ABSTRACT

The metabolic syndrome is an increasingly prevalent clinical syndrome, closely related to the risk of progression to type 2 diabetes, to cardiovascular disease (CVD) and to several cancers. Despite its prevalence (at about 20 % of many western populations and much higher in several high risk populations), it has been a controversial topic since it was first described, largely because of lack of agreement about criteria for definition and diagnosis. This has been further compounded by lack of clarity about how the syndrome should be treated. At the core of the pathophysiology of metabolic syndromeis a gradual and progressive distortion of normal metabolic homeostasis, affecting all ofthe major metabolically active organs and tissues.

KEY WORDS

Metabolic Syndrome , Obesity, Insulin resistance, Dyslypideia, Gastric bypass, Bariatric surgery

INTRODUCTION

The metabolic syndrome is described by the clustering of several risk factors for cardiovascular disease such as hypertension, dyslipidemia, central obesity, insulin resistance and high fasting plasma glucose. World Health Organization suggested for the above syndrome to be named the 'metabolic syndrome'. People with metabolic syndrome are at increased risk for developing diabetes mellitus and cardiovascular disease, as well as increased mortality from cardiovascular disease**(Marjani, 2012).**

Metabolic syndrome is difficult to define, due to its nonuniform classification and reliance on hard cutoffs in the evaluation of disorders with non-Gaussian distributions. Lipid partitioning among specific fat depots is associated with insulin resistance, which can lead to mitochondrial overload and dysfunctional subcellular energy use and drive the various elements of metabolic syndrome**(Weiss et al., 2013).**

Sympathetic nervous system overactivity is a key mechanism leading to hypertension in patients with the metabolic syndrome. Chronic sympathetic nervous system overactivity contributes to a further declineof insulin sensitivity

and creates a vicious circle that may contribute to the development of hypertension and of the metabolic syndrome and favors cardiovascular and kidney disease**(Canale et al., 2013).**

Worldwide prevalence of Metabolic Syndrome ranges from <10% to as much as 84%, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity).In general, the International.

Diabetes Federation estimates that one quarter of the world's adult population has the Metabolic Syndrome. Higher socioeconomic status, sedentary lifestyle, and high body mass index were significantly associated with Metabolic Syndrome. It was concluded that the differences in genetic background, diet, levels of physical activity, smoking, family history of diabetes, and education all influence the prevalence of the Metabolic Syndrome and its components. The observed prevalence of the Metabolic Syndrome in National Health and Nutrition Examination Survey was 5% among the subjects of normal weight, 22% among the overweight, and 60% among the obese. It further increases with age (10% in individuals aged 20–29, 20% in individuals aged 40–49, and 45% in individuals aged 60–69). The prevalence of Metabolic Syndrome varied from 8% to 43% in men and from 7% to 56% in women around the world. A Framingham Heart Study report indicated that a weight increase of ≥2.25kg over a period of 16 years was associated

with an up to 45% increased risk of developing the Metabolic Syndrome**(Kaur, 2014).**

In 2001, the National Cholesterol Education Program introduced the concept of Metabolic Syndrome. A diagnosis is based on having at least three out of five of the following: waist circumference > 40 inches in men or > 35 inches in women, triglycerides ≥ 150 mg/dL, HDL cholesterol < 50 mg/dL in women and < 40 mg/dL in men, blood pressure ≥ 135/85 mmHg and fasting serumglucose of ≥ 110 mg/dL). In 2005, the International Diabetes Federationsuggested a definition of Metabolic Syndrome. According to International Diabetes Federation an individual is diagnosed as having Metabolic Syndrome if they have central obesity (waist circumferenceof≥ 94 cm for men and ≥ 80 cm for women) and any two of the following factors: elevated triglycerides (≥ 150 mg/dL), decreased HDL cholesterol (< 40 mg/dL) in males and < 50 mg/dL in females), hypertension (systolic≥ 130 mmHg or diastolic ≥ 85 mmHg) and raised fasting plasma glucose (≥ 100 mg/dL) **(Marjani, 2012).**

Type 2 diabetes isa heterogeneous disorder and, while its causes have yet to be fully explained, obesity is considered the primary risk factor.It has been estimated that the risk of developing Type 2 diabetes is increased 93-fold in women and 42-fold in men who are severely obese rather than of healthy weight**(Dixon et al., 2011)**.

Prevention and treatment strategies for adult metabolic syndromefocus on weight management, as obesity and insulin resistance are known to be at the central axis of the definition, alongside pharmacotherapy of integrally linked conditions such as hypertension and dyslipidaemia. In children and adolescents, however, opportunities for pharmacotherapy are currently limited and interventions aimed at weight management remain the sole treatment paradigm in the majority of cases. This is primarily due to a lack of long-term data relating to the degree of cardiovascular disease and Type2 Diabetes risk from paediatric Metabolic Syndrome, as well as concerns relating to safety and side effect profiles of currently available pharmacotherapies in those who are still growing and developing, coupled with continuing concern about the recently recognised adverse effects of past and proposed anti-obesity drugs**(Sabin et al., 2012).**

Life style intervention (diet and exercise), behavioral management and drug therapy for obesity deliver a degree of weight loss that is usually modest (and therefore unattractive to patients) andshort-lived (6months to 1 year at best) and carry considerable side effects. Moreover, despite the attenuation of risk factors such as diabetes and dyslipidemia, trial evidence for an effect of these weight control approaches on reducing cardiovascular disease or mortality is still lacking. On the other hand, and perhaps as a consequence, surgery for the treatment of severe obesity is gaining increasing favor**(Ferrannini and Mingrone, 2009)**.

A number of surgical approaches to induce weightloss have been developped.In general, they can be grouped into purely restrictive, mostly restrictive, and mostly malabsorptive procedures.In the first group, the most common procedure is laparoscopic adjustable gastricbanding (LAGB), LAGB was associated with the loss of 32–70% of excess weight.

Probably the most common weight loss surgery is the Roux-en-Y gastric bypass (RYGB), in which the stomach is reduced to a small pouch (30ml)that is connected via a tight outlet to the jejunum just past the duodenum while the jejunal stump is anastomosed to the lower jejunum in a Y conformation.Here,a degree of gastric restriction comparable with that of LAGB is coupled with the bypass of the duodenum and upper jejunum, making RYGB amostly restrictive procedure.Between33and77% of excessweight can be lost following RYGB **(Ferrannini and Mingrone, 2009)**.

Roux-en-Y gastric bypass in diabetic patients results in remarkable control of diabetes, dyslipidemia, and hypertension, and is associated with a significant reduction in predicted risk of major complications including nephropathy, retinopathy, and cardiovascular disease and mortality in the range of 18-47% at long-term follow-up**(Aminian et al., 2014)**.

AIM OF THE WORK

To highlight the effect of weight loss induced by gastric bypass surgery on different elements of metabolic syndrome and its complications.

PATHOPHYSIOLOGY OF METABOLIC SYNDROME

The metabolic syndrome is an increasingly prevalent clinical syndrome, closely related to the risk of progression to type 2 diabetes, to cardiovascular disease (CVD) and to several cancers. Despite its prevalence (at about 20 % of many western populations and much higher in several high risk populations), it has been a controversial topic since it was first described, largely because of lack of agreement about criteria for definition and diagnosis. This has been further compounded by lack of clarity about how the syndrome should be treated. At the core of the pathophysiology of metabolic syndromeis a gradual and progressive distortion of normal metabolic homeostasis, affecting all ofthe major metabolically active organs and tissues**(Nolan and O'Gorman, 2013)**.

Metabolic syndrome is not a specific disease. The metabolic syndrome is a constellation of metabolic derangements such as insulin resistance, hyperinsulinemia, abdominal obesity, impaired glucose tolerance, dyslipidemia, hypertension, and a proinflammatory and prothrombotic state**(Thaman and Arora, 2013)**.

Metabolic Syndrome affects many biochemical events in biological systems, including reproductive function. It reduces the use of glucose inthe muscles while increasing fatty acid

intake. It elevates theamounts of TG in the liver, and the formation of very low-densitylipoprotein (VLDL) and its release into the circulation. Glucoserelease from the same tissue also increases, and the conversionof glucose to fatty acids accelerates**(Aydin et al., 2014)**.

Predisposing factors of Metabolic Syndrome

Lifestyle and Physical Activity

Modern humans live in an environment that provides much comfort but is designed to eliminate moving. Lack of exercise and sedentary work in industrialized countries has become more and more common. Over the past 5 decades, a substantial accumulation of epidemiological and experimental data has established a causal relationship between low levels of leisure-time physical activity (LTPA) and an increased risk of cardiovascular disease**(Baceviciene et al., 2013)**.

Physical inactivity and energy imbalance have resulted in an obesity epidemic. Both developed and developing countries face the challenges of obesity and its comorbidities such as diabetes mellitus and cardiovascular diseases. All of these non-communicable diseases affect an individual's physical and social functioning, as well as quality of life**(Chu and Moy, 2013)**.

The effect of physical activity on cardiometabolic risk is independent of other mediators of reduced cardiometabolic risk, specifically diet behavior. The inverse relation between cardiometabolic risk and physical activity is linear, Metabolic Syndrome presence has been associated with a threshold of daily steps below a range of 3100–6000 per day**(Huffman et al., 2014)**.

Higher physical activity levelsare associated with greater insulin sensitivity and HDL-cholesterol, and lower levels of blood pressure, adiposity and triglycerides. Moderate-To-Vigorous Physical Activity levels and patterns inall likelihood play an important role as a mediational path to a healthierbody weight, thus attenuating the risk of developing Metabolic Syndromein youth**(Gomes et al., 2014)**.

Inactivityleads to a greater postabsorptive and postprandial insulin response, without a change in plasma glucose concentrations. In addition to, or as a consequence of insulin resistance, bed rest studies have shown an increase in postprandial lipids due to a decrease in plasma clearance. This has been confirmed by a decrease in lipid oxidation and an increase in ectopic fat accumulation **(Nolan and O'Gorman, 2013)**.

Physical activity influences metabolic risk factors within body weight categories, where normal weight subjects with low

physical activity levels have higher metabolic risk than more active ones, and obese subjects with high levels of physical activity have a lower metabolic risk than those who are inactive**(Gomes et al., 2014)**.

The strategy of promoting daily physical activity of at least 30 min, while based on evidence of decreased cardiovascularrisk, is unlikely to offset the time spent engaged in sedentary activities. The dramatic increase in sedentary time in recent years, at the expense of light daily activities, has removed a significant portion of daily energy expenditure. This demonstratesstrong links between inactivity and risk factors of the metabolic syndrome, while the physiology of inactivity promotes insulin resistance, hyperlipidaemia and ectopic lipid accumulation**(Nolan and O'Gorman, 2013)**.

Dietary Habits

Most people have improper dietary regimens characterized by high intake of fats, refined sugar and NaCl. The high energy density of foods, affordable prices and good flavour characteristics in addition to reduced physical activity lead to wide spread obesity and related diseases **(Angelova and Boyadjiev, 2013)**.

The relationship between energy intake, body mass and the metabolic syndrome is well established. In the past few decades, daily energy intake has increased and this change is

positively associated with metabolic syndrome risk factors. Excessive nutrient intake, in itself, confers greater risk, but recent data suggest that specific nutrients can accelerate the development of the metabolic syndrome**(Nolan and O'Gorman, 2013)**.

Carbohydrates

Carbohydrates in general

During the epidemics of obesity and type 2 diabetes, caloric increases have been due almost entirely to increased carbohydrates. Continued stimulation of insulin production can lead to an anabolic state that favors triglyceride (TG)synthesis over lipolysis and generation of TG-rich lipoproteins. Additionally, accumulation of fat in the liver and secondarily, in the pancreas, create self-reinforcing cycles that are believed to contribute to the onset of type 2 diabetes. Fatty liver leads to impaired fasting glucose metabolism and increased export of very low-density lipoprotein (LDL)-TG, which, in turn, increases fat delivery to all tissues **(Angelova and Boyadjiev, 2013)**.

Role of Fructose

There are epidemiological links between fructose consumption, obesity and metabolic syndrome. Moreover, several studies have demonstrated that excess fructose

consumption causes features of metabolic syndrome in laboratory animals and humans**(Lyssiotis andCantley, 2013)**.

The major source of fructose worldwide is sucrose or table sugar, the other major source of fructose is high fructose corn syrup (HFCS), which was introduced in the early 1970s as an additional sweetener. Despite the similarity in their chemical structures, fructose and glucose are metabolized in completely different ways**(Khitan and Kim, 2013)**.

In the liver, fructosegets phosphorylated to form fructose-1-phosphate and, as a consequence, it becomes a substrate for aldolase, and produces higher levels of ATP and citrate that results in the synthesis of fatty acids. all the fructose consumed is taken up by the liver and immediately converted to fat, while glucose stays in the bloodstream for some period of time, either for energy source or conversion to glycogen and only after the energy demands are met it can be converted to fat. This elevation of blood glucose levels in the bloodstream high for a long time is essential to meet the energy demands of the brain since glucose is the only energy source for brain and is also good for the muscle so that it is utilized for muscular activity**(Das, 2014)**.

While fructose does not stimulate insulin secretion, it can have an indirect impact on insulin action and circulating blood glucose levels. A high fructose diet has been shown to increase

blood pressure in animals, possibly by increased sympathetic nervous system activity, and tissue specific inflammation by a variety of proinflammatory cascades including uric acid, cytokine production and oxidative stress.Therefore, fructose can directly or indirectly contribute to each of the risk factors for the metabolic syndrome**(Nolan and O'Gorman, 2013)**.

Fats

The quantity and quality of fats consumed in the diet can have important effects on prevention and/or improvement clustering metabolic abnormalities of the metabolic syndrome. Serum fatty acid composition mainly reflects dietary fat intake, but also endogenous fatty acid synthesis catalyzed by desaturases. Furthermore, high fat intake and serum fatty acid profile may influence the progression of obesity and insulin sensitivity**(Ristic-Medic and Vucic, 2013)**.

When the supply of dietary fat exceeds physiological requirements, lipid accumulates in plasma, subcutaneous and visceral adiposetissue as well as most tissues that regulate metabolism. The accumulation of adipose and ectopic fat is associated with most risk factors for the metabolic syndrome**(Nolan and O'Gorman, 2013)**.

Dietary fat quality affects the risk of diabetes, and insulin resistance and sensitivity in healthy, obese and diabetic individuals. High serum levels of saturated fatty acids (SFA)

were reported to predict the development of MetS, while the risk of diabetes was inversely associated with vegetable fat, polyunsaturated fatty acid (PUFA) intakes and higher serum levels of ω–6 (n–6) PUFAs, the risk of type 2 diabetes wassignificantly reduced with higher intakes of PUFA**(Nettleton et al., 2014)**.

However, the highest atherogenic potential have trans fatty acids (TFA), which are obtained from partial hydrogenation of plant oils. Thus industrial foods - cakes, cookies and crackers often contain a high content of TFA. They lead to an increase in total and LDL-cholesterol, as well as highly atherogenic lipoproteinand lower levels of HDL-cholesterol. Due to these effects, TFA are more atherogenic when compared to SFA**(Ristic-Medic and Vucic, 2013)**.

Both saturated and trans fatty acids trigger inflammatory processes in adipocytes by increasing the production of pro inflammatory cytokines that contribute to insulin resistance and the metabolic syndrome**(Nolan and O'Gorman, 2013)**.

Dietary guidelines to limit consumption of total fat and saturated fat as one way to reduce the cardio metabolic risk of abnormal plasma lipids, hypertension, insulin resistance, diabetes and obesity, suggested that diet-based approaches may be suitable target for prevention and treatment of the MetS**(Ristic-Medic and Vucic, 2013)**.