Seasonal variation of biochemical parameters of hemodialysis patients in a tropical climate area

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Abstract

The results of hemodialysis laboratory tests guide the monitoring of the patient's health conditions, nutritional status and the quality of the procedure. The objective is to analyze the seasonal variations of biochemical parameters of hemodialysis patients in a tropical area of Brazil. This is a longitudinal epidemiological study of the seasonal variation of repeated measurements for hemoglobin, hematocrit, calcium, potassium, phosphorus, glucose, glutamic-pyruvic transaminase, pre- and postdialysis urea, KtV, and urea reduction rate in hemodialysis patients in the city of Cáceres, Brazilian Pantanal in the year 2014, in the savannah tropical climate area. January was used as the reference month and linear mixed effects regression models were used. All laboratory variables analyzed presented significant seasonal variation in at least two months in 2014. Hemoglobin and hematocrit displayed the lowest values in autumn and the highest in winter. Calcium remained stable and showed two high peaks in autumn and winter. Phosphorus, potassium and glutamic-pyruvic transaminase showed higher values in autumn and lower values in spring. KtV, urea reduction rate, predialysis and postdialysis urea, had the lowest peaks in winter and the highest in spring. Glucose showed instability with a high peak in spring and a lower peak in autumn. It is concluded that the biochemical parameters of chronic renal patients on hemodialysis display seasonal variations related to climatic seasonal variation in a tropical savannah climate area in Brazil. The variations observed tend to become inverted in the months with higher and lower temperatures.

Keywords: Seasons. Climate. Kidney dialysis.

INTRODUCTION

Patients undergoing hemodialysis are vulnerable to seasonal variations. In outcomes such as mortality, studies show a higher incidence pattern during winter months compared to summer months[1,2]. In addition, seasonal variations have also influenced the trajectory of clinical and laboratory parameters of these patients, especially in blood pressure[3].

Blood pressure in hemodialysis patients was inversely related to ambient temperature in different climates (Mediterranean, Continental, Temperate and Subtropical), in studies conducted in Europe, North America and Asia[4-9]. Weight gain between hemodialysis sessions has also been related to meteorological variables, particularly temperature, relative humidity, atmospheric pressure and daily sun exposure in the Mediterranean, Temperate and Subtropical climates[6,7,10].

In hemodialysis, biochemical parameters are fundamental for monitoring the patient's health, the evolution or control of chronic kidney disease and comorbidities, the quality of hemodialysis and nutritional status[11-14]. In Brazil, according to RDC No. 154 of 2004, hemodialysis patients must undergo mandatory examinations

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at monthly, quarterly, semi-annual and annual periods, depending on the parameter, and always with medical doctor's monitoring of the results[15].

For the general population, the literature presents seasonal variations of laboratory tests[16,17]. In hemodialysis patients, these associations have been little explored, and divergent results have been described for biochemical parameters, even in studies conducted in the same climate and continent[8,9,18,19].

Due to the lack of information on the seasonal variation of laboratory parameters of hemodialysis patients in tropical climate countries, the influence of the seasons on laboratory parameters of hemodialysis patients is possible. Thus, the objective of this study is to analyze the seasonal variation of biochemical parameters of hemodialysis patients in a tropical climate area in Brazil.

METHODS

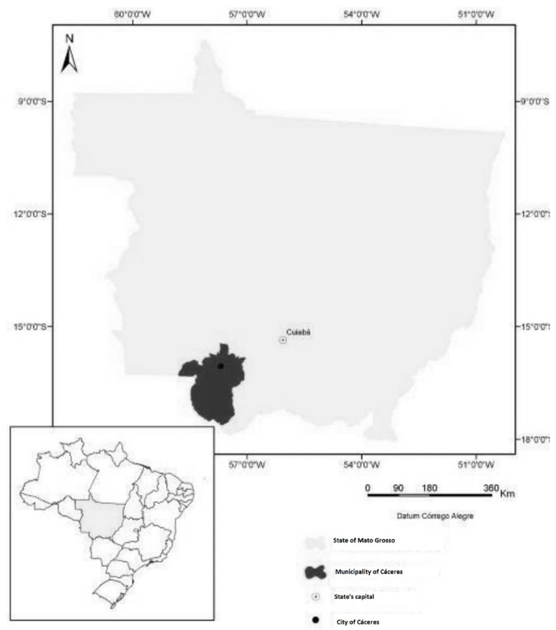
Study Design

This was a panel analysis epidemiological study of seasonal variation within laboratory test results of hemodialysis patients in the municipality of Cáceres, Mato Grosso state, from January to December 2014.

Population and Study Area

The study population consisted of 133 hemodialysis patients in 2014, attended at the hemodialysis unit located in Cáceres-MT, the Kidney Treatment Center Ltda (CTR). All patients older than 18 years who were on hemodialysis for more than three months in January 2014 were included in the study.

Cáceres is located in the state of Mato Grosso - Brazil, on the banks of the Paraguay River – the main tributary of the Brazilian wetland – 250 km from Cuiabá, the state capital. The city is 118m above sea level and has approximately 90,000 inhabitants, with an HDI of 0.801[19] (Figure 1). It has a climate classified as a tropical savannah (Aw), with an average temperature between 24.9 and 26.5°C. The months that may present below average temperatures are May, June, July and August, while in the other average temperatures are above 26°C[20]. A well-defined climate feature in the Pantanal region is marked by the rainy season (November to March) and drought (May to September)[21]. Other particularities are the high temperatures, especially in spring, with daily maximums reaching 40ºC; and in the months when cold masses migrate from the South, daily minimum temperatures may be below 10°C, with sudden changes in temperature and a short duration (two days on average)[22,23].



Source: Neves[23]

Figure 1 – Location of the municipality of Cáceres, Mato Grosso, Brazil.

Studies conducted in the Pantanal region of Mato Grosso state that high temperatures, especially in September, cause thermal discomfort with thermal sensation ranging from slightly hot to extremely hot[24]. In the "cooling" season, the thermal sensation is very cold, considering the climatology of the place, and possibly this sensation is influenced by the great thermal amplitude that occurs at this time[25]. In Cáceres, the combination of above average temperature and below average relative humidity - a fact common in August - generates thermal discomfort[21].

Study Variables

Biochemical Parameters

The data collected resulted from the monthly examinations performed according to RDC No. 154/2004[14], and obtained from the patients' records, are as follows: hemoglobin dosage (g/dL), hematocrit (%), free calcium (mg/dL), dosage potassium (mmol/L), phosphorus dosage (mg/dL), glutamic-pyruvic transaminase (GPT) (u/L), predialysis urea (mg/dL), postdialysis urea (mg/dL), KtV calculation, percentage of urea reduction rate (URR) (%) and glucose dosage (mg/dL) only for diabetic patients. The examinations were performed in the first week of each month. For purposes of sample characterization, data were also collected concerning date of birth, gender, race/skin color and underlying disease.

The biochemical variable units of measurement and the laboratory reference used in this study were those presented in the results of examinations performed by a laboratory accredited to the Unified Health System as a service provider for the hemodialysis unit.

Meteorological Variables

The meteorological data used were air temperature (maximum, minimum and daily average) and relative humidity (maximum, minimum and daily average) from January to December 2014, obtained from the automatic weather station of the National Institute of Meteorology (INMET), installed in Cáceres, MT (code - A941) and made available in a digital format through the INMET website[26].

Data management and analysis

In Brazil, the seasons are divided into fall (March 20 to June 20), winter (June 21 to September 21), spring (September 22 to December 20) and summer (December 21 to March 19)[26]. As the collections were performed during the first week of each month and to facilitate data interpretation, the seasons were defined as summer (January, February, March), autumn (April, May and June), winter (July, August and September) and spring (October, November and December).

The average temperature in Cáceres in 2014 was 25.9ºC. In September, in spring, the highest average was recorded at 28.5ºC and in July, in winter, the lowest average reached 22.3ºC. For relative air humidity, the annual average was 76%, where the lowest average was 63% in the winter (September) and the highest was 85% in the summer (February)[26].

Data were entered twice and subsequently validated. To verify the seasonal variation effects of laboratory test results, mixed-effect linear regression models suitable for longitudinal repeated-measure studies such as panel studies were used.

The dependent variables were the results of each patient's laboratory tests performed once a month during all months of 2014, while the independent variable was the time represented by the months of the year. A simple two-level model was constructed whose first level units refer to the repeated measurements of each second level unit. The simple model is described as:

$$Y_{tj} = \beta_{0j} + \sum_{r=1}^{11} \beta_r X_{rj} + e_{tj}$$

$$\beta_{0j} = \gamma_0 + u_{0j}$$

$$e_{tj} \sim N(0, \sigma^2) \text{ e } u_{0j} \sim N(0, \sigma_0^2)$$

Where:
t refers to level 1 units (days) t=1, ..., nj
j refers to level 2 units (patients) j=1, ..., 133.
b*0j* refers to the random coefficient
y*0* refers to level 2 coefficient (fixed)
u*0j* refers to the random term
X*rj* refers to the dummy variables associated with the months of February to December of the jth patient
b*r* corresponds to the fixed coefficients associated with the dummy variables.

The month of January was defined as the reference month to facilitate the interpretation of the data, since the follow-ups are the 12 months of the year. The analysis was performed in the R program (version 3.3.5) through the libraries lme4, lmerTest, effects and visreg. Associations were considered at a 5% significance level.

Ethical aspects

The study received a favorable opinion (no. 1.324.490) from the Research Ethics Committee of the State University of Mato Grosso CAAE: 4948715.0.0000.5166. All participants signed the Informed Consent Form (ICF).

RESULTS

Of the 133 hemodialysis patients, 81 (60.9%) were men; the average age was 54.9 years (age range 21 to 92 years); the average time in HD was 4.8 years (1 to 21 years in HD); most patients reported being white (49.6%); and the most prevalent underlying disease was arterial hypertension (45.8%) (Table 1). Hemoglobin and hematocrit presented mean values of 10.2g/dL and 30.6%, respectively, values lower than the reference for men and women. Calcium and GPT had means within the reference values. For potassium, phosphorus, predialysis urea, KtV, URR and glucose the means were higher than the reference values. There is no reference value for postdialysis urea, but an average below the recommended predialysis urea was observed (Table 2). Table 3 and Figure 2 show the seasonal variations in biochemical parameters. Hemoglobin and hematocrit showed the lowest values in autumn and the highest values in winter. Calcium had constant values with high peaks in autumn (May 6.50; p<0.001) and in winter (August 6.30; p<0.001). Potassium, calcium and GPT increased in autumn and decreased in spring. Predialysis urea and postdialysis urea had the highest peak in July and the lowest peak in August, both extreme values occurred in the winter. KTV and URR showed the same behavior throughout the year, the lowest peak in late summer (February) and the highest peak in late spring (November). Glucose values were inconsistent, with a high peak in spring (October) and the lowest in autumn (May) (Table 3 and Figure 2).

Table 1 – Characteristics of hemodialysis patients according to demographic variables, treatment time and underlying disease. Cáceres, MT, 2014.

Variables	N (133)
Age (years)	54.9±14.9
Time on hemodialysis (years)	4.8±3.8
Sex, N (%)	
Man	81 (60.9)
Woman	52 (39.1)
Race/ skin color, N (%)	
White	66(49.6)
Black	29(21.8)
Brown	38(28.6)
Base Disease, N (%)	
Diabetes Mellitus	21(15.9)
Glomerulonephritis	37(27.8)
Arterial hypertension	61(45.8)
Polycystic Kidney	5(3.8)
Diabetes Mellitus and High Blood Pressure	6(4.6)
Others	3(2.4)

Source: CTR Records (2014).

Table 2 – Descriptive analysis of laboratory variables of hemodialysis patients in Cáceres, MT, 2014.

Variables	N	No. observations	Average Standard Deviation	Mín	Máx	Laboratory reference values
Hemoglobin (g/dL)	133	1589	10.2±2.0	3.4	28.8	M 12.2 to 18.1 F 11.3 to 14.5
Hematocrit (%)	133	1590	30.6±6.0	9.3	48.4	M 35.5 to 53.7 F 36 to 48
Calcium (mg/dL)	133	1586	4.82±0.4	1.04	6.6	4.70 to 5.28
Phosphorus (mg/dL)	133	1588	5.46±0.9	1.0	81.0	2.5 to 4.5
Potassium (mmol/L)	133	1586	6.40±4.8	2.9	9.1	3.5 to 5.5
GPT (U/L)	133	1583	23.55±21.1	7.0	262.0	M 11 to 45 F 10 to 37
Pre Urea (mg/dL)	133	1585	134.3±40.5	35.0	279.0	10 to 50
Post Urea (mg/dL)	133	1585	45.4±19.7	10.0	142.0	-
Kt/V	133	1585	1.44±0.4	0.46	2.03	>1.2
TRU (%)	133	1585	66.1±10.3	34.0	89.0	>65
Glicose (mg/dl)	26	284	145.0±62.1	60.0	458.0	70 to 99

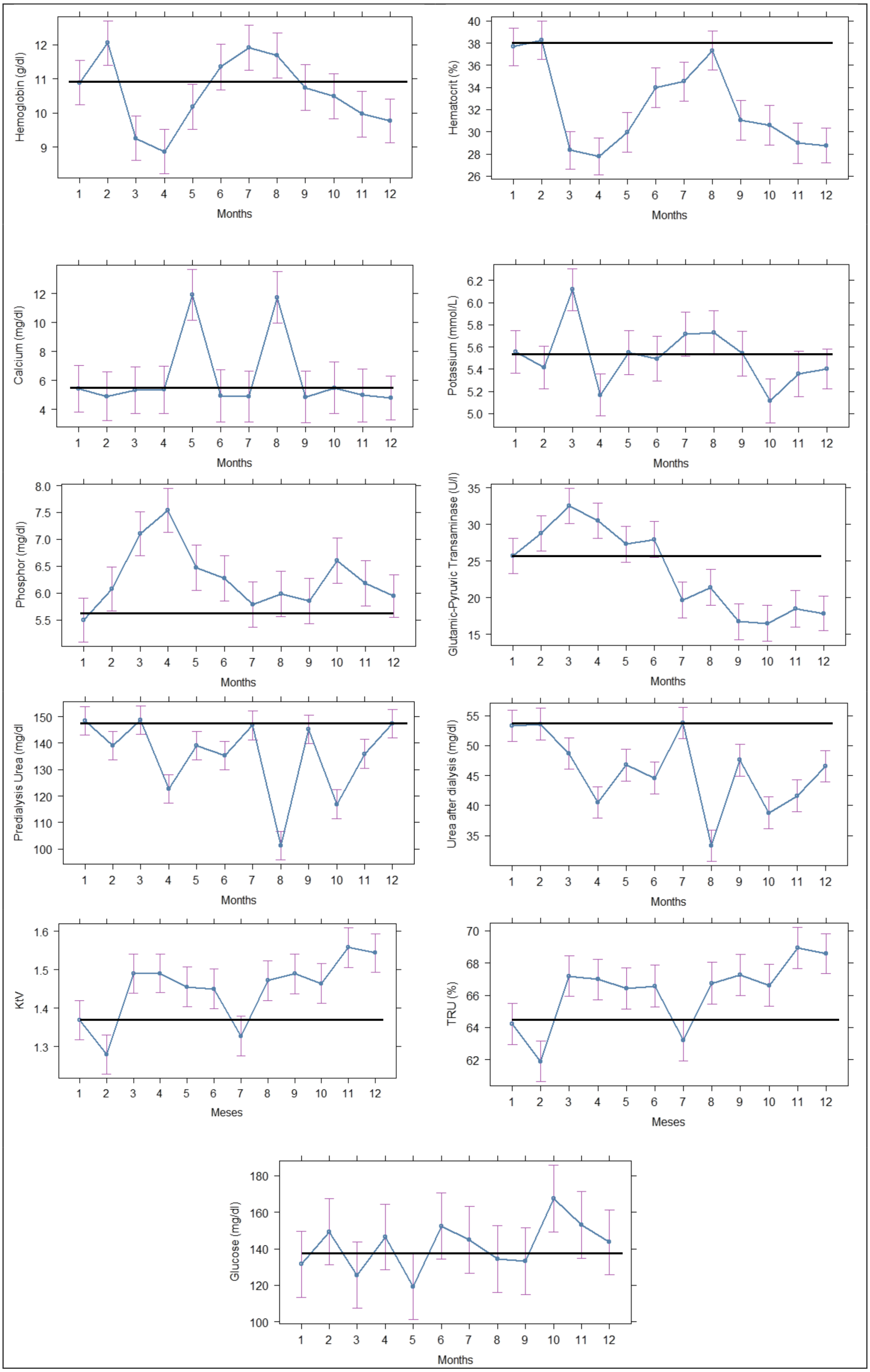
Source: CTR records, 2014. Legend: GPT: glutamic-pyruvic transaminase. Kt/V: formula for quantifying the dialysis dose. URR: Urea reduction rate. M: male. F: female.

Table 3 – Seasonal variations of laboratory variables by months of the year of hemodialysis patients in Cáceres, MT, 2014.

		Summer		Autumn			Winter			Spring	
Variable	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Hemoglobin	1.16**	-1.62**	-2.01**	-0.70**	0.46*	1.03**	0.80**	-0.13	-0.39**	-0.91**	-1.11*
Hematocrit	0.62	-9.33**	-9.88**	-7.72**	-3.69**	-3.13**	-0.33	-6.63**	-7.07**	-8.71**	-8.90**
Calcium	-5.31	-9.28	-5.85	6.50**	-4.81	-5.37	6.30**	-5.75	7.22	-4.57	-6.24
Potassium	-1.39	5.62**	-3.87**	-7.44	-6.15	1.61	1.72*	-1.33	-4.42	-1.97*	-1.53
Phosphorus	5.38**	1.61**	2.05**	9.81**	7.83**	2.96**	4.88*	3.63**	1.10*	6.92**	4.53**
GPT	3.09**	6.86**	4.78**	1.62*	2.27**	-5.99**	-4.26**	-8.92**	-9.17**	-7.16**	-7.81**
Predialysis Urea	-9.33**	0.45	-25.7**	-9.36**	-13.0**	-1.65	-47.1**	-3.09*	-31.4**	12.3**	-0.99
Postdialysis Urea	0.32	-4.59**	-12.7**	-6.50**	-8.68**	0.51	-19.9**	-5.67**	-14.4**	-11.6**	-6.74**
KtV	-8.95**	1.21**	1.22**	8.65**	8.16**	-4.07*	1.03**	1.20**	9.57**	18.9**	1.74**
URR	-2.32**	2.96**	2.77**	2.20**	2.35**	-1.03*	2.52**	3.05**	2.39**	4.71**	4.35**
Glucose&	17.7*	-5.91	14.8**	-12.1*	20.9**	13.4*	2.98	1.17	36.1**	21.4**	12.0*

Source: CTR Records (2014). January reference month. *p<0.05; **p<0.001. &Only diabetic patients.

Figure 2 – Seasonal variations of laboratory tests over the months. Cáceres, MT, 2014.



Source: CTR Records (2014). January reference month.

DISCUSSÃO

This is the first study on seasonal variations and biochemical parameters of hemodialysis patients in tropical climate areas such as the Brazilian Pantanal. Seasonal variations in biochemical parameters throughout the year suggest that changes in climate factors may have a direct effect on pathophysiological processes[27].

In studies carried out in the North American, European and Asian continents, some physiological and biochemical parameters of hemodialysis patients demonstrated seasonal variation, but with differences between the peaks in each climate[8,9,17,18,28,29]. The results found in this tropical climate study of hemoglobin, hematocrit and urea showed similarities of seasonal variation with other studies.

The hemoglobin and hematocrit seasonal variation was similar with the United States city climate8, and the seasonal variation of predialysis and postdialysis urea were equal to the Mediterranean and temperate seasonal variations[17,18,28,29]. The other biochemical parameters analyzed were not similar to other studies conducted in different climates/locations.

The differences between the results may be influenced by the climatic characteristics of the study sites, which present the four seasons with marked variations. In the Mato Grosso Pantanal region, there are few changes in temperatures throughout the year. However, what differs among the seasons is the increase in daily thermal amplitude and frequent cold winter days[30]. Other studies with hemodialysis patients were conducted in the United States[8,9], southern Croatia[17,18,28] and Japan[29], where the climate is well defined for the four seasons, with significant variations, especially in air temperature.

The highest hemoglobin and hematocrit values were found in the month with the lowest temperature, July in the winter, and the lowest values were in the fall in this tropical climate. In the USA, hematocrit also displayed seasonal variations between seasons; however, they observed a positive association with temperature, that is, the highest values in summer and the lowest in winter[8]. In another study also in the USA, there was no seasonal variation for hemoglobin[9]. In temperate regions such as Asia, a study with monthly assessment of biochemical parameters showed a higher hemoglobin value in autumn and a lower value in spring[29], which are different results from those found in this study. The reduction of hemoglobin in the winter in patients starting HD was described in a study conducted in temperate climate Japan, and a possible justification for this finding would be the dilution effect of excessive extracellular volume in winter, as suggested by the study's authors[29].

Potassium was higher in March in summer, unlike in a temperate area where HD patients' potassium was slightly higher in winter[29]. The increase in potassium in high temperature months is probably due to fruit intake[32]. However, during the warmer periods of the year (September and October) evaluated in the present study, potassium did not have high levels. In this study, the average temperature was high all year round, and the availability of tropical fruits is very large and easily accessible even in the patients' backyards[33].

Regarding the seasonal variation of glucose and phosphorus dosage in HD patients, there is speculation concerning the influence of seasonal variations due to hormonal physiological changes[17]. The glucose evaluated in this study was only for diabetic patients who were not necessarily fasting. Even so, seasonal variation was observed, which had the highest value in October, a month of high temperature and low relative humidity, which is in the spring.

For the diabetic population, fasting blood glucose results verified in Europe also point to seasonal variation, but the highest values were reported in winter[34] as well as for patients living in Mediterranean climate[18]. The seasonal variation observed in these studies was related to excessive food intake and decreased physical activity during winter[18,34].

Seasonal variation in phosphorus and GPT dosage was also described by Kovacic and Kovacic[17] for hemodialysis patients living in a Mediterranean climate area and by Yanai *et al.*[29] in a Temperate climate, with the highest values in the coldest months and lowest values in warmer months, as opposed to the findings of this study. Seasonal variation, especially for phosphorus, does not seem to be related to food intake but to neurohormonal influences[17].

Calcium was the test that had significant results for seasonal variation in just two months. In a temperate climate, calcium had monthly variations in HD patients, with higher values in autumn and lower values in spring[29]. In a study conducted in Sweden to assess the seasonal variation of calcium in people without pathologies, and controlling the seasonal variation of vitamin D and parathyroid hormone (PTH), calcium showed minimal seasonal variation, confirming that the calcium level is regulated internally and individually within a narrow range of variation, not suffering from external variations[35], which seems to corroborate our findings. In a study of primary hyperparathyroidism patients in southern Israel, calcium values were considered modest but significant, with higher levels in the fall; and it was suggested that this increase was linked to PTH and low Vitamin D levels[36].

Secondary hyperparathyroidism is prevalent among hemodialysis patients, ranging from 55 to 85%[37], and has a pathophysiological mechanism similar to the primary version38. Calcium variation may be linked to the presence of hyperparathyroidism in hemodialysis patients and may not be influenced by extreme factors. However, in the present study, PTH and vitamin D levels were not evaluated.

In the Mediterranean climate and in the temperate climate, predialysis and postdialysis urea showed seasonal variations, and the highest values were recorded in the colder months[17,18,28,29]. On the other hand, in the USA, in 15 cities, predialysis and postdialysis urea also showed seasonal variation, but the highest peak occurred in March, the spring[8]. In this study, predialysis and postdialysis urea showed higher values in winter when the average temperatures are lower than the general local average. A similar result was described for the Mediterranean and temperate climates[17,18,29]. Increased appetite in winter, higher protein and total fat intake, and decreased physical activity may be related to increased urea in the lower temperature month[8,35,39].

The appropriate dose of KtV for HD is 1.2[11], in this study, was identified in February alone, the average was 1.28 in all other months, and the average KtV was higher than the value considered adequate and displayed seasonal variations. When HD is poorly performed, i.e. KtV value is less than 1.2, there is a decrease in filtration of metabolites such as phosphorus, potassium and urea that rise in the bloodstream and the patient may develop symptoms such as nausea and vomiting, which may negatively alter food intake and interfere with test results[11]. However, this process does not seem to be present in the population studied.

In this study, KtV and URR showed variations every month of the year, different from Cheung *et al.*[8] and Kovacic, Roguljic and Kovacic[28], who did not find seasonal variations for KtV in the North American continent and in the Mediterranean climate. However, the result found in the present sample corroborates the seasonal variations found in predialysis and postdialysis urea, since URR and KtV represent the results of reduced urea after hemodialysis sessions.

Difficulties in comparing the seasonal variation of laboratory tests have already been described by other authors[8,17,29], and are related to the different therapeutic protocols, which usually follow the norms defined by each country.

Another limiting factor is the various methods of seasonal variation analysis, different collection periods, which make comparisons of the results difficult. Among the limitations, no clinical variables and/or medication use were analyzed, as well as the nutritional report data. Considering the evolution time of chronic kidney failure patients on hemodialysis, 12 months appears to be a short follow-up period, but it was sufficient to show the seasonal and monthly variations, the objective of this study.

The presence of seasonal variation in laboratory parameters demonstrates that professionals involved in the care of hemodialysis patients should take into account seasonal factors - especially in the colder and warmer months - when interpreting biochemical analyses, and prescribing drugs and dialysis parameters.

CONCLUSION

Biochemical parameters of chronic kidney failure patients on hemodialysis showed seasonal fluctuations related to climatic seasonal variation in an area with a tropical savannah climate in Brazil. The variations observed tended to inversely alter in the months with higher and lower temperatures.

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