Metabolic syndrome, diabetes, and hyperuricemia

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Purpose of review
To explore the causal relationship between metabolic syndrome, type 2 diabetes and hyperuricemia.

Recent findings
The prevalence of hyperuricemia in male adults with metabolic syndrome was increased and a large difference in prevalence of metabolic syndrome also existed in those with hyperuricemia compared with normouricemia. Even in those with normouricemia, higher serum uric acid levels were associated with metabolic syndrome. Serum uric acid was an independent risk factor for incident diabetes, and evidence showed that the patients with both gout and type 2 diabetes exhibited a mutual inter-dependent effect on higher incidences. Furthermore, obese patients often demonstrated insulin resistance and adipose tissue macrophage with low-grade inflammation, which is suggested to be the major contributor. Although alcohol intake is considered a risk for developing hyperuricemia, moderate alcohol intake showed a lower risk for developing type 2 diabetes and insulin resistance. Hyperinsulinemia reduces renal excretion of uric acid on the proximal tubular of the kidney leading to hyperuricemia, which has deleterious effects on endothelial function and on nitric oxide bioavailability, thus causing hyperinsulinemia.

Summary
We found evidence to suggest that insulin resistance plays a potentially key role in the causal relationship between metabolic syndrome, type 2 diabetes and hyperuricemia. Furthermore, it is likely that hyperuricemia and insulin resistance share a bidirectional causal effect.

Keywords
hyperuricemia, insulin resistance, metabolic syndrome, type 2 diabetes

INTRODUCTION

Uric acid is a final enzymatic product in the degradation of purine nucleosides and it has the ability to scavenge oxygen radicals and protect the erythrocyte membrane from lipid oxidation. Hyperuricemia is the major and primary risk factor of symptomatic gout [1], the clinical significance of which has been identified as the development of various comorbidities including gout, metabolic syndrome, coronary artery disease and type 2 diabetes [2–4], despite its major antioxidant property. Hyperuricemia also reflects insulin resistance in some studies [5▪,6▪], which is the basic pathophysiology of type 2 diabetes.

Metabolic syndrome represents a cluster of physiological and anthropometric abnormalities characterized by abnormally elevated glucose level, obesity, hypertension, elevated triglycerides and low high-density lipoprotein-cholesterol (HDL-c) [7]. These abnormalities are also characteristic of persons with hyperinsulinemia and hyperuricemia [8,9]. Metabolic syndrome is a major contributor to the development of type 2 diabetes, and other conditions which are similar to the associates of gout and hyperuricemia, including oxidative stress [10▪,11], mild kidney disease, endothelial dysfunction and chronic inflammation [12].

Apart from the well known causal associations of hyperuricemia leading to gout and of metabolic syndrome leading to diabetes, both hyperuricemia and metabolic syndrome are associated with hyperinsulinemia. Our previous study [13▪▪] has shown that patients with both gout and type 2 diabetes diseases exhibit a mutual inter-dependent effect on

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KEY POINTS

- Higher uric acid levels are associated with metabolic syndrome, and the reverse is also true.
- Insulin resistance may be a bridge between obesity and hyperuricemia.
- Alcohol intake does not show a simple linear relationship with insulin resistance, but rather, a U-shaped association.
- Hyperuricemia and insulin resistance share bidirectional causal effects.

higher incidences. The relationship is complex but insulin resistance is possibly a common link.

HYPERURICEMIA WITH METABOLIC SYNDROME

The metabolic syndrome is currently defined as having at least three of five characteristic signs (abdominal obesity, impaired fasting glucose, hypertriglyceridemia, low HDL-cholesterol, and elevated blood pressure) [14]. In patients with manifest atherosclerosis, both presence of more than three metabolic risk factors and the presence of a high waist circumference are associated with increased risk of future type 2 diabetes [15]. Some case series studies [16,17] reported that the prevalence of metabolic syndrome was high among patients with gout. Moreover, hyperuricemia has been associated with metabolic syndrome in studies [18–20] of both healthy individuals and patients. It may also precipitate cardiovascular diseases for which the metabolic syndrome is a strong risk factor. The most different in the prevalence of hyperuricemia was found in male adults with metabolic syndrome compared with nonmetabolic syndrome [17] and higher prevalence of metabolic syndrome was also found in men with hyperuricemia [17]. Even in those with normouricemia, higher serum uric acid levels were associated with metabolic syndrome [21▪]. In those with normal BMI, the prevalence of metabolic syndrome was more than 10-fold higher in those with uric acid levels of 10 mg/dl or greater compared with uric acid levels less than 6 mg/dl [22]. Thus, all the data shows us that those with hyperuricemia are always comorbiditied with metabolic syndrome.

Elevated mean serum uric acid levels were found to be significantly increased by the component number of metabolic syndrome [23▪], and furthermore, the prevalence of metabolic syndrome also increased significantly with uric acid levels [22,24]. Even in those with normal fasting glucose and normal glucose tolerance, serum uric acid was predicted independently by BMI, triglycerides and 2-hour glucose, and hyperuricemia was associated with obesity, hypertriglyceridemia and hypercholesterolemia [25▪]. In other studies [23▪,26], those in the highest quartile of uric acid levels, the risks were substantially higher for metabolic syndrome compared with those in lowest quartile of uric acid levels. This suggests that higher uric acid levels are associated with metabolic syndrome, and the converse is also true, that patients with hyperuricemia frequently have metabolic syndrome. Moreover, Facchini *et al.* [27] had suggested that insulin resistance is the pathophysiological mechanism for the association.

METABOLIC SYNDROME WITH INSULIN RESISTANCE

The abnormal components of metabolic syndrome usually lack a cogent conceptual pathogen to reflect the essential cause. However, insulin resistance is a common feature of patients with abnormal metabolic components. Insulin, secreted by pancreatic β-cells, causes cells to take up glucose from blood and when the cells have a reduced sensitivity to stimulation of glucose uptake or insulin in the face of normal or raised glucose concentration, the situation is defined as insulin resistance. If insulin resistance exists, more insulin needs to be secreted by the pancreas with resultant compensatory hyperinsulinemia. The result is glucose intolerance and hyperglycemia, and subsequent type 2 diabetes. In addition, hyperinsulinemia may aggravate insulin resistance by interfering with insulin-signaling pathways and further exacerbating insulin resistance [28–30].

Insulin resistance is thought to be an important correlate of other risk factors of the metabolic syndrome, such as dyslipidemia and hypertension. Patients with essential hypertension were always found to be associated with insulin resistance and even among the normotensive population, insulin resistance is shown to be associated with higher blood pressure levels [31]. Ferrannini observed that insulin has a direct effect on the dilatation of peripheral vasculature [32]. The average vasodilatory response was estimated to be in the range of 15–30% in those with high insulin exposure [33], but this effect is blunted in insulin-resistant individuals, especially in patients with type 2 diabetes. Furthermore, Hayden and Tyagi [34] also reviewed that hyperinsulinemia could lead to hypertension by activating renin–angiotensin system, and subsequently to decrease renal blood

flow, increase urate reabsorption and xanthine oxidase production, and result in hyperuricemia (Fig. 1) [34].

Insulin resistance also impacts on lipoprotein metabolism and is associated with an increase in triglycerides and depressed HDL levels. The ratio of triglycerides-HDL-cholesterol (TG-HDL-c) has been widely used as a simple marker to predict the association of patients with insulin resistance. Articles have discussed the efficacy of the TG-HDL-c ratio associate with insulin resistance for many population groups [35,36]. In a cross-sectional study [37], high levels of insulin sensitivity were inversely associated with the levels of TG-HDL-c ratio; and even in children and adolescents, the TG-HDL-c ratio is strongly associated with insulin resistance [38▪]. Yamashita *et al.* [39] provided the mechanism that insulin can inhibit HDL-mediated cholesterol efflux from human acute monocyte leukemia cell line derived macrophages through the inhibition of neutral cholesterol ester hydrolase and ATP-binding cassette transporter G1 expression in a vitro study.

Although many studies have demonstrated that insulin resistance existed in association with metabolic syndrome, and it can be considered to play a central role for it is not the sole cause for the components. However, it remains a well characterized pathophysiological mechanism to explain the appearance of several of them [32].

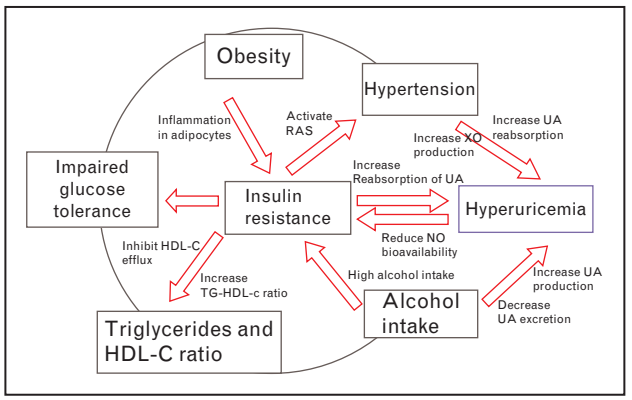

FIGURE 1. The image demonstrates interactions between the components of metabolic syndrome, insulin resistance and hyperuricemia. It shows hyperuricemia is associated with metabolic syndrome through the insulin resistance and kidney dysfunction; and that insulin plays a key role between them. Hyperuricemia may cause endothelial dysfunction and inhibition of nitric oxide bioavailability leading to subsequent hyperinsulinemia. Hyperinsulinemia also can increase uric acid reabsorption in the proximal tubules leading to hyperuricemia. Thus, hyperuricemia and insulin resistance share bidirectional causal effects. HDL-c, high-density lipoprotein-cholesterol; RAS, renin–angiotensin system; UA, uric acid; XO, xanthine oxidase.

OBESITY WITH INSULIN RESISTANCE

Obesity and type 2 diabetes are always complicated by insulin resistance; obesity is also associated with a state of chronic, low-grade inflammation that contributes to insulin resistance, type 2 diabetes, and increased risk for hyperuricemia and gout. Many clinical studies have shown a separate impact of fat distribution on insulin action, and an accumulation of fat in abdominal viscera has been reported to be strongly associated with insulin resistance independent of total adiposity [40]. In both humans and animal studies, inflammatory cells accumulate in adipose tissue with increasing body weight, and evidence is mounting that implicates these inflammatory cells as significant contributors to obesity-associated insulin resistance [41▪▪]. Although the pathogenesis of insulin resistance in obesity is multifactorial, there is evidence that adipose tissue macrophages with chronic, low-grade inflammation are a major contributor [42]. Furthermore, many regulators play a critical role in obesity-induced adipose tissue inflammation and insulin resistance by regulating macrophage recruitment, such as C–C motif chemokine receptor 5 (CCR5) [43], phosphoinositide 3-kinase (CPI3K)[44], dendritic cells [45] and adipose tissue size [46]. All of the information suggests a strong association between adipose tissue inflammation and insulin resistance in obesity.

Moreover, inflammatory mediators in adipose tissue have been shown to cause insulin resistance in adipocytes. For example, TNF-α-treated adipocytes exhibited decreased insulin signaling and subsequently decreased glucose uptake [41▪▪,47,48]. Another study [49] also showed that those patients with high insulin resistance after receiving 12 weeks of anti-TNF therapy demonstrated significant reduction in homeostatic model assessment -insulin resistance (HOMA-IR), and in a tumor necrosis factor-α receptor knockout mice study [50] also showed high-fat diet-induced obesity and insulin resistance were ameliorated via enhanced fecal bile acid excretion. It is suggested that insulin resistance may be a mediator between obesity and hyperuricemia, as insulin expression may be exacerbated by adipocytes, and insulin has been identified as a cause of hyperuricemia by inhibiting uric acid excretion.

ALCOHOL CONSUMPTION WITH INSULIN RESISTANCE

Alcohol intake is well known to be strongly associated with hyperuricemia. This may be due to raised urate production and diminished renal excretion. However, moderate alcohol intake has

been associated with a lower risk of type 2 diabetes [51,52], and is associated with decreased insulin resistance independent of BMI [53]. By contrast, chronic alcohol-related liver disease was found to be associated with increased expression of insulin [54], and there is evidence that chronic high-level ethanol consumption inhibits DNA synthesis and regenerative and reparative capacities of the liver, which may be due to inhibition of insulin signaling [55]. Moderate alcohol consumption may thus be protective against insulin resistance and the development of type 2 diabetes, whereas high intake seems to increase the risk. Alcohol intake does not show simple linear relationships with insulin resistance, but rather, a U-shaped curve [53,56].

HYPERURICEMIA WITH INSULIN RESISTANCE

Despite the fact that many studies have demonstrated an association between high serum uric acid and insulin resistance, the causal effect between them has not been fully explained. Uric acid – the end product of purine catabolism – was found to be associated with hypertension, obesity, dyslipidemia as well as hyperinsulinemia [25▪]. Those with higher serum uric acid were associated with a higher prevalence of insulin resistance even among normal fasting glucose and normal glucose tolerance patients [25▪]. Vuorinen-Markkola and Yki-Jarvinen [57] indicated that serum uric acid level is inversely correlated with insulin sensitivity, and uric acid was suggested to play an important role in the function of the β cell in patients with type 2 diabetes even in states prior to hyperuricemia [58▪]. A large epidemiologic study [59] also showed that high serum uric acid levels had a positive correlation with fasting serum insulin levels, and Tsouli *et al.* [60] have reviewed the association between elevated uric acid and insulin resistance.

Even though the association between hyperuricemia and insulin resistance has been well demonstrated, the causal effect between them should be further explored. Carnethon *et al.* [61] revealed a significantly higher risk of developing hyperinsulinemia with increased baseline uric acid level in a follow-up study among nondiabetic participants. In a recent study, Krishnan *et al.* [5▪] also demonstrated that those with hyperuricemia have 1.36 times the risk of developing insulin resistance in a 15-year follow-up study. Furthermore, in a mice study, Baldwin *et al.* [62▪] demonstrated that lowering uric acid in obese mice can reduce insulin resistance. All the data suggest that hyperuricemia can be detected prior to the development of hyperinsulinemia.

Although regarding the progressing causal effect of insulin resistance leading to hyperuricemia, hyperuricemia is usually the result of underexcretion of urate [63], and the renal clearance of urate has been shown to be inversely related to the degree of insulin resistance [27]. Moreover, hyperinsulinemia may decrease uric acid clearance by the kidneys [64,65]. Reaven *et al.* [66] attributed the presence of hyperuricemia in metabolic syndrome to a secondary response to hyperinsulinemia. The association has been attributed to the effects of insulin on proximal tubular urate transport of the kidney. In addition, drug treatments for improving insulin sensitivity were also shown to lower serum uric acid levels [67–70].

Therefore, one mechanism linking the association between hyperinsulinemia with hyperuricemia is a decrease of renal excretion of uric acid. Insulin can also enhance renal tubular sodium reabsorption [65,71], which in turn can reduce renal excretion of uric acid. Whatever the mechanisms of insulin on the renal tubules, be it direct stimulation of tubular ion exchange or acceleration of cellular metabolism [72], insulin can modify the handling of uric acid by the kidney, thus leading to hyperuricemia (Fig. 1).

Nakagawa *et al.* [73] showed that uric acid blocked acetylcholine-mediated arterial dilation, suggesting that uric acid can impair endothelial function. Moreover, in mice studies, endothelial nitric oxide synthase deficiency results in the features of insulin resistance and metabolic syndrome [74]. Because uric acid has been shown to reduce nitric oxide bioavailability [75,76], and reducing endothelial nitric oxide supply is a known mechanism for inducing insulin resistance [77], hyperuricemia may thus have a key role in the pathogenesis of insulin resistance (Fig. 1).

In summary we have reviewed the evidence that insulin may modify the handling of uric acid by the kidney, and contribute to hyperuricemia and the evidence that hyperuricemia may have a key role in the pathogenesis of insulin resistance by blocking endothelial nitric oxide supply. Thus, we speculate that hyperuricemia and insulin resistance share bidirectional causal effects (Fig. 1).

HYPERURICEMIA WITH TYPE 2 DIABETES

Hyperuricemia is a risk factor for type 2 diabetes, but the causal association between them is controversial. A large epidemiological study [78] of Japanese adult men showed that an elevation of serum uric acid levels increased the risk of type 2 diabetes. Although obesity has been recognized as a potential risk factor for type 2 diabetes, some studies

[79–81] have documented high rates of type 2 diabetes in the absence of classical obesity among some populations. These results suggest that other independent pathogenic factors may exist that could contribute to the occurrence of type 2 diabetes, such as hyperuricemia, and many studies [5▪,13▪▪,82] have suggested that elevated uric acid levels, hyperuricemia, or gout, have associations with the development of type 2 diabetes.

Dehghan *et al.* [83] demonstrated that serum uric acid is a strong and independent risk factor for diabetes in a 10-year follow-up study. Other studies [83,84] demonstrated a significant linear regression between serum uric acid levels and incident type 2 diabetes. However, diabetic patients who continue to be hyperuricemic appear to be at increased risk of developing diabetic complications, especially renal disease [85]. Although decreased kidney function can be highly associated with hyperuricemia, based on some epidemiological studies, hyperuricemia is an independent risk factor for kidney dysfunction in patients with diabetes mellitus. The causal association between hyperuricemia and type 2 diabetes may be mediated by kidney dysfunction as well as insulin resistance. However, not all studies have reached the same conclusion; a large prospective study [86] did not show an association between uric acid levels and type 2 diabetes, and an inverse association between serum uric acid levels and diabetes mellitus has also been observed [87,88].

CONCLUSION

We have reviewed the evidence that hyperuricemia is associated with metabolic syndrome as well as diabetes, and that insulin plays a key role between them. Hyperuricemia may precede insulin resistance and cause endothelial dysfunction and inhibition of nitric oxide bioavailability leading to subsequent hyperinsulinemia. However, hyperinsulinemia can reduce renal excretion of serum uric acid in the proximal tubules leading to hyperuricemia. Thus, there is evidence that the relationship between hyperuricemia and hyperinsulinemia may be a bidirectional causal effect. Similarly, the relationship between metabolic syndrome and hyperuricemia may be linked to insulin resistance.

Acknowledgements

None.

Conflicts of interest

No conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
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