

Exploration of the metabolic syndrome spectrum and its role in cardiovascular disease risk in Greece; the mediating effect of Mediterranean Diet: Results from the 10-year (2002-2012) follow-up of the ATTICA Study

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Abstract

Metabolic syndrome (MetS) is defined as a cluster of factors that increase the risk of cardiovascular disease (CVD). Its prevalence is rapidly increasing in Europe within the last decade, but to the best of our knowledge, there is no clear picture regarding its impact in Greece, while several definitions are being used to diagnose MetS presence. Moreover, there is no prospective data concerning the role of MetS in CVD risk for the Greek population. Thus, this review aimed to investigate which would be the most appropriate criteria for MetS diagnosis in Greeks, as well as to further explore the spectrum of MetS concerning CVD and their association to the adherence to the Mediterranean Diet through available epidemiologic evidence in Greece. Based on the Attica Study results, prevalence of Metabolic syndrome (MetS) varied from 20% to 51% according to definition used. Only the NCEP ATPIII revised definition highlighted that the MetS was significantly associated with CVD risk. After adjusting for several confounders each 1/55 increase in the MedDietScore, was associated with 3% lower risk for CVD incidence.

Key words: metabolic syndrome; mediterranean diet; cardiovascular disease; risk factors

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Introduction

The metabolic syndrome (MetS) constitutes a worldwide epidemic and is defined as a cluster of co-existing risk factors related to the development of atherosclerotic cardiovascular diseases (CVD), type 2 diabetes mellitus as well as increased all-cause mortality.¹ According to primary definitions, its main components were insulin resistance, central adiposity, dyslipidemia, arterial hypertension and endothelial dysfunction. Recently, various abnormalities such as chronic proinflammatory and prothrombotic conditions have been added to the entity of the syndrome, making its definition even more complex.^{2,3} Recently, inflammation process received increased attention concerning its role in the pathogenesis of various disorders ranging from insulin resistance and type 2 diabetes to fatty liver disease and CVD. It has been also demonstrated that MetS is associated with a chronic inflammatory response characterized by abnormal activation of several proinflammatory signaling pathways. Furthermore, regardless the presence or the progress of the MetS in an individual, C-reactive protein (CRP) levels independently predict the occurrence of future CVD events.² The latter has also been observed for other biological markers of inflammation such as interleukin-6 (IL-6) that have been positively associated with Body Mass Index (BMI) and fasting insulin levels.³ Besides the widely known and discussed components and the clinical implications of MetS, there is still no universally accepted pathogenic mechanism or use of consistent diagnostic criteria.⁴

Apart from all the aforementioned pathways linked to the presence of MetS either as the cause, or as the outcome, there are important highlighted lifestyle aspects strongly related to the presence of MetS, such as obesity. Presence of obesity enhances the risk of renal dysfunction promoting vascular damage.⁵ Observations among obese patients indicated that serum uric acid levels increase as a response to the glomerular filtration rate's (GFR) decrease and as a consequence, almost half of the patients with impaired renal function become hyperuricemic and this is the link between the two components of the

MetS that have been recently determined as such.⁶ Moreover, frequent physical activity and healthy dietary habits have been associated with favorable outcomes among subjects with metabolic disorders such as central adiposity and insulin resistance.⁷ The traditional Mediterranean Diet pattern is characterized by an abundance of plant foods, nuts, legumes, whole grains, moderate consumption of fish and poultry, low consumption of red meat, moderate consumption of wine (usually with meals) and high consumption of olive oil rich in monounsaturated fatty acids.^{7,8} The beneficial role of adhering to the Mediterranean Diet with regard to mortality from all causes, cardiovascular disease (CVD) and cancer, as well as obesity and type 2 diabetes has already been extensively reported^{7,9} and they are usually linked to anti-inflammatory properties such as inhibition of NADPH oxidase activity¹⁰, reduction of IL-6 levels¹¹, decreased levels of soluble vascular cell adhesion molecule-1¹², inhibition of proinflammatory cytokines synthesis such as TNF-alpha, IL-1, IL-2 and lower expression of adhesion molecules on the endothelium.¹³ Consequently, the protective effects of healthy dietary patterns such as Mediterranean diet against CVD could be mainly attributed to the lower generation of a proinflammatory milieu, but the above have rarely been studied in prospective studies.¹³

The effect of both inflammatory predictive ability of MetS and adherence to Mediterranean Diet on the 10-year CVD incidence in Greek population has been examined in detail by the prospective ATTICA Study. To our knowledge, this is the first time that the diagnostic criteria of the MetS have been evaluated in a large prospective study focused in the Greek population, by confirming the findings with the actual observed 10-year CVD risk. The Attica Study 10-year follow-up used three definitions for the MetS provided by the National Cholesterol Education Program Adult Panel III (revised NCEP ATP III)¹⁴, the International Federation (IDF)¹⁵ and the Harmonized definition.¹⁶ CVD events occurred in 317 subjects (accounting for 15.7% of the study sample); 40.7% of which occurred in subjects with MetS.¹⁶ Thus, the prior aim of this particular task was

Table 1. Different definitions of Metabolic Syndrome, presented in this review, with a list of their diagnostic criteria

Definition	Parameters included
NCEP:ATP III	Diagnosis: Three or more of the following: <ul style="list-style-type: none"> • waist circumference ≥ 102 cm for males or ≥ 88 cm for females • fasting serum triglycerides ≥ 150 mg/dl • High Density Lipoprotein serum levels < 40 mg/dl for males or < 50 mg/dl for females • systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg • fasting serum glucose ≥ 100 mg/dl
IDF	Diagnosis: Waist circumference ≥ 94 cm for males or ≥ 80 cm for females and two or more of the following: <ul style="list-style-type: none"> • fasting serum triglycerides ≥ 150 mg/dl • High Density Lipoprotein serum levels < 40 mg/dl for males or < 50 mg/dl for females • systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg • fasting serum glucose ≥ 100 mg/dl
Harmonized criteria*	Diagnosis: Three or more of the following: <ul style="list-style-type: none"> • waist circumference ≥ 94 cm for males or ≥ 80 cm for females • fasting serum triglycerides ≥ 150 mg/dl • High Density Lipoprotein serum levels < 40 mg/dl for males or < 50 mg/dl for females • systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg • fasting serum glucose ≥ 100 mg/dl

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to review and discuss the findings of the ATTICA Study that concerned the frame in which the MetS should be discussed in Greece. Specifically, the questions answered here by the ATTICA Study concerned the choice of the best diagnostic criteria for MetS among Greeks, its link to CVD risk through prospective study design and finally reveal which inflammatory biomarkers better predicted the 10-year CVD incidence and evaluate the potential mediating role of adherence to Mediterranean Diet in the pathway between MetS and 10-year risk for CVD.¹⁷

Definition

Several international health organizations, such as the World Health Organization (WHO), the European Group for the study of Insulin Resistance (EGIR), the National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII), the American Association of Clinical Endocrinology (AACE), the International Diabetes Federation

(IDF), and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI), have attempted to incorporate all the different parameters used to define MetS.⁴ In 2005, the NCEP: ATP III published a new set of criteria that included waist circumference, blood lipids, blood pressure and fasting glucose.¹⁴ The criteria being set by the NCEP: ATP III definition differed from both the glucocentric WHO and EGIR definitions as it was the first that considered the role of insulin resistance. The remaining four components of MetS were identical in the AHA/NHLBI definition to those of the IDF, with the exception of abdominal obesity that was defined differently. The IDF recommended that the threshold for waist circumference in Europeans should be 94 cm for men and 80 cm for women, while the AHA/NHLBI recommended cut-off points of 102 and 88 cm, respectively. Currently, the two most widely used definitions are those of the NCEP: ATP III and the obesity-centric IDF which focuses specifically on waist circumference, which is a surrogate measure

of central obesity.⁴ In 2009, new common-set criteria-called the Harmonized criteria - were introduced for international comparisons in 2009 and included agreed-upon cut points for different ethnic groups and sexes for the clinical diagnosis of the metabolic syndrome.¹⁸

Shortly, the revised NCEP ATP III definition includes three or more from the following; waist circumference (WC) ≥ 102 cm for males or ≥ 88 cm, TGL ≥ 150 mg/dl, HDL < 40 mg/dl for males or < 50 mg/dl for females, blood pressure $\geq 130/85$ mmHg, fasting glucose ≥ 100 mg/dl.¹⁴ The IDF definition describes MetS as having increased WC (≥ 94 cm for males or ≥ 80 cm for females) plus two of the following components; TGL ≥ 150 mg/dL, HDL < 40 mg/dL for males or 50 mg/dL for females, blood pressure $\geq 130/85$ mmHg, fasting glucose ≥ 100 mg/dL.¹⁵ Finally, the Harmonized criteria include three or more of the following features; WC ≥ 94 for males or ≥ 80 for females, TGL ≥ 150 mg/dL, HDL < 40 mg/dL for males or < 50 mg/dL for females, blood pressure $\geq 130/85$ mmHg, fasting blood glucose ≥ 100 mg/dL.¹⁸ (Table 1)

MetS and 10-year CVD risk in Greece

The MetS, as the concurrence of multiple metabolic abnormalities is associated with higher CVD risk through many different paths. In particular, the three components of atherogenic dyslipidemia (increased low-density lipoprotein (LDL), decreased HDL and high triglyceride concentrations) are individually associated with high CVD risk, while insulin resistance significantly increases the risk of developing type 2 diabetes mellitus which is a major risk factor for developing CVD. Presence of central obesity has associated with increased risk of CVD as a promoter of atherosclerosis through inflammation, increased arterial blood pressure and impaired endothelial function.¹³

Several epidemiological studies have confirmed the increased risk of CVD in individuals diagnosed with MetS, independently of the diagnostic criteria used.¹⁹⁻²⁵ Overall, a range of 1.5-3-fold higher risk of CVD and CHD mortality in comparison to healthy individuals has been reported in several prospective

studies, while a recent meta-analysis concluded that the presence of MetS was associated with a twofold increase in cardiovascular outcomes.²⁶ Contrarily, studies being held on older people, such as the Casale Monteferrato Study and PROSPER, failed to prove an association between MetS and risk of CVD.^{27,28} Due to these controversial results, recently, more studies aimed to investigate which of the proposed definitions of the MetS is particularly associated with increased CVD risk. Under this context, the 10-year follow-up of the ATTICA Study aimed to investigate the aforementioned issue as well as to provide a potential explanation regarding the role of inflammation and renal failure on CVD incidence.¹⁷ The prevalence of the MetS was estimated to be 20% according to the NCEP ATP III revised definition, 48.9% according to the IDF definition and 51% according to the Harmonized Criteria. Among the definitions, only the NCEP ATP III revised definition highlighted that the history of MetS was significantly associated (83% higher odds ratio) with CVD events, even after adjusting for several confounders such as age, sex, family history of CVD, physical activity, adherence to the Mediterranean Diet (MedDietScore) and smoking ($p < 0.001$).²¹ These findings confirmed that the choice of the appropriate MetS definition is of utmost importance for public health. More participants were classified as having the MetS using IDF and Harmonized definitions compared to the NCEP since the latter had different waist circumference cut-offs. On the other hand, the significant associations of the NCEP ATP III revised MetS definition is also confirmed by a recent meta-analysis, where NCEP defined MetS was associated with 200% higher risk for CVD events.²⁹

When the predictive role of inflammatory biomarkers (CRP, IL-6, uric acid and estimated GFR) were examined to explain the association of the three definitions of MetS with the 10-year CVD risk no significant differences were observed (all p 's > 0.40). This fact suggested that further investigation of inflammatory mediators of MetS on CVD incidence is needed, such as physical activity and dietary habits.

MetS and Mediterranean Diet in 10-year CVD risk

Many observational research studies suggested that Mediterranean Diet is as a prudent dietary pattern that was traditionally found in the Mediterranean area. Mediterranean Diet has been suggested to be protective against all-cause mortality, CVD, and cancer especially due to its antioxidant and anti-inflammatory properties.⁷ In the Greek cohort of the EPIC [European Prospective Investigation into Cancer and Nutrition] study, greater adherence to the Mediterranean Diet (2/9 increment in the Mediterranean Diet score) was associated with a 33% reduction in CHD mortality.³⁰ Moreover, according to the findings of the ATTICA Study, greater adherence to the Mediterranean Diet was associated with 20% lower CRP and 17% lower IL-6 levels as compared with subjects in the lowest tertile of adherence, after various adjustments.³¹ Since the presence of MetS is a risk factor for CHD, it was further investigated whether the level of adherence to the Mediterranean diet can alter CVD risk, when MetS is present.

After adjusting for several confounders (age, sex, family history of CVD, physical activity and smoking habits, as well as history of MetS), each 1/55

increase in the MedDietScore, was associated with 3% lower odds of CVD incidence (95%CI: 0.94-1.01). Furthermore, participants with lower adherence to Mediterranean Diet had double odds of developing a CVD event as compared to a moderate level of adherence. However, for subjects with higher level of adherence to this dietary pattern, no significant associations were observed.³²

Conclusions

The 10-year Attica Study follow-up confirmed that the MetS is positively associated with CVD development. Even though this inflammation-induced syndrome is present in the Greek population more investigation is needed in order to detect the specific inflammatory factors that accompany MetS and raise CVD risk. Adherence to the Mediterranean Diet seems to offer significant benefits regarding the prevention and treatment not only of the MetS as a whole but also of its components. As a result interventions should be encouraged in order to increase adherence to this dietary pattern and its health benefits. ◊

Conflict of interest: All authors declare no conflict of interest.

Περίληψη

Διερεύνηση του φάσματος των συνιστωσών του μεταβολικού συνδρόμου και του ρόλου του στον καρδιαγγειακό κίνδυνο στην Ελλάδα. Ο διαμεσολαβητικός ρόλος της Μεσογειακής διαίτας: Αποτελέσματα από το 10-ετη επανέλεγχο της μελέτης ΑΤΤΙΚΗ (2002-2012)

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Ως Μεταβολικό Σύνδρομο (ΜΣ) ορίζεται η συστάδα των παραγόντων που αυξάνουν τον καρδιαγγειακό κίνδυνο. Ο επιπολασμός του ΜΣ έχει αυξηθεί σημαντικά τις τελευταίες δεκαετίες στην Ευρώπη, όμως δεν υπάρχει ακόμα ξεκάθαρη εικόνα όσον αφορά στην εξέλιξη του στην Ελλάδα, ενώ ταυτόχρονα διάφοροι ορισμοί χρησιμοποιούνται για τη διάγνωση του ΜΣ. Επιπλέον δεν υπάρχουν δεδομένα από προοπτικές μελέτες που να έχουν μελετήσει την επίδραση του ΜΣ στον καρδιαγγειακό κίνδυνο στον ελληνικό πληθυσμό. Συνεπώς, η παρούσα ανασκόπηση είχε ως σκοπό να αναγνωρίσει ποια είναι τα καταλληλότερα κριτήρια για τη διάγνωση του ΜΣ στην Ελλάδα αλλά και να διερευνήσει το φάσμα των συνιστωσών του ΜΣ στον καρδιαγγειακό κίνδυνο και τη συσχέτισή τους με την προσκόλληση στη Μεσογειακή διαίτα λαμβάνοντας υπόψη τα διαθέσιμα επιδημιολογικά δεδομένα από την Ελλάδα. Σύμφωνα με τα ευρήματα της μελέτης ΑΤΤΙΚΗ, ο επιπολασμός το ΜΣ διευρύνεται από 20% έως 51%, ανάλογα με το χρησιμοποιούμενο διαγνωστικό κριτήριο. Μόνο ο αναθεωρημένος ορισμός του NCEP ΑΤΡΙΙΙ συσχετίστηκε με τον καρδιαγγειακό κίνδυνο. Μετά από διόρθωση για τους κλασσικούς παράγοντες καρδιαγγειακού κινδύνου, για κάθε 1/55 αύξηση στο MedDietScore, οδηγούσε σε 3% μείωση του καρδιαγγειακού κινδύνου.

Λέξεις ευρητηρίου: μεταβολικό σύνδρομο, μεσογειακή διαίτα, καρδιαγγειακή νόσος, παράγοντες κινδύνου

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