Research Article / Araştırma Makalesi

Comorbidities in Patients with Gout
Gut Hastalarında Eşlik Eden Komorbiditeler

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Abstract: Patients with gout frequently have multiple comorbidities, including hypertension(HT), cardiovascular disease (CVD), renal impairment, diabetes mellitus(DM), obesity, hyperlipidemia(HL) or metabolic syndrome. These comorbidities and their treatment may have an effect on the choice of therapeutic agent. This study was to identify the comorbidities of gout. The study retrospectively investigated the demographic, clinical, and biochemical variables and comorbid factors of patients diagnosed with gout who applied to the rheumatology department between December 2019 and April 2023. 384 gout patients were included (mean age 63.4 years; men 71.6%). 299 (77.9%) of the patients received a diagnosis for the first time. The number of patients with comorbidities was 319 (83.0%). Hypertension was the most common comorbidity, observed in 255 patients (58.5%). Other comorbid diseases were HL in 140 patients (36.4%), kidney disease in 132 patients (34.3%), coronary artery disease(CAD) in 120 patients (31.2%), DM in 100 patients (26.0%), heart failure in 65 patients (16.9%), osteoporosis in 45 patients (11.7%), liver disease in 26 patients (6.7%), stroke in 25 patients (6.5%), other diseases in 20 patients (5.2%), malignancy in 18 patients (4.6%) and the number of patients without any comorbidities was 65 (16.9%). Comorbidities in gout are very common and add further to the disease's morbidity and make its management challenging. Patients with gout should therefore screened for comorbidities and risk factors, which should be addressed as an important part of gout management.
Keywords: Gout, Comorbidity, Uric acid

Özet: Gut hastalarında sıklıkla hipertansiyon(HT), kardiyovasküler hastalık, böbrek yetmezliği, diyabet mellitus(DM), obezite, hiperlipidemi(HL) veya metabolik sendrom dahil olmak üzere birden fazla komorbidite bulunur. Bu komorbiditeler ve tedavileri gut' un seyrini ve tedavi edici ajan seçimini etkileyebilir. Bu çalışma gut' a eşlik eden hastalıkları belirlemek amacıyla yapıldı. Çalışmamızda Aralık 2019- Nisan 2023 tarihleri arasında romatoloji polikliniğine başvuran gut tanısı alan hastaların demografik, klinik, biyokimyasal değişkenleri ile komorbid faktörleri geriye dönük araştırıldı. Çalışmaya 384 gut hastası dahil edildi (ortalama yaş 63,4 yıl olup erkeklerin oranı %71,6). Hastaların 299' una (%77,9) ilk kez tanı konulmuştu. Komorbid hastalığı olan hasta sayısı 319 (%83,0) idi. Komorbid hastalıklar değerlendirildiğinde en sık görülen hipertansiyondu(255 hasta, %58,5). Eşlik eden diğer hastalıklar sırasıyla 140 hastada (%36,4) HL, 132 hastada (%34,3) böbrek hastalığı, 120 hastada (%31,2) koroner arter hastalığı, 100 hastada (%26,0) DM, 65 hastada kalp yetmezliği (%16,9), 45 hastada (%11,7) osteoporoz, 26 hastada (%6,7) karaciğer hastalığı, 25 hastada (%6,5) inme, 20 hastada (%5,2) diğer hastalıklar, 18 hastada (%4,6) malignite ve herhangi bir komorbiditesi olmayan hasta sayısı ise 65 (%16,9) idi. Gutta komorbiditeler çok yaygındır ve hastalığın morbiditesini daha da arttırır ve tedavisini zorlaştırır. Bu nedenle gut hastaları, gut tedavisinin önemli bir parçası olarak ele alınması gereken komorbiditeler ve risk faktörleri açısından taranmalıdır.
Anahtar Kelimeler: Gut, komorbidite, Ürik asit

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1. Introduction

Gout is the most common inflammatory arthritis and occurs when, sustained elevation of serum urate levels resulting in supersaturation of body tissues with urate, leads to the formation and deposition of monosodium urate crystals in and around the joints. The risk of gout increases with age, and it is thus more common in aging populations. Gout is more prevalent in men than in women. It is recognized as the most common form of inflammatory arthritis, with a prevalence of 0.9% to 2.5% in Europe, 3.9% in the USA 5% and over 6% in some Oceanic-Pacific ethnic groups(1-6). One acute attack may be the only manifestation, or acute inflammatory arthritis episodes (flares), often monoarticular, may recur. Acute gout attacks are painful and potentially disabling, needing immediate treatment. Gout is also associated with comorbidities that may impair well-being and reduce longevity(7). Many gout risk factors exist, including obesity, dietary factors and comorbid conditions(8). As well as a firmly established increased risk of cardiovascular disease, diabetes, hyperlipidemia, hypertension and chronic kidney disease in those with gout, novel associations of gout with other comorbidities have been reported, including atrial fibrillation, obstructive sleep apnoea, osteoporosis, hepatic disorders and malignancy(9-13). Increasing prevalence and incidence of obesity and comorbidities are likely to contribute substantially to the rising burden of gout.

The aim of the present study was to investigate the comorbidities of gout in a tertiary center rheumatology clinic.

2. Materials and Methods

2.1. Study design

This study includes patients who applied to the rheumatology outpatient clinic in Eskişehir Cıty Hospıtal with a diagnosis of gout between December 2019 and April 2023. The study included 384 patients aged between 18 and 89 years and diagnosed as gout according to the 2018 EULAR/ACR classification criteria(14). Patients who were diagnosed with gout attacks and treated by rheumatologists were included, while patients with other non-gout rheumatic diseases (connective tissue diseases, rheumatoid arthritis, spondyloarthropathies, calcium pyrophosphate disease, etc.) were excluded. Demographic data, comorbidities, laboratory data, and treatments of patients diagnosed with gout were recorded retrospectively. Demographic data; age, gender, body mass index, smoking and comorbidities were recorded. Laboratory indicators were examined including blood urea nitrogen (BUN), serum creatine (Cr), uric acid(UA), glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), total bilirubin (TB), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C); inflammatory indicators, involving erythrocyte sedimentation rate (ESR, normal range: 0–20 mm/H) and C- reactive protein (CRP, normal range: 0–5 mg/L). The estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation(15). eGFR levels lower than 60 mL/min/1.73 m2 were defined as decreased renal function. We defined hyperuricemia as a uric acid level ≥7 mg/dl for men and ≥6 mg/dl for women(16). Body mass index (BMI) was calculated using the standing height and weight recorded in the medical record at the time of gout diagnosis. BMI was categorized based on the World Health Organization classification: normal (18.5–24.9 kg/m2), overweight (pre-obese; 25–29.9 kg/m2), class I obesity (30–34.9 kg/m2), class II obesity (35–39.9 kg/m2), class III obesity (≥ 40 kg/m2)(17). Those with a BMI≥30 kg/m^2 were considered obese. This study was approved by the local ethics committee (approval date: 09/06/2023,decisionno: ESH/GOEK2023/32). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

2.2. Statistical analysis

When evaluating the study data, quantitative variables were determined by mean, standard

deviation, median, minimum and maximum values; qualitative variables were indicated by descriptive statistical methods such as frequency and percentage. The Independent Sample T test was used for two-group comparisons of normally distributed parameters, and the Mann-Whitney U test was used for two-group comparisons of non-normally distributed parameters. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 21. If $P<0.05$, the difference between the means was considered significant

3. Results

Characteristics of study group are listed in table 1. Patients were mostly male (n: 271, 71.6 %). The mean age was 63.4 ± 12 years, and women were older than men (67.4 ± 11 vs 60.1 ± 10 years, $p<0.001$). Of the gout patients, 346 (90.1%) were over 50 years old, while 38 (9.9%) were under 50 years old. Among the patients who applied, 85 (22.1%) had previously been diagnosed, while 299 (77.9%) were newly diagnosed. The number of patients who had their first attack was 110 (28.6%), the number of patients who had their second attack was 86 (22.3%), and the number of patients who had ≥ 3 attacks was 188 (48.9%).

Table 1. Patient characteristics and associated comorbidities

Variables	Overall, *n*(%)	Men, *n*(%)	Women, *n*(%)	Uric acid level, mg/dl, mean
Sex	384	275 (71.6)	109 (28.4)	8.2
Age, mean, years	63.4	60.1	67.4	
18-49	38 (9.8)	26 (9.4)	12 (11.0)	7.6
50-59	105 (27.3)	76 (27.6)	29 (26.6)	8.3
60-69	118 (30.7)	82 (29.8)	36 (33.0)	8.6
70-79	78 (20.3)	50 (18.1)	28 (25.6)	9.3
80-89	45 (11.7)	41 (14.9)	4 (3.6)	8.4
BMI, kg/m^2				
Underweight (<18.5)	6 (1.8)	6 (2.1)	0	6.8
Normal (18.5-24.9)	25 (6.5)	16 (5.8)	9 (8.2)	7.4
Overweight (25.0-29.9)	128 (33.3)	104 (37.8)	24 (22.0)	7.6
Class I Obesity (30.0 -34.9)	124 (32.2)	98 (35.6)	26 (23.8)	8.2
Class II obesity(35.0-39.9)	45 (11.7)	23 (8.3)	22 (20.1)	8.8
Class III obesity (≥ 40)	38 (9.8)	20 (7.2)	18 (16.5)	9.2
Unknown	18 (4.6)	8 (2.9)	10 (9.1)	7.8
Smoking				
Never	185 (48.1)	99 (36.0)	86 (78.8)	8.2
Current	100 (26.0)	88 (32.0)	12 (11.0)	8.5
Former	96 (25.0)	87 (31.6)	9 (8.2)	7.7
unknown	3 (0.7)	1 (0.3)	2 (1.8)	8.4
Major associated comorbidities				
Hypertension				
Coronary artery disease	225 (58.5)	175 (63.6)	50 (45.8)	8.8
Heart failure	120 (31.2)	80 (29.0)	40 (36.6)	8.4
Stroke	65 (16.9)	38 (13.8)	27 (24.7)	9.6
Diabetes mellitus	25 (6.5)	15 (5.4)	10 (0.9)	7.9
Hyperlipidemia	100 (26.0)	65 (23.6)	35 (32.1)	8.6
Renal disease	140 (36.4)	88 (32.0)	52 (47.7)	8.2
Hepatic disorders	132 (34.3)	94 (34.1)	38 (34.8)	8.8
Malignancy	26 (6.7)	15 (5.4)	11 (10.0)	7.9
Osteoporosis	18 (4.6)	10 (3.6)	8 (0.9)	7.2
Any comorbidity	45 (11.7)	15 (5.4)	30 (27.5)	7.6
Other	65 (16.9)	46 (20.3)	19 (34.8)	7.3
	20 (5.2)	16 (5.8)	4 (3.6)	7.4
Chronic kidney disease	132 (34.2)	94 (34.1)	38 (34.8)	8.8

GFR categories (ml/min/ 1.73 m2)				
G1≥90				
G2 60-89	225 (58.5)	175 (63.6)	77 (70.6)	7.5
G3a 45-59	17 (4.4)	12 (4.3)	5 (9.8)	8.0
G3b 30-44	25 (6.5)	17 (6.1)	8 (7.3)	8.6
G4 15-29	30 (7.8)	20 (7.2)	10 (9.1)	9.2
G5 <15	28 (7.2)	23 (8.3)	5 (4.5)	9.8
	32 (8.3)	28 (10.1)	4 (3.6)	9.7
Medication use				
Diuretic use	158 (41.8)	125 (45.4)	33 (30.2)	9.6
Aspirin	205 (53.3)	145 (52.7)	60 (55.0)	8.3
Statin	80 (20.8)	62 (22.5)	18 (16.5)	8.6
Gout-related medication				
Colchicine	32 (8.3)	25 (9.0)	7 (6.4)	6.8
Allopurinol	25 (6.5)	15 (5.4)	10 (9.1)	6.2
Febuxostat	3 (0.7)	3 (1.0)	0	5.8

GFR, glomerular filtration rate. Body mass index (BMI)

Prevalence of Comorbidities in the study population

The frequency of the comorbidities in the study group were as follows; obesity (n: 207, 53.9%), diabetes (n:100, 26 %), hyperlipidemia (n: 140, 36.4%), hypertension (n: 225, 58.5%), heart failure (n: 65, 16.9%), coronary heart disease (n: 120, 31.2%) and chronic renal failure (n: 132, 34.3%), stroke (n: 25, 6.5%), hepatic disorders (n: 26, 6.7%), malignancy (n: 18, 4.6%), osteoporosis (n: 45, 11.7%), other diseases (n: 20, 5.2%) and any comorbidity (65, 16.9).

Gout and Hypertension

The most common comorbidity among gout patients is hypertension. The mean age of patients with hypertension was 62.4 years. Of the patients with hypertension, 143 (63.5%) were using diuretic antihypertensive drugs.The mean uric acid level was 9.6 mg/dl in patients using diuretics and 7.3 mg/dl in those not using diuretics(p=0.04).

Gout and Obesity

The frequency of gout in patients with BMI ≥30 kg/m² was 53.9%. As shown in Table 1, an increase in BMI was associated with an increase in uric acid levels (p:0,03). The most common comorbidities associated with obesity were HT, DM, CAD, HL and renal diseases, respectively.

Gout and Cardiovascular Diseases

Heart failure and coronary artery disease are more common in women, while hypertension is more common in men. When we look at the long-term follow-ups of our patients, the follow-up rates were 78.4% in the first 6 months after diagnosis, 61.8% between 6 and 12 months, 38.6% between 12 and 24 months, 25.8% between 24 and 36 months, and 18.6% for ≥36 months. As time went on, the follow-up rates decreased. Therefore, an analysis of long-term mortalities could not be performed. Six patients with heart failure and seven patients with chronic kidney disease were lost during the follow-up period. Four of the deaths had both congestive heart failure and chronic renal failure. Heart failure had the highest mean uric acid level among comorbid diseases (UA: 9.6 mg/dl). All heart failure patients were using diuretics.

Gout and Coronary Artery Disease

After the diagnosis of gout, 18 patients (4.6%) experienced myocardial infarction, and 8 patients (2.0%) developed arrhythmia. Among the patients with CAD, 82.4% had HT, 32.5% had DM, 56.8% had HL, and 20.3% had chronic kidney disease. Among the 120 patients with CAD, the number of patients using diuretic antihypertensive drugs was 86, and the number of patients not using diuretic antihypertensive drugs was 34. The uric acid level was 8.4 mg/dl, which was higher than

the general patient average (ua: 8.2 mg/dl) (p: 0.62). The number of patients with CAD who smoked was 32. The number of patients with CAD and a BMI ≥30 kg/m² was 38 (31.6%).

Gout and Renal Disease

In 132 (34.1%) of the patients, GFR was <90 ml/min/1.73 m², and it was the most common comorbidity after HT and HL. As GFR decreased, uric acid levels increased. All patients were started on uric acid-lowering therapy after being diagnosed with gout. Allopurinol was given at higher doses for optimal uric acid levels compared to other comorbidities. During the follow-up period, 6 patients became routine dialysis patients. The number of patients with coronary artery disease who used diuretics was 56 (42.4%), and the number of patients with hypertension was 115 (87.1%). After diagnosis, 28 patients switched from diuretic antihypertensive drugs to losartan treatment.

Gout and Diabetes

Diabetes was present in 26.0% of the patients. The number of patients with a BMI ≥30 kg/m² was 55 (55.0%). The mean uric acid level was 8.6 mg/dl, and the number of patients using diuretic antihypertensive drugs was 48 (48.0%). The number of patients with accompanying chronic renal disease(CKD) was 32 (32.0%), the number of patients with HT was 68 (68.0%), and the number of patients with HL was 82 (82.0%). Metabolic syndrome component could not be evaluated as waist circumference measurement was not performed.

Gout and Other Comorbidities

Alzheimer's(n: 3, 0.7 %) and Parkinson's diseases(n: 1, 0.2 %), myelodysplastic syndrome(n: 2, 0.5 %), asthma(n: 5, 1.3 %), chronic obstructive pulmonary disease(n: 4, 1.0 %), obstructive sleep apnea syndrome (n: 2, 0.5 %), Crohn's disease(n: 2, 0.5 %), and pemphigus disease(n: 1, 0.2 %) are other comorbidities that are less common.

4. Discussion

With this study, we aimed to determine the comorbidities present at the time of diagnosis in patients with gout and to compare uric acid levels according to these comorbidities. In previous studies, the prevalence of HT, cardiac arrhythmias, heart valve disease, urolithiasis, HL, hypothyroidism, chronic lung disease, osteoarthritis, depression, anemia, and psoriasis has been found to be significantly higher in patients with gout compared to controls(18). In addition, in the years following the diagnosis, the likelihood of developing cancer, cardiovascular diseases, urolithiasis, kidney diseases, DM, HL, hypothyroidism, peptic ulcer disease, mild liver disease, osteoarthritis, rheumatic disease, depression, anemia and psoriasis were found to be higher in gout patients without a history of comorbidity compared to controls(18). In general, the burden of comorbidity is very high in the diagnosis of gout and the risk of developing new comorbidity is higher in gout patients than in the general population. In recent years, increasing risk factors for gout include obesity, age, DM, chronic kidney disease and aspirin usage.

The relationships between gout and various comorbidity categories are well known. For example, the relationship between gout and the components of metabolic syndrome is consistently reported. However, due to the retrospective nature of our study and the lack of waist circumference measurement, we could not evaluate metabolic syndrome among comorbid factors. As BMI increased, uric acid levels also increased(P=0.03). Therefore, gout should be considered in cases of sudden-onset arthritis of the toes and ankles in obese patients.

In general, the prevalence of comorbidities in our sample is similar to other previously published cohorts, but there are differences. For example, in the 2007-2008 NHANES prevalence study, HT was 74%, chronic renal disease was 71%, obesity was 53%, DM was 26%, and heart failure was 11%(19). In our study, the prevalence of HT was 58.5%, chronic renal disease was 34.2%, obesity was 53.9%, DM was 26%, and heart failure was 16.9%. We believe that geographic differences and dietary content contribute to these differences.

Gout is a known risk factor for cardiovascular diseases such as cerebrovascular disease,

congestive heart failure, and myocardial infarction, and collectively increases the risk of all-cause and cardiovascular mortality in gout patients[20, 21]. This relationship may be mediated by endothelial dysfunction caused by high uric acid and low-grade crystal-induced inflammation[22]. The follow-up periods of our patients were short, and mortality data could not be analyzed. However, during the follow-up period, six patients with heart failure and seven patients with chronic kidney disease were died. Four of the deceased patients had both heart failure and chronic kidney failure. Additionally, six patients became routine dialysis patients. Four patients with malignancy died.

When we look at the relationship between comorbidity and uric acid levels, the highest uric acid level was observed in heart failure and chronic kidney patients using diuretics. Especially, as GFR decreased, uric acid levels increased. Uric acid-lowering therapy was started in all patients with chronic kidney

disease diagnosed with gout. Patients with CKD had a high incidence of HT, HL, DM and CAD. Other comorbidities and medications should be questioned when gout is diagnosed in these patients.

The study has some limitations due to its retrospective design. The absence of a control group and insufficient information about alcohol consumption are among these limitations. Additionally, gout patients can receive treatment and follow-up from different specialists, which can lead to patients being lost to follow-up, resulting in insufficient mortality data.

The existence of comorbidity greatly complicates the management of gout and requires special attention in managing patients with gout. A comprehensive, multispecialty approach is needed to reduce the morbidity and mortality of gout and its associated health conditions in these patients.

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Ethics