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A comprehensive review on gout: the epidemiological trends, pathophysiology, clinical presentation, diagnosis and treatment

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Abstract

The current review was planned to assess updated knowledge about gout and to highlight the various areas which need to be focussed upon for better healthcare. Relevant articles published in English language were reviewed by utilising various databases including Google Scholar, Springer Link, Science Direct and MEDLINE. Data revealed a precipitating number of gout cases from the developed countries, while the developing countries on the other hand were found to be faced with an even higher threat. The risk factors and pathophysiology of gout are immaculate and clearly established. Hence, appropriate measures can be explored and worked on to pinpoint diagnosis, and economical treatment. In order to lessen the elevated global health burden along with revolutionising the patient's quality of life, an immediate action is required in certain aspects, like the adoption of a healthy modified lifestyle, a reduction in exposure to risk factors, robust prophylactic measures, bettering awareness, and an approach to early diagnosis followed by optimal treatment protocols.

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Key Words: Gout, Inflammation, Hyperuricemia, Allopurinol, Xanthine oxidase.

Introduction

Gout is well-known for decades as a chronic inflammatory condition of the joints.[1] In the past, gout was considered one of the benign diseases associated majorly with over-eating and to some extent of alcohol consumption. However, advanced studies and research revealed its roots in metabolic disorder, finding its origin with urate crystals, making deposits in joints, kidney, skin and various other tissues.[2] It is also termed "men's disease" owing to a high rate of incidence amongst males compared to females. The overall prevalence in men is estimated to be four times that of women. Females enjoy a comparative leverage because of the presence of estradiol that exhibits inhibitory action on urate crystal synthesis.[3] Gout finds a major association with a number of co-morbidities, like diabetes,[4] stroke, myocardial infarction (MI) and hypertension (HTN) amongst several others.[5] Altogether, with other co-morbidities, it gives a major rise in the rate of mortality and an overall decline in life expectancy.[5] Gout can be expressed as a raised serum uric acid, i.e., hyperuricemia, with levels reaching >6.8mg/dl. The rise in the levels of serum uric acid causes the generation of urate crystals, immediately followed by the formation of renal stones and backed with tophi that eventually lead to gouty arthritis.[1,3] The spectra of the disease extend from subclinical hyperuricemia, mapping its way to acute gouty arthritis and ultimately chronic tophaceous gout. The latter persists for a protracted duration and leads to a nastier stage called chronic arthopathic gout.[6] The prevalence of gout can be traced amongst some of the developed countries, while the rate is considerably high when seen with under-developed countries. Some of the initiating factors of the disease worth mentioning are high sugar intake, alcohol consumption, a high intake of meat and protein-rich diet. Acute pain, subcutaneous tophi, and persistence of low-

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grade inflammation for longer time cause deformation of joints, restricted mobility and permanent disability that negatively influences a patient's quality of life (QOL).[7] Deposition of the uric acid crystal may often damage kidneys and the condition may even progress to chronic nephritis. An immense increase in the economic burden of the disease has been observed worldwide, contributed majorly by malpractices, including suboptimal disease care, poor diagnosis, lack of communication between patient and healthcare providers, little awareness and understanding of the disease and unavailability of medicines.[8] Consequently, a greater number of the patients are witnessed by hospitals that in turn raise the overall cost of the treatment.[9] Presence of various co-morbidities makes the estimation of the exact economic burden of gout a bit difficult. However, steps can be taken to reduce this overall burden over the economy due to gout by promoting maximum awareness, controlling the symptoms, introducing a healthy lifestyle, timely and accurate diagnosis followed by optimised recovery protocols and treatment.[10]

The current narrative review was planned to provide streamlined information regarding gout, the most prevalent type of arthritis.[1,4,8]

Methods and Results

Literature was searched on various databases, including Google Scholar, Springer Link, Science Direct and MEDLINE, without any time limit. Search key words included: 'gout', 'gouty arthritis', 'hyperuricemia', 'gout economic burden' and 'prevalence, diagnosis and treatment for gout'. The search was narrowed down by referring articles exclusively subjected to human studies and published in the English language. Also, the search was restricted to research papers, literature reviews and systematic reviews.

The articles included focussed on the objectives of the current study and took a critical view on epidemiological trends, pathophysiology, clinical presentation, diagnosis and treatment of the gout. Articles excluded were the ones that lacked

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thorough information and did not comply with the objective of the present study, comprised epidemiological trends, pathophysiology, clinical presentation, diagnosis and treatment of the gout.

Of all the articles screened, 52 were shortlisted. After full-text review, 35(67.3%) articles were included.

Epidemiology: All around the globe, the human population is faced with frequently occurring inflammatory arthritis called gout.[1,4,8] Chang-Fu et al. published an epidemiological study revealing that the overall incidence and prevalence of gout has increased immensely over the past few years. The incidence of disease is uneven around the world and the occurrence is greater in the Pacific regions. Genetic factors can play a role as some ethnic groups are more prone to developing gout.[11] The United States of America (USA) and Europe top the chart with the highest number of gout affectees, with manifold increase over the last two decades. In Canada, the prevalence is considerably increased and in 2012, about 3.8% gout cases were reported.[12] The frequency of gout has increased in the USA in the past few years and the terns still continues. Approximately 8.3 million individuals are suffering from gout and the rate of incidence is higher in men (6.1 million) compared to women (2.2 million). The United Kingdom (UK) has reported having more than 700,000 people suffering from gout. The annual number of outdoor gout patients visiting the hospital in the United Kingdom is estimated to be four million.[13] As per another estimate, there are 4 males and 1.4 females in every thousand, annually affected by gouty arthritis, especially the ones aged >45 years.[1,3] On the other hand, the occurrence of hyperuricemia is prevalent in females, particularly in the post-menopausal ones. The rate of incidence is no lesser in the USA where almost 3 million self-reported cases of hyperuricemia were documented in a survey.[14] The high financial burden is linked to an increased prevalence of gout in the UK due to suboptimal treatment and management.[15] In New Zealand, around 9.3% to 13.9% of Māori men and 14.9% of Pacific island men suffer from severe

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gout.[16] A study conducted using nationwide data showed that the rate of gout incidence has substantially increased in the entire New Zealand population and the frequency is more (>25%) in the elderly Pacific and Māori men.[17] Higher number of hospital visits due to gout is reported in Asian than Caucasian subjects. The frequency of gout occurrence is reported to be high in mainland China,[18] while in Germany, the adult population shows >1% of gout patients. Not only European countries exhibit an alarming prevalence of high serum uric acid levels, but it is also evident is Asian countries, like Indonesia (18%), Taiwan (10-52%), Turkey (12%), China (6-25%), South Korea (5%) Thailand (9-11%) and Saudia Arabia (8%).[19] Till date, exact number of gout cases in Pakistan are not known and epidemiological statistics are required in order to evaluate risk factors and to have improved diagnosis.[20] Pathogenesis of the gout: Gout is a metabolic disorder resulting from the augmented formation of uric acid. It was first documented by Egyptians in 2640BC and it was known as the "disease of kings" as it is mostly associated with lifestyle. The term gout is coined from Latin word "gutta" meaning drop.[21] The heightening level of uric acid (>7mg/dl), primarily an end-product of purine metabolism, is the result of a disorder. Normally within the body, purines are transformed to the hypoxanthine, and then further transformed to uric acid by the action of hypoxanthine oxidase. Uric acid is converted to allantoin through the action of uricase, an enzyme excreted by the kidneys in mammals. The fundamental mechanism for the development of gout is an amplified serum level of uric acid following a reduced renal excretion.[22] The excretion of uric acid is mainly governed by renal secretion and absorption. The reabsorption process of uric acid is carried out by urate transporter-1. An amplified formation and dwindled excretion lead to a rise in the serum concentration of uric acid, which successively converts into monosodium urate crystals.[5] The presence of uric acid subsists as needle-shaped crystals, open for identification and consumption by the neutrophils and monocytes. The inflammatory response is initiated via

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the release of interleukin 1 (IL-1) and added cytokines, subsequently initiating an acute gout attack. This follows the action of neutrophils that with the ingested crystals grow closer and forming a tight packing. This ultimately advances to cell death, led by a unique pattern, presenting a phase specified as tophaceous gout.[23] The inflammosome encompassing a multi-molecular structure is a pro-cytokine, responsible for activating IL-1 that in turn exhibits the inflammatory response. Supplementary mediators are also part of the inflammation constitutes of IL-6 and alpha-tissue necrosis factor. Conversely, IL-1 inhibitors impede the discharge of IL-1 and, therefore, contribute to receding the inflammatory response. There were many mechanisms discovered by which uric acid stimulates the inflammation and have influence on innate immunity, and, hence, they are also known as "danger signal". However, further investigations are needed to know the cellular and molecular basis of the pathogenesis which would be helpful in recognising the new sites for drug-binding that can be beneficial in the treatment of gout. [24]

Clinical presentation and diagnosis: Acute gout manifests with symptoms of swelling, intense pain and soreness around the joints. An asymptomatic period may be experienced between the gout attacks that are referred to as inter-critical gout.[25] Acute gout is reported with high fever, leukocytosis and shedding skin throughout the inflamed area, closely resembling cellulite. The term "podagra" is specifically reserved for acute gout, referring to the condition when the very first metatarsophalangeal joints are influenced by the urate crystals. Acute gout comes with clear signs of flares with a distinct fashion presenting as immensely inflamed area accompanied by discomforting pain lasting for around 5-10 days.[26] The asymptomatic hyperuricemia can continue for a couple of years, while flares may dissolve within this duration. The crystals, on the other hand, may display propagation and intense pain accompanying inflammation, and ultimately may enter into the phase of chronic gout. In the case of chronic gout, production of tophi with unique features occurs that can be traced and

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diagnosed via physical examination and various imaging techniques. These tophi can be located in certain regions, namely cutaneous tissues, bones and articular spaces.[27] The presence of flare and pain makes routine activities and movement challenging for the patients, followed by permanent disability that adversely affect the patient's QOL.[2,5] The urate crystals are not limited to a particular organ, and, instead, may develop chalky deposit in the eyes though asymptomatic. A variety of eye pathologies, such as ulcerative keratitis, may occur following the crystals piling up in the cornea. This is a rare condition though.[28]

The diagnosis of the disease is based on the presence and identification of urate crystals coming through a smart and active clinical approach. This, besides being the gold standard diagnosis, is barely practised in routine. Failing to perform the synovial aspiration on a regular basis, the clinical diagnosis and judgment is based upon physical examination and patient history.[29] Some of the tools aiding in the detection of crystals are readily available, such as ultrasonography (USG) and microscopy. Another sensitive approach is a non-invasive dual-energy computed tomography (CT) technique that detects uric acid crystals. It offers diagnostic imaging by producing coloured images of crystals visible for a distinct identification of the subclinical tophus and the tophus volume. However, there is a need to refine the diagnostic methods.[30]

Prevention and treatment: High incidence of gout across the globe makes it necessary to have immediate identification of associated risk factors and lifestyle modifications to offer better prevention. Dietary habits, such as daily consumption of coffee, soft drinks and sugar, specifically fructose, increases the chances of gout. A controlled diet with partial or complete removal of precipitating factors and supported by healthy lifestyle promises prevention. Precautionary measures against gout incorporate the intake of more fluid and having a diet with low animal protein.[31] Routine ingestion of fresh vegetables, whole grains, nuts, fruits and dairy products gives an added advantage. A

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healthy routine with regular exercise, controlled body weight and use of vitamin C supplements, also limit the chances of gout. The management and treatment protocols of gout revolve around bringing down the serum level of uric acid, i.e., as low as 6mg/dl. In order to attain this status, medicines, like allopurinol and probenecid, play a pivotal role.[32] Drugs, for example, aspirin, diuretics, nicotinic acid, lactate infusion, testosterone, xylitol, ethambutol and pyrazinamide, should be taken cautiously as these may stimulate increased uric acid production and may worsen the gout. The regularly-acquired medicines to counter gout also include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and adrenocorticotropin hormone.[33] In addition, xanthine oxidase inhibitors, together with uricosuric, are frequently used. For the management of acute gout, the use of systemic corticosteroids stands out as the most effective means of treatment that comes with no substantial adverse effects.[34] In case of patients either resistant to or contraindicated with the use of allopurinol can switch therapy to febuxostat as a substitute drug for the treatment of gout.[35]

the current review does have a few limitations. It is a non-systematic review that included only articles related to human studies. Also, manuscripts for which full text was not available and that ones that were not published in the English language were also excluded.

Recommendations

It is suggested that advance molecular studies should be carried out to further explore the gout pathogenesis which would be helpful in recognising the targeted areas of drugs to counteract the disease.

Moreover, exploration of literature revealed that comprehensive epidemiological studies are not available, especially with regard to the developing countries. Such studies, as such, are recommended so that geographical variation, related risk factors and rate of morbidity and mortality with treatment outcomes over time can be evaluated.

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Conclusion

The distribution of gout, remains uneven, with developed countries more likely to face the economic burden via its negative influence of patients' QOL. There is a dire need for optimised treatment strategies.

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