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Screening for Chronic Kidney Disease in Relatives of Hemodialysis Patients

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Abstract
Objective: To estimate the prevalence and socioeconomic characteristics of Chronic Kidney Disease (CKD) in first and second-degree relatives of patients on hemodialysis Method: A questionnaire was applied on socioeconomic conditions, lifestyle, and personal pathological background. The formula of CKD-EPI and/or proteinuria greater than or equal to 1+ was used to characterize CKD. Analysis using the logistic regression model. Results: 408 individuals were evaluated and 12% had CKD. 6.61% had a glomerular filtration rate (GFR) ≤ 60 mL / min / 1.73 m2 and 5.39% proteinuria in the urine. The variables associated with the presence of CKD were age (OR = 1,60; 95% IC = 1,31-1,96), PAS (OR: 1,69; 95% IC: 1,24-2,28), PAD (OR: 1,52; 95% IC: 1,18-1,96) and blood glucose (OR: 2,03; 95% IC: 1,38-2,99). Conclusion: It is necessary to implement routines for systematic evaluation that prevent or delay the loss of renal function, in addition to measures that improve the pre-dialysis clinical conditions of this population.
Keywords: Chronic kidney disease, Family, Glomerular filtration rate.
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1.1 INTRODUCTION

With the aging of the population and the advent of cardiovascular diseases, many authors have considered chronic kidney disease (CKD) as the "millennium epidemic". Even in developed countries, CKD is a serious global public health problem due to its increasing morbidity and mortality, incidence and prevalence, as well as high economic costs to health systems (Wen et al., 2014; Saran et al., 2017).

As a nearly asymptomatic disease in its early stages, the actual prevalence of CKD is still unknown, even in countries like Japan and the United States (USA) that have a robust database on the pathology (Mills et al., 2015). According to a meta-analysis carried out with approximately 100 studies, it is estimated that the prevalence is

around 15% (Hill et al., 2016). In Brazil, few studies have addressed the prevalence of CKD, especially if we consider those that used the criteria for defining CKD proposed by Kidney Disease Improving Global Outcomes (KDIGO). Data from a systematic review that used studies with different methodologies for the diagnosis of CKD, including self-referral, found prevalences in Brazil that ranged from 1.43% to 27.20% (Marinho, Penha, Silva & Galvão, 2017).

Alarmed by the economic and health impact of CKD, many countries have turned their efforts to strategies that allow early diagnosis. Early diagnosis provides delayed decline in renal function, decreased need and length of hospital stay, reduces the initial costs of dialysis treatment, increases the likelihood of a preemptive transplant, improves the patient's clinical conditions before dialysis treatment, ensures permanent vascular access before dialysis, and decreases morbidity-mortality (Cooper et al., 2010; Lopez-Vargas, Tong, Sureshkumar, Johnson & Craig, 2013).

Most studies are aimed at patients with cardiovascular diseases, diabetes, and hypertension, groups that are known to be at risk for CKD, however, relatives of patients with CKD also belong to the risk group, even though they are not so studied (Obrador, Mahdavi-Mazdeh & Collins, 2011).

Despite the scarcity, some studies have already evaluated relatives of patients with CKD and demonstrated a high prevalence of the pathology (Wei et al., 2012), such as the 49.3% found by Jurkovitz et al (Jurkovitz, Franch, Shoham, Bellenger & McClellan, 2002). Thus, it is justified that there is not only an active search for these individuals but also proposals for their early care.

Therefore, this study aimed to estimate the prevalence and socioeconomic characteristics of CKD in first and second-degree relatives of patients on hemodialysis.

2.1 METHODS

This is a cross-sectional study carried out with first and second-degree relatives of patients with CKD undergoing hemodialysis in three reference services in the municipalities of Açailândia and Imperatriz, southern Maranhão. Data were collected from September 2017 to March 2018 by direct invitation through hemodialysis patients or by publicizing the study in each clinic.

This study occurred in two stages. In the first stage, CKD screening was performed in first and second-degree relatives of patients on hemodialysis, and individuals diagnosed as having CKD were invited to return to participate in a reassessment of their clinical status after three months.

To calculate the sample size, it was used the STATA 13.0 software (Stata Corp College Station, Texas, USA) and the significance level (α) of 5%, test power of 80%, a tolerable error of 4 %, plus 10% of possible losses in first and second-degree relatives of patients undergoing hemodialysis with an estimated prevalence of 595 people per million inhabitants in Brazil. For this study, a convenience sample was used, totaling 408 respondents.

Inclusion criteria were age ≥ 18 years, both sexes, and first or second-degree relatives of patients with CKD who were on hemodialysis for more than three months.

An adapted questionnaire from the PREVINA-SE (Kirsztajn & Bastos, 2015) study and the Screening for Occult Renal Disease (SCORED) study, which has already been validated for Brazil, was applied (Magacho et al., 2012) Data on socioeconomic, anthropometric, and clinical aspects, life habits, and CKD personal and family history were collected (Malachias et al., 2016).

Subsequently, blood pressure, height, and weight were measured. The blood was collected after a minimum fasting of 10 hours to measure blood glucose, urea, and creatinine. Participants were instructed to bring a sample of the first-morning urine, which was not collected in case of infection, fever, or menstrual period. CKD was defined with an estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m^2 and/or the presence of a protein greater than 1 + in the urine sample (Romão, 2004). The following formula was used: CKD-EPI [(eGFR= 141 x min (Cr/κ, 1)α x max (Cr/κ, 1)-1,209 x 0.993age x 1,018 (if woman) x 1,159 (if Afro-American)).

In the second phase of the study, individuals with CKD repeated urea and creatinine when eGFR ≤ 60 mL/min /1.73 m2 or 24-hour proteinuria for patients with ≥ 1 + protein in the first-morning urine sample.

As mentioned, the data were analyzed using the STATA 14.0 software (Stata Corp., College Station, Texas, USA). Descriptive statistics included the calculation of absolute, relative frequencies, mean, and standard deviation. The association between the explanatory variable and the response variable was performed using the Chi-square test. Logistic regression analysis was also performed to verify the association of events, the odds ratio (Odds ratio, OR) was used. The variables that presented $p \leq 0.20$ were considered for the multivariate analysis employing multiple logistic regression, considering the hierarchy. Variables with $p \leq 0.10$ were maintained in the hierarchical model for the control of residual confusion of variables. The 95% confidence intervals (95% CI) and level of statistical significance ($p \leq 0.05$) were considered.

This study was approved by the Research Ethics Committee of CEUMA University (nº 1.055.539). All participants signed the Free and Informed Consent Form (ICF).

3.1 RESULTS

408 relatives of chronic kidney patients undergoing hemodialysis were studied, with a mean age of 39 years (± 14.22), of whom 259 (63.5%) were women, 224 children (54.9%), and 128 (31.3 %) brothers. Regarding race, the majority referred to themselves as brown (68.87%). Regarding family income, 167 (40.9%) belonged to class D / E and 153 (37.5%) were illiterate / incomplete elementary II. The diagnosis of CKD was made in 49 (12%) participants, of which 27 (55.10%) had GFR ≤ 60 ml/min /1.72 m2 and 22 (44.89%) had proteinuria ≥ 1 + on examination morning urine (Table 1).

The practice of physical activity and smoking were also questioned. Of the participants, 146 (35.78%) reported practicing some physical activity, of which 15 (30.61%) were diagnosed with CKD. 38 (9.31%) individuals reported smoking, of these three (6.12%) had CKD. When the chi-square test was applied, there was an association between CKD and kinship ($p < 0.001$) and age ($p < 0.001$) (Table 1).

Regarding previous knowledge about CKD and hemodialysis, 280 (68.6%) had no knowledge about CKD, and 214 (52.45%) did not know about hemodialysis. The association of both knowledge of kidney disease and HD with the presence of CKD was tested using the chi-square test, with no significant association ($p = 0.65$ and $p = 0.19$, respectively) (Table 2).

Regarding diabetes and hypertension, all responses were self-reported. Of the 359 participants without kidney disease, 20 (5.57%) reported diabetes and only 15 (4.18%) were being treated. In the group diagnosed with CKD, 07 (14.29%) participants declared themselves diabetic and under treatment. Regarding hypertension, 57 (15.88%) claimed to be hypertensive, of which 49 (13.65%) were being treated. In the CKD group, 15 (30.61%) reported arterial hypertension, of whom 13 (26.53%) underwent treatment (Table 2).

Systolic Blood Pressure (SBP) was found to be above normal values (> 140 mmHg) in 50 (12.25%) participants, of whom 34 (8.33%) previously declared to be hypertensive. The mean SBP was 119 mmHg (± 16.22). Regarding the Diastolic Blood Pressure (DBP), 81 (19.85%) were above normal (> 90 mmHg), of 39 (9.55%) self-declared hypertensive. The mean DBP was 79.64 mmHg (± 10, 2). Among participants diagnosed with CKD, the mean SBP was 127 mmHg (± 22.31) and the DBP was 83 mmHg (± 12, 2) (Table 3).

There were 72 (17.6%) people with blood glucose between 100-126 mg/dl, of whom six (1.47%) were already diabetic, 39 (9.56%) had blood glucose levels above 126.0 mg/dl and 20 (4.90%) were diagnosed with diabetes during the study. Among self-reported diabetics, 19 (48.71%) had higher levels considered above clinical control by the Brazilian Diabetes Society (SBD) (> 130.0 mg/dl). The average blood glucose level was 95.58 mg/dl (± 43.15) in participants without CKD and 109.6 mg/dl (± 34.5) in patients diagnosed with CKD (Table 3).

In the group without CKD, 134 (33.17%) were overweight and 98 (24.26%) were obese. The average body mass index (BMI) in participants without CKD was 26.6 kg/m2 (± 5.1). In the CKD group, the average was 28.0 kg/m2 (± 4.38) (Table 3).

There was an association with the variable age (OR: 1.60; 95% CI: 1.31-1.96; $p < 0.01$), SBP (OR: 1.69; 95% CI: 1.24-2, 28; $p < 0.001$), DBP (OR: 1.52; 95% CI: 1.18-1.96; $p < 0.001$) and blood sugar level (OR: 2.03; 95% CI: 1.38-2, 99, $p < 0.001$) and CKD (Table 4).

CKD was classified into five stages according to the criteria adopted by K/DOQI (2002). It was found 21 (42.85%) in stage 3A and 10.20% in 3B (Table 5).

After three months, participants with CKD were reassessed, except for eight (16.32%) individuals due to refusal or change of address (city), as shown in Table 6.

4.1 DISCUSSION

The prevalence of CKD found in the first phase of this study was comparable to most of those that have already been executed, even with the average age (39 years) lower than those performed using the KEEP profile, such as KEEP Japan, in which the average age was 59.7 years, with age being a well-established risk factor for CKD (Takahashi, Okada & Yanai, 2010; Obrador et al., 2010; Brown et al., 2003). After the reassessment in three months, we had a 38.75% decrease from the initial value. As in the study by Afolabi, Abioye-Kuteyi, Arogundade & Bello (2009) the group diagnosed with CKD by the proteinuria criterion was the one that showed the greatest return to normal parameters. This fact corroborates the need for reassessment of these individuals and questions the real prevalence of CKD, especially in studies that used proteinuria as the only criterion and without reassessment. When compared with studies carried out in Brazil, a higher prevalence was observed, such as that found by Passos et al. (2003). According to our knowledge, only Bastos et al. (2009) reassessed the interviewees after three months, obtaining a smaller decrease in prevalence (from 12.4% to 9.6%). However, a minority of research carried out in Brazil adopts both proteinuria and GFR and a reassessment in three months for the diagnosis of CKD, as carried out in this study.

When individuals were stratified according to the degree of renal dysfunction, values similar to those reported by most international studies were obtained, with a predominance of stage 3, as occurred in the American KEEP study (stage 1: 21%; stage 2: 19%; stage 3: 33% and stage 5: 3%) (Brown et al., 2003) This

allows intervening in the natural evolution of the disease and can preserve kidney function if this diagnosis is made early. In Brazil, few studies have stratified participants, among which the one with the largest number of individuals was ELSA-Brasil, finding 1.5% in stage 1, 2.6% in stage 2, 4.0% in stage 3, 0.6% in stage 3b, 0.2% in stage 4 and 0.1% in stage 5 (Barreto et al., 2016). As in the present study, there was no predominance of participants in stage 3 of CKD.

Although there is no justification in the literature, it is observed that there is a higher prevalence of CKD in women (Obrador et al., 2010; Lima, Kesrouani, Gomes, Cruz & Mastroianni-Kirsztajn, 2012), including in the studies conducted by Freedman, Soucie & McClellan (1997) and Wei et al. (2012) who evaluated relatives of patients with kidney disease. In this study, even without obtaining statistical significance between the sexes, it was observed that the majority of participants with CKD were women, especially in more advanced stages, but it was not possible to determine a cause/effect relationship.

Risk factors already established, such as hypertension and diabetes, behaved similarly to worldwide studies, demonstrating that relatives of kidney patients have several associated risk factors. In the NHANES studies 1988-1994 and 1999-2002 and in the KEEP studies Mexico, Japan, and the USA, this association was well established (Takahashi, Okada & Yanai, 2010; Obrador et al., 2010; Brown et al., 2003; NHANES 2013-2014, 2013). In the present study, the values found for Systemic Arterial Hypertension (46.93%) and diabetes (26.52%) were similar to those found by Bastos et al. (2009) corroborating its importance for CKD. These pathologies have been associated with CKD. It seems reasonable to think that families that have individuals who have lost kidney function due to these pathologies are more likely to develop CKD.

Other “new” risk factors such as obesity and smoking have been associated with CKD, but it was not possible to establish this association, probably due to the low percentage of obese and smokers in this sample (25.92 and 3.7% respectively) which are in opposition to what was reported in the KEEP USA (44 and 45%, respectively) (Passos et al., 2003). The values in the present study were closer to those reported in a survey conducted in Egypt that also did not observe any association of these factors with CKD (Gouda et al., 2011). On the other hand, the regular practice of physical exercise has also not been shown to have a protective effect on CKD in this sample.

CKD has a worldwide distribution; however, it is important to remember that in countries with an economic profile similar to Brazil, the lower economic and educational classes are the most affected, either due to lack of access to the health or information system (Brown et al., 2003). In the present study, most participants diagnosed with CKD had lower levels of education (63.26%) and social class (75.51%). When asked about the knowledge that this population had about CKD and hemodialysis and there is a high prevalence of non-knowledge about CKD (68.62%) and hemodialysis (52.45%) in the same way as the results found by Khalil and Abdalrahim (2014) in which about half of the study participants had no information about the pathology. Even though it is not possible to demonstrate statistical significance for these variables, it is believed that the greater clarification about CKD, can contribute positively so that a greater number of relatives of chronic renal patients seek to assess their renal health early.

5.1 CONCLUSION

It is clear that there is still a long way to go before the real prevalence of CKD is precisely known, especially in Brazil.

The methodology used in this study was based on the use of the criteria established for the correct diagnosis and staging of CKD, accepted internationally, with results similar to those already published in the literature, confirming the need for public health measures aimed at the early diagnosis of CKD in Brazil.

The relatives of patients with CKD are at risk, and unlike hypertensive and diabetic patients who have specific health policies, they go unnoticed even in hemodialysis clinics, where they often take their relatives for dialysis. There are findings of several participants with relevant renal dysfunction, including stage 5, which justifies the implementation of simple routines, especially in hemodialysis clinics, to identify and clinically measure this population early.

CKD is a silent pathology for patients and doctors. It has high costs for the health system and the quality of life of the patient and his family. "Any" gain in time without dialysis justifies the creation of simple routines to identify CKD early.

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Table 1. Sociodemographic, epidemiological and clinical characteristics of 408 relatives diagnosed or not with chronic kidney disease.

Variable	eGFR-EPI + Proteinuria		p-value
	With CKD n (%)	Without CKD n (%)	
Relationship			0.01
Brother / sister	12 (24.49)	116 (32.31)	
Father / mother	12 (24.49)	27 (7.52)	
Son / daughter	21 (42.86)	203(56.55)	
Grandchildren	4 (8.16)	12 (3.34)	
Cousins	0 (0.00)	1 (0.27)	
Gender			0.54
Female	33 (67.35)	226 (62.95)	
Male	16(32.65)	133 (37.05)	
Race			0.48
Brown	36 (73.47)	245 (68.25)	
White	8 (16.33)	53 (14.76)	
Black	5 (10.20)	61 (16.99)	
Age group			< 0.01
18-29 years	8 (16.33)	109 (30.36)	
30-39 years	14 (28.57)	109 (30.36)	
40-49 years	3 (6.12)	69 (19.22)	
50-59 years	6 (12.24)	45 (12.53)	
60-69 years	9 (18.37)	20 (5.57)	
> 70 years	9 (18.37)	7 (1.95)	
Social-economic class			0.58
A	0 (0.00)	1 (0.28)	
B1	1 (2.04)	4 (1.11)	
B2	0 (0.00)	16 (4.46)	
C1	9 (18.37)	72 (20.06)	
C2	15 (30.61)	123 (34.26)	
D/E	24 (48.98)	143 (39.83)	
Education level			0.24
Illiterate / incomplete elementary II	24 (48.98)	129 (35.93)	
Complete elementary II / incomplete high-school	7 (14.29)	67 (18.66)	
Complete high-school / incomplete higher education	17 (34.69)	138 (38.44)	
Complete higher education	1 (2.04)	25 (6.96)	
Practice of physical exercise			0.42
Yes	15(30.61)	131(36.49)	
No	34 (69.39)	228 (63.51)	
Smoking			0.41
Yes	3 (6.12)	35 (9.75)	
No	46 (93.88)	324(90.25)	

Table 2. Results on knowledge of CKD and hemodialysis and pathological antecedents (hypertension and diabetes) in patients with and without chronic kidney disease.

Variable	eGFR-EPI + Proteinuria		p-value
	With CKD n (%)	Without CKD n (%)	
Knows CKD			0.65
Yes	14 (28.57)	114 (31.75)	
No	35 (71.43)	245 (68.25)	
Knows Hemodialysis			0.19
Yes	19 (38.78)	175 (48.75)	
No	30 (61.22)	184 (51.25)	
Diabetes			0.03
Yes	7 (14.29)	20 (5.57)	
No	38 (77.55)	322 (89.69)	
Does not know	4 (8.16)	17 (4.74)	
Treats diabetes			0.03
Yes	7 (14.29)	15 (4.18)	
No	42 (85.71)	344 (95.82)	
Hypertension			0.04
Yes	15 (30.61)	57 (15.88)	
No	33 (67.35)	292 (81.34)	
Does not know	1 (2.04)	10 (2.79)	
Treats hypertension			0.01
Yes	13 (26.53)	49 (13.65)	
No	36 (73.47)	310 (86.35)	

Table 4. Logistic regression of variables commonly associated with CKD: age, kinship, diabetes, blood glucose, hypertension, SBP, DBP, and whether knows hemodialysis.

Variable	Odds-ratio (OR)	Confidence interval	P-value
Age	1.60	0.00 – 1.31	< 0.001
Kinship	1.03	0.75 – 1.41	0.82
Diabetes	1.64	0.04 – 1.01	< 0.05
Hypertension	1.62	0.95 – 2.78	< 0.05
SBP	1.69	1.24 – 2.28	<0.001
DBP	1.52	1.18 – 1.96	<0.001
Glycemia	2.03	1.38 – 2.99	<0.001
Knows HD	0.66	0.36 – 1.22	0.1

SBP: systolic blood pressure; DBP: diastolic blood pressure; CKD: chronic kidney disease; HD: hemodialysis

Table 5. Characteristics of socioeconomic variables of participants diagnosed with chronic kidney disease.

Variable	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 5
n = 49	11 (22.44)	11 (22.44)	21 (42.85)	05 (10.20)	01 (2.04)
Average age	31.72	37.45	60.14	64.40	49.00
Kinship					
Brothers	-	03 (27.27)	01 (4.76)	01 (20.00)	01 (100.00)
Parents	-	01 (9.09)	7 (33.33)	03 (60.00)	-
Children	11 (100.00)	05 (45.45)	8 (38.10)	-	-
Grandchildren	-	02 (18.18)	4 (19.05)	01 (20.00)	-
Cousins	-	-	01 (4.76)	-	-
Gender					
Male	03 (27.27)	06 (54.54)	05 (23.81)	02 (40.00)	-
Female	08 (72.72)	05 (45.45)	16 (76.19)	03 (60.00)	01 (100.00)
Race					
Brown	07 (63.63)	09 (81.81)	16 (76.19)	04 (80.00)	-
White	01 (9.09)	02 (18.18)	4 (19.05)	-	01 (100.00)
Knowledge on CKD/HD					
Knows CKD	06 (54.54)	05 (45.45)	03 (27.27)	0.0 (0.00)	-
Knows HD	05 (45.45)	07 (63.63)	06 (54.54)	01 (20.00)	-
Economy class					
B1	01 (9.09)	-	-	-	01 (100.00)
B2	-	-	-	-	-
C1	02 (18.18)	02 (18.18)	04 (19.05)	01 (20.00)	-
C2	06 (54.54)	04 (36.36)	04 (19.05)	01 (20.00)	-
D/E	02 (18.18)	05 (45.45)	13 (61.90)	03 (60.00)	01 (100.00)
Education level					
Illiterate / Incomplete elementary	02 (18.18)	04 (36.36)	14 (66.67)	04 (80.00)	-
Complete elementary / incomplete high-school	02 (18.18)	03 (27.27)	01 (4.76)	-	01 (20.00)
Complete high-school / incomplete higher education	06 (54.54)	04 (36.36)	06 (28.57)	-	-
Complete higher education	01 (9.09)	-	-	01 (20.00)	-
Smoking					
	01 (9.09)	01 (4.76)	00 (0.00)	0.0 (0.00)	01 (9.09)
Physical exercise					
	03 (27.27)	04 (36.36)	07 (33.33)	01 (20.00)	0.0 (0.00)

Table 6. Characteristics of clinical variables of participants diagnosed with chronic kidney disease separated by stages.

Variable	Stage 1 n (%)	Stage 2 n (%)	Stage 3a n (%)	Stage 3b n (%)	Stage 5 n (%)
Systolic Blood Pressure					
Normal	07 (63.63)	07 (63.63)	07 (33.33)	-	01 (100.00)
Pre-hypertension	04 (36.36)	03 (27.27)	07 (33.33)	01 (20.00)	-
Systolic hypertension stage 1	-	01 (9.09)	04 (19.05)	03 (60.00)	-
Systolic hypertension stage 2	-	-	01 (4.76)	01 (20.00)	-
Systolic hypertension stage 3	-	-	02 (9.52)	-	-
Diastolic Blood Pressure					
Normal	10 (90.90)	06 (54.54)	09 (42.85)	01 (20.00)	01 (100.00)
Pre-hypertension	01 (9.09)	-	04 (19.05)	03 (60.00)	-
Diastolic hypertension stage 1	-	04 (36.36)	03 (14.28)	-	-
Diastolic hypertension stage 2	-	01 (9.09)	03 (14.28)	01 (20.00)	-
Diastolic hypertension stage 3	-	-	02 (9.52)	-	-
Body Mass Index (BMI)					
Low weight	01 (9.09)	-	-	-	-
Normal weight	04 (36.36)	01 (9.09)	07 (33.33)	01 (20.00)	01 (100.00)
Overweight	05 (45.45)	05 (45.45)	09 (42.86)	02 (40.00)	-
Obesity 1	01 (9.09)	04 (36.36)	04 (19.05)	02 (4000)	-
Obesity 2	-	01 (9.09)	-	-	-
Obesity 3	-	-	01 (4.76)	-	-
Glycaemia					
Normal	07 (63.63)	06 (54.54)	08 (38.09)	02 (40.00)	01 (100.00)
Changed fasting glycaemia	01 (9.09)	02 (18.18)	09 (42.85)	-	-
Diabetes	01 (9.09)	03 (27.27)	04 (19.05)	03 (60.00)	-