Prevalence of Albuminuria and Associated Factors among Gout Arthritis Patients in Cipto Mangunkusumo Hospital

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Abstract

Background: Gout arthritis associates with many comorbodities such as hyperuricemia, hypertension, hyperglycemia, obesity, and dyslipidemia, which are also factors for the development of/or predisposition factors of chronic kidney diseases (CKD). Albuminuria is a predictor factors for CKD. Screening for albuminuria is needed to be done in patients with high risk of CKD. This research was conducted to examine the prevalence of albuminuria and the associated factors in gout arthritis patients.

Method: This research was a cross-sectional study from gout arthritis patients' medical records in Cipto Mangunkusumo Hospital. We included all gout patients who treated within 2011−2015. Subjects with chronic kidney disease, in kidney replacement therapy, hypertension ≥ 10 years, and diabetes ≥ 5 years were excluded. Albuminuria was determined by urine dipstick result of protein ≥ 1+. Factors associated were age, sex, hyperuricemia, hypertension, stage of hypertension, hyperglycemia, obesity, dyslipidemia, uric acid level, and body mass index (BMI). Data associated with the factors were recorded and the associations were tested with chi square, fisher's exact, or independent t-test.

Result: from 54 subjects included in this research, the prevalence of albuminuria was 20.4%. There were no significant associations between all factors and albuminuria tested by chi square and fisher's exact test. Independent t-test's results also showed no significant associations between all the factors and albuminuria

Conclusion: The prevalence of albuminuria in gout arthritis patient was 20.4%. There were no significant associatons between age, sex, hyperuricemia, hypertension, hyperglycemia, obesity, dyslipidemia, uric acid level, and body mass index (BMI) tested with albuminuria in gout arthritis patients in Cipto Mangunkusumo Hospital from 2011−2015.

Keywords: Prevalence, Albuminuria, Gout Arthritis, Risk Factors

Introduction

Gout arthritis is a common disease in Indonesia, 1.7% male population suffer from this disease.[1] Gout arthritis is caused by the precipitation of uric acid in joints occured in hyperuricemic patients. Hyperuricemia is defined when plasma uric acid level reaches ≥ 6.8 mg/dL in normal body temperature.[2] The precipitation will lead inflammation involving complement system activation and phagocytosis. Activation of complement system makes neutrophils attracted to get out to synovial fluid compartment, while phagocytosis leads production of IL-1β through the activation of NLRP3 inflammasome. IL-1β will increase the proliferation, differentiation, and apoptosis of cells, and the influx of neutrofil to synovial fluid compartement. These processes will induce continuous inflammation, and lead the release of matrix metalloproteinase (MMP), an enzyme that can erode the bones.[2,3]

There are 4 phases of gout arthritis: asymptomatic, acute gout, intercritical phase, and chronic gout. Acute phase or gout attacks happens several hours with clinical symptoms, includes swollen joint and sharp pain in metatarsophalangeal I, ankle, achilles, knee, wrist, fingers, or elbow. The attack will be followed by resolution phase. Intercritical phase is an asymptomatic phase between two attacks. In several cases, intercritical phase are not found between the attacks, thus the phase is classified as chronic phase. In chronic phase, tophi can be developed in fingers, hands, knees, ankles, elbows, and antihelix.[4]

Gout arthritis decreases the patients' life quality, 21.1% of the patients suffer from moderate disability.[5] Gout arthritis and hyperuricemia could also induce kidney injury that will lead to a chronic kidney disease. Gout nephrolitiasis and urate nephropathy are the etiology of kidney injury in gout arthritis and hyperuricemic patients.[6] Moreover, chronic kidney disease (CKD) is the most prevalent comorbidities of gout patients in Indonesia (53.08%).[7] The previous statement were supported by the studies conducted by Roughley MJ, et al. [8] and Krishnan, et al. [9] The incidence of kidney injury was increasing three times in the group with serum uric acid ≥ 9.0 mg/dL and twice in the 7.0−8.9 mg/dL group.[10]

Gout patients often have comorbidities such as hypertension, dyslipidemia, diabetes, and obesity, which could increase the risk of developing kidney disease.[9] Hypertension may induce arteriolopathy, glomerulosclerosis, and tubulointerstitial fibrosis, whereas hyperglycemia in diabetic patients could lead to diffuse mesangial sclerosis, hypertrophy of mesangium cells, and membrane thickening

glomerulopathy.[11–13] Dyslipidemia and obesity can increase the release of free radicals that could damage glomeruli capilers and mesangium cells, thus leading kidney injury.[14,15] These conditions show us that gout patients are vulnerable to develop kidney injury and chronic kidney disease. Therefore, screening for chronic kidney disease is needed to be performed in all gout patients. Albuminuria is known as a screening tool for CKD and end-stage renal disease.[16–18] The usage of urine dipstick with albuminuria category ≥ +1 is reported as good as albumin-creatinin ratio with category ≥ 30 mg/g.[19,20] Therefore, we decided to conduct this research to find out the prevalence of albuminuria and risk factors associated in gout arthritis patients in RSUPN Cipto Mangunkusumo.

Method

This is a cross sectional study, done using secondary data from medical records of all patients who have diagnosed gout and treated in RSUPN Cipto Mangunkusumo between January 2011 and December 2015. Gout diagnosis is made by the rheumatologists and given code as ICD 10 (International Classification of Disease 10) of M10.0. Gout was diagnosis using diagnostic criteria in RSUPN Cipto Mangunkusumo which is also adapted from American College of Rheumatology Guideline in 1987. Patients who have history of chronic kidney disease consistent with KDIGO criteria (the presence of kidney injury and/or GFR < 60 ml/min/1.73 m^2) prior or at the time when gout arthritis diagnosis made, history of diabetes mellitus ≥5 years, history of hypertension ≥10 years, and no data of dipstick urinalysis were excluded from this study.

Data collected were included age when diagnosus was made, sex, weight, height, body mass index (BMI), serum uric acid (sUA), blood glucose test (HbA1C, random blood glucose, fasting blood glucose, or 2-hours-post-prandial blood glucose), blood lipid test (HDL, LDL, total cholesterol, or triglyceride), blood pressure test, dipstick urinalysis test, history of hypertension, diabetes, dyslipidemia or other illnesses, and previous treatment related to gout arthritis and its risk factors.

Independent variables in this study were risk factors in 2 types of data: categorical and numerical. Risk factors in categorical data were defined as: sex (men/women), age (>60 years old / ≤ 60 years old), hyperuricemia (severe = sUA ≥9.0 mg/dL, mild = sUA 7.0−8.9 mg/dL, and normal = <7.0 mg/dL), obesity (BMI ≥ 25 kg/m^2), hypertension (history of hypertension or consumption of hypotension agent), stage of hypertension (Stage I = systolic pressure < 160 mmHg or diastolic pressure <100 mmHg, Stage II = systolic pressure ≥ 160 mmHg atau diastolic pressure ≥ 100 mmHg), dyslipidemia (total cholesterol ≥ 240 mg/dL or LDL ≥ 160 mg/dL or HDL < 40 mg/dL or trigliserida ≥150 mg/dL or history of dyslipidemia or consumption of hypolipidemic agents), and hyperglycemia (2-hr PP ≥ 140 mg/dL or FBG ≥ 100 mg/dL or RBG ≥200 mg/dL or HbA1C >5.6% or history of diabetes mellitus or consumption of hypoglycemic agents).[10,22–28] Risk factors in numerical data were serum uric acid, body mass index, and age. The dependent variabel was albuminuria, defined as urine dipstick ≥ +1 with categorical data (yes/no).[18–20]

All data were recorded in secondary data form made by researcher and then inserted in statistical packages for social sciences (SPSS) for windows version 20.0. Independent t-test was used to analyze numerical-categorical data. Chi square test was used to analyze categorical-categorical data. Fisher's exact test was used if the data did not meet the criteria to be analyzed by chi square test.

Result

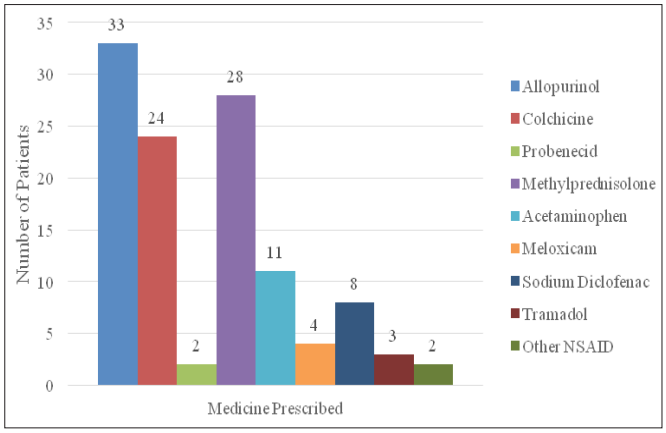
There were 191 patients who were diagnosed with gout or ICD 10 M10.0 during period January 2011 – December 2015, 137 samples were excluded consistent to exclusion criteria. Excluded samples were mainly due to the lack of urine dipstick data and had developed chronic kidney disease prior to the study. Other 54 patients was accounted as subjects. From these subjects, 40.4% suffered from gout arthritis less than 1 month, while 25.0% had chronic gout (more than 5 years). Tophi were developed in 38.9% subjects. Major subjects were male (88.9%) and aged below 60 years old (79.6%), with mean age was 50.80 ± 13.05 years old. Severe hyperuricemia was found in 30 subjects (58.8%) with mean serum uric acid level was 9.27 ± 2.82 mg/dL. Most subjects also suffered from dyslipidemia (72.2%). Hypertension found in 50% of subjects, 44% of them were stage-2 hypertension. As many as 40.7% of subjects suffered from hyperglycemia, while obesity happened in 44.4% of subjects, with the mean BMI was 26.69 ± 5.17 kg/m^2. The prevalence of albuminuria in gout arthritis patients was 20.4% (table 1).

Table 1. Characteristics of Gout Arthritis Patients in RSUPN Cipto Mangunkusumo in 2011−2015

Characteristics	N (%)
Age	
> 60 year-old	11 (20.4%)
≤ 60 year-old	43 (79.6%)
Sex	
Men	48 (88.9%)
Hyperuricemia	
Severe (≥ 9.0 mg/dL)	30 (58.8%)
Mild (7.0-8.9 mg/dL)	10 (19.6%)
Normal (< 7.0 mg/dL)	11 (21.6%)
No data	3
Hypertension	27 (50.0%)
Stage 1	8 (40.0%)
Stage 2	12 (60.0%)
No data	7
Hyperglycemia	22 (40.7%)
Obesity	24 (44.4%)
Dyslipidemia	39 (72.2%)
Albuminuria	11 (20.4%)
Duration of Illness	
< 1 month	21 (40.4%)
1-6 months	1 (1.9%)
6-12 months	7 (13.5%)
1-3 years	4 (7.7%)
3-5 years	6 (11.5%)
> 5 years	13 (25.0%)
Missing data	2
Tophus	21 (38.9%)

Allopurinol was the most prescribed medicine for subjects (33 patients). Metyhlprednisolone and colchicine were two other agents that were prescribed less frequent then NSAID in order to reduce the inflammation occurred in acute attack (figure 1). For hypertension treatment given to 27 subjects, angiotensin-converting enzyme inhibitor was the most anti-hypertensive agent used. Most patients (56.4%) with dyslipidemia frequently got statins rather than other agents.

Figure 1. Treatment Characteristics for Gout Arthritis Patients in RSUPN Cipto Mangunkusumo in 2011-2015



Tabel 2. Associations between Age, BMI, and Serum Uric Acid with Albuminuria

Risk factors	Albuminuria		p value	Mean difference (95% CI)
	Yes (N,%)	No (N,%)		
Age	56.00 ± 12.47 (11, 20.4%)	49.47 ± 13.00 (43, 79.6%)	0.140	6.53 (-2.21 – 15.28)
UA	9.98 ± 2.94 (9, 17.7%)	9.12 ± 2.80 (42, 82.3%)	0.411	0.86 (-1.23 – 2.94)
BMI	23.81 ± 2.89 (8,18.6%)	27.35 ± 5.37 (35,81.4%)	0.071	- 3.54 (-7.52 – 0.45)

UA: Serum Uric Acid; BMI: Body Mass Index

Table 3. Associations between Risk Factors and Albuminuria and the Statistical Test Used

Risk Factors	Albuminuria		p	OR (95% CI)
	Yes N (%)	No N (%)		
Age				
> 60 years old	4 (36.%)	7 (63%)	0.206	2.939 (0.675–12.798)
≤ 60 years old	7 (16.3%)	36 (83.7%)		
Sex				
Men	10 (20.8%)	38 (79.2%)	1.000	1.316 (0.38–12.574)
Women	1 (16.7%)	5 (83.3%)		
Hyperuricemia				
Severe	6 (20.0%)	24 (80.0%)	0.720	1.500 (0.330–6.822)
Mild and normal	3 (14.3%)	18 (85.7%)		
Missing data	3			
Hypertension				
Yes	6 (22.2%)	21 (77.8%)	0.735	1.257 (0.333–4.748)
No	5 (18.5%)	22 (81.5%)		
Stage of Hypertension				
Controlled and Stage 1	0 (0.0%)	8 (100.0%)	0.118	Could not be computed*
Stage 2	4 (33.3%)	8 (66.7%)		
Hyperglycemia				
Yes	5 (22.7%)	17 (77.3%)	0.721	1.275 (0.335–4.843)
No	6 (18.8%)	26 (81.2%)		
Obesity				
Yes	2 (8.3%)	22 (91.7%)	0.111	0.197 (0.035–1.123)
No	6 (31.6%)	13 (68.4%)		
Missing data	11			
Dyslipidemia				
Yes	9 (23.1%)	30 (76.9%)	0.708	1.950 (0.369–10.304)
No	2 (13.3%)	13 (86.7%)		

Severe hyperuricemia (≥9.0 mg/dL), mild and normal hyperuricemia (<9.0 mg/dL)

* The risk of stage of hypertension couldn't be computed as there was one cell that had 0 value

Independent T-test was used to analyze the association between age, BMI, and serum uric acid with albuminuria. It showed that there were no significant associations between all the risk factors with albuminuria (p value >0.05). However, there was quite a difference in mean age between the two groups (6.53 years; 95% CI -2.21–15.28). Moreover, the mean BMI of albuminuria group was lower than the non-albuminuria group (23.81 ± 2.89 vs 27.35 ± 5.37 kg/m^2, respectively), making it more interesting because this result was contradictive to others (table 2). When other factors were analyzed by chi square and fisher's exact test, there were no significant associations between all risk factors and albuminuria (table 3).

Discussion

This study showed us that 88.9% subjects were men, which is similar to the study conducted by Limanjaya, et al (81.96%).[7] Fewer women suffered from gout arthritis because of the estradiol effect which decrease uric acid serum level and prevent gout arthritis.[29] Most of gout patients were younger than 60 years old, with mean age at 50.80 ± 13.05. It is consistent with the previous study which stated the mean gout patients at 50.5 ± 13.0 years old,[30] and also consistent with theory which said that gout arthritis occurred frequently in the age of 50s.[31]

The mean of serum uric acid level found in this study (9.27 ± 2.82 mg/dL) was higher than in the study by Chen J, et al.[32] However, this result correlates with gout pathogenesis. Patients with uric acid serum more than 8 mg/dL are more likely to suffer from monosodium urate crystallization rather than patients with lower level of uric acid serum.[33] The prevalence of hyperuricemia in this study was also higher

than the previous study conducted in Indonesia by Darmawan, et al. which was found only 24.3% patients. The difference might be occured because of the different subject population, as we conducted a hospital-based study while this previous study conducted a population-based study.[1]

Hypertension prevalence in this study was lower than Krishnan, et al. (93%) and Choi, et al. (69.1%). It is proved that the different of races, lifestyles, and ages of subjects are affected the prevalence of hypertension..[9,34] However, the prevalence we found was higher than general Indonesian population (9.5%). This fact showed us that hypertension is more likely to happen in gout patients than in general population. It is in accordance with the result of study conducted by Yu, et al. (OR 7.21; 95% CI 7.00−7.44).[35,36] The less prevalence showed by this study also happened in hyperglycemia (40.7% in this study, vs 70.8%, 48.4%, and 53.7% in Chen J, et al, Choi, et al, and Fraile, et al, respectively).[32,34,37] The difference was caused by the different inclusion criteria and targeted population, which made the different races, lifestyles and characteristics of other illness between these studies.[21,38–40] However, the prevalence we found was higher than general Indonesian population (10.0%).[41] It indicates that hyperglycemia is also more likely to happen in gout patients than in general population.

Prevalence of dyslipidemia in subjects (72.2%) was higher than Choi, et al study (53.7% for hypertriglyceridemia and 47.4% for low HDL level) and than general Indonesia population prevalence (48.9% of low HDL level, 33.9% of high LDL level, and 24.8% of high total cholesterol level).[34,42] This might be happened due to the different inclusion criteria of dyslipidemia used in this study, which include all aspects of blood lipid test, thus the findings was bigger. The other findings with higher prevalence were also occured in obesity (44.4%), with mean BMI is also higher than Chen J, et al study (23,5% and mean BMI 25.0 ± 3.2 kg/m^2). The difference is happened due to the different criteria of obesity used in Chen J, et al study which defined obsesity with BMI > 27 kg/m^2.[32]

The prevalence of albuminuria in this study (20.4%) was higher than other studies, such as Yu and Berger (14.9%)[43] and Kuo, et al (9.8%).[44] The difference of population, leads to the different races and lifestyles, could explain this difference. Asian race is a predisposing factor of albuminuria compared to Caucasian (OR 1.42; IK 1.26−1.61).[21] Both race and lifestyle were risk factors of albuminuria which was not included in this study.[21,38–40]

There were no significant associations between all the risk factors with albuminuria. No significat association of albuminuria with age, sex, and other hyperuricemia factors might be happened due to the characteristic of gout patients. Gout patients are tend to be occured at the population with age 50s (in ≤ 60 years old group), men, and had severe hyperuricemia, with or without albuminuria, thus making it difficult to differentiate between the groups. The medications given to gout patients, such as allopurinol and colchicine, could also disturb the result of this study due to their protective effect to the kidney. [45–47] However, the prevalence of albuminuria was increasing from 16.3% in ≤ 60 years old group to 36.4% in the older group, which is consistent with Ramirez, et al. (*adjusted* OR 2.7; IK 95% 2.2−3.3).[48]

We found hyperglycemia had no association with albuminuria. This result was different from other studies[49,50] Hyperglycemia in diabetes patients could alter the basal membrane of glomerulus after 3−5 years.[13,51] The method to determine hyperglycemia in this study could not detect a long-term hyperglycemia condition, so this could be the reason why we found no association in this study. Meanwhile, for dyslipidemia, since our study used fewer sample size than other studies, the different rate of dyslipidemia observed in this study (9.8%) can not used to detect a significant difference.[26,52] Moreover, the majority of dyslipidemia patients in this study had used statin (56.4%), which could decrease the rate of albuminuria or proteinuria.[53]

Obesity also did not have any significant association with albuminuria. This result is also different from the others.[50,52] However, the prevalence of albuminuria in obese group was lower than in non-obese group (8.3% and 31.6%, respectively). The mean BMI of albuminuria group was lower than non-albuminuria group. All patients in non-obese group which developed albuminuria had other illnesses which were associated with albuminuria, such as tuberculosis, chronic heart failure, gout nephropathy, pneumonia, and stroke.[54–58]

Hypertension did not have any significant assosciation with albuminuria either. This result was inconsistent with the other studies due to the different characteristics of population, sample size, and method to determine albuminuria.[11,24,50,52] Moreover, most hypertension patients used angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) which can decrease the incidence of proteinuria and prevent end-stage renal disease (ESRD).[59,60] All albuminuria happened in stage-2 hypertension patients. This fact was consistent with the other studies which showed that high systolic or/and high diastolic pressure were the risk factors of proteinuria.[48,61] No significant association observed in this study was due to the fewer sample size and the missing data. Therefore, we recommend perform a bigger study to prove the association between hypertension (high systolic and diastolic pressures) and albuminuria in gout arthritis patients.

In spite of the fact that there were no significant association between the observed factors and albuminuria, this study showed us that there is a lot number of albuminuria occurring in gout patients. Since albuminuria has a predictive value on chronic kidney disease, the future study should seek the association between albuminuria and the incidence of chronic kidney disease in gout patients. Moreover, the fact that all gout patients who had stage-2 hypertension suffered from albuminuria were an indication that systolic and diastolic pressures were risk factors of albuminuria in gout patients. Therefore, precaution actions should be taken when dealing with gout patients who had stage-2 hypertension to prevent the progression of albuminuria. Future studies should also address the exact limit of blood pressure needed in gout patients in order to prevent the occurance of albuminuria and chronic kidney disease.

Lack of significant correlation found in this study was due to minimal sample size and data limitation, we do not assess the data of lifestyle which potentially confound the result. Thus, future studies should have a bigger sample size and measure

the population' lifestyle, as well as the other confounders like other comorbidities, and medicine taken by subjects. The use of other albuminuria test methods (albumin-creatinine ratio or 24-hour urine collection) is suggested to get numerical data, so that it is possible for future studies to seek the correlation between the risk factors and albuminuria more accurately.

Conclusion

The prevalence of albuminuria in gout patients in RSUPN Cipto Mangunkusumo in 2011−2015 was 20.4%. There were no significant correlation between age, sex, hyperuricemia, obesity, hypertension and stage of hypertension, hyperglycemia, and dyslipidemia with albuminuria. However, the prevalence of albuminuria was considerably high, especially in patients who had stage-2 hypertension. Therefore, preventive actions to those patients and future studies related to albuminuria's association with chronic kidney disease incidence in gout patients are needed.

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