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Randomized Control Trials

Long-term consumption of a mediterranean diet or a low-fat diet on kidney function in coronary heart disease patients: The CORDIOPREV randomized controlled trial

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SUMMARY

Background & aims: Lifestyle and dietary habits influence kidney function, playing an important role in the prevention and development of chronic kidney disease (CKD). The effectiveness of the Mediterranean diet in preserving kidney function has been seen in primary prevention. However, no scientific evidence is currently available to determine which dietary pattern is more effective in the management of CKD in secondary cardiovascular disease prevention. Thus, our aim was to evaluate the efficacy of the long-term consumption of two healthy dietary patterns (a Mediterranean diet rich in extra-virgin olive oil (EVOO) compared to a low-fat diet rich in complex carbohydrates) in preserving kidney function in coronary heart disease (CHD) patients.

Methods: CHD patients (n = 1002) from the CORDIOPREV study were randomized to follow a Mediterranean diet (35% fat, 22% MUFA, <50% carbohydrates) or a low-fat diet (28% fat, 12% MUFA, >55% carbohydrates). Kidney function was assessed by the determination of serum creatinine-based estimated glomerular filtration rate (eGFR) at baseline and after 5-years of dietary intervention. Patients were classified according to their type 2 diabetes (T2DM) status, using baseline eGFR (normal eGFR: ≥ 90 mL/min/1.73 m^2; mildly-impaired eGFR: 60 to <90 mL/min/1.73 m^2, severely-impaired eGFR: <60 mL/min/1.73 m^2) to evaluate its influence on the progression of kidney function. Multiple linear regression analysis were performed to determine the contribution of different clinical and anthropometric parameters to changes in eGFR.

Results: Although eGFR declined after both dietary interventions compared to baseline (all $p < 0.001$), the Mediterranean diet produced a lower decline of eGFR compared to the low-fat diet in patients with T2DM ($p = 0.040$). This effect was also observed when the overall population was considered ($p = 0.033$). No significant differences were observed in eGFR between the two diets in non-T2DM patients. In

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addition, this differential effect of the Mediterranean diet was mainly observed in patients with mildly-impaired eGFR in which this diet slowed eGFR progression ($p = 0.002$).
Conclusions: The long-term consumption of a Mediterranean diet rich in EVOO, when compared to a low-fat diet, may preserve kidney function, as shown by a reduced decline in eGFR in CHD patients with T2DM. Patients with mildly-impaired eGFR may benefit more from the beneficial effect of the consumption of the Mediterranean diet in preserving kidney function. These findings reinforce the clinical benefits of the Mediterranean diet in the context of secondary cardiovascular disease prevention.
Clinical trial registration: URL, http://www.cordioprev.es/index.php/en.
Clinicaltrials.gov number, NCT00924937.

1. Introduction

Chronic kidney disease (CKD) is a global health problem that affects more than 10% of the general adult population, imposing a significant economic burden on both the health-care system and society [1,2]. CKD is characterized by an age-related decline in kidney function that is accelerated by type 2 diabetes (T2DM), obesity, hypertension and increased levels of inflammation and oxidative stress [3–5]. CKD is bidirectionally associated with cardiovascular disease (CVD). In fact, CKD is considered an independent risk factor for cardiovascular events and for all-cause and cardiovascular death [1,6]. Recent evidence has pointed out that CKD is also associated with adverse outcomes in patients with CVD. Thus, the concomitant presence of CKD and coronary heart disease (CHD) is found to be closely linked to a greater likelihood of comorbid conditions compared with either of them alone [7].

The earlier subclinical stages of CKD usually go undetected, which results in the progression and worsening of the disease to end-stage renal disease, which requires dialysis or kidney transplantation [8,9]. This renal impairment is exacerbated in T2DM patients, as demonstrated by increased macro- and microvascular complications and the high mortality rates in this population [10]. Therefore, there is a need to establish preventive and effective strategies that may modulate CKD incidence and delay its progression.

Lifestyle and dietary habits have been shown to influence kidney function, playing a key role in the prevention and development of CKD. The beneficial effect of diet on kidney function is, in part, due to the reduction of the cardiovascular risk factors associated with the development and incidence of the CKD, which are also involved in the pathogenesis of the disease. Although previous dietary studies have focused on single nutrients and foods, the study of overall dietary patterns may provide a more powerful tool for assessing dietary habits by evaluating the synergistic and cumulative effects of specific nutrients on CKD [11].

In this context, the Mediterranean diet, which is rich in minimally-processed plant-based foods and monounsaturated fat (MUFA) from olive oil (mainly virgin or extra-virgin olive oil –VOO and EVOO, respectively), but lower in saturated fat (SFA), meat and dairy products, is an increasingly popular dietary pattern which is widely recognized for its health benefits, such as CVD prevention, due its capacity to reduce cardiovascular risk factors [12]. The effectiveness of the Mediterranean diet in preserving kidney function and delaying CKD progression has been reported in primary prevention both in observational and dietary intervention studies [13–16]. However, no scientific evidence is currently available to determine which dietary pattern is most effective in the management of CKD in secondary cardiovascular disease prevention.

Considering all the above, in this secondary prevention study, we evaluate the efficacy of the long-term consumption of two healthy dietary patterns (a Mediterranean diet rich in EVOO compared to a low-fat diet rich in complex carbohydrates) in delaying the impairment of kidney function in CHD patients with and without T2DM.

2. Methods

2.1. Design and study population

The current work was conducted within the framework of the CORDIOPREV study (Clinicaltrials.gov number NCT00924937). Full details of the design and methods have been reported previously [17]. Briefly, the CORDIOPREV study is an ongoing prospective, randomized, single-blind, controlled trial, based on an intention-to-treat analysis, including 1002 patients with CHD, who had their last coronary event more than six months before enrolment. Patients were recruited from November 2009 to February 2012, mostly at the Reina Sofia University Hospital Cordoba, Spain, but also from other hospitals in the neighboring provinces of Cordoba and Jaen. Details of the rationale and study methods, including the inclusion and exclusion criteria, cardiovascular risk factors and the patients' baseline characteristics, have been described recently [17]. To summarize, patients were eligible if they were aged 20–75, with established CHD but without clinical events in the last six months, with the intention of following a long-term monitoring study, with no other serious illnesses and a life expectancy of at least five years. All the patients gave their written informed consent to participate in the study. The study protocol was approved by the Human Investigation Review Committee at Reina Sofia University Hospital, following the institutional and Good Clinical Practice guidelines.

2.2. Randomization and dietary intervention

Randomization was performed by the Andalusian School of Public Health, as previously described (Fig. 1). The study dietitians were the only members of the intervention team to know about each participant's dietary group. Briefly, the randomization was based on the following variables: sex (male, female), age (<60 and ≥ 60 years old) and previous myocardial infarction (yes, no). Each patient was randomly stratified, in addition to the conventional treatment for CHD, to one of two potentially healthy diets: (a) the Mediterranean diet, with a minimum of 35% of total calories from fat [22% MUFA, 6% polyunsaturated (PUFA), and <10% SFA], 15% proteins, and a maximum of 50% carbohydrates and (b) a low-fat, high complex carbohydrate diet, as recommended by the National Cholesterol Education Program, with <30% of total calories from fat (12–14% MUFAs, 6–8% PUFAs, < 10% SFAs), ≥55% from carbohydrates and 15% from protein. In both diets, the cholesterol content was adjusted to <300 mg/day. Both study diets included foods from all major food groups, but no total calorie restriction was set. Full details on dietary assessment, adherence and recommendations, as well as follow-up

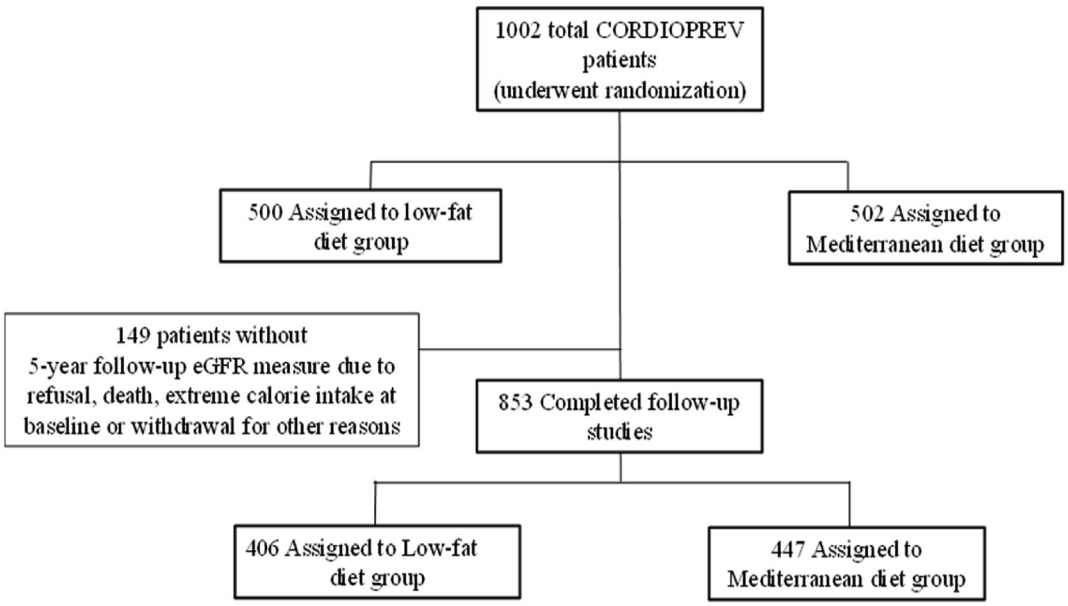

Fig. 1. (Flow diagram). Screening and randomization flow-chart of the CORDIOPREV study and the evaluation of kidney function. CORDIOPREV, CORonary Diet Intervention with Olive oil and cardiovascular PREVention.

visits, have been published elsewhere [17,18]. No intervention to increase physical activity or lose weight was included. Participants in both intervention groups received the same intensive dietary counselling. The present study was conducted over a follow-up period of 5 years. Details of the specific recommended diets, mean baseline values and changes in energy and nutrient intake after 5 years of intervention with both dietary patterns have been previously described [18].

In our study, although both dietary models share common characteristics in some of their major components (i.e. high intake of vegetables, fruit, legumes, and whole grains), patients consuming the Mediterranean diet also had a high intake of oily fish, nuts, and extra virgin olive oil, together with a low intake of harmful foods such as red/processed meats and pastries/commercial bakery products [18].

2.3. Anthropometric measurements and laboratory tests

The measurement of the anthropometric and biochemical parameters has been previously described [19]. Serum and urine creatinine concentrations were determined by the modified Jaffé colorimetric method and measured by spectrophotometry (Bio-Systems SA, Barcelona, Spain). Inter-assay and intra-assay coefficients of variation were <4.0% for serum creatinine and <3.0% for urinary creatinine, respectively.

2.4. Evaluation of kidney function

Kidney function was evaluated by determining the serum creatinine (sCr)-based estimated glomerular filtration rate (eGFR), calculated using the CKD-Epi (CKD Epidemiology Collaboration) equation (4) [49] as follows: for women, for sCr level <0.7 mg/dL (<62 mmol/L), eGFR (mL/min/1.73 m^2) = 144 × (sCr in mg/dL/0.7) −0.329 × (0.993 age); for sCr level >0.7 mg/dL (>62 mmol/L), eGFR (mL/min/1.73 m^2) = 144 × (sCr in mg/dL/0.7) −1.209 × (0.993 age). For men, for sCr level <0.9 mg/dL (<80 mmol/L), eGFR (mL/min/1.73 m^2) = 141 × (sCr in mg/dL/0.9) −0.411 × (0.993 age); for sCr level >0.9 mg/dL (>80 mmol/L), eGFR (mL/min/1.73 m^2) = 141 × (sCr in mg/dL/0.9) −1.209 × (0.993 age).

All 1002 patients completed the evaluation of kidney function at baseline (all of them with eGFR ≥30 mL/min/1.73 m^2) as one of the inclusion criteria of the study [17]. Of these patients, 853 completed the 5-year follow-up kidney function study (n = 143 patients did not provide eGFR data and n = 6 patients had extreme values for total energy intake: < 500 kcal/day or > 3500 kcal/day for women and <800 kcal/day or > 4000 kcal/day for men, according to the established criteria proposed by Willet et al. [20]) (Fig. 1). Baseline characteristics of those patients who completed the evaluation of kidney function study (during follow-up) compared to patients who did not complete it are shown in Supporting Table 1.

In order to analyze the influence of eGFR at baseline on the evolution of kidney function during the 5-years of dietary intervention, we classified the population into three categories according to eGFR at baseline: a) normal eGFR (≥90 mL/min/1.73 m^2, n = 514), b) mildly-impaired eGFR (60 to <90 mL/min/1.73 m^2, n = 286) and c) severely-impaired eGFR (<60 mL/min/1.73 m^2, n = 53).

We also evaluated the urinary albumin-to-creatinine ratio (UACR), both at baseline and after 5-years of follow-up, which was calculated as the urinary albumin concentration divided by the creatinine concentration in mg/g. This method, based on a spot urine test, yields results comparable to those from a 24-h urine collection [21].

2.5. Diabetes status criteria

To evaluate the influence of T2DM on kidney function, patients were assessed according to whether they had T2DM (n = 540) or not (n = 462) at baseline of the study. T2DM was diagnosed according to the American Diabetes Association (ADA) diagnosis criteria: fasting plasma glucose ≥126 mg/dL and 2 h plasma glucose in the 75 gr OGTT ≥200 mg/dL and/or hemoglobin glycated (HbA1c) plasma levels ≥6.5% [22].

2.6. Statistical analyses

The statistical analyses were carried out using SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The data are presented as

the mean ± standard error of the mean (SE) for continuous variables and as proportions for the categorical variables.

To evaluate the changes occurring in time, we calculated the Δ changes (changes produced between post- and pre-intervention in each diet). We also evaluated the group differences, defined as the differences in the Δ changes in the Mediterranean group compared with the Δ changes in the low-fat group.

The Kolmogorov–Smirnov normality test was performed to evaluate the distribution of the quantitative variables and continuous variables that deviated significantly from the assumption of normality were transformed. Categorical variables were compared using Chi–Square tests. With the continuous variables, between-group changes were assessed with an unpaired t test or univariate ANOVA, as required. To evaluate the data variation according to diet and time (baseline to 5 years), repeated-measures ANOVA analyses were used, as well as post hoc multiple comparisons analysis using the Bonferroni correction.

Age, sex, BMI, hypertension, T2DM status, energy and pharmacological treatments (use of lipid-lowering and antihypertensive drugs) at baseline were tested as covariates in all the tests/assays. Differences were considered significant when $p < 0.05$.

To determine the contribution of different clinical and anthropometric parameters to changes in eGFR, we performed a multiple linear regression analysis using the Δ changes in eGFR after 5 years of dietary intervention as the dependent variable. Age, sex, BMI, diabetes status, dietary group allocation, baseline eGFR categories and pharmacological treatment (use of lipid lowering and antihypertensive drugs) at baseline were included in the analysis, assuming that all the predictor variables were quantitative or categorical, and the outcome variable was quantitative, continuous, and unbounded.

3. Results

3.1. Baseline characteristics of the study population

The baseline anthropometric and biochemical characteristics of all the CHD patients who underwent the baseline study of kidney function and were assigned to randomized dietary groups are presented in Table 1. No significant differences were observed between randomized dietary groups. Moreover, the group of patients who did not complete the follow-up kidney function study were older and contained a higher percentage of current smokers compared to those who completed it (Supporting Table 1).

Baseline characteristics of the patients according to baseline eGFR categories are shown in Supporting Table 2. Patients with severely-impaired eGFR were older and showed higher levels of HbA1c compared to patients with normal and mildly-impaired eGFR (all $p < 0.05$). Moreover, both severely and mildly-impaired eGFR patients exhibited higher HOMA-IR, fasting insulin, triglycerides and UACR levels, as well as a higher percentage of former smokers with oral antidiabetic drug consumption compared to patients with normal eGFR (Supporting Table 2). On the other hand, T2DM patients were generally older and contained a higher percentage of patients with obesity and antidiabetic and/or antihypertensive treatment at baseline, compared to non-T2DM patients (all $p < 0.05$). T2DM patients also exhibited lower eGFR and higher UACR and HOMA-IR, fasting glucose, insulin, HbA1c and triglycerides levels compared to non-T2DM patients (all $p < 0.05$) (Supporting Table 3).

3.2. Effect of the dietary intervention on kidney function

The effect of each dietary intervention (Δ changes produced between post- and pre-intervention) on eGFR are shown in Fig. 2. In the total population, although eGFR declined after both dietary models compared to baseline (all $p < 0.001$), the Mediterranean diet produced a lower decline of eGFR compared to the low-fat diet ($p = 0.033$). In fact, after the Mediterranean diet, the eGFR decline rate was 1.58 mL/min/1.73 m^2 lower compared to the low-fat diet during the 5 years of follow-up (Fig. 2). When the baseline eGFR categories were considered, this differential effect of the Mediterranean diet was observed only in patients with mildly-impaired eGFR at baseline. In these patients, the Mediterranean diet slowed eGFR progression, while eGFR declined after the low-fat diet compared to baseline ($p = 0.002$). The eGFR decline rate was 2.49 mL/min/1.73 m^2/ml/min/1.73 m^2 lower after the Mediterranean diet compared to the low-fat ($p = 0.040$) (Fig. 3A).

We observed no changes in UACR after the consumption of either dietary model (Δ 6.58 ± 3.69, $p = 0.337$ and Δ 9.23 ± 3.52, $p = 0.159$ after low-fat and Mediterranean diet, respectively) or between diets.

Changes in the treatment regimens of the patients after 5 years of follow-up are shown in Supporting Table 4. There were no differences between the two dietary groups regarding drug treatment.

3.3. Diabetes status influences dietary effect on eGFR

The influence of diabetes status on changes in eGFR after dietary intervention is shown in Fig. 3B. We observed that, although eGFR decreased after both dietary interventions compared to baseline (all $p < 0.001$) in both non-T2DM and T2DM patients, the Mediterranean diet produced a lower decline of eGFR compared to the low-fat diet in T2DM patients ($p = 0.040$). In fact, after the Mediterranean diet, the eGFR decline rate was 2.07 mL/min/1.73 m^2 lower compared to the low-fat diet during the 5-years of follow-up. No significant differences were observed in eGFR between dietary groups in non-T2DM patients.

3.4. Independent determinants of changes in eGFR by multiple linear regression analysis

In a stepwise multiple linear regression analysis using changes in eGFR after 5 years of dietary intervention as the dependent variable, baseline eGFR categories ($B = -6.082$, $p = <0.001$) appear as the most contributive factor in changes in eGFR. Sex ($B = -3.107$, $p = 0.001$), presence of diabetes ($B = -2.387$, $p = 0.001$), allocation to the Mediterranean diet (versus low-fat diet) ($B = 1.474$, $p = 0.041$) and age ($B = -0.153$, $p = 0.001$) were also significant contributors to changes in eGFR (Table 2).

4. Discussion

To the best of our knowledge, no previous controlled clinical trials have evaluated the long-term effect of dietary patterns on kidney function in secondary cardiovascular disease prevention. In this randomized, controlled clinical trial, conducted in a large sample of patients with CHD, we found that the 5-year consumption of a Mediterranean diet, compared to a low-fat diet, may preserve kidney function, as assessed by eGFR, in patients with T2DM. This effect was also observed when the overall population was considered. Both dietary interventions had a similar impact on kidney function in non-T2DM patients. Our data also supported the view that patients with mildly-impaired eGFR may benefit more from the beneficial effect of consumption of the Mediterranean diet in preserving kidney function.

A progressive decline in eGFR reflects the natural aging process, which is estimated by an annual decline in eGFR of ≈1 mL/min/1.73 m^2 in healthy individuals [23]. Nevertheless, chronic diseases such as hypertension and T2DM influence this process, aggravating

Table 1
Baseline clinical and metabolic characteristics, lipid profiles and treatment regimens of the total CHD patients by randomized groups.

	Total population (n = 1002)	Low-fat diet group (n = 500)	Mediterranean diet group (n = 502)	*p* value*
Age, years	59.5 (0.2)	59.5 (0.4)	59.7 (0.4)	0.696
Male, %	82.5	82.6	82.5	0.957
Weight, kg	85.1 (0.4)	85.4 (0.7)	84.9 (0.6)	0.605
BMI, kg/m^2	31.1 (0.1)	31.2 (0.2)	31.0 (0.1)	0.647
Obesity, %[a]	56.0	58.0	54.1	0.226
SBP, mm Hg	138.8 (0.6)	139.0 (0.9)	138.5 (0.9)	0.821
DBP, mm Hg	77.2 (0.3)	77.3 (0.5)	77.2 (0.5)	0.991
Hypertension, %[b]	68.5	67.9	69.2	0.604
eGFR, ml/min/1.73 m^2	89.2 (0.5)	89.5 (0.7)	88.9 (0.8)	0.628
UACR, mg/g	61.84 (11.9)	61.7 (10.9)	41.7 (6.0)	0.110
Type 2 diabetes, %[c]	53.9	56.7	51.0	0.076
Fasting glucose, mg/dL	113.7 (1.2)	112.8 (1.6)	114.7 (1.8)	0.435
HbA1c, %	6.65	6.67	6.63	0.616
HOMA-IR	3.65 (0.26)	3.26 (0.20)	4.03 (0.48)	0.151
Fasting insulin, mU/L	11.0 (11.2)	10.85 (0.5)	11.13 (0.5)	0.694
Total cholesterol, mg/dL	159.0 (31.2)	159.0 (29.9)	159.1 (32.4)	0.945
LDL-cholesterol, mg/dL	88.5 (0.8)	88.2 (1.1)	88.9 (1.2)	0.596
HDL-cholesterol, mg/dL	42.2 (0.3)	42.1 (0.5)	42.3 (0.5)	0.788
Triglycerides, mg/dL	135.4 (2.2)	136.0 (3.2)	134.8 (3.1)	0.502
Smoking habits, %				
Never smokers	25.7	24.1	27.4	0.223
Current smokers	9.68	10.7	8.72	0.170
Former smokers	64.6	65.2	63.9	0.793
Medication use, %				
Lipid-lowering drugs	85.6	86.3	85.0	0.544
Oral antidiabetic drugs	34.8	35.3	34.4	0.791
Antihypertensive drugs	90.0	91.8	88.2	0.073

Data are mean (standard error) or percentage of participants. P value for comparisons between groups calculated with Chi-square tests for categorical variables or independent t-test test for quantitative variables. *Low-fat diet group vs. Mediterranean diet group, $p < 0.05$.
CHD, coronary heart disease; BMI, body max index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; HbA1c, glycated hemoglobin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.
[a] Obesity was defined as a BMI ≥30 kg/m^2.
[b] Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive therapy.
[c] Type 2 diabetes was defined as being diagnosed as diabetic before the start of the study (350, 34.9%) and those diagnosed by a fasting blood glucose level ≥126 mg/dL on two occasions, or a 2-h plasma glucose level ≥200 mg/dL during a 75-g oral glucose-tolerance test, during the first procedures of the study.

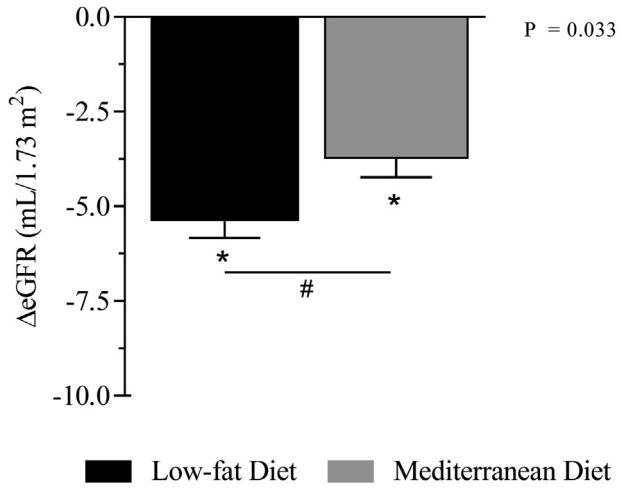

Fig. 2. Effect of dietary intervention on eGFR in patients with coronary heart disease. Data are presented as Δchanges produced between post- and preintervention ± standard error of the mean. Variables were compared using the analysis of variance (univariate ANOVA) adjusted by age, sex, hypertension and baseline BMI. Low-fat diet (n = 406) and Mediterranean diet (n = 447). Differences were considered to be significant when $p < 0.05$. * Significant differences between post and pre-intervention. # Significant differences between Mediterranean diet and low-fat diet. Abbreviation: eGFR, estimated glomerular filtration rate.

GFR decline [23]. In this context, evidence pointed out that the presence of CHD can directly affect kidney function, which in turn contributes to the progression and worsening outcomes of CHD [24]. However, the mean yearly rate of decline in eGFR after the Mediterranean diet observed in our study in the overall population was <1 mL/min/1.73 m^2. It should be highlighted that our population comprises patients who have suffered a previous cardiovascular event, and who are described as being prone to an accelerated eGFR decline over and above that imposed by natural aging [25]. This slowing down in the eGFR progression was not observed after consumption of the low-fat diet.

Different clinical studies have evaluated the influence of the Mediterranean diet on the incidence and prevention of CKD, mainly in primary prevention [26]. Most of them have found associations between this dietary pattern and renal outcomes based on both cross-sectional and prospective studies which used available scores for adherence to a Mediterranean diet [16,27–29]. In this context, two cross-sectional studies in healthy Greek populations reported that a greater adherence to the Mediterranean diet was associated with a reduced albuminuria and creatinine clearance rate by the Mediterranean Diet Quality Index for children and adolescents [27] and the Mediterranean Diet Score [16,29], respectively. Other systematic reviews and meta-analysis on prospective observational studies determined, using the Mediterranean Diet Scale [28], that a 1-point increment in adherence to the Mediterranean diet was associated with a 10% lower CKD risk [26]. In fact, a population-based cohort of 1110 Swedish elderly men, after a 10-year follow-up, showed, according to the Mediterranean Diet Score [29], that the adoption of the Mediterranean diet was related to better kidney function, evaluated by sCr-based eGFR, as in our study. Conversely, a low adherence to the Mediterranean diet was linked to a worse survival rates among those individuals with manifest CKD [11].

There are few dietary intervention clinical studies assessing the effect of consumption of a Mediterranean dietary pattern on parameters related to kidney function from the perspective of CKD

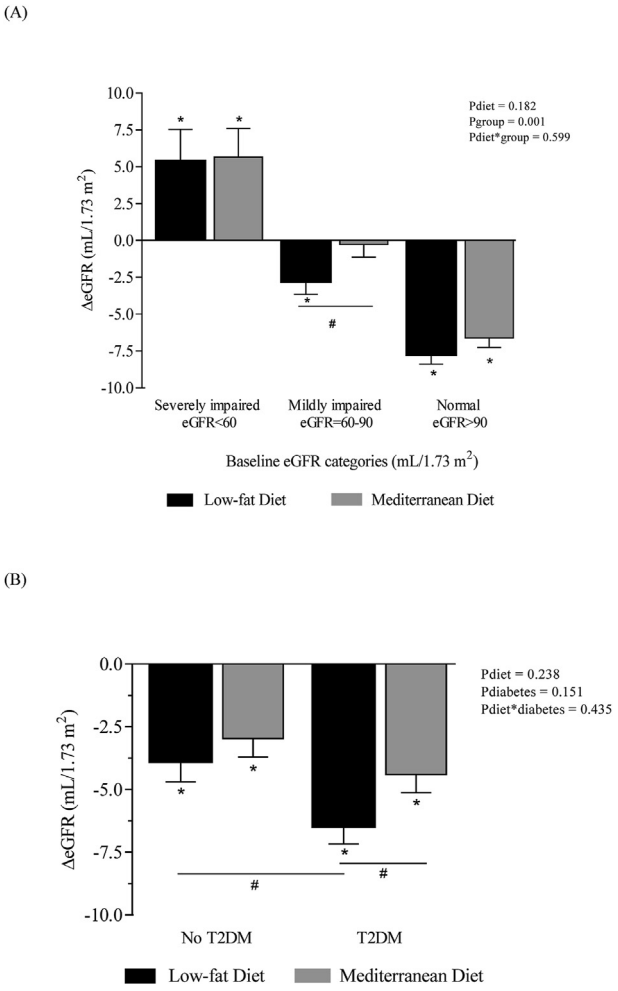

Fig. 3. Changes in eGFR (mL/min/1.73 m^2) during dietary intervention in patients with coronary heart disease. (A) According to baseline eGFR categories and (B) According to diabetes status. Data are presented as Δchanges produced between post- and preintervention ± standard error of the mean. Variables were compared using the analysis of variance (univariate ANOVA), adjusted by age, sex, hypertension and baseline BMI. Severely-impaired eGFR (n = 53), Mildly-impaired eGFR (n = 286) and Normal eGFR (n = 514). No T2DM (n = 400) and T2DM (n = 453). Differences were considered to be significant when $p < 0.05$. * Significant differences between post and pre-intervention. # Significant differences between groups. Global p-values: p (diet): diet effect; p (group): baseline eGFR category effect; p (diet × group): diet by baseline eGFR category interaction; p (diabetes): diabetes effect; p (diet × diabetes): diet by diabetes interaction. Abbreviations: eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus.

prevention. An earlier report from the PREDIMED study, a primary prevention study, evaluated the effect of a 1-year consumption of three different dietary interventions (two Mediterranean diets supplemented with either EVOO or nuts and a control diet) on kidney function in elderly participants without CHD but at high CVD risk. The authors found that eGFR increased in the 3 treatment groups compared to baseline, with no differences between dietary interventions both in the total population and when the presence or absence of T2DM were considered separately [14]. These results are partly in line with our data, in which both the Mediterranean diet and the low-fat diet led to increased eGFR without any differences in those patients with severely-impaired eGFR (<60 mL/min/1.73 m^2). The apparent inconsistency in the results may have arisen from differences in the design of the PREDIMED and CORDIOPREV studies, such as the type of population (non-CHD participants in primary prevention, versus patients with CHD in

Table 2
Predictors of 5-year change in eGFR in patients with CHD.

Independent variables	Unstandardized coefficients		Standardized coefficients	P value
	B	SE		
Age, y	−0.153	0.045	−0.126	0.001
Women (*vs* Men)	−3.107	0.953	−0.109	0.001
Baseline eGFR categories	−6.082	0.655	−0.340	<0.001
Allocation into Mediterranean diet (*vs* Low-fat diet)	1.474	0.719	0.068	0.041
T2DM at baseline, yes	−2.387	0.732	−0.110	0.001

Constant = 16.72; R = 0.115.
Predictive variables tested by stepwise method: age, BMI, sex (men: 0, women:1), presence of T2DM (no: 0, yes: 1), dietary group allocation (Low-fat diet: 0, Mediterranean diet: 1), baseline eGFR categories (severely-impaired eGFR ≤60 mL/min/1.73 m^2: 0, mildly-impaired eGFR 60–90 mL/min/1.73 m^2: 1, normal eGFR >90 mL/min/1.73 m^2: 2), use of lipid lowering drugs and use of antihypertensive drugs (no: 0, yes: 1), alcohol intake (no drinkers: 0, consumption <8 g/day: 1, consumption 8–16 g/day: 2, consumption >16 g/day: 3), smoking (no smoker: 0, former smoker: 1, current smoker: 2) assuming that all variables were quantitative or categorical, and the outcome variable was quantitative, continuous, and unbounded. Differences were considered to be significant when $p < 0.05$.

secondary prevention) and length of dietary intervention period (1 year versus 5 years of follow-up). Patients with CHD and lower eGFR are at higher risk of poor outcomes compared with those with normal eGFR (≥90 mL/min/1.73 m^2) [30]. In particular, CHD patients with an eGFR <60 mL/min/1.73 m^2 showed an increased risk of all-cause and cardiovascular mortality [31]. Our findings therefore reinforce the importance of healthy dietary interventions to ameliorate the impairment of kidney function, particularly among these vulnerable population groups.

In a recent weight-loss intervention-based study, PREDIMED-Plus, the 1-year consumption of an energy-reduced Mediterranean diet and increased physical activity (intervention group) led to a lower decline in eGFR, in comparison with the control group, who were given the usual advice recommending a Mediterranean diet, in overweight/obese adults with metabolic syndrome [13]. In this study, the eGFR decline rate was ≈0.6 mL/min/1.73 m^2 lower in the intervention group than in the control group, which could be partly attributed, according to the authors, to weight loss in the patients following this diet. In our study, the 5-year consumption of the Mediterranean diet, with no reduced energy, was able to achieve a mean yearly eGFR decline rate of ≈0.3 mL/min/1.73 m^2 lower than the low-fat diet in the overall population, without weight loss or increased physical activity in CHD patients. As the authors found in the PREDIMED-Plus study, this rate was more marked in patients with mildly-impaired eGFR (60 to <90 mL/min/1.73 m^2), where the Mediterranean diet (but not the low-fat diet) was able to prevent eGFR decline, which also highlights the importance of taking preventive and intervention measures in populations at risk.

Given the higher rate of development of renal dysfunction in diabetic populations, compared to non-diabetics [3], our data also found that, among the total population analyzed, those who presented baseline T2DM were more likely to benefit from consuming the Mediterranean diet, showing a lower eGFR decline compared to the low-fat diet. Although the exact underlying molecular mechanisms are not well-known, the effect of the Mediterranean dietary pattern on eGFR-based kidney function may be partially explained by its impact on cardiometabolic risk factors, such as improving plasma lipid levels, high blood pressure or oxidative stress/inflammation [32–34]. Given that endothelial dysfunction is known to be related to renal function [35], we have recently found, in the context of CORDIOPREV study, that a 1-year consumption of the Mediterranean diet, compared to the low-fat diet, improved endothelial function in CHD patients, even in those with T2DM

[19,36]. This diet also produced a better balance of endothelial homeostasis, reducing endothelial injury and improving those processes related to regenerative endothelial capacity [36–38]. Indeed, diets rich in MUFA reduce insulin resistance and restored endothelium-dependent vasodilatation in diabetic patients [39].

Another plausible cause for the beneficial effect of the Mediterranean diet on kidney function on T2DM patients may be its ability to reduce the levels of advanced glycation end products. These cytotoxic compounds, with oxidant and pro-inflammatory properties, are found in increased concentrations in diabetics compared to non-diabetics [40–42], and are closely involved in the development of kidney disease, particularly in the context of diabetes [43].

Of note, there were no differences between the two dietary intervention groups in the medical treatments received, including antihypertensive agents, particularly angiotensin-conversing enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), which are considered renoprotective because of their blood pressure-lowering and antiproteinuric effects [44]. This could partly explain the lack of any significant effects on UACR observed in our study.

Our study has a number of strengths. Firstly, given the bidirectional association between CHD and CKD, our results present a dietary strategy as a clinical and therapeutic tool that could better reduce the high recurrence of cardiovascular and/or CKD complications in these patients, through the consumption of a Mediterranean diet than a low-fat diet. Secondly, the study presents a randomized design that involves two different dietary patterns involving a large number of patients. Moreover, this is a comprehensive dietary intervention comparing two healthy dietary patterns. Although dietary compliance during such an extended period could be a key factor, in this case, adherence to the recommended dietary patterns was excellent, as shown by the rigorous dietary assessment measurements [17,18]. The lack of a standard control diet could be considered a limitation. Nevertheless, as our study has been developed in the framework of the CORDIOPREV trial, a cohort of patients with diagnosed CHD in secondary prevention, due to ethical criteria the use of a standard diet was not considered during the design phase of the study. Following different guidelines and international consensus documents [45–48], we chose to test the long-term effect of two active intervention arms (low-fat diet vs. Mediterranean diet) with proven benefits in patients at high cardiovascular risk.

Our study also has other limitations. First, our population consisted of CHD patients, which prevents generalization of the findings to other populations. However, these patients make up one of the populations in which dietary changes have been shown to have a significant impact on health. Second, eGFR was not determined using a direct measurement such as inulin or iothalamate, or 24-h urinary creatinine clearance, as these procedures are costly and time-consuming and are not suited to the routine detection of kidney disease. Also, morning spot urine test samples were used to estimate the albumin excretion rate (expressed as UACR), while a 24-h urine collection is considered the gold standard test to determine albuminuria.

5. Conclusions

The long-term consumption of a Mediterranean diet rich in EVOO, when compared to a low-fat diet, may preserve kidney function, as shown by a reduced decline in eGFR in CHD patients with T2DM. Patients with mildly-impaired eGFR may benefit more from the beneficial effect of the consumption of the Mediterranean diet in preserving kidney function. These findings reinforce the clinical benefits of the Mediterranean diet in the context of secondary cardiovascular disease prevention.

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Author contributions

Alicia Podadera-Herreros: Investigation and Writing-Original Draft. Juan F. Alcala-Diaz: Formal analysis and Validation. Francisco M. Gutierrez-Mariscal: Methodology and Investigation. Jose Jimenez-Torres: Data curation. Silvia de la Cruz-Ares: Software and Supervision. Antonio P. Arenas-de Larriva: Resources. Magdalena P. Cardelo: Validation. Jose D. Torres-Peña: Resources. Raul M. Luque: Supervision. Jose M Ordovas: Writing - Review & Editing. Javier Delgado-Lista: Supervision and visualization. Jose Lopez-Miranda: Visualization and Funding acquisition. Elena M Yubero-Serrano: Conceptualization, Writing - Review & Editing, Funding acquisition.

Conflict of interest

The authors declare that they have no current or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.12.041.

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