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REVIEW

The link between abdominal obesity, metabolic syndrome and cardiovascular disease

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Abstract *Aim:* The prevalence of metabolic syndrome has increased dramatically in recent years, and the cluster of metabolic abnormalities it encompasses results in increased cardiovascular morbidity and mortality. The role of abdominal (visceral) obesity and the underlying molecular and cellular mechanisms central to this association have been the subject of intensive research in recent times. The aim of this review is to correlate data in this area, highlighting the central role of excess visceral fat and its secreted adipokines, and to review existing and emerging therapies.
Data synthesis: Data were generated from a search of the PubMed database using the terms 'abdominal obesity', 'metabolic syndrome', 'insulin resistance', 'adipokines', 'interleukin-6 (IL-6)', 'adiponectin', 'tumour necrosis factor-alpha (TNF-α)' and 'cardiovascular disease'.
Conclusion: Metabolic syndrome is associated with a pro-inflammatory state, and the role of visceral obesity is thought to be central to this. Visceral obesity leads to alteration of the normal physiological balance of adipokines, insulin resistance, endothelial dysfunction and a pro-atherogenic state. In association with this, the presence of conventional cardiovascular risk factors such as hypertension, dyslipidaemia and smoking results in a significantly elevated cardiovascular and metabolic (cardiometabolic) risk. Better understanding of the molecular mechanisms central to this association has led to the development of potential therapeutic agents.

Introduction

Metabolic syndrome is linked with abdominal obesity and is associated with a clustering of abnormalities (including impaired glucose tolerance, dyslipidaemia and hypertension) that together lead to a significantly increased risk of cardiovascular disease (CVD).

Definition of metabolic syndrome

There are currently six separate definitions of metabolic syndrome, these being from the World

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Health Organization (WHO) [1], the European Group for the Study of Insulin Resistance (EGIR) [2], the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATPIII) [3], the American Association of Clinical Endocrinologists (AACE) [4], the International Diabetes Federation (IDF) [5] and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) [6]. The main diagnostic features are summarised in Table 1. Despite common features across the definitions, there are specific parameters in which they differ. The initial WHO and EGIR classifications require the measurement of insulin resistance and are primarily used in the research environment. The mechanisms used for determining insulin resistance rely on labour-intensive mechanisms such as the oral glucose tolerance test and the hyperinsulinaemic euglycaemic clamp. The ATPIII criteria were developed to be applicable in the outpatient setting (but in contrast to other definitions do not have mandatory diagnostic criteria), and have remained as the backbone for the subsequent IDF and AHA/NHLBI statements. The IDF classification has central obesity as a diagnostic criterion, whereas the AACE criteria do not include this measurement for diagnosis.

Abdominal obesity and insulin resistance are believed to be the main physiological forces resulting in the adverse cardiovascular profile in metabolic syndrome [7]. This is highlighted by abdominal obesity being the only mandatory diagnostic criterion in the IDF classification. The IDF classification was drawn up to give a consensus worldwide definition and acknowledged the ethnic differences in CVD risk for a given degree of adiposity (Table 2).

Table 1 A comparison of some of the most widely used definitions for metabolic syndrome

WHO (1999)	EGIR (1999)	ATPIII (2001)	IDF (2005)
Diabetes, impaired fasting glucose, glucose intolerance or insulin resistance (defined by hyperinsulinaemic, euglycaemic clamp mechanism), plus two or more of the following:	Insulin resistance deemed by fasting insulin values, plus two or more of the following:	Three or more of the following:	Central obesity (ethnic specific values), plus any two of the following:
• BMI $>30\ kg/m^2$, or waist to hip ratio >0.9 (M) or >0.85 (F)	• Central obesity with WC ≥ 94 cm (M) or ≥ 80 cm (F)	• WC >102 cm (M), >88 cm (F)	• TG >1.7 mmol/L or on specific treatment
• TG ≥ 1.7 mmol/L or HDL-C <0.9 (M) or <1.0 mmol/L (F)	• TG >2.0 mmol/L or HDL <1.0 mmol/L	• TG >1.7 mmol/L	• HDL-C <1.03 mmol/L (M), <1.29 mmol/L (F) or on specific treatment
• BP $>130/90$ mmHg	• BP $\geq 140/90$ mmHg or on antihypertensive medication	• BP $\geq 135/85$ mmHg or antihypertensive medication	• BP $\geq 130/85$ mmHg or on anti-hypertensive treatment
• Albumin excretion $>20\ \mu g/min$	• FBG ≥ 6.1 mmol/L	• FPG ≥ 6.1 mmol/L	• FPG ≥ 5.6 mmol/L or previously diagnosed type 2 diabetes

BMI: body mass index; BP: blood pressure; F: female; M: male; FPG: fasting plasma glucose; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; WC: waist circumference.

Prevalence of metabolic syndrome

The prevalence of metabolic syndrome will clearly vary depending on the definition applied, the ethnicity and age of the study population [8]. This is eloquently highlighted by a recent study of American adults [9]. Based on NCEP parameters, the unadjusted prevalence of metabolic syndrome was approximately 35% in all participants; when IDF criteria were applied to the same population group, this figure rose to 39%. Interestingly, the NCEP glycaemia parameter used in this study was >100 mg/dL (5.6 mmol/L; fasting plasma glucose), which is 10 mg/dL (0.5 mmol/L) lower than the cut-off value in the NCEP guidelines [3]. A similar study 11 years before, using NCEP criteria had shown an age-unadjusted prevalence of 21.8%, highlighting the significant increase in prevalence of metabolic syndrome in recent years [10]. The

Table 2 Ethnic-specific values for waist circumference (adapted from the IDF consensus worldwide definition of the metabolic syndrome, available at http://www.idf.org) [5]

Country/Ethnic group		Waist circumference
Europids (in USA, the ATPIII values are likely to be used in clinical practice)	Male	≥94 cm
	Female	≥80 cm
South Asians	Male	≥90 cm
	Female	≥80 cm
Japanese	Male	≥85 cm
	Female	≥90 cm
East Mediterranean and Middle East population	Male	Use European cut-off values until more specific data are available
	Female	

prevalence of metabolic syndrome in an Italian cohort (using NCEP parameters) was 18% and 15% in women and men respectively, demonstrating the variation seen between different geographical populations [11].

Abdominal obesity, metabolic syndrome and all-cause mortality

Waist circumference (WC) is directly related to all-cause mortality when adjusted for body mass index (BMI) [12], highlighting the importance of visceral over subcutaneous fat deposits and the incorporation of WC measurement in the diagnosis of metabolic syndrome [2,3,5]. The DECODE study, an amalgamation of European data from different centres, reported a significant increase in all-cause mortality and cardiovascular mortality in individuals with metabolic syndrome [13]. The overall hazard ratios for all-cause and cardiovascular mortality in men with the metabolic syndrome compared with those without were 1.44 and 2.26, respectively, with a similar trend in women [13]. Similar data have been presented in isolated studies of British, Scandinavian and American populations [14—17]. Direct comparison of data between studies can be difficult as some groups exclude patients with type 2 diabetes from their metabolic cohort, whilst others include these individuals. The inflammatory marker C-reactive protein (CRP) has been shown to statistically enhance the relationship between metabolic syndrome and coronary heart disease events [15]. A recent comparison of the metabolic syndrome definitions [3,5,6] and their predictive value for early atherosclerotic lesions, showed that the AHA/NHBLI definition for men, and the IDF definition for women, were the strongest predictors of coronary atherosclerosis when using carotid intima-media thickness as a surrogate marker [17].

Mechanistic link between abdominal obesity, metabolic syndrome and cardiovascular disease

One of the most challenging aspects of metabolic syndrome is understanding the cellular mechanisms that link the constellation of metabolic abnormalities with the pathophysiological effects that later manifest as clinical disease. The diagnostic criteria for metabolic syndrome clearly include conventional risk factors for cardiovascular disease such as hypertension and adverse lipid profile [18].

Obesity and atherosclerosis have been hypothesised to have an inflammatory aetiology [19—22]. Immune cells play an important role in all stages of the atherosclerotic process, and at a cellular level their interaction with the endothelium is thought to be a key process in early atheroma formation [23]. Associated with this is a reduction in nitric oxide (NO), a key regulator of endothelial homeostasis, and an increase in reactive oxygen species and oxidative stress, resulting in endothelial dysfunction and a pro-atherogenic vascular bed [24]. The molecular and cellular mechanisms underlying the relationship between obesity, metabolic syndrome, and its association with increased cardiovascular risk are incompletely understood and have led to focused research on the function of adipose tissue.

Obesity and inflammation

The link between obesity and inflammation was first proposed over a decade ago with the finding that the pro-inflammatory cytokine, tumour necrosis factor-alpha (TNF-α), was overexpressed in obesity [21]. Subsequent studies have demonstrated that the plasma levels of other inflammatory mediators (interleukin-6 [IL-6], CRP) [25] are also elevated. Adipose tissue is able to express many of these pro-inflammatory molecules, with macrophage infiltration into white adipose tissue demonstrated and proposed as a potential source of production [26].

Intriguingly recent studies have demonstrated that high fat intake is associated with oxidative stress and activation of nuclear factor kappa-beta (NF-κB), a pro-inflammatory transcription factor

[27,28]. A diet rich in fruit and fibre is reported to not induce significant inflammation compared to an equicalorific high fat diet [29].

Obesity and insulin resistance

Insulin has important physiological effects on the endothelium, increasing NO availability and stimulating vasodilatation, and is proposed to act in an anti-atherogenic manner overall [30,31]. Insulin-resistant states are associated with impaired vascular response to insulin and endothelial dysfunction [32,33]. Obesity is associated with insulin resistance [13]. Insulin resistance is also associated with increased cardiovascular risk, with meta-analyses demonstrating a statistically positive correlation between fasting plasma insulin and the risk of cardiovascular death independent of conventional risk factors (in a non-diabetic study group) [13].

Adipocytokines

Adipose tissue is now hypothesised to be the largest endocrine organ in the body, secreting a large number of biologically important substances termed adipokines [34]. The best-characterised adipokines are adiponectin, leptin, tumour necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) [13]. Other identified adipokines include plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, resistin, visfatin and glucocorticoids. These adipokines are postulated as a potential link between abdominal obesity and the vasculature, and have been shown to mediate insulin resistance [31,35]. A detailed account of all the adipokines are outside the scope of this review and there have been several recent focused reviews of this area that readers may wish to consult [34—36].

Serum levels of the pro-inflammatory adipokines IL-6 and TNF-α are elevated in obesity [25,37]. Human forearm studies have shown that TNF-α induces insulin resistance and inhibits endothelial-dependent vasodilatation [38], and research suggests that the main action of TNF-α in endothelial dysfunction is through mediating insulin resistance [39]. Increased serum and adipose IL-6 levels are negatively correlated with insulin sensitivity [40]. Human studies have also demonstrated that carotid artery distensibility is inversely related to visceral adipose mass, which is directly associated with increased serum IL-6 and CRP [25], while animal models show reduced endothelial vasodilatation in response to IL-6, which is hypothesised to be a result of reduced NO availability [41]. The intracellular enzymes, inhibitor of NF-κB kinase (IKK) and Jun N-terminal kinase (JNK), have been put forward as important intracellular mediators of inflammation and insulin resistance in the endothelial cell, potentially working through mechanisms dependent on NF-κB [42—44].

Adiponectin is secreted exclusively by adipose tissue, with plasma levels negatively correlated with obesity [45]. This paradoxical decrease in secretion in the presence of increasing adiposity is not understood. The exact physiological role of adiponectin is incompletely understood, but it is hypothesised to have an anti-inflammatory and protective role against atherosclerosis, and to be an insulin sensitizer [36]. There are several molecular weight forms of adiponectin, and the physiological actions of each and how they interact with the two adiponectin receptors identified is currently under investigation [34,36]. Hypoadiponectinaemia is associated with high body mass index, insulin resistance, dyslipidaemia, endothelial dysfunction, and increased risk of cardiovascular disease [46—48]. Adiponectin has a number of vasculo-protective functions on the endothelium, including stimulating NO production in endothelial cell models through the enzyme AMP-activating kinase (AMPK), an intracellular target of the anti-diabetic agents metformin and the thiazolidinediones [49,50]. Whilst hypoadiponectinaemia has been shown to play a causative role in atherosclerosis [51], its role as a predictive marker of future vascular events is less clear [52—54]. Intriguingly, modulation of the inflammatory response through cross talk between adipokine-initiated signalling pathways has been proposed, with adiponectin suppressing NF-κB signalling in response to TNF-α [55], suggesting that the change in serum concentrations of these adipokines may be a key factor in the transition from normal physiological conditions to pathological processes.

Free fatty acids

Visceral adiposity is associated with elevated free fatty acids (FFA). This results in an increased cardiovascular risk profile with impaired endothelial function, vascular smooth muscle cell (VSMC) proliferation and alteration of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels [56].

Proposed link between abdominal obesity, metabolic syndrome and cardiovascular disease

Obesity results in a pro-inflammatory state with increased visceral fat deposits and alteration of

adipokine secretion, with concomitant insulin resistance. In the vasculature, the cumulative effects of these changes result in alterations of NO/superoxide balance, resulting in endothelial dysfunction and increased cardiovascular risk through atheroma formation. This problem is further exacerbated by increased FFAs and the presence of 'traditional' cardiovascular risk factors (Fig. 1).

Managing the underlying CVD risk associated with metabolic syndrome

Reducing visceral fat

Reduction of adipose mass through exercise is well characterised to reduce the incidence of type 2 diabetes [57,58]. The increased CVD risk associated with metabolic syndrome can be reduced to the level of normal weight peers with high levels of activity/fitness [59]. Weight loss has been shown to improve endothelial dysfunction [60], with a loss of 5—10% of body weight conveying benefit. Both orlistat and sibutramine reduce visceral obesity and improve metabolic parameters in obesity [61,62]. Orlistat has been demonstrated to have differing effects on conduit and resistance vessels [60,61]. There are concerns that sibutramine can adversely affect blood pressure, and caution must be taken in individuals with pre-existing heart disease. There are limited data comparing the effects of orlistat and sibutramine head to head [62]. Combined sibutramine and lifestyle intervention has been shown to result in greater weight loss than each factor in isolation [63]. Gastric banding has been shown to significantly reduce abdominal adiposity and improve metabolic profile, providing another therapeutic option in morbidly obese patients [64].

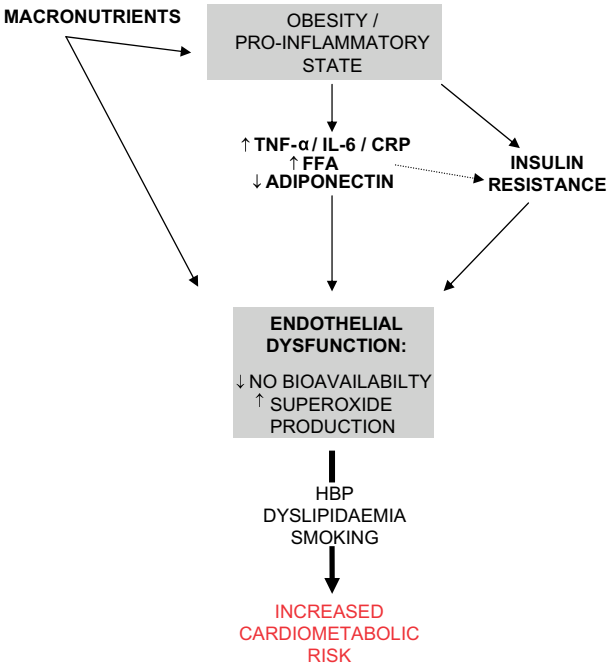

Figure 1 Potential mechanisms linking abdominal obesity, metabolic syndrome and cardiovascular disease. TNF-α: tumour-necrosis factor alpha; IL-6: interleukin-6; FFA: Free Fatty Acids; CRP: C-reactive protein; ↑: increase; ↓: decrease.

Emerging therapies

The endocannabinoid receptors are thought to play a key role in feeding signalling in the hypothalamus and are proposed to have a major role in FFA synthesis in the liver. Activation of cannabinoid receptor-1 (CB_1) results in increased feeding and serum lipid production [65]. Rimonabant, a CB_1 blocker, has shown significant reduction in weight loss, WC and triglycerides, with significant increases in HDL-C and insulin sensitivity in obese patients (in combination with a hypocaloric diet) [66]. Rimonabant treatment in patients with a higher risk of cardiovascular and metabolic disease (i.e. who are overweight or obese with untreated dyslipidaemia) provided similar changes in metabolic parameters, with additional significant increases in plasma adiponectin and LDL-cholesterol particle size [67].

The potential role of aspirin and intracellular enzyme inhibitors in blocking pro-inflammatory pathways mediated by IKK/JNK is currently being investigated [68,69].

Conclusion

The association between abdominal obesity, metabolic syndrome and CVD is well characterised. The prevalence of metabolic syndrome is rising, and new diagnostic criteria have been published to correct for ethnic differences in determining cardiovascular risk for a given level of abdominal adiposity. This takes into account the central role that visceral fat is proposed to play in the development of cardiovascular and metabolic diseases, and indicates how WC measurements may be useful in aiding patient identification in a clinical setting. Increased visceral fat is associated with a shift in the normal balance of the adipokines resulting in a pro-inflammatory state. Therapeutic options in the treatment of the clustering

of cardiometabolic risk factors are limited, with the prevention of excess visceral fat accumulation being favourable, although this may be a challenge to implement in practice. As better understanding of the underlying molecular mechanisms develops, more potential therapeutic targets will be identified. Clinical data that are currently available for the CB_1 blocker rimonabant show promising results in terms of improved multiple cardiometabolic risk factors. Modulation of inflammatory pathways known to be activated by insulin resistance states are also currently under investigation.

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