Review Article

Metabolic syndrome in the Mediterranean region: Current status

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ABSTRACT

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities including abdominal obesity, impaired fasting glucose, hypertension and dyslipidemia. It seems to affect about one-fourth to one-fifth of the Mediterranean population, and its prevalence increases with age, being similar for both sexes and depending on the region and the definition used, with the National Cholesterol Education Program-Adult Treatment Panel-III (NCEP-ATPIII) definition being the most effective in the identification of glucose intolerance and cardiovascular risk. Except for these, MetS is associated with fatty liver disease, some forms of cancer, hypogonadism, and vascular dementia. The Mediterranean diet seems to be an ideal diet in patients with MetS, being rich in fibre, monounsaturated and polyunsaturated fats, and low in animal protein; and decreases the prevalence of MetS and cardiovascular disease risk. Except for weight loss, multifactorial intervention including insulin resistance reduction and normoglycemia, management of dyslipidemia, optimizing blood pressure and administration of low-dose aspirin for patients at high or moderately high cardiovascular disease (CVD) risk are additional targets. The present review provides current understanding about MetS in the Mediterranean region, focusing on its prevalence, clinical significance, and therapeutic strategy.

Key words: Dyslipidemia, impaired glucose tolerance, Mediterranean diet, Mediterranean region, metabolic syndrome

Introduction

Metabolic syndrome (MetS) represents a constellation of cardiovascular risk factors, such as hyperglycemia, dyslipidemia [involving elevated triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C)], hypertension and abdominal obesity, which predispose the individual to increased risk of developing diabetes mellitus (DM) and cardiovascular disease (CVD).[1,2] It reflects our modern's world sedentary lifestyle, overnutrition, and resultant excess adiposity. It was first described by Reaven in 1988 as "syndrome X" or "insulin resistance syndrome".[3] Since then, several studies and definitions have been conducted and copious piece of literature has been produced.

Despite its growing prevalence worldwide, there is still lack of a uniformly accepted definition and great controversy with regard to the pathogenesis of MetS. The most widely accepted definition is that proposed by the National Cholesterol Education Program-Adult Treatment Panel-III (NCEP-ATPIII) criteria, which requires 3 or more of the following parameters: waist circumference (WC) >102 cm in men and >88 cm in women, HDL-C <40 mg/dl (<1.04 mmol/l) in men and <50 mg/dl (< 1.29 mmol/l) in women, TG ≥150 mg/dl (≥1.7 mmol/l), blood pressure (BP) ≥130/85 mmHg and fasting glucose ≥110 mg/dl (≥6.1 mmol/l).[4] There are other two commonly used definitions, one proposed by the International Diabetes Federation (IDF)[5] and one by the American Heart Association (AHA) and the National Heart Lung and Blood Institute (NHLBI).[6] According to the IDF definition, MetS is diagnosed if an individual has abdominal obesity, that is WC ≥94 cm in Europid men and ≥80 cm in Europid women and ≥2 of the remaining 4 criteria of the NCEP-ATP III definition.

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Cut-off points for hypertension, TG and HDL-C levels are the same but blood glucose levels are considered abnormal at lower levels [≥100 mg/dl (5.6 mmol/L)].[5] The definition proposed by the AHA/NHLBI in 2005 retained most of the NCEP-ATPIII criteria but adopted the same WC thresholds for some ethnic groups (e.g., Asians) and lower cut-off points for fasting glucose levels [≥100 mg/dL (5.6 mmol/L)] with the IDF definition.[6] Recently, the 2009 Joint Interim Societies (JIS) MetS definition was proposed which tried to unify the above three definitions. This uses the same thresholds for BP, TG, and HDL-C considers WC based on ethnicity [≥94 cm (men) or ≥80 cm (women) for a Mediterranean population, although it is not a mandatory criteria] and fasting glucose levels [≥100 mg/dL (5.6 mmol/L)]. Three or more of these criteria are required for diagnosis.[7] All these criteria are presented in Table 1.

There is no available unifying pathogenetic mechanism for the components of MetS. MetS is closely linked to IR and abdominal obesity, which develop as a result of an atherogenic diet and sedentary lifestyle in a metabolic susceptible individual.[8] Factors predisposing to this phenotype are genetic defects in insulin signalling pathways and mitochondrial function, advancing age and certain drugs, such as corticosteroids.[9] Specific genes, especially those that encode for 11β-hydroxysteroid dehydrogenase type 1, adiponectin, β3-adrenergic receptor, endocannabinoid receptors, may predispose to the development of MetS.[9] Finally, since the clinical features of MetS are shared by Cushing's syndrome it has been proposed that cortisol may contribute to the pathogenesis of both states. Increasing body of evidence has shown higher circulating cortisol levels in patients with MetS compared with healthy subjects despite being within the normal range, increased activity of cortisol in the periphery and dysregulation of the hypothalamic-pituitary-adrenal axis.[10]

The purpose of the present review is to provide knowledge about current status of the MetS in the Mediterranean population, focusing also on optimal therapeutic strategies.

Epidemiological Data

The prevalence of MetS is dependent on the population studied, determined by age, sex, race, or ethnicity, as well as on the definition used. In a large study of the United States (US) population using the NCEP-ATPIII criteria, the unadjusted and age-adjusted prevalence of the MetS was 21.8% and 23.7%, respectively.[11] Lower prevalence has been reported for other populations, such as among Korean adults (15.7% in 1998 and 14.4% in 2001, using the NCEP-ATP III criteria).[12] Data from the National Health and Nutrition Examination Survey (NHANES) III 1988-1994 or NHANES 1999-2000 involving the US population did not indicate any gender difference in prevalence.[13] Nevertheless, in two studies, the Mexico City Diabetes Study[14] and the Korean National Health and Nutrition Survey[12] women had a higher prevalence of the MetS than men. On the other hand, a recent study of the Finnish population demonstrated that the prevalence of the MetS based on both the NCEP-ATPIII and IDF definitions was higher in men than women.[15] The prevalence of MetS is lower in white, non-Hispanic women than men, and higher in African-American women than men.[9]

However, there are also conflicting data regarding the changes in prevalence. The age-adjusted prevalence of

Table 1: Comparison of the four definitions of metabolic syndrome

	NCEP-ATPIII, 2001	AHA/NHLBI, 2005	IDF, 2005	JIS, 2009
Criteria required	Any ≥3 of	Any ≥3 of	Mandatory: Waist circumference ≥94 cm (Europid men) or ≥80 cm (Europid women) Plus ≥2 of:	Any ≥3 of
Fasting blood glucose	fasting glucose ≥110 mg/dl (≥6.1 mmol/l)	fasting glucose ≥100 mg/dl (≥5.6 mmol/l)	fasting glucose ≥100 mg/dl (≥5.6 mmol/l)	fasting glucose ≥100 mg/dl (≥5.6 mmol/l)
High-density lipoprotein cholesterol	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women
Triglycerides	≥150 mg/dl (≥1.7 mmol/l)	≥150 mg/dl (≥1.7 mmol/l)	≥150 mg/dl (≥1.7 mmol/l)	≥150 mg/dl (≥1.7 mmol/l)
Waist circumference	≥102 cm (men) ≥88 cm (women)	≥102 cm (men) ≥88 cm (women)		≥94 cm (men) or ≥80 cm (women) for Mediterranean population
Hypertension	≥130/85 mmHg or specific treatment for this disorder	≥130/85 mmHg or specific treatment for this disorder	≥130/85 mmHg or specific treatment for this disorder	≥130/85 mmHg or specific treatment for this disorder

NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III, IDF: International Diabetes Federation, AHA: American Heart Association, NHLBI: National Heart Lung and Blood Institute, JIS: Joint Interim Society statement

the MetS increased from 27% in the NHANES III 1988-1994 to 32.9% in NHANES 1999-2000 (P = 0.014) in U.S. women, although it did not change in U.S. men (from 31.4-31.8%; p=0.866).[13] In the San Antonio Heart Study, an increase in the prevalence of the MetS was also demonstrated in both men and women, as well as Mexican Americans and non-Hispanic whites.[16] Nevertheless, the Mexico City Diabetes Study[14] and the Korean study[12] did not show any increase trend in the prevalence of the MetS, while in the Finnish study the prevalence increased significantly only in women during the years 1992-2002.[15]

Regarding Mediterranean population, in a representative cross-sectional study in Greece, including 4,153 adults older than 18 years, the age-standardized prevalence of the MetS was 23.6%.[17] The prevalence was similar in men (24.2%) and women (22.8%) (P = 0.3), as it was seen in the US population, and increased with age in both sexes, being 4.8% among participants aged 19−29 years and 43% for participants over 70 years old (P for trend < 0.0001). Most of those with MetS had ≥3 components of the syndrome (61%), with abdominal obesity (82%) and arterial hypertension (78%) being the most common of them in both sexes.[17] The prevalence of MetS in Italian adults >18 years seems to be lower, in particular, 18% in women and 15% in men, increasing from 3% among subjects aged 20−29 years to 25% in subjects aged 70 years or older.[18] In another Italian cohort of patients older than 65 years, the prevalence of MetS was 25.9% in non-diabetic men and 55.2% in non-diabetic women.[19]

The prevalence of MetS is much higher in patients with DM (78.2% with NCEP-ATPIII and 89.5% with IDF criteria in a Spanish cohort), being even higher in sedentary diabetic patients (with NCEP-ATPIII definition: 86.2% and with IDF: 93.9%).[20] The prevalence of MetS is also higher in specific patient populations than that reported for the general population, such as those with hypertension (59%),[21] coronary acute syndrome (about 51%),[22,23] hypertriglyceridemia (about 79%),[24] current smokers, subjects with heavy compared with moderate carbohydrate intake, physical inactivity, alcohol intake, lower household income, and those living in an urban area.[9]

As far as the definition criteria are concerned, the prevalence appears to be higher using the IDF criteria in comparison with NCEP-ATPIII.[9,25,26] Analysis of cross-sectional data from nearly 10,000 subjects from the general Greek population comparing the four different definitions (including the JIS one) in terms of the MetS prevalence and predictive value of MetS-related CVD risk, demonstrated much higher prevalence with the IDF and JIS definitions compared with the NCEP-ATPIII and AHA/NHLBI ones. The prevalence of CVD in those with MetS according to IDF and JIS was similar to the whole study population.[25] The age-adjusted prevalence of MetS defined by NCEP-ATPIII and AHA/NHLBI was 24.5% and 26.3%, respectively (P = 0.09), whereas that of IDF and JIS-defined MetS was 43.4% and 45.7% (P < 0.0001, for both comparisons), although the calculated vascular event risk was lower in those with IDF-defined MetS.[25]

Similar data have been conducted by other Mediterranean cohorts. In an Italian cohort of about 3,000 participants, the IDF definition produced a relevant increase in the prevalence of MetS, particularly in older subjects, when compared with NCEP-ATPIII criteria. Moreover, NCEP-ATPIII definition seems to be more effective than IDF in the identification of glucose intolerant subjects.[26] A Spanish cohort showed also a higher overall prevalence with the JIS criteria. In this study of Mediterranean population, the prevalence of MetS using the new definition increased significantly with age, being 4 times higher in individuals over 60 years than those younger than 40 years (P < 0.0001).[27] Interestingly, in a Spanish sample of elderly patients (>65 years) when the IDF definition was applied, the total prevalence was 48.9%, while the prevalence according to NCEP-ATPIII criteria was 46.8%, with a higher prevalence of MS in females than males and a steady decrease as the age of patients increased, both for the ATP III and the IDF definition.[28] These data indicate that IDF and JIS are not useful enough tools in identifying patients at increased CVD risk. Another study from Greece showed that the use of IDF definition results in increased labelling of elderly patients with the diagnosis of MetS, failing, however, to identify more at high risk of stroke.[29] Similar data were reported from a study in a hypertensive Mediterranean population, which indicated a higher prevalence of MetS according to the IDF and JIS definitions compared with that of the NCEP-ATPIII in both genders.[30] Nevertheless, IDF and JIS are more appropriate for Asian populations.[17]

In terms of gender-specific differences in CVD risk factors, a Greek study showed that arterial hypertension and hypertriglyceridemia were more common in men (89.6% vs 84.2% and 86.8% vs 74.2%, respectively; P < 0.001), while women presented with lower HDL-C and higher prevalence of abdominal obesity (58.2% vs 66.2% and 85.8% vs 97.1%, respectively; P < 0.001).[31] The 10-year risk of fatal CVD events using different scores was higher in men (6.3% +/- 4.3% vs 2.7% +/- 2.1%; P < 0.001).[31]

Clinical Significance

The main utility of diagnosing MetS is the identification of people at high risk of CVD beyond low-density-

lipoprotein cholesterol (LDL-C) levels and at high risk of developing DM. Recent data indicate that MetS is a better predictor than glucose intolerance for the development of DM.[8] It is well known that MetS is associated with increased risk of cardiovascular morbidity and mortality.[1,2] In terms of the prevalence of CVD in patients of the Mediterranean region, it is significantly higher in those with MetS than those without (29.4% vs 9.6% in a recent study).[32] Interestingly, subjects with the MetS but no DM have the same CVD prevalence (24.1%) with those with DM without the MetS (25.4%), but lower than those with both the MetS and DM (40.7%). The odds ratio (OR) of prevalent CVD in all patients with MetS was 1.94 in a Greek study (95% CI = 1.35−2.47)[31] and 1.40 (CI = 1.02−1.97) in an Italian cohort.[19] Moreover, patients with both MetS and DM had an OR of 3.04 (95% CI = 1.98−4.11) and in those of MetS but no DM the OR was1.48 (95% CI = 1.12−1.92).[32] Higher OR (4.37, CI: 3.25−5.87) of CVD in individuals with both MetS and DM was shown from another Mediterranean cohort.[33] Nevertheless, this study failed to show an independent association of MetS with CVD in patients with or without DM, after further adjustment for its individual components, arguing against of an additional information provided by diagnosing MetS.[33] In both Mediterranean men and women a significant association of MetS with stroke (OR = 1.67, 95% CI: 1.02−2.75 in men and OR = 1.72, CI: 1.01−2.93 in women) and DM (OR = 4.58, CI, 3.12−6.74 in men and OR = 5.15, CI: 3.23−8.20 in women) has been reported.[19]

A recent Italian study in patients over 65 years old and MetS showed also an increased risk in all-cause [hazard ratio (HR):1.41 (95% CI: 1.16−1.72)], P = 0.001) and cardiovascular mortality [HR: 1.60 (1.17−2.19), P = 0.003]. In this study, high glucose levels in both sexes and low HDL-C in women were independent predictors of mortality.[34] In another study from the Mediterranean region, MetS was associated with carotid intima-media thickness (IMT), an early marker of atherosclerosis. In particular, subjects with MetS had a significantly higher prevalence of a carotid IMT >0.80 mm and of carotid plaques compared with those without MetS. This correlation was evident for TG and fibrinogen levels.[35] Conflicting data have emerged regarding the ability of MetS to predict CVD risk independently of its components. A meta-analysis reported a relative risk (RR) of cardiovascular events and death of 1.78 (95% CI: 1.58−2.00), being stronger in women and remaining significant after adjusting for traditional CVD risk factors (RR: 1.54, 95% CI: 1.32−1.79).[36] On the other hand, others failed to show an independent prediction of CVD with MetS, different from the sum of its components.[37]

Except for CVD and DM, MetS is also associated with as higher urinary albumin excretion, lower glomerular filtration rate (GFR) and a greater prevalence of chronic kidney disease, independently of its individual components (OR:1.33, 95%CI: 1.03−1.71).[21] Other co-morbidities include non-alcoholic fatty liver disease[38] sleep-disordered breathing,[39] and hypogonadism in males, according to the results of a recent meta-analysis.[40] Furthermore, MetS has been associated with increased incidence of some types of cancer. A recent meta-analysis including a case-control study of Mediterranean (Italian) population indicated an increased risk of pancreatic cancer (RR: 1.55, 95% CI: 1.19-2.01), with DM being the key component for this correlation.[41] In another recent study, MetS in postmenopausal women was significantly associated with increased incidence of breast cancer (OR = 1.75, 95% CI: 1.37−2.22) and this risk was higher at older age.[42] One of the proposed mechanisms for this association may be related to increased insulin and insulin-like growth factor-I (IGF-I) activities observed in MetS. Elevated serum insulin concentrations observed in MetS and IR states increase the level and bioavailability of IGF-I, which in turn plays a key role in the development and progression of several cancers.[43] Finally, studies from the Mediterranean region indicated an association of MetS with increased risk of vascular dementia (adjusted HR: 3.82; 95% CI: 1.32−11.06)[44] and, in those with mild cognitive impairment, MetS was linked to increased progression to dementia (HR: 4.40; 95% CI: 1.30−14.82).[45]

Therapeutic Approach

Lifestyle modification based on a diet low in saturated and high in unsaturated fats, high in complex unrefined carbohydrates and fibre and low in added sugars and sodium combined with regular moderate to intense physical activity (at a minimum of 30 minutes/day) and smoking cessation, remains the cornerstone of therapeutic approach in patients with MetS.[9] Carbohydrates should constitute 40−65%, protein 10−35% (except those with nephropathy) and fats 20−35% of the total calorie intake. More specifically, saturated fats must be limited to <7%, trans-fatty acids to <1%, and cholesterol to <200 mg/day, while monounsaturated fats should be consumed, as they have beneficial effects on atherogenic dyslipidemia. In addition, n-3-polyunsaturated fatty acids (mainly from fish), which also have cardioprotective effects, should constitute about 10% of calorie intake.[9,46] Both low-glycemic load (LGL) diet and low-fat diet can reduce body weight, but the LGL diet appears to be more suitable for subjects with MetS.[47]

The Mediterranean diet seems to fulfil the aforementioned features of an ideal diet in patients with MetS. It is rich in fibre, monounsaturated and polyunsaturated fats, low in animal protein, and based mainly on fruit, vegetables, fish, nuts, whole grains, and olive oil.[9] The Mediterranean diet seems to be effective in reducing the prevalence of MetS and associated CVD.[48] It is also associated with longer life span[49] and prevention from some forms of cancer.[50] The healthiest components of the Mediterranean vary among the Mediterranean countries. However, fish, olive oil, red wine and vegetables are four essential components of such diet in all the countries. One form of such diet is the "Spanish Ketogenic Mediterranean Diet" (SKMD), which is a protein ketogenic diet including virgin olive oil as the principal source of fat (≥30 ml/day), green vegetables and salads as the main source of carbohydrates, fish as the main source of proteins and moderate red wine intake (200−400 ml/day).[51,52] Recent studies have shown that SKMD is effective in losing weight and safe in ameliorating all the components of the MetS, even in cases of not achieving the optimal body mass index (BMI).[51,52]

Regarding exercise, it may be beneficial beyond its effect on weight loss by selectively removing abdominal fat. It has been shown that aerobic exercise has a dose-response effect on visceral adiposity.[53] Furthermore, an intensive exercise intervention strategy seems to be further beneficial in patients with MetS. Indeed, a study in the Mediterranean population showed that a supervised aerobic and resistance training plus structured exercise counselling was superior to counselling alone as it resulted in significantly greater improvement in all the components of MetS, as well as inflammation, IR and CVD risk scores.[54]

Pharmaceutical intervention for losing weight includes only orlistat at the moment. Orlistat acts by reducing fat absorption via binding to gastric and pancreatic lipases, partially inhibiting the hydrolysis of TG into absorbable free fatty acids and monoacylglycerols.[53] This has been found to result in significant weight loss compared with placebo, but rebound weight gain, if discontinued.[55,56] In association with a hypocaloric diet, orlistat exerts a favourable effect on several CVD risk factors, including BP, fasting glucose, TG, and LDL-C levels in patients with MetS and type 2 DM.[57] Moreover in a large prospective study, orlistat plus lifestyle interventions reduced the incidence of type 2 DM by 37% in high-risk patients compared with placebo and lifestyle changes.[58] Sibutramine has previously been used as an appetite suppressant.[53] A recent study, the Sibutramine Cardiovascular OUTcomes (SCOUT) trial, conducted to assess the drug's cardiovascular safety in high-risk patients, demonstrated a 16% risk increase for the time from randomization to the first occurrence of a primary CVD event. The study also showed a 28% increased risk for nonfatal myocardial infarction (MI), and 36% for nonfatal stroke, although the rates for cardiovascular death and death from any cause were not increased.[59] For these reasons the drug was recently withdrawn from the market in the US, Canada, and Europe. According to the National Institute of Health (NIH) guidelines on obesity, pharmaceutical therapy for weight loss can be considered in patients with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of co-morbidities related to excess adiposity. In more severe cases of BMI ≥40 kg/m^2 or ≥35 kg/m^2 in the presence of significant co-morbidities, bariatric surgery may be considered.[9,60]

In addition to weight loss, multifactorial intervention including IR reduction and normoglycemia, management of dyslipidemia, lowering BP and administration of low-dose aspirin for patients at high or moderately-high CVD risk (10-year CVD risk ≥10%) is advisable.[9] Although no pharmacologic agent is currently approved to raise insulin sensitivity, metformin has been shown to reduce the progression to type 2 DM in patients with impaired glucose tolerance (IGT).[61] However, there are no cardiovascular end-point studies in patients with MetS treated with metformin. Thiazolidinediones (pioglitazone, rosiglitazone) may be an alternative option for insulin sensitivity. Pioglitazone seems to have a more beneficial effect than rosiglitazone on the plasma lipid profile.[62] In a recent randomized-controlled prospective study in adults with IGT pioglitazone reduced the risk of conversion of IGT to type 2 DM by 72% compared with placebo, although it was associated with significant weight gain and edema.[63] In another prospective trial, pioglitazone significantly reduced the risk of death, nonfatal MI and stroke compared with placebo in patients with type 2 DM.[64] On the other hand, rosiglitazone has been removed from the treatment algorithm of the American Diabetes Association and the European Association for the Study of Diabetes since it significantly increased the risk of MI and death from CVD.[65] Of note, significant concern has risen recently for pioglitazone due to a reported association with bladder cancer.[66]

In terms of dyslipidemia, LDL-C should be the main target of cholesterol-lowering therapy.[4] Each 10% decrease in LDL-C or 10% increase in HDL-C is associated with an 11% risk decrease for CVD.[67] Initiating treatment for LDL-C depends on the absolute CVD risk based on the number of risk factors present and the Framingham score.[4] For lower-risk patients (presence of 0-1 major risk factors and an estimated 10-year CVD risk of <10%

according to the Framingham score), the LDL-C goal is <160 mg/dl. For moderate-risk patients (presence of ≥2 risk factors and an estimated 10-year CVD risk of <10%), the LDL-C goal is <130 mg/dl. For moderately high-risk patients (presence of ≥2 risk factors and an estimated 10-year CVD of 10−20%), the LDL-C goal is <130 mg/dl, optionally <100 mg/dl. For high-risk patients [presence of coronary heart disease (CHD) or equivalent co-morbidities such as non-coronary forms of clinical atherosclerotic disease, DM, and multiple (≥2 CVD risk factors with an estimated 10-year risk of >20%], the LDL-C goal is <100 mg/dL, optionally <70 mg/dL when both CHD and DM are present.[4] A secondary target of cholesterol-lowering therapy is non-HDL-C. When TG levels are ≥200 mg/dl and the LDL-C goal has been achieved, the aim should be to decrease non-HDL-cholesterol to 30 mg/dl greater than LDL-C.[4]

Statins are the mainstay of treatment of dyslipidemia in MetS. They are the major LDL-C-lowering agents and reduce LDL-C by 25−45% depending on the dose and specific type of statin used. Statins also increase HDL-C by 5−10% and reduce TG by 7−30%.[4,9] They have several other effects independent of lipid-lowering, which include modulating endothelial function, stabilizing plaque and anti-inflammatory and antithrombotic effects, which further contribute to reducing the CVD risk associated with these drugs.[68] These pleiotropic actions have been shown in patients with impaired fasting glucose or IGT and the MetS.[68] Interestingly a recent Greek study comparing the estimated CVD (e-CVD) risk in patients with MetS when achieving LDL-C <100 mg/dl or <130 mg/dl by atorvastatin, showed greater reductions in e-CVD risk and actual CVD risk when the goal was <100 mg/dl. The reductions at 6 months were >50% in all patients and were even greater during the next 3 years.[69]

If the LDL-C goal is not achieved, other lipid-lowering drugs can be added to statins depending on the lipid profile of the individual patient. Ezetimibe or bile acid sequestrants such as colesevelam are effective in lowering LDL-C by 15−20%.[9] Plant sterols and stanols, which are available as food additives in a variety of dairy products, including margarine and yogurt, have a modest effect on LDL-C in combination with statins.[70] Moreover, fibrates decrease TG levels by 25−50% and LDL-C by up to 30% and increase HDL-C by 5−15%.[4,9] Fibrates, especially gemfibrozil, reduce CVD end points in patients with atherogenic dyslipidemia and MetS.[71] Omega-3 polyunsaturated fatty acids are particularly efficacious in lowering TG, decreasing these by 20−40%, although they raise LDL-C by 5−10% with no effect on HDL-C.[4,9] Finally, niacin is another alternative for reducing TG and non-HDL-C, either as monotherapy or in combination with LDL-C-lowering agents. It is the most potent agent for elevating HDL-C (5−15%), and for increasing the particle size of HDL-C.[4,9,72] It is also the only drug that lowers lipoprotein (a) levels in diabetics.[73]

Additional targets in order to minimize CVD risk in patients with MetS are reducing BP to <130/80 mmHg in patients with coronary heart disease, DM or chronic kidney disease, whereas for patients without these co-morbidities the target is <140/90 mmHg (preferably with angiotensin II converting enzyme inhibitors or angiotensin II receptor antagonists). In addition, low-dose aspirin is advisable for patients at high or moderately-high risk (10-year CHD risk of 10% or more).[4,9] For lower-risk patients, the benefit of aspirin must be weighed against the risk of hemorrhage.

Conclusion

MetS seems to affect about one-fourth to one-fifth of the Mediterranean population, with an increasing prevalence with age, being similar for both sexes and depending on the region and the definition used. The NCEP-ATPIII definition is the most effective in the identification of glucose intolerance and CVD risk. Except for these, MetS is associated with fatty liver disease, some forms of cancer, hypogonadism and vascular dementia. The Mediterranean diet seems to be an ideal diet in patients with MetS, being rich in fibre, monounsaturated and polyunsaturated fats and low in animal protein. It decreases the prevalence of both MetS and CVD risk. In addition to weight loss, multifactorial intervention, including IR reduction and normoglycemia, management of dyslipidemia, optimizing BP and administration of low-dose aspirin for patients at high or moderately-high CVD risk, should be considered.

References

1. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, *et al*. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709-16.
2. Obunai K, Jani S, Dangas GD. Cardiovascular morbidity and mortality of the metabolic syndrome. Med Clin North Am 2007;91:1169-84.
3. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
4. Grundy SM, Hansen B, Smith SC Jr, Cleeman JI, Kahn RA; American Heart Association; National Heart, Lung, and Blood Institute; American Diabetes Association. Clinical management of metabolic syndrome: Report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Circulation 2004;109:551-6.

5. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome: A new worldwide definition. Lancet 2005;366:1059-62.
6. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, *et al*. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.
7. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, *et al*; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the Metabolic Syndrome. A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.
8. Cameron AJ, Zimmet PC, Soderberg S, Alberti KG, Sicree R, Tuomilehto J, *et al*. The metabolic syndrome as a predictor of incident diabetes mellitus in Mauritius. Diabet Med 2007;24:1460-9.
9. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, *et al*. The metabolic syndrome. Endocr Rev 2008;29: 777-822.
10. Anagnostis P, Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Clinical review: The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. J Clin Endocrinol Metab 2009;94:2692-701.
11. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. JAMA. 2002;287:356-9.
12. Park HS, Kim SM, Lee JS, Lee J, Han JH, Yoon DK, *et al*. Prevalence and trends of metabolic syndrome in Korea: Korean National Health and Nutrition Survey 1998-2001. Diabetes Obes Metab 2007;9:50-8.
13. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. adults. Diabetes Care 2004;27:2444-9.
14. Lorenzo C, Williams K, Gonzalez-Villalpando C, Haffner SM. The prevalence of the metabolic syndrome did not increase in Mexico City between 1990-1992 and 1997-1999 despite more central obesity. Diabetes Care 2005;28:2480-5.
15. Hu G, Lindström J, Jousilahti P, Peltonen M, Sjöberg L, Kaaja R, *et al*. The increasing prevalence of metabolic syndrome among Finnish men and women over a decade. J Clin Endocrinol Metab 2008;93:832-6.
16. Lorenzo C, Williams K, Hunt KJ, Haffner SM. Trend in the prevalence of the metabolic syndrome and its impact on cardiovascular disease incidence: the San Antonio Heart Study. Diabetes Care 2006;29:625-30.
17. Athyros VG, Bouloukos VI, Pehlivanidis AN, Papageorgiou AA, Dionysopoulou SG, Symeonidis AN, *et al*. The prevalence of the metabolic syndrome in Greece: the MetS-Greece Multicentre Study. Diabetes Obes Metab 2005;7:397-405.
18. Miccoli R, Bianchi C, Odoguardi L, Penno G, Caricato F, Giovannitti MG, *et al*. Prevalence of the metabolic syndrome among Italian adults according to ATP III definition. Nutr Metab Cardiovasc Dis 2005;15:250-4.
19. Maggi S, Noale M, Gallina P, Bianchi D, Marzari C, Limongi F, *et al*. Metabolic syndrome, diabetes, and cardiovascular disease in an elderly Caucasian cohort: The Italian Longitudinal Study on Aging. J Gerontol A Biol Sci Med Sci 2006;61:505-10.
20. Rodríguez Bernardino A, García Polavieja P, Reviriego Fernández J, Serrano Ríos M. Prevalence of metabolic syndrome and consistency in its diagnosis in type 2 diabetic patients in Spain. Endocrinol Nutr 2010;57:60-70.
21. Leoncini G, Viazzi F, Agabiti Rosei E, Ambrosioni E, Costa FV, Leonetti G, *et al*. Metabolic syndrome and chronic kidney disease in high-risk Italian hypertensive patients: The I-DEMAND study. J Nephrol 2011 in press.
22. Jover A, Corbella E, Muñoz A, Millán J, Pintó X, Mangas A, *et al*. Prevalence of metabolic syndrome and its components in patients with acute coronary syndrome. Rev Esp Cardiol 2011;64:579-86.
23. Miller AM, Alcaraz Ruiz A, Borrayo Sánchez G, Almeida Gutiérrez E, Vargas Guzmán RM, Jáuregui Aguilar R. Metabolic syndrome: Clinical and angiographic impact on patients with acute coronary syndrome. Cir Cir 2010;78:113-20.
24. Ascaso JF, Millán J, Mateo-Gallego R, Ruiz A, Suarez-Tembra M, Borrallo RM, *et al*. Prevalence of metabolic syndrome and cardiovascular disease in a hyper-triglyceridemic population. Eur J Intern Med 2011;22:177-81.
25. Athyros VG, Ganotakis ES, Tziomalos K, Papageorgiou AA, Anagnostis P, Griva T, *et al*. Comparison of four definitions of the metabolic syndrome in a Greek (Mediterranean) population. Curr Med Res Opin 2010; 26:713-9.
26. Mannucci E, Monami M, Bardini G, Ognibene A, Rotella CM. National cholesterol educational program and international diabetes federation diagnostic criteria for metabolic syndrome in an Italian cohort: Results from the FIBAR Study. J Endocrinol Invest 2007;30:925-30.
27. Bernal-Lopez MR, Villalobos-Sanchez A, Mancera-Romero J, Jansen-Chaparro S, Baca-Osorio AJ, Lopez-Carmona MD, *et al*. Why not use the HbA1c as a criterion of dysglycemia in the new definition of the metabolic syndrome? Impact of the new criteria in the prevalence of the metabolic syndrome in a Mediterranean urban population from Southern Europe (IMAP study. Multidisciplinary intervention in primary care). Diabetes Res Clin Pract 2011;93:e57-60.
28. De Luis DA, Lopez Mongil R, Gonzalez Sagrado M, Lopez Trigo JA, Mora PF, Castrodeza Sanz J; *et al*. Prevalence of metabolic syndrome with International Diabetes Federation Criteria and ATP III Program in patients 65 years of age or older. J Nutr Health Aging 2010;14:400-4.
29. Milionis HJ, Kostapanos MS, Liberopoulos EN, Goudevenos J, Athyros VG, Mikhailidis DP, *et al*. Different definitions of the metabolic syndrome and risk of first-ever acute ischaemic non-embolic stroke in elderly subjects. Int J Clin Pract 2007;61:545-51.
30. Mikhailidis DP, Lioudaki E, Vrentzos GE, Mavrogeni H, Zeniodi MH, Ganotakis ES, *et al*. Prevalence of metabolic syndrome according to different definitions in a hypertensive population. Angiology 2011 in press.
31. Chimonas T, Athyros VG, Ganotakis E, Nicolaou V, Panagiotakos DB, Mikhailidis DP, *et al*. Cardiovascular risk factors and estimated 10-year risk of fatal cardiovascular events using various equations in Greeks with metabolic syndrome. Angiology 2010;61:49-57.
32. Athyros VG, Mikhailidis DP, Papageorgiou AA, Didangelos TP, Ganotakis ES, Symeonidis AN, *et al*. Prevalence of atherosclerotic vascular disease among subjects with the metabolic syndrome with or without diabetes mellitus: the METS-GREECE Multicentre Study. Curr Med Res Opin 2004;20:1691-701.
33. Bruno G, Fornengo P, Segre O, Novelli G, Panero F, Perotto M, *et al*. What is the clinical usefulness of the metabolic syndrome? The Casale Monferrato study. J Hypertens 2009;27:2403-8.
34. Zambon S, Zanoni S, Romanato G, Corti MC, Noale M, Sartori L, *et al*. Metabolic syndrome and all-cause and cardiovascular mortality in an Italian elderly population: The Progetto Veneto Anziani (Pro.V.A.) Study. Diabetes Care 2009; 32:153-9.

35. Antonini-Canterin F, La Carrubba S, Gullace G, Zito C, Di Bello V, Di Salvo G, *et al*. Association between carotid atherosclerosis and metabolic syndrome: Results from the ISMIR study. Angiology 2010;61:443-8.
36. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, *et al*. Metabolic syndrome and risk of incident cardiovascular events and death: A systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007;49:403-14.
37. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, *et al*. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005;28:385-90.
38. Chen SH, He F, Zhou HL, Wu HR, Xia C, Li YM. Relationship between nonalcoholic fatty liver disease and metabolic syndrome. J Dig Dis 2011;12:125-30.
39. Nakra N, Bhargava S, Dzuira J, Caprio S, Bazzy-Asaad A. Sleep-disordered breathing in children with metabolic syndrome: The role of leptin and sympathetic nervous system activity and the effect of continuous positive airway pressure. Pediatrics 2008;122:e634-42.
40. Corona GM, Forti GM. Testosterone and metabolic syndrome: A meta-analysis study. J Sexual Med 2011;8:272-283
41. Rosato V, Tavani A, Bosetti C, Pelucchi C, Talamini R, Polesel J, *et al*. Metabolic syndrome and pancreatic cancer risk: A case-control study in Italy and meta-analysis. Metabolism 2011;60:1372-8.
42. Rosato V, Bosetti C, Talamini R, Levi F, Montella M, Giacosa A, *et al*. Metabolic syndrome and the risk of breast cancer in postmenopausal women. Ann Oncol 2011 in press.
43. Pollak MN. Insulin, insulin-like growth factors, insulin resistance, and neoplasia. Am J Clin Nutr 2007;86(suppl):820S-2S.
44. Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, *et al*. Metabolic syndrome and the risk of vascular dementia: The Italian Longitudinal Study on Ageing. J Neurol Neurosurg Psychiatry 2010;81:433-40.
45. Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, *et al*. Metabolic syndrome, mild cognitive impairment, and progression to dementia: The Italian Longitudinal Study on Aging. Neurobiol Aging 2011;32:1932-41.
46. American Diabetes Association. Evidence based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Diabetes Care 2002;25:202-12.
47. Klemsdal TO, Holme I, Nerland H, Pedersen TR, Tonstad S. Effects of a low glycemic load diet versus a low-fat diet in subjects with and without the metabolic syndrome. Nutr Metab Cardiovasc Dis 2010;20:195-201.
48. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, *et al*. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: A randomized trial. JAMA 2004;292:1440-6.
49. Trichopoulou A, Kouris-Blazos A, Wahlqvist M, Gnardellis C, Lagiou P, Polychronopoulos E, *et al*. Diet and overall survival in elderly people. Br Med J 1995;311:1457-60.
50. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, *et al*. Mediterranean diet pyramid: A cultural model for healthy eating. Am J Clin Nutr 1995;61:1402S-6S.
51. Pérez-Guisado J, Muñoz-Serrano A. A pilot study of the Spanish ketogenic mediterranean diet: An effective therapy for the metabolic syndrome. J Med Food 2011;14:681-7.
52. Pérez-Guisado J, Muñoz-Serrano A, Alonso-Moraga A. Spanish Ketogenic Mediterranean diet: A healthy cardiovascular diet for weight loss. Nutr J 2008;7:30.
53. Yanovski SZ, Yanovski JA. Obesity. N Engl J Med 2002;346:591-602.
54. Fallucca F, Pugliese G, Missori S, Ribaudo MC, Alessi E, Strollo F, *et al*. Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: A randomized controlled trial: The Italian Diabetes and Exercise Study (IDES). Arch Intern Med 2010;170:1794-803.
55. Anagnostis P, Selalmatzidou D, Sapranidis M, Panagiotou A, Stergios A, Polyzos SA, *et al*. Comparative effects of sibutramine and orlistat on weight loss, glucose metabolism and leptin levels in non-diabetic obese patients: A prospective study. Indian J Endocrinol Metab 2011 in press.
56. Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, *et al*. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: A randomized controlled trial. JAMA 1999;281:235-42.
57. Didangelos TP, Thanopoulou AK, Bousboulas SH, Sambanis CL, Athyros VG, Spanou EA, *et al*. The Orlistat and Cardiovascular risk profile in patients with metabolic syndrome and type 2 Diabetes (ORLICARDIA) Study. Curr Med Res Opin 2004;20:1393-401.
58. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. Xenical in the prevention of diabetes in obese subjects (XENDOS) study: A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004;27:155-61.
59. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, *et al*. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010;363:905-17.
60. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, *et al*. Bariatric surgery: A systematic review and meta-analysis. JAMA 2004;292:1724-37.
61. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, *et al*. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
62. Miyazaki Y, DeFronzo RA. Rosiglitazone and pioglitazone similarly improve insulin sensitivity and secretion, glucose tolerance and adipocytokines in type 2 diabetic patients. Diabetes Obes Metab 2008;10:1204-11.
63. DeFronzo RA, Tripathy D, Schwenke DC, Banerji M, Bray GA, Buchanan TA, *et al*. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med 2011;364:1104-15.
64. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, *et al*. Secondary prevention of macrovascular events in patients with type 2 diabetes in the Proactive Study (Prospective pioglitazone clinical trial in macrovascular events): A randomised controlled trial. Lancet 2005;366:1279-89.
65. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.
66. Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. Diabetes Care 2011;34:1369-71.
67. Zhao XQ, Krasuski RA, Baer J, Whitney EJ, Neradilek B, Chait A, *et al*. Effects of combination lipid therapy on coronary stenosis progression and clinical cardiovascular events in coronary disease patients with metabolic syndrome: A combined analysis of the Familial Atherosclerosis Treatment Study (FATS), the HDL-Atherosclerosis Treatment Study (HATS), and the Armed Forces Regression Study (AFREGS). Am J Cardiol 2009;104:1457-64.
68. Krysiak R, Gdula-Dymek A, Bachowski R, Okopien B. Pleiotropic effects of atorvastatin and fenofibrate in metabolic syndrome and different types of pre-diabetes. Diabetes Care 2010;33:2266-70.
69. Athyros VG, Ganotakis E, Kolovou GD, Nicolaou V, Achimastos A, Bilianou E, *et al*. Assessing the treatment effect in metabolic syndrome without perceptible diabetes (ATTEMPT): A prospective-randomized

study in middle aged men and women. Curr Vasc Pharmacol 2011 [In Press].
70. Plat J, van Onselen EN, van Heugten MM, Mensink RP. Effects on serum lipids, lipoproteins and fat soluble antioxidant concentrations of consumption frequency of margarines and shortenings enriched with plant stanol esters. Eur J Clin Nutr 2000;54:671-7.
71. Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, *et al*. Diabetes, plasma insulin, and cardiovascular disease: Subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med 2002;162:2597-604.
72. Guyton FS. Long-term efficacy and safety of ezetimibe/simvastatin co administered with extended-release niacin in hyperlipidaemic patients with diabetes or metabolic syndrome. Diabetes Obes Metab 2010;12:983-93.
73. Pan J, Lin M, Kesala RL, Van J, Charles MA. Niacin treatment of the atherogenic lipid profile and Lp(a) in diabetes. Diabetes Obes Metab 2002;4:255-61.

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