What men should know about metabolic syndrome, adiposopathy and ‘sick fat’

The term ‘metabolic syndrome’ (MetSyn) is a term created to identify common atherosclerotic cardiovascular disease (CVD) risk factors that often cluster together (1). MetSyn was never intended to describe an underlying pathophysiological process. Other challenges with MetSyn include that: (i) multiple definitions exist for the same syndrome; (ii) multiple other terms describe same or similar syndrome and (iii) the diagnosis of MetSyn may not provide any better prediction of future disease than an assessment of its individual risk factors (2–4). From a clinical management standpoint, the term ‘metabolic syndrome’ may not be a particularly instructive or effective term in patient education (5). In contrast, since the 1940s (6), the data support visceral adiposity as an example of a unified, pathophysiological contributor to the abnormalities associated with MetSyn, such as high glucose levels, high blood pressure, high triglyceride levels, reduced high density lipoprotein cholesterol levels and increased CVD risk (7).

What men should know about the ‘metabolic syndrome’

The importance of the pathogenic potential of adipose tissue is codified in national and international guidelines regarding the diagnosis of MetSyn. Visceral adiposity increases waist circumference, which is not only a component of the diagnostic criteria of some MetSyn definitions (8), but is also the only diagnostic criteria required for other MetSyn definitions (9). This is of clinical relevance, because while all adipose tissue depots may have both fat mass and pathogenic metabolic potential (10), visceral adiposity may be especially pathogenic compared with other fat depots, such as peripheral subcutaneous adipose tissue. The increase in adiposopathic potential with visceral adiposity is because of its location (portal delivery to the liver), relative increase in metabolic activity, as well as its inherent differences in pre-adipocyte differentiation, lipolysis, lipogenesis, activity of adipocyte receptors and secretion of adipocyte factors (7). Thus, an increase in visceral adiposity is most associated with adverse metabolic consequences. Most applicable to this discussion is that an increase in visceral adiposity helps to account for the increased CVD risk found in men compared with women of the same age (6).

What men should know about ‘sick fat’

An increase in adipose tissue can cause morbidities because of the accumulation of fat mass alone. Additionally, increasing body weight (as may be reflected by the body mass index) is directly associated with an increased prevalence of metabolic diseases, such as type 2 diabetes mellitus, high blood pressure and dyslipidaemia (11). Furthermore, longitudinal data, even in the young, support that increased adiposity increases the onset or worsening of metabolic abnormalities (12). As importantly, a reduction in body weight among overweight individuals often improves metabolic disease (13), and thus weight reduction in overweight patients with metabolic diseases is a mainstay recommendation by regulatory agencies and many medical organisations. The relationship between increased body fat and metabolic disease can be explained by the wealth of data supporting adipocyte hypertrophy and visceral adiposity, as causing adipose tissue dysfunction results in pathogenic endocrine and immune responses leading to metabolic morbidities (7).

Specifically, adipose tissue is an active endocrine organ, whose dysfunction can ‘cause’ metabolic disease. Examples of normal adipose tissue endocrine function include associated factors involved in metabolic processes important for human health, such as angiogenesis, adipogenesis, extracellular matrix dissolution and reformation, lipogenesis, growth factor production, glucose metabolism, production of factors associated with the renin-angiotensin system, lipid metabolism, enzyme production, hormone production, steroid metabolism, immune response, haemostasis and element binding. Adipose tissue also has receptors for traditional peptides and glycoprotein hormones, receptors for nuclear hormones, other nuclear receptors, receptors for cytokines or adipokines...
with cytokine-like activity, receptors for growth factors, catecholamine receptors and other receptors. Adipose tissue is also an active immune organ, whose dysfunction (e.g. increase in pro-inflammatory factors and/or decrease in anti-inflammatory factors) can also promote metabolic disease. Pro-inflammatory responses involve adipose tissue affiliated factors such as those with cytokine activity, acute phase response proteins, proteins of the alternative complement system, chemotactic/chemoattractants for immune cells and eicosanoids/prostaglandins. Anti-inflammatory responses involve adipose tissue factors such as adiponectin, annexin-1, anti-inflammatory interleukins, transforming growth factor-beta, bone morphogenetic factor, nitric oxide and interleukin-1 receptor antagonist (7).

Thus, in summary, adiposopathy or ‘sick fat’ can generally be defined as anatomic and pathophysiological adipose tissue abnormalities that contribute to metabolic disease. Adiposopathy is promoted or ‘caused’ by positive caloric balance and sedentary lifestyle in genetically or environmentally susceptible patients. (Figure 1) Anatomical abnormalities typically found with adiposopathy or ‘sick fat’ include adipocyte hypertrophy, visceral adiposity, growth of adipose tissue beyond its vascular supply, increased number of adipose tissue-associated immune cells and ectopic fat deposition in other body organs. On a cellular level, adiposopathy is associated with intra-adipocyte organelle dysfunction (e.g. mitochondria and endoplasmic reticulum) (14, 15) and impaired adipogenesis (7). Adiposopathy leads to an increase in circulating free fatty acids, and the pathophysiological disruption of the otherwise physiological endocrine and immune function of adipose tissue promotes or worsens hyperglycaemia, high blood pressure and dyslipidaemia that are all major atherosclerotic coronary heart disease (CHD) risk factors. This helps to explain why adipose tissue anatomic findings, such as an increase in visceral adiposity, independently increase CHD risk (16). Other metabolic abnormalities of adiposopathy include non-alcholic steatohepatitis or fatty liver, hyperuricemia and increased cancer risk (e.g. cancer of the prostate in men, and cancer of the breast and uterus in women). Finally, adiposopathy may contribute to hypoandrogenaemia in men and hyperandrogenaemia in women. This helps to explain why: ‘One of the biochemical consequences of obesity is often a closer approximation of the genders with regard to sex hormone levels.’ (17)

Yet another example wherein adiposopathy or ‘sick fat’ may approximate the genders is in regard to MetSyn and CVD risk. As noted earlier, for the same age, men generally have higher CVD risk than

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**Figure 1** Simplified flow diagram of the relationship between adiposopathy and illustrative metabolic disease
women. However, while it is unclear that hyperglycaemia (a component of MetSyn) itself increases CVD risk (11), women with type 2 diabetes mellitus (T2DM) and no history of CVD appear to have a higher 10-year cumulative risk for CVD compared with men without T2DM and no history of CVD. Furthermore, not only do T2DM women with CVD have risk for a future CVD event similar to that of T2DM men with CVD, but also T2DM women with CVD may have a higher risk of a future fatal CVD event than their men counterparts (18). If it is assumed that the increase in CVD in patients with diabetes mellitus is not substantially because of hyperglycaemia, then an alternative explanation for this increased CVD risk is that the same underlying pathophysiologic process causing T2DM is also causing other metabolic abnormalities that increase CVD risk. Adiposopathy or ‘sick fat’ is such a potential cause, as it promotes or worsens high blood sugar, high blood pressure and dyslipidaemia that are all components of MetSyn and which are all major CVD risk factors.

What men should know about management of adiposopathy or ‘sick fat’

A detailed description of adiposopathy treatments is beyond this short perspective discussion and is reviewed elsewhere (19–24). (Table 1) In general, at least for the past decade: ‘An emerging concept is that the development of antiobesity agents must not only reduce fat mass (adiposity) but must also correct fat dysfunction (adiposopathy).’ (25) This suggests that overweight men with metabolic diseases due to adiposopathy or ‘sick fat’ benefit from interventions that improve adipocyte and adipose functionality (19,20,22).

For example, while often not associated with long-term efficacy, perhaps the most cost-effective way for an individual overweight man (or women) to improve adiposopathy-related metabolic diseases (such as those currently classified by MetSyn) is through appropriate nutrition and increased physical activity (13,26). This is of clinical importance.
because many clinicians prefer to treat the underlying cause of disease (adiposopathy), rather than the consequences of disease (hyperglycaemia, high blood pressure, dyslipidaemia, etc.) (11) Other options beyond lifestyle changes include drug therapies and bariatric surgery (22,26). Unfortunately, for the population of men (and women) at large, existing nutritional and physical activity public health efforts have not reversed the epidemic of obesity and its adverse mass and metabolic consequences.

Table I describes examples of adiposopathy treatments and their effects upon illustrative and selected factors associated with adipose tissue that otherwise contribute to metabolic disease. Table I also describes how antidiabetes mellitus therapies may have similar effects as the above, likely because these therapies have direct or indirect effects upon adipose tissue function, and because adiposopathy is a direct contributor to hyperglycaemia (4,7,11,17). In review of this table, a notable finding is the substantial amount of published knowledge regarding how various interventions reduce androgens in women with polycystic ovarian syndrome. In contrast, less published data exist regarding the effect of these same interventions in increasing androgens and decreasing estrogens in obese men. This is of clinical importance given the high rate of hyperandrogenaemia, hyperestrogenaemia, reduced sperm concentration and reduced sperm count in obese men (27). Clearly, more work needs to be carried out to better understand steroidogenesis in men, and the potential improvement in such endocrine function, as it pertains to therapies directed at improving adipose tissue function.

Conclusion

For over half a century, basic scientists have understood the pathogenic potential of adipose tissue. Similarly, clinicians and patients are well aware that an increase in body fat increases the risk of metabolic disease. But it is only in the past decade or so that many scientific organisations and clinical scientists have begun to acknowledge what has been common knowledge among basic scientists and clinicians, which is that adipose tissue is an active endocrine and immune organ with pathogenic potential (21). As such, over the next decade, clinicians and patients may find the term ‘obesity’ being relegated to describing fat-mass related pathology. Clinicians may find the term ‘metabolic syndrome’ replaced with ‘adiposopathy’ and ‘sick fat’ as scientific and clinical terms, respectively, which better describe the adverse metabolic consequences of dysfunctional adipocytes and pathogenic adipose tissue. From a patient standpoint, men should better understand that fat weight gain may cause their fat to become ‘sick,’ which may then contribute to metabolic diseases such as high glucose levels, high blood pressure and dyslipidaemia. The good news is that fat weight loss often treats ‘sick fat’ and results in improvements in metabolic diseases, such as those defined by the ‘metabolic syndrome.’ As such, clinicians may find that: ‘A discussion as to how increasing body weight may cause their fat to become ‘sick,’ or how losing body weight may cause their fat to become ‘healthier’, might be better than discussing the diagnostic components defining the ‘metabolic syndrome.’” (21)

Disclosure

The authors have nothing to disclose regarding this manuscript.

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