Metabolic Syndrome

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Introduction to Metabolic Syndrome

The metabolic syndrome (MetS) is a cluster of the most dangerous heart attack risk factors, and up to a quarter of the world's adults might have MetS. In general, cardiovascular diseases (CVD) are the most common cause of death in the world. As most patients show no obvious symptoms prior to the first incident, identification of risk factors and early intervention are important. Hypercholesterolemia is a well-established strong risk factor and is a primary target for the prevention of CVD (Fig. 1, see chapter "Hyperlipidemia"). MetS has been identified as the second target. It was previously called syndrome X [1] and insulin resistance syndrome [2], as low insulin sensitivity occurs frequently in this condition (Fig. 1).

Multiple definitions for the diagnosis of MetS exist, yet all require at least three of the following: (1) obesity, especially abdominal obesity (expressed by increased waist circumference); (2) dyslipidemia, expressed by raised serum levels of triglycerides or lowered high-density lipoprotein cholesterol (HDLc); (3) elevated blood pressure; (4) and raised fasting plasma glucose (see also chapters "Hyperlipidemia", "Hypertension", and "Diabetes mellitus", respectively) [3]. Moreover, subjects with MetS often show impaired glucose tolerance, insulin resistance, and postprandial abnormalities in lipids.

Abdominal obesity (also termed android obesity [4] or upper body obesity [5]), glucose intolerance, dyslipidemia, and hypertension form "the deadly quartet for CVD" [6]. Studies of abdominal body fat distribution using computed tomography (CT) have revealed that the accumulation of visceral fat in intra-abdominal cavity is more closely related to lipid, glucose, and blood pressure abnormalities rather than absolute body weight or abdominal subcutaneous fat [7]. Thus, the increase of visceral fat area correlates with a cluster of obesity-related risk factors even in mildly obese subjects and is a critical step in MetS development [8]. Finally, from a diagnostic point of view, the waist circumference is an easy-to-measure surrogate marker of visceral fat.

MetS usually occurs in association with sedentary lifestyle (overeating and physical inactivity). It has become a global health problem all over the world and is also increasing in Asian countries, where large numbers of people are living. Although the frequency of people with body mass index (BMI) above 30 is still lower in Asians compared to Caucasians and Africans, MetS, type 2 diabetes, and CVD have also become a serious health problem in Asia.

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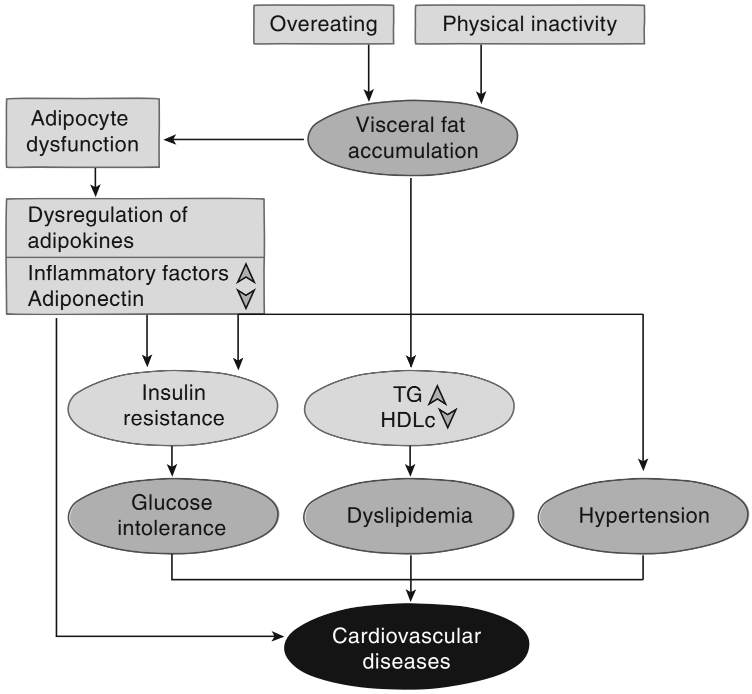

Fig. 1 Changes in metabolic syndrome. Accumulation of visceral fat is associated with a cluster of obesity-related risk factors, including hypertension, dyslipidemia, and glucose intolerance. Overproduction of adipocyte-derived inflammatory factors and reduction in antiatherogenic adiponectin level (summarized as "dysregulation of adipokines") also contribute to the development of cardiovascular disease. *TG* triglycerides (also called triacylglycerols), *HDLc* high-density lipoprotein cholesterol

Since dyslipidemia, hyperglycemia and hypertension are common disorders, these risk factors sometimes gather even in a lean individual without visceral fat accumulation. However, MetS is different from a condition randomly clustering multiple risk factors (Fig. 1).

Pathophysiology of the Metabolic Syndrome

Visceral Obesity

Visceral adipose tissue is present in the mesentery and omentum, where innumerable vessels run from the digestive tract to the liver. In response to energy demand, visceral adipose tissue rapidly hydrolyzes triglycerides and delivers the products, free fatty acids (FFA) and glycerol, to the liver via the portal vein, which resynthesizes energy substrates (triglycerides and glucose) for distant tissues (see chapters "Overview" under the part "Liver" and "Overview" under the part "Fat tissue") [9]. When the visceral fat accumulates, large amounts of FFA are transferred to liver and systemic circulation, leading to abnormalities in glucose and lipid metabolism, and endothelial dysfunction in MetS.

Another pathogenetic condition in visceral obesity is a dysfunction of adipocytes, especially abnormalities of adipocyte-derived factors, so-called adipokines (see chapter "Overview" under the part "Fat tissue") [10]. Oxidative stress and relative hypoxia due to insufficient blood supply are postulated to cause dysfunction of and damage to hypertrophied adipocytes. The latter secrete various inflammatory adipokines including monocyte chemotactic protein-1 (MCP-1) as an alarm signal, which recruits macrophages into the adipose tissue. Macrophages surround and remove the damaged adipocytes and produce proinflammatory cytokines, such as tumor necrosis factor α (TNFα), thus triggering a chronic inflammatory process in the adipose tissue. In addition, hypoxia induces hypoxia-inducible factor 1α, a transcription factor that enhances the expression of plasminogen activator inhibitor 1 in adipocytes. Importantly, in MetS, these proinflammatory and prothrombotic adipokines spread from the adipose tissue to the whole body via the bloodstream, triggering insulin resistance in muscle [11] and thrombus formation in arteries [12].

Adiponectin is a protein specifically produced by adipocytes and abundantly present in plasma. The protein suppresses (1) TNFα-induced expression of adhesion molecules in vascular endothelial cells, (2) growth factor-induced proliferation of smooth muscle cells, and (3) foam cell transformation of macrophages (see chapter "Atherosclerotic heart disease") [12]. In addition to these antiatherogenic activities, adiponectin also has insulin-sensitizing activity and stimulates FFA utilization by activation of AMP-dependent protein kinase (AMPK) and peroxisome proliferator-activated receptor α [13–16]. However, in visceral obesity, plasma levels of adiponectin are decreased. In sum, the dysregulation of adipokines is postulated as a molecular basis of various pathogenetic conditions associated with MetS (Fig. 2) [17].

Dyslipidemia

Triglyceride-rich VLDL is over-synthesized in visceral obesity. Thus, elevation of plasma triglyceride levels is a major feature of MetS.

After hydrolysis of triglycerides, the size of LDLs decreases (see chapter "Hyperlipidemia"). These smaller LDLs are prone to atherogenic oxidative change. Accumulation of VLDL remnants and decrease of HDLc promote atherosclerosis (see below).

Insulin Resistance

Insulin resistance and prediabetic and diabetic conditions are common features of MetS. Impaired metabolism of FFA and dysregulation of adipokines are postulated as mechanisms of insulin resistance in muscle. Muscle cells preferentially metabolize FFA, and glucose uptake is suppressed when the plasma level of FFA is elevated. Additionally, proinflammatory adipokines, such as TNFα, inhibit insulin signaling in muscle and adiponectin expression. Adiponectin normally activates AMPK and increases FFA utilization and thus acts as insulin-sensitizing hormone. However, in MetS, a decrease of adiponectin leads to insulin resistance. In turn, insulin resistance in muscle causes postprandial hyperinsulinemia. Subsequent rise in fasting blood glucose and hyperinsulinemia occur due to hepatic insulin resistance. In this condition, suppression of gluconeogenesis in the fasting state is impaired. The influx of large amounts of FFA from accumulated visceral fat to the liver and the decrease of adiponectin may contribute to hepatic insulin resistance.

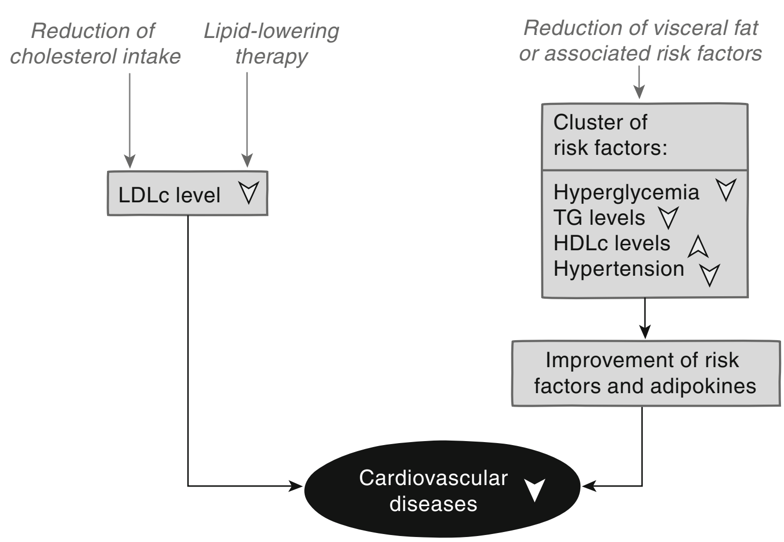

Fig. 2 Effects of treatment of metabolic syndrome on metabolism. Treatment of the multiple risk factors involved in metabolic syndrome apart from increased low-density lipoprotein cholesterol (*LDLc*, left side) aims to reduce visceral fat or directly targets individual risk factors. Reduction of visceral fat improves dysregulation of several adipokines and the whole cluster of risk factors. LDLc levels can be targeted by reducing cholesterol intake and lipid-lowering therapies. *TG* triglycerides (also called triacylglycerols), *HDLc* high-density lipoprotein cholesterol

Hypertension

Hyperinsulinemia promotes urinary reabsorption of sodium chloride in the kidney. Thus, subjects with MetS sometimes develop salt-sensitive hypertension (see chapter "Hypertension").

Additionally, adipocytes synthesize angiotensinogen (see chapter "Overview" under the part "Kidney") and consequently its levels are high in obesity, further contributing to hypertension.

Elevation of plasma FFA causes vascular endothelial dysfunction, resulting in an impairment of vasodilation activity. Increased sympathetic activity is also reported in subjects with MetS.

Atherosclerosis

Ultimately, MetS increases the risk of atherosclerosis. Hyperglycemia, hypertension, and increased FFA can damage the vascular endothelium (see chapters "Diabetes mellitus" and "Hypertension"). Increased levels of VLDL remnants, small-sized LDLs, and low HDLc levels promote the formation of lipid-rich atheromatous plaques (see chapter "Atherosclerotic heart disease"). Hypoadiponectinemia, hyper-inflammatory-cytokinemia and high levels of thrombotic factors accelerate the atherogenic process and trigger the rupture of plaques with the possibility of a lethal outcome.

Treatment of Metabolic Syndrome and Impact on Metabolism

Since MetS subjects often have type 2 diabetes [18], dyslipidemia, and hypertension, physicians may prescribe medicines according to these conditions (see chapters "Diabetes mellitus", "Hyperlipidemia ", and "Hypertension", respectively). As visceral fat accumulation is a key factor in the progression of MetS and underlies multiple risk factors, the primary management strategy is to reduce accumulated visceral fat [17].

Overwhelming evidence indicates that weight reduction alleviates glucose intolerance, hypertriglyceridemia, hypo-HDL-cholesterolemia, and hypertension. Reduction of visceral fat ameliorates the cluster of multiple CVD risk factors simultaneously (Fig. 2). As such, a change in lifestyle is the first-line treatment in MetS. This generally includes cardiovascular exercise, generally increased physical activity, and a restricted calorie intake.

To date, there is no single pharmacological treatment available, specifically tailored for the entire cluster of multiple disturbances involved in MetS.

Perspectives

With increasing comforts in the world, the average life span increased. However, reduced physical activity and excessive intake of nutrition lead to increased visceral fat and obesity causing type 2 diabetes, hypertension, dyslipidemia, and CVD. A strategy to combat and prevent MetS is critically required. Therefore, education and promotion of healthy lifestyle remains our most important and effective tool to prevent and treat MetS.

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