ABSTRACT

**Aim**: determine renal function and factors that influence reduction in renal function among Minahasanese with chronic gout arthritis and tophi.

**Methods**: this is a descriptive cross-sectional study where study subjects are recruited using multi-stage sampling. The data are descriptively processed using T-test, Pearson correlates, and multiple regression analysis.

**Results**: the proportion of mild, moderate, and severe reductions in renal function in Minahasanese with chronic gout arthritis and tophi were as follows: 25 patients (69.7%), 7 patients (19.5%), and 5 patients (11%). According to Pearson correlation, only urinary uric acid excretion \( r=0.626, p=0.000 \). The same findings were found using multiple regression, only urinary uric acid excretion is significant \( p=0.001 \).

**Conclusion**: most Minahasanese with chronic gout arthritis and tophi suffer from a mild reduction in renal function associated with the amount of uric acid excreted in the urine, but not associated with age, serum uric acid level, duration of gout arthritis, or tophi. Correlation with hypertension and use of NSAID are not evident in this study.

**Key words**: chronic gout arthritis, tophi, uric acid excretion.

INTRODUCTION

Long-standing recurrent attacks of acute gout arthritis with severe hyperuricemia can cause deposits of monosodium uric crystals into the body tissue, including the joints, around the joints, blood vessels and renal tissue, as well as can causing the formation of uric acid renal stones.\(^1,2\) Before uric acid lowering drugs are found, 60% of patients with untreated gout arthritis will develop tophi in 10 years.\(^2,3\)

The prevalence rate of tophi among patients with gout arthritis varies from 3%, in a study by the Mayo Clinic, up to 21% at the Veterans Affairs Medical Center in Los Angeles, California.\(^4\) In Europe, gout arthritis is the cause of 1% of hemodialysis cases and renal transplant.\(^5\) While the prevalence of gout arthritis among Minahasanese is quite high, which is up to 29.2%.\(^3\)

The risk for renal disorder due to gout is closely related to the degree of hyperuricemia, particularly among patients with tophi.\(^1,4\) Uric acid sedimentation accompanied by inflammation in the renal interstitial tissue (uric nephropathy) and uric acid sedimentation (uric acid nephropathy) can be a process that bases the renal dysfunction in patients with gout.\(^1\) Nevertheless, other conditions that are almost always found with hyperuricemia, such as hypertension and diabetes mellitus, could ignite renal damage.\(^1,6,7\)

This study aims at determining renal function and factors that play a role in reducing renal function among patients from the Minahasa ethnic group suffering from chronic gout arthritis with tophi.

METHODS

This descriptive cross-sectional study was conducted from January to July 2000, with a study sample of Minahasanese with chronic gout arthritis with tophi. The diagnosis of gout arthritis is established based on the criteria for gout arthritis from the American College of Rheumatology (ACR), 1977, quoted from 6 Section C (findings of 6 out of 12 clinical signs and symptoms, laboratory or radiological findings); which includes more than one incidence of acute arthritis, maximal inflammation in a day, monarticular arthritis, redness in the joints, severe pain and swelling – particularly in the first metatarsophalangeal joint, unilateral arthritic attacks usually in the first metatarsophalangeal joint, also possibly in the tarsal joint, tophi, hyperuricemia, radiological findings of asymmetrical joint swelling,
subcortical cyst without erosion and no growth of microorganisms in joint fluid culture from the joint that suffers from inflammation during attacks.

The exclusion criteria were diabetes mellitus, heart disease, lung tuberculosis, hematological disease, and skin disease; use of diuretics, nicotinic acid, or low dose aspirin; as well as patients with acute attacks of gout arthritis and those unwilling to participate in the study.

The diagnosis of hyperuricemia was established based on the criteria from the Council for International Organisations of Medical Sciences (CIOMS), which is over 7 mg/dl for males and over 6 mg/dl for females, and uric acid excretion per 24 hours is considered low if less than 300 mg/dl, normal if 300-800 mg/dl and high if over 800 mg/dl on a low purine diet. The diagnostic criteria for hypertension is based on that of the Seventh National Committee on Detection, Evaluation, and Treatment of High Blood pressure (JNC VII) 2003. A diagnosis of anemia is established if the hemoglobin level is less than 12 g/dl. Renal function is established based on clearance creatinine test (CCT) obtained using the cockcroft-gault formula, which is (140-age) x bodyweight divided by (72 x serum creatinine), with 85% correction for females. Glomerular filtration rate (GFR) is considered normal if the CCT is equal to or over 90 ml/minute, slightly reduced if the CCT is 89 to 60 ml/minute, moderately reduced if the CCT is 59 to 30 ml/minute, and severely reduced if the CCT is 15 to 29 ml/minute; while renal failure is established if the CCT is less than 15 ml/minute.

Patients that met the study requirements underwent preparation using a low purine and free from alcohol, non steroidal anti inflammatory agents (NSAIDs), and uricosurics, for 5 days, and then blood samples were taken after a 10-hour fast. Urinary uric acid examination was conducted by collecting urine for 24 hours, using thymol as a preservative, and then measured as 24 hour excretion. In addition, midstream urinalysis was performed and blood samples taken for hemoglobin level, serum uric acid and serum creatinine enzymatic assessment using Cobas Mira auto-analyzer.

The study results were descriptively analyzed using

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age (year)</th>
<th>Hemoglobin (g/dl)</th>
<th>Serum uric acid (mg/dl)</th>
<th>24 hour uric acid excretion (mg/dl)</th>
<th>Duration of Illness (years)</th>
<th>Duration of tophi (years)</th>
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<tbody>
<tr>
<td>Subcortical cyst</td>
<td>30-39</td>
<td>&lt; 12</td>
<td>≤ 7</td>
<td>&lt; 300</td>
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<td>≥ 12</td>
<td>7.1-8.9</td>
<td>300-800</td>
<td>1-19</td>
<td>10-19</td>
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<tr>
<td></td>
<td>50-59</td>
<td></td>
<td>9-10.9</td>
<td>&gt;800</td>
<td>20-39</td>
<td>20-29</td>
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<td></td>
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<td></td>
<td>≥ 11</td>
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<td>≥ 40</td>
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<tr>
<td></td>
<td>≥ 70</td>
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Table 1. Distribution of Creatinine Clearance Test (CCT) According to Age, Hemoglobin Level, Serum Uric Acid Level, 24-Hour Uric Acid Excretion, Duration of Illness, and Duration of Tophi
percentage, T-test, as well as correlation and multiple regression analysis.

RESULTS

There were 41 patients with chronic gout arthritis with tophi, but only 36 patients fulfilled the criteria, all of which were males with an age range of 31 to 76 years (± 53.56 years). The distribution serum uric acid level according to age group can be found in Figure 1.

The range of hemoglobin level is 7.5 to 17.9 (± 13.77), serum uric acid level is between 5.6 to 13.9 mg/dl (± 9.35 mg/dl), uric acid excretion 24 hour between 48 to 831 mg/dl (± 327.3) and CCT between 22 to 89 ml/minute (± 53.25) in this study. 25 patients (69.5%) had a low GFR reduction, 7 patients (19.5%) had moderate GFR reduction, and 5 patients (11%) had severe GFR reduction. The duration of gout arthritis ranged from 0 to 53 years (± 18.47 years) and the duration of tophi ranges from 1 to 31 years (± 7.92 years). The distribution of CCT according to age, hemoglobin level, serum uric acid level, 24-hour uric acid secretion, duration of gout arthritis and duration of tophi can be found in Table 1.

According to Pearson correlation analysis, hemoglobin level and 24-hour uric acid excretion demonstrated significant correlations with CCT and duration of tophi (r=0.427; p=0.009 and r= 0.626; p=0.000 respectively). While multiple regression between age, serum uric acid, 24-hour uric acid excretion, duration of arthritis, and duration of tophi found, only 24-hour uric acid excretion to have significant influence with CCT (p=0.001).

Hypertension was found in 50% of cases, and based on statistical analysis using T-test, no significant difference was found between the CCT of hypertensive and non-hypertensive patients (p=0.05). Abnormal midstream urine was found in 19 patients (52.7%), consisting of proteinuria in 3 patients (8.3%), hematuria in 9 patients (25%) and leukocyturia in 7 patients (19.4%). History of use of short-acting non-steroidal anti-inflammatory agents (NSAID) was found in all patients (100%), with a frequency of use of 3 to 5 days for every pain attacks. None of the patients had previously used uricosuric agents. A family history of joint pain was found in 27 patients (75%).

DISCUSSION

Chronic renal failure is a cause of death in gout patients as found by the study by Tablot and Terplan,11 who evaluated 166 patients with of gout arthritis, 23 of whom died with chronic renal failure. Steele, quoted from 12 stated that hyperuricemia could cause renal dysfunction, as was supported by Klineberg et al, quoted from 12 who said that hyperuricemia could cause renal failure, even when no symptom was present (asymptomatic hyperuricemia). On the other hand, other researchers, such as Berger and Yu, quoted from 13 said that they did not find negative effects on renal function among patients with untreated
hyperuricemia. Fessel quoted from 13 also stated that no reduction in renal function was found in patients with asymptomatic hyperuricemia who underwent 4 years of observation.

Balance of uric acid in the body is regulated through the excretion of most uric through the kidneys, and a small proportion through the gastrointestinal tract through a passive process.1,5,14,15 Total uric excretion is reduced progressively along with the progress of kidney disease.1,14 During this stadium, hyperuricemia could be severe, or more severe acute attacks with tophi formation could occur, or on the other hand uric-induced kidney damage could occur through secondary mechanisms, known as uric monosodium crystal formation in the kidney parenchyme.12,14,15 Further reduction of kidney function could be caused by microtophi.1,11,14 The presence of microtophi, uric crystal aggregation, lymphocytes, monocytes, giant cells, and fibroblast in the interstitial tissue are characteristic changes in uric nephropathy.11,13 In patients with uric nephropathy, kidney tophi is found in the medullar pyramid, which could occur from tubular sedimentation or interstitial primary crystallization.1,11,15 The primary abnormality found in uric nephropathy is in the form of inability to concentrate urine.1,11,14

In this study, renal dysfunction is found in all patients with chronic gout arthritis with tophi, most of which is in the form of mild reduction of GFR, found in 25 patients (69.5%). Two patients (5.6%) were found with asymptomatic hyperuricemia with a CCT of 78 and 21 ml/minute each. Serum uric acid levels of 9-10.9 mg/dl were found in 18 patients each (50.4%), but no significant correlation was found between CCT and serum uric acid level (r=-1.954; p=0.276). In this study, 24-hour urinary uric excretion was found mostly in low levels (< 300 mg/dl), which is in 18 patients (50%), followed by normal excretion in 17 patients (47.22%); and statistically there was a correlation between reduced CCT and 24-hour excretion (r=0.626; p = 0.000). Histopathological renal abnormalities cannot be determined since patients did not undergo renal biopsy.

Primary nephropathy occurs due to interstitial uric or uric monosodium sedimentation or tubular uric acid formation,16 while secondary nephropathy occurs due to overlap between infectious factors with hypertension, or both. The actual mechanism of secondary nephropathy due to hypertension that could aggravate kidney abnormality is still unclear.11,13,15 In this study, 18 patients (50%) were found with hypertension, but it is unclear whether hypertension plays a role in the development of kidney dysfunction. However, it can be stated that hypertension in chronic gout arthritis with tophi facilitates reduction of kidney function.

Urinary abnormality such as mild proteinuria and abnormal urinary sedimentation is a common finding among patients with gout arthritis with renal abnormality.5,13 Midstream urinary abnormality is found in 19 patients (52.7%).

Patients who have never suffered from hyperuricemia but have developed tophi due to physico-chemical saturation, reside in a generally colder area, and tissue aging.17 Acute attacks is associated with reduced serum uric acid level, and thus normal uric acid levels are found during acute attacks; uric acid diuresis also occurs during acute attacks.7,17 In this study, 5 patients had serum uric acid levels of ≤ 7 mg/dl.

More than 80% of study patients with nephropathy suffer from tophi have suffered from gout for over 10 years, and mostly have not been adequately treated.7,14 In general, it takes a long time between the first symptom of gout until the development of tophi.6 After 10 years from the first attack, it turns out that over 50% of patients have not demonstrated tophi formation, but most have developed minimal sedimentation, and tophi formation is found in most patients 20 years later.4 Age is also a factor that plays a small role to CCT reduction; the duration of gout also plays a role, albeit minimally, but this cannot be clearly distinguished from the aging process.13 In this study, 17 patients (47.2%) were found to have suffered from gout arthritis for 20-39 years, and the time lapse between the development gout arthritis and the development of tophi of less than 10 years was found among 26 patients (72.2%). On statistical analysis, no correlation was found between reduction in CCT and age (r=-0.20; p=0.242), the duration of gout arthritis (r=0.050; p=0.774) and the duration of tophi (r=-0.095; p=0.583).

Erythropoetin deficiency anemia in patients with reduced kidney failure occurs at a CCT of less than 30 ml/minute in non-diabetic patients.9 In this study, there is a significant correlation between CCT reduction and hemoglobin level.

Chronic NSAID use can influence renal function, and almost all patients with tophi have suffered from reduced kidney function, where they are all NSAID users.4,18 All patients in this study use NSAID during acute attacks but not continuously. In this study, the role of NSAIDs in the reduction of kidney function cannot be eliminated.
CONCLUSION

Reduced renal function of various degree can occur in all study subjects, which come from the Minahasa ethnic group, who suffer from chronic gout arthritis with tophi. Nevertheless, most (69.5%) of study subjects suffer from mild renal dysfunction, and should undergo continuous evaluation, considering the potential for renal dysfunction among Minahasanese with gout arthritis and tophi in this study. Urinary uric acid excretion is significantly correlated with reduced renal function among Minahasanese with chronic gout arthritis and tophi; while age, serum uric acid level, duration of gout arthritis and tophi is not significantly correlated with reduced renal function. Correlation with other factors that can influence reduced kidney function, such as hypertension and NSAID, is not established in this study. Renal biopsy is required in order to establish histopathological changes.

REFERENCES