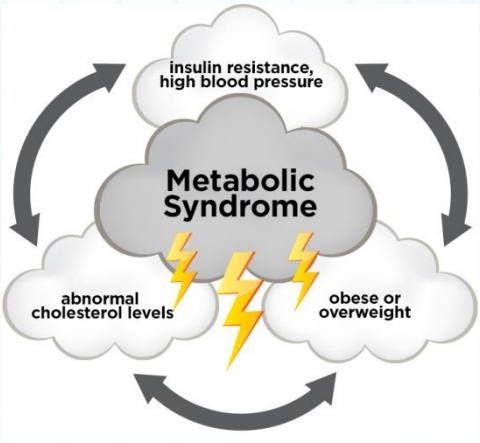
Metabolic syndrome



Metabolic syndrome is a disorder of energy utilization and storage, diagnosed by a co-occurrence of three out 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 increases the risk of developing cardiovascular disease and diabetes. Some studies have shown the prevalence in the USA to be an estimated 34% of the adult population, and the prevalence increases with age.

Metabolic syndrome is also known as metabolic syndrome X, cardiometabolic syndrome, syndrome X, insulin resistance syndrome, Reaven's syndrome (named for Gerald Reaven), and CHAOS (in Australia).

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

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.

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

Causes

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 factors are genetics, aging, diet (particularly sugar-sweetened beverage consumption), sedentary behavior or low physical activity, disrupted

chronobiology/sleep, mood disorders/psychotropic medication use, and excessive alcohol use. 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 (TNFα), and others. Some have pointed to a variety of causes, including increased uric acid levels caused by dietary fructose.

It is generally accepted that the current food environment contributes to the development of metabolic syndrome: our diet is mismatched with our biochemistry. 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, arguably creates a backlog of the products of mitochondrial oxidation, a process associated with progressive mitochondrial dysfunction and insulin resistance.

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). 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. HPA-axis dysfunction may explain the reported risk indication of abdominal obesity to cardiovascular disease (CVD), type 2 diabetes and stroke. Psychosocial stress is also linked to heart disease.

Overweight

Central obesity is a key feature of the syndrome, reflecting the fact that the syndrome's prevalence is driven by the strong relationship between waist circumference and increasing adiposity. However, despite the importance of obesity, patients who are of normal weight may also be insulin-resistant and have the syndrome.

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.

Aging

Metabolic syndrome affects 44% 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.

Diabetes mellitus type 2

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. 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. Hypoadiponectinemia has been shown to increase insulin resistance, and is considered to be a risk factor for developing metabolic syndrome.

Coronary heart 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.

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.

Psychiatric illnesses

People with schizophrenia, schizoaffective disorder or bipolar disorder may have a predisposition to metabolic syndrome that is exacerbated by a 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% of patients with schizophrenia meet criteria for metabolic syndrome; the prevalence is higher in women than in men.

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 TNFα and alter levels of a number of other substances (e.g., adiponectin, resistin, and PAI-1). TNFα has been shown not only to cause the production of inflammatory cytokines, but also possibly to trigger cell signaling by interaction with a TNFα receptor that may lead to insulin resistance. 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 TNFα 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.

The central role of the cannabinoid system in the development of metabolic syndrome is indisputable. Endocannabinoid overproduction and dysbalance may exacerbate corticolimbic reward system dysfunction, and contribute to executive dysfunction (e.g., impaired delay discounting), perpetuating unhealthy behaviors. The brain is crucial in development of metabolic syndrome, modulating peripheral carbohydrate and lipid metabolism.[citation needed]

Metabolic syndrome is a risk factor for neurological disorders.

The metabolic syndrome can be induced by overfeeding with sugar or fructose, particularly concomitantly with high-fat diet. The resulting short-chain fatty acid production, and general oversupply of n-6 fatty acids are important determinants of metabolic syndrome. In particular, arachidonic acid metabolism appears to be a factor in the pathogenesis of metabolic syndrome: arachidonic acid (with its precursor - linoleic acid) serve as a substrate to inflammatory factor production (prostaglandins and leukotrienes), whereas arachidonic acid-containing diacylglycerol (DAG) is a precursor to the endocannabinoid (2-arachidonoylglycerol) and is a by-product of fatty acid amide hydrolase (FAAH)- mediated metabolism of anandamide (produced from N-arachidonoyl phosphatidylethanolamine).

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.

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. 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 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.

IDF

The International Diabetes Federation 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.

WHO

The World Health Organization 1999 criteria[38] 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

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

NCEP

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

•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)

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.

•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

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.[42] 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 aspolycystic 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.[36]

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.

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), and a healthy, reduced calorie diet. 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. The International Obesity Taskforce states that interventions on a sociopolitical level are required to reduce the development of the metabolic syndrome in populations.

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. Some subsequent studies support the authors' findings, while others dispute them.

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. 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. 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.

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.

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. This drug could have been used to treat metabolic syndrome but was removed from the market by Merck in 2013 due to business reasons.

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

Epidemiology

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

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