

## Can Mediterranean Diet Counteract Metabolic Syndrome Diffusion?

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### THE METABOLIC SYNDROME

Metabolic syndrome (MetS) is a pathophysiological condition identified by a cluster of risk factors linked to the development of cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM) and some types of cancer, pathologies that are the leading cause of mortality in the western world<sup>[1-3]</sup>. Throughout the last decades several organizations have attempted to formulate guidelines for diagnosis of MetS, but there was a disagreement over these diagnostic criteria. Despite this disagreement all formulations identified five diagnostic parameters: high plasmatic levels of triglycerides, low plasmatic levels of High Density Lipoprotein cholesterol (HDL-C), hypertension, elevated fasting glucose or hyperglycemia and abdominal obesity. Diagnostic differences among various directives mainly concerned the combinations of these parameters<sup>[4]</sup>. Generally abdominal obesity was considered a “conditio sine qua non” in the diagnosis of MetS. In 2009 a committee of several scientific associations including the International Diabetes Federation (IDF), the American Heart Association (AHA), the International Atherosclerosis Society (IAS) and others proposed a harmonized definition of MetS for adults in order to solve the differences among previously proposed diagnostic criteria: for the diagnosis of metabolic syndrome is required positivity on at least three of the five parameters listed above, and obesity was no longer accounted as a necessary<sup>[5]</sup>. Moreover MetS is also associated with chronic low-grade inflammation, elevated oxidative stress, prothrombotic state and endothelial dysfunction, that throughout the development of insulin resistance, atherogenic dyslipidemias and dysfunctional lipoprotein lead to the increased risk of CVD and T2DM<sup>[6]</sup>.

MetS is therefore a multifactorial condition whose development is regulated by a complex interaction between genetic and environmental factors<sup>[7]</sup>. Nevertheless seems that hereditary factors contribute

### ABSTRACT

Over the past decades, the prevalence of the metabolic syndrome (MetS), a health condition identified by a cluster of risk factors linked to the development of cardiovascular disease, type 2 diabetes mellitus and some types of cancer, has dramatically increased in the world. The rising of MetS incidence and progression appear related to Westernization of dietary habits in the world, with a corresponding increase in the consumption of meat or meat products, snacks, baked desserts and sugar-sweetened beverages not only in the Western countries, but also in the Mediterranean region and among the Eastern populations. Otherwise epidemiological evidence suggests that a high dietary intake of fruits, vegetables, fish and whole grains can improve all the risk factors related to MetS. Particularly adherence to the Mediterranean diet seems to have positive effects on the prevalence and progression of the MetS. In this article we reviewed cohort studies, cross-sectional studies and clinical trials, showing new evidence supporting the beneficial role of adherence to the Mediterranean dietary pattern on the MetS progression. Analysis of the literature suggests that Mediterranean diet should be considered as a healthy and sustainable lifestyle playing a key role in primary and secondary prevention of MetS and its components.

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marginally to the development of MetS and genetic predisposition has been estimated explain only 10% of MetS cases<sup>[7,8]</sup>. Alternatively numerous environmental correlates have been identified and lifestyles, especially dietary habits and physical inactivity, are universally recognized as the main risk factors. Particularly, epidemiological evidences suggest that diet is probably more relevant for the development of MetS than is sedentary lifestyles<sup>[4,8-10]</sup>.

## DIETARY EFFECTS ON METABOLIC SYNDROME

Over the past decades, the prevalence of the metabolic syndrome has dramatically increased, not only in Western countries, but also in the Mediterranean region and among the Eastern populations. This appears related to Westernization of dietary habits, with a corresponding increase in the consumption of meat or meat products, snacks, baked desserts and sugar-sweetened beverages, which provide high amounts of saturated fatty acids (SFA) and simple carbohydrates as added sugars<sup>[4,11-15]</sup>. Otherwise epidemiological evidence suggests that a diet high in intake of fruits, vegetables, fish and whole grains can improve all the risk factors related to MetS<sup>[4,9,16]</sup>. Besides it is well known that a reduction of SFA dietary intake is strictly related to both improvement of blood lipid profile and cardiovascular events incidence reduction. On the other hand, the evidences from epidemiologic and clinical studies are consistent in finding that the reduction of cardiovascular risk (CVR) depends by nutrients used for replacing SFA. Specifically it has been demonstrated that replacement of SFA with unsaturated fat acids (UFA), either monounsaturated (MUFA) or polyunsaturated (PUFA) ones, is effective in improving CVR<sup>[17-20]</sup>. Particularly a recent meta-analysis showed that dietary sources of MUFA are crucial to determine their cardioprotective effects. In fact only vegetable cis-MUFA, and specifically oleic acid, seem to be associated with a reduction of CVR<sup>[21]</sup>.

Furthermore vegetable UFA, as well as fish  $\omega$ 3, concentrations have been inversely related to inflammatory markers<sup>[22,23]</sup> and oxidative stress<sup>[24-26]</sup>. Again fruits, vegetables, and other plant-based foods, as well as whole grain, contain a unique blend of bioactive components including resistant starches, vitamins, minerals, phytochemicals and antioxidants that may provide desirable health benefits reducing the risk of the development of chronic diseases<sup>[27,28]</sup>. Increasing evidence suggests that the health benefits of fruits, vegetables, whole grains, and other plant foods are attributed to the synergy or interactions of bioactive compounds and other nutrients in whole foods. Therefore, consumers should obtain the required mix of nutrients, antioxidants and bioactive compounds from their balanced diet with a wide variety of fruits, vegetables, whole grains, and other foods for optimal nutrition, health, and well-being, not from single dietary supplements<sup>[27]</sup>. Moreover, commonly, various foods are consumed together leading to a complex interaction among the various nutrients. For all these reasons the assessment of the interaction between dietary factors and metabolic diseases as well as MetS should be focused to the overall dietary pattern<sup>[4]</sup>.

## MEDITERRANEAN DIET AND METABOLIC SYNDROME

Interestingly the dietary features above reported look like the principles of Mediterranean diet (MD). MD, first described by Ancel Keys in 1960s, is the dietary pattern characteristic of the region around Mediterranean sea. There are several differences among eating habits of the several Mediterranean countries, but

all these populations show a similar dietary pattern. MD pattern is characterized by a high consumption of olive oil, fruit, vegetables, tree nuts, legumes and whole grain, moderate to high consumption of fish, moderate consumption of poultry, milk and dairy products and low consumption of beef and reed meat. Furthermore non Islamic populations make low-moderate use of wine<sup>[29,30]</sup>. The high use of olive oil and tree nuts guarantee an high UFA:SFA ratio, with a particularly high presence of cis-MUFA (oleic acid), moreover nuts and fish assure a high  $\omega$ 3: $\omega$ 6 ratio. Likely whole grain, fruit, vegetable and legumes provide an optimal mix of bioactive components, vitamins, minerals, phytochemicals and antioxidants, the latter contained in wine, too. MD cardioprotective effects are well known and widely documented by either epidemiological studies and clinical trials<sup>[31-36]</sup>, and in the last decade has been identified also an important protective role of this dietary pattern against development of the MetS<sup>[3,4,29]</sup>.

Ten years ago the ATTICA, a cross-sectional study examining 2,282 Greek subjects without any evidence of CVD or T2DM, showed that adherence to a MD pattern was associated with a 20% lower risk to develop MetS<sup>[37]</sup>. At the same time an Italian clinical trial conducted on 180 patients with MetS found, after two years of intervention, a 48% net reduction in the prevalence of MetS in subjects assigned to a MD pattern. Additionally body weight, inflammatory markers and insulin resistance decreased more and endothelial function improved in MD group than in control group (a cardiac-prudent low fat diet)<sup>[38]</sup>.

These findings were confirmed in 2007 by the SUN, a prospective cohort with a 6 years follow-up enrolling 2,563 subjects at low CVR. Adherence to the MD evaluated with a modified Mediterranean Diet Scale (mMDS) was associated with a 80% reduction of MetS Risk<sup>[39]</sup>. Similarly The Framingham Offspring Cohort followed for 7 years 2,730 participants without T2DM. Participants with higher adherence to the Mediterranean diet showed a lower incidence of the MetS and better values for the majority of the syndrome parameters. In fact MD adherence was significantly associated with lower waist circumference, fasting plasma glucose, insulin resistance (HOMA-IR) and triglyceride (TG) concentration, and higher HDL-Cholesterol (HDL-C) plasma level, while no relations with blood pressure were found<sup>[40]</sup>. A most recent French 6-year prospective study, enrolling 3,232 subjects, detected similar findings, showing an inverse relation between adherence to MD and MetS risk as well as with several MetS traits. MD adherence was, indeed, inversely associated with waist circumference, systolic blood pressure and TG plasma level, and directly associated with HDL-C concentration. Furthermore in this study several scales for the assessment of MD adherence were compared showing similar results among different scales<sup>[41]</sup>.

A cross-sectional study conducted on 808 high CVR participants of the PREDIMED protocol showed an inverse association between adherence to MD and prevalence of MetS and its components. In particular, subjects with a high MD adherence had the 47% and 54% lower odds of prosecuting respectively low HDL-C and high TG blood concentration. Hence, even in a population at elevated CVR, higher adherence to MD pattern is associated with a lower odds ratio of MetS<sup>[9]</sup>. Other three cross-sectional studies, two carried out in Greece, one in Italy, related low adherence to MD with a higher prevalence of MetS and vice versa a high adhesion to MD pattern with lower presence of MetS<sup>[42-44]</sup>.

The association of MD adherence with incidence of the MetS over 25 years has been assessed in 4,713 African American and white adults enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA). The study showed that incidence of MetS and its components was lower in people with higher adherence to MD.

Further, after a subdivision in 5 categories of adherence to MD, MetS incidence decreased from the lower to the higher adherence with an highly significant trend<sup>[45]</sup>.

Recently, a secondary analysis of PREDIMED participants, all adults at high CVR, compared the effect of three energy-unrestricted dietary pattern on incidence and prevalence of MetS. The three dietary patterns analysed were MD supplemented with extravirgin olive oil, a MD supplemented with nuts and finally a low-fat diet (control group). Data showed no association between MDs and incidence of MetS, but was disclosed a significantly effect of MDs on reversion of MetS, that results in a net reduction of the syndrome prevalence<sup>[46]</sup>. The lack of effect on MetS incidence is explained by authors with the consideration that, differently from previous studies, in this clinical trial diets were ad libitum without any energy restriction. Moreover, participants were older and at high CVR, and the assessment of incidence and reversion of MetS were a secondary goal of the PREDIMED trials, so results cannot be generalized. However the trial showed a clear MD effect on the reduction of MetS prevalence in a high CVR population.

On the other hand two cross-sectional studies showed a lack of association between MD and MetS prevalence. The first was a study performed on 578 subjects from the Canary Islands general population that indicated no association between adherence to MD and development of the MetS. However MD showed a protective effect on several MetS criteria, particularly on blood pressure, glycaemia, insulin resistance and lipid profile<sup>[47]</sup>. The other study enrolled 832 young Greek male navy recruits, and observed lack of association between MD and MetS prevalence was probably due to both young age of subjects ( $22.5 \pm 2.8$  years old) and to the very low MD adherence with high prevalence of westernized diet among this cohort<sup>[48]</sup>.

Only two out of thirteen studies analyzed found no relationship between MD and MetS prevalence, and both did not report conclusive results: one of them showed a protective role of MD on MetS component, the other one was carried out on a cohort with misappropriated features. In conclusion, overall results of the studies examined do suggest that adherence to a MD is associated with lower MetS prevalence and progression and this dietary pattern has favourable effects on the MetS components, suggesting that MD should be considered a valuable support to counteract the increasing diffusion of MetS. Taking in account of the results showed seems most important follow the whole dietary pattern of MD rather than undergo to some recommendations and rules, emphasizing that the Mediterranean diet should be seen as a healthy and sustainable lifestyle whose adoption plays a key role in primary and secondary prevention of MetS and its components.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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