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Clinical and nutritional factors associated with dialysis initiation and mortality in chronic kidney disease

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Abstract

Background: Chronic kidney disease is worldwide recognized as a public health problem due to high rates of morbidity and mortality. At the end stage of the disease, which the glomerular filtration rate is equal or less than 15 ml/min/1.73 m^2, dialysis initiation is usually indicated. In the absence of a consensus on the best time of beginning, the aim of this study was to identify clinical and nutritional factors associated with clinical outcomes with the start of dialysis and death.

Methods: In a prospective cohort of 82 patients, clinical (underlying renal disease, renal survival time, systolic and diastolic blood pressure, estimated glomerular filtration rate) and nutritional data (protein intake, anthropometry, bioelectrical impedance test, and strength handgrip) were collected. We used mean and standard deviation or median and association of the variables with the outcome entry into dialysis or death, and a Cox regression model was applied. Statistical significance was $p < 0.05$.

Results: Fifty-eight patients were included in group 1—G1 (without dialysis)—and 24 patients in group 2—G2 (dialysis). The groups were different in blood urea nitrogen ($p = <0.001$), serum creatinine ($p = 0.003$), estimated glomerular filtration rate ($p = 0.002$), and serum phosphorus ($p = 0.002$). After multivariate analysis, only serum albumin (HR 0.342, $p = 0.004$) and glomerular filtration rate (HR 0.001, $p = 0.001$) were associated with entry into dialysis and death.

Conclusions: We concluded that lower levels of serum albumin and glomerular filtration rate values are associated with entry into dialysis or death.

Keywords: Chronic kidney disease, Albumin, Dialysis

Background

Chronic kidney disease (CKD) is defined as the presence of functional or structural abnormalities in the kidneys for at least 3 months, with damaging implications for health [1]. It is diagnosed by a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 and recognized worldwide as a serious public health problem, associated with high morbidity and mortality [1, 2].

Individuals achieving the final stage of CKD or with an estimated glomerular filtration rate (eGFR) equal to 15 ml/min/1.73 m^2 is increasing. At this stage, renal replacement therapy (RRT) is usually indicated, but a consensus about the best time of initiation and the best method to be applied does not exist [3].

The number of dialysis patients exceeds 1.4 million in the world, with an annual increase of 8% [4]. Recent epidemiological data shows that nephrology accompaniment in pre-dialysis is essential for better treatment planning, maintenance of clinical and nutritional status, and reduce mortality in this population [3].

Until the 80s, the beginning of dialysis was indicated only when patients had serious uremic complications. After this period, several observational studies compared outcomes in patients beginning dialysis with different levels of GFR. There were no benefits with the early onset of RRT, and dialysis indication to patients with lower

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levels of GFR was not associated with high morbidity and mortality. These studies have shown that dialysis indication based on clinical symptoms, such as azotemia, hyperphosphatemia, hyperkalemia, lack of appetite, and weight loss, in addition to GFR levels, is most suitable and is associated with better clinical outcomes [1–3].

Protein energy wasting has been highlighted in pre-dialysis and can be caused by factors not only related to starvation as well as those inherent to kidney disease, such as anorexia, metabolic acidosis, electrolyte changes, biochemical changes, increased circulation inflammatory cytokines, and comorbidities associated with CKD, such as infection, diabetes, and cardiovascular disease [3, 4]. Dietary and nutritional factors, such as increased protein intake, increased acids intake, and higher body mass index, associated with metabolic syndrome, are related to greater progression of chronic renal disease [1, 5].

The knowledge of clinical and dietary factors associated with progression of CKD are essential for maintenance of interventions required to delay initiation of dialysis. The aim of the study was to identify clinical and nutritional factors related to entry into dialysis and occurrence of death in CKD patients in pre-dialysis stage.

Methods

Patients and methods

This is a prospective cohort study with patients aged over 18 treated in pre-dialysis ambulatory, in Dialysis Unit of the Botucatu School of Medicine.

Demographic (age and sex) and clinical data (baseline kidney disease, diagnosis of *diabetes mellitus* (DM) and blood pressure), corresponding to follow-up beginning, were obtained from medical records and records of the Dialysis Unit.

Patients were divided into two groups: group 1 (G1): patients who did not start dialysis and remained in ambulatory treatment and group 2 (G2): patients with dialysis indication or patients that died during follow-up. The follow-up time was 1 to 13 months, from the time of inclusion.

Demographic and clinical assessments

All patients were evaluated monthly according to pre-dialysis ambulatory routine at the Dialysis Unit. Demographic (age, sex, and stage of CKD) and clinical data (underlying renal disease, renal survival time, systolic and diastolic blood pressure, eGFR [6]) were collected from medical records.

Nutritional assessment

Nutritional status was assessed by protein intake quantification, anthropometry, bioelectrical impedance test (BIA), and handgrip strength.

Protein intake was estimated by protein equivalent of nitrogen appearance (PNA) [7, 8]. Anthropometric measurements were performed during outpatient nutritional care, including body weight (kg), height (cm), triciptal subcutaneous skinfold (TSF) (mm), skinbicipital (TSB) (mm), subscapularis skinfold (SEF) (mm), and suprailiac skinfolds (SIF) (mm), and arm muscular circumference (AC) (cm). Body mass index (BMI) (kg/m^2) and middle arm muscle circumference (MAMC) (cm) [7] were calculated according to anthropometric formulas.

Monofrequency BIA was performed by Biodynamics brand Model 450 and registered values: resistance (ohm), reactance (ohm), phase angle (Å) (°), total body water (l), intracellular water (l), and extracellular (l). The patients were motionless during the assessment. Volume status was considered by the equation: total body water determined by BIA minus body water obtained by Watson's formula [9].

Handgrip strength was evaluated by hydraulic dynamometer Jamar®. The patients were instructed to sit with adduced shoulder, elbow flexed to 90°, and neutral forearm. The avaliators asked the patients to make the appliance holding for 3 s with the rest periods of 30 s between trials on the same arm. The highest value was considered.

Laboratory measures

The laboratory measurements of routine medical consultation were considered at the time of inclusion of patient.

Blood samples were determined from measurements of the biochemical markers: calcium (mg/dl), phosphorus (mg/dl), albumin (g/dl), total cholesterol (mg/dl), triglycerides (mg/dl), creatinine (mg/dl), urea (mg/dl), and glucose (mg/dl). Inflammatory and hematological markers such as serum C-reactive protein (mg/dl) (CRP) and hemoglobin concentration (g/dl) were also collected.

Statistical analysis

Data were expressed as mean ± standard deviation, median (interquartile range), or percentage, as appropriate. Paired t test and the Mann-Whitney test, according to normality distribution of the variables, were used to compare groups G1 and G2. Frequency analysis used the chi-square test for categorical variables and Fisher's exact test for not categorical variables.

A multiple logistic regression model with stepwise procedure was used to identify, among the studied variables, independent of dialysis predictors. Initially, univariate models were generated using the chi-square test for categorical variables and logistic regression for continuous variables, and variable that showed a lower than 20% of statistical probability with random association with outcomes was selected for the multivariate model.

A Cox regression model was used to assess the independent predictors of the composite outcome of occurrence (dialysis or death) and the variables with statistical probability lower than 20% of association random with the outcome of univariate analysis were included in Cox regression analysis, adjusted for age, sex, PCR and the presence of diabetes.

The criterion for statistical significance for all analysis corresponded to a value of $p < 0.05$.

Results

Eighty-two patients were evaluated in the period of 1–13 months.

Tables 1 and 2 describe the baseline characteristics of the study population and differences between groups. G1 showed higher eGFR ($p = 0.002$), lower serum urea ($p = <0.001$), lower serum creatinine ($p = 0.003$), and lower serum phosphorus ($p = 0.002$) compared to G2.

Table 3 shows mean values of anthropometric parameters and handgrip strength. Differences between group variables were not found.

BIA variables and hydration status also did not differ between groups, according to Table 4.

Table 5 reports association of clinical, laboratory, and nutritional variables and the occurrence of dialysis and/or death. According to the Cox regression model, only eGFR and serum albumin were associated independently and negatively to dialysis initiation and death.

Table 1 Baseline clinical characteristics of all patients (82) included in the study

Variables	Prevalence	Mean and standard deviation
Age (years)		59.8 ± 14.9
Men/women (%)	53/47	
Stage CKD (%)		
Stages 1–3	7.3	
Stages 4–5	92.7	
Primary cause (%)		
Diabetes mellitus	40	
Arterial hypertension	36	
Polycystic kidneys	4.8	
Renal survival time (months)		6.7 ± 3.9
Systolic blood pressure (mmHg)		146.9 ± 23.1
Diastolic blood pressure (mmHg)		83.2 ± 15.4
BUN (mg/dl)		137.5 ± 42.5
Serum creatinine (mg/dl)		5.1 ± 1.8
eGFR (ml/min)		12.1 ± 6.2
Albumin (g/dl)		4.0 ± 0.5
Proteinuria (g/day)		3.0 ± 4.1
CRP (mg/dl)		1.3 ± 1.3
PNA (g/kg/day)		0.73 ± 0.2

CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *CRP* C-reactive protein, *PNA* protein equivalent of nitrogen appearance

Table 2 Differences in baseline characteristics among patients with progression (G2) or not (G1) to dialysis or death

Variables	G1	G2	*p*
Age (years)	58.8 ± 13.6	62.2 ± 17.9	0.342
Men/Women	31/27	13/11	0.854
Stage CKD (%)			
Stages 1–3	6 (10.3%)	0	0.173
Stages 4–5	52 (89.7%)	24 (100%)	
Primary cause (%)			
Diabetes mellitus	23 (39.6%)	10 (41.6%)	0.937
Arterial hypertension	22 (37.9%)	8 (33.3%)	0.888
Polycystic kidneys	2 (3.4%)	2 (8.3%)	0.577
Renal survival time (months)	7.1 ± 3.8	5.8 ± 3.9	0.241
Systolic blood pressure (mmHg)	145.4 ± 21.5	151.2 ± 27.2	0.343
Diastolic blood pressure (mmHg)	83.1 ± 16.0	83.6 ± 14.0	0.795
BUN (mg/dl)	125.3 ± 35.0	166.9 ± 45.4	<0.001
Serum creatinine (mg/dl)	4.6 ± 1.3	6.3 ± 2.4	0.003
eGFR (ml/min)	13.1 ± 6.3	9.5 ± 5.4	0.002
Phosphurus (mg/dl)	4.9 ± 0.9	5.8 ± 1.1	0.002
Albumin (g/dl)	4.0 ± 0.4	3.8 ± 0.7	0.156
Proteinuria (g/day)	3.0 ± 4.3	3.2 ± 3.7	0.621
CRP (mg/dl)	1.2 ± 1.2	1.4 ± 1.4	0.753
PNA (g/kg/day)	0.72 ± 0.3	0.75 ± 0.3	0.634

CKD Chronic kidney disease, *eGFR* estimated glomerular filtration rate, *CRP* C-reactive protein, *PNA* Protein equivalent of nitrogen appearance, *G1* group 1, *G2* group 2

Discussion

Lower levels of albumin and decreased glomerular filtration rates were associated with higher risk of dialysis initiation and death.

There is no consensus indicating better tools for TRS indication actually, so this study intended to identify nutritional and clinical factors related to entry into dialysis and occurrence of death. We found that serum albumin and renal function, as measured by eGFR, were related to these outcomes, independent of the inflammatory status.

Due to albumin nephro-protective role through several pathways, such as prevention of oxidative damage, renal vasodilation, and colloidal osmotic pressure, hypoalbuminemia (serum values below 3.5 mg/dl) is associated with unfavorable clinical outcomes and independent factor of progression of CKD [6].

Decreased values of serum albumin were associated with rapid decline in renal function and mortality in CKD patients in pre-dialysis, playing as a strong

Table 3 Anthropometric variables and handgrip strength among patients with progression (G2) or not (G1) to dialysis or death

Anthropometric parameters	Total	G1	G2	*p*
BMI (kg/m^2)	26.8 ± 7.9	25.4 ± 8.1	27.4 ± 7.9	0.321
AMC (cm)	26.0 ± 4.1	26.5 ± 4.7	25.8 ± 3.9	0.344
Handgrip (kg)	23.3 ± 12.4	20 (14.5–28.7)	20 (14.5–28.7)	0.647

BMI body mass index, *AMC* arm muscle circumference, *G1* group 1, *G2* group 2

indicator of wasting [8]. In this study, although BMI median values were classified as healthy for this population, lower serum albumin was predictor of adverse outcomes, regardless of PCR values, a common marker in the clinical practice of the inflammatory state.

Using subjective and objective assessment methods, such as medical history, dietary intake, lab tests, body composition with BIA, and skinfold measurements and, most recently, handgrip strength manual, has been recommended [10, 11].

Nutritional assessment and evaluation of muscle function enable to diagnose nutritional and functional impairments and, consequently, allows early interventions to avoid unfavorable outcomes, such as decreased quality of life, sarcopenia, and early death [12, 13].

In addition to serum albumin, eGFR was associated to entry into dialysis and occurrence of death. These factors play an important role in renal impairment and indication of dialysis [3, 11].

Study with 447 children and adolescents with GFR 30 to 90 ml/min/1.73^2, aimed to identify factors of progression of kidney disease through repeated measurements of GFR. After 1 year of follow-up, it was found that hypoalbuminemia was responsible for reducing the input dialysis time [14].

Renal function decline is also related to clinical factors such as blood pressure and poor glycemic control, proteinuria, volemic state, and others [15]. Although no significant association were find between body volume and outcomes, a recent study described practical aspects of volume control in chronic kidney population, and fluid overload in pre-dialysis patients was associated with high mortality rates from cardiovascular causes [16].

Table 4 Electrical bioimpedance variables and hydration status among patients with progression (G2) or not (G1) to dialysis or death

Bioimpedance data	Total	G1	G2	*p*
Phase angle (°)	5.9 ± 1.1	5.6 ± 1.2	6.0 ± 1.1	0.248
Extracellular water (l)	18.7 ± 5.4	17.4 (14.6–2.6)	18.7 (15.5–21.3)	0.939
Intracellular water (l)	20.6 ± 6.8	20.7 ± 8.4	20.5 ± 6.1	0.915
Total body water (l)	38.5 ± 9.6	37.6 ± 9.3	38.8 ± 9.7	0.609
Estimated volume by Watson (l)	36.4 ± 7.8	35.1 ± 7.0	36.9 ± 8.2	0.338
Hydration status (l)	2.0 ± 3.5	1.5 (−0.2–6.1)	1.4 (0.0–3.9)	0.895

G1 group 1, *G2* group 2

Table 5 Associations between clinical, laboratory, and nutritional variables and the occurrence of entrance on dialysis and death, according to the Cox regression model

Variables	*p* (univariate)	*p* (multivariate)	HR	95% CI
Albumin (g/dl)	0.016	0.004	0.342	0.163–0.716
Phosphorus (mg/dl)	0.000	0.111		
eGFR (ml/min)	0.000	0.001	0.001	0.585–0.865
Phase angle (°)	0.059	0.440		
CRP (mg/dl)	0.052	0.498		

eGFR estimated glomerular filtration rate, *CRP* C-reactive protein

There is no consensus about renal function obtained by eGFR, or based on serum creatinine, for targeting start of dialysis. However, the best RRT indication is based on assessment and clinical symptoms [11].

Conclusion

Chronic kidney disease progression can be influenced by modifiable factors, such as wasting and hypoalbuminemia, and non-modifiable factors, such as the disease per se and impaired renal function.

The results of this study showed that decreased values of serum albumin and renal function, as assessed by decreased eGFR, are factors that influence the start in dialysis and death in patients with end-stage CKD.

Abbreviations

Å: Phase angle; AMC: Arm muscle circumference; BIA: Bioelectrical impedance test; BMI: Body mass index; BSF: Biciptal subcutaneous skinfold; BUN: Blood urea nitrogen; CKD: Chronic kidney disease; CRP: C-reative protein; DM: *Diabetes mellitus*; eGFR: Estimated glomerular filtration rate; G1: Group 1; G2: Group 2; GFR: Glomerular filtration rate; MAMC: Middle arm muscle circumference; PNA: Protein equivalent of nitrogen appearance; RRT: Renal replacement terapy; SEF: Subescapular skinfold; SIF: Suprailiac skinfold; TSF: Triciptal subcutaneous skinfold

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the Botucatu Medical University repository. The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

MCO contributed to conception and design of the study, acquisition and interpretation of the data, and drafting the article. TMP contributed to the conception and design of the study and the acquisition of the data. CRG and LCM contributed to the analysis and interpretation of the data. ALB, MNBB, and FCV contributed to conception and design of the study in drafting the article, revising it critically for important intellectual content and final approval of the version. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethic Committee of Botucatu Medical School, protocol number (37744214.1.000.5411). All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Consent for publication

This manuscript does not contain any individual's person's data in any form (including individual details, images, or videos), has not been previously published, and is not under consideration elsewhere.

Competing interests

The authors declare that they have no competing interests.

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