ORIGINAL RESEARCH

Zinc Deficient Intake in Hemodialysis Patients: A Path to a High Mortality Risk

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Background: Zinc is essential for human nutrition and plays an important role in hemodialysis (HD) patients. The aim of this study is to analyze the relationship between zinc intake and mortality in HD patients.

Methods: This is a longitudinal, prospective, multicenter study with 582 HD patients from 37 dialysis centers. We recorded clinical and body composition parameters. Dietary intake and physical activity data were obtained using the Food Frequency Questionnaire and International Physical Activity Questionnaire. All statistical tests were performed using SPSS 24.0 software. A *P* value lower than 0.05 was considered statistically significant.

Results: Patients' mean age was 67.8 ± 17.7 years and median HD vintage was 65 (43-104) months. About 53.6% of the patients presented a deficient daily intake of zinc. Patients with the highest zinc intake were those who had a higher lean tissue index ($P = .022$), energy ($P < .001$), and protein ($p = .022$) intakes. Zinc intake was positively correlated with energy ($r = 0.709$) and protein intake ($r = 0.805$) and negatively correlated with the malnutrition screening tool score ($r = -0.087$). A higher energy, protein, and lower carbohydrates intake, as well as lower HD vintage and higher lean tissue index were predictors of zinc intake. A higher mortality risk was observed in patients with zinc intake below the recommended values, even after the adjustment for age, presence of diabetes, gender, dialysis vintage, albumin, lean tissue index, energy intake/kilogram, and level of physical activity ($P = .021$).

Conclusion: There is a high prevalence of HD patients with an inadequate zinc intake, which is related to worse nutritional and body composition parameters and with a higher mortality risk.

Introduction

FOLLOWING NUTRITIONAL RECOMMENDATIONS is one of the cornerstones in hemodialysis (HD) and contributes to keep patients stable by preventing negative outcomes related to an impaired nutritional status. Macronutrient and mineral intake, especially phosphorus, sodium, and potassium, as well as liquid consumption, should be routinely assessed in these patients.[1] However, other non-routinely monitored micronutrients, such as trace elements, also play an important role in patient health.[2]

Zinc is an essential trace element for human nutrition and plays an important role as a co-factor for enzymes that protect against oxidative damage as part of the antioxidant defense system.[3] It is required for cellular processes and immune function[2,4] and participates in energy, protein, carbohydrate, and lipid metabolism.[5]

Its deficiency is associated with anorexia, decreased taste acuity with a loss in taste buds, growth retardation, impotence, alopecia, glucose intolerance, hyperlipidemia, and impaired neurological and immune systems.[1,5,6] Causes of deficiency in patients on HD are multifactorial. Inadequate nutritional intake, malabsorption (due to ingestion of absorption inhibitors such as phytates, folic acid, and dietary fiber) or malabsorption syndrome, drug intake (oral iron supplements, calcium-based phosphate binders), and excessive losses (dialysate-driven losses) may promote zinc deficiency. Taste and smell impairment, due to chronic uremia present in these patients, contribute to a reduced food intake, including zinc deficiency and also protein energy wasting.[1,2,6-9]

The recommended dietary allowance of zinc for the general population is 8 mg/day for women and 11 mg/day for men, whereas the European Best Practice Guideline on Nutrition and Chronic Kidney Disease recommends a daily intake between 8 and 12 mg for women and 10 and 15 mg for men.[1] The recent KDOQI clinical practice guideline on nutrition in chronic kidney disease suggests not to routinely supplement zinc in HD patients since there is little evidence that it improves nutritional, inflammatory, or

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micronutrient status.[7] This micronutrient is absorbed in large quantities from protein-rich foods such as fish and shellfish (especially oysters), red meat, milk and milk products, poultry and eggs, and legumes, nuts and whole grain cereals are also good sources.[2] As zinc is completely bound to proteins and 60%–70% to albumin, low protein diets affect zinc absorption.[10]

Considering an adequate zinc intake of key importance, and simultaneously considering the lack of studies evaluating the relationship between its consumption and survival in HD patients, the aim of this study is to analyze the relationship between zinc intake and mortality in HD patients.

Materials and Methods

Study Design and Setting

We carried out a longitudinal, prospective, multicenter study with patients from 37 dialysis centers from November 2018 to November 2019.

Sample Size

We used the sample size computed for a longitudinal mortality study (that has not yet been published) 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.[11] 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.

The 600 patients of the sample were randomly selected among the 4600 patients on HD in the 37 dialysis centers: patients fulfilling the inclusion criteria were randomly selected equally from each dialysis center.

Inclusion and Exclusion Criteria

Patients were eligible for this study if they were aged ≥18 years, underwent a 4-hour in-center HD session 3 times a week for ≥15 months (with an online hemodiafiltration technique), had accepted to participate, and had signed an informed consent. According to most of the studies a dialysis vintage of 3 months is defined, 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 hemodialysis 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/insufficiency, and immunosuppressive or corticosteroid medication.

Data Analysis

Etiology of the chronic kidney disease, 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 external laboratories. Serum albumin was measured by the colorimetric technique with bromocresol green.

For the data analysis, patients were divided in 3 groups: daily zinc intake below/within/above the recommended values (between 10 and 15 mg for men and 8 and 12 mg for women).[1]

Body Composition

The assessment of body composition included lean tissue index (LTI), fat tissue index, body cell mass, % relative overhydration (overhydration/extracellular water pre-dialysis), total body water, extracellular water, and intracellular water. 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 5-1,000 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 in the hand and 2 in the foot contralateral to the vascular access. To obtain the clinically relevant output parameters, 2 advanced physiological models are used in the Body Composition Monitor: a volume model describing electrical conductance in a cell suspension[12] and a body composition model calculating the 3 principal body compartments: overhydration, lean tissue, and adipose tissue.[13]

All output parameters have been validated against the gold standard reference methods in various studies involving more than 500 patients and healthy controls.

Regarding the quality of measurements, all exceeded 95%.

Malnutrition

We used the malnutrition screening tool (MST) to assess malnutrition risk at the beginning of the study.[14] This consists of a simple and reliable tool to identify patients at risk of malnutrition and is routinely used in the nutrition appointments in our dialysis units. Three main components are evaluated in this score: weight loss (score: 0 or 2), amount of weight lost (score: 1–4), and poor food intake or poor appetite (score: 0 or 1).

Food Frequency Questionnaire

We assessed dietary intake through a semi-quantitative FFQ conducted by a trained dietitian in a face-to face interview during the HD treatment. It has been developed and validated for the Portuguese population.[15,16] It has 95 food items, 9 categories of frequencies (from "never or less than once a month" to "6x 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 United States 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.[17]

International Physical Activity Questionnaire

The short version of the International Physical Activity Questionnaire validated for the Portuguese population was used to assess the physical activity level[18] and conducted by a dietitian in a face-to-face interview, in the same day as the FFQ. Patients were asked about time spent (days per week and minutes per day) performing physical activity of different intensity levels (vigorous, moderate, walking) and sitting.

Statistical Analysis

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

For the analysis, patients were divided in 3 groups, depending on their zinc intake. Differences were evaluated using one-way analysis of variance for variables normally distributed and Kruskal-Wallis test for variables not normally distributed. The categorical variables were analyzed using the chi-squared test. We used the Spearman correlation coefficient to assess the relationship between zinc intake and the variables of interest.

We evaluated the prognostic differences of risk stratification in the study population using Kaplan–Meier curves and log-rank test. The Cox proportional hazard model was used to measure all potential variables and determine the significance of variables for prediction of 12-month mortality and the hazard ratio of death and 95% confidence interval were obtained. Primarily, a univariate Cox model was used to identify the association of zinc intake with mortality; posteriorly, the multivariable Cox regression models were conducted using covariates that have been described as significant predictors of mortality or covariates of clinical concern including age, presence of diabetes, gender, dialysis vintage, albumin, LTI, energy intake/kilogram, level of physical activity. Statistical analysis was performed using the SPSS software, version 24 (IBM SPSS, Inc., Chicago, IL) and a P value $<.05$ was considered statistically significant.

Ethical Issues

The dialysis 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

From the 600 patients selected for the study, 18 patients refused to participate in the study (3%) as they did not accept to answer the FFQ. Therefore, we collected data from 582 patients.

The mean age was 67.8 ± 17.7 years, 41.4% were female, 31.6% had diabetes mellitus, and the median HD vintage was 65 (interquartile range 43-104) months.

Of the whole sample, 53.6% presented a deficient intake of zinc (mean intake = 9.6 ± 4.1 mg/day). The lowest intake was 2.1 mg/day and the highest 42.7 mg/day. Mean intake in women was 8.3 ± 3.2 mg/day with 51.2% presenting a low intake, whereas for men data were 10.4 ± 4.4 mg/day and 55.3%, respectively.

Patients with the highest zinc intake were those who had higher LTI, energy, and protein intakes. Other differences among the groups are presented in Table 1.

Zinc intake was positively correlated with energy and protein intake and negatively with the MST score (Table 2).

Foods that presented the highest positive correlations (coefficient ≥0.25) with zinc intake were: beef/pork (r = 0.538), cheese (r = 0.373), eggs (r = 0.336), rice (r = 0.305), ham-processed meat (r = 0.284), codfish (r = 0.258), yogurt (r = 0.263), and whole-grain bread (r = 0.250). All of them with a P-value $<.001$.

During the 12 months of the follow-up period, the overall mortality was 5% (29 deaths occurred). About 7.4% of the patients with low zinc intake died, whereas this value was lower in the group of patients with an intake within the recommended values and above (2.1% and 2.6%, respectively). Therefore, the lowest survival was observed in patients with zinc intake below the recommendations (log-rank test; $P = .019$) (Fig. 1). No statistically significant association was observed between zinc intake survival curves and hospitalization.

Patients with a zinc intake below the recommended intake values did not present a higher risk of hospitalization ($P = .170$). However, in the Cox regression analysis, a 4.1 times higher mortality risk was observed in patients with zinc intake below the recommended intake values ($P = .017$), even after the adjustment for age, presence of

Table 1. Differences Between Groups of Zinc Intake (mg/d) and Variables of Interest

Parameter	Zinc Intake <10 (Men) or <8 (Women) (n = 312)	Zinc Intake 10-15 (Men) or 8-12 (Women) (n = 194)	Zinc Intake >15 (Men) or >12 (Women) (n = 76)	*P* Value
Zinc intake (mg/d)*	6.8 ± 1.7	11.1 ± 1.8	16.9 ± 4.0	–
Age* (y)	69 ± 13	68 ± 13	61 ± 16	**<.001**
HD vintage (mo)†	64 (43-97)	60 (43-94)	58 (42-87)	.743
Gender (%female)	39.7	45.9	38.2	.321
DM (%)	31.4	32.5	30.3	.934
Kt/V†	1.7 (1.6-1.9)	1.7 (1.5-1.9)	1.6 (1.4-1.9)	.137
nPCR (g/Kg/day)*	1.14 ± 0.26	1.21 ± 0.25	1.23 ± 0.26	**.022**
Albumin (g/dL)†	4.0 (3.8-4.3)	4.0 (3.8-4.2)	4.1 (3.9-4.3)	.384
C-reactive protein (mg/L)*	10.7 ± 14.6	11.1 ± 15.2	8.1 ± 8.8	.817
Hemoglobin (g/dL)†	11.1 (10.6-11.7)	11.4 (10.7-11.2)	11.2 (10.8-11.4)	.339
Total cholesterol*	167.7 ± 40.2	170.2 ± 43.1	177.7 ± 40.9	.511
HDL-C (mg/dL)†	45 (35-54)	43 (38-54)	41 (33-56)	.887
LDL-C (mg/dL)*	89.2 ± 38.2	98.4 ± 37.9	91.9 ± 29.2	.445
TG (mg/dL)†	127 (92-173)	135 (93-175)	122 (101-197)	.978
Dry weight (kg)†	67.5 (60.0-75.5)	71.3 (62.5-80.5)	73 (63.8-84.7)	**.037**
Body mass index (kg/m^2)†	25.0 (22.0-28.1)	27.0 (23.2-29.9)	25.8 (23.2-29.4)	.259
Lean tissue index (kg/m^2)†	12.5 (10.8-14.3)	11.7 (10.3-14.1)	12.9 (11.5-15.3)	**.022**
Fat tissue index (kg/m^2)†	12.2 (8.9-15.5)	14.7 (10.3-18.3)	13.0 (10.2-16.5)	.116
Daily energy intake (Kcal)	1561 (1281-1826)	2146 (1807-2517)	2984 (2596-3423)	**<.001**
DEI/kilogram (Kcal/kg)	23.1 (19.1-27.7)	30.0 (24.1-36.3)	42.4 (33.4-51.4)	**<.001**
Carbohydrates (%DEI)†	54.5 (49.9-58.9)	53.3 (48.2-56.8)	49.3 (45.2-56.1)	**.002**
Protein (%DEI)†	15.7 (14.6-17.6)	17.3 (15.7-19.2)	17.6 (16.3-19.4)	**<.001**
Fat (%DEI)†	27.8 (24.5-31.9)	29.5 (26.6-32.9)	31.4 (25.9-35.5)	**.004**
MST	0.47 ± 0.67	0.42 ± 0.63	0.36 ± 0.61	.324
Hospitalizations (number)*	0.32 ± 0.73	0.34 ± 0.64	0.29 ± 0.69	.889
Hospitalizations (length)*	4.6 ± 14.6	5.4 ± 14.1	2.6 ± 8.4	.329
WHO recommendations for physical activity (%)	19.6	17	28.9	.085

DEI, daily energy intake; DM, diabetes mellitus; Kt/V, dialysis adequacy; nPCR, normalized protein catabolic rate; TG, triglycerides; WHO, World Health Organization.
Bold values indicate $P < .05$.
*Mean ± standard deviation.
†Median (interquartile range).

diabetes, gender, dialysis vintage, albumin, LTI, energy intake/kilogram of body weight, and level of physical activity (95% confidence interval 1.2-13.6, $P = .021$) (Table 3).

Discussion

In our study, 53.6% of the patients presented a deficient intake of zinc and the mean intake was 9.6 ± 4.1 mg/day. Studies on HD patients report a zinc intake below the recommendations in 45% of the patients[19] and mean intakes ranging from 5.8 ± 2.8 to 6.1 ± 0.49 mg/day.[10,20]

Table 2. Correlations Between Zinc Intake and Energy, Macronutrients and Malnutrition Screening Tool

Dietary Zinc Intake	*r*
DEI/kilogram (Kcal/kg)	0.709*
Protein/kilogram	0.805*
% Carbohydrates	−0.224*
% Protein	0.272*
% Fat	0.145*
MST	−0.087†

DEI, daily energy intake; MST, malnutrition screening tool.
*$P < .001$.
†$P < .05$.

HD patients are susceptible to develop zinc deficiency due to an inadequate dietary intake, dialysate zinc losses, and a reduced gastrointestinal zinc absorption.[21,22] This is of particular concern, as up to 78% of adult patients on HD may be zinc deficient.[23] Dvornik et al[24] estimated zinc concentrations immediately before and after dialysis and concluded that serum zinc concentrations were highly dependent on HD treatment as in 64% patients serum zinc concentrations decreased. Serum or plasma zinc reflects the dietary zinc intake and reference data are available for most age and sex groups. The assessment of dietary zinc intake at the population level is recommended as it will provide information about the dietary patterns that may be associated with zinc adequacy or inadequacy and can help to identify populations or subpopulations at elevated risk for inadequate zinc intakes.[25]

In our study, we found that an insufficient zinc intake was an independent predictor of death in HD patients, even in the adjusted model. The inadequate serum zinc level in

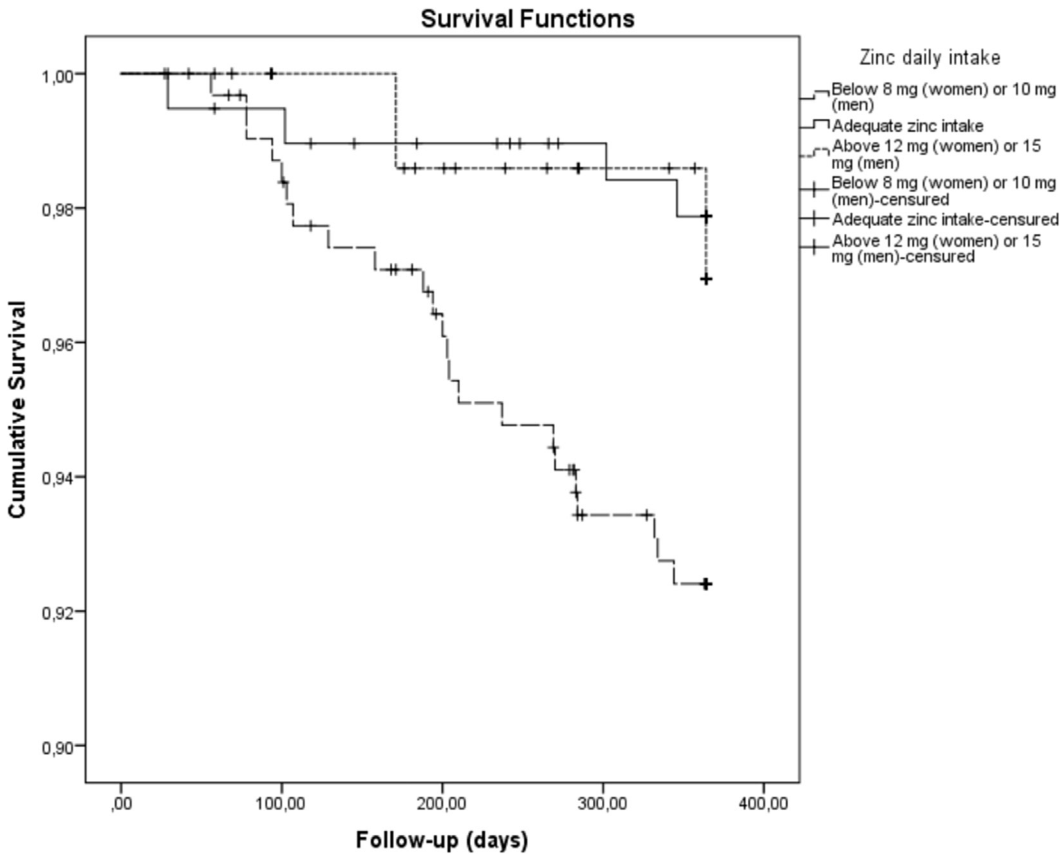

Figure 1. Survival curve for the 3 groups of patients (n = 582; log-rank χ^2 = 7.883; $P < .019$).

adult HD populations has also been described as an independent predictor of both overall mortality and hospitalization, due to infectious diseases.[26] Other contributing risk factors for morbidity and mortality rates in these patients include protein energy wasting, oxidant-antioxidant imbalance, progressive inflammation, impaired immune responsiveness, as well as infection, and zinc deficiency can be related to all of these complications.[27,28] A reduced food intake, which includes protein, may result in zinc deficiency and, in the medium term, can result in protein energy wasting.[1] In our study, patients with a deficient zinc intake presented higher scores on the MST and lower intake of energy and protein which are protein energy wasting related parameters. Therefore, there might be a beneficial relationship between zinc intake and patient's nutritional status.

The association between inadequate zinc consumption and lower energy intake has already been described[29] and zinc supplementation in HD patients has shown to increase food intake.[30] Our data show a lower daily energy intake with higher proportion of carbohydrates and lower of proportion of protein and fat in patients with a deficient zinc intake. Zinc food sources have changed over time, with zinc being obtained about equal amounts from foods of animal and plant sources to being predominantly obtained from animal foods, with this source appearing to be better absorbed.[31] In our study, we found that zinc was mainly obtained from animal sources such as red meat, cheese, and eggs and also from rice.

Patients with lower zinc intake were older and with lower dry weight, probably related with the lower consumption of energy and protein also observed in this group

Table 3. Cox Proportional Hazard Univariate and Multivariate Model for All-Cause Mortality

	HR (95% CI)	*P* Value	HR_a (95% CI)	*P* Value
Zinc daily intake <8 mg (women) or <10 mg (men)*	3.7 (1.3-10.6)	.017	4.1 (1.2-13.6)	.021

CI, confidence interval; HR_a, hazard ratio adjusted for: age, presence of diabetes, gender, dialysis vintage, albumin, lean tissue index, energy intake/kilogram, and level of physical activity.

*Recommended zinc intake for hemodialysis patients.

of patients, which commonly occurs in elderly patients.[8] Along with the decreased protein intake, mild cases of zinc deficiency may present non-fat weight loss[8] but zinc supplementation has shown to improve this status in HD patients[32] with increases in fat free mass and body fat percentages.[20] Indeed, some studies trying to examine the effects of zinc supplementation on nutritional status in HD patients have found an increase in albumin levels and in protein catabolic rate.[20,28,33] In our data, we did not observe differences in fat tissue index; however, patients in the highest level of zinc intake presented higher LTI. This observation is probably related to the fact that this group of patients were those who had higher intakes of energy and mainly protein. These results can also be related with the role of zinc in the protein synthesis which increases protein levels[10] possibly contributing to muscle synthesis.

Hypercholesterolemia and hypertriglyceridemia have been reported in previous studies on zinc-deficient diets, which could induce cardiovascular events and insulin resistance in chronic kidney disease patients.[34] In our study, despite that the highest calorie intake and fat (% daily energy intake) consumed have been observed in patients with higher zinc intakes, there were no changes in blood lipids based on zinc intake levels.

The group of patients with a higher zinc intake included a bigger percentage of physically active patients; however, we did not observe statistical differences between the 3 groups. A recent systematic review reported that dietary zinc intake was higher in exercise groups compared to control in half of the studies; therefore, authors deemed the effects of exercise training on dietary zinc intake to be equivocal.[35] The higher total zinc intake could be derived from the increased amount of food consumed but the influence of changing dietary patterns, as a result of exercise, on zinc status and related outcomes has not yet been clarified.[35]

In HD patients, a zinc supplementation of 50 mg zinc per day for 3-6 months should be considered when existing chronic inadequate protein/energy intake and symptoms evoking zinc deficiency (impaired taste or smell, skin fragility, impotence, peripheral neuropathy).[1] However, routine zinc supplementation is not recommend since the evidence that it improves nutritional, inflammatory or micronutrient status is considered to be insufficient.[1,7] Finally, as there are some drugs frequently prescribed to HD patients which may promote zinc deficiency, such as calcium-based phosphate binders and oral iron supplements, we consider that medications prescribed should be taken into account when assessing nutritional status and adjusting zinc dietary intake in patients undergoing HD treatment.

Our study comprises a large sample size, drawn from 37 dialysis units located in different geographical areas, which gives us a broad perspective, although we cannot disregard the fact that retrospective questionnaires were used, which rely on the accuracy of patients' recollections. There are other limitations related with the application of the FFQ. On the one hand, the FFQ used in this study has not been validated in an HD population. On the other hand, no information was collected regarding what were patients eating during the year of assessment for mortality as they could have changed the dietary intake reported in the FFQ.

In conclusion, there is a high prevalence of HD patients with an inadequate zinc intake, which is related with worst nutritional and body composition parameters and with a higher mortality risk. Food sources that most contribute to increase zinc consumption are also rich in protein, which is also an extremely important nutrient for these patients.

Practical Application

Zinc intake should be monitored and dietary advice should encourage the intake of zinc-rich foods to achieve the recommended daily intake. However, future studies with an appropriate design of food-based interventions should be performed.

Credit Authorship Contribution Statement

Cristina Garagarza: Conceptualization, Methodology, Investigation, Visualization, Writing - original draft, scientific project and agree with the contents of the manuscript. **Ana Valente:** Investigation, Writing - review & editing, scientific project and agree with the contents of the manuscript. **Cristina Caetano:** Investigation, scientific project and agree with the contents of the manuscript. **Inês Ramos:** Investigation, scientific project and agree with the contents of the manuscript. **Joana Sebastião:** Investigation, scientific project and agree with the contents of the manuscript. **Mariana Pinto:** Investigation, scientific project and agree with the contents of the manuscript. **Telma Oliveira:** Investigation, Writing - review & editing, scientific project and agree with the contents of the manuscript. **Aníbal Ferreira:** Writing - review & editing, scientific project and agree with the contents of the manuscript. **Catarina Sousa Guerreiro:** Supervision, Writing - review & editing, scientific project and agree with the contents of the manuscript.

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