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A changing paradigm for prevention of cardiovascular disease: emergence of the metabolic syndrome as a multiplex risk factor

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The traditional major risk factors for cardiovascular disease (CVD) are cigarette smoking, hypertension, elevated serum cholesterol, and hyperglycaemia (diabetes). The majority of patients with CVD have multiple risk factors. In recent years a common pattern of multiple risk factors has emerged. This is the metabolic syndrome, which is driven largely by obesity. The metabolic syndrome is particularly important because it is a multiplex risk factor for both CVD and Type 2 diabetes. Although obesity is the primary cause of the metabolic syndrome, there are other endogenous and exogenous factors.

Chronic cardiovascular disease (CVD) is insidious and multifactorial in aetiology. It is the leading killer in developed countries and is emerging as such throughout the world. How might we explain this rising prevalence of cardiovascular disease? Is it due to better prevention and treatment of infectious disease—to healthier living conditions? To urbanization? To more sedentary lifestyles? To changing types of food consumed? Or can it be explained by living longer in general? Presumably all of these factors are involved.[1] Regardless, the growing risk for CVD creates a new type of public health and clinical challenge.

The most common form of CVD is atherosclerotic cardiovascular disease (ASCVD). Fifty years of research has uncovered many of the causes of ASCVD. These causes are named risk factors. We now know that modification of several risk factors will reduce the risk for ASCVD. The critical challenge thus becomes: how can we favourably modify risk factors at both clinical and public health levels and in many countries?

Even if lifestyle intervention in populations at risk is theoretically the most effective, the chronicity of the problem makes it difficult to place prevention on political agendas that give priority on seemingly more urgent issues. But failure to incorporate prevention measures in the health-care agenda will ultimately add substantially to the already enormous health-care costs that are plaguing national budgets. These considerations call for analysis of resources and priority. To examine these, it may be valuable to briefly examine each of the major risk factors and make an assessment of where we stand.

Cigarette smoking

Smoking is a major preventable cause for ASCVD. According to the World Health Organization, about one-third of all adult men smoke.[2,3] In the Western Pacific Region, approximately two-thirds of men smoke. Smoking rates in women are increasing rapidly as well. Currently one in 10 of all adults die from smoking-caused illnesses, and it is projected that by 2030 one in six will succumb to smoking-related diseases. The smoking problem is largely one of public health. Where smoking rates have declined, there have been intense educational programmes and also legislative changes to discourage the habit. Where smoking rates are increasing, similar measures are needed.

Hypertension

Elevations of blood pressure further add to the rising prevalence of ASCVD worldwide. Blood pressure tends

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to rise with age; and as the population ages, the prevalence of hypertension increases in parallel. Worldwide at least one-fourth of adults have hypertension. Prevalence is highest in the elderly population.[4] The public health approach has had little impact on hypertension prevalence. Most of the problem is handled clinically. Unfortunately, only about half of treated individuals are adequately controlled. Why is this so? Some of the factors include the expense of medication, the need for multiple medications, the asymptomatic manifestation of the condition, lack of adequate follow-up, and in many regions, overall deficiency of health-care resources.

Elevated serum cholesterol

A third major risk factor is elevated serum cholesterol. This elevation signifies an increase in apolipoprotein B (apo B)-containing lipoproteins. Levels of serum cholesterol vary widely throughout the world, and they relate in no small part to dietary intakes.[5] Populations that have relatively high intakes of saturated fats and cholesterol exhibit higher cholesterol levels than those in which these intakes are low. In the past, most efforts to control high cholesterol levels rested on the public health approach. Indeed in several countries this effort met with considerable success.[6] In recent years, however, with the advent of potent drugs for cholesterol lowering, drug therapy has been used increasingly in clinical practice. Drugs are prescribed mostly in the middle-aged and older population; where this has occurred on a large scale, a definite reduction in average cholesterol levels in this portion of the population has occurred.[7]

Hyperglycaemia

An elevation of plasma glucose (diabetes) is commonly associated with ASCVD. Diabetes is increasing at an alarming rate. According to the International Diabetes Federation's diabetes atlas (http://www.eatlas.idf.org/), there are approximately 246 million people with diabetes in the adult population. The total was 194 million in 2003. Type 2 diabetes makes up about 85–95% of all cases of diabetes in developed countries and an even higher proportion in developing countries. It is commonly stated that hyperglycaemia (diabetes) is another major risk factor for ASCVD. There is no doubt that patients with diabetes, particularly, those with type 2 diabetes, are at increased risk for ASCVD. Nonetheless the question must be raised whether hyperglycaemia *per se* can account for the increase in risk. Although considerable evidence suggests that hyperglycaemia is atherogenic,[8] type 2 diabetes is commonly associated with other ASCVD risk factors. Thus, it remains uncertain how much of the increase in risk can be attributed to hyperglycaemia as such and how much is the result of associated risk factors.

Metabolic syndrome

This condition represents a clustering of risk factors of endogenous origin (metabolic risk factors).[9,10] An important discovery was that metabolic risk factors commonly cluster. When this occurs, risk for ASCVD is compounded. Thus the metabolic syndrome can be called a multiplex risk factor for ASCVD. Depending on the country, between 15 and 30% of the adult population exhibits the metabolic syndrome. The syndrome is accompanied by an approximately twofold increase in risk for ASCVD. In addition, persons with the metabolic syndrome who do not have diabetes have an approximate fivefold increase for developing this condition.[9] And about 85% of individuals with type 2 diabetes have the metabolic syndrome.[11]

Do established risk factors explain all of CVD?

Considerable controversy exists about how much the established risk factors discussed earlier contribute to the ASCVD. Estimates vary between 50 and 90%. This difference is largely due to how the risk-factor contribution is viewed. For example, we can ask how much ASCVD would be reduced if all risk factors were to be eliminated from the population. Epidemiological studies suggest that if cholesterol and blood pressure levels were optimal and if smoking and diabetes were nonexistent, ASCVD rates up to advanced age would be reduced by about 90%.[12] But assuming a population in which risk factors are common, what is their contribution to risk? These same studies suggest that less than 50% of variation in risk can be explained by established risk factors. Thus, many other factors must come into play on a base of established risk factors to modify the extent and time of onset of ASCVD. Among the former, the metabolic syndrome appears to be of increasing importance.

Understanding atherogenesis

To develop a rational strategy for both public health and clinical prevention of ASCVD, it is necessary to understand the pathogenic processes whereby the disease develops. Priority for prevention can be matched with longitudinal development of the disease. Above all, atherosclerosis is a chronic inflammatory process. The primary factor initiating the development of atherosclerosis appears to be the presence of excess lipoproteins containing apo B.[13,14] Most apo B in circulation is carried in low-density lipoproteins (LDL); but in some persons, a substantial portion of apo B is transported in triglyceride-rich lipoproteins (TGRLP). Both LDL and TGRLP almost certainly are atherogenic lipoproteins.[13] In the absence of some elevation of these lipoproteins, ASCVD is rare.[14,15] The higher their level, the more rapidly will atherosclerosis advance. The strong relationship between serum lipoprotein concentrations and risk for ASCVD has been confirmed by many epidemiological studies.[16]

In the presence of elevated apo B-containing lipoproteins, other factors can accelerate atherogenesis.[17] These exacerbating risk factors include cigarette smoking along with several factors of endogenous (metabolic) origin. Among the latter are elevations in blood pressure and glucose, reduced concentrations of high-density lipoproteins (HDL), and prothrombotic and proinflammatory states. These endogenous risk factors often cluster in an individual, producing the 'metabolic syndrome'.[9,10]

When arterial lesions have reached an advanced stage, atherosclerotic plaques can become unstable; at this point they are prone to rupture. When rupture occurs, the subintimal region is exposed to the blood stream, initiating thrombosis. The latter produces acute CVD syndromes, e.g. myocardial infarction and stroke. A prothromobotic state, common in the metabolic syndrome, can exacerbate propagation of thrombi, worsening the clinical event.[9] Some plaques do not rupture but progress to advanced occlusion. This produces stable angina pectoris or peripheral arterial disease. Advanced obstruction may require revascularization.

Risk factors and atherosclerotic cardiovascular disease

Is some elevation of serum cholesterol necessary for atherogenesis?

The relationship between several risk factors (smoking, hypertension, and diabetes) and ASCVD was early accepted; but a relation with cholesterol was widely doubted. Cholesterol skepticism persisted despite several types of evidence indicating an important role of cholesterol — animal models, genetic forms of hypercholesterolaemia, and prospective human studies.[13] Only after controlled clinical trials showed that serum cholesterol lowering substantially reduces risk for ASCVD was the 'cholesterol hypothesis' accepted.[13,18] Now after all these years it appears that cholesterol elevations in the form of atherogenic lipoproteins are required for atherosclerosis and ASCVD. In populations where serum cholesterol levels are very low the rates of clinical ASCVD are correspondingly low.[14,16] Importantly, a recent study[15] demonstrated that individuals who have a genetic form of very low cholesterol levels manifest virtually no ASCVD throughout life. Indeed, in populations that carry very low cholesterol concentrations, other risk factors—cigarette smoking, hypertension, and diabetes—seemingly elicit little or no ASCVD.[14,15] These other conditions can produce other adverse cardiovascular and non-cardiovascular effects, but ASCVD remains low.

How do lipoproteins initiate atherogenesis?

Atherogenic lipoproteins are proinflammatory agents that can filter into the arterial subendothelial space. The higher their serum level, the greater the amount entering the arterial wall. There, some lipoproteins escape harmlessly back into the circulation. Another portion, however, remains entrapped in the extracellular matrix.[19] The latter falls victim to attack by bioactive molecules and various enzymes.[20] These modify lipoproteins and convert them into proinflammatory agents. These agents induce inflammation in several ways, e.g. endothelial dysfunction and chemoattraction of monocytes to form macrophages. Macrophages further engulf modified lipoproteins, producing foam cells. These excess lipids in turn kill macrophages then build up extracellularly.

Role of other risk factors in atherogenesis.

All of the metabolic syndrome risk factors exacerbate inflammation once it has been started by atherogenic lipoproteins. In the past decades, many pathways have been identified whereby each of the metabolic risk factors—low HDL,[21–29] elevated blood pressure,[30–37] hyperglycaemia,[38–49] abnormal thrombogenic factors,[49–53] and high levels of cytokines[9]—accentuate inflammatory processes and promote atherogenesis (*Table 1*).

Metabolic syndrome: a multiplex CVD risk factor

The essence of the metabolic syndrome: clustering of metabolic risk factors for ASCVD

The concept of the metabolic syndrome grew out of the recognition that endogenous risk factors cluster in individuals.[9,10] These risk components consist of atherogenic dyslipidaemia, vascular dysfunction, elevated glucose, a prothrombotic state, and a proinflammatory state. Each of the major components contains several subcomponents (*Table 2*). Moreover, other metabolic disorders commonly accompany the metabolic syndrome, e.g. type 2 diabetes, fatty liver, cholesterol gallstones, obstructive sleep apnoea, and polycystic ovary disease. Risk factor clustering accounts for an increasing proportion of all ASCVD risk worldwide. The presence of the metabolic syndrome approximately doubles risk of ASCVD over the short term (5–10 years).[9] Over a lifetime, the risk differential will be even greater.

Is prediabetes a risk factor for ASCVD?

Prediabetes represents a borderline elevation of glucose levels, either during fasting or after a meal. Its presence clearly signifies increased risk for type 2 diabetes. It is commonly called a factor for ASCVD;[54] yet, the majority of patients with prediabetes carry several other metabolic risk factors that likely account for a higher risk.[55] The overlap between metabolic syndrome and prediabetes creates considerable confusion. In fact, the metabolic syndrome without prediabetes is a risk factor for diabetes.[56] Thus, the metabolic syndrome itself is a 'prediabetic' state. Whether a borderline elevation of glucose, independent of other components of the

Table 1 Reported mechanisms for promotion of atherogenesis by metabolic risk factors

Reduced HDL	Functions of HDL (impaired with reduced HDL) Reverse cholesterol transport Protects against endothelial dysfunction Inhibition of expression of endothelial cell adhesion molecules Anti-inflammatory Anti-thrombotic Stimulation of prostaglandin synthesis Inhibition of platelet activation
Elevated blood pressure	Endothelial dysfunction Increased: PDGF-beta and PDGF-beta receptors on vascular smooth muscle cells PKC-independent herbimycin A-sensitive activation Class A scavenger receptor expression on monocytes/macrophages Mechanotransduction in vascular smooth muscle cells Activation of arterial JNK/SAPK and ERK Activation of arterial MAP kinase
Elevated plasma glucose	Increased entrapment of LDL Collagen cross-linking Glycation of extracellular matrix Increased modification of LDL Oxidation of LDL Glycation of LDL Increased prothrombotic state Platelet dysfunction Endothelial dysfunction Activation of macrophages Increased AGE receptors Enhanced cytokine release Increased smooth muscle proliferation Modified insulin signalling in smooth muscle cells
Prothrombotic state	Elevations of: Plasminogen activator inhibitor-1 [PAI-1] Fibrinogen Factor VIIa Prothrombin fragment 1+2 [F1+2] Soluble CD40 ligand [sCD40L]
Proinflammatory state (increased circulating cytokines)	Activation of multiple inflammatory pathways in the arterial wall

metabolic syndrome, is directly atherogenic has not been resolved.

Table 2 Major components and subcomponents of metabolic risk factors of the metabolic syndrome

Major components	Subcomponents
Atherogenic dyslipidemia	Lipoprotein elevations Triglyceride-rich lipoprotein (TGRLP) Apolipoprotein B-containing lipoproteins Small LDL particles Reduction of high density lipoproteins (HDL)
Elevated blood pressure	Endothelial dysfunction Microvascular dysfunction
Elevated plasma glucose	Impaired fasting glucose Impaired glucose tolerance Clinical hyperglycemia (type 2 diabetes)
Prothrombotic state	Elevations of: Plasminogen activator inhibitor-1 [PAI-1] Fibrinogen Factor VIIa Prothrombin fragment 1+2 [F1+2] Soluble CD40 ligand [sCD40L]
Proinflammatory state	Elevations of inflammatory cytokines Elevations of acute phase reactants C-reactive protein (CRP) Fibrinogen Serum amyloid-A (SAA) Markers of inflammation CD40 ligand (sCD40L)
Associated conditions	Fatty liver Cholesterol gallstones Obstructive sleep apnoea Polycystic ovarian disease

Can patients with type 2 diabetes also have the metabolic syndrome?

The majority of individuals with type 2 diabetes have multiple ASCVD risk factors.[55] Some investigators, however, contend that type 2 diabetes is already an established disease and that to extend the metabolic syndrome into diabetes is confusing.[57] But such a conclusion is not logical. For example, hypercholesterolaemia and hypertension are risk factors for major cardiovascular events whether ASCVD is present or not. If so, why cannot the metabolic syndrome, a multiplex risk factor for ASCVD, still be present in patients with type 2 diabetes? In truth, individuals with diabetes plus the metabolic syndrome stand at particularly high risk for ASCVD.[58] This greater risk is due not only to a clustering of risk factors but to the likely atherogenicity of marked hyperglycaemia; several mechanisms are proposed whereby diabetic-level hyperglycaemia promotes atherosclerosis[38–49] (*Table 1*).

Pathogenesis of the metabolic syndrome

What causes the metabolic syndrome?

The metabolic syndrome is multifactorial; therefore it is not surprising that controversy exists about its

Table 3 Pathogenesis of the metabolic syndrome

Exogenous lifestyle factors	Endogenous susceptibility	
	Generalized susceptibility	Regional susceptibilities
Obesity	Dysregulation of master metabolic pathways	Pancreatic beta-cell defects
Physical inactivity	Adipose tissue disorders	Arterial stiffening
Atherogenic diet	Ethnic and racial susceptibility	Disorders in lipoprotein pathways
	Endocrine dysfunction	Coagulation and fibrinolytic dysregulation
	Metabolic ageing	

pathogenesis.[59] A simplified schema of pathogenesis is proposed in *Table 3*. According to this scheme, exogenous lifestyle factors, particularly obesity, represent the primary driving force behind development of the syndrome. Epidemiological data support the importance of these factors. But why is it that many sedentary, obese people do not develop the metabolic syndrome? Seemingly a second level of causation, here called endogenous susceptibility, must contribute as well. Factors contributing to endogenous susceptibility are an inherent insulin resistance, dysfunctional adipose tissue, endocrine dysfunction, metabolic ageing and other genetic predispositions.[59] Finally, additional factors linking the individual metabolic risk factors modify the expression of the syndrome. Examples include pancreatic beta-cell dysfunction that accentuates hyperglycaemia, arterial stiffening that exacerbates hypertension, and disorders affecting specific metabolic risk factors, e.g. lipoprotein disorders and dysfunction of the coagulation and fibrinolytic systems. The pathogenesis of metabolic syndrome can serve as a guide to therapy. Essentially, therapy can be directed at the three levels of pathogenesis and in the following order: treatment of exogenous lifestyle factors, treatment of endogenous susceptibility, and treatment of individual risk factors.

Is the metabolic syndrome a 'syndrome'?

One criticism of the metabolic syndrome as a concept is that its aetiology is too complex for it to be considered a single entity.[57] Certainly the syndrome results from the combination of multiple causes. The idea that it has a single pathogenesis—such as insulin resistance—is no longer tenable. But are not many chronic diseases, not to mention the individual risk factors, multifactorial in origin? Indeed each individual metabolic risk factor has both exogenous and endogenous factors in their own causation; causality of multiple risk factors together must be even more complex. Yet risk factor clustering is real; consequently, it is reasonable to call the clustering of metabolic risk factors a syndrome.[60]

How important are lifestyle factors in the syndrome?

Both exogenous lifestyle factors and endogenous susceptibility factors contribute to risk factor clustering. Nonetheless their relative contributions seemingly vary among individuals and populations.[61] Some populations, such as South and Southeast Asians, manifest particularly enhanced susceptibility to the metabolic syndrome and diabetes.[61] Even so, without excess body fat metabolic abnormalities do not blossom. In other regions, like North America and Europe, obesity is clearly the major force driving development of the syndrome for most individuals.[62]

How important is upper body obesity (abdominal obesity)?

Two general types of obesity are recognized: predominant lower body (gluteofemoral) obesity and upper body (truncal) obesity. The latter is often called 'abdominal obesity' because upper body fat accumulation is more clinically evident in the abdomen. Also, waist circumference is a good surrogate for total truncal fat.[63] Many reports indicate that predominant abdominal obesity is more commonly associated with the metabolic syndrome than is gluteofemoral obesity.[64] Why then does abdominal obesity have the greater impact? One view holds that fat deposited in the upper body is metabolically different from lower body fat. Another is that abdominal fat is a marker for excess visceral (intraperitoneal) fat that in turn is uniquely related to the development of the syndrome.[65] A third concept is that abdominal obesity reflects a relative deficiency of total body adipose tissue, reducing the total storage capacity for fat. If the latter holds, there could be a tendency for accumulation of fat in other tissues, such as muscle and liver, which could drive development of the metabolic syndrome. Which of these account for the predominant role of abdominal obesity has not been resolved.

Is lower body fat protective?

If gluteofemoral adipose tissue were to be deficient, then a nutrient overload could exceed the total storage capacity of adipose tissue. As mentioned before, this could result in ectopic fat accumulation in muscle and liver — predisposing to the metabolic syndrome. This theory is supported by observations that accumulation of fat in the gluteofemoral region appears to be protective against the metabolic syndrome.[63,66] This 'adipose-tissue deficiency' theory of predominant abdominal obesity, although attractive, remains to be proven.

Is 'visceral obesity' the real culprit?

Many investigators evoke the 'visceral-obesity theory' for the pathogenesis of the metabolic syndrome.[63–65] Two

mechanisms are suggested. First, visceral adipose tissue releases its products, particularly, non-esterified fatty acids (NEFA), directly into the portal circulation; these flood the liver and accumulate therein. This stimulates increased production of TGRLP (leading to atherogenic dyslipidaemia) and enhances glyconeogenesis (leading to hyperglycaemia). Second, visceral adipose tissue may be metabolically unique, causing excessive release of a variety of adipokines into the circulation, which promote development of the metabolic syndrome.

Not all investigators hold to the visceral obesity theory. Some propose that abdominal subcutaneous adipose tissue carries as much or more pathogenic significance as visceral obesity.[63,67,68] Support for the importance of subcutaneous adipose tissue comes from the fact that its absolute mass is considerably greater than that of visceral fat. Therefore, subcutaneous adipose tissue releases even more NEFA and various adipokines into the circulation than does the visceral bed. Also, several metabolic studies indicate that truncal subcutaneous adipose tissue correlates more strongly with insulin resistance than does visceral obesity,[69] but visceral adipose tissue appears to be more strongly related to dyslipidaemia.[63] In other words, different adipose tissue beds may affect the various risk factors differently.

Finally, if the adipose-tissue deficiency theory of the metabolic syndrome is valid, visceral obesity could be a marker for an adipose-tissue deficiency; in this case, an adipose-tissue deficiency and not visceral fat *per se* could be responsible for ectopic fat accumulation and metabolic risk factors.

Treatment of the metabolic syndrome

Is obesity the prime target of metabolic syndrome treatment?

For several years the metabolic syndrome was thought to be the result of endogenous susceptibility (e.g. insulin resistance).[70,71] But the increasing prevalence worldwide now makes it clear that obesity is the driving force. Thus, more investigators contend that prevention or management of obesity is the primary aim for coping with the growing epidemic of the metabolic syndrome.[1,18] Several reports indicate that weight reduction will reduce all of the cardiovascular risk factors of the syndrome[72] and will delay onset of type 2 diabetes.[73] This creates the challenge of how to institute more effective lifestyle therapies into clinical practice. Of importance is the observation that even moderate weight reduction (e.g. 7–10% of total body weight) will substantially improve all of the metabolic risk factors.[74] This fact makes the challenge of mitigating the metabolic syndrome through lifestyle changes less daunting.

A related question is whether obesity is an appropriate target for drug therapy. The pharmaceutical industry and academia are increasingly focused on identifying appetite-regulating targets in the brain and developing new drugs for these targets. Although at least two anti-obesity drugs are approved for use, they are not widely used in clinical practice. Nonetheless, this is a promising area for drug development. For example, an endocannabinoid receptor inhibitor, rimonabant, has been approved for treatment of obesity in Europe. This drug seemingly has fewer side effects than the other available anti-obesity drugs. Current thinking is that effective weight-loss drugs could become first-line drug therapy for patients with multiple cardiovascular risk factors, e.g. the metabolic syndrome.

Systemic endogenous susceptibility as a potential drug target for the metabolic syndrome

The pharmaceutical industry dreams of developing a drug that will mitigate metabolic susceptibility of the metabolic syndrome. Such a treatment could simultaneously modify all of the risk factors. One goal for research is to identify master metabolic regulators that are potential drug targets, and if modified, would improve multiple risk factors. Candidates for master metabolic regulators are various nuclear receptors[75] [e.g. PPAR gamma[76] and RXR[77]], AMP kinase,[78] ectonucleotide pyrophosphatase phosphodiesterase 1,[79] beta-arrestins,[80] SIRT1,[81] SREBPs,[82] transcriptional coactivator PGC1-alpha,[83] and endocannabinoid receptors.[84] A few promising agents have been identified that can modify metabolic risk factors acting on some of these receptors; but the ideal drug for metabolic susceptibility is far from being developed.

Limiting treatment to individual risk factors: the crisis in polypharmacy

All of the metabolic risk factors—atherogenic dyslipidaemia, elevated blood pressure, elevated plasma glucose, and a prothrombotic state—are potential targets for drug therapy. In patients in whom short-term risk is high, drug therapies may be necessary. But in such cases, multiple drugs often are required. When enough drugs are added, the patients become subject to the adverse effects of polypharmacy.[85] The latter is particularly a problem in patients with type 2 diabetes. Thus, the costs and dangers of polypharmacy are the major drawbacks of treatment of individual risk factors. Although a physician often has no other option, polypharmacy is by no means ideal. At present, early intervention, particularly with lifestyle change, is the only option that will delay the onset of advanced forms of metabolic syndrome and a high-risk status; but more targeted drug therapy directed against general metabolic susceptibility could eventually become a preferable treatment of the syndrome.

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