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Expert Opinion

Metabolic syndrome: new targets for an old problem

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1. Introduction

Metabolic syndrome comprises pathological features that include insulin resistance, visceral obesity, arterial hypertension and dyslipidemia, which increase the risk of developing cardiovascular diseases [1]. Abdominal obesity and insulin resistance are believed to be the core features of etabolic syndrome; however, inflammation, endothelial dysfunction, uric acid levels and oxidative stress are also thought to be associated with insulin resistance and metabolic syndrome [2].

Obesity is considered to be one of the most important determinants of the low-grade chronic inflammation present in metabolic syndrome, however, there are normal-weight individuals with metabolic syndrome . Furthermore, in some classical inflammatory diseases, such as systemic lupus erythematosus, the higher prevalence of metabolic syndrome is better explained by insulin resistance rather than obesity [3]. This reinforces the importance of insulin sensitivity as proposed in the original concept by Reaven [1]. Therefore, in addition to the continuous efforts to expand the knowledge on the beneficial effects of anti-obesity therapy, the development of new drugs with fewer side effects to overcome insulin resistance is needed.

Although increased metabolic syndrome prevalence has been considered a consequence of the obesity and diabetes mellitus pandemic, several issues are still subjects of debate, mainly the aforementioned issues inflammation, endothelial dysfunction, uric acid levels and oxidative stress.

2. Role of inflammation and endothelial dysfunction in metabolic syndrome

The understanding of the pathophysiological mechanisms that modulate metabolic syndrome has led to the identification of new therapeutic targets. Initially, pro-inflammatory cytokines produced in adipocytes, known as adipokines or adipocytokines, and positive acute-phase reactant proteins, demonstrated primarily by elevated levels of serum C-reactive protein, were considered the main target to avoid insulin resistance and some drugs like statins, besides their well known hypocholesterolemic effect, have been used to decrease the inflammatory state [4]. Recently, however, adiponectin has also emerged as one of the most robust candidates for therapeutic intervention. Adiponectin inhibits TNF-α production, adhesion molecule expression and NF-κB signaling, a pivotal pathway in inflammatory reactions in endothelial cells [5]. Ouchi *et al.* [5] showed that adiponectin suppressed TNF-α-induced NF-κB activation through a cAMP-dependent pathway in human aortic endothelial cells. Besides its anti-inflammatory action, which is not associated with pro-inflammatory cytokines [6], adiponectin enhances insulin sensitivity and has anti-atherogenic properties. Adiponectin levels are lower in patients with obesity, type 2 diabetes mellitus, arterial hypertension and metabolic syndrome [7]. These data indicate that a decrease in adiponectin is the main link between obesity and metabolic syndrome. Some therapies, such as antihypertensive drugs like ACE inhibitors [8], fish oil n-3 polyunsaturated fatty acids and soy-based products [9] augment adiponectin levels.

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It has been shown in experimental studies that adiponectin enhances NO production in cultured aortic endothelial cells, significantly increases eNOS (83%), reduces iNOS (70%) in hyperlipidemic rats [10] and improves obesity-related hypertension in mice [11]. Adiponectin augments blood flow by enhancing NO production and activating eNOS and may act as a modulator of vascular remodeling by suppressing smooth muscle cell migration, which possibly plays a role in the regulation of atherosclerosis [12]. In addition, human studies have also shown that hypoadiponectinemia is closely linked to endothelial dysfunction in healthy, and in hypertensive subjects [13].

Endothelial dysfunction is considered a hallmark in the pathophysiology of metabolic syndrome and it can be evaluated by several means, including the assessment of NO metabolite (NOx) levels. Some studies have reported a decrease in serum NOx levels in patients with metabolic syndrome [2]. NO has been considered the principal mediator of vasodilatation caused by endothelial cells, plays a major role in regulating blood pressure and its deficient bioactivity is an important component of hypertension [14]. Hypertensive subjects have increased generation of reactive oxygen species (ROS), which scavenge NO, thereby reducing NO bioavailability [14]. Furthermore, NOx have shown significant inverse correlation with body mass index (BMI), abdominal circumference and insulin resistance measured by homeostasis model assessment–insulin resistance (HOMA-IR), suggesting that obesity and decreases in insulin action are directly associated with the reduction of serum NOx levels in metabolic syndrome [2]. Also, oxidative stress mediated byROS /reactive nitrogen species (ROS/RNS) has shown increased levels in patients with metabolic syndrome [15], and ROS have been correlated positively with serum NOx levels [2]. Notwithstanding this positive correlation, NOx levels in patients with metabolic syndrome were decreased when compared with a control group [2]. The reduction in NOx levels is coherent with both endothelium dysfunction and increased oxidative stress. This statement is supported by the fact that NO is consumed in a reaction with superoxide anion yielding a strong oxidant species, $ONOO^-$, which in turn accelerates the lipid peroxidation reaction [16]. The peroxinitrite production is also supported by the elevated levels of nitrotyrosine. Therefore, antihypertensive agents, mainly ACE inhibitors [8,14], and non-pharmacological therapies, such as fish oil and soy-based products [9] that increase NO, may favor the decrease of hypertension, an important feature in metabolic syndrome patients.

3. Role of uric acid on metabolic syndrome

There is supporting evidence that uric acid may have a pathogenic role in the metabolic syndrome. Nakagawa *et al.* [17] suggested a causal role of uric acid in fructose-induced metabolic syndrome showing that uric acid dose -blocked acetylcholine-mediated arterial dilatation, suggesting that uric acid can impair endothelial function. In addition, they verified that allopurinol, a xanthine oxidase inhibitor that lowers serum uric acid, was able to decrease systolic blood pressure, improve insulin sensitivity, and normalize triacylglycerol levels in fructose-induced metabolic syndrome. Insulin has a physiological action on renal tubules, causing a reduction in uric acid clearance; which could explain the higher uric acid levels found in metabolic syndrome. Although uric acid may have a protective effect due to its antioxidant properties (it is responsible for 60% of total antioxidant capacity), it is clear that its dominant effect in metabolic syndrome is deleterious [18,19]. It has been shown that uric acid reduces NO bioavailability in various cell types via mechanisms involving redox control and also activating arginase and depleting NO. In addition, markedly increased levels of uric acid (> 6.2 mg/dl or 370 μM) are known to cause gout and nephrolithiasis, but more importantly have been associated with an increased risk of developing cardiovascular disease, particularly hypertension and metabolic syndrome. Hence, the classical view of uric acid as a simple and innocent bystander has been challenged. There is now a more complex understanding of its dual role: as a consequence of hypertension and metabolic syndrome, but also as a cause of hypertension and probably implication in the etiology of metabolic syndrome [20]. Even with a normal range of serum acid concentration, the risk of metabolic syndrome was found to be elevated in proportion to uric acid concentration [20].

An increase in uric acid has been also considered a component of the metabolic derangement verified in metabolic syndrome in adults, as well as in adolescents and children. Simão *et al.* [19] have previously reported that a group of patients with metabolic syndrome presented higher uric acid concentration compared with a healthy control group and that the uric acid had a positive significant correlation with waist circumference, fasting glucose, fasting insulin and HOMA, and a negative significant correlation with high-density-lipoprotein-cholesterol [19]. The most significant correlation verified in that work was between uric acid and insulin resistance. Insulin resistance has been considered the underlying condition that triggers the development of metabolic disturbances in metabolic syndrome. There is evidence to support the association between uric acid concentration and insulin resistance. First, the degree of insulin resistance has been shown to be directly related to uric acid concentration. Second, drugs that improve insulin sensitivity, such as metformin, troglitazone, sibutramine and orlistat, can also lower uric acid concentration. Third, after multiple logistic regression analysis, only uric acid concentration and fasting insulin were independent predictors of nonalcoholic fatty liver disease, which is another common characteristic of metabolic syndrome. Fourth, both alcohol and thiazide diuretic agents may contribute to the development of hyperuricemia and insulin resistance [20]. All together, these data strongly indicate the need for prospective studies to verify if

drugs that lower uric acid concentration have long-term beneficial effects on cardiovascular risk factors, especially those related to metabolic syndrome.

4. Role of oxidative stress in metabolic syndrome

The imbalance between pro-oxidant and antioxidant mechanisms has been considered one of the most important pathophysiological mechanisms of chronic diseases. This lack of equilibrium may be responsible for both the cause and/or consequences of chronic diseases such as metabolic syndrome and thus, oxidative stress has also been considered a hallmark of metabolic syndrome. Although its precise role is still debated, as a cause or consequence, some attempts have been made to decrease cardiovascular risk. In general, human studies have not shown beneficial effects when antioxidant supplements were tried. In contrast, some foods, dietary patterns and drugs have demonstrated that decrease in oxidative stress was associated with favorable clinical aspects. For instance, statins and ACE inhibitors, drugs used in the treatment of hypercholesterolemia and hypertension, respectively, may decrease oxidative stress and/or increase total antioxidant capacity [21].

5. Expert opinion

The understanding of the pathophysiological mechanisms that explain the development of metabolic syndrome has evolved in recent years. Decreased adiponectin levels, an anti-inflammatory adipocytokine, have been considered the link between obesity and the development of metabolic syndrome. Besides all the beneficial action on insulin sensitivity and atherogenesis, adiponectin stimulates eNOS, which could justify the favorable effects on hypertension obtained with pharmacological and non-pharmacological therapy. Human studies which have analysed adiponectin and NO levels concomitantly are still scarce. Clearly, more studies designed to confirm this interaction are needed. Another issue that deserves attention is the role of uric acid in metabolic syndrome. Uric acid has an ambivalent role; its contribution to total antioxidant capacity is around 60%. On the other hand, it is well known that its deleterious effects predominate in metabolic syndrome. It is still unclear which of the following detrimental roles of uric acid are more important: mediating the effects of conventional risk factors in the development of the atherosclerotic disease; mediating the effects of an anti-inflammatory status or mediating the effects of a pro-inflammatory status. Previous studies, which showed an inverse relationship between uric acid levels and adiponectin, seem to reinforce the former two hypotheses. Long-term studies to verify the consequences of decreasing uric acid concentration below the present recommendations in asymptomatic patients are warranted.

Foods and supplements with antioxidant activity can have some beneficial actions in metabolic syndrome therapy. Currently, several studies have been performed to investigate food and dietary patterns which associate a decrease in insulin resistance and cardiovascular risk with an increase in total antioxidant capacity, such as the Mediterranean diet. Theoretically, the use of antioxidants supplements, such as vitamin C or vitamin E could attenuate oxidative damage that occurs in metabolic syndrome; however, studies on this subject are still insufficient. Some experimental reports have already demonstrated an increase in plasma total antioxidant capacity and a decrease in lipid and protein oxidative processes, but human studies, in general, have not shown beneficial results with these supplements. Certainly, more cohort studies are warranted to verify long-term beneficial effects of antioxidants in metabolic syndrome therapy.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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