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Original Research Article

A REVIEW ON METABOLIC SYNDOME: BIOCHEMICAL INVESTIGATIONS

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Abstract: In the last few years, the metabolic syndrome (MetS) has attracted increased attention. Metabolic syndrome defined as a group of interconnected biochemical, physiological, metabolic and clinical risk factors such as hypertension, obesity, glucose intolerance, dyslipidemia and inflammation that lead to many fatal diseases as atherosclerotic cardiovascular disease, stroke and type 2 diabetes mellitus. This review tends to go over the main points of the essential mechanisms involved in induction models of MetS by diet regimen based on high-fat high fructose/sucrose (HFHF) added to normal chow. Management of metabolic syndrome should undergo several axes such as increasing physical activity, modification of lifestyle and healthy food besides. Moreover, medications can be used to control the symptoms of different disease related to metabolic syndrome. Finally, we can conclude that the main and prevalent risk factors for the pathophysiology of Metabolic Syndrome are Insulin resistant, abdominal obesity. Also, physical inactivity and chronic inflammation which provide a possible explanation of the cause of the metabolic syndrome until now which designates the energetic relationship between a number of contributing factors.

Key words: metabolic syndrome; diabetes mellitus; insulin resistance; obesity

Introduction

Metabolic syndrome (MetS) is recognized as sequence of linked biochemical, physiological, clinical and metabolic factors that tend to directly raise the risk of atherosclerotic cardiovascular disease (CVD), type 2 diabetes mellitus and all of these factors could lead to mortality (1). It consists of a set of conditions that do not have a single reason but can be caused due to many contributing elements such as genetic or environmental factors (2). Insulin resistance (IR), hypertension, heredity type 2 diabetes mellitus and racial background are unavoidable hereditary elements that enormously elevated the hazard of creating MetS (3). Moreover, aging is another fundamental unalterable risk factor for MetS. On the other hand, environmental hazard factors for MetS are possibly controllable. These incorporate the sedentary life, physical latency, and bad dietary patterns. Metabolic syndrome could eventually induce other medical complications such as; extended hazard of type 2 diabetes mellitus, cardiovascular disease (CVD), non-alcoholic fatty liver

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disease, kidney and pancreatic dysfunction, liver, pancreas, bladder, and breast cancers (4).

Epidemiology of metabolic syndrome

The propagation of the MetS has been increasing all over the world together with obesity, influencing equally developing and developed countries (5), due to the presence of different definitions of MetS, it's difficult to estimate the frequency but it varies from 10-84% across racial groups, gender, countries, and age (6). Epidemiologic studies demonstrated that the metabolic syndrome appears widely in ethnic groups including Asian-Indians, African-Americans, Mexican-Americans, Caucasians, and Chinese with varying prevalences of both the metabolic syndrome and its components (6).

USA use data from The National Health and Nutrition Examination Survey (NHANES 1999–2000) and (2009–2010) to make the comparative analysis, using the 2009 harmonized definition of MetS (7), demonstrated that the last decades the prevalence of MetS reduced from 25.5 to 22.9% (8). This result was seen obviously in Caucasians may be due to the usage of the drugs for the treatment of dyslipidemia and hypertension. Although, higher rates of prevalence (almost 40%) elicit when using the NHANES 1999–2002 data and the definition of International Diabetes Foundation (IDF) of the syndrome (9), which need central obesity to be one of the three factors; As the prevalence of abdominal obesity increased from 45.4 to 56.1% since 1999 till 2010, the thresholds for waist circumference were strongly lowered, also hyperglycemia increased from 12.9% reach to 19.9%, while the other parameters, as blood pressure were decreases from 32.3 to 24.0% and hypertriglyceridemia reduced from 33.5 to 24.3% due to use of antihypelipidemic agents (8). On the other hand, the prevalence is increased for Asians and Mexican-Americans when using the lower thresholds of waist circumference (10). In an Australian population-based survey, according to the IDF definition, the prevalence of the MetS was 29.1% and 19.3% according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) definitions (11). Another study using various definitions of the metabolic syndrome In Brazil found that the mean prevalence was 30% (12). While in Europe, the prevalence ranges from 10 to 30% (13). Also, in the Norwegian the predominance of the MetS according to IDF was 29.6% when compared to the NCEP-ATP III was 25.9% (14). Although in France according to the NCEP-ATP III definition, the MetS was found in men 16% and in women 11% (15).

Recently in China statistical-analysis including about 220,000 people, reported that the incidence of MetS was 19.2% in men and 27.0% in women, while noticed that MetS increased with increasing age in urban areas. Another study notes that the most common MetS component is hypertension in men with percent 52.8% followed by abdominal obesity in women with percent 46.1% (16).

In India the prevalence was 18.3% according to the NCEP-ATP III definition and 25.8% according to IDF (17), and significantly increases in urban areas (18) especially in Indian immigrants in USA (19). While in Japan Rates were lower 8% in men and 10% in women (20). Harzallah et al. (21) reported that the prevalence of MetS in Arab countries increased in female more than male by using the IDF criteria, while the prevalence decreased when using World Health Organization (WHO) or NCEP-ATP-III criteria (21). In Tunisia the prevalence of the MetS about 27% in male and 39% in the female, while in Iran and Turkey was about 33.1%. Generally, by using any definition, the MetS risk factors are higher in women than in men due to the significant differences of obesity and HDL-C and hypertension (22).

The risk of IR also the risk of developing the MetS increases in the family with the history of CVD or type 2 DM (23). Also varying in metabolic syndrome phenotypes and different clusters of components across ethnic groups and countries (24). Another study noticed that the predominance of the MetS increased with age, disregarding of sexual category (6). These data harmonized

with another study done in several countries and ethnic groups (25). An important study in children showed that the prevalence of MetS increased with increasing of type 2 DM and severity of obesity degree (26). Another study in the USA done in youth reported that the occurrence of the MetS was 11.9% in the overweight, 3.3% in children and 29.2% in the obese (27). Also, in NHANES 2001–2006, the prevalence was higher in Hispanic and Caucasian boys when compared to black adolescents (28). The prevalence of MetS was higher in boys and older children (26).

Origination of metabolic syndrome

Over the years, numerous definitions for MetS have been developed. The first definition was provided by world health organization (WHO), which placed insulin resistance and/or impaired glucose tolerance as an important high risk factor and considered it to be a necessary condition for the diagnosis of MetS (29). Later on, other definitions were developed by different organizations (30-34). The newest defining criteria have been provided by the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity (35) as presented in Table (1). Despite the fact that the grouping criteria contrast from each other, almost every one of them incorporates a combination of the following factors: abdominal obesity, blood pressure, diabetes and biochemical indicators (36).

MetS is a theory more than a diagnosis. The current definition of MetS includes many parameters such as hyperinsulinemia or IR, dyslipidemia, hypertension, and obesity, with a particular stress on central adiposity (40). Many other factors can influence MetS such as drugs like corticosteroids, antidepressants, antipsy-chotics, antihistamines which cause weight gain and obesity (41).

Obesity and MetS

The most causal component of MetS is obesity. Adipocytes generate different types of biologically active fragments (adipokines) including adiponectin, plasminogen activator inhibitor–1 (PAI-1), resistin, leptin, and TNF-α. Dysregulated generation of these adipokines participates in the pathogenesis of obesity associated with metabolic syndrome. In obesity, developing of IR and atherosclerosis is due to decrease in adiponectin in plasma (42). The correlation between obesity and type 2DM created the term ‘diabesity’ to confirm the strong relationship between these two conditions (43). Central obesity linked with insulin resistance, type 2 DM, metabolic syndrome and atherosclerotic cardiovascular disease (CVD). Central obesity is considered a low-grade inflammatory state, as it associated with increased secretion of interleukin-6(IL-6) and tumor necrosis factor-alpha (TNF-α) from adipose tissue that consequently elevated level of plasma C - reactive protein (CRP) which is an inflammatory marker associated with increased risk of myocardial infarction in these individuals. Moreover, obesity is associated with markedly decrease level of adiponectin, which has an important role in improving insulin signaling and protection against atherosclerosis (44) as showed in Figure (1).

Insulin resistance and MetS

Insulin resistance has a fundamental role in the progress of MetS. Multiple factors may lead to IR development. The most prominent of them are weight gain, sedentary lifestyle, and heredity factors. Moreover, other factors that could contribute to IR development are high-carbohydrate diets, ageing, drugs like steriods and androgens (45). Insulin resistance eventually will cause malfunction of β-cells in the pancreas and leads to hyperglycemia and T2DM (46). Patients who suffer from IR should not necessarily be obese, but may only suffer from poor distribution of fat, which is concentrated in the upper body especially the abdomen that strongly correlates IR with MetS (47).

Impaired glucose tolerance and IR are combined with increased CVD incidence. The mechanisms by which IR accelerate CVD risk include the production of glycation end products, elevated blood pressure, proinflammatory and prothrombotic states and dyslipidemia, which is caused by the increased flux of free fatty acids from adipose tissue to the

liver. Many organs could be affected metabolically by IR such as; adipose, hepatic and skeletal muscles tissues (48). IR may also have a direct effect on small and large blood vessels, which lead to hypertension, cellular proliferation and inflammatory responses in the wall of blood vessels (atherogenesis). Insulin resistance and MetS could also increase the risk for ischemic heart disease (49). Although obese people have increased the risk of insulin resistance, type 2DM and CVD, not every obese individual is insulin resistant or at high risk of diabetes and CVD (50).

In obese individual, impaired metabolism of non-esterified fatty acid (NEFA) could participate in developing the insulin-resistant state. The adipocytes in those obese individuals are characteristically in a hyperlipolytic states that are resistant to the insulin induced antilipolytic action. Moreover, the produced NEFA enter to the liver could affect liver metabolism, that increase liver production of hepatic glucose and IR .in summary impaired NEFA metabolism considered as insulin secretion stimulation the may cause of IR (51). Insulin is a hormone secreted by β-cells of pancreas responsible for in maintaining the glucose balance and also of some anabolic functions. It controls blood glucose level by regulating glucose uptake of muscle, liver, peripheral and fatty tissues. Moreover it has a role in fat metabolism by stimulating the synthesis of fat in the liver and fat cells (52).

Accumulation of free fatty acids (FFA) is the main reason for development of IR. The FFA is released in blood circulation in the lipolysis process of lipoprotein rich with TAG by action of lipoprotein lipase enzyme and through the action of the cyclic AMP-dependent hormone sensitive lipase enzyme and also by the action of lipoprotein lipase (53). Insulin hormone plays important role in stimulation of lipogenesis and prevention of lipolysis in adipose tissue and activation of lipoprotein lipase which play an important role in the transfer of triacylglycerol from blood lipoproteins into the tissues. IR cause inadequate secretion of insulin from pancreas so increase lipolysis process lead to accumulation of FFA. In muscles, FFA deactivates protein kinase C. In the rats fed a high-fat diet, IR cause deficiency in insulin-stimulated insulin receptor substrates in livers (54).

Type 2 diabetes and MetS

Diabetes mellitus is a metabolic disease that identified by hyperglycemia due to abnormalities either in insulin secretion, action or both (55). People who are not diabetic, but have metabolic syndrome are at higher risk to develop diabetes. The patients have a metabolic disorder syndrome are five times at risk of getting type2 DM since there is already glucose dysregulation (56). According to the American diabetes association diagnosing diabetes can fall under 4 major categories: Type 1, Type 2, Gestational diabetes mellitus (GDM) (57).

Type 2 diabetes mellitus (T2DM) is the commonest type of diabetes and is often referred as noninsulin-dependent diabetes" or "adult-onset diabetes" In T2DM there is a dysregulation of carbohydrate, lipid and protein metabolism as a result of impaired insulin secretion, insulin resistance or both. When a patient has T2DM, this puts him at a high risk for the suffering of CVD and MetS (58). Thus, the combination of these previous factors could lead to the development of MetS. Moreover, the incidence of MetS varies with the race and the age of the study population (59).

Table 1: Clinical diagnosis of metabolic syndrome by different organization

	ORGANIZATION				
Clinical measurements	**WHO (1998) (29)**	**EGIR (1999) (39)**	**NCEP/ATPIII (2001) (31)**	**AACE (2003) (38)**	**IDF (33, 37)**
Insulin resistance	IGT,IFG ,T2DMor lowered insulin sensitivity + any 2 factors of following	Plasma insulin > 75 thpercentile + any 2 of following	None Butany 3 of following 5 features	IGT or IFG + any of following	NONE
Body weight	Waist to hip ratio Men ≥ 90 cm Women ≥ 85 cm	WC in Men ≥ 94 cm Women ≥ 80 cm	WC in Men ≥ 102 cm Women ≥ 88 cm	BMI ≥ 25 kg/m^2	Increased WC (population specific)
Triacylglycerol	TAG ≥150 mg/dl	TAG ≥ 150 mg/dl	TAG ≥ 150 mg/dl	TAG ≥ 150 mg/dl	TAG ≥ 150 mg/dl
HDL-c	Men < 35 mg/dl Women < 39 mg/dl	Men < 39 mg/dl Women < 39 mg/dl	Men < 40 mg/dl Women < 50 mg/dl	Men < 40 mg/dl Women < 50 mg/dl	Men < 40 mg/dl Women < 50 mg/dl
Glucose	IGT, IFG or T2DM	IGT, IFG but not diabetes	>110 mg/dl includes diabetes	IGT, IFG but not diabetes	≥100 mg/dl include diabetes
Blood pressure	≥ 140/90 mm/Hg	≥ 140/85 mm/Hg	≥ 130/85 mm/Hg	≥ 130/85 mm/Hg	≥ 130/85 mm/Hg

IGT: impaired glucose intolerance, IFG: impaired fasting glucose, T2DM: type 2 diabetes mellitus, WC: waist circumference; BMI: body mass index, TAG: triacylglycerol. WHO: World Health Organization, EGIR: the European Group for Study of Insulin Resistance, AACE: American Association of Clinical Endocrinologists, IDF: International Diabetes Foundation, ATPIII: Adult Treatment Panel III.

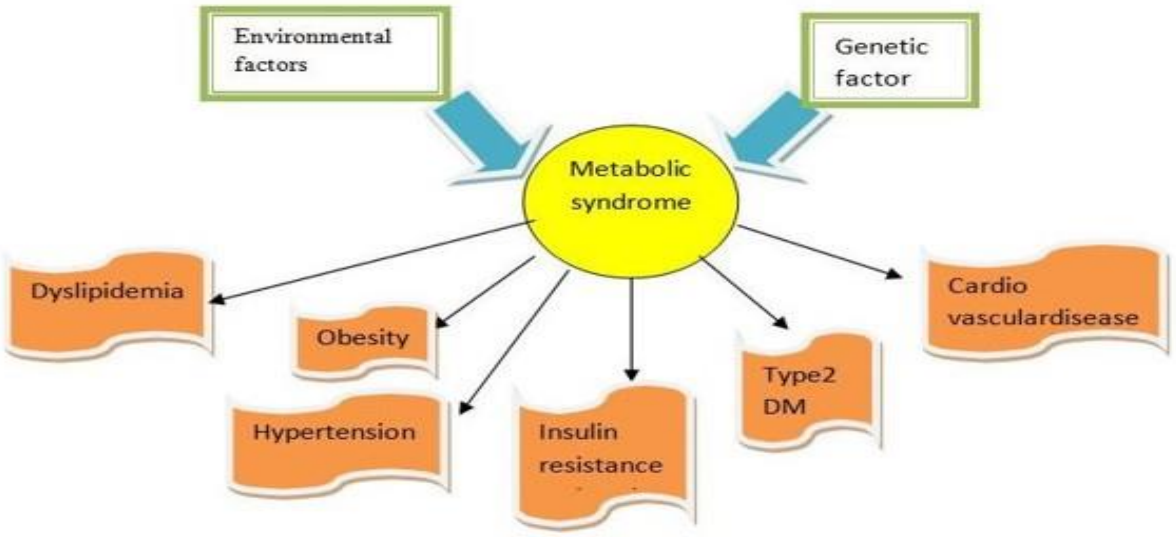

Figure 1: Etiology of MetS and risk factors affecting it

MetS and Oxidative Stress

Researches indicate that increased oxidative stress (OS) cause exaggeration in MetS symptoms such as T2DM, atherosclerosis, insulin resistance and inflammation (60). Oxidative stress generated due to the imbalance between reactive oxygen species (ROS) production and antioxidants efficiency, so OS occurred due to increase in ROS production or shortage in antioxidant system. ROS generated from the aerobic system through oxidation system ($O2^-$, H_2O_2, OH^- is a highly active product cause damage to the cellular component of the body, DNA denaturation and lipid peroxidation (61). ROS destroys many biological processes inside cellular system such as lipid peroxidation, carbohydrates oxidation, oxidation of nucleic acid base lead to deformation of DNA and mutation (62) (Figure 2).

Antioxidants divided into enzymatic catalase (CAT), superoxide dismutases (SOD), and glutathione peroxidase (GPX)) and non-enzymatic (vitamin C, vitamin E, β-carotene, reduced glutathione, and numerous phytochemicals). The body should keep its antioxidant level balanced either by dietary intake and/or de novo synthesis (63).

Oxidative stress plays a key role in the induction of many metabolic diseases such as diabetes, obesity, cardiovascular disease. In diabetes, it causes impairment release of insulin from β-cells of pancreas, inadequate uptake of glucose by cells. In obesity, it causes deformation of abdominal and visceral fats (64).

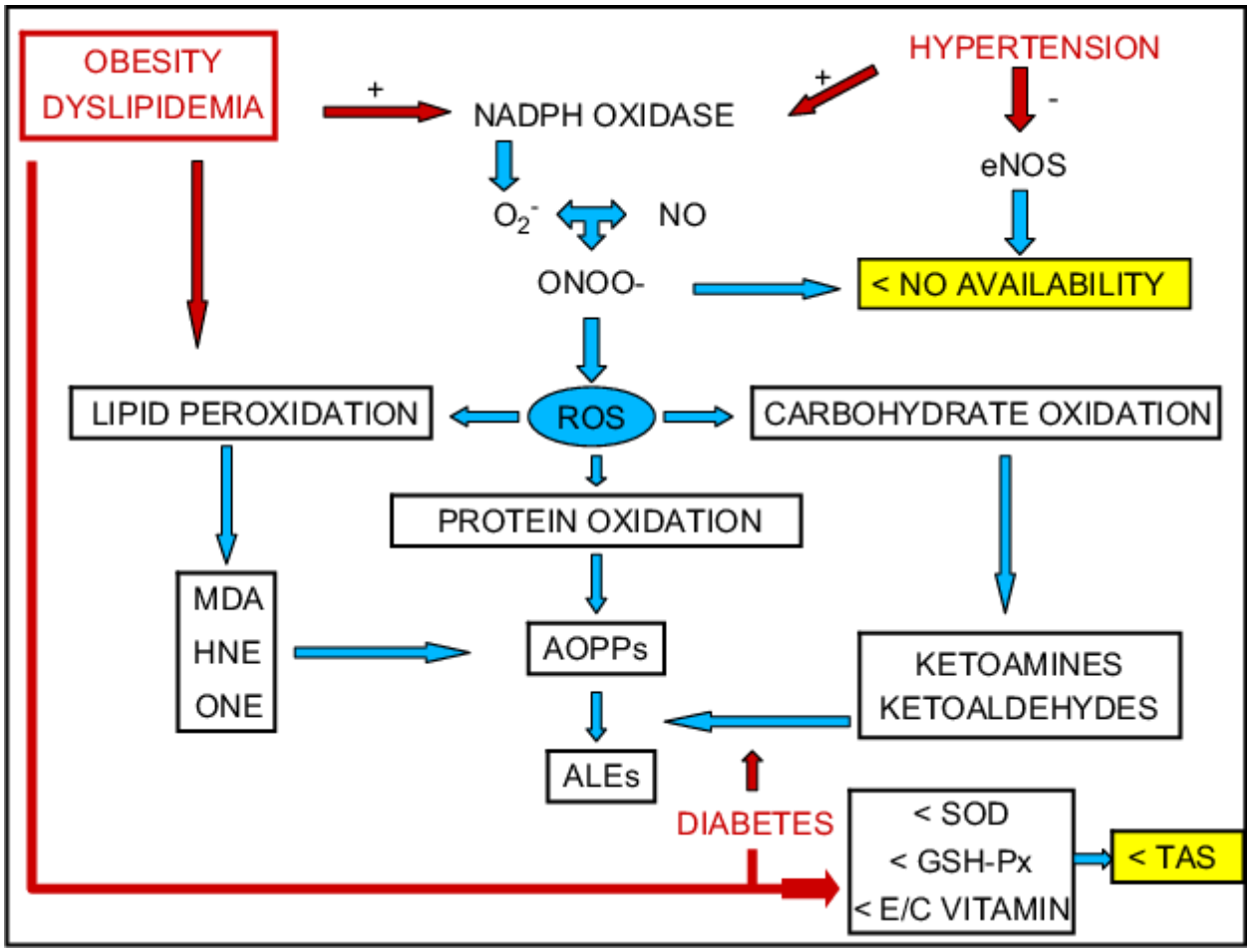

Figure 2: Role of oxidative stress in developing of MetS. MetS is affected by oxidative compounds lead to oxidation of lipids, carbohydrates and proteins (derived from Hopps et al. (64)

Abbreviations: O_2: superoxide anion; NO: nitric oxide; ONOO_: peroxinitrite; ROS: reactive oxygen species; eNOS: endothelial NO synthase; MDA: malonyldialdehyde; HNE: 4-hydroxynonenal; ONE: 4-oxy-2-nonenal; AOPPs: advanced oxidized plasma protein; ALEs: advanced lipoxidation end-products; SOD: superoxide dismutase; GSH-Px: glutathione peroxidase; and TAS: total antioxidant status.

Inflammation and MetS

According to previous studies, abdominal obesity results in systemic low-grade inflammation which causes IR and MetS. In patients who suffer from obesity or Type 2DM, investigate from plasma levels of coagulation, white blood cell counts, acute phase proteins, and some pro-inflammatory cytokines and chemokines are always elevated. Those previously mentioned inflammatory biomarkers often tend to decrease when the patient begin lifestyle changes in favor of reducing weight and weight loss. Some experimental data revealed that the site of inflammation in the obese and Type 2DM patient is mainly located in the liver, adipose tissue, muscle and pancreas (65). In animal models as well as humans suffering from obesity and DM there will be an infiltration of macrophages to these inflammation sites, these macrophages are important for the production of pro-inflammatory cytokines which are TNF-α, IL-6, and IL-1b (66). They promote insulin resistance through acting in the autocrine and paracrine way through interrupting with insulin signaling in peripheral tissue by stimulation of two pathways (the c-JUN N-terminal kinase (JNK) and nuclear factor-kappa B (NF-kB) pathway). In obese and Type 2DM patients, these pathways are activated and play major central act in building up tissue inflammation (67) as presented in Figure (3).

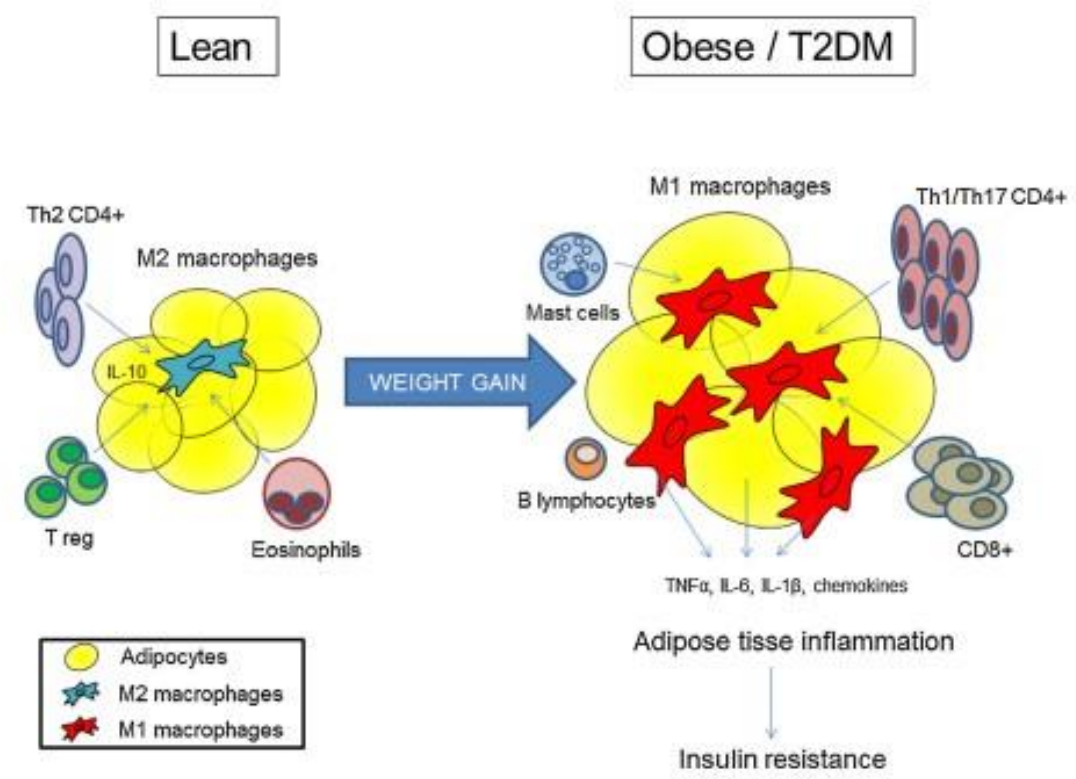

Figure 3: Role of inflammation of adipose tissue in developing of MetS and type 2 DM (derived from Esser et al. (65)

The main and prevalent risk factors for MetS are IR and abdominal obesity. Also, physical inactivity and chronic inflammation has a significant role in MetS (68). IR and hyperinsulinemia were closely correlated to the disturbed metabolic symptoms cluster (69). Visceral fat accumulation, which caused by physical inactivity and over nutrition, leading to an unusually high circulation of FFA, consequently appear of lipotoxic effects and IR and leading eventually to a state of hyperglycemia. Therefore, IR, ecological factors, inflammation and obesity provide a possible explanation of the cause of the metabolic syndrome until now which designates the energetic relationship between numbers of contributing factors (68).

Genetic mechanisms

Genes may affect in the propagation of the MetS in different ways each key of the syndrome parts high blood pressure, obesity, dysglycemia and dyslipidemia have a genetic basis, for which the main candidate genes can identify (70). This relation might facilitate the emergence of the syndrome. For an example, there is a difference in the expression of adiponectin gene (ADIPOQ), which associated with visceral obesity (71). Also, blood pressure has been correlated with differences in expression of angiotensinogen gene (AGT) (72), in addition to changes in apolipoproteins C-III genes (APOC3) and apolipoproteins E genes (APOE), which correlated with concentrations of plasma lipid (73,74). Thus, variants connected with the individual components of the MetS phenotype could interpretive correlation with the entire syndrome. Moreover, some candidate gene products may act within the main pathway which can affect different syndrome component, and possible single-gene associations have been identified. For an example glucocorticoid receptor gene (NR3C1), the gene associated with hypertension, obesity and insulin resistance (75). ADIPOQ associated with dyslipidemia, diabetes, and hypertension, β3 subunit of G protein (GNB3) gene, which associated with obesity and hypertension (76). Changes in expression of some genes which encode for

certain transcription factors as sterol regulatory element-binding protein 1 (SREBP1) and for-khead box protein C2 (FOXC2) are associated with concentrations of trigly-cerides in plasma and insulin sensitivity. These genes may be the maestro for association with the development of the whole metabolic syndrome (77,78).

The Metabolic Syndrome heritability

Study on family and twin showed a heritable interference in MetS factors clustering (79). For example, the study done in United States on 2,508 men twin pairs, the appearance of diabetes, obesity, and hypertension can be noticed in 31.6% of monozygotic pairs but noticed only 6.3% of dizygotic pairs (80). On the same line, a similar demonstration for heritable factors showed in a twin of female pairs. Also, another study on 432 people from 68 Japanese American families, significant genetic interference and effects were noted on all components of the MetS, especially dyslipidemia, about 50% of the changes were related to genetic influences (81). All above studies suggested that all causative genes underlying the MetS has motivated research to make more studies on the rare monogenic forms of the syndrome and also study the common trait by various approaches, including genetic linkage and association analysis (82).

Experimental Induction of MetS

There are different models of induction MetS in animals that allow scientists to study and investigate. One of these methods is genetic one by using specific species of rats; another method is by drugs that cause the destruction of β-cells of pancreas such as streptozotocin (STZ) or alloxan, but his type of induction is different from the human model. The most common and easiest way to induce MetS is by diet but it needs a long time of experimental, this method mimics to the human model of diet causing the metabolic disorder. As human dietary is more complex than animal diet, so the combination of the different types of foods (fat and carbohydrates) is added to reach the same model of human regimen (83).

In the field of MetS researches, rats and mice are the most well-known animal models. Different dietary systems have been used to initiate MetS in animals. They included the utilization of either a single kind of eating routine or a mix of weight control plans, for example a) high fructose b) high-sucrose c) high-fat d) high fructose/ high-fat e) high-sucrose/high-fat diets or f) high fat/high fructose/high sucrose diet. It was proved that using high-fat high-fructose/sucrose eating regimen (HFHF) in rodent chow is the fundamental method for induction of MetS mimic the human ones (84,85) (Table 2).

Accordingly, chow is a high fiber eating routine containing complex sugars with fats of vegetable sources. Chow is reasonable to make and is attractive to rodents. Fiber is regularly given by cellulose (86). The HFHF eating regimen used to induce MetS in animals usually contain high quantities of sugar (fructose/ sucrose), fat or both (87). This model had utilized generally little amounts of these added substances, planning to mimic nearly the cafeteria diet, these eating regimens were related with essentially higher caloric admission (88).

Table 2: Different dietary methods for induction of metabolic syndrome in animals

Methods	Effect on normal rats
1. High fructose 66% for 2weeks	This diet results in hyperinsulinemia , hypertriglyceridemia , increase in blood pressure and insulin resistance (89).
2. High sucrose 8% for 5weeks	This model results in mild hypertension and tachycardia (90).
3. High fat 60% lard for 120 days	Obesity, insulin resistance (91).
4. High sucrose34%+ high fat 21% for 2 or 4 weeks	High body fat percentage and impaired glucose tolerance along with hyperinsulinemia and insulin resistance (92).
5. High fructose 17.5% and fructose 25% in drinking water+ high fat 20% for 16 weeks	Metabolic syndrome and cardiovascular such as hypertension, hypertrophy, ventricular fibrosis and endothelial dysfunction (83).
6. High fat 30%+ high fructose 40% + high sucrose 10% (HFHF) diet for 12 weeks	The fundamental method for induction of MetS mimics the human ones (93).

Sugars can be separated into simple (e.g. monosaccharides and disaccharides) and complex (e.g. oligosaccharides and polysaccharides) forms. Carbohydrates are one of the basic supplements that act as short-term fuel in the body since they are the simpler process than fats. Carbohydrates digestion starts in the small digestive tract to form glucose particles, then it is absorbed by the circulatory system and transported to the liver through the entry vein. When carbohydrates exceed the daily limits of the body need, blood glucose concentration will stay high and insulin is secreted by the pancreas to enable cells to take up glucose. Then, glucose is metabolized in the following pathways (a) breakdown during the process glycolysis to supply the body with energy (b) changed over to glycogen in liver and muscles (c) transferred under insulin effect in the adipose tissue to develop fatty acids (lipogenesis) (94).

Extended utilization of carbohydrates causes elevated glucose levels in the blood. Therefore, the pancreas pumps more insulin into the bloodstream to decrease the blood glucose. So, the carbohydrates changes to fats that stored in adipose tissue. The sensitivity of insulin is also decreased. There is strong correlation between insulin resistance and high carbohydrate intake (95).

Fructose is a monosaccharide, which is available with glucose in general food items. The impact of mixing fructose and glucose together is more effective in inducing MetS than the impact of using fructose alone (96). Fructose is the favored sugar that usually added to the animal nourishment or drinking water and the most prominent model uses 10% fructose solution (97). After fructose absorption it's delivered via the portal vein to the liver, then it undergoes different metabolic pathways it may be oxidized, change into glucose, stored as glycogen, or enter the process of de novo lipogenesis (DNL). The major difference between fructose and glucose is the higher tendency of fructose to enter in the process of DNL, as the fructose is the key element in de novo lipogenesis (96). Massive fructose uptake by the liver is due to fructose consumption, fructose utilization brought about enormous fructose absorption by the liver. Fructose is changed to fructose-1-phosphate by the phosphofructokinase enzyme in the presence of ATP. It is trailed by the cleavage of fructose-1-phosphate into glyceraldehyde and dihydroxyacetone which may convert to triacylglycerol or glycogen. (97).

In glycolysis process phosphofructokinase (PFK) is the rate-limiting enzyme, enabling fructose convert to fructose-1, 6-bisphosphate, then changed to pyruvate through the procedure of glycolysis. At this status, fructose is associated with a few procedures: (a) some of the fructose is changed into lactate from pyruvate, (b) another part produces triose-phosphate which promptly changes into glucose or on the other hand glycogen through gluconeogenesis, (c) carbons determined from the fructose can be changed over into unsaturated fats, and (d) the hindrance of hepatic lipid oxidation by fructose favors very low density lipoproteins (vLDL)- triacylgly-

cerol synthesis and unsaturated fat re-esterification (98).

The negative effect of fructose on health is influenced by the amount of fructose consumed (99). An extensive inflow of fructose into the liver causes an increase of triacylglycerol and cholesterol production due to its lipogenic properties, in this way diminished insulin sensitivity and promoting insulin resistance and glucose intolerance (61, 100). Sucrose, or table sugar, is a disaccharide found in cane and beet sugar. It is converted into its constituent fructose and glucose by the catalyst sucrase enzyme (101).

Glucose uptake in glucose digestion is adversely controlled by phosphofructokinase, prompting the persistent passage of fructose into the glycolytic pathway. Overabundance fructose will be changed over into fat in the liver as fructose is a superior substrate for unsaturated fat combination contrasted with glucose. In this way, fructose is the primary dynamic fixing adding to the advancement of MetS in creatures after sucrose utilization (102). Administration of sucrose in drinking water in animal labs lead to stimulates insulin resistance, obesity, triacylglycerols, cholesterol, (LDL-c), and free unsaturated fats cause exaggeration of MetS (103).

High-fat diets have been widely used to initiate MetS in the clinical trial. It has been demonstrated that a high-fat eating regimen is potent in inducing hyperglycemia, insulin resistance, dyslipidemia and elevated plasma free fatty acids (104,105). Triacylglycerol is the main constituent of body fat; it is an ester derivative of three unsaturated fat chains and glycerol. Lipid digestion starts with the procedure of lipolysis. A lot of glycerol and fatty acids diffuse into the circulation system. Plasma free unsaturated fats are significant substrates for hepatic vLDL-c and triacylglycerol generation (106). Roughly 70 % of free fatty acids will be re-esterified (lipogenesis) to produce triacylglycerol. The rate of re-esterification is correlated with the rate of glycerol-3-phosphate generation through glycolysis process and the rate of unsaturated fat discharge from adipocytes (107).

A proper treatment and control of dyslipidemia, hypertension and an excellent glycaemic control are needed in case the patient suffers from diabetes while, already having a metabolic disorder. The clinical researchers recommended the drug therapy choice besides lifestyle modifications is essential to reach the ideal glycaemic goal as a prophylactic way against many long-term microvascular complications (i.e. retinopathy, nephropathy, and neuropathy) and macrovascular ones (i.e. heart attack and stroke) (58).

Management and controlling of MetS

The cornerstone in the treatment of MetS is depending on lifestyle modify, a development in physical fitness which leads to progress in body fat circulation and cardiovascular health, reduce body mass index (BMI) and treatment of diabetes mellitus type 2. ATP III launched some instructions for the healthy diet that must contain a lot of fibers from fruits and vegetables, also food that it has to contain omega-3 and omega-6such as olive oil, tuna, fish and canola oil. Individuals must avoid the cafeteria diet, junk food, and food contains saturated and hydrogenated fats. Sugars intake must be controlled in the MetS patients and preferred to replace with artificial sweaters sugar. Moreover, whole grains are healthier to use instead of rice and bakeries (108).

The first guidelines to control MetS directed to increase daily physical activities and exercises as walking, swimming, ride bikes, gymnastics, but the most important is to keep on these regular exercises and for a long time. Moreover, a proper diet control must be followed to reduce obesity, IR, type2DM; also we can keep blood pressure, TAG, LDL-c and cholesterol within normal ranges by following lifestyle regimen (108,109). The second guideline is to use drug medications for treatment of MetS disease such as metformin for treatment of IR and statins for treatment of high cholesterol as it inhibits reductase enzyme lead to improving CVD diseases. Also, fibrates used to relieve the symptoms of athe rogenic, dyslipidaemia and enhance CVD diseases (110,111).

Management of diabetes mellitus varies according to many factors such as type 2 DM, the age of patients and severity of the disease. These entire factors play role in putting the suitable strategy for managing the disease. Maintaining the glycemia and decreasing the long term hazards and risks of diabetes is done through pharmacological therapy. In case of T2DM several drug classes are used including: a) Insulin sensitizers (Biguanides – Thiazolidinediones); b) Insulin secretagogues (Sulfonylureas – Meglitinide derivatives); c) Alphaglucosidase inhibitors; d) Glucagonlike peptide–1 (GLP-1) agonists; e) Dipeptidyl peptidase IV (DPP-4) inhibitors; f) Selective sodium-glucose transporter-2 (SGLT-2) inhibitors; g) Insulin; h) Amylinomimetics (112). Although there are many pharmaceutical drugs in the markets, scientists tends to use medicinal plants to treat diabetes because of the less harmful side effects of plants medications and the natural formulation than manufactured ones (113).

Conclusion

Finally, we can conclude that the main and prevalent risk factors for the pathophysiology of MetS are IR and abdominal obesity. Also, physical inactivity and chronic inflammation have a significant role in MetS. For the understanding of the MetS, it starts from the noticing that IR and hyperinsulinemia were closely correlated to the disturbed metabolic symptoms cluster. Visceral fat accumulation, which caused by physical inactivity and overnutrition, leading to an unusually high circulation of FFA, consequently appear of lipotoxic effects and IR and leading eventually to a state of hyperglycemia. Therefore, IR, ecological factors, inflammation, and obesity provide a possible explanation of the cause of the metabolic syndrome until now which designates the energetic relationship between a number of contributing factors.

This review determines different issues related to the metabolic syndrome which needs additional research for an explanation. Firstly need to improve strategies to achieve and sustain long-term weight reduction and increased physical activity. Moreover, a lack of understanding of the genetic and metabolic contributions to the causation of the syndrome stands in the way of developing new therapeutic approaches. The need exists, therefore, for additional basic and clinical research designed to better understand pathophysiology from the standpoint of genetics, molecular biology, and cellular signaling.

Conflict of interest

None of the authors have any conflict of interest to declare.

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