

An Overview of Metabolic Syndrome in Turkish Population

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Abstract

Metabolic Syndrome (MetS) is a significant reason of morbidity affecting gradually more people both in the world and in our country. In this growth getting towards pandemic, basic changes in nutritional habits with sedentary life style and some characteristics which come with heredity play role. Prevalence of atherosclerotic cardiovascular disease also increases day after day. Genetic endowment and environmental factors that have changed over years are holding the responsibility. Metabolic Syndrome in definition has the importance which emphasizes that certain risk factors cause development of cardiovascular disease and diabetes mellitus (DM) together, not individually. Several guidelines have been published recently in order to easily detect MetS which has been nearly an epidemic worldwide. The present review touches upon the epidemiology, etiopathogenesis and treatment approaches of MetS in Turkey and in the world so as to enlighten healthcare professionals.

Keywords: Diabetes mellitus; Poly-metabolic syndrome; Cardiovascular diseases

Introduction

Metabolic Syndrome is a disorder in which several cardiovascular risk factors such as insulin resistance, impaired glucose tolerance, DM, obesity, abdominal adiposity, dyslipidaemia, hypertension and coronary heart disease are combined. It is described with different terms such as insulin resistance syndrome, syndrome X, poly-metabolic syndrome, deadly quartet, cardio-metabolic syndrome, dysmetabolic syndrome and Reaven syndrome. Reaven has pointed out the frequent togetherness of various risk factors firstly in 1988 and specified that this togetherness which he called "syndrome X" increased the risk of developing cardiovascular diseases [1]. World Health Organization (WHO) defined MetS in 1998 as the existence of DM, impaired fasting glucose, impaired glucose tolerance or insulin resistance in addition to at least two conditions among hypertension (>160/90 mmHg), hyperlipidaemia, central obesity and micro albuminuria [2]. International Diabetes Federation (IDF) has published a global guideline in 2005 that different thresholds were described according to different ethnic groups [3]. Based on the relevant guideline, abdominal obesity and high concentrations of triglycerides demonstrated insulin resistance. Therefore, diagnosis of central obesity should be sought; additionally at least two of high triglycerides, low High Density Lipoprotein-cholesterol (HDL-C), high blood pressure and high fasting glucose level diagnoses should be present in order to diagnose the MetS. Different thresholds of central obesity for different races were accepted in this guideline as distinct from WHO and National Cholesterol Education Program (NCEP-ATP III) guidelines. Abdominal obesity has been defined as the waist circumference above 94 cm and 80 cm for European men and women, above 90 cm and 80 cm for Chinese and South Asian men and women and 85 cm and 80 cm in Japanese men and women, respectively [3]. In Turkey, in the MetS diagnosis guideline published by the Society of Endocrinology and Metabolism of Turkey in 2005; a diagnosis guide was prepared including WHO MetS diagnosis criteria with insulin resistance of 1998 and IDF's guidelines. According to the relevant guideline, at least one of DM or impaired glucose tolerance or insulin resistance and at least two of hypertension, dyslipidaemia, and abdominal obesity are the diagnostic criteria [4].

Epidemiology of Metabolic Syndrome

Prevalence of MetS has recently been increasing. Based on NCEP-ATP III criteria, MetS prevalence in men and women in the USA is 33.7% and 35.4%, respectively while it is seen in 39.9% of USA men and 38.1% of USA women according to IDF criteria [5]. From 1999-

2000 to 2009-2010, the age-adjusted prevalence of MetS was reported to decrease from 25.5% to 22.9% in the US population [6]. In Abu Dhabi, MetS was found in 29.0% and 31.5% of non-diabetics using IDF and ATP III criteria, respectively [7]. Overall MetS prevalence of age-standardized sample in underdeveloped parts of Eastern India was found to be 33.5%, being 24.9% in males and 42.3% in females [8]. An updated report of MetS including 24670 individuals in Spain shows 31% prevalence (women 29%, men 32%) [9]. According to another study, among 7488 Chinese adults; up-to-date prevalence of MetS was 21.3% and 18.2% based on definitions of revised NCEP-ATP III and IDF criteria, respectively [10]. In 4341 subjects from Peninsular and East Malaysia, based on the WHO, ATP III, IDF and Harmonized definitions, the overall prevalence of MetS were 32.1%, 34.3%, 37.1% and 42.5%, respectively [11]. Prevalence of MetS in urban population of upper Assam was found to be 32.8% among 502 subjects, being higher in females (45.9%) than in males (21.5%) [12]. Prevalence of MetS according to NCEP ATP-III criteria were 20.1% (15.9% in males and 23.9% in females) and 38.1% according to IDF criteria (39.7% in males and 36.6% in females) in Slovak population [13]. Among 901 data of participants from Colombia, 41% were determined to have MetS [14].

In Turkish population, 9.2 million adults aged over 30 years had MetS in 2000 according to Turkish Adult Risk Factor Study (TEKHARF) and 53% of people with coronary heart disease had MetS at the same time [15]. The 2012 scan of TEKHARF cohort demonstrates that MetS prevalence has reached to 53% in adults aged over 40 years with an increment rate of 1.3% over a 12-year period. The results of the latest scan focus on regional differences of MetS in Turkey; the prevalence is the highest in Southeast Anatolia, increasing in Mediterranean region while it is getting regressed in Marmara and the lowest in Aegean region. Today's prevalence of MetS in a 3800-participant cohort is 54.5% in women and 45.1% in men [16]. The results of Metabolic Syndrome Research (METSAR) conducted with 4529 subjects in 2004 demonstrated a MetS prevalence of 35%, being higher in women than

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men (41.1% vs. 28.8%) in adults aged over 20 years. Increase in age leads to increase in MetS prevalence in both genders with a prevalence of 49% in subjects aged over 70 years. These findings are based on waist circumference thresholds in men and women with assessment of 102 cm for men and 88 cm for women. Prevalence of MetS rises further when current borders for waist circumference are regarded (94 cm and 80 cm) [17]. There has been 4057 subjects recruited to Prospective Urban Epidemiological Study (PURE TURKEY) for MetS in 2010 and a waist circumference of >94 cm for men and >80 cm for women were accepted as MetS criteria; the prevalence in men was 41.4% while 43.5% in women. The study has also found a 57.7% of MetS prevalence in subjects aged 60-64 years which shows that by the increase in age, MetS is seen more frequently in Turkey. The same study has also revealed a remarkable rate of obesity in women and men, being 63.6% and 34.5%, respectively [18]. Prevalence of MetS in a sample representing Turkish population, using ATP III guidelines, was reported to be 33.9% and differed significantly in men (28.0%) and women (39.6%) [19]. A study of MetS among adults in the Mediterranean region of Turkey included 767 people aged 20 to 83 years old from 4 provinces; and prevalence of MetS was 34.6% (male, 31.2%; female, 37.3%) and 28.8% (male, 23.1%; female, 33.5%) according to IDF and ATP III criteria, respectively [20]. The prevalence of MetS was found to be very high in many large and small scale studies in Turkey and it is definite that main condition which deteriorates metabolism and coronary health of our population is the MetS [16].

Etiopathogenesis of Metabolic Syndrome

A single genetic, infectious or environmental factor that can explain etiopathogenesis of all components of MetS has not been defined yet. However, its aetiology can be examined in three categories: obesity/adiposity disorders, insulin resistance and independent factors such as vascular, hepatic and immunologic origin molecules. Although there is a polygenetic predisposition, sedentary life and unhealthy nutrition exacerbate the prognosis.

The idea that insulin resistance underlies MetS has been fortified by many guidelines and researches. Insulin resistance is the critical characteristic and sign point of MetS. Increase in insulin resistance and adipose tissue seems to be in collaboration with type 2 DM. On one hand, while plasma lipoprotein lipase (LPL) activity decreases and plasma triglycerides increase, on the other hand, degradation of HDL-C accelerates due to increased LPL activity in the liver during insulin resistance. One of the characteristics of insulin resistance is increased plasma free fatty acids (FFAs) concentration [21]. These FFAs stimulate accumulation of triglycerides in the liver. The discovery that adipose tissue, besides being energy storage, releases several peptide complement factors and cytokines to bloodstream as an endocrine organ, is revolutionary in terms of understanding the relation between insulin resistance and obesity. Molecules like interleukin-6 (IL-6) and tumour necrosis factor- α (TNF- α) which are released from adipose tissue, have also negative effects on metabolism [22].

Adiponectine is a plasma protein that is released from adipose tissue. It facilitates the clearance of plasma glucose, triglycerides and FFAs and it suppresses glucose production in the liver [23]. Furthermore, it inhibits the negative effects of inflammatory mediators which are important in atherogenesis processes by accumulating on the walls of injured blood vessels. Level of adiponectine declines in obese subjects and interestingly the regulation of adiponectine level are done in the omental adipose tissue instead of subcutaneous adipose tissue [24]. This mechanism is consistent with the link between visceral obesity and MetS and insulin resistance. Distribution of body fat is also an

important risk factor for insulin resistance. This has been systematically reviewed firstly by Vague et al in 1956 in which obesity was classified as "android" and "gynoid". It was determined that android type obesity was more related to DM and coronary heart disease when compared with gynoid type [25]. The connection between visceral obesity and insulin resistance results from metabolic characteristics of fat tissue accumulating in omental and paraintestinal area. Because visceral adipose tissue is basically more resistant to the effects of insulin and susceptible to lipolytic enzymes, it increases triglyceride synthesis in the liver by providing the passage of more FFAs to portal system and it may deteriorate first transition metabolism of insulin [26,27]. Apart from these, insulin resistance is also correlated with prothrombotic state accompanying MetS. It stimulates hyperinsulinemia and production of fibrinogen and plasminogen activator inhibitor-1 (PAI-1) which induces prothrombotic states that has a role in atherogenesis [28].

Dietary Factors Underlying Metabolic Syndrome

The aetiology of MetS which is one of the diet-related polygenic disorders [29] involves a complex interaction between genetic, metabolic and environmental factors including especially dietary habits [30]. Lifestyle changes (diet and physical activity) are thought to be the most important contributors to increasing incidence of MetS [31]. The consequences of excess energy intake that characterizes MetS are obesity, insulin resistance, hyperlipidaemia, and hypertension which show that causes of MetS are largely dietary in origin [32]. Therefore, the risk of MetS was found to increase due to a Western diet or a diet with high-glycaemic-load while Mediterranean diet and Dietary Approaches to Stop Hypertension (DASH) diet may reduce the risk [33]. Also, a recent investigation on the association of MetS with Chinese-style diet showed that eating poultry with skin and eating a bean-free diet may be associated with high MetS risk [33]. These kinds of high-energy, carbohydrate-rich, hyperlipidaemic diets which contain high amounts of fats, animal proteins, sugars, fructose, refined grains, salt, sweetened beverages and low amounts of fibre, fruits-vegetables, beans, whole grains, nuts were linked to excess cholesterol and saturated fatty acids (SFA) intake [33], to inflammatory state induced by high energy (largely from fats) intake that causes insulin resistance and the problem of excess energy disposal [32], to proinflammatory milieu marked by high levels of cytokines which could induce insulin resistance, dyslipidaemia and endothelial dysfunction [30], to elevated triglyceride, fasting blood glucose levels and systolic blood pressure, and to reduced HDL-C due to high percentage of energy intake from carbohydrates and high intake of refined grains and rice [34] and were hence found to lead to MetS and its gradually increasing prevalence.

Excessive exposure to dietary fat may play a key role in MetS development [29]. High prevalence of obesity and MetS in some developing countries was thought to result from high dietary fat intake and low physical activity level [33]. The amount and kind of dietary fatty acids can deteriorate some parameters involved in MetS due to their influence on plasma triacylglycerol, total cholesterol and Low Density Lipoprotein-C (LDL-C) concentrations by SFAs or on reducing HDL-C concentrations and increased LDL oxidation induced by Polyunsaturated Fatty Acids (PUFAs). Trans fatty acids have several implications in MetS since they are strongly associated with rise in inflammatory processes, plasma triacylglycerol and cholesterol, and reduction in HDL-C [35]. Dietary fat composition, particularly high portions of saturated fat and monounsaturated fatty acids (MUFAs), has been found to represent an important environmental factor which may relate to MetS risk. This increased risk has been attributed to elevated plasma Complement component 3 (C3) concentrations, which is a novel cardio-metabolic risk factor and an acute phase response protein

by high inflammatory state, by more oxidized oleic acid that negatively affects insulin sensitivity, by stimulating adipocyte C3 production from chylomicrons and in association with low HDL-C concentrations, impaired insulin sensitivity, hyperinsulinaemia and abdominal obesity [29]. It seems that dietary factors underlying MetS are as dominant as other aetiological ones. Especially in individuals predisposed to MetS display greater sensitivity to unhealthy eating habits such as high intake of total dietary fats [29].

Frequently Detected Conditions in Metabolic Syndrome in Turkey as in the World

Obesity

Obesity is an important risk factor for development of MetS and the recent rise in obesity is regarded as the triggering factor for expansion of it [36]. Obesity is a chronic low-grade inflammatory state that predisposes to development of insulin resistance and MetS [29]. Abdominal obesity which is associated with nutrition is accepted to form basis for dyslipidaemia, hyperglycaemia, hypertension and accordingly, cardiovascular diseases. Increment in insulin resistance induced by metabolically active molecules that are released from visceral adipocytes (leptin, resistin, IL-6, TNF- α , PAI-1), is the most important pathogenic factor during this process. Turkish Diabetes Prevalence Study (TURDEP-II) (2010) findings show that of subjects aged over 20 years, 37% are overweight (BMI 25-29.9 kg/m²), 35.9% are obese (BMI >30 kg/m²) while 53% have abdominal obesity³⁷. When the forthcoming threat that up to 60% of obese people will develop MetS [31] is thought, obesity becomes, therefore, the primarily precaution to be taken in Turkey.

Hypertension

Insulin resistance generally underlies essential hypertension. The hypertensive effect of insulin that is expected through stimulation of central sympathetic activity and water and sodium retention from kidneys is balanced with the hypotensive effect induced by peripheral vasodilatation in normal physiological conditions. In the presence of insulin resistance, due to additional resistance to peripheral vasodilator effect, hypertension is thought to occur by the unbalanced vasopressor effect. Besides that the rates of awareness, being under treatment and control in terms of hypertension are low worldwide, there are significant differences between countries [37]. Prevalence, Awareness and Treatment of Hypertension in Turkey (Patent) study showed the hypertension prevalence as 31.8%, the rates of awareness, being under treatment and control as 40%, 31% and 8%, respectively in Turkey by 2003 [28].

Hyperlipidaemia

Dyslipidaemia which is developed by visceral obesity and insulin resistance in patients with MetS is characterized with low concentration of HDL-C and high concentrations of triglyceride. There is an increase in atherogenic and Very Low Density Lipoprotein (VLDL) subgroups while LDL-C is generally in normal levels. Hypertriglyceridemia and low levels of HDL-C increase the risk of cardiovascular disease [38]. In Turkey, blood lipid levels were determined in the scope of METSAR in 4259 individuals; concentrations of total cholesterol were 173.6 mg/dl and 179.6 mg/dl while triglyceride levels were 148.3 mg/dl and 129.7 mg/dl in men and women, respectively. Levels of LDL-C were 98.5 mg/dl in men and 100.5 mg/dl in women, HDL-C levels were 46.3 mg/dl in men and 52 mg/dl in women with a general mean level of 49.2 mg/dl [15].

Insulin resistance, impaired glucose tolerance, diabetes mellitus

Risk of developing DM in patients with MetS has been determined to be 2 to 34 fold higher [39]. Albeit all type 2 diabetics do not develop insulin resistance, overt DM or impaired glucose tolerance is the first step of MetS diagnostic process; an additional insulin resistance is not sought. Insulin resistance increases atherosclerosis and cardiovascular disease risk independent from other risk factors. Approximately, in one thirds of patients with impaired glucose tolerance, overt DM may develop within 10 years. In 1997-1998 TURDEP-I data showed the prevalence of DM as 7.2%, impaired glucose tolerance as 6.7% in 24788 Turkish adults, being more prevalent in women. These data demonstrate a higher prevalence of DM in our country compared with many others [40]. The follow-up of TURDEP-I, TURDEP-II findings of 26499 Turkish adults in 2010 have shown a DM prevalence as 13.7% with a 90% rise within 12 years. Moreover, DM starts at a 5-year earlier age in 2010 compared with 1998 in our country. The rise in DM prevalence is not specific to our country. It is growing rapidly worldwide however; the rate in Turkey is very high [41].

Cardiovascular disease risk

Cardiovascular disease risk is more than 1.5 fold in patients with MetS. The presence of MetS, not obesity, is the condition that raises risk [39]. In a meta-analysis including 951.083 patients and 87 clinical studies in which NCEP and revised NCEP definitions were used for MetS diagnosis; MetS was found to increase cardiovascular disease risk at 2.35 fold, cardiovascular mortality 2.40 fold, all-cause mortality 1.58 fold, myocardial infarction risk 1.99 fold and stroke risk 2.27 fold. Cardiovascular risk was also found higher in women than men with MetS. Predisposition of postmenopausal women to abdominal obesity than men, a different cholesterol profile of women than men, a stronger relation of high triglyceride concentration with coronary artery diseases in women than men and women-specific risk factors such as polycystic ovary syndrome, hormone replacement treatment and gestational DM may have role in this higher risk [42].

Treatment Approaches in Metabolic Syndrome

The primary approach should be the arrangement of lifestyle because MetS is also a consequence of environmental factors. The aim is preventing DM and cardiovascular diseases. Weight loss with a proper nutrition and physical activity program provides a corrective impact of all disorders observed in MetS.

Dietary therapy and exercise

It is obligatory to educate the patient about healthy living. As a non-pharmacological approach; lifestyle and behaviour changes aiming weight loss with dietary therapy and exercise is the basis of MetS management. These interventions are the most effective and the cheapest approaches for preventing both insulin resistance and cardiovascular disease and DM development. Adiposity and physical detraining are important risk factors for mortality. With an appropriate exercise program, energy expenditure and insulin sensitivity are increased, in this manner cardiovascular event risk and MetS development are decreased [38]. Current clinical evidences exhibit that approaches including exercise for 100-150 minutes per week or preferentially 150-300 minutes per week and only 5-7% loss in weight are even adequate to prevent MetS, have favourable impact on lipid disorders, glucose tolerance and hypertension and decrease type 2 DM onset in 58% within three years [39].

The "realistic goal" in obesity treatment is not reaching the ideal

body weight; it is losing 10% of current weight within six months. With this goal, a medical nutrition therapy planned by dietitians with appropriate energy and nutrients intake is essential for weight control. Regular physical activity enables reaching this goal and maintenance of targeted body weight. In case of need and prescription, medicinal therapy or bariatric surgery (especially for those with BMI >40 kg/m²) may be used.

Traditional Mediterranean diet is one of the important choices in preventing MetS and coronary heart disease. Eating regular Mediterranean diet provides decline in concentrations of inflammation and coagulation markers and decreases cardiovascular events and mortality. The components of Mediterranean diet, especially olive oil, have favourable effects on health. It contains MUFA and polyphenolic compounds. Besides being more resistant to oxidation, oleic acid, MUFA of the olive oil, was also found to protect LDL-C from oxidation by its Oropain substance. There are data showing that subjects, who decrease the intake of saturated fat and increase the intake of olive oil, have higher levels of HDL-C and lower levels of LDL-C. It is also advocated that the best adipose tissue structure is provided by Mediterranean diet which includes MUFA, omega-3 fatty acids, soluble fibre, fruits-vegetables, and whole grains [40]. On the other hand, DASH diet that is rich in low-fat dairy foods, calcium and potassium, and low in sodium compared to Mediterranean diet, may have greater benefit for MetS with high content of flavonols, flavanones, carotenoids and phytosterols which could improve antioxidant capacity and reduce oxidative stress. This shows that dietary therapies for MetS reduction may have mechanisms other than the impact of weight reduction on MetS. In addition, a well adherence to healthy diets is associated with reduced inflammation and reduced MetS incidence [30]. Some specific dietary components (total dietary fibre, soluble fibre, insoluble fibre, fruit fibre, cereal fibre and legume fibre) were shown to have a protective effect on MetS. In Tehran Lipid and Glucose Study, risk of MetS decreased with 1 g increases of total dietary fibre, soluble and insoluble fibre intakes in 1000 kcal. The reduction in odds of MetS was 8% for total dietary fibre, 11% for soluble fibre and 7% for insoluble fibre. Especially soluble fibre was reported to improve insulin resistance by delaying gastric emptying, slowing absorption and digestion of carbohydrates [43]. A diet rich in phytoestrogens may be another protective and/or treating approach for MetS because they have been determined to involve in the down-regulation of pro-inflammatory cytokines, to increase insulin sensitivity and reverse cholesterol transport, to exert antioxidant effects and to increase energy expenditure through Peroxisome Proliferator-Activated Receptor (PPAR) pathway and mechanisms and they may help reduce triglycerides by balancing HDL/LDL ratio [31].

Smoking and drinking are obviously risk factors for cardiovascular, metabolic and hepatic complications in patients with MetS and these factors should be mentioned while talking about lifestyle changes.

Pharmacological therapy

Pharmacological therapy is required when lifestyle changes fall short. Decreasing LDL-C is the primarily goal for dyslipidaemia. Statins are used for reaching this goal [42]. Fibrate therapy may be thought for high concentrations of triglycerides and low concentrations of HDL-C [44]. The effects of antihypertensive medicines on metabolic parameters as well as on blood pressure should be taken into consideration in MetS. It is expected to control the blood pressure, prevent target organ damage, and positively influence metabolic parameters or at least not to affect them negatively. There is not yet a treatment choice targeting fibrinogen and PAI-1 in order to prevent prothrombotic states, nevertheless acetylsalicylic acid seem to be quite effective as an antiplatelet therapy.

It is efficient in primary and secondary protection of coronary events and a promising agent in primary protection of MetS. Struggling with proinflammatory part of MetS is getting more interest nowadays [42].

Conclusion

MetS is a risk factor causing atherosclerotic cardiovascular diseases and type 2 DM. Although diagnostic criteria differ in guidelines, those criteria conceptually are in correspondence with each other. Definition of MetS in clinical practice is going to appear as an approach which can contribute to struggling with multi-cardiovascular risks. On the other hand, the prevalence of MetS is more quickly increasing in Turkey than worldwide. Adhering to healthy diets may reduce the risk of MetS because it is well known that fighting with adverse effects of MetS without changing eating habits is not possible. There is also a superfast increase in the health outcomes of MetS (especially DM) in Turkey. Therefore, health authorities and health care professionals in Turkey should strive to implement the strategies by which prevalence of risk factors for MetS is reduced. Also, they should focus on determining the best therapeutic and preventive practices with regard to reasons of differences between MetS prevalence in geographical regions of Turkey.

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