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Role of parathyroid hormone in anorexia on maintenance hemodialysis patients

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SUMMARY

Background and aim: Anorexia, which is a common condition in patients on hemodialysis (HD), is characterized by impaired appetite, a subjective condition that hinders anorexia diagnosis. Anorexia is frequently associated with protein energy wasting and inflammation, increasing morbidity and mortality risk. The aim of the study was to evaluate the association between appetite and nutritional, inflammatory, hormonal, and dietary intake parameters in patients on maintenance HD.
Methods: Cross-sectional study with clinical, laboratory, and anthropometric parameters, body composition, muscle function, and dietary intake assessment. To evaluate appetite, a three simple questions questionnaire previously validated was used. After appetite classification, the sample was dichotomized in "normal appetite" and "impaired appetite" and compared. Multiple logistic regression was used to identify association between variables and outcome.
Results: 125 patients on HD were included, aged 60.6 ± 14.12 years old, median HD vintage 35.5 months. In dichotomized sample, 78.4% patients showed "normal appetite", and 21.6% "impaired appetite". "Impaired appetite" was independently associated with increased serum PTH (OR 1.001; 95% CI 1.000–1.002; $p = 0.03$), low zinc intake (OR 0.860; 95% CI 0.746–0.991; $p = 0.03$) and lower urea serum (OR 0.982; 95% CI 0.965–0.999; $p = 0.04$). Both groups showed insufficient dietary intake.
Conclusions: Appetite was independently associated with increased serum of PTH, low serum concentration of urea, and low zinc intake which may infer association of appetite with mineral bone disease, protein intake and zinc deficiency.

1. Introduction

In chronic kidney disease (CKD), a progressive decrease in protein and energy body stores often occurs, characterizing Protein Energy Wasting (PEW). PEW is a specific type of malnutrition involving factors inherent to CKD, such as hypercatabolic state, uremic toxins retention, and inflammation, with consequent appetite reduction and higher risk of morbidity and mortality [1–3].

The association between PEW and inflammation in patients with CKD implies appetite reduction with consequent decrease in food intake, micronutrients deficiency, muscle weakness and disability, reduced quality of life, increase in hospitalizations, morbidity and mortality [4–7].

Loss of appetite is a condition of variable prevalence (6–50%) among patients undergoing hemodialysis [6–8]. Due to its subjective character, there is a great dificult to diagnose loss of appetite and there is no gold standard instrument to assess it. Nevertheless it shows a strong influence on nutritional status and responses to dialytic therapy in clinical practice [9]. Studies assessing appetite in patients on hemodialysis suggest that appetite reduction plays a central role in the association between PEW and inflammation, which is determinant in increase of morbidity and mortality rates [5,6].

Due to the importance of appetite in PEW progress, studies associating it with nutritional, hormonal, and inflammatory parameters may be important for further therapies to improve appetite. In addition, due to the subjective character of appetite evaluation, objective parameters that predict appetite loss may be useful.

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Thus, the aim of this study was to verify the association between self-reported appetite with clinical, laboratory, nutritional (anthropometric, body composition, muscle function and dietary intake), hormonal, and inflammatory parameters in patients with CKD undergoing maintenance hemodialysis.

2. Materials and methods

2.1. Study design and patients

This was a cross-sectional study with patients with CKD on maintenance hemodialysis in the Clinics Hospital of Botucatu Medical School (Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu, Brazil). Patients over 18 years old undergoing hemodialysis treatment for at least three months and that agreed to participate in this research were included. Those with end-stage liver diseases, cancer, antiretroviral treatment, chronic inflammatory diseases, acute infections or using antibiotics by up to the previous month of data collection were excluded. This study was approved by the Research Ethics Committee of the Botucatu Medical School and consent form was individually obtained.

2.2. Appetite assessment

To characterize “current appetite”, the first three questions from the HEMO Study questionnaire were applied [5,9]. The first question was: “during the past week (7 days), how would you rate your appetite?”, with the following options of answer: 1) Very good, 2) Good, 3) Regular, 4) Bad or 5) Very bad. In the second question, patients were asked if there were any changes in their appetite in the previous week and, if so, the third question was whether it decreased or increased. After characterization of “current appetite” with the first question, the sample was dichotomized. Patients who classified their appetite as “very good” or “good” were considered with “normal appetite”, and those who classified it as “regular”, “bad” or “very bad” were considered with “impaired appetite”. The application of the questionnaire was carried out by a single researcher in one moment.

2.3. Clinical parameters evaluation

The following information was obtained from electronic medical records: sex, age, hemodialysis vintage, presence of diabetes and hypertension, main cause of end stage renal disease, dose of erythropoietin, use of high-flow dialysis filter, Kt/V and normalized protein catabolic rate (nPCR).

2.4. Laboratory analysis

Venous blood samples were collected before the second dialysis session of the week. Biochemical [serum calcium, phosphorus, potassium, alkaline phosphatase, albumin, total cholesterol, triglycerides, HDL-cholesterol, creatinine, urea, glucose, and bicarbonate (dry biochemistry, Vitros, Johnson & Johnson®)], hematological [hematocrits, hemoglobin, total lymphocyte counting, iron, ferritin and transferrin saturation (cythochemistry, impedance, absorbance and flow cytometry, fluorometry, Pentra ABX 120, Horiba®), serum iron (dry chemistry, VITROS DT, Johnson & Johnson®)], inflammatory markers [serum concentration of C reactive protein - CRP (fixed-point immunochemical method)] and hormonal parameters [25-hydroxyvitamin D (chemiluminescence, Architect, Abbott®), leptin (ELISA, RayBio®, Norcross), and parathyroid hormone (PTH) (chemiluminescence, Architect, Abbott®)] were determined.

2.5. Anthropometric assessment

Evaluation was carried out after dialysis session in the non-fistula implanted arm. Triceps (TSF), bicipital, subscapular, and supra-iliac skinfolds thickness, mid-arm circumference (MAC), body weight and height were measured. Using these data, body mass index (BMI), body fat percentage [10,11], mid-arm muscle circumference (MAMC) were calculated. The following formula was used: MAMC (cm) = MAC (cm) − [TSF (mm) x 0,314]) and percent standard of MAMC was calculated using percentile distribution tables [12].

2.6. Bioelectrical impedance evaluation

Single-frequency bioelectrical impedance analysis was performed (Biodynamics, 450). This analysis was carried out 20 min after hemodialysis session in patients in supine position. Electrodes were placed in the opposite side of vascular access in the dorsal region of hand and foot. Values of resistance, reactance, phase angle, total body water, percentage of intra and extracellular water, adipose tissue and free fat mass were considered.

2.7. Muscle function evaluation

Muscle function was evaluated with handgrip strength on the opposite side of fistula using Jamar® hydraulic dynamometer (Sammons Preston, Masan, Korea) with precision of 1 kg. Patients were instructed to self-adjust the dynamometer to better adapt it to their hands and obtain a better performance. Patients were told to press the equipment using their maximum strength in response to voice commands. Three tests were carried out and the maximum value obtained was considered.

2.8. Food intake assessment

Dietary intake was evaluated using 24-hour dietary recalls of patients. Participant were asked to report all foods and beverages consumed in the previous 24-hours, to a single interviewer. Kilocalories per current body weight (kcal/kg/day), protein per current body weight (g/kg/day), total sodium, potassium, phosphorus, and zinc intake were considered.

2.9. Statistical analysis

Data were expressed with mean ± standard deviation, median (minimum and maximum) or percentage, when appropriate. For comparison between groups with “normal appetite” and “impaired appetite”, t Student's test was used for parametric distribution variables, and a generalized linear model was used for non-parametric distribution variables.

Logistic regression analyses with continuous variables were used to investigate the association with the outcome “impaired appetite”. The variables with statistical probability inferior to 20% were selected for multivariable logistic regression model with backward procedure. Collinearity between variables was tested. CRP and leptin values were logarithmically converted. Analyses were performed using SAS 9.2 and SPSS 22.0. Statistical significance criterion for all analyses was $p < 0.05$.

3. Results

This study enrolled 125 hemodialysis patients with age ranging from 25 to 91 years, with predominance of males (56.8%). Diabetic nephropathy was the main cause of end stage chronic kidney disease, followed by hypertensive nephrosclerosis (32 and 20%, respectively).

Regarding evaluation of appetite, most patients classified their appetite as "good" (63.2%). Only three patients reported a "very bad" appetite, and all of them denied positive or negative changes compared to the previous week.

The sample was divided in two groups: the first one with 98 patients (78.4%) that showed "normal appetite", and the second one with 27 patients (21.6%) with "impaired appetite". Not statistical difference was found in the comparison of clinical variables between the groups (Table 1).

Regarding laboratory parameters, patients with "impaired appetite" showed higher serum iron, transferrin saturation index, and alkaline phosphatase and lower urea and 25-hydroxyvitamin D levels. About nutritional characteristics, those with "impaired appetite" presented higher percentage of body fat when measured by anthropometry ($p = 0.02$). There was no difference in muscle function or other anthropometric variables between the groups. According to recommendations, energy and protein intake were insufficient in both groups. Group with "normal appetite" and "impaired appetite" had median energy and mean protein intake 18.4 kcal/kg/day and 0.9 g/kg/day, 17.8 kcal/kg/day and 0.7 g/kg/day, respectively, with no statistical difference [13]. Comparing the groups, patients with "impaired appetite" showed lower zinc intake than patients with "normal appetite". All the variables that showed significant difference is represented in Table 2.

After univariate models, the selected variables for multivariable logistic regression model were: serum urea, transferrin saturation, zinc intake, PTH, CRP, and protein intake. Sex, age, hemodialysis vintage, leptin, and BMI were included for adjustment. Serum urea and zinc intake were positively associated with appetite, while PTH was negatively associated with appetite (Table 3).

4. Discussion

The present study assessed the association between appetite and clinical, biochemical, nutritional, hormonal and inflammatory parameters. "Impaired appetite" was independently associated with increased serum PTH, low zinc intake and low serum urea.

A relevant association found in this study was between "impaired appetite" and PTH serum levels. PTH is an uremic toxin that, in high concentrations, is responsible for metabolic and structural achievements such as anorexia, hyperlipidemia, carbohydrate intolerance, immune dysfunction, cardiac hypertrophy, and high bone turnover, releasing bone markers such as alkaline phosphatase [17,18]. In univariate analysis, those with impaired appetite had higher alkaline phosphatase and lower vitamin D, both characteristics of bone mineral disease in CKD.

Jiang et al. pointed out that patients submitted to parathyroidectomy improved their nutritional status with higher albumin serum levels and BMI [18]. In addition, experimental studies indicated PTH as the responsible for protein metabolism disturbs, with consequent increase of proteolysis in the skeletal muscle of patients on hemodialysis, leading to fatigue, muscle atrophy, weight loss and malnutrition [17,19,20]. Therefore, PTH is associated with poorer nutritional status, and perhaps, appetite may be involved in PEW development.

After identifying the influence of parathyroid hormone-related protein (PTHrP) on the development of cachexia in cancer patients, Kir et al. questioned whether high serum PTH levels due to CKD secondary hyperparathyroidism would not present the same action in the development of wasting [21]. In an experimental model with nephrectomized rats, the authors showed that PTH and PTHrP, both acting through the same receptor, activate the protein kinase A (PKA), which promotes the expression of genes involving thermogenesis (e.g. uncoumpling protein 1-UPC1), leading to white adipose tissue "browning", with increase of O_2 consumption and energy expenditure, and decrease of body fat mass, both white and brown adipose tissue, and muscle mass [21]. Besides this mechanism, literature shows the interaction of PTH with insulin resistance, obesity, diabetes and inflammation, conditions that are presented in CKD patients, worsening wasting and possibly involving the impaired appetite [22,23]. Our study reinforces the

Table 1
Comparison of clinical characteristics according appetite classification of 125 patients on maintenance hemodialysis.

Clinical variables	All (n = 125)	Normal appetite (n = 98)	Impaired appetite (n = 27)	p
Age (years)	60.6 ± 14.1	60.3 ± 14.0	61.9 ± 14.5	0.59
Sex [Male (%)]	71 (56.8)	57 (58.1)	14 (51.8)	0.55
Presence of diabetes [n (%)]	52 (41.6)	38 (38.7)	14 (51.8)	0.22
Presence of hypertension [n (%)]	101 (80.8)	79 (80.6)	22 (81.4)	0.91
Main cause of end stage renal disease [n (%)]				0.89
Diabetic nephropathy	40 (32)	31 (31.6)	9 (33.3)	
Hypertensive nephrosclerosis	25 (20)	20 (20.4)	5 (18.5)	
Undetermined	15 (12)	12 (12.2)	3 (11.1)	
Glomerular diseases	13 (10.4)	12 (10.2)	3 (11.1)	
Others	32 (25.6)	25 (25.5)	7 (25.9)	
Dialysis vintage (months)	35.5 (7; 266)	30.2 (7; 266)	39.7 (7; 256)	0.46
Kt/V	1.4 ± 0.2	1.4 ± 0.18	1.5 ± 0.23	0.67
Erythropoietin (IU/week)	4000 (0; 36000)	4000 (0; 36000)	4000 (0; 24000)	0.13
Dialysis filter [High flow performance (%)]	99 (79.2)	77 (78.5)	22 (81.4)	0.74

Table 2
Comparison of laboratory and nutritional parameters (food intake and anthropometry) with significant results of 125 patients according to appetite classification.

Laboratory variables	Normal appetite (n = 98)	Impaired appetite (n = 27)	p
Alkaline phosphatase (mg/dl)	110 (49; 528)	119 (67; 1157)	0.003
Serum urea (mg/dl)	116.4 ± 28	101.7 ± 30.5	0.01
Serum iron (μg/dl)	73.5 (10; 238)	80 (17; 1,218)	<0.001
Transferrin Saturation (%)	35.3 (1.1; 136.2)	38.4 (12.8; 499.7)	<0.01
Vitamin D (ng/l)	30.5 ± 11.5	25.6 ± 10	0.04
Body fat[a] (%)	29.4 ± 8.3	34.2 ± 8.3	0.03
Zinc (mg/day)	7.9 ± 4.2	5.7 ± 3.0	0.004

[a] Body fat: estimated by athropometry – sum of four skinfolds.

Table 3
Multiple logistic regression for “impaired appetite”.

Variables	OR (95%CI)	P
Serum Urea	0.982 (0.965; 0.999)	0.04
PTH	1.001 (1.000; 1.002)	0.03
Zinc intake	0.860 (0.746; 0.991)	0.03
CRP	2.955 (0.924; 9.447)	0.06

Variables included: serum urea, transferrin saturation, zinc intake, PTH, CRP and protein intake normalized for body weight.
Variables included in adjustments: sex, age, hemodialysis vintage, leptin, and BMI.

findings of these recent experimental studies, hypothesizing there is an impact of PTH high levels on PEW, not only related to fat and muscle mass decrease, but inducing anorexia as well.

Chronic inflammation is featured in PEW, in part due to its effects on appetite. “Impaired appetite” group showed lower levels of serum vitamin D, which could be associated with chronic inflammation and elevated serum alkaline phosphatase levels [24,25]. High levels of alkaline phosphatase are an indication of high bone turnover, a common characteristic of CKD related to mineral bone disorders [26].

Lower zinc intake among patients with "impaired appetite" was observed in this study. Average daily intake of zinc (5.7 mg) in the group with “impaired appetite” was lower than the recommendations, regardless of patient's sex. According to the Dietary Reference Intakes (DRI's), zinc estimated average requirement (EAR) intake is 9.4 mg/day for men and 6.8 mg/day for women [27]. Zinc is an essential metal involved in biochemical processes, and its deficiency is associated with anorexia, weight loss, oxidative stress, and cognitive and growth delay [28,29]. Castro et al. showed hypozincemia in 89% of a sample of 28 patients of the same dialysis unit of this research, with no association with dialytic modality [30]. Low zinc intake was also reported by Aranha et al. in another Brazilian sample of hemodialysis patients [31]. These results possibly indicate a low consumption of zinc food sources in dialytic populations. Thus, it is suggested that low zinc intake in Brazilian samples could be due the high cost of zinc food sources, such as crayfish, red meat, whole grains, oil seeds, vegetables, and tubers. Moreover, some of these products may be restricted in diets for hemodialysis patients, due to high phosphate or potassium content.

Zinc deficiency has been observed in hemodialysis patients and can occur because of proteinuria, calcitriol deficiency, which affects zinc absorption in the intestine, inflammation, hypoalbuminemia, and loss through dialysis procedure [28–31]. Moreover, low zinc intake may be one of the reasons of zinc deficiency in CKD patients, and may be associated with anorexia [28,31,32]. Aranha et al. found a negative correlation between plasma concentrations of leptin and zinc in hemodialysis patients, however, they found no association of both with impaired appetite or nutritional status [31]. Leptin, which is a protein produced primarily by adipocytes and metabolized in kidney, is involved in energy metabolism and appetite regulation. The production of leptin is proportional to the amount of white fat mass [33]. Although body fat percentage was higher in “impaired appetite” group, leptin levels were not related to appetite in our sample. A possible explanation is that in CKD, leptin levels are usually increased due to other reasons, such as decreased filtration rate, chronic inflammation and hyperinsulinemia [34]. In cases of leptin resistance, such as in CKD, leptin has been linked to decreased bone mass. Leptin may also act as a proinflammatory adipokine, activating inflammatory pathways that leads to poorer bone health [35]. Moreover, there is a relationship between zinc deficiency and inflammation, and zinc supplementation lead to an anti-inflammatory effect in hemodialysis patients [32,36].

Lower urea levels have also been associated with “impaired appetite”. Among several factors attributed to appetite reduction in patients with CKD, uremic toxicity is of the most traditional representatives, since after dialysis onset this symptom tends to improve [8,37]. Carrero et al., also found association of serum urea with worsen nutritional status of patients with CKD [37]. Urea, a 60Da molecule which is the final product of protein metabolism and nitrogen compounds, is a good marker of protein intake and dialysis adequacy [38]. Thus, lower levels of serum urea found in patients with “impaired appetite” revealed low food intake, as already indicated by the values of energy and protein intake found in this study. Moreover, nutrition guidelines for hemodialysis patients recommend 35 kcal/kg and 1,2 g/kg [13].

Patients with “impaired appetite” had a higher percentage of body fat, evaluated by anthropometry. Our data agree with the literature concerning higher production and release of pro-inflammatory substances in patients with increase in adipose tissue stores, which represents a possible cause of appetite reduction [39,40]. These substances are known as adipokines and represent important inflammatory markers such as: leptin, interleukin 6, tumor necrosis factor-α, resistin, among others [39,41,42]. Several studies have already addressed the association between serum levels of leptin and CRP, once leptin stimulates acute phase protein production of liver cells [42]. In addition, transferrin, an acute phase protein strongly influenced by inflammation, showed to be lower in these patients, probably because of the inflammatory state. Hence, inflammation in patients undergoing hemodialysis has been pointed out as an important mediator of anorexia in this population [2].

A relationship between altered markers of mineral and bone disorders – such as increased levels of alkaline phosphatase and PTH, and vitamin D deficiency – and worse outcomes, as renal osteodystrophy, vascular calcification, cardiovascular disease, hospitalization and mortality has been already described [26,43]. Thus, based on our findings, we hypothesized there is influence of mineral and bone disorders markers on appetite of hemodialysis patients. Further studies are needed to confirm this relationship.

This research has some methodological limitations: this is a cross-sectional single center study with no control group. Since anorexia is associated with several variables, longitudinal assessments of appetite would establish a causal relationship among the evaluated parameters. The lack of gold standard tools to evaluate appetite in CKD represents a limitation, even if applied by only one researcher. The lack of plasma levels measurements of zinc and specific inflammatory markers hinders the evaluation of zinc deficiency and inflammatory profile of these patients, respectively. Despite such limitations, this research was able to show significant associations among diminished appetite and higher PTH levels in a hemodialysis sample of patients.

5. Conclusion

Appetite was independently associated with increased serum PTH, low zinc intake and low serum concentration of urea. In addition, it is possible to suggest the involvement of inflammation due to the negative association between CRP and appetite. Besides PTH association with appetite in multivariate analysis, other bone mineral metabolism markers were associated with appetite in univariate analysis, showing the involvement of bone mineral disorders in appetite impairment, and further malnutrition status. As soon, clinically strengthened the role for parathyroid hormone and possibly the inflammation in “Impaired appetite” affecting the intake of essential micro and macronutrients such as zinc and protein. Despite the difficulty of appetite evaluation due to its subjective character, early detection of appetite decrease would prevent nutritional status deterioration, and allow interventions that would also contribute to hospitalization, morbidity and mortality rates reduction in patients undergoing hemodialysis.

Statement of authorship

M. C. C. B. Ribeiro, F. C. D. Vannini and J. C. T. Caramori contributed to the conception and design of the research; M. C. C. B. Ribeiro, F. C. D. Vannini, B. P. Vogt and J. C. T. Caramori contributed to the acquisition, analysis, or interpretation of the data; M. C. C. B. Ribeiro and J. C. T. Caramori drafted the manuscript; M. C. C. B. Ribeiro, B. P. Vogt and J. C. T. Caramori critically revised the manuscript; and M. C. C. B. Ribeiro, B. P. Vogt, F. C. D. Vannini and J. C. T. Caramori agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

Conflict of interest statement and funding sources

The authors declare they have no conflicts of interest. A master's degree scholarship was provided to MCCB, and a doctorate scholarship was provided to BPV by Coordination of Improvement of Higher Education Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), an organization of the Brazilian federal government under the Ministry of Education.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.07.008.

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