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# Metabolic syndrome update

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ABSTRACT

The metabolic syndrome is a multiplex risk factor for atherosclerotic cardiovascular disease and type 2 diabetes. It is composed of atherogenic dyslipidemia, elevated blood pressure, insulin resistance and elevated glucose, a pro-thrombotic state, and a pro-inflammatory state. Excess energy intake and concomitant obesity are the major drivers of the syndrome. Lifestyle intervention can reverse metabolic risk factors, but at times, drug therapies or bariatric surgery may be required to control more overt risk factors.

**Key words:** Metabolic syndrome, Diabetes, Dyslipidemia, Hypertension, Nutrition, Obesity.

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The metabolic syndrome is a multiplex risk factor for atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes [1]. It doubles risk for ASCVD and, in patients without diabetes, increases risk for type 2 diabetes fivefold [2]. The metabolic syndrome occurs commonly throughout the world, ranging in prevalence from 10% to 40% [3]. The syndrome occurs most often in populations characterized by excessive nutrient intake and physical inactivity [4], but underlying metabolic and genetic susceptibilities are critical factors as well.

## Definition of metabolic syndrome

The metabolic syndrome consists of five factors for ASCVD: atherogenic dyslipidemia, elevated blood pressure, dysglycemia, a pro-thrombotic state, and a pro-inflammatory state [5] (Fig. 1). They occur most commonly in obese persons. Atherogenic dyslipidemia comprises elevations in plasma triglycerides and apolipoprotein B (apo B), and reductions in high-density lipoproteins (HDL). Elevated blood pressure includes both overt and borderline hypertension. Dysglycemia consists of either prediabetes or diabetes. Abnormalities in coagulation factors and blood platelets make up a pro-thrombotic state. A pro-inflammatory state results from inflammatory mediators acting on a variety of tissues. The contribution of each of these components to cardiovascular risk undoubtedly varies among individuals but, in combination, they double the risk for ASCVD.

Several attempts have been made to craft a clinical definition of the syndrome. The most commonly accepted is a recent consensus definition [4] (Table). It includes abdominal obesity as a key (but not necessary) component, elevations in serum triglyceride and glucose, increased blood pressure, and reduced levels of HDL cholesterol (HDL-C). The presence of three or more of these constitutes a clinical diagnosis.

## Pathogenesis

An early hypothesis was that insulin resistance is the cause of metabolic syndrome [6,7]. Without question, insulin

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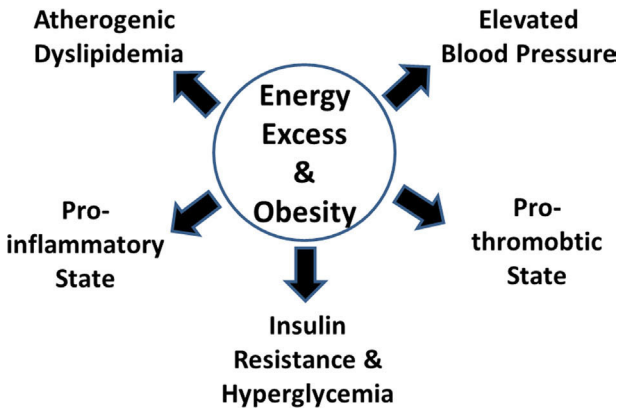


**Fig. 1 – Relationships between energy excess/obesity and risk factors of the metabolic syndrome. Available evidence indicates that excess energy intake and concomitant obesity are major causes of all the metabolic risk factors.**

resistance contributes to hyperglycemia. Its role in causing other metabolic risk factors is uncertain.

Another view sees obesity (or energy imbalance) as the main cause. Since obesity strongly associates with all metabolic risk factors, its role is plausible. A related view contends that positive caloric balance underlies the metabolic syndrome (Fig. 1). Obesity is a useful clinical indicator of a state of overnutrition but this does not necessarily mean that an excess of adipose tissue is the true cause. For example, caloric restriction, even in the presence of continuing obesity, reverses most metabolic risk factors [8]. This suggests that a positive energy imbalance (overnutrition) takes precedence over excess adipose tissue as the primary cause of the syndrome [9].

## Components of metabolic syndrome

### *Upper-body obesity*

Most persons with the metabolic syndrome are categorically obese (BMI $\geq$ 30 kg/m$^2$) [10]. Among them, individuals with predominant upper-body obesity are most prone to metabolic syndrome. Fat in the upper body can be either intraperitoneal (visceral) or subcutaneous. Excess visceral fat associates strongly with the metabolic syndrome [11,12]. But in addition, excessive amounts of upper-body subcutaneous fat are accompanied by greater risk for metabolic syndrome [13–16]. In persons with upper-body obesity, the amount of subcutaneous fat typically exceeds that of visceral fat by twofold or threefold [17].

It is commonly believed that obesity supplies excess fat to various organs or tissues, especially muscle and liver. Fat overload in tissues is referred to as ectopic fat [18]. A mediator between adipose-tissue fat and ectopic fat appears to be a high plasma level of non-esterified fatty acids (NEFA) [19]. Ectopic fat in muscle associates strongly with insulin resistance [18]. In the liver, excess fatty acids can be burned completely or partially degraded to ketone bodies. The remaining fatty acids are re-esterified into triglycerides, which are incorporated into very-low-density lipoproteins (VLDL); the latter are secreted into the circulation.

In another form of obesity, adipose tissue locates predominately in the lower body. This is called lower-body obesity or gluteofemoral obesity. This pattern is more common in women, but can be found in men. It accompanies a lower prevalence of metabolic syndrome than occurs with upper-body obesity [16]. A reason for this difference may be that individuals with lower-body obesity have a lower rate of release of NEFA into the circulation. Some articles suggest that lower-body adipose tissue actually protects against metabolic syndrome [16,20]; if so, the mechanism is not entirely clear.

It is widely believed that the excess body weight in obese persons consists largely of adipose-tissue triglyceride; however, in fact, excess weight divides almost equally between fat mass and lean body mass [21]. The burning of a portion of excess energy by lean mass may protect against the adverse effects of overnutrition. In some individuals, overnutrition is well tolerated without development of risk factors, whereas in others, metabolic risk factors appear [22].

Recent studies reveal that adipose tissue contributes a host of bio-active peptides (adipokines) that may influence

**Table – Criteria for clinical diagnosis of the metabolic syndrome.**

| Measure | Categorical cut points |
|---|---|
| Elevated waist circumference[a] | $\geq$102 cm in males<br>$\geq$88 cm in females |
| Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator[b]) | $\geq$150 mg/dL (1.7 mmol/L) |
| Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator[b]) | <40 mg/dL (1.0 mmol/L) in males<br><50 mg/dL (1.3 mmol/L) in females |
| Elevated blood pressure (anti-hypertensive drug treatment in a patient with a history of hypertension is an alternate indicator) | Systolic $\geq$130 and/or diastolic $\geq$85 mmHg |
| Elevated fasting glucose[c] (drug treatment of elevated glucose is an alternate indicator) | $\geq$100 mg/dL |

HDL-C indicates high-density lipoprotein cholesterol.
[a] Waist circumference cut points used in the USA. Cut points for other populations are listed in the parent document [4].
[b] The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose *n*-3 fatty acids presume high triglycerides.
[c] Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the current criteria [4].