The metabolic syndrome

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The metabolic syndrome is a common metabolic disorder that results from the increasing prevalence of obesity. The disorder is defined in various ways, but in the near future a new definition(s) will be applicable worldwide. The pathophysiology seems to be largely attributable to insulin resistance with excessive flux of fatty acids implicated. A proinflammatory state probably contributes to the syndrome. The increased risk for type 2 diabetes and cardiovascular disease demands therapeutic attention for those at high risk. The fundamental approach is weight reduction and increased physical activity; however, drug treatment could be appropriate for diabetes and cardiovascular disease risk reduction.

The concept of the metabolic syndrome has existed for at least 80 years.[1] This constellation of metabolic disturbances, all risk factors for cardiovascular disease, was first described in the 1920s by Kylin, a Swedish physician, as the clustering of hypertension, hyperglycaemia, and gout.[2] Later, in 1947, Vague drew attention to upper body adiposity (android or male-type obesity) as the obesity phenotype that was commonly associated with metabolic abnormalities associated with type 2 diabetes and cardiovascular disease.[3]

Over the past two decades, a striking increase in the number of people with the metabolic syndrome worldwide has taken place. This increase is associated with the global epidemic of obesity and diabetes.[4] With the elevated risk not only of diabetes but also of cardiovascular disease from the metabolic syndrome,[5] there is urgent need for strategies to prevent the emerging global epidemic.[4] The metabolic syndrome is a master of disguise since it can present in various ways according to the different components that constitute the syndrome.

The metabolic syndrome is also known as syndrome X,[6] the insulin resistance syndrome,[7] and the deadly quartet.[8] The constellation of metabolic abnormalities includes glucose intolerance (type 2 diabetes, impaired glucose tolerance, or impaired fasting glycaemia), insulin resistance, central obesity, dyslipidaemia, and hypertension, all well documented risk factors for cardiovascular disease. These conditions co-occur in an individual more often than might be expected by chance. When grouped together, they are associated with increased risk of cardiovascular disease.[9,10] Lemieux and colleagues[11] have suggested the importance of abdominal obesity and the so-called hypertrigly-ceridaemic waist phenotype as a central component.[11] Although some strong positions have been taken, the cause of the syndrome is still not settled,[12] as discussed in more detail later.

Defining the metabolic syndrome

While the concept of the metabolic syndrome was accepted, and even while controversies have raged about its cause, it was not until 1998 that there was an initiative to develop an internationally recognised definition. In an attempt to achieve some agreement on definition, and to provide a tool for clinicians and researchers, a WHO consultation proposed a set of criteria.[13] Subsequently, the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III)[14] and the European Group for the Study of Insulin Resistance[15] have formulated definitions. These definitions agree on the essential components—glucose intolerance, obesity, hypertension, and dyslipidaemia—but do differ in the detail and criteria (table 1).

The WHO definition and that of the European Group for the Study of Insulin Resistance agree in that they both include either glucose intolerance or insulin resistance as an essential component.[13,15] However, for the NCEP:ATP III definition,[14] this criterion is not included. Additionally, the cut-off points for criteria of each component of the cluster and the way of combining them to define the metabolic syndrome differ between the definitions of the WHO and European Group for the Study of Insulin resistance and the definition of the NCEP:ATP III.

The WHO proposal was designed as a first attempt to define the syndrome. The report clearly stated that the definition would be modified as new information became available about the components and their predictive power.[13] In retrospect, it is apparent that the WHO definition was better suited as a research tool whereas the NCEP:ATP III definition[14] was more useful for clinical practice. Clinicians prefer simple tools with which to assess patients and improve their management, and it is generally agreed that the NCEP:ATP-III definition is simpler for practice. It requires only a fasting assessment of blood glucose, whereas the WHO definition can require an oral glucose tolerance test. Furthermore, because an accurate assessment of insulin resistance requires a more complicated test (eg, the hyperinsulinaemic euglycaemic

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Search strategy and selection criteria

We searched PubMed with the terms "metabolic syndrome", "insulin resistance", "coronary heart disease", "diabetes mellitus", "inflammation", "hypertension", "insulin secretion", "CRP", "cytokines", and "adiponectin".

WHO, 1999	European Group for the Study of Insulin Resistance, 1999	ATP III, 2001
Diabetes or impaired fasting glycaemia or impaired glucose tolerance or insulin resistance (hyperinsulinaemic, euglycaemic clamp-glucose uptake in lowest 25%)	Insulin resistance—hyperinsulinaemia: top 25% of fasting insulin values from non-diabetic population	
Plus 2 or more of the following	Plus 2 or more of the following	3 or more of the following
Obesity: BMI >30 or waist-to-hip ratio >0·9 (male) or >0·85 (female)	Central obesity: waist circumference ≥94 cm (male) or ≥80 cm (female)	Central obesity: waist circumference >102 cm (male), >88 cm (female)
Dyslipidaemia: triglycerides ≥1·7 mmol/L or HDL cholesterol <0·9 (male) or <1·0 (female) mmol/L	Dyslipidaemia: triglycerides >2·0 mmol/L or HDL cholesterol <1·0	Hypertriglyceridaemia: triglycerides ≥1·7 mmol/L
Hypertension: blood pressure >140/90 mm Hg	Hypertension: blood pressure ≥140/90 mm Hg and/or medication	Low HDL cholesterol: <1·0 mmol/L (male), <1·3 mmol/L (female)
Microalbuminuria: albumin excretion >20 μg/min	Fasting plasma glucose ≥6·>1 mmol/L	Hypertension: blood pressure ≥135/85 mm Hg or medication
		Fasting plasma glucose ≥6·1 mmol/L

Table 1: Comparison of definitions of the metabolic syndrome

clamp technique), its application in an epidemiological or clinical setting is impractical, although the Homeostasis Model Assessment (HOMA) model could be used as an alternative method.[16]

Yet another attempt at a definition came from the American Association of Endocrinology,[17] who have referred to the cluster as the insulin resistance syndrome. They suggest that four factors should be the "identifying abnormalities" of the syndrome. These are elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, and elevated fasting and postload (75 g) glucose. Obesity is not a component of their definition. Given the mounting evidence that central obesity is a major risk factor for type 2 diabetes and cardiovascular disease,[11,14] this omission is rather surprising.

Since several definitions of the syndrome are in use, it is difficult to compare prevalence and impact between countries. Fortunately, there is now a chance for a more rational approach. In May, 2004, a group of experts was convened by the International Diabetes Federation (IDF) to attempt to establish a unified definition for the metabolic syndrome and to highlight areas where more research into the syndrome is needed. A similar process has been initiated jointly by the National Heart, Lung and Blood Institute (NHLBI) and the American Heart Association. Further consideration of the definition by the ATP III panel is expected to follow. Ultimately, the combined efforts of the IDF and NHLBI–American Heart Association will result in a new definition(s) of the metabolic syndrome that will be suitable for use in clinical practice worldwide.

A major issue for the IDF consensus consultation was the fact that criteria used for obesity in Asian and other populations could be different from those used in the west. The importance of obesity as a risk factor for several diseases including type 2 diabetes, cardiovascular disease, hypertension, gallstone disease, and certain cancers, is well documented.[18] Yet, the amount of obesity associated with increased risk differs between populations. The WHO criteria that define overweight and obesity in terms of comorbidities are not necessarily appropriate for Asian populations. This issue was addressed in 2000 by a group convened by the International Association for the Study of Obesity and

supported by WHO (Western Pacific Region) and the International Obesity Task Force. They redefined overweight as body-mass index (BMI) >23 and obesity as >25 in Asians. Central obesity was defined as >80 cm for women and >90 cm in men.[19]

More recently, a working party with representation from WHO (Geneva), the International Society for the Study of Obesity, and the International Obesity Task Force re-emphasised the fact that obesity-associated risk is a continuum and that there are interethnic differences in the relations between various obesity indices and the risks of cardiovascular disease.[20] They noted that in urban Asians, the BMI range of 23–24 has an equivalent risk of type 2 diabetes, hypertension, and dyslipidaemia as a BMI of 25–29·9 in white people. This finding will probably be taken into account when the new IDF definition is published.

Prevalence

Comparisons of published prevalence for different populations are difficult despite attempts to reach agreement on the definition of the metabolic syndrome.[1] Many studies compare prevalences using different criteria, and perhaps their main achievement is to reinforce the need for a standardised international definition. Cameron and others[1] have published a detailed review about the prevalence of the syndrome with different criteria (table 1).

Figure 1 presents studies from various countries. They differ with respect to study design, sample selection, year that they were undertaken, precise definition of the metabolic syndrome used, and age and sex structure of the population. Although the obesity criteria in NCEP:ATP-III are not necessarily appropriate for Asian groups,[20] figure 1 only shows prevalences established with NCEP:ATP-III criteria rather than the WHO's.

Despite differences in the design of these studies and other variables, certain inferences can be made. For example, even for studies involving participants in the same age-groups, there is wide variation in prevalence in both sexes. In those studies that include people 20–25 years and older, the prevalence varies in urban populations from 8% (India) to 24% (USA) in men, and from 7% (France) to 43% (Iran) in women.

An interesting example of the effect of ethnic origin on the metabolic syndrome is a comparison of the prevalence of the syndrome in the USA with lower prevalence in non-Hispanic white people compared with Mexican Americans, and in African American men compared with non-Hispanic white and Mexican American men.[21]

A very consistent finding is that the prevalence of the metabolic syndrome is highly age-dependent. This pattern is clear in Iran where the prevalence is less than 10% for both men and women in the 20–29 year age-group, rising to 38% and 67%, respectively, in the 60–69 year age-group.[22] Similarly, in a French population, the prevalence rises from <5·6% in the 30–39 year age-group to 17·5% in the 60–64 year age-group.[22] Additionally, the prevalence of the metabolic syndrome in the USA (national health and nutrition examination survey [NHANES III]) increased from 7% in participants aged 20–29 years to 44% and 42% for those aged 60–69 years and at least 70 years, respectively.[21]

Until recently, type 2 diabetes and the metabolic syndrome have been regarded as a disease of adults.[4] However, with increasing rates of obesity in young people, it is clear that the disease can begin at different ages in all ethnic groups, and that type 2 diabetes and the metabolic syndrome can be evident in childhood.[23–26] However, estimates of prevalence are difficult because of the problem of producing an appropriate definition of the syndrome in children and adolescents. In the USA, Weiss and colleagues[26] reported that the prevalence of the metabolic syndrome increased with severity of obesity, and reached 50% in severely obese youngsters. Each half-unit increase in BMI was associated with an increase in the risk of the metabolic syndrome in overweight and obese people (odds ratio 1·55), as was each unit of increase in insulin resistance as assessed with the HOMA model (odds ratio 1·12 for each additional unit of insulin resistance). The prevalence of the metabolic syndrome increased significantly with increasing insulin resistance after adjustment for ethnic group and degree of obesity. C-reactive protein concentrations increased and adiponectin concentrations decreased with increasing obesity. The researchers concluded that the prevalence of the metabolic syndrome is high in obese children and adolescents, and it increases with worsening obesity. Biomarkers of an increased risk of adverse cardiovascular outcomes are already present in these youngsters.

In Taiwan, a screening study of 3 million students (aged 6–18 years)[24] showed that people with type 2 diabetes had higher mean BMI, cholesterol, and blood pressure than did those with a normal fasting glucose, and, even at this young age, the metabolic syndrome was present. Similar results have also been reported in Hong Kong Chinese children.[25] Finally, data from the
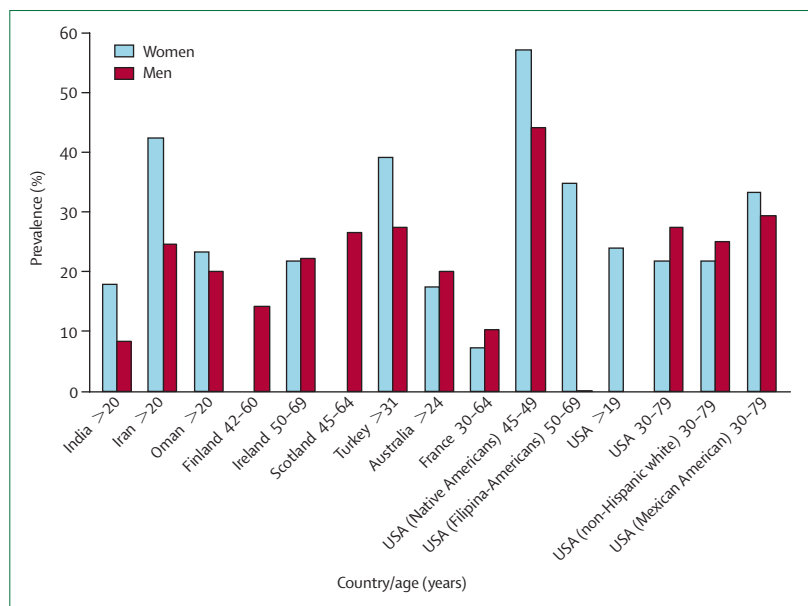

Figure 1: **Prevalence of the metabolic syndrome from ATPIII definition**
Adapted from Cameron et al.[1]

12–19 years age-group in the NHANES III study, with NCEP:ATP-III criteria modified for adolescents, reported that the prevalence of the metabolic syndrome in adolescents was 4·2%.[27]

Relation to predictability of diabetes and cardiovascular disease

The metabolic syndrome is associated with an increased risk of both diabetes[5] and cardiovascular disease.[9,10,28,29] Several studies have indicated that the metabolic syndrome predicts future diabetes.[30,31] However, since impaired fasting glucose and impaired glucose tolerance are components of the NCEP:ATP-III and the WHO definitions respectively, this finding might not be a surprise.

In the DECODE study involving European men and women,[32] non-diabetic people with the metabolic syndrome had an increased risk of death from all causes as well as from cardiovascular disease.[32] The overall hazard ratios for all-cause and cardiovascular disease mortality in people with the metabolic syndrome compared with those without it were 1·44 and 2·26 in men and 1·38 and 2·78 in women after adjustment for age, blood cholesterol concentrations, and smoking.

In two other prospective European studies,[9,10] the presence of the syndrome predicted increased cardiovascular disease and coronary heart disease mortality. Again, this finding is not unexpected since the metabolic syndrome comprises established risk factors for cardiovascular disease. In these two studies, as well as the Verona Diabetes Complications Study,[33] the relative hazard ratios for cardiovascular disease outcomes ranged from 2 to 5. In addition, applying the ATP III criteria to

10 537 NHANES III participants resulted in a significant association between the metabolic syndrome with prevalent myocardial infarction and stroke.[34] With a new metabolic syndrome definition(s) imminent, it will be important to establish whether there are differences between ethnic groups in prediction using this new definition(s). From this point of view, the findings of the INTERHEART study[35] could be of great importance. This study looked at putative cardiovascular risk factors in nearly 30 000 people in 52 countries and from all inhabited continents of the world. Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity accounted for most of the risk of myocardial infarction worldwide in both sexes and at all ages in all regions. This result suggests that approaches to cardiovascular disease prevention can be based on similar principles worldwide.

In another study, the Diabetes Predicting Model and the Framingham Risk Score were used to examine the relative value of the metabolic syndrome in predicting type 2 diabetes and cardiovascular disease, respectively.[36] Initially 1709 non-diabetic participants in the San Antonio Heart Study were followed up for 7·5 years, and 195 developed type 2 diabetes. Over the same interval, 156 of 2570 participants experienced a cardiovascular disease event. The sensitivity for predicting diabetes using the ATP III definition of the metabolic syndrome was 66% and the false positive rate was 28%. The sensitivity and false positive rate for the prediction of cardiovascular disease were 67% and 34%, respectively. At corresponding false positive rates, the two predicting models had significantly higher sensitivities, and, at corresponding sensitivities, significantly lower false positive rates than the metabolic syndrome for both outcomes. Thus, in the San Antonio Heart Study, the metabolic syndrome proved inferior to established predicting models for either type 2 diabetes or cardio-vascular disease.

Mechanisms underlying the metabolic syndrome

Insulin resistance
The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance. Insulin resistance has traditionally been defined with a glucocentric view—ie, when a defect in insulin action results in fasting hyperinsulinaemia to maintain euglycaemia. Yet, even before fasting hyper-insulinaemia develops, postprandial hyperinsulinaemia exists.

A major contributor to the development of insulin resistance is an overabundance of circulating fatty acids. Plasma albumin-bound free fatty acids are derived mainly from adipose tissue triglyceride stores released through the action of the cyclic AMP-dependent enzyme hormone sensitive lipase. Fatty acids are also derived through the lipolysis of triglyceride-rich lipoproteins in tissues by the action of lipoprotein lipase.[37] Insulin is important to both antilipolysis and the stimulation of lipoprotein lipase. Of note, the most sensitive pathway of insulin action is the inhibition of lipolysis in adipose tissue.[38] Thus, when insulin resistance develops, the increased amount of lipolysis of stored triacylglycerol molecules in adipose tissue produces more fatty acids, which could further inhibit the antilipolytic effect of insulin, creating additional lipolysis.

Upon reaching insulin sensitive tissues, excessive fatty acids create insulin resistance by the added substrate availability and by modifying downstream signalling (figure 2). In muscle, fatty acids can impair activation of protein kinase C-λ and protein kinase C-ζ.[39] Moreover, the generation of excess acyl CoAs or acyl-CoA derivatives such as ceramide can diminish Akt1 activation.[40] In the liver of rats fed a high-fat diet, insulin resistance can be attributed to a defect in insulin-stimulated insulin receptor substrate-1 and insulin receptor substrate-2 tyrosine phosphorylation. These changes were associated with activation of protein kinase C-ε and c-Jun N-terminal kinase-1.[41] However, in the liver there seems to be some discrepancy in the metabolic effects of free fatty acids on insulin-mediated glucose and lipid metabolism. While circulating free fatty acids increase hepatic glucose production and diminish inhibition of glucose production by insulin,[42] lipogenesis, a pathway related to both the stimulatory effects of such acids and insulin on sterol response element binding protein-1c,[43] continues.

Studies of (1) insulin resistant people with obesity and/or type 2 diabetes,[44] (2) offspring of patients with type 2 diabetes,[45] and (3) the elderly[46] have identified a defect in mitochondrial oxidative phosphorylation that relates to the accumulation of triglycerides and related lipid molecules in muscle. Moreover, in murine models of obesity, another subcellular organelle could be involved, the endoplasmic reticulum. In mice made deficient in the endoplasmic reticulum X-box binding protein-1, hyperactivation of c-Jun N-terminal kinase-1 increases serine phosphorylation of insulin receptor substrate-1 and insulin resistance.[47] Thus, more basic mechanisms of insulin resistance are being discovered over time. 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.

Obesity and increased waist circumference
Although the first description of the metabolic syndrome was in the early 20th century,[2] the worldwide obesity epidemic has been the most important driving force in the much more recent recognition of the syndrome. Despite the importance of obesity in the model, we should remember that patients of normal weight can also be insulin resistant.[48]

For several definitions of the metabolic syndrome, waist circumference is included.[13–15] Mechanistically, a distinction between a large waist due to increases in subcutaneous adipose tissue versus visceral fat is debated. This distinction can be made with computed tomography or magnetic resonance imaging.[49] With increases in intra-abdominal or visceral adipose tissue, a higher rate of flux of adipose tissue-derived free fatty acids to the liver through the splanchnic circulation 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 (ie, glucose production, lipid synthesis, and secretion of prothrombotic proteins such as fibrinogen and plasminogen activator inhibitor 1).[50] 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 free fatty acid flux and metabolism, the relative predominance of visceral rather than subcutaneous adipose tissue with increasing waist circumference in Asians and Asian Indians[51] renders the relative prevalence of the syndrome higher than in African-American men in whom subcutaneous fat predominates.[52] However, there is evidence that the elevated postprandial free fatty acid release in upper body obese women originates from the non-splanchnic upper body fat, and not from the visceral depot.[53] These results suggest that visceral fat might be a marker for, but not the source of, excess postprandial free fatty acids in obesity.

In the setting of partial or complete lipoatrophy, insulin resistance and the metabolic syndrome typically coexist.[54] Evidence from these less common disorders does support a genetic basis of the syndrome including single gene defects in peroxisome-proliferator activated receptor-λ, lamin A/C, 1-acylglycerol-3-phosphate, O-acyltransferase, seipin,[55] the β-2 adrenergic receptor,[56] and adiponectin.[57]

Dyslipidaemia
In general, with increases in free fatty acid flux to the liver, increased production of apo B-containing triglyceride-rich very low-density lipoproteins (VLDL) occurs.[58] The effect of insulin on this process is somewhat complex. In the setting of insulin resistance, increased flux of free fatty acids to the liver increases hepatic triglyceride synthesis; however, under physiological conditions, insulin inhibits rather than increases the secretion of VLDL into the systemic circulation.[59] This response in part is an effect of insulin on the degradation of apo B.[60] Yet, insulin is also lipogenic, increasing the transcription and enzyme activity of many genes that relate to triglyceride biosynthesis.[61] Whether or not this pathway remains

operational in the setting of systemic insulin resistance has not been completely addressed. Additionally, insulin resistance could also reduce the concentrations of lipoprotein lipase in peripheral tissues (ie, in adipose tissue more than muscle).[62] This alteration in lipoprotein lipase, however, seems to contribute less to the hypertriglyceridaemia than does the overproduction of VLDL. Nevertheless, hypertriglyceridaemia is an excellent reflection of the insulin resistant condition and is one of the important criteria for diagnosis of the metabolic syndrome.

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 hypertriglyceridaemia, a decrease in the cholesterol content of HDL results from decreases in the cholesteryl ester content of the lipoprotein core with variable increases in triglyceride making the particle small and dense, a function in part of cholesteryl ester transfer protein.[63] This change in lipoprotein composition also results in an increased clearance of HDL from the circulation.[64] The relation of these changes in HDL to insulin resistance are probably indirect, arising in concert with the changes in triglyceride-rich lipoprotein metabolism.

In addition to HDL, the composition of LDL is also modified in a similar way. In fact, with fasting serum triglycerides >2·0 mmol/L, almost all patients have a predominance of small dense LDL.[65,66] This change in LDL composition is attributable to relative depletion of unesterified cholesterol, esterified cholesterol, and phospholipid with either no change or an increase in LDL triglyceride.[67,68] Small dense LDL might be more atherogenic than buoyant LDL because (1) it is more toxic to the endothelium; (2) it is more able to transit through the endothelial basement membrane; (3) it adheres well to glycosaminoglycans; (4) it has increased susceptibility to oxidation; and/or (5) it is more selectively bound to scavenger receptors on monocyte-derived macrophages;[69,70] however, this contention is not entirely accepted.[71] In some studies, this alteration in LDL composition is an independent risk factor for cardiovascular disease.[72] However, more often this association is not independent, but related to the concomitant changes in other lipoproteins and other risk factors.[73]

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 to mediate glucose uptake and metabolism in insulin sensitive tissues (ie, muscle and adipose tissue). The relation between impaired fasting glucose or impaired glucose tolerance and insulin resistance is well supported by human, non-human primate, and rodent

studies. To compensate for defects in insulin action, insulin secretion and/or clearance must be modified to sustain euglycaemia. If this compensation fails, defects in insulin secretion predominate.

Insulin resistance in pancreatic islet β cells implies that signals that generate glucose-dependent insulin secretion have been adversely modified, and fatty acids are prime candidates. Although free fatty acids can stimulate insulin secretion, increasing and prolonged exposure to excessive concentrations results in falls in insulin secretion.[74] The mechanism for this alteration has been attributed to lipotoxicity through several potential different mechanisms.[75–77]

Insulin also can feedback on its own secretion. The importance of this system comes from 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;[78] however, the β-cell specific knockout of the insulin receptor produces progressive glucose intolerance and diabetes.[79] In people with genetic predispositions to development of diabetes, the presumed stress of the insulin resistant environment on β-cell function causes glucose intolerance and ultimately higher risk of diabetes.

Hypertension

The relation between insulin resistance and hypertension is well established,[80] and relates to several different mechanisms. First, it is important to note that insulin is a vasodilator when given intravenously to people of normal weight,[81] with secondary effects on sodium reabsorption in the kidney.[82] Evidence indicates that sodium reabsorption is increased in white people but not Africans or Asians with the metabolic syndrome.[83] In the setting of insulin resistance, the vasodilatory effect of insulin can be lost,[84] but the renal effect on sodium reabsorption preserved.[85] Fatty acids themselves can mediate relative vasoconstriction.[86] Insulin also increases the activity of the sympathetic nervous system,[87] an effect that might also be preserved in the setting of the insulin resistance.[88] However, when assessed by concentrations of fasting insulin, HOMA or the HOMA insulin resistance index (HOMA-IR),[16] insulin resistance contributes only modestly to the increased prevalence of hypertension in the metabolic syndrome.[89]

Other manifestations

Insulin resistance is accompanied by many other alterations that are not included in the diagnostic criteria for the metabolic syndrome (panel). Increases in apo B and C-III, uric acid, prothrombotic factors (fibrinogen, plasminogen activator inhibitor 1), serum viscosity, asymmetric dimethylarginine, homocysteine, white blood cell count, pro-inflammatory cytokines, the presence of microalbuminuria, non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis, obstructive sleep apnoea, and polycystic ovarian disease are all associated with insulin resistance.

Non-alcoholic fatty liver disease (fatty liver) is common; however, in non-alcoholic steatohepatitis both triglyceride accumulation and inflammation coexist.[90] Non-alcoholic steatohepatitis in particular is becoming an important health problem that is present in 2–3% of individuals in the USA and other western countries.[91] As the incidence of overweight/obesity and the metabolic syndrome increases, this disease could become one of the more frequent causes of end stage liver disease and hepatocellular carcinoma.

Cigarette smoking[92] and sedentary lifestyle[93] can also produce many of the major criteria of the syndrome and beyond. Increases in apo B and C-III,[94] and non-alcoholic steatohepatitis[95] are tied to the effects of fatty acids on VLDL production by the liver, and in the case of apo B and C-III provide evidence of an increased number of proatherogenic particles in the circulation. Hyperuricaemia results from defects in insulin action

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Panel: Changes associated with insulin resistance

Lifestyle
Cigarette smoking
Sedentary behaviour

Lipoproteins
Increased apo B
Decreased apo A-1
Small dense LDL and HDL
Increased apo C-III

Prothrombotic
Increased fibrinogen
Increased plasminogen activator inhibitor 1
Increased viscosity

Inflammatory markers
Increased white blood cell count
Increased interleukin 6
Increased tumour necrosis factor α
Increased resistin
Increased C-reactive protein
Decreased adiponectin

Vascular
Microalbuminuria
Increased asymmetric dimethylarginine

Other
Increased uric acid
Increased homocysteine
Non-alcoholic steatohepatitis
Polycystic ovaries syndrome
Obstructive sleep apnoea

on the renal tubular reabsorption of uric acid,[96] whereas the increase in asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, relates to endothelial dysfunction.[88] An extended form of endothelial pathophysiology in insulin resistant states could be microalbuminuria.[97]

Proinflammatory cytokines

The association of the metabolic syndrome with inflammation is well documented.[98] The increases in proinflammatory cytokines including interleukin 6, resistin, tumour necrosis factor α (TNFα) and C-reactive protein[99] reflect overproduction by the expanded adipose tissue mass (figure 2).[100] Evidence suggests that monocyte-derived macrophages reside in adipose tissue and might be at least in part the source of the generation of proinflammatory cytokines locally and in the systemic circulation.[101,102] There is increasing evidence that insulin resistance in the liver, muscle, and adipose tissue is not only associated with the abundance of proinflammatory cytokines (and relative deficiency of the anti-inflammatory cytokine adiponectin), but is a direct result of this burden.[91] It remains unclear, however, how much of the insulin resistance related to the adipose tissue content of macrophages is paracrine versus endocrine.

As a general index of inflammation, C-reactive protein concentrations vary by ethnic origin and within ethnic groups by fitness.[103,104] For instance, concentrations of C-reactive protein were higher in healthy Indian Asians than in European white people and were related to greater central obesity and insulin resistance in Indian Asians.[104] At present it remains unclear whether these differences when adjusted for other covariates will relate to different rates of development of diabetes and/or cardiovascular disease.

Adiponectin

Adiponectin is an anti-inflammatory cytokine that is produced exclusively by adipocytes. Adiponectin both enhances insulin sensitivity and inhibits many steps in the inflammatory process.[105] In the liver, it inhibits both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production.[106] In muscle, it increases glucose transport and enhances fatty acid oxidation, effects that are partly due to the activation of AMP-kinase.[102] In mice, decreased circulating concentrations of adiponectin could be important in producing changes in metabolism consistent with the metabolic syndrome,[107,95] with reductions in adiponectin also apparent in people with the syndrome.[108,96] The relative contribution of the deficiency in this cytokine versus the overabundance of the proinflammatory cytokines remains unclear. Some reports link low concentrations of adiponectin to myocardial infarction[109] and to the progression of subclinical coronary heart disease.[110]
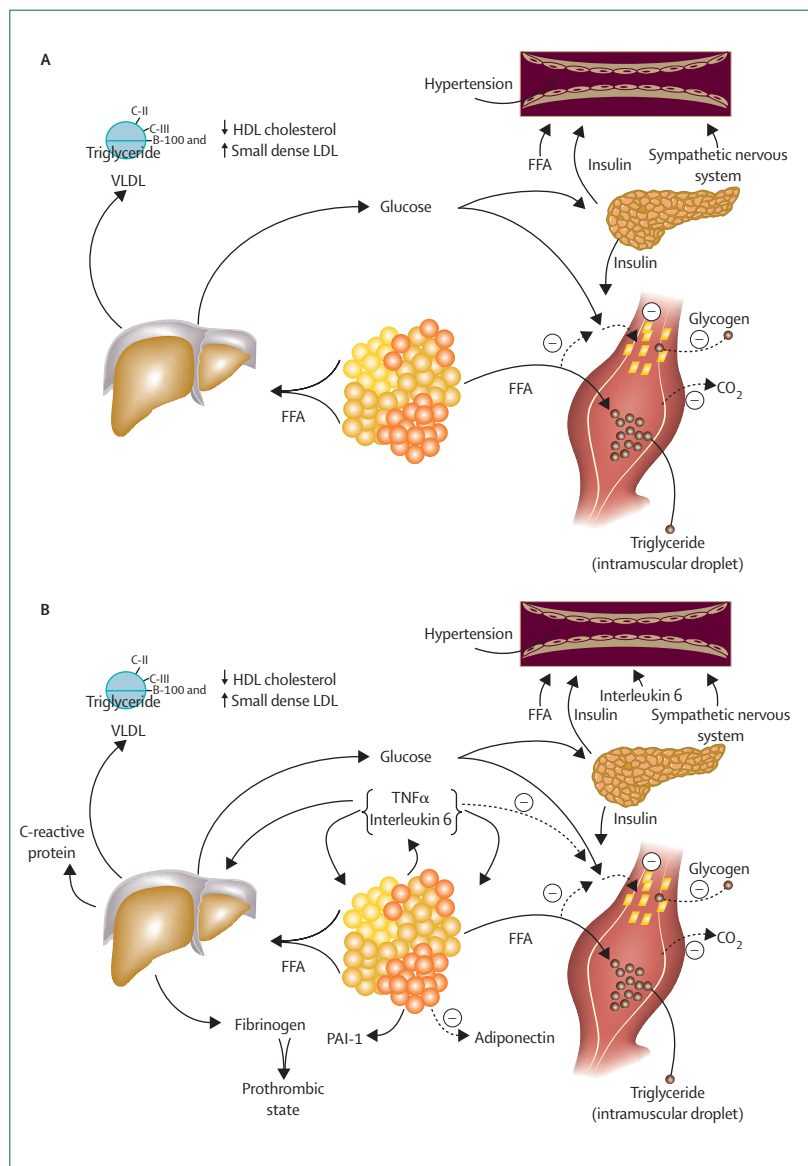
Figure 2: **Pathophysiology of the metabolic syndrome (insulin resistance)**

A: Free fatty acids (FFA) are released in abundance from an expanded adipose tissue mass. In the liver, FFA produce an increased production of glucose, triglycerides and secretion of very low density lipoproteins (VLDL). Associated lipid/lipoprotein abnormalities include reductions in high density lipoprotein (HDL) cholesterol and an increased density of low density lipoproteins (LDL). FFA 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 triglyceride (TG). Increases in circulating glucose and to some extent FFA increase pancreatic insulin secretion resulting in hyperinsulinemia. Hyperinsulinaemia may result in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and contribute to the hypertension as might increased levels of circulating FFA.

B: Superimposed and contributory to the insulin resistance produced by excessive FFA is the paracrine and endocrine effect of the proinflammatory state. Produced by a variety of cells in adipose tissue including adipocytes and monocyte-derived macrophages, the enhanced secretion of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) among others results in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFA. 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 FFA 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 results in a pro-thrombotic state. 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. PAI1=plasminogen activator inhibitor 1. FFA=free fatty acids.

Beyond insulin resistance

Despite the substantial amount of evidence in support of the notion that the metabolic syndrome is an insulin resistance syndrome, quantification of insulin action in vivo is not always strongly related to the presence of the syndrome.[111] Several key questions are raised. First, if the metabolic syndrome is a consequence of only insulin resistance, is the definition appropriately constructed? Second, is it possible that the current components and their relation to the metabolic syndrome exist as three-factor or four-factor aggregates—eg, insulin or glucose, lipids or lipoproteins, blood pressure, and obesity assessments (BMI, waist circumference)?[112] Third, do other mechanisms remain to be discovered? And fourth, if other mechanisms exist, do some components of the syndrome need to be grouped with insulin resistance and the others separately?

An alternative concept suggested by Unger[113] to explain the metabolic syndrome is leptin resistance.[113] In general, conditions in which leptin deficiency or resistance are present are associated with triglyceride accumulation in non-adipose organs (eg, liver, muscle, and the islets).[113] This pathophysiology could relate to the absence of down regulation of sterol response element binding protein 1c by leptin[114] and/or the inability of leptin to activate AMP-kinase in muscle.[115] Leptin also seems to lower insulin secretion,[116] but 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.[117]

Management of metabolic syndrome

The presence of the metabolic syndrome carries increased risk for cardiovascular disease[10,118] and type 2 diabetes.[117] Some affected people are at high or moderately high risk for major cardiovascular disease events in the short term (<10 years); others are at less risk in the short term, but carry a fairly high long-term risk.[119] In the latter group, therapeutic lifestyle modification is first-line therapy, but if 10-year risk is high, drug therapy to modify cardiovascular disease risk factors might be required as well.[120] For this reason, a 10-year risk assessment is needed in all those who have a diagnosis of the metabolic syndrome.

Risk assessment

Several approaches are available to estimate 10-year risk for cardiovascular disease (or coronary heart disease).[120,121] These risk engines incorporate the major risk factors for cardiovascular disease: cigarette smoking, blood pressure, total cholesterol, HDL cholesterol, age, sex, and sometimes other risk factors such as diabetes. In some guidelines,[120] diabetes counts as a high-risk condition independent of other risk factors. According to the Framingham Heart Study, adding abdominal obesity, triglycerides, and fasting glucose to the Framingham risk algorithm yields little or no increase in power of prediction;[119,122] however, in the Quebec Cardiovascular Study concentrations of fasting insulin, triglycerides, apo B, small dense LDL, and waist circumference all proved important determinants.[11,123] The PROCAM risk algorithm[124] also includes triglycerides and a family history of premature coronary heart disease.[124] Whether adding further factors—abdominal obesity, apo B, small LDL, C-reactive protein, and insulin and glucose concentrations—to the current definition of the metabolic syndrome will enhance risk prediction for cardiovascular disease has not been rigorously tested, but elevated C-reactive protein seems to carry increased risk for coronary heart disease beyond standard criteria.[125,126]

The finding of IFG or IGT nonetheless signifies a higher risk for type 2 diabetes.[127] It is noteworthy that when the NCEP:ATP-III and WHO criteria for the metabolic syndrome were compared in subjects with or without a history of cardiovascular disease, the age-adjusted prevalence was 23·9% according to the ATP III definition and 25·1% according to the WHO definition.[128] Estimates differed substantially for some subgroups—in African-American men, the WHO estimate was 24·9%, compared with the ATP III estimate of 16·5%. Yet, NCEP:ATP-III and WHO criteria were similar at identifying the relative risk for cardiovascular disease in the presence and absence of the metabolic syndrome.

The incidence of cardiovascular disease in Asian people is much less than in white people,[129] and the Framingham risk algorithm reportedly overestimates the risk of coronary heart disease in Asians.[130] This finding suggests that evaluation of cardiovascular disease risk based on a database of mainly white people could be inappropriate for Asians. This possibility certainly needs to be considered seriously in the diagnosis and approach to prevention and treatment of cardiovascular disease in these populations with the metabolic syndrome.

Management of underlying risk factors

Although the metabolic syndrome appears to be more common in people who are genetically susceptible, acquired underlying risk factors—being overweight or obese, physical inactivity, and an atherogenic diet—commonly elicit clinical manifestations. Clinical management should first focus on management of these underlying risk factor independent of an individual's risk status (table 2).

Obesity

Abdominal obesity is the body fat parameter most closely associated with the metabolic syndrome.[120,131] As noted previously, definitions of abdominal obesity vary according to population. Clinical management of obesity should adhere to several well-established principles.[5] Effective weight reduction improves all risk factors

associated with the metabolic syndrome,[132] and it will further reduce the risk for type 2 diabetes.[133,134]

Weight reduction is best achieved by behavioural change to reduce energy intake and by physical activity to enhance energy expenditure.[132] Caloric intake should be reduced by 500–1000 calories per day to produce a weight loss of 0·5–1·0 kg per week. The goal is to reduce bodyweight by about 7–10% over 6–12 months, followed by long-term behaviour modification and maintenance of increased physical activity. To date, weight reduction drugs have not been particularly effective for treatment of obesity; on the other hand, in the USA, bariatric surgery has been used increasingly to treat patients with morbid obesity.[135] The effectiveness and safety of bariatric surgery in patients with the metabolic syndrome has been quite encouraging with 95% of patients free of the syndrome 1 year after the operation.[136] Longer periods of observation after weight stabilisation are, however, needed.

Physical inactivity

Current guidelines[137] recommend practical, regular, and moderate regimens of physical activity (eg, 30 min moderate-intensity exercise daily). Regular and sustained physical activity will improve all risk factors of the metabolic syndrome.[27,93] Sedentary activities in leisure time should be replaced by more active behaviour such as brisk walking, jogging, swimming, biking, golfing, and team sports. Combination of weight loss and exercise to reduce the incidence of type 2 diabetes in patients with glucose intolerance should not be dismissed.[138]

Atherogenic and diabetogenic diets

There is general agreement that persons with the metabolic syndrome should adhere to a set of dietary principles: low intakes of saturated fats, trans fats, and cholesterol, reduced consumption of simple sugars, and increased intakes of fruits, vegetables, and whole grains.[120] More controversial is the relative amounts of carbohydrate and unsaturated fats. Some investigators favour lower fat intakes, whereas others recommend higher fat diets.[139] Low-fat diets have been advocated to promote weight reduction,[140] whereas higher monounsaturated fat intakes diminish postprandial glycaemia, reduce serum triglycerides, and raise concentrations of HDL-cholesterol.[139]

Management of metabolic risk factors

The metabolic risk factors that are part of the definition of the syndrome include atherogenic dyslipidaemia, elevated blood pressure, and elevated plasma glucose; however, we will also consider the prothrombotic state and a proinflammatory state. Effective treatment of the underlying risk factors will reduce the severity of all of the metabolic risk factors. However, if people are found to be at particularly high risk or if a given risk factor is

severely abnormal, drug therapy may be necessary. Approaches to each risk factor can be considered briefly.

Atherogenic dyslipidaemia

This condition consists of elevations of triglycerides and apo B, small LDL particles, and low HDL cholesterol. 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) reduce risk for major cardiovascular disease events in high risk patients with the metabolic syndrome by reducing all apo B containing lipoproteins.[141,142] Fibrates mitigate atherogenic dyslipidaemia and appear to reduce the risk for cardiovascular disease in patients with the metabolic syndrome.[143] Their use in combination with statins is particularly attractive, but carries some increased risk for myopathy. This increase in risk with a statin plus fibrate has been particularly noted for the fibrate gemfibrozil.[144] A higher risk from the combination could result from pharmacological interaction of gemfibrozil with the statin to produce higher concentrations of the statin in the

	Therapeutic goals and recommendations
Abdominal obesity	Goal: 10% weight loss first year, thereafter continued weight loss or maintain weight Recommendation: caloric restriction; regular exercise; behaviour modification
Physical inactivity	Goal: regular moderate-intensity physical activity Recommendation: 30–60 min moderate-intensity exercise daily
Atherogenic diet	Goals: reduced intakes of saturated fats, trans fats and cholesterol Recommendations: saturated fat ,7% of total calories; reduce trans fat; dietary cholesterol <200 mg daily; total fat 25–35% of total calories
Cigarette smoking	Goal and recommendation: complete smoking cessation
LDL-C	Goals: High-risk patients*—LDL cholesterol <1 g/L (2·6 mmol/L) Therapeutic option—LDL cholesterol <0·7 g/l (1·8 mmol/L) Moderately high-risk patients†—LDL cholesterol <1·3 g/L (3·4 mmol/L) Therapeutic option—LDL cholesterol <1 g/L (2·6 mmol/L) Moderate-risk patients‡—LDL cholesterol <1·3 g/L (3·4 mmol/L) Recommendations: high-risk patients—lifestyle therapies§ and LDL-cholesterol lowering drug to achieve recommended goal Moderately high-risk patients—lifestyle therapies; add LDL-cholesterol lowering drug if necessary to achieve recommended goal when baseline LDL cholesterol ≥1·3 g/L (3·4 mmol/L) Moderate risk patients—lifestyle therapies; add LDL-cholesterol lowering drug if necessary to achieve recommended goal when baseline LDL cholesterol ≥1·6 g/L (4·1 mmol/L)
High triglyceride or low HDL-C	Goal: insufficient data to establish goal Recommendation: High-risk patients—consider adding fibrate (preferably fenofibrate) or nicotinic acid to LDL-lowering drug therapy
Elevated blood pressure	Goals: blood pressure <135/<85 mm Hg. For diabetes or chronic kidney disease: blood pressure <130/80 mm Hg Recommendation: lifestyle therapies; add antihypertensive drug(s) when necessary to achieve goals of therapy
Elevated glucose	Goal: maintenance or reduction in fasting glucose if >1 g/L (5·5 mmol/L). Haemoglobin A1C <7·0% for diabetes Recommendation: lifestyle therapies; add hypoglycaemic agents as necessary to achieve goal fasting glucose or haemoglobin A1C
Prothrombotic state	Goal: reduction of prothrombotic state Recommendation: High-risk patients—initiate low-dose aspirin therapy; consider clopidogrel if aspirin is contraindicated Moderately high-risk patients—consider low-dose aspirin therapy
Proinflammatory state	Recommendations: no specific therapies

*High-risk patients: those with established atherosclerotic cardiovascular disease, diabetes, or 10-year risk for coronary heart disease >20%. ‡Moderately high-risk patients: those with 10-year risk for coronary heart disease 10–20%. ‡Moderate risk patients: those with metabolic syndrome but 10-year risk for coronary heart disease <10%. §Lifestyle therapies include weight reduction, regular exercise, and antiatherogenic diet.

Table 2: Targets, goals, and recommendations for clinical management of metabolic syndrome

blood.[145] Recent studies suggest that fenofibrate combined with a statin is less likely to cause myopathy than is gemfibrozil.[146] The combination of a statin with a low dose of nicotinic acid is an alternative to a statin plus fibrate.[147] Although low doses of nicotinic acid can be tolerated by most patients with the metabolic syndrome, some patients might find it difficult to take on a long-term basis. For patients with diabetes, nicotinic acid can raise glucose concentrations, but as long as the dose is kept relatively low, it does not produce substantial deterioration of glycaemic control in most patients.[148]

Blood pressure
Mild elevations of blood pressure can often be controlled with lifestyle changes, but if hypertension persists despite such therapies, antihypertensive drugs are usually required.[149] The benefits of blood pressure reduction for reducing major cardiovascular disease has been well established through many clinical trials,[149] including those in patients with type 2 diabetes.[150] Some investigators believe that angiotensin-converting enzyme (ACE) inhibitors or angiotension receptor blockers are better first-line therapy for metabolic syndrome patients, especially when type 2 diabetes is present,[151] but the issue of the most effective drug has not been entirely resolved.[152]

Insulin resistance and hyperglycaemia
Lifestyle intervention can reduce the risk for conversion of IFG/IGT to type 2 diabetes.[133,134,138] Preliminary reports indicate that metformin or thiazolidinediones also reduce risk for type 2 diabetes in people with IFG or IGT.[133,153] On the other hand, no clinical trial evidence indicates that these drugs will reduce risk for cardiovascular disease events in patients with the metabolic syndrome. Currently, metformin or thiazolidinediones are not recommended solely for the prevention of diabetes. The cost-effectiveness of this approach has not been established.

When patients with type 2 diabetes concomitantly exhibit other features of the metabolic syndrome they are at particularly high risk for cardiovascular disease. Clinical trials show that high priority should be given to treatment of dyslipidaemia[154] and hypertension.[149] Glycaemic control to a haemoglobin A1c of less than 7% will reduce microvascular complications and could decrease risk for macrovascular disease as well.[155]

The use of lipid-altering, antihypertensive and hypoglycaemic drugs can modify insulin sensitivity and bodyweight. Metformin and thiazolidinediones improve insulin sensitivity but have discrepant effects on bodyweight: metformin reduces weight whereas thiazolidinediones increase it.[156,157] The increase in weight in patients treated with insulin secretagogues (sulfonylureas and repaglinide or nateglinide) and insulin results mostly from improved glycaemic control and increases in caloric intake as a result of

hypoglycaemia. With the exception of nicotinic acid, lipid-altering drugs do not affect insulin sensitivity or weight, whereas the effect of antihypertensive drugs is more complex. β-adrenergic blockers and thiazide diuretics might decrease insulin sensitivity but less so at low doses, whereas ACE inhibitors and angiotensin II receptor antagonists have variable effects.[151] By uncertain mechanisms, ACE inhibitors and angiotensin II receptor antagonists seem to decrease the incidence of type 2 diabetes.[158]

Prothrombotic state
This risk factor is characterised by elevations of fibrinogen, plasminogen activator inhibitor 1, and possibly other coagulation factors. The only available clinical approach to an increased risk for arterial thrombosis in patients with diabetes is low-dose aspirin or other antiplatelet drugs.[159] These drugs are universally recommended unless contraindicated in patients with established cardiovascular disease. Their efficacy in patients with type 2 diabetes in the absence of cardiovascular disease has not been established through clinical trials, although they are widely recommended. In other people with the metabolic syndrome, aspirin prophylaxis is a therapeutic option when the risk for cardiovascular disease events is judged to be relatively high.[160]

Proinflammatory state
This condition can be identified by elevated cytokines (eg, TNFα and interleukin 6) as well as by elevations in acute phase reactants (C-reactive protein and fibrinogen). An elevated concentration of C-reactive protein is widely thought to be an indicator of a proinflammatory state and to be associated with higher risk for both cardiovascular disease and diabetes.[161] Lifestyle therapies, especially weight reduction, will reduce concentrations of this cytokine and thus can mitigate an underlying inflammatory state.[162] No specific anti-inflammatory drugs are available to treat the proinflammatory state. However, several drugs used to treat other metabolic risk factors—statins, fibrates, and thiazolidinediones—have been reported to reduce concentrations of C-reactive proteins.[163,164] The drugs, however, cannot be recommended specifically to reduce a proinflammatory state independent of other risk factors.

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