International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 8; Issue 08 (C); August 2019; Page No.19748-19751
DOI: http://dx.doi.org/10.24327/ijcar.2019.3825.19751

Review Article

EFFECT OF BARIATRIC OPERATIONS ON GOUT DISEASE: LITERATURE REVIEW AND RETROSPECTIVE STUDY ON 68 GOUT PATIENTS

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Article History:
Received 13th May, 2019 Received in revised form 11th June, 2019 Accepted 8th July, 2019 Published online 28th August, 2019

Key words: Bariatric operations on Gout Disease

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. Accumulative evidences have pointed out that gout disease is highly associated with obesity and metabolic syndrome. Moreover, it was 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 to a reduction in the serum uric acid levels.

The prevalence of gout is increasing worldwide, and obesity is one of the most common risk factors for gout development.[1] Weight loss is associated with a reduction in serum urate levels[2-4] and with a lower incidence of gouty arthritis.[4], [5] The American College of Rheumatology and the European League against Rheumatism guidelines recommend weight loss for gout management in obese subjects.[6 ,7]

Bariatric surgery is the most effective means of achieving substantial and sustained weight loss in obese subjects.[8]

METHODS

2200 obese subjects from Assia medical center from January 2011 until January 2017, of them 201 patients had gout disease, of them 68 had follow up in our system, the rest of the patients (133patients) don't have follow up so we exclude them from the study. All patients were preoperatively diagnosed with gout and were taking medications such as non-steroidal anti-inflammatory drugs (NSAIDs) or allopurinol and passed bariatric operations such as sleeve gastrectomy, roux en y gastric bypass, laparoscopic adjustable gastric band or one anastomosis gastric bypass.

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We reviewed all these patients retrospectively. Parameters assessed included weight, body mass index (BMI), weight loss, type of bariatric operation, uric acid level before and until 2 years after the operation, a medical history of gout, any onset of acute gouty attacks after the operation.

RESULTS

These patients had a mean age of 50.7 (range 20 to 74) years and a mean BMI of 41.1 kg/m2. 17 patients (25%) presented with acute gouty attacks in the first month postoperatively.

58 patients (85%) had at least one gout attack until one year before the operation in comparison to 23 patients (33%) one year after the operation.

There was a decrease in uric acid level after the operation at one year and two years with p value less than 0.001.

In our series, the prevalence of gout was of 9.1% and the incidence of acute attacks was 25% in the patients with a previous diagnosis of gout in the first month after the operation. There was resolution of the disease due to weight loss in our series of 46 patients (67%).

LITERATURE REVIEW

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 economic burden for the individual and the community [9]. The disease is in association with co-morbidities, and even has an impact on mortality [10].

Symptoms

Acute gout appears as a form of arthritis, characterized by joint inflammation, commonly occurring in the first meta-tarsophalangeal joint, reaching maximal intensity within 24 hours. Involvement of the inter-tarsal, ankle and knee joints is also common, while involvement of hand, wrist and olecranon

bursal is present only in patients who have been suffering from the disease for many years [11].

Gout is mostly diagnosed by its clinical presentation of swelling and redness of the first meta-tarsophalangeal 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 meta-tarsophalangeal joint and subcortical cyst without erosions on radiography. The disease is usually followed with hyperuricemia, defined as a plasma urate level higher than 420 μmol/l (7.0 mg/dl) in males and 360 μmol/l (6.0 mg/dl) in females [12].

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 [13]. 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 [14].

As a result of high serum uric acid levels, monosodium urate monohydrate (MSU) crystals are formed, inducing local and systemic inflammatory response, resulting with the activation of caspase-1, interleukin -1β and 6, tumor necrosis factor α, and neutrophil chemotactants [15] Consequently, enormous amounts of neutrophils are recruited to the joint, sustaining the inflammatory response and induce damage the surrounding tissues. [16]

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However, it is important to mention that a large majority of people with hyperuricemia do not have gout; but the risk of gout increases with increasing serum urate level. Also, the co-morbidities of gout, renal and cardiovascular diseases, are commonly associated with asymptomatic high levels of serum uric acid [17].

Frequency

The prevalence of gout is increasing worldwide, probably due to population aging, changes in diet and lifestyle, and increasing rates of obesity [17]. 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 [18]. 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 [18].

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 [19]. Obesity was found in many prospective cohort studies as one of the strongest risk factor for hyperuricemia and gout. [20].

Additional risk factors include: Increasing age; Genetic Factors including: SLC22A12-SLC22A12 which encodes urate anion transporter 1, SLC2A9-SLC2A9 which encodes glucose transporter type 9, and BCG2 which encodes the adenosine triphosphate -binding transporter 2. Mutation in this genes, which are involved in renal urate transport, were found in gout patients and may explain certain subjects' predisposing for developing hyperuricemia and gout [18) alcohol consumption, especially beer and liquor [18]; increased consumption of meat and seafood [18]; fructose intake [18]; use of diuretics; and taking various medications such as β-blockers and angiotensin-II receptor antagonists [21].

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 [18]. Calcium-channel blockers and losartan appear to reduce the risk of developing hyperuricemia and gout [21].

Diabetes, hyper-triglyceridemia and hypercholesterolemia are associated with significantly increased risk of gout flares in patients with prevalent gout [22].

Co-morbidities

Gout is associated with a number of serious co-morbidities, such as: hypertension, diabetes mellitus type 2, ischemic heart disease, kidney disease and obesity [23]. It is also associated with premature death due to a high frequency of co-morbidities [17]. Indeed, increased risk of death in gout patients with renal dialysis and cardiovascular diseases has been demonstrated [11]. 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% [17]. Gout was found to be associated with high risk of coronary heart disease, heart failure, atrial fibrillation, aortic stenosis, ischemic stroke and peripheral vascular disease [17]. Moreover, drugs targeting those co-morbidities were found to be associated with increased risk of gout [17]. In addition to that, links between increased serum levels of uric acid and brain dysfunction, low performance on memory-related tasks, as well as ageing-related illnesses and Parkinson's disease have been reported [24].

The prevalence of metabolic syndrome is 62.8% in patients with gout, compared with 25.4% in non-gout patients [25]. 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 [17]. 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 [17].

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 [23]. In patients with frequent attacks and contraindications to colchicine, NSAIDs, corticosteroids, and interleukin-1 blocker should be considered [Richette 2016].

Allopurinol, used to decrease high blood uric acid levels, should be started during an acute attack (at 50-100 mg per day or less in those with severe renal impairment) and last according to the serum uric acid levels monitored every two to five weeks [23]. 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 [26]. 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 [27].

Weight control appears to lower serum uric acid levels, thus diet plays a very important part in gout management [25].

DISCUSSION

Overweight and obesity are becoming endemic and are associated with insulin resistance, type 2 diabetes, dyslipidemia, hypertension, cholelithiasis, various malignances, non-alcoholic steato-hepatitis, gastro-esophageal reflux, obstructive sleep apnea, degenerative joint disease, lower back pain, polycystic ovary syndrome, as well as a remarkable reduction in life expectancy [28].

Abdominal adiposity, obesity, as well as weight change were all found to be associated with increased risk to develop gout [19] [29].

Interestingly, the risk of recurrent gout attacks and its association to obesity have been contradictory. Zhang *et al*. reported that there was no association between BMI and the risk of recurrent attacks of gout [30]. Cea Soriano *et al*. screened a large British data base of newly diagnosed gout patients in comparison to matched controls and found out a significantly smaller extent of association between obesity and recurrent gout attacks than between obesity and the risk of gout development [31]. On the other hand, 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 [32].

In our series17 patients (25%) presented with acute gouty attacks in the first month postoperatively.

58 patients (85%) had at least one gout attack until one year before the operation in comparison to 23 patients (33%) one year after the operation.

There was a decrease in uric acid level after the operation at one year and two years with P value less than 0.001.

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 [28, 29]. Moreover, retrospective cohort studies have demonstrated that bariatric surgery leads to a decrease in mortality [28]

In most studies, serum uric acid levels are a strong predictor of mortality from cardiovascular disease in healthy middle-aged men [33]. Other studies suggest that serum uric acid is a strong and independent risk factor for diabetes [34]. Bariatric surgery is currently the most effective intervention for weight loss and long-term weight maintenance.

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This has been consistently demonstrated in numerous randomized controlled trials and cohort studies [35]. So there is indirect effect of bariatric surgery on decreasing mortality from these chronic diseases alongside the effect on gout disease.

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, TNFα secretion from peripheral blood mononuclear cells [29]. 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.

Hence, it can be assumed that the weight loss influences the outbreak of the disease through regulation of the inflammatory responses to MSU crystals. 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.

In our study 25 % of patients who followed previous diagnosis of gout experienced an acute attack at the first month postoperatively.

Remarkably, a significant reduction in serum uric acid levels was observed 12-months after bariatric surgery.

There was no significant difference between one type of operation over other. In relation to effect on gout or uric acid level.

There was no correlation between gout disease changes and sex, age of the patient or BMI.

CONCLUSION

Shortly after the surgery, there is higher incidence of gout attacks in the first month post-operatively so we recommend preoperative prophylactic treatment for these patients but in the long run (≥ 1 year after the surgery) incidence of gout attacks were reduced.

Serum uric acid levels decreased significantly after the operation at one year and two years follow-up.

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