

Clinical Scenario of the Metabolic Syndrome

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Keywords

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Summary

The term metabolic syndrome (MeS) refers to a cluster of associated symptoms composed of impaired fasting glucose, abdominal obesity, hypertension, and dyslipidemia. MeS is associated with an increased risk of cardiovascular and diabetes-associated morbidity and mortality. The increased amount of visceral fat together with a chronic inflammatory state predisposes to the development of arteriosclerosis. Furthermore, insulin resistance (IR) and dyslipidemia are associated with fatty liver disease. In addition, MeS is linked to non-cardiovascular diseases such as cancer as well as psychiatric or endocrine disorders. Here, we discuss the clinical impact of MeS in cardiovascular and non-cardiovascular diseases to highlight the importance of prevention, early diagnosis, and multifactorial treatment of high-risk individuals.

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Cardiovascular System

Fat Distribution

The metabolic syndrome (MeS) increases overall cardiovascular mortality by a factor of 1.5–2.5 [1]. Over the last decades, the relevance of fat distribution for the development of cardiovascular disease (CVD) and metabolic disorders was recognized despite the finding of so-called metabolically healthy obese people, a phenomenon first described by Sims about 15 years ago [2]. Localization of the excess amount of adipose tissue appears to be a key for developing cardiovascular and metabolic diseases. Furthermore, in contrast to subcutaneous fat, excess visceral fat increases the risk for developing insulin resistance (IR) and other features of MeS [3].

The waist-to-hip ratio appears to be superior to the body mass index (BMI) when assessing the individual disease risk since it identifies people with a relatively low BMI but increased intra-abdominal fat accumulation [4]. In line with these findings, it has been shown that the waist-to-hip ratio and waist and hip circumferences are superior to BMI in predicting the risk of myocardial infarction [5]. An even better diagnostic parameter of visceral fat than waist circumference alone appears to be the combination of an increased waist circumference and elevated fasting triglyceride concentrations [6]. It has been shown that high triglycerides together with elevated waist circumference are associated with a higher cardiometabolic risk profile, as displayed by a hazard ratio for future coronary artery disease of 2.40 in men and of 3.84 in women [7]. Beyond the risk for coronary heart disease, excess visceral fat has been found to be associated with hypertension [8]. In comparison to other influencing factors, the waist circumference in men and women showed the strongest association to systolic and diastolic blood pressure [9].

The pathophysiological link between visceral fat and cardiovascular disease is certainly multifactorial. One mechanism might be the association of visceral and ectopic fat accumulation, e.g. fatty degeneration of cardiac cells. It has been shown that visceral obesity is the best predictor for epicardial and pericardial fat [10]. Moreover, weight loss associated with a decrease of visceral fat in severely obese subjects significantly reduces epicardial fat thickness [11]. Pericardial fat correlates with adiposity, vascular calcification, and further cardiovascular risk factors [12]. In particular, epicardial fat appears to be related to the presence, severity, and recurrence of atrial fibrillation as a most critical factor for stroke [13]. Visceral adiposity in contrast to subcutaneous fat facilitates arteriosclerosis, hypertension, and fat accumulation of the heart, thereby heralding an increased risk of CVD (fig. 1).

Chronic Inflammation in Adipose Tissue

Chronic low-grade inflammation caused by activated macrophages in visceral adipose tissue may also contribute to cardiovascular risk in patients with MeS [14]. It has been shown that low C-reactive protein (CRP) levels in metabolically healthy obese pa-

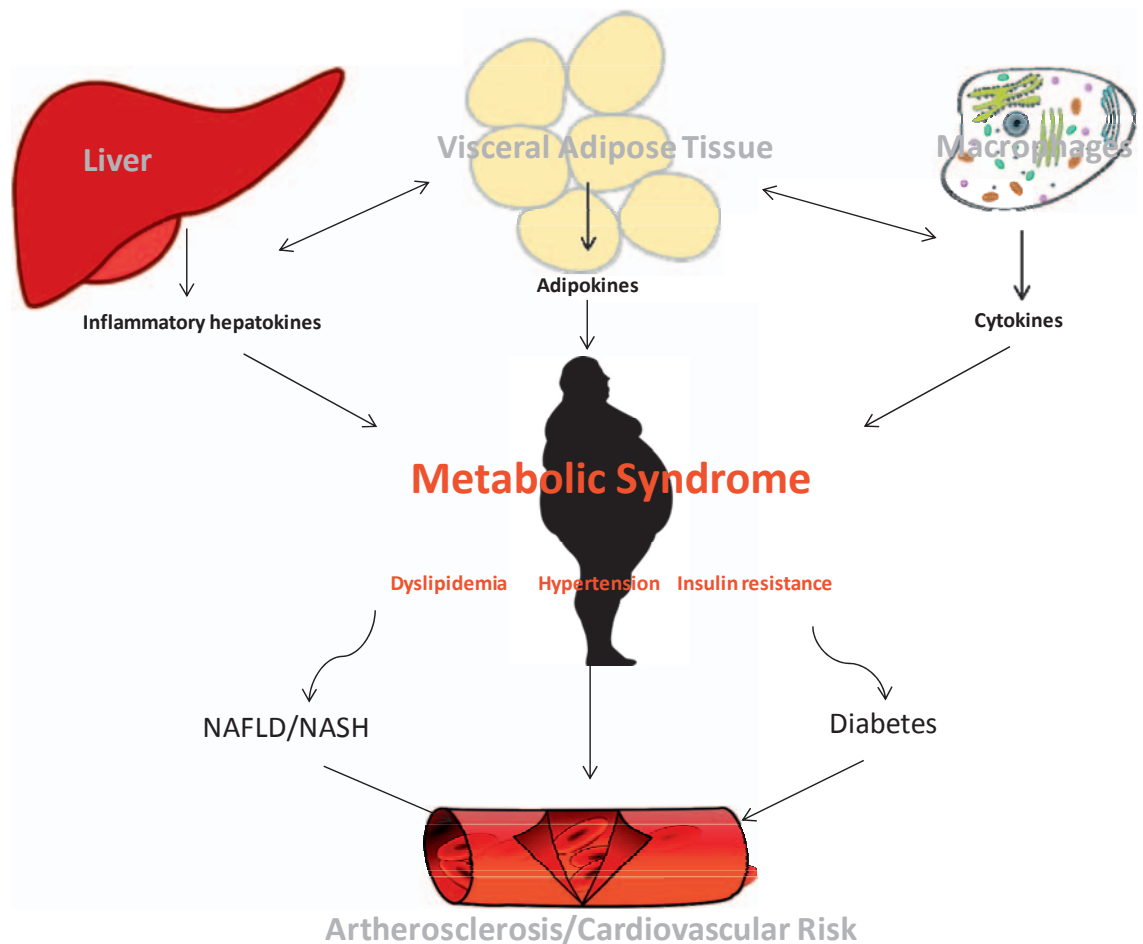


Fig. 1. Pathogenesis of elevated cardiovascular risk in the MeS.

tients were associated with a similar risk for CVD as compared to metabolically healthy normal-weight persons [15]. The mechanism of obesity-related inflammation is not fully understood yet. One possible explanation is obesity-induced systemic oxidative stress, which leads to a stimulation of NADPH oxidase activation, thereby disrupting normal adipocytokine profiles [16]. Adipose tissue of obese patients expresses large amounts of proinflammatory cytokines such as tumor necrosis factor (TNF)-alpha or interleukin (IL)-6. Furthermore, adipose tissue macrophages are elevated in obesity and perpetuate inflammatory pathways, e.g. by being responsible for almost all adipose tissue TNF-alpha expression [17].

Leptin and Other Adipokines

The probably most relevant adipokine is leptin, whose main role resides in signaling peripheral energy status to the brain. Its key physiological functions are to reduce appetite, increase energy expenditure, and improve insulin sensitivity [18]. Leptin is mostly synthesized and secreted by white adipocytes [19]. It has been shown that hyperleptinemia is associated with CVD such as atherosclerosis [20]. The development of leptin resistance, in analogy to IR, appears to be of major relevance for the genesis and maintenance of obesity. This resistance may occur at several sites, namely at the blood-brain barrier and at specific hypothalamic nuclei such as the arcuate nucleus and other nuclei associated with reward-re-

lated eating behavior [21]. Bypassing the blood-brain barrier may represent a means to overcome at least one site of this resistance [22]. In conclusion, elevated leptin levels and leptin resistance are associated with obesity, IR, myocardial infarction, and congestive heart failure [23].

Adiponectin, an adipocyte-derived protein, is an important adipokine protective for the development of MeS and capable of increasing insulin sensitivity [24]. Adiponectin suppresses glucose production in the liver and enhances fatty acid oxidation in skeletal muscle, resulting in beneficial metabolic sequelae [25]. Adiponectin levels have been shown to be significantly reduced in obesity [26]. With regards to chronic inflammation processes, this peptide is inversely associated with CRP levels independently of all other MeS factors [27]. Moreover, adiponectin appears to play a major role in the central regulation of energy metabolism. As such, adiponectin complexes have been shown in human cerebrospinal fluid [28]. In animal models, intracerebroventricular injection of adiponectin led to a decrease in body weight and an increase in energy expenditure [29].

Effects for the development of CVD also exist for homocysteine, a product of demethylation of methionine. This amino acid appears to be relevant in the pathogenesis of atherogenesis by inducing prothrombotic and proinflammatory effects, increased oxidative stress, endothelial dysfunction, and smooth muscle cell prolifer-

eration [30]. Elevated plasma homocystein levels are associated with increased cerebro-cardiovascular events in MeS [31]. In obese patients, homocysteine concentrations are elevated and correlate well with serum levels of leptin [32].

Insulin Action

Impairment of insulin action is one key feature of MeS. Conceptually, both IR and impaired pancreatic insulin secretion lead to a decrease of insulin action. It has been shown that IR contributes to the development of arteriosclerosis [33], thereby increasing cardiovascular risk. Furthermore, IR may contribute to other cardiovascular risk factors such as increased blood pressure, dyslipidemia, and diastolic dysfunction [34]. A major risk factor for the development of IR is visceral obesity [35]. Increased waist circumference, skin alterations like pseudoacanthosis nigricans, and fatty liver disease might serve as clinical indicators for IR.

IR may occur in several tissues, e.g. also in the brain as a so-called 'central insulin resistance' among other factors induced by excessive intake of calories and saturated fatty acids [36]. As a consequence, this may lead to attenuated satiety signals and increased hunger. IR in the liver is followed by increased glucose production due to insufficient suppression of gluconeogenesis. Moreover, excessive delivery of free fatty acids from adipose tissue further perpetuates hepatic IR and promotes non-alcoholic fatty liver disease (NAFLD) [37]. NAFLD, being tightly correlated with hepatic IR [38], is a strong predictor for the development of diabetes mellitus type 2 [39]. Further progression of NAFLD triggers hepatic inflammation, i.e. steatohepatitis leading to fibrosis and even cirrhosis [40]. Moreover, IR of adipose tissue leads to elevated levels of triglycerides and free fatty acids as a consequence of increased lipolysis [41]. Accumulation of fatty acids in the pancreas might further result in diminished insulin secretion from pancreatic β -cells [42, 43]. Impaired insulin secretion in combination with IR further worsens the metabolic consequences of MeS.

Lipid Metabolism

Another key feature of MeS is dyslipidemia as characterized by elevated levels of triglycerides and free fatty acids as well as decreased levels of high-density lipoproteins (HDL) [44]. Low-density lipoproteins (LDL) and total cholesterol levels are mostly within the normal range, while HDL and LDL particles are smaller in visceral obesity and MeS [45]. This is driven by an exchange of cholesterol ester molecules against triglyceride molecules in the core of the lipoproteins. Subsequently, HDL and LDL particles are more likely to deliver their lipid content to the liver, thereby forming small dense particles [46]. This dyslipidemic state is one of the main risk factors for developing arteriosclerosis [47]. Whether hypertriglyceridemia represents an independent risk factor is not yet verified in humans [48], but remnants of triglyceride-rich lipoproteins are highly atherogenic [49]. The low density and altered

Table 1. Association between obesity and relative risk of cancer: meta-analysis of studies from 1985–2011 (modified according to [80])

Cancer	Relative risk (95% confidence interval)	
	women	men
Esophagus	2.04 (1.18–3.55) ^a	1.23 (0.58–2.60)
Colon	1.19 (1.04–1.36) ^a	1.57 (1.48–1.65) ^a
Rectum	1.03 (0.74–1.44)	1.22 (0.91–1.64)
Pancreas	1.34 (1.22–1.46) ^a	1.36 (1.07–1.73) ^a
Gallbladder	1.82 (1.32–2.50) ^a	1.47 (1.17–1.85) ^a
Thyroid gland	1.03 (0.87–1.23)	1.12 (0.72–1.72)
Non-Hodgkin lymphoma	0.91 (0.86–0.97) ^a	1.09 (0.98–1.21)
Breast, postmenopausal	1.25 (1.07–1.46) ^a	–
Kidney	1.72 (1.58–1.88) ^a	1.57 (1.38–1.77) ^a

^aStatistically significant $p < 0.05$.

structure of LDL cholesterol in MeS particularly promotes the development of arteriosclerosis by stimulating resident macrophages and triggering inflammation within the vascular wall [50]. Less effective binding to the LDL receptor also attenuates the clearance of small LDL particles. Furthermore, expression of the LDL receptor is reduced in the presence of IR. Antiatherogenic features of HDL are based on an increased cholesterol efflux from the vascular wall and inhibition of the uptake of LDL into macrophages [51].

Other Obesity-Associated Diseases

Cancer

In MeS, there is an increased risk for developing cancer with sex-specific differences (table 1). However, there is still a debate on the underlying mechanisms. Again, IR, hyperinsulinemia, and chronic subclinical inflammation might directly and indirectly promote cellular dedifferentiation and thus tumorigenesis. Due to stimulation of cell survival, cell proliferation, and angiogenesis, cancer progression is facilitated [52]. Insulin acts as a growth factor, and hyperinsulinemia, as often prevalent in MeS, may cause a more rapid and aggressive growth of cancers such as colorectal carcinoma, pancreatic carcinoma, liver cancer, and others [53]. Adipocytes represent a central mediator of the inflammatory response in obese patients. They are secreting not only proinflammatory cytokines or adipokines but also growth factors such as insulin-like growth factor 1 or vascular endothelial growth factor. Through these growth factors, PI3K/Akt signaling is stimulated, which is involved in the regulation of cell survival, cell proliferation, and cell migration. Thus, chronic inflammation in adipose tissue promotes hyperplasia, tumor growth, and metastasis formation [52]. Moreover, abdominal obesity induces significant changes in adipose stem cells, which may initiate breast cancer formation through estrogen-dependent pathways (table 1) [54].

Hyperuricemia

In recent years, hyperuricemia has been recognized as a part of MeS, since high serum uric acid is clearly correlated with the prev-

alence of MeS [55]. Furthermore, higher levels of serum uric acid increase the risk of developing type 2 diabetes [56] and are associated with several components of MeS such as IR [57], hypertension [58], and arteriosclerosis [59]. Atherogenic effects are probably mediated by higher activity of pro-oxidant in comparison to anti-oxidant forms of xanthine oxidoreductase. Increased vascular inflammation may result from this alteration [60, 61].

Blood Clotting

Impaired blood clotting has been observed in MeS, which increases the risk for cardiovascular events [62]. Beside atherothrombotic cardiovascular events, there is also a higher rate of thromboembolism. Both are provoked by reduced activity of vasodilators and an increased expression of vasoconstrictors as a consequence of endothelial dysfunction. This dysfunction appears to result from chronic inflammation, dyslipidemia, and hypertension. Furthermore, a higher platelet activity and enhanced coagulation, displayed by higher fibrinogen and plasminogen activator inhibitor levels, are observed [63]. Enhanced coagulation could be caused by altered hepatic production of coagulation factors and proinflammatory cytokines because of hepatic IR [64]. In addition, there is evidence for an influence of several adipokines, such as leptin and adiponectin, on platelet function [65].

Psychiatric Disorders

Depressive disorders are often associated with metabolic disturbances like hypertension, increased cardiovascular risk, chronic inflammation, and altered insulin signaling [66]. The prevalence of MeS is threefold higher in patients with psychiatric disorders compared to the general population. This includes depression, bipolar disorders, and schizophrenia [67]. Numerous mechanisms behind these findings are being discussed, encompassing vascular changes, subclinical hypercortisolism, and failure of coping strategies.

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Endocrine System

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) constitutes one of the most common endocrine disorders in young women of reproductive age [68] and is closely related to MeS. The prevalence of visceral obesity in women with PCOS varies between 61 and 76% [69]. As in MeS, visceral obesity in PCOS is associated with elevated levels of LDL, triglycerides, and cholesterol as well as decreased levels of HDL and results in an increased risk of arteriosclerosis [70]. Clearly, PCOS is related to an impaired metabolic homeostasis and thus with an elevated cardiovascular risk [71].

Subclinical Hypercortisolism

The link between hypercortisolism and MeS was recognized based on similar clinical manifestations. In particular, subclinical hypercortisolism, which is defined as disturbed hypothalamus-pituitary-adrenal (HPA) axis activity without symptoms of an overt Cushing's syndrome or presence of an adrenal incidentaloma, has been linked to MeS [72]. In contrast, it has also been postulated that MeS is associated with a hyperactivity of the HPA axis [73, 74]. The prevalence of subclinical hypercortisolism has been estimated to be 0.2–2.0% in the adult population and thereby represents a key suspect for developing MeS [75]. Still, and despite the correlation of subclinical hypercortisolism with visceral obesity [76], hypertension [77], IR [78], and increased cardiovascular risk [79], the clinical significance in MeS still remains unclear.

Disclosure Statement

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