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Plenary Lecture

Mechanisms of the components of the metabolic syndrome that predispose to diabetes and atherosclerotic CVD

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The metabolic syndrome represents a summation of obesity-driven risk factors for atherosclerotic CVD and type 2 diabetes. Definitions of the syndrome vary but in general agree closely in identifying subjects. The relationships between the metabolic syndrome and atherosclerotic CVD and diabetes also vary, with relative risks of approximately 1·5–3·0 and approximately 3·0–5·0 respectively. Insulin resistance appears to explain much of the pathophysiology of the syndrome. Both increased fatty acid flux and an excess of circulating pro-inflammatory cytokines are likely mediators. With increased waist circumference, increases in fatty acid delivery to the liver result in higher rates of hepatic glucose production and increases in the secretion of apoB-containing lipoproteins. Concomitant changes in HDL ensue, including a replacement of the cholesterol content with TAG, an accelerated clearance from the plasma and thus a reduced number of HDL particles. Typically also present are increases in small dense LDL. Hypertension in part relates to the insulin resistance, but may involve other mechanisms. Impaired fasting glucose often relates to defects in insulin secretion in addition to insulin resistance, and probably more than any other component of the syndrome predicts the increased incidence of type 2 diabetes. Although not included in the diagnostic criteria, increases in pro-inflammatory cytokines and pro-thrombotic factors, in addition to decreases in plasma adiponectin, may also contribute to the increased incidence of atherosclerotic CVD and diabetes. In general, the greater the number of metabolic syndrome components, the greater the risk for these outcomes. The cytokines and pro-thrombotic factors also appear to contribute.

Metabolic syndrome: Insulin resistance: Atherosclerotic CVD: Type 2 diabetes

The metabolic syndrome: definition

The metabolic syndrome is a recently defined set of criteria that has been prompted by the worldwide obesity epidemic. Although multiple definitions have been offered, to make the approach to the metabolic syndrome easier, perhaps the criteria proposed by the National Cholesterol Education Program Adult Treatment Program III Committee (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) and/or those of the International Diabetes Federation (Alberti *et al*. 2005) should be emphasized (Table 1). The sensitivity for the presence of the syndrome may be greater with the International Diabetes Federation criteria because an expanded waist circumference must be present. A case in point is the higher prevalence of the syndrome in the National Health and Nutrition Examination Survey III population using the International Diabetes Federation *v*. National Cholesterol Education Program Adult Treatment Program III Committee definitions (Ford, 2005).

Recent controversy has surrounded the diagnosis. In the latter half of 2005 a joint statement by the American Diabetes Association and the European Association for the Study of Diabetes (Kahn *et al*. 2005) has raised a number of concerns about the scientific merit of the metabolic syndrome. Many of these points are valid and need further consideration, but responses to follow justify the continued importance of the syndrome to scientists and practitioners

Abbreviations: CRP, C-reactive protein; LPL, lipoprotein lipase.

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Table 1. National Cholesterol Education Program Adult Treatment Program III Committee (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001; NCEP:ATPIII 2001) and International Diabetes Federation (Alberti *et al.* 2005; IDF) criteria for the metabolic syndrome

NCEP:ATPIII 2001	IDF criteria for central adiposity*		
Three or more of the following:	Waist circumference		
Central obesity: waist circumference (cm)	M (cm)	F	Ethnicity
M>102, F>88	≥94	≥80	Europid, Sub-Saharan African, Eastern and Middle Eastern
Hypertriacylglycerolaemia: TAG ≥1500 mg/l or specific medication	≥90	≥80	South Asian, Chinese and ethnic South and Central American
	≥80	≥90	Japanese
Low HDL-cholesterol for M<400 mg/l and for F<500 mg/l, or specific medication	Two or more of the following:		
Hypertension: blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic or specific medication	Fasting TAG >1500 mg/l or specific medication		
Fasting plasma glucose ≥1000 mg/l or specific medication or previously diagnosed type 2 diabetes	HDL-cholesterol for M<400 mg/l, for F<500 mg/l, or specific medication		
	Blood pressure >130 mmHg systolic or >85 mmHg diastolic or previous diagnosis or specific medication		
	Fasting plasma glucose ≥1000 mg/l or previously diagnosed type 2 diabetes		

M, males; F, females.
*In this analysis, the following thresholds for waist circumference (cm) were used: M: white ≥94, African-American ≥94, Mexican-American ≥90; F: white ≥80, African-American ≥80, Mexican-American ≥80. For participants whose designation was 'other race, including multiracial' the thresholds (cm) that were once based on Europid cut-off points (M ≥94, F ≥80) and South Asian cut-off points (M ≥90, F ≥80) were used. For participants who were considered 'other Hispanic' the IDF thresholds for ethnic South and Central Americans were used.

(Grundy *et al.* 2005; Grundy, 2006). With time, consolidation of the definition, mechanisms, implications and therapeutics will ensue.

Metabolic syndrome: risk for atherosclerosis and type 2 diabetes mellitus

The metabolic syndrome confers risk for atherosclerotic CVD and type 2 diabetes. It is important to note that the selection criteria, end points and the interval for outcome evaluation used in the many trials have varied. Thus, broad sweeping conclusions related to the impact of the metabolic syndrome on any outcome need to be carefully considered.

Atherosclerotic CVD

The risk for new-onset CHD in patients with the metabolic syndrome in the absence of diabetes has varied substantially from population to population but averages between about 1·5-fold and 3-fold higher (Eckel *et al.* 2005). However, the population-attributable risk for the development of CHD over a follow-up period of 8 years in middle-aged men and women with the metabolic syndrome in the Framingham Offspring Study was found to be 34% and 16% respectively (Rutter *et al.* 2005). Use of the Framingham risk scoring system for patients without diabetes but with the metabolic syndrome enhances the predictability of CHD. Elevations in C-reactive protein (CRP) also influence this risk, and more so in patients with the metabolic syndrome and type 2 diabetes (Rutter *et al.* 2005).

Although the metabolic syndrome is a substantial predictor of CHD and atherosclerotic CVD in general (which includes CHD and stroke), there is a paucity of information about the specific risk of stroke and peripheral vascular disease. In the absence of diabetes and previous atherosclerotic CVD the relative risk of ischaemic stroke in Finnish men with the metabolic syndrome was found to be approximately 2·5 (Kurl *et al.* 2006). In the Framingham Offspring Study both the metabolic syndrome and diabetes were found to predict ischaemic stroke, with the population-attributable risk being greater for patients with the metabolic syndrome than for patients with diabetes alone (19% *v.* 7%), particularly in women (27% *v.* 5%; Najarian *et al.* 2006).

Type 2 diabetes

Overall, the risk for type 2 diabetes in patients with the metabolic syndrome is 3-fold–5-fold higher (Eckel *et al.* 2005). In an 8-year follow-up of middle-aged men and women in the Framingham Offspring Study the population-attributable risk for developing type 2 diabetes was found to be 62% and 47% respectively (Wilson *et al.* 2005). Clearly, patients with impaired fasting glucose or impaired glucose tolerance have a high risk for type 2 diabetes; a risk that may be independent of other components of the metabolic syndrome. However, in the Insulin Resistance Atherosclerosis Study (Hanley *et al.* 2005) the definitions of the International Diabetes Federation (Alberti *et al.* 2005) and the National Cholesterol Education Program Adult Treatment Program III Committee (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) were shown to predict type 2 diabetes equally well despite not requiring the use of oral glucose tolerance testing or measures of insulin resistance or microalbuminuria. The risk for new-onset type 2 diabetes may be as strong for the metabolic syndrome as for impaired glucose tolerance and may not require the presence of impaired fasting glucose as a predictor.

Mechanisms for CHD and type 2 diabetes mellitus underlying the metabolic syndrome

Insulin resistance

The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin

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resistance (Eckel *et al*. 2005). Insulin resistance has been most often defined using a glucocentric view, i.e. when a defect in insulin action results in fasting hyperinsulinaemia to maintain euglycaemia. Yet, even before fasting hyperinsulinaemia develops, postprandial hyperinsulinaemia exists. A series of biomarkers are available to assess the presence of insulin resistance, including fasting insulin, the homeostatic model assessment, pro-insulin and TAG:HDL-cholesterol, yet a number of limitations exist for each one. Although the modified intravenous tolerance test of Bergman (Boston *et al*. 2003) has proved useful in research settings, its practical application is lacking. The euglycaemic clamp continues to be the gold standard.

A major contributor to the development of insulin resistance is circulating fatty acids. Albumin-bound NEFA are derived predominantly from TAG stores in adipose tissue. Historically, the cAMP-dependent enzyme hormone-sensitive lipase was considered to be the lipolytic enzyme; however, recent evidence from murine models indicates that adipose TAG lipase may be more important (Haemmerle *et al*. 2006). Lipoprotein lipase (LPL) also provides fatty acids but through the lipolysis of circulating TAG-rich lipoproteins (Eckel, 1989). Insulin is important to both anti-lipolysis and the stimulation of LPL in adipose tissue. Importantly, the most sensitive pathway of insulin action is the inhibition of lipolysis (Jensen *et al*. 1989). Paracrine regulation of lipolysis in adipose tissue may also be an important contributor to the circulating NEFA burden. One such paracrine affecter is the cytokines. With increasing adipose tissue mass, infiltration of monocyte-derived macrophages occurs and inflammatory cytokines are released. This local effect promotes additional impairment in the anti-lipolytic effect of insulin, creating more lipolysis (Suganami *et al*. 2005).

In muscle excessive fatty acids decrease insulin sensitivity (Fig. 1(a)). Increased fatty acid availability results in the accumulation of intramyocellular fatty acyl-CoA, which then unfavourably modifies a number of downstream pathways including: insulin signalling; insulin-(in)dependent glucose transport and phosphorylation; insulin-stimulated glycogen synthesis; insulin-stimulated oxidative phosphorylation (ATP synthesis); accumulation of TAG; expression of PPARγ coactivator-1 and PPARγ coactivator-1-controlled genes involved in mitochondrial biogenesis and oxidative phosphorylation and potentially the initiation of inflammatory processes by activation of protein kinase C and NF-κB; expression of matrix metalloproteinases (for review, see Roden, 2005). This effect of fatty acids on muscle insulin sensitivity is more attributable to SFA than unsaturated fatty acids (Storlien *et al*. 2000; Lee *et al*. 2006).

In human subjects the infusion of a lipid emulsion with the simultaneous administration of intravenous heparin to release lipases and then lipoprotein-TAG fatty acids into the plasma compartment results in insulin resistance (Boden *et al*. 2002), which leads to defects in insulin action not only in skeletal muscle but also in the liver (Boden, 2003). In the liver of high-fat-fed rats insulin resistance can be attributed to a defect in insulin-stimulated insulin receptor substrate-1 and insulin receptor substrate-2 tyrosine phosphorylation. These changes have been associated with activation of protein kinase C-ε and c-Jun N-terminal kinase-1 (Samuel *et al*. 2004). Yet, while circulating fatty acids increase hepatic glucose production and diminish the inhibition of glucose production by insulin (Boden & Shulman, 2002), lipogenesis as a result of the stimulatory effects of fatty acids and insulin on sterol response element-binding protein-1c continues (Shimomura *et al*. 1999). Very recent evidence has demonstrated that the pharmacological inhibition of the lipid biosynthetic enzymes acetyl-CoA carboxylase-1 and -2 increases fat oxidation and reduces hepatic steatosis and insulin resistance (Savage *et al*. 2006).

More detailed studies in human subjects have examined the cellular and molecular basis of insulin resistance in more detail (Petersen *et al*. 2003, 2004; Barbato *et al*. 2004), and in insulin-resistant subjects with obesity and/or type 2 diabetes and in the elderly a defect in mitochondrial oxidative phosphorylation has been identified. More recently, a common variant in mitochondrial DNA at bp 16189 (T→C transition) has been associated with the metabolic syndrome in Chinese adults (Weng *et al*. 2005). Although the mitochondrial ribosomal RNA and transfer RNA are encoded by mitochondrial DNA in human subjects, all proteins involved in mitochondrial translation are encoded by nuclear genes. Moreover, increasingly nuclear genes associated with the metabolic syndrome are being recognized (Matsunaga & Muramatsu, 2005).

Murine models of the metabolic syndrome are becoming more evident. In mice made deficient in the endoplasmic reticulum X-box-binding protein-1 hyperactivation of c-Jun N-terminal kinase increases serine phosphorylation of insulin receptor substrate-1 and insulin resistance (Ozcan *et al*. 2004). Among other models addressing the mechanism of the metabolic syndrome in rodents are mice lacking the fatty acid-binding proteins aP2 and mal1. These mice exhibit a striking phenotype with strong protection from diet-induced obesity, insulin resistance, type 2 diabetes and fatty liver disease (Maeda *et al*. 2005).

A new report (Shuldiner & McLenithan, 2004) indicates that PPARγ coactivator-1α and -1β mRNA levels decrease with age in individuals with a genetic variant in PPARγ coactivator-1α, and that these decreases correlate with alterations in whole-body glucose and fatty acid oxidation. These data provide insights into how aging modifies genetic susceptibility to alterations in oxidative phosphorylation and type 2 diabetes.

Oxidative stress has also been viewed as a cellular mechanism for insulin resistance. One enzyme that initiates base excision repair of ring-fragmented purines and some pyrimidines is neil1. In the absence of oxidative stress neil1-knock-out (neil1 −/−) and heterozygotic (neil1 +/−) mice develop severe obesity, dyslipidaemia and hepatic steatosis with more modest hyperinsulinaemia (Vartanian *et al*. 2006).

Thus, with time more basic mechanisms of insulin resistance are being discovered. Presumably, these biochemical changes in insulin-mediated signalling pathways result in decreases in insulin-mediated glucose transport and metabolism in the metabolic syndrome as well.

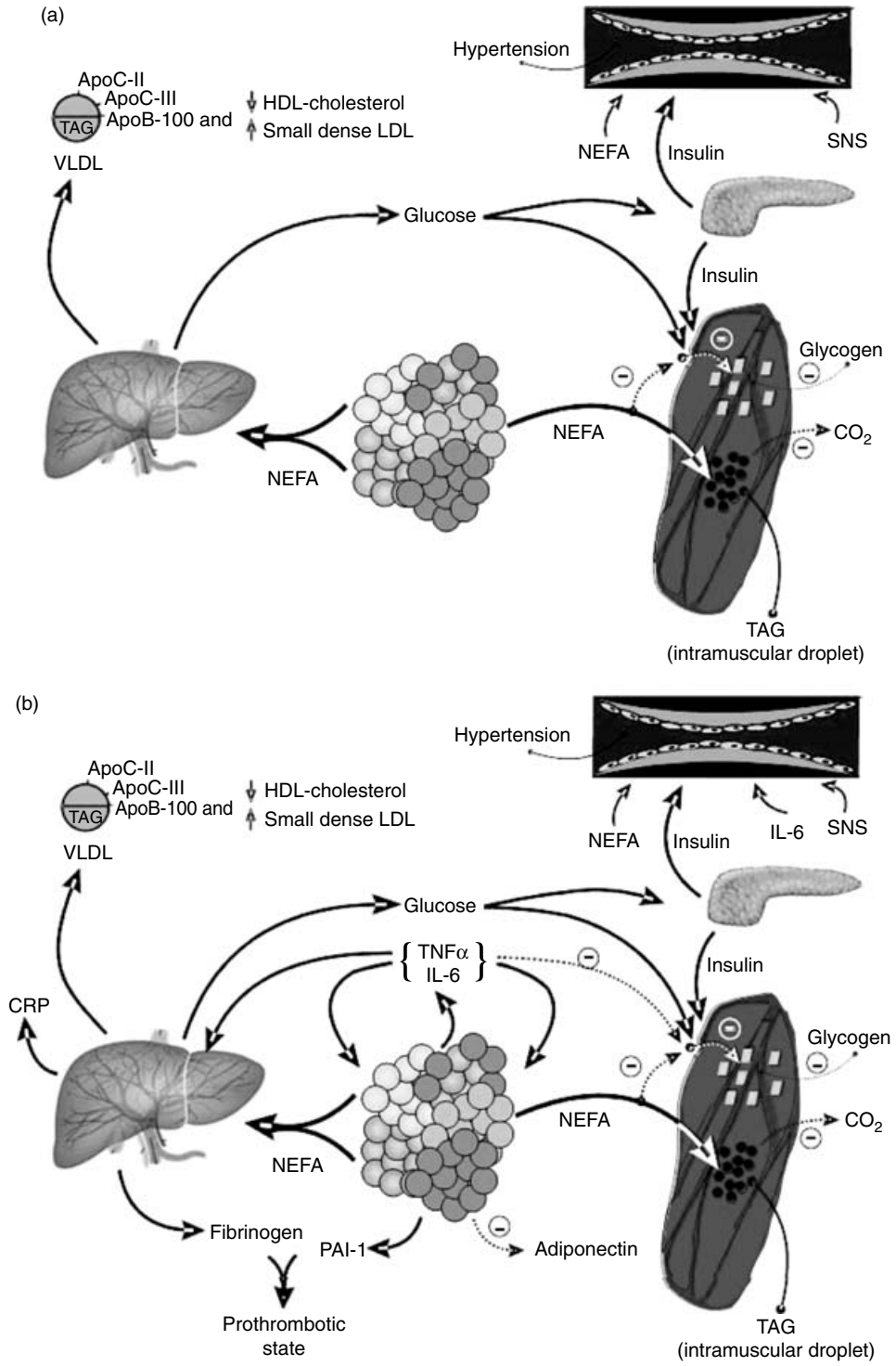

Fig. 1. Pathophysiology of the metabolic syndrome (insulin resistance and NEFA), (a) NEFA are released in abundance from an expanded adipose tissue mass. In the liver NEFA result in an increased production of glucose and TAG and secretion of VLDL. Associated lipid and lipoprotein abnormalities include reductions in HDL-cholesterol and an increased density of LDL. NEFA also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation in TAG. Increases in circulating glucose, and to some extent NEFA, increase pancreatic insulin secretion, resulting in hyperinsulinaemia. Hyperinsulinaemia may result in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and contribute to the hypertension, as might increased circulating levels of NEFA. (b) Superimposed and contributory to the insulin resistance produced by excessive NEFA is the paracrine and endocrine effect of the pro-inflammatory state.

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Obesity and increased waist circumference

Although the first description of the metabolic syndrome occurred in the early 20th century (Kylin, 1923), the worldwide obesity epidemic has been the most important driving force for the much more recent recognition of the syndrome. Despite the importance of obesity in the model, it is relevant to remember that patients who are normal weight may also be insulin resistant (Ruderman *et al*. 1998).

For the International Diabetes Federation (Alberti *et al*. 2005) definition of the metabolic syndrome the waist circumference as defined must be increased (Table 1). It is important to distinguish between a large waist circumference that is a result of increases in subcutaneous adipose tissue from that in which the visceral depot is expanded. This distinction can be made using computerized tomography or MRI (Lee *et al*. 2004). With increases in intra-abdominal or visceral adipose tissue a higher rate of flux of adipose tissue-derived NEFA to the liver would be expected, whereas increases in abdominal subcutaneous fat would release lipolysis products into the systemic circulation and avoid more direct effects on hepatic metabolism, i.e. glucose production, lipid synthesis, lipoprotein secretion and the secretion of pro-thrombotic proteins such as fibrinogen and plasminogen activator inhibitor-1 (Aubert *et al*. 2003).

Despite these potential differences in mechanisms related to excessive abdominal adipose tissue distribution, the clinical diagnosis of the metabolic syndrome does not distinguish between increases in subcutaneous and visceral fat. Yet, perhaps by a mechanism related to NEFA flux and metabolism, the predominance of visceral *v*. subcutaneous adipose tissue with increasing waist circumference in Asians and Asian Indians (Bajaj & Banerji, 2004) renders the relative prevalence of the syndrome higher than that in African-American men in whom subcutaneous fat predominates (Tanaka *et al*. 2003). However, there is evidence that the elevated postprandial NEFA release in upper-body obese women originates from the non-splanchnic upper body fat, and not from the visceral depot (Guo *et al*. 1999). These results suggest that visceral fat may be a marker for, but not the source of, excess postprandial fatty acids in obesity.

The amount of epicardial fat assessed by echocardiography could be a simple and practical tool for cardiovascular risk stratification in clinical practice and research (Iacobellis *et al*. 2005). Epicardial fat is a metabolically-active organ that generates various bioactive molecules, some of which might markedly affect cardiac function. This small 'visceral fat' depot is now recognized as a rich source of NEFA and a number of bioactive molecules, such as inflammatory cytokines and adiponectin. Presently, validation and more clinical significance are needed.

Murine examples of the impact of body fat distribution on insulin resistance and the metabolic syndrome include mice with over-expression of 11-hydroxysteroid dehydrogenase 1 that have elevated intra-adipose corticosterone levels but normal circulating corticosterone levels (Masuzaki *et al*. 2001). These mice exhibit central obesity, hypertension, impaired glucose tolerance and hypertriacylglycerolaemia. Conversely, mice that fail to express 11-hydroxysteroid dehydrogenase 1 are resistant to the development of metabolic syndrome (Kotelevtsev *et al*. 1997).

More recent studies have shown that the ectopic expression of very low levels of uncoupling protein 1 in epididymal fat reverses both insulin and leptin resistance. Uncoupling protein 1 expression in epididymal fat improves glucose tolerance and decreases food intake in both diet-induced and genetically-obese mouse models (Yamada *et al*. 2006). Moreover, in wild-type mice local-nerve dissection in the epididymis or pharmacological afferent blockade blunts the decrease in food intake, suggesting that afferent-nerve signals from intra-abdominal adipose tissue regulate food intake.

In the setting of partial or complete lipoatrophy insulin resistance and the metabolic syndrome typically co-exist (Garg & Misra, 2004). Evidence from these less-common disorders does support a genetic basis of the syndrome, including single-gene defects in PPAR-λ, lamin A/C, 1-acylglycerol-3-phosphate, O-acyltransferase, seipin (Hegele, 2003), the β-2 adrenergic receptor (Dallongeville *et al*. 2003) and adiponectin (Fumeron *et al*. 2004).

Dyslipidaemia

With increased NEFA flux to the liver, increased production of apoB-containing TAG-rich VLDL occurs (Lewis *et al*. 1995). The effect of insulin on this process is somewhat complex. In the setting of insulin resistance the increased flux of NEFA to the liver increases hepatic TAG synthesis; however, under physiological conditions insulin inhibits rather than increases the secretion of VLDL into the systemic circulation (Lewis & Steiner, 1996). This inhibitory effect in part is an effect of insulin on the

Produced by a variety of cells in adipose tissue, including adipocytes and monocyte-derived macrophages, the enhanced secretion of IL-6 and TNFα, among others, results in more insulin resistance and lipolysis of adipose tissue TAG stores to circulating NEFA. IL-6 and other cytokines also are increased in the circulation and may enhance hepatic glucose production, the production of VLDL by the liver and insulin resistance in muscle. Cytokines and NEFA also increase the production of fibrinogen and plasminogen activator inhibitor-1 (PAI-1) by the liver that complements the overproduction of PAI-1 by adipose tissue. This action results in a pro-thrombotic state. Higher circulating levels of cytokines also stimulate the hepatic production of C-reactive protein (CRP). Reductions in the production of the anti-inflammatory and insulin-sensitizing cytokine adiponectin are also associated with the metabolic syndrome and may contribute to the pathophysiology of the syndrome. ↑, Increased; ↓, reduced; ⊖, effects relatively reduced. (From Eckel *et al*. 2005, with permission from Elsevier.)

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degradation of apoB (Taghibiglou *et al*. 2002). Yet, insulin is also lipogenic, increasing the transcription and enzyme activity of many genes that relate to TAG biosynthesis (Foufelle & Ferre, 2002). Not completely addressed is whether or not this pathway remains operational in the setting of systemic insulin resistance.

In addition, insulin resistance may also reduce the level of LPL in peripheral tissues, i.e. in adipose tissue more than in muscle (Eckel *et al*. 1995). This alteration in LPL, however, appears to contribute less to the hypertriacylglycerolaemia. However, mutations in the LPL gene affect LPL expression and are associated with both dyslipidaemia and insulin resistance (Holzl *et al*. 2002; Ma *et al*. 2003; Goodarzi *et al*. 2004). Recent evidence even suggests that levels of LPL mass in pre-heparin plasma may be a quantitative indicator of whole-body insulin resistance (Miyashita & Shirai, 2005).

The other major lipoprotein disturbance in the metabolic syndrome is a reduction in HDL-cholesterol. This reduction is a consequence of changes in HDL composition and metabolism. In the presence of hypertriacylglycerolaemia a decrease in the cholesterol content of HDL is a consequence of decreases in the cholesteryl ester content of the lipoprotein core, with variable increases in TAG making the particle small and dense, a function in part of cholesteryl ester transfer protein (Murakami *et al*. 1995). Although HDL typically possess many features that appear to contribute to the association between increased HDL-cholesterol and protection from atherosclerosis, HDL may be modified to become pro-inflammatory (Ansell *et al*. 2005). The ability of HDL to inhibit or paradoxically to enhance vascular inflammation, lipid oxidation, plaque growth and thrombosis reflects changes in specific enzyme and protein components, e.g. increases in serum amyloid A, an acute-phase reactant and pro-inflammatory molecule (Kontush & Chapman, 2006). This change in lipoprotein composition also results in an increased clearance of HDL from the circulation (Brinton *et al*. 1991; Chan *et al*. 2006). Thus, reductions in plasma levels of apoA-1 (a reflection of HDL particle number) are seen.

The relationship between these changes in HDL and insulin resistance is probably indirect, occurring in concert with the changes in TAG-rich lipoprotein metabolism. Although small dense HDL particles are typically better lipid acceptors, the formation of HDL that are small and dense in the setting of the dyslipidaemia of the metabolic syndrome may attenuate anti-atherogenic properties (Kontush & Chapman, 2006). Thus, low circulating levels of HDL-cholesterol might, therefore, be associated with small HDL particles of abnormal structure and composition with defective functionality.

In addition to HDL, LDL are also modified in composition in a similar way. In fact, with fasting serum TAG of $>2{\cdot}0$ mM almost all patients have a predominance of small dense LDL (de Graaf *et al*. 1993; Manzato *et al*. 1993). This change in LDL composition is attributable to relative depletion of non-esterified cholesterol, esterified cholesterol and phospholipid with either no change or an increase in LDL-TAG (Halle *et al*. 1999; Kwiterovich, 2002). Small dense LDL may be more atherogenic because they are more toxic to the endothelium, more able to transit through the endothelial basement membrane, more likely to adhere to arterial wall glycosaminoglycans, have increased susceptibility to oxidation and/or are more selectively bound to scavenger receptors on monocyte-derived macrophages (Packard, 1996; Krauss, 1995). However, the direct relationship between small dense LDL and the natural history of atherosclerotic CVD is not entirely accepted (Lada & Rudel, 2004; Jungner *et al*. 2006). In some studies this alteration in LDL composition is an independent risk factor for CVD (Zambon *et al*. 1999). Recently, the effects of gemfibrozil on NMR-measured LDL and HDL particle subclasses, not reflected by conventional lipoprotein-cholesterol measures, has helped to explain the beneficial effect of the fibrate in patients with low HDL-cholesterol and CHD. However, most often the association between particle composition and atherosclerotic CVD events is not independent, but related to the concomitant changes in other lipoproteins and other risk factors (Sacks & Campos, 2003). It is possible that when circulating levels of LDL-cholesterol are lower, measurements of LDL particle number may ultimately prove to be more useful.

Glucose intolerance

The defects in insulin action in glucose metabolism include deficiencies in the ability of the hormone to suppress glucose production by the liver and kidney and mediate glucose uptake and metabolism in insulin-sensitive tissues, i.e. muscle and adipose tissue. The relationship between impaired fasting glucose or glucose tolerance and insulin resistance is well supported by human studies (Abdul-Ghani *et al*. 2006). To compensate for defects in insulin action insulin secretion and/or clearance must be modified to sustain euglycaemia. On failure of this compensation defects in insulin secretion rather than insulin clearance predominate.

Insulin resistance in pancreatic islet β-cells implies that the signals that generate glucose-dependent insulin secretion have been adversely modified, and fatty acids are prime candidates. Although NEFA can stimulate insulin secretion, increasing and prolonged exposure to excessive levels results in decreases in insulin secretion (Lee *et al*. 1994). The mechanism for this alteration has been attributed to lipotoxicity through a number of potential different mechanisms (Shimabukuro *et al*. 1998; Yaney & Corkey, 2003; Boucher *et al*. 2004; Joseph *et al*. 2004).

Insulin also feeds back on its own secretion. The importance of this feedback relates to experiments in rodents in which the insulin receptor is tissue-specifically deleted. When the insulin receptor is deleted in skeletal muscle hyperglycaemia does not result (Bruning *et al*. 1998); however, the β-cell-specific knock-out of the insulin receptor produces progressive glucose intolerance and diabetes (Kulkarni *et al*. 1999). In human subjects with genetic predispositions to develop diabetes the presumed stress of the insulin-resistant environment on β-cell function produces glucose intolerance and ultimately the higher risk of diabetes.

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Hypertension

The relationship between insulin resistance and hypertension is well established (Ferrannini *et al*. 1987), and relates to several different mechanisms. Insulin is a vasodilator when given intravenously to normal-weight subjects (Steinberg *et al*. 1994), with secondary effects on Na re-absorption in the kidney (DeFronzo *et al*. 1975). Of interest, Na re-absorption is increased in Caucasians but not in Africans or Asians with the metabolic syndrome (Barbato *et al*. 2004). In insulin-resistant subjects the vasodilatory effect of insulin may be lost (Tooke & Hannemann, 2000), but the renal effect on Na re-absorption preserved (Kuroda *et al*. 1999). Insulin also increases the activity of the sympathetic nervous system (Anderson *et al*. 1991), an effect that may also be preserved in the setting of the insulin resistance (Egan, 2003). In addition, fatty acids themselves can produce vasoconstriction (Tripathy *et al*. 2003).

The spontaneous-hypertensive rat is a widely-studied model of hypertension that exhibits metabolic abnormalities that share features with the human metabolic syndrome. Genetic-linkage studies have revealed a defective *CD36* gene encoding a membrane fatty acid transporter and hyperinsulinaemia in the spontaneous-hypertensive rat. However, there is no unifying mechanism that can explain these phenotypes as a consequence of a defective *CD36* gene (Tanaka *et al*. 2006). Of interest, the hearts of CD36-defective spontaneous-hypertensive rats exhibit uncoupling of glucose oxidation from its uptake and enhanced protein O-linked N-acetylglucosaminylation, suggesting increased glucose shunt through the hexose monophosphate pathway. Thiamine repletion in the CD36-defective spontaneous-hypertensive rat results in correction of the uncoupling of glucose oxidation to glucose uptake, reduced protein O-linked N-acetylglucosaminylation and the expression of mRNA involved in the hexose monophosphate shunt, renin–angiotensin system and adipokines in epididymal adipose tissue, and reduced hypertension and hyperinsulinaemia.

Subjects with CD36 mutations have also been identified (Yamashita *et al*. 2006). In addition to mild hypertension and dyslipidaemia, whole-body insulin-mediated body glucose uptake is reduced in CD36-deficient patients, indicating the presence of insulin resistance. The frequency of CD36 deficiency is also higher in patients with CHD than in control subjects.

Yet, despite the plethora of potential mechanisms by which insulin resistance might cause hypertension, with the current level of understanding insulin resistance appears to contribute only moderately to the increased prevalence of hypertension in the metabolic syndrome (Hanley *et al*. 2002).

Other manifestations

Insulin resistance is accompanied by many other alterations that are not included in the diagnostic criteria for the metabolic syndrome (Table 2). Increases in apoB and apoC-III, uric acid, pro-thrombotic factors (fibrinogen, plasminogen activator inhibitor-1), serum viscosity, asymmetric dimethylarginine, homocysteine, leucocyte count, pro-inflammatory cytokines, the presence of microalbuminuria, non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis, polycystic ovarian disease, obstructive sleep apnea and cholesterol gallstones and a decrease in adiponectin are all associated with insulin resistance.

Table 2. Other alterations that accompany insulin resistance that are not included in the diagnostic criteria for the metabolic syndrome

Lifestyle
Cigarette smoking
Sedentary behaviour
Lipoproteins
↑ ApoB
↓ ApoA-1
Small dense LDL and HDL
↑ ApoC-III
Pro-thrombotic
↑ Fibrinogen
↑ Plasminogen activator inhibitor-1
↑ Viscosity
Inflammatory markers
↑ Leucocytes
↑ IL-1
↑ IL-6
↑ IL-18
↑ TNFα
↑ Resistin
↑ C-reactive protein
↓ Adiponectin
Vascular
Microalbuminuria
↑ Asymmetric dimethylarginine
Other
↑ Uric acid
↑ Homocysteine
Non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis
Polycystic ovary syndrome
Obstructive sleep apnea

↑, Increased; ↓, decreased.

Cigarette smoking (Eliasson *et al*. 1994) and a sedentary lifestyle (Lakka *et al*. 2003) can also produce many of the major criteria of the syndrome and beyond. Increases in apoB, apoC-III (Onat *et al*. 2003) and non-alcoholic steatohepatitis (Medina *et al*. 2004) are tied to the effects of fatty acids on VLDL production by the liver, and in the case of apoB and apoC-III provide evidence of an increased number of pro-atherogenic particles in the circulation. Hyperuricaemia reflects defects in insulin action on the renal tubular re-absorption of uric acid (Facchini *et al*. 1991), whereas the increase in asymmetric dimethylarginine, an endogenous inhibitor of NO synthase, relates to endothelial dysfunction (Egan, 2003). An extended form of endothelial pathophysiology in insulin-resistant states could be microalbuminuria (Rowley *et al*. 2003). Insulin resistance is also associated with gall bladder disease (Nervi *et al*. 2006). Bile is typically more lithogenic when

it contains a higher cholesterol:bile acids and phospholipids. The primary reason for lithogenic bile in obese patients is an increase in total body cholesterol synthesis, possibly secondary to the overload of tissues with fatty acids that are precursors for cholesterol synthesis (Grundy, 2004).

Pro-inflammatory cytokines. The association between the metabolic syndrome and inflammation is well documented (Sutherland *et al*. 2004). The increases in pro-inflammatory cytokines including IL-6, IL-18, resistin, TNFα and CRP (Fernandez-Real & Ricart, 2003; Fig. 1(b)) reflect overproduction by the expanded adipose tissue mass (Trayhurn & Wood, 2004). Recent evidence (Weisberg *et al*. 2003; Xu *et al*. 2003) suggests that in adipose tissue monocyte-derived macrophages reside and may be at least in part the source of the generation of pro-inflammatory cytokines locally and in the plasma. Insulin resistance in the liver, muscle and adipose tissue is not only associated with the abundance of pro-inflammatory cytokines (and relative deficiency of the anti-inflammatory cytokine adiponectin), but a direct result of this burden (Neuschwander-Tetri & Caldwell, 2003). It remains unclear, however, how much of the insulin resistance related to the adipose tissue content of macrophages is paracrine *v*. endocrine.

As a general index of inflammation, CRP levels vary with ethnicity, level of fitness, and gender (Chambers *et al*. 2001; LaMonte *et al*. 2002; Patel *et al*. 2006). For instance, CRP concentrations are higher in healthy Indian Asians than in European whites and relate to greater central obesity and insulin resistance in Indian Asians (Chambers *et al*. 2001). In the Bogalusa Heart Study plasma CRP levels were found to show a significant race (black> Caucasian; $P = 0{\cdot}01$) and gender (female>male; $P = 0{\cdot}0001$) difference (Patel *et al*. 2006). At present, it remains unclear whether these differences in CRP when adjusted for other covariates will relate to different rates of development of diabetes and/or atherosclerotic CVD. Of interest, a state of low-grade systemic inflammation evidenced by higher levels of CRP has been found in subjects with a normal BMI who show subclinical insulin resistance but no other metabolic abnormalities (Bo *et al*. 2005).

Within the setting of the metabolic syndrome increases in inflammatory markers do affect CHD mortality (Coppola *et al*. 2006; Langenberg *et al*. 2006; Linnemann *et al*. 2006). Increases in CRP also appear to impact on the incidence of peripheral vascular disease in patients with diabetes and the metabolic syndrome (Vu *et al*. 2005). In addition, elevated CRP concentrations are a predictor of diabetes in the general Japanese population, an effect independent of obesity and insulin resistance (Doi *et al*. 2005). A similar observation has been reported in west of Scotland men (Sattar *et al*. 2004). When the risks for atherosclerotic CVD and diabetes are considered sufficient data appear to have been accumulated to modify the definition of the metabolic syndrome to include a measure of inflammation (Haffner, 2006).

Visfatin (also known as pre-B-cell colony-enhancing factor) is a cytokine that is highly expressed in visceral fat and its blood levels correlate with obesity (Stephens & Vidal-Puig, 2006). Circulating visfatin concentrations are increased by hyperglycaemia. This effect is suppressed by exogenous hyperinsulinaemia or somatostatin infusion. Glucose signalling for visfatin release in adipocytes involves the phosphatidylinositol 3-kinase/Akt pathway (Haider *et al*. 2006). Additional insight into mechanisms and the relationship between this cytokine and atherosclerotic CVD and diabetes is needed.

A large amount of information indicates that inflammation may be involved in the initiation as well as the development of hypertension. Evidence from animal models as well as patients have indicated that hypertension may exert pro-inflammatory actions through the increased expression of several mediators, including leucocyte adhesion molecules, chemokines, growth factors, heat-shock proteins, endothelin-1, and angiotensin. This association between inflammation and hypertension relates to previous documentation that endothelial dysfunction and increased serum levels of CRP are present in patients with hypertension (Li *et al*. 2005).

Elevated levels of the protease inhibitor plasminogen activator inhibitor-1 are well known molecular markers of the metabolic syndrome. However, it has been proposed that plasminogen activator inhibitor-1 could also act as an aetiological factor in the development of metabolic syndrome and its sequelae. This effect could be a result of plasminogen activator inhibitor-1 inhibition of the activity of members of the proprotein convertase class of serine proteases (Griffiths & Grainger, 2006).

Adiponectin. Adiponectin is an anti-inflammatory cytokine that is produced exclusively by adipocytes. Adiponectin has been shown to both enhance insulin sensitivity and inhibit many steps in the inflammatory process (Nawrocki & Scherer, 2004). In the liver adiponectin inhibits both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production (Combs *et al*. 2001). In muscle adiponectin increases glucose transport and enhances fatty acid oxidation, effects that result in part from the activation of AMP kinase (Xu *et al*. 2003). Adiponectin and the two receptors of adiponectin adipoR1 and adipoR2 are all associated with body composition, insulin sensitivity and metabolic variables (Bluher *et al*. 2006).

Recent evidence suggests that the high-molecular-weight form of adiponectin has better predictive power in relation to insulin resistance and the metabolic syndrome than plasma total adiponectin level (Hara *et al*. 2006; Lara-Castro *et al*. 2006). Moreover, adiponectin relates strongly to levels of HDL-cholesterol. The relationship appears to be a consequence of a strong negative correlation between adiponectin and the fractional clearance rate of apoA-1 (Verges *et al*. 2006). Interestingly, there are reports that link low levels of adiponectin to myocardial infarction (Pischon *et al*. 2004) and to the progression of subclinical CHD (Maahs *et al*. 2005).

In mice decreased circulating levels of adiponectin appear to be important in producing metabolic changes consistent with the metabolic syndrome (van Puijenbroek *et al*. 1996; Yamauchi *et al*. 2003; Ohashi *et al*. 2006). Reductions in adiponectin are also apparent in human subjects with the metabolic syndrome (Bergman *et al*. 2004; Matsuzawa *et al*. 2004). Additional properties of

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adiponectin related to the metabolic syndrome have recently emerged. Adiponectin-knock-out mice develop hypertension when maintained on a high-salt diet, but in the absence of insulin resistance (Ohashi *et al*. 2006). The hypertension of adiponectin-knock-out mice is associated with reduced mRNA levels of endothelial NO synthase and PGI2 synthase in aorta and low levels of endothelial NO synthase metabolites and PGI2 synthase in plasma. Moreover, adiponectin therapy lowers the elevated blood pressure and corrects the altered mRNA to normal. In addition, adiponectin-induced cyclooxygenase-2-dependent synthesis of PGE2 in cardiac cells and cyclooxygenase-2 inhibition reverses the inhibitory effects of adiponectin on TNFα production and infarct size (Shibata *et al*. 2005). Overall, adiponectin is thought to be cardio-protective (Ouchi *et al*. 2006). Presently, the relative contribution of the deficiency in adiponectin *v*. the overabundance of the pro-inflammatory cytokines remains unclear.

Beyond insulin resistance

An alternative concept suggested by Unger (2003) to explain the metabolic syndrome is leptin resistance. In general, conditions in which leptin deficiency or resistance are present are associated with TAG accumulation in non-adipose organs, e.g. liver, muscle and the islets. This pathophysiology could relate to the absence of down-regulation of sterol response element-binding protein-1c by leptin (Kakuma *et al*. 2000) and/or the inability of leptin to activate AMP kinase in muscle (Minokoshi & Kahn, 2003). Leptin also appears to decrease insulin secretion (Cases *et al*. 2001; Sung *et al*. 2005), a result secondary to suppressor of cytokine signalling-3-mediated transcriptional inhibition of pre-proinsulin gene expression (Laubner *et al*. 2005). Leptin resistance could relate to the hyperinsulinaemia that develops in the setting of the metabolic syndrome before defects in insulin secretion lead to the development of diabetes (Seufert, 2004).

In addition to linking adiposity and central nervous circuits to reduce appetite and enhance energy expenditure, leptin has been shown to increase overall sympathetic nerve activity, facilitate glucose utilization and improve insulin sensitivity. In addition, leptin is capable of regulating cardiac and vascular contractility through a local NO-dependent mechanism (Ren, 2004). The recent discovery that leptin and insulin share many of the same signalling pathways (Xu *et al*. 2005) suggests that both peptides could share responsibility for the metabolic syndrome.

Summary

Nearly all the criteria included in the metabolic syndrome relate to or are a cause of insulin resistance and confer increased risk for atherosclerotic CVD and diabetes. Moreover, most of the components that relate to the syndrome but are not included in the definition, e.g. pro-inflammatory cytokines, also relate to insulin resistance and atherosclerotic CVD and diabetes risk. With time, the syndrome will hopefully be clarified in definition and mechanisms so that the relationship with atherosclerotic CVD and diabetes will result in targeting either the syndrome or the individual components to reduce risk. At present, an emphasis on lifestyle is most appropriate to address the syndrome; in addition, steps should be taken to modify risk factors.

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