Mediterranean Diet: A Dietary Pattern Related to Nutritional Benefits for Hemodialysis Patients

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Objectives: In adults with chronic kidney disease, not on dialysis, there is a recent recommendation suggesting the prescription of a Mediterranean diet pattern but there is still no evidence to suggest a specific dietary pattern for hemodialysis (HD) patients. The aim of this study was to identify dietary patterns in HD patients and analyze their relationship with nutritional status, physical activity, and survival.

Design and Methods: This was a longitudinal prospective multicenter study with 12 months of follow-up that included 582 HD patients from 37 dialysis centers. Clinical parameters, dietary intake, and physical activity were assessed. Dietary patterns were derived from principal component analysis. A p-value lower than 0.05 was considered statistically significant.

Results: Three different dietary patterns were identified: "Mediterranean," "Western," and "low animal protein." Patients in the Mediterranean pattern group showed higher intakes of protein (P = .040), omega 3 fatty acids (P < .001), vitamins B12 (P < .001), B6 (P < .001), C (P < .001), D (P < .001), folic acid (P < .001) and presented a higher practice of moderate physical activity (P = .010). Despite the lower number of deaths that occurred in the Mediterranean dietary pattern group, we did not observe a statistically significant lower mortality risk (P = .096).

Conclusions: The Mediterranean style pattern was associated with a better nutritional intake profile and lifestyle related factors such as a higher practice of moderate physical activity in HD patients.

Keywords: diet; nutrition; body composition; mortality; dialysis

Introduction

CURRENTLY, RECOMMENDATIONS FOR hemodialysis (HD) patients focus on achieving a sufficient energy and protein intake without exceeding phosphorus, potassium, sodium, and fluid intake limits.[1] While this single nutrient approach could be more difficult to attain, the recommendation to follow a specific dietary pattern, which considers qualitative and quantitative aspects of the diet, could be easier for patients to adhere and may play a more important role in clinical outcomes.[2]

Dietary pattern analysis has emerged as an alternative and complementary approach to investigate associations between dietary intake and health outcomes. Instead of looking at individual nutrients or foods, pattern analysis examines the effects of the overall diet.[3] Actually, dietary guidelines have moved away from focusing on single foods or nutrients to a more encompassing dietary pattern approach.[4]

The nutritional status of HD patients is closely related to the type of food items consumed, their amount and frequency.[1] It is well-known that lifestyle modification, including healthy diets and exercise, has beneficial effects in the general population.[5,6] Moreover, a greater adherence to the Mediterranean diet pattern contributes to reduce the risk of overall mortality, cardiovascular diseases, coronary heart disease, myocardial infarction, overall cancer incidence, neurodegenerative diseases, and diabetes.[7-10] A healthy dietary pattern, encouraging higher intakes of vegetables, fruit, legumes, nuts, whole grains, fish, and low-fat dairy, and lower intakes of red and processed meats, sodium, and sugar-sweetened beverages has been associated with a lower incidence of chronic kidney disease (CKD).[11] Furthermore, in patients with CKD, a greater adherence to healthy dietary patterns has been associated with lower risk for disease progression and all-cause mortality.[11-13]

Despite that, in adults with CKD, not on dialysis, there is a recent recommendation suggesting the prescription of a Mediterranean diet[1] pattern for improving lipid profiles,

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there is still no evidence to suggest a specific dietary pattern for HD patients and few studies have been published focusing on dietary patterns and health outcomes in this population.

The aim of this study was to identify dietary patterns in HD patients and analyze their relationship with nutritional status, physical activity, and survival.

Materials and Methods

Study Design and Setting

We carried out a longitudinal prospective multicenter study with patients from 37 HD centers from November of 2018 until November of 2019.

Sample Size

We calculated the sample size assuming a type I error (alpha) of 0.05, a type II error (beta) of 0.2, a proportion of exposed cases (q1) of 0.287 and a relative hazard of 0.460, based on the data previously published regarding body composition as a mortality predictor in HD patients.[14] Considering a number of events needed of 64, an annual mortality rate of 13.3% in 2015 in our country and 10% of refusal margin, the total required sample size was 600 patients.

These 600 patients were selected among the 4,600 patients undergoing HD in 37 dialysis centers: patients fulfilling the inclusion criteria were randomly selected equally from each dialysis center and 18 patients refused to participate in the study (3%). Therefore, we collected data from 582 patients.

Inclusion and Exclusion Criteria

Patients were eligible for this study if they were aged ≥18 years, underwent a 4 hours in-center HD session 3 times a week for ≥15 months (with an online hemodiafiltration technique), agreed to participate and had signed an informed consent. In many studies of HD subjects, the accepted HD vintage is 3 months but as the food frequency questionnaire (FFQ) reports the food habits over the last 12 months before its application; we considered a minimum dialysis vintage of 15 months.

All patients were dialyzed with high-flux membranes (Helixone®, Fresenius®) and ultrapure water in accordance with the criteria of ISO regulation 13959:2009—Water for HD and related therapies. Patients were ineligible if they met any of the following criteria: low comprehension of the country language, severe neurological or mental disorder, active neoplastic disease, major amputation (lower/upper extremities), enteral or parenteral feeding, severe alcohol or drug addiction, hepatitis C with viral replication, liver disease, and immunosuppressive or corticoid medication.

Data Analysis

Etiology of the CKD, demographic, anthropometric, biochemical, and dialysis treatment data were obtained from the dialysis units database in the same month as the face-to-face interviews. We collected blood for the biochemical analysis before the midweek HD session. All the laboratory measures were tested using identical methods in different laboratories.

Body Composition

The assessment of body composition included lean tissue index (LTI), fat tissue index (FTI) and relative overhydration (OH) (%) (OH/extracellular water predialysis [ECW]). These parameters were collected from 521 patients and analyzed through bioimpedance spectroscopy with the Body Composition Monitor® (Fresenius Medical Care Deutschland GmbH, Germany).

The Body Composition Monitor takes measurements at 50 frequencies in a range of 5 KHz-1000 KHz. The measurement was performed approximately 30 minutes before the midweek HD session by placing 4 conventional electrodes in the patient, who was lying in the supine position: 2 on the hand and 2 on the foot contralateral to the vascular access. To obtain the clinically relevant output parameters, two advanced physiological models are used in the Body Composition Monitor.

- A volume model describing electrical conductance in a cell suspension enabling the calculation of total body water (TBW) and ECW as well as intracellular water (ICW).[15]
- A body composition model calculating the 3 principal body compartments OH, lean tissue and adipose tissue from ECW and TBW information.[16]

All output parameters have been validated against the gold standard reference methods in various studies involving more than 500 patients and healthy controls. The reference methods include: ECW—bromide dilution; ICW—total body potassium (TBK); TBW—deuterium dilution; lean tissue mass—Dual Energy X-ray Absorptiometry (DEXA); Adipose Tissue Mass—4 compartment modeling, DEXA, air displacement plethysmography and underwater weighing; body cell mass—magnet resonance tomography, TBK; OH—by expert clinical assessment.

Regarding the quality of measurements, all exceeded 95%.

Food Frequency Questionnaire

We assessed dietary intake through a semi-quantitative FFQ conducted by a dietitian in a face-to face interview during the HD treatment. It has been developed and validated for the Portuguese population.[17,18] It has 95 food items, 9 categories of frequencies (from "never or less than once a month" to "six or more times a day"), and a section with predetermined average portions. The frequency of intake and the mean portions of each food item were registered and illustrated through a book with 131 colored photos, serving as a visual auxiliary for the patients. The respondent was asked to describe her or his diet over the last 1-year period. To estimate dietary intake, the frequency reported for each item was multiplied by the respective portion (in grams) and by a factor for seasonal variation of food items which are eaten in specific times during the year. This questionnaire gives information regarding the average daily amount of macro and micronutrients consumed. The conversion of food item into nutrients was done with the Food Processor Plus software (ESHA Research, Salem, Oregon) containing the nutritional data from the US Department of Agriculture and adapted to typical Portuguese foods. The nutrient content of Portuguese foods was added to the original database using the Portuguese food composition table.[19] For the data analysis, food items with a mean intake ≤ 5 g/day were excluded.

Twenty food groups were created according to similar nutritional characteristics: milk and milk products; fish; white bread, rice, pasta and potatoes; cookies and sweets; vegetables; fruit; wine and beer; caffeinated drinks; red meat; processed meat; eggs; chicken and turkey; olive oil; fish patties and beef croquettes; home-made fried potatoes; whole grain bread; soft drinks; barley drinks; vegetables soup; beans, peas and chickpeas.

Finally, dietary patterns were derived based on these twenty food groups which were individually adjusted for total energy intake. The different dietary patterns identified in this study were named according to the food groups with the highest factor loadings.

International Physical Activity Questionnaire

The short version of the International Physical Activity Questionnaire, which is validated for the Portuguese population, was used to assess the physical activity level[20] and conducted by a dietitian in a face-to face interview, in the same day as the FFQ. Patients were asked about the time spent (days per week and minutes per day) performing physical activity of different intensity levels (vigorous, moderate, and walking) and sitting.

Statistical Analysis

Categorical variables were presented as frequency (percentages) and continuous variables as mean ± standard deviation or as median and interquartile ranges. Data distribution was tested with the Kolmogorov–Smirnov test.

Principal component analysis was used to derive the dietary patterns. The principal component analysis with varimax rotation and Kaiser normalization was used to enhance the difference between loadings to improve the interpretability of factors. The number of dietary patterns retained was determined based on eigenvalue >1.5 (which indicates the total variance explained by a given factor), scree plot examination and interpretability of the derived patterns. Patients were assigned to factor scores computed for each pattern identified, which indicated adherence to that pattern. Patients were categorized into the pattern for which they presented the highest factor score.

Mean differences were evaluated using one-way analysis of variance for variables normally distributed and Kruskal-Wallis test for variables not normally distributed. In variables where statistically significant differences were observed between the 3 groups, values across groups were compared with Bonferroni post hoc tests and significance values adjusted for multiple comparisons.

The categorical variables were analyzed using the Pearson's chi-square test.

The cumulative survival graph for all-cause mortality was generated using the Kaplan–Meier analyses, and log-rank test was used to compare the survival rates between the groups. Cox's hazard proportion analysis was used to estimate the hazard ratios for all-cause mortality, according to the dietary pattern. Multivariate analysis included adjustment for age, gender, presence of diabetes, HD vintage, presence of diabetes, and albumin.

Statistical analysis was performed using the SPSS software (version 26.0; IBM SPSS, Inc., Chicago, IL, USA) and a p-value <.05 was considered statistically significant.

Ethical Standards

The HD company and the Faculty of Medicine ethics committees approved this study and all patients who decided to participate had signed an informed consent form beforehand. The study was conducted according to the Declaration of Helsinki.

Results

The mean age of patients was 67.8 ± 17.7 years and the median HD vintage was 65 (interquartile range: 43-104) months. Etiology of all patients was as follows: diabetes mellitus 21.5%; unspecified CKD 19.1%; hypertension 13.9%; nephrotic syndrome 9.1%; polycystic disease 8.4%; other causes (known) 18.5%; and unknown 9.5%.

Regarding residual diuresis, the % of patients with renal diuresis ≥200 mL/24 hours) was 59.5%.

With respect to the intake of vitamin supplements, 89.2% of the patients were prescribed with folic acid, 88.3% with B-complex vitamins, and 32.1% with vitamin D supplement.

Three different dietary patterns were identified (Table 1).

- "Mediterranean" (33.5% of the patients) with higher intake of vegetables (91 ± 81 g/day), beans, peas and chickpeas (19 ± 27 g/day), fish (72 ± 49 g/day), olive oil (13 ± 13 g/day), eggs (25 ± 25 g/day), and lower intake of dairy products (182 ± 168 g/day).
- "Western" (31.3% of the patients) with higher intake of soft drinks (92 ± 141 mL/day), home-made fried potatoes (10 ± 18 g/day), caffeinated drinks (121 ± 131 mL/day), red and processed meat (98 ± 242 g/day), and lower intake of fruit (161 ± 110 g/day), and vegetables soup (44 ± 60 mL/day).

Table 1. Factor Loadings for Three Dietary Patterns Derived by Principal Components Analysis

	Components		
Food Groups	Mediterranean	Western	Low Animal Protein
Milk and milk products	−0.378	−0.290	−0.164
Fish	**0.473**	−0.195	−0.071
White bread, rice, pasta, and potatoes	−0.208	−0.137	−0.799
Cookies and sweets	−0.045	0.263	**0.385**
Vegetables	**0.622**	0.001	0.056
Fruit	0.109	−0.416	0.075
Wine and beer	0.173	−0.046	−0.035
Caffeinated drinks	0.079	**0.390**	0.033
Red meat	0.158	**0.366**	0.004
Processed meat	−0.262	**0.379**	0.125
Eggs	**0.326**	0.122	−0.213
Chicken and turkey	0.202	0.155	−0.174
Olive oil	**0.448**	−0.073	0.022
Fish patties and beef croquettes	0.233	−0.165	−0.171
Home-made fried potatoes	−0.163	**0.512**	0.024
Whole grain bread	−0.005	−0.100	**0.694**
Soft drinks	−0.080	**0.633**	−0.133
Barley drinks	0.025	−0.296	−0.194
Vegetables soup	−0.136	−0.317	**0.377**
Beans, peas, and chickpeas	**0.521**	0.082	0.168

Data expressed as factor loading (correlation coefficient between each food group and dietary pattern). Food groups with factor loadings ≥0.30 were bolded to indicate main food groups in each component.

- "Low animal protein" (35.2% of the patients) with higher intake of whole grain bread (141 ± 126 g/day), cookies and sweets (39 ± 68 g/day), vegetables soup (170 ± 170 mL/day) and lower intake of white bread, rice, pasta, and potatoes (186 ± 112 g/day).

Differences in clinical parameters, body composition, and nutritional intake between the dietary patterns are described in Table 2. For multiple comparisons, adjusted p-values of those variables where differences were observed between any of the dietary patterns are presented in Table 3. Serum sodium, protein intake (g/day), and FTI did not differ among any of the dietary patterns in multiple comparisons tests.

Other biochemical parameters were studied, such as, serum bicarbonate, calcium/phosphorus product and hemoglobin but did not show any statistically significant differences. Differences in the relative overhydration (%) were also not observed. Besides these results, no statistically significant differences were observed in the intake of saturated fat, polyunsaturated fat, monounsaturated fat, or iron among the 3 different patterns.

Patients following the Mediterranean pattern showed higher intake of protein, omega 3 fatty acids, vitamins B12, B6, C, D, folic acid, and presented a higher practice of moderate physical activity. Furthermore, comparing with the group of patients in the low animal protein dietary pattern, a higher LTI was observed.

Despite no statistically significant differences were observed in 12-month survival curves between the three patterns identified in our study, 6 (1.0%) patients following a Mediterranean dietary pattern died, whereas 8 (1.4%) deaths were registered in the Western pattern group and 15 (2.6%) died among patients who followed a low animal protein pattern ($P = .163$) (Figure 1).

Regardless the lower number of deaths that occurred in the Mediterranean dietary pattern group, in the multivariate model, the COX regression analysis did not show a statistically significant survival advantage for patients following a Mediterranean dietary pattern (95% confidence interval: 0.166–1.159; $P = .096$) (Table 4).

Discussion

In this longitudinal, prospective multicenter study, including 582 HD patients, three different dietary patterns were identified: "Mediterranean" (33.5% of the patients), "Western" (31.3% of the patients) and "low animal protein" (35.2% of the patients). These patterns represent the habitual intake of our HD study population and suggest that their overall intake may be similar to that of the general population, despite the specific nutritional recommendations typically given to these patients. From our main findings, we point out that the Mediterranean dietary pattern was associated with a better nutritional intake profile regarding vitamins and omega 3 fatty acids. What is more, patients following this dietary pattern, presented an adequate body composition status and a higher practice of moderate physical activity. Further, despite the lower number of deaths that occurred in the Mediterranean dietary pattern group, we did not observe a statistically significant lower mortality risk in this group of patients ($P = .096$).

Table 2. Patient's Characteristics Depending on the Dietary Pattern

	Mediterranean (n = 195)	Western (n = 182)	Low-Animal Protein (n = 205)	*P*
Age (y)*	68.1 ± 13.0	62.8 ± 15.3	71.8 ± 11.4	**<.001**
Hemodialysis vintage (months)†	64 (43-92)	65 (44-111)	66 (41-110)	.584
Presence of DM (%)	11.9	7.0	12.7	**.006**
Intradialytic weight gain (%)†	3.2 (2.4-4-2)	3.2 (2.3-4.1)	3.0 (2.4-3.9)	.579
Kt/V†	1.72 (1.5-1.9)	1.66 (1.5-1.9)	1.71 (1.5-1.9)	.996
Body composition				
Dry weight (Kg)†	70.7 (61.4-80.0)	67.9 (60.5-76.0)	68.5 (60.0-78.5)	.353
Body mass index (kg/m^2)†	26.0 (22.3-29.7)	25.2 (22.1-28.4)	25.6 (23.2-28.9)	.351
Lean tissue index (kg/m^2)†	12.2 (10.5-14.3)	12.8 (11.1-14.9)	11.7 (10.3-13.4)	**<.001**
Fat tissue index (kg/m^2)†	13.5 (10.3-17.0)	11.9 (7.8-15.6)	13.9 (10.3-17.5)	**.007**
Biochemical parameters				
Potassium (mEq/L)*	5.2 ± 0.6	5.2 ± 0.7	5.3 ± 0.7	.643
Potassium>6.0 (%)	13.4	13.6	16.4	.661
Sodium (mmol/L)*	139 ± 3	140 ± 3	139 ± 3	**.037**
Phosphorus (mg/dL)*	4.2 ± 1.1	4.4 ± 1.2	4.2 ± 1.2	.138
Phosphorus>5.5 (%)	15.1	18.9	13.2	.315
Calcium (mg/dL)*	8.90 ± 0.75	8.97 ± 0.73	9.02 ± 0.75	.274
Albumin (g/dL)†	4.0 (3.8-4.2)	4.1 (3.9-4.3)	4.0 (3.9-4.2)	.063
C-reactive protein (mg/L)*	8.6 ± 13.8	10.7 ± 12.8	11.9 ± 15.9	.605
Dietary intake (day)				
Energy (Kcal)†	1831 (1467-2357)	1754 (1383-2287)	1818 (1478-2248)	.743
Energy (Kcal/Kg)†	25.3 (19.9-33.3)	27.5 (20.3-33.8)	26.4 (20.9-33.1)	.980
Protein (g/kg)†	1.1 (0.9-1.5)	1.1(0.8-1.5)	1.1 (0.9-1.3)	.176
Protein (g)†	77.3 (60-104)	72(52-99)	73.3 (59-94)	**.040**
Carbohydrates (g)†	231 (166.286)	233 (184-291)	253 (206-294)	.079
Total fat (g)†	57.8 (44.5-78.6)	56.8 (41-81)	56 (45-74)	.612
Fiber (g)†	18.7 (14.7-25.6)	15.5 (12.6-20.4)	23.3 (18.4-28.9)	<.001
Omega 3 fatty acids (g)†	1.0 (0.8-1.4)	0.9 (0.6-1.2)	0.8 (0.7-1.1)	<.001
Vitamin B12 (mcg)†	6.1 (3.9-8.6)	4.4 (2.6-7.4)	4.2 (3.0-6.7)	<.001
Vitamin B6 (mg)†	1.4 (1.1-1.8)	1.2 (0.9-1.6)	1.3 (1.0-1.6)	<.001
Folic acid (mcg)†	214 (163-294)	193 (139-242)	210 (175-277)	<.001
Vitamin C (mg)†	80 (51-118)	56 (39-78)	65 (47-91)	<.001
Vitamin D (mcg)†	3.0 (2.0-4.4)	2.3 (1.6-3.3)	2.2 (1.6-3.1)	<.001
Calcium (mg)†	617 (442-873)	602 (394-881)	699 (520-933)	**.020**
Phosphorus (mg)†	1015 (807-1401)	1004 (745-1299)	1134 (873-1385)	**.012**
Potassium (mg)†	2329 (1816-3131)	2168 (1638-2647)	2375 (1797-2980)	**.001**
Magnesium (mg)†	236 (193-300)	213 (172-275)	279 (214-343)	<.001
Sodium (mg)†	2105 (1529-2741)	2152 (1607-2951)	2322 (1784-2824)	.294
PA				
Moderate PA (min/week) *	127 ± 331	81 ± 212	55 ± 140	**.010**
Vigorous PA (min/week)*	21 ± 149	22 ± 218	2.3 ± 18	.338
Walking (min/week)*	103 ± 192	106 ± 317	73 ± 140	.273

DM, diabetes mellitus; PA, physical activity.
*Mean ± SD.
†Median (IQR); Kt/V–dialysis adequacy.

Patients following a Mediterranean dietary pattern where those with the highest omega 3 fatty acids intake (1.0 g/day). This amount almost reached the National Academies of Science, Engineering, and Medicine recommendation for the adequate intake which is 1.1 g/day for women and 1.6 g/day for men.[21] Bossola et al. revealed lower intakes of this fatty acid by HD patients (0.5-0.6 g/day).[22] The most recent guidelines recommend a daily intake of 1.3-4 g omega-3/day in order to reduce triglycerides and low-density lipoprotein cholesterol and increase high-density lipoprotein levels.[1]

The content of vitamin C in the diet was clearly insufficient for patients in the Western and low animal protein dietary patterns which are in line with data presented by other authors with values ranging from 30 to 64 mg/day.[23-25] However, better intakes were registered in the Mediterranean dietary pattern (80 mg/day). Regarding this vitamin, the recommended intake is of at least 90 mg/d for men and 75 mg/d for women and should be supplemented, also in HD patients, to reach this amount.[1] On the other hand, the intake of folate was profoundly deficient in all the groups. The recommended

Table 3. Bonferroni Post hoc Analysis for Variables With Statistically Significant Differences With Corrected *P*-Value for Multiple Comparisons

Variable	Dietary Pattern Multiple Comparison	*P*
Age (y)	Mediterranean * Western	<**.001**
	Western * low animal protein	<**.001**
	Low animal protein * Mediterranean	**.015**
Moderate PA (min/wk)	Mediterranean * Western	.184
	Western * low animal protein	.869
	Low animal protein * Mediterranean	**.008**
Lean Tissue Index (kg/m^2)	Mediterranean * Western	.271
	Western * Low animal protein	**.001**
	Low animal protein * Mediterranean	.473
Fiber (g/day)	Mediterranean * Western	<**.001**
	Western * low animal protein	<**.001**
	Low animal protein * Mediterranean	<**.001**
Omega 3 fatty acids (g/day)	Mediterranean * Western	**.026**
	Western * low animal protein	1.000
	Low animal protein * Mediterranean	**.001**
Vitamin B12 (mcg/day)	Mediterranean * Western	**.001**
	Western * low animal protein	1.000
	Low animal protein * Mediterranean	<**.001**
Vitamin B6 (mg/day)	Mediterranean * Western	**.007**
	Western * low animal protein	.995
	Low animal protein * Mediterranean	.172
Folic acid (mcg/day)	Mediterranean * Western	**.007**
	Western * low animal protein	**.028**
	Low animal protein * Mediterranean	1.000
Vitamin C (mg/day)	Mediterranean * Western	<**.001**
	Western * low animal protein	.085
	Low animal protein * Mediterranean	**.037**
Vitamin D (mcg/day)	Mediterranean * Western	<**.001**
	Western * low animal protein	1.000
	Low animal protein * Mediterranean	<**.001**
Calcium (mg/day)	Mediterranean * Western	.706
	Western * low animal protein	**.004**
	Low animal protein * Mediterranean	.580
Phosphorus (mg/day)	Mediterranean * Western	.980
	Western * low animal protein	**.028**
	Low animal protein * Mediterranean	.107

(*Continued*)

Table 3. Bonferroni Post hoc Analysis for Variables With Statistically Significant Differences With Corrected P-Value for Multiple Comparisons (*Continued*)

Variable	Dietary Pattern Multiple Comparison	*P*
Potassium (mg/day)	Mediterranean * Western	**.046**
	Western * low animal protein	**.028**
	Low animal protein * Mediterranean	1.000
Magnesium (mg/day)[2]	Mediterranean * Western	**.002**
	Western * low animal protein	<**.001**
	Low animal protein * Mediterranean	**.006**

dietary allowance (RDA) for folate in adults is listed as 400 μg (mcg)/day.[26] Despite the higher intake observed in patients following the Mediterranean dietary pattern (214 mcg/day), this amount did not reach the recommendations. However other authors have found even lower intakes in HD patients (102-158 mcg/day).[23] The most recent guidelines for HD patients do not mention folic acid supplementation as part of the hyperhomocysteinemia management as there is no evidence demonstrating reduction in adverse cardiovascular outcomes but recommend routine supplementation when its deficiency/insufficiency is present.[1] This recommendation also exists for vitamins B12 and B6. The RDA for vitamin B6 in adults <51 years is 1.3 mg/day and for older people 1.7 mg/day (men) and 1.5 mg/day (women) whereas for vitamin B12 is 2.4 mcg/day.[26] The group of patients that reached the highest intakes was the Mediterranean dietary pattern group for both vitamins. However, only vitamin B12 intake was clearly above the recommendation. The RDA for vitamin D is 15 mcg for adults (19-70 years) and 20 mcg for adults >70 years.[27] Again, in our data we observed a very low intake of vitamin D which have also been pointed out in other studies with HD patients (2.0-3.5 mcg/day).[23,28] However, a significant higher intake was attained by patients in the Mediterranean pattern group (3.0 mcg/day).

Some recent studies have derived dietary patterns from the habitual reported intake of HD patients but very few have examined dietary patterns and mortality in these population.[29-31] Comparing to our data, Tsuruya et al. identified three similar patterns in a Japanese HD population which they called "vegetables group," "fish group," and "meat group."[30] What is more, they found an association between adverse clinical outcomes, including mortality and an unbalanced diet, characterized by a much larger intake of vegetables than meat or fish. A lower number of dietary patterns emerged in the study of

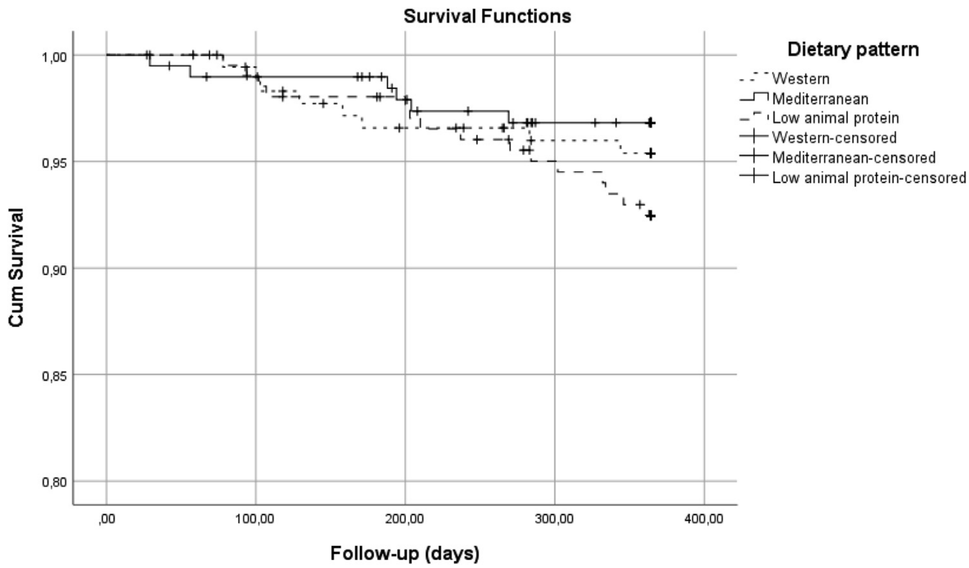

Figure 1. Kaplan-Meyer survival curves for all cause-mortality by dietary pattern (12 months of follow-up): $P = .163$.

Saglimbene et al. where the authors observed a "fruit and vegetable" diet and a "Western" diet, with these patterns being consistent across ten European countries and Argentina.[31] On the contrary, in this study there was a lack of association with mortality. In a substudy of the DIET-HD study, through the derivation of the Mediterranean and Dash diet scores, no association with cardiovascular or all-cause mortality was observed, despite the different methodology approach.[29] Similarly, Tallman et al. reported only two major patterns in an African American HD population: a "low sweetened beverage" and a "high sweetened beverage".[32] These authors aimed to analyze several health outcomes such as: patient's quality of life, daily nutrient intake as well as other biochemical parameters. Results showed lower quality of life among patients with high intake of sugar sweetened beverages and reduced intake of protein and vegetables. The low refined sugar consumption was associated with a decreased intake in energy, sugars, and vitamin C and with an increased intake of zinc, chromium, selenium, and cholesterol. In the study of Saglimbene et al. the highest quartile of the "Western" dietary pattern presented higher intakes of energy, protein, carbohydrates, fat, phosphorus, and sodium and lower intakes of sugar and potassium relatively to the mean intakes observed in the highest quartile of the "fruit and vegetable" dietary pattern.[31]

Our data showed that the dietary pattern that we defined as Mediterranean was associated with a better nutritional intake profile regarding vitamins and healthy fatty acids, showing the highest intakes omega 3 fatty acids, vitamins B12, B6, C, D, and folic acid. Moreover, the Mediterranean pattern presented higher intakes of fiber and magnesium when compared to the Western pattern.

Khor et al. aimed to analyze the relationship between different dietary patterns and serum phosphate levels in HD patients. Patients in the higher tertile of the "home food" dietary pattern, characterized by a higher consumption of plain rice, nonvegetables, fish and shellfish, poultry, pork, refined bread, fruit and soybean, presented a lower energy intake and inorganic phosphate intake, as well as lower serum phosphate levels, and higher animal protein intake and organic animal phosphate compared to those patients in the highest tertile of the "sugar sweetened beverages" group.[33] For this reason, authors state that a "home food" dietary pattern is the answer to patients facing the phosphate-protein dilemma. Different findings were reported by Tsuruya et al. where the "well-balanced" dietary pattern presented higher serum phosphorus levels even with a lower phosphorus mean intake.[30] In our study, phosphorus intake was higher in the low animal protein dietary pattern, but statistically significant differences were only observed when comparing to the Western dietary pattern. Interestingly, despite that lower mean serum phosphate levels were seen in the Mediterranean and low animal protein, comparing with the Western pattern, no statistical differences were observed in these values between the 3 dietary patterns identified. On the other hand, the highest protein intake (g/day) was observed within the Mediterranean dietary pattern giving a positive contribution to the increased protein needs once CKD patients start HD treatment. When assessing the g of protein per Kg body weight the 3 groups reached the recommendation (1.0-1.2 g/kg body weight per day).[1] Despite the highest intake of protein in the Mediterranean dietary pattern, the same trend was not observed regarding phosphorus intake (as protein-rich foods are also rich in phosphorus) or in serum

Table 4. Cox Proportional Hazard Univariate and Multivariate Model for All-cause Mortality

Indicator: *Low Animal Protein* DP	HR (95% CI)	*P*	HR_a (95% CI)	*P*
Mediterranean DP	0.43 (0.17-1.10)	.077	0.44 (0.17-1.16)	.096
Western DP	0.62 (0.26-1.45)	.268	0.75 (0.30-1.89)	.542

DP, dietary pattern; HR, hazard ratio adjusted for: age, presence of diabetes, gender, dialysis vintage, albumin.

phosphorus highlighting one more benefit of the Mediterranean dietary pattern. We hypothesize that this finding can be related with the type of phosphorus consumed (organic versus inorganic), which we did not differentiate in this study.

Still regarding biochemical parameters, our data showed that patients following a Mediterranean dietary pattern presented lower serum sodium levels, but post-hoc analysis did not show differences among any of the dietary patterns. We also observed that no statistically significant differences were observed regarding sodium intake. Despite sodium mass balance in HD patients is primarily dependent on dietary salt intake it also depends on sodium removal during dialysis treatment.[34] In fact, there has been there increasing interest on individualizing the Na + dialysate prescription with the aim of reducing fluid overload and achieving better cardiovascular outcomes.[35,36] Moreover, in anuric patients, the water intake and extrarenal water losses during the inter-dialysis interval also influence predialysis serum sodium concentration.[37]

The results of Tsuruya et al. showed a lower salt intake in a "well-balanced" dietary pattern. Although the lower potassium intake in this group of patients, mean serum potassium was the same among the 2 groups (well-balanced diet versus unbalanced). In our data, notwithstanding the differences observed in potassium intake, these results did not reflect in the serum potassium levels. Patients on HD are frequently taught to limit the consumption of potassium rich foods such as fruits, vegetables, legumes, whole grains, nuts, and processed foods but some authors have questioned this approach and whether dietary potassium and, specially, its food source affects serum potassium levels.[38] Our study group has recently published an article where this issue is discussed, and we concluded that following the dietary approaches to stop hypertension diet, which is characterized by the intake of potassium-rich foods, especially plant-based sources, is not associated with increased serum potassium levels in HD patients. Furthermore, a higher adherence to the dietary approaches to stop hypertension dietary pattern predicted lower serum potassium levels.[39] The lack of association between dietary potassium intake and serum potassium levels can be due to other several nutritional factors such as the bioavailability of dietary potassium (which is influenced by the consumption of other nutrients and constituents in the foods), fiber intake, foods alkali content, potassium sources, cooking methods as well as muscle mass, given that increased muscle mass can provide a greater capacity for potassium uptake.[40,41] Dietary-consumption data indicate that westernized diets are high in processed foods, high in sodium content, and low in potassium,[40] results that we can confirm through the data presented in this study.

Sualeheen et al. identified four different patterns in a group of Malaysian HD patients, including an "eating out-sugar sweetened beverages", "home food", "eating out noodles" and "eating out rice" patterns.[42] The major conclusion of this study was that a high adherence to a "home food" pattern was associated with a higher hand grip strength and serum albumin levels as well as with a lower malnutrition inflammation score and diet monotony index comparing with less adherent patients, which represents a better nutritional status. Our data did not show any statistically significant difference between C-reactive protein levels among the three groups; however, the lower C-reactive protein mean level observed in the Mediterranean pattern possibly indicates a trend to a decreased inflammation in patient's adherent to this pattern. It is important to note that, despite the older age of patients in the Mediterranean dietary pattern group compared with the Western dietary pattern, no differences in albumin were observed among the 3 groups of patients and mean levels were within the target values, highlighting another potential benefit of following the Mediterranean dietary pattern.

Regarding body composition parameters, the Mediterranean dietary pattern median LTI and FTI values were between the data observed on the other groups showing interesting nutritional benefits of following a Mediterranean pattern, in the context of an HD population. On the other hand, after running post hoc analysis, those following a Western diet presented a higher LTI compared to patients in the low animal protein group. This finding could be related to the patient's age as patient's mean age was the lowest in the Western group and the patients in the low animal protein were the oldest. In the study by Sualeheen et al. no differences in body composition were observed between the three consumption levels of the different dietary patterns analyzed.[42] In HD patients, several studies have shown that any gain in body weight is associated with better survival, where both fat mass and fat-free lean body mass also confer survival advantage.[43] What is more, Noori et al. suggested that the survival advantage of fat mass was superior to that of lean body mass and that low baseline body fat percentage and fat loss over time were independently associated with higher mortality even after adjustment.[44]

Finally, to our knowledge, this is the first study that has also analyzed the possible relationship between physical activities in HD patients following different dietary patterns. Sedentary lifestyle is associated with a low adherence to healthier dietary patterns, including fruits and vegetables, and has the tendency to be associated with unhealthier patterns, rich in animal fats and sweets.[45] In our study, patients following a Mediterranean dietary pattern were those practicing the highest levels of moderate physical activity and statistically significant differences were observed when comparing to the low animal protein group. Despite being observational, these results, point potential advantages of the "Mediterranean" dietary pattern also at this level, once the benefits of a regular physical activity practice are well described for the HD population.[46,47]

It is worth noting that this study involved a large sample size, drawn from 37 dialysis units representative of different geographical areas in the country, which gives us a broad perspective and the fact that, to date, very few studies have been published in this field. As a limitation we point the fact that retrospective questionnaires were used which rely on the accuracy of patients' recollections and the follow-up period which could be extended to ensure stronger conclusions.

Conclusion

Three different dietary patterns were identified in this HD population. We highlight that the pattern which was closer to the well-known Mediterranean diet was associated with a better nutritional intake profile regarding vitamin B6, B12, C, D, folic acid, and omega 3 fatty acids. Additionally, patients following this dietary pattern reported a higher practice of moderate physical activity. Furthermore, a lower number of deaths occurred in the Mediterranean dietary pattern group; however, we did not observe a statistically significant lower mortality risk in this group of patients.

Practical Applications

With these results, we have shown that following a Mediterranean dietary pattern is associated with benefits for HD patient's health at the nutritional intake profile level and in lifestyle related factors such as a higher practice of moderate physical activity. Therefore, recommending HD patients to follow a "Mediterranean lifestyle" instead of a Western or low animal protein diets would provide health benefits for this population.

Credit Author Statement

All coauthors have participated in this scientific project and agreed with the contents of the manuscript. Cristina Garagarza contributed to conceptualization, methodology, investigation, visualization, and writing-original draft preparation. Ana Valente and Telma Oliveira contributed to investigation, writing-review, and editing. Cristina Caetano, Inês Ramos, Joana Sebastião, and Mariana Pinto contributed to investigation. Aníbal Ferreira contributed to writing-review and editing. Catarina Sousa Guerreiro contributed to supervision, writing- reviewing, and editing.

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