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Original Article

The Frequency of ANA-positivity and Inflammatory Markers in COVID-19

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ABSTRACT

Background: Immune system activation plays an important role in pathogenesis and mortality in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The inflammatory response during the disease is caused by the innate and adaptive immune systems. Anti-nuclear antibody (ANA) positivity rate increases in SARS-CoV-2-positive patients due to adaptive immune system activation. This study aims to investigate the association between ANA-positivity rate and pulmonary symptoms, and inflammatory markers (C-reactive protein [CRP] and fibrinogen).

Material and Methods: One hundred five consecutive patients with the diagnosis of COVID-19 were included in this cross-sectional study. Participants were divided into groups according to the ANA and pulmonary symptom status. Clinical (gender, age) and biochemical (hemogram, liver function tests, kidney function tests, D-Dimer, CRP, and fibrinogen) were compared between the groups and the impact of ANA positivity on pulmonary symptoms development was assessed.

Results: Of the 105 patients, 60 of them had no pulmonary symptoms. The remaining 45 patients had at least one pulmonary symptom. ANA immunofluorescence assay (IFA) positivity rate was 19% (20/105 patients) in the study group. 60% of the ANA-positive patients were positive at 1/160, 30% at 1/320 and 10% at 1/1000 titer. ANA-IFA positivity rate was found higher among patients with pulmonary symptoms; however, the difference was not statistically significant (26.7% vs. 8/60 13.3%, respectively; p=.085). The CRP and fibrinogen levels were (6.9 vs. 3.4, p=.132, and 346.5 vs. 326, p=.183) among ANA positive and negative patients. Twelve (63.2%) patients with ANA-positivity had pulmonary symptoms, and 33 (39.3%) patients with ANA-negativity had pulmonary symptoms (p=0.058).

Conclusions: Although there is no difference between patients with or without pulmonary symptoms, ANA, which may reflect the pathogenetic role of adaptive immune dysregulation, can often be detected in patients with Coronavirus disease 2019.

Keywords: Antibodies, antinuclear, immunology, autoimmunity, COVID-19

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first detected in December 2019. The severity of this disease, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), varies significantly in clinical ways. The disease has a broad spectrum of symptoms from asymptomatic to respiratory failure characterized by SARS. While it primarily affects the respiratory system, COVID-19 may also affect many systems that have cellular access receptors for the virus such as the cardiovascular, gastrointestinal, renal, and central nervous systems (1). COVID-19-related mortality is usually associated with coagulopathy, cytokine storm syndrome, and multi-organ failure (2). Many antiviral drugs have been tried against the disease, but no drug has proven efficacy yet (3). However, corticosteroid

therapy can significantly prevent immune-mediated lung injury and decrease mortality (4). Immune system activation plays an important role in pathogenesis and mortality in SARS-CoV-2 infection. The inflammatory response during the disease is caused by the innate and adaptive immune systems. Cytokines, which are an important part of the inflammatory process, are produced by various immune cells including innate immune system components such as macrophages, dendritic cells, natural killer cells, and components of the adaptive immune system such as T and B lymphocytes (5). Antinuclear antibody (ANA) positivity increases in SARSCoV-2-positive patients due to adaptive immune system activation (6). We aimed to investigate the effect of ANA positivity on pulmonary symptoms in addition to routine laboratory tests.

MATERIALS AND METHODS

Study Design and Participants

Between the 1st of August and the 30th of September 2020, the patients diagnosed with SARS-CoV-2 were evaluated in terms of eligibility for inclusion in the study. A positive result in polymerase chain reaction (PCR) analysis of a sample collected on a nasopharyngeal swab was defined as a COVID-19 case. 105 patients aged >18 years who were diagnosed with SARSCoV-2 by PCR and hospitalized were included in this cross-sectional study. Of the 105 patients, 60 had no pulmonary symptoms, and the remaining 45 patients had pulmonary symptoms (dyspnea, tachypnea, cough, pulmonary infiltrate) and 1 patient was transferred to the intensive care unit (ICU) who was ANA-negative. The symptom frequencies of the study group were presented in Table 1. The oxygen saturation of all patients without pulmonary symptoms was above 92% in room air and they were hospitalized for close follow-up. 86 patients were scanned with thorax computed tomography (CT) for the presence of pulmonary findings. While thorax CT was normal in 35 (33.3%) patients, at least one pulmonary finding was detected in 51 (48.6%) patients.

Patients diagnosed with rheumatologic, immunological disease, malignancy, end-stage heart, and renal failure, advanced liver failure, and used immunosuppressive drugs for other reasons were excluded from the study. The patients were evaluated for the presence of an ANA-related disease by anamnesis and physical examination. The previous ANA status of the participants is unknown.

Laboratory examinations

Serum urea, creatinine, complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), D-dimer, ferritin, CRP, fibrinogen, and lactic dehydrogenase (LDH) levels were recorded in all patients. Antibodies to nuclear antigens were detected using the HELMED ANA screen multiplex autoimmune assay. Specimens demonstrating reactivity for any nuclear antigen were additionally tested using indirect immunofluorescence on HEp-2 cells at a dilution of 1:160. The blood samples were collected on the first hospitalization day for ANA detection and the collected samples were studied later simultaneously.

Ethical approval

This study was carried out in accordance with the Declaration of Helsinki. All participants have been informed. Consent of all participants was obtained. The study was approved by the Ankara Dışkapı Training and Research Hospital ethics committee and the Ministry of Health (Date: 06.07.2020, Approval number: 91/20).

STATISTICAL ANALYSIS

Numerical data are presented as mean (standard deviation) or median (min-max) according to their suitability for normal distribution. The presentation of categorical data was presented as n (%), and the chi-square test was used for comparisons. Mann Whitney U test or Student t test was used to compare numerical data. A univariate regression analysis was performed for ANA status and pulmonary symptoms presence. If the P-value < .05, it was considered statistically significant.

RESULTS

Of 105 patients with COVID-19, the ANA-IFA positivity rate was 44 (41.9%) in the whole study group

Table 1. Demographics, clinical, and laboratory findings, and comorbidities of the patients

Demographics		**Comorbidities, n (%)**	
Age, years, mean (SD)	40.3 (14.9)	Hypertension	16 (15.2)
Sex, Male, n (%)	44 (41.9)	Chronic obstructive pulmonary disease / Asthma	9 (8.6)
Laboratory, n (%) ANA-positivity		Thyroid disease	7 (6.7)
1/160	12 (11.4)	Coronary artery disease	4 (3.8)
1/320	6 (5.7)	Diabetes mellitus	3 (2.9)
1/1000	2 (1.9)	Chronic renal failure	2 (1.9)
Symptoms, n (%)			
Asymptomatic cases	19 (18.1)	Anosmia	9 (8.6)
Fever	30 (28.6)	Diarrhea	7 (6.7)
Sore Throat	21 (20)	Cough	39 (37.1)
Headache	20 (19)	Dyspnea	23 (21.9)
Arthralgia/myalgia	28 (26.7)	Cough and/or Dyspnea	45 (42.9)

(20/105 patients). Twelve (60%) of the ANA-positive patients were positive at 1/160, six (30%) at 1/320, and two (10%) at 1/1000 titer. Demographics, clinical and laboratory findings, and comorbidities of the patients are shown in Table 1. While 28 (46.7%) of the patients without pulmonary symptoms were male, 16 (35.6%) of the patients with pulmonary symptoms were male. There was no significant difference in gender between the two groups. The median age was 39.5 (18-87) in patients without pulmonary symptoms and it was 40 (18-83) in those with pulmonary symptoms. There was no significant difference in age between the two groups. Hemoglobin (Hgb), white blood cell (WBC), neutrophil, lymphocyte, thrombocyte, urea, creatinine, AST, ALT, LDH, D-dimer, and ferritin levels were similar in both groups. The CRP and fibrinogen values were significantly higher in patients with pulmonary symptoms. The data were presented in Table 2.

ANA-IFA positivity was found to be a higher frequency among patients with pulmonary symptoms, but the difference was not significant (12/45 (26.7%) vs. 8/60 (13.3%) respectively). While 12 (63.2%) ANA-positive patients had pulmonary symptoms, only 33 (39.3%) ANA-negative patients had pulmonary symptoms (p=0.058). In the univariate analysis, ANA status was not significantly associated with the presence of pulmonary symptoms (95% CI 2.64 (0.94-7.42) p=.064).

White blood cells and leukocytes were higher in patients with ANA-positivity. There was no difference in the other laboratory results in the subgroups of positive and negative ANA (Table 3).

DISCUSSION

Pneumonia is the most common serious complication of COVID-19 infection. It is characterized by fever, cough, shortness of breath, and bilateral infiltration on lung imaging. In those patients, adult respiratory distress syndrome (ARDS) usually develops after the second week. This does not only result from an uncontrolled viral replication but also an explosive immune response in the host (7). In this study, we investigated the association between ANA (an indicator of an adaptive immune response) and pulmonary symptoms in the early period of COVID-19.

There is a high prevalence of antibodies against nuclear antigens in COVID-19 patients. A recent study demonstrated that ANA was positive in 50% of patients, and 92% of 11 intensive care unit (ICU) patients (6). The patients with severe pulmonary symptoms who were followed up in the intensive care unit had a high frequency of ANA positivity (6). Similarly, 25% (16/64) of the COVID-19 patients in the study conducted by Lerma et al. had a positive result in the ANA test and 75% (12/16) of them were followed up in the ICU (8). Additionally, Lerma et al. emphasized that patients with ANA positivity (14/16, 88%) had weak reactivity and two patients with strong ANA positivity had a history of systemic lupus erythematosus (8). In our study, the frequency of ANA-positivity was lower than in those three studies. In our study, the patients had low ANA positivity since none of them required ICU. The titer was 1/160 in most of the ANA-positive patients [12/20 (60%)], which was in line with the study of Lerma et al. Although ANA is the hallmark of many autoimmune diseases, it can also be found commonly in acute illnesses including viral infection (9,10). Acute infections have been associated with ANA positivity, which does not indicate subsequent autoimmune disease but reflects transient auto reactive B and plasma cell activation (10). ANA positivity rate was 33.3% in a prospective study involving 33 consecutive patients followed by Pascolini et al. (11). During the follow-up nine of 33 patients (27.2%) needed ICU, and four of them died. Although the ANA positivity rate was higher among the patients who died, this difference was not significant (57% vs. 26.9%, respectively; p=0.10).

Table 2. Laboratory parameters in patients with COVID-19 are stratified according to the presence or absence of pulmonary symptoms.

	Patients without pulmonary symptoms	Patients with pulmonary symptoms	P value
WBC	5145 (497-12250)	5260 (950-13960)	.526
Neutrophil	2735 (1000-9850)	3250 (170-8200)	.433
Lymphocyte	1500 (530-5010)	1440 (610-3510)	.629
Thrombocyte (10^3/μL)	214.5 (94-371)	226 (64-512)	.204
Urea (mg/dL)	24.6 (5.1-60)	26 (13-57.8)	.897
Creatinine (mg/dL)	0.75 (0.46-1.91)	0.76 (0.47-1.35)	.995
AST (U/L)	19 (11-125)	19 (12-147)	.636
ALT (U/L)	19 (5-185)	20 (4-141)	.943
LDH (U/L)	179 (118-474)	200 (117-557)	.143
D-dimer	0.26 (0.17-2.21)	0.27 (0.20-2.30)	.645
Ferritin (mg/L)	95.9 (6.67-421)	107 (8.1-200)	.333
CRP (mg/L)	2.74 (1-253.2)	5.02 (0.30-278.5)	.009
Fibrinojen (mg/dL), mean (SD)	320.9 (73.8)	379.6 (100.9)	.001

Unless otherwise stated, values are presented as median (min-max). WBC; white blood count, AST; aspartate aminotransferase, ALT; alanine aminotransferase, LDH; Lactic dehydrogenase, CRP; C-reactive protein

It has been reported that the levels of some blood markers may be associated with the severity and mortality of COVID-19 patients (12,13). Of these clinical parameters, serum CRP is an important marker that changes significantly in severe COVID-19 patients (14). It is a non-specific, acute-phase inflammatory protein whose expression is increased in response to tissue damage, inflammation, and infection (15). Increased CRP levels in COVID-19 patients may be associated with disease severity and disease progression (13). Wang et al. showed that severe cases and 7.7% of non-severe COVID-19 patients who progressed to severe disease after hospitalization had pulmonary symptoms and significantly higher CRP concentrations compared to non-severe cases (median 43.8 vs. 12.1 mg/L) (14). Another study showed that having an elevated CRP level at baseline may be a valuable early marker in predicting the probability of disease progression in COVID-19 patients (16). It emphasized that this could help healthcare professionals to identify these patients at an early stage for early treatment. We also found that CRP levels were significantly higher in the patients with pulmonary symptoms at the beginning of COVID-19 disease. Therefore, COVID-19 patients with high CRP levels at the time of diagnosis should be closely watched in terms of the risk of progression, even if they do not have symptoms yet to meet the criteria for severe disease. Fibrinogen is a glycoprotein and a positive acute phase reactant that is produced in the liver. Fibrinogen also plays a role in fibrin formation as the last step in induced coagulation. Intravascular coagulation and even disseminated intravascular coagulation (DIC) can be present in COVID-19 patients and lead them to death. D-dimer increases and fibrinogen levels decrease when DIC develops (17). In the study of Han et al., the levels of fibrinogen and degradation products were higher in COVID-19 patients compared to healthy controls as well as higher levels of severe COVID-19 patients compared to mild patients (18). Tang et al. showed that fibrinogen and antithrombin activity levels were also significantly lower in nonsurvivors, which suggested that Conventional coagulation parameters during COVID-19 were significantly associated with prognosis (17). In the present study, fibrinogen levels were significantly higher in the patient group with pulmonary symptoms and it was considered an independent risk factor for pulmonary symptoms. Therefore, pulmonary involvement and COVID-19 progression should be considered in patients with increased fibrinogen at the time of diagnosis. Moreover, low fibrinogen levels in follow-up should be a warning for DIC development.

Limitations of the study

The present study has some limitations such as the data consists of only the patients who applied in 2 months period and the patients with mild symptoms were enrolled in the study. The study cohort involves relatively a small sample size of patients and the patients' previous ANA status is unknown. In addition, autoantibodies other than ANA were not examined and their interactions are not available in this study.

CONCLUSION

While ANA-positivity was detected in 19% of our patients, the difference between patients with and without pulmonary symptoms in terms of ANA positivity was not statistically significant. The low number of patients and/or our selection of patients with the mild disease might have caused this outcome. ANA, which may reflect a pathogenetic role of adaptive immune dysregulation, can often be detected in COVID-19 patients. The significance of ANA-positivity in the acute phase of the infection is unclear and prospective studies involving large-scale patient groups are needed.

DECLARATIONS

Declaration of conflicting interests: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Table 3. Comparison of laboratory parameters of anti-nuclear antibody positive or negative patient groups

	ANA positive patients	ANA negative patients	P
WBC	6315 (2630-12250)	5030 (497-13960)	.034
Neutrophil	3965 (830-9850)	2850 (170-8200)	.042
Lymphocyte	1570 (690-5010)	1420 (530-4210)	.308
Thrombocyte (10^3/µL)	229 (64-334)	215 (84-512)	.194
Urea (mg/dL)	24.8 (14-57.8)	26.9 (5.1-60)	.290
Creatinine (mg/dL)	0.76 (0.47-1.35)	0.74 (0.46-1.91)	.977
AST (U/L)	20.8 (12.4-147.3)	19 (11.6-144)	.263
ALT (U/L)	19 (10-185)	19.8 (4-141)	.668
LDH (U/L)	202.5 (144-479)	182 (117-557)	.157
D-dimer	0.27 (0.2-2.3)	0.25 (0.17-1.94)	.201
Ferritin (mg/L)	105.5 (19.6-1087)	101 (6.67-2000)	.524
CRP (mg/L)	6.9 (0.3-253.2)	3.4 (0.1-278.5)	.132
Fibrinojen (mg/dL)	346.5 (242-631)	326 (143-679)	.183

ANA; anti-nuclear antibody; ALT; alanine aminotransferase, AST; aspartate aminotransferase, CRP; C-reactive protein, LDH; lactic dehydrogenase, WBC; white blood count.

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Original Article

Impact of Serum Albumin Levels on Arterio-Venous Fistula Maturation in End-Stage Renal Disease Patients with Diabetes Mellitus

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ABSTRACT

Background: Diabetes mellitus (DM) is a well-known risk factor for the prolongation of arterio-venous fistula (AVF) maturation and hypoalbuminemia. In this study, we studied the impact of the serum albumin levels during AVF creation on AVF maturation duration in diabetic patients.

Material and Methods: This single-center observational study was carried out using the data of 131 hemodialysis patients. Sixty-seven individuals with AVF were included in the study and were divided into two groups; diabetics and non-diabetics. Serum albumin levels during AVF creation were noted. The maturation period was described as the interval between the creation and cannulation time of AVF providing a minimum of 250 ml/min blood flow during the hemodialysis session (week). The demographic and clinical features of the individuals were noted and compared.

Results: Twenty-five individuals were in the diabetic and 42 were in the non-diabetic group. Serum albumin level was lower (3.50±0.44 vs 3.84±0.32) during AVF creation in the diabetic group; $p<0.001$. A negative correlation was observed between preoperative serum albumin level and AVF maturation time; $p=0.003$ and $r=0,132$. Additionally, maturation duration was significantly higher among diabetics (6.6 vs 5.1 weeks). Serum CRP levels were similar between the two groups ($p=0.057$).

Conclusion: Longer AVF maturation time in diabetic patients is closely related to low serum albumin levels. Low serum levels of albumin should be considered when evaluating ESRD patients with DM for AVF creation.

Keywords: Arteriovenous fistula, diabetes mellitus, hypoalbuminemia, hemodialysis

INTRODUCTION

Diabetes mellitus (DM) is the leading cause of the end-stage renal disease (ESRD) in the whole World (1,2). A timely created arteriovenous fistula (AVF) is crucial in chronic kidney disease (CKD) patients when the disease is progressing to ESRD. However, the exact time to create AVF in ESRD patients with DM has not been described.

Hypoalbuminemia is a common clinical finding in the course of diabetic nephropathy (DNP) and correlates closely with mortality and poor renal outcome (3,4). Hypoalbuminemia occurs either due to severe proteinuria (especially, when clinical features of the nephrotic syndrome are apparent) or to chronic inflammation in DM (3). Hypoalbuminemia, proteinuria, and vascular endothelial injury are closely associated with each other, and the majority of cardiovascular events are explained by those factors and their interactions (5). Regardless of the pathogenesis of hypoalbuminemia (inflammation, protein malnutrition, protein loss), hypoalbuminemia is associated with worse outcomes (5-8).

Hypoalbuminemia and diabetes both have adverse impacts on all types of surgical operations (9-12). DM has a negative impact on AVF remodelling and AVF maturation duration (12-14). DM and hypoalbuminemia both might have a worse impact on AVF maturation time. In this study, we investigate the impact of serum albumin levels on AVF maturation duration in diabetic

patients with ESRD.

MATERIALS AND METHODS

Study Design and Participants

This single-center retrospective case-control study was conducted in 2021 in a university-affiliated private hospital. A total of 131 hemodialysis patients were evaluated and 67 of those whose first vascular access route was an AVF were included in the study (64 of 131 patients had started chronic hemodialysis therapy with a temporary or permanent catheter). The patients were divided into two groups; patients with DM and non-DM. The clinical and laboratory of the individuals were noted from the local computer software of the hospital.

Laboratory examinations and clinical measurements

Serum albumin, C-reactive protein (CRP), and hemoglobin levels of the individuals on the operation day of AVF were noted. An AVF that provided a 250 ml/min blood flow rate, was considered a maturated AVF. The duration from the operation day to the maturation day was considered the maturation duration. If an additional AVF creation operation or AVF-related reintervention was necessitated the first operation was considered as AV fistula dysfunction. The second operation was considered a different case. Serum albumin, CRP, and hemoglobin levels on the maturation day/week were also compared between the two groups.

Thirty-two patients were detected to have residual urine from the registries of the hemodialysis center and hospital, however, the 24-h urine analysis revealing proteinuria amount in the AVF maturation periods was not available.

Exclusion criteria

The patients with chronic liver disease, congestive heart failure, malabsorption syndromes, and >1 gr/day proteinuria also were excluded.

Ethical approval

This study was carried out in accordance with the ethical principles for medical research of Declaration of Helsinki. The consent form is not available since the study is in a retrospective design. The study was approved by the ethics committee of scientific research of Medicana International Ankara Hospital (Date: 28.01.2022, Approval number: BSH-2022/01-B).

STATISTICAL ANALYSIS

Statistical analysis was conducted using SPSS (version 13.0). In the first step, all data were tested for normality by using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The normally distributed (parametric) data are presented as the mean±standard deviation and the non-normally distributed (nonparametric) data are presented as the median (minimum-maximum). The independent samples t-test was used to compare continuous parametric variables between the groups. Mann-Whitney U test was utilized to compare non-parametric variables. Pearson's or Fisher's exact test was used to compare the categorical variables. A Paired test was used to compare preoperative and postoperative serum albumin and CRP levels. Univariate and multivariate Cox regression analyses were performed to identify the impact of the laboratory data and clinical features of the individuals on the maturation duration. P-value <0.05 was considered statistically significant.

RESULTS

A total of 67 hemodialysis patients were evaluated. Forty-six of those were male and 21 were female individuals. DM and hypertension were ESRD's most common etiological factors (36.7% and 29.9%, respectively) (**Table 1**). The diabetic and non-diabetic groups were of similar age and gender (p=0.175 and p=0.142, respectively). The mean canulation duration of a maturated AVF (time period from the creation time to first canulation time in which AVF provided a > 250 ml/min blood flow) in the diabetic group was 6.6 weeks while in the nondiabetic group was 5.1 weeks (p=0.036) (**Table 2**). Preoperative serum albumine (PSA) levels were lower in the diabetic group at the

Table 1. The clinical and laboratory features of the participants

Age, year	49.92±17.62
Gender, male/female, n=	46/21
***Preoperative serum albumin, gr/dl**	3.71 gr/dl
****Postoperative serum albumin, gr/dl**	3.74 gr/dl
Hemoglobin, gr/dl	10.4 mg/dl
Serum creatinine, mg/dl	6.34 mg/dl
CRP, mg/dl	2.12 (0,01-22)
CKD, etiology	DM (37.3%), HT (29.9%), PCKD; 4.5%, GN; 7.5%, Unknown; %20.9

CRP, c-reactive protein, CKD; chronic kidney disease, DM; diabetes mellitus, HT; hypertension, PCKD; polycystic kidney disease, GN; glomerulonephritis. *serum albumin at the time of AVF creation, ** serum albumin at the time of AVF canulation

Table 2. The comparison of the diabetic and non-diabetic patients at the time of arteriovenous fistula creation

	Diabetic, N=25	Non-diabetic, N=42	P value
Age, year	54.04±15.72	47.47±18.39	0.142
Gender, male/female, n=	20/5	26/16	0.175
***Preoperative serum albumin, gr/dl**	3.50±0.44	3.84±0.32	**<0.001**
****Postoperative serum albumin, gr/dl**	3.72±0.46	3.76±0.57	0.766
Hemoglobin	10.52±	10.39±1.51	0.740
Serum creatinine, mg/dl	5.98±1.23	6.35±2.12	0.125
CRP, mg/dl	3.80(0.02-22)	1.70(0.01-12)	0.057
AVF maturation duration, week	6.60±2.73	5.09±2.80	**0.036**

CRP; c-reactive protein. *serum albumin at the time of AVF creation, ** serum albumin at the time of AVF cannulation, AVF; arteriovenous fistula

time of AVF creation (3.5±0.44 gr/dl vs 3.84±0.32 gr/dl and p<0.001) and were negatively correlated with AVF maturation duration r=0.132 and p=0.003) (**Figure 1**). C-reactive protein level was higher in the diabetic group however the distinction was not statistically significant (3.80[0.02-22] mg/dl vs 1.70[0.01-12] mg/dl and p=0.077). CRP levels positively correlated with AVF maturation duration (r=0.149 and p=0.011) (**Figure 2**). However, serum albumin and CRP levels did not reveal a correlation with each other (p=0.150). Older age also correlated with the prolongation of AVF maturation duration (r=0.096 and p=0.011) (**Figure 3**). Univariate regression analysis indicated that age, lower serum albumin levels, HD duration, CRP, and DM had an impact on AVF maturation duration (p<0.05) (**Table 3**). Multivariate analysis

Figure 1. Lower preoperative serum albumin level is negatively correlated with the maturation duration of AVF fistula

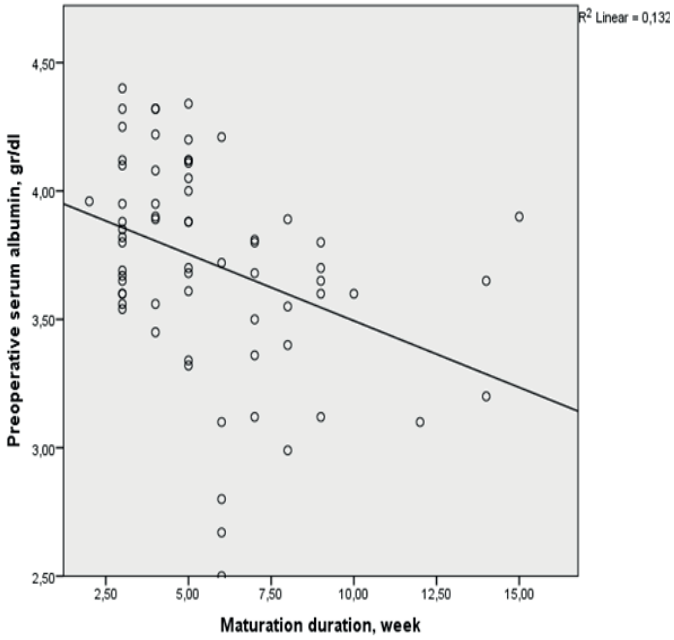


Figure 2. Higher CRP levels correlated with prolongation of AVF maturation duration

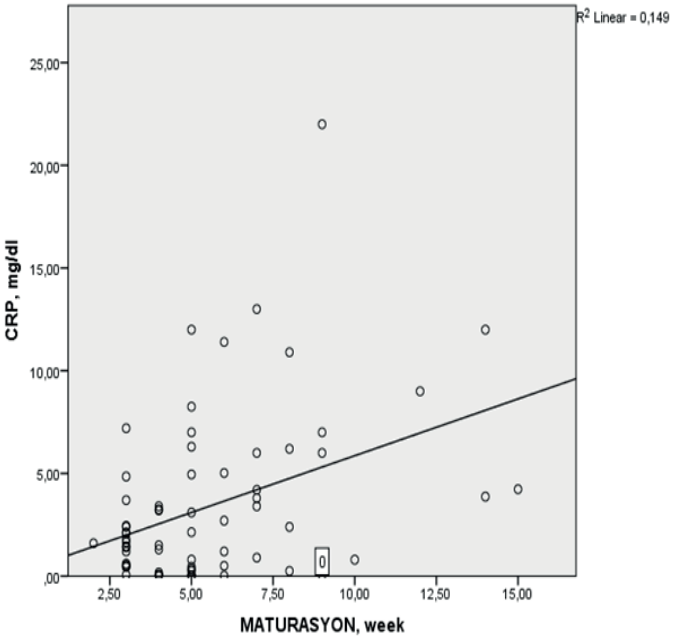
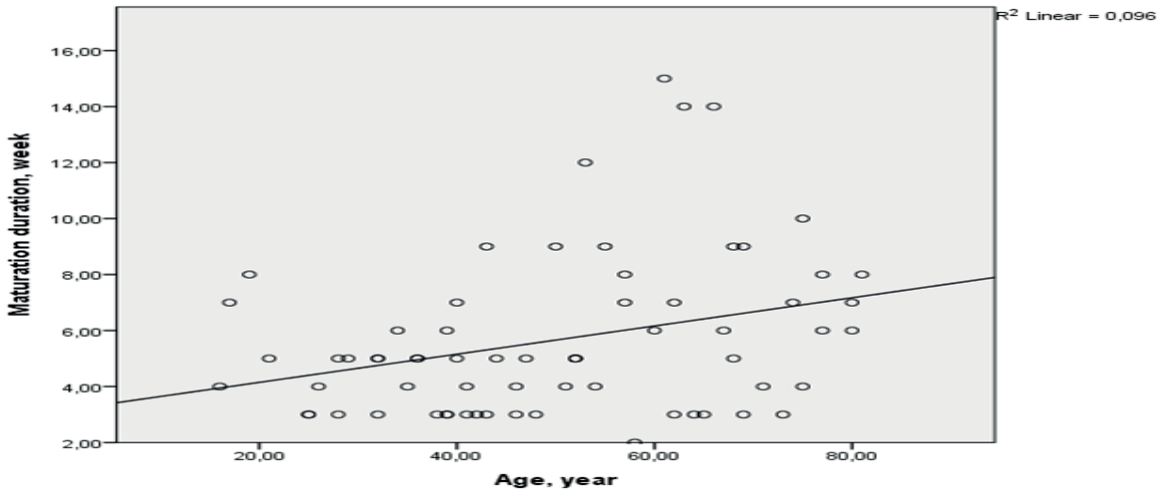


Table 3. The clinical and laboratory features of the participants

	Univariate		Multivariate	
	P value and 95% CI		P value and 95% CI	
Age, years	**0.011**	0.012 – 0.089	**0.048**	0.000 – 0.075
Hgb, g/dl	0.217	-0.722 – 0.167	-	-
CRP, mg/dl	**<0.001**	0.111 – 0.430	**0.004**	0.078 – 0.393
Preoperative serum albumin, g/dl	**0.003**	-4.150 - -0.923	0.122	-3.129 - -0.380
DM	**0.036**	-2.909 - -0.101	0.748	-1.647 – 1.192

Hgb; hemoglobin, CRP; c-reactive protein

Figure 3. Age positively correlates with maturation duration



demonstrated that preoperative CRP and age are the only factors that determine maturation duration ($p<0.05$) (Table 3). Postoperative serum albumin and CRP levels were found to be partially improved during the time of AVF cannulation compared to the preoperative levels in the diabetic group.

DISCUSSION

Arteriovenous fistula creation is the preferred vascular access route in diabetic hemodialysis patients, however, maturation duration is longer compared to nondiabetic ESRD patients. Determining factors that might have an impact on AVF maturation duration will provide benefits in evaluating diabetic patients before AVF creation. This small cohort demonstrates that age and preoperative CRP are the main factors that impact AVF maturation duration.

Strong evidence suggests that DM is more likely to cause AVF dysmaturation or failure. The pathophysiological mechanisms of DM that negatively impacts vascular endothelium are the focus of interest. The increased release of inflammation biomarkers such as interleukin-6, vascular cellular adhesion molecule-1, and monocyte chemoattractant protein-1, and thromboaggregation (increased von Willebrand factor release and platelet aggregation) lead to thrombosis based on vascular intimal injury (15,16). In this study, DM had an impact on AVF maturation duration, however, in multivariate regression analysis, this impact disappeared probably due to the low sample size of the cohort.

Small increases in CRP which is an indirect sign of low-level inflammation predict the likelihood of cardiovascular injury both in diabetic and nondiabetic populations (17). Further, local CRP increase suggests diabetic atherosclerosis plaques in diabetic individuals (17). Zadeh et al. suggested that CRP before AVF surgery is an indicator of fistula function (18). In our study, preoperative CRP level was higher among diabetic patients compared to nondiabetic ESRD patients and positively correlated with the prolongation of AVF maturation duration.

Reduced serum albumin is associated with increased adipose tissue inflammation, adiposity, and dysglycemia in type 2 DM. Hypoalbuminemia may be a consequence of a decreased act of insulin on protein synthesis or chronic inflammation involving infiltration of macrophage into adipose tissue (19). Additionally, at the time of AVF creation, ESRD patients may have malnutrition. Whether the cause of hypoalbuminemia is inflammation or malnutrition, it has a clear association with AVF failure (20,21). In our study, ESRD patients with DM were hypoalbuminemic and hypoalbuminemia negatively correlated with AVF maturation duration. However, surprisingly CRP and hypoalbuminemia did not exhibit a significant relation, and in multivariate regression analysis, CRP was a stronger predictor for AVF maturation duration than presurgical albumin levels. We think in this cohort hypoalbuminemia is further related to malnutrition rather than inflammation. The anabolic activity of the body likely improved due to alleviation in the uremic state, the patients gained appetite, and serum albumin levels significantly increased following initiating hemodialysis. Although serum CRP levels decreased following initiating hemodialysis, a correlation between improvement in CRP and postoperative serum albumin levels was not available.

Low hemoglobin level is associated with worse AVF survival, especially when hemoglobin level < 8 gr/dl (22). In this study, hemoglobin levels were > 10 gr/dl, and probably this level of hemoglobin is beneficial for AVF maturation as reported by Gheith et al (23).

Advanced age is another risk factor for worse AVF survival, or failure (23,24). In our cohort, older age was found to correlate with AVF maturation duration.

Predicting worse outcomes by using useful tools can provide better healthcare for ESRD patients. Since a

prolonged AVF maturation duration can be expected in ESRD patients with a higher level of CRP, older age, and hypoalbuminemia, avoiding to use of a temporary central catheter, struggling with malnutrition as a cause of hypoalbuminemia, and evaluating the older ESRD patients carefully before AVF creation, are essential.

This study has some limitations; including low-sample size, not taking into account the site of AVF, the presence of catheter simultaneously, comorbidities, and medicine use such as angiotensin-converting enzyme inhibitors. However, the content will provide some data to physicians in considering an AVF creation.

CONCLUSION

AVF creation in diabetic ESRD patients is a challenge and requires a complete evaluation that involves inflammation, malnutrition, and anemia correction.

DECLARATIONS

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Original Article

Is Obesity an Obstacle to Being A kidney Donor? Experiences from A High-Volume Center

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ABSTRACT

Background: Donor obesity is considered a relative contraindication to kidney donation by most transplant centers because of concerns about short-term and long-term morbidity and mortality. In this study, the impact of kidney donor body mass index (BMI)on perioperative and postoperative morbidity was investigated.

Material and Methods: We included all individuals (n= 170) who donated their kidneys for living kidney transplants performed at our hospital between November 2017 and October 2018. We divided kidney donors into four groups according to their BMI; normal (< 25 kg/m^2), overweight (25 - 29.9 kg/m^2), class I obesity (30 - 34.99 kg/m^2), and class II obesity (> 35 kg/m^2). We compared preoperative and postoperative blood pressure, estimated glomerular filtration rate (eGFR), and proteinuria values. p< 0.05 was considered statistically significant in all analyzes.

Results: 32.9% of the donors had normal weight, 31.7% were overweight, 28.8% had class I obesity, and 9.4% had class II obesity. The mean postoperative hospital stay was 2.2(2-4) days, and there was no difference between donors with and without obesity (p > 0.05). The only parameter negatively correlated with low eGFR at 12 months postoperatively was donor age (p= 0.024 and r= 0.290). There was no correlation between eGFR and BMI (p=0.125 and r=0.065). No difference was observed in donors' blood pressure measurements after kidney donation. Postoperative proteinuria was positively correlated with BMI (p= 0.02, r= 0.296).

Conclusion: Donor candidates with obesity may be considered donors for patients with end-stage renal disease for whom there are no other suitable living kidney donors after a thorough perioperative evaluation.

Keywords: Living kidney donor, obesity, end-stage renal disease, renal transplant

INTRODUCTION

Kidney transplantation is the ideal renal replacement therapy for patients with end-stage renal disease (ESRD). It offers important advantages such as better quality of life and longer life expectancy compared with dialysis options (1). In particular, the long-term results of transplantation procedures with living donors have been quite successful. However, because there are not enough donors, many ESRD patients in our country and in the world rely on dialysis. Currently, more than twenty thousand ESRD patients in our country are on the deceased donor waiting list because they do not have a living donor (2).

Certain conditions such as active infections, severe cardiopulmonary problems, and malignancies identified in donor candidates during the screening process in which they are considered as donors definitely disqualify them from being donors (3). However, in some "gray areas," such as donor obesity, there can be significant differences in approach between countries and centers. Often, a body mass index (BMI) > 35 kg/m2 or > 40 kg/m2 precludes donor eligibility. Currently, the clinical practice guideline Kidney Disease: Improving Global Outcomes for the evaluation and care of living kidney donors (KDIGO) recommends consideration of BMI as part of the risk assessment of donor candidates. However,

no clear recommendation is made to reject candidates with high BMI (4). The main reason for concern about donors with high BMI in kidney transplantation is the risks of perioperative complications that can harm the donor even in the early (prolonged wound healing, infections, thromboembolism, etc.) or late (development of renal disease) stages (5-11). However, the prevalence of obesity is increasing worldwide, and donor obesity is one of the most important problems increasingly faced by many transplant centers (11-15). Therefore, every data regarding the short- and long-term morbidity and mortality of kidney donors with obesity are of great value.

In our high-volume center where 5-8% of annual kidney transplants are performed in Turkey, donor candidates of ESRD patients who do not have other suitable living donors with a BMI > 35 kg/m2 are also accepted. In this study, the effect of the BMI at the time of the operation on the morbidity of the kidney donors in the living kidney transplantation operations performed in our center was evaluated.

MATERIALS AND METHODS

Study Design and Participants

One hundred ninety-two kidney transplants performed at the Organ Transplant Center of Istanbul Yeni Yuzyil University Private Gaziosmapaşa Hospital between November 2017 and October 2018 were retrospectively reviewed. All living donors (n = 170) were included in our study. Diabetics with good glycemic control are accepted as kidney donors in our center if the recipient has no other suitable donor and has the following characteristics: patients over 50 years old, not more than 10 years old with diabetes and no signs of end-organ damage (proteinuria, left ventricular hypertrophy, coronary artery disease, diabetic neuropathy, and nephropathy, etc.).

Laboratory examinations and clinical measurements

Donor's age, sex, BMI, surgical technique (allograft harvesting), preoperative eGFR, protein excretion rate, systolic and diastolic blood pressure, and length of hospital stay were recorded. These parameters were also recorded 12 months postoperatively. Daily protein excretion was determined by the protein-creatinine ratio in spot urine. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaborative 2009 equation (CKD-EPI) via an online calculator website; http://www.mdrd.com/.

Definition and classification

The definition and classification of obesity were established according to the American Diabetes Association - Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Medical Care in Diabetes-2022 (16). Accordingly, four groups were formed: Normal weight (BMI: 18.5-24.9), overweight (BMI: 25-29.9), class I obesity (BMI: 30-34.9), class II obesity (BMI > 35) (four subjects had BMI greater than 40 kg/m2, and we included them in the class II group because the sample size was too small to determine class III).

Ethical approval

This study was carried out in accordance with the Declaration of Helsinki. The consent form is not available since the study is retrospective. The study was approved by the ethics committee of scientific research of Istanbul Yeni Yuzyil University.

STATISTICAL ANALYSIS

Data were analyzed using SPSS (Statistical Package for the Social Sciences) version 23.0. The normality of continuous variables was tested using the Kolmogorov-Smirnov test. Descriptive data were expressed as mean + standard deviation (SD) and median (minimum-maximum). Groups were compared using the one-way ANOVA test for parametric variables, and the difference between groups was examined using the post hoc Tukey test. The Kruskal-Wallis test was used to compare nonparametric variables among the four groups. $P < 0.05$ was considered significant at the 95% confidence interval.

RESULTS

A total of 170 kidney donors were included in our study. The epidemiological and laboratory data are shown in Table 1. The number of male and female donors was equal. In 85.9% of the donors, the kidney grafts were harvested using laparoscopic techniques (**Table 1**). According to their BMI, 32.9% of the donors were of normal weight, 31.7% were overweight, 25.8% had class I obesity, and 9.4% had class II obesity. Four individuals had a BMI greater than 40 kg/m2, but because of the small sample size, they were included in the class II group. 22 donors were hypertensive, and the number of hypertensive donors was similar in all groups ($p > 0.05$). Postoperative hospital stay was similar in the donors with obesity and normal-weight (mean 2.2[1-4] days).

The mean eGFR reduction in donors at 12 months was 36.54±11.25 ml/min/1.73 m^2. Donor age was the only parameter negatively correlated with low eGFR ($p = 0.024$ and $r= 0.290$). No correlation was found between BMI and posttransplant 12 months eGFR ($p=0.125$ and $r=0.065$).

Systolic and diastolic blood pressure values correlated with BMI ($p=0.036$, $r=0.256$). However, the increase in blood pressure after kidney donation showed no significant change between the donors with obesity and normal-weight ($p > 0.05$).

Table 1. Epidemiological and laboratory characteristics of the donors

Parameters	Value
Age, years	85/85
Gender, male/female, n	85/85
Surgery technique •Laparoscopic, n •Open, n	 146 (% 85.9) 24 (% 14.1)
Preoperative eGFR	105.60 ± 12.42
Preoperative proteinuria, mg/day	30.7 (4.2-164)
Hypertension, n	22
Diabetes mellitus, n	2
Systolic blood pressure, mmHg	115 ± 11
Hospital stay, day	2.1 (1 - 4)
Discharge serum creatinine, mg/dL	1.08 ± 0.22
Postoperative 12. Months serum creatinine, mg/dL	1.13 ± 0.21

BMI; body mass index, eGFR; estimated glomerular filtration rate

The amount of protein excretion rate did not change at the end of the 12th month in donors with and without obesity (p>0.05) (**Table 2**). Posttransplant proteinuria decreased in donors (except the Class 1 obesity group), however, the reduction rate did not reach a statistically significant level (p>0.05). The rate of decrease in proteinuria was more pronounced in the obesity class II (p = 0.09). BMI was positively correlated with proteinuria in pre-and and postoperative periods (p = 0.03 and r= 0.312 and p = 0.02, r= 0.296, respectively).

DISCUSSION

Most transplant centers evaluate donors with obesity based on their local surgical experience and recipient and donor requirements. However, obesity, particularly more severe than class I (class II, class III, and super obesity), is generally considered a relative contraindication to donation. Although individuals with obesity are not ideal donors, they may be considered kidney donors in some cases. However, more data on long-term follow-up are needed. In this study, approximately 35.2% of the donors had a BMI over 30 kg/m2. Donors with obesity did not have longer hospital stays. One-year outcomes of high BMI donors were similar to normal weight donors in terms of eGFR, protein excretion rate, and blood pressure change.

Few studies address the health consequences of kidney donation in individuals with high BMI. However, the evidence available to date has not shown a significant difference between donors with and without obesity (17,18). Rea et al. demonstrated an increase in arteriolar hyalinosis and significant tubular vacuolization in biopsies from donors with obesity but found similar results for iothalamate GFR and albuminuria at 12-month follow-up (18). Previous studies have reported an initial GFR reduction of up to 20-35% after kidney donation and stable renal function over the years (19,20). Short-term recovery of renal function is worse in older donors and those with high BMI (19). Londen et al. reported that the decline in renal function after donation reaches 38 ml/min and that possible complications such as preeclampsia should be considered, especially in women with high BMI (21). Tavakol et al. and Thukral et al. reported similar results in their studies (22,23). In our study, the rate of change in eGFR and protein excretion levels after the donation was similar in individuals with and without obesity. The rate of decline in eGFR was approximately 35 ml/min/1.73 m2 in all donors after donation and was independent of BMI. The protein excretion rate was higher in donors with higher BMI and correlated with both preoperative and postoperative BMI. However, the protein excretion rate did not increase after donation. In contrast, a nonsignificant decrease was observed in donors with a BMI of > 35 kg/m^2. A slight (but statistically nonsignificant) weight loss in donors with a BMI > 35 kg/m2 may have led to a decrease in protein excretion rate; because all donors with a higher BMI were advised by our transplant team to lose weight before surgery and were informed about the increased risks.

Individuals with high BMI usually have higher blood pressure than normal-weight people. Therefore, some authors reported that their risk of blood pressure elevation is higher after kidney donation (23,24).

Ramcharan et al, in their study examining the long-term data (20-37 years) of 256 living kidney donors, found that 38% of the donors had elevated blood pressure and 50% of them started antihypertensive drug therapy. However, they reported that serum creatinine and protein excretion rates remained constant (25). A meta-analysis of more than 5000 donors concluded that, given the blood pressure changes in similar age groups, blood pressure increased by 5 mmHg in donors between 5 and 10 years after kidney donation. However, this meta-analysis was not considered to indicate the risk ratio for donors with higher BMI (26). However, the authors claimed that the remaining renal function of kidney donors did not deteriorate faster than would be expected due to the aging process (26). In our study, there was an increase in blood pressure values of approximately 2-3 mmHg in both donor groups. However, we could not detect the postoperative dietary behavior and weight changes of the donors, which is an important limitation of this study.

Although our study did not aim to demonstrate obesity-related postoperative complications, the hospital stay is no longer in donors with obesity than in normal-weight

Table 2. The comparison of the groups according to BMI

	[A]Normal weight, N= 56	[B]Overweight, N= 54	[C]Class I Obesity, N= 44	[D]Class II Obesity, N= 16	P value
Age, year	43.50 ±13.19	46.96±12.58	50.13±11.34	43.87±13.92	A vs B; p=0.16, A vs C; **p<0.05** A vs D; p=0.92 C vs D; p=0.08, B vs C; p=0.19 B vs D; p=0.40 (Post hoc Anova and Tukey's p values)
Preoperative BMI, kg/m^2	23.45±1.89	27.34±3.45	32.19±3.12	37.84±4.2	A vs B; **p<0.05**, A vs C; **p<0.001,** A vs D; **p<0.001,** B vs C; **p=0.02**, B vs D; **p=0.001** C vs D; **p=0.03 (**Post hoc Anova and Tukey's p values)
Postoperative BMI, kg/m^2	24.87±2.39	28.65±4.16	33.42±3.95	36.15±5.1	A vs B; **p<0.05**, A vs C; **p<0.001,** A vs D; **p<0.001,** B vs C; **p<0.001**, B vs D; **p=0.001** C vs D; **p=0.04 (**Post hoc Anova and Tukey's p values)
Surgery technique • Laparoscopic • Open	 46 10	 47 7	 38 6	 15 1	P > 0.05 (Anova)
Preoperative eGFR, ml/min	105.58±11.72	105.10±13.64	105.43±13.07	107.25±9.19	A vs B; p=0.84, A vs C; p=0.95 A vs D; p=0.60 B vs C; p=0.90 B vs D; p=0.55, C vs D; p=0.61 (Post hoc Anova and Tukey's p values)
Postoperative 12 months eGFR, ml/min	71.39±13.59	67.16±13.69	67.79±l5.00	70.11±l4.12	A vs B; p=0.10, A vs C; p=0.21 A vs D; p=0.96 B vs C; p=0.82, B vs D; p=0.33, C vs D; p=0.45 (Post hoc Anova and Tukey's p values)
Systolic blood pressure, mmHg (Mean measurements during preoperative hospitalization)	112(80-140)	114(90-160)	117(100-160)	119(100-140)	A vs B; p=0.34, A vs C; **p<0.05** A vs D; **p<0.05** B vs C; p=0.10 B vs D; p=0.06, C vs D; p=0.48 (Post hoc Anova and Tukey's p values)
Systolic blood pressure, mmHg (Mean measurements postoperative 12-month outpatient polyclinic visits)	115(90-140)	116(90-160)	119(110-170)	122(110-160)	P>0.05 (Anova)
Diastolic TA, mmHg (Mean measurements during preoperative hospitalization)	70.89±6.68	73.70±7.59	73.86±5.79	76.25±+9.57	A vs B; **p<0.05**, A vs C; **p<0.05**, A vs D; **p<0.05**, B vs C; p=0.90 B vs D; p=0.27 C vs D; p=0.24 (Post hoc Anova and Tukey's p values)
Diastolic TA, mmHg (Mean measurements postoperative 12-month outpatient polyclinic visits)	73.05±7.72	77.28±8.32	78.12±6.43	80.55±9.78	P>0.05 (Anova)
Preoperative proteinuria, mg/day (Mean measurements during preoperative hospitalization)	12.4 (4.2-80.6)	27.6 (19.2-49.3)	32.2 (9.7-164)	46.3 (8.3-124.3)	A vs B; **p<0.001,** A vs C; **p<0.001**, A vs D; **p<0.001**, B vs C; p=0.06, B vs D; **p=0.03,** C vs D; p=0.07 (Post hoc Anova and Tukey's p values)
Postoperative proteinuria, mg/day (Mean measurements postoperative 12-month outpatient polyclinic visits)	10.3 (3.8-76.2)	22.56 (11.05-51.45)	33.3 (10.1-140.4)	42.4 (16.3-133.5)	A vs B; **p<0.05,** A vs C; **p<0.001**, , A vs D; **p<0.001**, B vs C; **p=0.04**, B vs D; **p=0.02,** C vs D; p=0.10 (Post hoc Anova and Tukey's p values)
Hospital stay following surgery, day	2.1(1-3)	2.2(2-3)	2.1(2-3)	2.3(2-4)	A vs B; p=0.27, A vs C; p=0.51 A vs D; p=0.30, B vs C; p=0.65 B vs D; p=0.77, C vs D; p=0.57 (Post hoc Anova and Tukey's p values)

donors. Therefore, it can be indirectly assumed that the complication rate in the early perioperative period did not increase in donors with obesity in our cohort. Moreover, previous studies have shown that laparoscopic kidney donation is safe (27,28). However, prolonged intraoperative time, which is one of the major problems faced by the surgical team, might be an expected problem in donors with obesity.

Limitations of the study include the lack of metabolic assessment of donors, the lack of data on medication use (antihypertensives, etc.), the assessment of blood pressure with only one measurement in the office, and the relatively short follow-up period.

CONCLUSION

We consider that individuals with obesity, in conjunction with a good perioperative evaluation process, may be considered donors for ESRD patients for whom there are no other suitable living donors.

DECLARATIONS

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Review

Pregnancy and The Kidneys: A Brief Systematic Review

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ABSTRACT

Significant anatomical and physiological changes occur in kidneys during pregnancy. These need to be well defined to discriminate real nephrological disorders. Pregnancy may cause a predisposition to some kidney diseases, and it is not surprising that women with already-known kidney disorders may face challenges during this period. Management is more complicated than in the general population as both maternal and fetal health should be considered. In this report, besides anatomical and physiological changes that occur in pregnancy, common nephrological disorders like hypertension, urinary tract infections, and acute and chronic kidney injury are reviewed.

Keywords: Pregnancy, hypertension, urinary tract infection, acute kidney injury, chronic kidney injury

RENAL ANATOMICAL CHANGES IN PREGNANCY

Renal size increases by 1 cm during pregnancy because of increased vasculature and interstitial volume. Physiologic hydronephrosis may occur due to mechanical compression by the enlarging uterus and smooth muscle relaxation related to progesterone. It is commonly more prominent on the right side as the uterus usually undergoes rotation with tilting to the right. Ureteric compression may cause urine stasis which may increase the likelihood of urinary tract infections (UTIs), nephrolithiasis, and pyelonephritis. Loss of bladder tone may cause symptoms like urinary frequency, urgency, and incontinence (1).

RENAL PHYSIOLOGICAL CHANGES IN PREGNANCY

Blood volume increases progressively throughout the pregnancy. Systemic vascular resistance and so the systemic blood pressure decrease. Increased blood volume and reduced systemic vascular resistance accompanied by increased sympathetic activity lead to an increase in heart rate and cardiac output. Systemic vasodilation causes renal vascular dilatation and increased glomerular filtration which causes a reduction in serum creatinine, blood urea nitrogen, and uric acid levels (2). Urinary protein and glucose excretion also increase. Sodium is filtrated and reabsorbed more due to the activated renin–angiotensin–aldosterone system, and sodium retention may contribute to the increased plasma volume (1). Normal plasma osmolality threshold decreases and plasma osmolality becomes 270 to 275 mOsm/kg. A fall in serum sodium level by 5 mEq/L occurs (3).

Changes in the immune system (shift from a T helper cell type 1 to a T helper cell type 2 phenotype and increase in the number of regulatory T cells) occur in pregnancy to establish fetal tolerance. This may impact the behavior of autoimmune diseases (2).

HYPERTENSION IN PREGNANCY

Hypertension in pregnancy is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (average of at least two measurements) (4,5). Blood pressure should be measured with a validated and calibrated device and with a standardized technique (5). The prevalence of hypertension in pregnancy continues to increase due to advanced maternal age and cardiometabolic risk factors like obesity. It can cause maternal and fetal mortality, and morbidity (4).

Hypertension in pregnancy can be classified as chronic arterial hypertension, preeclampsia

superimposed upon chronic arterial hypertension, gestational hypertension, and preeclampsia.

• **Chronic arterial hypertension** is considered when the hypertension is diagnosed before the 20th week of gestation and/or persists longer than 12 weeks postpartum. These women have an increased risk for superimposed preeclampsia and other maternal complications like heart failure, stroke, pulmonary edema, acute kidney injury (AKI) or death, and fetal complications like intrauterine growth retardation, placental abruption, preterm delivery, and fetal loss (2,3,6). Physiologic decrease in blood pressure may mask hypertension in early pregnancy (2).

• **Preeclampsia superimposed upon chronic arterial hypertension** is considered in the presence of worsening hypertension with new-onset proteinuria and/or significant new end-organ dysfunction after 20 weeks of gestation in a patient with chronic hypertension. Maternal and fetal morbidities increase with superimposed preeclampsia (7).

• **Gestational hypertension** is considered when pregnant patients had high blood pressure after the 20th week of gestation. Blood pressure normalizes in the postpartum period (2). These women have an increased risk for superimposed preeclampsia. Blood pressure usually resolves after 12 weeks in the postpartum period (3).

• **Preeclampsia** is considered in the presence of new-onset hypertension after 20 weeks of gestation and urinary protein excretion ≥ 300 mg/d or urine protein/creatinine ratio (UPCR) ≥ 0.3 g/g (2). Risk factors for preeclampsia are shown in **Table 1**. The amount of proteinuria is not associated with maternal or fetal outcomes (7). In the absence of proteinuria clinical features of severity (**Table 2**) may help diagnosis (2). Serum uric acid is often greater than expected.

Table 1. Risk factors for preeclampsia (3)

•Advanced maternal age
•Nulliparity
•Being pregnant with more than one baby
•Preeclampsia in a previous pregnancy
•Family history of preeclampsia
•Chronic hypertension
•Diabetes mellitus
•Chronic kidney disease
•Autoimmune disease
•>10 years since the previous pregnancy
•Obesity

Table 1. Clinical features of severity (7)

•Thrombocytopenia (Platelets < 100000/μL)
•Renal insufficiency (Serum creatinine >1.1 mg/dL or doubling of serum creatinine concentration in the absence of another kidney disease)
•Impaired liver function (Liver transaminases 2× upper limits of normal)
•Pulmonary edema
•New-onset cerebral or visual symptoms

HELLP (Hemolysis, Elevated liver enzymes, Low Platelets) syndrome is a subtype of preeclampsia with hemolysis (microangiopathic blood smear; schistocytes and burr cells, serum bilirubin ≥1.2 mg/dL, low serum haptoglobin or lactate dehydrogenase ≥2 times the upper level of normal), elevated liver enzymes (≥2 times the upper level of normal), and thrombocytopenia (<100,000 cells/microL) (8).

Eclampsia develops when a seizure occurs in a preeclamptic patient (9).

Preeclampsia is associated with later-life cardiovascular risk. Patients who had preeclampsia should receive counseling before their next pregnancy (7).

Maternal benefits of lowering blood pressure and the potential fetal risks due to reductions in uteroplacental circulation should be considered (4,10). Lowering blood pressure aggressively is usually not recommended (4). Bed rest or salt restriction was not shown to reduce preeclampsia risk (11). Treatment should be initiated usually when the blood pressure is ≥150-160/100-110 mmHg (2). Target blood pressure is usually accepted as <140/90 mmHg (3,6).

Oral nifedipine, oral/intravenous labetalol, or intravenous hydralazine may be used for severe hypertension (≥170/110 mmHg). Methyldopa, labetalol, and long-acting nifedipine are oral antihypertensive agents that may be used for non-severe hypertension in pregnancy (5). Diuretics are not preferred as they may cause volume depletion, and angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), renin inhibitors, and mineralocorticoid receptor antagonists are contraindicated as they are teratogenic (7).

Delivery is the preferred treatment for preeclampsia, especially after 37 weeks of gestation, and for the ones with severe clinical features (2). Maternal and fetal conditions should be considered in the delivery decision. Corticosteroids should be administered between 25 and 34 weeks to decrease the risk of respiratory distress syndrome in infants (3).

Magnesium sulfate is used in the treatment and prevention of eclampsia (5).

Low-dose aspirin is recommended to prevent preeclampsia in high-risk patients, and preferably should be initiated before 16 weeks of gestation (5,12). Oral calcium supplementation (500 mg/d) may be suggested for women with poor dietary intake of calcium (<900 mg/day) to prevent preeclampsia (5).

URINARY TRACT INFECTIONS IN PREGNANCY

UTIs are common in pregnancy and are classified as lower UTIs (asymptomatic bacteriuria or acute cystitis) and upper UTIs (acute pyelonephritis). Enterobacteriaceae and Escherichia coli are responsible for most of the cases (13).

•Asymptomatic bacteriuria is diagnosed when a urine sample shows 10^5 colony-forming units (CFU)/mL without symptoms of UTI ideally in two consecutive urine cultures. In pregnant women, asymptomatic bacteriuria should be treated as it can turn to symptomatic acute cystitis or even pyelonephritis and can increase the risk for adverse fetal outcomes (preterm birth, low birth weight, and perinatal mortality) (13).

•Symptoms like frequency, dysuria, or strangury may indicate acute cystitis. 10^2 organisms/ml is sufficient to diagnose the presence of pyuria and symptoms (13).

•Symptoms like fever, dysuria, and loin pain may indicate acute pyelonephritis with generally more than 10^5 organisms/ml in the urine (3,14).

Management of UTIs in Pregnancy

Penicillins (with or without beta-lactamase inhibitors), cephalosporins, aztreonam, and fosfomycin are generally accepted as safe in pregnancy. Supportive treatment and intravenous antibiotics (preferably broad-spectrum beta-lactams) should be administered for acute pyelonephritis (14).

Antibiotic prophylaxis is suggested for the ones who have persistent bacteriuria. Prophylaxis should be considered in patients with recurrent UTI (2 episodes during pregnancy) (3).

ACUTE KIDNEY INJURY

Pregnancy-related AKI may cause maternal and fetal morbidity and mortality (15). Pregnancy-related AKI increases the risk of preterm births, low birth weights, and neonatal intensive care unit admissions (16). Older maternal age, preeclampsia, antepartum/postpartum haemorrhage, infections (eg; sepsis) lower socioeconomic status, obesity, and comorbidities like diabetes, hypertension, and chronic kidney disease are the risk factors for AKI in pregnancy (15-17).

Pregnancy-related AKI is not well defined. Serum creatinine usually decreases below 0.8 mg/dL in pregnancy. Therefore, even a seemingly normal creatinine may be indicative of pregnancy-related AKI (16). Serum creatinine checked in early pregnancy may help the diagnosis of AKI later on (15,16).

Prerenal, renal, and postrenal causes should be sought. In the first trimester, volume depletion due to hyperemesis gravidarum may cause prerenal AKI (16). Hemorrhage, pulmonary embolism, heart failure, or sepsis are some of the other reasons that may cause prerenal AKI, and these may also result in ischemic acute tubular necrosis if the injury is severe. Acute fatty liver of pregnancy, amniotic fluid embolism or severe preeclampsia, and HELLP syndrome may cause acute tubular necrosis. Severe hypotension may result in acute cortical necrosis (2). Postrenal AKI may be more common in the second and third trimesters due to the compression of the gravid uterus on the ureter (16).

Urinalysis, urine microscopy, comprehensive metabolic panel, coagulation panel, and serological work may help with differential diagnosis. Serum complement levels may be found elevated due to increased synthesis by the liver in pregnancy. A kidney ultrasound may be used to exclude postrenal etiologies (16). Renal biopsy may be considered in the first and second trimesters if the diagnosis is needed for urgent therapy (18).

Supportive care and specific treatment options (if a specific cause of pregnancy-related AKI is defined) should be administered (16). Dialysis may be required in some patients, and it is associated with increased mortality (2).

Pregnancy-related AKI may increase the risk of hypertension CKD in long term (11,16).

CHRONIC KIDNEY INJURY

Pregnant patients with chronic kidney injury (CKD) may have fetal or maternal complications including preeclampsia, preterm delivery, low birth weight, deterioration in kidney functions, and increased mortality. (19) Fertility rate is lower in patients with more advanced kidney disease (3). The higher the stage of CKD, the greater the risk of adverse pregnancy outcomes. Glomerular nephropathies, autoimmune diseases, and diabetic nephropathy may have poorer outcomes. CKD increases the risk of preeclampsia and hypertension in pregnancy (11).

Euvolemia should be aimed to avoid dehydration and pulmonary edema. Thromboprophylaxis with low molecular weight heparin is recommended for patients with nephrotic-range proteinuria if there is no contraindication. In the presence of additional risk

factors, thromboprophylaxis may also be considered for patients with non-nephrotic range proteinuria. Anemia can be treated with parenteral iron and erythropoietin-stimulating agents if indicated. Vitamin D supplementation is also suggested for patients who have vitamin D deficiency. Non-calcium-based phosphate binders and calcimimetics should be discontinued. Maternal urea concentration, gestation, renal function trajectory, fluid balance, biochemical parameters, blood pressure, and symptoms of uremia should be all considered when taking the decision about dialysis initiation (19).

If patients with the end-stage renal disease get pregnant, their dialysis treatment should be intensified (frequency and duration) (11). Dialysis duration should be more than 20 hours/week to maintain serum urea nitrogen target near-normal (<50 mg/dL). Residual renal function should also be considered. Although a successful pregnancy is possible for patients under peritoneal dialysis or hemodialysis perinatal mortality and preterm delivery may be more common. Pregnancy may cause the formation of anti-HLA antibodies which may be a problem to find a suitable kidney donor in the future (2).

Fertility improves after renal transplantation. Risks for pregnancy complications are also lower in comparison to dialysis patients (2). Renal transplant patients are usually advised to wait at least 1 year for stable graft function before pursuing pregnancy. Immunosuppressive treatment should be arranged. Prednisolone, azathioprine, and tacrolimus/cyclosporine are the immunosuppressive agents preferred (2). Renal transplant patients have a higher risk of complications than in the general population (11). Mycophenolate should be withdrawn 3-6 months before conception. Aspirin is suggested to prevent preeclampsia (19).

SPECIFIC RENAL DISEASES IN PREGNANCY

Specific renal diseases like diabetic nephropathy, lupus nephritis, and vasculitis, reflux nephropathy, congenital abnormalities of the kidney and urinary tract (CAKUT), and glomerulonephritis are not reviewed in this report.

DISCLOSURES

Ethics Committee Approval Number: Not necessary
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Case Report

Acute Pancreatitis After a Late Period of Metformin Intoxication in a Non-Diabetic Patient

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ABSTRACT

Metformin, an oral antidiabetic drug, is the first-line treatment modality for the treatment of non-insulin-dependent diabetes mellitus. Metformin is more commonly associated with gastrointestinal side effects. Acute pancreatitis due to metformin is very rare. We present a case of acute pancreatitis after a late period of metformin intoxication in a non-diabetic patient. Because acute pancreatitis can appear in the late period of metformin intoxication, the emergency physician should be vigilant for this condition.

Keywords: Acute pancreatitis, metformin, intoxication

INTRODUCTION

Metformin, an oral antidiabetic drug in the biguanide class, is the first-line treatment modality for the treatment of non-insulin-dependent diabetes mellitus and the most widely prescribed antidiabetic drug in the world. It's also used in the treatment of polycystic ovary syndrome, non-alcoholic fatty liver disease, and premature puberty (1). Metformin is more commonly associated with gastrointestinal side effects, including diarrhea, cramps, nausea, vomiting, and increased flatulence. However, the most serious adverse effect and potentially life-threatening complication of metformin is lactic acidosis (2). Acute pancreatitis due to metformin is very rare and this adverse effect results from a combination of drug overdose and renal failure (3,4). Furthermore, there is limited knowledge regarding the course of metformin intoxication without renal failure in non-diabetic patients. Herein, we present a case of late edematous pancreatitis following metformin intoxication in a non-diabetic patient with normal renal function.

CASE

A 26-year-old man admitted to the emergency department with epigastric pain, nausea, and vomiting for one day. He had a history of hospitalization in the intensive care unit owing to a suicide attempt with 60 grams of metformin use one week before his admission to our clinic. He had been hospitalized for five days and was discharged after successful treatment with activated charcoal gastric lavage, intravenous hydration, and a single four-hour hemodialysis session without anyother organ failure for side effects of metformin overdose and lactic acidosis. He had no history of trauma, smoking, alcohol consumption, or use of herbal or illicit drugs. On physical examination, he was afebrile, with a blood pressure of 125/75 mm/Hg, and a pulse of 78 beats per minute. His abdominal examination revealed tenderness in the epigastric region, but no rigidity or rebound was detected. The remainder of the examination was normal.

Results of the blood tests were as follows; white-cell count: 9300 per cubic millimeter, hemoglobin level: 14.4 g/dl (reference range: 13.6-17.2 g/dl), platelet count: 20700/mm3, aspartate aminotransferase: 23 U/L (reference range: 0-34 U/L), alanine aminotransferase: 42 U/L (reference range: 10- 49 U/L), alkaline phosphatase: 61 U/L (reference range: 40-129 U/L), gama glutamyl transferase: 67 U/L (reference range: 8-73 U/L), total bilirubin: 0.7 mg/dL (reference range:0.3-1.2 mg/dL), direct bilirubin: 0.2 mg/dL (reference range: 0-0.2 mg/dL), total protein: 7.2 g/dl, albumin: 4.2 g/dl, glucose: 93 mg/dL, lactate dehydrogenase: 247 U/L (reference range: 120-246 U/L), pancreatic amylase: 303 U/L (reference range:13-53 U/L), lipase: 320 U/L (reference range: 6-51 U/L), creatinine: 1.1 mg/dL (reference range: 0.7-1.3 mg/dL), and urea: 32 mg/dL (reference range: 19-48 mg/dl). The electrolyte levels were in the normal range and arterial blood gases had a pH of 7.37 and a lactate level of 1.53 mmol/L (reference range: 0-1.8 mmol/L). The level of lipid profiles and thyroid-

stimulating hormone were normal. C-reactive protein level was 8.2 mg/L (reference range: 0-8 mg/L). Polymerase-chain-reaction tests were negative for hepatitis B, hepatitis C, and human immunodeficiency virus. An ultrasonographic examination of the abdomen showed that the vertical size of the liver was 12 cm. This examination also revealed a mild increase in liver echo density with no gall stones and splenomegaly and an increase in the pancreatic body with the hypoechoic pattern. An abdominal computed tomography scan detected a diffusely enlarged pancreas with low density from edema, and acute pancreatitis was confirmed by radiologic imaging. The patient was treated with intravenous fluids and a proton pump inhibitor. Within two days, the patient's abdominal pain improved and serum pancreatic amylase and lipase levels recovered. The patient was discharged three days after the hospitalization and tested well at the follow-up.

DISCUSSION

The patient was diagnosed with mild edematous pancreatitis after metformin intoxication in the late period due to the clinical presentation of epigastric pain, the lack of multi-organ failure, high levels of amylase and lipase, the lack of other known causes of acute pancreatitis, and the conformable radiological findings for the diagnosis of acute pancreatitis. The most important causes of acute pancreatitis are alcohol consumption and gallstones. Drug-induced acute pancreatitis is generally considered to be a rare condition, accounting for approximately 2% of all causes of acute pancreatitis (5). Furthermore, metformin accounts for a very small percentage of the drugs that induce acute pancreatitis. Hence, metformin's involvement in the complication is an extremely rare event.

Metformin is more commonly associated with gastrointestinal side effects, but the most serious adverse effect and life-threatening complication of this drug is lactic acidosis, with mortality greater than 30% (2,6). The exact molecular mechanism underlying metformin-induced acute pancreatitis is still unknown. However, available evidence suggests that acute pancreatitis due to metformin is probably caused by the overexpression and prolonged activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), by the drug overdose or/and with renal insufficiency (7).

Recommended daily dose of metformin is <2550 mg (2). If administered within these doses, metformin activates AMPK, a liver enzyme that plays an important role in insulin signaling and cellular energy homeostasis. This activation leads to hepatic fatty acid oxidation and ketogenesis, inhibition of lipogenesis, stimulation of skeletal muscle fatty acid oxidation and glucose uptake, and modulation of insulin secretion by pancreatic beta-cells. Additionally, this process suppresses hepatic glucose production, increases insulin sensitivity, enhances peripheral glucose uptake, increases fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract (8).

On the other hand, administration of metformin above the recommended daily dose (>2550 mg), can lead to pancreatic beta cell damage due to overstimulation of the AMPK signaling pathway. This is in line with a previous study where the pancreatic beta-cell function was shown to be impaired in vivo by overexpression of AMPK (9) (**Figure**). Prolonged activation and overexpression of AMPK will tend to decrease beta-cell function, leading to acinar cell damage and intracellular leakage of digestive enzymes from ductules. This leakage is associated with pancreatic inflammation

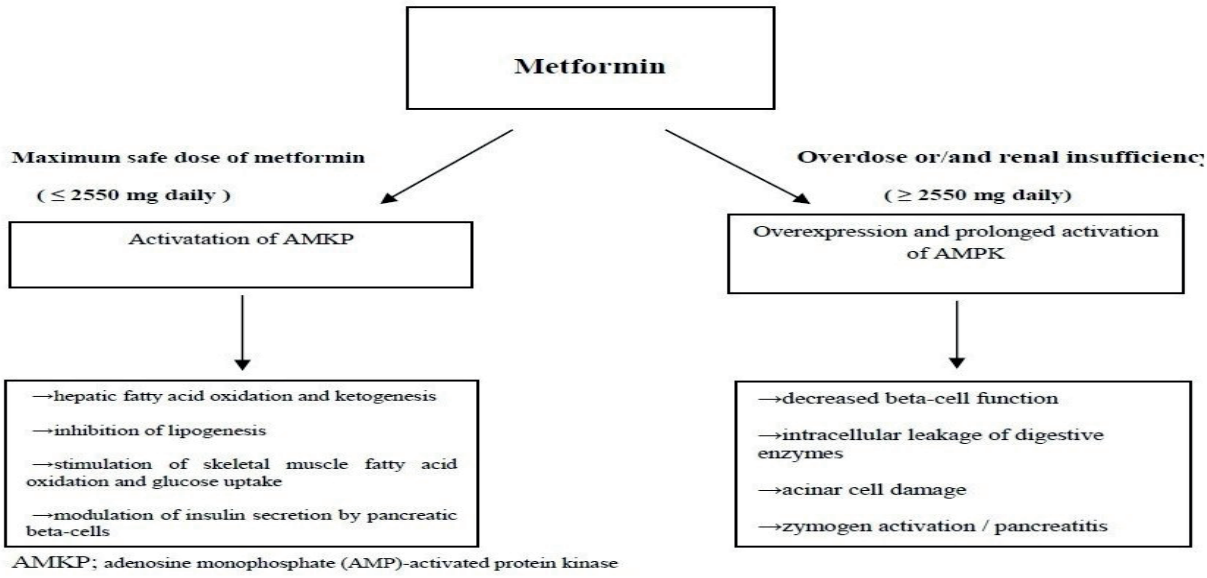

Figure. Dose-dependent effects of metformin on AMPK activation (adapted from Reference 9).

through zymogen activation. Dose-dependent effects of metformin on AMPK activation are shown in the Figure.

Metformin is cleared from the body by tubular secretion and excreted in the urine without any change. Therefore, overdoses of metformin and renal dysfunction will tend to cause an accumulation of the drug and trigger pancreatitis via the aforementioned prolonged activation of the AMPK signaling pathway.

A few cases of pancreatitis have been reported with metformin. Among the published case reports, metformin-induced pancreatitis was attributed to metformin overdose, patients' comorbidities, a combination of other drugs (angiotensin-converting enzyme inhibitor, non-steroidal anti-inflammatory), and renal failure (4,6,7,10).

There is no knowledge of the course of metformin intoxication without renal failure in non-diabetic patients in the late period. This is the first case of metformin-associated late-acute pancreatitis due to overdose-dependent side effects of metformin in a patient with non-comorbidities and no-renal impairment. Because acute pancreatitis can appear in the late period of metformin intoxication, the emergency physician should be vigilant for this condition.

DECLARATIONS

Acknowledgment: Not applicable
Ethics Committee Approval Number: Not necessary
Informed Consent: Not necessary
Referee Evaluation Process: Externally peer-reviewed
Conflict of Interest Statement: Authors declare no conflict of interest.

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Case Report

Irritant Contact Dermatitis at Peritoneal Dialysis Exit Site Due to Misuse of Nitrofurazone: Case Series

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ABSTRACT

Erythema around the catheter exit site in peritoneal dialysis patients occurs usually due to exit-site infections, but also rarely develops due to noninfectious causes. The absence of purulent drainage, pain, or edema, and the characteristic appearance of lesions with negative culture results are supporting findings for irritant contact dermatitis. Here we discussed the development of irritant contact dermatitis around the catheter exit site due to the misuse of nitrofurazone in peritoneal dialysis patients. Nitrofurazone should be avoided in exit-site care due to its irritant potential.

Keywords: Irritant contact dermatitis, nitrofurazone, peritoneal dialysis

INTRODUCTION

Erythema around the peritoneal dialysis (PD) catheter in a PD patient occurs usually due to catheter exit-site infection. Catheter exit-site infection is a leading risk factor for peritonitis which may cause PD failure, and even death (1,2). Daily topical application of antibiotic-containing preparations to the exit site is recommended in current PD guidelines to reduce exit-site infection risk (3). Erythema around the PD catheter may rarely develop due to noninfectious reasons like a thermal burn, friction, chemical irritant exposure, and allergic reasons (4). Here we presented PD patients with irritant contact dermatitis due to misuse of topical nitrofurazone.

CASES

A total of four PD patients aged 45-64 years admitted with erythema and itching around the PD catheter exit site. Patients denied abdominal pain, fever, cloudy dialysate, and purulent drainage from the exit site. They started to use topical antibiotic cream for exit-site care regularly after recommended being in the PD unit. We learned that nitrofurazone was first used in the hospital as it was the only available topical antibiotic cream, and they continued to use nitrofurazone without a prescription due to its low price. Their vital signs were stable. Abdominal examination was normal (**Table 1**). The lesions around the catheter exit site had a sharp demarcation and were limited to the contact area in all patients. Vesicles on the erythematous base were observed (**Figure 1**). Demographic and clinical features were summarized in the table. Irritant contact dermatitis due to nitrofurazone was diagnosed in all cases. Chronic irritant contact dermatitis was thought in case 4 due to hyperpigmented erythematous plaque with squam and sharp demarcation. Nitrofurazone was discontinued. The topical steroid was started. Findings were regressed in the follow-up (**Figure 2**).

DISCUSSION

Erythema around the PD catheter should be accepted as infectious until proven otherwise, but noninfectious reasons should also be considered in the differential diagnosis (1). Contact dermatitis around the PD catheter exit site was reported in a few patients: one due to gentamicin, two children and one adult due to povidone-iodine, another case due to octenidindihydrochloride+phenoxyethanol, one silicon allergy due to Tenckhoff PD catheter (1,4-7). In our

Table 1. Clinical features of patients

	Case 1	Case 2	Case 3	Case 4
Age (years)	64	45	54	54
Gender	Female	Male	Female	Female
Primary kidney disease	DNP	DNP	DNP	Glomerulonephritis
PD program	APD	CAPD	CAPD	APD
Duration of PD (months)	20	13	6	18
Erythema around catheter	Present	Present	Present	Present
Itching	Present	Present	Present	Present
Abdominal pain	Absent	Absent	Absent	Absent
Fever	Absent	Absent	Absent	Absent
Cloudy diyalisate	Absent	Absent	Absent	Absent
Drainage around catheter	Absent	Absent	Absent	Absent
Trauma to exit-site	Absent	Absent	Absent	Absent
Recent changes in use of bandage	Absent	Absent	Absent	Absent
Recent change in the use of povido-ne-iodine	Absent	Absent	Absent	Absent
Exit-site culture	Negative	Negative	Negative	Negative
Topical agent used	Nitrofurazone	Nitrofurazone	Nitrofurazone	Nitrofurazone
Frequency of exit-care	Every other day	1 in 3 days	1 in 3 days	3 per week

DNP; diabetic nephropathy, PD; peritoneal dialysis, APD; assisted peritoneal dialysis CAPD; continuous ambulatory peritoneal dialysis

cases, irritant contact dermatitis was developed due to topical nitrofurazone application around the exit site.

Irritant contact dermatitis is the most common type of contact dermatitis. It occurs due to physical, mechanical, or chemical irritation. Activation of the natural immune system is the underlying pathophysiology. Skin barrier disruption may lead to cellular changes, an increase in proinflammatory mediators, and T lymphocyte activation. The concentration of the irritant substance, duration of exposure, and frequency of exposure may affect the irritant potential of the substance (9). In our cases, lesions appeared after the increase in the frequency of application.

The international society of peritoneal dialysis (ISPD) suggests the use of topical application of antibiotic cream like mupirocin or gentamicin to the catheter exit site (3). Nitrofurazone is a broad-spectrum antibiotic that is more commonly used for ulcer, burn, or skin infections. It has a relatively high risk of contact dermatitis (10). Topical nitrofurazone application was not recommended for routine PD exit-site care. We describe for the first time irritant contact dermatitis

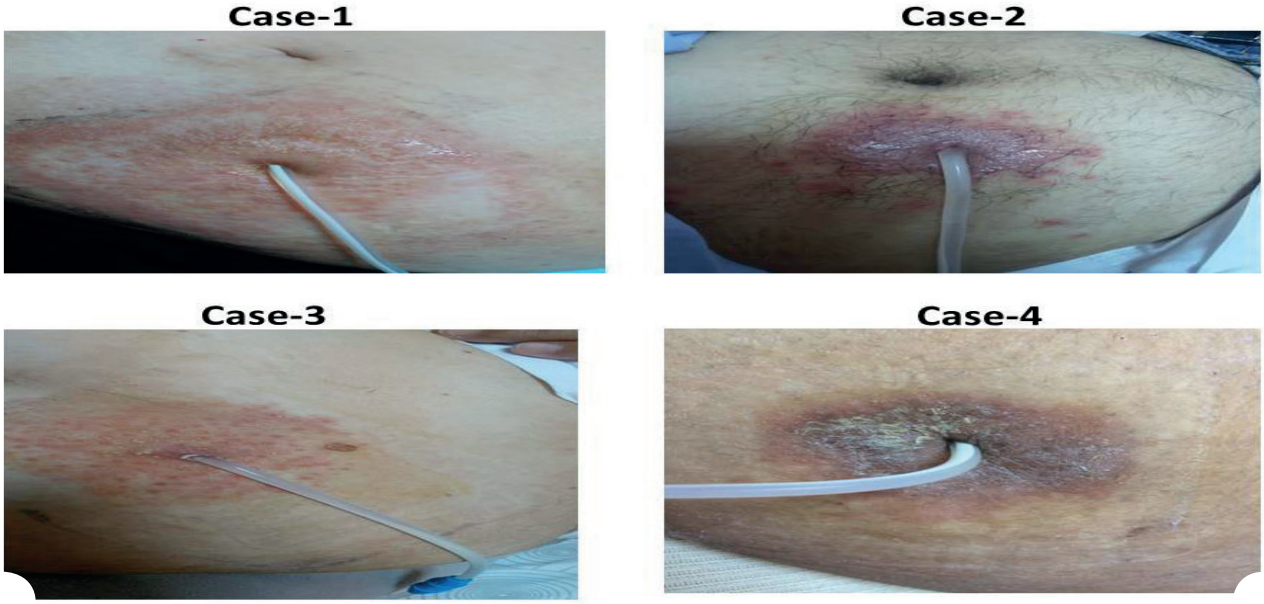

Figure 1. Peritoneal dialysis catheter exit-site at diagnosis

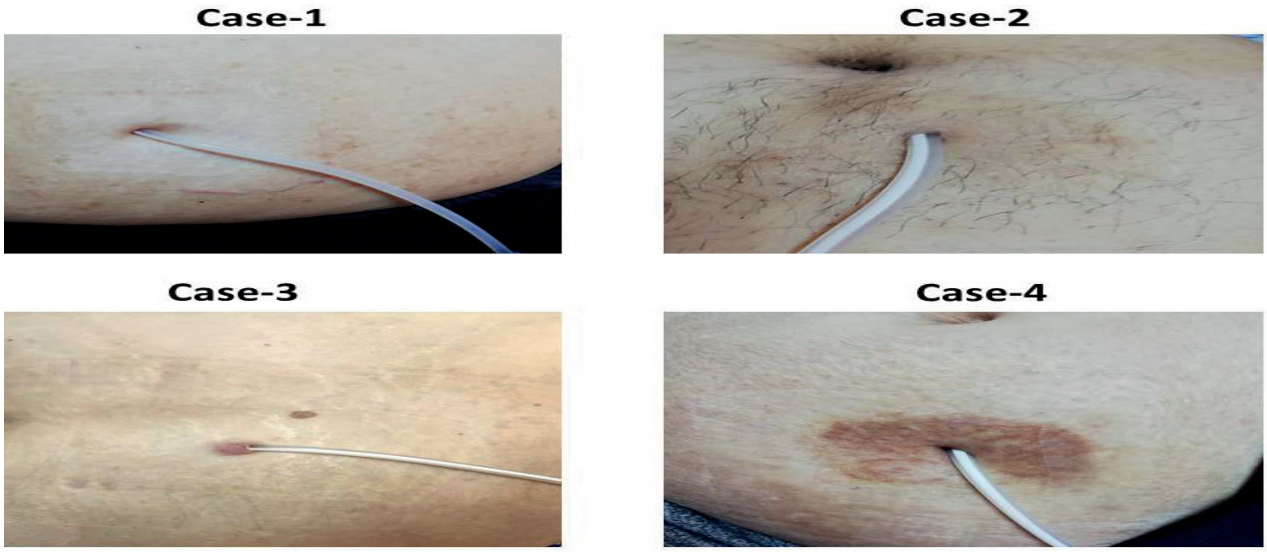

Figure 2. Peritoneal dialysis catheter exit site after one month

around the PD catheter exit site due to misuse of topical nitrofurazone.

Diagnosis of irritant contact dermatitis is usually clinical (9,11). Patients with acute irritant contact dermatitis may admit with erythema, edema, exudation, bulls, and erosions. Burning, pain, and itching may coexist. The lesion is limited to the contact area with sharp demarcation (9). Besides the characteristic appearance of the rash, negative Gram stain and culture of the PD exit site and favorable response to the withdrawal of the suspected agent may support irritant contact dermatitis (11). Lesion regresses by the discontinuation of contact, but may take weeks to months depending on the severity. Recurrent contact may lead to the development of chronic irritant dermatitis. A patch test may be carried out to exclude allergic contact dermatitis (9). Skin biopsy and immunofluorescence examination may be also used to confirm the diagnosis (6,8). Withdrawal of irritant factors is necessary for the treatment. The use of topical steroids in treatment is controversial (9). Irritant contact dermatitis was diagnosed by typical history and physical examination in our cases. The absence of purulent drainage with negative culture results was supporting findings, and lesions improved after the withdrawal of nitrofurazone.

In conclusion, a differential diagnosis of exit-site infection should include irritant contact dermatitis. Misdiagnosis of irritant contact dermatitis may cause deterioration of lesions due to continuous exposure to an irritant factor and may cause unnecessary use of antibiotics (1). Topical agents used for exit-site care in PD patients should be checked during routine visits, and nitrofurazone should be avoided due to its irritant potential.

DISCLOSURES

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Author Contributions: All authors contributed to the writing of this paper and approved the final version.

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