ORIGINAL ARTICLE

Effects of Italian Mediterranean organic diet vs. low-protein diet in nephropathic patients according to MTHFR genotypes

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Abstract

Background Several reports associate an Italian-style Mediterranean diet (IMD) with lower risk of cardiovascular disease and morbidity. The present study aimed to explore the effects of an Italian Mediterranean organic diet (IMOD) versus low-protein diet (LPD) in chronic kidney disease (CKD) patients, according to patients' carrier status for the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism.

Methods A total of 40 male patients with CKD and stable renal function (Kidney Disease Outcomes Quality Initiative stages 2 and 3) were classified according to MTHFR polymorphism as carrier T(+) or non carrier T(−). At the time of enrolment (T0) patients' diet consisted of LPD; they were then administered IMD for 14 days (T1), thereupon IMOD for 14 days (T2). Patients underwent a complete medical history, body composition assessment and biochemical analysis.

Results Baseline homocysteine levels were on average 8.24 mol/l higher (95 % confidence interval 6.47, 10.00) among T(+) than T(−) and the difference was statistically significant (p < 0.001). We found a significant interaction between MTHFR status and the effect of both the IMD and IMOD on homocysteine levels compared to LPD (p for interaction <0.001). Both the IMD and IMOD resulted in significant variations of anthropometric and laboratory measurements.

Conclusions IMD and IMOD diets could represent a viable alternative to LPD in CKD patients on conservative therapy. The effect of these diets seems to be influenced by MTHFR genotypes.

Keywords Body composition · Cardiovascular disease risk · Chronic kidney disease · C677T MTHFR polymorphism · Italian Mediterranean organic diet

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Introduction

In patients with chronic kidney disease (CKD), the rate of mortality from cardiovascular disease is 10- to 20-fold higher than that seen in the general population, even after correction for age, sex, race and the presence of diabetes [1]. Hyperhomocysteinemia has been identified as a predictor of atherosclerotic complications in the general population. It is also frequent among patients with renal failure [2] and several studies have shown that in CKD hyperhomocysteinemia is a risk factor for cardiovascular complications [3]. Hyperhomocysteinemia at an earlier stage of renal disease could also accelerate the progression of chronic renal disease. Homocysteine (Hcy) causes endothelial cell dysfunction and injury via production of reactive oxygen species during its autoxidation [4].

Hyperhomocysteinemia enhances vascular smooth muscle cell proliferation [5], increases platelet aggregation, acts on the coagulation cascade and fibrinolysis, directly inducing or acting in a synergistic manner with other risk factors to create a prothrombotic environment [6].

Serum and intracellular levels of Hcy are regulated by remethylation to methionine or trans-sulfuration to cysteine. The methyl donor in the vitamin B12-dependent remethylation is 5-methyltetrahydrofolate generated from the reduction of the 5,10-methylenetetrahydrofolate reductase (MTHFR) enzyme. Elevated plasma concentrations of total Hcy (tHcy) depend chiefly on genetic defects in the enzymes involved in homocysteine metabolism or in nutritional deficiency of the vitamin cofactors. A common C/T mutation at nucleotide position 677 (C677T) has been identified in the gene coding for MTHFR. This genetic mutation causes a valine for alanine substitution, which decreases MTHFR activity and tends to increase tHcy concentrations in individuals who are homozygous for the T/T genotype [7]. Two other MTHFR polymorphisms have been identified (G1793A and A1298C) [8]. A study has shown that in a large population of kidney transplant recipients, the patients carrying the MTHFR G1793A mutation had approximately 4 nmol/l higher plasma Hcy concentrations compared to individuals with the corresponding wild-type alleles [9].

Several observational studies have provided scientific evidence that diets rich in fruit, vegetables, legumes, whole grains, fish, and low-fat dairy products are associated with lower incidence of various chronic diseases, including atherosclerosis, cardiovascular diseases, and cancer. Since the early 1990s, growing evidence indicates that the Mediterranean diet, a concept first proposed by Keys in the mid-1980s, has a beneficial influence on health and longevity. Previous studies have demonstrated that the Mediterranean diet (MD) with a lower risk of coronary heart disease (CHD) morbidity and mortality [10–12].

The mechanisms by which the Mediterranean diet exerts its favorable effects on the cardiovascular system are diverse and a number of plausible explanations have been provided, including regulation of arterial blood pressure levels, body weight, blood lipid concentrations, inflammation and coagulation processes, and endothelial function.

It has been suggested that organic products could contain 10–50 % more phytochemicals than non-organic products. Previous data highlighted a possible impact on human health of a Mediterranean diet comprising organic products versus conventional, due to the effect on the total plasma anti-oxidant capacity, i.e. an increase in plasma antioxidant capacity was observed in the subjects receiving the organic diet [13].

Conscious that, regardless of its organic or conventional origin, a well-balanced diet is necessary to improve health and that the administration of a single or a few organic foods within the habitual diet would probably not reveal any beneficial effect, we undertook the present study to explore the effects of the Italian Mediterranean organic diet (IMOD) versus the low-protein diet (LPD) on chemical–clinical parameters and body composition in CKD patients, according to the C677T MTHFR polymorphism.

Subjects and methods

Study population

In order to avoid potential confounding factors following menstrual cycle hormone fluctuations, we excluded women from the study. A total of 50 male patients (mean age 46.25 ± 5.97 years; range 42–54) with CKD and stable renal function [stages 2 and 3 according to the Kidney Disease Outcomes Quality Initiative (K-DOQI) 2003 classification] were recruited from the Department of Internal Medicine, Hypertension and Nephrology Unit, "Tor Vergata" University Hospital, Rome (Italy) according to the level of kidney function. We selected 40 patients with GFR <70 and >45 ml/min corresponding to stages 2 and 3 CKD of K-DOQI 2003 [14]. The causes of primary renal failure were chronic glomerulonephrites. All patients were managed with standard conservative treatment. Participation in the study included a complete medical history to gather information on health status, current medications including supplements of vitamins and minerals, alcohol consumption, smoking, physical activity (PA) and family history of chronic diseases. Data on PA were collected using a simple questionnaire that grades the level of PA into five categories (sedentary, light, moderate, heavy and agonistic) based on the time spent in activities of daily living on programmed physical exercise. No change of total energy intake (kcal/die) was required during the course of the study, nor was there any change in subjects' physical activity during the study, and no change in resting metabolic rate (RMR) was expected.

The subjects were categorized into body mass index (BMI) subgroups according to World Health Organization (WHO) criteria [15–17]. Moreover, gender and age were also used to classify the total population. Patients were classified based on carrier status for the MTHFR polymorphism as: carrier T(+) or non carrier T(−).

All patients gave their informed consent before entering the study. The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the "Tor Vergata" University Medical Ethical Committee, Rome, Italy.

Diet assessment

Compliance was assessed by 3-day diet records (3DDRs) completed during the study. Participants were asked to complete a 3-day weighed diet record including 2 week-days and 1 weekend day at baseline and after 7 days of dietary intervention. Detailed instruction on how to collect diet records was verbally given to each participant by a trained researcher. Written instructions were also included in the 3DDR booklet provided. A researcher reviewed all 3DDRs upon return for completeness and accuracy.

Low protein diet (LPD)

In CKD, nutritional therapy means designing diets to reduce the patient's intake of proteins, phosphorus and sodium, while preserving adequate energy intake. Different nutritional strategies can be devised according to the protein needs of the patient [18]. At the time of enrolment (T0) our patients had been following a diet with controlled protein intake [recommended dietary allowance (RDA) 0.7 g/kg/day of protein] and low-phosphorus intake (phosphorus 300–400 mg/day) for 6 months. The potential renal acid load index was −10.39 mEq/100 g [19]. The sodium chloride content of the LPD was kept between 2 and 5 g/day according to individual needs. The energy intake was 2,000 kcal/day.

The macronutrient composition of the dietary regimen was as follows: carbohydrates, 50.2 % kcal/day; proteins, 12.8 % kcal/day; total fat, 29.3 % kcal/day [saturated fat 14.34 g; polyunsaturated fatty acids (PUFA) 8.06 g: 5–6 % of n-6 PUFA and 1–2 % of n-3 PUFA; monounsaturated fatty acids (MUFA), 38.47 g; cholesterol consumption of 160 mg/day], 17.2 g of fibre, folic acid 328 mcg, pyridoxine 1.4 mg, cyanocobalamin 2.1 mg per day. No alcoholic beverages were allowed except 100 ml/day of red wine (7.7 % kcal/day). The plan for each subject was obtained from a dietetic software package (Dietosystem, DS Medica, Milan, Italy).

Italian Mediterranean diet (IMD) and Italian Mediterranean organic diet (IMOD)

For 14 days (T1) all selected subjects consumed conventional products according to the IMD, the so-called Nicotera diet [20, 21]. Following this, for a further 14 days (T2) they followed an exclusively "organic" diet, according to the IMOD [22, 23]. The potential renal acid load index was −10.47 mEq/100 g [19]. The sodium chloride content of LPD was kept between 2 and 5 g/day according to individual needs. The energy intake was 2,000 kcal/day.

The macronutrient composition of the dietary regimen was as follows: carbohydrates, 54.75 % kcal/day; proteins, 14.9 % kcal/day (0.9 g/kg/day); total fat, 22.65 % kcal/day (saturated fat 14.07 g; PUFA 6.62 g: 5–6 % of n-6 PUFA and 1–2 % of n-3 PUFA; MUFA, 32.55 g; cholesterol consumption of 147.83 mg/day), 30.16 g of fibre, folic acid 421.60 mcg, pyridoxine 1.82 mg, cyanocobalamin 2.79 mg per day. No alcoholic beverages were allowed except 100 ml/day of red wine (7.7 % kcal/day). The plan for each subject was obtained from a dietetic software package (Dietosystem, DS Medica, Milan, Italy). The only differences in composition between IMD and IMOD were: folic acid >450 mcg, pyridoxine 2.18 mg and cyanocobalamin 3.38 mg *per die*. The Italian RDA were incorporated to ensure adequate vitamin and mineral intake [24]. The potassium intake met the dietary reference intakes of the Institute of Medicine of the National Academies, Washington, DC, USA. The IMD and IMOD were evaluated by a dietetic software package (DS Medigroup, Milan, Italy).

MTHFR genotype

Genomic DNA was extracted from peripheral whole blood using the QIAamp DNA Mini Kit (Quiagen, Valencia, CA, USA). MTHFR was selected for genotyping. The C677T polymorphism of the MTHFR gene was screened by the restriction fragment–length polymorphism after digestion with HinfI restriction enzyme, as previously described [7]. The TT and the CT genotypes were grouped and indicated as T carriers T(+), while the CC genotype were named as T non carriers T(−). Among the general European population, genotype frequencies are: CC = 45 %, CT = 45 %, TT = 10 %. The genotype distribution observed in European hemodialysis patients was: CC 51.2 % (n = 41), CT 37.5 % (n = 30) and TT 11.2 % (n = 9).

Anthropometric measurements

Anthropometric parameters were measured according to standard methods [25]. BMI was calculated as body weight divided by height squared (kg/m^2).

Dual X-ray absorptiometry (DXA)

The total body composition was assessed by DXA (iDXA, G.E. Medical Systems, WI, USA), according to the previously described procedure [26]. The coefficient of variation (CV) (standard deviation [SD]/mean) for repeated measurements is 1.0–2.2 % in our laboratory depending on the application. Subjects were classified as pre-obese/obese according to a World Health Organization (WHO) Technical Report and a WHO Technical Report Series [27, 28].

Analysis of blood samples

Fasting blood samples were collected, and analyzed according to standard techniques by the accredited Clinical Chemical Laboratories of the "Tor Vergata" Policlinico (PTV) of Rome, Italy.

GFR estimation

The estimated GFR (e-GFR) was calculated using the CKD epidemiology collaboration (CKD-EPI) formula [29].

Statistical analysis

The main aim of the study was to analyze whether the presence of the MTHFR C677T polymorphism would modify the effect of two different diets, IMD and IMOD, on circulating levels of homocysteine. Repeated measurements for each patients were analyzed with the use of random-intercept linear mixed models with homocysteine as the dependent variable; the effect modification by MTHFR status on the prescribed diet was investigated by including in the model an interaction term between MTHFR status and diet. Marginal means and differences with 95 % confidence intervals (CI) were estimated from the model, using the LPD as reference, and reported according to MTHFR status.

We also analyzed the main effects of the IMD and IMOD on a number of other anthropometric and laboratory variables with random-intercept linear mixed models with each measured parameter as dependent variable and diet as explanatory variable. For these analyses, we chose a conservative approach and only looked at contrasts between LPD and IMD and IMOD when the overall test for the effect of diet was statistically significant. Furthermore, to avoid over-inflation of the type I error from multiple testing, the Bonferroni correction was applied: with 12 preplanned comparisons, the corrected p value for statistical significance was fixed at p = 0.004.

A χ^2 test was also used to evaluate the Hardy–Weinberg equilibrium of the observed genotype frequencies with respect to the general population. The level of significance was fixed at p ≤ 0.05 for all procedures. Statistical analysis was performed using computer software packages (SPSS for Windows, version 13.0, SPSS, Chicago, IL, USA; and Stata version 12.1, StataCorp, TX, USA).

Results

Among 50 Caucasian Italian males subjects recruited for the study, 7 were excluded at screening (two had prostate cancer and five were diabetic), and 3 were withdrawn for

Table 1 Baseline characteristics of overall study group

Characteristics	
Number of patients	40
Age (years)	46.25 ± 5.97*
Gender (male, female)	40 M, 0 F
Likely underlying renal disease	
Immunoglobulin (Ig)A glomerulonephritis	14
Membrano-proliferative glomerulonephritis	16
Primary glomerulonephritis not histologically defined	10

* Data are expressed as mean ± SD

missing data in some of the variables considered. Thus, a total of 40 subjects completed the study, and their data were eligible for data analysis. The demographic and clinical characteristics of the participants are presented in Table 1.

The distribution of the MTHFR genotypes in our study group was compatible with the Hardy–Weinberg equilibrium (p ≤ 0.05). The T allele frequency was 45 %, and the CC, CT, and TT genotype frequencies were 55 % (n = 22), 35 % (n = 14), and 10 % (n = 4), respectively. The T allele frequency in our sample was similar to that in other white populations [30].

The degree of compliance was high in all groups but was greater in LPD (99.5 %) than IMOD (98.4 %) and IMD (94.6 %) (p = 0.05). However the degree of palatability was higher in IMOD (99.4 %) and IMD (94.6 %) than in LPD (60.0 %) (p = 0.05).

Baseline homocysteine levels were on average 8.24 mol/l higher (95 % CI 6.47, 10.00) among T(+) participants than T(−) and the difference was statistically significant (p < 0.001). We found a significant effect modification of MTHFR status on the effect of both the IMD and IMOD on homocysteine levels compared with that of the LPD (p for interaction <0.001). In particular, among T(−) patients homocysteine levels for IMD did not differ significantly from LPD (average difference −0.25 mol/l, 95 % CI −1.92, 1.43; p = 0.77), whereas they were significantly lower for IMOD (average difference −2.17 mol/l, 95 % CI −3.85, −0.49; p = 0.01). Conversely, among T(+) patients homocysteine levels were significantly lower, with respect to LPD, for both IMD (average difference −3.08 mol/l, 95 % CI −4.94, −1.23; p = 0.001) and IMOD (average difference −9.18 mol/l, 95 % CI −11.04, −7.33; p < 0.001). Compared with IMD, homocysteine levels after IMOD were lower for both T(−) patients (average difference −1.92 mol/l, 95 % CI −3.60, −0.24; p = 0.03) and T(+) patients (average difference −6.10 mol/l, 95 % CI −7.96, −4.24; p < 0.001). The relationships between diet and MTHFR status on homocysteine levels are illustrated in Fig. 1.

Since we did not find any significant interaction between MTHFR status and diet on the other measured variables, we only report the main effects of each diet without further stratification for MTHFR status. Since the overall test for differences between diets was statistically significant for all the measured parameters, we performed paired comparisons between diets for each parameter (Table 2). The e-GFR during the entire study period did not change significantly.

Discussion

Several studies have found that adherence to IMD, for its particular combination of micro- and macronutrients, is associated with beneficial effects on metabolic syndrome, cardiovascular disease, and major chronic degenerative diseases, reducing the overall and cardiovascular mortality, and with improved weight management [31–34]. Our results demonstrate that the administration of IMOD, according to the Nicotera diet guideline, is associated with

Levels of homocysteine on different diets based on MTHFR status

Fig. 1 Levels of homocysteine with different diets based on MTHFR genotypes. Time periods 1, 2 and 3 refer to LPD, IMD and IMOD, respectively. *LPD* low protein diet, *IMD* Italian Mediterranean diet, *IMOD* Italian Mediterranean organic diet

a variety of benefits in CKD patients. This study, for the first time, describes an important gene–environment interaction in CKD patients, providing evidence of an interaction between a genetic variant of MTHFR, the C677T polymorphism, and a balanced IMD/IMOD nutritional intervention and its influence on biochemical values, anthropometric and body composition parameters.

The variant homozygous genotype of MTHFR affects genomic DNA methylation through an interaction with folate [35] and it is associated with elevated plasma homocysteine levels [36–39]. Moreover, as proposed by Lambrinoudaki et al. [40], the genetic variants affecting Hcy metabolism may result in impaired tHcy catabolism which, at a cellular level, may lead to tissue dysfunction thus causing metabolic disturbances and related body composition modification. Because of the association of MTHFR C677T polymorphism with cardiovascular disease risk [41] osteoporosis and sarcopenia [42], we considered the T(+) carriers as 'at risk' subjects.

The IMOD was associated with significant changes in body composition of all patients, despite no alteration in total energy intake (kcal/day), physical activity and life style during the course of the study. In particular, the effect of the nutritional interventions was associated with significant changes in body composition, e.g. a significant reduction of total body (TB)Fat ($p < 0.05$) and BMI ($p < 0.05$), and a significant increase of TBLean ($p < 0.05$). The enhancement of TBLean is directly correlated to the increase of body cell mass and, consequently, of the resting metabolic rate. Therefore, while prescribing an isocaloric diet we observed a significant weight loss, in terms of BMI and TBFat, during IMD and IMOD diets compared to the LPD.

Liu et al. [42] recently demonstrated that MTHFR gene variants are associated with lean mass, sustaining findings linking genetic determination of BMI and lean mass to chromosome 1p36, where the MTHFR gene is located. Moreover, epidemiological studies have found that tHcy
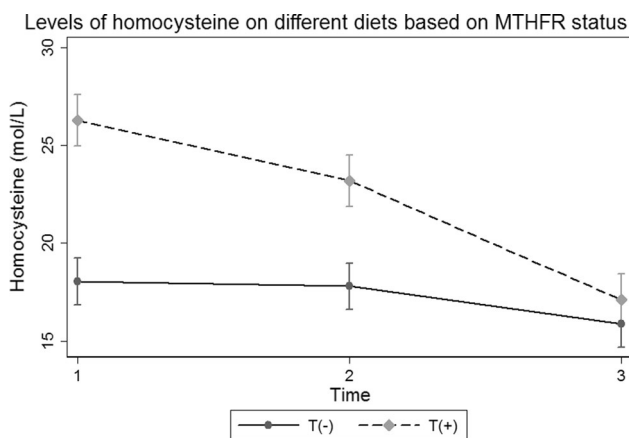
Table 2 Anthropometric and laboratory parameters according to diet

Parameter	LPD	IMD	IMOD
BMI (kg/m^2)	32.0 (30.5, 33.5)	26.9 (25.5, 28.4)*	25.6 (24.2, 27.1)*#
Total body fat (kg)	21.6 (20.2, 22.9)	23.4 (22.0, 24.8)*	16.3 (14.9, 17.7)*#
Total body lean (kg)	52.9 (51.2, 54.6)	53.5 (51.8, 55.3)	54.8 (53.1, 56.5)*
Urea (mg/dl)	86.0 (71.2, 100.7)	84.2 (69.4, 98.9)*	80.6 (65.8, 95.3)*#
Creatinine (mg/dl)	1.90 (1.72, 2.07)	1.80 (1.63, 1.98)*	1.70 (1.52, 1.87)*#
Total cholesterol (mg/dl)	186 (180, 193)	182 (162, 175)*	168 (162, 175)*#
Calcium (mg/dl)	9.89 (9.73, 10.06)	9.91 (9.75, 10.07)	9.34 (9.18, 9.50)*#
Phosphate (mg/dl)	4.90 (4.73, 5.07)	4.20 (4.03, 4.37)*	3.65 (3.48, 3.82)*#
Potassium (mEq/l)	4.89 (4.83, 4.96)	4.90 (4.84, 4.97)*	4.70 (4.64, 4.77)*#
Vitamin B12 (mg/dl)	571 (501, 642)	574 (504, 645)	518 (448, 588)*#
Albuminuria (mg/24 h)	96.4 (61.9, 130.8)	94.4 (59.9, 128.9)	71.8 (37.3, 106.2)*#

Data are presented as marginal means and 95 % CI

LPD low protein diet, *IMD* Italian Mediterranean diet, *IMOD* Italian Mediterranean organic diet, *BMI* body mass index

* $p < 0.05$ vs. LPD; # $p < 0.05$ vs. IMD

correlates with lean mass and BMI [43]. Although further biochemical studies are needed to elucidate the molecular mechanisms that underlie and explain the relationship between MTHFR, TBFat and TBLean, herein we have highlighted a significant reduction of tHcy levels in T(+) carriers, combined with a reduction of TBFat, and an increase of TBLean after IMOD nutritional intervention.

Moreover, the increase in muscle mass following the IMOD nutritional intervention could mean a reduction in risk of sarcopenia for CKD patients. Reduction in lean body mass per se is an important risk factor for sarcopenia, a serious health problem that has not yet received sufficient attention. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and increased morbidity and mortality [44]. It has been demonstrated that the MTHFR gene is highly expressed in skeletal muscle, and the formation of muscles is associated with the simultaneous formation of homocysteine in connection with creatine/creatinine synthesis [45]. The recovery of muscle mass and the simultaneous reduction of tHcy and of other risk factors such as total cholesterol, phosphate and albuminuria levels, confirm the higher quality of the IMOD nutritional intervention in comparison to recommended dietary plans.

In 1989, the National Authorities of USA together with an expert advisory group of academic nephrologists sponsored and conducted a multicenter prospective study known as the modification of diet in renal disease (MDRD) study, in order to test the hypothesis that restricting dietary protein and lowering blood pressure could slow the progression of renal disease among 1,840 patients with various stages of chronic kidney disease. The results of this study, published in 1994, showed that dietary protein restriction had a slight beneficial effect on declining renal function only in patients with moderate renal disease and the benefit of lowering blood pressure was only seen in patients with albuminuria greater than one gram per day [46].

Although low-protein diets have often been recommended as a means of slowing the progression of CKD [47, 48], adherence to these diets is poor because of the lack of variety in menus and the limitations on consumption of many foods [49]. Moreover, reduced food intake in these patients often worsens the situation and increases the chances of inadequate intake of micronutrients such as folate and vitamins B6 and B12, abundant in protein-rich foods [50, 51]. These vitamins are known to be involved in the metabolism of homocysteine, with deficient levels favoring hyperhomocysteinemia. This cardiovascular risk factor is particularly worrisome in patients with CKD. In patients with uremia the mortality rate attributable to cardiovascular disease is 30 % higher than in the general population, and hyperhomocysteinemia is the most prevalent risk factor [52].

Recently, the recognition of phosphate as an independent risk factor for cardiovascular disease even among non chronic kidney disease patients, as well as a risk factor for rapid deterioration of renal function among dialysis patients and experimental animals, set the investigation in another direction independent of protein diet and energy consumption. Moreover, the recent discovery of the critical role of FGF-23 and Klotho protein in phosphate homeostasis indicate the possibility that inorganic phosphate may be a toxic element for blood vessels, heart and kidneys [53–55].

In our study, we demonstrated a significant reduction of hyperphosphatemia after both diets, associated with an improvement in the lipid profile, which suggests less need of lipids for endothelial cell repair, and a lower risk for CVD. Albuminuria reflects a generalized impairment of endothelium and represents a marker of increased cardiovascular risk and of progression of renal failure [56]. In our study, at T2, in CKD patients, there was a significant reduction of albuminuria.

A limitation of this study is the relatively small sample size. However, it was large enough to provide us with adequate statistical power. Another limitation is the short time of observation, although this would have counterbalanced the frequently observed phenomenon of low compliance to dietary instructions. A further limitation is the potential carryover from one diet to another, that could have potentially biased our results. It is important to note that subjects experienced the most dramatic weight loss during the first quarter of the meal plan, because they were very compliant to the administered diet. Thus, in our study the IMD and IMOD nutritional interventions were programmed for a duration of only 2 weeks respectively, in order to reveal the true impact on weight loss, body composition and laboratory parameter changes.

Our data also provide a basis for personalized dietary recommendations based on the individual's genetic makeup and information from other factors such as body composition and biochemical values, in the context of a nutritional intervention assigned to CKD patients.

In conclusion, our data highlight that a dietary pattern rich in some beneficial food groups such as fruit and vegetables, from organic agricultural practice, can reduce the incidence of cardiovascular disease risk in CKD subjects, reducing fasting baseline phosphate, total cholesterol concentrations, and albuminuria. In particular, with regard to the MTHFR polymorphism, we observed a significant reduction of tHcy in T(+) carriers after IMD and in both genotypes after IMOD. This may lead to a lower incidence of CVD and could be of particular significance in CKD patients. We suggest that IMOD may

play a role in longevity and quality of life of CKD patients, pointing towards the beneficial value of organic food consumption.

Furthermore, prescription of IMOD may represent an appropriate primary therapeutic option for the global CVD risk prevention, in particular in CKD patients on conservative therapy, in line with recommendations of the Italian Pharmaceutical Agency (Agenzia Italiana del Farmaco, AIFA) note n.13 guidelines (D.G.R. 1209/2002), the National Cholesterol Education Program (NCEP), the American Heart Association (AHA), and the Therapeutic Lifestyle Change (TLC) [57].

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