



Original/Valoración nutricional

Late referral for chronic kidney disease patients: nutritional point of view

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Abstract

The prevalence of late referral of patients with chronic kidney disease (CKD) is high and has been associated with a worse CKD prognosis, however few studies have been conducted from a nutritional perspective.

Objective: Characterize the nutritional status of patients with CKD at first attendance in a nephrology service, with early (ER) and late referral (LR).

Methodology: It was a cross-sectional study with patients older than 18 years referred to the Nephrology service of a University Hospital. The referral groups were classified according to estimated glomerular filtration rate (eGFR) as: LR (eGFR<15ml/min/1.73m²) or ER (eGFR>15 ml/min/1.73m²) based on the Kidney Disease Outcomes Quality Initiative. Nutritional evaluation included subjective global assessment (SGA), anthropometric, laboratory and bioelectrical impedance data. The SAS® software was used for statistical analysis.

Results: Seventy-five patients were evaluated, 29% of them belonging to the LR group. This group showed a greater previous weight loss (-7.0 ± 3.5 versus -2.8 ± 7.0 Kg) and lower values for all anthropometric and body composition variables. In general, the laboratory results of the LR group also were worse. According to the SGA, all LR patients had some degree of malnutrition (50% with severe malnutrition against 28.8% in ER), showing significantly lower results for GFR (21.4 + 12.2 ml/min/1.73 m²), albumin (3.9 + 0.3 g/dL), serum bicarbonate (22.8 + 5.1 mmol/L) and phase angle (5.3+ 0.6 θ). Renal function was positively correlated with percent adequacy of arm circumference (r=0,40; p<0,01) and albumin (r=0,45; p<0,01).

Conclusion: The LR group showed a worse nutritional status showing that, for the nutritional point of view, the delayed referral brings substantial losses that can make difference in future treatment, thus demonstrating the importance of early nutritional monitoring for this population.

(Nutr Hosp. 2015;31:1286-1293)

DOI:10.3305/nh.2015.31.3.7939

Key words: Nutritional status. Chronic kidney disease. Late referral.

LATE REFERENCIA DE LOS PACIENTES
CON ENFERMEDAD RENAL CRÓNICA:
PUNTO DE VISTA NUTRICIONAL

Resumen

La prevalencia de la referencia tardía de los pacientes con enfermedad renal crónica (ERC) es alta y se ha asociado con un pronóstico peor ERC, sin embargo pocos estudios se han llevado a cabo desde una perspectiva nutricional.

Objetivo: Caracterizar el estado nutricional de los pacientes con ERC con la primera cita en un servicio de nefrología, con temprana (ER) y la remisión tardía (LR).

Metodología: Se realizó un estudio transversal con pacientes mayores de 18 años a que se refiere el servicio de Nefrología del Hospital Universitario. Los grupos de referencia se clasificaron de acuerdo a la tasa estimada de filtración glomerular (TFG) como: LR (TFG <15 ml / min / 1.73m²) o ER (TFG> 15 ml / min / 1.73m²), basado en la Kidney Disease Outcomes Quality Initiative. Evaluación nutricional incluyó la evaluación subjetiva global (SGA), antropométricas, de laboratorio y los datos de impedancia bioeléctrica. El software de SAS ® se utilizó para el análisis estadístico.

Resultados: Fueron evaluados setenta y cinco pacientes, el 29% de ellos pertenece al grupo LR. Este grupo mostró una pérdida mayor de peso anterior (-7,0 ± 3,5 frente a -2,8 ± 7,0 Kg) y los valores más bajos para todas las variables antropométricas y de composición corporal. En general, los resultados de laboratorio del grupo LR también eran peores. De acuerdo con el SGA, todos los pacientes tenían LR algún grado de desnutrición (50% con desnutrición severa contra 28,8% en ER), que muestra resultados significativamente más bajos de la TFG (21,4 + 12,2 ml / min / 1,73 m²), albúmina (3,9 + 0,3 g / dL), bicarbonato sérico (22,8 + 5,1 mmol / L) y ángulo de fase (5.3+ 0,6 θ). La función renal se correlacionó positivamente con el porcentaje de adecuación de la circunferencia del brazo (r=0,40; p<0,01) y albúmina (r=0,45; p<0,01).

Conclusión: El grupo LR mostró un peor estado nutricional muestra que, para el punto de vista nutricional, la remisión tardía trae pérdidas sustanciales que pueden hacer la diferencia en el tratamiento futuro, lo que demuestra la importancia de la vigilancia nutricional precoz para esta población.

(Nutr Hosp. 2015;31:1286-1293)

DOI:10.3305/nh.2015.31.3.7939

Palabras clave: Estado nutricional. Enfermedad renal crónica. La referencia tardía.

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Recibido: 29-VIII-2014.
Aceptado: 12-X-2014.

Introduction

Chronic Kidney Disease (CKD) is a clinical syndrome characterized by renal damage and progressive and irreversible loss of kidney function¹. The increased prevalence of CKD has led to its recognition as a public health problem in Brazil and in the world, especially due to the high costs for the health system, the high morbidity and mortality of this population, and the adverse consequences for affected individuals².

In order to control the complications caused by CKD, to attenuate the progression of the disease and to optimize its treatment, in addition to preparing the patients for dialysis or kidney transplantation, international guidelines recommend that patients with CKD be referred early to a nephrologist for the assessment and management of the disease³.

Many studies have indicated that late referral is associated with a poorer prognosis for CKD^{4,5}. It involves higher rates of progression to renal dysfunction, higher complication rates and a higher risk to require emergency dialysis, resulting in increased morbidity-mortality, higher treatment costs, and a worse quality of life^{6,7,8,9}. Despite this recognized health impairment due to late referral, few studies have been conducted using a nutritional perspective^{10,11,12}.

Starting from a glomerular filtration rate (GFR) of 60 mL/min/1.73 m², the patients should be regularly submitted to assessment of nutritional status. The ideal way to monitor the nutritional status of these patients includes a combination of various clinical, laboratory and anthropometric parameters in order to circumvent the limitation of each method when employed separately^{13,14}.

Among the complications of CKD to which late referral may contribute is protein-energy malnutrition (PEM). The causes of this condition are multifactorial, being mainly related to the dietary restrictions of pre-dialysis treatment, the clinical conditions determined by the disease itself (anorexia, gastrointestinal and hormonal disorders, and metabolic changes), and poly medication^{15,16,17,18}.

Most of the patients who start dialysis treatment without previous nutritional monitoring have symptoms of malnutrition such as weight loss and changes in anthropometric and laboratory parameters¹⁹. Thus, the application of a nutritional care plan seems to be the main protective factor against the worsening of PEM, since nutritional monitoring and education are key factors in order to secure motivation and adherence to the diet^{20,21}.

Considering nutritional status as an important prognostic factor in the evolution of CKD and in view of the lack of information about the patients referred to nephrology services, it is essential to be aware of the nutritional status of these patients in order to improve the nutritional care provided to them. Thus, the main objective of the present study was to characterize the nutritional status of patients with CKD under conser-

vative treatment with early or late referral to a nephrology service.

Subjects and Methods

Design

An observational cross-sectional study was conducted between October 2009 and December 2010 on 75 patients with pre-dialysis CKD referred to the Nephrology Service of a University Hospital in Ribeirão Preto, São Paulo, Brazil for the first time and aged 18 years or older. Individuals with acute kidney injury, prior kidney transplantation or dialysis and those for whom the disease could not be differentiated as acute or chronic according to their medical records were excluded.

The study was approved by the Research Ethics Committee of the University Hospital, Medical School of Ribeirão Preto, University of São Paulo, and all patients gave written informed consent to participate.

Sample size was calculated from a pilot sample previously obtained from a CKD population. The formula of Singer (1997) was used and the level of significance was set at 0.05. For a test power of 0.8, the result of the calculation was a total sample of 70 patients²².

Time of referral

The classification of late referral was based on the definition of the K/DOQI Guidelines, using as a criterion a GFR of <15 mL/min/1.73 m², estimated from the formula of Cockcroft-Gault, which uses age, current weight and plasma creatinine concentration²³. On this basis, the patients were assigned to two groups, i.e., those with a late referral (GFR <15 mL/min/1.73 m²) and those with an early referral (GFR >15 mL/min/1.73 m²).

Anthropometric measures

The same trained nutritionist performed the anthropometric evaluation of all patients under fasting conditions. Weight was measured with a scale with 0.1 kg precision and height with a stadiometer with 0.1 cm precision (Filizola S/A, São Paulo, Brazil). Body mass index (BMI) was calculated as weight divided by height squared. A cutoff point of ≥ 24.9 kg/m² was used to classify excess weight for adults and a cutoff point of ≥ 27.0 kg/m² was used to classify excess weight for elderly subjects²⁴.

The following anthropometric indices were assessed: the patient's current weight expressed as a percentage of ideal weight (%); measurement of the arm circumference (AC) expressed as a percentage of adequacy in relation to the ideal values for gender and age^{25,26}; and waist circumference (WC) classified according to the World Health Organization (WHO)²⁷.

The percentage of weight change was calculated based on the current weight in relation to the habitual weight and classified as gain, significant loss (<10%) or severe loss (> 10%) in the last 6 months²⁸. Patients whose clinical condition did not permit anthropometric assessment were only submitted to subjective global assessment and to laboratory work-up.

Body composition was evaluated by tetrapolar bioelectrical bioimpedance analysis (BIA) (Biodynamics 450, Biodynamics Corporation, Seattle, WA, USA) which provides data regarding body water, lean mass, phase angle and fat mass, using a current of 800 μ A and 50 kHz. The measurements were performed according to manufacturer instructions.

A researcher experienced in using the scored Subjective Global Assessment (SGA) assessed all subjects²⁹. Each subject was classified as well-nourished (SGA A), moderately or suspected of being malnourished (SGA B), or severely malnourished (SGA C). The scored SGA consists of the four medical components (weight loss, nutrition impact symptoms, intake and functional capacity) and a physical examination assessing fat, muscle stores and fluid status plus global assessment of nutritional status.

Biochemical evaluation

Blood samples were collected from the patients after a 12-h overnight fast. Biochemical evaluation included the determination of lipid profile, serum albumin, total protein, urea, creatinine, calcium, phosphorus, blood count, glucose and venous blood gases (pH and bicarbonate - HCO_3^-). All exams were carried out in the Central Laboratory of the University Hospital of the institution.

The lipid profile, consisting of total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL-c) and high density lipoprotein (HDL-c), was determined. The following desirable reference values were considered: <200 mg/dL TC, <150 mg/dL TG and < 100 mg/dL LDL-c, and for HDL-c, values higher than 40 mg/dL for men and higher than 50 mg/dL for women³⁰.

The reference value used for serum albumin was ≥ 4.0 g/dL (K/DOQI, 2000) and the reference value used for glucose was > 100 mg/dL³¹. Metabolic acidosis was defined as serum bicarbonate concentrations of less than 22 mmol/L³².

Statistics

Data are reported as mean and standard deviation for continuous variables and as frequencies and percentages for categorical variables. Spearman correlation was used to determine associations between estimated GFR and nutritional parameters. The nonparametric Wilcoxon test was applied to analyze

differences between the late referral (LR) and early referral (ER) groups regarding the continuous variables, and the Fisher exact test was used to analyze differences regarding the categorical variables. The level of significance was set at 5%. ANOVA was used to compare the patients according to SGA classification, followed by the Tukey post-test when the null hypothesis was rejected. The SAS[®] software (version 9.2, 2008, SAS Institute Inc. Cary, NC, USA) was used for all analyses.

Results

Seventy-five patients under conservative treatment were assessed, 29% of them belonging to the LR group and 71% to the ER group. Mean patient age was 64.8+11.6 years and 73% were elderly persons (> 60 years). Patient distribution according to kidney function is presented in table I.

According to BMI, most subjects (63%) were overweight and obese. When each group was considered separately, the percentage of overweight in ER patients was even higher (68%). Concerning abdominal circumference, 75% of the patients were found to be at higher risk for metabolic complications associated with obesity.

Nutritional assessment revealed that 54% of the patients had suffered a weight loss of up to 10% in the last 6 months. The LR group showed lower values for all the anthropometric and body composition variables, except for the percentage of weight change, which indicated a greater weight loss in this group (Table II). In agreement with the anthropometric assessment, in general the laboratory data for the LR group were worse than those for the ER group (Table III).

The lipid profile showed changes in large part of the subjects compared to reference values. Hypertriglyceridemia was present in 47% of cases, elevated LDL-c in 57% and hypercholesterolemia in 40%. It is important to point out that 37% of the patients showing normal serum TC levels were taking lipid-lowering drugs. Fasting glycemia levels were higher than the reference values in 44% of the patients.

Table I
Patient distribution according to CKD staging

Stage	Glomerular filtration rate* (ml/min/1.73 m ²)	n (%)
II	60-89	7 (9.3%)
III	30-59	20 (26.7%)
IV	15-29	26 (34.7%)
V	<15	22 (29.3%)

*Glomerular filtration rate estimated using the formula of Cockcroft-Gault²³.

Table II
Comparison of the anthropometric variables between groups according to late or early referral

Variables	Sample (n=75)	Late referral (n=22)	Early referral (n=53)	p-value
Change in weight (%)	-3.9 ± 6.5	- 7.0 ± 3.5	- 2.8 ± 7.0	<0.01
Adequacy of IMW (%)	126.1 ± 23.8	113.5 ± 16.6	131.3 ± 24.4	<0.01
BMI (kg/m ²)	27.3 ± 5.2	24.5 ± 3.6	28.4 ± 5.3	<0.01
Adequacy of AC (%)	97 ± 14.1	89.4 ± 10.9	99.4 ± 14.2	0.01
AbC (cm)	97.2 ± 13.3	86.6 ± 11.1	100.7 ± 12.1	<0.01
Phase angle (θ)	5.7 ± 0.9	5.2 ± 0.7	5.9 ± 0.9	0.01
Fat mass (%)	20.4 ± 8.3	23.7 ± 6.8	29.6 ± 7.6	0.02

*Nonparametric Wilcoxon test. Data are reported as mean ± SD. IMW: ideal mean weight; BMI: body mass index; AC: arm circumference; AbC: abdominal circumference.

Table III
Comparison of the laboratory variables between groups according to late and early referral

Variables	Late referral (n=22)	Early referral (n=53)	p-value
Hemoglobin (g/dl)	10.7 ± 1.53	13.1 ± 2	<0.01
Hematocrit (%)	32.9 ± 4.10	39.6 ± 5.7	<0.01
Lymphocytes (10 ³ mm ³)	1.7 ± 0.86	2.1 ± 0.6	0.03
TIBC	186 ± 51.45	223.2 ± 84.5	0.02
Glycemia (mg/dl)	105.1 ± 51.6	127.2 ± 60	0.04
Albumin (g/dl)	3.92 ± 0.26	4.2 ± 0.3	<0.01
Total proteins (g/dl)	6.6 ± 0.5	6.9 ± 0.4	0.04
Urea (mg/dl)	107.2 ± 42.3	75.4 ± 41.1	<0.01
Creatinine (mg/dl)	5.6 ± 2.3	2.3 ± 1.1	<0.01
Phosphorus (mg/dl)	5.6	4.05	<0.01
Total calcium (mg/dl)	8.5	9.5	<0.01
Blood pH	7.3 ± 0.1	7.6 ± 0.1	<0.01
Serum bicarbonate	20.7 ± 4.3	26.4 ± 4.3	<0.01

*Nonparametric Wilcoxon test. Data are reported as mean ± SD. TIBC: Total iron-binding capacity.

There were associations between kidney function and parameters of nutritional assessment. There was a significant positive correlation between GFR and phase angle (Figure 1) and between renal function and albumin (Figure 2). The prevalence of hypoalbuminemia in the total sample was 37%.

Metabolic acidosis was identified in 28% of the patients. Significant positive correlations were observed between serum bicarbonate levels and nutritional status variables such as albumin (Figure 3).

Patient classification according to the SGA is presented in table IV. Half the patients in the LR group had severe malnutrition and no patient was classified as well nourished.

When the laboratory and anthropometric variables were compared according to SGA, the patients classified as malnourished were found to have significantly lower GFR, albumin, serum bicarbonate and phase angle values and a greater weight loss. However, only albumin differed between categories B and C and only phase angle and GFR differed between categories A and B (Table IV, Table V).

Discussion

The main findings of the present study were a high prevalence of patients with late referral (LR) to the

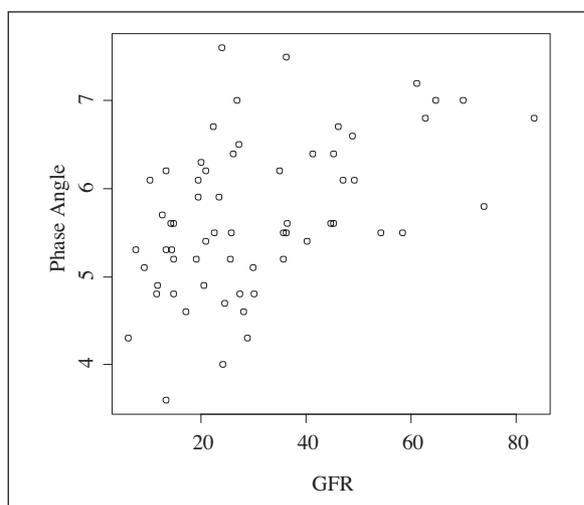


Fig. 1.—Correlation Spearman between GFR and phase angle (CCS=0,48; $p<0,01$).

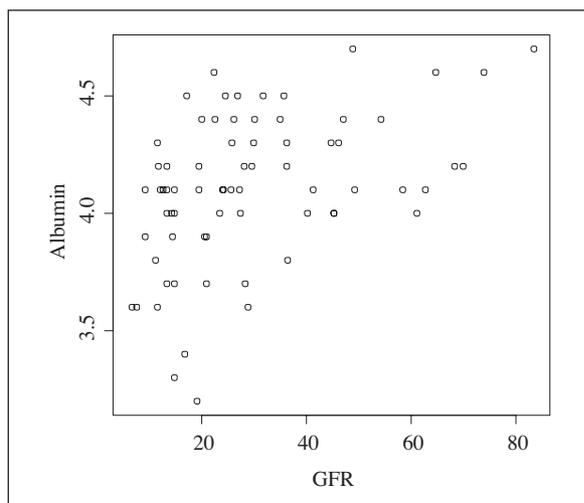


Fig. 2.—Correlation Spearman between renal function and albumin (CCS=0,45; $p<0,01$).

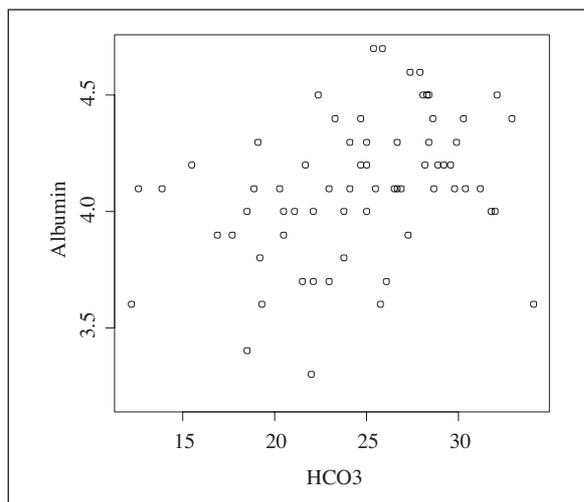


Fig. 3.—Correlation Spearman between serum bicarbonate levels and albumin (CCS=0,4; $p<0,01$).

nephrology service of a university hospital and the fact that these patients showed a worse nutritional status according to the SGA and most of the anthropometry, laboratory and body composition parameters compared to the ER group.

The definition of “late referral” is somewhat arbitrary and quite heterogeneous. Most studies usually assess the prevalence of LR on the basis of the difference in time between referral to the nephrologist and beginning of dialysis treatment. However, since there is no established definition, different times are used as cut-off points, among them 1, 3, 4, 6 or even 12 months before dialysis treatment^{4,33,34,35,36,37}.

This criterion based on the difference in time is used in prospective or retrospective studies. However, due to the cross-sectional nature of our study, we could not use this classification. For this reason, we selected the LR criterion considered in the guidelines of the K/DOQI based on stage 5 of CKD (GFR<15 ml/min/1.73 m²)³. According to the systematic review study of Navaneethan et al. (2008), this diversity of criteria is responsible for the wide variation in the prevalence of LR reported in the literature (15 to 80%), impairing a possible comparison between studies⁹.

The high percentage of LR patients detected in the present study (29%) agrees with literature data. Navaneethan et al. (2007), in a retrospective US study on 204 patients, compared the two classifications of LR and detected a value of 22% according to the criterion of kidney function (GFR<15 ml/min/1.73 m²) and a value of 26% according to the time criterion (6 months before dialysis)¹². Similar results were obtained in a study conducted in Italy on 673 patients³³. Recently, Hommel et al. (2012) detected an even higher LR percentage (38%)³⁷. Thus, the literature shows that up to 64% of CKD patients are still referred late⁴.

Our findings show that kidney function was positively correlated with phase angle, with LR patients showing lower phase angle values. This reduction has been considered to reflect damage to the cell membrane, cell death, increased ratio between intra- and extracellular water, and decrease body cell mass^{38,39}. From

Table IV
Classification of nutritional status of groups late and early referral according to Subjective Global Assessment*

Classification	Late referral (n=22)	Early referral (n= 53)	Sample
A	0	17 (32.7%)	17 (22.9%)
B	11 (50%)	20 (38.5%)	31 (41.9%)
C	11 (50%)	15 (28.8%)	26 (35.2%)

* Detsky, 1987 (29) A: Well nourished; B: Mild to moderate malnutrition; C: Severe malnutrition.

Table V
*Comparison of the nutritional variables according to classification by the Subjective Global Assessment**

Variables	Classification SGA			p-value
	A	B	C	
eGFR (ml/min/1.73 m ²)	47 + 16 ^a	26.3 + 16.7 ^{b,c}	21.4 + 12.2 ^b	p<0.01
Albumin (g/dl)	4.3 + 0.2 ^a	4.1+0.2 ^{a,c}	3.9 + 0.3 ^b	p<0.01
Serum bicarbonate (mmol/L)	28.0 + 2.9 ^a	24.7+ 5.1 ^{a, b}	22.8 + 5.1 ^b	p<0.01
Change in weight (%)	-1 + 5.2 ^a	-3.8 + 6.5 ^{a, b}	-6.1 + 6.7 ^b	p<0.01
Phase angle (θ)	6.4+ 0.7 ^a	5.6+ 0.9 ^{b,c}	5.3+ 0.6 ^b	p<0.01

Data are reported as mean ± SD. ANOVA: p-value < 0.01; Tukey post-test.

SGA: Subjective Global Assessment; eGFR: Estimated glomerular filtration rate.

*Detsky, 1987 (29). A: Well nourished; B: Mild to moderate malnutrition; C: Severe malnutrition.

a clinical viewpoint, the phase angle is considered to be an important marker in the determination of increased risk of morbidity in various pathological conditions^{11,40}, particularly in CKD patients before dialysis. Caravaca et al. (2011) established that a phase angle of 5.3° is of prognostic value for survival⁴¹.

BMI assessment revealed a high percentage of overweight and obesity (63%), especially in the ER group. Brazilian studies have detected lower percentages of excess weight in CKD patients, of the order of 25 to 50%^{10,42}. There still is controversy about the best measure for the determination of obesity in these patients. Some studies that evaluated the relationship between obesity and adverse outcome in CKD using BMI obtained conflicting results, which were partially due to the determination of total body mass without differentiating between fat and lean mass^{43,44,45}. Evidence suggests that abdominal circumference is a more reliable tool for the detection of visceral adiposity, being a better predictor of morbidity and cardiovascular risk compared to BMI⁴⁶. When the abdominal circumference was analyzed in the present population, most individuals were found to be at higher risk to develop metabolic complications.

Positive correlations were detected between kidney function and anthropometric variables. GFR was correlated with BMI and with percent adequacy of arm circumference, indicating that the progressive loss of kidney function is accompanied by a decline of nutritional status markers and is intimately linked to an increased risk of malnutrition, as also reported by Campbell et al. (2008)²⁰. In agreement with these results, considering all the anthropometric variables measured, the LR group showed a worse nutritional status than the ER group.

Herget-Rosenthal et al. (2010) also observed that LR patients had a poorer nutritional status when assessed according to serum albumin concentration (< 3.5 g/dl) and BMI (<20 kg/m²), and identified malnutrition as an independent factor associated with mortality⁴⁷. Thus, during the pre-dialysis phase, malnutrition seems to be a predictor of increased number of hos-

pitalizations and deaths and of progression to dialysis therapy regardless of GFR²⁰.

Another clinical tool with established prognostic value for CKD and used to assess nutritional status is the SGA, which is commonly used to determine the prevalence of malnutrition and to identify patients at higher risk for morbidity and mortality⁴⁸. Stenvinkel et al. (2002) reported that CKD patients classified as malnourished according to the SGA showed significantly higher mortality rates than patients classified as well nourished when the data were adjusted for age, diabetes and cardiovascular diseases¹⁶.

The beginning and the severity of PEM are related to the level of kidney function, with a higher prevalence of nutritional damage being usually observed below a GFR of 60 ml/min/1.73 m² and being reflected on lower albumin, serum bicarbonate and cholesterol values³. These changes were present in our study, in which malnutrition detected according to the SGA was associated with the more advanced phases of CKD and with significantly lower levels of albumin, serum bicarbonate and phase angle and a greater weight loss.

LR patients also showed worse laboratory results characterizing nutritional status compared to ER patients. In particular, metabolic acidosis, which is a common complication of CKD especially when GFR reaches levels close to 20 ml/min/1.73 m², was present in almost one third of the patients, a result lower than those reported in the literature considering the same cut-off point. Leal et al. (2009) observed a 50% frequency of metabolic acidosis in a sample with characteristics similar to those of the subjects studied here⁴².

The reduction of serum bicarbonate levels is associated with various adverse effects including bone disease, hypoalbuminemia and increased risk of death^{42,49}. In addition, it plays an important role in the pathogenesis of PEM, which involves increased protein degradation of skeletal muscle in the presence of acidosis, with its correction possibly contributing to

a reduction of this degradation⁵⁰. In the present study we observed various significant positive correlations between serum bicarbonate level and nutritional status variables such as albumin, total proteins, fat mass, percent fat and percent adequacy of arm circumference. When we compared the bicarbonate levels according to SGA classification, we noted that category A patients had significantly higher levels than category C patients.

Hypoalbuminemia was present in 37% of the subjects and its frequency was significantly higher in the LR group compared to the ER group. It is important to remember that low albumin levels may reflect not only the deterioration of nutritional status, but also the presence of inflammation, proteinuria, systemic diseases, advanced age, and degree of hydration. Thus, albumin should be used in combination with other parameters for the assessment of nutritional status¹⁶.

Regarding the lipid profile, a high percentage of patients with dyslipidemias as well as significantly lower HDL levels was observed in the LR group. However, this prevalence may be even higher since 37% of the patients with normal serum cholesterol levels were taking lipid-lowering medication. Recently, Chen et al. (2013) demonstrated that increases in TC and LDL-c are associated with a more rapid progression of CDK, being considered risk factors for renal replacement therapy in stage 3-5 patients⁵¹.

There is evidence that pre-dialysis nephrology care independently affects the clinical outcomes^{8,52,53}. The main objective of nutritional treatment during this phase is to maintain and/or recover the nutritional status, to attenuate the uremic symptoms, to control the metabolic disorders, and to delay the rate of kidney disease progression⁵⁴. Thus, it is extremely important to maintain these patients under nutritional monitoring throughout CKD treatment, since this is a period that must be used to offer the patient the best possible conditions for the beginning of dialysis.

However, since most epidemiological investigations are devoted to the study of patients kept under dialysis treatment, it is essential to start new studies, mainly during earlier CKD phases in order to provide better nutritional care to this population.

Conclusion

Despite the limitations of the present study such as a small sample size and the use of a LR criterion little employed in the literature, the results obtained demonstrated that patients with late referral presented a greater deterioration of nutritional status. Thus, it is essential for patients with CKD to receive an earlier diagnosis during the pre-dialysis period and to be referred in a timely manner to multiprofessional nephrology teams, in order to delay dialysis or to start dialysis program in a better health condition.

Acknowledgement

The authors acknowledge Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for granting a Master's fellowship (2009/ 06553-6) and for financial aid (2010/11179-3).

References

1. Kalista-Richards M. The kidney: medical nutrition therapy-yesterday and today. *Nutr Clin Pract*. 2011 Apr;26(2):143-50.
2. Kim do H, Kim M, Kim H, et al. Early referral to a nephrologist improved patient survival: prospective cohort study for end-stage renal disease in Korea. *PLoS One*. 2013;8(1):e55323.
3. National Kidney Foundation: KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39:S1-S266.
4. Sprangers B, Evenepoel P, Vanrenterghem Y. Late referral of patients with chronic kidney disease: no time to waste. *Mayo Clin Proc*. 2006;81(11):1487-1494.
5. Innes A. The detection of advanced chronic kidney disease by surveillance of elevated plasma creatinines a five-year experience. *Nephrol Dial Transplant* (2008) 23: 2571-2575.
6. Levin A. Consequences of late referral on patients outcomes. *Nephrol Dial Transplant* (2000) 15 (Suppl 3): 8-13.
7. Kazmi WH, Obrador GT, Khan SS, Pereira BJJ, Kausz AT. Late nephrology referral and mortality among patients with end-stage renal disease: a propensity score analysis. *Nephrol Dial Transplant* (2004) 19: 1808-1814.
8. Chan MR, Dall AT, Fletcher KE, Lu N, Trivedi H: Outcomes in patients with chronic kidney disease referred late to nephrologists: a meta-analysis. *Am J Med* 2007;120:1063.e2-1070.e2.
9. Navaneethan SD, Aloudat S, Singh S. A systematic review of patient and health system characteristics associated with late referral in chronic kidney disease. *BMC Nephrology* 2008, 9:3.
10. Carvalho KT, Silva MIB, Bregman R. Nutritional profile of patients with chronic renal failure. *Journal of Renal Nutrition*, 2004 Apr;14(2):97-100.
11. Bellizzi V, Scalfi A, Terracciano V. Early changes in bioelectrical estimates of body composition in chronic kidney disease. *J Am Soc Nephrol* 17: 1481-1487,2006.
12. Navaneethan SD, Nigwekar S, Sengodan M, et al., Referral to nephrologists for chronic kidney disease care: is non-diabetic kidney disease ignored? *Nephron Clin Pract* 2007;106:c113-c118
13. Vegine PM, Fernandes AC, Torres MR, Silva MI, Avesani CM. Assessment of methods to identify protein-energy wasting in patients on hemodialysis. *J Bras Nefrol*. 2011 Mar;33(1):55-61.
14. Bellizzi V, Di Iorio BR, Brunori G, et al. Assessment of nutritional practice in Italian chronic kidney disease clinics: a questionnaire-based survey. *J Ren Nutr*. 2010 Mar;20(2):82-90
15. Chazot C, Laurent G, Charra B, et al. Malnutrition in long-term haemodialysis. *Nephrol Dial Transplant* 2001;16:61-9.
16. Stenvinkel P, Barany P, Chung SH, Lindholm B, Heimbürger O. A comparative analysis of nutritional parameters as predictors of outcome in male and female ESRD patients. *Nephrol Dial Transplant*. 2002 Jul;17(7):1266-74.
17. Guarnieri G, Antonione R, Biolo G: Mechanisms of malnutrition in uremia. *J Renal Nutr* 13(2):153-157, 2003.
18. Espinosa Cuevas MA, Navarrete Rodriguez G, Villeda Martinez ME, et al. Body fluid volume and nutritional status in hemodialysis: vector bioelectric impedance analysis. *Clin Nephrol*. 2010 Apr;73(4):300-8.
19. Kaysen GA, Johansen KL, Cheng SC. Trends and outcomes associated with serum albumin concentration among incident dialysis patients in the United States. *Journal of Renal Nutrition*, Vol 18, No 4 (July), 2008: pp 323-331
20. Campbell KL, Ash S, Davies PS, Bauer JD. Randomized controlled trial of nutritional counseling on body composition and diet

- tary intake in severe CKD. *American Journal of Kidney Diseases*, 2008 May;51(5):748-58. doi: 10.1053/j.ajkd.2007.12.015.
21. Fouque D, Pelletier S, Mafra D. Nutrition and chronic kidney disease. *Kidney International* (2011) 80, 348–357
 22. Singer J. Estimating sample size for continuous outcomes, comparing more than two parallel groups with unequal sizes. *Statistical in medicine*. 1997 Dec 30;16(24):2805-11.
 23. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31-41, 1976
 24. Lipschitz DA. Screening for nutritional status in the elderly. *Primary Care* 1994. 21(1): 55–67.
 25. Blackburn GL, Thornton PA. Nutritional assessment of the hospitalized patients. *Med Clin North Am*. 63;1103-115, 1979.
 26. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr* 1981, 34: 2540-5.
 27. World Health Organization (WHO). Waist Circumference and Waist–Hip Ratio - Report of a WHO Expert Consultation, Geneva, 8-11 December 2008.
 28. Blackburn GL, Bistrrian BR, Maini BS, Schlamm HT, Smith MF. Nutritional and metabolic assessment of the hospitalized patient. *JPEN J Parenter Enteral Nutr*. 1977;1(1):11-22.
 29. Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? *JPEN J Parenter Enteral Nutr* 1987;11(1):8-13.
 30. The Third Report of the National Cholesterol Education Program (NECP). Expert Panel on Detection. Evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;16;285(19):2486-97
 31. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care* 29:S4-S85, 2006 (suppl 1).
 32. Kirsztajn GM, Souza E, Romão Jr JE, Bastos MG, Meyer F, Andrada NC. Doença renal crônica (pré-terapia renal substitutiva): diagnóstico. Projeto Diretrizes, 2011.
 33. Di Napoli A, Valle S, d'Adamo G, et al. Predialysis Study Group of Lazio. Survey of determinants and effects of timing of referral to a nephrologist: the patient's point of view. *J Nephrol*. 2010 Sep-Oct;23(5):603-13.
 34. de Jager DJ, Voormolen N, Krediet RT, et al. Association between time of referral and survival in the first year of dialysis in diabetics and the elderly. *Nephrol Dial Transplant*. 2011 Feb;26(2):652-8. doi: 10.1093/ndt/gfq438.
 35. Fischer MJ, Ahya SN, Gordon EJ. Interventions to reduce late referrals to nephrologists. *Am J Nephrol*. 2011;33(1):60-9. doi: 10.1159/000322704.
 36. Kumar S, Jeganathan J, Amruthesh. Timing of nephrology referral: influence on mortality and morbidity in chronic kidney disease. *Nephrourol Mon*. 2012 Summer;4(3):578-81. doi: 10.5812/numonthly.2232.
 37. Hommel K, Madsen M, Kamper AL. The importance of early referral for the treatment of chronic kidney disease: a Danish nationwide cohort study. *BMC Nephrol*. 2012 Sep 10;13:108. doi: 10.1186/1471-2369-13-108.
 38. Barbosa-Silva MC, Barros AJ, Wang J, Heymsfield SB, Pierson RN. Bioelectrical impedance analysis: population reference values for phase angle by age and sex. *Am J Clin Nutr*. 2005; 82(1):49- 52.
 39. Oliveira CMC, Kubrusly M, Mota RS, Silva CA, Choukroun G, Oliveira VN. The phase angle and mass body cell as markers of nutritional status in hemodialysis patients. *Journal of Renal Nutrition*, 2010 Sep;20(5):314-20. doi: 10.1053/j.jrn.2010.01.008.
 40. ESPEN Guidelines. Kylea UG, Bosaeus I, De Lorenzoc AD, et al.. Bioelectrical impedance analysis—part II: utilization in clinical practice. *Clinical Nutrition* (2004) 23, 1430–1453
 41. Caravaca F, Martínez del Viejo C, Villa J, Martínez-Gallardo R, Ferreira F. Estimación del estado de hidratación mediante bioimpedancia espectroscópica multifrecuencia en la enfermedad renal crónica avanzada prediálisis. *Nefrología* 2011;31(5):537-44.
 42. Leal VO, Delgado AG, Leite M. Influence of renal function and diet on acid-base status in chronic kidney disease patients. *J Ren Nutr*. 2009 Mar;19(2):178-82. doi: 10.1053/j.jrn.2008.08.010.
 43. Kalantar-Zadeh K, Streja E, Kovesdy CP, et al. The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. *Mayo Clin Proc*. 2010 Nov;85(11):991-1001.
 44. Kramer H, Shoham D, McClure LA, et al. Association of waist circumference and body mass index with all-cause mortality in CKD: The REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. *Am J Kidney Dis*. 2011 Aug;58(2):177-85.
 45. Evans PD, McIntyre NJ, Fluck RJ, McIntyre CW, Taal MW. Anthropomorphic measurements that include central fat distribution are more closely related with key risk factors than BMI in CKD stage 3. *PLoS One*. 2012;7(4):e34699.
 46. Burton JO, Gray LJ, Webb DR, et al. Association of anthropometric obesity measures with chronic kidney disease risk in a non-diabetic patient population. *Nephrol Dial Transplant*. 2012 May;27(5):1860-6.
 47. Herget-Rosenthal S, Linden QC, Hollenbeck M. How does late nephrological co-management impact chronic kidney disease? – An observational study. *Int J Clin Pract*, December 2010, 64, 13, 1784–1792.
 48. Lawson JA, Lazarus R, Kelly JJ. Prevalence and prognostic significance of malnutrition in chronic renal insufficiency. *J Ren Nutr* 2001 Jan;11(1):16-22.
 49. Yaqoob MM. Acidosis and progression of chronic kidney disease Muhammad M. *Current Opinion in Nephrology and Hypertension* 2010, 19:489–492.
 50. Chiu YW, Kopple JD, Mehrotra R. Correction of metabolic acidosis to ameliorate wasting in chronic kidney disease: goals and strategies. *Semin Nephrol*. 2009 Jan;29(1):67-74.
 51. Chen SC, Hung CC, Kuo MC, et al. Association of dyslipidemia with renal outcomes in chronic kidney disease. *PLOS ONE*. 2013;8(2):E55643. DOI: 10.1371/JOURNAL.PONE.0055643.
 52. Curtis BM, Ravani P, Malberti F, et al. The short- and longterm impact of multidisciplinary clinics in addition to standard nephrology care on patient outcomes. *Nephrol Dial Transplant*. 2005; 20:147–154.
 53. Khan SS, Xue JL, Kazmi WH, et al. Does predialysis nephrology care influence patient survival after initiation of dialysis? *Kidney Int*. 2005;67:1038–1046.
 54. Filipowicz R, Beddhu S. Optimal nutrition for predialysis chronic kidney disease. *Adv Chronic Kidney Dis*. 2013 Mar;20(2):175-80. doi: 10.1053/j.ackd.2012.12.007.