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Prevalence of hypouricemia, possible causes and clinical outcome

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Abstract

Hypouricemia is usually defined as serum uric acid level <2.0 mg/dL. Hypouricemia has no symptoms and usually does not require treatment. But it can lead to nephrolithiasis clinically and acute kidney damage after exercise. There are many possible causes of hypouricemia, such as malignancy and diabetes mellitus. In this study, we aimed to investigate the prevalence and possible causes of hypouricemia and clinical outcomes. Patients who applied to the Kahramanmaraş Necip Fazıl City Hospital between January 2016 and December 2017 and patients with serum uric acid levels were included in the study. Individuals with serum uric acid levels <2 mg/dl were screened and their diagnoses and treatments were noted. Renal ultrasonography was also evaluated for nephrolithiasis in patients with hypouricemia. A total of 59755 patients were included in the study. The prevalence of hypouricemia was determined as 0.88% (531/59755). The prevalence of hypouricemia was determined as 0.74% (365/49286) in the outpatient and 1.58% (166/10469) in the hospitalized patients. Of the patients diagnosed with hypouricemia, 77.9% were female and 22.0% were male. The prevalence of hypouricemia among female patients was found to be 1.06% (414/38701) and 0.55% (117/21054) among male patients. Possible causes include malignancy, diabetes mellitus, hypertension, pregnancy, intracranial pathology, burns and drugs. Clinically, acute renal failure, hyponatremia, chronic kidney disease and nephrolithiasis were detected. There were no illnesses or drug use stories in 114 cases. As a result, the prevalence of hypouricemia was found to be 0.88%. It was found higher in hospitalized patients and women.

Keywords: Hypouricemia, malignancy, nephrolithiasis

Introduction

Hypouricemia is usually defined as a serum uric acid level below 2.0 mg / dL. Hypouricemia has no detectable symptoms and therefore does not require treatment. However, it is a biochemical symptom which should be considered because it may be related to primary or secondary tubulopathy and other underlying conditions [1]. Hypouricemia may develop depending on genetic mutations or medical diseases and medications. Urate transport mechanisms are known as urate transporter 1 (URAT 1) and glucose transport 9 (GLUT9). URAT1 is also known as SLC22A12 and GLUT9 is also known as SLC2A9. Some mutations which occur in URAT1 and GLUT9 may lead to hereditary renal hypouricemia [2-3].

Fractional excretion of uric acid is generally evaluated in the diagnosis of hypouricemia. Reduced fractional excretion of serum uric acid is associated with defect in uric acid production. The

causes of hypouricemia and reduced fractional uric acid excretion are known as xanthinuria, allopurinol, rasburicase, neoplasia and liver disease. Hypouricemia and increased fractional excretion of serum uric acid are associated with defect in the proximal transport mechanism of uric acid. The causes of increased fractional uric acid excretion include salicylate, contrast agent, total parenteral nutrition, neoplasia, Wilson syndrome, inappropriate ADH release, primary and secondary fanconi syndrome, cystinosis, myeloma heavy chain and hereditary renal tubular hypouricemia. Hypouricemia appears secondary to extracellular volume extension in inappropriate ADH disease. In this here, along with sodium the absorption of uric acid from the proximal tubule decreases [4].

Material and Methods

The study was conducted in January 2016 and December 2017 in Kahramanmaraş Necip Fazıl City Hospital. The study included patients with serum uric acid levels. Hypouricemia was defined as serum uric acid level below 2 mg / dl. Biochemistry parameters were evaluated by scanning the files of patients with serum uric acid level <2 mg / dl and their diagnoses and treatments were

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noted. Besides, their renal ultrasound was evaluated to assess renal calculi in patients with hypouricemia.

Statistics; Variables such as representative serum uric acid level were stated as average values. Diseases along with hypouricemia and variables such as nephrolithiasis were evaluated as frequencies. Statistical significance was accepted as $p < 0.05$. All statistical analysis was performed using SPSS version 20.0 (IBM Co., Armonk, NY, USA).

Results

A total of 59755 patients were included in the study. The average age of the patients was 48.2 ± 17.7 (18-99) years. The prevalence of hypouricemia was 0.88% (531/59755). The prevalence of hypouricemia was 1.58% (166/10469) in hospitalized patients and 0.74% (365/49286) in outpatients. Of the patients with hypouricemia, 77.9% were female and 22.0% were male. The frequency of hypouricemia among women was 1.06% (414/38701) and 0.55% (117/21054) among men. The prevalence of hypouricemia was higher in hospitalized patients and in women. When the serum uric acid level was evaluated as ≤ 2 mg / dl, the prevalence of hypouricemia was 1.17% (the prevalence of hypouricemia in women was 1.44% and 0.69% in men). The average serum uric acid level was 4.7 ± 1.62 (0.1-19.5). The serum uric acid level was found to be 34.69% between ≥ 2 mg/dl and ≤ 4 mg/dl, 55.47% between >4 mg/dl and ≤ 7 mg/dl, 5.93% between >7 mg/dl and <10 mg/dl, 1.33 % in the level ≥ 10 mg/dl.

In our study, the possible causes of hypouricemia and accompanying diseases were given in Table 1. Coronary artery disease, inflammatory colitis, liver disease, cerebral palsy, psychosis, hydatid cyst and granulomatosis infection were found to be as the other causes. A total of 58 (10.9%) patients had medicine use (5.5% angiotensin converting enzyme or angiotensin receptor blocker, 1.9% acetylsalicylic acid, 1.5% allopurinol, 1.1% warfarin, 0.8% angiotensin converting enzyme + acetylsalicylic acid and 0.2% angiotensin converting enzyme + warfarin). Among malignant patients, as most frequently 18.6% lung cancer, 11.4% gastric cancer, 10% breast cancer, 10% hematologic, 8.6% pancreatic cancer, 8.6% colon cancer, 5.7% prostate cancer and 27.1% other cancers were detected.

Acute kidney damage was detected in 22 (4.1%) patients. Among these patients, three patients had no previous disease, while other patients had additional diseases (diabetes, hypertension, cerebrovascular disease, tumor, Alzheimer's disease). The frequency of chronic kidney disease was detected as 1.7%. Among its causes, two patients had isolated chronic kidney disease, while the other patients had additional diseases (diabetes, anemia, hypertension, malignancy, coronary artery disease). Hyponatremia was detected in a total of 12 (2.3%) patients, isolated hyponatremia was found in three patients; additional diseases were existing in the other patients (anemia, diabetes, tumor, cerebral palsy). Nephrolithiasis was detected in 13 (2.4%) patients, five patients had no previous pathology, the other patients had additional diseases (anemia, diabetes, hypertension, tumor).

Table 1. Possible causes and diseases of hypouricemia

Possible Causes	% (patients)
Anemia	% 14.3 (76)
Tumor	%11.9 (63)
Diabetes mellitus	%10.2 (54)
Pregnancy	% 9.8 (52)
Anemia+Pregnancy	%2.6 (14)
Hypertension	%4 (21)
Anxiety	%5.1 (27)
Diabetes mellitus +hypertension	%2.4 (13)
Diabetes mellitus+anemia	%2.4 (13)
Diabetes mellitus+cancer	%1.3 (7)
Anxiety+anemia	%1.7 (9)
Collagen tissue diseases	%2.3 (12)
Cerebrovascular disease	%2.1 (11)
Epilepsy	%1.3 (7)
Burnt	%1.1 (6)
Intracranial pathology	%0.94 (5)
Hypertension+coronary artery disease	%0.6 (3)
Hypothyroidis	%0.6 (3)
Diabetes mellitus+Hypertension+Coronary artery disease	%0.4 (2)
Diabetes mellitus+Coronary artery disease	%0.4 (2)
Diabetes mellitus+Hypertension+anemia	%0.4 (2)
Alzheimer	%0.4 (2)
Diabetes mellitus+Cerebrovascular disease	%0.4 (2)
Hypertension+ Cerebrovascular disease	%0.4 (2)
Isolated acute kidney disease	%0.56 (3)
Isolated nephrolithiasis	%0.94 (5)
Isolated chronic kidney disease	% 0.4(2)
Isolated hyponatremia	%0.56 (3)
Idiopathic	%19.3 (103)
Others	% 1.31(7)

Discussion

In our study, the prevalence of hypouricemia was found to be 0.88% (1.58% in hospitalized patients; 0.74% in outpatients). Hypouricemia was higher in hospitalized patients and women. In the study of Son and his friends, the prevalence of hypouricemia (serum uric acid < 2.0 mg/dL) was found to be 1.39% (424/30757). 68.4% of the patients with hypouricemia were women. The prevalence of hypouricemia was found to be 4.14% (299 / 7.222) in the hospitalized patients, 0.53% (125 / 23.534) in the outpatients, 1.03% (134 / 13.032) in the male patients and 1.64% (290 / 17.725) in female patients [5]. The prevalence of hypouricemia (serum uric acid level less than 2.0 mg/dL.) as detected as 0.51% in a study conducted in Turkey [6]. In a study conducted in Japan (hypouricemia is taken ≤ 2), the prevalence of hypouricemia was found to be 0.1191% in Tokyo (0.310% in women and 0.068% in men), 0.579% in Yonago (1.237% in women and 0.318% in men). The prevalence of hypouricemia was 4 times higher in women than men [7].

Serum uric acid level is detected significantly lower in diabetics than non-diabetic patients in consequence of increasing urinary

clearance. It has been reported that hypouricemia develops in patients with diabetes [8]. In the study conducted in China, the residual of serum uric acid level were found to be up to 7mmol / L in fasting glucose level. However, it was showed serum uric acid level decreased when fasting glucose level was > 7 mmol / L. After oral glucose tolerance test, a reverse relationship was found between glucose and serum uric acid in patients with plasma glucose level> 8mmol / l [9]. In the study of Gotoh and his friends, it was emphasized that there may be a relationship between glycosuria and serum uric acid reduction [10]. In the study conducted in type 2 diabetic patients, hypouricemia was found to be associated with poor metabolic control, hyper filtration, and late onset or decreased progression nephropathy [11]. In diabetic patients with normal renal function, serum uric acid levels were significantly lower in diabetic patients than in the control group [12].

Hereditary renal hypouricemia should be considered in patients with hypouricemia and increased fractional uric acid excretion (> 10%). Hereditary renal hypouricemia may lead to clinically nephrolithiasis and acute kidney damage after exercise [13]. Hereditary xanthinuria develops in consequence of lack of xanthine dehydrogenase enzyme. Autosomal recessive passes. In the lack of enzyme xanthine and hypoxanthine cannot be destroyed by uric acid. The lack of xanthine dehydrogenase enzyme is called type 1 xanthinuria. Type 2 xanthinuria develops as a result of both xanthine dehydrogenase and aldehyde oxidase deficiency. Clinically, it may result in hematuria, urinary tract infections, nephrolithiasis, acute kidney damage, crystallinity and chronic kidney disease. Hypoxanthine and xanthine increase in urine and blood. Besides, hypouricemia and hypouricosuria develop in patients [14]. In the study conducted by Son and his friends, malignancy which is the most common cause of hypouricemia was found to be 43.4%. (solid tumor 39.9%, hematologic 3.5%). Other causes was found to be diabetes mellitus 28.3%, drugs 14.6 (allopurinol, angiotensin receptor blocker, salicylate, febuxostat, warfarin), intracranial disease 9.1% and rarely obstructive jaundice, renal tubular acidosis and ulcerative colitis [5]. In the study of Bugdaycı and his friends, the causes of hypouricemia was found to be 16% diabetes mellitus, 15% hypertension, 4% solid tumor and drugs (11% losartan, 7% losartan + fenofibrate, 1% allopurinol, 5% salicylate) [6].

In our study, acute kidney damage was 4.1%, chronic kidney disease was 1.7%, hyponatremia was 2.3% and nephrolithiasis was 2.4%. In the study conducted in Japan, nephrolithiasis was found to be 1.2%, kidney disease was 2.3% and depression was found to be 1.2% [7]. In a study investigating the relationship between renal function and hypouricemia, hypouricemia was found to be associated with decreased renal function in men, but no such relationship was found in women [15]. In the study of Çetin and his friends, patients with anemia who beta thalassemia was minor was compared with non-anemia and control patients. Increased fractional uric acid excretion, hypouricemia and increased uric acid excretion were detected in patients with anemia [16]. In our study, anemia (14.3%) was the most common type along with hypouricemia.

Conclusion

In conclusion, hypouricemia drew rarely interest by researchers. However, hypouricemia may lead to clinically nephrolithiasis and acute kidney damage after exercise. It is thought that it develops as

a result of glomerular hyper filtration in diseases such as diabetes and hypertension. It may develop as a result of renal tubular damage and nutritional deficiency in patients with malignancy. Besides, in malignant patients the underlying cause whether or not develop as a result of genetic defects in uric acid transport mechanisms will be illuminated by studies (especially ABCG2 gene mutations). When laboratory hypouricemia is detected, precautions should be taken in terms of nephrolithiasis and acute kidney damage

Competing interests

The authors declare that they have no competing interest

Financial Disclosure

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Ethical approval

Ethical Committee Kahramanmaraş Sutcu Imam University 03.01.2018/04.

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