An Overview about Management of Metabolic Syndrome

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Abstract

The definition of MetS encompass the presence of obesity and two of the three following criteria: high blood pressure, impaired glucose metabolism, elevated non-high-density lipoprotein (non-HDL) cholesterol level (atherogenic dyslipidaemia). Obesity is a disorder of energy homeostasis which manifests as excessive adipose tissue accumulation. It is diagnosed based on the body mass index (BMI) assuming that values above 30 kg/m2 confirm the diagnosis. The BMI, however, does not provide information on adipose tissue distribution (visceral or femoral- gluteal), so waist circumference measurements are used (the midpoint between the iliac crest and the lowest rib along the midaxillary line defines the measurement level). Weight loss is one of the primary interventions to positively affect all MetS conditions. The imbalance between energy intake and expenditure is the key cause of overweight and obesity, which are a part of the metabolic syndrome. Several plant extracts, spices, herbs, and essential oil extracts have apparent benefit in the management of patients with MetS but cannot be considered as an alternative for pharmacotherapy. However, these may be a promising field in the development of novel therapies. The crucial effects of physical activity include increase of HDL-C levels, reduction of triglyceride levels, improvement of glycaemic control due to increased tissue sensitivity to insulin, and blood pressure reduction.

Keywords: Metabolic syndrome, management

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Introduction

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that includes hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia. MetS, also is labeled as 'insulin resistance syndrome', 'syndrome X', 'hypertriglyceridemic waist', and 'the deadly quartet', MetS is strongly associated with an increased risk of developing atherosclerotic

cardiovascular disease (CVD). Any patient diagnosed with metabolic syndrome should at least be seen as a high cardiovascular risk patient ***(1).***

American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI) criteria are widely used for the diagnosis of MetS that require the presence of any 3 out of 5 metabolic traits for the diagnosis. These include: hypertension (>130/85 mmHg), abdominal obesity (a waist circumference of ≥102 cm in men, ≥88 cm in women, elevated triglycerides (TG ≥150 mg/dl), reduced plasma high-density lipoprotein cholesterol (HDL <40 mg/dl in men and <50 mg/dl in women), and impaired glucose tolerance (>100 mg/dl) ***(2).***

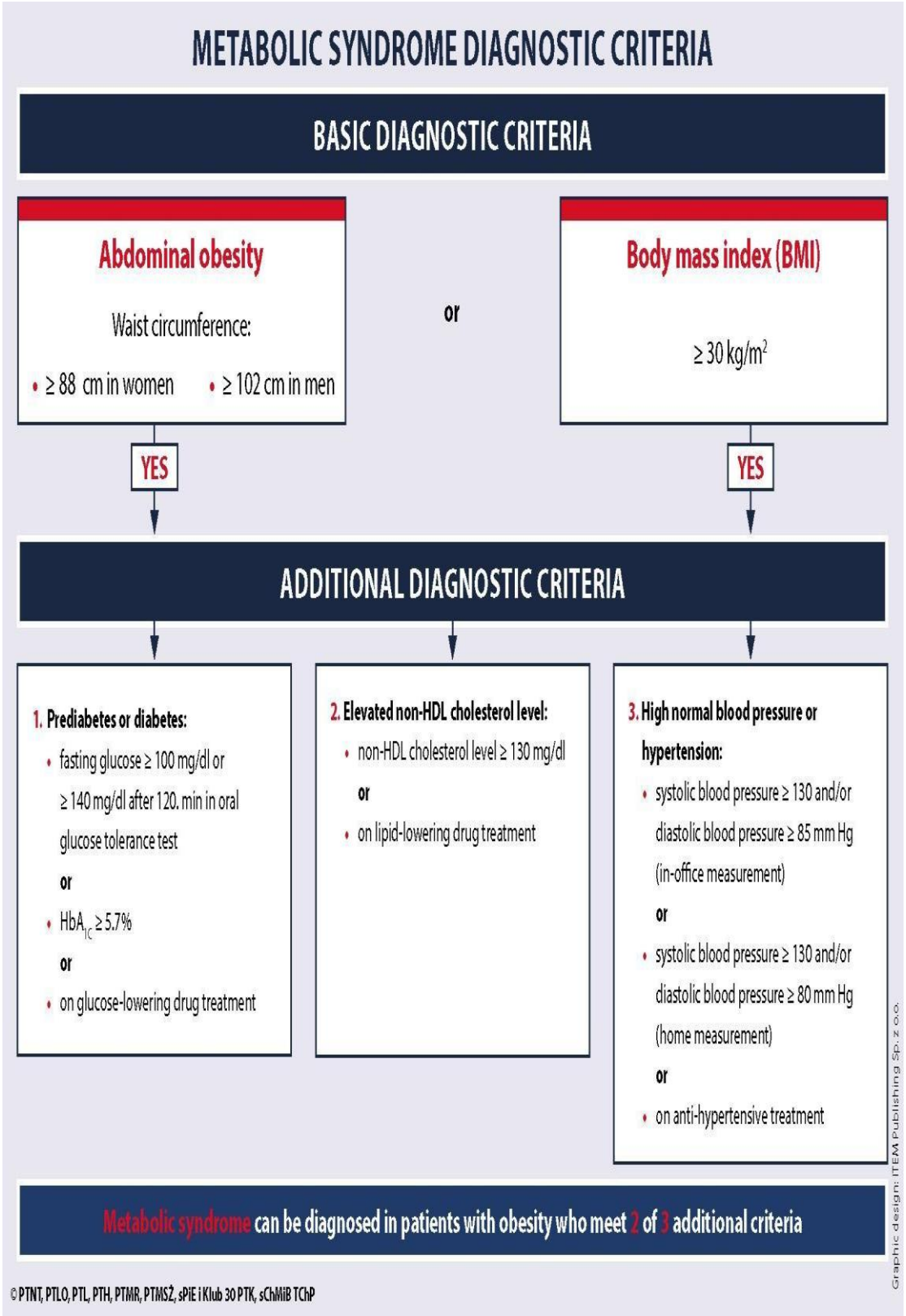
The prevalence of MetS has been reported as 27.3% in the Arabian Gulf Region.A number of factors can be attributed to this high prevalence, including lifestyle changes and rapid urbanization of the region in the last 40 years.According to the Center of Disease Control and Prevention (CDC), there is about 35% increase in MetS prevalence in The United States since the appearance of the term in the 1980still 2012 ***(3).***

Diagnostic criteria of metabolic syndrome

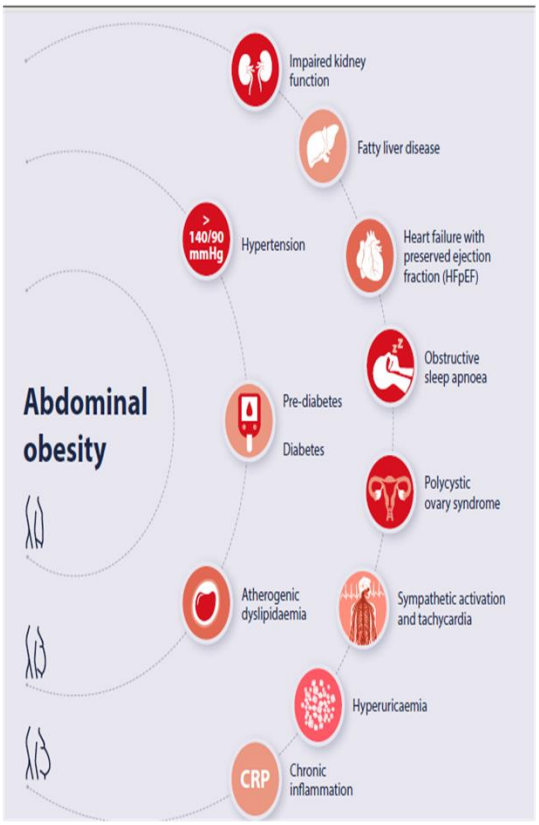
The definition of MetS encompass the presence of obesity and two of the three following criteria: high blood pressure, impaired glucose metabolism, elevated non-high-density lipoprotein (non-HDL) cholesterol level (atherogenic dyslipidaemia) The MetS diagnostic criteria are presented in ***(1).***

Furthermore, apart from the main components, MetS also encompasses additional conditions as impaired kidney function, hepatic steatosis, obstructive sleep apnoea, heart failure with preserved ejection fraction, polycystic ovary syndrome, chronic inflammation, sympathetic activation and hyperuricaemia ***(1).***

Obesity is a disorder of energy homeostasis which manifests as excessive adipose tissue accumulation. It is diagnosed based on the body mass index (BMI) assuming that values above 30 kg/m2 con- firm the diagnosis. The BMI, however, does not provide information on adipose tissue distribution (visceral or femoral- gluteal), so waist circumference measurements are used (the midpoint between the iliac crest and the lowest rib along the midaxillary line defines the measurement level). According to the criteria of the International Diabetes Federation (IDF), central obesity is diagnosed in European adults based on the waist circumference of 80 cm and 94 cm in women and men, respectively. A significantly increased risk of metabolic complications is found in women with a waist circumference of 88 cm and men with a waist circumference of 102 cm ***(1).***



Metabolic syndrome diagnostic criteria *(1).*



multisystem affection of metabolic syndrome *(1).*

Obesity as a basic element of metabolic syndrome

Atherogenic dyslipidaemia

Patients with MetS often have atherogenic dyslipidaemia, which includes elevated triglyceride levels, low HDL levels and normal to elevated LDL levels, with predominance of small, dense low-density lipoprotein (sdLDL) which additionally increases the CV risk *(4).*

Impaired glucose metabolism

Type 2 diabetes mellitus and MetS share common underlying mechanisms including insulin resistance and metabolic abnormalities linked to the excess adipose tissue and its dysfunction. Hyperglycaemia and lipid abnormalities (mainly hypertriglyceridemia) develop as a result of impaired tissue sensitivity to insulin. Increased insulin release from islet β-cells gradually leads to their exhaustion, followed by pre-diabetes and diabetes. *(5).*

Hypertension

There is a positive, linear correlation between BMI and the risk of hypertension, observable as early as the first decades of life *(6).*

All patients with hypertension concomitant with metabolic syndrome should be offered non-medical management aiming at significant lifestyle modifications, to include in particular:weight loss, reduced salt intake and increased physical activity *(6)*.

Impaired kidney function

The obesity-related mechanisms of nephron damage are not fully known. The postulated mechanisms included a combination of haemodynamic, metabolic and inflammatory abnormalities. Sympathetic activation, activation of the renin-angiotensin-aldosterone system (RAAS) and physical compression may contribute to hypertension, which, alongside metabolic disorders (e.g. diabetes), glomerular hyperfiltration and inflammation, may cause kidney injury *(6)*.

Hyperuricaemia

Experimental and clinical studies have indicated the role of uric acid in the development of different components of the metabolic syndrome: hypertension, diabetes, fatty liver disease, and chronic kidney disease. Uric acid has been postulated to irreversibly react with nitric oxide, causing endothelial dysfunction and development of hypertension. Nitric oxide deficiency leads to reduced blood flow to insulin-sensitive tissues, which exacerbates insulin resistance. Patients with higher serum uric acid levels have higher cardiovascular morbidity and mortality than those with lower serum uric acid levels *(7)*.

Sympathetic overdrive and tachycardia

High C-reactive protein (CRP) concentration , elevated white blood cell count and with increased inflammatory state in insulin resistance are assosciated with tachycardia in patients with MetS. Inflammation, on the other hand, plays the key role in pathogenesis and progression of atherosclerosis *(1)*. Tachycardia is a cardiovascular risk factor. which is also an indication for a medical intervention in those patients. Resting HR > 80 bpm in a patient with MetS suggests a higher CV risk *(8)*.

Inflammation

Higher levels of leptin in patients with metabolic syndrome correlate with atherogenesis and inflammation in obesity, through its effect on proinflammatory cytokine and fibrinogen release *(9)*.

Management of Metabolic syndrome

Diet

Weight loss is one of the primary interventions to positively affect all MetS conditions. The imbalance between energy intake and expenditure is the key cause of overweight and obesity, which are a part of the metabolic syndrome *(10)*.

To lose approximately 0.5 kg a week, a well-balanced diet is recommended, which reduces the daily caloric intake by 500–600 kcal *(1)*.

In patients with obesity and pre-diabetes, the treatment goal should be a weight loss of at least 5–7%. In patients with obesity and diabetes, the treatment goal should be a weight loss of at least 7–15% *(11)*.

It is recommended to reduce the intake of the trans-unsaturated fatty acids (present in highly processed foods, including commercial bakery products and some hydrogenated fats) and saturated fatty acids present in meat, dairy, coconut and palm oil (the benefits include reducing triglyceride levels and increasing the HDL-C level) *(12).*

It is recommended to Increase the amount of dietary fibre, by eating e.g. pulses, vegetables, fruit and whole- grain products (the benefits include reducing triglyceride levels, increasing the HDL-C level, improved control of blood pressure, body weight and glycaemia) Vegetables are also a good source of potassium, which positively affects blood pressure regulation *(13).*

It is recommended to Increase the intake of the omega-3 fatty acids, by eating e.g. fish (the benefits include reducing triglyceride levels) *(13).*

It is recommended to reduce the proportion of dietary carbohydrates (especially simple) to below 50% of all caloric intake, in particular by reducing the intake of sugary drinks (the benefits include reducing triglyceride levels) *(14).*

It is recommended to reduce salt intake (the benefits include decreasing blood pressure) *(13).*

Nutraceuticals

Several plant extracts, spices, herbs, and essential oil extracts have apparent benefit in the management of patients with MetS but cannot be considered as an alternative for pharmacotherapy. However, these may be a promising field in the development of novel therapies *(15).*

physical exercise

The crucial effects of physical activity include increase of HDL-C levels, reduction of triglyceride levels, improvement of glycaemic control due to increased tissue sensitivity to insulin, and blood pressure reduction *(1).* The latest guidance by the European Society of Cardiology recommends that to reduce all-cause mortality, CV mortality, and morbidity, the physical activity of an adult per week should be at least : *(13).*

- 150–300 min of moderate-intensity aerobic physical activity (defined as difficulty speakingin full sentences during the exercise);
- 75–150 min of vigorous intensity aerobic physical activity (defined as inability to speak during the exercise); or an equivalent combination of moderate and vigorous intensity activity *(13).*

Management of Metabolic syndrome comorbidities

Management of Obesity:

The goal of obesity treatment is to stop its progression, that is, further body weight increase, and subsequently to lose weight. Even a modest weight loss of 5% to 10% of total body weight is likely to produce health benefits *(16).*

Medical management of obesity

Medical treatment is a part of a complex management strategy and is used when non-medical interventions prove ineffective *(17).*

Medical management should also be considered in all patients with BMI

30 kg/m2 as well as those with BMI 27 kg/m2 and at least one overweight- related disease. Thus, all patients with MetS should be considered a priori as potential clients for medical treatment. ***(11)***.

Currently, the following drugs are approved and available for the treatment of obesity : orlistat, a lipase inhibitor; bupropion hydrochloride and naltrexone hydrochloride in a fixed-dose combination medication; and glucagon like peptide-1 receptor agonists (GLP-1RA) ***(11)***.

GLP-1RA should be used as a drug of choice in patients with overweight and obesity with comorbid MetS, pre-diabetes, type 2 diabetes mellitus, hypertension, atherosclerosis. Liraglutide is the only drug whose efficacy and safety have been provenin patients with obesity before or after bariatric surgery.

Naltrexone/bupropion in a fixed-dose combination medication should be primarily considered in patients with obesity comorbid with depression and those whose body weight increased following smoking cessation. It should also be considered in patients whose obesity is due to snacking. Orlistat is recommended as the second or third choice therapy ***(11)***.

Multidisciplinary approach to the management of obesity

Obesity management encompasses the cooperation between the patient and the multidisciplinary team of different healthcare professionals, including physicians representing various medical specialties, dieticians, psychologists and physiotherapists ***(17)***.

Surgical management of obesity

Bariatric surgery can lead to a complete, permanent weight loss and remission of obesity-related diseases, such as type 2 diabetes mellitus, hypertension, and dyslipidaemia components of MetS.

Based on their BMI levels, the following patients are eligible for bariatric surgery:

- those with BMI > 40 kg/m2;
- those with BMI of 35–39.9 kg/m2 and > 1 obesity-related disease (e.g. type 2 diabetes mellitus, hypertension, severe osteoarthritis, dyslipidaemia, severe Obstructive Sleep Apnea);
- those with BMI of 30–35 kg/m2 and type 2 diabetes mellitus which remains uncontrolled despite appropriate medical treatment ***(18)*** .

Pre-operative weight loss (5–10%) is indicated laparoscopic technique, considered the 'gold standard' in bariatric surgery. The procedure should be decided upon on a case-to- case basis, considering the patient's preferences, age or comorbidities ***(19)***.

Management of pre-diabetes

The management of pre-diabetes primarily involves reducing insulin resistance, mainly through weight loss. Weight loss of 5% improves glycaemic control, blood pressure and lipid profile, thus significantly reducing the risk of type 2 diabetes mellitus and its CV complications. ***(20)***

Metformin should be considered to prevent the development of type 2 diabetes mellitus in the following groups of patients with pre-diabetes: those aged < 60 with BMI ≥ 35 kg/m2, and women with a history of gestational diabetes *(21)*

Glucagon-like peptide-1 receptor agonists (GLP-1RA) can be considered in patients with BMI ≥ 27 kg/m2 to reduce the risk of progression of pre-diabetes to type 2 diabetes mellitus (liraglutide – target dose of 3 mg; semaglutide – target dose of 2.4 mg) *(22).*

Management of diabetes

In cases with concomitant overweight/ obesity, atherosclerotic cardiovascular disease, chronic kidney disease or very high cardiovascular risk, dual therapy involving metformin and another agent with a proven effect on cardiovascular risk, GLP-1RA or sodium glucose co-transporter 2 inhibitor (SGLT2i) is recommended. According to the American and European guidelines, GLP-1RA or SGLT2i monotherapy is possible in patients with type 2 diabetes mellitus *(23).*

Management of dyslipidaemia

Lipids levels in addition to cardiovascular risk scores determine the treatment indication which include : *(*4*).*

- High-intensity statin therapy up to the maximum tolerated dose to achieve the target LDL cholesterol level for a given risk group. For primary prevention, with If the maximum tolerated dose of a statin and ezetimibe fail to reduce the LDL cholesterol level to the target values; (*proprotein convertase substilisin / kesxin type 9*) PCSK9 inhibitor can be considered . For secondry prevention the combination of the maximum tolerated dose of a statin and ezetimibe and PCSK9 inhibitor is recommended .

The combination therapy using omega-3 fatty acids (PUFA, at 2– 4 g/day) and statin can be considered in patients with triglyceride concentrations above 2.3 mmol/l (200 mg/dl) despite statin treatment; The combination therapy using choline fenofibrate and statin can be considered as a part of primary prevention in patients with triglyceride concentrations above 2.3 mmol/l (200 mg/ dl) whose LDL cholesterol levels have been reduced to the target values, especially where the HDL cholesterol levels are low; The combination therapy using choline fenofibrate and statin should be considered in high-risk patients with triglyceride concentrations above 2.3 mmol/l (200 mg/dl) whose LDL cholesterol levels have been reduced to the target values, especially where the HDL cholesterol levels are low *(*4*).*

Hypertension

Choosing anti-hypertensive drugs *(24):*

The first-line treatment should involve a combination of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor blocker (ARB) with a dihydropyridine calcium-channel blocker or a thiazide/thiazide-like diuretic (preferably in a fixed dose combination). *(24).*

Where the target blood pressure fails to be achieved, the third anti- hypertensive medication should be added after 6–8 weeks, for the treatment to involve a combination of an ACE inhibitor

or ARB with a dihydropyridine calcium-channel blocker and a thiazide/thiazide-like diuretic (preferably in a fixed dose combination) ***(24).***

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