

Body composition changes and cardiometabolic benefits of a balanced Italian Mediterranean Diet in obese patients with metabolic syndrome

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Body composition changes and cardiometabolic benefits of a balanced Italian Mediterranean Diet in obese patients with metabolic syndrome

Nicola Di Daniele · Luigi Petramala · Laura Di Renzo · Francesca Sarlo · Domenico Giovanni Della Rocca · Mariagiovanna Rizzo · Valentina Fondacaro · Leonardo Iacopino · Carl J. Pepine · Antonino De Lorenzo

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Abstract Metabolic syndrome (MS) is a cluster of metabolic alteration associated with a higher risk of cardiovascular disease and overall mortality than the single alterations alone. The Italian Mediterranean Diet (IMD) can exert a positive effect on cardiovascular risk and related morbidity and mortality. The aim was to evaluate the benefits of dietary intervention based on a typical IMD on body composition, cardiometabolic changes and reduction in cardiovascular disease in patients with MS. Eighty White Italian subjects with MS were prescribed a balanced hypocaloric IMD. We investigated dietary habits and impact of the diet on health

status, blood biochemical markers, anthropometric measurements and body composition during a 6-month follow-up period. Body composition, fat mass and distribution were assessed by Dual X-ray absorptiometry. Adherence to the IMD led to a decrease in body weight (102.59 ± 16.82 to 92.39 ± 15.94 kg, $p < 0.001$), body mass index (BMI) (38.57 ± 6.94 to 35.10 ± 6.76 , <0.001) and waist circumference (112.23 ± 12.55 vs 92.42 ± 18.17 cm, $p < 0.001$). A significant loss of total body fat especially in waist region was observed. The MS was resolved in 52 % of the patients. Significant improvements in systolic and diastolic blood pressure and fasting glucose occurred. Low-density lipoprotein cholesterol was reduced from 128.74 ± 33.18 to 108.76 ± 38.61 mg/dl ($p < 0.001$), triglycerides from 169.81 ± 80.80 to 131.02 ± 63.88 mg/dl ($p < 0.001$). The present results suggest that a dietary intervention based on a typical IMD effectively promotes weight loss and reduces the growing burden of cardiovascular risk factors that typifies patients with MS.

Nicola Di Daniele, Luigi Petramala, Laura Di Renzo equally contributed to this work.

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Keywords Italian Mediterranean Diet · Body composition · Metabolic syndrome · Cardiovascular disease

Introduction

High blood glucose is the third leading cause of premature mortality globally [1]. The general focus of diabetes prevention has concentrated on intervening among individuals at high risk for the disease. Several authors have estimated that a 1 % decrease in BMI across the United States population would prevent more than 2 million new cases of diabetes over the next 20 years [2]. Therefore, high-risk management strategies remain important as long as the

disease is widely prevalent, and intervention to target population level behavior is critically needed.

To this aim, the clustering of certain metabolic factors (e.g., abdominal obesity, dyslipidemia and elevated blood pressure) linked to insulin resistance (e.g., MS) has been documented to identify patients at increased risk for type 2 diabetes, as well as CVD and overall mortality [3, 4]. These metabolic abnormalities contribute to a pro-inflammatory/pro-thrombotic state that likely plays a pivotal role in both pathogenesis and complications of atherosclerosis, leading to the clinical CVD (e.g., myocardial infarction and stroke).

The MS is a growing health problem worldwide with a prevalence in developed countries estimated at 25–35 % of adults [5, 6]. This variability essentially depends on the diagnostic criteria (ATP III, IDF and WHO) for MS and the sampled population [7]. An estimated increase in up to 35 % in prevalence, in parallel with the increasing prevalence of obesity and diabetes, was observed in the last two decades. A similar increase has also involved the Mediterranean population [8].

Although a unifying definition of the MS does not exist [9–11], there is a worldwide agreement about the role of insulin resistance and abdominal obesity as the main pathophysiological mechanisms for the development of metabolic disorders characterizing the MS [8].

Lifestyle changes (LC) interventions, such as dietary changes and physical activity, have a main role in treatment of the MS [9]. Given the rising prevalence of the syndrome, a dietary approach is among the LC that might significantly help prevent and treat the metabolic imbalance.

Since the studies first showing longer life expectancy in the Mediterranean region [8], observational studies have provided evidence that adherence to a MD is associated with lower risk for CVD [12–14]. The MD is typically rich in fruit, vegetables, legumes, whole grains, fish and low-fat dairy products. Mechanisms responsible for these favorable effects are multiple and interrelated: antioxidant and anti-inflammatory properties [15], lower arterial blood pressure levels and blood lipid concentrations, reduced body weight [16].

The aim of this study was to evaluate the effect of Italian Mediterranean Diet (IMD), the so-called Nicotera Diet [17, 18], on prevalence of MS, as well as its determinants (blood pressure, waist circumference, glycaemia and lipid metabolism) and body composition in subjects presenting to a center for management of obesity-related diseases.

Materials and methods

Study design

We used prospective, cohort design with repeated measures. After screening and subject selection they entered a

baseline period. After baseline measurements subjects were entered the *intervention period* and were followed at 4-week intervals. Final assessment was made *at 6 months*. Patients who did not complete the 6-month dietary regimen were considered non-compliant and excluded from further study. In our case-control study, patients were used as controls of themselves.

Subjects

Between March 2009 and February 2010, 105 obese subjects with suspected MS according to the current International Diabetes Federation guidelines for metabolic syndrome [6] were screened by medical and nutritional staff of the Obesity Centre of Nicotera Hospital (VV, Italy). Subjects with a history or symptoms of coronary artery, cerebrovascular or peripheral artery disease, heart failure, renal or hepatic diseases or smoking were excluded, as well as those with established type 2 diabetes. Renal disease was defined as serum creatinine >1.5 mg/dl or albuminuria >300 mg/dl. It was ascertained that none were taking lipid-lowering or antidiabetic medications, insulin, nitro derivatives or systemic corticosteroids.

At baseline, subjects underwent complete medical history review (e.g., health status, current medications, alcohol consumption, smoking, physical activity and dietary habits with a validated food-frequency questionnaire), physical examination, blood biochemical analysis, BP and anthropometric measurements and DXA evaluation. Participants were assigned to three registered dietitians and received a balanced hypocaloric IMD. They were also instructed not to modify physical activity (PA) behaviors during the 6-month intervention period.

All measurements were re-evaluated at each visit, in addition to a 30-min session with a dietitian to verify dietary regimen compliance. During the intervention period, the same dietitian conducted 10–15-min motivational telephone calls with participants to enhance dietary compliance.

This study was conducted in accordance with the Declaration of Helsinki guidelines and approved by a local ethical committee (“Tor Vergata” University Medical Ethical Committee, Rome, Italy). Study design was clearly written in lay person language and provided to each study subject. All participants provided written informed consent to participate.

Diagnosis of MS

The MS was defined according to International Diabetes Federation (IDF) guidelines [6]. Diagnosis required central obesity, defined as waist circumference ≥ 94 cm for European men and ≥ 80 cm for European women, plus any two of the following four factors: TG level ≥ 150 mg/dL or specific

treatment for this lipid abnormality; HDL cholesterol <40 mg/dL in males and <50 mg/dL in females or specific treatment for this lipid abnormality; systolic blood pressure (SBP) \geq 130 or diastolic blood pressure (DBP) \geq 85 mm Hg or antihypertensive treatment; fasting plasma glucose \geq 100 mg/dL or previously diagnosed type 2 diabetes.

Diet Assessment

Dietary intakes over the past 12 months were collected by a validated food-frequency questionnaire that included 127 food items and three portion-size pictures for 17 items [19]. The alimentary diary and nutrient intake were analyzed using diet analyser software INDALI. Daily and weekly food intake in grams was calculated from food intake frequency and portion sizes. This information was used to assess the adequacy and adherence to MD.

Dietary intervention

Although there are many forms of MD, we used the Italian IMD, the so-called Nicotera Diet [18]. Total daily energy content of the diet was determined on an individual basis, taking into account RMR, calculated for the Italian population [20].

The macronutrient's composition of the dietary regimen was as follows: carbohydrates (55–60 %); proteins (15–20 %, half comprised of vegetable proteins); total fat (less than 30 %; saturated fat <10 %; PUFA 6–10 %: 5–6 % of n-6 PUFA and 1–2 % of n-3 PUFA; MUFA about 15 %; trans-fatty acids <1 %; cholesterol consumption <300 mg per day), sodium chloride <5 g and 30 g of fibers per die. No alcoholic beverages were allowed except 100 ml/day of red wine. The weekly frequency of consumption of animal foods was 3–4 times for fish, 1–2 for meat, 1 for eggs, 1 for cheese. The daily intake of carbohydrates was mainly derived from wheat (pasta and bread), other cereals and legumes (at least 3 times/week). The daily intake of fruit and vegetables was more than 400 g. Extra-virgin olive oil was consumed daily in the amount of 20–25 g. No change in total energy intake (Kcal/day) was required during the experimental time.

The composition of the diet in terms of foods and food combinations was planned to obtain an animal to vegetable protein ratio as close to 1:1 as possible. Nutritional indices like the PRAL, renal NAE, CSI, GI, AI, TI and MAI were calculated for each individual diet by the dietetic software using published formulas [21]. We report the values of the above indices obtained by assuming a mean energy value of 6,5 MJ (1500 kcal). They were -17,7 for PRAL, 31,7 for NAE, 9,8 for CSI, GI < 70, AI = 0,25, TI = 0,46 and MAI = 5.2. The IMD was evaluated by a dietetic software package (DS Medigroup, Milan, Italy).

Clinical and anthropometric measurements

Anthropometric measurements were performed according to standard methods after a 12-h overnight fast without clothes or shoes. Waist circumference was measured at the horizontal plane that corresponds with the narrowest point between the crest iliac and the bottom rib. Hip circumference was measured at the largest point when observed on a horizontal plane, and these circumferences were used to calculate waist-to-hip ratio. BMI was calculated as body weight (kg)/height (m)². The BP was taken using a mercury sphygmomanometer from the right upper arm after the subject was seated quietly for at least 5 min (average of three measurements).

Dual X-ray absorptiometry (DXA)

Body composition was determined by means of DXA (Lunar model DPX-IQ, GE healthcare) fan beam scanner. It assesses both whole and segmental body soft tissues, fat and lean mass, and bone tissue. Default software readings provided lines positioned to divide the body into six compartments (head, trunk, arms, legs, android and gynoid areas). For each region of the whole body, fat and lean body mass and bone mineral content were determined. Subjects were given complete instructions on the testing procedure (no exercise in the 24 h before the test, taking cotton t-shirt, shorts and socks). The coefficients of variation intra and inter subjects were 2.2 % for fat mass and 1.1 % for lean body mass. The effective radiation dose from this procedure was about 0.01 mSv.

Blood biochemical analysis

Blood samples (10 mL) were collected into sterile tubes containing EDTA (evacuated tubes), via vein puncture early in the morning (07:00–09:00) after an overnight fast (12 h) and were immediately placed on ice. Serum laboratory tests included fasting glucose, total cholesterol, HDL, LDL and TG at baseline and after 7 days. Fasting plasma glucose concentrations were measured using the glucose oxidase method with an automated glucose analyzer (COBAS INTEGRA 400, Roche Diagnostics, Indianapolis, IN, USA), serum lipid profile components were determined by standard enzymatic colorimetric techniques (Roche143 Modular P800, Roche Diagnostics, Indianapolis, IN, USA). Analyses were carried out by the accredited Clinical Chemical Laboratories of the Hospital of Nicotera, Italy. Atherogenic indices were calculated as follows: total cholesterol (mg/dL)/HDL cholesterol (mg/dL) (normal value <5 for men and <4.5 for women), LDL cholesterol (mg/dL)/HDL cholesterol (mg/dL) (normal value <3.5 for men and <3 for women), log [triglycerides (mg/dL)/HDL

(mg/dL)] (normal value <0.5). Risk categories and target levels for total cholesterol/HDL cholesterol, LDL cholesterol/HDL cholesterol in primary and secondary prevention, stratified by gender, were considered [22].

Statistical analysis

Sample size was selected to provide a statistical power of 95 % to detect a reduction of 50 % for the MS, with $\alpha = 0.05$. Continuous variables are presented as mean \pm standard deviation (SD), and differences were evaluated by the paired Student *t* or Wilcoxon test, depending on the shape of the distribution curve. Categorical variables are expressed by count and percentage and compared by χ^2 or Fisher's exact test when appropriated. The Pearson coefficient was used for measuring linear correlation between variables. Correlations were evaluated by univariate and stepwise forward multivariate regression analysis.

The probability values are two-sided; a probability value <0.05 was considered to indicate statistical significance. Statistical analysis was performed using a computer software package (SPSS for Windows, version 13.0; SPSS, Chicago, IL, USA).

Results

Patient characteristics:

At Baseline

Of the 105 obese patients enrolled, 80 were included: 21 were excluded because of non-compliance with the dietary regimen (poor adherence and motivation, inability to accept the checks provided, missing data on dietary intake during observational period, without reporting side effects related to dietary intervention) reducing the final evaluable cohort to 59 subjects (26.3 % drop out). Demographic and MS characteristics are summarized in Table 1. Men and women were 25 and 34, respectively; mean BMI was 35.83 ± 4.26 kg/m² in male group and 40.60 ± 7.84 kg/m² in female group. Mean daily dietary intake was 2010 kcal/day, macronutrient's composition of the dietary regimen was as follows: carbohydrates 55.4 %, proteins 17.6 %, total fat 27 %, fibers 21.3 g/day, cholesterol consumption 450 mg/day, fruits and vegetables 280 g/day.

At 6 months

Dietary intervention was associated with marked reduction in obesity at 6 months. Mean body weight decreased from 101.53 ± 18.60 to 92.41 ± 18.17 kg ($p < 0.001$), as well

Table 1 Baseline Characteristics according to gender

Parameters	Men (n = 25)	Women (n = 34)
Age	48.7 \pm 13	51.4 \pm 11.5
Weight (kg)	104.5 \pm 17.3	99.3 \pm 19.4
BMI (Kg/m ²)	35.8 \pm 4.3	40.6 \pm 7.8
Obesity (%)		
I degree (BMI 30–35 kg/m ²)	52.0 (n = 13)	32.4 (n = 11)
II degree (BMI 35–40 kg/m ²)	28.0 (n = 7)	29.4 (n = 10)
III degree (BMI > 40 kg/m ²)	20.0 (n = 5)	38.2 (n = 13)
Waist circumference (cm)	113.1 \pm 9.1	111.6 \pm 14.7
SBP (mmHg)	137.4 \pm 15.2	133.2 \pm 14.1
DBP (mmHg)	87.8 \pm 10.3	84.0 \pm 9.3
Fasting glucose (mg/dl)	110.5 \pm 16.7	112.6 \pm 23.8
HDL-C (mg/dl)	44.9 \pm 9.0	48.4 \pm 16.7
Triglycerides (mg/dl)	151.6 \pm 60.0	170.6 \pm 85.1

Parameters are expressed as mean \pm SD

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* HDL cholesterol

Table 2 Anthropometric characteristics at baseline and 6 months of dietary intervention

Parameters	Baseline	At 6 months	<i>p</i> value
Weight (kg)	101.5 \pm 18.6	92.4 \pm 18.2	<0.001
BMI (Kg/m ²)	38.6 \pm 6.9	35.1 \pm 6.8	<0.001
Waist circumference (cm)	112.2 \pm 12.6	92.4 \pm 18.2	<0.001
Hip circumference (cm)	119.7 \pm 14.3	113.3 \pm 13.4	<0.001
Waist/hip ratio	0.9 \pm 0.1	0.9 \pm 0.1	0.003

Parameters are expressed as mean \pm SD

NS not significant, *BMI* body mass index

as other obesity-related anthropometric parameters (BMI, waist and hip circumference and waist/hip ratio, Table 2). Physical activity levels did not change during the course of the investigation. Body composition analysis by DXA resulted in reduction in total body fat ($p < 0.001$) and total body lean ($p < 0.001$; Table 3). The body fat mass reduction was distributed to those regions where adipose tissue is metabolically active, such as trunk and android (waist) region.

MS components

After dietary intervention, the prevalence of the MS decreased by 56 % in men and 47 % in women. The BP, fasting blood glucose and triglycerides levels showed the most changes. Systolic BP decreased from 135.02 ± 14.61 to 123.72 ± 11.87 mmHg ($p < 0.001$) as did diastolic BP (85.65 ± 10.07 to 76.01 ± 7.57 mmHg, $p < 0.001$). A concomitant decrease in fasting plasma glucose (113.59 ± 21.42

Table 3 Body composition measured by DXA in study subjects at baseline and after 6 months of dietary intervention

Parameters	Baseline	At 6 months	<i>p</i> value
Total body fat			
%	42.5 ± 7.5	39.8 ± 8.5	<0.001
Kg	42.1 ± 12.9	36.9 ± 11.3	<0.001
Total body lean			
%	58.4 ± 9.8	61.1 ± 10.3	<0.001
Kg	54.9 ± 14.6	52.9 ± 11.5	0.088
Android body fat			
%	52.5 ± 5.6	48.9 ± 7.1	<0.001
Kg	4.5 ± 1.5	3.8 ± 1.3	<0.001
Trunk body fat			
%	46.2 ± 5.7	43.5 ± 6.8	<0.001
Kg	43.1 ± 11.2	36.8 ± 11.4	<0.001

Parameters are expressed as mean ± SD

Table 4 Metabolic syndrome parameters and atherogenic lipid indices at baseline and 6 months of dietary intervention

Parameters	Baseline	At 6 months	<i>p</i> value
SBP (mmHg)	135.2 ± 14.6	123.72 ± 11.9	<0.001
DBP (mmHg)	85.7 ± 10.1	76.01 ± 7.6	<0.001
Fasting glucose (mg/dl)	113.6 ± 21.4	100.65 ± 16.9	<0.001
Total-C (mg/dl)	205.7 ± 33.5	180.18 ± 38.1	<0.001
HDL-C (mg/dl)	45.9 ± 10	47.97 ± 14	0.339
LDL-C (mg/dl)	128.7 ± 33.2	108.76 ± 38.6	<0.001
Triglycerides (mg/dl)	169.8 ± 80.8	131.02 ± 63.9	<0.001
Total-C/HDL-C	4.6 ± 1.6	4.05 ± 1.4	0.003
LDL-C/HDL-C	2.9 ± 1.1	2.50 ± 1.1	0.002
Log TG/HDL-C	0.5 ± 0.2	0.42 ± 0.3	0.001

Parameters are expressed as mean ± SD

NS not significant, SBP systolic blood pressure, DBP diastolic blood pressure, Total-C total cholesterol, HDL-C HDL cholesterol, LDL-C LDL cholesterol

to 100.65 ± 16.85 mg/dL; $p < 0.001$) and plasma TG (169.81 ± 80.80 to 131.02 ± 63.88 mg/dL, $p < 0.001$) was observed. The HDL-cholesterol fraction did not change (Table 4).

LDL-cholesterol and atherogenic indices

Compared to baseline, there was a reduction in total cholesterol (205.75 ± 33.45 to 180.18 ± 38.10 mg/dL; $p < 0.001$) and LDL cholesterol (128.74 ± 33.18 to 108.76 ± 38.61 mg/dL; $p < 0.001$) (Table 4). A decrease in atherogenic lipid indices (total cholesterol/HDL cholesterol index, $p = 0.003$; LDL cholesterol/HDL cholesterol index, $p = 0.002$) was observed.

Table 5 Correlation analysis between metabolic syndrome parameters, atherogenic indices and body composition of abdominal region

	Waist circumference (cm)	Android body fat (Kg)
SBP (mmHg)	0.16	0.15
DBP (mmHg)	0.93	0.13
Fasting glucose (mg/dl)	0.37 ²	0.20
Total-C (mg/dl)	0.9	0.01
HDL-C (mg/dl)	-0.17	-0.26
LDL-C (mg/dl)	0.16	-0.05
Triglycerides (mg/dl)	0.28	0.44 ¹
Total-C/HDL-C	0.33 ¹	0.31
LDL-C/HDL-C	0.23	0.17
Log triglycerides/HDL-C	0.32 ¹	0.46 ¹

¹ $p \leq 0.05$, ² $p \leq 0.01$

SBP systolic blood pressure, DBP diastolic blood pressure, Total-C Total Cholesterol, HDL-C HDL Cholesterol, LDL-C LDL Cholesterol

Correlation analysis

Waist circumference was positively correlated with fasting glucose, total cholesterol/HDL cholesterol index and Log TG/HDL-C index (Table 5). DEXA-derived abdominal body fat was positively correlated with TG, total cholesterol/HDL cholesterol index and Log TG/HDL-C index.

To identify parameters linked to effects of MD to promote weight loss and reduce the growing burden of cardiovascular risk factors that typify patients with MS, we used a multiple regression model in which age, sex, and baseline waist are used as independent variables and delta of waist circumference (Δ WC) is used as the dependent variable. Using this analysis, age, sex and baseline waist circumference did not appear as independent and significant predictor of reduction in Δ WC ($R^2 = 0.075$; $F = 1.49$; $p = 0.227$).

Discussion

In this observational study, we found that a balanced hypocaloric (mean reduction in calories intake/day about 500 KCal) IMD in obese Italian patients was associated with multiple beneficial changes among obese subjects with MS. The results indicate that adherence to IMD, without implementation of additional physical activity, was associated with relevant reduction in prevalence of the MS by about half (-52 %) in obese subjects. The subjects were enrolled in obese-related diseases specialized center, thus the dietary intervention led to important improvement in central obesity, and, especially, reduction in atherogenic dyslipidemia, high BP levels and insulin resistance/glucose

intolerance, which represent a group of risk factors for CVD and other diseases such as diabetes and cancer.

Previous epidemiological and interventional studies have demonstrated the beneficial effects of the MD on the reduction in CVD, diabetes type 2, several types of chronic degenerative disease and cancers as well as cardiovascular and overall mortality [8, 23]. In the Attica study [24], adherence to the MD was inversely associated with better fasting indices of glucose homeostasis in normoglycemic patients.

In a previous study, we evaluated differences in time trends of cancer morbidity and mortality in Nicotera, one of the Italian rural areas analyzed in the “Seven Countries Study”, from 1960 to 1996. Progressive loss of traditional dietary habits and increased consumption of animal source and high-glycemic index foods led to an average decrease in MAI from 9.4 to 2.8 in males and from 11.4 to 2.5 in females over that period, in conjunction with a progressively increasing cancer incidence [25].

The MD is a high carbohydrates/moderate-high fat pattern with a high monounsaturated/saturated fat ratio. It is characterized by a high consumption of cereals (e.g., pasta and other whole grain foods), legumes, fruits, vegetables, fish, olive oil, nuts, moderate consumption of wine, low-fat dairy products and low consumption of meat products, with specific recommended composition of the dietary regimen.

The types of carbohydrates consumed are important, especially with low-glycemic index (e.g., whole grains, legumes, vegetables). In several studies, whole grain and fiber intake was inversely associated with a lower incidence of the MS [26] and with improved insulin sensitivity, lower fasting and 2-h plasma insulin concentrations, lower total and LDL cholesterol [27].

In a two-year dietary intervention trial, comparing effects of different diets (low-fat, restricted-calorie; Mediterranean, restricted-calorie; or low-carbohydrate, non-restricted-calorie) on moderate obese subjects, the Mediterranean diet yielded the most favorable changes in fasting plasma glucose and insulin levels among diabetics [28].

Olive oil is a prime component of the MD and excellent MUFA source. Substitution of energy intake from trans-fats for that from MUFA improves insulin sensitivity [29]. A similar protective effect against insulin resistance and diabetes has been observed in hyperlipidemic patients after isocaloric substitution of the energy intake from trans-fat for that from PUFA, whose main source is fish, an important component of the MD [30]. A diet rich in PUFA, especially the n-3 fatty acids, may also raise HDL cholesterol levels and lower triglyceride levels [31]. As regards, in patients affected by type 2 diabetes, Rizza et al. showed a significant improvement of endothelial function associated to reduction in pro-atherogenic and

inflammatory markers (reduction in TNF- α levels and triglycerides, increase in adiponectin) after dietary supplementation with n-3 PUFA (fish oil), confirming antioxidant and anti-inflammatory properties of n-3 PUFA [32].

In our study, the greater differences among the MS components during the observation period occurred in triglyceride and both systolic and diastolic BP levels. MUFA helps reduce BP levels, need of antihypertensive medication and risk of developing hypertension [33]. Another essential component of the MD is red wine, rich in polyphenols, whose beneficial effects on vascular homeostasis and oxidative stress may promote a better BP control.

Although not measured in our study, several studies have confirmed coexistence of low-grade chronic inflammation, adiponectin levels and insulin resistance in MS patients [34]. An inverse association was observed between typical Mediterranean food consumption (especially olive oil and nuts) and circulating markers of inflammation in patients at cardiovascular high risk [35]. The antioxidant and anti-inflammatory features of the MD may justify use to modulate oxidative and inflammatory burdens that trigger and promote metabolic abnormalities in the MS. Visceral obesity, main independent risk factor for MS development, contributes to a pro-inflammatory state through an overproduction of pro-inflammatory cytokines (e.g., interleukin-6), chemokines and acute phase proteins [36].

In clinical practice, evaluation of body fat through measurements like BMI can lead to a considerable misclassification of obesity prevalence [37]; therefore, it is necessary to adopt a standardized and reliable method for assessment of whole and segmental body composition. Of note, “normal weight obese” people, such as subjects, especially women, with normal weight and normal BMI but with elevated fat mass (>30 %), are exposed to an oxidative stress related to metabolic abnormalities occurring in obesity [38] that represent important risk factors for CVD development.

Globally, the prevalence of metabolic syndrome is increasing, largely because of obesity resulting from poor diets and sedentary lifestyles. Prevalence estimates vary widely between populations [39, 40] and 35 % of people in high-income countries [41] have metabolic syndrome. Furthermore, it has consistently been shown that the prevalence of metabolic syndrome increases with age [42].

A recent meta-analysis of 13 studies including 3907 participants with metabolic syndrome indicates the benefits of both lifestyle and pharmacological interventions to reverse metabolic syndrome. Lifestyle interventions appear to be the most effective; however, the trials were too heterogeneous to be able to make firm conclusions about which aspects of lifestyle interventions, at a detailed level, are most effective [43].

In the current study, a balanced hypocaloric dietary regimen based on the IMD was associated with reduction in waist circumference, BMI and total body weight at 6 months. The DXA confirmed that fat loss was localized in the abdominal region, where adipose tissue acts as a metabolically active organ to promote abnormalities leading to increased risk of CVD, diabetes and overall mortality.

Our study has several limitations that should be noted. This study was conducted in specialized obesity center, evaluating obese subjects by medical and nutritional experts focused on weight management, and these results may not extend beyond such an environment. Furthermore, follow-up was limited to only 6 months of dietary intervention, and although compliance was good (74 %), the ability to maintain this rate for longer periods, as required to translate to disease prevention, is unknown. Clearly, additional studies are needed to assess longer-term benefits of dietary intervention, persistence of these improvements and required amount of antioxidants in the diet, which may further improve the effectiveness of dietary intervention.

This prospective study provides evidence that adherence to a typical IMD promotes weight loss and is associated with favorable effects on the metabolic abnormalities characterizing the MS.

The assessment of body composition through precise instrumental methods demonstrates the effectiveness of the MD to reduce fat mass, especially where adipose tissue shows metabolically active properties.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. World Health Organization (2009) Global health risks: mortality and burden of disease attributable to selected major risk factors. World Health Organization, Geneva, Switzerland
2. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. (2011) Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet*. 27; 378 (9793): 815–825
3. Janghorbani M, Amini M (2011) Associations of hip circumference and height with incidence of type 2 diabetes: the Isfahan diabetes prevention study. *Acta Diabetol*. doi:10.1007/s00592-011-0351-4
4. Wannamethee SG, Shaper AG, Lennon L, Morris RW (2005) Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch Intern Med* 165(22):2644–2650
5. Ervin RB (2009) Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003–2006. *Natl Health Stat Report* 13:1–7
6. Alberti KG, Zimmet P, Shaw J (2005) IDF epidemiology task force consensus group: the metabolic syndrome a new worldwide definition. *Lancet* 366:1059–1062
7. Panagiotakos DB, Polychronopoulos E (2005) The role of Mediterranean diet in the epidemiology of metabolic syndrome: converting epidemiology to clinical practice. *Lipids Health Dis* 12:4–7
8. Keys A, Menotti A, Karvonen MJ et al (1986) The diet and 15-year death rate in the seven countries study. *Am J Epidemiol* 124(6):903–915
9. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15(7):539–553
10. Grundy SM, Cleeman JI, Daniels SR et al (2005) Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 112(17):2735–2752
11. Expert Panel on Detection (2001) Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285(19):2486–2497
12. Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C (2004) Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: the ATTICA Study. *J Am Coll Cardiol* 44(1):152–158
13. Knuops KT, de Groot LC, Kromhout D et al (2004) Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA* 292(12): 1433–1439
14. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A (2008) Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 337:a1344
15. Rallidis LS, Lekakis J, Kolomvoutsou A et al (2009) Close adherence to a Mediterranean diet improves endothelial function in subjects with abdominal obesity. *Am J Clin Nutr* 90(2):263–268
16. Psaltopoulou T, Naska A, Orfanos P, Trichopoulos D, Moutokalakis T, Trichopoulou A (2004) Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am J Clin Nutr* 80(4):1012–1018
17. Fidanza F, Alberti A, Fruttini D (2005) The Nicotera diet: the reference Italian Mediterranean diet. *World Rev Nutr Diet* 95:115–121
18. De Lorenzo A, Noce A, Bigioni M et al (2010) The effects of Italian Mediterranean organic diet (IMOD) on health status. *Curr Pharm Des* 16(7):814–824
19. Shai I, Shahar DR, Vardi H, Fraser D (2004) Selection of food items for inclusion in a newly developed food-frequency questionnaire. *Public Health Nutr* 7(6):745–749
20. De Lorenzo A, Tagliabue A, Andreoli A, Testolin G, Comelli M, Deurenberg P (2001) Measured and predicted resting metabolic rate in Italian males and females, aged 18–59 year. *Eur J Clin Nutr* 55(3):208–214

21. Alberti-Fidanza A, Fidanza F (2004) Mediterranean adequacy index of Italian diets. *Public Health Nutr* 7(7):937–941
22. Millán J, Pintò X, Muñoz A et al (2009) Lipoprotein ratios: physiological significance and clinical usefulness in cardiovascular prevention. *Vasc Health Risk Manag* 5:757–765
23. Sofi F, Abbate R, Gensini GF, Casini A (2010) Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* 92(5):1189–1196
24. Panagiotakos DB, Tzima N, Pitsavos C et al (2007) The association between adherence to the Mediterranean diet and fasting indices of glucose homeostasis: the ATTICA Study. *J Am Coll Nutr* 26:32–38
25. De Lorenzo A, Andreoli A, Sorge RP et al (1999) Modification of dietary habits (Mediterranean diet) and cancer mortality in a southern Italian village from 1960 to 1996. *Ann N Y Acad Sci* 889:224–229
26. McKeown NM, Meigs JB, Liu S et al (2004) Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diabetes Care* 27:538–5346
27. Perez-Jimenez F, Lopez-Miranda J, Pinillos MD et al (2001) A mediterranean and a high-carbohydrate diet improve glucose metabolism in healthy young persons. *Diabetologia* 44:2038–2043
28. Shai I, Schwarzfuchs D, Henkin Y et al (2008) Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 359(3):229–241
29. Martínez-González MA, Sánchez-Villegas A (2004) The emerging role of Mediterranean diets in cardiovascular epidemiology: monounsaturated fats, olive oil, red wine or the whole pattern? *Eur J Epidemiol* 19(1):9–13
30. Brunner EJ, Wunsch H, Marmot MG (2001) What is an optimal diet? Relationship of macronutrient intake to obesity, glucose tolerance, lipoprotein cholesterol levels and the metabolic syndrome in the Whitehall II Study. *Int J Obes Relat Metab Disord* 25:45–53
31. Skulas-Ray AC, West SG, Davidson MH, Kris-Etherton PM (2008) Omega-3 fatty acid concentrates in the treatment of moderate hypertriglyceridemia. *Expert Opin Pharmacother* 9:1237–1248
32. Rizza S, Tesaro M, Cardillo C, Galli A, Iantorno M, Gigli F, Sbraccia P, Federici M, Quon MJ, Lauro D (2009) Fish oil supplementation improves endothelial function in normoglycemic offspring of patients with type 2 diabetes. *Atherosclerosis* 206(2):569–574
33. Rasmussen BM, Vessby B, Uusitupa M & the KANWU Study Group. (2006). Effects of dietary saturated, monounsaturated, and n-3 fatty acids on BP in healthy subjects. *Am J Clin Nutr*; 83: 221–226
34. George A, Deemer SE, Dixie L (2010) Thompson Adiponectin is associated with risk of the metabolic syndrome and insulin resistance in women. *Acta Diabetol* 2010:8. doi:[10.1007/s00592-010-0192-6](https://doi.org/10.1007/s00592-010-0192-6)
35. Salas-Salvado J, Garcia-Arellano A, Estruch R et al (2008) Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. *Eur J Clin Nutr* 62(5):651–659
36. Carr DB, Utzschneider KM, Hull RL et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes*. 2004; 53b(8): 2087–2094
37. De Lorenzo A, Deurenberg P, Pietrantuono M et al (2003) How fat is obese? *Acta Diabetol* 40(Suppl 1):S254–S257
38. Di Renzo L, Galvano F, Orlandi C et al (2010) Oxidative stress in normal-weight obese syndrome. *Obesity (Silver Spring)* 18(11): 2125–2130
39. Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. *Endocrinol Metab Clin North Am* 2004; 33: 351–375.] but indicate that between 13 and 30% of people in developing countries
40. Mohan V, Deepa M (2006) The metabolic syndrome in developing countries. *Diabet Voice* 51:15–17
41. Ford ES, Giles WH, Mokdad AH (2004) Increasing prevalence of the metabolic syndrome among US adults. *Diabetes Care* 27: 2444–2449
42. Eckel RH, Grundy SM, Zimmet PZ (2005) The metabolic syndrome. *Lancet* 365:1415–1428
43. Dunkley AJ, Charles K, Gray LJ, Camosso-Stefinovic J, Davies MJ, Khunti K (2012) Effectiveness of interventions for reducing diabetes and cardiovascular disease risk in people with metabolic syndrome: systematic review and mixed treatment comparison meta-analysis. *Diabet Obes Metabol* 14:616–625