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Review Article

A MAJOR HEALTH HAZARD: METABOLIC SYNDROME

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ABSTRACTS

The constellation of dyslipidemia (hypertriglyceridemia and low levels of high-density lipoprotein cholesterol), elevated blood pressure, impaired glucose tolerance, and central obesity is identified now as metabolic syndrome, also called syndrome X. Soon, metabolic syndrome will overtake cigarette smoking as the number one risk factor for heart disease among the U.S. population. The National Cholesterol Education Program–Adult Treatment Panel III has identified metabolic syndrome as an indication for vigorous lifestyle intervention. Effective interventions include diet, exercise, and judicious use of pharmacologic agents to address specific risk factors. Weight loss significantly improves all aspects of metabolic syndrome. Increasing physical activity and decreasing caloric intake by reducing portion sizes will improve metabolic syndrome abnormalities, even in the absence of weight loss. Specific dietary changes that are appropriate for addressing different aspects of the syndrome include reducing saturated fat intake to lower insulin resistance, reducing sodium intake to lower blood pressure, and reducing high-glycemic–index carbohydrate intake to lower triglyceride levels. A diet that includes more fruits, vegetables, whole grains, monounsaturated fats, and low-fat dairy products will benefit most patients with metabolic syndrome. Family physicians can be more effective in helping patients to change their lifestyle behaviors by assessing each patient for the presence of specific risk factors, clearly communicating these risk factors to patients, identifying appropriate interventions to address specific risks, and assisting patients in identifying barriers to behavior change.

Keywords: Health, Metabolic syndrome

INTRODUCTION

Cardiovascular disease (CVD) refers to the class of diseases that involve the heart and/or blood vessels (arteries and veins). While the term technically refers to any disease that affects the cardiovascular system, it is usually used to refer to those related to atherosclerosis (arterial disease). Diseases of the heart alone caused 30% of all deaths, with other diseases of the cardiovascular system causing substantial further death and disability. It is the number 1 cause of death and disability in the United States and most European countries.

There are many risk factors which associate with (but are not all causes of) various forms of cardiovascular disease. These include the following:

- Non-modifiable Risk Factors

O Age
O Gender, men under age 64 are much more likely to die of coronary heart disease than women, although the gender difference declines with age. (The gender difference is less pronounced in blacks than in whites, but it is still significant).
O Genetic factors/Family history of cardiovascular disease.

- Modifiable Risk Factors

O Tobacco smoking .
O Insulin Resistance & Diabetes Mellitus .
O Hypercholesterolemia (Elevated Cholesterol Levels) and Abnormal Lipoprotein Particle Profile (Cholesterol Subtypes).
O Obesity, especially central or male-type obesity; apart from being linked to diabetes, this form of obesity independently increases cardiovascular risk, presumedly by inducing an inflammatory and procoagulant state.
O High blood pressure .
O Elevated heart rate.
O Physical inactivity/Sedentary lifestyle
O Absence of key nutritional elements, such as omega-3 fatty acids and polyphenol antioxidants .
O Exposure to high levels of environmental noise
O Stress
O Depression [1].

Many of above risk factors often cluster together, and commonly refered as metabolic syndrome (MetS). Demographic changes combined with the increasing prevalence of obesity and physical inactivity are generally assumed to be the driving forces, but as discussed above, urbanization is one of the most important factors explaining the increasing problem with the metabolic syndrome in a global perspective[2].

The metabolic syndrome has received increased attention in the past few years. This cluster of the most dangerous heart attack risk factors includes: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure.

According to International Diabetes Federation (IDF)

- A quarter of the world's adults have metabolic syndrome.
- People with metabolic syndrome are twice as likely to die from, and three times as likely to have a heart attack or stroke compared with people without the syndrome.
- People with metabolic syndrome have a five-fold greater risk of developing type 2 diabetes.
- Up to 80% of the 200 million people with diabetes globally will die of cardiovascular disease.
- This puts metabolic syndrome and diabetes way ahead of HIV/AIDS in morbidity and mortality terms yet the problem is not as well recognized[3].

The main reason why the metabolic syndrome is attracting scientific and commercial interest is that the factors defining the syndrome are all factors associated with an increased morbidity and mortality in general and from CVD in particular [2].

Calcium channel blockers have been long back introduced in clinical practice and are being used effectively with promising results. In addition to their antihypertensive efficacy, they are reported to possess antioxidant activity[4].

The National Cholesterol Education Program's Adult Treatment Panel III report (NCEP ATP III) identified the metabolic syndrome as a multiplex risk factor for cardiovascular disease (CVD) that is deserving of more clinical attention.

In 1988, Reaven noted that several risk factors like Dyslipidemia, Hypertension and Hyperglycemia, commonly cluster together. This clustering he called Syndrome X, and he recognized it as a multiplex

risk factor for CVD. Reaven and subsequently others postulated that insulin resistance underlies Syndrome X, hence the commonly used term insulin resistance syndrome. Other researchers use the term metabolic syndrome for this clustering of metabolic risk factors[5].

Although the modern era of what we now call the 'metabolic syndrome' or the 'insulin resistance syndrome' seems to have started less than two decades ago with the description of syndrome X by G.M. Reaven in the late 1980s, the history of this syndrome is much longer. In particular, a considerable number of scientists, starting as early as almost 90 years ago, have described the very common coexistence of the various components of the syndrome, including hypertension, and some of them gave several names to this clustering[6].

History

The term "metabolic syndrome" dates back to at least the late 1950s, but came into common usage in the late 1970s to describe various associations of risk factors with diabetes that had been noted as early as the 1920s.

- The Marseilles physician Dr. Jean Vague, in 1947, observed that upper body obesity appeared to predispose to diabetes, atherosclerosis, gout, and calculi.
- Avogaro, Crepaldi and co-workers described six moderately obese patients with diabetes, hypercholesterolemia, and marked hypertriglyceridemia all of which improved when the patients were put on a hypocaloric, low carbohydrate diet.
- In 1977, Haller used the term "metabolic syndrome" for associations of obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia and Hepatic steatosis when describing the additive effects of risk factors on atherosclerosis.
- The same year, Singer used the term for associations of obesity, gout, diabetes mellitus, and hypertension with hyperlipoprotenemia.
- In 1977 and 1978, Dr. Gerald B. Phillips developed the concept that risk factors for myocardial infarction concur to form a "constellation of abnormalities" (i.e., glucose intolerance, hyperinsulinemia, hyperlipidemia [hypercholesterolemia and hypertriglyceridemia] and hypertension) that is associated not only with heart disease, but also with aging, obesity and other clinical states. He suggested there must be an underlying linking factor, the identification of which could lead to the prevention of cardiovascular disease; he hypothesized that this factor was sex hormones.
- In 1988, in his Banting lecture, Gerald M. Reaven proposed insulin resistance as the underlying factor and named the constellation of abnormalities Syndrome X. Reaven did not include abdominal obesity, which has also been hypothesized as the underlying factor, as part of the condition.

The terms "Metabolic Syndrome," "Insulin Resistance Syndrome "and" Syndrome X" are now used specifically to define a constellation of abnormalities that is associated with increased risk for the development of type 2 diabetes and atherosclerotic vascular disease (e.g., heart disease and stroke)[7].

Definition and Diagnosis

The World Health Organization (WHO) was the first to publish an internationally accepted definition for metabolic syndrome in 1998, but the criteria that have received the most widespread acceptance and use are those proposed as a part of ATP3 (the third report of the National Cholesterol Education Research Program (NCEP) experts Adult Treatment Panel (ATP) on detection, evaluation and treatment of high blood cholesterol in adults[8].

WHO criteria

WHO criteria viewed insulin resistance as a required component for diagnosis of metabolic syndrome. A potential disadvantage of the WHO criteria is that special testing of glucose status beyond routine clinical assessment may be necessary to diagnose metabolic syndrome.

Table 1: WHO criteria for diagnosis of metabolic syndrome [5,19,33].

Insulin Resistance, Identified By 1 of the Following:
• Type 2 diabetes
• Impaired fasting glucose
• Impaired glucose tolerance
• Or for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions
Plus any 2 of the following:
• Antihypertensive medication and/or high blood pressure (≥ 140 mm Hg systolic or ≥90 mm Hg diastolic)
• Plasma triglycerides ≥150 mg/dL (≥1.7 mmol/L)
• HDL cholesterol <35 mg/dL (<0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) in women
• Body mass index (BMI) >30 kg/m^2 and/or waist:hip ratio >0.9 in men, >0.85 in women
• Urinary albumin excretion rate ≥20 µg/min or albumin:creatinine ratio ≥30 mg/g

National Cholesterol Education Program

ATP III criteria:

Criteria of ATP III (Adult Treatment Panel III) are shown in Table 2. When 3 of 5 of the listed characteristics are present, a diagnosis of metabolic syndrome can be made. The primary clinical outcome of metabolic syndrome was identified as coronary heart disease (CHD) / CVD. Abdominal obesity, recognized by increased waist circumference, is the first criterion listed. Its inclusion reflects the priority given to abdominal obesity as a contributor to metabolic syndrome. Also listed are raised triglycerides, reduced high-density lipoprotein-cholesterol (HDL-C), elevated blood pressure, and raised plasma glucose. Cut points for several of these are less stringent than usually required to identify a categorical risk factor, because multiple marginal risk factors can impart significantly increased risk for CVD. Explicit demonstration of insulin resistance is not required for diagnosis; however, most persons meeting ATP III criteria will be insulin resistant. Finally, the presence of type 2 diabetes does not exclude a diagnosis of metabolic syndrome[5,19].

Table 2: ATP III clinical identification of the metabolic syndrome[5,19]

Risk Factor	Defining Level
Abdominal obesity, given as waist circumference	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/ dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

EGIR criteria

Following the publication of the WHO definition in 1999, the EGIR (European Group for the Study of Insulin Resistance) proposed a modified version to be used in non-diabetic subjects only, which is simpler to use in epidemiological studies since it does not require a euglycaemic clamp to measure insulin sensitivity (Table 3).EGIR proposed the use of fasting insulin levels to estimate insulin resistance and impaired fasting glucose (IFG) as a substitute for IGT. It also had slightly modified cut-points for hypertension, triglycerides (TGs), highdensity lipoprotein (HDL) cholesterol and altered measures and cut-points for central obesity based on waist circumference[19].

Table 3: EGIR definitions for metabolic syndrome[19,34].

Risk Factor	Defining Level
Central obesity, given as waist circumference	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥2.0mmol/L
HDL cholesterol	<1.0 mmol/dL(39mg/dl)
Blood pressure	≥140/≥90 mm Hg
Fasting glucose	≥6.1mmol/L mg/dL

Components of Metabolic Syndrome

ATP III identified 6 components of the metabolic syndrome that relate to CVD:

- Abdominal obesity.
- Atherogenic dyslipidemia.
- Raised blood pressure.
- Insulin resistance ± glucose intolerance.
- Proinflammatory state.
- Prothrombotic state[5,35].

Abdominal obesity

Abdominal obesity is the form of obesity most strongly associated with the metabolic syndrome. It presents clinically as increased waist circumference. Obesity is a common feature of metabolic syndrome. Each 5% increase in weight at age 20 is associated with a nearly 200% greater risk of full-blown metabolic syndrome by middle age. The strong association of obesity with other components of metabolic syndrome makes it the major risk-defining factor of metabolic syndrome[5]

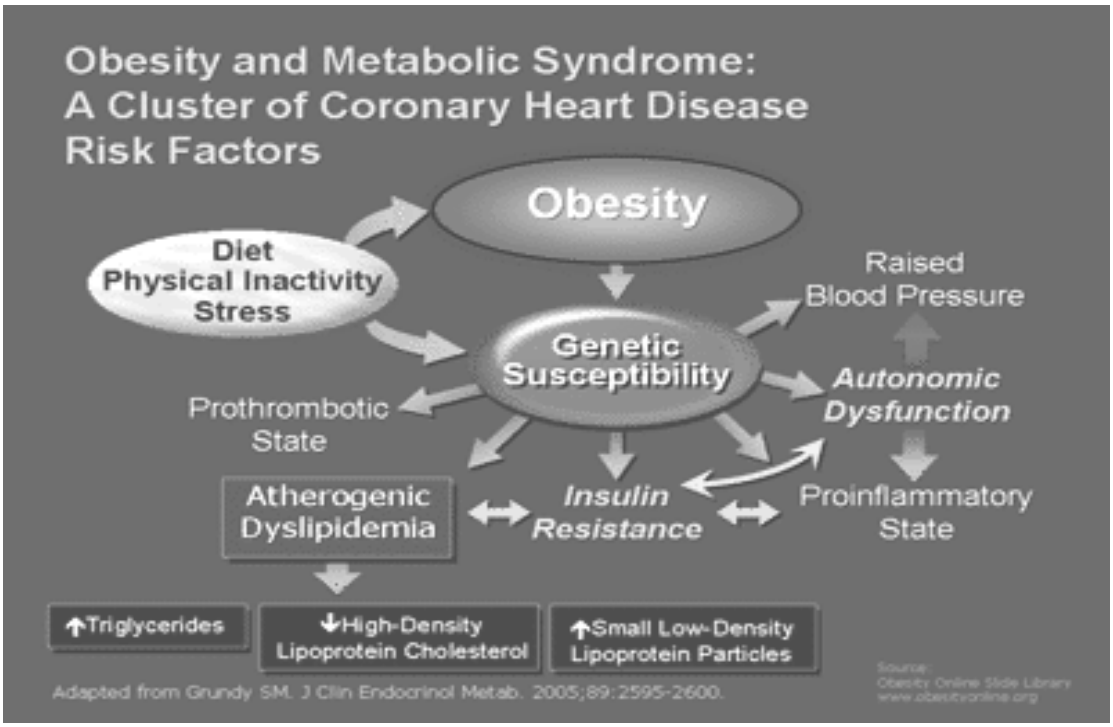

Fig. 1: Obesity and metabolic syndrome[9].

Body fat distribution, especially visceral adipose tissue accumulation, has been found to be a major correlate of a cluster of diabetogenic, atherogenic, prothrombotic and proinflammatory metabolic abnormalities referred to as the metabolic syndrome.

Thus several other adipose tissue secretions may influence the development of metabolic syndrome. These multiple pathways makes it difficult to differentiate between the more important and less important ones and leading complexity provides a great challenge for basic and clinical research[10].

Atherogenic dyslipidemia

Atherogenic dyslipidemia manifests in routine lipoprotein analysis by raised triglycerides and low concentrations of HDL cholesterol. A more detailed analysis usually reveals other lipoprotein abnormalities, eg, increased remnant lipoproteins, elevated apolipoprotein B, small LDL particles, and small HDL particles. All of these abnormalities have been implicated as being independently atherogenic[5]. Dyslipidaemia, the hallmark of the metabolic syndrome, is summarised as (a) increased flux of free fatty acids, (b) raised TG values, (c) low high density lipoprotein (HDL) cholesterol values, (d) increased small, dense low density lipoprotein (LDL) values, and (e) raised apolipoprotein (apo) B values (Table 4). Dyslipidaemia is widely established as an independent risk factor for cardiovascular disease[11].

Dietary triglycerides are absorbed by the small intestine, secreted into the lymph system, and enter the systemic circulation as chylomicrons via the thoracic duct. Muscle and adipose tissue remove some of the triglyceride from the chylomicron and the chylomicron remnant is taken up by the liver and metabolized into a cholesterol rich lipoprotein. Although most of the triglyceride found in blood is absorbed from the small intestine, the liver produces and secretes a small amount of triglyceride. Apolipoproteins are proteins associated with lipids that assist with their assembly, transport, and metabolism. Defects in any of these structural proteins or the enzymes they interact with may result in a clinical dyslipidemia.[12]

Table 4: Fasting abnormalities in lipid, lipoprotein, apolipoprotein values, and in enzymes or proteins involved in the metabolic syndrome[11].

Lipids	Lipoproteins	Apolipoprotein	Enzymes, proteins
Increased FFA	Increased VLDL	Increased apo B-100 and apo B-48	Decreased L
Increased TGs	Increased small dense LDL	Decreased apo A	Increased HL
	Decreased HDL		Increased CETP

FFA: Free Fatty Acid; TG: Triglyceride; VLDL: Very Low Density Lipoprotein; LDL: Low Density Lipoprotein; HDL, High Density Lipoprotein; apo: apolipoprotein; LPL: Lipoprotein Lipase; HL: Hepatic Lipase; CETP: Cholesteryl Ester Transfer Protein.

An important component of atherogenic dyslipidemia is central obesity, which is defined as increased waist circumference and has recently been identified as a chief predictor of the metabolic syndrome in certain patients. Another recent study found that both body mass index and waist circumference were highly predictive of eventual development of the metabolic syndrome.

Raised blood pressure (Hypertension)

Elevated blood pressure strongly associates with obesity and commonly occurs in insulin-resistant persons. Hypertension thus commonly is listed among metabolic risk factors. However, some investigators believe that hypertension is less "metabolic" than other metabolic-syndrome components. Certainly, hypertension is multifactorial in origin. For example, increasing arterial stiffness contributes significantly to systolic hypertension in the elderly. Even so, most conference participants favored inclusion of elevated blood pressure as one component of the metabolic syndrome[5].

Increased blood pressure is considered an important component of metabolic syndrome. More than 85% of those with metabolic syndrome, even in the absence of diabetes, have elevated blood pressure (BP) or hypertension. The association of elevated BP with the metabolic syndrome is strongly linked through the causative pathway of obesity. Hypertension is the leading metabolic syndrome risk factor that predisposes to increased cardiovascular morbidity and mortality, and is additionally an important risk factor for development of chronic kidney disease in the presence of obesity, the metabolic syndrome, and microalbuminuria. Control of blood pressure in persons with the metabolic syndrome may prevent a significant number of coronary heart disease events. The primary modality of treatment is lifestyle intervention with reduced caloric intake and increased physical activity[13].

Predictors of hypertension include age, obesity, alcohol consumption, and glucose intolerance. Modan et al suggested a relationship between insulin levels and blood pressure in 1985, and Ferrannini et al reported that in a lean cohort, hypertensive participants were more insulin resistant than were nonhypertensive participants. Reaven included hypertension in his description of syndrome X. A number of other reports have found that hyperinsulinemia and/or insulin resistance are correlated with hypertension. Several groups have hypothesized that hyperinsulinemia and/or insulin resistance may play a role in the etiology of hypertension. Insulin has been shown to stimulate the sympathetic nervous system, increase renal sodium retention, modulate cation transport, and induce hypertrophy of vascular smooth muscle. However, the association between insulin and hypertension has been controversial, with a number of studies finding no association between insulin and blood pressure. Acute insulin infusions in humans and animals were found, in most studies, to have a vasodilator hypotensive rather than a hypertensive effect. Ferrannini et al have proposed that insulin resistance might lead to hypertension because of diminished insulin-induced vasodilation and the imbalance between its pressor and depressor effects[14]. Additionally, endothelin-1 may play a crucial role in the pathogenesis of hypertension in insulin resistant subjects probably due to increased endothelin-1 release in response to insulin[15].

Insulin resistance

Hyperinsulinemia and insulin resistance, the cornerstones of metabolic syndrome, are associated with several metabolic and cardiovascular disorders that include hypertension and diabetes mellitus[16]. It is considered as a prime component, than obesity, by many researchers because of its strong association with several other metabolic risk factors[5].

Insulin resistance is present in the majority of people with the metabolic syndrome. It strongly associates with other metabolic risk factors and correlates univariately with CVD risk. These associations, combined with belief in its priority, account for the term insulin resistance syndrome. Even so, mechanisms underlying the link to CVD risk factors are uncertain, hence the ATP III's classification of insulin resistance as an emerging risk factor. Patients with longstanding insulin resistance frequently manifest glucose intolerance, another emerging risk factor. When glucose intolerance evolves into diabetes-level hyperglycemia, elevated glucose constitutes a major, independent risk factor for CVD[5]. Insulin resistance is strongly associated with arterial hypertension and a pathogenetic role in the development of arterial hypertension[17].

Insulin resistance (impaired insulin action) contributes to many disease processes. These include type 2 diabetes and the cluster of cardiovascular risk factors known as 'metabolic syndrome', as well as polycystic ovarian syndrome, nonalcoholic fatty liver disease[18].

Insulin resistance is present in the majority of people with the MetS. It strongly associates with a number of other MetS components; however, the association with hypertension is weak. Insulin resistance correlates univariately with the risk of Type 2 diabetes and CVD. Although not all studies have shown it to be an independent CVD risk factor, a recent meta-analysis has shown a significant association in non-diabetic males and females between surrogate measures of insulin resistance and incident CVD. The mechanisms underlying the link between insulin resistance and CVD still need further investigation[19].

Excessive insulin causes damage to the whole body, including

· **Endothelium**. The inner lining or endothelium of the arterial walls comes under attack by excess insulin. The risk of arterial blood clots, which can cause heart attacks or strokes, is increased. The pathophysiology is very complicated. It is clear, however, that the damages include reduced nitrous oxide activities (which could lead to hypertension), increased platelet and monocyte adhesion, increased pro-coagulant activity, impaired fibrinoloytic activity, and impaired degradation of glycosylated fibrin. The net result: increased blood pressure, increased formation of atherosclerotic plaques, increased thrombus formation, angina, and heart attack. The risk of cardiovascular disease is significantly increased when the endothelium is damaged.

· **Pancreas.** Type 2 diabetes develops when the pancreas ultimately "burns itself out" from the excessive demand for insulin production which it cannot keep up in an insulin resistance state. Only 20% of people with excessive insulin due to insulin resistance develop diabetes. The rest continues to produce enough insulin to meet the demand.

· **Ovaries.** The ovary, being exposed to consistently higher levels of insulin, increases its testosterone secretion accordingly, the ovary being insulin sensitive. It is a major factor in the development of polycystic ovary syndrome.

· **Cancer.** Some research indicates it might also increase the risk of prostate, colon and breastcancer.

· **Premature Aging.** Metabolic Syndrome also generates high levels of cell-damaging free radicals and causes premature aging.

Some researchers believe it can also increase the risk of Alzheimer's disease.

· **Kidneys.** Excessive insulin leads to sodium retention. Fluids follow sodium, resulting in excessive fluid in the body and ultimately hypertension, a condition that is present in 50% of those with Metabolic Syndrome [20].

The current understanding of the pathophysiology of insulin resistance suggests that multiple mechanisms are involved in its pathogenesis[20].

Table 5: Mechanisms of insulin resistance[20]

- Impaired muscle glycogen synthesis due to a defect in muscle glucose transport.
- Changes in insulin receptor isoform expression and insulin/IGF-hybrid receptor abundance.
- Defects in insulin signaling cascade.
- Defects in GLUT4 expression and function.
- Increased expression and/ or function of phosphatases and inhibitors.
- Enhanced production of inflammatory molecules.

Proinflammatory state

A proinflammatory state, recognized clinically by elevations of C-reactive protein (CRP), is commonly present in persons with metabolic syndrome. Multiple mechanisms seemingly underlie elevations of CRP. One cause is obesity, because excess adipose tissue releases inflammatory cytokines that may elicit higher CRP levels[5]. Chronic, sub-clinical inflammation is another important feature of metabolic syndrome. Dietary high in refined starches, sugar and saturated and tranc-fatty acids, and poor in natural antioxidant and fiber from fruits, vegetables and whole grains may cause an activation of the innate immune system, most likely by an excess proinflammatory cytokine production associated with reduced production of anti-inflammatory cytokines[21] Resulting oxidative stress then reduces availability of nitric oxide and promotes redox-sensitive expression of intracellular adhesion molecule (ICAM)-1 and vascular adhesion molecule (VCAM)-1. These cell-surface glycoproteins facilitate the attachment of blood-borne leukocytes to the endothelium and are crucial for the resulting low-grade inflammation[22].

The reasons for a link between inflammation and metabolic syndrome are not fully understood. One explanation may be that adipose tissue in obese persons with the metabolic syndrome releases increased amounts of cytokines into the circulation; this in turn accounts for a greater production of CRP by the liver. Another possibility is that insulin resistance per se is responsible for a higher production of cytokines. Regardless of mechanism, the finding that patients with metabolic syndrome exhibit characteristics of a proinflammatory state provides a new and exciting connection between inflammation and metabolic processes. This connection promises to yield new insights into pathways whereby the metabolic syndrome leads to atherosclerosis and acute coronary syndromes. Undoubtedly, the connections between inflammation and metabolism are complex and present a challenge for new research. [23]

Though the etiology of obesity represents a complex interaction of genetics, diet, metabolism, and physical activity, there is considerable evidence to suggest that it could be an inflammatory condition. C-reactive protein is a sensitive marker for systemic inflammation and is produced by the liver. A positive association between body mass index (BMI) and CRP has been described in otherwise healthy adults. Overweight children have increased concentrations of CRP compared with normal-weight children. A strong relation exists between elevated CRP levels and cardiovascular risk factors, fibrinogen, and high-density lipoprotein cholesterol, suggesting that inflammation occurs throughout life in the development of atherosclerosis and cardiovascular disease.

Inflammation has a role in the pathogenesis of atherosclerosis, and atherosclerosis, in turn, is common in subjects with obesity, hypertension, hyperlipidemia, diabetes mellitus, and insulin resistance. IL-6 levels are elevated in cardiovascular disease and are predictive of future ischemic events. It was reported that weekly injections of recombinant IL-6 resulted in significant increases in IL-6, IL-1ß, and TNF-α, and fibrinogen levels, and increased atherosclerosis in ApoE-deficient mice compared with controls. This led to the conclusion that pro-inflammatory cytokines and acute phase proteins such as CRP participate in the development and progression of atherosclerosis. [14]

In prospective observational studies, CRP concentration has consistently been linked with cardiovascular events as well as with high-risk vascular phenotypes including high blood pressure, diabetes, and the metabolic syndrome.[20] Recently some investigators have shown that CPRs are released by human adipocytes in response to inflammatory cytokines indicating that vascular inflammation and obesity are correlated. This, it is not surprising that CRP reflects metabolic syndrome, as CRP levels not only correlate with TGs, obesity, blood pressure, and fasting glucose, but also with insulin sensitivity, endothelial dysfunction and impaired fibrinolysis.[26]

It is evident from the preceding discussion that almost all components of metabolic syndrome X are associated with low-grade systemic inflammation. In view of the presence of systemic inflammatory response in metabolic syndrome X, "systemic inflammatory metabolic syndrome" (SIMS) may be a more appropriate term to describe it. [24]

Prothrombotic state

A prothrombotic state, characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen, also associates with the metabolic syndrome. Fibrinogen, an acute-phase reactant like CRP, rises in response to a high-cytokine state. Thus, prothrombotic and proinflammatory states may be metabolically interconnected[5].

Metabolic syndrome is accompanied by large number of coagulation and fibrinolytic abnormalities consisting of increased levels of clotting factors (tissue factor, factor VII and fibrinogen) as well as inhibition of the fibrinolytic pathway (increased plasminogen activator inhibitor-1 and decreased tissue plasminogen activator activity). Simultaneously, The presence of endothelial dysfunction and dyslipidemia triggers platelet aggregability, thus further increasing the risk of thrombotic events both in the arterial and venous system.

Apart from endocrine and metabolic disturbances, the metabolic syndrome also has characteristics of a prothrombotic state.[27] Obesity per se increases the risk for venous thromboembolism by approximately twofold.[36] This prothrombotic state probably reflects the effects of dysfunctional adipocytes (i.e. visceral fat accumulation), inflammatory activation and changes at various levels of the coagulation system, resulting in increased thrombin generation, decreased fibrinolysis and platelet hypercoagulability[27].

Activation of the coagulation cascade

The accumulation of visceral fat cells is a hallmark of the metabolic syndrome. These cells produce a wide array of paracrine and endocrine substances including cytokines and hormones. These 'dysfunctional' adipocytes constitute a key factor in maintaining a pro-inflammatory and insulin-resistant state[27]. Increased levels of fibrinogen are associated with both chronic inflammation and insulin resistance in the metabolic syndrome. Fibrinogen is not only of pivotal importance for regulating thrombin activity and providing the final substrate for thrombus formation, but is also of predictive value for future cardiovascular disease. In parallel, low-grade chronic inflammation has been associated with increased release of soluble Tissue factor (TF) and factor VII. The highly vascularized adipose tissue has been proposed as a major source of TF release in vivo. Accordingly, weight loss is associated with a significant fall in soluble TF levels in patients with metabolic syndrome. Factor VII activity correlates to both BMI and triglyceride levels owing, in part, to the formation of lipoprotein surface remnants during lipolysis. The simultaneous increase in both soluble TF and factor VII clearly

enhances the risk of activation of the coagulation cascade. Accordingly, thrombin generation tends to be enhanced in obese patients with impaired glucose tolerance. The latter finding highlights the importance of natural inhibitors of the coagulation cascade in the metabolic syndrome. However, data on coagulation inhibitors are inconsistent[27].

Hypofibrinolysis

Abnormal fibrinolysis is one of the best-documented parts of the metabolic syndrome. As a specific chapter is written about this topic in this issue, we will only briefly touch on this subject. Fibrinolysis is tightly controlled by the balance of tissue plasminogen-activator (t-PA) and PAI-1. The physiological role of PAI-1 is to inhibit plasminogen activators such as t-PA to control the rate of fibrin degradation (Figure 2). Indeed, BMI appears to be associated with increased levels of fibrin degradation in large cohort studies. Epidemiological surveys have convincingly demonstrated a positive association between elevated PAI-1 levels and increased cardiovascular risk[27]. Under physiological conditions, secretion of PAI-1 is stimulated by insulin, FFAs and chronic inflammation[57]. Subjects with the metabolic syndrome will therefore have increased PAI-1 levels for the following reasons. Firstly, chronic inflammation contributes to the increase in PAI-1. Secondly, PAI-1 levels are positively associated with the amount of visceral fat. Thirdly, insulin resistance is associated with enhanced lipolysis in adipose tissue, resulting in increased supply of FFAs to the liver. The increased flux of FFAs catalyzes the induction of PAI-1 gene expression and PAI-1 production. Finally, decreased plasma t-PA activity is related to insulin resistance in patients with characteristics of the metabolic syndrome. Overall, these changes contribute to attenuation of plasminogen conversion, resulting in a hypofibrinolytic state[27].

Mechechanism of Metabolic Syndrome

The pathophisiological basis of metabolic syndrome is divided into four stages as follows:

- Early-stage disease: genetics, visceral adiposity and lifestyle
- Mid-stage disease: adipocytokines, insulin resistance and inflammation
- Late-stage: clinical features of the metabolic syndrome (Dyslipidemia-the hallmark feature, high blood pressure)
- Final-stages: complications of the metabolic syndrome (increased CVD risk, diabetes mellitus)[7]

Pathophysiology of Metabolic Syndrome

The primary cause is insulin resistance. Insulin resistance correlates with visceral fat measured by waist circumference or waist to hip ratio. The link between insulin resistance and cardiovascular disease probably is mediated by oxidative stress, which produces endothelial cell dysfunction, promoting vascular damage and atheroma formation. Hormonal changes for the development of abdominal obesity. One study11 demonstrated that persons with elevated levels of serum cortisol (caused by chronic stress) developed abdominal obesity, insulin resistance, and lipid abnormalities. The investigators concluded that this inappropriate activation of the hypothalamic-pituitary-adrenal axis by stress is responsible for the link between psychosocial and economic problems, and acute myocardial infarction.

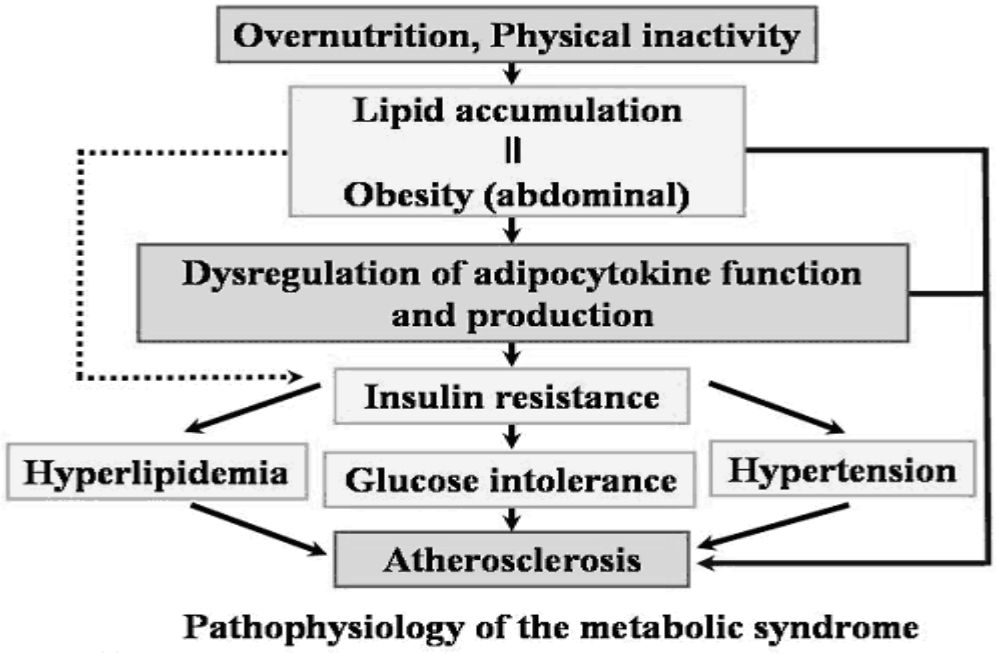

Fig. 3: Pathophysiology of metabolic syndrome[28]

Nutritional factors influencing the development of Metabolic Syndrome

Diets high in carbohydrates, particularly sugars and even more particularly sucrose and fructose, increase serum triacylglycerol concentrations and decrease serum HDL cholesterol and may therefore increase the risk of CVD. Data from Hudgins et al using liquid or solid diets show that sucrose increases serum triacylglycerol concentrations, but starch does not. Thus, the design of many studies of total carbohydrate and serum triacylglycerols are somewhat confounded by the co variation of sugars and total carbohydrate intake. Carbohydrate is increased whereas the ratio of sugars to total carbohydrate is kept constant. For example, Reaven's group has consistently reported increased fasting and postprandial triacylglycerol concentrations with diets with 60% of energy from carbohydrate than with diets with 40% of energy from carbohydrate in which the ratio of sugars to starch was constant at one-third of the total. The intake of total sugars in the high-carbohydrate group was

18% of energy, compared with 12% of energy in the low-carbohydrate group, and the intake of sucrose was 8% of energy and 12% of energy, respectively. Although neither of these diets is considered high in sucrose (ie, ≥20% of energy), the increase in serum triacylglycerol concentrations may be due partly to the increase in sucrose rather than to the increase in total carbohydrate. In support of this possibility, an early study from Reaven's laboratory showed that, when the sucrose content of diet was held constant at 13% of energy (20 g), but total carbohydrate was increased from 40% of energy to 60% of energy, the increase in fasting triacylglycerol was attenuated, and insulinemia was unchanged. Similarly, Vidon et al found no effect on fasting serum triacylglycerol concentrations when the carbohydrate content of the diet was increased from 40% of energy to 55% of energy with fructose held constant at 18–20 g/d. Taken together, these studies suggest that, if the content of triacylglycerol-raising sugars (ie, sucrose and fructose) in the diet is kept in the moderate range, total dietary carbohydrate can be increased to 55% or 60% of energy without risking an increase in fasting serum triacylglyerol concentrations [30].

Although fructose does not appear to acutely increase insulin levels, chronic exposure seems to indirectly cause hyperinsulinemia and obesity through other mechanisms. One proposed mechanism involves GLUT5, a fructose transporter that is found to have significantly higher expression levels in young Zucker obese rats compared to lean controls. As the rats age and become diabetic, GLUT5 abundance and activity is compromised, causing an even more marked insulin resistance over lean rats, implying a possible role of GLUT5 receptors in the pathology of metabolic syndrome associated with fructose feeding and insulin resistance Increased free fatty acids (FFA) in diabetic subjects and fructose fed models play a role in the inflammatory state of insulin resistance. If FFA are not removed from tissues, as occurs in fructose fed insulin resistant models, there is an increased energy and FFA flux that leads to the increased secretion of TG. Another theory explaining how chronic fructose overnutrition can lead to type 2 diabetes is the hexosamine hypothesis, where hexosamine flux is thought to regulate glucose and satiety-sensing pathways. With overexpression of glutamine:fructose-6-phosphate amidotransferase, the key regulatory enzyme in hexosamine synthesis, the liver produces excess fatty acids, skeletal muscle becomes insulin resistant, and hyperinsulinemia results. This pathway of excess hexosamine flux leads to long-term storage of energy, and eventually obesity and type 2 diabetes. [31]

Therapeutic Interventions

The first line treatment is change of lifestyle (i.e., caloric restriction and physical activity). However, drug treatment is frequently required. Generally, the individual disorders that comprise the metabolic syndrome are treated separately. Diuretics and ACE inhibitors may be used to treat hypertension. Cholesterol drugs may be used to lower LDL cholesterol and triglyceride levels, if they are elevated, and to raise HDL levels if they are low. Use of drugs that decrease insulin resistance, e.g., Metformin And Thiazolidinediones, is controversial; this treatment is not approved by the U.S. Food and Drug Administration.

A 2003 study indicated that cardiovascular exercise was therapeutic in approximately 31% of cases. The most probable benefit was to triglyceride levels, with 43% showing improvement; but fasting plasma glucose and insulin resistance of 91% of test subjects did not improve. Many other studies have supported the value of increased physical activity and restricted caloric intake (exercise and diet) to treat metabolic syndrome[7].

Table 6: Treatment strategies for metabolic syndrome[20,84]

Metabolic Syndrome Feature	Therapeutic Lifestyle Changes	Pharmacological Therapies
Central obesity	• Calorie restriction • Aerobic exercise • Reduce Weight	• Lipase inhibitors • Neuronal reuptake inhibitors
Low HDL	• Low saturated fat, rich in monounsaturated fats • Aerobic exercise • Moderate alcohol intake • Stop Smoking	• Niacin • PPAR-alfa agonists
High triglycerides	• Carbohydrate and calorie restriction • Aerobic exercise	• PPAR-alfa agonists • Niacin • Omega-3 fish oils
Small dense LDL	• Reduced saturated fat • Aerobic exercise	• HMG-CoA reductase inhibitors • Niacin • PPAR-alfa agonists
Insulin resistance, Glucose intolerance	• Carbohydrate and calorie restriction • Aerobic exercise • Increase Dietary Fibers	• Thiazolidinediones • Alfa-glucosidase inhibitors
High blood pressure	• Calorie restriction • Low fat, low salt • Aerobic exercise • Limit alcohol consumption	• Antihypertensive agents as per JNC-7

CONCLUSION

The MS is a clustering of cardiovascular risk factors. The diagnosis is not difficult to establish using blood pressure, waist circumference and some additional laboratory results. The prevalence of MS is increasing due to changes in lifestyle. Patients with the MS have a two to four times higher risk of dying from atherosclerotic disease. Studies have shown more atherosclerosis and increased rates of its progression in MS patients. Also, these patients seem to be more vulnerable to events at comparable levels of atherosclerosis. Treatment starts with lifestyle intervention: exercise and weight reduction. Medical intervention strategies using blood pressure-lowering agents, statins, fibrates and metformin seem the most appropriate to date; TZD may be added to this list in the future. Evidence regarding risk assessment and optimal medical strategies will be an important aspect of vascular research in the coming years.

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