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Hypereosinophilic syndrome: Case series and review of the literature

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ABSTRACT

Hypereosinophilic Syndrome (HES) is caused by the uncontrolled proliferation of eosinophils generally associated with conditions such as allergic reactions or parasitic infections. This syndrome is characterized by excessive eosinophil production (>1500/mm^3) that persists for more than six months and cannot be explained by secondary causes. HES symptoms can affect different body organs, and usually, nonspecific symptoms include fever, malaise, fatigue, rash, shortness of breath, and myalgia.

HES is a rare disease with multiorgan involvement, including the skin, joints, kidneys, vascular system, gastrointestinal tract, cardiac and pulmonary systems. The main feature of this disease is that overproduced eosinophils accumulate in organs and cause organ damage. Cardiac involvement plays a critical role in determining morbidity and mortality, and cardiac and large vessel thrombosis with severe clinical manifestations can also be observed.

Treatment aims to reduce the absolute eosinophil count, improve symptoms, and prevent disease progression. Pharmacologic therapy aims to maintain targeted eosinophil levels below 1.5 x 10^9/L (1500 cells/µL) to reduce the symptoms of eosinophilic disease and prevent organ damage. Furthermore, indications for emergency treatment should be rapidly assessed and initiated promptly in appropriate patients.

This paper will discuss the diagnosis, clinical manifestations, treatment modalities, and management challenges of HES in detail through two rare case examples.

Keywords: Hypereosinophilia, eosinophil, hypereosinophilic syndrome

Eosinophils typically increase in conditions such as allergic reactions or parasitic infections, but in some cases, they can multiply uncontrollably and accumulate in tissues with damaging effects. Hypereosinophilic syndrome (HES) is a disease characterized by excessive eosinophil production (>1500/mm^3) that persists for more than six months and cannot be explained by secondary causes.[1,2] Symptoms may vary depending on which organs of the body it affects. It can often be challenging to identify the underlying causes of this disease. A multidisciplinary approach is required in the diagnosis and treatment process.

The main clinical manifestations include nonspecific findings such as fever, malaise, fatigue, rash, dyspnea, and myalgia.[2] HES is a rare disease with multiorgan involvement, including skin, joints, kidney, vascular, gastrointestinal, cardiac, and pulmonary systems. The main feature of the disease is that overproduced eosinophils accumulate in organs and cause organ damage. Cardiac involvement is the most crit-

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ical organ involvement, determining morbidity and mortality.[3,4] In addition, severe clinical pictures characterized by cardiac and large vessel thrombosis may also be observed.[5]

In this article, we will discuss the diagnosis, clinical manifestations, treatment methods, and complexity of HES with two accurate case reports. This article, discussed in the light of current literature, will guide healthcare professionals who recognize and treat this rare disease and raise awareness.

CASE PRESENTATION

Case 1

A 67-year-old male patient presented to our clinic with complaints of malaise and rash on the legs. The patient had a known diagnosis of hypertension and had not changed his medication recently; his complaints had been present for about one year, and no significant response was obtained in the treatments performed by dermatology and cardiovascular surgery. Further investigations were planned after an elevated eosinophil count (1940/mm^3 (24.7%)) was noted. It was observed that eosinophil levels had been at 1700/mm^3 for about eight months, and previous eosinophil levels were within the normal range. Parasitic examination and tests for brucellosis were negative. No significant laboratory results were found in the evaluation regarding vasculitis, and no monoclonal band increase was observed in electrophoresis. FIP1L1-PDGFRA gene fusion screening, lymphocyte phenotyping, and peripheral smear were performed. No pathologic findings other than eosinophilia were found in the peripheral smear, while gene fusion screening results and lymphocyte phenotyping were negative. Computed tomography (CT) of the lung showed no involvement, and echocardiography showed no evidence of cardiac involvement or thrombus. Magnetic resonance angiography revealed a thrombus in the lower extremity, and anticoagulant therapy was initiated. As a result of the evaluations, the patient was diagnosed with idiopathic HES, and corticosteroid treatment was started. The patient received 1 mg/kg methylprednisolone treatment, and as a result of improvement in laboratory and clinical findings, the patient was discharged and taken to an outpatient clinic follow-up.

Case 2

A 34-year-old male patient presented to our outpatient clinic with complaints of early fatigue, weakness, intermittent leg rash, and shortness of breath. He had no known comorbidities and did not describe any medication use. Electrocardiography and chest radiography revealed no significant pathology in the outpatient evaluation. Laboratory results showed normal thyroid, renal, and liver function tests and no anemia. The eosinophil count was 2445/mm^3 (28.6%), and the patient was admitted to our clinic for further evaluation. In the evaluation of the patient, it was observed that eosinophil levels had been high for the last year. Parasite examination and tests for brucellosis were negative. No additional pathology was detected in the peripheral smear. The bcr-abl and myeloproliferative tests ordered because of chronic eosinophilia were negative. FIP1L1-PDGFRA gene fusion screening and lymphocyte phenotyping were performed. No gene fusion clonal T lymphocyte was detected due to the screening. The d-dimer result of the patient who described shortness of breath was within normal range, and no pulmonary involvement was found on lung computed tomography. In the cardiologic evaluation of the patient, echocardiography revealed a moderate decrease in ejection fraction and suspicious thrombus appearance, and warfarin treatment was initiated. The patient was considered to have idiopathic HES, and 60 mg/day methylprednisolone treatment was initiated. After the treatment, the patient's complaints improved significantly, and eosinophil counts returned to normal. The patient, whose eosinophil count was normalized and clinical symptoms improved with treatment, was discharged with the recommendation of cardiology and internal medicine outpatient clinic follow-up.

DISCUSSION

The percentage of eosinophils in peripheral blood is 3-5%, and the absolute count is between 350-500/µL (1). Eosinophilia, which refers to an increase in eosinophils in peripheral blood, is classified as mild (upper limit 1500/µL), moderate (1500-5000/µL), and severe (>5000/µL).[6,7] Hypereosinophilia is generally used for values above 1500/µL.[8]

Hypereosinophilic syndrome is a multisystemic disease and may present with simple clinical symptoms or severe clinical outcomes. It occurs as a result of eosinophil infiltration in the affected organ. Although it is mainly observed in the age group of 20-50 years, it can occur at any age.[9] Male predominance is remarkable, as in our cases.10 Although the actual prevalence of the disease is not known precisely, it

Table 1. Hypereosinophilic syndrome diagnostic criteria

1. Eosinophil count of 1,500/μL or higher for at least 6 months (this does not apply in the presence of symptoms requiring eosinophil-lowering therapy)
2. Exclusion of secondary and clonal eosinophilia
3. Presence of evidence of organ involvement
4. Absence of phenotypically abnormal and/or clonal T lymphocytes

was found to be between 0.36 and 6.3 per 100,000 in a data-based study.[11]

Secondary causes include parasitic infections, allergic diseases, drug side effects, T-cell lymphomas, and various carcinomas that should be excluded for diagnosing HES. Recently, eosinophilic syndromes that cannot be categorized as secondary have been divided into clonal and idiopathic categories. HES is primarily evaluated in the idiopathic eosinophilia category. In the absence of organ damage, the definition of idiopathic eosinophilia should be preferred instead of HES.[8] The World Health Organization (WHO) has classified clonal eosinophilia into two subcategories.12 Current diagnostic criteria for HES are given in Table 1.[13]

1. Myeloid/lymphoid neoplasms with eosinophilia and mutations (PDGFR α/β or FGFR1).

2. Chronic eosinophilic leukemia, not otherwise specified

Generally, symptoms have a slow onset and may not always be specific. While malaise, fatigue, chronic cough, rash, and myalgias may be observed, they may also present with a clinical picture with a high risk of mortality with severe thrombosis and cardiac and neurologic involvement.[14] In both of our cases, complaints of weakness and fatigue were at the forefront, and our second patient described dyspnea. Table 2 shows the HES variants and their characteristics.[15] The occurrence rate of HES-related complications such as dermatologic (rash), pulmonary (cough and dyspnea), gastrointestinal, cardiac, neurologic, and others are 37%, 25%, 14%, 5%, and 4%, respectively.[16]

Cardiac involvement

Cardiac involvement usually occurs in three stages. The early necrotic stage is usually asymptomatic and may involve the endocardium and myocardium. Rarely, it may cause acute heart failure. It is followed by a stage in which thrombi develop in the damaged endocardium and may cause peripheral embolism. The final stage is the fibrotic stage, which results in restrictive cardiomyopathy. Advanced heart failure and valvular pathologies may accompany.[17,18]

Echocardiography may appear normal in the acute necrotic stage. There may be a chance of diagnosis in the early stage with magnetic resonance. Endomyocardial biopsy is helpful in definitive diagnosis in the ear-

Table 2. The HES variants and their characteristics

HES variant	Defined abnormalities	Clinical and laboratory features
Myeloid variant	PDGFRB and FGFR1 rearrangements JAK2 point mutation and translocation	↑ Serum B12 Anemia and/or thrombocytopenia Hepatomegaly and/or splenomegaly Circulating leukocyte precursors
T-cell lymphocytic HES	Abnormal IL-5 producing T cells	Prominent skin manifestations (including plaques, erythroderma, urticaria) Polyclonal hypergammaglobulinemia
Familial HES	5q 31-33 mutation	Congenital asymptomatic eosinophilia, autosomal dominant
Idiopathic HES		Multi-system involvement
Specific/defined syndromes associated with Hypereosinophilia	Examples include episodic angioedema with eosinophilia, eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss), other disorders associated with immune dysregulation.	Marked eosinophilia in the setting of an underlying disorder associated with eosinophilia; the exact role of eosinophils in disease manifestations remains unclear

HES: Hypereosinophilic syndrome

ly stage.19 The second stage of heart disease involves thrombus formation along areas of damaged endocardium. The tissue factor, believed to be very important in thrombus formation, is directly expressed by eosinophils. The main complication of intracardiac thrombus formation is that it leads to embolic strokes, ischemia of the extremities, and other embolic events.[20] In the fibrotic stage, echocardiography may show mitral or tricuspid regurgitation, cardiomegaly, restrictive cardiomyopathy, or T-wave inversions. Echocardiography may show intracardiac thrombus.

Neurologic involvement

Neurological involvement may include peripheral polyneuropathy and encephalopathy with central infiltration, depending on the location of eosinophil infiltration. Cerebral thromboembolism may result from intracardiac thrombi and may present as embolic strokes or transient ischemic episodes. Magnetic resonance imaging may reveal multiple infarcts. Encephalopathy may manifest as behavioral changes, confusion, ataxia, and memory loss. Affected patients may also have upper motor neuron damage signs, such as increased muscle tone, deep tendon reflexes, and positive Babinski response.[21]

Cutaneous involvement

Cutaneous manifestations are usually nonspecific, resemble urticarial and dermatitis-like lesions, and are frequently seen in patients with HES. Common cutaneous manifestations of HES include eczema (involving the hands, flexural areas, or scattered plaques), erythroderma, generalized thickening of the skin (lichenification), dermographism, recurrent urticaria and angioedema.[22]

Biopsies of papular or nodular lesions show perivascular infiltration with eosinophils and mild to moderate perivascular neutrophilic and mononuclear infiltrates without vasculitis. Less commonly, mucosal ulcers, which are often difficult to treat, develop in the mouth, nose, pharynx, esophagus and stomach, or penis or anus.[9]

Lung involvement

Pulmonary involvement may range from normal lung imaging to restrictive pulmonary disease. While some patients may complain of a chronic dry cough, they may also present with restrictive disease due to diffuse infiltrations.[23] Pulmonary involvement is common in HES and may result from eosinophilic infiltration of the lung followed by fibrosis, heart failure, or pulmonary embolism. In a Mayo Clinic study, respiratory symptoms were reported in 63 percent of patients. The most common presenting symptoms were shortness of breath (45%), cough (39%) and wheezing (24%). Abnormal chest radiography or computed tomography (CT) findings were seen in 43 percent of patients and included parenchymal infiltrates (37%), pleural effusion (14%), intrathoracic lymphadenopathy (12%) and pulmonary embolism (4%).24

Gastrointestinal involvement

Gastrointestinal involvement may manifest as abdominal pain, nausea, and diarrhea. Eosinophilic gastritis, enterocolitis, or colitis may be seen due to eosinophil infiltration. Hepatitis and focal hepatic lesions may be observed as hepatic involvement.9

Treatment

The main aim of treatment is to reduce the absolute eosinophil count, improve signs and symptoms, and prevent disease progression.[25]

The timing of treatment in patients depends on the severity of Hypereosinophilia (HE) and the presence of signs and symptoms.[26]

If patients have symptoms of hyperleukocytosis due to extremely high levels of eosinophils, even if rarely present, hypercellularity should be rapidly reduced. Most patients are asymptomatic and have less severe eosinophil levels. Pharmacologic therapy aims to reduce the signs and symptoms of eosinophilic disease and maintain levels below 1.5 x 10^9/L (1500 cells/µL) to help prevent the development of end-organ damage.

The choice of therapeutic agent in patients to be treated depends on the presence or absence of FIP1L1-PDGFRA fusion. The myeloid variant with a fusion defect (i.e., PDGFRA-positive HES) is initially treated with imatinib mesylate, while patients with other HES types are initially treated with glucocorticoids.

Indications for emergency treatment: There are conditions indicating emergency treatment in HES patients.[9,27,28]

1) Extremely high eosinophil levels (i.e., absolute eosinophil count [AEC] >100 x 10^9/L; >100,000 cells/µL).

2) Signs and symptoms of leukostasis (i.e., pulmonary or neurologic dysfunction with a white blood cell count >50 x 10^9/L [>50,000 cells/µL]).

3) Signs and symptoms or other evidence of potentially life-threatening complications of HES (i.e.,

acute heart failure, thromboembolic events).

4) In patients with lung involvement, urgent treatment is required in patients showing eosinophil-associated disease (i.e., extensive interstitial infiltrates, ground-glass opacities, condensation) consistent with clinical symptoms.

Corticosteroids are the treatment of choice for HES. In patients for whom emergency treatment is indicated, the most preferred agent is corticosteroids. Imatinib, rituximab, cyclophosphamide, and hydroxyurea are the other main agents tried in treatment. Although various immunosuppressive agents have been tested over time, corticosteroids have maintained their position in treatment.[29] In terms of holistic therapy, it is essential to perform additional treatments for the system involved in the disease and to treat complications.

CONCLUSION

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: NY, AEÖ, NK; Study Design: NY, AEÖ, NK; Supervision; NY, AEÖ, NK; Funding: NY, AEÖ, NK; Materials: NY, AEÖ, NK; Data Collection and/or Processing: NY, AEÖ, NK; Analysis and/or Data Interpretation: NY, AEÖ, NK; Literature Review: NY, AEÖ, NK; Critical Review: NY, AEÖ, NK; Manuscript preparing: NY, AEÖ, NK.

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The association between serum perilipin-2 and kidney disease progression of patients with autosomal dominant polycystic kidney disease

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ABSTRACT

Objectives: We aimed to evaluate the relationship between serum perilipin-2 / adipophilin (PLIN-2 / ADRP) levels and clinical course in patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD).

Methods: 80 ADPKD patients with Chronic Kidney Disease (CKD) G1-G4 status, among the patients who were regularly followed up in the nephrology outpatient clinic between 2012 and 2019, were included in the study. CKD-G5 patients were excluded from the study. Baseline PLIN-2/ADRP levels were measured. Patients were divided into 2 groups according to the median serum PLIN-2/ADRP level. During the follow-up period, data such as blood pressure, height-adjusted total kidney volume (HtTKV), proteinuria, complete blood count, and biochemical tests were recorded.

Results: In the patients with serum PLIN-2 / ADRP level above the median value (11.675 ng / mL), BMI was significantly higher than the other group ($p<0.001$). The female sex ratio was found to be significantly increased in patients with serum PLIN-2 /ADRP levels above the median value. Serum PLIN-2/ADRP levels were found to increase as eGFR decreased in ADPKD patients, but it was not statistically significant. In patients with high baseline mean PLIN-2/ADRP levels, the mean eGFR decline was found to be 20 ml/min/1.73 m^2. However, the mean eGFR decrease in the other group with a low baseline PLIN-2/ADRP value was found to be 16 ml/min/1.73 m^2 after 7 years of follow-up.

Conclusion: PLIN-2 / ADRP levels increased in female ADPKD patients and it is positively associated with BMI increase. Increased serum PLIN-2 / ADRP levels may be a harbinger of faster kidney function decline.

Keywords: Perilipin-2, Autosomal Dominant Polycystic Kidney Disease, female sex, body mass index

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Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common hereditary disease of the kidney that progresses to kidney failure (KF). Genetic causes of ADPKD in the mutations in the PKD1 gene on chromosome 16 and the PKD2 gene on chromosome 4 in the PKD2 genes are formed.[1] The most important complications in ADPKD patients are KF and cardiovascular diseases .[2] ADPKD can be considered as a multisystemic disease in terms of concomitant cystic (such as hepatic, pancreatic) and non-cystic (such as intracranial aneurysm and heart valve disorders) involvement in other organs rather than a kidney disease alone.[3]

Treatment options to slow the progression of the disease in ADPKD are limited. Especially in recent years, positive results have been obtained in preventing the decrease in the estimated glomerular filtration rate (eGFR) with the use of V2 receptor antagonists. However, significant inflammatory and fibrotic changes occur in the renal tubular epithelium before eGFR decline. There are ongoing numerous studies on the role of cell proliferation, apoptosis, fluid secretion, and extracellular matrix in the course of this progressive disease.[4] Recently, studies on ADPKD have been increasing on biomarkers, cytokines, receptors, and molecules that can predict disease progression.[5]

Perilipines (PLINs) are part of the protein group that reacts with the intracellular neutral lipid droplets. PLINs are located on the surface of oil droplets. They highly phosphorylate adipocyte proteins. PLIN is phosphorylated after cyclic adenosine monophosphate (cAMP) activates protein kinase A (PKA). PLIN moves away from the surface of the lipid droplet. It allows hormone-sensitive lipase (HSL) to hydrolyze the triglyceride (triacylglycerol [TAG]) nucleus. The most well-defined and most important droplet proteins are PLINs. There are 5 types currently known: PLIN-1-5.[6]

PLIN-2 / adipophilin (also known as adipocyte differentiation-related protein [ADRP]) is commonly expressed in adipogenic cells in tissues such as the lung, steatotic liver, adrenal cortex, and testis. PLIN-2 / ADRP is associated with droplets and is destroyed in the absence of neutral lipids. Its expression is connected to the number of neutral lipids in the cell and overexpression of PLIN-2 / ADRP occurs in increased droplet formation.[7,8] Diseases associated with lipid droplet (LD) accumulation are on the rise. For this reason, researchers concentrated on studies on PLINs. PLIN-2 / ADRP has been studied as a biomarker in some types of diseases including atherosclerosis and kidney cancer.[9-12]

In recent years, there has been growing interest in the potential role of PLIN-2 / ADRP in kidney disease. This biomarker has been shown to be linked to kidney cancer and atherosclerosis. Studies have shown that PLIN-2/ADRP expression is increased in various renal conditions, such as acute kidney injury (AKI), chronic kidney disease (CKD), and diabetic nephropathy. This increase in PLIN-2 / ADRP expression is thought to be due to several factors, including oxidative stress, inflammation, and metabolic dysregulation. Therefore PLIN-2 / ADRP expression can increase the production of reactive oxygen species (ROS) that can damage kidney cells. The expression of PLIN-2 / ADRP can also block the activity of PPARα, a transcription factor that helps to protect kidney cells from damage. In addition, PLIN-2 / ADRP expression can increase protein secretion from kidney cells, which can lead to proteinuria. Taken together, these findings suggest that PLIN-2 / ADRP is a potential target for the development of new treatments for kidney disease.[13] In addition to being accompanied by vascular dysfunction and renal cystic proliferation, metabolic abnormalities are also evident in patients with ADPKD.[14] Currently, an inexpensive, widely applicable biomarker that can predict the progression to KF in patients with ADPKD has not been fully found. Therefore, we aimed to investigate the relationship between PLIN-2 / ADRP, and ADPKD, in terms of metabolic changes, kidney volume, and kidney disease progression.

METHODS

Patients and study design

We classified ADPKD patients who were consistently monitored at the nephrology outpatient clinic from 2012 to 2019 according to their CKD status, using the estimated glomerular filtration rate (eGFR). 80 ADPKD patients with CKD G1-G4 status were included. CKD G5 patients were excluded from the study. 15 PLIN-2 / ADRP levels were measured from blood stored in a -80 ° C cabinet obtained from the patients at baseline (sera of the patients in 2012). Patients were divided into 2 groups according to the median serum PLIN-2/ADRP level. All patients' data including blood pressure, height, weight measurements, height-adjusted total kidney volume (HtTKV), 24-h urine proteinuria, complete blood count, eGFR, CRP, lipid profile, albumin, uric acid, calcium, phosphorus, proteinuria were recorded during a routine control of

the patients. After all data were obtained, ADPKD patient groups were examined as CKD G1-G4 according to the status of CKD. Rapid progression of ADPKD was defined as an eGFR decrease of ≥ 5 ml/min/1.73m2 yr at 1 year or ≥2.5 ml/min/1.73m2 per yr over 5 yr or Mayo image class 1C, 1D, or 1E .16 An informed consent form was obtained from all patients included in the study. The Ethics Committee of XXXX University Clinical Research granted approval for this study by decision dated November 07, 2018, and number 2018/561.

Statistical analysis

Data normality and variance homogeneity were evaluated using histograms and q-q plot graphs and Shapiro-Wilk's test. Levene's test was used to test variance homogeneity. For continuous variables in between groups, the two-way t-test and Mann-Whitney U test were used. For categorical variables, Pearson's chi-squared test and Fisher's exact test were used. To compare the means between variables with more than two groups, we used one-way ANOVA and Kruskal-Wallis test for continuous variables, and Pearson's chi-squared test, and Fisher's exact test for categorical variables. Pairwise comparisons between groups were performed using Tukey's test, Tamhane's T2 test, Siegel-Castellan test, and Bonferroni-corrected z test. To compare the means between dependent groups, a t-test was used for dependent samples. Receiver operating characteristic (ROC) analysis was used to determine the cut-off point for the PLIN-2 / ADRP variable to assess its relationship with disease progression. The Youden index was used to find the cut-off point. The analyses were performed using R 3.2.0 (www.r-project.org) and TURCOSA Analytical statistical software programs. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Forty-three patients (54%) were female and 37 (46%) were male. Patients were examined in 4 groups according to CKD G1-G4 status. The mean age of the patients was 39.45 ± 10.57, 54.43 ± 7.29, 62.43 ± 12.26, 58.00 ± 4.16, respectively from CKD G1 to G4. Between groups, the presence of hypertension correlated with the severity of kidney failure. The median systolic blood pressure (mmHg) of the patients was 123.43±16.36, 133.81±18.50, 134.29±16.50, 147.14±14.96, respectively from CKD G1 to G4 (p=0.003). Body mass index was significantly increased in CKD G4 patients compared to CKD G1 patients (p=0.006) (Table 1).

Serum uric acid levels were similar in CKD G2 and G3 patients, but there was a statistically significant increase in CKD G4 patients when compared with other groups (p<0.001). When serum PLIN-2 / ADRP levels were compared, no significant difference was found between the groups (p=0.439). However, the mean serum PLIN-2 / ADRP levels were increased in line with the CKD stage progression. When the groups were compared in terms of height-adjusted Total Kidney Volume (HtTKV), there was a significant increase in kidney volume in patients with CKD G4 compared to the other stages (p =0.006). HDL levels were found

Table 1. Demographic and clinical comparison of ADPKD patients with basal values according to stage

Variables	Groups CKD G1 (>90 ml/dk; n=38)	CKD G2 (60-89 ml/dk; n=21)	CKD G3 (30-59 ml/dk; n=14)	CKD G4 (15-29 ml/dk; n=7)	*p*
Age (year)	39.45± 10.57[a]	54.43±7.29[b]	62.43±12.26[b]	58.00±4.16 [b]	**<0.001**
Gender %(Male)	12(31.6)[a]	14(66.7)[b]	8(57.1)[ab]	3(42)[ab]	0.057
Hypertension% (Yes)	19(50)[a]	21(100)[b]	12(85.7)[b]	7(100)[b]	**<0.001**
Status (ex)	0(0)	0(0)	2(14.3)[a]	1(14.3) [a]	0.033
SBP (mmHg)	123.43±16.36[a]	133.81±18.50[ab]	134.29±16.50[ab]	147.14±14.96[b]	**0.003**
DBP (mmHg)	78.95±12.36[a]	84.76±10.66[ab]	80.36±7.95[ab]	92.86± 9.51[b]	0.014
Body Mass Index (kg/m²)	24.26±4.50[a]	26.33±4.19[ab]	27.21±2.88[ab]	29.71±4.27[b]	0.006

Data: n (%), mean ± SD and median (25-75persentyl).
Different superscripts in the same row indicate a statistically significant difference between the groups. SBP: Systolic blood pressure. DBP: diastolic blood pressure
CKD G1–G4: Chronic Kidney Disease GFR category[15]

Table 2. Biochemical comparison of ADPKD patients with basal values according to stage

Variables	Groups				*P*
	CKD G1 (>90 ml/dk; n=38)	CKD G2 (60-89 ml/dk; n=21)	CKD G3 (30-59 ml/dk; n=14)	CKD G4 (15-29 ml/dk; n=7)	
Hemoglobin (g/dl)	13.59±1.74[a]	14.34±1.6[a]	13.71±1.97[a]	13.04±2.31[a]	0.312
PLIN-2/ADRP (ng / mL)	11.83 (10.18-12.73)[a]	11.12 (9.60-12.11)[a]	12.12 (9.92-12.95)[a]	12.84 (7.30-13.56)[a]	0.439
CRP (mg/L)	3.40 (3.25-3.45) [a]	3.40 (3.28-6.76) [a]	3.61 (3.19-7.05) [a]	3.40 (3.17-7.20) [a]	0.461
eGFR* (ml/min/1.73m^2)	114.50 (106.50-121.0)[a]	72.0 (65.90-80.0)[cd]	36.40 (31.60-54.72)[bd]	26.10 (21.50-27.0)[b]	**<0.001**
Total cholesterol (mg/dl)	189.61±351[a]	195.86±34.65[a]	190.71±47.8[a]	183.71±15.41[a]	0.871
Triglycerides (mg/dl)	100.5 (77.0-129.75)[a]	171.0 (104.5-258.5)[b]	179.5 (108.5-260.75)[b]	105.0 (84.0-126.0)[ab]	**0.001**
LDL (mg/dl)	113.76± 32.52[a]	121.62±29.05[a]	123.29±38.27[a]	114.00±20.78[a]	0.704
HDL (mg/dl)	49.26±11.11[a]	41.48±8.49[bc]	37.71±12.88[b]	44.00±7.23[abc]	**0.003**
Albumin (g/dl)	4.20 (3.90-4.50) [a]	4.20 (3.95-4.35) [a]	3.80 (3.45-4.22)[a]	4.0 (3.20-4.20)[a]	0.066
Uric acid (mg/dl)	4.32± 1.10[a]	6.21±1.48[b]	7.40±1.69[bc]	8.11±1.20[c]	**<0.001**
Calcium (mg/dl)	9.32±0.43[a]	9.34±0.41[a]	9.10±0.65[a]	9.27±0.41[a]	0.450
Phosphorus (mg/dl)	3.27±0.57[a]	3.09±0.46[a]	3.22±0.45[a]	3.40±0.56[a]	0.491
Proteinuria (g/24h)	0.10 (0.08-0.14) [a]	0.10 (0.09-0.17) [a]	0.31 (0.16-0.65) [b]	0.20 (0.10-0.90) [ab]	**<0.001**
HtTKV (ml/m)	502.50 (271.0-848.0)[a]	870.50 (352.50-1246.50)[b]	1124.0 (666.25-1303.5)[b]	1782 (995.5-3230.0)[b]	**0.006**

* Calculated by CKD-EPI method.

Different superscripts in the same row indicate a statistically significant difference between the groups. eGFR: Glomerular filtration rate
CRP: C reactive protein,
DBP: Diastolic blood pressure, SBP: Systolic blood pressure, LDL: Low-density lipoprotein,
HDL: High-density lipoprotein, HtTKV: height-adjusted Total Kidney Volume
PLIN-2/ADRP: Perilipin-2/Adipose Differentiation-Related Protein
CKD G1–G4: Chronic Kidney Disease GFR category[15]

to be higher in G1 CKD patients than in G4 CKD patients. This difference was statistically significant (p=0.003).

Proteinuria level was found to be higher in G4 CKD patients than in G1 CKD patients, consistent with CKD stages (p<0.001) (Table 2).

The median serum PLIN-2 /ADRP level measured in patients with ADPKD was 11.675 ng/mL. The female patients were found to be significantly increased in patients with serum PLIN-2 /ADRP levels above the median value (p<0.001). Similarly, body mass index was significantly higher in patients with serum PLIN-2 / ADRP levels above the median value (p <0.001) The hemoglobin median value was found to be significantly decreased in patients with serum PLIN-2/ ADRP levels above the median value (p<0.001). By following the GFR values of the patients between 2012 and 2019, the percentage change in the average annual glomerular filtration rate (ΔGFR%) was calculated. ΔGFR was observed to be increasing in patients with serum PLIN-2/ADRP levels above the median value. However, it is not statistically significant (p=0.343) (Table 3).

A cut-off value for serum PLIN-2 / ADRP was found 11.97 in ROC analysis (Table 4). When the effect of serum PLIN-2 / ADRP level on rapid progression was examined in the ROC curve analysis, the area under the ROC curve was found to be 0.53 (0.40-0.67). There was no statistically significant difference (p=0.237) (Figure 1).

Table 3. Demographic, clinical, and biochemical comparison of ADPKD patients with baseline values according to median serum PLIN-2 / ADRP level

Variables	PLIN-2/ADRP (ng / mL) ≤11.675 (n=40)	>11.675 (n=40)	*p*
Age (year)	48.48±14.37	49.58± 12.76	0.718
Gender %(Male)	31(77)	6(15)	**<0.001**
Hypertension% (Yes)	31(77.5)	28(70)	0.446
Status (ex)	2(5)	1(2.5)	0.556
SBP (mmHg)	130.13±19.59	130.13±16.73	0.999
DBP (mmHg)	80.38±11.11	83.50±12.04	0.232
Body Mass Index (kg/m²)	24.08±3.57	27.53±4.56	**<0.001**
Hemoglobin (g/dl)	14.54±1.63	12.985±1.65	**<0.001**
CRP (mg/L)	3.40(3.21-3.45)	3.40(3.28-4.60)	0.598
eGFR* (ml/dk)	87.55± 31.66	80.90± 37.08	0.513
Total cholesterol (mg/dl)	185.30±36.85	196.65±34.44	0.162
Triglycerides (mg/dl)	113(84-174)	124(95-193)	0.624
LDL (mg/dl)	113.38±32.81	121.15±30.39	0.307
HDL (mg/dl)	41.83±11.40	47.65±10.85	0.022
Albumin (g/dl)	4.17(3.82-4.30)	4.15(3.8-4.40)	0.739
Uric acid (mg/dl)	5.86± 1.94	5.52±1.91	0.427
Calcium (mg/dl)	9.33±0.47	9.25±0.47	0.452
Phosphorus (mg/dl)	3.18±0.526	3.26±0.52	0.583
Proteinuria (g/gün)	0.13(0.10-0.28)	0.10(0.09-0.19)	0.301
HtTKV (ml/m)	848(436-1236)	739(239-1122)	0.255
ΔGFR %	22.05(11.13-42.63)	24.90(15.03-42.07)	0.343

* Calculated by CKD-EPI method.
Data: n (%), mean ± SD and median (25-75persentyl).
SBP: Systolic blood pressure DBP: Diastolic blood pressure
eGFR: Glomerular filtration rate, CRP: C reactive protein, LDL: Low-density lipoprotein,
HDL: High-density lipoprotein HtTKV: height-adjusted Total Kidney Volume
PLIN-2/ADRP: Perilipin-2/Adipose Differentiation-Related Protein
ΔGFR: Percent change in average annual glomerular filtration rate

The relationship between annual eGFR values and serum PLIN-2 / ADRP level between 2012-2019 of the patients was analyzed. Mean eGFR values were higher in patients with serum PLIN-2 / ADRP levels below the mean value in both 2012 and 2019. In this group, the eGFR was 87.55 ± 31.66 ml/min/1.73 m2 in 2012. The mean eGFR value of the patients with serum PLIN-2 / ADRP levels above the mean value was 80.90 ± 37.08 ml/min/1.73 m2 in 2012. In ADPKD patients with high baseline mean PLIN-2/ADRP levels, the mean eGFR loss at the end of 2019 was found to be approximately 20 ml/min/1.73 m2. However, the mean eGFR loss in the other group was found to be approximately 16 ml/min/1.73 m2 at the end of 2019 (Figure 2 and Figure 3).

Table 4. ROC analysis results for rapid progression of serum PLIN-2 /ADRP levels in ADPKD

Variable	CUT-OFF	Diagnostic Measurements SEN (95% CI)	SPE (95% CI)	PPV (95% CI)	NPV (95%CI)
PLIN-2/ADRP	11.97	0.55 (0.40-0.69)	0.61 (0.42-0.78)	0.69 (0.50-0.80)	0.46 (0.32-0.66)

CI: Confidence interval, SEN: Sensitivity, SPE: Specificity, PPV: Positive Predictive Value,
NPD: Negative Predictive Value Değer PLIN-2/ADRP: Perilipin-2/Adipose Differentiation-Related Protein

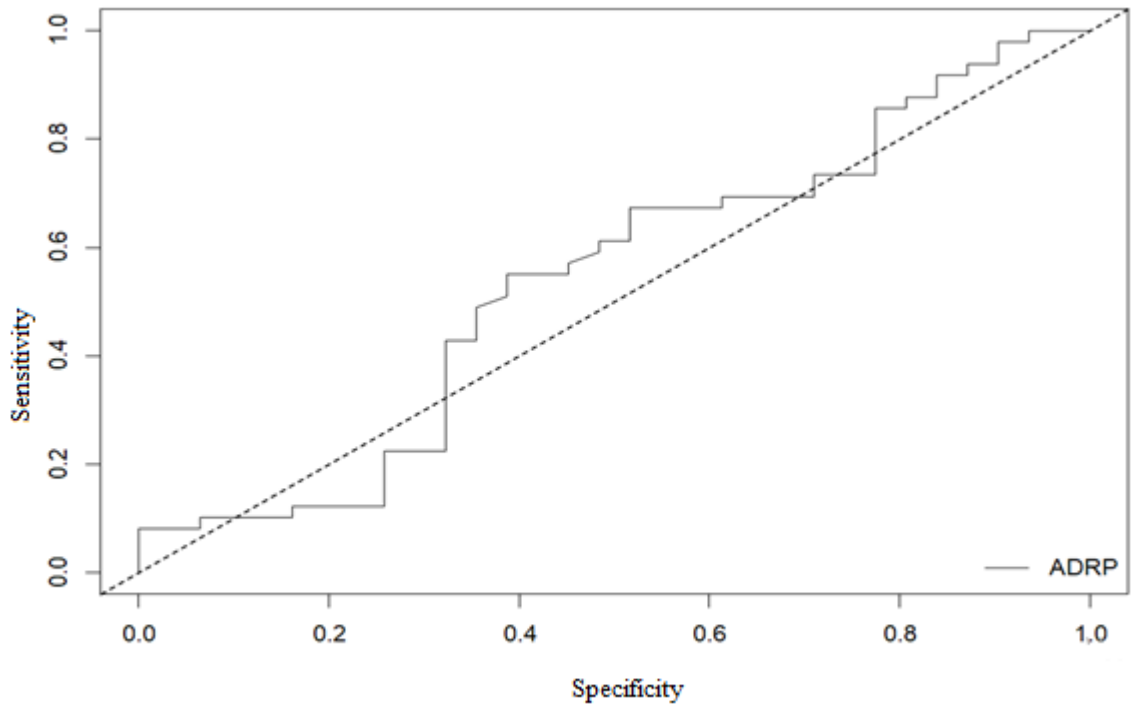

Figure 1. ROC analysis curve of the sensitivity and specificity of the effect of serum PLIN-2 / ADRP level on rapid progression in ADPKD

DISCUSSION

ADPKD stands as the most prevalent hereditary renal disorder, affecting millions of individuals worldwide. Extensive research has uncovered numerous crucial molecular and cellular mechanisms that contribute to the development of ADPKD. However, despite these advancements, many aspects of the disease still remain elusive. Unraveling the complex molecular and cellular mechanisms underlying this debilitating disease, as well as finding biomarkers that can predict disease progression, will pave the way for the

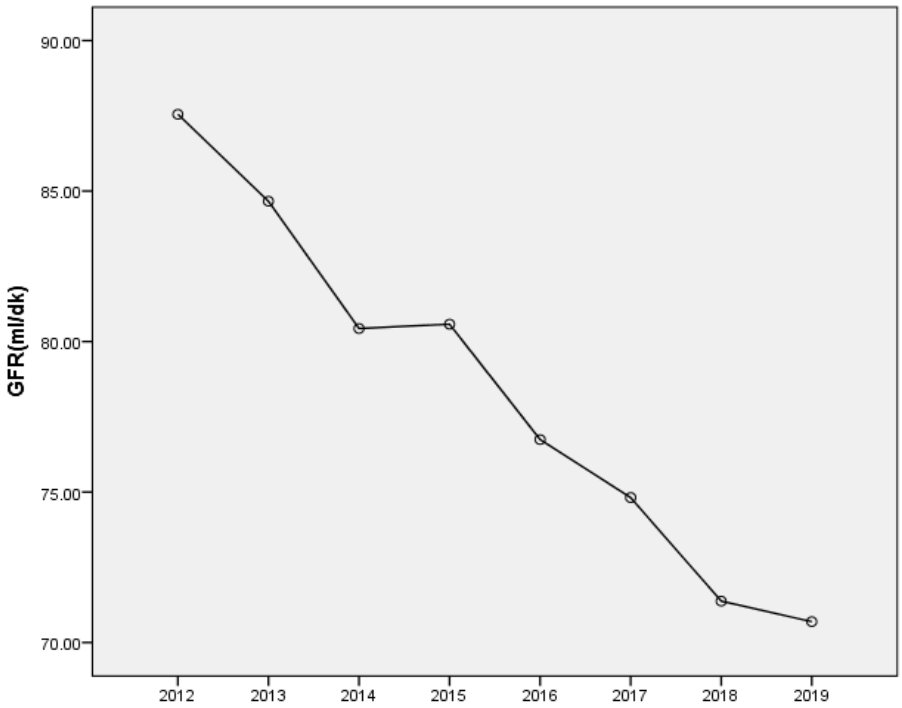

Figure 2. Mean eGFR course between 2012-2019 in patients with serum PLIN-2 / ADRP levels below the mean value

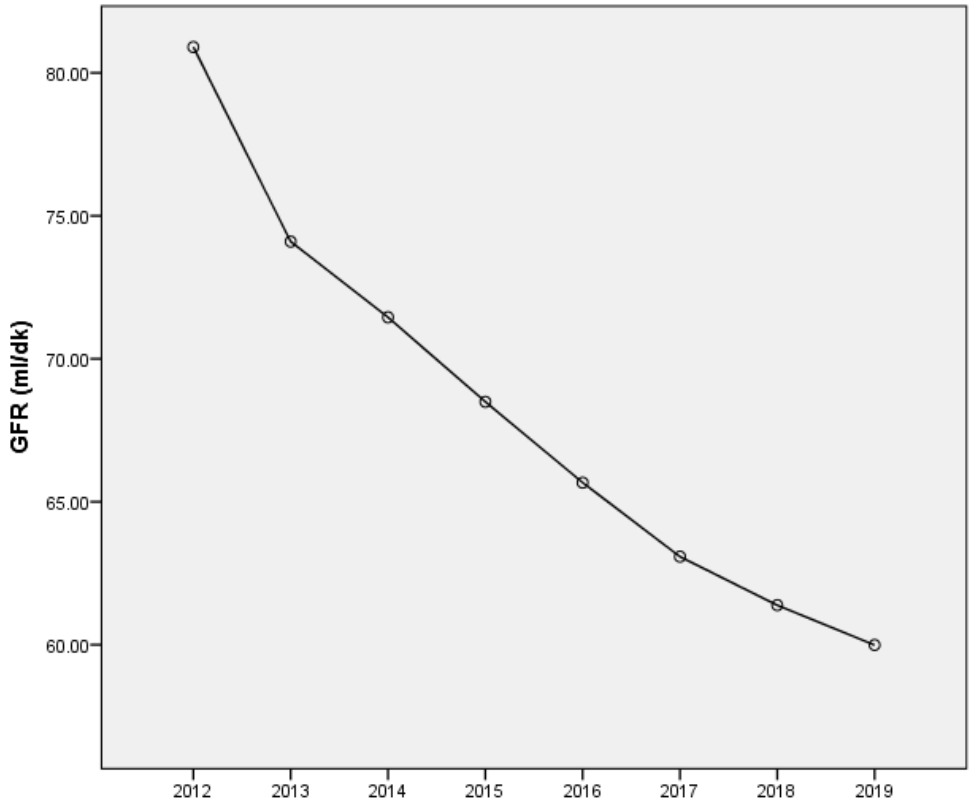

Figure 3. Mean eGFR course between 2012-2019 in patients with serum PLIN-2 / ADRP levels above the mean value

development of new targeted therapies that will alleviate the burden of ADPKD and improve the quality of life of affected individuals. The clinical course of ADPKD is variable, but the disease typically progresses slowly over time. The factors that influence prognosis in ADPKD include the age of onset, the severity of the disease, and the presence of other medical conditions.

Our study presents three significant discoveries. Firstly, high levels of PLIN-2 / ADRP are associated with increased BMI which may affect the clinical course of ADPKD. Secondly, PLIN-2 / ADRP is increased in female patients with ADPKD compared to male counterparts. Lastly, patients with high levels of PLIN-2 / ADRP are prone to faster kidney disease progression compared the patients with low levels of PLIN-2 / ADRP however the difference was not found to be statistically significant.

Perilipines (PLINs) have emerged as part of the group of proteins that react with the intracellular neutral lipid droplets. PLINs localized on the surface of the oil droplets have been found to highly phosphorylate adipocyte proteins, regulating lipolysis via cAMP and PKAF.[6] Based on metabolic disorders in uremic patients, by Axelsson *et al*., examined human adipocyte cells that were kept in uremic serum. In the study, it was found that the rate of spontaneous lipolysis was 30% higher in cells kept in uremic serum. In a study evaluating uremic serum and human adipocyte cells, the relationship between PLIN and uremia was investigated. It has been proposed that the increase in lipolysis in CKD may be associated with a decrease in PLIN synthesis.[17]

Unfortunately, there is currently no study in the literature that reveals the correlation between serum PLIN-2/ADRP levels and eGFR. However, in our study, eGFR values were significantly decreased in patients above the median value of PLIN-2/ADRP. While the mean eGFR value was 80.90±37.08 ml/min in this group, the mean eGFR was 87.55 ± 31.66 ml/min in patients with below the PLIN-2 / ADRP median value. In addition, the annual average percentage of eGFR change (ΔGFR) was evaluated. It was found that the change was higher in patients with serum PLIN-2 / ADRP levels above the median value. The BMI value was statistically significantly increased in patients with serum PLIN-2 / ADRP levels above the median value ($p<0.001$). A preclinical study conducted on mice has revealed a significant connection between PLIN-2/ADRP and obesity. This study demonstrates that hepatocyte-specific actions of PLIN-2/ADRP are central to the initiation and pathological progression of non-alcoholic fatty liver disease (NAFLD) through its effects on immune cell recruitment and fibrogenesis in obese and insulin-resistant mice. Conversely,

extra hepatocyte PLIN-2/ADRP actions support NAFLD pathophysiology through effects on obesity, insulin resistance, and inflammation.[18] A recent clinical study found that PLIN-2/ADRP levels do not change with age, but women have higher PLIN-2/ADRP levels than men. In addition, a strong relationship was found between PLIN-2/ADRP levels and BMI.[19] In our study, patients with high PLIN-2/ADRP levels mostly consisted of obese patients. A significant correlation was found between high PLIN-2/ADRP levels and BMI in our study, consistent with the literature ($p<0.001$). Furthermore, a significant correlation was found between female ADPKD patients and PLIN-2/ADRP levels. Supporting the previous knowledge, PLIN-2/ADRP levels were higher in female patients than in males ($p<0.001$).

In a 2017 study by Nowak *et al*., overweight and especially obesity were connected with the rate of progression in patients with early-stage ADPKD. In another study of this group, this relationship was once again demonstrated.[20, 21] In addition, Kocyigit *et al*. in a study with ADPKD patients who met the criteria for metabolic syndrome progressed significantly more rapidly than those who did not, during the 12-month follow-up period.[22] These studies mentioned above clearly demonstrated the relationship between obesity and kidney disease progression in ADPKD patients. In our study, it was shown that decreased eGFR was associated with increased BMI, consistent with the current literature.

In a large retrospective cohort study of ADPKD patients followed for many years, men had worse kidney function at a given age. In another retrospective study, the median age of onset of KF was 4 years younger in men than in women (52 versus 56 years).[23] The actual gender effect is unknown, as none of these studies were population-based. Larger population numbers are needed to fully see the gender relationship. However, the male gender stands out as a risk factor for ADPKD patients. In our study, patients with high PLIN-2/ADRP levels were women. Therefore, it suggests that high PLIN-2/ADRP levels may be associated with female gender and fat mass. In other words, PLIN-2/ADRP levels in ADPKD patients may be related to factors such as female hormones, BMI, and fat mass.

CONCLUSION

In conclusion, PLIN-2 / ADRP is associated with increased BMI and female sex in the ADPKD population. Taking into account these findings along with other research studies, the rise in serum PLIN-2 / ADRP levels provides valuable insights into the prediction of rapid progression. Although the current findings may not have been deemed statistically significant, it is crucial to clarify the link between the level of serum PLIN-2 / ADRP and ADPKD. This can be achieved through the utilization of a more extensive sample size and an extended follow-up duration.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The Ethics Committee of Erciyes University Clinical Research granted approval for this study by decision dated November 7, 2018 and number 2018/561.

Authors' Contribution

Study Conception: MC, EE, IK; Study Design: MC, EE, IK; Supervision; EE, IK; Funding: MC; Materials: CK, ACG; Data Collection and/or Processing: CK, GZ, ACG; Analysis and/or Data Interpretation: GZ; Literature Review: MC, EE; Critical Review: MC, EE, IK; Manuscript preparing: MC, EE, IK.

Main points

•As BMI increases in the ADPKD population, the median value of serum PLIN-2/ADRP level increases.

•The median value of serum PLIN-2/ADRP level was higher in female ADPKD patients than in males.

•As eGFR decreased in ADPKD patients, serum PLIN-2 / ADRP levels were found to increase, but it was not statistically significant.

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Angiotensin converting enzyme inhibitors related cough and associated medications

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ABSTRACT

Objectives: Angiotensin-converting enzyme inhibitors (ACEi) are among the main anti-hypertensive medications. While they are generally well tolerated, dry cough is one of their important side effects, with a frequency of up to 10 percent. Medications that are associated with increased ACEi-related cough frequency are not well described. We wanted to evaluate medications that might have an effect on ACEi-related cough.

Method: This study was designed as a post-hoc analysis of our previously published study. Patients who were on ACEi were identified, and demographics, comorbidities, laboratory data, and medications were retrieved via electronic medical records. Patients who reported cough and whose cough ceased after ACEi withdrawal were defined as having an "ACEi-related cough." Patients were grouped according to their ACEi-related cough presence.

Results: One hundred and twenty-one patients were included in the study, of whom 14 experienced ACEi-related coughs. All medications except for low dose acetylsalicylic acid (ASA) and calcium channel blockers (CCB) were similar between the groups. Low dose ASA use was significantly higher among patients who experienced ACEi-related cough (50% vs. 16.8%, p=0.04). On the other hand, CCB use was associated with lower ACEi-related cough (7.7% vs. 35.5%, p=0.03). Medications other than ASA and CCB, demographics, comorbidities, and laboratory data were similar across the groups.

Discussion: ACEi-related cough risk is higher among patients on low dose ASA and lower among patients on CCB. Further studies are needed to demonstrate if there is a "safe" acetylsalicylic acid dose that is not associated with ACEi-related cough.

Keywords: hypertension, angiotensin converting enzyme inhibitors, acetylsalicylic acid, calcium channel blockers, cough

Hypertension is a significant contributor to cardiovascular risk, alongside conditions like coronary artery disease. Its management involves implementing lifestyle modifications and utilizing medicines. Several prominent categories of drugs used to treat hypertension, such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), are commonly included in the treatment plans of many individuals with high blood pressure.[1,2] In addition to treating hypertension, ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) are often prescribed for patients with albuminuric diabetic renal disease and heart failure with reduced ejection fraction.[3,4] The latest hyperten-

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sion guidelines recommend the use of dual combination therapy, namely the addition of either an ACE inhibitor or an ARB to either calcium channel blockers or thiazide diuretics. Although ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) are typically well tolerated, ACEi is linked to a dry cough that requires discontinuation of the medication and a switch to ARB in 5 to 10 percent of patients, with other reports indicating rates as high as 30 percent.[5,6] According to reports, this condition is less prevalent in people with hypertension but more prevalent in patients with coronary artery disease and diabetes mellitus.[6] The precise mechanism behind ACEi-related cough is not well understood. However, the most probable explanation for the dry cough is that ACEi inhibits the breakdown of bradykinin and substance P, resulting in the constriction of airway smooth muscles and subsequent coughing.[7] Various factors have been suggested and defined to elucidate the reasons why certain patients develop a cough as a result of ACE inhibitor (ACEi) use while others do not. These factors encompass lung congestion caused by heart failure, varying levels of bronchial activity, heightened sensitivity of airway sensory nerve fibers to bradykinin, a reduced ability to break down bradykinin, and genetic variations in the bradykinin gene.[6] In addition to ACE inhibitors, various medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), beta-blockers, and acetylsalicylic acid (ASA), have the potential to trigger bronchospasm and result in coughing.[8] A study with ASA has shown that ASA has a bimodal effect on ACEi-related cough: While intermediate doses can lower ACE-related cough, low ASA doses have no effect.[9]

This study aimed to examine the impact of medications that are known to cause dry cough when used alone (such as ASA, beta-blockers, NSAIDs, etc.) or medications commonly used in hypertensive patients taking ACE inhibitors but not directly linked to dry cough when used alone (such as metformin, calcium channel blockers, proton pump inhibitors, etc.) on ACE inhibitor-induced cough.

METHODS

Design

This study was designed as a post-hoc analysis of our previously published study on hypertensive patients. Our previous study's aim was to evaluate the renal side effects of ACEi and ARBs via machine learning algorithms. During that study, some patients who were already on ACEi therapy were detected to report a chronic cough that had ceased after ACEi withdrawal, and we defined this cough as an "ACEi-related cough." In this study, we acquired the clinical characteristics of the patients who were on ACEi, and we grouped them as patients who experienced ACEi-related cough ("Cough" group) and patients who did not experience ACEi-related cough ("No Cough" group).

Clinical Data

- The following clinical data were acquired for the analysis:
- Demographics: Age and sex
- Comorbidities: diabetes mellitus (DM), coronary artery disease (CAD), heart failure (HF), chronic kidney disease (CKD), pulmonary disease, active malignancy, connective tissue disorders
- Medications: thiazide diuretics, calcium channel blockers (CCB), beta blockers, loop diuretics, insulin, metformin, nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, statins, and acetylsalicylic acid (ASA)
- Laboratory Values: Urea, glomerular filtration rate (GFR), creatinine, uric acid, sodium, potassium, calcium, glucose, low-density lipoprotein (LDL), triglyceride, and albumin

Statistics

For descriptive statistics, continuous variables were presented as "mean (±standard deviation)" or "median (interquartile range)" according to their distribution pattern. Categorical variables were presented as "numbers (percentages)". For comparison of continuous variables' between-group differences, the student's t-test or Mann-Whitney U test was used according to the variables' distribution patterns. Pearson's chi-squared test ($\chi 2$ test) (or Fisher's exact test when needed) was used for comparison of categorical variables' between-group differences. Two-sided significance testing was performed to calculate p-values, and p-values less than 0.05 were considered significant. All analyses were conducted using IBM SPSS Software version 23.0 (SPSS Inc., Chicago, IL), licensed to the institution where the study was carried out.

Ethics

Patients were assigned an anonymous identification number to protect confidentiality. The processing of the data did not require informed consent, and

written informed consent was not obtained due to the study's retrospective design. The study complies with the principles outlined in the Declaration of Helsinki, and this study was approved by the Hacettepe University Institutional Review Board (Project number GO22/734).

RESULTS

One hundred and twenty-one patients who were on ACEi therapy were included in the study. Of those, 14 (11.5%) experienced an ACEi-related cough, while 107 (88.5%) did not. The median age was 62, and there was a slight female dominance that did not show a difference between the groups.

The two most common comorbidities were diabetes mellitus and coronary artery disease, with frequencies of 42.1% and 33.9%, respectively. Coronary artery disease, the primary indication for acetylsalicylic acid use, was almost identical in the no-cough and cough groups (33.6% vs. 35.7%, p=1). Diabetes mellitus and heart failure frequencies, which were associated with higher ACEi-related cough risk, were similar between the two groups (41.1% vs. 50%, p=0.52, and 4.7% vs. 7.1%, p=0.53, respectively). Although pulmonary disorders were more common among patients who experienced ACEi-related cough (6.5% vs. 21.4%),

Table 1. Characteristics of patients grouped by their cough status

	TOTAL n = 121	NO COUGH n = 107	COUGH n = 14	p
Demographics				
Age	62 (14)	62 (15)	58 (10)	.13
Female sex	72 (59%)	65 (60.7%)	7 (50%)	.44
Comorbidities				
Diabetes mellitus	51 (42.1%)	44 (41.1%)	7 (50%)	.52
Coronary artery disease	41 (33.9%)	36 (33.6%)	5 (35.7%)	1
Heart failure	6 (5%)	5 (4.7%)	1 (7.1%)	.53
Chronic kidney disease	6 (5%)	6 (5.6%)	0	1
Pulmonary disease	10 (8.3%)	7 (6.5%)	3 (21.4%)	.09
Active malignancy	2 (1.7%)	1 (.9%)	1 (7.1%)	.21
Connective tissue disorders	8 (6.6 %)	6 (5.6%)	2 (14.3%)	.23
Medications				
Thiazide diuretics	47 (39.2%)	40 (37.4%)	7 (40%)	.25
Calcium channel blockers	39 (32.5%)	38 (35.5%)	1 (7.7%)	**0.03**
Beta blockers	42 (34.7%)	39 (36.4%)	3 (21.4)	.37
Loop diuretics				
Insulin	16 (13.3%)	14 (13.1%)	2 (15.4%)	.68
Metformin	43 (35.5%)	37 (34.6%)	6 (42.9%)	.56
Nonsteroidal anti-inflammatory drugs	15 (12.5%)	13 (12.1%)	2 (15.4%)	.66
Proton pump inhibitors	31 (25.8%)	28 (26.2%)	3 (23.1%)	1
Acetylsalicylic acid	25 (20.7%)	18 (16.8%)	7 (50%)	**.004**
Statins	21 (17.4%)	16 (15%)	5 (35.7%)	.067
Laboratory Values				
Urea	30 (14)	30 (15)	32 (13)	.97
Glomerular filtration rate	93 (21)	91 (22)	101 (18)	**.017**
Creatinine	.80 (.27)	.80 (.29)	.74 (.19)	.63
Uric acid	5.6 (1.8)	5.4 (1.8)	5.9 (2.3)	.68
Sodium	139 (3)	139 (3)	138 (3)	.5
Potassium	4.2 (.5)	4.2 (.5)	4 (.7)	.06
Calcium	9.6 (.7)	9.6 (.7)	9.4 (.8)	.19
Glucose	108 (25)	108 (23)	106 (33)	.93
Low density lipoprotein	113 (56)	113 (58)	114 (44)	.70
Triglyceride	150 (103)	151 (104)	131 (103)	.82
Albumin	4.3 (.5)	4.3 (.5)	4.1 (.8)	.30

this difference did not reach statistical significance (p=0.09). All other comorbidity frequencies were also similar between the groups (p>0.05).

Regarding biochemical characteristics, two groups did not differ except for the GFR. GFR was slightly higher in ACEi-related cough patients compared to the non-cough group (101 vs. 91, p = 0.017).

The most common medications were thiazide diuretics, metformin, and beta blockers (39.2%, 35.5%, and 34.7%, respectively). Calcium channel blockers (CCB) were used by 39 patients (32.5%) in total, and CCB use was significantly more common among patients who did not experience ACEi-related cough (35.5% vs. 7.7%, one-sided p=0.03). Acetylsalicylic acid (ASA) was used by 25 patients (20.7%), and ASA use was significantly more common among patients who experienced ACEi-related cough (50% vs. 16.8%, p=0.004). All medication uses other than ASA and CCB were similar across the groups (p>0.05). Table 1 illustrates in detail the clinical characteristics of patients according to their ACEi-related cough status.

DISCUSSION

This study illustrated that acetylsalicylic acid and calcium channel blockers are associated with higher and lower angiotensin-converting enzyme inhibitor-related cough, respectively. A dry and persistent cough is a well-described side effect of ACEi. Although all ACEi can produce dry coughs, perindopril is associated with lower ACEi-related coughs, due in part to its higher tissue potency.[10,11] Alongside ACEi, several medications, some of which may be used concomitantly with ACEi, also have an effect on cough. While many of them may increase cough incidence (e.g., beta blockers), some have the potential to reduce cough (e.g., calcium channel blockers).[8] It has been shown that the addition of calcium channel blockers reduces cough compared to ACEi monotherapy.[12] Possible mechanisms include inhibition of prostaglandin synthesis and decreased central transmission of cough reflexes.[6] Regarding ASA, a previous study was able to demonstrate that intermediate-dose ASA could suppress ACEi-related coughs while low-dose ASA could not suppress them. Our findings illustrate that low-dose ASA is associated with an even higher ACEi-related cough compared to a lack of ASA. To the best of our knowledge, this is the first study to demonstrate the association between ASA use and higher ACEi-related associations. Prostaglandins (PG) have been proposed to play a major role in ACEi-related cough. It is known that ASA irreversibly inhibits cyclooxygenase, the first enzyme in PG synthesis, converting arachidonic acid to PG-H2.[9] This mechanism can explain the intermediate dose of ASA's suppressing effect on ACEi-related cough but cannot elucidate the dose-dependent observation.

We acknowledge the limitations of our study. Firstly, this study was a retrospective analysis and prone to many limitations of retrospective studies. Secondly, the number of patients in both the total and cough groups was small; therefore, differences that are slightly above the p value of 0.05 (e.g., statin use, pulmonary disease presence) might be due to the small sample size. Thirdly, we did not take into account the CCB and ACEi types and doses; hence, we do not know whether different doses and types are associated with different cough frequencies. Lastly, these patients were receiving ACEi for hypertension but not for heart failure with reduced ejection fraction or albuminuric diabetic renal disease, so the findings might not be generalizable for indications other than hypertension.

In conclusion, clinicians should be aware of the fact that ACEi-related coughs are more common among patients who are on ASA. CCB can be more suitable than thiazides when added to ACEi due to the lower ACEi-related cough with CCB. Further studies on large patient numbers and different patient backgrounds are needed to clarify the association between acetylsalicylic acid use and ACEi-related cough.

CONCLUSION

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Hacettepe University. (Decision number: 2022/12-29, date: 5.7.2022).

Authors' Contribution

Study Conception: ATG; Study Design: ATG, MÖ;

Supervision; ATG, MÖ; Funding: ATG, MÖ; Materials: ATG, MÖ; Data Collection and/or Processing: ATG, MÖ; Analysis and/or Data Interpretation: ATG, MÖ; Literature Review: İD; Critical Review: ATG, MÖ; Manuscript preparing: ATG, MÖ.

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Thyroid nodules frequency in patients with chronic kidney disease (ckd) who undergoing hemodialysis

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ABSTRACT

Objectives: In our study; we examined the frequency of thyroid nodules, which are very common in the general population, in patients with Chronic Kidney Disease (CKD) who undergoing hemodialysis.

Methods: Our study was performed between 01.01.2020 and 01.04.2020 at Van Yuzuncu Yil University Faculty of Medicine, Dursun Odabaş Medical Center. 57 patients with CKD aged between 18-90 years were included in the study. Thyroid ultrasonography were performed on the patients. Subsequently, TSH, fT4 and fT3 laboratory tests, which are the routine tests in all CKD patients, were requested. Presence, number, location, size of thyroid nodules, isthmus thickness and total thyroid volume were recorded.

Results: 26 of the patients in our study were female and 31 were male. The mean age of the patients 51,98± 18,22. The thyroid volume was 16,57±9,97 mL. Thyroid nodules were detected in 27 (%47,4) of 57 patients. Thyroid nodules were seen to be more common in female gender and with increasing age. Also there was positive correlation between dialysis duration and thyroid nodule. %92,6 of the patients in our study were euthyroid.

Conclusion: We found that the frequency of thyroid nodules increased in patients with CKD who undergoing hemodialysis. We found that thyroid nodules were more common in women and with increasing age. In addition, we found that the longer the dialysis duration, the more frequent the thyroid nodule. Routine thyroid USG was recommended to patients with CKD who undergoing hemodialysis.

Keywords: Thyroid nodule, Chronic Kidney Disease, Hemodialysis

Thyroid dysfunctions and nodular goiter are more common in patients diagnosed with CKD than in the normal population.[1] Changes in thyroid function occur in patients diagnosed with CKD. These changes are; decrease in free-circulating thyroid hormones, changes in the peripheral metabolism of thyroid hormones, decrease in binding to carrier proteins, decrease in the storage of iodine in the thyroid gland. Euthyroidism, hypothyroidism or subclinical hypothyroidism is more common in patients diagnosed with end-stage renal failure. The decrease in Total T4 (TT4), free T4 (fT4), Total T3 (TT3) and free T3 (fT3) is more common. However, the reason for this situation is still unclear.[2]

Benign and malignant nodules in the thyroid gland are more common in end-stage renal failure than in healthy people.3 In different studies, thyroid volume was found to be increased in approximately 14% of

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patients diagnosed with end-stage renal failure, and thyroid nodules were detected in 36.8 - 59.4% of patients.[2,3]

METHODS

Approval was obtained from the Ethics Committee of Van Yüzüncü Yıl University Faculty of Medicine Dursun Odabaş Tıp Merkezi before starting the prospective study, which we plan to conduct to investigate the frequency of thyroid nodules in patients diagnosed with Chronic Kidney Disease (CKD) and receiving hemodialysis treatment (Date: 20/12/2019 Decision No: 03). The study was started after the written informed consert form was received from all the patients. Our study was conducted at Van Yüzüncü Yıl University Faculty of Medicine Dursun Odabaş Tıp Merkezi between 01.01.2020-01.04.2020. A total of 57 patients between the ages of 18 and 90 with a diagnosis of CKD and receiving hemodialysis treatment were included in the study. Through face-to-face interviews, the patients' age, gender, hemodialysis time, whether they have thyroid disease and the medications they use were questioned in detail.

Thyroid ultrasonography (with GE LOGIQ P5 ultrasonography device) was performed by the same endocrinologist at the Endocrinology Clinic of Van Yuzuncu Yil University Faculty of Medicine to all of the patients participating in the study. The dimensions of the thyroid lobes, the thickness of the isthmus, nodules, if any, the location, number and size of nodules of the patients were recorded. The thyroid volume of each lobe was calculated separately. The width (cm) × length (cm) × depth (cm) × 0.479 formula was used when calculating thyroid volume. The total thyroid volume was calculated by summing the volume of both right and left thyroid lobes. The volume of the isthmus was not taken into account when calculating the thyroid volume.

After that, TSH, fT4 and fT3 laboratory tests, which are routinely requested in all CKD patients, were requested. TSH levels were studied with the Architect ci16200 TM device. Reference range was accepted as 0.35-4.94 µIU/mL for TSH.

As a result of thyroid ultrasonography, according to the recommendations of the "American Thyroid Association" (ATA) guidelines, it was recommended to perform a thyroid fine needle aspiration biopsy on nodules with a high potential for malignancy. Those with subnormal TSH were again offered radionuclide thyroid screening in accordance with the recommendations of the ATA manual.

Those who were not within the specified age range at the time of diagnosis, did not have the diagnostic criteria for CKD disease, had previously undergone thyroid surgery, had any malignancies at the time of diagnosis and pregnant women were not included in the study.

RESULTS

A total of 57 patients diagnosed with CKD and undergoing hemodialysis, including 26 (45.61%) women and 31 (54.39%) men, were included in our study. The mean age of the patients in our study group was 51.98±18.22. There was a significant difference between the mean ages of male and female patients (p=0.036) (table 1).

When looking at Table 2, it was seen that 47.4% of the kidney failure patients included in the study (27 patients) had thyroid nodules. When the evaluation was performed according to gender, 16 (61.5%) female and 11 (35.5%) male patients were found to have thyroid nodules. It was found that there was significant difference between gender and whether thyroid nodule (p=0.05). As a result of the analysis, it was found that the patients with nodules were the most female patients.

74.1% of the patients included in the study (20 patients) had one nodule and 25.9% (7 patients) had more than one nodule. In this case, it was found that the vast majority of the patients included in the study

Table 1. The Average Age of the Patients Participating in the Study According to Their Gender

Gender	Number	Age Average	Standart Deviation	Minimum	Maximum	P value
Female	26	57,46	17,813	18	91	
Male	31	47,39	17,536	20	80	
Total	57	51,98	18,221	18	91	0,036

Table 2. The Relationship between Gender and Whether There is a Thyroid Nodule or Not

			The detected of a thyroid nodule		Total
			Detected	Not detected	
Gender	**Female**	Number	16	10	26
		Gender%	61,5%	38,5%	100,0%
	Male	Number	11	20	31
		Gender%	35,5%	64,5%	100,0%
Total		Number	27	30	57
		Gender%	47,4%	52,6%	100,0%
		P value: 0.05			

had a nodule (Table 3). It was found that the average age of hemodialysis patients with thyroid nodules included in the study was 57.96±16.07 and the average age of hemodialysis patients without thyroid nodules was 46.6±18.61. It was found that there was a significant difference between age and thyroid nodule (p=0.02). In the current study, hemodialysis patients with a thyroid nodule were found to have one nodule, two nodules, or three nodules. The average size of the first nodules of the patients was 8.70±5.10 mm, the average size of the second nodules was 16 ± 11.81 mm and the average size of the third nodules was 8.50±2.12 mm.

It was found that the average age of hemodialysis patients with thyroid nodules included in the study was 57.96±16.07 and the average age of hemodialysis patients without thyroid nodules was 46.6±18.61. It was found that there was a significant difference between age and thyroid nodule (p=0.02). In the current study, hemodialysis patients with a thyroid nodule were found to have one nodule, two nodules, or three nodules. The average size of the first nodule of the patients was 8.70±5.10 mm, the average size of the second nodules was 16±11.81 mm and the average size of the third nodules was 8.50±2.12 mm.

The average TSH values of the patients included in the study were 1.69±1.05 and the average ST4 values were 0.82±0.29. There were no differences when considering the status of thyroid nodule or absence of TSH, ST4 values (p=0.61; p=0.09). The average ST3 values of patients were 2.50. The average ST3 values of patients who had thyroid nodules were 2.37. The average ST3 values of patients who didn't have thyroid nodules were 2.62. ST3 values of patients with thyroid nodules and those without thyroid nodules differ (p=0.05). It was found that the ST3 values of hemodialysis patients with nodules were lower (Table 4)

The average hemodialysis time of all patients was 5.96±5.27, the average hemodialysis time of patients with thyroid nodules was 8.11±5.90 and the average of patients without thyroid nodules was 4.03±3.77. It was found that there was a significant difference between hemodialysis patients with a thyroid nodule and without a thyroid nodule. The hemodialysis time of patients with thyroid nodule detection is longer than in patients without thyroid nodule detection (p=0.00). The average thyroid volume of all patients was 15.29±8.16, the average thyroid volume of pa-

Table 3. Having a single or multiple nodule in patients with a thyroid nodule

			Detected	Not detected	
Number of thyroid nodules	**0 nodule**	Number	0	30	30
		Total%	0,0%	100,0%	52,6%
	1 nodule	Number	20	0	20
		Total%	74,1%	0,0%	35,1%
	2 nodules	Number	5	0	5
		Total%	18,5%	0,0%	8,8%
	3 nodules	Number	2	0	2
		Total%	7,4%	0,0%	3,5%
	Total	Number	27	30	57
		Total%	100,0%	100,0%	100,0%
P value: 0,000					

Table 4. Descriptive Statistics And Comparative Results of Thyroid Nodule Absence Status

	Thyroid nodule	Number	Average	Standart Deviation	Minimum	Maximum	P value
TSH	**Detected**	27	1,6141	1,04493	0,08	4,54	0,613
	Not detected	30	1,7563	1,06113	0,08	5,45	
	Total	57	1,6889	1,04651	0,08	5,45	
fT4	**Detected**	27	0,7478	0,33104	0,04	1,55	0,087
	Not detected	30	0,8780	0,22886	0,09	1,50	
	Total	57	0,8163	0,28689	0,04	1,55	
fT3	**Detected**	27	2,3737	0,52320	1,05	3,66	0,051
	Not detected	30	2,6200	0,40733	1,93	3,39	
	Total	57	2,5033	0,47792	1,05	3,66	
Duration of hemodialysis(year)	**Detected**	27	8,11	5,899	1	20	0,003
	Not detected	30	4,03	3,774	1	19	
	Total	57	5,96	5,268	1	20	
Thyroid volum (mL)	**Detected**	27	18,2122	9,90283	5,10	40,30	0,009
	Not detected	30	12,6637	5,06279	5,70	23,70	
	Total	57	15,2919	8,16190	5,10	40,30	

tients with thyroid nodules was 18.21±9.90 and the average thyroid volume of patients without thyroid nodules was 12.66 ± 5.06. There were differences between patients with thyroid nodules and those without thyroid nodules (p= 0.01). It was found that kidney failure patients with thyroid nodules had higher thyroid volumes (Table 4)

DISCUSSION

Thyroid nodules constitute the most common group of diseases belonging to the thyroid gland in society. The clinical importance of thyroid nodules is the functional status of the nodule, whether it is malignant, whether it causes pressure symptoms and signs.[4]

Both environmental and genetic factors play a role in the formation of thyroid nodules.[5] The prevalence of nodular goiter may vary depending on the iodine intake of the society in which the research was conducted, as well as depending on techniques such as palpation or USG used in scans.6 In this study, we investigated the frequency of thyroid nodules in patients diagnosed with CKD and undergoing hemodialysis.

There are numerous studies investigating the frequency of thyroid nodules in our country.[7,8] In Erzurum province, one of the iodine-deficient regions, the prevalence of thyroid nodules in the adult population was found to be 2.1% by palpation and 18% by ultrasonography.[7] In the 2023 thyroid diseases diagnosis and treatment (TEMD) guideline, it was reported that the frequency of thyroid nodules detected by ultrasonography in our country was 23.5% between the ages of 18-65 and 37.4% over the age of 65.[4]

The relationship between thyroid gland and kidney function has been known for a long time.[9] According to numerous studies, it has been found that CKD affects the metabolism of thyroid hormones and the thyroid gland structurally. These structural changes can be in the form of diffuse goiter, single thyroid nodule or multinodular goiter. Benign and malignant thyroid nodules are observed more frequently in patients with CKD than in the normal population.[10-13] According to studies in the literature, thyroid nodules were detected in 36.8 - 59.4% of patients diagnosed with CKD and undergoing hemodialysis.[14-16] According to a study conducted by Kutlay S and his colleagues in our country, thyroid nodules were detected in 36.8% of hemodialysis patients in areas with moderate iodine deficiency.[14] In a study conducted by Pakfetrat M *et al*. in Iran, the rate of thyroid nodules in patients undergoing hemodialysis was found to be 43.7%.[16] In two different studies conducted by Miki H *et al*. and Lin C *et al*., the thyroid nodule rate in hemodialysis patients was found to be 55% and 59.8%.[15,17] Similar to other studies in our study, we detected a thyroid nodule in 47.4% of patients diagnosed with CKD who underwent hemodialysis.

According to the 2023 TEMD guideline, the incidence of thyroid nodules in female is higher than in male.4 In studies conducted by Lin C *et al*. and Kaptein EM *et al*., it was found that thyroid nodule is more common in female hemodialysis patients.[15,18] In our study, when the evaluation was made according to

gender, we detected thyroid nodules in 16 (61.5%) female and 11 (38.5%) male patients. As a result of our analysis, we found that the patients who were found to have nodules, similar to the other studies, were the most female patients (p=0.05).

In the 2023 TEMD guideline and other studies, it has been observed that the frequency of thyroid nodules increases with age.[4,19] We found that the average age of kidney failure patients with thyroid nodules included in our study was 57.96±16.07, and the average age of kidney failure patients without thyroid nodules was 46.6±18.61. We found that there was a significant difference between age and thyroid nodule (p=0.02). In our study, similar to the TEMD guideline and other studies, we found that the frequency of thyroid nodules increases with increasing age.

When looking at the TSH values in different studies, it was found that hypothyroidism is often found in hemodialysis patients. However, there are also studies that have found euthyroidism.1[4,20] In a study conducted by Ibrahim Ihab A and his colleagues, it was found that the TSH values of hemodialysis patients were in the normal range.[12]

In our study, we have found that TSH values between 0-0,34 mlU/L (7,4%) and between 0,35-5,47 mlU/L (92,6%) who have had thyroid nodules. And we have found that TSH values between 0-0,34 mlU-/L (3,3%) and between 0,35-5,47 mlU/L (96,7%) who haven't had thyroid nodule. In our study, we found that the majority of patients' TSH values were in the normal range who had thyroid nodule.

In the studies conducted by Kutlay S *et al*. and Lebkovska U *et al*., it was found that the frequency of diffuse goiter and nodular goiter increases when the duration of dialysis increases.[14,21] In our study, when we looked at the relationship between the duration of hemodialysis of patients and the thyroid nodule, we found that there was a significant relationship. In our study, similar to the other studies, we found that thyroid nodule is observed more frequently when the duration of dialysis increases.

CONCLUSION

In our study, we detected thyroid nodules in 27 (47.4%) of 57 hemodialysis patients. In addition, we found that a thyroid nodule is more common in female than in male and a thyroid nodule is more common with increase age. The frequency of thyroid nodules by gender and age, were similar to the thyroid nodule studies in hemodialysis patients performed in our country and around the world.

In our study, we found that there is a significant relationship between the duration of dialysis and a thyroid nodule. We found that the incidence of thyroid nodules increased as the duration of dialysis increased.

When we looked at the TSH values of the patients in our study, we found that our patients had more euthyroidism.

Due to the high frequency of thyroid nodules in hemodialysis patients, we found that it is appropriate to routinely screen patients undergoing dialysis for the presence of nodules using thyroid ultrasonography.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Yüzüncü Yıl University İstanbul, Turkey. (Decision number: 06, date: 18.12.2019).

Authors' Contribution

Study Conception: MA, MA, YD; Study Design: MA, MA, YD; Supervision; MA, MA, YD; Funding: MA, MA; Materials: MA, MA; Data Collection and/or Processing: MA, MA; Analysis and/or Data Interpretation: MA, MA; Literature Review: MA, MA; Critical Review: MA, MA, YD; Manuscript preparing: MA, MA, YD.

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Why magnesium level check should be part of standard diabetes care?

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ABSTRACT

Objectives: The aim of this study was to investigate the effectiveness of routine magnesium monitoring in patients with diabetes during follow-up.

Methods: A retrospective observational clinical study was conducted, encompassing 387 participants aged 18 years and older, with and without diabetes. The control group comprised patients without diabetes. The group with diabetes consisted of 237 patients (134 women, 103 men), while the control group consisted of 150 patients (85 women, 65 men). Hypomagnesemia was diagnosed at <1.6 mg/dL. The study compared the groups based on the frequency of hypomagnesemia and clinical characteristics.

Results: The prevalence of hypomagnesemia was 8.8% (13.8% in patients with diabetes, 1.3% in the control group; p=0.001), with a magnesium level of 1.93±0.24 mg/dL (1.85±0.25 mg/dL in patients with diabetes, 2.06±0.16 mg/dL in the control group; p=0.001).

The study found that the prevalence of hypomagnesemia was significantly higher in patients with diabetes, particularly those with advanced age, longer duration of diabetes, impaired glycemic control, and previous hypomagnesemia diagnosis. Moreover, the use of proton pump inhibitors (PPIs) and diuretics were more common in patients with diabetes with hypomagnesemia. Conversely, the frequency of SGLT-2 inhibitor use was lower in patients with hypomagnesemia.

Discussion: This study suggests that routine magnesium measurement should be considered as a part of standard evaluation, especially for patients with diabetes exhibiting the aforementioned risk factors, and emphasizes the significance of acknowledging PPI and diuretic usage in such cases.

Keywords: Magnesium, diabetes mellitus, risk factors

Magnesium is an important ion involved in almost every mechanism in the cell, including energy homeostasis, protein synthesis, and DNA stability, and hypomagnesemia is defined as a magnesium concentration of 1.6 mg/dL or <2 standard deviations from the general population mean.[1] Hypomagnesemia may develop due to chronic disease, alcoholism, drugs, gastrointestinal or renal loss and many other reasons. Signs and symptoms can range from mild tremor and malaise to cardiac ischemia and death. It is an important electrolyte disorder that can be observed in 2% of the general

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population, 12% of hospitalized patients, 60-65% of patients hospitalized in intensive care units, and 14-48% of those with type 2 diabetes.[2-4] It has been reported that magnesium levels are lower in patients with diabetes than in those without diabetes, and that mutations in magnesotropic genes, low dietary Mg intake, autonomic neuropathy or impaired intestinal Mg absorption due to diarrhea triggered by metformin use, drugs such as diuretics, immunosuppressives and proton pump inhibitors, metabolic acidosis and insulin resistance may be related to this.[5] On the other hand, it has been reported that hypomagnesemia is associated with poor glycemic control and micro/macro vascular complications and development of foot ulcers in patients with diabetes.[6] Magnesium is not a routine monitoring parameter in patients with diabetes in daily practice. However, in parallel with the increase in laboratory investigations, asymptomatic or incidental hypomagnesemia cases are frequently encountered. The aim of this study was to determine the frequency of hypomagnesemia and clinical features associated with hypomagnesemia in patients with type 2 diabetes.

METHODS

Two hundred and thirtyseven patients with a confirmed diagnosis of type 2 diabetes mellitus and 150 controls aged ≥18 were included in this retrospective, observational, clinical study among consecutive patients attending the outpatient clinics of an university hospital department of Internal Medicine. Patients with advanced kidney and heart failure, chronic liver disease, cancer or malabsorption disorder were excluded from the study. Study protocol was approved by local ethics committee (approval date and number:0581/2022). The study was conducted in accordance with Declaration of Helsinki.

Study design

Demographic characteristics, comorbid conditions, duration of diabetes, type of diabetes, treatment features, presence of hypomagnesemia detected in previous admissions, use of drugs known to have an effect on magnesium levels (such as diuretic, antibiotic, proton pump inhibitor, immunosuppressive, digitalis) of patients who met the inclusion criteria.

Previous and current laboratory data (glucose, HbA1c, creatinine, alanine aminotransferase, total cholesterol, LDL cholesterol, triglyceride, magnesium) were obtained from medical records.The diagnosis of hypomagnesemia was accepted as the hospital laboratory lower limit reference value of <1.6 mg/dL.

Diabetes and control groups were compared according to the frequency and clinical features of hypomagnesemia. The clinical features of patients with hypomagnesemia and normal magnesium who have diabetes were also analyzed. Multivariate logistic regression analysis was performed to identify clinical features associated with hypomagnesemia.

Diabetes mellitus diagnosis

Patients were diagnosed with diabetes mellitus if they had one of the following: Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) or 2 h glucose ≥200 mg/dL (11.1 mmol/L) during oral glucose tolerance test, or HbA1c ≥6.5% (48 mmol/mol) or a random plasma glucose ≥200 mg/dL (11.1 mmol/L) in a patient with symptoms of hyperglycemia.[7]

Laboratory analysis

Fasting glucose concentrations were determined using the hexokinase method. Serum creatinine was assayed using the kinetic Jaffe method. For alanine transaminase concentrations, an enzymatic (without P-50-P, NADH) method was used. Fasting plasma total cholesterol, HDL and LDL cholesterol, and triglyceride concentrations were determined using enzymatic methods (Abbott Architect c16000 and c8000, Abbott). A Tosoh HLC-723 G8 (Tosoh G8) (Tosoh, Japan) (variant-mode) ion exchange high-performance liquid chromatography system was used for HbA1c measurements. Magnesium was studied on Roche/Hitachi cobas 8000 c, Mannheim, Germany.

Statistical Analyses

NCSS (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA) program was used. Shapiro Wilks test and Box Plot graphs were used to evaluate the conformity of the data to normal distribution. Student t-test was used for the evaluation of two quantitative groups with normal distribution and Mann Whitney U Test was used for the evaluation of two quantitative groups without normal distribution. Pearson Chi-Square Test, Fisher's Exact Test and Fisher Freeman Halton test were used to compare qualitative data. Logistic Regression Analysis was used to determine the risk factors affecting low magnesium. The results were evaluated at 95% confidence interval and significance was evaluated at $p<0.05$ level.

RESULTS

A total of 387 patients (219 females, 168 males) were included in the study. The group with diabetes consisted of 237 individuals (134 female, 103 male, mean age: 60.87±10.86 years), while the control group comprised 150 cases (85 female, 65 male, mean age: 59.56±11.46 years).

The clinical characteristics of the groups are detailed in Table 1. Age and gender distributions were comparable between the groups. Hypomagnesemia was observed in 8.8% of all cases, with a mean magnesium level of 1.93±0.24. The frequency of patients with hypomagnesemia in their previous admissions was 14.2%, and no patients exhibited hypermagnesemia.

The group with diabetes showed a higher prevalence of hypomagnesemia compared to the control group (13.5% vs. 1.3%, p=0.001), with lower mean magnesium levels (1.85±0.25 mg/dL versus 2.06±0.16 mg/dL, p=0.001), and a higher reported incidence of hypomagnesemia in previous records (20.3% vs. 4.7%, p=0.001). Fasting glucose, HbA1c, and triglyceride levels were higher, whereas total cholesterol, LDL cholesterol, and HDL cholesterol levels were lower in the diabetic group (p<0.01 for all). The frequencies of patients using antihypertensive drugs, including diuretics and proton pump inhibitors, were higher in the group with diabetes than in the group without diabetes (p<0.01 for all).

The comparison of clinical and laboratory features of patients with diabetes experiencing hypomagnesemia and those with normal magnesium are given in Tables 2 and 3.

In the diabetic group with hypomagnesemia, mean age (p=0.001), mean duration of diabetes (p= 0.023), frequency of patients with hypomagnesemia at previous admissions (p=0.001), frequency of patients using proton pump inhibitors (p=0.011), patients using mixed insulin frequency (p= 0.018) and fasting glucose

Table 1. Clinical characteristics of the groups

	Total (n=387)	DM- (n=150)	DM+ (n=237)	p
Age (sd)	60.36±11.1	59.56±11.46	60.87±10.86	0.137
Female (n,%)	219 (56.6)	85 (56.7)	134 (56.5)	
Male (n,%)	168 (43.4)	65 (43.3)	103 (43.5)	0.980
Frequency of previous hypomagnesemia (n,%)	55 (14,2)	7 (4,7)	48 (20,3)	**0.001**
Laboratory				
Glucose (mg/dL)	128,04±58,48	91,89±12,80	150,92±64,30	**0,001**
HbA1C (%)	6,86±1,80	5,59±0,36	7,66±1,89	**0,001**
Creatinine (mg/dL)	0,82±0,22	0,82±0,17	0,83±0,25	0,663
Glomerular filtration rate (mL/dk/1.73 m^2)	88,5±18,35	89,49±15,72	87,88±19,84	0,779
Alanine aminotransferase	19,8±12,67	20,64±15,27	19,27±10,70	0,505
Total cholesterol (mg/dL)	192,35±46,44	203,64±40,73	185,2±48,45	**0,001**
LDL cholesterol (mg/dL)	109,56±38,46	120,33±35,07	102,75±39,02	**0,001**
HDL cholesterol (mg/dL)	51,34±13,71	54,57±13,71	49,29±13,35	**0,001**
Triglyceride (mg/dL)	159,03±90,9	145,6±86,11	167,52±92,98	**0,007**
Magnesium (mg/dL)	1,93±0,24	2,06±0,16	1,85±0,25	**0,001**
Prevalence of hypomagnesemia (n,%)	34 (8,8)	2 (1,3)	32 (13,5)	**0,001**
Use of hypomagnesemia-related medication				
Diuretics (n,%)	82 (21,2)	18 (12,0)	64 (27.0)	**0,001**
Proton pump inhibitor (n,%)	81 (20.9)	8 (5,3)	73 (30.8)	**0.001**
Antibiotics (n,%)	2 (0.5)	2 (1,3)	0 (0,0)	0,150
Immunosuppressive (n,%)	0 (0,0)	0 (0,0)	0 (0,0)	-
Digital (n,%)	2 (0,5)	0 (0,0)	2 (1,8)	0.524
Comorbidities				
Hypertension (n,%)	191 (49,4)	43 (28,7)	148 (62,4)	**0.001**
Coronary artery disease (n,%)	60 (15,5)	12 (8,0)	48 (20,3)	**0.001**
Chronic kidney disease (n,%)	16 (4,1)	3 (2,0)	13 (5,5)	0.118
Hypothyroidism (n,%)	58 (15,0)	23 (15,3)	35 (14,8)	0.879

Table 2. Comparison of clinical characteristics of diabetic patients with and without hypomagnesemia

	Hypomagnesemia (+) (n=32)	Hypomagnesemia (-) (n=205)	*p*
Age (mean±SD)	66.56±9.39	59.98±10.82	**0.001**
Duration of diabetes (years) (mean±SD)	15,19±9,38	11,33±7,73	**0.023**
Frequency of previous hypomagnesemia (n,%)	14 (43.8)	34 (16,6)	**0.001**
Diabetes type (n,%)			
Type I	1 (3,1)	6 (2,9)	1.000
Type II	31 (96,9)	199 (97,1)	
Gender (n,%)			
Female	21 (65,6)	113 (55,1)	0.263
Male	11 (34,4)	92 (44,9)	
Duration of diabetes (n, %)			
<10 years	12 (37,5)	113 (55,1)	0.063
≥10 years	20 (62,5)	92 (44,9)	
Diabetes treatment (n, %)			
Insulin	0 (0,0)	13 (6,3)	
Oral antidiabetic	24 (75,0)	134 (65,4)	0,503
Insulin+ oral antidiabetic	8 (25,0)	56 (27,3)	
Lifestyle treatment	0 (0,0)	2 (1,0)	
Comorbidities (n,%)			
Hypertension	24 (75)	124 (60.5)	0,115
Coronary artery disease	5 (15,6)	43 (21)	0,484
Chronic kidney disease	1 (3.1)	12 (5.9)	1.000
Hypothyroidism	3 (9.4)	32 (15,6)	0.434
Diabetic neuropathy	8 (25)	54 (26.3)	0.872
Gastroparesis	0 (0)	1 (0,5)	1.000
Retinopathy	2 (6.3)	8 (3.9)	0.629
Hypomagnesemia-related drug use (n,%)			
Diuretics	9 (28.1)	55 (26.8)	0.878
Proton pump inhibitor	16 (50)	57 (27.8)	**0,011**
Antibiotics	0 (0)	0 (0)	-
Immunosuppressive	0 (0)	0 (0)	-
Digital	0 (0)	2 (1.0)	1.000

levels (p= 0.032) were higher than the diabetic group with normal magnesium levels, and the frequency of patients using SGLT-2 inhibitors (p= 0.001) was lower. In the multivariate logistic regression analysis, age (ODDS: 1.064, 95% CI; 1.020-1.110, p= 0.004) and fasting glucose levels (ODDS: 1.006, 95% CI; 1.001-1.011, p= 0.027) were independent risk factors for hypomagnesemia.

DISCUSSION

The results of this study revealed that the frequency of hypomagnesemia is high in patients with diabetes and that age and fasting glucose levels are the major determinants of hypomagnesemia.

Increasing data reveal that the prevalence of hypomagnesemia is high in patients with diabetes, although it varies according to study design and population characteristics, and hypomagnesemia is mostly associated with advanced age, diabetes duration, diabetes severity, treatment characteristics, and diabetic micro- and macrovascular complications.[8-10]

For example, in an observational cohort study including 929 patients with type 2 diabetes treated in primary care, the frequency of hypomagnesemia was found to be 9.6%, and it was shown that age, duration of diabetes, body mass index, HbA1c, metformin, sulfonylurea, and DPP-4 inhibitor use were negatively associated with magnesium concentration.[4]

Similar to our study, in an observational study conducted on outpatients with type 2 diabetes, the frequency of hypomagnesemia was found to be 12.9%, and it was stated that hypomagnesemia was associated with poor glycemic control and contributed to the development and progression of micro- and

Table 3 Comparison of treatment and laboratory characteristics in diabetics with and without hypomagnesemia

	Hypomagnesemia (+) (n=32)	Hypomagnesemia (-) (n=205)	*p*
OAD usage (n,%)			
Metformin	28 (87,5)	164 (80,0)	0.314
Sulfonylurea	4 (12,5)	13 (6,3)	0.259
DPP4-i	19 (59,4)	95 (46,3)	0.170
GLP-1 agonist	0 (0,0)	6 (2,9)	1.000
Glitazone	4 (12,5)	25 (12,2)	1.000
SGLT2-i	2 (6,3)	81 (39,5)	**0.001**
Acarbose	1 (3,1)	6 (2,9)	1.000
No OAD use	0 (0,0)	17 (8,3)	0.139
Insulin usage (n,%)			
Basal insülin	4 (50,0)	57 (82,6)	0.053
Bolus insülin	3 (37,5)	24 (34,8)	1.000
Basal plus	0 (0,0)	4 (5,8)	1.000
Mix insülin	4 (50,0)	8 (11,6)	**0.018**
Laboratory (mean±SD)			
Fasting glucose (mg/dL)	174,13±74,66	147,30±61,95	**0,032**
HbA1c (%)	7,82±1,82	7,63±1,91	0.463
Creatinine (mg/dL)	0,81±0,19	0,83±0,25	0.751
GFR	84,11±16,28	88,46±20,32	0.074
Total cholesterol (mg/dL)	183,78±37,03	185,42±50,07	0.859
LDL cholesterol (mg/dL)	96,31±31,55	103,76±40,03	0.317
HDL cholesterol (mg/dL)	51,06±12,18	49,01±13,52	0.321
Triglycerides (mg/dL)	172,53±83,58	166,74±94,53	0.450
Spot urine protein/creatinine ratio	0,42±0,94	0,27±0,69	0.292
Glycemic control (n,%)			
<%7	14 (43,8)	92 (44,9)	0.905
≥%7	18 (56,3)	113 (55,1)	

macrovascular complications of diabetes.[11]

Second; The reason is that the cases using proton pump inhibitors were found to be significantly higher both in the group with diabetes than in the non-diabetic group and in individuals with diabetes and hypomagnesemia compared to those with normal magnesium.

In fact, it is a well-known phenomenon that proton pump inhibitors are associated with the development of hypomagnesemia and is thought to be due to decreased intestinal magnesium absorption, mainly through the transient receptor potential melastatin-6 and -7 (TRPM6/7).[12]

In this respect, it may not be a surprising finding that PPI use is high in individuals with diabetes with dyspeptic complaints such as diabetic gastroparesis. However, the fact that half of the individuals with diabetes and hypomagnesemia were using PPI reveals the necessity of questioning the use of PPI in individuals with diabetes and hypomagnesemia.

Third; The prevalence of SGLT-2 inhibitor users in individuals with diabetes with normal magnesium levels was found to be significantly higher than in individuals with diabetes and hypomagnesemia. This finding raises questions as to whether this is coincidental or whether the use of SGLT-2 inhibitors has a protective effect against hypomagnesemia. In a meta-analysis of randomized controlled trials, it was observed that SGLT-2 inhibitors moderately but significantly increase magnesium levels as a class effect, suggesting that this may be associated with increased magnesium absorption in the renal proximal tubule.[13] Case reports have shown that SGLT-2 inhibitors improve magnesium levels in individuals with diabetes with refractory hypomagnesemia.[14,15]

In this respect, although the cause-effect relationship could not be fully established in our study, considering the literature, this finding supports the idea that the use of SGLT-2 inhibitors may be a therapeutic option, especially in individuals with diabetes with refractory

hypomagnesemia.

Although the use of mixed insulin was found to be higher in the group with diabetes with hypomagnesemia compared to the group with diabetes with normal magnesium levels, although it was found to be statistically significant, it was considered as a coincidental finding due to the low number of cases.

CONCLUSION

This study suggested that the frequency of hypomagnesemia is high in individuals with diabetes and that magnesium measurement should be a part of routine screening, especially in individuals with diabetes with advanced age, long diabetes duration, impaired glycemic control, and previously diagnosed hypomagnesemia.

On the other hand, it is one of the important results of this study that the use of proton pump inhibitors should be considered in the approach to the individual with diabetes with hypomagnesemia. More comprehensive studies are needed to evaluate the positive effects of SGLT-2 inhibitors on hypomagnesemia.

Limitations

The retrospective design, the fact that the cases did not receive magnesium treatment at the time of admission or before, alcohol use known to have an effect on magnesium, anthropometric measurements, micro and macrovascular complications, and conditions leading to renal loss such as 24-hour urine magnesium excretion could not be evaluated clearly and accurately.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of İstanbul Medeniyet University, İstanbul, Turkey. (Decision number: 2022/0581, date: 05.10.2022).

Authors' Contribution

Study Conception: MU,MVK; Study Design: MU; Supervision; MU,MVK; Materials: EP,AT,Eİ,MMA; Data Collection and/or Processing: P,AT,Eİ,MMA; Analysis and/or Data Interpretation: MU,MVK; Critical Review: MU,MVK; Manuscript preparing: MU,MVK.

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