Review Article

An update on inflammatory markers in metabolic syndrome

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ABSTRACT

Metabolic syndrome is an emerging global threat as a major health burden. It is widely presumed that Metabolic syndrome is associated with a low grade chronic inflammatory phenomenon. This inflammatory state is due to the imbalance between the pro and anti-inflammatory cytokines. Studies have been performed on various inflammatory markers in metabolic syndrome like hsCRP, TNF-alpha, Adiponectin, IL-6, IL-10. Articles were chosen from indexed journals from various search engines. Pro inflammatory cytokines like hsCRP, TNF – alpha, Interleukin -6 were found to be increased and anti-inflammatory cytokines like Interleukin – 10 were reduced in metabolic syndrome.

Keywords: Metabolic syndrome, Cytokine, Inflammatory marker, hsCRP, Interleukin

INTRODUCTION

Globally, MetS is a key community health challenge due to rapid urbanization, sedentary lifestyle, and excess energy intake. MetS defines a group of cardio metabolic risk factors namely central obesity, glucose intolerance, hyperinsulinemia, low high density lipoprotein (HDL) cholesterol, high triglycerides (TG), and systemic hypertension that impact individuals to develop type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD). It is defined by the global harmonized definition as having three of the five following features: increased triglycerides (TG), low levels of high-density lipoprotein (HDL)-cholesterol, plasma glucose >100 mg/dL, increased waist circumference (WC), and hypertension (HTN). In India, a recent rise in MetS has been attributed to the shift in lifestyles both in the urban and in the rural areas. Worldwide prevalence of MetS ranges from <10% to as much as 84%, and the prevalence of MetS in Asian Indians has been documented to be from 11% to 41%. Independent studies have established the close association of pro-inflammatory state with increased atherogenesis.

METHODS

Indexed and cited journals were searched using search engines like Pubmed, Cochrane reviews and Google scholarly utilising key words like Metabolic syndrome, inflammatory markers (hsCRP, TNF-alpha, IL-6, IL-10). Studies, reviews and meta-analysis done in humans and published in English language were chosen. Articles were quantitatively reviewed using PICOS. The articles were chosen from all over the world, published in the past 23 years.

DISCUSSION

C-reactive protein (CRP) is an acute-phase reactant and levels may increase up to 1000-fold in response to major infection or trauma.[1] In normal clinical practice CRP values below 10 mg/L are considered normal. Higher values indicate infection, inflammation, or necrosis. The increased serum concentration of high-sensitivity CRP (hsCRP) is a marker of low-grade inflammation, and sensitive immunoassays are capable to detect also very low serum CRP concentrations (<1 mg/L). Even slightly

elevated serum concentrations of hsCRP predict clinical manifestations of atherosclerotic CVD.[2-4] Although serum CRP concentrations may increase in response to acute illness concentrations are remarkably stable over a long period when measured in asymptomatic adults.[5]

CRP is primarily secreted by the liver in response to a variety of inflammatory cytokines. Elevated plasma CRP concentrations have been reported in individuals with abdominal obesity, especially in the obese with large depots of visceral adipose tissue.[5] Elevated CRP concentrations accompanying obesity may signify an increased concentration of adipocytokines and a proinflammatory state, which is associated also with insulin resistance.[6] In obesity, white adipose tissue is characterized by increased production and secretion of a wide range of inflammatory molecules including TNF-α and IL-6. These cytokines may have local effects on adipose tissue physiology and also systemic effects on other organs.[7] Process linked to chronic inflammation decrease insulin action, whereas insulin resistance leads to worsening of inflammation.[8]

TNF-α is a pro-inflammatory cytokine that is produced and secreted from adipocytes. TNF-α is increased in the adipose tissue and skeletal muscle of insulin-resistant humans.[9] Within adipose tissue, TNF-α causes adipocyte insulin resistance and impairs insulin signaling.[10] Via downregulation of lipoprotein, lipase inhibits lipid storage in adipose tissue.[10] TNF-α has important effects on whole-body lipid metabolism, raising serum triglyceride levels by stimulating very-low-density lipoprotein cholesterol production.

IL-6 has been classified as a cytokine with both pro- and anti-inflammatory actions.[11,12] On average, 30% of circulating IL-6 in resting conditions originate from adipose tissue.[13] Abdominal adipose tissue releases more IL-6 than subcutaneous adipose tissue.[14] During exercise, IL-6 is produced locally in working skeletal muscle, and low muscle glycogen content stimulates the production.

During exercise, IL-6 contributes to the maintenance of glucose homeostasis, stimulates adipose tissue lipolysis and may also inhibit the effect of TNF-α. On the other hand, it has been proposed that IL-6 alters insulin sensitivity, increases hepatic production of fibrinogen and CRP, is procoagulant, and stimulates adhesion of circulating leukocytes to the vascular endothelium. IL-6 also stimulates the central and the sympathetic nervous systems and might result in hypertension contributing to a higher concentration of angiotensin II, which is a potent vasoconstrictor. Data from population-based studies have shown that elevation of IL-6 predicts total and cardiovascular mortality.[15-17]

AMP-activated protein kinase (AMPK) is a major regulator of energy balance, glucose and lipid metabolism at both cellular and whole-body levels.[18] AMPK switches cells from an anabolic state where nutrients are taken up

and stored into a catabolic state where they are oxidized.[18] IL-6 may mediate or modify some of the AMPK actions in muscle and adipose tissue.[19] As IL-6, also AMPK is activated by exercise and absence of glucose. In a recent animal study, IL-6 knockout mice had decreased AMPK activity and developed components of the metabolic syndrome, such as obesity, dyslipidemia and glucose intolerance.[19]

Adiponectin is an anti-inflammatory cytokine produced by adipocytes that circulate at relatively high levels in the blood.[20,21] Adiponectin activates AMPK, improves insulin sensitivity, inhibits inflammation, and may have direct anti - atherosclerotic effects.[22] Adiponectin levels are reduced in obese individuals; especially in those with abdominal obesity.[23] Reduced adiponectin levels contribute to insulin resistance, hyperglycemia, and endothelial dysfunction. In a recent study, lower adiponectin levels were associated with most of the components of the metabolic syndrome and the metabolic syndrome itself.[24]

Cytokines and free fatty acids increase also the production of fibrinogen and coagulation factor, PAI-1, in the liver, which complements the overproduction of PAI-1 by especially visceral adipose tissue. Aging is associated with increased inflammatory activity.[25,26] In a cohort of 81-year old men and women, aging was associated with increased circulating levels of TNF-α, and high inflammatory activity was associated with increased prevalence of clinical diagnosis of atherosclerosis.[27] Limited data on the association of low-grade inflammation with the metabolic syndrome are available in the elderly, especially from long-term studies.[28]

Cross-sectional studies have found associations of hsCRP with metabolic syndrome and its components, including obesity, insulin resistance, dyslipidemia, elevated blood pressure, and endothelial dysfunction.[28-37] Prospective studies in middle-aged individuals have observed that increased serum hsCRP concentrations predict the development of the metabolic syndrome and type 2 diabetes.[38-40]

Interleukin-10 (IL-10), a cytokine, contains variable anti-inflammatory properties and controls insulin sensitivity and cholesterol uptake and efflux in macrophages.[41-43] IL-10 is produced from many organs, including spleen. It acts via the IL-10 receptor to activate the JAK/STAT pathway and exerts immunosuppressive effects by blocking IκK activity or by inducing tyrosine phosphorylation of STAT-3.[44,45] IL-10 are produced largely from activated B cells of spleen, and recent studies suggest that spleen-derived IL-10 has important suppressing effect on destructive immune responses induced by obesity.[46,47] IL-10 derived from spleen had a defensive outcome against pathological inflammation in liver and IL-10 and recovers liver fibrosis.[47,48] However, obesity is related with minimal production IL-10 by the spleen.[45] IL-10 levels were below the normal value in metabolic syndrome of 50 obese Caucasian women compared to 50 age matched control

non-obese women. In the earlier study, IL-10 levels were observed to be raised in obese Caucasian women and low IL-10 levels have been related with the metabolic syndrome.[49] But, studies regarding the association between IL-10 and inflammatory markers such as CRP and IL-6, are limited.

CONCLUSION

Metabolic syndrome is associated with a chronic inflammatory state as a result of imbalance between the pro and anti-inflammatory factors. Further studies are suggested to look for possible therapeutic implications of targeted anti-inflammatory therapy.

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