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Glycoinsulinemic parameters associated with vitamin D status in patients with chronic kidney disease undergoing dialysis therapy

Parâmetros glucoinsulinêmicos como fatores associados ao estado de vitamina D em pacientes com doença renal crônica submetidos a tratamento de diálise

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ABSTRACT

Evidence indicates that the physiological role of vitamin D goes beyond regulating classical domains of minerals and hormones. It is reported that the low status of Vitamin D may contribute to the occurrence of metabolic disorders, with emphasis on insulin resistance, atherosclerotic events and metabolic syndrome. In this sense, this study aimed to verify the association between metabolic and anthropometric parameters and vitamin D status in patients with chronic kidney disease undergoing hemodialysis. This was a cross-sectional study conducted with 95 patients with chronic kidney disease treated at clinics in Teresina, Piauí, Brazil. Lipid and inflammatory profile, glycemia, insulin and vitamin D status were determined. Data were analyzed using STATA software, adopting significance level of $p < 0.05$. The results pointed to a significant association between vitamin D concentrations and adiposity of patients. It was observed that the high blood glucose and HOMA-IR values presented statistical association with vitamin D concentrations, and conditioned greater chances of their inadequacy. There was no correlation between nutrient concentrations and cytokines evaluated in the study. Therefore, it was concluded that the increase in levels of glycoinsulinemic parameters (insulin and HOMA-IR) seems to influence vitamin D status in patients with chronic kidney disease. **Keywords:** Cytokines; Glycemia; Hemodialysis; Hypercholesterolemia; Kidney disease; Metabolic processes; Metabolic syndrome.

RESUMEN

La evidencia indica que el papel fisiológico de la vitamina D va más allá de regular los dominios clásicos del eje mineral y hormonal. Hay trabajos que muestran que el bajo nivel de vitamina D puede contribuir a la aparición de trastornos metabólicos, con énfasis en la resistencia a la insulina, eventos ateroscleróticos y síndrome metabólico. En este sentido, el objetivo de este estudio fue verificar la asociación entre parámetros metabólicos y antropométricos y el estado de vitamina D en pacientes renales crónicos en hemodiálisis. Se trata de un estudio transversal realizado con 95 pacientes con enfermedad renal crónica atendidos en consultas externas de Teresina, Piauí, Brasil. Se determinó el perfil lipídico e inflamatorio, la glicemia, la insulina y el estado de vitamina D. Los datos se analizaron utilizando programa STATA, con un nivel de significancia de $p < 0,05$. Los resultados apuntaron a una asociación significativa entre las concentraciones de vitamina D y la adiposidad de los pacientes. Se observó que los valores elevados de glucosa en sangre y HOMA-IR se asociaron estadísticamente con las concentraciones de vitamina D y condicionaron mayores posibilidades de su insuficiencia. No hubo correlación entre las concentraciones de nutrientes y las citocinas evaluadas en el estudio. Por tanto, se concluyó que el aumento de los niveles de parámetros glucoinsulinémicos (insulina y HOMA-IR) parece influir en el estado de la vitamina D en pacientes con enfermedad renal crónica.

Palabras clave: Citoquinas; Glicemia; Hemodiálisis; Hipercolesterolemia; Nefropatía; Procesos metabólicos; Síndrome metabólico.

INTRODUCTION

According to epidemiological data, the prevalence of chronic kidney disease (CKD) varies between 8 and 16% of the world population and, in the context of global health, is increasing at alarming rates^{1,2}. Among its several metabolic implications, it constitutes a risk factor for vitamin D deficiency, which has attracted attention because it represents a public health problem still prevalent in emerging and developed countries^{3,4,5}.

Although there is no consensus regarding the ideal levels of 25(OH)D (vitamin D reserve), its deficiency in a population is defined by most specialists as values below 20 ng/mL (<50 nmol/L) in the blood⁶. The high prevalence of deficiency/insufficiency of this vitamin in patients with CKD may result from factors such as: lack of exposure to sunlight by individuals with chronic diseases, reduction of skin synthesis of cholecalciferol in response to sunlight, as well as decreased intake of source foods, urinary loss of 25(OH)D, and impairments on tubular resorption of 25(OH)D. These factors can still be aggravated by renal phosphorus retention in the early stages of CKD, which can contribute to the reduction of production of 1,25(OH)D directly and increased FGF-23^{7,8}.

The evidence indicates that the physiological role of vitamin D goes beyond only regulating the classical domain of the calcium-phosphorus-PTH axis⁹. The low status of vitamin D can not only contribute to the development of cardiovascular diseases (CVD) and renal dysfunctions, but is also strongly associated with Metabolic Syndrome (MetS), which is recognized as a complex set of risk factors interrelated with metabolic alterations, CKD and atherosclerotic events^{10,11}.

It is suggested that vitamin D concentrations are correlated with dyslipidemia. The connection between hypercholesterolemia and hypovitaminosis D is explained from a defect in low density lipoprotein (LDL) receptors and therefore in cholesterol absorption^{12,13}. Therefore, in addition to vitamin D directly reducing the level of serum triglycerides by increasing calcium in the serum via intestinal

absorption, it also indirectly impairs the synthesis and secretion of triglycerides in the liver^{13,14}. Not yet disregarding the participation of vitamin in the suppression mechanism of PTH, which also alters lipid fractions¹⁵.

In addition, experimental studies have shown that vitamin D is also a basic and necessary factor for normal insulin secretion, especially by reducing the resistance to insulin action by calcium-phosphorus metabolism and the insulin receptor gene^{16,17,18,19}.

Finally, the role of this vitamin is also recognized in the control of inflammation by acting as immunomodulator and regulator of the transcription of genes involved in the inflammatory response. Specifically, the cells that produce calcitriol also express the Vitamin D Receptor (VDR) and the enzymes needed to metabolize vitamin D3 (1 α -, 25-, and 24-hydroxylases). Therefore, changes in their serum concentrations compromise the protective performance of defense cells (T cells), and promote the release of inflammatory markers^{20,21}.

Given the physiological importance of vitamin D, the impact of CKD on worldwide mortality and the relationship between serum concentrations of this nutrient and the prevalence of complications, the present study aimed to associate anthropometric, glycoinsulinemic, inflammatory and lipid profiles with the status of vitamin D of CKD patients undergoing hemodialysis.

METHODS

Research Design and Sample

This multicenter, cross-sectional and quantitative study was conducted in accordance with the Guidelines of the Declaration of Helsinki and Resolution N°. 466/2012 of the National Health Council²², and received ethical approval under opinion N° 2.527.329, issued by the Ethics and Research Committee of the Federal University of Piauí (CEP-UFPI).

The study corresponds to a section of the data from the research project entitled "Cardiovascular Risk and its Association with Metabolic Syndrome in Patients with

Chronic Kidney Disease in Hemodialysis Therapy", linked to the Graduate Program in Food and Nutrition of the Federal University of Piauí-PPGAN/UFPI.

The sample size was estimated considering the total number of patients (n= 727) registered and under treatment in three specialized clinics located in Teresina-PI, and adopting the 95% confidence interval, margin of error of 5% and prevalence of 0.048% of hemodialysis patients in the state of Piauí in 2016²³, incorporating the sample 95 participants, of both sexes, diagnosed with CKD undergoing dialysis therapy in the three selected treatment centers, which serve approximately 69% of renal patients on hemodialysis in the municipality of Teresina.

The eligibility criteria defined were: a) patients with CKD in hemodialysis treatment for at least six months; b) over 20 years and ≤ 59 years; c) preserved cognitive ability; d) absence of history of recent infections (less than three months); e) absence cancer, tuberculosis, acquired immunodeficiency syndrome, chronic obstructive pulmonary disease, severe cardiovascular disease, cerebrovascular disease and symptomatic heart failure (CHF) diagnosis; f) absence of amputations or physical disabilities that would prevent anthropometric evaluation. Pregnant and lactating participants were considered ineligible, and aspects such as race and sex had no distinguishing value for the study.

All patients were aware of the objectives, procedures, risks and benefits of the research, and confirmed acceptance by signing the Free and Informed Consent Form (TCLE). Through interviews, sociodemographic, lifestyle, and anthropometric data were obtained, which were compiled in previously tested forms. The clinical characteristics were consulted in the medical records. Biological material was collected to determine the lipidogram, glycemia, insulin and serum vitamin D.

Anthropometric Parameters

The evaluation was based on the measurement of anthropometric variables of interest. Body Mass Index (BMI) was obtained through the ratio between dry weight and height square. The classification of nutritional status was based on the cut-off points defined by the World Health Organization²⁴. To determine the Waist/Hip Ratio (WHR), previously measured WC values (with inelastic measuring tape, positioned in the relaxed abdominal region and at the midpoint between the last rib and the iliac crest), were applied to the CK values (evaluated at the hip region, in the maximum extension of the buttocks). The cutoff points suggested by Lean et al. were adopted²⁵ and Pereira et al.²⁶ for WC and WHR, in this order, for cardiovascular risk classification. Neck Circumference (NC) was measured using inelastic measuring tape, positioned at the height of the cricothyroid cartilage. In men who presented some prominence, NC was measured below the region. The values obtained were classified according to Cardiovascular Risk (CVR) based on the study by Ben et al.²⁷. The Conicity Index (CI) was also determined using

the formula pre-established by Valdez²⁸, and was classified as proposed by Pitanga et al.²⁹.

Collection of Biological Material

Blood samples were collected in the morning, between 5 and 7 hours, and patients were previously instructed to fast at least 12 hours. Procedures were performed at participating clinics by a qualified professional. A total sample of 9 mL of blood was obtained, of which 4 mL were distributed in vacuum tubes containing Diaminotetraacetic Ethylene Acid (EDTA) and 5 mL in tubes with clot activator for subsequent biochemical analyses of the study.

Specific Biochemical Parameters

Vitamin D

Vitamin D was determined by the total vitamin D 25(OH) access assay, this is a competitive two-step bonding enzyme immunoassay. In the initial incubation, the sample was added to a reaction vessel with a BPD release agent and paramagnetic particles coated with monoclonal antibodies anti-25(OH) vitamin D. A 25(OH) vitamin D is released by BPD and binds to monoclonal antibodies anti-25(OH) vitamin D immobilized in the solid phase. Subsequently, an alkaline 25(OH) vitamin D-phosphatase analogue conjugate is added that competes for binding to immobilized anti-25(OH) vitamin D monoclonal antibodies. After a second incubation, materials attached to the solid phase are retained in a magnetic field, while unbound materials are removed by washing. Then the chemiluminescent substrate is added to the container and the light generated by the reaction is measured with a luminometer. Light production is inversely proportional to the concentration of 25(OH) vitamin D in the sample. The amount of analyte present in the sample is determined from a stored multipoint calibration curve.

Serum Glucose Concentration, Insulin and HOMA-IR Calculus

The analysis of serum fasting glucose concentrations was performed using the dry chemistry method. The values that were between 75 and 99 mg/dL for fasting glucose were considered adequate for glycemic control, and values above 126 mg/dL indicated altered glycemia, according to the ADA³⁰. The evaluation of serum insulin concentration was performed according to the chemiluminescence method, and the concentration interval 6-27 U/mL was adopted as reference. The evaluation of insulin resistance was performed by calculating the Homeostasis Model Assessment (HOMA), which is used to evaluate insulin sensitivity or resistance and pancreatic β cell function from insulin and fasting glucose concentrations converted to concentration expressed in mmol/L by multiplying the value in mg/dL by 0.0555. HOMA-IR was calculated using the formula of Matthews et al.³¹.

Lipid Profile

Serum concentrations of triglycerides, total cholesterol and HDL-cholesterol were determined according to the

dry chemistry method. The LDL-cholesterol fraction was calculated as proposed by Friedwald et al.³² obeying the reference values of the updated version of the ADA³⁰.

Determination of serum inflammatory cytokines

For the determination of serum levels of TNF- α IL-1 β , IL-6, IL-8, IL12P70 and IL-10, blood serum was used, adopting the flow cytometry technique with the use of a commercial BD kit[™] Cytometric Bead Array (CBA) Human with respective cytokines, from BD Bioscience, following manufacturer instructions, at the Nathan Portella Tropical Diseases Institute. The procedure was also used to prepare the standard curve. In the same sample, four populations of beads with different fluorescence intensities were conjugated with a specific capture antibody for each cytokine, forming the bead curves, then read on the FACSCantoll flow cytometer.

Statistical Analysis

Stata[®], v.12 (Statacorp, College Station, Texas, USA) software was used for data organization and analysis. The Shapiro-Wilk test was applied to verify data normality. The association between the variable serum vitamin D status and the variables that reflect inflammation, insulin resistance, and blood glucose and lipid profile was tested by Pearson's Chi-Square test (χ^2) or Fisher's Exact test when appropriate. The strength of the association was tested based on the prevalence ratio (PR) estimated by Poisson regression with robust variance. The differences in means were compared between the groups according to the presence of inadequacy of serum vitamin D using the Student's t-test for the parametric variables and the Mann-Whitney test for non-parametric variables. The 95% Confidence Interval and statistical significance of $p < 0.05$ were adopted.

RESULTS

The sample came from a low-income population (up to one minimum wage), with low education, average age of 40.9 ± 10.6 years, 66.3% were male, comorbidities strongly associated with cardiovascular diseases, such as diabetes (22.0%) and hypertension (63.4%), with hemodialysis time between 2 and 5 years, non-smokers and ex-alcoholics.

There was a preponderance of adequacy of vitamin D levels in the sample studied (80%). The means of the participants' anthropometric data are presented in table 1. The results show mean values of weight, height, BMI, WC, NC, and WHR were statistically higher in males.

Table 2 shows the association between vitamin D status and anthropometric and adiposity parameters. It was observed that higher values of NC condition 3.24 times more likely to have vitamin D. Table 3 below shows the estimate of food consumption of the study population. It was observed that protein and lipid intake was statistically higher in females, and that low dietary intake of vitamin D predominated, with no significant difference between sexes.

Regarding glycoinsulinemic parameters and lipid profile (Table 4), it was observed that high blood glucose and HOMA-IR values presented a statistical association with the vitamin D status of the patients. Table 5 recognizes that high blood glucose values were 2.27 times more likely to have vitamin D inadequacy, as well as the increase in HOMA-IR, also conferred 2.41 times more chances of presenting the same diagnosis. Table 6 below shows the proposed correlation coefficients between vitamin D concentrations and the cytokine profile evaluated in patients. No correlation was observed between the variables.

Table 1. Measures of dispersion of anthropometric variables of patients with CKD undergoing hemodialysis, according to sex. Teresina - PI, 2020.

Parameters	Sex			p
	Total (n= 95) Mean $\pm$ SD	Female (n= 32) Mean $\pm$ SD	Male (n= 63) Mean $\pm$ SD	
Weight (kg)	63.0 $\pm$ 14.6	54.9 $\pm$ 11.4	67.1 $\pm$ 14.4	0.000*
Height (m)	1.63 $\pm$ 0.09	1.56 $\pm$ 0.06	1.66 $\pm$ 0.09	0.000*
BMI (kg/m ²)	23.6 $\pm$ 4.4	22.3 $\pm$ 3.9	24.2 $\pm$ 4.5	0.040
WC (cm)	86.0 $\pm$ 13.9	78.3 $\pm$ 12.7	89.9 $\pm$ 12.9	0.000*
NC (cm)	36.7 $\pm$ 4.1	33.2 $\pm$ 3.4	37.7 $\pm$ 3.6	0.000*
HC (cm)	93.7 $\pm$ 8.4	91.8 $\pm$ 9.8	94.7 $\pm$ 7.5	0.111
WHR	0.91 $\pm$ 0.09	0.84 $\pm$ 0.08	0.94 $\pm$ 0.08	0.000*

*Student t test. SD: Standard Deviation. BMI: Body Mass Index; WC: Waist Circumference; NC: Neck Circumference; HC: Hip Circumference; WHR: Waist-Hip Ratio; High CVR when: ≥ 94 cm for men and ≥ 80 cm for women; WHR ≥ 0.95 for males and ≥ 0.80 for females; NC ≥ 37 cm for men and ≥ 34 cm for women.

Table 2. Association between Vitamin D Status and Anthropometric Parameters and Adiposity of CKD Patients.

Variables	Suitable		Unsuitable		p	PR	CI 95%
	n	%	n	%			
BMI (kg/m ²)							
Underweight	9	90.0	1	10.0	0.749*	1.00	-
Normal	44	80.0	11	20.0		2.00	0.290-13.96
Overweight	23	76.7	7	23.3		2.33	0.320-16.90
WC							
<94 cm M e <80 cm F	45	80.4	11	19.6	0.917	1.00	-
≥94 cm M e ≥80 cm F	31	79.5	8	20.5		1.04	0.460-2.37
NC							
<37 cm M e <34 cm F	40	90.9	4	9.1	0.020*	1.00	-
≥37 cm M e ≥34 cm F	36	70.6	15	29.4		3.24	1.15-9.08

*Pearson's Chi-Square test. * Fisher's exact test with significant association (p<0.05). M= Male; F= Female; BMI= Body Mass Index; WC= Waist circumference; NC= Neck Circumference; PR= Prevalence Ratio; CI= Confidence Interval.

Table 3. Estimation of Dietary Intake of CKD Patients according to sex, Mean±SD.

Dietary Consumption	Total (n= 95)	Female (n= 32)	Male (n= 63)	p
Energy (kcal/kg)	25.8±10.6	26.6±9.8	25.4±10.9	0.729
CHO (%)	56.1± 32.0	55.6±20.1	56.3±36.7	0.295
PTN (g)	82.1±27.4	81.0±25.0	82.6±28.6	0.843
PTN (g/kg)	1.40±0.6	1.60±0.6	1.30±0.6	0.043
LIP (%)	17.1±9.7	18.0±5.1	16.6±11.4	0.017
Vitamin D (mcg)	5.50±14.4	6.20±16.9	5.20±13.0	0.909

*Test from Mann Whitney. SD: Standard Deviation. CHO: Carbohydrate; PTN: Protein; LIP: Lipid. Reference values: Energy= Adults: 35 kcal/kg/day; CHO= 50-60% of the TEV; LIP= 25-35% of the TEV; PTN= 1.2 g/kg/day; Vitamin D 600IU (15mcg). TEV: Total Energy Value.

Table 4. Measurements of Blood Glucose, HOMA-IR and Lipid Profile of Participants according to Vitamin D Concentrations.

Variables	Mean $\pm$ SD	n	CI 95%	p
Glucose**				
<100	47.8 $\pm$ 14.8	68	40.2 – 47.4	0.023
$\geq$ 100	37.0 $\pm$ 16.0	27	30.6 – 43.3	
HOMA-IR*				
<3.0	44.0 $\pm$ 15.1	65	40.3 – 47.8	0.042
$\geq$ 3.0	37.1 $\pm$ 15.2	30	31.5 – 42.8	
TC (mg/dL) *				
<200	41.8 $\pm$ 15.7	90	38.5 – 45.1	0.981
$\geq$ 200	42.0 $\pm$ 8.30	05	31.7 – 52.3	
LDL*				
<100	42.6 $\pm$ 15.6	72	38.9 – 46.3	0.380
$\geq$ 100	39.4 $\pm$ 14.6	23	33.0 – 45.7	
HDL*				
$\leq$ 40/50	42.9 $\pm$ 14.2	16	35.4 – 50.5	0.758
>40/50	41.6 $\pm$ 15.7	79	38.1 – 45.1	
TG*				
<150	43.7 $\pm$ 15.2	56	39.7 – 47.8	0.149
$\geq$ 150	39.1 $\pm$ 15.4	39	34.1 – 44.1	

*Student t test. **Mann Whitney test. SD= Standard Deviation; CI= Confidence Interval; TC= Total cholesterol; LDL= Low Density Lipoprotein; HDL= High Density Lipoprotein; TG= Triacylglycerol.

Table 5. Prevalence Ratio of Blood Glucose, HOMA-IR and Lipid Profile on Vitamin D Status among CKD Patients on Hemodialysis.

Parameters	Status Vitamin D				p	PR	CI 95%
	Suitable (n= 76) n°	%	Unsuitable (n= 19) n°	%			
Glucose							
<100	58	85.3	10	14.7	0.041	1.00	–
$\geq$ 100	18	66.7	9	33.3		2.27	1.03 – 5.00
HOMA-IR							
<3.0	56	86.2	9	13.8	0.027	1.00	–
$\geq$ 3.0	20	66.7	10	33.3		2.41	1.09 – 5.32
TC (mg/dL)							
<200	72	80.0	18	20.0	0.681*	1.00	–
$\geq$ 200	4	80.0	1	20.0		1.00	0.160 – 6.11
LDL							
<100	59	81.9	13	18.1	0.402	1.00	–
$\geq$ 100	17	73.9	6	26.1		1.44	0.620 – 3.38
HDL							
$\leq$ 40/50	13	81.2	3	18.8	0.599*	1.00	–
> 40/50	63	79.8	16	20.2		1.08	0.350 – 3.30
TG							
<150	47	83.9	9	16.1	0.251	1.00	–
$\geq$ 150	29	74.4	10	25.6		1.60	0.710 – 3.57

*Pearson's Chi-Square test; *Fisher's exact test; PR= Prevalence Ratio; PR estimated by Poisson Regression. CI= Confidence Interval; TC: Total Cholesterol; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglycerides.

Table 6. Linear correlations between serum vitamin D levels and cytokines.

Cytokines	Serum Vitamin D Correlation Coefficient	p
TNF- α (pg/mL)	0.02	0.829
IL-1 β (pg/mL)	0.04	0.705
IL-6 (pg/mL)	-0.10	0.325
IL- 8 (pg/mL)	0.11	0.310
IL-10 (pg/mL)	0.10	0.318
IL-12P70 (pg/mL)	0.09	0.386

*Pearson's correlation. TNF- α = Tumor Necrosis Factor-Alpha; IL= Interleukin.

DISCUSSION

In this study, we sought to gather evidence regarding the association between vitamin D and glycemic, lipid and inflammatory parameters evaluated in CKD patients undergoing hemodialysis.

Considering that CKD is a risk for hypovitaminosis D, an aspect frequently reported in the literature, the findings of this study were contrary to the most expected hypothesis, since only 20% of the sample presented vitamin D inadequacy, with an average value of 41.8 ng/mL.

It is possible that this low prevalence of vitamin deficiency is due to the fact that the study population lives in a locality with a tropical climate, which allows greater sun exposure and consequently higher production of serum levels of 25(OH) D. Another important aspect was the predominance (66.3%) of males in the sample, which according to literature is a population with a lower prevalence of vitamin D deficiency, compared to females, in which incidence rates are more expressive³³. Moreover, because it is a group composed of adults (mean age of 40.9 $\pm$ 10.6 years) undergoing hemolytic treatment for more than 2 years, it is considered that the existence of follow-up and professional guidance contributes to conscious support to the dietary plan directed to CKD, which reflects considerably on lifestyle and diet, resulting in the maintenance of ideal levels of the nutrient in question.

On the other hand, the study by Diniz et al.³⁴, which investigated a patient with pre-dialysis CKD, found vitamin D deficiency/insufficiency in 72.6% of the sample. The authors consider that the presence of renal dysfunction and nephrotic proteinuria, possibly due to urinary losses of vitamin D linked to its plasma-binding protein, were the main explanations for this result.

Other literature, such as that by Blair et al.³⁵, who proposed to investigate patients in 5 dialysis centers in Massachusetts, observed that 92.4% of the individuals had vitamin D levels lower than 40 ng/mL, and that 80% had levels equal to or lower than 31 ng/mL. In addition, researchers found that

vitamin D (25(OH)D) deficiency seems to be more prevalent in stage 5 CKD. Similarly, Cupisti et al.³⁶ found that vitamin D deficiency was predominant (66.4%) in the 269 patients evaluated, while insufficiency was seen in only 16.5% of the sample, without proof of the relationship between vitamin D deficiency and renal function.

In addition to the evaluation of the vitamin D profile, anthropometric parameters such as BMI, WC, WHR and NC were also evaluated, which demonstrated adequacy compared to reference values, with statistically higher values in males ($p < 0.05$). Only NC was superior to desirable cutoff points, which suggested abdominal fat accumulation, and, therefore, greater predisposition to atherosclerotic events.

The relationship between vitamin D status and adiposity in the general population is supported by vitamin sequestration in adipose tissue, voluminous dilution or negative feedback mechanisms triggered by increased circulation of 1,25-dihydroxyvitamin D3, others assume that heavier individuals may participate less in outdoor activity, can also wear more clothing than thinner individuals, thus decreasing sun exposure and limiting endogenous production of calcitriol in the skin. However, it is still unclear whether adiposity should be considered when determining dietary requirements for vitamin D³⁷.

The recognition of BMI sensitivity to scale the risk of vitamin D inadequacy was not proven in this study. There are controversial results in the literature on the subject, however, it is necessary to highlight that BMI does not distinguish content of lean mass and adipose mass, and there is evidence that associates the concentrations of 25(OH)D positively with muscle stocks and negatively with fat stocks³⁸, so that the use of other adiposity indices could be more effective to glimpse the relationship of vitamin D over body composition.

Using a two-way genetic approach, authors confirm that high BMI leads to a lower concentration of 25(OH) D³⁹. In the current study the mean BMI values indicated normal weight, thus concentrations of vitamin D were close to normal levels.

Also regarding the relationship between vitamin D status and adiposity, the higher NC measurements showed a higher chance of vitamin D inadequacy in these patients. Zanon et al.⁴⁰ concluded that NC is an alternative to estimate body fat. Similarly, a study of 1,053 adults with a mean age of 39 years from five cities in Brazil found a close association between NC, visceral and subcutaneous fat deposition, and MetS⁴¹. The NC measurement demonstrates an association with atherogenesis, arterial hypertension and low HDL levels⁴². Similarly, the prevalence of hypertension, diabetes, dyslipidemias, obesity and changes in anthropometric markers were higher in individuals with increased NC; these findings suggest that decreased muscle mass and excess adiposity show associations with CKD and MetS⁴³.

Usual food intake showed a high probability of inadequate energy and macronutrients. The average caloric value of 25.8 kcal/kg/day classifies the diet of participants

as hypocaloric, which can contribute to negative energy balance, conditioning the mobilization of protein reserves to supply the caloric demand increased by the hypercatabolic character of the disease⁴⁴. It is emphasized that the achievement of nutritional needs constitutes a challenge among these patients due to anorexia being very prevalent in this population, resulting from uremic symptomatology, the effects of drug interactions, associated comorbidities, and also endocrine-metabolic alterations responsible for marked catabolism and significant loss of nutrients by dialysis treatment, especially^{45,46,47}.

The average protein intake was 1.3 g/kg/day, which is equivalent to a contribution of 20.9% of the total caloric value, indicating a hyperprotein intake and was statistically higher in women. Therefore, it was observed that habitual consumption of proteins was adequate for hemodialysis patients, since the protein needs of these patients is higher, due to losses during the dialysis process (10 to 12 g/session) and also because a decrease in plasma concentration of amino acids and peptides leads to muscle proteolysis. This fact suggests that participants may have received some specific nutritional guidance, particularly women, who tend to progress more slowly to an advanced stage of CKD compared to men, regardless of etiology, as they reveal a more disciplined behavior regarding the search for health services in the earlier stages of symptoms and better a dietary treatment.

The findings of this study are similar to those of Machado et al.⁴⁸, Araújo et al.⁴⁹, Vaz et al.⁵⁰, Ribeiro et al.⁵¹ which showed low energy consumption, attributing to hormonal and inflammatory changes. Alvarenga et al.⁵² found energy consumption of 20.5 ± 11.7 kcal/kg/day and protein of 0.87 ± 0.50 g/kg, which are both below recommendations.

Authors reported that a protein intake below the recommendations, associated with lower energy intake and catabolic effects of the disease, may result in negative nitrogen balance and expose patients to the risk of malnutrition^{53,54,55}.

The insufficient dietary intake of vitamin D observed in this study can be explained by the group's eating habits, characterized by low consumption of foods rich in vitamin D, such as: oily fish, mainly cod liver oil, canned tuna, salmon and sardines, egg yolk, mushrooms, liver and milks enriched with vitamin.

Body composition and body fat distribution are related to complications such as insulin resistance (IR), since adipose tissue receives the influence of several signs, insulin, cortisol and catecholamines. In response, tissue secretes other substances that act both locally and systemically, participating in several metabolic processes, such as: leptin, adiponectin, Tumor Necrosis Factor Alpha (TNF- α), among others. These play a fundamental role in insulin resistance, with abdominal fat having the greatest impact in this process⁵⁶.

It is also noteworthy that the cross-talk between vitamin D concentrations and IR is based on the action of 1,25 (OH)D on the increase in transcription of insulin receptor

genes⁵⁷. Genes stimulate the flow of calcium from cells, the transport of glucose in muscle⁵⁸ and also regulate the release of endocrine disruptors, such as nuclear PPAR (Peroxisome Proliferative Activated Receptor), capable of affecting insulin sensitivity⁵⁹. In addition, as expected, vitamin D deficiency may favor the expression of inflammatory cytokines, such as interleukins, IL-1, IL-6, TNF- α , which are involved in the biological mechanisms of insulin action resistance and Nuclear Factor Kappa-Beta (NF- κ B)^{17,60}.

In view of the mechanisms mentioned above, it is possible to explain the significant association between glycemia and HOMA-IR with vitamin D observed in this study. It is also noteworthy that the prevalence ratio showed high values of blood glucose and HOMA-IR, which revealed 2.27 and 2.41, respectively, more chances of vitamin D inadequacy.

A study by Kostoglou et al.⁶¹ showed a relationship between vitamin D levels and glycemic control in Type 2 Diabetes Mellitus. These findings may have therapeutic implications, as cautious vitamin D supplementation may improve glycemic control in Type 2 diabetes mellitus. Talaei et al.¹⁷ found results that prove the benefit of vitamin D supplementation for the significant reduction of insulin and HOMA-IR in patients with DM2. Authors also reported that the effects of vitamin D on insulin resistance was significant when vitamin D concentration was between 40 to 60 ng/ml (100-150nmol/l), but when vitamin D was lower or higher than this concentration, no influence on insulin resistance was observed. In the present study, the mean vitamin D value obtained (41.8 ng/mL) corroded with the above-mentioned findings and reinforced the effects of the nutrient on insulin resistance.

Other literature, such as the study by Lim et al.⁶², also found that low levels of 25(OH)D were associated with lower glycemic control, and even greater use of insulin in Asian populations with Type 2 Diabetes and stage 3 or 4 of CKD. In contrast, Hoffmann et al.⁶³ found that body composition, and not glycemic control, were associated with vitamin D status in an outpatient population of adults with DM and CKD.

It is also suggested that other determinants proposed for IR in patients with CKD could be present in the sample, such as: excess visceral fat, decreased physical activity and accumulation of uremic toxins.

It is noteworthy that the role of inflammation in the pathogenesis and especially in the progression of CKD has shown that patients with CKD have a pro-inflammatory phenotype that is accentuated as the renal lesion continues towards its terminal stage. In this study, despite the fact that these patients were in stages 4 or 5 of renal injury, no linear correlation was evidenced between cytokines and serum vitamin D, attributing this finding to the mean levels of Vitamin D found in this study. The results of Azizieh et al.³³ point to a possible role of vitamin D as a contributing factor for the balance of cytokines towards an anti-inflammatory role in inflammatory situations, as observed in CKD.

Studies by Azizieh et al.³³ and Peterson et al.⁶⁴ found no

statistically significant relationship between concentrations of 25(OH)D and IL-6, IL-10. Peterson et al.⁶⁴ observed a significant inverse relationship between the concentrations of 25(OH)D and TNF- α . In a study by Turk et al.⁶⁵, involving patients with hemodialysis with elevated Parathyroid Hormone (PTH) demonstrated that both oral and intravenous supplementation of 1.25(OH)₂ was able to significantly decrease IL-6 concentrations after 6 months of treatment, which was attributed to the inverse relationship between 25(OH)D and PTH.

Among the limitations observed in this study, the main ones are cited: the relatively small sample size and the proposed methodological (cross-sectional) design, which does not allow determining cause and effect. Furthermore, the investigation of the inflammatory profile focused on the evaluation of cytokine levels only in serum, which suggests a possible quantification bias, especially considering that these markers have very short half-life.

CONCLUSION

This study concluded that high values of NC and glycoinsulinemic parameters evaluated conditioned higher chances of inadequate vitamin D concentrations in CKD patients.

Considering the need to control serum vitamin D levels for bone mineral balance, immune defense, lipid profile control and insulin sensitivity optimization, which when compromised worsen the renal condition, it is suggested the implementation of nutritional education strategies aimed at the interrelated promotion of healthy eating habits, adequate sun exposure and physical activity.

It would be of great interest to conduct further studies in patients with other chronic diseases and inflammatory conditions, excluding confounding factors such as differences in participant characteristics, vitamin D status and associated comorbidity states, to elucidate not only the causal link between vitamin D deficiency and worsening glycemic control, as well as the possible immunomodulatory action of the nutrient in the pathophysiological scenarios of interest.

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