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ORIGINAL ARTICLE

Patient empowerment and the Mediterranean diet as a possible tool to tackle prediabetes associated with overweight or obesity: a pilot study

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Abstract

Aim The objective of this study was to investigate the effect of implementation of short-term patient empowerment as applied to Mediterranean diet (MD) adherence on metabolic and anthropometric parameters in prediabetic overweight or obese subjects.

Methods The sample included 42 subjects with prediabetes, aged 18–75 years and with body mass index (BMI) ≥ 25 kg/m^2, who received dietary advice on MD by nutritionists during session groups every 2 weeks for 4 months. Data on energy caloric intake and macronutrient consumption were collected using a 7-day food diary record. Adherence to MD was investigated through the PREvención con DIeta MEDiterránea (PREDIMED) questionnaire. No advice was given regarding caloric restriction and physical activity. At baseline and at the end of the study, each subject underwent anthropometric, metabolic, and nutritional assessments.

Results Approximately 40.5% of subjects had achieved restoration of normal glucose tolerance by the end of the study. Fasting plasma glucose, glycated hemoglobin (HbA1C), BMI, waist circumference, blood pressure, visceral adiposity index, triglycerides, and total and LDL cholesterol levels were significantly decreased, while HDL cholesterol had significantly increased by the end of the study. The subjects significantly increased adherence to MD, as assessed by the PREDIMED questionnaire at follow-up. A reduction of prevalence of the metabolic syndrome was also reported. Interestingly, the PREDIMED score correlated with HbA1C values at follow-up, after adjusting for BMI and total caloric intake.

Conclusions Implementation of short-term patient empowerment as applied to MD adherence was shown to improve anthropometric and metabolic parameters in prediabetic overweight or obese subjects. This is of considerable importance, given that diet must be the cornerstone of treatment in patients at high risk of developing type 2 diabetes.

Keywords Prediabetes · Mediterranean diet · Type 2 diabetes · Overweight · Obesity · Empowerment

Introduction

Prediabetes is associated with increased risk of type 2 diabetes and diabetic-related complications, such as cardiovascular diseases [1]. The Diabetes Prevention Program (DPP) [2] and ACT NOW [3] studies have reported that the rate of conversion of prediabetes to type 2 diabetes is 7–10% per year, with no significant difference in ethnicity. The most important therapeutic strategy to prevent progression from prediabetes to overt type 2 diabetes is lifestyle intervention focused on physical activity and a healthy diet. However, there is no specific dietary pattern recommendation to prevent type 2 diabetes in

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either the general or the at-risk population. The American Diabetes Association recommends dietary strategies that decrease calories and intake of dietary fat, while it encourages the intake of dietary fiber and foods containing whole grains as well as the reduction of sugar intake, e.g., sweetened beverages [4]. Studies have reported healthful diets to be effective in the reduction of type 2 diabetes, although the dietary patterns used in these studies were very heterogeneous, thus not permitting any firm conclusions to be drawn [5]. The Mediterranean diet (MD) seems to be a promising approach to fight diabetes at new diagnosis, even without caloric restriction. The healthy dietary pattern of the Mediterranean diet is characterized by high consumption of vegetables, legumes, grains, fruits, nuts, and olive oil; moderate consumption of fish and wine; and low consumption of red and processed meat and whole-fat dairy products [6]. Lower incidence of type 2 diabetes has been observed with increasing adherence to MD in Southern Europe [7]. Furthermore, better glycemic control and a delay in starting antidiabetic drugs have been observed in diabetic subjects following MD compared to subjects following a low-fat diet [8]. The PREvención con DIeta MEDiterránea (PREDIMED) study compared the long-term effect of MD plus virgin olive oil or nuts with a low-fat diet on the incidence of type 2 diabetes. Although caloric restriction was not recommended, MD has been reported to be effective in the prevention of diabetes [9]. In particular, MD is recommended by the American Diabetes Association (ADA) due to its beneficial effects on glycemic control and cardiovascular risk factors, but only as an alternative to a lower fat, higher carbohydrate eating pattern [9]. A systematic review with meta-analyses on the efficacy of MD on the management of type 2 diabetes and prediabetic states indicated that MD was associated with better glycemic control and cardiovascular risk factors than control diets, including a lower fat diet, thus suggesting that it is suitable for the overall management of type 2 diabetes [10].

In addition, another important tool that could be a promising approach to tackle prediabetes is the empowerment of patients regarding the lifestyle to be adopted. Empowerment has long been considered an important and integral component of management of diabetes [11]. Diabetic self-management education, whether delivered on an individual basis or in a group setting, has been shown to improve glycemic control and cardiovascular risk factors [12, 13].

Based on the results of the PREDIMED study, we aimed to investigate the short-term effect of MD on metabolic control in prediabetic overweight or obese subjects. Given the paramount importance of empowerment in the management of type 2 diabetes, we decided to deliver knowledge on MD to patients through informative talks with nutritionists, with the aim of empowering prediabetic subjects regarding this dietary pattern.

Materials and methods

Study design and participants

This study was part of a health promotion intervention funded by the National Center for Prevention and Control of Diseases of the Italian Ministry of Health 2010. The study design was a 4-month pilot study carried out in participants with prediabetes with overweight or obesity, investigating the short-term effect of MD on metabolic parameters. The subjects were enrolled in different Diabetes Outpatient Clinics in the metropolitan area of Naples, which were coordinated by the Unit of Endocrinology of the Dipartimento di Medicina Clinica e Chirurgia, at the University “Federico II” of Naples, Italy, and included 42 participants. The work was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was approved by the Ethical Committee of the University of Naples “Federico II” Medical School (n. 05/14). The purpose of the protocol was explained to all patients, and written informed consent was obtained. The study was conducted without support from the pharmaceutical industry. Eligible participants for the study were adult subjects (aged 18–75 years) with prediabetes, diagnosed according to glycated hemoglobin (HbA1c) recommended by the ADA guidelines (5.7–6.4%) [4] and BMI $\geq$ 25 kg/m^2, who were not taking any antidiabetic drugs, without cardiovascular diseases, without clinical events, and with no other serious diseases. Participants with overt type 2 diabetes were excluded. Other exclusion criteria were alcohol or drug abuse and history of allergy or intolerance to olive oil.

Procedures

Trained nutritionists were responsible for all aspects of the behavioral intervention promoting MD. Briefly, nutritionists gave dietary advice to participants by holding session groups every 2 weeks for 4 months. The sessions consisted of informative talks on MD, without offering any advice on energy restriction and without promoting physical activity. The general recommendations for MD were as follows: use of extra virgin olive oil for cooking and dressing of salads and other dishes; consumption of two or more servings (125 g/serving) per day of vegetables (at least one of them as salad); three or more servings per day of fresh fruit; three or more servings per week of legumes; three or more servings per week of fish or seafood; three or more servings per week of nuts or seeds; white meats instead of red meats or processed meats; and regular preparation of a homemade sauce with tomato, garlic, onion, and spices with olive oil to dress vegetables, pasta, rice, and other dishes. Optionally, among alcohol drinkers, moderate consumption of red wine (seven glasses/week) was also allowed. Recommendations were also given to avoid or limit the consumption of butter, cream, fast food, sweets, pastries, and sugar-sweetened beverages.

Adherence to MD

As already reported [14], adherence to MD was evaluated using the previously validated 14-item questionnaire for the assessment of PREDIMED [15]. A qualified nutritionist administered the questionnaire during a face-to-face interview with all enrolled subjects. Briefly, for each item, scores 1 and 0 were assigned; the PREDIMED score was calculated as follows: score 0–5, lowest adherence; score 6–9, average adherence; and score ≥ 10, highest adherence [15].

Dietary assessment

As previously reported [6], data were obtained during a face-to-face interview between the patient and a qualified nutritionist. Dietary assessment data were collected using a 7-day food record [16, 17]. The dietary interview enabled quantification of foods and drinks by using a photographic food atlas (≈ 1000 photographs) of known portion sizes to ensure accurate completion of the records [18]. On day 1 of the diary, the nutritionists, trained in standardized protocols, provided participants with instructions on how to complete the diary at the health check and asked them to recall the previous day's intake. Participants prospectively completed the remaining 6 days. The subjects returned the records to the nutritionist, who asked supplemental questions if necessary. Data were stored and processed using commercial software (Terapia Alimentare Dietosystem® DS-Medica, http://www.dsmedica.info). As regards quantities and qualities of foods consumed, the software is able to calculate not only the daily caloric intake but also the quantities of macronutrients (protein; total, complex, and simple carbohydrates; fibers; total fat, saturated fatty (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA): n-6 PUFA, n-3 PUFA, and n-6/n-3 PUFAs ratio; and cholesterol).

Anthropometric measurements

All anthropometric measurements were taken with subjects wearing light clothes and without shoes. In each subject, body mass index (BMI) was calculated as weight (kg)/height (m^2). Height was measured to the nearest 1 cm using a wall-mounted stadiometer. Body weight was determined to the nearest 100 g using a calibrated balance beam scale. Waist circumference (WC) was measured to the closest 0.1 cm with a non-extensible tape. The measurements were made with the subject standing upright, feet together, arms hanging freely at the sides, and breathing normally. WC was measured at the midpoint between the inferior costal margin and the upper iliac crest. Hip circumference (HC) was measured as the maximum circumference around the buttocks posteriorly and the symphysis pubis anteriorly and measured to the nearest 0.5 cm. In all individuals, systolic (SBP) and diastolic (DBP) blood pressures were measured three times, 2 min apart, with a random zero sphygmomanometer (Gelman Hawksley Ltd., Sussex, UK) after the subject had been sitting for at least 10 min. The average of the second and third readings was recorded.

Physical activity level was investigated with a standard questionnaire and was expressed according to whether the participant habitually engaged at least 30 min/day of aerobic exercise (YES/NO).

Laboratory tests

Venous blood samples were taken from the antecubital vein between 8 and 10 a.m. after an overnight fast of at least 8 h, collected in vacutainer tubes containing EDTA, and stored at − 80 °C until processed. All biochemical analyses, including total cholesterol and triglycerides, were performed with a Roche Modular Analytics System in the Central Biochemistry Laboratory of our Institution. Low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol were determined by direct method (homogeneous enzymatic assay for the direct quantitative determination of LDL cholesterol and HDL cholesterol). Fasting plasma glucose concentration was measured by the glucose oxidase method. HbA1c was measured with high-performance liquid chromatography (HPLC). The intra-assay coefficients of variations (CV) were < 5.5%.

Visceral adiposity index

The visceral adiposity index (VAI) was calculated with the following sex-specific formula, with TG levels expressed in millimoles per liter and HDL levels expressed in millimoles per liter [19, 20]:

$$\text{Male}$$
$$\text{VAI} = \left(\frac{\text{WC}}{39.68 + (1.88 \times \text{BMI})}\right) \times \left(\frac{\text{TG}}{1.03}\right) \times \left(\frac{1.31}{\text{HDL}}\right)$$
$$\text{Female}$$
$$\text{VAI} = \left(\frac{\text{WC}}{36.58 + (1.89 \times \text{BMI})}\right) \times \left(\frac{\text{TG}}{0.81}\right) \times \left(\frac{1.52}{\text{HDL}}\right)$$

Criteria defining metabolic syndrome

According to the National Cholesterol Education Program (NCEP)-Adult Treatment Panel (ATP III) definition, metabolic syndrome (MetS) is present if three or more of the following five criteria are met: WC over 102 cm and 88 cm (in males and females, respectively), blood pressure over 130/85 mmHg, fasting triglyceride level over 150 mg/dL, fasting HDL cholesterol level less than 40 mg/dL and 50 mg/dL (in males and females, respectively), and fasting glucose over 100 mg/dL (NCEP-ATP III 2000).

Outcomes

The main outcome of interest was changes of HbA1c values after a mean of 4 months of follow-up. Changes in anthropometric measurements, blood pressure, fasting plasma glucose, lipid profile, and total energy, as well as the daily macronutrient intake and adherence to MD at the end of intervention, were pre-specified secondary outcomes in this study.

Statistical methods

Data are expressed as mean ± SD or as median plus range according to variable distributions evaluated by the Kolmogorov-Smirnov test. Differences between the two groups were analyzed by the Wilcoxon paired test or Student's paired *t* test, when appropriate. The chi-square (χ^2) test was used to test the significance of differences in frequency distributions. The correlations between variables were performed using Pearson *r* or Spearman's *rho* correlation coefficients, when appropriate. Univariate proportional odds ratio (OR) models, 95% confidence interval (IC) and adjusted R^2, were performed to assess the association among quantitative variables (all food items of the PREDIMED questionnaire as YES and NO, and PREDIMED score as low, average, and high adherence). In these analyses, we entered only those variables that had a P value < 0.05 in the univariate analysis (partial correlation). To avoid multicollinearity, variables with a variance inflation factor (VIF) > 10 were excluded. Values ≤ 0.05 were considered statistically significant. Data were stored and analyzed using the MedCalc® package (Version 12.3.0 1993–2012 MedCalc Software bvba-MedCalc Software, Mariakerke, Belgium). Since there were no similar studies in the literature, we performed a priori sample size calculations using G POWER software.

Results

Subject characteristics

All participants in the study completed the PREDIMED questionnaires and the 7-day food records. The resulting total sample size, estimated according to a global effect size of 0.8 with type I error of 0.05 and a power of 95%, is 35 subjects in each group. Thus, we decided to enroll 42 subjects in each group, adjusting the sample size for 20% anticipated dropouts.

The study population, aged 60.5 (37.0–71.0) years, consisted of 21 females (50%). The mean of BMI was 32.23 ± 6.08 kg/m^2.

The baseline anthropometric measurements, blood pressure, fasting plasma glucose (FPG) and HbA1c, lipid profile, VAI, and physical activity of each participant are reported in Table 1. In particular, WC was higher than sex-specific cutoffs in 90.5% (38 subjects). Physical activity on at least 5 days per week was reported in 59.5% (25 subjects).

Figure 1 shows that in the case of prevalence of single metabolic risk factors and MetS, fasting glucose was higher than specific cutoffs in 81.0% (34 subjects), while presence/absence of MetS was diagnosed in 54.8% (23 subjects).

Response frequency of dietary components included in the PREDIMED questionnaire of the subjects at baseline is reported in Table 2. Extra virgin olive oil was the most consumed food item (71.4%), followed by fish (57.1%). According to the PREDIMED score, a large percentage of subjects demonstrated average adherence (PREDIMED score 6–9) to MD (57.1%, 24 subjects) (Fig. 2). In Table 3, we report total energy and daily macronutrient intakes obtained from the 7-day food records.

The results of the univariate proportional odds ratio model, performed to assess the association of percentage of HbA1c with food items of the PREDIMED questionnaire, are reported in Table 4. The components of MD that were the major determinants of HbA1C were extra virgin olive oil ($P = 0.025$), vegetables ($P = 0.007$), fruit ($P = 0.048$), legumes ($P < 0.001$), fish ($P = 0.028$), and nuts ($P < 0.001$), whose consumption seems to have a beneficial effect on HbA1C values. By contrast, the highest odds of consumption of red meats ($P = 0.017$), butter ($P = 0.028$), soda drinks ($P = 0.007$), and commercial sweets and confectionery ($P = 0.023$) seemed to have a negative effect on HbA1C values. In addition, the higher score of adherence to MD was negatively associated with percentage of HbA1c ($r = -0.564$, $P < 0.001$), independently of BMI and total energy intake ($r = -0.501$, $P = 0.001$).

Follow-up results

Seventeen subjects (40.5%) achieved restoration of normal glucose tolerance by the end of the study.

After the 4-month dietary intervention, there was a significant decrease of both HbA1C ($P < 0.001$) and FPG ($P < 0.001$) (Table 1).

Figure 1 shows the difference of the prevalence in the single metabolic risk factors and MetS after 4 months of follow-up. BMI, WC, SBP/DBP, VAI, and total and LDL cholesterol levels were significantly decreased, while HDL cholesterol had significantly increased by the end of the study ($P < 0.001$). In addition, there was a significant reduction in triglycerides ($P = 0.027$), and the subjects exhibited statistically significant differences compared with baseline for MetS

Table 1 Clinical and metabolic characteristics of the subjects at baseline and after 4 months of dietary intervention

Parameters	Baseline $n = 42$	After 4 months $n = 42$	P value
BMI (kg/m^2)	32.23 ± 6.08	30.60 ± 5.79	*< 0.001*
WC (cm)	104.55 (89.0–133.0)	100.0 (87.0–130.2)	*< 0.001*
HC (cm)	106.00 (72.1–136.5)	108.05 (78.0–139.0)	0.361
SBP (mmHg)	130.00 (100.0–155.0)	120.00 (90.0–140.0)	*< 0.001*
DBP (mmHg)	85.00 (60.0–95.0)	70.00 (60.0–85.0)	*< 0.001*
Fasting glucose (mg/dL)	125.36 ± 15.26	115.60 ± 12.54	*< 0.001*
HbA1c (%)	6.30 (6.0–6.5)	5.85 (5.3–6.8)	*< 0.001*
Total cholesterol (mg/dL)	187.62 ± 42.63	174.76 ± 39.21	*< 0.001*
HDL cholesterol (mg/dL)	45.00 (26.0–80.0)	51.00 (35.0–78.0)	*< 0.001*
LDL cholesterol (mg/dL)	107.97 ± 37.43	94.45 ± 33.49	*< 0.001*
Fasting triglycerides (mg/dL)	166.00 (57.0–443.0)	146.00 (58.0–253.0)	*0.027*
VAI	5.86 (1.41–17.02)	4.18 (1.69–10.89)	*0.001*
Physical activity			
Yes	25 (59.5%)	34 (81.0%)	0.056
No	17 (40.5%)	8 (19.0%)	

After 4 months, the patients exhibited statistically significant differences compared with baseline for anthropometric measurements, metabolic profiles, and cardiometabolic indices. Data are expressed as mean ± SD or as median plus range according to variable distributions evaluated by the Kolmogorov-Smirnov test. The paired *t* test or Wilcoxon paired test was used for the significance differences between the two groups. The chi-square (χ^2) test was used to test whether groups were associated with physical activity. A *P* value in italics denotes a significant difference ($P < 0.05$)

BMI, body mass index; *WC*, waist circumference; *HC*, hip circumference; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *HbA1c*, hemoglobin A1c; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *VAI*, visceral adiposity index

presence/absence ($P = 0.049$). No difference was found in terms of physical activity ($P = 0.056$).

Considering the response frequency of dietary components included in the PREDIMED questionnaire, statistically significant differences were observed (Table 2). In particular, the subjects had increased consumption of vegetables ($P = 0.003$), legumes ($P = 0.001$), fish/seafood ($P = 0.033$), nuts ($P < 0.001$), and poultry ($P = 0.001$) and had reduced consumption of red/processed meats, butter, cream, margarine, soda drinks, commercial sweets, and confectionery ($P < 0.001$). In addition, the PREDIMED score was increased (6.21 ± 1.85 vs. 10.52 ± 2.31, $P < 0.001$), and, as shown in Fig. 2, the percentage of subjects with a high adherence to MD (PREDIMED score ≥ 10) was significantly increased (4.8 vs. 73.8%; $\chi^2 = 39.13$, $P < 0.001$).

Table 3 shows the differences of total energy and daily macronutrient intakes. The subjects experienced a significant reduction in total energy intake ($P < 0.001$). In addition, all daily macronutrient intake was modified after 4 months, resulting in a significantly increased consumption of fiber ($P < 0.001$) and a significant decrease of simple carbohydrates ($P < 0.001$), fat ($P < 0.001$), and cholesterol ($P < 0.001$). No changes were recorded regarding the consumption of protein ($P = 0.347$), while a trend toward a positive association with complex carbohydrates was observed ($P = 0.086$).

The components of MD that were the major determinants of HbA1C were extra virgin olive oil ($P = 0.02$), vegetables ($P = 0.015$), legumes ($P = 0.015$), fish ($P = 0.006$), and nuts ($P = 0.022$), whose consumption seems to have a beneficial effect on HbA1C values. In contrast, the highest consumption of red meats ($P = 0.044$), soda drinks ($P = 0.008$), and commercial sweets and confectionery ($P = 0.014$) seemed to have a negative effect on HbA1C values (Table 4). As expected, delta variations of HbA1c correlated with delta variations of total energy and daily macronutrient intakes obtained from the 7-day food records, except for n-3 PUFA ($P = 0.498$) after 4 months of follow-up (Table 5). Figure 3 shows the correlation between delta variations of HbA1c and delta variations of PREDIMED score at 4 months of follow-up ($r = 0.552$, $P < 0.001$).

As already noted at baseline, the higher score of adherence to MD was negatively associated with a lower percentage of HbA1c ($r = -0.919$, $P < 0.001$), independently of BMI and total energy intake ($r = -0.799$, $P < 0.001$).

Discussion

In this nutrition intervention study, we found that a non-calorie-restricted, traditional MD decreased HbA1C values in

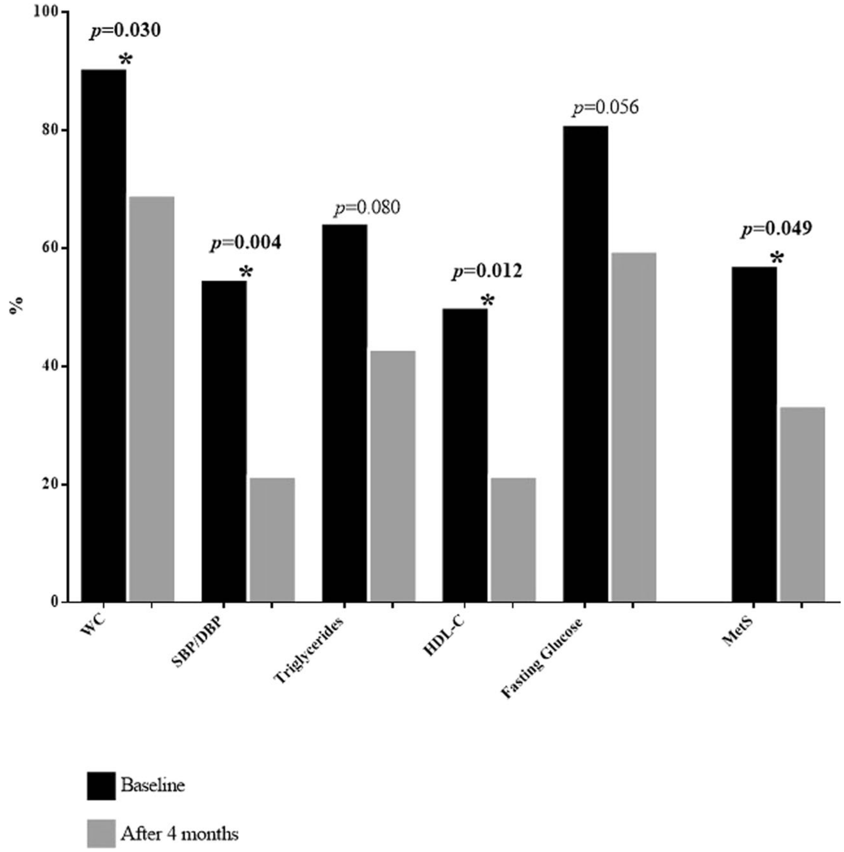

Fig. 1 Frequency of metabolic risk factors and MetS in patients at baseline and after 4 months. After 4 months, the patients exhibited statistically significant differences compared with baseline for some parameters of the MetS. In particular: WC (90.5 vs. 69.0%; $\chi^2 = 4.72$, $\boldsymbol{P} = \mathbf{0.030}$), SBP/DBP (54.8 vs. 21.4%; $\chi^2 = 8.53$, $\boldsymbol{P} = \mathbf{0.004}$), triglycerides (64.3 vs. 42.9%; $\chi^2 = 3.06$, $P = 0.080$), HDL-C (50.0 vs. 21.4%; $\chi^2 = 6.27$, $\boldsymbol{P} = \mathbf{0.012}$); fasting glucose (81.0 vs. 59.5%; $\chi^2 = 3.65$, $P = 0.056$), and MetS presence/absence (57.1 vs. 33.3%; $\chi^2 = 3.89$, $\boldsymbol{P} = \mathbf{0.049}$) at baseline and after 4 months, respectively. Data are expressed as percentage. The chi-square (χ^2) test was used to test the significance of differences between the two groups. A P value in bold type denotes a significant difference ($P < 0.05$). *WC*, waist circumference; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *HDL-C*, high-density lipoprotein cholesterol; *MetS*, metabolic syndrome

prediabetic subjects with overweight or obesity after a median follow-up of 4 months. The improvement of HbA1C values was accompanied by a significant reduction in all anthropometric measurements, blood pressure, lipid profile, and VAI, and a significant increase in HDL cholesterol. At the end of the study, prediabetic subjects were found to have increased adherence to MD and a significant change in food cues, preferring vegetables, legumes, fish/seafood, nuts, and poultry to red/processed meats, butter, cream, margarine, soda drinks, and commercial sweets and confectionery. Our results confirm previous studies highlighting the role of change of lifestyle as a key player in the management of prediabetes [11–13]. In our study, the nutritionists provided knowledge on MD, thus empowering prediabetic subjects in awareness of what constitutes a healthy diet, such as MD, as a key component in/an essential part of prediabetes management. As previously reported, patient empowerment is of paramount importance in diabetes education, increasing diabetic individuals' knowledge concerning self-care, skills, self-awareness, and the sense of personal autonomy [21]. Usually, diagnosis of type 2 diabetes arouses a range of emotional responses that threaten people's social and personal identity; thus, there is the need to construct new identity representations. Raballo et al. investigated the perceptions of diabetes care and diabetes in a large cohort of Italian patients followed long term by group or usual care [22]. These authors developed and validated an educational model, reporting that group treatment was effective in reinforcing communication and peer identification, and suggested that it can be applied to everyday practice in busy diabetes clinics. In particular, their educational model achieved its clinical aims by promoting awareness, self-efficacy, positive attitudes toward diabetes and the setting of care, an internal locus of control, and empowerment in the patients. In China, diabetic subjects enrolled in an empowerment-based self-management program, improved diet management and blood glucose self-monitoring [23]. A cluster-randomized clinical trial was carried out in people with type 2 diabetes participating in seven group meetings, each one lasting around 2 h. At the end of the study, there was an improvement in glycemic levels, as demonstrated by glycated hemoglobin

Table 2 Response frequency of dietary components included in the PREDIMED questionnaire at baseline and after 4 months

	Questions	Baseline $n = 42$		After 4 months $n = 42$		*P* values
		n	%	*n*	%	
1	Use of extra virgin olive oil as main culinary lipid	30	71.4	30	71.4	0.809
2	Extra virgin olive oil > 4 tablespoons	21	50.0	22	52.4	1.000
3	Vegetables ≥ 2 servings/day	20	47.6	34	81.0	0.003
4	Fruits ≥ 3 servings/day	18	42.9	27	64.3	0.080
5	Red/processed meats < 1/day	21	50.0	35	83.3	< 0.001
6	Butter, cream, margarine < 1/day	18	42.9	39	92.9	< 0.001
7	Soda drinks < 1/day	10	23.8	36	85.7	< 0.001
8	Wine—glasses ≥ 7/week	12	28.6	18	42.9	0.255
9	Legumes ≥ 3/week	20	47.6	37	88.1	0.001
10	Fish/seafood ≥ 3/week	24	57.1	34	81.0	0.033
11	Commercial sweets and confectionery ≤ 2/week	11	26.2	37	88.1	< 0.001
12	Tree nuts ≥ 3/week	13	31.0	35	83.3	< 0.001
13	Poultry more than red meats	21	50.0	36	85.7	0.001
14	Use of sofrito sauce ≥ 2/week	22	52.4	27	64.3	0.376

After 4 months, most of the questions of the PREDIMED questionnaire were answered positively. Data are expressed as percentage of response obtained with the PREDIMED questionnaire. *PREDIMED*, PREvención con DIetaMEDiterránea [9]

results [24]. Accordingly, in our study also, empowerment has been proven to reinforce the motivation of diabetic subjects and the ability to believe in themselves, thus reducing the stress related to the inability of managing the disease. Furthermore, all the subjects enrolled in our study lived in the same metropolitan area, therefore sharing similar food habits. As result of empowerment, they were enabled to change their food habits in a healthy way, using foods and recipes that, in fact, already belong to their own nutritional tradition. Since, as mentioned, all the subjects lived in the same area, they switched their dietary pattern to the intake of similar food, thus reducing possible bias.

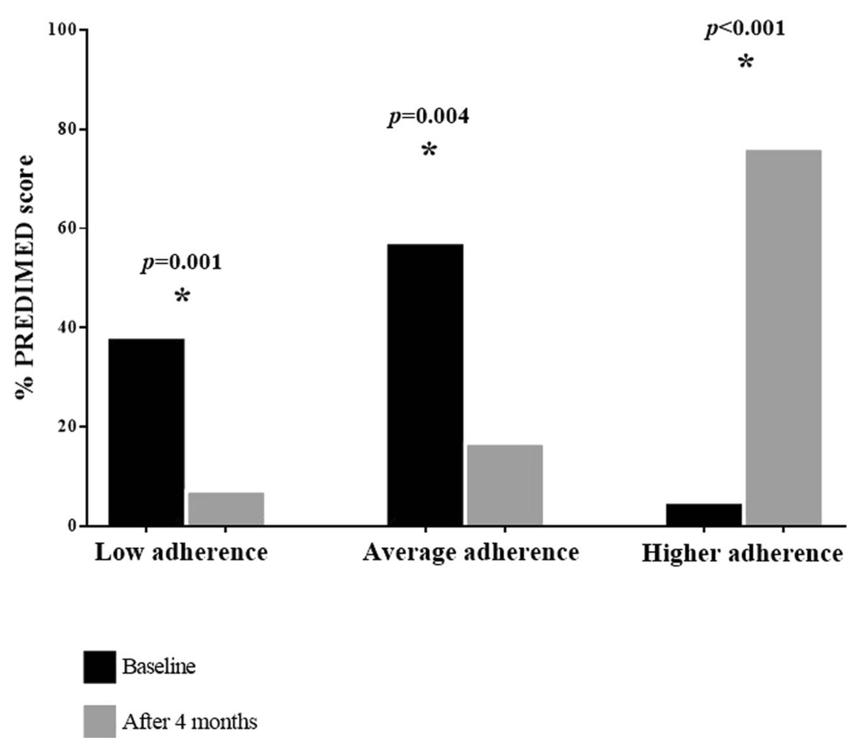

Fig. 2 Difference of adherence MD in the PREDIMED score at baseline and after 4 months. After 4 months, the patients exhibited statistically significant differences compared with baseline for the adherence MD in the PREDIMED score. In particular: low adherence of MD (38.1 vs. 4.8%; $\chi^2 = 11.95$, $\boldsymbol{P = 0.001}$), average adherence of MD (57.1 vs. 21.4%; $\chi^2 = 9.78$, $\boldsymbol{P = 0.002}$), and higher adherence of MD (4.8 vs. 73.8%; $\chi^2 = 39.13$, $\boldsymbol{P < 0.001}$) at baseline and after 4 months, respectively. Data are expressed as percentages

Table 3 Total energy and macronutrient intake of patients at baseline and after 4 months

Parameters	Baseline $n = 42$	After 4 months $n = 42$	*P* value
Total energy (kcal)	2512.07 ± 501.64	2238.21 ± 564.80	< 0.001
Protein (g of total kcal)	98.23 ± 17.25	94.47 ± 22.72	0.347
Carbohydrate (g of total kcal)	345.49 ± 78.50	304.79 ± 76.93	< 0.001
Complex (g of total kcal)	208.83 ± 50.15	203.72 ± 51.67	0.086
Simple (g of total kcal)	136.67 ± 34.16	101.07 ± 25.36	< 0.001
Fiber (g/day)	16.27 ± 5.56	19.30 ± 4.19	< 0.001
Fat (g of total kcal)	81.90 ± 21.69	71.24 ± 19.17	< 0.001
SFA (g of total kcal)	33.40 ± 10.53	23.35 ± 6.03	< 0.001
MUFA (g of total kcal)	28.27 ± 7.62	31.78 ± 8.45	0.021
PUFA (g of total kcal)	20.40 ± 15.56	16.12 ± 14.09	0.015
n-6 PUFA (g/day)	17.79 ± 15.82	12.89 ± 14.31	0.005
n-3 PUFA (g/day)	2.61 ± 0.80	3.22 ± 1.26	0.006
n-6/n-3 PUFAs ratio	7.92 ± 8.24	4.76 ± 6.42	0.004
Cholesterol (mg/day)	155.93 ± 50.32	135.48 ± 38.38	< 0.001

The patients' increased knowledge of MD resulted not only in food restriction but also in the switch to healthier food preferences. As a result, the subjects experienced an improvement in HbA1C values, which, notably, was partially explained by weight loss. In fact, a higher score of adherence to MD was inversely associated with percentage of HbA1c, after adjusting for BMI and total energy intake, thus suggesting that the MD food cluster could have beneficial metabolic properties besides weight loss. This assumption was supported by the fact that most of the components of MD share antioxidant properties due to polyphenols. Olive oil, nuts, red wine, legumes, fruits, and vegetables, key MD components, are all polyphenol-rich foods that have been reported to have beneficial effects on glucose metabolism [25]. The consumption of olive leaf extract (500 mg) resulted in a significant decrease of HbA1C and fasting plasma insulin levels in type 2 diabetic subjects [26]. Similar results were found by de Bock et al., who demonstrated an improvement of pancreatic β-cell function and insulin resistance after olive oil administration in middle-aged overweight men [27]. In addition, one of the main characteristics of traditional MD is the moderate intake of wine consumed with meals. Wine, particularly red wine, is

Table 4 Univariate proportional odds ratio model to assess the association between circulating levels of HbA1c and food items included in the PREDIMED questionnaire

	Questions	Baseline				After 4 months			
		OR	*P* value	95% IC	R^2	OR	*P* value	95% IC	R^2
1	Use of extra virgin olive oil as main culinary lipid	0.004	0.025	0.001–0.490	0.138	0.032	0.002	0.003–0.292	0.269
2	Extra virgin olive oil > 4 tablespoons	0.528	0.721	0.016–17.61	0.003	0.064	0.005	0.009–0.445	0.217
3	Vegetables ≥ 2 servings/day	0.003	0.007	0.001–0.205	0.188	0.105	0.015	0.017–0.641	0.153
4	Fruits ≥ 3 servings/day	0.021	0.048	0.001–0.974	0.096	0.209	0.060	0.041–1.065	0.088
5	Red/processed meats < 1/day	132.66	0.017	2.384–7381.08	0.144	0.112	0.044	0.013–0.940	0.104
6	Butter, cream, margarine < 1/day	91.94	0.028	1.641–5153.47	0.123	0.001	0.110	0.001–18.962	0.276
7	Soda drinks < 1/day	> 999.00	0.007	22.42–> 999.0	0.281	0.002	0.008	0.001–0.206	0.323
8	Wine—glasses ≥ 7/week	0.149	0.341	0.003–7.515	0.022	0.211	0.107	0.032–1.396	0.069
9	Legumes ≥ 3/week	0.001	< 0.001	0.000–0.001	0.538	0.002	0.015	0.001–0.307	0.288
10	Fish/seafood ≥ 3/week	0.011	0.028	0.000–0.610	0.123	0.001	0.006	0.000–0.087	0.462
11	Commercial sweets and confectionery ≤ 2/week	394.34	0.023	2.249–> 999	0.145	0.012	0.014	0.001–0.416	0.214
12	Tree nuts ≥ 3/week	0.001	< 0.001	0.000–0.001	0.504	0.120	0.022	0.020–0.732	0.134
13	Poultry more than red meats	0.103	0.217	0.003–3.797	0.037	0.243	0.185	0.030–1.969	0.042
14	Use of sofrito sauce ≥ 2/week	0.025	0.058	0.001–1.133	0.089	0.400	0.327	0.064–2.505	0.023

Table 5 Correlation between Δ HbA1c with energy and nutrient intake

Parameters	ΔHbA1c	
	r	*P* values
Total energy (kcal)	0.955	< 0.001
Protein (g of total kcal)	0.439	0.004
Carbohydrate (g of total kcal)	0.899	< 0.001
Complex (g of total kcal)	0.753	< 0.001
Simple (g of total kcal)	0.921	< 0.001
Fiber (g/day)	−0.633	< 0.001
Fat (g of total kcal)	0.922	< 0.001
SFA (g of total kcal)	0.914	< 0.001
MUFA (g of total kcal)	−0.469	0.002
PUFA (g of total kcal)	0.371	0.015
n-6 PUFA (g/day)	0.374	0.015
n-3 PUFA (g/day)	−0.107	0.498
n-6/n-3 PUFAs ratio	0.393	0.010
Cholesterol (mg/day)	0.899	< 0.001

HbA1c, hemoglobin A1c; *SFA*, saturated fatty; *MUFA*, monounsaturated fatty acids; *PUFA*, polyunsaturated fatty acids

rich in phenolic compounds, including flavonoids (anthocyanins, tannins, and catechins), stilbenes like resveratrols, tyrosols, and hydroxytyrosols. Evidence suggests that red wine is rich in polyphenols that are responsible for improvement in insulin resistance, as measured by HoMA-IR [28]. Nuts, which are a well-known source of unsaturated fatty acids, fiber, antioxidant vitamins, minerals, and other bioactive compounds, are also consumed in high amounts in MD. Ellagic acid, which is found in significant amounts in nuts, has been demonstrated to have positive effects on diabetes control [29]. In addition, plasma values of urolithin A glucuronide,

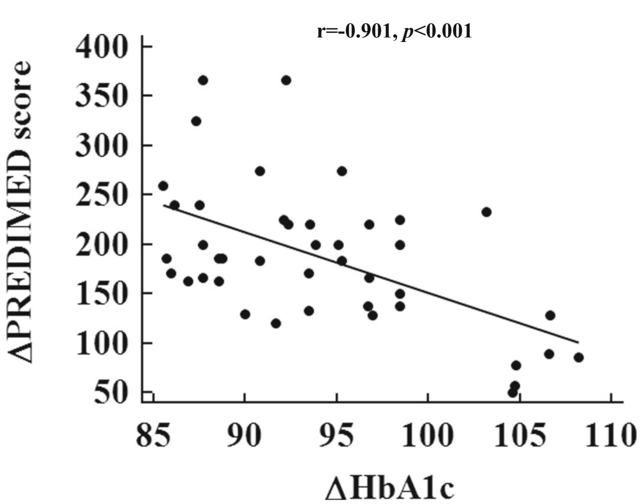

Fig. 3 Correlation between delta variation of HbA1c values and delta variation of PREDIMED score at 4 months of follow-up ($r = 0.552$, $P < 0.001$)

which is a metabolite of dietary ellagic acid, have been inversely correlated with insulin resistance measured by HoMA-IR [30].

One of the most relevant results of our study was that subjects experienced weight loss without receiving any advice relating to reducing caloric intake or to modifying their habitual physical activity. This effect could be explained by the low energy density (defined in terms of available dietary energy per weight, i.e., energy content/weight of food or kJ/g), of MD food components [31, 32]. Furthermore, strict adherence to MD has also been associated with high fiber intake and high diet volume (water content) of food. All these mechanisms lead to a delayed gastric emptying rate and slowed digestion and absorption which, in turn, slows the rate of glucose absorption, reduces plasma insulin levels, and elicits earlier satiety, resulting in a reduction of total caloric intake [33, 34]. Finally, we found an improvement in both systolic and diastolic blood pressures after MD dietary intervention; this possibly explained by the high mineral content of plant foods, which tend to reduce arterial blood pressure (including potassium, magnesium, and calcium) [35]. In addition, the high antioxidant content of plant foods and olive oil may also contribute to the health of the vascular system [36].

Although this study shows promising results, it is not free of limitations. All the subjects were of Caucasian ethnicity living in Southern Italy; therefore, our results might not be capable of extrapolation to other populations with a different ethnic distribution. Furthermore, the lack of control groups following other types of diet did not allow for investigation of what dietary pattern is more effective in the short-term improvement of metabolic control in prediabetic subjects with overweight or obesity.

In summary, our study shows that a short-term dietary intervention focused on MD, even not recommending caloric restriction, in prediabetic subjects with overweight or obesity, reduced HbA1C values and improved several anthropometric and metabolic outcomes. We would therefore recommend the adoption of this nutritional intervention in prediabetes associated with overweight or obesity. Further studies are needed to investigate whether there is a beneficial impact of MD on the long-term risk of developing type 2 diabetes in prediabetic subjects in different population samples.

Compliance with ethical standards

The work was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was approved by the Ethical Committee of the University of Naples "Federico II" Medical School (n. 05/14). The purpose of the protocol was explained to all patients, and written informed consent was obtained.

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