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Interplay between fat, muscle, bone mass, and oteophytes and risk for tophaceous gout

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ABSTRACT

Tophaceous gout is a common arthritis caused by the deposition of urate crystals and is related to limited joint function. Although there are reports that uric acid (UA) is associated with bone mineral density (BMD), little is known about the relationship between UA, osteophytes, and muscle. This cross-sectional case–control study was performed in patients with tophaceous gout. The control group included patients without gout. All subjects underwent BMD and body composition analyses. Age, sex, alcohol consumption, smoking, and radiography of both knees were recorded. Adjusted ORs for tophaceous gout were calculated using the logistical regression models. A total of 150 male patients were enrolled, including 65 individuals with tophaceous gout and 85 without gout. The mean age of the patients with tophaceous gout was 59.94±12.40 years, while that of individuals without gout was 61.29±11.57 years (p=0.492). Patients with tophaceous gout have a higher mean body mass index, fat mass, appendicular lean mass, BMD, and osteophytes. Multiple logistic regression analysis revealed that fat mass (OR 2.01, 95% CI 1.27 to 3.18), appendicular lean mass (OR 4.27, 95% CI 1.86 to 9.83), and osteophytes (OR 5.88, 95% CI 1.72 to 20.13) were significantly associated with tophaceous gout. In the current study, higher fat mass, high muscle mass, and osteophyte formation were found to increase the risk of tophaceous gout, as the association is the most than can be inferred from a cross-sectional study. Therefore, reducing body fat and weight management may prevent tophaceous gout.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Gout is closely related to the intake of high-purine foods, alcohol consumption, and obesity. In addition, some studies have revealed a relationship between gout and fat accumulation. This hints that the store of visceral fat instead of subcutaneous fat in gout is related to metabolic abnormalities and hyperuricemia

WHAT THIS STUDY ADDS

⇒ This study had shown for the first time that the association between tophaceous gout and risk factors is largely determined by fat mass.

⇒ Patients with tophaceous gout have a higher mean body mass index (BMI), fat mass, appendicular lean mass, bone mineral density, and osteophytes. Multiple logistic regression analysis revealed that fat mass, appendicular lean mass, and osteophyte were significantly associated with tophaceous gout.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings may have clinical implications in primary prevention strategies for chronic diseases, which may require monitoring of high visceral adipose tissue fat mass and consequent high plasma uric acid levels as potential prognostic factors. Besides, as part of the imaging evaluation in future tophaceous gout studies, the evaluation of new bone formation (NBF) may prove the pathogenesis and impact of NBF in the disease. However, this study reports only total fat mass and BMI. No measures of visceral fat or distinction between visceral and subcutaneous fat are mentioned.

INTRODUCTION

Tophaceous gout is a metabolic disorder that is often associated with recurrent attacks of gout resulting from the chronic deposition of monosodium urate crystals in involved joints. Hyperuricemia is the most important cause of gout development. It may be due to an decreased excretion, increased production of uric acid (UA) or both.[1 2] If not treated properly, it may lead to cardiovascular disease or chronic kidney disease.

Gout is closely related to the intake of high-purine foods, alcohol consumption, and obesity. In addition, some studies have revealed a relationship between gout and fat accumulation.[3] This hints that the store of visceral fat instead of subcutaneous fat in gout is related to metabolic abnormalities and hyperuricemia.[4] Therefore, reducing visceral fat should be a priority when caring for patients with gout.

In contrast, negative correlation has been found between UA levels and osteoporosis.[5 6] It has revealed UA can be associated with higher bone mineral density (BMD) at the lumbar spine and hip.[2] A study found higher serum UA levels reduced the rate of bone loss by 9.7 years.[7]

Tophaceous gout has some radiological changes, such as tophi and intra-articular erosions. Hypertrophic bone changes have also been noted.[8 9] These findings may provide reasons about the mechanisms of bone remodeling in tophaceous gout. However, whether it can fully explain that the correlation between bone density and tophaceous gout remains uncertain.

Although UA, fat mass, and bone density have been reported, there is not enough information on predictors of tophaceous gout. Therefore, the aim of this study was to conduct a case–control study to understand the factors to predict risk of tophaceous gout.

MATERIALS AND METHODS

We conducted a cross sectional case–control study in patients with tophaceous gout. The control group included patients without gout. All patients were recruited at the rheumatology clinic at Kaohsiung Chang Gang Memorial Hospital.

Study group

Diagnostic criteria for gout

We selected patients with gout according to the 2015 American College of Rheumatology/European League Against Rheumatism criteria. We recruited those with tophaceous gout.[10]

Inclusion criteria

1. Study group: Those with tophaceous gout were included.
2. Control group: Osteoarthritis Kellgren and Lawrence (K-L) grade 1 or 2.

Exclusion criteria:

1. Those with K-L grade 3 or 4.[11]
2. Those with infectious arthritis or rheumatoid arthritis.

General characteristics, covariates, and comorbidities

Subjects received a questionnaire to assess the existence of disease, medications being taken, and lifestyle variables. The subjects were asked to list medications and diseases in a questionnaire to be completed at home. Then, the research assistant checks the completeness and accuracy of the questionnaire in the presence of the subjects. Detailed interviews were conducted to confirm the presence of specific diseases (such as osteoporosis, coronary heart disease, diabetes, and osteoarthritis) that the subjects listed under their close cooperation. If in doubt, please provide written instructions certified by the responsible doctor.

The biochemical parameters examined included hemoglobin, urea, creatinine, calcium, phosphorus, and glycohemoglobin.

Radiography of knee joint

Both knees were imaged in weight-bearing position. All radiographs were read by a single trained observer, by K-L criteria.[11] The presence of osteophytes[12] in the medial and lateral tibiofemoral compartments of the knees will be recorded. All the degrees of joint space and osteophyte were clubbed together and recorded as presence or absence.

Dual-energy X-ray absorptiometry (DXA)

The BMD of the femoral neck, total hip and lumbar spine were assessed using DXA.[13] Total fat mass and appendicular muscle mass was assessed using a whole-body DXA (Lunar iDXA; GE Healthcare, Tokyo, Japan), and index was calculated as kilogram per square metre.

Radiography of knee joint

Both knees were imaged in weight-bearing position. All radiographs were read by K-L criteria.[11]The presence of osteophytes[12] in the medial and lateral tibiofemoral compartments of the knees were recorded. Those with either bilateral knee joints were recorded as presence or absence of joint space narrowing or osteophyte.

Statistical analysis

A t-test is used to compare continuous variables between groups, while a χ^2 test is used to assess the association between categorical variables. Logistic regression analysis is used to examine the association between the presence of tophaceous gout with osteophytes, BMD, muscle mass, and other parameters. A p value less than 0.05 is considered statistically significant. All statistical analysis uses SPSS V.23.0.

RESULTS

A total of 150 male patients were enrolled, including 65 with tophaceous gout and 85 without gout. Table 1 shows the comparison of the characteristics between patients with tophaceous gout and patients without gout. The mean age of the patients with tophaceous gout was 59.94±12.40 years,

Table 1 Characteristics of the patients enrolled in the study

Variables	Tophaceous gout (n=65)	Non-gout group (n=85)	P value
Age (years), mean±SD	59.94±12.40	61.29±11.57	0.492
Body mass index (kg/m^2), mean±SD	28.38±5.10	24.42±3.17	<0.001
Smoking, n (%)	7 (10.8)	14 (16.5)	0.225
Alcohol consumption, n (%)	7 (10.8)	8 (10.4)	0.496
Fat mass/height^2 (kg/m^2), mean±SD	9.73±3.80	6.91±1.78	<0.001
Appendicular lean mass/height^2 (kg/m^2), mean±SD	7.61±1.06	6.77±0.81	<0.001
Lumbar spine BMD (g/cm^2), mean±SD	1.03±0.15	1.11±0.32	0.08
Femur neck BMD (g/cm^2), mean±SD	0.72±0.11	0.68±0.10	0.017
Total hip BMD (g/cm^2), mean±SD	0.94±0.13	0.89±0.13	0.036
Knee joint space narrowing, n (%)	30 (46.2)	40 (47.1)	0.522
Knee osteophyte, n (%)	16 (24.6)	8 (9.4)	0.011

BMD, bone mineral density.

while that of the patients without gout was 61.29±11.57 (p=0.492). The mean body mass index (BMI) of the group with tophaceous gout (28.38±5.10 kg/m^2) was higher than that of the group without gout (24.42±3.17 kg/m^2) (p<0.001). Moreover, the fat mass and appendicular lean mass were found to be higher in patients with tophaceous gout (p<0.001). The total hip BMD was also higher in the group with tophaceous gout (p=0.038). There was no significant difference found between the lumbar spine and femoral neck BMD between the group with tophaceous gout and the group without gout. In addition, there was more osteophyte formation in the knee joint in the group with tophaceous gout (p=0.011). In this study, most of the study patients had K-L grade 2.

Logistic regression analysis showed that a high fat mass (p=0.003, OR 2.01, 95% CI 1.27 to 3.18) and a high muscle mass was associated with tophaceous gout (p=0.001, OR 4.27, 95% CI 1.86 to 9.83). Additionally, knee osteophyte formation was found to be associated with tophaceous gout (p=0.005, OR 5.88, 95% CI 1.72 to 20.13). In contrast, a higher femoral neck and total hip BMD was not associated with tophaceous gout (p>0.05) (table 2).

DISCUSSION

Although tophaceous gout is a common disease, its relationship with body composition remains uncertain. This study analyzed the relationships between these factors. The main finding of the study is that patients with high fat, high muscle mass and osteophyte formation have a higher risk of tophaceous gout.

According to reports, after adjusting for variables, the positive correlation between plasma UA and fat mass is still significant.[14] Visceral fat has been shown to be related to overproduction of UA as compared with subcutaneous fat in obese subjects[15] because it has metabolic activity and regulates many adipocytokines related to insulin resistance.[16] Insulin resistance can increase circulating plasma UA levels, increase renal tubular reabsorption of UA, and reduce urinary UA excretion.[17]

In the current study, the formation of osteophytes increased the risk of tophaceous gout. Quantitative analysis has demonstrated that new bone formation (NBF) is closely related to joint disease in tophaceous gout.[18] The features of NBF in tophaceous gout are osteophytes, sclerosis, and bone spurs. The findings that bone erosion and osteophyte are closely related to all the features of NBF indicate that bone loss and NBF may be related during remodeling of joints affected by tophaceous gout. In fact, the monosodium urate (MSU) crystals in tophus are surrounded by inflammatory cells and fibrovascular area in which there is organized collagen deposition.[19] It is suspected that those cause the formation of fibrovascular areas and can also lead to production of NBF. Apart from bone resorption markers such as interleukin-1 and tumor necrosis factor a (TNFa),[20 21] in the tophi, there is also transforming growth factor b (TGFb) to be found.[20] TGFb may lead to NBF.[22] Activation of bone morphogenetic protein and Wnt signaling pathway may also cause NBF patterns in joints affected by tophaceous gout.[23–25] So in future tophaceous gout studies, evaluating NBF as part of imaging evaluation may provide information on the mechanism and influence of NBF in the disease.

It is reported that there is a relationship between UA and bone density.[26] Those with high-serum UA are correlated with a less risk of osteoporosis and fractures.[27] High UA had lower urinary N-terminal telopeptide-1, a marker of bone resorption; this may explain the reason.[2] Our research results are consistent with the results of most previous studies and support the hypothesis that UA is beneficial to human bone health.

A kidney transplantation study showed serum UA is correlated with muscle strength and muscle mass.[28] Apart from this, the correlation had also been found in other studies.[29 30] UA may have benefit on bone; this may be by its antioxidant effect. UA may react with several oxidants and consists most of the antioxidant effect in plasma.[31] Lines of evidence have proven oxidative stress to be important in bone loss.[32 33] In this study, our findings suggest the benefit of UA on bone may be mediated by muscle mass. Previous studies have shown that some muscle-derived cytokines (eg, myostatin, insulin-like growth factor 1) may regulate bone metabolism, so there is interplay between the muscle and bone.[34] So, greater muscle mass is associated with better bone health.

Strengths and limitations

The study has its strength. This is the first to report a good relationship between tophaceous gout and lipid mass, muscle mass, and osteophyte formation. However, the limitations of this study need further attention. First, we did not measure antioxidants and antioxidant enzymes in plasma that may cause residual confounding effects, although we had adjusted for many other potential confounding factors. Second, this cross-section study limited its generalization, although the values of baseline and follow-up tophaceous gout data had been presented. Third, we use DXA instead of the golden method of MRI or CT to measure skeletal muscle mass[35 36]; however, DXA is a convenient method in clinical practice to measure muscle mass.

In conclusion, this study has shown for the first time that the association between tophaceous gout and risk factors is largely determined by fat mass (a specific measure of fat deposition) rather than BMI. Our findings may have clinical implications in primary prevention strategies for chronic

Table 2 Risk factors to predict tophaceous gout

Variables	Regression coefficient	SE	Wald	P value	OR (95% CI)
Body mass index	−0.281	0.167	2.817	0.093	0.76 (0.54 to 1.05)
Fat mass/height^2	0.699	0.233	8.994	0.003	2.01 (1.27 to 3.18)
Appendicular lean mass/height^2	1.452	0.425	11.651	0.001	4.27 (1.86 to 9.83)
BMD, femoral neck	−1.212	4.356	0.077	0.781	0.3 (0 to 1518.04)
BMD, total hip	−0.395	3.725	0.011	0.916	0.67 (0 to 998.91)
Osteophyte	1.771	0.628	7.951	0.005	5.88 (1.72 to 20.13)

BMD, bone mineral density.

diseases, which may require monitoring of high visceral adipose tissue fat mass and consequent high-plasma UA levels as potential prognostic factors. Besides, as part of the imaging evaluation in future tophaceous gout studies, the evaluation of NBF may prove the pathogenesis and impact of NBF in the disease.

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Competing interests None declared.

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Ethics approval This study involves human subjects and was approved by the institutional review board of Kaohsiung Chang Gung Memorial Hospital (IRB number 201800414A3). The subjects gave written informed consent to participate in the study before taking part.

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