Metabolic syndrome: nature, therapeutic solutions and options

Altan Onat
†Istanbul University, Cerrahpaşa Medical Faculty, Istanbul, Turkey

Introduction: Metabolic syndrome (MetS) defines the clustering in an individual of multiple metabolic abnormalities, based on central obesity and insulin resistance. In addition to its five components, prothrombotic and proinflammatory states are essential features. The significance of MetS lies in its close association with the risk of type 2 diabetes and cardiovascular disease (CVD). This field being an evolving one necessitated the current review.

Areas covered: The areas covered in this review include the so far unproven concept that enhanced low-grade inflammation often leads to dysfunction of the anti-inflammatory and atheroprotective properties of apolipoprotein A – I (apoA-I) and HDL particles, which further increases the risk of diabetes and CVD. It was emphasized that lifestyle modification is essential in the prevention and management of MetS, which includes maintenance of optimal weight by caloric restriction, adherence to a diet that minimizes postprandial glucose and triglyceride fluctuations, restricting alcohol consumption, smoking cessation and engaging in regular exercise. Drug therapy should target the dyslipoproteinemia and the often associated hypertension or dysglycemia. Statins are the drugs of first choice, to be initiated in patients with MetS at high 10-year cardiovascular risk. Such treatment is inadequate if fasting serum triglycerides remain at > 150 mg/dl, when niacin should be combined. Fibrates, omega 3 fatty acids, metformin, angiotensin-converting enzyme inhibitors and pioglitazone are additional options in drug therapy.

Expert opinion: Research on MetS in subpopulations prone to impaired glucose tolerance and insulin resistance has indicated that proinflammatory state and oxidative stress are often prominently involved in MetS, to the extent that evidence of impaired function of HDL and apo A-I particles is discernible by biological evidence of functional defectiveness via outcomes studies and/or correlations with inflammatory and anti-inflammatory biomarkers. A sex difference has been clear in this development.

Keywords: abdominal obesity, atherogenic dyslipidemia, cardiovascular disease risk, diabetes mellitus, HDL dysfunction, metabolic syndrome

1. Introduction

Metabolic syndrome (MetS) refers to the concurrence in an individual of multiple metabolic abnormalities associated with cardiovascular disease (CVD). When initially described by Reaven [1], greater weight was afforded to insulin resistance and lesser weight to central obesity than is now considered. The definition recommended by the Adult Treatment Panel (ATP-III) of the National Cholesterol Education Program (NCEP) [2] constituted an important step to our understanding of the physiopathology and to its identification by simple clinical criteria. Presence of three out of five criteria was required to identify MetS, namely abdominal obesity (≥ 102 cm in males, ≥ 88 cm in females), elevated serum fasting triglycerides (≥ 150 mg/dl), low high-density lipoprotein cholesterol (HDL-C; < 40 mg/dl in
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1.1 Pathogenesis, modification of criteria and current consensus definition

In agreement with the American Diabetes Association, which reduced the threshold of impaired fasting glucose to 100 mg/dl, the National Heart, Lung, and Blood Institute/American Heart Association (NHLBI/AHA) modified the dysglycemia criterion of the ATP-III definition of MetS, lowering it to 100 mg/dl [3]. The International Diabetes Federation (IDF) set abdominal obesity as an obligatory component and, importantly, recommended different thresholds for this parameter in diverse ethnicities [4]. This was due to increased recognition that the threshold of atherogenic dyslipidemia and signs of enhanced low-grade inflammation associated with abdominal obesity varies in main ethnic groups. IDF recommended that the cutoff for abdominal obesity in Europeans be 94 cm in men and 80 cm in women. Finally, a joint committee of several related associations recently produced a joint statement that harmonized the definition of MetS with respect to abdominal obesity [5]. It was recommended that abdominal obesity not be an obligatory component for which national or regional cut points for waist circumference can be used. The proinflammatory and prothrombotic states had been recognized already by the ATP-III as components, without being included among the criteria for clinical diagnosis of MetS in the joint interim statement.

1.2 Prevalence of MetS

The prevalence of MetS increases with age and varies with ethnicity and race. Moreover, a plateau is reached earlier in men than women: while males onwards of 50 years of age reach a plateau of highest prevalence, females, exhibiting a steep rise after menopause, reach the highest prevalence past age 60 years.

In the USA, MetS is estimated to prevail in 34% of adults (aged 20 years or over) according to the National Health and Examination Survey 2003–2006 using revised ATP-III criteria [6]. This percentage was about 5 points higher than the estimate in the period 1988–1994. In nondiabetic European adults, a prevalence of 15% was reported using modified WHO criteria [7].

Higher MetS prevalence has been observed in Middle Eastern populations: 39% among Turks [8] and 33.2% among Iranians [9], using the original ATP-III definition. On the other hand, lower prevalence of MetS was found in East Asian populations: for example ~14% in a relatively small population sample in East China with waist circumference modification of the ATP-III criteria [10].

MetS develops in far fewer adolescents than in adults, though this trend is rising. For instance, among US adolescents, this prevalence was estimated at 6.4% [11]. An IDF consensus report [12] recommended similar abdominal obesity cutoffs to adults in adolescents aged 16 years or over, but 90th percentile waist circumference values in those aged <16 years. The application of the MetS model has not yet been validated in adolescents in whom the impact of growth and puberty on reference values is variable.

1.3 Gender difference

Gender impacts obviously waist girth, the common measure of abdominal obesity. But the difference in the IDF-recommended cutoffs of waist circumference across genders varies strikingly [4]. Whereas a 14-cm lower cutoff is considered for women compared with men as the threshold in Westerners, the threshold recommended by the related organization compared with men is 5 cm lower for Chinese and 5 cm higher for Japanese women [5]. Our recommended thresholds in waist circumference among Turkish adults entail a 7-cm lower value in females [13].

More importantly, gender influences the response of proinflammatory state to overall adiposity and, in particular, central obesity and also the associated impaired function of HDL particles. Women are affected to a greater extent by this process, which is described in more detail below. Moreover, the association of inflammatory mediators is
largely independent of the ATP-III MetS components in men, but these mediators tend to act in conjunction with the components in women.

Finally, the impact of MetS on subsequent cardiovascular risk has been demonstrated to be higher in women, by a third, in a systematic review and meta-analysis of longitudinal studies [14].

1.4 Proinflammatory state and oxidative stress in MetS

The main shortcoming of current definitions of MetS, derived from practical necessity, is the lack of inclusion of any measure of proinflammatory state and oxidative stress, though clearly recognized – along with prothrombotic state – in its concept [2,3]. The multicenter Insulin Resistance Atherosclerosis Study had shown a linear relation between the inflammatory marker C-reactive protein (CRP) and the number of metabolic disorders [15]. The second shortcoming of defining MetS is not recognizing that a major component – lack of intact HDL function – does not fully overlap with reduced cholesterol concentration in HDL, but rather with impairment in its function or in its main apolipoproteins, which can either be assayed or established epidemiologically in prospective studies for outcomes of cardiometabolic risk. These statements do not aim to criticize the justifiable restriction of current criteria of the MetS components that have served and are still serving as a useful tool in identifying individuals with a cluster of risk variables at high risk of type 2 diabetes and CHD.

Experience over the past decade, however, has shown that both of the two shortcomings described, associated in fact with each other, is not an uncommon phenomenon in certain subsets of populations at high risk of diabetes or CHD [16-18], or even the middle-aged and elderly populations at large, such as the Turks (Figure 1) [19,20]. It is important that clinicians are aware of this possibility.

Proinflammatory state and/or oxidative stress, derived mainly but not exclusively from nutrients containing excess fatty acids, is a very complex mechanism underlying cardiometabolic disorders (Table 1). The best biomarker for this process is CRP [21-23] but still does not reflect the whole process for which other markers have been reported in connection with MetS. These include inflammatory markers such as fibrinogen [24], apolipoprotein (apo) B [25], apo E [26], complement C3 [27], or markers of oxidative stress such as gamma-glutamyl transferase (GGT) [28-30], uric acid [31,32], low total bilirubin [33,34], chemokines and cell adhesion molecules. We found that CRP and complement C3, in particular, are largely nonoverlapping. In a population-based nondiabetic Swedish cohort, lipoprotein-associated phospholipase was associated with MetS, and each was additively related to increased risk for incident CVD [35]. It is likely that atherogenic small, dense, low-density lipoprotein (LDL) particles lay underneath these associations which illustrate the clustering of an inflammatory mediator with ATP-III-defined MetS.

1.5 HDL dysfunction

The existence of enhanced proinflammatory state and/or oxidative stress, in turn, promotes another adverse process, namely the development of HDL dysfunction [19,36], an unproven concept hitherto not widely appreciated, and which encompasses the anti-inflammatory and atheroprotective activities of HDL particles itself or its apolipoproteins A – I (or A-II or C-III) [37]. The consequent increase in HDL concentration [38] leads to heterogeneity in protective function of high levels of HDL-C [2]. We have obtained evidence among Turks (unpublished data) for the aggregation of lipoprotein (a) to apo A-I to form an immune complex, which constitutes a major risk factor of CHD at a magnitude approaching that of conventional risk factors.

These processes may cause misclassification of people actually with MetS into non-MetS in the case of only two major criteria (abdominal obesity and elevated triglycerides) in conjunction with HDL dysfunction being present. Such misclassification evidently may yield inconsistencies or variances in the impact of MetS. These considerations could lead to some adjustments (perhaps inclusion of a CRP level) in the future for identifying individuals with MetS.

1.6 Significance of MetS as a risk factor for type 2 diabetes and coronary heart disease

Numerous prospective studies have assessed the significance of MetS as a risk factor for type 2 diabetes [38] and CVD or death [7,8,39-44] using the ATP-III or WHO definitions, or their modifications. Gami et al. [14] reviewed systematically results of 172 – 573 individuals in 37 studies with respect to incident CVD and death. The relative risk (RR) was 1.78 (95% CI 1.58 – 2.00). In seven studies that provided separate risk estimates for both genders, the stated risk was higher for women compared with men (RR = 2.63 vs 1.98; p = 0.09). The authors concluded that people with MetS are at increased risk of cardiovascular events.

MetS has been found to be of high predictive value for type 2 diabetes [39,45-49]. Incident diabetes was found to be associated approximately fivefold higher in people with MetS than without [46]. On the whole, there were no great differences among the various MetS definitions with regard to their predictive ability of diabetes risk [47,48].

The issue of whether the cardiovascular risk conferred by MetS is greater than the risk imparted by the sum of individual components has been debated. Pooled results of three studies that simultaneously adjusted for MetS and its components showed an increased risk of CVD or death (RR = 1.54, 95% CI 1.32 – 1.79). The stated issue may not be as yet fully resolved because true cases of MetS with a pronounced element of enhanced low-grade inflammation or HDL dysfunction may be misclassified at present as indicated above.

The genetic polymorphism related most selectively to serum triglycerides, thereby, to MetS, is the -1131T > C polymorphism of the APOA5 gene. For every C allele of the -1131T > C polymorphism inherited, mean triglycerides
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were 16% higher in a meta-analysis, which concluded that these findings were consistent with a causal association between triglyceride-mediated pathways and CHD [50]. Excess risk for hypertriglyceridemia was associated with the minor C allele also among Turks in both genders and, in women, for atherogenic dyslipidemia and MetS, after adjustment for confounders [51].

2. Lifestyle modification in prevention and management of metabolic syndrome

In patients at risk of and with MetS, dietary strategies and lifestyle modification with improving physical inactivity, smoking cessation and limiting alcohol consumption are mainstays of prevention and management because such factors play a central role in the metabolic abnormalities underlying MetS (Table 2) [52].

It is recognized that macronutrient intake may induce oxidative stress and inflammatory responses. Postprandial hyperlipidemia representing raised levels of triglycerides, chylomicrons and remnant lipoproteins, induces oxidative stress and inflammation, added to the effects of postprandial hyperglycemia [53]. Postprandial hypertriglyceridemia, rather than fasting triglyceride levels, has been associated with increased cardiovascular events [54,55]. Ingestion of excess high-calorie, easily digestible foods causes abnormal surges in blood glucose and triglyceride levels [51]. Excess plasma glucose and free fatty acids outstrip the capacity of oxidative phosphorylation and induce production of free radicals such as superoxide anion [56]. This post-prandial oxidant stress triggers atherogenic changes, including increases in LDL oxidation, sympathetic tone, vasoconstriction and thrombogenicity [50,56]. The glycemic index of a food defines the increment in the area under the postprandial glucose curve after ingestion of 50 g of a specific food compared with that after ingestion of 50 g of oral glucose. Studies demonstrated that diets rich in high-glycemic-index, low-fiber foods independently increase the risk of both CVD and diabetes [57]. However, this issue remains controversial as consumption of test foods with a decreased glycemic load, when incorporated into a habitual diet, did not ameliorate metabolic risk markers in overweight subjects [58].

2.1 Improving postprandial dysglycemia and dyslipidemia

Diets that include large amounts of fresh unprocessed plants, with moderate levels of lean protein and omega 3 fatty acids or monounsaturated fats as well as of low levels of carbohydrates and saturated and trans fats, and that are rich in antioxidants substantially improve postprandial glucose and lipid levels [50,57]. Minimally processed plants such as vegetables, fruits, nuts, seeds and grains increase postprandial glucose and triglycerides to a lesser degree than do processed foods [59]. Green leafy vegetables such as broccoli and spinach, fruits such as grapefruits and cherries are recommended in this context [50].

Intake of dietary antioxidants is beneficial against the development of oxidative stress. Dietary antioxidants exist in deeply pigmented plant-based foods and certain drinks – such as berries, red wine, dark chocolate, tea and pomegranates – and, additionally, help protect the vascular endothelium from postprandial oxidant stress and inflammation [60]. The calorie-free herb cinnamon, rich in antioxidants, diminishes the postprandial glucose fluctuations, in part by slowing gastric emptying [61].

It has been found that chronic consumption of a diet high in processed carbohydrates leads to excess visceral fat, which predisposes to insulin resistance and low-grade inflammation and, in turn, to hypertension and CVD; whereas restriction of refined carbohydrates improves postprandial dysglycemia and dyslipidemia [62]. Via effects of delaying gastric emptying, slowing digestion and diminishing the postprandial fluctuations of glucose and triglyceride levels, dietary fiber is important in improving postprandial changes [63].

The traditional salad dressings of the Mediterranean diet, namely vinegar and olive oil, are beneficial for the patient with MetS. Vinegar diminishes postprandial glycemia, probably owing to slowed gastric emptying by acetic acid, and thus improves the meal-induced oxidant stress [50]. Lean protein not comprising saturated fat is considered to have anti-inflammatory and cardioprotective properties. Egg white, fish, lean meat including game meat and poultry breast meat blunt postprandial inflammation [62].

2.2 Calorie restriction for weight loss

An obvious issue is the sizes of the portions that determine the total calorie intake as well as the postprandial glucose spikes. Hence, portion control is of great relevance to the health effects of any diet. A reduction in the macronutrient intake...
in the obese subject reduces both oxidative stress and inflammatory mediators [64]. Reduction of caloric intake is particularly more effective in improving postprandial oxidative stress by restricting processed carbohydrates, saturated and trans fats [60,62].

Even modest weight loss of 5–10% decreases postprandial glycemia and lipidemia and reduces the risk of incident diabetes [62]. Effectiveness of caloric restriction is augmented by diets low in processed foods and high in vegetables, fruits, nuts, egg white, lean meat, soy protein and wholewheat, which improve inflammation, insulin sensitivity, lipids and blood pressure [65].

### 2.3 Restricting alcohol consumption

Though chronic excessive alcohol use has been known for a long time to lead to hypertension, CHD and death [66], it is generally recognized that a J-shaped dose–response relationship exists between drinking and risk of various vascular events [67]. Indeed, moderate chronic alcohol intake, defined at present as one to two drinks a day for women and two to four drinks for men, is associated with a better life expectancy [68] and with lower risk of CHD [66] in the general population. Most of the beneficial effect of moderate drinking is considered to be mediated by elevation in HDL-C [69] and moreso by improved fibrinolytic activity [70].

We found that gender modulated the response of cardiometabolic risk variables to moderate alcohol consumption among Turks inasmuch as men showed a log-linear positive association of drinking categories with blood pressure, serum low-density lipoprotein-cholesterol (LDL-C), apo B and CRP, while women responded with lower triglycerides and CRP [71]. This was reflected in a prospective analysis of 1900 Turkish adults that risk of incident MetS tended to be reduced in women alone, not in men, after adjustment for age, physical activity and smoking status [72]. The reduced risk may be mediated by the inverse association of alcohol intake with circulating complement C3 [27].

### 2.4 Avoiding physical inactivity

Lack of exercise has been considered a fundamental factor in the worldwide obesity epidemic observed in the last few decades. Physical inactivity lowers insulin sensitivity in skeletal muscles and magnifies the postprandial fluctuations of plasma glucose and triglycerides.

Postprandial triglycerides and glucose have been shown to be lowered substantially by walking for 90 min [73] or even by light-intensity exercise [74], whereas long cumulative sedentary time was associated with higher 2-h glucose levels [74]. Improvements in lipoprotein profile, including in lipoprotein particle sizes, in 111 sedentary overweight adults were related to the amount (jogging 20 miles a week) of physical activity rather than to its intensity or improvement in fitness [75]. Thus, exercise exerts beneficial effect by improving inflammation by both lowering postprandial metabolic alterations as well as by avoiding the accumulation of abdominal fat [74]. In a systematic review of the literature on the influence of physical activity on abdominal fat, 7 out of 10 controlled trials using imaging techniques to measure change in abdominal fat in overweight or obese subjects reported significant reductions compared with controls [76].

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### Table 1. Manifestations of proinflammatory state and its consequences in metabolic syndrome (MetS).

<table>
<thead>
<tr>
<th>Manifestation of inflammation</th>
<th>Specific biomarkers</th>
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<tbody>
<tr>
<td>Independent prediction of MetS</td>
<td>C-reactive protein [19-21], fibrinogen [22], apoB [23], apoE [24], complement C3 [25], GGT [26-28], uric acid [29,30], low total bilirubin [31,32]</td>
</tr>
<tr>
<td>Dysfunction of apolipoprotein A-I and HDL (reviewed in [33])</td>
<td>Lack of protection against diabetes and coronary heart disease and even induction of these diseases by apoA-I [17] and HDL-cholesterol [18] – mediated by aggregation of lipoprotein(a) to apoA-I and, possibly, by excess phospholipid transfer protein</td>
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### Table 2. Prevention and management of metabolic syndrome.

<table>
<thead>
<tr>
<th>Type of management</th>
<th>Specific options</th>
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| **Lifestyle modification** (cornerstone of management) | Caloric restriction  
Diet to minimize postprandial glucose and triglyceride fluctuations  
Restricting alcohol consumption  
Smoking cessation in men and some women  
Engaging in regular exercise |
| **Drug therapy** | Statins in individuals at high cardiovascular disease risk  
Niacin or fibrates (added to statins) to reduce fasting triglycerides to < 150 mg/dl  
Omega 3 fatty acids, low dose or 4 g/day |
| **Other options** | Metformin, 850 mg b.i.d.  
Pioglitazone to improve atherogenic dyslipidemia  
ACE inhibitors or angiotensin receptor blockers  
Hormone-replacement therapy in selected women only in their first decade of menopause |
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Exercise results in a fall in the markers of inflammation such as plasma CRP level [77]. Though its mechanism is not clear, the development of diabetes is clearly prevented and the risk is reduced among prediabetic people by exercise [78].

2.5 Discontinuance of cigarette smoking

There is general agreement on smoking cessation as a major lifestyle change in men with MetS, given the cardiovascular and noncardiovascular health hazards [79-81]. This is so despite the fact that discontinuance of smoking is followed by weight gain in both genders. In ethnic groups in whom smoking leads to abdominal obesity or to weight gain, smoking cessation is critical for a better outlook, regardless of gender.

However, in the prevention of MetS and in women with MetS, the effect of smoking is variable, beneficial effects offsetting the hazardous ones, depending on following observations. The relationship between cigarette smoking and obesity/diabetes is confounded by ethnicity, sex, effect of smoking on adiposity, serum insulin levels and on its influence on subclinical inflammation/oxidative stress. In the analysis of NHANES (National Health and Nutrition Examination Survey) II, cigarette-smoking US men and women had a lower age- and sex-controlled BMI than nonsmokers and gained substantially less weight after age 25 years [79]. Also among Swiss adults, the multivariably adjusted odds ratio for obesity versus normal weight was significantly lower among female smokers compared with nonsmokers, and similarly in males smoking fewer than 20 cigarettes daily [82].

Evidence is available that fasting insulin levels are slightly lower among smokers than nonsmokers and that, in an environment of prevalent insulin resistance and proinflammatory state/oxidative stress, not only is an impaired HDL function a major adverse determinant of cardiometabolic risk, but also the effect of cigarette smoking loses hazardous features and may emerge even as beneficial with regard to cardiometabolic risk [36]. Female gender significantly interacts with this situation.

In fact, our prospectively elicited observations in Turks may be summed up as smoking being associated with lower risk of abdominal obesity in both sexes. It significantly protected women against the development of type 2 diabetes after adjustment for age [83]. This effect was mainly via protection from obesity though a separate modest inhibiting effect on visceral fat accumulation could also be documented [84], as well as an inhibiting effect on serum levels of apo C-III [36] and complement C3 [27]. Thus, women who do not gain weight in the course of smoking need not be urged to discontinue light to moderate smoking, aiming to avoid obesity-related hazards of hypertension and diabetes upon smoking cessation. However, such women still need cautioning for potential cardiovascular and cancer risk.

It is worth emphasizing repeatedly that effective lifestyle change can improve all five components of MetS and is the cornerstone of prevention and management taking precedence to drug therapy.

3. Drug therapy for the dyslipoproteinemia and other individual risk factors

A Consensus Conference report of the American Diabetes Association recommends drug therapy in subjects with MetS and a high (≥ 20%) 10-year CHD risk, and drug administration based on the number and magnitude of their risk factors in those with a 10-year risk < 20% [85]. The primary objective in CVD risk reduction is stated as lowering LDL-C values. This is particularly of value in many patients with MetS who have (familial) combined hyperlipidemia. Drug therapy is suggested to be instituted in addition to lowering saturated and trans fat to < 7% of calories and dietary cholesterol intake to < 200 mg/day, lowering excess body weight and increasing soluble fiber consumption [85].

The choice of drug for this purpose is statins, which exert beneficial effects mediated by LDL-C lowering, modest effects on HDL-C and by anti-inflammatory effects. In rare cases of patients who are intolerant to statins, niacin or ezetimibe constitute a second line of drugs as monotherapy. Nicotinic acid combined with a statin selectively decreases small, dense LDL particles [86].

In patients with MetS at high CHD risk but without diabetes or CHD, statins should be initiated at LDL-C concentrations > 100 mg/dl. Treatment goal in such cases is to lower LDL-C concentrations to < 100 mg/dl or apo B levels to < 90 mg/dl.

The Consensus Conference report specifies that in patients with MetS and known clinical CHD or in those with diabetes plus one nonlipid risk factor (such as hypertension), the LDL-C treatment goal be < 70 mg/dl and apo B levels < 80 mg/dl [85].

3.1 Improving the atherogenic dyslipidemia

Second-level therapeutic importance has been assigned to approaches directed at lowering triglyceride-rich lipoproteins (triglycerides > 200 mg/dl) and raising reduced HDL-C concentrations in addition to lifestyle counseling [82]. In individuals on statin therapy who continue to have low HDL-C or elevated non-HDL-C, or if apo B levels remain elevated, combination therapy is recommended.

The preferred agent for combination with a statin is nicotinic acid since evidence for reduction in CVD events with niacin seems better than with fibrates [87,88]. Although insulin resistance has been associated with niacin, use of niacin at 1.5 g/day in diabetes did not significantly increase A1C levels [89,90].

3.2 Statin use and increased risk of diabetes and mortality

Usage of statin drugs has been reported to increase modestly the risk of incident diabetes [91,92]. The hazard ratio in a meta-analysis of statin trials has been described as 1.09 (95% CI 1.04 – 1.13) [88]. In addition, in a recent meta-analysis of 11 studies in a high-risk primary prevention setting, the use of statins was not associated with a significant reduction (RR = 0.91) in the risk of all-cause mortality [93]. Critical is the high-risk primary prevention setup which probably included HDL dysfunction.
for the high-risk setting. A plausible explanation is still needed. In our experience, statin drugs promoted hypertriglyceremic dyslipidemias independently of other variables such as waist girth, apo E and dysfunctional apo A-I in women with hypertriglyceridemia and elevated apo B. We have epidemiologic evidence to hypothesize that, in a proinflammatory milieu, statins may elevate concentrations of Lp(a) so that Lp(a) and apo A-I aggregate, thereby rendering the latter dysfunctional and ultimately promoting comparatively risk of type 2 diabetes and CHD. Obesity and MetS interacted with rosuvastatin therapy among subjects at high cardiovascular risk by demonstrating poor risk reduction in post hoc analyses of the JUPITER trial [94].

3.3 Fibrates
Several studies showed benefit of fibrates in reducing nonfatal myocardial infarction but not mortality or fatal myocardial infarction. These include the FIELD study with fenofibrate in people with diabetes [95], the older Helsinki Heart study [96] and the BIP trial with bezafibrate [97]. In the secondary prevention VA-HIT trial with gemfibrozil [98], nearly 1500 men having low HDL-C were examined as to whether measurement of HDL subpopulations provided information additional to the modest increases in HDL-C level relative to CVD-risk reduction. Gemfibrozil therapy was associated with decreases in the small, lipid-poor preβ-1 HDL (with apo A-I) and with increases in the small α-3 and preα-3 HDLs, but also with decreases in the large, lipid-rich α-1 and α-2 HDL. This indicated that, rather than changes in HDL subpopulations with gemfibrozil, diminution in inflammation might account for the CVD risk reduction.

The ACCORD (action to control cardiovascular risk in diabetes) lipid trial [99] showed not only the safety of fenofibrate–statin combinations, but also strongly suggested that patients with high triglycerides are those who benefit most from fibrates. A total of 5518 randomized patients were followed up over a mean of 4.7 years. The combination of fenofibrate (160 mg/day) and simvastatin fell short of significantly decreasing the primary cardiovascular outcome in the whole cohort compared with simvastatin alone, but reduced cardiovascular risk by 31% in a prespecified diabetic patient subgroup with high (≥ 204 mg/dl) triglyceride and low (≤ 34 mg/dl) HDL-C levels. A recent meta-analysis of fibrate [100] confirmed this distinction and indicated a 15% reduction in cardiovascular events per 0.3 mmol/liter improvement in the mentioned high triglyceride levels. Caution is deemed in women who did not experience benefit from combination therapy in the ACCORD trial.

3.4 Omega 3 fatty acids
Plasma triglycerides are lowered effectively by n3 fatty acids at high doses of at least 4 g daily and are a good adjunct to statin use in individuals in whom triglycerides remain high. In MetS, n3 fatty acids decrease the hepatic secretion of large very-low-density lipoproteins (VLDL) converting them to LDL [101]. Since cardiovascular outcome studies using high doses are lacking [85,102], evidence of objective benefit is unclear [103,104]. But low-dose omega 3 fatty acids could be used after an acute coronary event in view of two trials having demonstrated in patients with previous coronary artery disease reduction in all-cause mortality and sudden death [105] or major coronary events [106].

3.5 Metformin
Metformin may be used for its antihyperglycemic and triglyceride-lowering properties. Metformin (850 mg b.i.d.) at 12 months was shown to decrease serum CRP by a significant 14% in women with impaired glucose tolerance compared with the placebo group [107]. The reduction did not reach significance in men.

3.6 Pioglitazone
Pioglitazone, a peroxisome proliferator activated receptor-γ agonist, is beneficial on atherogenic dyslipidemia, raising HDL-C and decreasing triglycerides as well as lowering LDL particle number [108]. In 360 randomized diabetic patients with coronary artery disease, favorable effects of pioglitazone on triglyceride/HDL-C ratio correlated with delayed atheroma progression in the PERISCOPE (pioglitazone effect on regression of intravascular sonographic coronary obstruction prospective evaluation) study [109]. Persons with prediabetes (on ramipril treatment) randomly assigned to rosiglitazone in the DREAM trial [110] demonstrated a substantial reduction of outcome for diabetes or death compared with those assigned to placebo. South Asians experienced a smaller and Latinos a larger preventive effect. This effect of rosiglitazone (which is not yet on the market) was not sustained 1.6 years after therapy was discontinued in the DREAM-ON trial [111].

3.7 Niacin
Pooled data from five double-blind, placebo-controlled studies conducted in 1996 – 2002 in 432 patients with dyslipidemia treated with various doses of extended-release niacin were analyzed [112]. These showed that, at daily doses of 1 – 2 g, triglycerides were reduced by 14 to 33%, HDL-C was raised by 16 to 25% and lipoprotein(a) was reduced by 9 to 23%. Women respond to this drug possibly slightly better. Flushing occurred in every four out of five patients treated; low-dose aspirin was administered in order to reduce this effect, which led to withdrawal in few of them. Niacin-induced flushing is mediated by a stimulation of production of several prostaglandins. Laropiprant, a selective prostaglandin DP(1) receptor antagonist [113], may inhibit such a sensation of cutaneous vasodilation and burning when added to extended-release niacin [113,114].

In a review on glycemic regulation in dyslipidemic patients concerning the effects of niacin alone or in combination with statins, on fasting insulin and HbA1c were assessed to be modest and amenable to adjustment in hypoglycemic regimens [115]. Reductions in incidence of cardiovascular effects and the
degree of atherosclerotic progression in patients with atherogenic dyslipidemia were found to outweigh the mild effects on glycemic regulation. In a comparative evaluation of carotid intima-media thickness [116] in patients with optimal LDL-C and low HDL-C, the addition to statins of niacin-ER led to significant regression whereas the addition of ezetimibe led to progression despite greater reduction in LDL-C with the latter regimen.

3.8 Focus on hypertriglyceridemia

The recommendations outlined above are rational, yet are insufficient in a substantial proportion of individuals with MetS. The clinician should not be satisfied with reaching the treatment goal for LDL-C when fasting triglycerides remain above 150 mg/dl or when the ratio of triglyceride:LDL-C is persistently high, raising suspicion of proinflammatory state/oxidative stress, indicative of high cardiometabolic risk. Hypertriglyceridemia results from hepatic hypersecretion or decreased catabolism of triglyceride-rich lipoproteins. Keeping in mind that the development of both diabetes and CVD is critically related in individuals with MetS to hypertriglyceridemia and the associated proinflammatory state and potentially to the accompanying dysfunction of HDL and apo A-I particles, fasting serum triglycerides should be normalized by drug therapy.

In abdominally obese Turkish men aged over 45 years a triglyceride:LDL-C ratio of ≥ 4.5 and/or CRP > 2.5 mg/liter, and in women aged over 50 years a triglyceride level > 150 mg/dl (1.7 mmol/liter) and/or complement C3 level > 1.3 g/liter are the most appropriate markers regarding impaired anti-inflammatory or atheroprotective HDL function (unpublished data). Though trials are lacking, in such instances drug therapy as described above should be directed towards lowering fasting triglycerides to below 150 mg/dl, especially in women, concomitantly with strict adherence to dietary principles and increased exercise [117].

3.9 Medication against hypertension and low-grade inflammation

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have both antihypertensive and anti-inflammatory effects. Hence, they have been used as important options in preventing diabetes and CHD [118]. The HOPE, ALLHAT and VALUE trials reported secondary end point data showing reduction in incident type 2 diabetes in hypertensive patients. Since none was specifically designed to investigate new-onset diabetes, two large clinical trials – ONTARGET and TRANSCEND – have been conducted. In comparing telmisartan 80 mg daily with ramipril 10 mg daily, telmisartan was not better than ramipril in the outcome of new-onset diabetes nor in the primary outcome of vascular disease and mortality [119].

The finding in ONTARGET and TRANSCEND [120] that decline in cognitive function (as a manifestation of microvascular brain disease) was related to (micro)albuminuria, cross-sectionally and at 5 years’ follow-up, and that participants treated with ramipril and/or telmisartan had lower odds for decline in cognitive function than those treated with placebo, indicates that these drugs may be beneficial via anti-inflammatory or antioxidative effects in MetS patients who have hypertension and proinflammatory state.

In the NAVIGATOR trial, in individuals at high risk because of impaired glucose tolerance (IGT) and cardiovascular risk factors, neither the selective AT1 receptor antagonist valsartan, nor the short-acting insulin-secreting agent nateglinide improved cardiovascular prognosis; and risk of new-onset diabetes diminished (by 14%) only with valsartan [121].

Statins are recognized also to reduce serum CRP. The JUPITER trial in apparently healthy men and women without hyperlipidemia but with elevated CRP levels (≥ 2 mg/liter) using rosuvastatin (20 mg daily) showed halving of the CRP levels and reduction of the primary end point of CVD and death (HR = 0.56, 95% CI 0.46 – 0.69) [122]. However, the influence of pravastatin and atorvastatin on markers of oxidative stress in hypercholesterolemic subjects has been variable, reducing oxidized LDL and Lp-PLA2 but not affecting other markers; thus, their clinical utility is not yet defined [123].

3.10 Medication for weight reduction

Weight reduction is beneficial for most patients with MetS in which area orlistat, an inhibitor of gastrointestinal lipase activity, has been the drug most widely used. In a 4-year, randomized, placebo-controlled study of obese patients with normal or IGT, added to lifestyle changes, orlistat allowed additional weight loss by a mean of 3 kg and significantly reduced the incidence of type 2 diabetes, mainly in IGT patients [124]. With the exception of a higher incidence of mild to moderate gastrointestinal events, adverse events were similar in the two treatment groups. Some improvement of cardiovascular risk factors was noted, though components of atherogenic dyslipidemia were not favorably influenced.

Efficacy of orlistat in the maintenance of weight loss following a very-low-energy diet in abdominally obese patients with dyslipidemia and impaired fasting glucose was evaluated [125]. Orlistat added to lifestyle change was associated with maintaining an extra 2.4 kg of weight reduction for up to 3 years and with reduced incidence of type 2 diabetes.

3.11 Hormone-replacement therapy in postmenopausal women

Effects of hormone-replacement therapy (HRT) on components of MetS were analyzed by pooling 107 trials [126]. Apart from reducing by 30% the risk of new-onset diabetes and levels of Lp(a) and fibrinogen, HRT reduced significantly fasting glucose and HOMA (Homeostatic Model Assessment) index in women with diabetes, but increased CRP levels by 38%. HRT may be considered in selected women with MetS only in their first decade of menopause in whom satisfactory reduction in components are not obtained and who remain
under close observation. But the risk of stroke was shown to rise modestly with hormone therapy [127].

It should be borne in mind that effects of all the discussed drugs and their outcome are derived not from studies based specifically on patients with MetS but rather on the general population or patients with various conditions related to cardiovascular risk. Two clinical trials recruiting large proportions of patients with MetS and diabetes and testing the addition of niacin to a statin are ongoing (AIM HIGH and HPS-2 THRIVE).

4. Conclusion

The MetS cluster quintuples the risk of type 2 diabetes and nearly doubles the CVD risk. The often-associated enhanced systemic low-grade inflammation may lead, especially in women, to the (thus far little-recognized) dysfunction of the anti-inflammatory and atheroprotective properties of apo A-I and HDL particles, which increases the risk of diabetes and CVD even more.

Lifestyle modification should take precedence in the approach to the prevention and management of MetS. Maintenance of optimal weight by caloric restriction, adherence to a diet that minimizes postprandial glucose and triglyceride fluctuations to ameliorate the atherogenic dyslipidemia, restricting alcohol consumption, smoking cessation and engaging in regular exercise are issues to be emphasized by the clinician to each individual with or at risk of MetS. Drug therapy should target the dyslipoproteinemia and the often-associated hypertension. Statins are the drugs of first choice, to be initiated in patients with MetS at high 10-year cardiovascular risk, aiming to reduce LDL-C concentration to < 100 mg/dl. Such treatment, even if at goal, needs to be complemented by niacin or fibrates if fasting serum triglycerides remain > 150 mg/dl, with the purpose of reducing the associated proinflammatory state.

5. Expert opinion

Metabolic syndrome (MetS) defines the clustering in an individual of multiple metabolic abnormalities, based on central obesity and insulin resistance; it is associated with a fivefold risk of type 2 diabetes and a twofold risk of CVD. Beyond its five classical components, a prothrombotic and a proinflammatory state are recognized elements. For the clinical identification of MetS, a series of definitions evolved to one of a joint statement, which recommended the use of national or regional waist circumference cut points with respect to abdominal obesity, which needed not to be an obligatory component.

Research on MetS has been suboptimal in population segments prone to IGT and insulin resistance. This has indicated that proinflammatory state and oxidative stress are often prominently involved in MetS to the extent that evidence of impaired function of HDL and apo A-I particles [18-20] is discernible by biological evidence of functional defectiveness, either by follow-up for outcomes of diabetes, CHD or by correlations with inflammatory and anti-inflammatory biomarkers [36]. Such research may point to the necessity to develop relatively simple criteria to be included in the current ones with the purpose of improved identification of MetS and reducing the possible misclassification of people actually with the MetS into non-MetS.

Gender differences in the response of proinflammatory state to overall adiposity or to central obesity and in the associated impaired function of HDL particles are areas that clearly merit additional investigation. Interaction of gender and cigarette smoking in the setting of proinflammatory state as well as in the associated dysfunction of HDL and apo A-I particles may yield confirmation of favorable or neutral overall effect of smoking in cardiometabolic risk observed among Turkish adults [36,80]. The influence of oxidative stress induced by postprandial dyslipidemia on Lp(a) and on apo A-I dysfunction deserves further research to clarify additional mechanistic aspects in MetS and cardiometabolic risk.

Finally, more studies are needed to assess the effect of statin therapy in people with MetS, specifically at high cardiovascular risk, especially on lipoprotein(a) and apo A-I dysfunction, which might explain the modest increase in new-onset diabetes [92] and virtual lack of benefit on overall mortality [93] or morbidity [94] in recently reported meta-analyses and trials.

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Declaration of interest

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Affiliation
Altan Onat1,2

1Address for correspondence

1Istanbul University,
Cerrahpaşa Medical Faculty,
Istanbul, Turkey
Tel: +90 212 351 6217;
E-mail: alt_onat@yahoo.com.tr

2Nisbetiye cad. 59/24, Etiler 34335,
Istanbul, Turkey