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The Correlation of Asymptomatic Hyperuricemia Patients and their Comorbidities at Sint Carolus Hospital in 2019

Cindy Oey[1], Emon Winardi Danudirgo[1], Bettia Bermawi[2]
[1]Internal Medicine Department, Sint Carolus Hospital
[2]Clinical Pathology Department, Sint Carolus Hospital

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Corresponding author:
E-mail address: *cindy_oey@yahoo.com*
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ABSTRACT

Background Gout is a progressive disease due to Mono Sodium Urate (MSU) crystal deposition at joints, kidney, and other connective tissue, caused by chronic hyperuricemia. In both developed and developing countries, there were increasing prevalence and incidence of gout in recent decades. Patients with hyperuricaemia are at risk of developing a variety of comorbidities, such as hypertension, chronic kidney disease, cardiovascular diseases, and metabolic syndromes. **Methods** Total 303 patients with asymptomatic hyperuricemia from Internal Medicine, Neurology, and Cardiology departments of Sint Carolus Hospital Jakarta admitted in January until December 2019 were recorded and analyzed for its comorbidities. **Result**s The number of asymptomatic hyperuricemia patients was higher that gouty arthritis, mostly men, middle-aged, with the median level of uric acid 7.7 mg/dl. The most frequent comorbidity found in this study was hypertension. Majority of the population has 2 comorbidities, higher UA level (>8 mg/dl) had more comorbidities compared to lower UA level (≥6.8-8 mg/dl), 4 vs 2 comorbidities respectively. Fisher exact test shown that higher UA level has a significant relatioship with the presence of hypertension, dyslipidemia, cardiovascular disease, chronic renal failure, stroke, and diabetes mellitus ($p < 0.05$). **Conclusion** This study describes that the presence of asymptomatic hyperuricemia often coexisted with hypertension and other comorbidities. Higher UA level correlates significantly to more comorbidities.

1. Introduction

Gout is a progressive disease due to Mono Sodium Urate (MSU) crystal deposition at joints, kidney, and other connective tissue, caused by chronic hyperuricemia.1 Prevalence of gout disease is 13.6 in 1000 men and 6.4 in 1000 women. Its prevalence is increasing with age, with 7% mean value in men aged >75 years-old and 3% in women aged >85 yo.1 Gout is a major health problem worldwide, with the prevalence varying from 0.1% to 10% in different regions. As in mainland China, a systematic review of data from 2000 to 2014 suggested the prevalence of hyperuricaemia and gout in the general population were 13.3% and 1.1%, respectively. In general, both developed and developing countries presented with

increasing prevalence and incidence of gout in recent decades.2 Hyperuricemia, defined as a serum urate concentration exceeding the limit of solubility (about 6.8 mg per deciliter [400 μmol per liter]). There are 3 spectrums of gout disease, asymptomatic hyperuricemia, acute gouty arthritis, and chronic gouty arthritis.1 Patients with hyperuricaemia or gout are at risk of developing a variety of comorbidities, such as hypertension, chronic kidney disease, cardiovascular diseases, metabolic syndromes, and psychiatric disorders.2 Many studies have addressed the correlation between hyperuricemic condition with those comorbidities.3 Hyperuricemia, a known correlate of oxidative stress, is a marker for adverse prognosis among individuals with heart failure.4 A large number of researchers have begun to consider uric acid as a serum indicator of glycometabolic disorders, because of a correlation between uric acid and glucose metabolism.5 Hyperuricemia is also found to be modestly increase the risks of both stroke incidence and mortality.6 The clinical manifestations of gout (acute gouty arthritis, gouty arthropathy, chronic tophaceous gout, uric acid urolithiasis, and gouty nephropathy) result from deposition of monosodium urate or uric acid crystals from supersaturated body fluids. The solubility of monosodium urate in extracellular fluids is influenced by a variety of factors, including pH, temperature, and sodium ion and protein concentrations.7 Uric acid is a final metabolite of purine metabolism in humans. Constituting the base components of nucleic acids (DNA, RNA), adenine and guanine are the purines with purine skeletons. Although there are two routes by which purine enters the human body, through oral intake or biosynthesis, a significantly higher amount of purines is biosynthesized than taken orally. As for oral intake, given that a unit of nucleic acid exists per cell, foods such as liver are rich in purines as they contain more cells. Purines that entered the body by ingestion are absorbed in the digestive tract and metabolized to uric acid, the final product. However, the amount is relatively low in comparison to the amount biosynthesized within the human body. The major energy source in humans, adenosine triphosphate (ATP) structure, centers on adenine, which is converted into hypoxanthine, xanthine, and eventually uric acid during ATP metabolism, and is subsequently excreted from the cell and into the blood. During this process, hypoxanthine is converted into xanthine and later, uric acid, with the activation of xanthine oxygenase (XO) and the production of reactive oxygen during metabolism. This reactive oxygen binds to nitric oxide (NO), a vasodilator substance, and inhibits its function, which is supposedly one of the factors involved in the development of arteriosclerosis. During the metabolism of fructose, a large amount of ATP is consumed resulting in the increased amount of uric acid. Recent increases in the rates of obesity, hypertension, diabetes, and cardiovascular disease are mainly caused by the elevated intake of sugars including fructose. In pathological conditions such as congenital heart failure and serious heart failure, aggravated anaerobic metabolism in tissues due to oxygen shortage tends to increase the levels of serum lactic acid. Additionally, the production of uric acid rises during intense exercise.Various factors are involved in the processes of uric acid production and secretion. In order to determine whether the cause of hyperuricemia is overproduction or underexcretion, uric acid or creatinine clearances are utilized for the diagnosis of the underlying disease.8 Several drugs are known to increase serum levels of uric acid, such as diuretics, aspirin, cyclosporine, theophylline, mycophenolate and ACE inhibitors.9 Although gout is a curable disease, its management is still not optimal in a large proportion of patients and there is still controversies regarding the urate lowering therapy (ULT) for asymptomatic hyperuricemia patients.1 Sircar et al provide additional evidence to the growing body of studies that suggest that hyperuricemia is not a benign condition and that urate-lowering therapy can mitigate kidney function

decline.3 Given the favorable side effect profile of urate-lowering therapy and the renal, cardiovascular, and cerebrovascular benefits from normalizing serum uric acid levels, the question should not be if, but rather when, patients with hyperuricemia should be treated.10,11 Obermayer et al may provide some guidance for when to initiate urate-lowering therapy in patients with asymptomatic hyperuricemic, noting that a serum uric acid level 9 mg/dL carries a 3-fold risk for kidney disease. Further studies are needed to determine which patients with CKD would derive maximum benefit from treatment and the minimum threshold of hyperuricemia required to experience benefits.3 Since the last 2006 recommendations, barriers to the effective treatment and cure of gout have been identified and the importance of the lack of knowledge of the disease and subsequent non-adherence to treatment have been emphasised. Moreover, an observational study showed that full patient education increased adherence to ULT, leading to a high rate (92%) of effectively treated patients at 12 months. Every person with gout should receive advice regarding lifestyle: weight loss if appropriate and avoidance of alcohol (especially beer and spirits) and sugar-sweetened drinks, heavy meals and excessive intake of meat and seafood. Low-fat dairy products should be encouraged. Regular exercise should be advised. Moreover, regular physical activity might decrease the excess mortality associated with chronic hyperuricaemia.12,13 Current urate-lowering therapy (ULT) includes three direct acting drugs (allopurinol, febuxostat, Rasburicase) and at least four 'indirect' drugs with other important targets (canagliflozin, losartan, fenofibrate and sevelamer).14 Thus, a major goal in managing gout is long-term reduction of serum urate concentrations to clearly subsaturating levels; such reduction, if maintained over time, will prevent or reverse the formation and deposition of urate crystals.7 Since excess uric acid not only has an adverse effect, but also acts preferably as a reducing substance, this dual nature needs to be considered hyperuricemia in patients with cardiovascular risks such as hypertension is considered as a risk factor for cardiovascular disease, and an appropriate intervention is likely necessary at an early stage.8 While there is a consensus to start ULT in cases of symptomatic hyperuricemia (gout, urate-nephrolithiasis), the very frequent conditions of asymptomatic hyperuricemia remains a major conundrum. The effect of asymptomatic hyperuricemia on kidney function has had fluctuating positions over decades. The conflicting results might indicate: (i) the presence of counterbalancing positive and negative effects on kidney function of both serum uric acid and urate-lowering agents, (ii) the presence of a subpopulation of patients, as yet unidentified, which could truly benefit from a urate-lowering therapy. Therefore, today the treatment of asymptomatic hyperuricemia is not recommended nor excluded by current guidelines of European League Against Rheumatism (EULAR), American Colleague of Rheumatology (ACR) and National Kidney Foundation (NKF).1,8 In the contrary, Japan Society for Nucleic Acid Metabolism has recommended to give the ULT for asymptomatic hyperuricemia patients with UA level >9 or >8 mg/dl in patiens with cardiovascular risk factors (renal impairment, hypertension, diabetes melitus, and ischemic heart disease).15 Serum uric acid has recently received attention in many studies as a potential biomarker to predict the development of hypertension, diabetes mellitus, and chronic kidney disease.16,17. Hyperuricemia can be easily detected in routine medical care. Hopefully that our study will encourage others to learn more about the potential use of hyperuricemia as a biomarker.

2.Methods

This is a cross-sectional descriptive study and was conducted using secondary data taken from medical records of Internal Medicine, Neurology, and Cardiology departments of Sint Carolus Hospital Jakarta admitted in January until December 2019.

The inclusion criteria of this study were asymptomatic hyperuricemia patients aged >17-years-old. The exclusion criteria were having history of- or currently having; (1) Hematologic malignancies (Acute Leukemia, Chronic Leukemia, Essential Thrombocythemia, Polycythemia Vera, Myelofibrosis); (2) Solid organ tumors (primary or metastase); (3) Multiple myeloma; (4) Treatment with chemotherapy agent ; (5) Tumor lysis syndrome; (6) Acute and Chronic Gouty Arthritis. Total sampling was used as the sampling method of this study. Hyperuricemia defined as a serum urate concentration exceeding 6.8 mg per deciliter.1 Asymptomatic hyperuricemia defined as having uric acid level as mentioned above and without symptoms of acute and chronic gouty arthritis. The diagnoses include their comorbidities were collected as listed on the medical records. The collected data was then analyzed using SPSS 16.

3.Results

Out of 5465 patients whom uric acid level were examined at Sint Carolus Hospital in 2019, there were 565 patients (10.34%) with high uric acid level. Then we separate the acute and chronic gouty arthritis from the asymptomatic hyperuricemia group, the prevalence were 149 patients (2.72%) and 303 patients (5.54%) respectively.

Table 1. Asymptomatic Hyperuricemia Patients Characteristics

Variables	Cases N=303(%)
Gender	
• Male	233 (76.9)
• Female	70 (23.1)
Age Groups	
• 20–40 years	69 (22.8)
• 41–60 years	167 (55.1)
• >60 years	67 (22.1)
Uric Acid level	
• >6.8-8 mg/dL	112 (37)
• >8 mg/dL	191 (63)

Table 2. Comorbidity characteristics of cases

Comorbidity	Cases N (%)
Hypertension	240 (79.2)
Dyslipidemia	194 (64)
Cardiovascular disease	115 (38)
Chronic renal failure	94 (31)
Stroke	47 (15.5)
Diabetes mellitus	148 (48.8)
No comorbidity	6 (2)
1 comorbidity	43 (14.2)
2 comorbidities	85 (28.1)
3 comorbidities	83 (27.4)
4 comorbidities	55 (18.2)
5 comorbidities	31 (10.2)

Table 3. Number of comorbidity by Uric Acid (UA) level

Number of comorbidity	UA >8 mg/dl (patient)	UA ≥6.8-8 mg/dl (patient)
1	1	42
2	12	73

3	25	58
4	43	12
5	29	2
0	2	4

Table 4. Analysis of Comobidities in Asymptomatic Hyperuricemia patients

Category	UA >8 mg/dl	UA >6,8-8 mg/dl	Total	P-Value
Hypertension				0.000
Yes	106 (44.2)	134 (55.8)	240(100)	
No	6 (10.5)	57 (79.2)	64 (100)	
Dyslipidemia				0.000
Yes	93 (11.1)	101 (88.8)	194	
No	19 (11.5)	90 (89.5)	(100)	
			109	
			(100)	
Cardiovascular disease				0.001
Yes	56 (48.7)	59 (51.3)	115	
No	56 (29.8)	132 (70.2)	(100)	
			188	
			(100)	
CRF				0.003
Yes	46 (48.9)	48 (51.1)	94 (100)	
No	66 (31.6)	143 (63.1)	209	
			(100)	
Stroke				0.000
Yes	30 (63.8)	17 (36.2)	47 (100)	
No	82 (32)	174 (68)	256	
			(100)	
Diabetes				0.000
Yes	84 (56.7)	64 (43.3)	148	
No	28 (18)	127 (82)	(100)	
			155	
			(100)	

4.Discussion

Natural history of Gout consists of three phases, such as asymptomatic hyperuricemia, acute gouty arthritis with intercritical phase, and chronic gouty arthritis.[1] We found that in our study, the number of asymptomatic hyperuricemia patients was higher than gouty arthritis (416 patients vs 149 patients, respectively).

The serum uric acid level is known to vary significantly depending on meals, lifestyle, gender, and previous use of diuretics. Since female hormones lower the serum uric acid levels, they tend to increase after menopause.[8] Our study populations consist of mostly male patients (76,9%) in middle-aged (median 49 years old) with high UA level (median 7.7 mg/dl) (Table 1).

Hyperuricemia, defined as a serum urate concentration exceeding the limit of solubility (about 6.8 mg per deciliter [400 μmol per liter]), is a common biochemical abnormality that reflects supersaturation of the extracellular fluid with urate and predisposes affected persons to gout.[1,7]

Patients with hyperuricaemia or gout are at risk of developing a variety of comorbidities, such as hypertension, chronic kidney disease, cardiovascular diseases, metabolic syndromes, and psychiatric disorders.[2] Many studies have addressed the correlation between hyperuricemic condition with those comorbidities.[3] A recent survey found that 5%–10% of patients with gout had at least seven comorbidities and that hypertension was presented in at least 74% patients with gout. These comorbid conditions add difficulties to gout management and affect patients' quality of life.[2] The most frequent

comorbidity found in this study was hypertension, there were 240 patients (79,2%) having hypertension as comorbidity in this study. Majority of the population has 2 comorbidities (Table 2). Table 3 shown that higher UA level (>8 mg/dl) has more comorbidities compared to lower UA level (≥6.8-8 mg/dl), mostly at 4 comorbidities vs 2 comorbidities. Fisher exact test (Table 4) analyzed about the relationship between each comorbidities with UA level. We concluded that higher UA level has a significant relatioship with each comorbidities ($p < 0.05$).

The incidence rates of heart failure was ~6 fold higher among those at the highest quartile of serum uric acid (>6.3 mg/dl) compared to those at the lowest quartile (<3.4mg/dl).

Hyperuricemia is a novel, independent, risk factor for heart failure in a group of young general community dwellers. This has implications for development of preventive strategies for heart failure. Hyperuricemia is associated with worse hemodynamic measures such as increased left atrial pressure and decreased cardiac index among patients with primary pulmonary hypertension, cor pulmonale and dilated cardiomyopathy in a small case series. Among those with established heart failure, hyperuricemia is a risk factor for adverse outcomes including mortality. Hyperuricemia is associated with worse hemodynamic measures such as increased left atrial pressure and decreased cardiac index among patients with primary pulmonary hypertension, cor pulmonale and dilated cardiomyopathy in a small case series. Among those with established heart failure, hyperuricemia is a risk factor for adverse outcomes including mortality hypertension. There have not been any studies that examined hyperuricemia as independent risk factors for heart failure risk among the general population. The single available study from Austria, did not account for confounders such as valvular heart disease and diuretics, and renal disease suggested that highest quantiles of serum uric acid was associated with elevated risk for death from heart failure.[4] Nevertheless, a completely different paradigm regarding hyperuricemia was being proposed, that is a role of sodium urate in cardiovascular disease. In 1999 the Framingham study supported the view that uric acid is not a risk factor for cardiovascular disease. Current guidelines (e.g. JNC-8) do not list uric acid as a risk factor. The main reason for this change in direction has been the strong association of uric acid levels and other known risk factors for cardiovascular disease (obesity, diabetes etc.). Interventional studies and metanalysis about urate-lowering therapy on cardiovascular disease do not support this approach to reduce cardiovascular risk. A previous Cochrane review reached the same result, even though it is possible that urate-lowering approach might have an effect on hypertension. Overall, the association between uric acid and cardiovascular disease appear to have the same dynamic of gouty nephropathy.[9] The risk of cardiovascular events, including death, is substantially higher in people with gout than in those without gout.[10] There were 115 patients (38%) having cardiovascular disease as comorbidity in this study (Table 2).

In both diabetic and non-diabetic group, serum uric acid correlated positively and significantly with serum creatinine (>1.3mg/dl), blood urea (>40mg/dl) and microalbuminuria ($p<0.05$). Though serum uric acid did not correlate with HbA1c and FBS ($p>0.05$) in both the group. In non-diabetics, males were 6.95 times likely to have hyperuricemia than females. Hyperuricemia may be associated with early onset or incipient nephropathy in both diabetes and non-diabetic patient. Hyperuricemia, a highly prevalent condition in the adult population, is associated with obesity and insulin resistance. Recent evidence has suggested that uric acid plays a role in immune activation and cytokine secretion. Moreover, uric acid has been identified as a mediator of endothelial dysfunction and systemic inflammation. Increasing evidence suggests that

hyperuricemia is an independent risk factor for impaired fasting glucose (IFG) and type 2 diabetes. Patients with hyperuricemia are at a significantly higher risk of progressing to Type 2 diabetes. A large number of researchers have begun to consider uric acid as a serum indicator of glycometabolic disorders, because of a correlation between uric acid and glucose metabolism.[5] There were 148 patients (48.8%) having diabetes as comorbidity in this study (Table 2).

Hyperuricemic patients have significant association for renal involvement more than in the normouricemic subjects in both diabetics and non-diabetics patients.[5] A large epidemiologic Japanese study identified hyperuricemia as a key predictor of end-stage renal disease over a 7-year period. This report was one of the first to identify women with hyperuricemia to be at greater risk for end-stage renal disease. In another study, Obermayr et al followed up 21,475 healthy volunteers for 7 years to determine whether hyperuricemia was an independent risk factor for new-onset kidney disease. The study confirmed that after adjustment for multiple risk factors, including baseline eGFR, age, sex, mean blood pressure, and metabolic syndrome, an elevated serum uric acid level (7-8.9 mg/dL) doubled the risk for incident kidney disease. Further, compared with those with lower serum uric acid levels, those with serum uric acid levels > 9 mg/dL had 3 times the risk for developing kidney disease. It is now apparent that hyperuricemia is more than just gout.[3] Thus we divided the group of UA level based on higher or below 8 mg/dl. There were 94 patients (31%) having chronic renal failure as comorbidity in this study (Table 2).

Hyperuricemia was associated with a significantly higher risk of both stroke incidence and mortality. Subgroup analyses of studies adjusting for known risk factors such as age, hypertension, diabetes, and cholesterol still showed that hyperuricemia was significantly associated with both stroke incidence and mortality. The pooled estimate of multivariate RRs did not differ much by gender. Our study suggests that hyperuricemia may modestly increase the risks of both stroke incidence and mortality. Future research is needed to determine whether lowering uric acid level has any beneficial effects on stroke.[6] The SUA level was significantly elevated in patients of acute stroke. Elevated SUA was associated with higher mortality, more in ischemic stroke patients. Hence, SUA can be considered as a risk factor and poor mortality outcome in patients of acute stroke.[11] There were 47 patients (15.5%) having stroke disease and 194 patients (64%) having dyslipidemia as comorbidity in this study (Table 2).

The weakness of this study is the bias of diagnostic approach and disease management conducted by each doctors with their own areas of expertise (Internist, Cardiologist, Neurologist).

Conclusion

This study describes that the presence of asymptomatic hyperuricemia often coexisted with hypertension and other comorbidities. Higher UA level correlates significantly to more comorbidities. Accordingly, we suggested that every person with hyperuricemia should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, hyperlipidaemia, hypertension, and diabetes, which should be addressed as an integral part of the management of hyperuricemia.

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