Redefining the Metabolic Syndrome: Contribution of Inflammatory and Sex Steroidal Antecedents

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Abstract

The MetS is a major health concern in the United States today being more prevalent in older individuals and in populations of specific racial/ethnic backgrounds. Although MetS is defined by a clustering of metabolic abnormalities including hyperglycemia, high blood pressure and central obesity, we propose the addition of pro-inflammatory adipokines (TNF-α, IL-6, Leptin, PAI-1) as well as CRP being incorporated into the physiological evaluation of those at risk for MetS. Much research exists to show that hyperinsulinemia and central obesity are integral to the development of MetS and that inflammatory adipokines and cytokines are increased in response to the development of insulin resistance and central obesity. However, questions remain as to whether or not these are the primary contributors or sole antecedents to the development of MetS. Androgenic steroids have also been proposed to contribute to the pathogenesis of MetS. More research is necessary to determine whether insulin resistance and central obesity mediate the relationship between androgens and MetS or whether androgenic sex steroids mediate the relationship between MetS and insulin resistance and/or central obesity or whether there is bidirectionality in aforementioned relationships.

Introduction

Approximately 34% of US adults meet the criteria for the metabolic syndrome (MetS) (Ervin, 2009) which consists of a clustering of metabolic abnormalities including hyperglycemia, dyslipidemia, and hypertension (Alberti et al 2009). These perturbations are associated with a two-fold greater risk of cardiovascular disease (CVD) and almost three-fold risk of type-2 diabetes (Ford 2005; Grundy 2008). Independent of aforementioned adverse health outcomes, MetS is often observed in those with fatty liver, gallstones, polycystic ovary syndrome, asthma, sleep disturbances, and certain types of cancer (Beilby, 2004).

Gender, age, and race differences are also found in men with MetS, showing greater prevalence rates compared to women (Regitz-Zagrosek V, 2006). Both men and women in their 40's and 50's are three times more likely than 20-39 year olds to have MetS, while women in their 60's are six times more likely to develop the syndrome than women in the youngest group (Ervin, 2009). Among men living in the US, rates are highest among Hispanic Americans and lower in African-Americans with Caucasian men falling somewhere in between. In women in the US, rates are highest in Hispanic women, lowest in Caucasian women, with African-Americans falling somewhat closer to Caucasian women (Church, 2004).

Although MetS is associated with increased risk of all-cause morbidity and mortality, there is variability in the criteria agreed upon by national organizations (see Table 1). Using the Adult Treatment Panel-III (ATP guidelines), equal weight is given to each component and one must possess three out of five components to meet the criteria for MetS. Although insulin resistance is highly predictive of the onset of diabetes, it is not a required criteria when using ATP guidelines. Conversely, using World Health Organization (WHO) guidelines, insulin resistance is required along with two additional criteria. Insulin resistance is defined by impaired fasting glucose, impaired glucose tolerance or type 2 diabetes. Even in those with normal fasting glucose, those in the lowest quartile for their specific population may be considered insulin resistant under specialized testing conditions. Thus, specialized testing of glucose status beyond routine clinical assessments may be required in addition to higher qualifications for blood pressure using these guidelines (Beilby, 2004). In contrast, the International Diabetes Federation (IDF) requires central obesity as a mandatory component along with any two of the remaining four components for a MetS diagnosis.

Table 1: Criteria for the Metabolic Syndrome According to Different Organizations

Characteristics	NCEP-ATP III [19]	IDF [20]	WHO[21]
Insulin Resistance, Impaired Glucose Tolerance or Impaired Fasting Glucose, and/or Diabetes	Fasting Glucose ≥ 6.1 mmol/L	Fasting Glucose ≥ 5.6 mmol/L	Glucose ≥7.0 mmol/L and/or 2 hr post glucose load ≥11.1 (diabetes) and/or fasting glucose < 7.0 mmol/L and 2 hr post glucose load ≥ 7.8 mmol/Liter or glucose >7.0mmol/L and 2 hr post glucose > 7.8 and <11.1mmol/L (impaired glucose tolerance) or fasting glucose ≥ 6.1 but < 7.0 mmol/L and 2 hr post glucose load < 7.8 mmol/L (impaired fasting glucose).
Waist Circumference	> 102cm, males > 88cm, females	> 94cm, males* > 80cm, females	> 0.90 males > 0.85 females or
BMI or WHR	-	-	BMI > 30kg/m^2 or WHR > 0.90 males > 0.85 females
HDL-cholesterol	< 1.04mmol/L males < 1.30mmol/L females	< 1.03mmol/L males < 1.29mmol/L females	< 0.90mm/L males < 1.0mmol/L females
Triglycerides	≥ 1.7mmol/L	≥ 1.7mmol/L	≥ 1.7mmol/L
Blood Pressure	≥130/≥85mmHg	≥130/≥85mmHg	≥ 140/≥90mmHg
Microalbuminuria			Urinary albumin excretion rate ≥ 20 μg/min or albumin/creatinine ratio > 3.4 mg/mmol

NCEP-ATP III: National Cholesterol Education Program- Adult Treatment Panel III, IDF: International Diabetes Federation, WHO: World Health Organization

*Specific to Europid populations

The exact pathogenesis of the MetS is not entirely clear. Historically, insulin resistance was considered the primary factor with a strong link to each of the MetS components (Church, 2004). Unhealthy lifestyle habits such as high fat/high sugar diets, excessive total calorie intake, and/or a lack of physical activity may over time induce insulin resistance. On a cellular level, this may result in blunted tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 leading to down-regulation of phosphatidylinositol 3-phosphate, thereby reducing GLUT-4 transporter activity.

Hyperinsulinemia, in compensation for the insulin resistant state, may result in metabolic perturbations associated with MetS including high blood pressure, central obesity, dyslipidemia, and hyperglycemia (De Fronzo and Ferrannini, 1997). However, research has shown heterogeneity in the strength of the relationship between insulin resistance and different components of the MetS both within and among different populations (Alberti, 1998). The theory of insulin resistance being the sole or primary contributing factor to MetS is not without question.

Much attention has focused upon obesity, specifically central obesity and its association with disorders of adipose tissue metabolism, as being a primary factor. Even more disconcerting is the spillover of excess triglycerides that may lead to ectopic fat distribution observed in the heart, liver, viscera, and skeletal muscle. Both central obesity and ectopic fat distribution are reported to play an important role in the pathophysiology of MetS (Sperling, 2015) as the IDF considers central obesity a mandatory component of MetS.

Inflammatory Factors and the Metabolic Syndrome

Obesity-related inflammation contributes to many of the pathological features associated with MetS increasing CVD and type 2 diabetes risk (Wisse, 2004). Inflammatory markers born out of hypertrophied fat cells, most notably, cytokines, chemokines, and hormone-like proteins collectively called adipokines, have been found to contribute to pro-inflammatory signaling by the liver, immune cells, and adipose tissue itself (Balistreri, 2010).

Expanded fat stores marked by macrophage infiltration accounts for most of the TNF-α production, which serves as a mediator of both local and systemic inflammation. TNF-α induces insulin resistance through serine phosphorylation of the insulin receptor and insulin receptor substrate-1, interrupting insulin signaling. TNA- α stimulates adipose tissue lipolysis, increasing free fatty acid circulation

adversely affecting the serum lipid profile (Grunfeld, 1991; Kern, 2001). Along with its suppressive effects on nitric oxide (Lau, 2005), TNF- α contributes to the increased risk of cardiac events (Bray, 2009). It also activates the transcription factor nucleus factor $_{k}\beta$ pathway, which in turn translocates to the nucleus where it activates inflammatory target genes and serves as a second messenger system for inflammatory cytokine signaling. Evidence suggests that TNF- α has a direct role in the development of MetS (Ho, 2013) and also increases the secretion of other pro-inflammatory cytokines such as IL-6 (Coelho, 2013).

IL-6 is also associated with insulin resistance and in fat tissue, is secreted by adipocytes, macrophages, and non-macrophage stromal vascular cells. Since IL-6 is pleiotropic and affects a variety of tissues distal to the site of release, it is difficult to determine the source of IL-6, which is produced by a number of different tissues and may have paradoxical actions (Carey & Fabbraio, 2004). Stimulation of IL-6 via exercise and skeletal muscle contraction, for example, mediates beneficial effects on glucose homeostasis. In contrast, after infusing glucose using euglycemic clamp techniques, IL-6 is associated with poor glucose control. Furthermore, pharmacologic agents that block or neutralize IL-6, can result in improvements in insulin resistance and glucose homeostasis (Fantuzzi, 2014).

Paradoxical pro and anti-inflammatory actions of IL-6 are likely related to the mode of delivery or stimulation (Carey & Fabbraio, 2004; Fantuzzi, 2014). Elevated circulating levels of IL-6 may be considered a marker of IL-6 resistance and concomitant with elevated TNF- α are often observed in obesity and in those with CVD (Erusan, 2012). Evidence suggests that IL-6 elevation as a result of hypertrophied adipocytes, is more likely the result of its positive association with obesity rather than a direct causal effect on insulin resistance. IL-6 is a significant factor enhancing hepatic synthesis of acute phase proteins contributing to chronic systemic inflammation via its actions on C-reactive protein (CRP)(Wisse, 2004).

CRP, a signaling product of IL-6, is a general non-specific marker of systemic inflammation released by the liver. Since CRP is associated with plaque instability and rupture, it is also considered a marker of the global assessment of CVD (Ridker, 2001). It is weakly associated with traditional risk factors such as serum lipids and lipoproteins, therefore it can be used to indicate at risk individuals with a normal lipid profile who may not be identified using traditional methods. CRP may also con-

tribute to the atherosclerotic process directly by operating at the level of vascular endothelial tissue to increase LDL-uptake and oxidation (LeMont, 2004), independently predicting myocardial infarction, peripheral artery disease, and stroke (Torres, 2003).

CRP is higher in women than men, higher in women using oral hormone therapy and higher in Black and Hispanic women specifically Mexican-American, compared to White women (Wee, 2008; Church, 2004). Interestingly, CRP is significantly lower in aerobically fit men independent of body fat (Tomaszewski, 2003). In women, CRP is more closely associated with body composition being significantly higher in obese women (Church, 2004). In fact, much of the race differences in CRP in women can be eliminated by controlling for obesity (Wee, 2008). In obese participants with CVD, elevated levels of CRP, IL-6, and TNF-α are correlated with a rise in leptin concentration (Erusan et al, 2012).

Leptin is a classic peptide hormone produced by mature adipocytes having structural similarities to cytokines. It is proinflammatory and strongly associated with insulin resistance (Chung et al, 2009) and CVD (Wallace, 2001). Leptin is also a centrally and peripherally acting adipokine hormone that participates in the regulation of food intake, energy expenditure, and glucose homeostasis (Ahima, 2006; Bruun, 2003). Adequate leptin levels signal repletion of energy stores, satiety, and a suppression of food intake while low leptin levels signal the need for increased food consumption and decreased energy expenditure (Leshan, 2006).

Typically leptin concentrations are decreased with weight loss and rise in proportion to adiposity. While this rise in leptin occurs to maintain energy homeostasis, obese individuals may be resistant to the action of leptin. Neuronal pathways activated to reduce appetite and increase energy expenditure with expanded adipose tissue stores, are not upregulated as expected and excess body weight is maintained (Wisse, 2004). Evidence shows that CRP binds to leptin, impairs insulin signaling and mediates leptin resistance (Chen, 2006). Current research suggests that the local induction of TNF-α and IL-6 by leptin provides the signal for obesity-related inflammation and CVD risk (Erusan, 2012).

Hypersecretion of aforementioned adipokines, particularly TNF-α, and free fatty acids increase the synthesis of plasminogen activation inhibitor-1 (PAI-1) (Samad, 1999). PAI-1 is a proinflammatory, prothrombotic and profibrotic adipokine secreted from platelets, endothelial cells and adipose tissue. PAI-1 suppresses fibrinolytic activity by inhibiting

plasminogen activator and urokinase-like plasminogen activator, thereby enhancing thrombosis.

Since PAI-1 plays an important role in hemostasis and is a known marker of endothelial dysfunction, it is also a strong risk factor for stroke and myocardial infarction (Gallistl et al 2000). PAI-1 is correlated with circulating insulin levels and in the insulin resistant state, elevated PAI-1 is often observed along with its pro-inflammatory constituents (TNF-α, IL-6). In fact, PAI-1 concentrations increase in stepwise fashion as one progresses from normal glucose levels to impaired glucose tolerance and finally, to type 2 diabetes (Festa, 1999). Because of the relationship between PAI-1 and insulin resistance, it is an excellent predictor of type 2 diabetes risk (Haffner, 2003). More recent evidence demonstrates that PAI-1 is related to MetS in both adults (Alessi and Vague, 2006) and adolescents (Gonzalez, 2012), however, whether it leads to obesity, inflammation, and MetS or is the result of obesity-related inflammation and MetS is unclear (Alessi and Vague, 2006).

It should be noted that aforementioned inflammatory (TNF- α, IL-6, C-RP, leptin) and thrombogenic (PAI-1) markers are often observed in the pre-diabetic and early angiogenic condition (Haffner, 2003) and may provide the basis for the constellation of risk factors associated with MetS. This has been proposed in the "common soil hypothesis" coined by Stern (1995) who suggested that CVD and type-2 diabetes are rooted in common antecedent conditions reflective of an unhealthy environment (i.e. less than optimal diet/sedentary lifestyle and/or poor genetics). This leads to the development of abdominal obesity and the insulin resistance state observed in MetS and is marked by pro-inflammatory, pro-thrombogenic adipokines and acute phase proteins.

Sex Steroids and the Metabolic Syndrome

Sex steroids also contribute to the MetS as human adipocytes express sex steroid receptors. While estrogen stimulates the size and proliferation of pre-adipocytes, androgens inhibit their differentiation having no effect on cellular hypertrophy or proliferation (Karastergiou, 2012). Estrogenic steroids including 17-β estradiol may possess anti-inflammatory properties as they serve to inhibit pro-inflammatory cytokines such as IL-1β and TNF- α (J.G. Gannon, 2014). Since the predominance of research with regard to MetS has been reported on androgens, the rest of the review will be confined to androgenic sex steroids.

Androgenic sex steroids including total testosterone (TT) and the more metabolically

active free testosterone (FT) are known to present a sexual dimorphism with regard to MetS. In men, elevated TT and FT are associated with reduced abdominal or central obesity and MetS risk, whereas in women, the converse is observed (Brand, 2011). Sex hormone binding globulin (SHBG) acts as a transport protein for testosterone that renders it inactive. Although the relationship between SHBG and MetS risk is stronger in women, the lower the SHBG, the greater the MetS risk in both genders (Brand, 2011). However, controversy exists as to whether insulin resistance or increased abdominal obesity mediates the relationship between androgenic steroids and MetS or vice versa. The answer to this question may lie in the underlying cause and pathogenesis of MetS.

In men, low testosterone levels are reported to lead to the development of central obesity (Khaw, 1992) while predicting risk for MetS (Laaksonen, 2004) and type 2 diabetes (Stellato, 2000). In a study of hypogonadal men, improvements in several components of the MetS were found (Kapoor, 2006) and a reversal of MetS was also observed (Heufelder, 2009) following testosterone administration. Following weight loss in obese men, increases in testosterone and SHBG are also found concomitant with improvements in components of the MetS (Niskanen, 2004). However, fat and insulin levels also decline with weight loss (Goodpastor, 2004) and since insulin has been shown to blunt SHGB and corresponding TT levels (Plymate, 1988; Mohr, 2006), the increase in TT following weight loss may be the result of reduction in adiposity and circulating insulin levels.

A positive relationship between insulin sensitivity and testosterone have been demonstrated independent of SHBG (Pitteloud, 2005). In an elegant study rooted in hypothalamic function, Pitteloud (2005) was able to demonstrate a strong positive relationship between insulin sensitivity and testosterone in lean, insulin resistant, and type 2 diabetic adult men. The fact that insulin stimulates gonadotropin releasing hormone increasing Leydig cell steroidogenesis does not negate the fact that insulin resistance acts to blunt testosterone production in men. It should be noted that inflammatory adipokines such as leptin and TNF-α are also associated with reductions in testosterone and since weight loss results in a rise in testosterone, this does suggest a link to adipocyte size and function (Pitteloud, 2005).

Brand (2011) reported a much stronger relationship between testosterone and MetS in men following WHO guidelines which place greater emphasis on insulin resistance and also IDF guidelines, which emphasize

central obesity compared to NCEP ATP III guidelines, which place equal emphasis on all MetS components. This suggests that insulin resistance or central obesity may be primary factors mediating the relationship between testosterone and MetS, although results remain questionable (Rees and Dayan, 2011).

In women, findings are also mixed. In one study, elevated TT/low SHGB at baseline was associated with increased risk of MetS (Torrens, 2009). In another study after controlling for visceral adipose tissue, a key marker of central obesity, androgenic steroids contributed more to several components of the MetS including diastolic blood pressure, fasting glucose, and serum lipoproteins (Perry, 2013). However, in the same study, visceral adipose tissue was found to contribute more to other components of the MetS including systolic blood pressure, insulin resistance, circulating insulin levels, and triglycerides. In obese women with polycystic ovary syndrome, weight loss using diabetes treatment agents resulted in decreased androgen levels and improvements in MetS components (Gambineri, 2006; Crave, 1995). However, insulin levels typically decline with weight loss and since insulin directly stimulates ovarian production of testosterone (Barbieri, 1986), improvements in MetS components may have been mediated by improvements in insulin sensitivity.

The sparse amount of prospective research and longitudinal studies in this field along with the complexity of the interrelationships among the risk factors themselves, make it difficult to ascertain whether insulin resistance, central obesity, or androgenic steroids serve as primary contributors to the development of MetS (Rees and Dayan, 2011). Therefore it is unclear as to whether insulin resistance and central obesity mediate the relationship between androgenic steroids and MetS or vice versa or both indicating a bi-directionality in relation to MetS.

In summary, the MetS is an important health concern that appears to be rooted in the development of insulin resistance and obesity, specifically central obesity. Although research supports the fact that inflammatory markers increase as a result of insulin resistance and central obesity, we propose the addition of pro-inflammatory adipokines to the physiological evaluation of those at risk for MetS. Furthermore, pro-inflammatory and pro-thrombotic adipokines promote the synthesis of other inflammatory proteins and adipokines and can be detected early on to identify risk for MetS. Androgenic steroids are also associated with MetS risk and have been reported to play a role in the pathogenesis of MetS.

More research is warranted to determine whether or not insulin resistance and/or central obesity are the primary contributors to MetS, thereby mediating the androgenic sex steroid relationship with MetS or vice versa or whether there is bidirectionality in aforementioned relationships with MetS.

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