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PREVALENCE OF HYPERURICEMIA AND GOUT AND THEIR RELATIONSHIP TO CERTAIN RISK FACTORS: A SYSTEMATIC REVIEW

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ABSTRACT **Background/ objectives:** The frequency of related comorbidities, all-cause mortality, and societal costs are all on the rise, and so is the burden of gout and hyperuricemia globally. This systematic review aims to investigate the recently published literature on the prevalence and risk factors of gout and hyperuricemia. **Methods:** PubMed, Web of Science, Science Direct, and Cochrane Library were systematically searched to include the relevant literature. Rayyan QRCI was used throughout this systematic approach. **Results:** Our results included eleven studies with a total of 204,759,079 patients diagnosed with gout and/ or hyperuricemia. The reported total prevalence of hyperuricemia was 40,169,245 (19.6%), and the prevalence of gout was 6,192,105 (3.02%). The included studies recorded a rising incidence of gout and hyperuricemia. **Conclusion:** Gout is thus an increasing problem over the world, and to address and improve widespread poor care, international cooperation efforts are needed. Hyperuricemia and gout affected males more than females. Older age, obesity, male gender, less activity, a diet heavy in purines, and lower educational levels all had an impact on blood UA concentration. These are high-risk populations that need to have their UA levels regularly checked.

KEYWORDS : Gout; Hyperuricemia; Uric acid; Risk factors; Systematic review.

INTRODUCTION

Gout is a type of arthritis caused by the deposition of monosodium urate (MSU) crystals in the joints after a sustained rise in uric acid levels over the MSU saturation point. Given that they raise uricemia, which is one of the main—if not the only—risk factors for MSU crystallization, certain dietary or lifestyle factors have been demonstrated to raise the risk of gout [1].

Gout and hyperuricemia appear to be separate but closely related diseases; 85–90% of hyperuricemic patients do not exhibit gout-like clinical symptoms. According to a previous study, asymptomatic hyperuricemia, intermittent gout, and chronic gout are the three stages that follow each other in the temporal link between hyperuricemia and gout [2].

The term "asymptomatic hyperuricemia" refers to hyperuricemia that does not exhibit gout-like symptoms. It has been demonstrated that the degree of hyperuricemia can accurately predict when flares will occur [3, 4]. Gout prevalence has increased by 100% in the past 30 years, which is out of line with the 42% increase in the global population or the increase in life expectancy [5]. According to the Global Burden of Disease Study from 2017, 41.2 million persons worldwide are predicted to have gout, which is more than double the number of those with rheumatoid arthritis [5, 6]. In the US alone, 9.2 million persons (3.9% of US adults) have gout [7]. Gout is more common and occurs more frequently in older persons and racial/ethnic minorities [8].

The understanding of gout risk factors has significantly advanced recently, with emphasis on the significance of obesity, lifestyle factors, comorbidities, and genetics. Most risk factors for gout make people more likely to have high uric acid levels. Recent investigations have confirmed the significance of hyperuricemia as a risk factor for the onset of gout. In the Malmö Preventative Study, the absolute risk of developing gout in adults with hyperuricemia (serum urate >405 mol/l (6.75 mg/dl)) was 13.3% in men and 17.7% in women after more than 25 years of follow-up, compared to 2.7% and 1.9%, respectively, in those with serum urate 360 mol/l (6 mg/dl) [9].

Obesity is a significant risk factor for gout and is believed to play a significant role in the disease's increased prevalence and incidence. In a 2018 meta-analysis, individuals with obesity (BMI 30 kg/m2) had a >2-fold higher risk of having gout than those with a BMI of 30 kg/m2 (adjusted RR (aRR) 2.24, 95% CI 1.76-2.86) [10].

Complex relationships exist between gout, hyperuricemia, and comorbidities, with some diseases predisposing to these conditions while others develop as a result of gout [11]. Recent studies have corroborated earlier findings with classic cardiovascular risk factors, CVD, and CKD (such as hypertension and hyperlipidemia). The occurrence of comorbidities before and after a first diagnosis of gout was examined in a significant study using data from the UK's Clinical Practice Research Datalink (CPRD) [56]. This investigation verified the well-known links between gout and later CVD and renal disease and the risk factors for gout, including hypertension, hyperlipidemia, and renal illness.

Hypertension and the use of diuretics both increase the risk of developing gout, according to a meta-analysis of cohort studies [11]. This systematic review aims to investigate the recently published literature on the prevalence and risk factors of gout and hyperuricemia.

Methodology

This systematic review was conducted in accordance with accepted standards (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA) [13].

Study Design and Duration

This was a systematic review conducted between July and August 2023.

Search strategy

A thorough search of four major databases, including PubMed, Web of Science, Science Direct, and Cochrane Library, was done to find the relevant literature. We restricted our search to English and considered each database's unique requirements. The following keywords were converted into PubMed Mesh terms and used to find the relevant studies; "Gout," "Hyperuricemia," "Uric acid," "Prevalence," and "Risk factors." The Boolean operators "OR" and "AND" matched the required keywords. Publications with full English text, available free articles, and human trials were among the search results.

Selection criteria

We considered the following criteria for inclusion in this review:

- Study designs that investigated the recently published literature on gout and hyperuricemia prevalence and risk factors.
- Studies conducted between 2020-2023.
- English language.
- Free accessible articles.

Data extraction

Rayyan (QCRI) was used to detect duplicates in the search strategy output [14]. The researchers refined the combined search results using a set of inclusion/exclusion criteria to assess the relevancy of the titles and abstracts. The reviewers thoroughly read each paper that matched the inclusion requirements. The writers discussed dispute-resolution techniques. The permitted study was uploaded using a previously generated data extraction form. The authors extracted data about the study titles, authors, study year, country, participants, gender, the prevalence of gout, the prevalence of hyperuricemia, risk factors, and main outcomes. A separate sheet was created for the risk of bias assessment.

Strategy for data synthesis

Summary tables were created using information from pertinent research to provide a qualitative analysis of the findings and study components. The most effective method for using the data from the included study articles was selected once the data for the systematic review were extracted.

Risk of bias assessment

The ROBINS-I risk of bias assessment method for non-randomized trials of treatments was used to assess the quality of the included studies [15]. The seven topics that were assessed included confounding, participant selection for the study, classification of interventions, deviations from intended interventions, missing data, assessment of outcomes, and selection of the reported result.

RESULTS

Search Results

A total of 405 study articles resulted from the systematic search, and 53 duplicates were deleted. Title and abstract screening were conducted on 352 studies, and 290 studies were excluded. 62 reports were sought for retrieval, and only 5 articles were not retrieved. Finally, 57 studies were screened for full-text assessment; 35 were excluded for wrong study outcomes, and 11 for the wrong population type. Eleven study articles were included in this systematic review. A summary of the study selection process is presented in **Figure 1.**

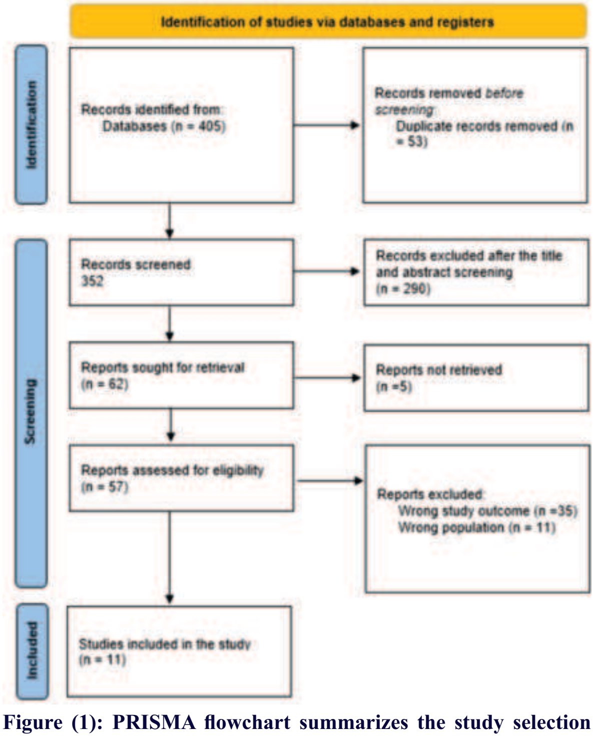

Figure (1): PRISMA flowchart summarizes the study selection process.

Characteristics of the included studies

Table (1) presents the sociodemographic characteristics of the included study articles. Our results included thirteen studies with a total of 204,759,079 patients diagnosed with gout and/ or hyperuricemia. Four studies were conducted in Saudi Arabia [16-19], four in China [20-23], one in Japan [24], one in the United Kingdom (UK) [25], and one in New Caledonia [26]. Five studies were retrospective in nature [16, 17, 19, 24], three were cross-sectional studies [١٨, 22, 26], and two were cohort studies [20, 25].

Table (2) presents the clinical characteristics. The reported total prevalence of hyperuricemia was 40,169,245 (19.6%), and the prevalence of gout was 6,192,105 (3.02%). The included studies recorded a rising incidence of gout and hyperuricemia. It is also reported that males were more affected than females [17, 18]. Old age, obesity, male gender, decreased exercise, purine-rich diet, and lower educational levels all had an effect on serum UA concentration, and these are considered high-risk groups which require regular monitoring for UA levels [18, 19, 21, 26]. Gout was associated with various cardiovascular (CVS) comorbidities [20, 25].

Table (1): Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Age range (months)	Males (%)
Dwid et al. 2020 [16]	Cross-sectional retrospective	Saudi Arabia	1978	53.4 ± 15	1511 (76.4)
Ghamri et al. 2022 [17]	Retro spective	Saudi Arabia	1206	44.3 ± 14.2	447 (37.1)
Shaikhomar & Header 2020 [18]	Cross-sectional	Saudi Arabia	100	46.89±17.01	77 (77)
Alenezi et al. 2020 [19]	Retro spective	Saudi Arabia	117	54.8	62 (53)
Han et al. 2023 [20]	Cohort	China	204,179,060	46.48 ± 0.20	NM
Zhang et al. 2023 [21]	Cross-sectional retrospective	China	642	47±16	605 (94.2)
Mu et al. 2023 [22]	Cross-sectional	China	58	50.7□± □17.5	49 (84.5)
Song et al. 2022 [23]	Cross-sectional retrospective	China	78,130	18->70	38013 (48.7)
Akari et al. 2022 [24]	Retrospective cohort	Japan	64,677	47.1±11.3	57 758 (89.3)
Zho et al. 2022 [25]	Cohort	UK	431,967	57.7 ± 7.93	194311 (44.9)
Bardin et al. 2022 [26]	Cross-sectional	New Caledonia	1144	37.7 ± 12	577 (50.4)

DISCUSSION

The prevalence of comorbidities associated with gout, all-cause mortality, and societal expenses are all on the rise globally. Gout is still not properly managed despite major improvements in knowledge of risk factors and treatment modalities. In this study, the reported prevalence of hyperuricemia was (19.6%), and gout was (3.02%).

A previous meta-analysis estimated the pooled prevalence of hyperuricemia in China was (13.3%) which was lower than our finding [27]. A recent global study reported that 5.21 million people aged 15 to 39 had gout worldwide in 2019, with the annual incidence significantly rising from 38.71 to 45.94 cases per 100,000 people between 1990 and 2019 [28]. Demographic characteristics like age, sex, and ethnicity have an impact on the occurrence of gout. Genetics, comorbidity patterns, and dietary variations based on ethnicity can all enhance gout risk. Gout prevalence in the non-Hispanic black population was 4.8% in the NHANES survey conducted in the USA for the years 2015 to 2016, 4.0% in the non-Hispanic white population, and 2.0% in the Hispanic population [29]

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Prevalence of hyperuricemia	Prevalence of gout	Conclusion	ROBIN-I
Dwid et al. 2020 [16]	1116 (56.4)	1978 (100%)	38.8% of patients were given allopurinol for trivial hyperuricemia, whereas 39% lacked a prescription reason the prescribing doctor had noted. Except in some circumstances, there is not any strong evidence to support the idea that treating asymptomatic hyperuricemia is beneficial.	Moderate
Ghamri et al. 2022 [17]	145 (12)	1206 (100%)	Hyperuricemia occurred 12% of the time and was more common in men than in women. The serum UA levels and lipid profile did not significantly correlate. Age, BMI, and sex all had an effect on serum UA concentration. Therefore, we suggest that elderly patients and patients who are obese be monitored for changes in serum UA concentrations.	Moderate
Shaikhomar & Header 2020 [18]	18 (18)	100 (100%)	Males comprised 100% of the hyperuricemic participants (18% of the total study population), and purine-rich diets, decreased exercise, and lower educational levels were probable causes. Hyperuricemia was also linked to an increase in visceral fat levels.	High
Alenezi et al. 2020 [19]	58 (49.6)	117 (100%)	A favorable relationship between serum ferritin, serum transferrin, and serum hemoglobin in Saudi patients and serum uric acid. Even in the absence of associated symptoms, undiagnosed hemochromatosis or iron overload should be considered when there are excessive uric acid values.	Moderate
Han et al. 2023 [20]	40,044,228 (19.6%)	9,158,600 (4.1%)	Patients with HF plus high uric acid (HUA) or gout were 1.37 and 1.45 times more likely to experience all-cause mortality in the long-term follow-up compared to patients without HUA or gout. Ambulatory patients with HUA or gout were also 2.46 and 2.35 times more likely to have HF.	High
Zhang et al. 2023 [21]	121 (18.8)	521 (81.2)	The DECT method to examine the systemic burden and location of urate deposition in symptomatic gout and asymptomatic hyperuricemia. The burden of urate deposition is greater in individuals with symptomatic gout, and the distribution is more evident in the foot/knee, even though preclinical urate deposition can occur in people with asymptomatic hyperuricemia.	Moderate
Mu et al. 2023 [22]	40 (68.9)	18 (31.1)	Patients with hyperuricemia and gout have higher levels of uric acid in their tears than healthy individuals. Tear IL1 levels and tear uric acid values had a statistically significant positive connection, indicating a relationship between ocular inflammation and hyperuricemia.	High
Song et al. 2022 [23]	13829 (17.7)	2500 (3.2)	In comparison to earlier studies of the Chinese population and even certain industrialized nations, the prevalence rates of HUA and gout among Chinese adults between 2015 and 2017 were significantly higher. It further reveals that a number of variables, such as sex, age, residency country, nationality, smoking, and further complicating metabolic disorders,	Moderate

			have varied effects on the morbidities of HUA and gout.	
Akari et al. 2022 [24]	46280 (71.5)	14519 (22.4)	A medication specifically designed to lower serum uric acid levels was not administered to nearly half of patients with newly diagnosed hyperuricemia and/or gout.	Moderate
Zho et al. 2022 [25]	62752 (14.5)	12508 (2.9)	There is a reliable correlation between gout and various forms of CVD and hyperuricemia. Additionally, while the MR studies in which we used only genetic variants for hyperuricemia and gout imply that gout is not a causal factor in the development of CVDs but rather that the level of blood urate is, our findings suggest that other gout-related factors may have an impact.	High
Bardin et al. 2022 [26]	658 (57.5)	38 (3.3)	In New Caledonia, gout and hyperuricemia were very common, even in persons with European ancestry.	Moderate

We also found that males were more affected than females [17, 18]. The GBD 2017 study also found that males accounted for a large portion of the gout burden [30]. Gout is more prevalent in middle-aged men than in women, particularly in premenopausal women [31-33]. It is yet unknown what causes the difference in gout incidence between sexes. Only a small number of studies have examined the causes of the variation in occurrence by sex, despite the fact that gout has been studied for decades [34].

Based on earlier research, a few potential causes of the sex difference in gout have been put forth. Women over 50 have a higher life expectancy and a higher prevalence of hypertension than men, which increases the likelihood that they may get gout [34]. Inappropriate prescribing has reportedly occurred more frequently in women than in males among adults over 65 [35]. There were no obvious differences found in a meta-analysis of studies that looked at gout risk variables according to sex [36].

We found that old age, obesity, male gender, decreased exercise, purine-rich diet, and lower educational levels all had an effect on serum UA concentration, and these are considered high-risk groups which require regular monitoring for UA levels [18, 19, 21, 26]. Recent research has emphasized the significance of hereditary and obesity-related variables as major contributors to hyperuricemia. According to a 2018 meta-analysis, genetic variation in urate levels was more common than dietary variations [37]. The population-attributable risk of obesity, however, was estimated to be 44%; in contrast, the population-attributable risks for the DASH diet and alcohol use were 9% and 8%, respectively [38]. This is despite the fact that the variances in hyperuricemia explained by obesity, non-adherence to the DASH diet, alcohol use, and diuretic use were generally low.

We also found that gout was associated with various CVS comorbidities [20, 25]. Cardiovascular disease (CVD) is the leading cause of death, and gout is linked to a 17% greater risk of all-cause mortality than those without gout [39]. In addition, those with renal illness had a 1.78 times higher risk of cause-specific mortality than those without gout [39]. Although rheumatoid arthritis has seen a decline in excess risk of premature mortality relative to the general population over time [40], this trend has not been seen in gout, with similar excess risk of mortality for patients diagnosed with gout between 1999 and 2006 and 2007 and 2014 [41].

CONCLUSION

In this systematic review, the prevalence of hyperuricemia and gout was relatively high, and this prevalence was markedly rising. Hyperuricemia and gout affected males more than females. Older age, obesity, male gender, less activity, a diet heavy in purines, and lower educational levels all had an impact on blood UA concentration. These are high-risk populations that need to have their UA levels regularly checked. Gout was also associated with CVS comorbidities. Gout is anticipated to be significantly influenced by comparable increases in the frequency of comorbidities and obesity, and efforts to reduce gout will be based in part on addressing these issues. Gout is thus an increasing problem over the world, and to address and improve widespread poor care, international cooperation efforts are needed.

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