Review of Modifiable Risk Factors for Gout in Asia

Faktor Risiko yang dapat Dimodifikasi pada Gout: Sebuah Tinjauan Pustaka

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Abstract

Gout is the most common inflammatory arthritis in the world, including in the Asia region. Gout is a debilitating, yet preventable disease. The general principle of gout prevention is to regulate circulating UA concentration and other related comorbidities. Identifying gout modifiable risk factors is paramount in gout prevention. This review aims to explain modifiable risk factors for gout, especially in the Asia region. Apart from urate-lowering therapy, modifying gout risk factors consisted of a low-purine diet, mild to moderate exercise, adequate sleep, elimination of smoking exposure, and regulation of comorbidities such as hypertension, obesity, metabolic syndrome, and kidney diseases, lowered the risk of hyperuricemia and gout in Asian population.

Keywords: *Gout; Disease Prevention; Modifiable Risk Factor; Morbidity; Lifestyle*

Abstrak

Gout merupakan penyakit arthritis tipe inflammatori yang paling umum ditemui di seluruh dunia, termasuk daerah Asia. Gout merupakan penyakit yang memiliki morbiditas tinggi, tetapi dapat dicegah. Prinsip umum pencegahan gout adalah regulasi asam urat pada serum dan penyakit komorbid lainnya. Sehingga, identifikasi faktor risiko yang dapat dimodikasi merupakan hal yang penting pada pencegahan gout. Tinjauan ini bertujuan untuk menjelaskan faktor risiko yang dapat dimodifikasi pada gout, terutama pada populasi Asia. Berdasarkan hasil pencarian, diit rendah purin, latihan fisik dengan intensitas ringan-sedang, tidur yang cukup, mengenyahkan paparan rokok, dan kontrol penyakit komorbid seperti hipertensi, obesitas, sindroma metabolik, dan penyakit ginjal dapat menurunkan risiko hiperurisemia dan gout pada populasi Asia.

Kata Kunci: Gout; Prevensi; Faktor Risiko; Morbiditas; Gaya Hidup

INTRODUCTION

Gout is the most common inflammatory arthritis in the world, including in the Asia region. The prevalence of gout was estimated from <1% to 6.8% with an incidence rate of 0.58-2.89 per 1.000 person-years.(1) Study in Hong Kong and China showed the prevalence of gout was 2.92% and 1.1%, respectively.(2,3) Meanwhile, prevalence of gout in Indonesia was unclear.

Gout is a debilitating disease. It negatively affects the quality of life (QoL). Studies among Chinese individuals showed that gout patients had poorer health-related QoL (SF-36 health survey) in both physical and mental components.(4) While another study showed that patients with gout had a higher work-absentee rate compared to control (22% vs 14%, p<0.0001) along with new-onset absenteeism for up to 1.47-folds (95%CI: 1.23-1.75).(5)

Despite its morbidity, gout is a preventable disease. The general principle of its prevention is to regulate circulating UA concentration and other related comorbidities.(6) Identifying gout modifiable risk factors is paramount in gout prevention. Therefore, this review aims to explain modifiable risk factors for gout, especially in the Asia region.

MATERIALS AND METHODS

This review was carried out by literature search on PubMed and Google Scholar in July 2022. The following keywords and their synonyms were applied during the search: "Gout", "Hyperuricemia", "Modifiable Risk Factors", and "Prevention". The Boolean operators ("AND", "OR", and "NOT") were applied to specify the search. All relevant reviews, cohorts, and trial articles published in the last 10 years were included to describe and explain the modifiable risk factors and prevention for gout in Asia. Studies that were conducted in non-Asia countries were excluded from this review.

GOUT

Uric acid (UA) is the final bioproduct of purine catabolism. The serum UA concentration is dependent on its production and excretion rate in urine. The UA has low solubility in water. Therefore, a concentration of 6.8 mg/dL or above is associated with oversaturated condition or hyperuricemia.(7)

Gout is a form of inflammatory arthritis and usually affects unilaterally. Gout is initiated by UA crystal deposition (monosodium urate) in the synovial fluid, followed by a sterile inflammation process. The most common joint affected by gout is the first metatarsophalangeal joint.(7,8)

Several risk factors are related to hyperuricemia and gout. These risk factors of gout are divided into modifiable and non-modifiable. Modifiable risk factors are substantial since regulation of these factors might benefit the patients.(9) Apart from urate-lowering therapy, modifiable risk factors include diet, exercise and sleep, smoking, and comorbidities regulation.

DIET

Dietary modification has been the main focus in the management of hyperuricemia and gout. A low-purine diet is associated with lower serum UA and gout. A recent meta-analysis explored several dietary factors in the risk of hyperuricemia and gout among Asians and Americans.(10) Red meat (OR:1.28, 95%CI: 1.17-1.40), seafood (OR:1.37, 95%CI: 1.15-1.63), alcohol (OR:2.12, 95%CI: 1.68-2.69, and fructose (OR:1.89, 95%CI: 1.70-2.09) were independent risk factors of hyperuricemia and gout. On contrary, soy products (OR: 0.79, 95%CI: 0.66-0.95) were protective factors against hyperuricemia and gout. Dairy products (OR: 0.50, 95%CI: 0.37-0.66) were only protective against hyperuricemia, while coffee (OR: 0.47, 95%CI: 0.37-0.59) and high-purine vegetables (OR: 0.86, 95%CI: 0.75-0.98) were only protective to gout. Similar results were observed among Chinese centenarians. Meat and seafood consumption was associated with hyperuricemia by 2.5 and 1.4-folds, respectively. While vegetable consumption was a protective factor (OR: 0.52, 95%CI: 0.32-0.85).(11)

Individuals with high meat food pattern intake (Beef, poultry, processed meat, eggs, fast food, cakes-biscuits, fats/oil, dairy products, and soft drink) was associated with more prevalent hyperuricemia (PR: 1.48, 95%CI: 1.12-2.10). Meanwhile, a traditional Chinese food pattern which is majorly composed of rice products, coarse grains, starchy tubers, fresh or pickled vegetables, pork, soy products, and tea, was associated with a lower prevalence of hyperuricemia with PR of 0.82 (95%CI: 0.43-0.92).(12)

A study in Northern Chinese populations also showed that a plant-based diet lowered the risk of hyperuricemia (OR: 0.70, 95%CI: 0.56-0.87). Both animal diet (high intake of poultry, livestock, fish and

shrimp, processed meats, and nuts) and specialized-diet (high intake of poultry, sugar-sweetened beverages, animal organs, and tea or coffee, and a low intake of snacks and desserts) increased the risk of hyperuricemia by 1.4-folds.(13)

A study in the Balinese population revealed that a mean dietary composition of 80% energy, 14% protein, 30% cholesterol, 55% carbohydrates, and purine of 85-94 mg could lower serum UA by 1.7 mg/dL ($p<0.001$). Combining this dietary composition with exercise could enhance the reduction to 2.3 mg/dL.(14)

EXERCISE AND SLEEP

Exercise is an important healthy lifestyle to maintain the body's metabolism process. In addition, sleep is also a substantial aspect of maintaining an optimal metabolic process. Recent studies showed that these factors also affected purine catabolism as well as gout development.

1. Exercise

Exercise is known to lower serum UA among individuals with hyperuricemia. One study from Bali, Indonesia showed that yoga for six weeks along with a low-purine diet significantly decreased UA by an average of 2.33 mg/dL compared to a low-purine diet only by 1.74 mg/dL ($p=0.04$). It was hypothesized yoga decreased UA by three mechanisms: bodyweight regulation, joint and circulation involvement, and mindfulness of the individual's body. The study recommended a 60-minute yoga exercise three times a week.(14)

Another study in Indonesia also explored the influence of spiritual care-ergonomic exercise on gout patients. Ergonomic exercise focuses on both physiologic muscle movement and breathing exercise. The ergonomic exercise was performed three times each week for four weeks. Interestingly, both serum UA and QoL were improved significantly. The mean serum UA was decreased by 2.29 mg/dL compared to control which increased serum UA by 0.42 mg/dL ($p<0.001$). The QoL was significantly improved by 42.7 points compared to control which dropped the QoL by 2.1 points.(15)

On contrary, a heavy and strenuous exercise such as long-distance running would increase serum UA. One study among healthy individuals showed that a 10-kilometers running was associated with serum UA elevation by 32% at 90 minutes after exercise ($p<0.05$) and 36% at 24 hours after exercise ($p<0.05$). Strenuous and heavy exercise induces oxidative stress and increases UA as an anti-oxidant compensatory mechanism.(16) Therefore, mild-moderate exercise is recommended for gout patients over heavy and strenuous exercise.

2. Sleep

Sleep is known to affect most metabolic processes in the body, including UA metabolism. Yet, available evidence demonstrated inconsistent results among Asians. Sleep hygiene along with exercise was shown to decrease serum UA and improve QoL in Indonesians with gout.(15)

Meanwhile, one study from more than 4.500 Taiwanese populations drew interesting conclusions. The short duration of sleep was associated with higher UA concentration, while poor quality of sleep (Pittsburgh Sleep Quality Index) was associated with lower UA concentration.(17) While other evidence from the Chinese population showed staying up late was not associated with hyperuricemia.(11)

Despite these inconsistent results, obstructive sleep apnea (OSA) was significantly associated with UA and hyperuricemia. Snoring, a sign of OSA, was more prevalent among individuals with hyperuricemia (31.3% vs 18.8%, $p<0.001$). on multivariate analysis, snoring was an independent risk factor for hyperuricemia with an odds ratio of 2.59 (95%CI: 1.84-3.64).(11) Similarly, patients with OSA had higher serum UA compared to healthy control (7.54 vs 5.38 mg/dL, $p=0.001$).(18) An surgical approach to OSA, uvulopalatopharyngoplasty, had been proven beneficial in reducing serum UA by 33%.(19) Based on these findings, adequate sleep might be beneficial in managing gout. The exact mechanism of how sleep affects UA is yet to be clear, more research is needed to elucidate the mechanism.

SMOKING

Smoking is a risk factor for most diseases, including hyperuricemia and gout. Active and passive smoking have distinguishable risks to the disease's development or progression. Recently, electronic cigarette (e-cigarette) usage is rising.

1. Active Smoking

Generally, hyperuricemia and gout are more prevalent among active smokers. A study among Indonesians showed that active smokers had a more 2.65 and 5.13-times risk of developing hyperuricemia and gout respectively. Subsequently, smoking duration (> 23 years), number of cigarettes per day (>16), and pack-year (>20) were associated with a higher risk of developing gout.(20)

Evidence among Korean populations showed a different influence of active smoking in males and females. Serum UA in males was less affected, while females were significantly affected. Active smoking increased the risk of hyperuricemia in Korean females by 1.81-2.00 times after several confounding adjustments.(21) Another study in 3.179 Korean females also showed active smoking resulted in a 2.67-folds risk of developing hyperuricemia.(22)

2. Passive Smoking

Passive or second-hand smoking exhibited inconsistent conclusions. Passive smoking increased the risk of hyperuricemia and gout by 3.58 and 7.17-folds, respectively.(20) On the contrary, passive smoking was not associated with hyperuricemia among Koreans.(21)

3. E-Cigarette

A recent study in Korea evaluated the effects of e-cigarettes on serum UA and the risk of hyperuricemia. The serum UA was elevated following increased e-cigarette exposure ($p=0.013$ in males and $p=0.007$ in females). The prevalence of hyperuricemia was also higher in those who were active and ever use e-cigarettes compared to control (26.6%, 19.2%, and 14.2%, $p<0.001$). Further analysis and confounding adjustments demonstrated active e-cigarette smokers had a 1.86-1.96 risk of developing hyperuricemia. This effect persisted in males, yet became statistically insignificant in females ($p>0.05$).(23)

COMORBIDITIES REGULATION

The antioxidant activity of UA had been studied in many metabolic diseases. Many studies revealed the relationship between these metabolic diseases with serum UA. Therefore, regulating these comorbidities is an important factor in preventing hyperuricemia and gout.

1. Hypertension

Numerous studies had successfully linked increased blood pressure with the risk of hyperuricemia and gout. Both pre-hypertension (systolic: 120-139 mmHg and/or diastolic: 80-89 mmHg) and hypertension (systolic: 140 mmHg or above and/or diastolic: 90 mmHg or above) increased the risk of hyperuricemia by 1.51 (95%CI: 1.22-1.87) and 1.53 (95%CI: 1.18-1.99), respectively.(24)

Another study on Singaporeans of Hokkien and Cantonese descent revealed a bi-directional association between hypertension and gout.(25) Hypertensive patients had 88% more risk of developing gout (95%CI: 1.61-2.21), while patients with gout had 18% (95%CI: 1.02-1.37) more risk of hypertension. A longer duration of hypertension also increased the risk of gout. About 5-9.9 years of hypertension would increase the risk of gout by 2.21-folds (95%CI: 1.77-2.77), while a duration of more than 10 years increased the risk by 2.44-folds (95%CI: 1.98-3.01).

One study from Indonesia gracefully constructed an equation model to evaluate the association between urate, blood pressure, and gout. The study concluded that increased systolic blood pressure possibly mediated gout development by urate (β:0.05, 95%CI Bias Corrected:0.02-0.08, $p < 0.001$).(26) Based on these findings, controlling systolic blood pressure is fundamental in reducing the risk of gout.

2. Obesity and Metabolic Syndrome

Association between obesity and metabolic syndrome (MetS) with gout had been well explored. Obesity and MetS are associated with the risk of hyperuricemia and gout.

Increased body mass index (BMI) and waist circumference was associated with hyperuricemia ($p=0.008$ and $p=0.010$, respectively).(27) A high baseline WC in the Chinese population was related to higher serum UA on 5 years of follow-up ($\beta=0.003$, $p=0.031$).(28) A study in Korean males concluded that every 1-kg fat reduction was related to 9% odds of achieving optimal serum UA. Meanwhile, the 1-kg fat gain was associated with a 0.05 mg/dL increase in serum UA.(29)

Insulin resistance is one component of MetS. Several insulin resistance indexes include glucose and triglycerides index (TyG), TyG index with body mass index (TyG-BMI), triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL-c), and metabolic score for insulin resistance (METS-IR). These indexes were positively correlated with higher serum UA which TG/HDL-c outperformed other indexes (AUC: 0.768, 95%CI: 0.726–0.811).(30)

Dyslipidemia, another aspect of MetS was also associated with hyperuricemia and gout. Increased TG and decreased HDL were associated with higher hyperuricemia incidence ($p<0.001$).(31) Evidence from China revealed TG was positively related ($r=0.116$. $p=0.003$), while HDL was inversely related to gout ($r=-0.282$, $p<0.001$).(32)

3. Kidney Diseases

The majority of UA is excreted through the kidney, hence any disruption of kidney function results in elevated serum UA and risk of gout. Chinese population with hyperuricemia had significantly higher serum urea and creatinine along with lower eGFR (all p<0.001). Subsequently, the following study also showed an inverse correlation between eGFR and hyperuricemia (β=-0.041, OR: 0.96, 95%CI: 0.94-0.98, p<0.001).(11) The serum UA was also higher among chronic kidney disease patients (9.55 vs 7.74 mg/dL, p=0.01).(33)

On the other hand, hyperuricemia accelerated kidney function deterioration. Serum UA of more than 6 mg/dL was associated with rapid eGFR declining by 12% (95%CI: 1.03-1.22) and became 60% (95%CI: 1.37-1.86) in patients with serum UA of more than 10 mg/dL.(34) Study in Thai populations gracefully showed that every 1 mg/dL increase of serum UA was associated with a higher risk of rapid eGFR declining and new-onset kidney diseases by 25% and 40%, respectively (OR: 1.25, 95%CI: 1.14-1.33 and OR:1.40, 95%CI: 1.26-1.49).(35)

CONCLUSION

. Gout is a debilitating, yet preventable disease. Modifying its risk factors such as a low-purine diet, mild to moderate exercise, adequate sleep, eliminating smoking exposure, and regulating comorbidities (hypertension, obesity, metabolic syndrome, and kidney diseases) lowers the risk of gout among the Asian population.

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