

Review Article

METABOLIC SYNDROME ASSOCIATED COMPLICATIONS

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ABSTRACT

Metabolic syndrome (MetS) is characterized by a cluster of disorders like obesity, insulin resistance, glucose intolerance, hypertension and dyslipidemia. All these disorders are responsible for the development of secondary morbid and co-morbid conditions. The current review focuses on the molecular pathogenesis of secondary late complications associated with metabolic syndrome including cognitive impairment, depressive disorder, neuropathy, arthritis and colorectal cancer.

Keywords: Arthritis, Cancer, Cognitive impairment, Depressive disorders, Metabolic syndrome, Neuropathy.

INTRODUCTION

Metabolic syndrome (MetS) is a multiple factorial condition that draws a parallel to various risks such as dyslipidemia, hypertension, and hyperglycemia. As per the new International Diabetes Federation (IDF), for a person to be defined as having metabolic syndrome they must have central obesity along with any two of the following four factors: Raised triglycerides (≥ 150 mg/dL), reduced HDL cholesterol (<40 mg/dL in males and <50 mg/dL in females), raised blood pressure (systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg) and raised fasting plasma glucose (FPG ≥ 100 mg/dL) [1]. According to previous reports about 20 to 30 % of world population is currently suffering from metabolic syndrome [2]. Mets have been associated with increase in age and BMI [3]. In MetS, there is a tendency to develop central obesity associated with an increase in circulatory free fatty acids [4]. This eventually leads to increase in blood pressure, insulin-resistance and hyperlipidemia [5]. Insulin resistance is often projected to be the major cause of Mets; however there are other factors like genetic variations in breaking down lipids in blood and age, which may contribute to its development [6]. Metabolic syndrome may give rise to a number of secondary complications which primarily include atherosclerosis and other cardiovascular disorders (reviewed in details by Reaven G 2002) [6]. Dementia, neuropathy, arthritis and colorectal cancer. The present review focuses on the mechanisms associated with the pathogenesis of late complications of MetS like cognitive impairment, depression, neuropathy, arthritis and colorectal cancer.

Cognition impairment and metabolic syndrome

Evidence suggests that MetS and associated factors such as visceral obesity, elevated triglycerides, elevated fasting blood glucose, high blood pressure and decreased HDL all have detrimental effects on cognition [7, 8]. Biological toxicity occurs with increase in plasma glucose levels causing protein glycation, alteration of redox potential and generation of reactive oxygen species [9]. The ensuing oxidative stress may lead to vascular damage. This microvascular dysfunction may prove to be detrimental to hippocampal neurons leading to cognitive deficit [10]. Release of excess glucocorticoids may augment natural fat and cause insulin resistance [11, 12]. Increased cortisol level due to stress has been correlated with signs of MetS [13]. Cortisol may also reduce the amount of insulin transported across the blood-brain barrier [14]. Glycemic control affects cognitive performance that relies mostly on hippocampal neurons [15]. Animal studies have shown that the transportation of glucose to the hippocampal neurons and glia is inhibited by glucocorticoids [16]. This may be due to excessive localization of cortisol and insulin receptors in the hippocampal regions of the brain [7, 17]. Some studies have also proposed the role of cerebral white matter lesions in the development of stroke, cognitive impairment and dementia

[18]. Large white matter hyper-intensities have been associated with disturbed cerebral perfusion in human volunteers. These studies have also shown cerebral metabolic abnormalities in white matter atrophy. Marred cerebral white matter is intertwined with attenuated cerebrovascular hemodynamics [19]. Elevated blood pressure, dyslipidemia and elevated fasting glucose levels associated with MetS have been implicated in subcortical white matter lesions, peri ventricular hyperintensities and silent ischemic brain lesions [20]. All of the above factors have been implicated in the pathogenesis of MetS associated cognitive deficits [7].

Metabolic syndrome associated neuropathy

Prevalence of impaired glucose tolerance has been associated with 40–50% of idiopathic neuropathy patients [21]. Mechanisms of injury include fatty deposition in nerves, extracellular protein glycation, mitochondrial dysfunction, and oxidative stress [22, 23]. Hyperglycaemia and hyperlipidemia associated with metabolic syndrome may cause cellular damage with production of reactive oxygen species leading to mitochondrial dysfunction and endoplasmic reticulum (ER) stress [24,25]. These changes not only lead to direct neuronal injury but also promote insulin-resistance mediated by excess nutrient, initiating tissue inflammation, which in turn may exacerbate insulin resistance.

In MetS. This is in C-reactive protein and pro-inflammatory state is well documented due to recruitment of leukocyte by chemokines via Jun N-terminal kinases (JNK) and inhibitor of nuclear factor κ B kinase (IKK) causing tissue damage. JNK and IKK also mediate further production of inflammatory and tissue-damaging signals by activation of nuclear factor κ B (NF κ B) [26, 27]. There is a strong correlation between NF κ B activation and release of pro-inflammatory cytokines like Interleukin-6 (IL-6) and Tumor necrosis factor α (TNF- α) leading to neuronal dysfunction in diabetic neuropathy. Advanced glycation end products (AGEs) may also stimulate NF κ B thus contributing to the disease process [28].

Metabolic syndrome associated depressive disorders

MetS have been associated with depressive disorders, while others have shown women with depressive disorders are more likely to develop metabolic syndrome [29, 30]. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis which is vital to the stress response has major implications in depressive disorders. Promotion of glucose uptake by insulin is hampered by excessive rise in glucocorticoids leading to deposition of body fat. Individuals suffering from mood disorders due to cortisol dys regulation often show increased frequency of MetS [31]. Activation of immunoinflammatory networks by alteration in insulin sensitivity may affect the neuronal or glial cells by oxidative stress mechanisms. The metabolic syndrome and insulin resistance are also strongly linked

with elevated inflammatory markers [27, 32]. Adipose tissue during obesity and metabolic syndrome has been associated with the secretion of pro-inflammatory cytokines such as TNF- α , resistin, IL-6 [33, 34]. Activated pro-inflammatory cytokines induce "sickness behaviour", a syndrome phenotypically similar to depressive disorders that include anorexia, sleep disturbance and decreased self care behaviour in rodents [35]. Depressive disorders have also been associated with increased cytokine levels in various clinical studies [36, 37]. Adipocytes are known to have receptors for Oestrogen, PPAR γ , Insulin like growth factor, insulin and leptin and may release an array of secretory products like leptin and oestrogen which can be associated with depressive disorders [38]. Reduced oestrogen levels have long been associated with anxiety and depression especially in women [39]. Oestrogen receptor α (ER- α) also plays an important role in oestrogen mediated regulation of metabolism [35]. Suppression of ER- α expression in the hypothalamic nuclei of female mice and rats develop a phenotype characteristic of metabolic syndrome marked by obesity and impaired glucose tolerance [40].

Arthritis and metabolic syndrome

Metabolic syndrome and Insulin resistance and obesity have been independently associated with psoriatic arthritis, which is characterized by joint pain, stiffness and swelling, underlined by a systemic inflammatory state [41, 42]. There is increased evidence that chronic inflammation and immune dysregulation may contribute to accelerated atherogenesis and may play a major role in all stages of atherosclerosis (i.e., atherogenesis, atheroma progression, and the development of thrombosis) [43]. Studies suggest that patients with rheumatoid arthritis (RA) have accelerated atherosclerosis. Thus, inflammation associated with RA may contribute to increased risk for metabolic syndrome and coronary-artery disease [44]. Pro-inflammatory cytokines like IL-1 β , TNF- α and C-reactive protein (CRP) have been shown to be up regulated in RA. While the healthy endothelium prevents adhesion of mononuclear cells, during inflammation they express adhesion molecules [selectins, vascular adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1]. Which promotes the adherence of monocytes to the endothelium, which is believed to be the earliest events in atherosclerogenesis [45]. Inflammatory cytokines like TNF- α may itself induce insulin resistance and suppression of glucose transporter (Glut)-4 expression by inhibiting insulin receptor autophosphorylation or by inducing serine phosphorylation of insulin receptor substrate (IRS)-1. Leptin produced by adipose tissues may also contribute to insulin resistance through phosphorylation of serine residues of IRS-1. The involvement of inflammatory cytokines in insulin resistance is mainly important for the following reasons. First, it correlates adipose tissue, a major source of inflammatory cytokines in patients with abdominal obesity with insulin resistance and MetS. Secondly, it provides a plausible explanation for the interplay between chronic inflammatory diseases like RA and MetS [46]. Thus although RA and MetS have often been observed to coexist and various plausible mechanisms may correlate them further studies need to be conducted to prove their association.

Metabolic syndrome and colorectal cancer

The role of insulin in the etiology of colorectal cancer is implicated by various observational and meta-analysis studies [47, 48]. Numerous epidemiological studies have shown a significant correlation between hyperinsulinemia and risk of colorectal cancers [49,50]. Mitogenic action of insulin via insulin receptors has been largely implicated in the association of MetS with colorectal cancer [51,52]. In MetS associate obesity, adipocytes have an important role in the pathogenesis of colorectal cancer. Adeponectin, the hormone secreted by adipocytes regulates not only glucose metabolism but also sensitizes peripheral tissue to insulin [53]. Clinical studies also demonstrate the association of visceral fat accumulation and decreased plasma adiponectin concentration in metabolic syndrome [54]. On the other side insulin resistance leading to reduction in adeponectine is the predominant feature associated with chronic hyperinsulinaemia. Insulin and IGF1 promote mitogenesis and inhibit apoptosis via caspase-mediated pathway in endothelial cells.

This leads to tumorigenesis by the action of insulin receptors (IRs) and IGF1 receptor (IGF1R) [55-57]. IGF 1 may also upregulate the secretion of vascular endothelial growth factor (VEGF), leading to angiogenesis [58]. Adiponectin also inhibits the production of TNF- α by macrophages and its destructive action on endothelial cells stimulates angiogenesis [59]. Reduction in circulatory adiponectin levels has inherent ability to induce tumorigenesis mediated by TNF- α [60]. Insulin inhibits transcription of IGFBP-1, which increases circulating IGFs [61]. High levels of circulating IGF-I increase cellular proliferation and inhibit apoptosis, increasing the risk for colorectal cancer [62]. Thus in MetS, tumorigenic action of insulin, adeponectine and IGF, and inhibitory action of adeponectin on TNF- α in macrophages are the primary cause of colorectal cancer. Recent studies also show the role of HMGA1 gene, key player in cancer progression to be a key regulator for insulin receptor (INSR) gene. Polymorphism in the HMGA1 is associated with the risk of insulin-resistance during metabolic syndrome [63]. While defects in HMGA1 protein causes reduced level of INSR expression and increased susceptibility to hyperinsulinemic state [64, 65].

CONCLUSION

Hyperlipidemia and hyperglycemia associated with MetS form the major basis for development of secondary complications. MetS induced oxidative stress may play important role in development of cognitive impairment, neuropathy and depressive disorders while its effect on cell proliferation, angiogenesis and apoptosis may contribute to the pathogenesis of colorectal cancer.

CONFLICT OF INTERESTS

Declared None

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