEFV* mutations (22). Additionally, patients with these mutations require higher doses of colchicine to prevent attacks compared to those with other genotypes. The *M694V* mutation predominantly affects FMF patients of North African Jewish descent, who are known to experience more severe

attacks. Moreover, a high prevalence of amyloidosis was detected before the use of colchicine (23). Ashkenazi Jews and Druze, who have a low frequency of the *M694V* mutation, tend to have milder versions of FMF with a lower prevalence of amyloidosis.

Genetic variants found in Exon 2 (e.g., E148Q, R202Q) and Exon 3 (P369S) typically present with a milder clinical presentation of FMF, often associated only with mild and nonspecific inflammatory symptoms. However, this is not always the case, as reports of more severe or atypical disease with these variants exist. For example, several studies have shown that *E148Q*, *P369S*, and *R408Q* can be found on a single allele (in cis) and may manifest as FMF-like disease or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) syndrome (24,25).

Additional studies conducted in Greece and Turkey have reported an association between the *R202Q* mutation and an inflammatory phenotype of FMF (26,27). Therefore, it has been observed that typical clinical features of FMF, especially arthritis, are observed in patients with compound mutations, including *R202Q* (25).

In Japan, where most mutations occur in Exons 2, 3, and 4, FMF tends to be mild and easily controlled with low-dose colchicine (28). Individuals with no or only one pathogenic *MEFV* mutation tend to have a milder disease compared to those with biallelic pathogenic variants (29). These observations indicate an additional role of environmental factors in the FMF phenotype.

Whether the *E148Q* mutation is merely a polymorphism or a sequence alteration causing the disease remains uncertain (30,31). The penetrance of the *E148Q* mutation is reduced, and *E148Q* homozygotes are either asymptomatic or may have mild disease. Additionally, amyloidosis is rare in individuals with these mutations. However, patients carrying the *E148Q* mutation along with an additional different mutation are almost always symptomatic. In one study, the penetrance of *M694V*/*E148Q* was found to be 17 times higher than that of *M694V*/-. This suggests that the *E148Q* mutation plays an active role when combined with the *M694V* mutation (32).

Considering other genetic factors, the incomplete penetrance and variable presentations of FMF suggest the presence of potential genetic factors that could influence the disease's presentation. Evidence that another gene may modulate the clinical features of the *MEFV* gene is demonstrated by the segregation of different alleles of the major histocompatibility class I chain-related gene A (*MICA*) among FMF patients with different clinical features. In a study evaluating 151 affected patients and family members for the presence of five common MICA alleles, the A-9 allele was strongly associated with early disease onset in *M694V* homozygotes, while the A-4 allele was found to impact the frequency of FMF attacks (33). The mechanism by which MICA or another closely linked gene influences the FMF phenotype is not yet clear.

In one study, the presence of the serum amyloid A1 (SAA1) alpha homozygous genotype was associated with a sevenfold increased risk of renal amyloidosis compared to other SAA1 genotypes (34).

EPIGENETIC

For a long time, conventional knowledge held that altering the DNA sequence was the only means to potentially induce phenotypic variation. However, in 1942, Waddington introduced the term "epigenetics", which explains changes in gene functions capable of being transmitted to subsequent generations without direct alterations to the DNA sequence itself (35,36).

The study of epigenetics facilitates the identification of various disease biomarkers, empowering researchers and healthcare experts to detect specific diseases based on associated epigenetic mechanisms at an early stage, before their full manifestation or progression. Such an approach is pivotal in formulating tailored treatment or prevention strategies for prospective patients (37).

Numerous epigenetic mechanisms have been studied, with DNA methylation, histone modification, and noncoding RNAs—particularly microRNAs (miRNAs)—emerging as the most extensively investigated within the spectrum of inflammatory diseases (38).

DNA Methylation

DNA methylation stands as a predominant epigenetic mechanism influencing gene expression and phenotype without altering the underlying DNA sequence. This process, primarily occurring within CpG islands of gene promoters, orchestrates chromatin remodeling, subsequently impacting transcriptional activity and protein levels (39).

In the context of FMF, investigations into the methylation status of the *MEFV* gene, a key player in the disease pathogenesis, have yielded conflicting results. While some studies suggested a potential link between *MEFV* methylation and disease severity, inconsistencies emerged, underscoring the complexity of epigenetic regulation in FMF manifestation (**Table 1**) (16,40-43).

Moreover, emerging evidence implicates epigenetic modifications in the regulation of inflammasome complexes, shedding light on novel pathways contributing to FMF pathophysiology. The epigenetic regulation of NLRP13 and NLRP3 inflammasomes, along with their impact on IL-1β expression, suggests a multifaceted interplay between epigenetics and

Table 1. Studies investigating DNA methylation in FMF

Study	Findings
Ulum et al. (2015) (40)	No correlation found between *MEFV* gene methylation and clinical symptoms in Turkish children diagnosed with FMF.
Kirectepe et al. (2011) (41)	Higher levels of *MEFV* gene methylation observed in FMF patients compared to healthy controls, associated with decreased gene expression.
Doğan et al. (2019) (42)	No correlation found between *MEFV* methylation and *MEFV* expression levels in pediatric FMF patients in Turkey.
Zekry et al. (2023) (43)	No significant difference observed in methylation levels of *MEFV* gene exon 2 between colchicine responders and nonresponders in FMF patients.

FMF; Familial Mediterranean Fever methylation

inflammatory processes in FMF (44).

Furthermore, insights into the potential influence of DNA methylation on colchicine responsiveness among FMF patients highlight the therapeutic implications of epigenetic variability. However, definitive conclusions regarding the efficacy of colchicine in methylation-associated cases await further elucidation through expanded research endeavors. While the results showed that the colchicine nonresponders had a greater methylation level of exon 2 of the *MEFV* gene than did the colchicine responders, these results were deemed to be nonsignificant (43).

Overall, while the role of DNA methylation in FMF etiology and treatment response remains an area of active investigation, it is evident that epigenetic mechanisms contribute significantly to the clinical heterogeneity and pathogenic mechanisms of this complex autoinflammatory disorder. Future studies elucidating the intricate interplay between epigenetic modifications and FMF phenotypes hold promise for advancing both diagnostic and therapeutic strategies in the management of this debilitating condition.

Histone Modification

Histone modification emerges as a pivotal epigenetic mechanism intricately intertwined with DNA methylation, collectively orchestrating chromatin dynamics and gene expression patterns throughout cellular growth and development (45). While histone modifications encompass a diverse array of biochemical alterations, including methylation, acetylation, phosphorylation, ubiquitination, and SUMOylation, their cumulative effects govern transcriptional activity either by directly modulating chromatin structure or via interactions with effector proteins (**Table 2**) (16,46-49).

Of particular interest is the role of histone modifications in the activation of the NLRP3 inflammasome, a central mediator of autoimmune and autoinflammatory disorders such as systemic lupus erythematosus, rheumatoid arthritis, and Behçet disease. Despite the well-established implications of histone modifications in these diseases, their role in FMF remains largely unexplored (**Table 3**) (16,50-52).

Notably, histone acetylation dynamics have been implicated in the regulation of the NLRP3 inflammasome, exemplified by studies demonstrating increased NLRP3 expression levels upon histone acetylation in various inflammatory contexts (48,49,53). Similarly, histone demethylation has been shown to modulate NLRP3 inflammasome activity, underscoring the intricate interplay between histone modifications and inflammatory responses.

The shared genetic and inflammatory features between FMF and Behçet disease warrant investigation into the potential role of histone modifications in FMF manifestation (54). Studies elucidating the impact of histone acetylation, histone demethylation,

Table 2. Histone modifications and their effects

Histone Modification	Effect on Gene Expression
Methylation	Can lead to either gene activation or repression, depending on the specific lysine or arginine residue methylated. Represses gene expression when occurring on H3K9, H3K27, and H4K20. Activates gene expression when occurring on H3K4, H3K36, and H3K79.
Acetylation	Activates gene expression by neutralizing the positive charge of lysine residues, allowing DNA to remain accessible to transcriptional machinery.
Phosphorylation	Generally results in the activation of gene expression.
Ubiquitination	Can lead to either the activation or repression of gene expression. Monoubiquitylation of H2A mainly represses gene expression, while that of H2B activates gene expression.
SUMOylation	Generally associated with transcriptional repression.

Table 3. Role of histone modifications in inflammasome regulation and autoinflammatory diseases

Inflammasome Regulation	Role of Histone Modifications
Activation of NLRP3 Inflammasome	Histone acetylation dynamics, such as increased acetylation of histones H3K9 and H4 in the promoter region of NLRP3, have been shown to increase its expression levels and activate the inflammasome.
Regulation of Behçet's Disease (BD) **Manifestation**	Histone modifications, particularly the regulation of histone acetylation by SIRT1, have been implicated in the manifestation of BD, suggesting potential treatment options targeting histone acetylation.

ubiquitination, and SUMOylation on inflammatory pathways in experimental models of FMF hold promise for expanding our understanding of epigenetic contributions to disease expression and potential therapeutic targets (**Table 4**).

In summary, exploring the role of histone modifications in FMF pathophysiology not only sheds light on the underlying mechanisms driving disease manifestation but also offers novel avenues for therapeutic intervention and personalized treatment strategies aimed at mitigating inflammation and improving patient outcomes. Further research in this area is imperative for unraveling the complex interplay between epigenetics and autoinflammatory disorders, ultimately paving the way for more effective management and targeted therapies.

miRNAs

microRNAs (miRNAs) is as pivotal regulators of gene expression, orchestrating intricate cellular processes through post-transcriptional mechanisms. These small noncoding RNA molecules, encompassing approximately 2600 mature forms in humans, exert their influence by modulating mRNA stability and translation, thereby impacting diverse biological pathways (55).

The role of miRNAs extends beyond intracellular functions, as they are actively secreted into extracellular fluids, serving as intercellular messengers that facilitate communication between cells (56). Through their interactions with target genes, miRNAs play a crucial role in modulating immune responses, with implications in both proinflammatory and anti-inflammatory processes. Several immune response mechanisms, such as the proliferation and differentiation of B and T cells, the amplification of monocytes and neutrophils, the stimulation of antibody production, and the secretion of inflammatory mediators, have been associated with miRNAs (57).

miRNAs have emerged as key players in the pathogenesis of FMF, influencing various mechanisms such as apoptosis, inflammation, and autophagy (58). Studies have identified differential expression patterns of specific miRNAs in FMF patients, particularly those homozygous for the *M694V* mutation, compared to healthy controls. These dysregulated miRNAs, such as miR-144-3p, miR-21-5p, and miR-451, are implicated in immune processes and cytokine regulation, suggesting their potential as biomarkers for disease activity and therapeutic targets (59).

Moreover, investigations into the association between specific miRNAs and FMF genotype have revealed intriguing findings, with miR-107 showing significant downregulation in patients carrying the *M694V* mutation (60). Such insights not only deepen our understanding of the molecular mechanisms underlying FMF but also hold promise for the development of personalized diagnostic and therapeutic strategies.

The studies exploring the therapeutic potential of miRNAs in FMF have identified miR-204-3p as a candidate for modulating the phosphoinositide 3-kinase gamma (PI3Kγ) pathway, a key mediator of inflammatory cytokine release. By targeting this pathway, miR-204-3p offers a potential avenue for mitigating inflammation and ameliorating disease symptoms in FMF patients (61).

The microarray analysis conducted by Latsoudis et al. highlighted elevated expression levels of miR-4520a in FMF patients, suggesting its involvement in FMF pathogenesis through the regulation of autophagy via the mTOR pathway (62). Similarly, investigations by Akkaya-Ulum et al. revealed differential expression of inflammatory pathway-related miRNAs in FMF patients, with distinct profiles observed in homozygous and heterozygous individuals (**Table 5**) (16,63). Notably, miR-197-3p emerged as a potential therapeutic target, with its overexpression demonstrating anti-inflammatory

Table 4. Histone modifications and their effects

Shared Features	Implications and Studies
Genetic Overlap	*MEFV* mutations, particularly *M694V*, have been associated with increased risk of Behçet's Disease (BD) in regions where both FMF and BD are prevalent.
Inflammatory Features	Shared pathophysiological features suggest potential shared mechanisms between FMF and Behçet's Disease, warranting further investigation.

Table 5. Studies Investigating miRNA Expression in FMF Patients

Study	Findings
Latsoudis et al. (2017) (62)	Higher expression of miR-4520a in FMF patients, targeting RHEB involved in autophagy regulation.
Akkaya-Ulum et al. (2017) (63)	Differential expression of miRNAs related to inflammatory pathways in FMF patients with *MEFV* mutations.
Akkaya-Ulum et al. (2021) (58)	Overexpression of miR-197-3p in FMF patients, exhibiting anti-inflammatory effects by targeting IL-1R1.
Karpuzoglu et al. (2021) (73)	Dysregulated expression of miRNAs involved in apoptosis in FMF children.
Abdelkawy et al. (2021) (65)	Evaluation of miR-181a and miR-125a as potential biomarkers of inflammation in FMF patients.

FMF; Familial Mediterranean Fever methylation, RHEB; ras homolog enriched in brain, miRNA; microRNA

effects by targeting IL-1R1 and modulating NF-κB signaling.

Furthermore, studies evaluating miRNA expression in FMF patients undergoing colchicine treatment have identified potential biomarkers associated with treatment response (64). The upregulation of miR-132, miR-15a, and miR-181a in colchicine-treated patients suggests their involvement in mediating the anti-inflammatory effects of colchicine. Additionally, investigations into the role of miRNAs in apoptotic pathways revealed dysregulated expression patterns in FMF children, further implicating miRNAs in disease progression.

Moreover, recent studies have explored the utility of miRNAs as biomarkers of inflammation in FMF, with miR-181a and miR-125a showing promise in this regard (**Table 6**) (16,65). Elevated levels of proinflammatory cytokines and decreased expression of anti-inflammatory miRNAs were observed in FMF patients compared to healthy controls, highlighting the potential of miRNAs as diagnostic and prognostic markers.

In conclusion, the dysregulation of miRNAs in FMF underscores their multifaceted roles in disease pathogenesis, treatment response, and inflammation. Further elucidation of miRNA-mediated mechanisms holds significant promise for the development of novel therapeutic strategies and personalized approaches for managing FMF. Additionally, the utility of miRNAs as biomarkers offers valuable insights into disease monitoring and prognosis, paving the way for improved clinical management of FMF patients.

Novel Therapies in FMF

Colchicine, a medication derived from the autumn crocus plant, has indeed been employed for centuries in treating various conditions, including gouty arthritis. Its mechanism of action was elucidated in the 1960s, and its effectiveness in treating FMF. Since its recognition as the treatment of choice for FMF in 1974, colchicine has transformed the management of this condition (66). Colchicine is subject to usage constraints owing to its narrow therapeutic index and the possibility of adverse effects. Gastrointestinal disturbances are prevalent, with about one-third of patients experiencing partial remission, while 5–10% do not respond to treatment (66).

The approval of novel IL-1 antagonists, such as canakinumab and anakinra, alongside the accumulated experience with alternative medications in targeted treatment contexts, is broadening the therapeutic repertoire available for managing FMF (66-68). Canakinumab has been found effective in controlling and preventing flares in patients with colchicine-resistant FMF (68).

The safety and efficacy of RIST4721, an oral antagonist of acidic CXC chemokine receptor 2 (CXCR2), in FMF subjects, is being investigated in a phase 2 study

Table 6. Key Findings and Implications of miRNA Studies in FMF

Key Findings	Implications
Dysregulated miRNA expression in FMF patients	Insight into molecular mechanisms underlying FMF pathogenesis.
Identification of miRNAs targeting inflammatory pathways	Potential therapeutic targets for modulating inflammation in FMF.
Association between miRNA expression and treatment response	Understanding mechanisms of action of colchicine and other treatments in FMF.
Dysregulated miRNAs in apoptotic pathways in FMF children	Implications for disease progression and potential therapeutic interventions.
Evaluation of miRNAs as biomarkers of inflammation in FMF	Potential diagnostic and prognostic markers for monitoring disease activity.

(69). Due to the proven role of TNF-α's involvement in FMF, studies have promised that TNF-α blockade agents like infliximab, etanercept, and adalimumab may demonstrate favorable outcomes in managing FMF attacks (70). Although FMF patients show alterations in the gut microbiota, the therapeutic role of a commercial probiotic formulation, Lactobacillus acidophilus INMIA 9602 Er-2 strain 317/402 (Narine), did not improve the quality of life and crisis onset in FMF patients, hence the need for additional investigations in this context (71). The potential role of CRISPR-Cas9 gene editing technology in various diseases such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes mellitus, psoriasis, and coeliac disease has been investigated recently (54). CRISPR-Cas9 may represent its immunomodulatory effects by regulating cytokines like IL-1, IL-36, and TNF-α, as well as T cell-related factors. However, these studies have remained in an experimental model (54,72).

CONCLUSION

The exploration of epigenetic mechanisms in FMF has revealed intricate regulatory pathways that contribute to the disease's pathogenesis and clinical manifestations. DNA methylation and histone modifications, two major epigenetic processes, play pivotal roles in gene expression regulation and chromatin remodeling, thereby influencing various aspects of FMF.

Studies have highlighted the involvement of DNA methylation in modulating the expression of the MEFV gene, which encodes the pyrin protein. While inconsistencies exist regarding the correlation between MEFV methylation and disease severity, emerging evidence suggests a potential link between MEFV methylation status and patient response to colchicine treatment. Additionally, investigations into the epigenetic regulation of inflammasome components, such as NLRP13 and NLRP3, have unveiled novel insights into FMF pathophysiology.

Moreover, histone modifications, including methylation, acetylation, and phosphorylation, have been implicated in the activation of the NLRP3 inflammasome and the regulation of inflammatory responses in FMF. Although research on histone modifications in FMF remains limited, insights from related autoimmune and autoinflammatory disorders provide valuable directions for future investigations.

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Case Report

Coexistence of Autosomal Dominant Polycystic Kidney Disease and Hereditary Distal Renal Tubular Acidosis in a Child: A Very Rare Case Report and Literature Review

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited cystic kidney disease that exhibits a variety of clinical manifestations due to multiple mutation types and a variety of penetration powers.

Renal tubular acidosis (RTA) is a group of transport defects secondary to reduced proximal tubular reabsorption of bicarbonate (HCO3-), the distal secretion of protons (hydrogen ion, H+), or both, resulting in impaired capacity for net acid excretion and persistent hyperchloremic metabolic acidosis with a normal anion gap (AG) 12±2 mmol/L. The above conditions are either secondary to other causes or primary, with or without known genetic defects.

ADPKD rarely can cause RTA, however, the potential heritage interactions of ADPKD and distal renal tubular acidosis (dRTA) mutations have not yet been identified. As far as we know, dRTA and ADPKD have not been reported in the same patient. Here we present a 4-year-old patient who was diagnosed with ADPKD with *PKD1* (NM_001009944.3): c.11014C>T (p.Arg3672Trp) heterozygous and type1 RTA (dRTA) with *SLC4A1* (NM_00342.4): c.1765C>T (p.Arg589Cys) heterozygous mutation, but no sign of cystic kidney disease in his mother despite having the same *PKD1* mutation. His father had an incomplete form of dRTA presented with a SLC4A1 mutation (with no metabolic acidosis, a urinary pH of 7, and a history of recurrent kidney stones). The child is being treated with 5–8 mEq/kg of citrate, and cyst growth seems to have stopped following a 2-year follow-up. The case highlights the importance of "two hits" or the coexistence of different abnormalities in the development of cystic formation in ADPKD.

Keywords: Polycystic kidney disease, *PKD1*, *PKD2*, *SLC4A1*, renal tubular acidosis, mutation

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is mainly caused by mutations in *PKD1* (80–85%) and *PKD2* (15–20%), which encode Polycystin 1 (PC1) and Polycystin 2 (PC2), respectively (1-3). The incidence of de novo ADPKD sequence variants is about 10% in affected cases (4). It affects around 1 in 1,000 live births (5-6). The disease is characterized by the formation of cysts in various locations in the kidneys, occurs in only a portion of the tubules in the nephrons, but mostly in the distal regions. Cysts development and growth usually start in utero and progress, but kidney function is typically conserved until the age of 30–40 years (1-6). The progressive development and growth of numerous bilateral kidney cysts, result in urine concentration defects, hypertension, acute and chronic pain, kidney stones, hematuria, urinary tract infections, and, most importantly, kidney function loss (7). ADPKD is usually an adult-onset disease in which approximately 70% of patients progress to kidney failure. Up to now, no interventions were shown to slow the rate of disease progression in ADPKD. The treatment of ADPKD has therefore been symptomatic, with the aim of reducing

morbidity and mortality associated with disease manifestations.

Renal tubular acidosis (RTA) is hyperchloremic metabolic acidosis with a normal anion gap (AG):12±2 mmol/L. Distal RTA (dRTA) can be secondary related to the causes such as obstructive uropathy, reflux nephropathy and chronic tubulointerstitial nephritis or primary with or without known genetic defects. Hereditary dRTA is a rare genetic disorder (8). The genetic cause is determined in only 70%–80% of patients (8-10). Three different transport proteins have been found as causes of dRTA; the B1/ATP6V1B1, a4/ATP6V0A4 subunits of the vacuolar-type H+-ATPase (H+-ATPase), and chloride–bicarbonate exchanger AE1/SLC4A1 band 3 (11,12). While the autosomal dominant form of dRTA is related to AE1 mutation, the autosomal recessive form is associated with mutations in genes *ATP6V1B1*, *ATP6V0A4*, and *SLC4A1*, which encode subunits a4 and B1 of V-ATPase, and the AE1 bicarbonate/chloride exchanger respectively (13).

In AE1 protein; the gene that encodes the Cl−/HCO3− exchanger, mutations usually present as dominant dRTA, but a recessive pattern has been recently described (13-16). Several studies have shown trafficking defects in the mutant protein rather than the lack of function as the major mechanism underlying the pathogenesis of dRTA from AE1 mutations. Hereditary dRTA typically presents in infancy, however, especially the appearance of dRTA, in individuals with autosomal dominant and recessive form of *SLC4A1* can be later according to other types of genetic defects (*ATP6V1B1* and *ATP6V0A4*) (11-15).

Dominant AE1 mutation can exhibit a complete or incomplete dRTA clinical transmission (14,15). The clinical variant of dRTA that presents with inadequate urinary acidification without spontaneous metabolic acidosis is termed incomplete dRTA (idRTA). Failure to acidify urinary pH <5.3 in the NH4Cl load was considered diagnostic for idRTA. These conditions significantly impact the quality of life in untreated individuals and can lead to growth failure, osteoporosis, rickets, and even kidney failure. Moreover, 8.33% of the patients presented with tubular proteinuria (urine protein <1 g/day) and low-molecular-weight proteinuria on urine protein electrophoresis. Metabolic acidosis is mild in *SLC4A1* mutations, and all cases with hereditary dRTA can develop nephrocalcinosis. Children with dRTA should be followed-up long-term for hearing ability, kidney function, and growth (17).

The primary objectives of dRTA treatment are correction of the metabolic acidosis and the avoidance of disease-related complications. Alkali in the form of a mixture of sodium and potassium citrate salts is recommended to be administered to maintain normal serum bicarbonate. The amount of alkali needed usually decreases with age. Infants require as much as 5–8 mEq/kg of citrate or HCO3-, whereas adults require only about 0.5–1 mEq/kg. Potassium supplementation is needed in the majority of patients with hypokalemic hereditary distal RTA.

CASE

TA 50-month male child suffering from dysuria, fever, and suprapubic pain was bought to the pediatric nephrology polyclinic. He was born from unrelated parents and on healthy until he had the urinary tract infection episodes onset 1 year ago. The patient's laboratory findings demonstrated mild proteinuria, leukocyturia, and a slightly increased CRP level. The whole blood count and the remaining biochemical parameters were found in normal ranges. However, urine pH was 5.5 and in an arterial blood gas analysis, pH; 7.26, K+; 2.42 mEq/L, HCO3-; 15 mmol/L were found. 24 hours urine collection revealed 7 mg/kg/day (>4 mg/kg/day) hypercalciuria, proteinuria and beta2 microglobulinuria in normal ranges. The anion gap (AG) was calculated as 13 mmol/L (AG:12±2 mmol/L). Considering all clinical and laboratory findings, the patient was diagnosed with dRTA and he was evaluated in terms of primary and secondary dRTA.

The kidney USG indicated anechoic corticopelvic cystic lesions in both kidneys, which cannot be clearly distinguished from the focal sequelae of caliectatic appearances. The abdominal and brain computed tomography (CT) also showed bilateral multiple kidney

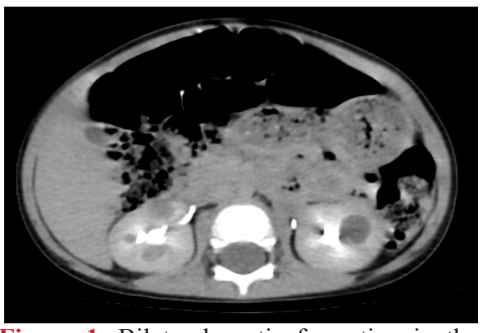

Figure 1. Bilateral cystic formation in the kidneys axial computed tomography image (no kidney stone)

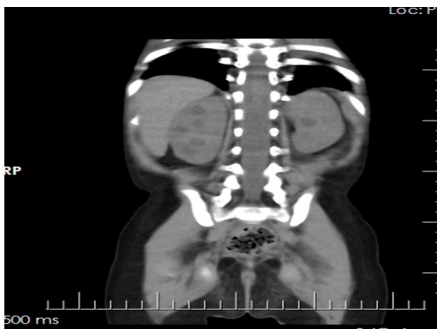

Figure 2. Bilateral cystic formation in the kidneys coronal computed tomography image (no kidney stone)

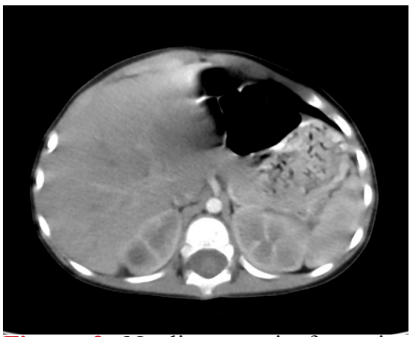

Figure 3. No liver cystic formation in the child's computed tomography images

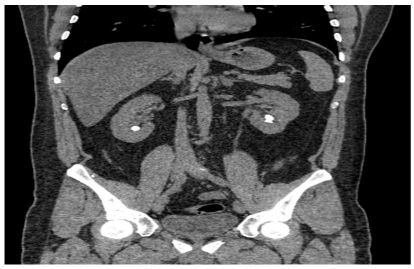

Figure 4. Bilateral kidney stones (Father's computed tomography image)

cystic formations with no intrinsic and peripheral contrast enhancement (the maximum sized cyst was in 12X8.5 mm in the right kidney lower pole) (**Figure 1-3**), but there was no sign of liver, brain, or pancreatic ductal cysts. The child has large cortical and corticomedullary cysts, considering the clinical view and the findings are suggestive of *PKD1* as the cause of cystic formation.

The patient was evaluated for PKD and primary known genetic defects of dRTA with whole genome sequencing analyzes. Both dRTA and ADPKD, genetically mutant have been reported in the child; with a Polycystin-1 (*PKD1*) pArg3672Trp heterozygous and type 1 RTA (dRTA) *SLC4A1* pArg 589Cys heterozygous mutation. The clinical features and the result of genetic analysis suggest that the child has a hereditary dRTA and ADPKD1.

The child was evaluated for hearing abilities, growth deficiency, rickets, and hereditary hemolytic anemia (a very rare complication), and was found negative for those. The patient was diagnosed that he has ADPKD and dRTA with no extra renal manifestations. The patient was put on potassium citrate salts treatment to correction of hypokalemia and metabolic acidosis, monitoring with blood $HCO3^-$ and urinary PH, and calcium level.

Meanwhile, the parents were evaluated for cystic kidney disease and RTA. Mother had no clinical signs of ADPKD and RTA, however, the father had a history of recurrent kidney stones without kidney cysts and metabolic acidosis (**Figure 4**). The genetic analysis panel of mother and father show that mother has *PKD1* (NM_001009944.3): c.11014C>T (p.Arg3672Trp) heterozygous and father has *SLC4A1* (NM_00342.4): c.1765C>T (p.Arg589Cys) heterozygous mutation.

Genotypic and phenotypic characteristics of patient, mother and father

- The child: The child has ADPKD with *PKD1* heterozygous mutations, and exhibits diffuse cystic formation in both kidneys. The child also has a hereditary dRTA related to the *SLC4A1* gene mutation.
- The mother (40 years old): Despite carrying the same mutations of the patient, she has no clinical sign of the ADPKD. She had no history of kidney stones and also the *SLC4A1* gene mutation is negative.
- The father (45 years old): The father has *SLC4A1* gene heterozygous mutation as the same of patient has, related to the hereditary dRTA. He has a history of kidney stones without metabolic acidosis, but with a failure to maximally lower urine pH (urinary pH was 7) (**Figure 4**). The father presentation reflects the variant of type of dRTA that is termed idRTA.

DISCUSSION

Although ADPDK is considered an adult disease, the phenotypic spectrum of ADPKD ranges from in utero onset to adequate kidney function at old age. About 2% of ADPKD cases occur in early childhood, and the severity of the disease makes it difficult to distinguish from autosomal recessive polycystic kidney disease. ADPKD has various presentation types due to concomitant different penetration poverty of the mutations. Similar genetically mutations may express varying severity of disease in members of the same family. The mechanism by which a heterozygous mutation results in cyst development is controversial. The pathogenesis underlying the polycystic kidney disease phenotypes is still unclear. All these variability's suggest that PKD mutations alone may not be sufficient for cyst development and support a two hit hypothesis, due to possible complex interaction of the affected gene with other factors (18,19). In addition to primary cilia defects, PKD cells exhibit many other cellular aberrations (dedifferentiation, increased proliferation and apoptosis, polarity defects, and altered gene expression) proposed to be associated with cystogenesis and/or cyst progression (20,21).

The "two hit' has been reported which they thought to be effective in cyst formation in ADPKD (18,19). Schlevogt et al. reported that the mutant *SEC61A1* results in enhanced proteasomal degradation and impairs biosynthesis of PC2 (22). Similarly, in our case, the coexistence of dRTA may promote the early and diffuse cystic formation.

To date, whole genome sequencing or next-generation sequencing of long polychain reaction products, and somatic mutations of PKD genes can be detected in >90% of kidney cysts (23). Studies reported that the cyst formations of disease is dosage of functional *PKD1* protein dependent, where incompletely penetrant alleles influence disease severity (24,25). Additionally, a dose of functional polycystin-1 that falls below a critical threshold may be important to promote cyst formation (24,25). In this case, the mother has the same heterozygous PKD mutation (NM_001009944.3): c.11014C>T (p.Arg3672Trp), however, in contrast to the child, she had no cystic formation in her kidneys at the age of 40 years. It supports the previous data arguing that *PKD1* and *PKD2* gene mutations are not solely enough to develop cyst formation. We could not study

the RNA expression of PC1, in the mother's urine, or the expression of RNA of mutant *PKD1*, in immortalized urine sediment cells. So it can be speculated that the mother functional PC1 level expected to be normal or high than critical threshold.

AE1 mutations causing dRTA were initially described by Bruce et al., and later by Karet et al. (13-16,26). AE1 mutations are classified as autosomal dominant and recessive dRTA (26,27). AE1 protein is encoded by the *SLC4A1* gene in humans and present in the basolateral face of α-intercalated cells of the collecting ducts of the nephron. Since AE1 is abundantly present on erythrocytes and helps maintain cytoskeleton structure as well as ion transport, hemolytic anemia (HA) may be seen in some types of hereditary dRTA associated with AE1 mutations. In cases with dominant AE1 mutations, erythrocytes are capable to maintain chloride/bicarbonate traffic (in contrast to α-intercalated cells), thus membrane functions remain intact and this explains the absence of HA. The only AD AE1 mutation causing HA with dRTA has been reported with A858D mutation from Malaysia and India (28,29). Most autosomal recessive AE1 mutations reported so far have been seen associated with HA as a result of Southeast Asia ovalocytosis or hemolytic spherocytosis (30,31). HA however, is not always present in autosomal recessive AE1 mutations. In this report, the child has dRTA with *SLC4A1* (NM_00342.4): c.1765C>T (p.Arg589Cys) heterozygous mutation but no other extra renal manifestation such as hemolytic anemia.

Heterozygous AE1 mutation can exhibit a complete or idRTA clinical transmission (18). Bruce et al. reported idRTA in 8 of 18 patients and over the follow-ups of 10 years, and 2 of 8 developed acidosis (26). Incomplete dRTA was also described in the father of 2 affected children from Brazil (32). Then after, *AD A888L* mutation was found in this family. The incomplete form of dRTA, like complete dRTA, presents with failure to maximally lower urine pH, but blood pH and plasma bicarbonate remain normal. In our case, *SLC4A1* heterozygous mutation has been described in the father; with low urine acidification capacity and kidney stones, and no metabolic acidosis. Given all of this, the father has idRTA and according to our knowledge, this is the first case from Turkey.

Genetic mutations responsible for inherited diseases often alter the structure of transcribed mRNA and the resulting protein, inducing instability in both. However, in our patient, we could not measure the mRNA activities.

CONCLUSION

This case underscores the diverse phenotypic manifestations of genetic mutations, as demonstrated by the child's presentation of both ADPKD and dRTA, while the mother carries the same *PKD1* mutation without exhibiting symptoms of ADPKD. The genetic analysis also revealed the father's heterozygous mutation in *SLC4A1*, leading to idRTA, further highlighting the variability in disease expression within families. The pathogenesis of ADPKD and dRTA involves intricate molecular mechanisms, including potential interactions between mutated genes and other cellular factors. The "two-hit" hypothesis, where secondary mutations or environmental factors exacerbate disease progression, may contribute to the early and diffuse cystic formation observed in this case. Moreover, in adults, even in the absence of metabolic acidosis, genetic testing should be considered if there is insufficient urine acidification capacity along with a history of kidney stones.

Treatment strategies for these conditions focus on managing symptoms and complications, such as metabolic acidosis and electrolyte imbalances, to improve patient outcomes and quality of life. The utilization of alkali therapy for correcting metabolic acidosis in dRTA and close monitoring of kidney function are crucial aspects of patient management.

DECLARATIONS

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Letter to Editor

Comparison of FDG and Ga-68 PSMA PET/CT Findings in a Case of Metastatic Hepatocellular Carcinoma

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To The Editor

Prostate-specific membrane antigen (PSMA) is a transmembrane protein secreted from the prostate epithelium. Ga-68 PSMA positron emission tomography/computed tomography (PET/CT) is a widely used imaging method for the visualisation of prostate cancer (1-3). PSMA expression has also been reported for some non-prostate malignancies including hepatocellular cancers (4,5). Demonstration of PSMA uptake in non-prostate malignancies may constitute an alternative for targeted therapies with 177 Lu-PSMA. Therefore, the use of PSMA-targeted imaging and therapy is expected to increase dramatically in the coming years (6,7). Hepatocellular carcinoma (HCC) is a primary malignant liver tumor originating from hepatocytes, more prevalent in populations with a high incidence of viral hepatitis, with approximately 80% developing on the background of chronic hepatitis B and C infections. It is the fifth most common cancer worldwide. The diagnosis of hepatocellular carcinoma includes imaging methods, biomarkers, and biopsy (1). Imaging techniques include ultrasonography, CT, and magnetic resonance imaging. Alpha-fetoprotein is examined as a biomarker (1). Biopsy is employed when a diagnosis cannot be made despite all other tests. It has been reported that 95% of HCC cases show PSMA uptake due to tumor neovascularization, and imaging with 68Ga-PSMA has been found to detect more cases compared to FDG (9), 18F-choline, and contrast-enhanced CT, especially in areas where FDG uptake is lower, indicating higher PSMA uptake (8-10). In this case study, we aimed to share the findings of a patient diagnosed with HCC who underwent whole body F-18 fluorodeoxyglucose (FDG) PET/CT imaging and Ga-68 PSMA PET/CT imaging and its contribution to diagnosis and staging. PSMA is involved in many malignancies such as glial, renal, lung, colorectal and hepatocellular cancers due to its tumor neovascularization properties.

Case: A 70-year-old male patient diagnosed with hepatocellular carcinoma (HCC) underwent FDG PET/CT imaging for initial staging (**Figure 1**). The imaging revealed an irregularly bordered mass approximately 199x151 mm in size at the level of liver segments 7-8-4-5 with a maximum SUV (SUVmax) of 5.9. In addition

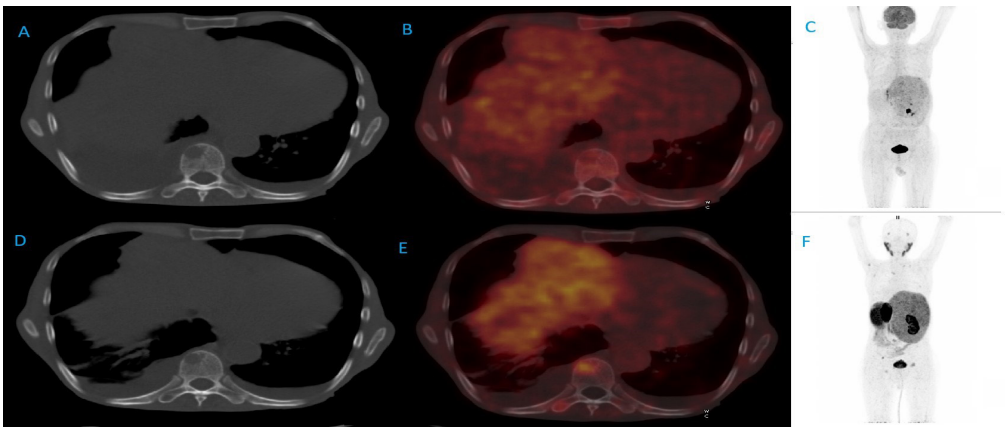

Figure 1. BFigure 1. Axial tomography image (A), axial positron emission tomography/computed tomography image (B), MIP image (C) in FDG PET/CT study and axial tomography image (D), axial positron emission tomography/computed tomography image (E), MIP image (F) in Ga-68 PSMA PET/CT study of lesions observed in T9 vertebral corpus and right transverse process of a patient with HCC.

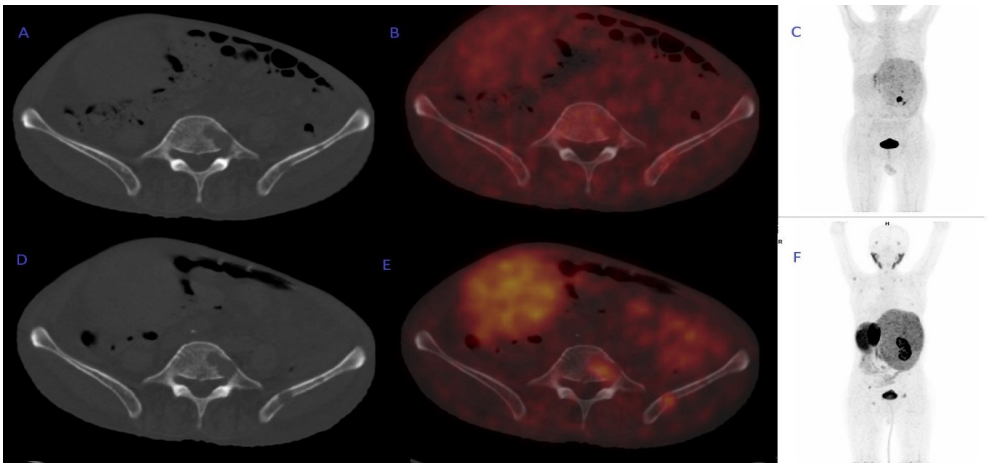

Figure 2. Lesions observed in the L5 vertebral body and left iliac bone of a patient diagnosed with HCC on FDG PET/CT study; axial tomography image (A), axial positron emission tomography/computerized tomography image (B), MIP image (C), and in the Ga-68 PSMA PET/CT study; axial tomography image (D), axial positron emission tomography/computerized tomography image (E), MIP image (F).of a patient with HCC.

to this lesion, multiple irregularly bordered masses and nodular lesions were observed in both lobes, with the largest being about 67 mm in diameter at the level of liver segment 6, where the SUVmax was 3.8. No pathological FDG uptake was observed in the widespread lytic lesions in the skeletal system seen on CT. In the differential diagnosis of mass lesions and bone metastases, Ga68 PSMA PET/CT imaging was conducted (**Figure 2**). It revealed increased PSMA uptake with an SUVmax of 6.9 in the irregularly bordered mass of approximately 199x151 mm at the level of liver segments 7-8-4-5. Besides this lesion, increased PSMA uptake with an SUVmax of 7.3 was found in multiple irregularly bordered masses and nodular lesions observed in both lobes, with the largest about 67 mm in diameter at the level of liver segment 6. Furthermore, in the skeletal system, significantly increased PSMA uptakes were detected with an SUVmax of 5.3 in the widespread lytic lesions. The role of F-18 FDG PET/CT imaging is generally limited in HCC cases due to the tumor's low metabolism. Ga-68 PSMA PET/CT is a current method used in prostate cancer imaging. However, increased PSMA expression has also been found in many non-prostate malignancies, including HCC. In our case, the PSMA uptake in the lytic lesions of the skeletal system was significantly higher than the FDG uptake.

In conclusion, Ga-68 PSMA PET/CT imaging can be used in many non-prostate related malignancies. We perform Ga68 PSMA PET-CT imaging to contribute to diagnosis and staging in patients who have undergone FDG PET-CT but do not show uptake. In this case, we can say that Ga-68 PSMA PET/CT was useful and superior in the detection of bone metastases in addition to the primary tumour. When evaluated on a case basis, it can be considered that tumours and metastases detected with PSMA may also be useful in the use of targeted therapies.

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Letter to Editor

Cancer Treatment with Immune Checkpoint Inhibitors in Kidney Recipients

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To The Editor

After an organ transplant, cancer stands as one of the three primary culprits leading to mortality, alongside cardiovascular disease and infection (1,2). Notably, advancements in screening, prophylaxis, and interventional therapies have contributed to a decline in the occurrence of cardiovascular disease and infection, enhancing post-transplant outcomes. However, immunosuppressive regimens remain be most important causes for increased cancer risk in this population. Research findings reveal a notable increase in the risk of cancer, ranging from two to four times the baseline rate, following organ transplantation (3).

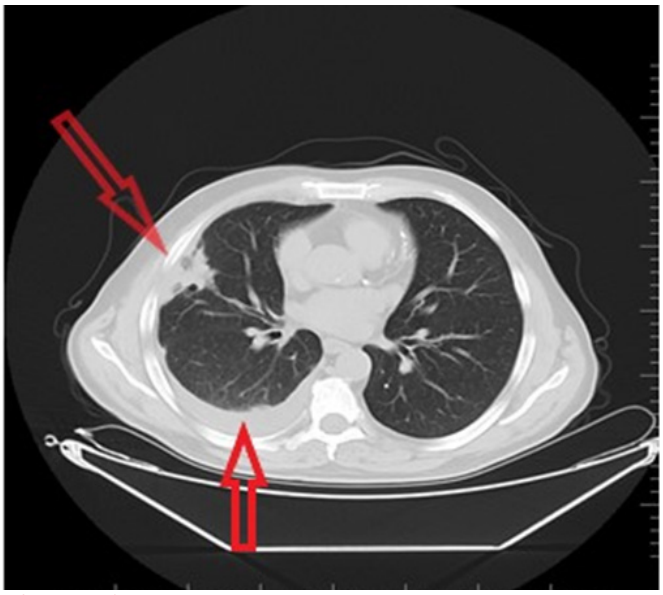
In the past decade, a transformative shift in cancer therapy has emerged through the targeted manipulation of the immune system via immunotherapy. This revolutionary approach involves the modulation of the patient's existing immune system using immune checkpoint inhibitors (ICIs), such as anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), anti-programmed cell death (PD1), and anti-programmed cell death ligand 1 (PDL1), resulting in sustained remissions across diverse tumor types (4,5). In the CheckMate-057 and CheckMate-017 trials, nivolumab demonstrated a significant enhancement in overall survival compared to docetaxel in patients with advanced non-small cell lung cancer experiencing disease progression following platinum-based chemotherapy (the median overall survival in patients who received nivolumab was 3 months longer (12.2 months vs 9.2 months) (6).

The utilization of immune checkpoint inhibitors in kidney transplant recipients is linked to markedly elevated rates of acute rejection (7). In a recent multicenter retrospective cohort study involving kidney transplant recipients (KTRs) with cancer receiving immune checkpoint inhibitors (ICIs), findings indicated that 42% of patients experienced acute graft rejection, with 65.5% of those cases progressing to end-stage kidney disease (ESKD) necessitating dialysis (8).

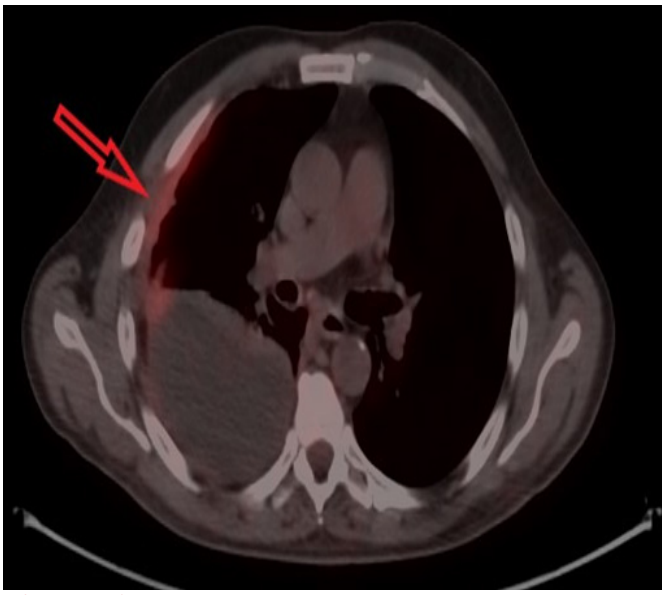
Given all, ICIs are potent to lead to posttransplant acute rejection and rejections mainly occur within the first month following initiating the treatment. Unfortunately, an acute rejection following an ICIs course will confuse all clinical outcomes, since the most potent anti-rejection treatment is not possible during an active malignancy (9). Moreover, the worsening allograft function will confuse the dosing of chemotherapy and increase unadorable hospitalization. So, considering an ICIs regimen + chemotherapy in an organ recipient under immunosuppressive treatment stands there as a crucial dilemma in modern medicine. Nevertheless, it is crucial to highlight that not all immunomodulators exhibit uniform effects regarding allograft rejection. For instance, studies indicate that nivolumab demonstrates a higher potency in inducing allograft rejection, whereas ipilimumab exerts a comparatively lesser impact on rejection outcomes (10).

In this context, here we present a briefcase to highlight the importance of the issue.

Case: A 53-year-old male patient, who lost his kidney in 2009 due to recurrent kidney stone obstruction and pyelonephritis, underwent a living donor transplant in 2016. A total of 300 mg (3 mg/kg total dose) of ATG was administered. The patient, with no history of rejection and stable renal function, presented to the organ transplantation clinic four months ago with complaints of persistent cough, fever, and right abdominal pain. Clinical, laboratory, and radiological examinations revealed findings related to lower right lung lobe infiltration and pleural effusion (**Picture 1**). The initial diagnosis was lobar pneumonia, and the second evaluation suggested lung cancer. Due to the preliminary diagnosis of malignancy, mycophenolic acid was discontinued, the tacrolimus dose was reduced by 50%,



Picture 1. Right lung-located involvement and ipsilateral pleural effusion (Arrows)



Picture 1. 18-FDG PET-CT demonstrates an increased pleaural glucose uptake (Arrow)

and the prednisolone dose was doubled. Additionally, 1.5 mg/day everolimus in divided doses was added to the treatment. The patient underwent a two-week treatment course comprising moxifloxacin, fluconazole, and oseltamivir (since the initial antibacterial treatment was ineffective, subsequent treatments were targeted to viral or fungal etiologies). A lung biopsy was scheduled for the patient who did not respond to this treatment and experienced fever, cough, chest pain, and high CRP.

Since the patient's lung biopsy was compatible with non-small cell lung cancer (squamous cell cancer), and squamous cell cancer was also detected cytologically in the pleural effusion fluid, the patient underwent lobectomy and pleurectomy + decortication surgery (PET-CT; **Picture 2**). PD-1 expression rate on malignant cells was approximately 80%. The patient was scheduled for chemotherapy, consisting of paclitaxel (175-225 mg/m2, every 3 weeks) + nivolumab (240 mg every 15 days).

At the first outpatient polyclinic control 4 weeks after the treatment of malignancy with administrating nivolumab, creatinine was found to be twice as high as the baseline value. Nivolumab treatment was discontinued, and the paclitaxel dose was halved. An allograft biopsy was performed since serum creatinine level continued to be elevated after 10 days (after excluding all possible causes of creatinine elevation). Biopsy findings were consistent with mixed-type acute rejection.

The patient was treated with 3 doses of 100 mg mini-pulse glucocorticoid and titrated to maintain the tacrolimus trough level at 5 ng/dl. Everolimus level was titrated to 5-8 ng/dl and monitored. Unfortunately, the patient's disease progression continues, and the estimated glomerular filtration rate (eGFR) at the last follow-up is 16 ml/min/1.73 m2. The clinical outcome is projected to be renal replacement therapy shortly (baseline serum creatinine was 1.3 mg/dl and current is 4.23 mg/dl).

In conclusion, the presented case underscores the intricate challenges at the intersection of organ transplantation and cancer therapy. The complex management of immunosuppression, coupled with the potential for acute rejection during cancer treatment, highlights the need for careful, individualized approaches. In renal transplant recipients, the use of ICIs should be carefully evaluated, with consideration given only to cases where these drugs can make a substantial contribution to patient survival.

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