Review Article
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Gout, obesity and bariatric surgery

Abstract

Gout is a common arthritis disease, characterized by high serum levels of uric acid. The disease is associated with many co-morbidities, such as: hypertension, type 2 diabetes, ischemic heart disease, kidney disease and obesity, and even has an impact on mortality. It appears as a form of arthritis, characterized by joint inflammation, commonly occurring in the first metatarsophalangeal joint.

Abdominal adiposity, obesity, as well as metabolic syndrome were all found to be associated with the increased risk of developing gout. Weight loss, associated with a reduction in serum urate levels, was found to lower incidence of gout. Many studies have demonstrated that weight loss following bariatric surgery resulted in reduced serum uric acid levels. Nevertheless, some studies have demonstrated that immediately after the surgical procedure, a significantly higher frequency of gout attacks was observed, which was significantly decreased after the first postoperative month up to 1 year. Thus, it is recommended that preoperative prophylactic treatment should be administered to patients with a history of gout and that serum uric acid levels should be followed shortly after the surgery to prevent an increase in the incidence of gout attacks.

Volume 8 Issue 4 - 2018

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Received: June 26, 2018 | **Published:** August 01, 2018

Introduction

Gout is a common arthritis disease, characterized by high serum levels of uric acid. Many risk factors were found to contribute to the development of the disease. Accumulated evidence has pointed out that gout is highly associated with obesity and metabolic syndrome. Moreover, it has been demonstrated by various clinical studies that upon major weight loss, the risk for the development of gout, as well as the frequency of attacks are reduced in correlation with a reduction in the serum uric acid levels.

In this review we will present the association between high levels of serum uric acid, gout and obesity. The beneficial effects of weight loss, especially by bariatric surgery, will be discussed.

Gout disease

Gout is both an inflammatory and a metabolic disease. It is accompanied by significant pain, functional impairment, increased work absence causing reduced productivity, reduced quality of life and presents an economic burden for the individual and the community.[1–3] The disease is associated with co-morbidities, and even has an impact on mortality.[4]

Symptoms

Acute gout appears as a form of arthritis, characterized by joint inflammation, commonly occurring in the first metatarsophalangeal joint, reaching maximal intensity within 24 hours. Involvement of the inter-tarsal, ankle and knee joints is also common, while the involvement of hand, wrist and olecranon bursal is present only in patients who have been suffering from the disease for manyyears.[5]

Gout is mostly diagnosed by its clinical presentation of swelling and redness of the first metatarsophalangeal joint. The American College of Rheumatology criteria are the most widely used guidelines for diagnosis of gout and include: Presence of characteristic urate crystals in the joint fluid, asymmetric swelling within a joint on radiography, attack of mono-articular arthritis, negative culture of joint fluid for microorganisms during attack of joint inflammation, development of maximal inflammation within one day, hyperuricemia, joint redness, more than one attack of acute arthritis, as well as pain or redness in the first metatarsophalangeal joint and subcortical cysts without erosions on radiography. The disease is usually followed with hyperuricemia, defined as a plasma urate level higher than 420µmol/l (7.0mg/dl) in males and 360µmol/l (6.0mg/dl) in females.[6]

Pathogenesis

Gout is caused by prolonged high serum levels of uric acid, possibly caused by inactive uricase, the enzyme responsible for the breakdown of uric acid to allantoin or by impairment of renal excretion. The balance between uric acid production and excretion determines its serum concentrations. High serum levels of uric acid appear to contribute to impaired nitric oxide production, endothelial dysfunction, increased vascular stiffness, inappropriate activation of the renin-angiotensin-aldosterone system, enhanced oxidative stress, and maladaptive immune and inflammatory responses.[7] Furthermore, hyperuricemia may not be benign and appears to be accompanying the worldwide obesity pandemic, metabolic syndrome, hypertension, diabetes and kidney and cardiovascular disease states.[8]

As a result of high serum uric acid levels, monosodium urate (MSU) crystals are formed, inducing local and a systemic inflammatory response, resulting in the activation of caspase-1, interleukin -1β and 6, tumor necrosis factor α, and neutrophil chemotactants.[5,9] Consequently, enormous amounts of neutrophils are recruited to the joint, sustaining the inflammatory response and inducing damage in the surrounding tissues.[10]

However, it is important to mention that the majority of people with hyperuricemia do not have gout. Nevertheless, the risk of gout raises with the increasing serum urate levels. In addition, the comorbidities of gout, renal and cardiovascular diseases, are commonly associated with asymptomatic high levels of serum uric acid.[11]

Frequency

The prevalence of gout is increasing worldwide, probably due to population aging, changes in diet and lifestyle, and increasing rates of obesity.[12–15] In the population under 65 years of age, males have a fourfold higher prevalence of gout than females. However, this ratio is reduced to 3:1 male to female over 65 years of age.[13] The mean age of gout onset is approximately 10 years older in females than males,

probably due to the estrogen's protection effect - enhancing the renal tubular urate excretion in pre-menopausal females.[16]

Risk factors

Overweight and obesity, metabolic syndrome, hypertension, high levels of blood cholesterol and chronic kidney disease have been associated with increased risk of gout.[17] Obesity was found in many prospective cohort studies as one of the strongest risk factor for hyperuricemia and gout.[18–22]

Additional risk factors include: Increasing age; Genetic Factors such as: SLC22A12—SLC22A12 which encodes urate anion transporter 1, SLC2A9—SLC2A9 encoding glucose transporter type 9, and BCG2 which encodes the adenosine triphosphate - binding transporter 2. Mutation in these genes, which are involved in renal urate transport, were found in gout patients and may explain certain subjects' predisposition for developing hyperuricemia and gout;[23] alcohol consumption, especially beer and liquor;[24] increased consumption of meat and seafood;[25] fructose intake;[26] use of diuretics; and taking various medications such as β-blockers and angiotensin-II receptor antagonists.[27]

On the other hand, low fat dairy products, coffee, supplementation of vitamin C and cherry consumption have been shown to be potentially protective against the development of gout by acutely lowering serum uric acid.[23] Calcium-channel blockers and losartan appear to reduce the risk of developing hyperuricemia and gout.[27]

Diabetes, hypertriglyceridemia and hypercholesterolemia are associated with significantly increased risk of gout flares in patients with prevalent gout.[28]

Co-morbidities

Gout is associated with a number of serious co-morbidities, such as: hypertension, type 2 diabetes, ischemic heart disease, kidney disease and obesity.[29] It is also associated with premature death due to a high frequency of comorbidities.[30] Indeed, increased risk of death in gout patients with renal dialysis and cardiovascular diseases has been demonstrated.[31–34] A recent meta-analysis of six studies revealed that the prevalence of chronic kidney disease of stage 3 or above in gout was estimated at 24%.[35] Gout was found to be associated with a high risk of coronary heart disease, heart failure, atrial fibrillation, aortic stenosis, ischemic stroke and peripheral vascular disease.[36] Moreover, drugs targeting those comorbidities were found to be associated with increased risk of gout.[37] In addition to that, links between increased serum levels of uric acid and brain dysfunction, low performance on memory-related tasks, as well as age-related illnesses and Parkinson's disease have been reported.[38]

The prevalence of metabolic syndrome is 62.8% in patients with gout, compared with 25.4% in non-gout patients. In the third National Health and Nutrition Examination Survey (NHANES) the prevalence of abdominal obesity was found to be 62.9% in gout patients vs. 35.3% in non-gout patients.[39]

Co-morbidities can also be a contraindication for drugs used in the management of acute flares of gout disease. For example, in patients with renal failure, colchicine and NSAIDs should not be used.[40]

Treatment

The American College of Physicians developed guidelines providing clinical recommendations for the management of gout. The recommendations are based on a systematic review of various randomized, controlled trials; systematic reviews; and large observational studies published between January 2010 and March 2016.

The treatment of gout patients is aimed to lower serum uric acid in order to allow MSU crystals to dissolve and to prevent the creation of further MSU in the joints, as well as to relieve the inflammation symptoms. According to the European League against Rheumatism (EULAR), non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine are considered as first-line agents for the treatment of acute gout attacks and should begin as soon as possible. Oral or intra-articular corticosteroids are recommended for those who cannot tolerate the above medications, or who have contraindications.[41] In patients with frequent attacks and contraindications to colchicine, NSAIDs and corticosteroids, interleukin-1 blocker should be considered.[42]

Allopurinol, used to decrease high blood uric acid levels, should be started during an acute attack (at 50–100mg per day or less for those with severe renal impairment) and should last until suitable serum uric acid levels, monitored every two to five weeks, are maintained.[29] However, according to the American College of Physicians long-term urate-lowering therapy is not recommended after a first gout attack or in patients with infrequent attacks.[43] If a decreased level of serum uric acid cannot be achieved with allopurinol, then febuxostat, a uricosuric drug or a combination of a xanthine oxidase inhibitor with a uricosuric drug should be considered. For patients with refractory gout, pegloticase is recommended.[42] Weight control appears to lower serum uric acid levels, thus the role of diet plays a very important part in gout management.[44] According to the British Society for Rheumatology Guideline for the Management of Gout from 2017, a well-balanced low in fat and sugars diet, and high in vegetables and fiber should be encouraged; excessive intake of alcoholic drinks and high purine foods should be avoided; inclusion of soy beans and vegetable sources of protein, and cherries in the diet are recommended.[45]

Obesity and gout

Overweight and obesity are becoming endemic and are associated with insulin resistance, type 2 diabetes, dyslipidemia , hypertension, cholelithiasis, various malignances, non-alcoholic steatohepatitis, gastro-esophageal reflux, obstructive sleep apnea, degenerative joint disease, lower back pain, polycystic ovary syndrome, as well as a remarkable reduction in life expectancy.[46]

Abdominal adiposity, obesity, as well as weight gain were all found to be associated with the increased risk of developing gout.[20,47,48] Men with a Body mass index (BMI) over 27.5 kg/m^2 were 16 times more likely to report gout attacks than men with a BMI<20 kg/m^2.[49]

Interestingly, the risk of recurrent gout attacks and its association to obesity have been contradictory. Zhang et al.,[50] reported that there was no association between BMI and the risk of recurrent attacks of gout.[50] Cea Soriano et al.,[51] compared a large British data base of newly diagnosed gout patients with matched controls and discovered a significantly reduced association between obesity and recurrent gout attacks than between obesity and the risk of gout development. In contrast, Nguyen has shown that a decrease in BMI reduced the risk of recurrent attacks of gout, while an increase in BMI augmented the risk of recurrent attacks of gout, suggesting that this could be a better tool to evaluate the association between obesity and the recurrence of gout attacks.[52]

Many studies have demonstrated that weight reduction upon low-calorie diets leads to reduced serum uric acid levels in people with obesity.[53] Weight loss, associated with a reduction in serum urate levels, was also found to lower incidence of gout.[25] Nielsen et al.,[41] performed a systematic review and found out that a weight loss of >7kg resulted in a beneficial effect on serum uric acid at medium-term/long-term follow-up and that weight loss of >3.5kg showed beneficial effects on gout attacks on medium-term/long-term follow-up.[54] Hence, The American College of Rheumatology and the European League against Rheumatism guidelines recommend weight loss for gout management in obese subjects.[41]

Bariatric surgery and gout

Bariatric surgery is currently the most effective intervention for weight loss and long-term weight maintenance. This has been consistently demonstrated in numerous randomized controlled trials and cohort studies.[55,56] Bariatric surgery is a safe and effective tool to achieve a marked weight loss. The eligibility criteria for accessing bariatric surgery includes the following: BMI≥40kg/m^2 or a BMI between 35 and 39.9kg/m^2 with comorbidity and previous unsuccessful weight loss efforts.[57] The rates of bariatric surgery procedures are increasing sharply. The surgical procedure usually results in a weight loss of 20–40kg and a 10–15kg/m^2 reduction in BMI.[58] Weight loss is maximal after 1–2 years and the weight slowly increases until year 8–10 after which body weight stabilizes.[59]

The common types of weight-loss surgery are laparoscopic Roux-en-Y gastric bypass, laparoscopic sleeve gastrectomy, laparoscopic one anastomosis gastric bypass, laparoscopic adjustable gastric banding and laparoscopic biliopancreatic diversion with or without duodenal switch.

Postoperative complications and side effects are common among obese patients. Venous thromboembolism and anastomotic leak are the most fearsome complications. Dumping syndrome occurs in about half of patients after gastric bypass during the first month. Nutritional deficiencies can be developed (mostly deficiencies of vitamin B12 and iron) and an increase in the incidence of gallstones has been observed.[60]

Over the years it has been evident that bariatric surgery restored insulin sensitivity and improved type 2 diabetes, lipid profile and blood pressure control, obstructive sleep apnea, and quality of life. Moreover, retrospective cohort studies have demonstrated that bariatric surgery leads to a decrease in mortality.[60,61]

In most studies, serum uric acid levels were a strong predictor of mortality from cardiovascular disease in healthy middle-aged men.[62] Other studies suggest that serum uric acid is a strong and independent risk factor for diabetes.[63]

Many studies have demonstrated that weight loss following bariatric surgery resulted in reduced serum uric acid levels in people with obesity and metabolic syndrome.[64] It seems that weight loss induced a significant reduction in the production of urate, as well as an increased renal clearance of urate.[65]

Furthermore, weight loss following bariatric surgery was found to be associated with reduced inflammatory responses to Monosodium Urate (MSU) crystals, including significant reductions in the production of interleukin-1β, 6 and 8, and TNFα secretion from peripheral blood mononuclear cells.[64,66] This response could contribute to reduce the risk of gout flares. Indeed, a significant reduction in the frequency of gout attacks after bariatric surgery was observed in many studies.[67–69] Interestingly, data from some studies revealed that weight loss among patients with uncontrolled gout resulted in a significant suppression in the frequency of gout attacks, regardless of a rather small reduction in serum uric acid levels. Hence, it can be assumed that the weight loss influences the outbreak of the disease through the regulation of inflammatory responses to MSU crystals.

Moreover, it has been shown that adoption of Low-Purine Diet, which is recommended for gout, reduced the risk of gout attacks after bariatric surgery in gout patients. Schiavo et al.,[69] studied the effect of postoperative low-purine diet on the frequency of gout attacks (n=24), as compared to a normal-purine diet (n=16) in 40 patients diagnosed with gout before the sleeve gastrectomy procedure. One year after the surgery, a significant decrease in serum uric acid levels was observed in both groups, with a more significant decrease noted in patients following low-purine diet compared to those on a normal-purine diet ($p<0.001$). This was also demonstrated by the allopurinol requirements and by the frequency of gout attacks ($p<0.001$). A year after the sleeve gastrectomy, the low-purine diet group no longer required allopurinol therapy, and suffered no gout attacks.[69] Thus, bariatric surgery has an indirect effect on decreasing mortality from these chronic diseases, alongside the effect on gout disease.

Table 1 presents studies published over the years in which various types of bariatric surgery in obese gout patients affected serum uric acid levels as well as the frequency of gout attacks.

Gout attacks may develop in the early post-operative period, within 8 days after surgery. Kang et al. compared patients with gout who developed postsurgical gout attacks with patients with gout who did not develop gout attacks after surgery. They discovered that elevated presurgical serum urate levels (>/=9mg/dl) and failure to administer colchicine prophylaxis were found to be risk factors for postsurgical gout. Postoperative gout attacks were found in patients who demonstrated higher pre-surgical serum uric acid levels and a more rapid and profound decrease in uric acid levels after surgery. The authors suggested that post-surgical gout attacks could be prevented by controlling pre-surgical uric acid levels.[70] In a study performed by Friedman et al.,[71] who monitored previous diagnoses of gout patients, 33.3% of them experienced an acute attack postoperatively.[71]

Nevertheless, some studies have demonstrated that the effect of bariatric surgery on serum uric acid levels and the frequency of gout attacks vary in time after the procedure. Romero-Talamáset et al.,[72] studied 99 bariatric surgery gout patients and compared them to 56 non-bariatric gout patients. Immediately after the surgical procedure, a significantly higher frequency of gout attacks was observed in the bariatric surgery group compared to that observed in patients who underwent other procedures. However, the incidence significantly decreased after the first postoperative month up to 1 year. Remarkably, a significant reduction in serum uric acid levels was observed 13-months after bariatric surgery.[72] Dalbeth revealed that among obese people with type 2 diabetes and with no history of gout, serum uric acid concentrations increased during the first days after a laparoscopic sleeve gastrectomy and reduced 1 year after surgery. It is thus suggested that the immediate post-surgery rise in serum uric acid levels is due to renal dysfunction associated with the surgery procedure and as a response to surgical tissue disruption, as well as metabolic effects, catabolism, or dehydration from fasting or rapid weight loss. Additionally, dramatic changes in serum uric acid levels might trigger gout attacks.[54,64, 65]

Table 1 presents studies published over the years in which various types of bariatric surgery in obese gout patients affected serum uric acid levels as well as the frequency of gout attacks

Author, publication, year	Study type	Patients	Results
Schiavo[69] Obes Surg. 2018	Retrospective	obese (n=40)	One year after the surgery the decrease in serum uric acid level of the low-purine diet group was more significant compared to the normal-purine diet group ($p < 0.001$)
Maglio[68] Ann Rheum Dis. 2017	Prospective	obese (n=3981) bariatric surgery (+) n=1982 bariatric surgery (-) n=1999	Bariatric surgery was associated with a reduced incidence of gout compared with usual care (adjusted HR 0.60, 95% CI 0.48 to 0.75, $p<0.001$)
Chen[67] Transplant Proc. 2016	Retrospective	morbid obesity, poorly controlled new-onset diabetes and gout after kidney transplantation (n=1)	Total remission of gout after 1 year of follow-up
Romero-Talamás[72] Surg Obes Relat Dis. 2014	Retrospective	obese, gout bariatric surgery (+) n=99 bariatric surgery (-) n=56	The incidence of early gouty attack in the first month after surgery was significantly higher in the bariatric group than the nonbariatric group (17.5% versus 1.8%, P = 0.003) In the bariatric group, 23.8% of patients had at least one gouty attack during the 12-month period before surgery, which dropped to 8.0% during postoperative months 1–13 (P = 0.005) There was a significant reduction in uric acid levels 13-months after bariatric surgery compared with baseline values (9.1 +/- 2.0 versus 5.6 +/- 2.5 mg/dL, P= 0.007)
Dalbeth[64] Ann Rheum Dis. 2014	Prospective	obese, type 2 diabetes (n=60) gout (n=12)	In gout patients, uric acid serum levels above therapeutic target levels were reduced from 83% at baseline to 33% one year after surgery (p=0.031)
Dalbeth[66] Ann Rheum Dis. 2013	Prospective	obese, type 2 diabetes (n=20)	Reduced uric acid serum levels and reduced inflammatory responses to Monosodium Urate (MSU) crystals upon mean follow-up of 256 days
Friedman[71] Surg Obes Relat Dis. 2008	Retrospective	obese (n=411) gout (21)	Only 33.3% of the gout patients had an acute attack postoperatively
Antozzi[65] Obes Surg. 2005	Retrospective	obese (n=1,240) gout (n=5)	2 out of gout patients had acute attacks during the postoperative period

Conclusion

In conclusion, the literature contains solid data indicating that obesity is associated with the increased risk of developing gout. Many studies have revealed that weight loss following bariatric surgery resulted in reduced serum uric acid levels and the amelioration of inflammatory responses to MSU crystals. Consequently, a decreased in risk to develop gout as well as lowering the frequency of gout attacks is demonstrated. However, in some of the studies, shortly after the surgery, a rise in serum uric acid levels in addition to a higher incidence of gout attacks was observed, while in the long run (≥1 year after the surgery) both serum uric acid levels and incidence of gout attacks were reduced. Thus, in view of these findings we recommend that preoperative prophylactic treatment should be administered to patients with a history of gout. Moreover, serum uric acid levels should be followed shortly after the surgery and treated accordingly in order to prevent an increase in the incidence of gout attacks.

Acknowledgments

None.

Conflicts of interest

The author declares there are no conflicts of interest.

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