ZINC AND CARDIOVASCULAR RISK IN NEPHROPATHIC PATIENTS UNDERGOING HEMODIALYSIS TREATMENT

Zinco e risco cardiovascular de pacientes nefropatas em tratamento de hemodiálise

Zinc y riesgo cardiovascular de pacientes con enfermedad del riñón en tratamiento de hemodiálisis

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ABSTRACT

Objective: To assess the relationship between zinc concentration and cardiovascular risk in patients with chronic renal failure on hemodialysis. **Methods:** Analytical retrospective cross-sectional study carried out in Fortaleza, Ceará, Brazil, in 2012 with 43 adult patients with chronic renal failure on hemodialysis (HD group) and 35 healthy individuals (control group). Socioeconomic and biochemical (total cholesterol - TC, low density lipoprotein - LDL, very low density lipoprotein - VLDL, high density lipoprotein - HDL and triglycerides - TG) were collected. Plasma zinc was determined using coupled plasma optical emission spectrometry. HD group' lipid profile was collected from medical records, and the controls' lipid profile was analyzed using the Bioclin® kit. Non-HDL cholesterol was = CT – HDL-C. Cardiovascular risk was assessed using the TG/HDL ratio, with risk when ≥ 3.8. Student's t test, Pearson's test or Spearman's test were used. **Results:** Zinc was below the recommended and lower ($p<0.001$) in the HD group (68.40μg/dL and 85.53μg/dL, respectively). HDL-c in the HD group was below the recommended (39.64±11.58). VLDL (29.02±14.03 mg/dL) in HD patients was higher ($p<0.001$) than in controls (15.47±10.65 mg/dL). LDL was higher in the HD group than in controls ($p=0.05$) and TG in the HD group (145.14±70.15 mg/dL) was higher ($p<0.001$) than in controls (77.35±53.25 mg/dL). The TG/HDL ratio in the HD group was 4.02±2.60 ($p=0.04$), indicating a higher cardiovascular risk. Individuals with higher TG/HDL had lower zinc ($p=0.011$). **Conclusion:** Patients on hemodialysis presented with zinc deficiency and high cardiovascular risk, but there was no correlation between zinc levels and lipid profile.

Descriptors: Renal Insufficiency, Chronic; Zinc; Renal Dialysis; Cholesterol.

RESUMO

Objetivo: *Investigar a relação entre concentração de zinco e risco cardiovascular em pacientes com insuficiência renal crônica em hemodiálise.* **Métodos:** *Estudo analítico, retrospectivo e transversal, realizado em Fortaleza, Ceará, em 2012, do qual participaram 43 adultos com insuficiência renal crônica em hemodiálise (grupo HD) e 35 saudáveis (CO - controle). Coletaram-se dados socioeconômicos*

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*e bioquímicos (colesterol total - CT, lipoproteína de baixa densidade - LDL, lipoproteína de muito baixa densidade - VLDL, lipoproteína de alta densidade - HDL e triglicerídeos - TG); determinou-se zinco plasmático por espectrometria de emissão óptica com plasma acoplado; coletou-se perfil lipídico do grupo HD do prontuário e do grupo CO por meio de kit Bioclin®. Obteve-se colesterol não-HDL pela fórmula: não-HDL = CT – HDL-c. Calculou-se risco cardiovascular pela razão TG/HDL, considerando risco quando ≥3,8. Análises por meio de testes t de Student, Pearson ou Spearman. **Resultados:** O zinco do grupo HD encontrou-se abaixo da referência e menor (p<0,001) em relação ao controle (68,40µg/dL e 85,53µg/dL, respectivamente). HDL no grupo HD mostrou-se abaixo da recomendação (39,64±11,58). VLDL (29,02±14,03mg/dL) do grupo HD foi maior (p<0,001) que no CO (15,47±10,65mg/dL). LDL do grupo HD maior que no CO (p=0,05) e o TG no grupo HD (145,14±70,15mg/dL) maior (p<0,001) que no CO (77,35±53,25mg/dL). Encontrou-se razão TG/HDL no grupo HD de 4,02±2,60 (p=0,04), indicando maior risco cardiovascular. Pacientes com maior relação TG/HDL apresentaram menores níveis de zinco (p=0,011). **Conclusão:** Os pacientes em hemodiálise apresentaram deficiência de zinco e possuíam elevado risco cardiovascular, porém sem correlação entre zinco e perfil lipídico.*

Descritores: *Insuficiência Renal Crônica; Zinco; Diálise Renal; Colesterol.*

RESUMEN

Objetivo: *Investigar la relación entre la concentración de zinc y el riesgo cardiovascular de pacientes con insuficiencia renal crónica en hemodiálisis. **Métodos:** Estudio analítico, retrospectivo y transversal realizado en Fortaleza, Ceará, en 2012, en el cual participaron 43 pacientes adultos con insuficiencia renal crónica en hemodiálisis (grupo HD) y 35 saludables (grupo CO - control). Se recogieron los datos socioeconómicos y bioquímicos (colesterol total - CT, lipoproteína de baja densidad - LDL, lipoproteína de muy baja densidad - VLDL, lipoproteína de alta densidad - HDL y triglicéridos - TG); se determinó el zinc plasmático por la espectrometría de emisión óptica por el plasma de acoplamiento inductivo; se recogió el perfil lipídico del grupo HD del historial clínico y el del grupo control a través del kit Bioclin®. Se obtuvo el colesterol no-HDL por la fórmula: no-HDL = CT – HDL-c. Se calculó el riesgo cardiovascular por la razón TG/HDL considerando riesgo cuando ≥3,8. Los análisis fueron a través de la prueba t de Student, Pearson o Spearman. **Resultados:** El zinc del grupo HD fue menor y abajo de la referencia (p<0,001) en comparación con el control (68,40µg/dL y 85,53µg/dL, respectivamente). La HDL del grupo HD se mostró abajo de la recomendación (39,64±11,58). El VLDL (29,02±14,03mg/dL) del grupo HD ha sido mayor (p<0,001) que en el CO (15,47±10,65mg/dL). La LDL del grupo HD ha sido mayor que en el CO (p=0,05) y el TG en el grupo HD (145,14±70,15mg/dL) mayor (p<0,001) que en el CO (77,35±53,25mg/dL). Se encontró la razón TG/HDL en el grupo HD de 4,02±2,60 (p=0,04) con menores niveles de zinc (p=0,011). **Conclusión:** Los pacientes en hemodiálisis presentaron deficiencia de zinc y tenían elevado riesgo cardiovascular, sin embargo, sin relación entre el zinc y el perfil lipídico.*

Descriptores: *Insuficiencia Renal Crónica; Zinc; Diálisis Renal; Colesterol.*

INTRODUCTION

Chronic renal failure (CRF) consists of renal damage with progressive and irreversible loss of kidney function, with hemodialysis (HD) being recommended as renal replacement therapy (RRT). CRF is a major public health problem in Brazil and the estimated total number of patients undergoing RRT in the country has been increasing rapidly. In 2013, there were approximately 100,397 patients, representing a 3% increase in relation to the past three years. The estimated prevalence for the same year was 499 patients per million population (pmp), with an incidence of 170 patients pmp. The number of deaths accounted for 17.9% of the causes of death in the country[1].

There is a growing interest in nutritional disorders and nutritional therapy in patients with CRF treated with HD. Low plasma zinc (Zn) levels are found in these patients, which can occur as a result of uremia, reduced renal function, diet, medication, losses in the HD treatment, increased fecal excretion or decrease of intestinal absorption[2-5]. Given its biological importance, Zn has been associated with several parameters that may predict unsatisfactory clinical outcomes, including changes in cholesterol profile, which may contribute to the increase of morbidity and mortality in patients with CRF[6,7].

One of the main alterations of the lipid profile present in patients submitted to HD is called uremic dyslipidemia and is characterized by hypertriglyceridemia, high VLDL (very low-density lipoprotein) and LDL (low-density lipoprotein) levels and low HDL (high-density lipoprotein) levels. The role of Zn in this process is poorly understood, but it is known that dietary mineral deficiency can reduce Zn levels in endothelial cells so that there may be damage related to oxidative stress, apoptosis, inflammation and metabolic changes, such as changes in lipid profile, leading to cardiovascular complications[8-10].

Cardiovascular complications are closely associated with mortality in patients with chronic kidney disease undergoing HD, and the number of deaths is 10 to 20 times higher than in the general population[11]. The pathophysiology of cardiovascular disease (CVD) in this population is complex and has been determined by the high prevalence of traditional risk factors such as obesity and dyslipidemia. Researchers have suggested the use of an index that has shown a strong relationship to cardiovascular risk, the TG/HDL-cholesterol ratio, which strongly predicts the risk of acute myocardial infarction and is acknowledged as

an independent atherogenic marker that is more significant than the other ratios (TC/HDL-c and LDL/HDL-c). In addition, it correlates directly with plasma type B LDL-C particles, which are more easily oxidized, thus becoming more atherogenic[12].

Adequate nutrition plays an essential role in the treatment of kidney diseases. Individualized dietary counseling should be combined with nutrition education programs to assist in the control and prevention of CRF complications. Considering the increase in morbidity and mortality due to the clinical treatment of CRF and the scarcity of data in this field of knowledge, the present study aimed to assess the relationship between zinc concentration and cardiovascular risk in patients with chronic renal failure on hemodialysis.

METHODS

This is an observational retrospective and cross-sectional study carried out with two groups: HD group, patients with CRF on HD (n=43) and control group (CO group), healthy participants (n=35). The HD group included adult patients with CRF on HD with no associated chronic diseases, such as cancer and diabetes, attending two specialized clinics for patients with kidney diseases in the city of Fortaleza, Ceará, Brazil. Patients were selected in a non-random and convenient manner from July to December 2012. The control group included volunteers from a public university in the state who were selected in a non-random and convenient manner. Individuals who were not diagnosed with renal failure or any chronic diseases were eligible.

Socioeconomic data (age, gender, ethnicity and education) were collected through a direct interview using a structured questionnaire. Venous blood samples were collected from the participants after a 12-hour fasting period using disposable plastic syringes and sterile needles. Blood was collected into glass tubes containing 30% sodium citrate as anticoagulant (10μL/mL of blood) for the analysis of Zn (10mL).

To ensure control of contamination by minerals, all glassware and polypropylene material used for analysis underwent a demineralization process using 30% nitric acid solution for a minimum period of 12 hours. Further, they were rinsed using deionized water, dried in a specific oven for demineralized material and kept in closed containers until the moment of use.

Zn level was determined using Inductively Coupled Plasma – Optic Emission Spectrophotometry (ICP-OES)[13] with the following analytical conditions: ICP-OES spectrometer (Varian/Agilent® 730 Series) with axially-viewed plasma and SVS-2 continuous flow sampler for sample injection. The device was set as follows: power: 1.4 kW; plasma flow (gas): 15 L/minute; auxiliary gas flow: 1.5 L/minute; spray chamber type: cyclonic; nebulizer flow: 0.7 L/minute. Calibration curves for the tested analytes were as follows: 1, 5, 10, 20, 50 and 100 ug/L in diluent solutions containing 3.0% (m/v) 1-butanol, 0.1% v/v) TAMA (high purity surfactant), 0.05% (v/v) HNO_3. Reference material was used to measure the accuracy of measurements - Seronorm L2 LOT 1003192 (SERO Norway®).

The dilution of the plasma samples consisted of 1:10, with v/v as follows: 3.0% (m/v) 1-butanol, 0.1% (v/v) TAMA (high purity surfactant), and 0.05% (v/v) nitric acid (HNO_3) to aid in the dissolution of trace elements in the samples. The acid concentration was kept to a minimum due to the precipitation or aggregation of cellular components into blood samples, thereby removing some analytes from the solution. The reference value chosen was 70μg/dL[14].

The analysis of the lipid profile was performed by collecting data on total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), VLDL, low-density lipoprotein cholesterol (LDL-c) and triglycerides (TG). Information on the HD group was obtained by consulting medical records. The analysis of the lipid profile data of the CO group followed the guidelines of the Bioclin® automation kit (QUIBASA, Brazil). Non-HDL cholesterol was determined as follows: Non-HDL cholesterol = TC – HDL-C.

The abnormality criteria selected for plasma lipids were based on the V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis[15]: TC > 200mg/dl; HDL-c <40mg/dl; LDL-c >100mg/dl; TG >150mg/dl and non-HDL cholesterol >130mg/dl.

The TG/HDL-c ratio, which was obtained using plasma TG and HDL-c values and the pre-established equation, was classified into risk for CVD when TG/HDL-c $\geq$3.8 for both genders[16].

The statistical analysis was performed using SPSS version 20.0. All continuous variables were tested for normality of distribution using the Kolmogorov-Smirnov test. Mean and standard deviation were used to describe the continuous numerical variables. Student's t-test was used to compare means and Pearson's or Spearman's tests were used to check for correlations.

This research is in accordance with Resolution 466/12 of the National Health Council and was approved by the Research Ethics Committee of the Health Secretariat of the State of Ceará under Approval No. 203.906. Participants were previously informed of the research objectives and signed a Free Informed Consent Form prior to data collection.

RESULTS

The HD group had a mean age of 50.8±18.5 years, with 53.5% (n=23) of its participants being men. The most predominant level of education was primary education (42.6%, n=18) and there was a prevalence of *Pardos* (mixed-race Brazilians), which accounted for 59.6% (n=26) of the patients. Most of the participants (74.2%, n=32) had an income of one minimum wage.

Table I shows the description of the groups as for the lipid and zinc profiles. With regard to plasma Zn, mean values were 68.40μg/dL in the HD group and 85.53μg/dL in the CO group. The level of this mineral in patients with CRF is below the reference parameters and significantly lower ($p < 0.001$) than the levels found in healthy individuals.

The TC level in the HD group was within the recommendation, with no differences in relation to the CO group. HDL-c levels were low in both groups and below the recommendation. Mean VLDL was 29.02±14.03 mg/dL in the HD group and 15.47 ± 10.65 mg/dL in the CO group, both within the reference values. However, the HD group presented a significantly higher mean in relation to the CO group ($p < 0.001$). LDL values in the HD group were higher than those in the CO group ($p = 0.05$); however, the levels were within the recommendation. The mean TG in patients with CRF (145.14±70.15 mg/dL) was significantly higher ($p < 0.001$) than the mean value in the group of healthy participants (77.35±53.25 mg/dL); however, the values are within the reference parameters. Non-HDL cholesterol levels showed no difference between the groups, with both groups presenting levels within the recommendation.

The mean TG/HDL-c ratio in the HD group was 4.02 ± 2.60. In the CO group the mean was significantly lower ($p = 0.04$), with a value of 2.59±3.6.

Plasma Zn did not correlate with lipid profile markers. However, individuals who presented higher TG/HDL-c ratio values and higher risk for CVD had lower mean Zn levels ($p = 0.011$) when compared to those without cardiovascular risk.

Table I - Lipid profile and plasma zinc of hemodialysis and control groups. Fortaleza, Ceará, 2012.

Biochemical variables	HD group	CO group	Reference Value*	p value
Total Cholesterol	154.23±33.50	165.67±59.86	< 200mg/dL	0.335
HDL-c	39.64±11.58	42.08±10.42	> 60 mg/dL	0.349
VLDL	29.02±14.03	15.47±10.65	< 30 mg/dL	0.000
LDL-c	85.56±27.64	108.87±60.49	< 100 mg/dL	0.052
Triglycerides	145.14±70.15	77.35±53.25	< 150 mg/dL	0.000
Non-HDL Cholesterol	114.59±32.66	123.59±59.95	< 130 mg/dL	0.446
Zinc**	68.40±5.09	85.53±5.86	70μg/dL	<0.001
TG/HDL-c	4.02±2.60	2.59±3.6	<3.8	0.046

HDL-c: High-density lipoprotein; VLDL: Very low-density lipoprotein; LDL-c: Low-density lipoprotein; TG: Triglycerides; HD: Hemodialysis; CO: Control; Results are described as mean ± SD; *Brazilian Society of Cardiology[15]; ** Gibson[14].

DISCUSSION

During HD treatment, some elements can accumulate in the body, and in certain situations microminerals, such as Zn, may enter the dialysate, leading to a deficiency of these elements[17,18]. In the present study, the Zn levels in patients with CRF were below (68.40 μg/dL) normal levels and lower ($p < 0.001$) than those in healthy participants, thus revealing that these patients have a deficit of this mineral. Other studies have also demonstrated a reduction in plasma Zn levels in HD patients, with values below the reference of 70 μg/dL and similar to those of the present study: 54.5±16.3 μg/dL[19]; 62.03±13.59 μg/dL[20]; 61.27 μg/dL[21].

Zn deficiency has been acknowledged as a prevalent condition in this population[17]. Several factors may contribute to a higher nutritional risk and specific nutrient deficiency, such as the reduction in food consumption, which is frequently present in these patients, especially in older individuals[22,23]. Furthermore, it is observed that 74.2% of the patients with CRF belong to the lower economic classes and have lower levels of education. The low socioeconomic level may be related to CRF complications due to the difficult access to the health system, to foods that are essentially zinc sources, and to nutritional guidelines[24].

According to the European Renal Association, a daily intake of 8 to 12mg of zinc for women and of 10 to 15mg for men on HD is recommended. Routine supplementation is not recommended; however, the use of 50 mg/day for three to six months may be considered in patients with chronic inadequate protein/energy intake and symptoms associated with zinc deficiency, such as changes in taste and smell, skin fragility, impotence and peripheral neuropathy[25]. In Brazil, there is no specific zinc recommendation for patients on HD. The country adopts the recommendations of the American Institute of Medicine, which recommends the intake of 8 mg/day for women (from the age of nine) and 11 mg/day for men (from the age of fourteen)[26]. However, there is a predominance of inadequate zinc intake among these patients[27].

The lack of Zn in patients with CRF can lead to clinical symptoms such as changes in taste, reduced immunocompetence, and several metabolic alterations, such as changes in the lipid profile[28]. Although there was no statistical correlation between Zn levels and lipid profile in the present study, there was a deficiency of this mineral in individuals on HD and they presented negative changes in their lipid profile, such as high VLDL, LDL and TG levels and low HDL levels.

There is a growing body of evidence showing that these lipid metabolism abnormalities contribute to the progression of kidney disease, and that the vicious cycle between renal dysfunction and dyslipidemia is activated, which seems to contribute to cardiovascular mortality. Cardiovascular complications are considered the main causes of death in this population, especially among those submitted to HD, and this prevalence increases 10 to 20 times[29].

A longitudinal study that assessed the relationship between TG/HDL-c and CRF found a significant relationship between them that, in addition to predicting cardiovascular outcomes, is also a parameter to identify the risk of developing and progressing CRF[30]. In present research, patients on HD presented a high TG/HDL-c ratio, thus indicating a higher risk of cardiovascular events. In addition, those who were classified as having cardiovascular risk presented a significantly lower mean (p=0.011) of Zn level than those who did not exhibited this risk.

Several educational methods addressing dietary habits of patients on HD have been developed and, due to the great difficulty of dietary adequacy in this public, there is a need for constant interventions on food behavior to foster adequate food choices and reduce risk in this population[31].

Given that, studies have been carried out to analyze the supplementation of this mineral as a strategy to reestablish Zn levels in HD patients[32,33]. This intervention may be an effective means of improving plasma levels of this mineral and consequently the lipid profile and of reducing cardiovascular events[34,35]. Therefore, the need for a more frequent monitoring of zinc blood levels in these patients is emphasized in order to minimize the possible damages caused by its deficiency. In addition, further research should be developed, especially on zinc, oxidative stress and CVD.

In this regard, the collaboration of the nutritionist with other health professionals should be part of the treatment of the disease, since nutritional status, especially with respect to specific nutrients, can positively or negatively interfere with the therapeutic results of CRF.

CONCLUSION

The hemodialysis patients analyzed presented zinc deficiency and had a high cardiovascular risk due to the high TG/HDL ratio. However, there was no correlation between zinc and lipid profile.

CONCLICTS OF INTEREST

The authors declare the are no conflicts of interest.

The manuscript used the same population analyzed in the thesis titled "Selenium x chronic renal failure: assessment of nutritional status of selenium in patients on hemodialysis treatment and healthy individuals living in Fortaleza, Ceará", **Ceará State University** (*Universidade Estadual do Ceará*), Health Sciences Center, Nutrition and Health Master's Degree Program, Fortaleza, 2013, **72 pages**.

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