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From Editor

Dear Readers,

It is with great pleasure that we present to you the latest issue of our journal, filled with insightful research and clinical findings across a diverse array of medical disciplines.

In this edition, we delve into the intricate interplay between allergic diseases and systemic side effects following COVID-19 vaccination, shedding light on an increasingly relevant topic in the context of global vaccination campaigns. Additionally, our contributors explore neuromuscular dysfunction and electrophysiological findings in patients with thyroid disorders, offering valuable insights into the management of these conditions. Amidst the challenges posed by the COVID-19 pandemic, our journal also addresses the prognosis and risks faced by renal transplant recipients, providing essential information for healthcare professionals involved in the care of these vulnerable individuals. Furthermore, we present an updated perspective on dyslipidemia and its implications for kidney health, along with discussions on diagnosing and treating monogenic hypertension in pediatric patients, offering valuable guidance for clinicians in managing these conditions effectively. We also showcase remarkable clinical cases, including the successful twin pregnancy of a peritoneal dialysis patient and a rare presentation of multiple and ectopic parathyroid adenoma, highlighting the complexity and diversity of medical conditions encountered in clinical practice.

We extend our heartfelt gratitude to all the authors, reviewers, and editorial staff whose dedication and expertise have made this issue possible. We hope that the contents of this journal will inspire further research, collaboration, and innovation in the field of medicine.

Thank you for your continued support and interest in our publication.

Sincerely,

Hacı Hasan Yeter
Issue Editor/Editorial Board Member
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The Science

Original Article

Are Allergic Diseases a Risk Factor for Systemic Side Effects After COVID-19 Vaccines?

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Abstract

Background: This study aims to evaluate local and systemic adverse reactions following COVID-19 vaccines in patients with a history of allergic diseases and to determine potential risk factors for emerging adverse events.

Methods: During the period from April 1, 2021, to September 30, 2021, a total of 648 adult patients who had been exposed to COVID-19 vaccines were enrolled in this retrospective case-control study. All vaccinated patients were asked to answer a detailed retrospective questionnaire, including systemic and local side effects.

Results: Six hundred forty-eight adult patients [Female: 446 (68.8%), Male: 202 (32.2%)] were enrolled in the study. After the 1st dose of COVID-19 vaccine, 24.1% of patients, and after the 2nd dose of COVID-19 vaccines, 67 patients (12.3%) developed side effects. Female gender, history of previous COVID-19 infection, and COVID-19 vaccine type administered were found to be independent risk factors for systemic side effects after COVID-19 vaccines. Premedication was found to be a protective factor for systemic side effects developing after COVID-19 vaccines.

Conclusion: Systemic side effects against COVID-19 vaccines are very low. Patients with allergic disease do not have an increased risk for systemic side effects that may develop after COVID-19 vaccines. Moreover, doubts or fears about possible side effects in the allergic patient group should not be an obstacle to COVID-19 vaccination.

Keywords: COVID-19, CoronaVac, Pfizer-BioNTech, vaccine side effects, allergies

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) was first reported in December 2019 and then spread all over the world in a short time and was accepted as a pandemic by the World Health Organization (WHO) in March 2020. In the 2 years following its identification, coronavirus disease 2019 (COVID-19) has killed more than 5 million people (1). There is still no effective treatment for the disease. Thus, herd immunity (mass vaccination and herd immunity) for virus protection seems to be the most effective way to turn back to the pre-pandemic period and end of pandemic. However, due to sociodemographic inequalities, vaccine supply problems and vaccine hesitancy, unfortunately, COVID-19 vaccination does not have the desired level and effect.

In Turkey, the first COVID-19 vaccination was started on January 13, 2021, with CoronaVac (Sinovac Biotech, China) to healthcare workers, and then the Pfizer-BioNTech COVID-19 vaccine was added to the vaccination calendar. After April 2021, individuals aged ≥ 60 started to be vaccinated. In December 2021, the total number of COVID-19 vaccines administered in Turkey was 125 million doses (2).

Unfortunately, Covid-19 vaccines also have many side effects and metabolic effects (3). Although the side effects reported with COVID-19 vaccines are usually minor and can be easily controlled with necessary interventions, these side effects lead to doubts about COVID-19 vaccines in patients during the periods when COVID-19 vaccination should be done most rapidly and intensively (4). Additionally, the rapid development and production phases of COVID-19 vaccines and the limited data of the post-vaccination period increase

these doubts.

In phase 2 and 3 of currently approved COVID-19 vaccines, patients with a known allergy or a history of anaphylaxis were excluded from the study (5). After the first Pfizer-BioNTech COVID-19 vaccine was administered, 2 anaphylaxis cases were reported in the media before 24 hours had passed (6). Also, during December 14–23 2020, 175 severe allergic reactions were reported after approximately 2 million Pfizer-BioNTech COVID-19 vaccine administrations, and 21 of these cases were reported to be anaphylaxis (7). This situation created doubts and unanswered questions about the risk of side effects of COVID-19 vaccines in patients with allergic diseases, as well well in patients and clinicians dealing with this patient group (8). Although there are studies on the efficacy and safety of COVID-19 vaccines, however, studies on the course of COVID-19 vaccines in allergic patients are limited. Therefore, our aim with this study was to evaluate local (LSE) and systemic (SSE) side effects after COVID-19 vaccines in patients with allergic diseases, especially allergic rhinitis, asthma, and chronic urticaria, and to determine possible risk factors for these side effects.

METHODS

Among the patients who applied to the allergy and immunology clinic in Konya City Hospital between April 1, 2021 and September 30, 2021, 648 adult patients who received any COVID-19 vaccine and agreed to participate were included in this retrospective case-control study.

An anonymous self-reporting based on a questionnaire related to safety and tolerance of vaccine was applied to the patients included in the study. This questionnaire included demographic data of patients and questions about LSE and SSE developed after vaccination. Age, gender, history of previous COVID-19 infection, COVID-19 vaccine type and number of doses, atopy status of patients, use of a drug that may affect the COVID-19 vaccine side effects, such as antihistamine, steroid and omalizumab before the COVID-19 vaccine, and demographic characteristics such as the presence of a doctor-diagnosed allergic disease were questioned in this survey. The local and systemic side effects developed after vaccination, the time elapsed between immunization and side effects, and the need for treatment for the side effects were also questioned. Information on atopy status, allergen sensitivity and allergic diseases of the patients were obtained from their files.

Patients with a diagnosis/history of asthma, urticaria/angioedema, rhinitis, drug allergy, venom allergy, and contact dermatitis were considered atopic. Pain, redness, swelling at the vaccination site were considered as LSE, and symptoms such as weakness, fatigue, myalgia, arthralgia, fever, headache were diagnosed as SSE. Patients with symptoms indicating that at least two of the skin, respiratory, cardiovascular, and gastrointestinal systems are affected after the COVID-19 vaccine (urticaria/angioedema, dyspnea, syncope, presyncope, hypotension, shock..) were considered anaphylaxis.

Patients who were treated with drugs that have the potential to affect local and systemic side effects such as antihistamine, oral steroid or omalizumab, and patients who were treated with antihistamine and/or steroid therapy to avoid the development of side effects before the COVID-19 vaccine were considered as the patient group who received premedication.

Ethics committee approval of the study was granted by University of Health Sciences Konya City Hospital Ethics Committee (Date: 15.10.2021, decision 2021/012). Written informed consent was obtained from all patients participating in the study.

STATISTICAL ANALYSIS

IBM SPSS 20.0 (Chicago, IL, USA) statistics software was used for the analysis of all data obtained during the study and recorded in the study form. Kolmogorov Smirnov test was used to determine whether or not the distribution of discrete and continuous numerical variables was in accordance with the normal distribution. Descriptive statistics were demonstrated as mean±standard deviation (SD) or median (minimum-maximum) for discrete and continuous numerical variables, and as number of cases and (%) for categorical variables. Chi-square was used to evaluate categorical variables, and t test or Mann Whitney U test was used to evaluate continuous variables. Independent risk factors for LSE and SSE were determined by univariant and multivariant binominal regression analysis. Parameters with $p < 0.2$, which are independent risk factors for LSE and SSE, were included in the univariant regression analysis. Parameters that were found to be significant in the univariant regression analysis were included in the multivariate regression analysis. For $p<0.05$, the results were considered statistically significant.

RESULTS

Six hundred and forty-eight adult patients [Female (F): 446 (68.8%), Male (M): 202 (32.2%)] participated in the study. Detailed clinical and laboratory characteristics of the patients are listed in Table 1. Pfizer-BioNTech vaccine was administered to 68.5% of the patients (648 patients), and double-dose COVID-19 vaccine was administered to 84% (544 patients). Ninety-six patients (14.8%) were premedicated with anti-allergic drugs before the administration of the COVID-19 vaccine. Among the patients, 35.2%, 22.8% and 26.5% were followed up for allergic rhinitis, asthma and chronic urticaria respectively.

Two hundred ninety-three patients (45.2% of the patients) reported side effects after the 1st dose of COVID-19 vaccine. The most frequently reported LSE was pain at the injection site (34.7 %) occurring within the first 4 hours (26.9%). The most frequently reported SSE was fatigue (14.5%) occurring within 24-72 hours (13.9%) after immunization. Among the patients who reported SSE, 44 (6.8%) needed treatment with antipyretic and anti-inflammatory drugs. Anaphylaxis requiring adrenaline injections developed in two patients (0.3%).

Five-hundred and forty-four patients received a 2nd dose of COVID-19 vaccine. One hundred and four of them (19.1%) developed LSE, and LSE most frequently developed after the 4th hour of the vaccine injection. Sixty-seven (12.3%) of the 544 patients who were administered the 2nd dose of the vaccine developed SSE. SSE occurred most frequently at 24-72 hours after the injection. Twelve patients needed treatment with antipyretic and anti-inflammatory drugs, but no case of anaphylaxis and adrenaline injection was reported. Thirteen patients (2%) developed COVID-19 infection despite being vaccinated. Data on all local and systemic side effects are summarized in **Table 1**.

Comparison of patient groups reporting or not reporting LSE after the 1st dose of COVID-19 vaccine, showed a significant difference was found between the two groups in terms of age, of the proportion of patients aged less than 50 years of the applied COVID-19 vaccines (CoronaVac vaccine vs Pfizer-BioNTech vaccine), the rate of premedicated patients, and the presence of allergic rhinitis ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$ and p: 0.002), respectively. On the other hand, there was a significant difference between patients who reported SSE after the 1st of COVID-19 vaccine and those who did not, in terms of gender, the proportion of patients aged less than 50 years, history of previous COVID-19 infection, applied COVID-19 vaccines, and premedication status (respectively p: 0.021, p: 0.012, p: 0.021, $p<0.001$, $p<0.001$, $p< 0.001$) (**Table 2a**).

Comparison of the patients that did and did not develop LSE after the 2nd dose of vaccine showed significant differences in terms of the rate of patients aged less than 50 years, the administered COVID-19 vaccines, the rate of premedicated patients, and the presence of allergic rhinitis (respectively p: 0.031, $p< 0.001$, $p< 0.001$, $p< 0.001$, p: 0.006). On the other hand, a significant difference was found between patients who reported SSE after the 2nd dose of vaccine and those who did not in terms of the ratio of patients aged less than 50 years, history of previous COVID-19 infection, the number

Table 1. Demographic, clinical and laboratory parameters of the study population and characteristics of LSE and SSE developing after COVID-19 vaccines

Parameters	Results	After 1st dose of COVID-19 vaccine n: 648	Results	After 2nd dose of COVID-19 vaccine n: 544	Results
Gender, Female n (%)	446 (68.8)	LSE	227 (35)	LSE	104 (19.1)
Age, year (mean,min-max)	41 (18-86)	SSE	156 (24.1)	SSE	67 (12.3)
Atopy n (%)	378 (58.3)	**Type of LSE, n (%)**		**Type of LSE, n (%)**	
Previous COVID-19 infection n (%)	96 (14.8)	Redness	6 (0.9)	Redness	2 (0.4)
COVID-19 vaccines n (%)		Local pain at injection site	225 (34.7)	Local pain at injection site	103 (18.9)
Pfizer-BioNTech n (%)	444 (68.5)	Swelling at injection site	19 (2.9)	Swelling at injection site	7 (1.3)
CoronaVac n (%)	204 (31.5)	**Time of LSE, n (%)**		**Time of LSE, n (%)**	
COVID-19 vaccine doses n (%)		Hyper acute (in 30 minutes):	3 (0.5)	Hyper acute (in 30 minutes):	2 (1.9)
Single dose n (%)	104 (16)	Acute (in 4 hours):	50 (7.7	Acute (in 4 hours):	16 (15.4)
Double dose n (%)	544 (84)	Late (After 4 hours):	174 (26.9)	Late (After 4 hours):	86 (82.7)
Premedications, n (%)	96 (14.8)	SSE after 1st dose of COVID-19 vaccine	156 (24.1)	SSE after 2nd dose of COVID-19 vaccine	67 (12.3)
Comorbidity n (%)		**Type of SSE, n (%)**		**Type of SSE, n (%)**	
Asthma	148 (22.8)	Fatique	94 (14.5)	Fatique	49 (9.1)
Chronic urticaria	171 (26.5)	Arthralgia	62 (9.6)	Arthralgia	43 (7.9)
Allergic rhinitis	227 (35.2)	Myalgia	51 (7.9)	Myalgia	33 (6.1)
Contact dermatitis	9 (1.4)	Headache	60 (9.3)	Headache	28 (5.1)
Pruritus	62 (9.6)	Fever	45 (6.9)	Fever	21 (3.9)
Venom allergy	13 (2.0)	38 °C>	39 (6)	38 °C>	17 (3.2)
Drug allergy	18 (2.8)	38 °C <	6 (0.9)	38 °C <	4 (0.7)
		Urticaria/ Angioedema	11 (1.7)	Urticaria/ Angioedema	5 (0.9)
COVID-19 infection after vaccinacion (n)	13 (2)	Dyspnea/ Wheezing	12 (1.9)	Dyspnea/ Wheezing	2 (0.4)
After 2 dose of Pfizer-BioNTech (n)	6	Nausea/ Vomiting	14 (2.2)	Nausea/ Vomiting	4 (0.7)
After 2 dose of CoronaVac (n)	6	Hypotension/ tachcardia/ syncope/ presyncope	13 (2)	Hypotension/ tachcardia/ syncope/ presyncope	3 (0.6)
After single dose of BioNTech (n)	1	**Time of SSE, n (%)**		**Time of SSE, n (%)**	
		In 24 hours	63 (9.7)	In 24 hours	13 (2.4)
Anapyhlaxis n (%)		24-72 hours	90 (13.9)	24-72 hours	53 (9.7)
After 1. dose	2 (0.3)	72h-7 days	2 (0.3)	72h-7 days	1 (0.2)
After 2. dose	-	After 7 days	1 (0.2)	After 7 days	-
		Treatment	44 (6.8)	Treatment	12 (2.2)

LSE: local side effects, SSE: systemic side effects, COVID-19: Coronavirus disease 2019

Table 2a. Comparison of LSE and SSE reported after 1st dose COVID-19 vaccines with demographic and clinical characteristics of patients

	After 1st dose of COVID-19 vaccines					
Parameters	LSE (+) n: 227	LSE (-), n: 421	p	SSE (+), n: 156	SSE (-), n: 492	p
Gender, female, n (%)	167 (73.6)	279 (66.3)	0.056	119 (76.3)	327 (66.5)	0.021
Age, year (mean,min-max)	38(17-71)	43(17-86)	<0.001	40.50(18-70)	41(18-86)	0.463
Age (<50 year),n (%)	181 (79.7)	260 (61.8)	<0.001	119 (76.3)	322 (65.4)	0.012
Presence of atopy, n (%)	146 (64.3)	232 (55.1)	0.230	101 (64.7)	277 (56.3)	0.062
History of previous COVID-19 infection n (%)	40 (17.6)	56 (13.3)	0.140	32 (20.5)	64 (13.0)	0.021
Pfizer-BioNTech vaccine, n (%)	202 (89)	242 (57.5)	<0.001	137 (87.8)	307 (62.4)	<0.001
Premedication n (%)	55 (24.2)	41 (9.7)	<0.001	38 (24.4)	58 (11.8)	<0.001
History of Asthma n (%)	42 (18.5)	106 (25.2)	0.053	37 (23.7)	111 (22.6)	0.764
History of Urticaria n (%)	52 (22.9)	120 (28.5)	0.124	43 (27.6)	129 (26.2)	0.740
History of Rhinitis n (%)	98 (43.2)	130 (30.9)	0.002	56 (35.9)	172 (35.0)	0.831
History of Pruritus n (%)	27 (11.9)	35 (8.3)	0.139	16 (10.3)	46 (9.3)	0.737
History of Drug allergy n (%)	3 (1.3)	15 (3.6)	0.132	2 (1.3)	16 (3.3)	0.267
History of Venom allergy n (%)	4 (1.8)	9 (2.1)	0.745	3 (1.9)	10 (2.0)	0.932
History of Contact dermatitis n (%)	3 (1.3)	6 (1.4)	0.914	1 (0.6)	8 (1.6)	0.360

LSE: local side effects, SSE: systemic side effects, COVID-19: Coronavirus disease 2019, ºPremedication before vaccination

of administered doses of COVID-19 vaccines, and the rate of premedicated patients (respectively p: 0.032, p< 0.001, p< 0.001, p< 0.001, and p< 0.001) (**Table 2b**).

As a result of the univariate and multivariate analysis, female gender, (Odds ratio (OR): 1.757, 95%Cl: 1.143-2.702, p: 0.010), history of previous COVID-19 infection, (OR: 1.762, 95%Cl: 1.068-2.906, p: 0.026), and COVID-19 vaccine type administered (Pfizer-BioNTech vaccine vs CoronaVac vaccine, OR: 4.443, 95% CI: 2.640-7.476, p<0.001) were found to be independent risk factors for SSE after the 1st dose of COVID-19 vaccine. Conversely, premedication (OR: 0.454, 95% Cl: 0.281-0.733, p<0.001), on the other hand, was found to be a protective factor for SSE developing after 1st dose of COVID-19 vaccines (**Table 3a** and **Table 3b**).

As a result of univariate and multivariate analysis, female gender gender (OR: 1.919, 95%Cl: 1.017-3.621, p: 0.044), history of previous COVID-19 infection (OR: 4.715, 95%Cl: 2.526-8.802, p<0.001), and the type of COVID-19 vaccine administered (Pfizer-BioNTech vaccine vs CoronaVac vaccine, OR: 4.486, 95% CI: 2.043-9.850) were found to be independent risk factors for SSE after the 2nd dose of COVID-19 vaccine. Conversely again, premedication (OR: 0.280, 95% CI: 0.141-0.560), on the other hand, was found to be a protective factor for SSE developing after 1st dose of CoVid-19 vaccines (Table 3a and Table 3b).

DISCUSSION

To our knowledge, our study is among the rare studies evaluating the impact of allergic diseases on tolerance of COVID-19 vaccines. The study showed three main and important results. Firstly, the most common LSE reported after COVID-19 vaccines is injection site pain, and the most common SSE is fatigue. Secondly, female gender, history of previous COVID-19 infection and Pfizer-BioNTech vaccine were found to be risk factors for SSE, but conversely, premedication was found to be protective. Lastly, the presence of allergic disease and atopy, especially allergic rhinitis, asthma and chronic urticaria, was not a risk factor for SSE developing after COVID-19 vaccine.

It has been reported in many studies examining the side

Table 2b. Comparison of LSE and SSE reported after 2nd dose of COVID-19 vaccines with demographic and clinical characteristics of patients

	After 2nd dose of COVID-19 vaccines					
Parameters	LSE (+), n: 104	LSE (-), n: 440	p	SSE (+), n: 67	SSE (-), n: 477	p
Gender, female, n (%)	74 (71.2)	294 (66.8)	0.395	51 (76.1)	317 (66.5)	0.113
Age, year (mean,min-max)	40.5(17-71)	42(17-86)	0.264	40(18-70)	42(17-86)	0.487
Age (<50 year),n (%)	78 (75.0)	281 (63.9)	0.031	52 (77.6)	307 (64.4)	0.032
Presence of atopy, n (%)	67 (64.4)	251 (57.0)	0.170	43 (64.2)	275 (57.7)	0.310
History of previous COVID-19 infection n (%)	20 (19.2)	56 (12.7)	0.085	23 (34.2)	53 (11.1)	<0.001
Pfizer-BioNTech vaccine, n (%)	92 (88.5)	270 (61.4)	<0.001	59 (88.1)	303 (63.5)	<0.001
Premedication n (%)	31 (29.8)	24 (5.5)	<0.001	17 (25.4)	38 (8.0)	<0.001
History of Asthma n (%)	19 (18.3)	114 (25.9)	0.103	16 (23.9)	117 (24.5)	0.908
History of Urticaria n (%)	31 (29.8)	127 (28.9)	0.849	18 (26.9)	140 (29.4)	0.675
History of Rhinitis n (%)	46 (44.2)	133 (30.2)	0.006	25 (37.3)	154 (32.3)	0.412
History of Pruritus n (%)	6 (5.8)	34 (7.7)	0.491	7 (10.4)	33 (6.9)	0.300
History of Drug allergy n (%)	2 (1.9)	16 (3.6)	0.380	2 (3.0)	16 (3.4)	0.874
History of Venom allergy n (%)	1 (1.0)	9 (2.0)	0.459	1 (1.5)	9 (1.9)	0.822
History of Contact dermatitis n (%)	1 (1.0)	7 (1.6)	0.632	0	8 (1.7)	0.604

LSE: local side effects, SSE: systemic side effects, COVID-19: Coronavirus disease 2019

Table 3a. Univariate and multivariate binomial regression analyses demonstrating the relationship between baseline characteristics and SSEs after 1st dose COVID-19 vaccines

	SSE After 1st dose of COVID-19 vaccines			
	Univariate Analysis		Multivariate Analysis	
Parameters	OR (95% CI)	P value	OR (95% CI)	P-value
Gender, female, n (%)	1.62 (1.073-2.454)	0.022	1.757 (1.143-2.702)	0.010
Age, year	0.993 (0.981-1.009)	0.264	0.999 (0.985-1.014)	0.917
Age (<50 year)	1.698 (1.123-2.566)	0.012	1.294 0(0.826-2.029)	0.261
Presence of atopy, n (%)	1.425 (0.981-2.071)	0.063	0.821 (0.552-1.221)	0.329
History of previous COVID-19 infection, n (%) *	1.726 (1.080-2.759)	0.023	1.762 (1.068-2.906)	0.026
Pfizer-BioNTech, vaccine, n (%)	4.345 (2.601-7.260)	<0.001	4.443 (2.640-7.476)	<0.001
Premedication, n (%) º	2.410 (1.526-3.805)	<0.001	2.203 (1.323-3.32)	<0.001
History of asthma, n (%)	1.067 (0.698-1.633)	0.764	1.210 (0.772-1.897)	0.405
History of urticaria, n (%)	1.071 (0.714-1.605)	0.740	1.196 (0.744-1.922)	0.461
History of rhinitis, n (%)	1.042 (0.715-1.517)	0.831	2.207 (0.729-6.683)	0.161
History of pruritus, n (%)	1.108 (0.608-2.018)	0.737	1.254 (0.656-2.398)	0.493
History of drug allergy, n (%)	0.386 (0.088-1.699)	0.208		
History of venom allergy, n (%)	0.945 (0.257-3.478)	0.932		
History of contact dermatitis, n (%)	0.390 (0.048-3.145)	0.377		

COVID: 2019 novel coronavirus, SSE: systemic side effects, *: COVID-19 infection status before vaccination, ºPremedication before vaccination

effects developed after COVID-19 vaccines that the most common LSE caused by COVID-19 is pain at the injection site, and the most common SSE is weakness/fatigue (9-13). Pain at the injection site was reported as the most common adverse event in the CoronaVac, phase 1 and 2 studies (14). The most frequently reported side effect after another inactive COVID-19 vaccine (BBV152) is pain at the injection site (15). Menni et al. reported a 71.9% incidence of LSE after the 1st dose of Pfizer-BioNTech vaccine and a 68.5% after the 2nd dose (16). In this study, the incidence of SSE was 13.5% after the 1st dose and 22.0% after the 2nd dose. Thomas et al reported that the most common LSE after Pfizer-BioNTech vaccine was mild-moderate pain at the injection site, and that fatigue was the most common SSE (17). In another cohort, side effects were reported in 64.9% of 8682 patients who received the 1st dose of Pfizer-BioNTech or Moderna vaccine, and 80.3% of patients who received the 2nd dose of these vaccines. In this cohort, the most common side effects after COVID-19 vaccines were fatigue and pain at the injection site (18). We think that both LSE and SSE rates are lower than in other studies because some of our patient group received various premedications that could prevent the development of LSE and SSE. However, the most common LSE and SSE symptoms support similar data in the literature.

Anaphylaxis after vaccination is rare and typically emerges within minutes of vaccination (19). The CDC COVID-19 Response Team reported that the rate of anaphylaxis after Pfizer-BioNTech vaccine was 11.1 per million (20). This rate is approximately 8 times the risk of anaphylaxis developing due to commonly used vaccines (1.31 per million) (21). In our study, after Pfizer-BioNTech and CoronaVac, anaphylaxis developed in a total of two patients, one different patient each. The rate of anaphylaxis was higher than previously reported (0.3% after the 1st dose of COVID-19 vaccine). This

Table 3b. Univariate and multivariate binomial regression analyses demonstrating the relationship between baseline characteristics and SSEs after 2nd dose COVID-19 vaccines

	SSE After 2nd dose of COVID-19 vaccines			
Parameters	Univariate Analysis		Multivariate Analysis	
Variables	OR (95% CI)	P value	OR (95% CI)	P-value
Gender, female, n (%)	1.609(0.889-2.911)	0.116	1.919(1.017-3.621)	0.044
Age, year	0.993(0.977-1.010)	0.410	-	-
Age (<50 year)	1.920(1.049-3.513)	0.034	1.753 (0.895-3.434)	0.102
Presence of atopy, n (%)	1.316(0.774-2.239)	0.311	-	-
History of previous COVID-19 infection, n (%) *	4.182(2.342-7.465)	<0.001	4.715(2.526-8.802)	<0.001
Pfizer-BioNTech, vaccine, n (%)	4.235(1.977-9.077)	<0.001	4.486(2.043-9.850)	<0.001
Premedication, n (%) º	3.922(1.356-4.239)	<0.001	3.571(1.243-3.968)	<0.001
History of asthma, n (%)	0.965(0.530-1.757)	0.908	1.297(0.669-2.515)	0.441
History of urticaria, n (%)	0.884(0.498-1.571)	0.675	2.987 (0.366-24.377)	0.307
History of rhinitis, n (%)	1.248(0.734-2.123)	0.413	1.243(0.615-2.511)	0.544
History of pruritus, n (%)	1.570(0.665-3.706)	0.304	1.886(0.734-4.847)	0.188
History of drug allergy, n (%)	0.788(0.098-6.319)	0.874	-	-
History of venom allergy, n (%)	-	-	-	-
History of contact dermatitis, n (%)	-	-	-	-

COVID: 2019 novel coronavirus, SSE: systemic side effects, *: COVID-19 infection status before vaccination, ºPremedication before vaccination

may be because our patient group consists of patients with a high tendency to anaphylaxis.

Women generally have stronger immune functions and higher antibody levels, but also develop more frequent side effects to vaccines including COVID-19 vaccines (22,23). In the study by Menni et al. women reported more side effects after COVID-19 vaccines (16). In their meta-analysis, Alhumaid et al. found female gender as a risk factor for anaphylaxis and non-anaphylactic reactions (24). In a cohort evaluating side effects of Pfizer-BioNTech and Moderna vaccines, it was reported that female gender was associated with higher odds in terms of both side effects and severe adverse effects (18). In our study also, the rate of SSE was higher in women after both 1st and 2nd dose of COVID-19 vaccines, although significance was attained only for SSE developing after the first dose. Additionally, the risk of developing SSE in women after COVID-19 vaccines was 1.9 times higher than in men. The difference in terms of SSE between genders may be caused by genetic, hormonal and immunological differences or the combination of these differences (25,26).

Previous COVID-19 infection is an important parameter that affects post-COVID-19 vaccine side effects, and, in many studies, this relationship has been investigated. Bandolli et al. reported that the rates of LSE after Pfizer-BioNTech vaccine were similar, but that SSE developed more frequently in patients with a history of previous COVID-19 infection compared to patients without previous infection (27). In the study by Mathioudakis et al. that previous COVID-19 infection is a risk factor for side effects, fever, breathlessness, flu-like illness and fatigue after COVID-19 vaccines (28). Another study stated that previous COVID-19 infection increased the risk of SSE by 2.9 times after Pfizer-BioNTech and a similar relationship was found for LSE (16). Beatty et al. reported that history of previous COVID-19 infection was associated with higher odds of adverse effects to COVID-19 vaccines (18). They suggested that the reason for this situation is that vaccines increase immunogenicity in infected individuals, thus inducing stronger humoral and T-cell responses in patients with previous COVID-19 infection, and increasing vaccine reactogenicity after COVID-19 vaccines (29,30). Although we did not reach a similar conclusion in our study, reporting more frequent side effects after the 2nd dose of COVID-19 vaccines may support these hypotheses. There are many studies in the literature reporting that more frequent side effects are observed after the 2nd dose of COVID-19 vaccines (10, 16,18,28,31), probably due to the boosting effect of the second injection on sensitized T cells and neutralizing antibodies formed after the 1st (immunizing) dose of the vaccines, similar to patients who have had a previous COVID-19 infection.

CoronaVac is an alum adjuvanted inactivated COVID-19 vaccine. Pfizer-BioNTech COVID-19 vaccine is an mRNA-lipid nanoparticle-based vaccine. It contains polyethylene glycol (PEG) derivatives as an adjuvant, affects both humoral and cellular steps of the adaptive immune system, and the incidence of side effects to this vaccine is relatively higher (32-34). In many studies, it has been reported that less LSE and SSE develop after inactivated COVID-19 vaccines administration than with protein subunit vaccines, RNA based vaccines and viral vector vaccines (9,11,14). Wu et al. reported that both local and systemic side effects are rarer after inactivated COVID-19 vaccines than after mRNA vaccines administration (23.7%-89.4% for LSE, 21%-83.3% for SSE) (9). In another meta-analysis, 31.75% of side effects were reported in patients immunized with inactivated virus vaccines and 81.76% in patients immunized with RNA-based COVID-19 vaccines (11). Likewise, in our study, both LSE and SSE were observed more frequently after Pfizer-BioNTech COVID-19 vaccine, and Pfizer-BioNTech vaccine, and this vaccine was found to be a risk factor for SSE.

Antihistamines, corticosteroids and omalizumab are the most frequently used treatments in allergic patients. Premedication with corticosteroids and antihistamines may theoretically suppress the immune response and reduce post-COVID-19 side effects, but premedication with these drugs before vaccination is not recommended (5,35). Some studies suggested that antihistamines protect against post-COVID-19 side effects, that these drugs have anti-viral effects, can bind to ACE2 and prevent the entry of Sars-CoV-2 virus into the cell (36,37). Similarly, in a study in 79.083 Spanish patients, Vila-Corcoles et al. found that antihistamines were protective for COVID-19 (38). In another study, 70 patients out of 80 who reported allergic(-like) complaints after the 1st dose of Pfizer-BioNTech vaccine received the 2nd dose of vaccine after allergic evaluation, and 89% of these patients developed no reaction or mildly reaction only after antihistamine premedication (39). Conversely, in a Turkish study conducted on healthcare workers who received CoronaVac, post-vaccine rashes, fever, chills, and headache were reported more frequently in patients receiving antihistamines (40). Unfortunately, our study was insufficient to comment on this issue because the ratio of the number of premedication patients to the general population was low. Hence, the potential relationship between antihistamine drugs and adverse effects of COVID-19 vaccines needs further research.

Another finding in our study was that allergic diseases, especially asthma, allergic rhinitis and chronic urticaria, or the presence of atopy are not risk factors for SSE developing after COVID-19 vaccines. Studies on the side effects of allergic diseases after COVID-19 vaccines are very limited. In a meta-analysis, Alhumaid et al. found

that history of atopy was a risk factor of anaphylactic and non-anaphylactic reactions to SARS-CoV-2 vaccines (Pfizer-BioNTech and Moderna vaccines). Inoue et al. reported that, although no cases of anaphylaxis were reported, the frequency of adverse events after COVID-19 vaccination was higher in allergic patients and that the duration of adverse events was longer (41). Nittner et al. reported that local side effects such as swelling and redness develop more frequently in allergic patients after Pfizer-BioNTech vaccine, that these side effects last longer, and that allergic individuals need medical intervention due to the side effects more frequently (x2) than non-allergic individuals (31). On the other hand, Beatty et al. reported that asthma was associated with lower odds in terms of both side effects and severe adverse effects after Pfizer-BioNTech and Moderna vaccines (18). EACCI (European Academy of Allergy and Clinical Immunology) declared that there is no contraindication for allergic patients to receive COVID-19 vaccines, except for patients with sensitivity to components of these vaccines, and that allergy to drugs, food, insect venom, or inhalant allergens (house dust mites, pollens, animal dander, molds) generally does not constitute a contraindication for any vaccine, including SARS-CoV-2 vaccines (42). Moreover, the American College of Allergy Asthma and Immunology (ACAAI) has stated that "Individuals with common allergies (foods, inhalants, latex, insects) are not more likely than the general population to develop allergic reactions to the Pfizer-BioNTech vaccine" (43). The results of our study, showing that neither the presence of atopy nor the presence of allergic disease was a risk factor for SSE after COVID-19 vaccines, agree with these recommendations.

The strength of our study is that the allergic diseases of the patients were diagnosed by a physician, self-reported allergy being typically much higher than confirmed allergy, and that the size of the population studied is important and includes numerous allergic patients. Our study also has some limitations. First, the data on side effects, and drug uses considered as premedication was obtained through personal notification. This makes possible a bias linked to social desirability. It is well known that reporting of side effects may vary among patients. Also, our study classified patients according to the allergic disease for which they were primarily followed. Other concomitant allergic diseases (diagnosed or undiagnosed) may have affected the results in some patients. Additionally, the number of patients diagnosed with venom allergy, drug allergy, and contact dermatitis was relatively low. The fact that the study was retrospective and included patients from only one ethnic background makes it difficult to generalize the results. These limitations may have impacted the power of statistical analyses in the patient groups.

CONCLUSION

In our study, CoronaVac and Pfizer-BioNTech COVID-19 vaccines were well-tolerated, and SSE against both vaccines was very low. Patients with allergic or atopic diseases do not have an increased risk for SSE that may develop after COVID-19 vaccines, so this should not have doubts in the minds of either clinicians or patients and prevent vaccination.

ETHICAL DECLARATIONS

Conflict of Interest Statement: The author declares no conflicts of interest related to this research.

Informed consent: Informed consent was taken from the patients.

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Ethical Issues: This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects.

Author Contributions: The authors declared that they all participated in the design, execution, and analysis of the study and that they approved the final version of the paper.

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Original Article

Neuromuscular Dysfunction and Electrophysiological Findings in Patients With Hypothyroidism and Hyperthyroidism

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Abstract

Background: We aimed to determine the frequency of neuropathy and myopathy in newly diagnosed hypothyroid and hyperthyroid patients and to investigate the correlation between serum creatine kinase (CK) concentration and thyroid dysfunction.

Methods: A total of 21 hyperthyroid, 19 hypothyroid, and 20 healthy control subjects were selected for the study. All participants underwent neuromuscular examinations for paresthesia, diffuse pain, muscle cramps, and muscle weakness. Electroneurophysiologic studies were performed on all participants.

Results: Neuromuscular complaints were observed more frequently in the hypothyroid and hyperthyroid groups compared to the control group. Myopathy was detected in 10% of the hypothyroid group and 4% of the hyperthyroid group. Polyphasia potential abnormality was detected in 21% of the hypothyroid group and 14% of the hyperthyroid group. CK elevation was found in 42% of patients in the hypothyroid group and 4% of patients in the hyperthyroid group. There was no correlation between symptoms and CK elevation or between myopathy and thyroid function levels. In the electroneurophysiologic study, 14% neuropathy was found in the hyperthyroidism group and 26% in the hypothyroidism group. In the hypothyroid group, polyneuropathy was found in 10%, and carpal tunnel syndrome was found in 10%. Absence of sensory action potential was found in 10% of the hyperthyroid group and 4% of the hypothyroid group, and low compound muscle action potential was found in 4% of the hyperthyroid group. There was no correlation between thyroid hormone levels and neuropathy.

Conclusion: Neuromuscular complaints and neuropathic findings are highly prevalent in patients with thyroid dysfunction. Neuromuscular symptoms may improve after treatment of thyroid disease. In future studies, comparing post-treatment electrophysiologic values with pre-treatment values and clinical values may more clearly demonstrate the effect of thyroid function on the neuromuscular system.

Keywords: Hypothyroidism, hyperthyroidism, neuromuscular

INTRODUCTION

Thyroid dysfunctions are significant endocrine disorders common among adults and may be associated with morbidity and mortality, especially in elderly individuals. Both hypothyroidism and hyperthyroidism can cause signs and symptoms of neuromuscular dysfunction (1,2). In hypothyroidism, myopathy characterized by proximal muscle weakness may be observed alongside mononeuropathy and sensorimotor axonal polyneuropathy. The prevalence of these symptoms and findings varies in different publications. In previous studies, the prevalence of neuropathy in hypothyroid patients ranged from 10% to 70%, while the prevalence of myopathy ranged from 20% to 80%. Electrophysiologic studies have shown that carpal tunnel syndrome (CTS) is the most common neuropathy in hypothyroidism (3-5).

In hyperthyroidism, myopathy, mononeuropathy, and sensorimotor axonal polyneuropathy may be observed with a less prevalence Neuropathy is less frequent

and typically subclinical in hyperthyroidism. It is believed that weight loss, weakness, infiltration of the tendon sheath with mucopolysaccharides, infiltrative dermopathy, and the direct effects of thyroid hormones on axonal function may contribute to the development of mononeuropathy in thyrotoxic patients. In hyperthyroid patients, the prevalence of myopathy ranged from 60% to 80%, while polyneuropathy and neuropathy were rarely reported, with low prevalence in a few publications (6-9).

The aim of our study was to investigate the prevalence of neuromuscular symptoms in newly diagnosed hypothyroid and hyperthyroid patients, to demonstrate neuromuscular dysfunction using electroneurophysiology, and to determine the possible correlation with creatine kinase (CK) concentration and serum thyroid hormone levels in the presence of neuropathy and myopathy.

METHODS

Twenty-one patients with hyperthyroidism (14 females/7 males) and 19 patients with hypothyroidism (17 females/2 males), who had not received a previous hormone replacement therapy, and whose symptoms had lasted for more than one month, were included in the study. Twenty healthy volunteers with no previous history of thyroid disease and who were clinically and biochemically euthyroid were assigned as the control group.

Patients over 65 and under 18 years of age, with chronic diseases (such as diabetes mellitus, malignancy, chronic liver disease, chronic renal failure, collagen tissue diseases), vitamin B12 and folic acid deficiency, chronic alcohol use, a history of drug use causing neuropathy and myopathy, and central or peripheral nervous system diseases were excluded.

Symptoms of the participants; such as paresthesia, muscle cramps, muscle weakness, and diffuse pain fatigue were noted. Subjective symptoms were thoroughly evaluated by performing physical examination. Serum creatinine kinase (CK) levels, nerve conduction studies, and needle electromyography (EMGs) were assessed retrospectively from hospital files.

Electroneurophysiologic studies were conducted using the Nihon Kohden Neuropack 2 device in all patients and the control group in accordance with the American Diabetes Association diabetic neuropathy protocol. Median motor conduction studies, ulnar, peroneal, and motor nerve conduction velocities, distal latencies, and compound muscle action potentials (CMAPs) were examined. In sensory conduction studies, median, ulnar, and sural nerve sensory conduction velocities, distal latencies, and sensory amplitude potentials (SAP) were measured. Deviations from reference values were recorded according to recommended protocols. The presence or absence of polyneuropathy (PNP) was determined by electrophysiologic involvement of more than one of the examined nerves, with pathologic findings of the involved nerves (SAP decrease, decrease in sensory conduction velocity, slowing, prolongation in motor nerve distal latency, CMAPS decrease in amplitude, slowing of motor conduction velocity, F-wave latency prolongation) evaluated based on the fulfillment of at least one of these criteria.

The presence of spontaneous muscle fibril activity (fibrillation potentials, positive sharp waves, fasciculations, or complex repetitive discharges) and signs of reinnervation activity (polyphasic or giant motor unit action potential) were measured. A visual analysis method was used to measure motor unit action potential (MUAP) values.

This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects.

STATISTICAL ANALYSIS

SPSS version 10.0 for Windows was used in the assessment of the study data. The distributions of numeric variables were assessed using both the Kolmogorov-Smirnov test and the Shapiro-Wilk test. Parametric variables were presents as mean ± standard deviation. Anova and posthoc Tukey tests were used in the comparison of multiple groups. Categorical variables were exhibited by number and percentage. Spearman correlation coefficient was applied for the analyses of nonparametric data. Pearson's chi-square test was used to compare categorical variables. The level of statistical significance was set at $P<0.05$.

RESULTS

A total of 40 patients (31 females and 9 males) with a diagnosis of hypo or hyperthyroidism were evaluated. The mean ages were 42.23±12.09 and 40.47±14.11 years in hypothyroidism and hyperthyroidism groups, respectively. The control group consisted of 20 healthy individuals with a mean age of 42.25±12.01 years (**Table 1**).

Table 1. Clinical and laboratory characteristics of hypothyroidism and hyperthyroidism patients

	Hypothyroidism (n=19)	Hyperthyroidism (n=21)	Control group (n=20)	P[1]	P[2]
Age (year)	40.47±14.11	42.23±12.09	40,38±9,27	0.870	0.571
sT3(pg/ml)	1.38±0.39	12.62±5.78	2.73±0.40	0.001*	0.001*
sT4 (ng/dl)	0.62±0.82	4.04±1.94	1.12±0.20	0.001*	0.001*
TSH (mIU/ml)	74.21±33.9	0.059±0.002	1.89±0.87	0.001*	0.001*
CK (IU/l)	336.21±140	80.52±64.88	83.12±37.46	0.001*	0.752

*: p<0.05, TSH: Tiroid Stimulan Hormon, fT4: free T4, fT3:serbest T3, CK: Creatinin Kinase. n: Patient number P1: Significance value between hypothyroidism and control group, P2: Significance value between hyperthyroidism and control group

Table 2. The neurological complaints of the patient and control groups

	Hypothyroidism (n:19)	Hyperthyroidism (n:21)	Control (n:20)	P[1]	P[2]
Weakness	15 (78.9 %)	17 (80.9 %)	6 (30%)	0.004	0.002
Cramps	16 (84.2%)	11 (52.3%)	2 (10%)	<0.001	0.006
Paresthesia	15 (78.9%)	10 (47.6%)	2 (10%)	<0.001	0.015
Diffuse pain	13 (68.4%)	14 (66.6%)	3 (15%)	0.001	0.001

n: Patient number P1: Significance value between hypothyroidism and control group, P2: Significance value between hyperthyroidism and control group

Clinical and laboratory features of the participants were given in **Table 1**. The neurological symptoms of patients including weaknes, cramping, paresthesia, diffuse pain were more common in hypothyroidism and hyperthyroidism groups compared the control group ($p<0.05$) (**Table 2**). The prevalence of symptoms in patients with abnormal thyroid hormone status as follows; weakness 80.9% (in hyperthyroidism) and 78.9% (in hypothyroidism), cramping 52.3% (in hyperthyroidism) and 84.2% (in hypothyroidism), paresthesia 47.6% (in hyperthyroidism) and 78.9% (in hypothyroidism), and diffuse pain 66.6% (in hyperthyroidism) and 68.4% (in hypothyroidism). The prevalence of neuromuscular complaints in the control group was lower than in the hypothyroid and hyperthyroid patient groups ($p<0.05$). Neurological examinations suggesting myopathy or polyneuropathy (PNP) did not reveal weakness, decreased deep tendon reflexes, or glove-sock-style sensory deficits.

Electrophysiologic studies revealed myopathy in 2 patients (10%) and polyphasia potential abnormalities in 4 patients (21%) in the hypothyroid group. In the hyperthyroidism group, myopathy was detected in 1 patient (4%) and polyphasia potential abnormalities in 3 patients (14%).

Since myopathy was detected in only 1 patient in the hyperthyroidism group, the relationship between CK and thyroid functions was not evaluated. In the hyperthyroidism group, serum CK concentration was elevated in 1 patient (4%). In hypothyroid patients, CK concentration was elevated in 8 patients (42%), and there was no significant correlation between serum T3 and T4 levels and myopathy ($p>0.05$).

There was no statistically significant correlation between neuromuscular symptoms and CK concentration in both groups ($p>0.05$). There was no significant difference in CK concentration between patients with electroneurophysiologically detected myopathy and patients without myopathy ($p>0.05$). There was no significant difference in sT3, sT4, and TSH values between patients with high CK concentrations and patients with normal levels ($p>0.05$).

The findings of the hypothyroidism and hyperthyroidism groups and the control group in the electroneurophysiologic studies are presented in **Table 3**. Median nerve motor and sensory amplitudes, as well as ulnar nerve sensory amplitude, were lower in hyperthyroid patients compared to the control group ($p<0.05$). Median nerve motor and sensory amplitudes were also lower in hypothyroid patients compared to the control group ($p<0.05$) (**Table 4**).

In the hypothyroidism and hyperthyroidism groups, decreased sural nerve sensory conduction velocity and absence of SAP were detected, although not statistically significant, sural nerve sensory conduction velocity was found to be lower than in the control group. This suggests that sensorial conduction may be impaired earlier than motor conduction in thyroid dysfunctions.

There was no statistically significant difference between the serum sT3 and sT4 levels of patients with neuropathy and thyroid patients without neuropathy ($p>0.05$). No electrophysiologic neuropathy was detected in the control group. The incidence of neuropathy was higher in patients with thyroid dysfunction compared to the control group, and this difference was statistically significant ($p<0.05$).

DISCUSSION

This study demonstrates that symptoms such as weakness, cramps, paresthesia, and pain are more common in patients with hypothyroidism and hyperthyroidism, and these patients may exhibit electroneurophysiological findings more frequently than individuals with normal

Table 3. Electroneurophysiologic Neuropathy Findings in Hypothyroidism-Hyperthyroidism and Control Group

	Hyperthyroidism (n:21)	Hypothyroidism (n:19)	Control (n:20)
Normal	18	14	20
Polyneuropathy	0	2	0
Sural conduction velocity decrease or no SAP	2	1	0
CTS	0	2	0
Peroneal CMAP amplitüd low	1	0	0

SAP: Sensory amplitude potential CTS:carpal tunnel syndrome CMAPS: compound muscle action potentials

Table 4. Comparison of the groups according to the electroneurophsiological findings

		Hyperthyroidism Group	Hypothyroidism Group	Control Group	Normal Value	P[1]	P[2]
	D lat	3.04± 0.08	3.10± 0.08	3.15± 0.05	<3.6 m/sn	0.2	0.51
Median	Amp	9.07± 0.97	9.19± 0.93	11.84± 0.95	> 5 mV	0.027*	0.034*
Motor	NCV	58.39± 0.83	56.54± 1.26	57.35± 0.82	> 49.96 m/sn	0.382	0.643
	F	27.66± 0.42	27.71± 0.55	26.99± 0.3	<29.7 m/sn	0.192	0.683
Median	NCV	46.07± 0.68	45.93± 1.27	46.97± 0.92	>41.26 m/sn	0.715	0.615
	Amp	25.54± 2.45	25.49± 2.5	31.22± 3.33	> 10 mV	0.044*	0.042*
	D lat	2.30± 0.04	2.40± 0.1	2.29± 0.03	<2.51 m/sn	0.824	0.97
Ulnar	Amp	10.22± 0.59	12.26± 0.7	13.06± 0.51	> 5 mV	0.002*	0.177
Motor	NCV	61.32± 1.41	58.04± 1.08	61.26± 1.22	> 50.61 m/sn	0.917	0.126
	F	27.35± 0.48	27.17± 0.38	27.20± 0.27	<30.26 m/sn	0.927	0.694
Ulnar	Amp	19.07± 1.27	21.02± 1.87	18.02± 0.87	> 8 mikroV	0.392	0.112
	NCV	43.32± 0.75	45.30± 0.87	44,57± 0,46	> 39.26 m/sn	0.667	0.627
	D lat	3.72± 0.11	4.39± 0.22	3.80± 0.15	<4.78 m/sn	0.705	0.039
Peroneal	Amp	6.05± 0.69	6.54± 0.74	8.04± 0.77	> 4 mV	0.087	0.423
Motor	NCV	47.19± 0.72	46.87± 0.77	48.24± 0.80	>41.83 m/sn	0.279	0.152
	F	45.88± 0.69	48.38± 0.9	46.62± 0.72	<55.38 m/sn	0.389	0.292
Sural	NCV	38.9	38.4	39.38± 0.72	> 34.68 m/sn	0.483	0.383
	Amp	15	20.8	27.65± 3.56	> 6 mikroV	0.327	0.173

D lat: Distal latency, Amp: Amplitude, NCV: Nerve conduction velocity, F: F latency, p1: Significance value between hyperthyroidism and control group, p2: Significance value between hypothyroidism and control group. *:P<0.05

thyroid hormone levels.

The prevalence of neuromuscular involvement in thyroid dysfunction varies between 20% and 80% (3,10-13). Approximately 40% of hypothyroid patients and 20% of hyperthyroid patients show predominantly sensory signs of sensorimotor axonal neuropathy early in the course of thyroid disease (3). In our study, the frequency of cramps increased in both patient groups, and fatigue complaints were reported by 80% of the patients, while the frequency of diffuse pain and paresthesia increased.

Although neuropathies seen clinically and electrophysiologically in hypothyroidism and hyperthyroidism are often sensorial, mixed sensorial and sensorimotor neuropathies may be present in the early stages of the disease. Motor nerve conduction velocity is generally within normal limits, but sensorial nerve action potentials may be decreased in the early stages of the disease (14).

Hypothyroidism affects many systems, including the central and peripheral nervous system. Some publications suggest that electroneurophysiological abnormalities, such as decreased motor and sensorial nerve conduction velocity, may be observed (15-16). Electrophysiological studies of peripheral neuropathy in hypothyroid patients yield findings varying between 17% and 72% (3,17,18). The development of peripheral neuropathy in hypothyroidism may be due to various causes, such as the accumulation of mucopolysaccharides in the endoneurium and perineurium, segmental demyelination, glycogen aggregates, and axonal degeneration (19). In a study by Khedr et al., an electroneurophysiological study was conducted in 23 patients with hypothyroidism, and it was found that the peripheral nervous system was affected in 52% of the patients, with entrapment neuropathy developing in 35% of them, myopathic changes in 9%, and axonal polyneuropathy in 9% (15). While neuropathy due to hypothyroidism has been demonstrated in studies, neuropathy due to hyperthyroidism is reported to be less common. Duyff et al. found a neuropathy rate of 19% in patients with hyperthyroidism in their study (3). In a study by Berlit et al., 27 hyperthyroid patients were examined neurophysiologically (20). Although motor nerve conduction velocities of the peroneal and median nerves were mostly normal in patients, 29.6% exhibited pathologic findings in the sensorial nerve conduction velocities of the sural nerve, and 22.2% had borderline findings.

In our study, among patients with thyroid dysfunction, the rate of neuromuscular complaints was higher than in the control group. Neuropathy rates were 26% in the hypothyroid patient group and 14% in the hyperthyroid patient group. Polyneuropathy was found in 10% of the hypothyroid patient group but not in the hyperthyroid patient group. However, the absence of sensory action potentials or decreased sural nerve conduction velocity was found in 9%, and low compound muscle action potential was found in 4% in the hyperthyroid patient

group. The reasons for the varying frequency of peripheral neuropathy in studies may be attributed to differences in the criteria used to diagnose peripheral neuropathy in the literature. Median nerve motor and sensorial amplitudes, as well as ulnar nerve sensorial amplitude, were lower in hyperthyroid patients compared to the control group. In hypothyroid patients, median nerve motor and sensory amplitudes were also lower than in the control group, with the decrease in sensory amplitude being more pronounced. The rate of sural sensory conduction velocity decrease was high in both patient groups. This suggests that sensory conduction is impaired earlier than motor conduction in thyroid dysfunctions. Akarsu et al. found that axonal motor fibers were mostly affected in hypothyroidism, while Duffy et al. emphasized that the sensory conduction system was affected earlier than the motor conduction system in thyroid dysfunctions based on electrophysiological findings (3,13).

Carpal tunnel syndrome is one of the most common entrapment neuropathies. In hypothyroidism, CTS is thought to develop due to mucinous infiltration of the median nerve perineurium and endoneurium. The association of hypothyroidism and CTS has been reported with varying rates in the literature. Suresh et al. reported that thyroid dysfunction (hypothyroidism or hyperthyroidism) slightly increased the rate of CTS in their study (21). Van Dijk et al. found a prevalence of hypothyroidism between 1.3% and 10.3% in patients with CTS in their review (22). While the rate of CTS in patients with subclinical hypothyroidism was found to be 12.5%, CTS was detected at a higher rate of 32.5-37.5% in patients with overt hypothyroidism (22-24). Apart from differences in diagnostic criteria, other factors, such as gender, advanced age, and duration of hypothyroidism, may influence the prevalence of CTS in hypothyroid patients (23).

There are few studies investigating the prevalence of CTS in patients with hyperthyroidism. Çakır et al. found a 7.1% prevalence of CTS with nerve conduction tests in patients with thyrotoxicosis (42 patients) (8). In their study, CTS was not detected in any of the 23 patients with subclinical thyrotoxicosis. In our study, the incidence of carpal tunnel syndrome was found to be 10% (2/19 patients) in the hypothyroid patient group, supporting the literature, while no carpal tunnel syndrome was observed in the hyperthyroid patient group.

Myopathy is a well-recognized complication of hypothyroidism. Khaleeli et al. found myopathy in 80% of 15 patients with severe hypothyroidism and suggested that myopathy was more frequent in patients with serous effusion and may be related to the degree of hypothyroidism (24). They found no statistical significance between myopathy and disease duration. Khedr et al. examined 23 hypothyroid patients electrophysiologically and found myopathy in 2 patients (9%), while Duyff et al. found a myopathy rate of 33% (3,15). Although the severity of myopathy is often correlated with the degree and duration of hypothyroidism in electrophysiological examinations, there is no consistent correlation between myopathy findings in muscle tissue obtained via needle biopsies and the duration and severity of hypothyroidism (11). EMG findings in hypothyroidism are quite variable, and EMG is often observed as normal. Rarely, typical myopathic patterns and abnormal spontaneous activities may be observed on EMG (24). These rate variations may be attributed to this variability.

The incidence of muscle dysfunction in hyperthyroidism can be up to 80%. However, although this rate seems to reflect the frequency of myopathy, it cannot be supported by electrophysiological studies. The mechanism of myopathy in hyperthyroidism is thought to be related to the decrease in muscle function due to the increased myosin alpha concentration in skeletal muscle with adrenergic stimulation of thyroid hormones (6). Duyff et al. found myopathic changes in 10% of 21 hyperthyroid patients electrophysiologically and reported a correlation between muscle weakness clinically and elevated T4 levels (3).

In our study, myopathy was found in 2 patients (10%), and electrophysiologically increased polyphasia was observed in 4 patients (20%) in the hypothyroid group. These findings were not correlated with TSH, sT3, sT4 values. In the hyperthyroid patient group, myopathy was detected in 1 patient (4%), and electrophysiologically increased polyphasia was observed in 3 patients (14%).

Serum CK concentration is usually elevated in hypothyroid patients. Rarely, hypothyroidism may cause severe skeletal muscle involvement and rhabdomyolysis. Elevated CK may be due to direct cellular damage, decreased cellular metabolism, or a reversible defect in glycogenolysis. Although some publications suggest that the degree of hypothyroidism is correlated with elevated CK levels, no consistent correlation has been observed between the severity of symptoms and serum CK concentration (25,26). In a case report of a patient with severe hypothyroidism, it was reported that rhabdomyolysis and axonal neuropathy developed, and the very high CK level decreased to normal after hormone treatment. In hyperthyroidism, serum CK levels generally do not change (27-29).

CONCLUSION

Our study, in patient with thyroid dysfunction, the rate of neuromuscular complaints was higher than in the control group. PNP and CTS were higher in the hypothyroid patient group compared to the control group, while

PNP and CTS were not detected in the hyperthyroid patient group. Sural conduction velocity decrease or no SAP rate was higher in both patient groups. Our electroneurophysiologic studies have shown that sensorial nerve conduction velocity is affected before motor nerve conduction velocity in early thyroid dysfunction. Again, electroneurophysiologically, the percentage of myopathy was found to be higher in the hypothyroid patient group than in the hyperthyroid patient group and control. There was no statistical correlation between serum TSH, T3 and T4 levels and neuropathy and myopathy in both patient groups. Although serum CK concentration was not correlated with the degree of disease and myopathy, it was found to be significantly higher in hypothyroid patients.

Although the mechanism by which thyroid dysfunction affects the neuromuscular system is still debated. Neuromuscular symptoms may improve after treatment of thyroid disease. In future studies, comparison of post-treatment electrophysiologic values with pre-treatment values and clinical values may show the effect of thyroid function on the neuromuscular system more clearly.

DECLARATIONS

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Prognostic and Risk Factors in Renal Transplant Recipients During the COVID-19 Pandemic

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Abstract

Background: We aim to compare potential factors that may affect the prognosis of kidney transplant recipients (KTRs) and hemodialysis patients (HDPs) with the diagnosis of COVID-19.

Method: This single-center retrospective study was conducted at the University of Health Science Diskapi Yildirim Beyazit Training and Research Hospital hospital. From March 1, 2021, to September 30, 2021, 110 individuals diagnosed with COVID-19 and ≥18 years old were included in our study. The study population comprised 29 kidney transplant recipients (KTRs) and 81 hemodialysis patients (HDPs). Data were collected from the hospital's software and included patient descriptive features, laboratory test results, medication records, demographic information, comorbidities, and clinical outcomes of COVID-19 diagnosis, such as mortality and discharge rates.

Results: A total of 110 patients (29 KTRs, 81 HDPs) were evaluated. There was no significant difference in mortality rates observed between the groups (p=0.117). Coronary artery disease (CAD) was found to be associated with mortality in both KTRs and HDPs (p=0.001 and p=0.021, respectively). A logistic regression analysis model identified age above 55 years as a significant mortality-related factor in HDPs (p=0.039). Pro-brain natriuretic peptide (pro-BNP) and procalcitonin levels at admission, and increase in serum creatinine, neutrophil count, lactate dehydrogenase (LDH), d-dimer, procalcitonin and urea urea during hospitalization were associated with death in KTRs (p<0.05).

Conclusion: This study highlights comparable mortality rates in KTRs and HDPs hospitalized due to COVID-19. Kidney injury (increase in creatinine, urea), presence of CAD, proBNP, D-dimer, LDH), and inflammation (increase in neutrophil count, procalcitonin) could be a predictor of mortality in KTRS with COVID-19. Despite ongoing debates on immunosuppressive medications, our findings suggest a potential role in mitigating COVID-19 severity. Additionally, age > 55 years is a strong indicator of in HDPs with COVID-19.

Keywords: COVID-19, CoronaVac, Pfizer-BioNTech, vaccine side effects, allergies

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is associated with an increased risk of morbidity and mortality among individuals with comorbidities such as chronic kidney disease (CKD) (1). Kidney transplant recipients (KTRs) pose significantly poorer prognoses in COVID-19 when compared to the general population. This increased vulnerability is associated with the presence of comorbidities and the impact of immunosuppressive therapy (2).

The preliminary data highlighted the disproportional higher COVID-19 fatality rates in the kidney transplanted population compared with the general population (3). Besides studies indicate that kidney transplantation provides a more favorable survival rate

during the COVID-19 pandemic compared to other renal replacement therapies, despite a few opposite claims (4-6). Hence, the specific impact of COVID-19 on KTRs remains uncertain.

Immunization stands as the most robust defense against diseases, however, studies including KTRs reveal a diminished antibody response, even after the second dose of an mRNA vaccine, when compared to the general population (7). It is a fact that KTRs are at risk since most of the available data are based on mRNA vaccination results of patients who have undergone solid organ transplants and considering that vaccination with mRNA is the most common method (8).

Adverse outcomes in individuals with COVID-19 were found to be correlated with various factors, including gender, age, lifestyle, and cardio-metabolic symptoms (9). The identification of prognostic factors holds pivotal importance in both the prevention and management of disease development in kidney transplant recipients (KTRs), a high-risk group susceptible to COVID-19. (10).

In this study, we aimed to investigate potential prognostic factors in KTRs and hemodialysis patients (HDPs), who were diagnosed with COVID-19 and required hospitalization.

METHODS

Study Design

This is a retrospective single-center case-control study. The standard treatments for COVID-19 patients aligned with the guidelines outlined by the Ministry of Health of the Republic of Turkey. The study ethics approval was obtained from the local clinical research ethics committee of our hospital (IRB no: 114/06). This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects

Patients and Protocols

The study encompassed adult individuals (≥18 years old) who were kidney transplant recipients (KTRs) and hemodialysis patients (HDPs) without a history of kidney transplantation. These participants sought medical attention at our hospital between March 01, 2021, and September 30, 2021, and were subsequently admitted to COVID-19 services or the intensive care unit. Inclusion criteria were based on positive COVID-19 PCR test results and the presence of ground glass opacities and/or mixed consolidation areas in lung computed tomography. HDPs were confirmed whether they had received an adequate previous hemodialysis treatment by inquiring about their records (patients with KT/V> 1.2 were included).

The immunosuppressive therapy consisted of prednisolone, mycophenolic acid, calcineurin inhibitors, or mammalian target of rapamycin (mTOR) inhibitors. Mycophenolic acid doses were reduced by half and prednisolone doses were doubled following the diagnosis of COVID-19. Based on lymphocyte counts and clinical course, mycophenolic acid therapy was interrupted when mandatory. One patient received anakinra (3x200mg intravenously) and three patients received tocilizumab (8 mg/kg, at a maximum dose of 800 mg). A patient treated with tocilizumab also received a cytokine filter therapy (Ultraflux EMiC2 Fresenius Medical Care Turkey).

After admission, laboratory and imaging tests were conducted as clinically indicated, encompassing complete blood counts, serum biochemistry, ferritin, procalcitonin, D-dimer, fibrinogen, N-terminal pro-brain natriuretic peptide (proBNP), C-reactive protein (CRP), and lactate dehydrogenase (LDH). Additionally, chest X-ray and computed tomography were performed. Symptoms, medical history, comorbidities, physical examination findings, age, gender, length of hospital stay, and the outcomes (death or discharge) were recorded from the hospital's software. ProBNP levels were specifically assessed on the initial day of admission. The changes in the study parameters were demonstrated by calculating a Δ (the difference between the baseline levels at admission [parameter-1] and the peak levels after admission [parameter-2] for the following tests: urea, creatinine, LDH, neutrophils, lymphocytes, ferritin, fibrinogen, D-dimer, procalcitonin, and CRP).

STATISTICAL ANALYSIS

Simple arithmetic means and percentages were employed to synthesize demographic and clinical data. The distribution characteristics of continuous variables were examined using the Shapiro-Wilk test and histograms. Continuous variables were summarized as the arithmetic mean ± standard deviation (SD) or median (minimum-maximum), depending on the type and distribution. Intergroup comparisons of parametric and nonparametric variables were carried out using the independent samples t-test and the Mann-Whitney U test, respectively. Categorical variables were compared using the chi-square test. Logistic regression was utilized to assess the effects of continuous variables on mortality and survival in both the kidney transplant recipients (KTRs) and hemodialysis patients (HDPs) groups. The analysis was conducted using Statistical Package for Social Sciences version 23 software. $P<0.05$ was assumed as significant.

RESULTS

The study encompassed a total of 110 patients, consisting of 29 KTRs and 81 HDPs. 43 individuals (39.1%) were women. **Table 1** presents the descriptive statistics

Table 1. Distribution of demographic characteristics, comorbidities and symptoms in KTRs and HDPs

		KTRs, N(%)		HDPs, N(%)		P value
Age (year)	≤55	16	55.2	32	39.5	0.144
	>55	13	44.8	49	60.5	
Sex	Female	10	34.5	33	40.7	0.553
	Male	19	65.5	48	59,3	
Prognosis	Discharge	25	86.2	58	71.6	0.117
	Death	4	13.8	23	28.4	
DM	Yes	20	69.0	46	56.8	0.251
	No	9	31.0	35	43.2	
HT	Yes	18	62.1	40	49.4	0.240
	No	11	37.9	41	50.6	
CAD	Yes	26	89.7	63	77.8	0.163
	No	3	10.3	18	22.2	
Cough	Yes	10	43.5	33	50.8	0.548
	No	13	56.5	32	49,2	
Dispnea	Yes	13	56.5	29	44.6	0.326
	No	10	43.5	36	55.4	
Diarrhea	Yes	20	87.0	59	90.8	0.604
	No	3	13.0	6	9.2	
Nausea Vomiting	Yes	20	87.0	63	96.9	0.076
	No	3	13.0	2	3.1	
Myalgia	Yes	13	56.5	51	78.5[a]	**0.042**
	No	10	43.5[b]	14	21.5	
Fever	Yes	18	78.3	38	58.5	0.090
	No	5	21.7	27	41.5	
Headache	Yes	21	91.3	61	93.8	0.678
	No	2	8.7	4	6.2	

KTRs; kidney transplant recipients, HDPs; hemodialysis patients, DM; diabetes mellitus, HT; hypertension, CAD: coronary artery disease

of categorical patient characteristics. The groups demonstrated similarity in terms of gender distribution, comorbidity rates, and age groups (divided into two groups as >55 and ≤55 years of age). The duration of hospital stay averaged 11.6±9.4 days for KTRs and 14.3±13.8 days for HDPs. 27 individuals died, constituting a mortality rate of 24.5%. The mortality rate was relatively higher in HDPs, however, no statistically significant difference was observed between the two groups (p=0.117). The frequency of myalgia as a presenting complaint was significantly higher in KTRs compared to HDPs (56.5% vs 21.5%, p= 0.042).

The mean age was 50.66±11.73 years and 58.89±14.22 years in KTRs and HDPs, respectively (p=0.006). In the HDPs group, the mean levels of urea-1, urea-2, creatinine-1, creatinine-2, ferritin-1, CRP-2, and ΔCRP, and the neutrophil-2/lymphocyte-2 ratio were significantly higher, and in the KTRs group, the mean levels of LDH-2, ΔLDH, and lymphocyte-2 were significantly higher (p<0.05) (Table 2).

The presence of coronary artery disease (CAD) was associated with mortality in the KTRs group (p=0.001), however, this association was found in individuals aged >55 years (p=0.039) and those with CAD in the HDPs group (p=0.021) (Table 3).

In the KTRs group, the levels of creatinine-2,

Table 2. Descriptive values of numerical characteristics of KTRs and HDPs groups

	Group	N	Mean	SD±	P value
Age (Year)	KTRs	29	50.66	11.73	**0.006**
	HDPs	81	58.89	14.22	
CCI	KTRs	29	2.93	1.49	0.655
	HDPs	81	2.79	2.05	
Urea1 (mg/dl)	KTRs	29	53.08	31.33	**0.001**
	HDPs	78	106.58	50.20	
Urea2 (mg/dl)	KTRs	29	62.90	37.23	**0.001**
	HDPs	72	130.36	57.23	
ΔUrea	KTRs	29	-9.82	22.55	0.080
	HDPs	72	-23.83	56.92	
Creatinine1 (mg/dl)	KTRs	29	1.66	1.16	**0.031**
	HDPs	78	9.93	21.04	
Creatinine2 (mg/dl)	KTRs	29	1.72	1.43	**0.001**
	HDPs	71	6.52	2.90	
ΔCreatinine	KTRs	29	-0.06	0.71	0.573
	HDPs	71	0.10	0.17	
Neutrophile1	KTRs	29	4572.93	1916.52	0.918
	HDPs	79	5929.49	5409.88	
Neutrophile2	KTRs	29	4712.00	3159.56	0.924
	HDPs	73	5753,01	4894,84	
Lenfocyte1	KTRs	29	1066.14	630.73	0.072
	HDPs	76	987,30	783,11	
Lenfocyte2	KTRs	29	1188.97	780.37	**0.001**
	HDPs	70	965.59	968.53	
LDH1 (mg/dl)	KTRs	27	268.37	163.85	0.101
	HDPs	69	322.75	149.97	
LDH2 (mg/dl)	KTRs	27	377.07	477.52	**0.020**
	HDPs	57	352,49	191,90	
ΔLDH	KTRs	27	-108.70	455.35	**0.024**
	HDPs	57	-20.61	186.46	
Ferritin1 (µg/L)	KTRs	22	663.60	894.19	**0.031**
	HDPs	67	2425.71	2612.37	
Ferritin2 (µg/L)	KTRs	23	963.87	1387.85	0.112
	HDPs	39	1900.67	1706.83	
Fibrinogen1 (g/L)	KTRs	22	470	164.43	0.820
	HDPs	75	477.84	134.05	
Fibrinogen2 (g/L)	KTRs	22	454.68	154.37	0.864
	HDPs	48	461.15	141.92	
ΔFibrinogen	KTRs	22	15.32	158.54	0.461
	HDPs	51	50.08	193.71	
D-dimer1 (µg/ml)	KTRs	24	1.71	4.40	0.187
	HDPs	75	3.70	4.09	
D-dimer2 (µg/ml)	KTRs	23	2.37	6.97	0.239
	HDPs	59	3.71	3.50	
ΔD-dimer	KTRs	23	-0.60	8.54	0.793
	HDPs	58	0.43	4.06	
Procalsitonin1 (µg/L)	KTRs	25	1.31	5.09	0.154
	HDPs	76	71.07	417.79	
Procalsitonin2 (µg/L)	KTRs	24	8.91	28.10	0.067
	HDPs	51	17.74	74.84	
ΔProcalsitonin	KTRs	24	-7.56	24.82	0.143
	HDPs	52	24,94	190,71	
Probnp (ng/L)	KTRs	24	1904.27	3711.01	0.122
	HDPs	73	17079.1	13052.15	
AST (mg/dl)	KTRs	29	38.36	55.94	0.617
	HDPs	77	27.89	26.07	
ALT (mg/dl)	KTRs	29	33.66	29.57	0.134
	HDPs	77	22.73	32.55	
CRP1 (mg/L)	KTRs	28	65.93	74.14	0.507
	HDPs	75	121.12	118.90	
CRP2 (mg/L)	KTRs	27	52.38	82.95	**0.017**
	HDPs	57	90.83	82.12	
ΔCRP	KTRs	27	15.94	77.85	**0.026**
	HDPs	57	36.94	127.04	
Neutrophile1/Lenfocyte1	KTRs	29	7.70	12.00	0.405
	HDPs	76	8.48	10.18	
Neutrophile2/Lenfocyte2	KTRs	29	8.26	14.69	**0.025**
	HDPs	68	9.41	12.17	

CCI; Charlson co-morbidity index, LDH; lactate dehydrogenase, AST; aspartate aminotransferase, ALT; alanine aminotransferase, CRP; c-reactive protein

neutrophil-1, neutrophil-2, LDH-2, D-dimer-2, procalcitonin-1, procalcitonin-2, proBNP, Δurea, ΔLDH, Δferritin, and Δprocalcitonin were significantly

Table 3. Evaluation of the relationship between mortality and categorical features in KTRs and HDPs

n %			Discharge		Death		
			n	%	n	%	p value
KTRs	Age (Year)	<=55	14	87.5	2	12.5	0.823
		>55	11	84.6	2	15.4	
	Sex	Female	8	80.0	2	20.0	0.482
		Male	17	89.5	2	10.5	
	DM	No	17	90.0	3	10.0	0.779
		Yes	8	77.8	1	22.2	
	HT	No	16	94.4	2	5.6	0.592
		Yes	9	72.7	2	27.3	
	CAD	No	25	84.6	1	15.4	0.001
		Yes	0	100.0	3	0.0	
HDPs	Age (Year)	<=55	27	84.4	5	15.6	0.039
		>55	31	63.3	18	36.7	
	Sex	Female	27	81.8	6	18.2	0.091
		Male	31	64.6	17	35.4	
	DM	No	36	78.3	10	21.7	0.128
		Yes	22	62.9	13	37.1	
	HT	No	31	77.5	9	22.5	0.245
		Yes	27	65.9	14	34.1	
	CAD	No	49	77.8	14	22.2	0.021
		Yes	9	50.0	9	50.0	

DM; diabetes mellitus, HT; hypertension, CAD; coronary artery disease

higher in non-survivors (p<0.05) (**Table 4**). In HDPs, Δneutrophil and ΔLDH were significantly higher and lymphocyte-2 was significantly lower in non-survivors. The values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have been reported as indicators of poor prognosis in COVID-19 within the general population, did not demonstrate a significant association with mortality in the comparative analysis of the two groups (p=0.924 vs p=0.218 and p=0.217 vs p=0.845, KTRs vs HDPs respectively).

We performed a univariate binary logistic regression analysis to evaluate the risk ratios of mortality-related factors. **Table 5** demonstrates the results from the logistic regression analysis. Only HDPs above 55 years of age had a significantly higher risk of death (OR: 3.135 (1.026-9.582) (p=0.045). The risk of death was significantly higher in patients with CAD in both groups (OR: 3.500 (1.167-10.498) (p=0.025).

DISCUSSION

It is controversial whether the course of COVID-19 is different in KTRs compared to HDPs. Identification of prognostic factors in KTRs is crucial to lower worse outcomes. In this study, mortality rates in KTRs and HDPs requiring hospitalization due to COVID-19 were similar and CAD was associated with mortality in both of the KTRs and HDPs groups.

The relationship between COVID-19 and mortality remains unclear in KTRs (4-6,11). Mortality rates in KTRs were reported as 28% by a study conducted at Columbia University, 25% in Spain, and 25% in Italy

Table 4. Comparison of survivors (discharge) and died (death) in the KTRs and HDPs groups.

	Group	Prognosis	N	Mean	SD±	P value
Age (Year)	KTRs	Discharge	25	50.16	11.71	0.579
		Death	4	53.75	13.15	
	HDPs	Discharge	58	57.88	15.15	0.257
		Death	23	61.43	11.42	
CCI	KTRs	Discharge	25	2.76	1.51	0.065
		Death	4	4.00	0.82	
	HDPs	Discharge	58	2.53	2.07	0.060
		Death	23	3.43	1.88	
Urea1 (mg/dl)	KTRs	Discharge	25	54.66	32.79	0.508
		Death	4	43.23	20.29	
	HDPs	Discharge	55	107.06	51.94	0.897
		Death	23	105.43	46.84	
Urea2 (mg/dl)	KTRs	Discharge	25	58.01	36.20	.076
		Death	4	93.48	31.82	
	HDPs	Discharge	49	128.54	58.86	0.697
		Death	23	134.23	54.67	
ΔUrea	KTRs	Discharge	25	-3.35	12.89	**0.049**
		Death	4	-50.25	29.79	
	HDPs	Discharge	49	-21.49	54.33	0.615
		Death	23	-28.80	63.08	
Creatinine1 (mg/dl)	KTRs	Discharge	25	1.65	1.21	0.926
		Death	4	1.71	0.90	
	HDPs	Discharge	56	11.37	24.69	0.339
		Death	22	6.27	2.51	
Creatinine2 (mg/dl)	KTRs	Discharge	25	1.52	1.26	**0.050**
		Death	4	2.98	1.94	
	HDPs	Discharge	49	6.74	3.23	0.265
		Death	22	6.04	1.96	
ΔCreatinine	KTRs	Discharge	25	0.13	0.28	0.126
		Death	4	-1.27	1.33	
	HDPs	Discharge	49	0.05	2.26	0.748
		Death	22	0.23	2.01	
Neutrophile1	KTRs	Discharge	25	4143	1473.56	**0.014**
		Death	4	7260	2396.50	
	HDPs	Discharge	56	6249.29	6017.74	0.627
		Death	23	5150.87	3512.42	
Neutrophile2	KTRs	Discharge	25	4086	2365.96	**0.050**
		Death	4	8625	4970.83	
	HDPs	Discharge	51	5427.06	4223.99	0.833
		Death	22	6508.64	6229.71	
ΔNeutrophile	KTRs	Discharge	25	57.08	2265.67	0.255
		Death	4	-1365	4879.87	
	HDPs	Discharge	51	129.22	5466.74	**0.050**
		Death	22	-1517.73	4053.07	
Lenfocyte1	KTRs	Discharge	25	1047.92	622.17	0.569
		Death	4	1180	772.14	
	HDPs	Discharge	53	1040.85	841.54	0.384
		Death	23	863.91	627.64	
Lenfocyte2	KTRs	Discharge	25	1256	772.56	0.154
		Death	4	770	798.42	
	HDPs	Discharge	47	1113	1135.29	**0.007**
		Death	23	664.35	325.39	

continues...

(12-14). According to the data provided by the European Kidney Association COVID-19 Database (ERACODA), the mortality prediction rate within 28 days was 21.3% in KTRs and 25.0% in HDPs (15). A multicenter study conducted in Turkey revealed a mortality rate of 12.5%

Table 4 (continues). Comparison of survivors (discharge) and died (death) in the KTRs and HDPs groups.

ΔLenfocyte	KTRs	Discharge	25	-208.08	651.67	0.486
		Death	4	410	1192	
	HDPs	Discharge	47	-79.70	1282.86	0.368
		Death	23	199.57	561.28	
Neutrophile1/ Lenfocyte1	KTRs	Discharge	25	6.40	9.81	0.411
		Death	4	15.80	21.75	
	HDPs	Discharge	53	9.16	11.73	0.919
		Death	23	6.94	4.93	
Neutrophile2/ Lenfocyte2	KTRs	Discharge	25	4.91	5.97	0.067
		Death	4	29.16	32.43	
	HDPs	Discharge	46	7.45	8.02	0.100
		Death	22	13.50	17.58	
LDH1 (mg/dl)	KTRs	Discharge	24	275.13	171.17	0.419
		Death	3	214.33	84.63	
	HDPs	Discharge	46	320.67	156.35	0.809
		Death	23	326.91	139.60	
LDH2 (mg/dl)	KTRs	Discharge	24	258.21	189.74	**0.041**
		Death	3	1328	1012.11	
	HDPs	Discharge	35	316.20	136.44	0.380
		Death	22	410.23	249.76	
ΔLDH	KTRs	Discharge	24	16.92	99.30	**0.007**
		Death	3	-1113.67	936.91	
	HDPs	Discharge	35	21.46	145.55	**0.050**
		Death	22	-87.55	225.32	
Ferritin1 (µg/L)	KTRs	Discharge	20	527.35	523.34	0.568
		Death	2	2026.10	2739.19	
	HDPs	Discharge	46	2103.18	2065.93	0.380
		Death	21	3132.19	3486.30	
Ferritin2 (µg/L)	KTRs	Discharge	21	708.71	703.21	0.126
		Death	2	3643	4094.15	
	HDPs	Discharge	25	1621.56	1131.40	0.650
		Death	14	2399.07	2394.83	
ΔFerritin	KTRs	Discharge	20	-144.45	332.20	**0.030**
		Death	2	-1616.90	1354.96	
	HDPs	Discharge	24	94.13	1760.72	0.694
		Death	14	-145.50	2162.14	
Fibrinogen1 (g/L)	KTRs	Discharge	19	480.95	169.29	0.445
		Death	3	400.67	132.67	
	HDPs	Discharge	53	484.13	139.22	0.532
		Death	22	462.68	122.40	
Fibrinogen2 (g/L)	KTRs	Discharge	19	473.11	147.72	0.164
		Death	3	338	173.67	
	HDPs	Discharge	33	451.24	141.50	0.479
		Death	15	482.93	145.29	
ΔFibrinogen	KTRs	Discharge	19	7.84	141.17	0.590
		Death	3	62.67	284	
	HDPs	Discharge	36	76.03	206.42	0.140
		Death	15	-12.20	147	
D-dimer1 (µgml)	KTRs	Discharge	21	1.66	4.69	0.060
		Death	3	2.04	1.44	
	HDPs	Discharge	52	3.68	4.04	0.735
		Death	23	3.76	4.30	

continues...

among KTRs, while another independent multicenter study from the same region reported mortality rates of 21% in KTRs and 25.4% in HDPs (4,16). In our study, mortality rates were found similar; 13.8% in KTRs and 28.4% in HDPs. This study demonstrates similar

Table 4 (continues). Comparison of survivors (discharge) and died (death) in the KTRs and HDPs groups.

D-dimer2 (µg/ml)	KTRs	Discharge	20	2.33	7.48	**0.028**
		Death	3	2.65	1.73	
	HDPs	Discharge	39	3.67	3.18	0.898
		Death	20	3.80	4.15	
ΔD-dimer	KTRs	Discharge	20	-0.60	9.13	0.523
		Death	3	-0.61	2.99	
	HDPs	Discharge	38	0.56	4.39	0.695
		Death	20	0.19	3.43	
Procalsitonin1 (µg/L)	KTRs	Discharge	21	0.30	0.50	**0.041**
		Death	4	6.61	12.70	
	HDPs	Discharge	54	40.51	257.44	0.986
		Death	22	146.07	669.19	
Procalsitonin2 (µg/L)	KTRs	Discharge	21	0.62	1.76	**0.010**
		Death	3	66.96	57.22	
	HDPs	Discharge	35	20.66	89.05	0.707
		Death	16	11.35	25.19	
ΔProcalsitonin	KTRs	Discharge	21	-0.32	1.43	**0.010**
		Death	3	-58.24	51.60	
	HDPs	Discharge	36	39.25	228.01	0.372
		Death	16	-7.28	27.62	
Probnp (ng/L)	KTRs	Discharge	20	994.62	2569.51	**0.004**
		Death	4	6452.50	5537.94	
	HDPs	Discharge	53	16736.87	12935.89	0.769
		Death	20	17985.85	13652.92	
AST(mg/dl)	KTRs	Discharge	25	27.65	17.18	0.217
		Death	4	105.28	141.15	
	HDPs	Discharge	54	29.27	28.62	0.845
		Death	23	24.67	18.97	
ALT (mg/dl)	KTRs	Discharge	25	33.46	30.22	0.924
		Death	4	34.92	29.19	
	HDPs	Discharge	54	25.95	37.50	0.218
		Death	23	15.17	13.70	
CRP1 (mg/L)	KTRs	Discharge	25	63.63	72.73	0.683
		Death	3	85.09	100.57	
	HDPs	Discharge	53	126.12	121.51	0.557
		Death	22	109.08	114.22	
CRP2 (mg/L)	KTRs	Discharge	24	42.70	72.56	0.123
		Death	3	129.79	137.05	
	HDPs	Discharge	39	74.23	63.43	0.074
		Death	18	126.82	105.92	
ΔCRP	KTRs	Discharge	24	23.52	62.12	0.589
		Death	3	-44.70	167.96	
	HDPs	Discharge	39	57.72	131.43	**0.012**
		Death	18	-8.07	106.82	

CCI; Charlson Comorbidity Index, LDH; lactate dehydrogenase, AST; aspartate aminotransferase, ALT; alanine aminotransferase, CRP; c-reactive protein

mortality rates in KTRs and HDPs to the previous reports from Turkey, in contrast to lower mortality rates reported from other countries. We believe that the relatively younger ages of KTRs in this study may have contributed to these results. There is a debate regarding the potential augmentation of COVID-19 severity risk associated with the use of immunosuppressive medications. This debate originates from the fact that medications used in transplant patients act on T cells, but not on memory T and B cells (17). In contrast, a recent study has indicated that therapeutic doses of tacrolimus potently

Table 5. Effects of demographic and biochemical parameters on mortality in KTRs and HDPs groups

	KTRs 95% C.I.for OR				HDPs 95% C.I.for OR			
		Lower	Upper	P value		Lower	Upper	P value
Age Group (>55 *vs* <=55)	1.273	0.154	10.530	0.823	3.135	1.026	9.582	**0.045**
Sex (Female *vs* Male)	2.125	0.252	17.927	0.488	0.405	0.140	1.174	0.096
CCI	1.729	0.830	3.602	0.144	1.244	0.975	1.587	0.079
HT	1.778	0.213	14.860	0.595	1.786	0.668	4.776	0.248
DM	0.708	0.063	7.919	0.780	2.127	0.798	5.670	0.131
CAD	72.000	3.512	1476.122	**0.006**	3.500	1.167	10.498	**0.025**
ΔUrea	0.890	0.796	0.995	**0.041**	0.998	0.989	1.007	0.610
ΔCreatinine	0.011	0.000	5.036	0.149	1.039	0.824	1.311	0.744
ΔNeutrophile	1.000	0.999	1.000	0.324	1.000	1.000	1.000	0.218
ΔLenfocyte	1.001	1.000	1.001	0.138	1.000	1.000	1.001	0.329
ΔLDH	0.984	0.958	1.011	0.235	0.996	0.993	1.000	**0.050**
ΔFerritin	0.997	0.994	1.000	0.092	1.000	1.000	1.000	0.704
ΔFibrinogen	1.002	0.994	1.002	0.573	0.997	0.994	1.001	0.145
ΔD-dimer	1.000	0.865	1.000	0.999	0.977	0.854	1.118	0.737
ΔProcalsitonin	0.881	0.522	1.488	0.636	0.975	0.939	1.013	0.191
ΔCRP	0.990	0.975	1.005	0.175	0.995	0.990	1.001	0.078
Neutrophile1/Lenfocyte1	1.045	0.979	1.116	0.190	0.971	0.909	1.038	0.393
Neutrophile2/Lenfocyte2	1.097	0.998	1.206	**0.050**	1.042	0.994	1.092	0.085

OR; Odds Ratio; CI; confidence interval for OR, CCI; Carlson-Comorbidity Index, LDH; lactate dehydrogenase, CRP; C-reactive protein, DM; diabetes mellitus, HT; hypertension, CAD; coronary artery disease

can suppress the proliferation of human coronaviruses in cell culture media (18). This data has given rise to a hypothesis suggesting that standard immunosuppressive therapy in KTRs may potentially inhibit cytokine release, thereby mitigating disease severity and reducing the associated risk of mortality. Moreover, numerous studies in the literature have indicated that various vaccines administered for prophylaxis against diverse infections might confer protection against COVID-19 (19,20). A study by Gürsel et al. has reported that different vaccines can protect against various pathogens, as shown in COVID-19 (21). Some attenuated vaccines, such as Bacillus Calmette-Guerin (BCG), which is listed on the vaccination schedule in our country, can protect against different pathogens of acute respiratory tract infections. The mechanism underlying the nonspecific immunization by the BCG vaccine is suggested to be through the induction of innate immunity (21). Genetic and racial differences are also considered to play an important role in COVID-19 (22).

In this study, there is no impact of age on mortality in KTRs. However, in the HDPs group, being older than 55 years was associated with mortality. Previous studies reported that hypertension (HT), diabetes mellitus (DM), and CAD are the most common comorbidities in non-survivor COVID-19 patients. CAD was the only factor associated with mortality in both KTRs and HDPs in the current study. Similarly, a recent study reported CAD first as the most common cause of mortality due to COVID-19 (23).

Previous studies reported a significant association between acute kidney injury with multi-organ failure and mortality in COVID-19 patients (24,25). In this study, increased urea and creatinine levels suggest an acute kidney injury associated with mortality in KTRs. Additionally, we assessed the influence of neutrophil and lymphocyte counts, the neutrophil/lymphocyte ratio, and levels of procalcitonin, ferritin, and CRP as inflammation parameters on the outcomes of COVID-19. In the KTRs group, inflammatory parameters linked with mortality included neutrophils, procalcitonin, and ferritin. Exacerbation of the inflammatory status in COVID-19 has been associated with an unfavorable prognosis in the general population (10). In this study, we revealed an increased inflammatory status in the KTRs who died. Although we noted lymphocytopenia in the KTRs group, aligning with recent research findings, this observation did not achieve statistical significance. The small number of KTRs and the lack of immunization results associated with vaccinations during the study period are the limitations of our study. During the study period, the patients completed the three-dose schedule of the vaccine. The patients in the KTRs group received attenuated vaccines as the standard first two doses. The patients received either attenuated or mRNA vaccines as the third dose depending on patient preferences. Because of the lack of results to evaluate the immune response, the effect of vaccination on mortality and prognosis could not be evaluated in the study. A recent study involving 30 transplant recipients revealed that, following the administration of the standard two doses of an mRNA vaccine, 6 individuals exhibited a poor immune response, while 24 showed no immune response at all. The study has subsequently reported the outcomes of immunization in this patient cohort with a third dose of the vaccine

(26). In the nonresponder group, the antibody titers on the 14th day following vaccination revealed a strong positive antibody response in 6/24 (25%) recipients and a negative response in 16/24 (67%) recipients. In their later report, the same team reported the results of vaccination of 18 KTRs with the fourth dose. In 3 out of 6 patients (3/18) (16.6%) with a negative antibody response after the third dose of an mRNA vaccine, the antibody response remained negative after the fourth dose (27).

As stated in the limited number of recent studies, the immune responses of KTRs receiving vaccines against COVID-19 do not appear as precise as those obtained in the general population. Our study may add value by identifying the factors affecting the prognosis and reporting the risk ratios during the era when the efficacy of vaccines in transplant recipients is still being discussed. To the best of our knowledge, this is the first study investigating the prognostic factors of COVID-19 in KTRs in Turkey.

CONCLUSION

This study highlights the comparable mortality rates in KTRs and HDPs hospitalized due to COVID-19. The association of CAD with mortality underscores the importance of recognizing specific risk factors in these populations. Despite the unresolved debate on the impact of immunosuppressive medications, our findings suggest a potential role of immunosuppressive regimens in inhibiting cytokine release, offering a novel perspective on managing COVID-19 severity in KTRs. The study's limitations, such as a small KTR sample size and a lack of immunization results, are acknowledged. Nevertheless, this research contributes valuable insights into the unique challenges faced by KTRs during the COVID-19 era.

ETHICAL DECLARATIONS

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Ethical Issues: This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects. The study ethics approval was obtained from the local clinical research ethics committee of our hospital (IRB no: 114/06).

Author Contributions: The authors declared that they all participated in the design, execution, and analysis of the study and that they approved the final version of the paper.

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Review

Dyslipidemia and Kidney: An Updated View

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Abstract

Dyslipidemia is a common concern in various kidney-related conditions, including chronic kidney disease, nephrotic syndrome, kidney transplant patients, and those undergoing dialysis. Dyslipidemia is a significant risk factor for atherosclerosis and cardiovascular diseases in these patient groups. Understanding the unique challenges and factors associated with dyslipidemia in these kidney-related conditions is essential for providing effective patient care and reducing cardiovascular risk. This review explores the relationship between dyslipidemia and kidney diseases, highlighting the key recommendations and considerations for managing lipid profiles in each population.

Keywords: Chronic kidney disease, dialysis, dyslipidemia, nephrotic syndrome, statins, transplantation

INTRODUCTION

The elevated plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides and high-density lipoprotein cholesterol (HDL-C) levels define dyslipidemia and having dyslipidemia is associated to the development of atherosclerosis and cardiovascular diseases (CVD). Patients with chronic kidney disease (CKD) shows significant changes in their lipid profiles and lipoprotein structure and function (1). They have also increased risk for atherosclerosis development from dyslipidemia.

Secondary causes of dyslipidemia include the nephrotic syndrome (NS), hypothyroidism, diabetes mellitus, excessive alcohol intake, obesity and chronic liver disease. 13-cis-retinoic acid, androgens, anticonvulsants, oral contraceptives, highly active anti-retroviral therapy, corticosteroids, diuretics, cyclosporine, beta-blockers, sirolimus are the drugs that are associated with secondary dyslipidemia. Genetic predisposition and low daily exercise also contribute to dyslipidemia. The major determinants of dyslipidemia in CKD patients are glomerular filtration rate (GFR), the presence of diabetes mellitus, severity of proteinuria, use of immunosuppressive agents, modality of renal replacement therapy, comorbidities and nutritional status (2).

In this chapter the association of dyslipidemia with kidney diseases is discussed.

Triglyceride-rich Lipoproteins

Concentrations of triglyceride-rich lipoproteins [very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), chylomicrons and their residues] begin to increase in the early stages of CKD and are highest in NS and in dialysis patients, especially in peritoneal dialysis (PD) patients. Approximately half of the CKD patients have triglyceride levels >200 mg/dl. The increased production and decreased catabolism of triglyceride- rich lipoproteins are the causes of high triglyceride levels in patients with renal dysfunction. Increased Apo C3 level is an important cause of decreased catabolism of triglyceride- rich lipoproteins. Secondary hyperparathyroidism also causes calcium deposition in the liver and other tissues. As a result, lipoprotein lipase deficiency may develop in these tissues and decreased catabolism of triglyceride- rich lipoproteins may ensue. Repetitive use of low molecular weight heparin in hemodialysis (HD) patients results in the release of the endothelial lipoprotein lipase enzyme and leads to decreased catabolism of triglyceride-rich lipoproteins. Glucose absorption from PD solutions induce hyperinsulinemia (hyperinsulinemia is also

frequently detected in CKD patients) and increased hepatic lipoprotein lipase synthesis and thereby to increased VLDL production.

Low-density Lipoprotein Rich Cholesterol

Approximately 20 to 30 % of the CKD patients have LDL-C >130 mg/dl. Different concentrations of plasma cholesterol levels are observed in CKD patients. In contrast to normal or low concentrations in HD patients, PD and NS patients have higher concentrations of plasma cholesterol levels. Lipid profiles in various kidney-related conditions is shown in Table 1. In non-dialysis dependent CKD patients with NS, increased production and decreased catabolism of LDL-C are responsible for hypercholesterolemia. One of the most important factors that determine cholesterol-rich lipoprotein level is proteinuria. 3-hydroxy-3-methylglutaryl coenzyme A reductase and cholesterol 7 alpha-hydroxylase enzymes are rate-limiting enzymes in cholesterol biosynthesis and catabolism, respectively. Gene expression of these enzymes is not seen in CKD patients without proteinuria. Decreased function of hepatic LDL receptors is also associated with slower LDL clearance. Acquired LDL receptor deficiency develops in patients with nephrotic proteinuria. Atherogenic small dense LDL particles are increased in CKD patients. Higher electronegative LDL-C levels increase the differentiation of monocytes into proinflammatory M1 macrophages. As a result, increased inflammation and accelerated atherosclerosis develops. In PD patients, the protein passing into the peritoneal fluid is high and therefore hepatic albumin synthesis is increased, as well as the synthesis of other proteins and cholesterol-rich lipoproteins by the liver. There is also the escape of apolipoproteins and intact lipoproteins into the peritoneal cavity, but its significance is not yet clear.

High-density Lipoprotein Cholesterol

Transport of excess cholesterol from the artery wall to the liver for removal (reverse cholesterol transport) is the main function of HDL-C. Reverse cholesterol transport is important for cellular cholesterol homeostasis and protect against atherosclerosis. HDL-related apolipoproteins (mainly apolipoprotein AI-II) and enzymes [paroxonase-1, platelet-activating factor acetyl-hydrolase, and lecithin-cholesterol acyltransferase (LCAT)] takes part in important roles for endogenous inhibition of inflammation, platelet adhesion and LDL oxidation. HDL-C exhibits antioxidative properties by increasing endothelial nitric oxide synthase activity and by reducing the formation of reactive oxygen particles. Patients with impaired renal function generally have decreased levels of HDL-related apolipoproteins, decreased activity of LCAT and increased activity of the cholesteryl ester transfer protein (CETP) which are responsible for decreased serum concentrations of HDL-C. The antioxidant and anti-inflammatory function of HDL particles and the quality of reverse cholesterol transport decreased in patients with kidney dysfunction. These data explain the association between HDL-c and increased mortality in CKD patients. HDL carbonylation caused by CKD has been found to be responsible for impaired platelet aggregation and is thought to contribute to the etiology of cardiovascular events.

Lipoprotein (a)

High Lipoprotein (a)(Lp(a)) concentrations are associated with increased risk of CVD in the general population. Lp(a) plays important roles in thrombosis, inflammation and atherosclerosis. Lp(a) is a LDL-C like lipoprotein and is separated from LDL-C by covalently bound apolipoprotein (a). A large gradient of Lp(a) concentration between the aorta and renal vein and increased apolipoprotein (a) fragments in the urine shows the role of the kidneys in degradation of Lpa(a). There is an inverse relation between plasma Lp(a) concentrations and GFR. Highest plasma Lp(a) concentrations especially the large apolipoprotein(a) isoforms are seen in NS and PD patients. PD patients have increased protein loss into the peritoneal cavity which leads to increased hepatic production of Lp(a). Lp(a) levels are also high in HD patients due to inflammation, malnutrition and decreased clearance.

Dyslipidemia in Chronic Kidney Disease

The kidney disease: Improving Global Outcomes guideline (KDIGO-2013) recommends measuring lipid panel that includes TC, LDL-C, HDL-C and triglycerides (3). Fasting does not affect HDL-C but affect mainly triglyceride values and to a lesser extent LDL-C. Annual measurement of lipid panel is also advised regardless of the patients are treated with statins or not. More frequently monitoring of lipids may be necessary for patients with markedly abnormal values.

Table 1. Lipid profiles in various kidney-related conditions

Parameters	Stage 1-5 CKD	Hemodialysis	Peritonealdialysis	Nephrotic syndrome
Total cholesterol	High*	Normal, low	High	High
LDL cholesterol	High*	Normal, low	High	High
HDL cholesterol	Low	Low	Low	Low
Triglycerides	High*	High	High	High
Lipoporotein (a)	High*	High	High	High

LDL: low density lipoprotein; HDL: high density lipoprotein; CKD: chronic kidney disease. The asterisks (*) indicate increasing plasma levels with decreasing glomerular filtration rate

Annual measurement allows assessment of compliance, optimal dosing of medications, consideration of additional antihyperlipidemic therapy including ezetimibe or consideration of additional diet or lifestyle modifications. Change in renal replacement therapy modality, occurrence of other causes of dyslipidemia, need for reassessment of 10-year cardiovascular risk or not already taking a statin are reasons to measure the lipid profile after the initial measurement. Substantial random within-patient variation in serum cholesterol levels can be observed. So, the compliance of patients to treatment is unprovable in some instances. Measurement of Lp (a) is essential part of cardiovascular risk evaluation and should be measured at least once in patients' lifetime (4). Lp(a) can also be checked when changes in the CKD stage occur. Specialist referral is essential for triglyceride levels >1000 mg/dl or LDL-C levels>190 mg/dl.

Diet should be prioritized in the treatment of dyslipidemia before drug therapy. Only a small amount of change develops in serum cholesterol, but no clinical benefit is observed with therapeutic lifestyle measures. Mediterranean-type diet is beneficial in CKD and kidney transplant patients; low protein diet has positive effects on lipid profile. It is known that a diet with an increased fiber content is associated with an improvement in quality of life and lipid profile. The nonpharmacologic management of hypertriglyceridemia among CKD patients include dietary modification, weight reduction, increased physical activity and reduced alcohol intake. A low-fat diet (less than 15 percent of total calories), reduction of monosaccharides and disaccharides and use of fish oils are essential part of this diet.

As discussed previously, the structure and function of HDL-C is changed in CKD patients. A study included patients with CKD stage G3-G4 found that HDL-C ≤40 mg/dl was related to a higher risk of mortality in both genders and HDL-C >60 mg/dl was related to a lower risk of mortality in women but not in men (5). Compared to individuals with HDL-C ≥40 mg/dl, those with HDL-C <30 mg/dl had higher risk for CKD development or progression. However, genetic studies revealed nonsignificant results between HDL-C and CKD, regarding causality.

Rare CKD patients who have serum total triglycerides >1000 mg/dl despite nonpharmacologic interventions may require fibrates in order to prevent pancreatitis. The effect of gemfibrozil in CKD patients with established coronary heart disease and HDL-C <40 mg/dl was evaluated with the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT). Gemfibrozil lowered the risk of coronary death and nonfatal myocardial infarction. However, gemfibrozil therapy had no effect on total mortality (6).

Management of LDL-C to reduce cardiovascular risk is not different from the general population. The increased relative risk for CVD in patients with CKD (including albuminuria with a normal GFR) make essential to prescribe statins. Data also showed that treatment with statins reduce cardiovascular risks. However, the relation between LDL-C and CVD disappears as the GFR decreases and some studies show no association which should be because of the inflammation and malnutrition those are usually seen at advanced stages of CKD.

Statins can be used either for primary or secondary prevention of CVD in non-dialysis CKD patients as patients without CKD. For primary prevention, the predicted 10-year absolute risk of having a major cardiovascular event can be used. Cardiovascular risk can be annually assessed in CKD patients with validated risk prediction tools. Statins can be used if the predicted risk is ≥7.5 to 10% but not if the risk is <5%. Statins can be offered to patients with predictive risk of 5-7.5%. Patients who have atherosclerotic vascular diseases should receive maximum statin dose, similar to patients from general population with atherosclerotic vascular diseases. Patients with estimated GFR <60 mL/min/1.73 m^2 or patients with an estimated GFR ≥60 mL/min/1.73 m^2 with other cardiovascular risk factors (diabetes, hypertension, smoking, low levels of HDL-C, high levels Lp(a)) and older than a ≥50 years of age are suitable for secondary prevention. Recent myocardial infarction or greater life expectancy favors patient's decision to receive statin, but more severe comorbidity or higher current pill burden does not. The frequently prescribed statin is atorvastatin for patients with CKD because it undergoes hepatic clearance. Atorvastatin may also have positive effects on renal function and proteinuria.

Because Lp(a) may be measured as part of the TC or LDL-C fraction; patients who do not achieve target LDL- C levels should be checked for high plasma Lp(a) concentration. There are no drugs that specifically lower Lp(a) levels. However, protein convertase subtilisin/kexin type 9 inhibitors (PCSK9) can reduce Lp(a) by 25 to 30%. PCSK9 is a proprotein convertase involved in the degradation of LDL receptors in the liver. PCSK9 inhibitors are human monoclonal antibodies that inhibit the binding of PCSK9 to the LDL receptors. Two large randomized placebo-controlled trials involving high cardiovascular risk patients demonstrated that the PCSK9 inhibitors evolocumab (FOURIER trial, n= 27,564) and alirocumab (ODYSSEY trial, n= 18,924) reduce LDL-C levels significantly more than statins and significantly decrease cardiovascular morbidity and mortality independent of baseline LDL-C levels. Post-hoc analysis of these trials demonstrated that the efficacy and safety of alirocumab and evolocumab were comparable among subjects with and those without estimated GFR

Table 2. Summary of 4D, AURORA, SHARP studies

	Die Deutsche Diabetes Dialyse Studie(4D)	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA)	Study of Heart and Renal Protection (SHARP)
Study Design	Germany, 178 centers median follow up: 4 years, aged: 18-80 years old, 1255 diabetic hemodialysis patients, randomized controlled trial: atorvastatin 20 mg versus placebo	280 centers in 25 countries, median follow-up: 3.8 years, aged: 50-80 years old, 2776 patients on hemodialysis, randomized controlled trial: rosuvastatin 10 mg versus placebo	Median follow-up 4.9 years, aged ≥40 years old, 9270 patients (3023 on dialysis and 6247 not) no history of coronary intervention or myocardial infarction
Primary End Points	Composite of death from cardiac causes, nonfatal myocardial infarction and stroke	Death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke	Major vascular events, such as non-fatal myocardial infarction, non-fatal stroke, arterial revascularization and vascular death, doubling of baseline serum creatinine, the development of end-stage renal disease
Secondary End Points	Death from all causes and all cardiac and cerebrovascular events	Death from all causes and individual cardiac and vascular events	Fatal vascular events, non- vascular mortality, Hospitalization for heart failure, coronary revascularization procedures
Results	Primary end point: No significant effect Secondary end point: The risk of all cardiac events combined was reduced by 18 % increased incidence of stroke, although the numbers were small	Primary end point: No significant effect Secondary end point: No significant effect	Reduces the risk of major atherosclerotic events in a wide range of patients with chronic kidney disease. No significant impact on all-cause mortality

<60 mL/min/1.73 m²(7). The role of PCSK9 inhibitors in the treatment of dyslipidemia or cardiovascular risk reduction in CKD patients remains to be studied. Novel antisense oligonucleotides against apolipoprotein(a) and lipoprotein apheresis are other options to reduce Lp(a). Nearly 90% of the Lp(a) concentrations can be lowered with antisense oligonucleotides. However, it is not known whether this treatment decreases cardiovascular events or not. Dramatic lowering of cardiovascular events is observed with lipoprotein apheresis.

Dyslipidemia in Dialysis Patients

The lipid profile in HD patients is similar to patients with non-dialysis CKD. LDL-C is not suitable to assess cardiovascular risk in dialysis patients. Regardless of LDL-C levels, an increased risk of CVD is seen in majority of dialysis patients. Therefore, interventions to reduce LDL-C and cardiovascular events in the general population are not mostly beneficial in dialysis patients. Because a subgroup of dialysis patients can benefit from statin therapy, patients should be periodically evaluated for statin therapy. The issue of whether statins are effective in lowering the risk of a cardiovascular event in dialysis patients was addressed in the 4-D, AURORA and SHARP trials. Summary of 4D, AURORA, SHARP Studies is shown in **Table 2**.

The 4D Study (Die Deutsche Diabetes Dialyse Studie) was the first placebo-controlled randomized conrolled trial (8). Compared to 1.3% decline of LDL-C with plasebo, atorvostatin decreased the median LDL-C level by 42% over 4 weeks. Over a median follow-up of 4 years, there was only an 8% non-significant decrease in the primary composite endpoint in the atorvastatin treated group. Despite no effect on overall mortality, the rate of all cardiac events reduced by 18%. The rate of fatal and non-fatal cardiac events and death from any cause was significantly reduced in subgroup of patients with pre-treatment LDL-C>145 mg/dl. Therefore, diabetic HD patients with high LDL-C may be target for statin therapy.

A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), is the other placebo-controlled RCT (9). LDL- C levels reduced significantly with rosuvastatin versus no change with placebo after 3 months. At a median follow-up period of 3.8 years, the incidence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke was similar in two groups. All-cause mortality was also not significantly different between the groups. Therapy with statins did not provide benefit in patients with diabetes or elevated C-reactive protein levels.

The Study of Heart and Renal Protection (SHARP) trial evaluated the efficacy of simvastatin plus ezetimibe compared with placebo in lowering cardiovascular morbidity in patients with CKD of whom 3023 were dialysis patients (10). They have no history of coronary intervention or myocardial infarction. A trend toward

benefit for lowering the incidence of the atherosclerotic cardiovascular events in the antihyperlipidemic therapy arm was observed during a median follow-up of 4.9 years. However, the SHARP trial was not powered to detect an effect on subgroups and there was no evidence that the effect differed according to the presence of end stage renal disease (ESRD) at baseline. Thus, the SHARP trial may be interpreted as showing efficacy for LDL cholesterol lowering and cardiovascular benefit in dialysis patients.

In addition, one meta-analysis showed a modest benefit in atherosclerotic-related events, while another found no benefit of statin treatment in all-cause mortality, cardiovascular mortality, and major cardiovascular events (11-12).

Unfortunately, as discussed above, lipid-lowering treatments are not as effective in reducing cardiovascular risk in dialysis patients as they are in the general population or in non-dialysis CKD patients. This should be because, compared to the general population, the pathophysiology and spectrum of CVD begin to differ from early to advanced stages of CKD, and the difference is more pronounced in dialysis patients. The process of atherosclerosis differs in dialysis patients compared to general population. Uremia-related risk factors including hyperphosphatemia, anemia, hyperhomocysteinemia, oxidative stress, malnutrition, inflammation and many of the traditional Framingham risk factors for atherosclerosis are frequently seen in dialysis patients and they contribute to atherosclerotic process. Accumulation of asymmetric dimethylarginine, Lp(a) and IDL also play important roles in the initiation and progression of coronary atherosclerosis. In addition to atherosclerosis; arterial stiffness, vascular calcification, left ventricular hypertrophy, left ventricular diastolic dysfunction, congestive cardiomyopathy and sudden cardiac death from arrhythmias are commonly seen in dialysis patients. Most deaths in dialysis patients are not associated with coronary artery disease and therefore cannot be replaced by statins or other lipid-lowering therapies.

The KDIGO guideline work group agree that statin therapy is not routinely initiated in dialysis patients including PD patients. Statin therapy should also be continued in patients who are already receiving statins or a statin/ezetimibe combination at the time of initiation of dialysis. It is stated that statins may be beneficial in a subgroup of HD patients with significant atherosclerotic disease and hyperlipidemia. Liu et al. reported that hypercholesterolemia was an independent risk factor for all-cause and CVD mortality in a subset of ESRD patients without serological evidence of inflammation or malnutrition. Patients with very high LDL cholesterol (>190 mg/dl) may also benefit from treatment. It is mostly unnecessary to include ezetimibe in the regimen as long as the LDL-C and the non-HDL C targets can be achieved with statin and/or other measures alone.

Since the PD patient group was small in number in the SHARP study, cardiovascular benefit could not be achieved in this group of patients despite lowering the cholesterol level. Data from a retrospective cohort study using propensity score matching showed reduced mortality in the statin arm in PD patients.

Hypertriglyceridemia is not usually treated with pharmacologic therapy in dialysis patients, partly because the relationship between serum triglyceride levels and clinical outcome is uncertain, the propensity of dialysis patients to develop side effects from drugs and the prevalence of polypharmacy in this population. Therapeutic lifestyle changes should be advised with avoiding malnutrition.

Effects of PCSK9 inhibitors on cardiovascular outcomes in patients with ESRD is unknown.

Dyslipidemia in Kidney Transplant Patients

Dyslipidemia is a frequent complication after kidney transplantation, even when allograft function is normal or near normal. Increases in TC and LDL-C levels are the most common abnormalities and elevated triglyceride levels are also frequently noted. A recent study showed that kidney transplantation by itself has beneficial effects on the lipid profile when compared to ESRD period. Improvement in HDL-C and triglyceride levels following kidney transplantation has been associated with successful engraftment and better graft function. Pre-transplant high-intensity statin therapy was also met with a survival benefit after transplantation. Given that allograft failure is the principal risk to a patient's health, dyslipidemia may be tolerated, even if it is related to immunosuppressive therapy and cannot be optimally treated. Because dyslipidemia have adverse effects on kidney graft function, use of antihyperlipidemic therapy is also reasonable.

Glucocorticoid withdrawal may lower TC and triglyceride levels in kidney transplanted patients (13). However, these benefits must be considered in the context of higher acute rejection risk, as well as a possible increased risk of allograft loss and recurrent glomerulonephritis. In addition, glucocorticoid elimination may not yield a net benefit in the overall lipid profile, since it may depress protective HDL-C levels to the same extent as TC as a result, the HDL-C to TC ratio remains unchanged. Nonetheless, reducing glucocorticoids may have other cardioprotective benefits, including improved blood pressure and glucose tolerance. There is also dose dependent effects of cyclosporin with elevations in TC and LDL-C concentrations and with reductions in HDL-C levels (14). Use of tacrolimus instead of

cyclosporine may have beneficial effects on serum lipid levels. The mammalian target of rapamycin (mTOR) inhibitors are frequently associated with dyslipidemia, particularly associated to hypertriglyceridemia. Studies comparing patients receiving sirolimus to patients receiving calcineurin inhibitors (CNI) showed that those on sirolimus had higher levels of triglycerides, LDL-C and TC in the first few months after transplantation, but these differences decreased at later timepoints. Sirolimus-treated patients were also more likely to be on lipid-lowering drugs in these studies (15). The antiproliferative and cardioprotective effects of mTOR inhibitors and the reduction in CNI-related risk factors may offset the adverse effects of mTOR inhibitor–associated hyperlipidemia. If dyslipidemia occurs cyclosporine can be converted to tacrolimus, sirolimus can be discontinued and low dose prednisone can be continued considering the risk of rejection.

There are no definitive data of statin-related improvement in atherosclerotic CVD outcomes in patients with kidney transplant patients, although there is suggestive evidence of benefits. The ALERT trial found beneficial effect of early initiation of statin therapy on posttransplant cardiovascular outcomes. Compared to patients who used statin therapy within the first 4 years after transplantation had risk reduction of 64% compared to 19% reduction in patients who had started therapy after ten years (16). Kidney transplant recipients with established atherosclerotic CVD, should receive maximum doses of statins, similar to nontransplant patients with established atherosclerotic CVD. Statin therapy is appropriate for patients> 40 years old without established atherosclerotic CVD if their estimated 10-year atherosclerotic CVD risk is >10%. Statin therapy is also suggested to patients>30 years old without established atherosclerotic CVD. For adult kidney transplant recipients between 8 to 29 years old without established atherosclerotic CVD, the decision to treat with statin therapy should be individualized, considering patient preferences and a relatively small expected atherosclerotic CVD reduction over 10 years versus the risks of polypharmacy and drug toxicity. Data evaluating the use of ezetimibe or statin and ezetimibe combination in the transplant population are limited. Ezetimibe and statins block intestinal absorption of dietary cholesterol and inhibits hepatic cholesterol synthesis; respectively. Ezetimibe can be used by transplant recipients who are refractory to the highest tolerated statin dose or as a second-line agent in those who are intolerant to statin.

PCSK9 inhibitors are not recommended given the lack of data on efficacy and safety in kidney transplanted patients.

Dyslipidemia in Nephrotic Syndrome

Patients with the NS frequently have marked elevations in serum TC and LDL-C. This is due to a combination of increased biosynthesis and impaired catabolism of lipoproteins. They also have marked elevations in the plasma triglycerides and Lp(a) concentrations. Total HDL-C levels are usually normal or reduced in the NS and there is often a pronounced decline in the cardioprotective HDL2 fraction. The severity of the hyperlipidemia is inversely related to the fall in plasma oncotic pressure. Some nephrotic patients diagnosed with renal amyloidosis and lupus nephritis may have no lipid abnormalities.

Patients with the NS have been shown to have elevated plasma PCSK9 levels that correlate with the degree of proteinuria, levels of TC, non-HDL-C and LDL-C. Hyperlipidemia results from altered expression of PCSK9. In one series of nephrotic patients who went into remission, a decrease in plasma cholesterol was accompanied by a reduction in plasma PCSK9. The impairment of reverse cholesterol transport is also observed in patients with NS and may contribute to proteinuria and disease progression in a number of glomerular disorders. Fatty acid uptake and accumulation of triglycerides in the kidney cortex have been shown to cause glomerular damage in experimental models of NS (17). CKD can also develop due to podocyte damage and mesangial cell proliferation. In addition, serum free fatty acid elevation may predict the development of acute kidney injury in NS.

It seems likely that patients with persistent NS and hyperlipidemia are at increased risk for atherosclerotic CVD, particularly if other cardiovascular risk factors are present. Spontaneous or drug-induced resolution of the NS reverses the hyperlipidemia (18). Because the nephrotic state is transient in minimal change disease with corticosteroid treatment and do not subject the patient to prolonged hyperlipidemia, there is no increased risk of coronary death as in other patients diagnosed with NS. Thus, intensive lipid-lowering therapy to prevent CVD may be warranted in patients with chronic NS who do not achieve disease remission.

A lipid panel at the time of diagnosis and repeat lipid panel every three months as long as the patient remains nephrotic can be obtained. It is important to note that most commonly used CVD risk calculators have not been validated in patients <40 years old and do not include NS as a potential factor in the estimation of the risk. So, nephrotic patients who do not have preexisting CVD risk factors could not be accurately assessed with CVD risk calculators.

The reduction in protein excretion with angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) may be associated with a 10 to 20%decline in the plasma levels of TC and LDL-C and Lp(a). The magnitude of these changes appears

to be related to the degree of fall in protein excretion, but they can occur with little or no elevation in the plasma albumin concentration. Evidence for the effect of low protein diets on the lipid profile in patients with nephrotic level proteinuria is also lacking. Decreased protein intake was also reported with decreasing serum TC and LDL levels.

In patients with the NS, the management of hyperlipidemia focuses primarily on treatment of the NS (Immunosuppressive therapy as well as supportive measures, such as treatment with an ACE inhibitor or ARB). Lifestyle modifications and lipid-lowering therapy may be indicated for selected patients, such as those with persistent NS and hyperlipidemia despite treatment of the underlying kidney disorder. However, evidence to guide the optimal therapy of hyperlipidemia in this patient population is limited. Although these lifestyle modifications have not been well studied in patients with the NS, these have been shown to have beneficial effects on preventing cardiovascular morbidity and mortality in the general population.

All patients with the NS should receive lipid-lowering therapies for primary or secondary prevention of CVD as appropriate based upon their assessed CVD risk. In patients with NS who do not have an indication for primary or secondary CVD preventive therapies, the optimal approach to pharmacologic lipid-lowering therapy is uncertain. Thus, the pharmacologic lipid-lowering therapy should be considered by weighing the potential benefits and risks of treatment. If the NS resolves within three to six months, pharmacologic lipid-lowering therapy is not initiated unless indicated for primary or secondary CVD prevention based upon the patient's CVD risk and GFR. If the NS does not resolve within three to six months, a lipid profile is repeated and pharmacologic lipid-lowering therapy with a statin is initiated if the LDL-C is >100 mg/dl or if indicated for primary or secondary CVD prevention based upon the patient's estimated CVD risk and GFR. In rare patients with an LDL-C ≤100 mg/dl who have isolated severe hypertriglyceridemia (>400 mg/dl), treatment with omega-3 fatty acids or a fibrate is required.

Statins are the preferred first-line agents for treatment of hyperlipidemia in patients with the NS. The optimal LDL-C target in patients with the NS is not known. Titration of the statin dose to target an LDL-C goal of <100 mg/dl in view of the increased CVD risk in patients with the NS is recommended. Antiproliferative and anti-inflammatory properties of statins and their ability to reduce systolic or diastolic blood pressure, C-reactive protein, endothelin-1 levels are features of statins that protect patients against CVD besides their lipid-lowering effects.

If the target LDL-C value is not achieved with maximally tolerated statin therapy, or if the drug is not tolerated, additional second-line agents may be required. Second-line therapies including ezetimibe, PCSK9 inhibitors, fibrates, bile acid sequestrants, nicotinic acid, omega-3 fatty acids and LDL apheresis can be used for patients who may not be able to tolerate a statin or may not be able to achieve the target LDL-C despite treatment with a maximally tolerated statin. These second-line therapies can also be used in patients who have concomitant hypertriglyceridemia that is not responsive to statin therapy. The efficacy of these second-line therapies is variable and use of these agents is often limited by side effects.

Adverse Effects with Statins and Fibrates

Reduced renal excretion of medications, polypharmacy and high prevalence of comorbidity makes CKD patients vulnerable to medication-related adverse events. So, reduced doses of statins are generally recommended in patients with advanced CKD. Statins are contraindicated in lactation, pregnancy and active liver disease or states when the transaminase levels are three times or more than the upper limit of normal. KDIGO guidelines recommend measuring transaminase levels before starting statin therapy. However, further measurements of transaminase levels are not necessary if the patient has no related symptoms. Statins are also associated with adverse muscle events and it is shown that routine monitoring of creatine kinase levels in the absence of symptoms of myopathy is not essential. In SHARP trial, despite no evidence of increased risk of rhabdomyolysis or liver dysfunction, some patients receiving simvastatin plus ezetimibe were significantly more likely to discontinue the drug.

Atorvastatin, lovastatin and simvastatin are all metabolized by CYP-3A4 and drug-drug interactions of statins with macrolides, azole antifungals, non-dihydropyridine calcium channel blockers, cyclosporine, tacrolimus, and sirolimus should be taken into account when statins are started. Coadministration of a statin with cyclosporine (cyclosporin inhibits CYP450 3A4) can increase statin levels and the risk of myotoxicity. In addition, cyclosporin inhibits OATP1B1/SLCO1B1-mediated hepatic uptake of statins, resulting in significant medication interaction. Therefore, in cyclosporin-treated patients, all statins should be introduced at low doses and up titrated. A nonsignificant but high risk of hemorrhagic and fatal stroke was also reported in the previously reported randomized controlled trials.

The risk of fibrate related myositis and rhabdomyolysis is higher in patients with CKD. Fenofibrate should not be used in patients with estimated GFR less than 30 mL/min/1.73 m². Fibrates when used with statins are also

more likely to produce muscle toxicity (17). Elevations in serum creatinine concentrations have been noted in patients taking fibrates, while such changes are often reversible and their relation to true alterations of GFR is unclear, such elevations may complicate the assessment of other conditions such as acute rejection. Acute kidney injury due to biopsy-verified proximal tubule dysfunction was also reported in three kidney transplant recipients treated with fenofibrate.

CONCLUSION

The management of dyslipidemia in patients with CKD involves a multifaceted approach. Management of LDL-C to reduce cardiovascular risk is not different from the general population for non-dialysis dependent CKD patients. However, the relation between LDL-C and CVD disappears as the GFR decreases. The effectiveness of lipid-lowering treatments, particularly statins, in dialysis patients remains a topic of debate. While studies like 4D, AURORA, and SHARP offer insights, the diverse pathophysiology of CVD in dialysis patients challenges the applicability of general population guidelines. In kidney transplant recipients, dyslipidemia is a common concern post-transplantation. The dynamic nature of lipid profiles, influenced by immunosuppressive therapies and allograft function, underscores the need for personalized approaches. Nephrotic syndrome presents unique challenges, the transient nature of some cases necessitates cautious lipid-lowering therapy decisions. Management focuses on treating the underlying kidney disorder.

Throughout these diverse scenarios, the challenge lies in balancing the benefits and risks of pharmacological interventions, considering the specific needs of each patient. Adverse effects, drug interactions and individual response to treatment underscore the importance of close monitoring and a tailored approach to dyslipidemia management in the complex landscape of kidney-related disorders. The emergence of new therapeutic options, such as PCSK9 inhibitors, raises intriguing possibilities but requires further investigation in CKD populations.

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Review

Diagnosis and Treatment of Monogenic Hypertension in Children

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Abstract

Hypertension (HT) is a common public health problem that develops due to primary and secondary causes. The prevalence of HT in children and adolescents is 3.6%. In childhood HT, complex and polygenic factors such as genetic, environmental, adaptive, neural, and hormonal mechanisms play a role. Among these factors, genetic factors are estimated to contribute to the development of HT by 30-60%; however, known genetic factors explain only 3% of the cases.

Monogenic inherited HT is associated with a mutation in a single gene, with or without the influence of mineralocorticoids, leading to increased sodium reabsorption and intravascular volume expansion. Typically, HT in these patients has an early onset, a family history of HT, is associated with electrolyte imbalance, and shows a clinical course refractory to treatment.

In treating monogenic inherited HT, understanding functional genetic mutations enables the utilization of highly effective pharmacogenetic pathways. This knowledge provides the opportunity to tailor treatments specifically to target the primary pathophysiological mechanism of the condition. Sodium-dependent, low renin levels, and monogenic inherited HT treatment are based on a low-sodium diet and block the pathological sodium reabsorption mechanism.

Diagnosis can be made through physical examination, blood pressure measurement, and measurement of renin, aldosterone, cortisol, and potassium levels. Monogenic inherited HTs are rare. Early diagnosis ensures blood pressure control early on, reducing the morbidity and mortality associated with HT. Genetic tests are necessary to confirm the diagnosis, make a differential diagnosis, and choose appropriate treatment.

Clinical manifestations of monogenic inherited HT in some patients extend beyond HT. Other systemic symptoms may accompany HT or manifest at certain stages of life. This article discusses monogenic inherited HT that manifests in the early stages of life, emphasizing the clinical aspects of HT.

Keywords: Hypertension, monogenic inherited, pharmacogenetics, Liddle syndrome, Geller syndrome

INTRODUCTION

Monogenic inherited hypertension (HT) syndromes refers to specific genetic mutations that interfere with normal renal and adrenal regulation of blood pressure and follows Mendelian inheritance models (1-3). In these patients, HT develops due to increased sodium reabsorption, excessive aldosterone synthesis, and enzyme deficiencies that regulate the synthesis and deactivation of adrenal steroid hormones. Clinical manifestations of HT occur as a result of intravascular volume expansion, with or without the influence of mineralocorticoids (3-5). Monogenic inherited HTs are rare. Early diagnosis is crucial for reducing the morbidity and mortality associated with HT since they can be treated (3,6-9).

The known monogenic inheritance causes of HT are characterized by abnormal sodium transport, volume expansion, and low renin in the kidneys. Several rare syndromes with monogenic inheritance that manifest with very high HT in early life have been identified (3). These include Liddle syndrome, glucocorticoid-remediable aldosteronism (GRA), apparent mineralocorticoid excess (AME), Gordon syndrome (GS), MR over-sensitivity

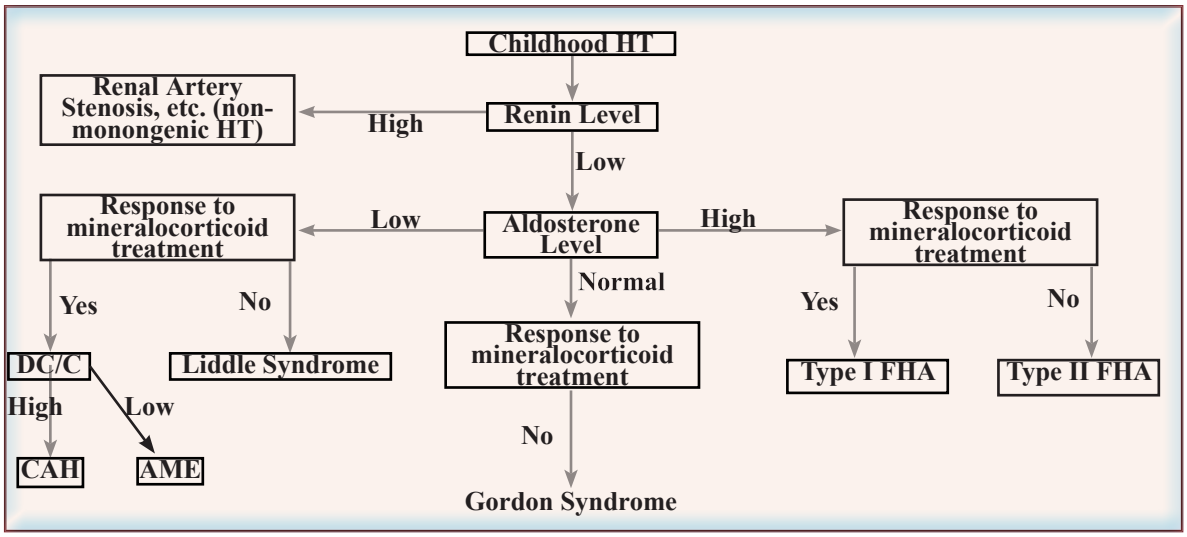

Figure 1. Diagnostic approach to childhood hypertension. DCC; deoxycortisol cortisol ratio, CAH; congenital adrenal hyperplasia, FHA; familial hyperaldosteronism (Adopted from Reference 1)

syndrome, and congenital adrenal hyperplasia (CAH). Low-renin hypertension (LRH) should be suspected in children with a family history of early-onset, severe, and resistant HT, or a history of cerebrovascular events and death due to heart failure. Hypokalemia, except in Gordon syndrome, is a common feature in most LRH cases.

EPIDEMIOLOGY

Hypertension is a significant public health problem in adults, leading to serious morbidity and mortality. The prevalence of HT is reported to be 32.6%. However, in children and adolescents, the prevalence of HT is 3.6% (1). The Human Genome Project, initiated in 2001, paved the way for large-scale genomic studies in populations. In studies conducted so far, more than 30 genes and over 1477 single-nucleotide polymorphisms (SNPs) associated with blood pressure have been identified. It is estimated that genetic factors contribute to 30-60% of the development of HT, but known genetic factors explain only 3% of hypertensive cases (2). Only a small fraction of these is related to monogenic inherited HT.

CAUSES OF MONOGENIC INHERITED HYPERTENSION

Monogenic inherited hypertension manifests in two forms, depending on its dependence on mineralocorticoids or independence (**Table 1** and **Figure 1**).

CHARACTERISTICS AND DIAGNOSIS

Monogenic inherited hypertension typically begins in early life and is characterized by a family history of hypertension. It is associated with electrolyte metabolism disorders and shows a clinical course refractory to treatment. Early diagnosis is crucial, especially in hypertensive children with a family history of early-onset hypertension. Suspicions of hypertension-related disease with a mutation in a single gene should arise, especially if plasma renin levels are suppressed, and distal tubular sodium absorption is increased. The clinical phenotypes of monogenic inherited hypertension can range from mild symptoms, including normotension or normokalemia, to life-threatening conditions. Routine mutation analysis is not always recommended in hypertensive patients' non-hypertensive siblings if renin, aldosterone, and serum electrolytes are normal.

While single-gene PCR-based tests have been successfully used in genetic identification, using whole-

Table 1. Key features of monogenic inherited hypertension types

Mineralocorticoid Dependent	Mineralocorticoid Independent
Mineralocorticoids are one of the key hormones that regulate sodium and potassium balance in the body. Single-gene inherited HT syndromes are based on the excess effect of mineralocorticoids and the resulting increase in intravascular volume. • Excessive effect of mineralocorticoids (apparent mineralocorticoid excess), • Treatable with glucocorticoids-aldosteronism (glucocorticoid-remediable aldosteronism), • Due to 11β-hydroxylase or 17α-hydroxylase deficiency (congenital adrenal hyperplasia). • Familial Hyperaldosteronism Type II-III-IV (FH-II-III-IV)	It refers to single gene inherited hypertension syndromes that develop in association with increased sodium reabsorption, independent of mineralocorticoids. • Liddle Syndrome • Gordon Syndrome

HT; hypertension, FH; familial hyperaldosteronism

genome DNA sequencing and exome sequencing is now possible for the diagnosis of rare monogenic inherited syndromes. Although the causes of monogenic inherited hypertension are rare, identifying them in childhood is beneficial for successful treatment and avoiding associated morbidity and mortality.

For diagnosis, routine physical examination, blood pressure measurement, and laboratory measurements of plasma renin activity, aldosterone, cortisol, and potassium should be performed. Genetic tests are useful for confirming the diagnosis and making a differential diagnosis. The differential diagnosis should consider secondary causes of hypertension, such as renal parenchymal diseases, renal artery stenosis, adrenal gland neoplasms, hyperthyroidism, and excessive dietary salt intake. While a definitive diagnosis in patients with a mutation in a single gene can be made through genetic analysis, in some cases, a possible diagnosis can be reached based on clinical features, laboratory results, and the response to specific pharmacological drugs (such as those with a low sodium diet and drugs blocking sodium reabsorption mechanisms).

The term "low-renin hypertension (LRH)," describing an HT phenotype with low renin activity and no prominent hyperaldosteronism, is used by the European Society of Hypertension (ESH) (6). Metabolic alkalosis is prevalent in the majority of cases, while metabolic acidosis is associated with GS (10).

Plasma Renin Activity and Aldosterone Levels: Testing and Interpretation

Plasma renin activity (PRA) and plasma aldosterone levels are measured from a blood sample taken from an upper-arm vein after the patient has been lying on their back for more than 30 minutes in the early morning, on an empty stomach. Test results can be influenced by the patient's position, specific foods, beverages, and medications, so care must be taken when collecting the blood sample. The normal daily diurnal range for plasma renin activity is 0.17–5.38 ng/mL/h, and for aldosterone, it is 2.5–39.2 ng/dL.

In cases where there are signs of increased aldosterone production, such as high blood pressure, muscle weakness, and low potassium levels, blood samples for renin activity measurement are taken from a vein in the arm. Some centers may also perform selective blood sampling from the kidneys or adrenal veins. In these patients, abnormal plasma aldosterone concentrations can be detected along with serum potassium and metabolic acid-base disorders. Normally, hypertension and low potassium levels suppress aldosterone synthesis and release.

In primary aldosteronism (PA), the most distinguishing test is the aldosterone-renin ratio (ARR). An ARR >30 (ng/dL and ng/mL/h) is indicative of the evaluation of patients with primary PA, such as familial hyperaldosteronism type I (FH-I/GRA) and familial hyperaldosteronism type II (FH-II) (10). In the case of an ARR >10 in a child with FH-I/GRA, genetic analysis is recommended (11). Genetic analysis is also suggested in cases of early-onset hypertension diagnosis and hypokalemia in a family member.

MONOGENIC INHERITED HYPERTENSION SYNDROMES

1. Apparent Mineralocorticoid Excess

AME is a rare autosomal recessive disorder characterized by high blood pressure due to a deficiency of the 11-beta-hydroxysteroid dehydrogenase type 2 (HSD11B2) enzyme in the kidneys. It has been identified in fewer than 100 patients in the last 25 years. The gene encoding HSD11B2 (HSD11B2) is located on chromosome 16q22. Mutations in the HSD11B2 gene result in insufficient synthesis of the HSD11B2 enzyme. As a consequence of the deficiency, cortisol levels rise because cortisol cannot be adequately converted to cortisone due to the lack of HSD11B2. This inappropriate activation of the mineralocorticoid receptor (MR) leads to symptoms of hyperaldosteronism (12).

Activation of MRs in renal tubule cells specifically increases sodium reabsorption through epithelial sodium channels (ENaC) and leads to an extracellular volume expansion. Cortisol has high affinity for both glucocorticoid and MRs. Consequently, low plasma renin and aldosterone levels result in hypokalemia and metabolic alkalosis (13).

These patients are often of low birth weight. Early-onset hypertension is accompanied by metabolic alkalosis and severe hypokalemia. Diagnosis can be made by the ratio of tetrahydrocortisol and allotetrahydrocortisol, metabolites of cortisol in urine, to the concentration of tetrahydrocortisone. The normal ratio is 1:1, but in AME patients, this ratio can be as high as 6.7–33. The conversion rate of cortisol to cortisone measured after cortisol infusion in AME patients is only about 0–6%, compared to what is observed in healthy individuals (14). The optimal diagnostic test can be performed with 11-tritiated cortisol injection, but this technique is not widely used due to the rarity of tritiated cortisol. Patients with AME can be treated with spironolactone and triamterene, which reduce sodium reabsorption and potassium secretion.

2. Familial Hyperaldosteronism

Familial hyperaldosteronism is characterized by early-onset hypertension accompanied by high aldosterone, low plasma renin activity, and hypokalemia. The early onset suggests an inherited cause of primary hyperaldosteronism. Four different types of familial

Table 2. A brief distinction for FH subtypes

	Genetic Variation	Pathophysiology	Presentation
Type I	CYP11B1/CYP11B2 gene	ACTH induces transcription of CYP11B2	GK-suppressive HA
Type II	CLCN2 mutation	Increased Cl^- efflux leads CYP11B2 transcription	Early-onset PA
Type III	KCNJ5 mutation	Increased NA^+ efflux leads CYP11B2 transcription	Sever early-onset PA (T158A, I157S, E145Q, G151R) Mild PA: (G151E, Y152C)
Type IV	CACNA1H mutation	Increased Ca^{2+} efflux leads CYP11B2 transcription	Early onset

CLCN2; chloride channel protein 2, KCNJ5; potassium voltage-gated channel subfamily J member 5, ACTH; adrenocorticotropic hormone, PA; primary aldosteronism, HA, GK; glucocorticoid, HA; hyper aldosteronism

hyperaldosteronism have been identified to date (Table 2).

a.Type I FH (Glucocorticoid-Remediable Aldosteronism): GRA is an autosomal dominant inherited hypertensive disorder characterized by elevated plasma aldosterone levels, low plasma renin activity, and abnormal steroid synthesis. The aldosterone synthase (CYP11B2) hyperactivity in these patients can be suppressed by glucocorticoids. It is also known as familial hyperaldosteronism type I.

Two adjacent genes, CYP11B1 (11β-hydroxylase) and CYP11B2 (aldosterone synthase), are located on chromosome 8q. The chimeric gene resulting from unequal crossovers between these two genes codes for a hybrid protein that increases aldosterone production independently of renin, due to its ability to stimulate aldosterone production (15). The chimeric gene is activated not only by low blood volume, angiotensin II, and high serum potassium levels but also by adrenocorticotropic hormone (ACTH) in these patients. Under ACTH stimulation, aldosterone is synthesized from the zona fasciculata along with cortisol. This results in a significant increase in aldosterone concentration, leading to increased potassium excretion and enhanced water reabsorption with sodium chloride (16).

GRA patients exhibit severe symptoms of hypertension along with mild hypokalemia and metabolic alkalosis. Despite low plasma renin levels, aldosterone concentrations may be normal (9). The confirmation of the diagnosis involves conducting a dexamethasone suppression test and determining the aldosterone-to-renin ratio (ARR) and hybrid steroids (18-oxocortisol and 18-hydroxycortisol) levels in urine, which helps distinguish elevated aldosterone due to ACTH influence (17). Confirmatory diagnosis often involves sequencing analysis of the chimeric CYP11B1/CYP11B2 gene.

Due to the risk of cerebral aneurysm and associated bleeding during puberty, these patients should undergo MRI angiography for monitoring (18). Treatment involves using low-dose glucocorticoids (prednisolone 2.5-5 mg/day) to suppress the stimulatory effect of ACTH on aldosterone synthesis and MR antagonist drugs such as spironolactone or eplerenone to reduce aldosterone effects. ENaC antagonists like amiloride and triamterene can also be used (19, 20). Since renin synthesis is suppressed in GRA patients, antihypertensive drugs such as ACE inhibitors and β-blockers have no role in treatment.

b.Type II FH: Pathogenic variants that functionally increase the voltage-gated chloride channel ClC-2, encoded by the chloride channel protein 2 (CLCN2) gene expressed in the zona glomerulosa layer of the adrenal gland, regulate the depolarization of the cell membrane through the activation of voltage calcium channels. This, in turn, regulates the expression of CYP11β-2, an enzyme for aldosterone biosynthesis, leading to conditions such as aldosterone-producing adenoma or idiopathic bilateral adrenal hyperplasia.

Clinical symptoms associated with FH-II-related hypertension typically develop in adulthood (21). Mutation analysis is the standard method for the definitive diagnosis of FH-II. Unlike FH-I, FH-II does not respond to glucocorticoids; therefore, in FH-II, unilateral adrenalectomy along with the use of MR antagonists is recommended for symptom improvement.

c.Type III FH-III: In FH-III, pathogenic mutations leading to functional increases in the KCNJ5 (potassium voltage-gated channel subfamily J member 5) gene result in the loss of potassium selectivity in the potassium channel of the zona glomerulosa cell. This leads to an increased influx of sodium into the cell, lowering the cell's depolarization threshold (22). Consequently, aldosterone synthesis and secretion increase in adrenal glomerulosa cells. Patients with FH-III present with severe hypertension, hypokalemia, and bilateral hyperplasia (23). In most cases, bilateral adrenalectomy is often required.

d.Type IV FH-IV: In FH-IV, pathogenic mutations leading to functional increases in the CACNA1H gene, encoding the T-type voltage-gated calcium channel Cav3.2, result in excessive calcium entry into adrenal zona glomerulosa cells, leading to hyperaldosteronism (24,25). Additionally, somatic mutations in CACNA1H, including KCNJ5, ATP1A1, and ATP2B3, have been identified in over 50% of patients with aldosterone-producing adenomas (26,27). The identification of new genetic forms in primary aldosteronism may necessitate reclassification.

3.Liddle Syndrome (Pseudo-Hyperaldosteronism)

Liddle syndrome is an autosomal dominant disorder characterized by severe hypertension, low plasma renin activity, and low plasma aldosterone levels. Mutations that lead to ENaC hyperactivity play a role in the pathogenesis of the disease.

Functional ENaC is a heterotrimer composed of α (or δ), β, and γ subunits. Each subunit has two transmembrane domains, extracellular loops or rings, and large extracellular loops. ENaC in the kidneys is primarily expressed in the principal cells of the aldosterone-sensitive distal nephron. These cells are found in the distal convoluted tubule, connecting tubule, and collecting duct, where hormonally controlled, rate-limiting sodium reabsorption occurs. Increases in ENaC activity lead to inappropriate sodium retention, while decreases in activity result in natriuresis and diuresis. ENaC activity is regulated by various factors, including aldosterone. In principal cells, aldosterone activates MR to "upregulate" the positive regulators of the channel. Aldosterone also causes a trophic increase in ENaC transcription through the MR pathway.

In Liddle syndrome, mutations in the SCNN1A, SCNN1B, and SCNN1G genes, encoding the α, β, and γ subunits of ENaC, respectively, result in changes that confer hyperfunction to ENaC. Mutations in the β and γ subunits cause the carboxy terminus (early stop codon) of the ENaC molecule it encodes to be shortened due to heterozygous mutations in the SCNN1B and/or SCNN1G genes in LS. Since the mutant ENaC protein lacks the Nedd 4-2 binding region, it cannot be tagged for metabolism. In these patients, ENaC sodium sensitivity and sodium reabsorption are increased independently of the effects of mineralocorticoids (28-31).

In LS, early-onset salt-sensitive hypertension, hypokalemia, metabolic alkalosis, low PRA, and low aldosterone levels are detected. Urinary potassium concentration is high, and sodium levels are low in these patients. Treatment for hypertension involves a salt-free or low-sodium diet and the use of potassium-sparing diuretics, such as amiloride or triamterene, with direct inhibition of ENaC. MR inhibitors like spironolactone have no place in the treatment.

4. Gordon Syndrome (Pseudo-Hypoaldosteronism/ Hypoaldosteronism Type 2)

Gordon syndrome is a rare inherited form of monogenic hypertension associated with hyperkalemia and metabolic acidosis. After its recognition in the 1960s, a phenotype-genotype correlation was observed in families with Gordon syndrome, and subsequently, four genes, WNK1, WNK4, KLHL3, and CUL3, were shown to play a role in the disease pathogenesis. The encoded proteins Kelch-like 3 and Cullin 3 interact to form a ring-like complex with WNK-kinase 4. This interaction, under normal conditions, inhibits the renal outer medullary potassium channel (ROMK) by affecting the sodium-chloride cotransporter (NCC) and ENaC, promoting normokalemia and normotension. WNK-kinase 1 has an inhibitory effect on WNK-kinase 4. Mutations in WNK1, WNK4, KLHL3, and CUL3, all result in the accumulation of WNK-kinase 4, leading to hypertension, hyperkalemia, and metabolic acidosis (35-38). Only a small fraction of patients with GS have been associated with mutations in WNK1 and WNK4. Hypertension associated with mutations in the CUL3 gene emerges early and is much more severe; it progresses with profound acidosis and severe hyperkalemia (38).

The clinical phenotype of patients with GS is the same for mutations in any of the four proteins (WNK1, WNK4, CUL3, and KLHL3), and similar electrolyte imbalances are observed. Affected individuals initially present with hyperkalemia, normal serum sodium levels, hyperchloremic metabolic acidosis, and hypercalciuria. Plasma renin activity is suppressed, and aldosterone levels are incongruently low with hyperkalemia. Chronic mineralocorticoid-resistant hyperkalemia and hypertension are observed. The sodium-chloride cotransporter is located on the apical surface of the distal tubule; it facilitates the reabsorption of 5-10% of filtered NaCl and is inhibited by thiazide. Treatment with thiazide diuretics dramatically improves electrolyte abnormalities and blood pressure by inhibiting NCC (39,40).

5. Congenital Adrenal Hyperplasia

Congenital Adrenal Hyperplasia (CAH), an autosomal recessive disorder caused by mutations in the CYP11B1 and CYP17A1 genes associated with cortisol biosynthesis. CYP11B1 and CYP17A1 code for 11β-hydroxylase and 17α-hydroxylase, respectively. Deficiency in either 11β-hydroxylase or 17α-hydroxylase leads to the excessive production of 21-hydroxylated steroid intermediates with mineralocorticoid effects, resulting in hypertension (5). The overproduction of these intermediates is due to increased ACTH production resulting from the loss of the negative feedback effect of cortisol (41). Elevated levels of 11-deoxycorticosterone

(DOC) lead to excessive MR activation and low renin activity. In girls with 17α-hydroxylase deficiency, impaired steroidogenesis occurs in both the adrenals and gonads, leading to the absence of secondary sexual characteristics and amenorrhea. Depending on the severity of mutations, patients with 11β-hydroxylase deficiency may present with genital ambiguity, hirsutism, premature bone maturation, and early puberty (42).

Virilization, a phenotypic manifestation of CYP11B1 deficiency, may also develop due to excessive androgen production, depending on the severity of the mutations and the presence of the CYP11B/β1 hybrid gene resulting from recombination between the CYP11B2 and CYP11B1 genes.

Diagnosis is typically based on clinical symptoms, and confirmation is achieved through mutation studies for 11β-hydroxylase and 17α-hydroxylase. Affected individuals show early-onset hypertension, hypernatremia, hypokalemia, and low renin activity. Treatment for hypertension involves the use of the MR antagonist spironolactone and dexamethasone.

In the most common cause of KAH, 21-hydroxylase deficiency, unlike deficiencies in 11β-hydroxylase and 17α-hydroxylase, there is sodium loss, and hypertension does not develop.

6. Familial Glucocorticoid Resistance

Inactivating mutations in the NR3C1 gene, located in the chromosomal region 5q31-q32, can lead to familial glucocorticoid resistance, and they can be inherited in both autosomal recessive and dominant patterns. Mutant glucocorticoid receptors (GRs) fail to respond to cortisol (43,44). Consequently, there is an increase in cortisol and ACTH levels. Due to elevated ACTH, there is an overproduction of mineralocorticoids and androgens. Cortisol has a high affinity for both glucocorticoid and MRs. In these patients, in addition to an increase in mineralocorticoids, there is also MR activation in renal tubules mediated by hypercortisolism. Clinical findings include hypertension, hypokalemia, low renin and aldosterone levels, hirsutism, and precocious puberty in females (45). Affected individuals do not develop a Cushingoid appearance due to GRs insensitivity. These patients are diagnosed with high cortisol levels through genetic analysis.

Nightly low-dose dexamethasone treatment suppresses ACTH secretion and corrects excessive glocorticoids, hypercortisolism, and hyperandrogenism. MR antagonists such as spironolactone and eplerenone are effective in controlling hypertension in individuals with familial glucocorticoid resistance.

7. Geller Syndrome

Hypertension resulting from a heterozygous mutation in the MR, due to changes in ligand selectivity and activation of the nuclear receptor, is known as Geller Syndrome (46,47). Normally, both the GRs and MR have high affinity for cortisol due to their structural similarities (48). However, aldosterone exhibits a clear MR specificity. In healthy individuals, cortisol activation of MR is prevented by the conversion of cortisol to cortisone.

In Geller syndrome, the mutant MR shows increased sensitivity to other steroid hormones like progesterone. In females with a heterozygous MR mutation, hypertension develops during pregnancy due to elevated progesterone levels and increased MR sensitivity. In males with a heterozygous MR mutation, cortisol binds to MR with sensitivity comparable to aldosterone, resulting in hypertension (49).

These patients typically present with hypertension at a young age, decreased plasma renin activity (PRA), and low serum aldosterone levels. When progesterone levels rise significantly during pregnancy, this mutation can lead to severe hypertension. Patients with Geller syndrome must adhere to a low-salt diet, and their pregnancy should be closely monitored. Spironolactone has alternative binding sites on MR, and binding to these sites (MRL810 alternative binding parameter) can cause spironolactone to exert a severe agonistic effect, leading to electrolyte imbalance and hypertension (paradoxical activation) (8).

8. Brachydactyly Autosomal Dominant Hypertension (ODHB)

ODHB is a condition characterized by autosomal dominant inheritance due to a mutation in the PDE3A gene. Individuals with ODHB typically exhibit short stature, hypertension that progresses with age independently of salt intake, and altered baroreflex regulation (50,51). Additionally, affected individuals show thickening and shortening of metacarpals and phalanges, characterized by typical E brachydactyly (52,53). If hypertension is left untreated, it often leads to cerebral hemorrhage, resulting in death usually before the age of 50.

The PDE3A gene is located on chromosome 12 and encodes phosphodiesterase 3A (PDE3A), a member of the cyclic nucleotide phosphodiesterase (cGI-PDE) family inhibited by c-GMP. Functional analyses have shown that mutations in PDE3A increase protein kinase A-mediated phosphorylation of PDE3A. The mutation-related increase in PDE3A activity leads to enhanced cAMP hydrolysis and reduced cAMP levels. The increased cAMP hydrolysis causes a decrease in phosphoprotein levels stimulated by phosphorylated vasodilators. Hypertension results from vasoconstriction and increased peripheral vascular resistance associated with these changes.

Clinical manifestations develop due to the mutation causing a functional increase in PDE3A in the gene. These mutations contribute to hypertension by increasing peripheral vascular resistance, accompanied by characteristic skeletal changes. Affected individuals are not sensitive to salt, and they exhibit normal renin, aldosterone, and catecholaminergic responses to decreased and increased vascular volume.

Hypertension emerges in childhood and progresses over time. Diagnosis typically occurs in childhood, and early treatment can reduce the likelihood of stroke (55). Studies have demonstrated significant reductions in hypertension with the use of antihypertensive drugs, beta-blockers, alpha-blockers, calcium channel blockers, and ACE inhibitors, either in combination or as monotherapy (56). Research is ongoing to explore measures aimed at increasing cGMP to address cAMP deficiency.

9. Familial Pheochromocytoma

In individuals with familial pheochromocytoma, specific mutations are identified, leading to severe paroxysmal hypertension attacks with elevated levels of epinephrine and norepinephrine. It can be associated with various syndromes. Von Hippel-Lindau disease is linked to bilateral pheochromocytomas, retinal and cerebellar angiomas, kidney, and pancreatic cysts, and renal cell carcinoma. The mutation causing this disease has been identified on 3p25.3, and it is also a tumor suppressor gene defect (57). RET, a proto-oncogene, is associated with non-syndromic pheochromocytoma as well as multiple endocrine neoplasia syndrome type 2 (MEN 2). MEN 2 is an autosomal dominantly inherited disorder due to a mutation on chromosome 10q11.21. MEN 2 has two subtypes: MEN 2A, associated with pheochromocytoma, medullary thyroid carcinoma, and hyperparathyroidism; and MEN 2B, associated with pheochromocytoma, medullary thyroid carcinoma, and mucosal neuromas. Pheochromocytoma is also linked to neurofibromatosis type I caused by mutations in the NF1 gene located on chromosome 17q11.2. Studies have shown that solitary pheochromocytomas may contain mutations in the mentioned genes. A study on solitary tumors reported that 86% of them included copy number alterations in genes associated with familial pheochromocytoma, with NF1 alterations being the most common in 26% of the tumors (59).

Initially, it was believed that 10% of pheochromocytomas were familial, and 90% were sporadic. New technology in genetic testing has revealed that 50% of pheochromocytomas are sporadic, and 15-25% are associated with germ line mutations (60).

According to the Endocrine Society clinical practice guidelines, the treatment for functional pheochromocytomas involves initiating antihypertensive therapy followed by tumor resection. Treatment should begin with alpha-adrenergic antagonists (e.g., phenoxybenzamine or doxazosin) before surgery. Other antihypertensives, especially dihydropyridines and beta-adrenergic antagonists, may be used additionally. Blood pressure and catecholamine metabolism should be carefully monitored throughout the perioperative process. Due to the association of pheochromocytoma with various neoplastic syndromes mentioned above, genetic testing may be recommended as a prognostic and preventive indicator (61).

CONCLUSION

In conclusion, monogenic inherited hypertension in children presents a complex interplay of genetic, environmental, and hormonal factors. While the prevalence of hypertension in children is relatively low, understanding and diagnosing monogenic forms are crucial for effective management. Genetic testing plays a pivotal role in confirming diagnoses and guiding tailored treatments, targeting the specific genetic mutations underlying these conditions.

Early identification of monogenic hypertension allows for the implementation of targeted therapeutic strategies, including low-sodium diets and drugs that address the pathological sodium reabsorption mechanisms. Additionally, recognizing associated syndromes and manifestations beyond hypertension is essential for comprehensive patient care.

Despite the rarity of these monogenic inherited forms, their impact on morbidity and mortality emphasizes the importance of early intervention. Ongoing research and advancements in genetic testing contribute to our understanding of these conditions, paving the way for improved diagnostic accuracy and therapeutic options. In the realm of pediatric hypertension, a multidisciplinary approach that integrates clinical, genetic, and pharmacogenetic insights is essential for optimizing patient outcomes and reducing the long-term consequences of monogenic hypertension.

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Letter to Editor

Succesfully Completed Twin Pregnancy of a Peritoneal Dialysis Patient

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Dear Editors,

Maintenance dialysis patients with end-stage renal disease rarely conceive, with annual incidences of 0.3–2.7% and successful multiple pregnancies rarer (1). Here, we want to present a rare case of a patient with end-stage renal disease (ESRD) having a successful twin pregnancy.

The 31-year-old female patient, who has been undergoing continuous ambulatory peritoneal dialysis (CAPD) for the past 1.5 years due to end-stage renal failure associated with focal segmental glomerulosclerosis, presented with an unplanned twin pregnancy of 7 weeks. This pregnancy is the patient's second, and her previous pregnancy from 3 years ago ended in stillbirth following preeclampsia.

The patient's blood pressure was regulated with 30 mg of nifedipine, and the daily urine volume was 1000 cc. In the laboratory tests, blood urea nitrogen (BUN) is 36 mg/dL, creatinine is 6.71 mg/dL, and hemoglobin is 10.3 g/dL, with no pathology detected in other tests.

She wished to go on with CAPD. Dialysis treatment was planned with 4 changes of 2000 cc dialysis solutions, including 3 sets of 1.36% and 1 set of 2.27% glucose. During follow-up, the patient did not require additional treatment beyond iron replacement and antihypertensive medication. As her pregnancy progressed, her exchanges caused mild pain. We successfully reduced the dialysis volume gradually from 2000 cc to 1200 cc and increased the frequency of changes gradually up to 8 times a day, thereby alleviating the patient's symptoms. During this process, her weekly Kt/V values ranged between 1.6 and 1.8. After 22 weeks, BUN and creatinine values increased. She experienced drainage issues and daily UF rate decline from 1000 cc to 500 cc. She refused to switch to hemodialysis (HD) despite our efforts. In this case, we continued the dialysis treatment with automated peritoneal dialysis (APD). We planned a nightly APD with solutions containing 2.27% glucose, involving 10 exchanges of 1000 cc each. Adequate dialysis was hardly maintained.

She needed an immediate cervical cerclage after a severe vaginal discharge and bleeding at 24 weeks. Ultimately, she was persuaded for HD. Until week 32, she was on a hemodialysis program, including 3 hours of hemodialysis and 1000-1500 cc ultrafiltration daily, for 6 days a week. During this process the patient's BUN and creatinine values regressed uncomplicatedly to the recommended levels for pregnant hemodialysis patients and the daily diuresis volume ranged between 400-500 cc (2). At that time she developed preeclampsia. As she had severe preeclampsia in her previous unsuccessful pregnancy, we offered emergent C/S.

Ultimately, after reaching 32 weeks and 6 days of gestation, she delivered two robust twins. As a precaution, both infants were monitored in the NICU for one day. Without complications, the mother and twins were discharged. After two weeks of HD, the patient returned to CAPD. In five years of follow-up, she received a live transplant and maintained 0.7 mg/dL creatinine with both children growing normally.

Maintenance of residual renal function (RRF) and continuous daily ultrafiltration are advantages of PD over HD. Pregnancy outcomes improve with these factors. Nevertheless, due to the reduced occurrence of pregnancy rates in women undergoing PD and the limited availability of data, the majority of authors and guidelines suggest transitioning to HD before conception or the first trimester (3).

Daily and extended hemodialysis schedules strain patients and healthcare institutions. Women with significant residual renal function (RRF) or who cannot quickly transition to intensive HD may benefit from preserving PD during part of the pregnancy or incorporating HD.

The optimal PD prescription during pregnancy depends on factors like RRF and tolerated dwell volume. In patients with decreased dwell volume, transitioning from CAPD to automated peritoneal dialysis (APD) with an increased number of exchanges can provide more optimal Kt/V values as such is our case. Published data provides diverse techniques. Several PD patients have successfully switched to HD in the last trimester. Occasionally, cases completing a whole pregnancy on PD have been described (4).

In conclusion, considering RRF, laboratory data and patient preference we believe a hybrid, individualized approach is the optimal strategy for pregnant PD patients. Our case serves as an example of successful hybrid dialysis treatment for pregnant PD patients, providing guidance in the management of this group of patients.

DECLARATIONS

Conflict of Interest Statement: The authors declares no conflicts of interest related to this letter.

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Letter to Editor

A Rare Case of Multiple and Ectopic Parathyroid Adenoma

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Dear Editors,

Primary hyperparathyroidism (P-HPT) is an endocrine disorder caused by the autonomous overproduction and secretion of parathyroid hormone (PTH) by one or more abnormal parathyroid glands. Patients are mostly between the ages of 40-70, with a higher incidence in females compared to males. Most patients with P-HPT have hypercalcemia and elevated PTH levels (5,6). In primary HPT, the main issue is the growth of one or more abnormal parathyroid glands and the inappropriate secretion of PTH from these glands relative to serum calcium levels. Solitary parathyroid adenoma and diffuse parathyroid hyperplasia, more rarely multiple adenomas, and parathyroid carcinoma, are significant pathologies resulting in primary hyperparathyroidism. Pathologically functioning parathyroid cells in parathyroid adenoma show lower sensitivity to high calcium levels than normal. Therefore, since the serum calcium set point is at a higher threshold, the circulating calcium level is maintained at much higher levels. In parathyroid hyperplasia, there is a general increase in the number of parathyroid cells that produce and secrete excess PTH but maintain normal sensitivity to calcium. Both conditions cause hypercalcemia, but there is a difference in PTH levels (7). In P-HPT cases; solitary parathyroid adenoma is the most common cause, accounting for 85-90%. Various literatures report multiple parathyroid adenomas at different rates, ranging from 2-11%. Other causes of primary hyperparathyroidism include parathyroid hyperplasia, which accounts for 15% of all cases, while carcinomas, which are rarer, are responsible for only 1% of cases (1,2). In the treatment of P-HPT; the traditional surgical approach is the removal of all hyperfunctioning parathyroid glands. This is possible with a good parathyroidectomy operation that includes bilateral neck exploration. Bilateral neck exploration is based on the evaluation of all parathyroid glands and then the removal of one or more glands that appear pathological (5). However, due to the long duration of the operation and the high rates of mortality and morbidity, preoperative diagnostic studies are becoming increasingly important. The diagnosis of P-HPT is made with clinical and laboratory examinations. The purpose of parathyroid imaging is to locate abnormal parathyroid glands in the preoperative period, to shorten the operation time, and to reduce morbidity rates (8). In this context, parathyroid scintigraphy with technetium-99m-hexakis-2-methoxy-isobutyl isonitrile (Tc-99m MIBI) is a current method widely used to determine the presence, number, and localization of parathyroid adenomas. In our case, we aimed to provide an overview of the imaging and treatment processes through a case of four parathyroid adenomas, one of which is ectopically located, a rare condition detected by Tc-99m MIBI parathyroid scintigraphy.

Case

A 21-year-old female patient presented with widespread bone pain. Investigations revealed high serum calcium and parathyroid hormone levels, and bone densitometry showed low bone mineral density for her age. A diagnosis of primary hyperparathyroidism was made. Preoperative ultrasound examination detected suspicious nodules compatible with parathyroid adenomas: two in the right lobe and one in the left lobe of the thyroid gland. Additionally, preoperative Tc-99m MIBI parathyroid scintigraphy reported suspicious activity consistent with adenomas in both lobes, persisting in early (20 min) and late images (120 min) (**Image 1**). During surgery, three parathyroid glands were excised with the support of an intraoperative gamma probe, and adenomas were confirmed in frozen sections. However, due to the lack of significant improvement in intraoperative parathyroid hormone levels, a complementary thyroidectomy was performed. Subsequently, a parathyroid adenoma located within the thyroid tissue was identified in the thyroidectomy specimen. Postoperative serum calcium and PTH levels showed significant improvement.

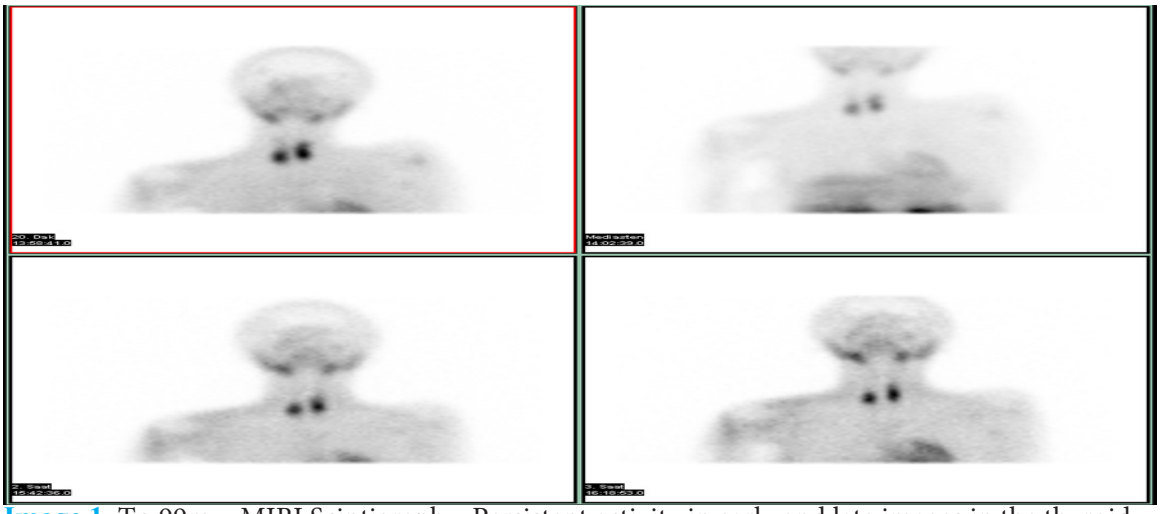

Image 1. Tc-99m – MIBI Scintigraphy: Persistent activity in early and late images in the thyroid gland region.

Multiple parathyroid adenomas have been reported in 2-11% of cases with P-HPT (2). In 6-16% of cases, one or more hyperparathyroidism adenomas are found in an ectopic position. Multiple and ectopically located parathyroid adenomas, though rare, are encountered in routine endocrine practice and often present with persistent and recurrent hyperparathyroidism (3,4). 80-95% of patients with P-HPT are treatable with a simple parathyroidectomy after the first surgery (9). In cases where a cure is not achieved, persistent hypercalcemia immediately after surgery or recurrent hypercalcemia after a long period of normal serum calcium levels is observed (10). In our case, despite the significant contribution of preoperative Tc-99m MIBI scintigraphy in identifying multiple parathyroid adenomas, the persistent intraoperative hyperparathyroidism necessitated the search for a new ectopic adenoma focus. With the help of intraoperative gamma probe signals from thyroid tissue, an ectopically located intrathyroidal adenoma was detected. We confirmed that essential components of curative treatment in parathyroid adenoma cases are preoperative scintigraphic imaging (USG and Tc-99m MIBI scintigraphy) and intraoperative PTH measurements. In this context, it should not be forgotten that in primary hyperparathyroidism cases, Tc-99m-MIBI scintigraphy and intraoperative gamma probe use are crucial for localizing hyperfunctioning parathyroid pathologies preoperatively and especially for identifying hyperfunctioning adenomas with typical or atypical locations in cases of resistant hyperparathyroidism in parathyroid surgery (2).

In conclusion, Tc-99m MIBI parathyroid scintigraphy, widely used for determining the number and location of lesions before adenoma surgery in patients newly diagnosed with primary hyperparathyroidism, is a current method that reduces the duration, complications, and scope of the procedure.

DECLARATIONS

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