

Metabolic syndrome

Metabolic syndrome is a clustering of at least three of five of the following medical conditions: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low high-density lipoprotein (HDL) levels.

Metabolic syndrome is associated with the risk of developing cardiovascular disease and diabetes.^{[1][2]} Some studies have shown the prevalence in the USA to be an estimated 34% of the adult population,^[3] and the prevalence increases with age.

Metabolic syndrome and prediabetes may be the same disorder, just diagnosed by a different set of biomarkers.

The syndrome is thought to be caused by an underlying disorder of energy utilization and storage. The cause of the syndrome is an area of on-going medical research.

1 Signs and symptoms

The main sign of metabolic syndrome is central obesity (also known as visceral, male-pattern or apple-shaped adiposity), overweight with adipose tissue accumulation particularly around the waist and trunk.^[4]

Other signs of metabolic syndrome include high blood pressure, decreased fasting serum HDL cholesterol, elevated fasting serum triglyceride level (VLDL triglyceride), impaired fasting glucose, insulin resistance, or prediabetes.

Associated conditions include hyperuricemia, fatty liver (especially in concurrent obesity) progressing to nonalcoholic fatty liver disease, polycystic ovarian syndrome (in women), erectile dysfunction (in men), and acanthosis nigricans.

2 Cause

The exact mechanisms of the complex pathways of metabolic syndrome are under investigation. The pathophysiology is very complex and has been only partially elucidated. Most patients are older, obese, sedentary, and have a degree of insulin resistance. Stress can also be a contributing factor. The most important risk factors are diet (particularly sugar-sweetened beverage consumption),^[5] genetics,^{[6][7][8][9]} aging, sedentary behavior^[10] or low physical activity,^{[11][12]} disrupted chronobiology/sleep,^[13] mood disorders/psychotropic

medication use,^{[14][15]} and excessive alcohol use.^[16] There is debate regarding whether obesity or insulin resistance is the cause of the metabolic syndrome or if they are consequences of a more far-reaching metabolic derangement. A number of markers of systemic inflammation, including C-reactive protein, are often increased, as are fibrinogen, interleukin 6, tumor necrosis factor-alpha (TNF- α), and others. Some have pointed to a variety of causes, including increased uric acid levels caused by dietary fructose.^{[17][18][19]}

It is generally accepted that the current food environment contributes to the development of metabolic syndrome: our diet is mismatched with our biochemistry.^[20] Weight gain is associated with metabolic syndrome. Rather than total adiposity, the core clinical component of the syndrome is visceral and/or ectopic fat (i.e., fat in organs not designed for fat storage) whereas the principal metabolic abnormality is insulin resistance. The continuous provision of energy via dietary carbohydrate, lipid, and protein fuels, unmatched by physical activity/energy demand creates a backlog of the products of mitochondrial oxidation, a process associated with progressive mitochondrial dysfunction and insulin resistance.

2.1 Stress

Recent research indicates prolonged chronic stress can contribute to metabolic syndrome by disrupting the hormonal balance of the hypothalamic-pituitary-adrenal axis (HPA-axis).^[21] A dysfunctional HPA-axis causes high cortisol levels to circulate, which results in raising glucose and insulin levels, which in turn cause insulin-mediated effects on adipose tissue, ultimately promoting visceral adiposity, insulin resistance, dyslipidemia and hypertension, with direct effects on the bone, causing "low turnover" osteoporosis.^[22] HPA-axis dysfunction may explain the reported risk indication of abdominal obesity to cardiovascular disease (CVD), type 2 diabetes and stroke.^[23] Psychosocial stress is also linked to heart disease.^[24]

2.2 Overweight

Main article: Central obesity

Central obesity is a key feature of the syndrome, being both a symptom and a cause of it in that the increasing adiposity often reflected in high waist circumference

both often results from and often contributes to **insulin resistance**. However, despite the importance of obesity, patients who are of normal weight may also be insulin-resistant and have the syndrome.^[25]

2.3 Sedentary lifestyle

Physical inactivity is a predictor of CVD events and related mortality. Many components of metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly **central**); reduced HDL cholesterol; and a trend toward increased triglycerides, blood pressure, and glucose in the genetically susceptible. Compared with individuals who watched television or videos or used their computers for less than one hour daily, those who carried out these behaviors for greater than four hours daily have a twofold increased risk of metabolic syndrome.^[25]

2.4 Aging

Metabolic syndrome affects 60% of the U.S. population older than age 50. With respect to that demographic, the percentage of women having the syndrome is higher than that of men. The age dependency of the syndrome's prevalence is seen in most populations around the world.^[25]

2.5 Diabetes mellitus type 2

Main article: **Diabetes mellitus**

The metabolic syndrome quintuples the risk of type 2 diabetes mellitus. Type 2 diabetes is considered a **complication** of metabolic syndrome. In people with impaired glucose tolerance or impaired fasting glucose, presence of metabolic syndrome doubles the risk of developing type 2 diabetes.^[26] It is likely that prediabetes and metabolic syndrome denote the same disorder, defining it by the different sets of biological markers. The presence of metabolic syndrome is associated with a higher prevalence of CVD than found in patients with type 2 diabetes or IGT without the syndrome.^[25] Hypoadiponectinemia has been shown to increase insulin resistance,^[27] and is considered to be a risk factor for developing metabolic syndrome.^[28]

2.6 Coronary heart disease

Main article: **Coronary disease**

The approximate prevalence of the metabolic syndrome in patients with coronary heart disease (CHD) is 50%, with a prevalence of 37% in patients with premature

coronary artery disease (age 45), particularly in women. With appropriate cardiac rehabilitation and changes in lifestyle (e.g., **nutrition**, **physical activity**, **weight reduction**, and, in some cases, **drugs**), the prevalence of the syndrome can be reduced.^[25]

2.7 Lipodystrophy

Main article: **Lipodystrophy**

Lipodystrophic disorders in general are associated with metabolic syndrome. Both genetic (e.g., **Berardinelli-Seip congenital lipodystrophy**, **Dunnigan familial partial lipodystrophy**) and acquired (e.g., **HIV-related lipodystrophy** in patients treated with highly active antiretroviral therapy) forms of lipodystrophy may give rise to severe insulin resistance and many of metabolic syndrome's components.^[25]

2.8 Psychiatric illnesses

People with **schizophrenia**, **schizoaffective disorder** or **bipolar disorder** may have a predisposition to metabolic syndrome that is **exacerbated** by sedentary lifestyle, poor dietary habits, possible limited access to care, and antipsychotic drug-induced adverse effects. It has been found in Australia that 67% of patients with either bipolar disorder or schizoaffective disorder, and 51%^[29] of patients with schizophrenia meet criteria for metabolic syndrome; the prevalence is higher in women than in men.^[30]

3 Pathophysiology

It is common for there to be a development of **visceral fat**, after which the **adipocytes** (fat cells) of the visceral fat increase **plasma** levels of **TNF- α** and alter levels of a number of other substances (e.g., **adiponectin**, **resistin**, and **PAI-1**). **TNF- α** has been shown not only to cause the production of inflammatory **cytokines**, but also possibly to trigger cell signaling by interaction with a **TNF- α receptor** that may lead to insulin resistance.^[31] An experiment with rats fed a diet with 33% **sucrose** has been proposed as a model for the development of metabolic syndrome. The sucrose first elevated blood levels of **triglycerides**, which induced **visceral fat** and ultimately resulted in insulin resistance. The progression from visceral fat to increased **TNF- α** to insulin resistance has some parallels to human development of metabolic syndrome. The increase in adipose tissue also increases the number of immune cells present within, which play a role in inflammation. Chronic inflammation contributes to an increased risk of hypertension, atherosclerosis and diabetes.^[32]

The involvement of the **endocannabinoid system** in the development of metabolic syndrome is

indisputable.^{[33][34][35]} Endocannabinoid overproduction may induce reward system dysfunction^[34] and cause executive dysfunctions (e.g., impaired delay discounting), in turn perpetuating unhealthy behaviors. The brain is crucial in development of metabolic syndrome, modulating peripheral carbohydrate and lipid metabolism.^{[33][34]}

The metabolic syndrome can be induced by overfeeding with sugar or fructose, particularly concomitantly with high-fat diet.^[36] The resulting oversupply of omega-6 fatty acids, particularly arachidonic acid (AA), is an important factor in the pathogenesis of metabolic syndrome. Arachidonic acid (with its precursor - linoleic acid) serve as a substrate to the production of inflammatory mediators known as eicosanoids, whereas the arachidonic acid-containing compound diacylglycerol (DAG) is a precursor to the endocannabinoid 2-arachidonoylglycerol (2-AG) while fatty acid amide hydrolase (FAAH) mediates the metabolism of arachidonic acid into anandamide.^[35] Anandamide can also be produced from *N*-acylphosphatidylethanolamine via several pathways.^[35] Anandamide and 2-AG can also be hydrolyzed into arachidonic acid, potentially leading to increased eicosanoid synthesis.^[35]

Metabolic syndrome is a risk factor for neurological disorders.^[37] Metabolomic studies suggest an excess of organic acids, impaired lipid oxidation byproducts, essential fatty acids and essential amino acids in the blood serum of affected patients. However, it is not entirely clear whether the accumulation of essential fatty acids and amino acids is the result of excessive ingestion or excess production by gut microbiota.

4 Diagnosis

A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity published a guideline to harmonize the definition of the metabolic syndrome.^[38] This definition recognizes that the risk associated with a particular waist measurement will differ in different populations. Whether it is better at this time to set the level at which risk starts to increase or at which there is already substantially increased risk will be up to local decision-making groups. However, for international comparisons and to facilitate the etiology, it is critical that a commonly agreed-upon set of criteria be used worldwide, with agreed-upon cut points for different ethnic groups and sexes. There are many people in the world of mixed ethnicity, and in those cases, pragmatic decisions will have to be made.

The previous definitions of the metabolic syndrome by

the International Diabetes Federation^[39] and the revised National Cholesterol Education Program are very similar and they identify individuals with a given set of symptoms as having metabolic syndrome. There are two differences, however: the IDF definition states that if body mass index (BMI) is greater than 30 kg/m², central obesity can be assumed, and waist circumference does not need to be measured. However, this potentially excludes any subject without increased waist circumference if BMI is less than 30. Conversely, the NCEP definition indicates that metabolic syndrome can be diagnosed based on other criteria. Also, the IDF uses geography-specific cut points for waist circumference, while NCEP uses only one set of cut points for waist circumference regardless of geography. These two definitions are much more similar than the original NCEP and WHO definitions.

4.1 IDF

The International Diabetes Federation^[39] consensus worldwide definition of the metabolic syndrome (2006) is: Central obesity (defined as waist circumference[#] with ethnicity-specific values) AND any two of the following:

- Raised triglycerides: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality
- Raised blood pressure (BP): systolic BP > 130 or diastolic BP > 85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose (FPG): > 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

If FPG is > 5.6 mmol/L or 100 mg/dL, an oral glucose tolerance test is strongly recommended, but is not necessary to define presence of the syndrome.

[#] If BMI is > 30 kg/m², central obesity can be assumed and waist circumference does not need to be measured

4.2 WHO

The World Health Organization 1999 criteria^[40] require the presence of any one of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following:

- Blood pressure: ≥ 140/90 mmHg
- Dyslipidemia: triglycerides (TG): ≥ 1.695 mmol/L and high-density lipoprotein cholesterol (HDL-C) ≤ 0.9 mmol/L (male), ≤ 1.0 mmol/L (female)

- Central obesity: waist:hip ratio > 0.90 (male); > 0.85 (female), or body mass index > 30 kg/m²
- Microalbuminuria: urinary albumin excretion ratio ≥ 20 µg/min or albumin:creatinine ratio ≥ 30 mg/g

4.3 EGIR

The **European Group for the Study of Insulin Resistance** (1999) requires insulin resistance defined as the top 25% of the fasting insulin values among nondiabetic individuals AND two or more of the following:

- Central obesity: waist circumference ≥ 94 cm or 37 inches (male), ≥ 80 cm or 31.5 inches (female)
- Dyslipidemia: TG ≥ 2.0 mmol/L and/or HDL-C < 1.0 mmol/L or treated for dyslipidemia
- Hypertension: blood pressure ≥ 140/90 mmHg or antihypertensive medication
- Fasting plasma glucose ≥ 6.1 mmol/L

4.4 NCEP

The US National Cholesterol Education Program Adult Treatment Panel III (2001) requires at least three of the following:^[41]

- Central obesity: waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 35 inches (female)
- Dyslipidemia: TG ≥ 1.7 mmol/L (150 mg/dl)
- Dyslipidemia: HDL-C < 40 mg/dL (male), < 50 mg/dL (female)
- Blood pressure ≥ 130/85 mmHg (or treated for hypertension)
- Fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dl)

4.5 American Heart Association

There is confusion as to whether, in 2004, the AHA/NHLBI intended to create another set of guidelines or simply update the NCEP ATP III definition.^{[42][43]}

- Elevated waist circumference:
 - Men — greater than 40 inches (102 cm)
 - Women — greater than 35 inches (88 cm)
- Elevated triglycerides: Equal to or greater than 150 mg/dL (1.7 mmol/L)
- Reduced HDL (“good”) cholesterol:

- Men — Less than 40 mg/dL (1.03 mmol/L)
- Women — Less than 50 mg/dL (1.29 mmol/L)

- Elevated blood pressure: Equal to or greater than 130/85 mm Hg or use of medication for hypertension
- Elevated fasting glucose: Equal to or greater than 100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia

4.6 Other

High-sensitivity C-reactive protein has been developed and used as a marker to predict coronary vascular diseases in metabolic syndrome, and it was recently used as a predictor for **nonalcoholic fatty liver disease** (steatohepatitis) in correlation with serum markers that indicated lipid and glucose metabolism.^[44] Fatty liver disease and steatohepatitis can be considered as manifestations of metabolic syndrome, indicative of abnormal energy storage as fat in ectopic distribution. Reproductive disorders (such as **polycystic ovary syndrome** in women of reproductive age), and erectile dysfunction or decreased total testosterone (low testosterone-binding globulin) in men can be attributed to metabolic syndrome.^[45]

4.7 Rheumatic diseases

There are new findings regarding the comorbidity associated with rheumatic diseases. Both **psoriasis** and **psoriatic arthritis** have been found to be associated with metabolic syndrome.^[46]

5 Prevention

Various strategies have been proposed to prevent the development of metabolic syndrome. These include increased physical activity (such as walking 30 minutes every day),^[47] and a healthy, reduced calorie diet.^[48] Many studies support the value of a healthy lifestyle as above. However, one study stated these potentially beneficial measures are effective in only a minority of people, primarily due to a lack of compliance with lifestyle and diet changes.^[11] The **International Obesity Taskforce** states that interventions on a sociopolitical level are required to reduce development of the metabolic syndrome in populations.^[49]

The **Caerphilly Heart Disease Study** followed 2,375 male subjects over 20 years and suggested the daily intake of a pint (~568 ml) of milk or equivalent dairy products more than halved the risk of metabolic syndrome.^[50] Some subsequent studies support the authors’ findings, while others dispute them.^[51] A systematic review of four **randomized**

controlled trials found that a paleolithic nutritional pattern improved three of five measurable components of the metabolic syndrome in participants with at least one of the components.^[52]

6 Management

The first line treatment is change of lifestyle (e.g., Dietary Guidelines for Americans and physical activity). However, if in three to six months of efforts at remedying risk factors prove insufficient, then drug treatment is frequently required. Generally, the individual disorders that compose 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. Weight loss medications may result in weight loss.^[53] As obesity is often recognized as the culprit behind many of the additional symptoms, with weight loss and lifestyle changes in diet, physical activity, the need for other medications may diminish.

A 2003 study indicated 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.^[11] Many other studies have supported the value of physical activity and dietary modifications to treat metabolic syndrome. Some natural compounds, like ursolic acid, have been suggested as a treatment for obesity/metabolic syndrome based on the results of extensive research involving animal models; it is argued, however, that there is still a lack of data regarding the use of ursolic acid in humans, as phase-II/III trials of that drug have not been carried so far.^[12]

Restricting the overall dietary carbohydrate intake is more effective in reducing the most common symptoms of metabolic syndrome than the more commonly prescribed reduction in dietary fat intake.^[54]

The combination preparation simvastatin/sitagliptin (marketed as Juvisync) was introduced in 2011 and the use of this drug was to lower LDL levels and as well as increase insulin levels.^[55] This drug could have been used to treat metabolic syndrome but was removed from the market by Merck in 2013 due to business reasons.^[56]

High-dose statins, recommended to reduce cardiovascular risk, have been associated with higher progression to diabetes, particularly in patients with metabolic syndrome. The biological mechanisms are not entirely understood, however, the plausible explanation may lie in competitive inhibition of glucose transport via the so-

lute carrier (SLC) family of transporters (specifically *SLCO1B1*), important in statin pharmacokinetics.

7 Epidemiology

Main article: Epidemiology of metabolic syndrome

Approximately 20 – 25 percent of the world's adult population has the cluster of risk factors that is metabolic syndrome.^[57] In 2000, approximately 32% of U.S. adults had the metabolic syndrome.^{[58][59]} In more recent years that figure has climbed to 34%.^{[59][60]}

8 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.^{[61][62]}

- The Marseilles physician Dr. Jean Vague, in 1947, observed that upper body obesity appeared to predispose to diabetes, atherosclerosis, gout and calculi.^[63]
- Avogadro, Crepaldi and coworkers 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.^[64]
- 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.^[65]
- The same year, Singer used the term for associations of obesity, gout, diabetes mellitus, and hypertension with hyperlipoproteinemia.^[66]
- In 1977 and 1978, Gerald B. Phillips developed the concept that risk factors for myocardial infarction concur to form a “constellation of abnormalities” (i.e., glucose intolerance, hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia, and hypertension) 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.^{[67][68]}
- 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.^[69]

The terms “metabolic syndrome,” “insulin resistance syndrome,” and “syndrome X” are now used specifically to define a constellation of abnormalities associated with increased risk for the development of type 2 diabetes and atherosclerotic vascular disease (e.g., heart disease and stroke).

9 Controversy

The clinical value of using “metabolic syndrome” as a diagnosis previously has been debated due to different sets of conflicting and incomplete diagnostic criteria. These concerns have led the [American Diabetes Association](#) and the [European Association for the Study of Diabetes](#) to issue a joint statement identifying eight major concerns on the clinical utility of the metabolic syndrome diagnosis.^[70] The principal argument has been that when confounding factors such as obesity are accounted for, diagnosis of the metabolic syndrome has a negligible association with the risk of heart disease.^[71]

Naturally, since the metabolic syndrome is a disorder of energy distribution and storage, fat accumulation explains for a significant proportion of cardiovascular risk. However, obesity without metabolic syndrome does not confer a significant cardiovascular risk, whereas metabolic syndrome without obesity is associated with a significant risk of diabetes and cardiovascular disease. This association of metabolic syndrome with diabetes can be illustrated by generalized [lipodystrophy](#) (near complete absence of adipose tissue). The animals and humans with generalized lipodystrophy develop signs of metabolic syndrome in the absence of adipose tissue; and the metabolic syndrome progresses to type 2 diabetes. Adipose tissue transplantation in transgenic mice with lipodystrophy can cure the type 2 diabetes. It has not been contested that cardiovascular risk factors tend to cluster together; the matter of contention has been the assertion that the metabolic syndrome is anything more than the sum of its constituent parts. [Phenotypic heterogeneity](#) (for example, represented by variation in metabolic syndrome factor combinations among individuals with metabolic syndrome) has fueled that debate. However, more recent evidence suggests that common triggers (for example, excessive sugar-intake in the environment of overabundant food) can contribute to the development of multiple metabolic abnormalities at the same time, supporting the commonality of the energy utilization and storage pathways in metabolic syndrome.

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 Figure 1. Biosynthesis pathways of anandamide (AEA)
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11 Further reading

Bhat RA. *Factor Analysis of Metabolic Syndrome Components in North Indian Population of Kashmir*. J Med Soc 2015; 29: 83-87.

12 External links

- Metabolic Syndrome X at the Stanford University Pharmacogenomic Knowledge Base

13 Text and image sources, contributors, and licenses

13.1 Text

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