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Original/*Otros*

The association of selenium status with thyroid hormones and anthropometric values in dyslipidemic patients

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Abstract

Background: **Selenium (Se) is an essential micronutrient that performs physiological functions in the metabolism of thyroid hormone and may have an association with anthropometric variables relevant to cardiovascular disease. Aim: To study the associations between Se status, thyroid hormones and anthropometric variables in dyslipidemic patients.Methods: Eighty-three patients were assessed in a cross-sectional study. Blood samples were analyzed for Se and thyroid hormones. Anthropometric measurements were taken, and dietary Se intake was investigated.**

Results: **Mean plasma Se concentrations were low in the patients, at 88.7 ± 16.7 μg/L. Patients with plasma Se ≥ 95 μg/L were found to have a higher body mass index (BMI) (30.74 ± 4.31 vs 27.68 ± 5.63 kg/m², *P* = 0.02) and waist-to-height ratio (0.65 ± 0.05 *vs* 0.59 ± 0.07, *P* = 0.003) when compared to those with concentrations between 80 and 94 μg/L. Se intake associated positively with T_3L/T_4L ratio (*r* = 0.273; *P*= 0.03), BMI (*r*= 0.257, *P*= 0.04) and WC (*r*= 0.299, *P*= 0.02). Conclusion: The patients with the highest normal plasma Se concentrations were found to have increases in the anthropometric variables we investigated. There is a need for further study in order to elucidate these findings. Furthermore, we found a positive association between Se intake and the most metabolically active form of the thyroid hormones.**

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Key words: *Selenium. Thyroid hormones. Anthropometry. Dyslipidemia.*

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RELACIÓN ENTRE LOS NIVELES DE SELENIO, LAS HORMONAS TIROIDEAS Y LA ANTROPOMETRÍA EN PACIENTES CON DISLIPIDEMIA

Resumen

Contexto: **El selenio (Se) es un micronutriente esencial que realiza las funciones fisiológicas en el metabolismo de la hormona tiroidea y pueden tener una asociación con las variables antropométricas pertinentes a la enfermedad cardiovascular.**

Objetivo: **Estudiar la asociación entre el estado de Se, hormonas tiroideas y las variables antropométricas en pacientes con dislipidemia.**

Métodos: **Ochenta y tres pacientes fueron evaluados en un estudio transversal. Se analizaron muestras de sangre para Se y hormonas tiroideas. Las medidas antropométricas fueron tomadas, y la ingesta de la dieta Se fue investigado.**

Resultados: **La media de las concentraciones de Se en plasma fueron bajas en los pacientes, a 88,7 ± 16,7 mg / l. Se encontró que los pacientes con niveles plasmáticos de Se ≥ 95 mg / L de tener un índice de masa corporal (IMC) (30.74 ± 4.31 vs 27.68 ± 5.63 kg / m 2, P = 0,02) y la relación cintura-estatura (0,65 ± 0,05 vs 0,59 ± 0,07, P = 0,003) en comparación con aquellos con concentraciones entre 80 y 94 g / l. Ingesta de Se asoció positivamente con relación T3L / T4L (r = 0,273, p = 0,03), índice de masa corporal (r = 0,257, P = 0,04) y WC (r = 0,299, P = 0,02).**

Conclusión: **Se encontró que los pacientes con las más altas concentraciones de Se en plasma normal tener incrementos en las variables antropométricas que investigamos. Hay una necesidad de un mayor estudio para dilucidar estos hallazgos. Además, se encontró una asociación positiva entre el consumo de Se y la forma más metabólicamente activa de las hormonas tiroideas.**

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Palabras clave: *Selenio. Hormonas tiroideas. La antropometría. La dislipidemia.*

Introduction

Cardiovascular disease (CVD) is among the main causes of death around the world.

The 2010 overall rate of death attributable to CVD in the EUA was 235.5 per 100 000[1]. It is estimated that 23% of the deaths from ischemic heart diseases are related on by excess weight[2].

Thyroid hormones are related to cardiovascular health[3] and, within normal range, have been associated with body weight and waist circumference (WC)[4,5]. As for the thyroid gland itself, it contains the highest selenium (Se) content of the entire human body[6]. Se status may have an influence on thyroid hormones[7], given its importance in the conversion of the metabolically active form of these hormones and protecting the thyroid gland from the oxidative damage that arises during the synthesis of these hormones[3,6].

There is a lack of studies investigating plasma concentrations and intake of Se in association with anthropometric parameters in a dyslipidemic population[8,9]. Such analysis has clinical relevance due to the importance that changes in body weight have on cardiovascular health[2]. Our hypothesis is that plasma concentrations, Se intake and thyroid hormones are interrelated, as well as related to anthropometric parameters. The aim of this study, therefore, is to evaluate the association that plasma concentration and intake of Se have with thyroid hormones and anthropometric variables.

Pacients and methods

Ethical Concerns

All patients involved in this study were informed of the procedures to which they would be subjected and signed a written consent form. This study was approved by the Clinical Research Ethics Committee of the INC (National Institute of Cardiology) (316/2011).

Pacients

Patients were recruited at the National Institute of Cardiology. s We studied dyslipidemic patients in the secondary level of health care, all of whom were using lipid-lowering medication.

The entry criteria included euthyroid, dyslipidemic, hypertense, between 45 and 85 years of age, of both sexes, given overall nutritional orientation by the nutritional outpatient unit, and did not alter the dosage of lipid-lowering medication during the three months prior to joining the study. Subjects were excluded if they had past history of disease or use of thyroid medication; use of medication for treating cardiovascular diseases that affect thyroid function, such as amiodarone and propranolol; having suffered an acute cardiovascular event within the last six months, chronic kidney disease with a glomerular filtration rate < 60 mL/minute/1.73m^2 [(10)], or malignancy; use of oral contraceptives or hormone replacement therapy; and participation in a rigorous physical activity/weight loss program during the three months preceding the study.

Of the 97 participants initially recruited over the phone from the INC Atherosclerosis and Cardiovascular Prevention Outpatient Clinic (Rio de Janeiro, Brazil), 83 dylipidemic and hypertensive patients (49 males and 34 females) were eligible (Fig. 1). Among those who did not meet the inclusion criteria, three were shown to have hyperthyroidism; three, hypothyroidism; two, chronic kidney disease with a glomerular filtration rate < 60 mL/minute/1.73m^2; and one was found to have malignancy.

Approach

This was a a cross-sectional study between July 2011 and June 2012.

A questionnaire was used to general information and specifics regarding any medication, practice of physical activities, and dietary habits. Blood samples were taken to determine levels of plasma Se and thyroid hormones, as well as lipid profile. Furthermore, we carried out an anthropometric assessment to determine weight, BMI, waist circumference (WC) and waist-to-height ratio (WHtR).

Analysis of the association , plasma Se and thyroid hormone levels ,with anthropometric variables was based on tertiles of study-participant plasma Se concentrations. We also analyzed the associations between Se intake, thyroid hormones and anthropometric variables.

Definitions

Patients were considered dyslipidemic if they were using a lipid-lowering medication or were found to have serum LDL ≥ 160 mg/dL or triglycerides ≥ 150mg/dL or if high-density lipoprotein (HDL) levels were < 40 mg/dL in men and < 50mg/dL in women. These alterations could occur on their own or in association with one another[11].

Patients were considered to be hypertensive if they were taking antihypertensive drugs or were found to have an average blood pressure ≥ 140/90 mmHg[12].

The cutoff points for being classified as having euthyroidism were as follows: TSH of 0.45-4.50 μUI/mL; T4L of 0.7-1.48 ng/dL; T3 of 0.58-1.59 ng/mL; T3L of 1.71-3.71 pg/mL[13].

Normal plasma Se concentrations were estimated according to levels of the mineral required for attaining maximum glutathione peroxidase activity—a normal range, between 95 and 150 μg/L[14]. The re-

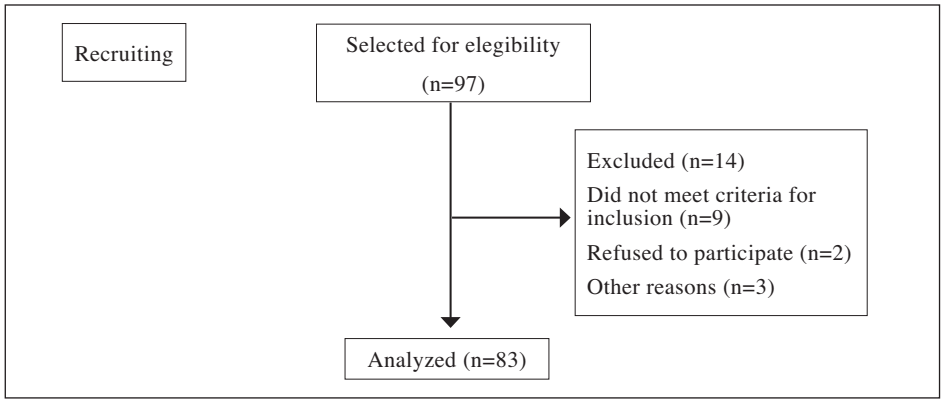

Fig. 1.—Flowchart of study participants

commended Se intake is 55 μg/day for both sexes, according to Dietary Reference Intake (DRI)[15].

We define as eutrophic a BMI between 18.5 and 24.9 kg/m^2, overweight as a BMI between 25 and 29.9 kg/m^2, and obese as a BMI ≥ 30 kg/m^2. [16]

we defining increased WC as being ≥ 88 cm in females and ≥ 102 cm in males[17]WHtR was considered a determinant of increased coronary risk when ≥ 0.52 in men and ≥ 0.53 in women[18].

Questionnaires were employed to assess physical activity[19]. Individuals were classified as either sedentary, if they practiced no physical activity, or moderately inactive, since none of them was found to expend more than 100 kcal of energy through physical activity per day.

Variables investigated

Body weight was taken using an electronic anthropometric scale (Filizola®, São Paulo, Brazil) with a 180 kg maximum capacity and accurate to 100g. Height measurements were taken using a stadiometer accurate to the 1mm (Standard Sanny®, São Paulo, Brazil). Using the weight and height measurements to calculate it, BMI was defined as weight (kg)/height (m)^2 [(16)].

WC was ascertained using measuring tape accurate to the 0.1 cm (Standard Sanny®, São Paulo, Brazil)[17], and WHtR was determined by dividing WC (cm) by height (cm)[18].

We used WHtR due to its importance as an anthropometric indicator of obesity and predictor of increased coronary risk[18].

Fasting blood for biochemical profile was draw after 12-hour fast and was analyzed INC Laboratory for Clinical Analysis (Rio de Janeiro, Brasil) using equipment (ARCHITECT *ci*8200, Abbott ARCHITECT®, Abbott Park, IL, USA) and commercial kits (Abbott ARCHITECT *c*8000®, Abbott Park, IL, USA).

Serum concentrations of TSH and the thyroid hormones total triiodothyronine (T3), free triiodothyronine (T3L) and free thyroxine (T4L) were analyzed using chemiluminescence microparticle immunoassay (CMIA). The free triiodothyronine/free thyroxine ratio (T3L/T4L ratio) was obtained using the conventional units of measure.

Serum concentrations of triglycerides, total cholesterol and HDL-c were determined using the enzymatic colorimetric method: glycerol phosphate oxidase/peroxidase, oxidase/peroxidase cholesterol and direct detergent, respectively. The LDL-c values were obtained using the formula of Friedewald et al. (1972)[20].

The plasma Se concentrations were analyzed in samples collected in VACUETTE® Trace Elements NH Sodium Heperin tubes and kept at -70ºC until the moment analysis was performed. These concentrations were determined by atomic absorption spectrometry using a mass spectrometer with an inductively coupled plasma source (NexION™300 ICP-MS, PerkinElmer, Massachusetts, USA). This analysis was carried out at LABSPECTRO, at the Pontifical Catholic University of Rio de Janeiro, Brazil.

Habitual dietary Se intake was assessed using a food frequency questionnaire (FFQ) validated[21] using the Food Processor software version 12 (EshaResearch, 1984, Salem, MA, USA).

Statistical analysis

All results were expressed as mean ± standard deviation (SD) for quantitative variables and as percentages for qualitative variables. We checked for the normality of the variables by using the Kolmogorov-Sminorv statistical test.

We used the Spearman test to analyze the association between Se intake and the variables under study.

When investigating the associations between the plasma Se concentrations in tertiles of the sample population and thyroid hormones and anthropometric variables, we used the Kruskal-Wallis test with a post-hoc Mann-Whitney U test to compare between the two groups. We employed the chi-squared test to assess the difference in prevalence of increased waist circumfe-

rence according to the tertiles showing plasma Se concentrations.

A P value < 0.05 was considered statistically significant. Statistical analysis was carried out using SPSS software (version 12, SPSS Inc., Chicago, IL, USA).

Results

Table I shows detailed information on clinical and laboratory variables of the study population.

The mean age in the total group was 60.7 ±10.2 years of age. Men and woman were distribute equally (83 patients,49 of them men) Of them, 33.7% were moderately inactive, while 66.3% were sedentary.

Elevated prevalence of overweight/obese (73.5%), with abdominal obesity with increased WHtRs (n=73, 89%) and increased WC (n=50, 61%). The percentage for adequate BMI was 26.5%, WC was 39%, and WHtR was 11%.

We found that 65.1% of the patients had plasma Se at levels below the baseline values, that is, low concentrations of plasma Se (88.7 ± 16.7 μg/L, minimum: 50 mcg/L and maximum: 122 mcg/L). Additionally, 55% of the patients were found to have Se intake below DRI recommendations.

Table I
Laboratorial, anthropometric and dietary characteristics of the study participants

Variable	*Mean ± SD*	*Median*	*Range p25 – p75*
Plasma Se – μg/L	88.66 ± 16.73	88	78.00 – 101.00
TSH – μUI/mL	2.55 ± 1.64	2.1	1.52 – 3.21
T4L – ng/dL	1.19 ± 0.15	1.2	1.11 – 1.29
T3– ng/mL	1.04 ± 0.21	1	0.92 – 1.19
T3L – pg/mL	2.94 ± 0.44	2.93	2.68 – 3.19
T3L/T4L Ratio	2.51 ± 0.49	2.5	2.19 – 2.82
Total cholesterol – mg/dL	216.87 ± 87.79	205	157.00 – 260.00
LDL-c – mg/dL	130.95 ± 58.07	118	89.00 – 154.00
HDL-c – mg/dL	38.65 ± 12.79	35	30.00 – 47.00
Triglycerides – mg/dL	194.02 ± 131.19	168	120.00 – 235.00
BMI – kg/m2	29.13 ± 5.02	28.58	25.55 – 32.18
WC – cm	100.66 ±12.19	99.5	93.50 – 108.00
WHtR	0.62 ± 0.07	0.62	0.57 – 0.66

Se, selenium; TSH, thyroid stimulating hormone; T4L, free thyroxin; T3, total triiodothyronine; T3L, free triiodothyronine; LDL-c, low density lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio.

Table II
Comparison of average serum thyroid hormone values and anthropometric and dietary variables studied, by tertiles of plasma Se concentrations

Variables	*Plasma Se Tertiles*		
	1st tertile (n = 26) 50 – 79 μg/L	*2nd tertile (n = 29) 80 – 94 μg/L*	*3rd tertile (n = 28) 95 – 122 μg/L*
TSH – μUI/mL	2.50 ± 1.80	2.48 ± 1.13	2.66 ± 1.95
T_4L –ng/dL	1.21 ± 0.14	1.18 ± 0.12	1.17 ± 0.18
T_3L–pg/mL	2.90 ± 0.52	3.05 ± 0.30	2.85 ± 0.46
T_3L/T_4L Ratio	2.43 ± 0.57	2.60 ± 0.33	2.49 ± 0.56
BMI – kg/m^2*	29.03 ± 4.66	27.68 ± 5.63	30.74 ± 4.31
WC – cm*† ‡	100.84 ± 10.61	94.65 ± 11.99	106.96 ±10.89
WHtR*	0.62 ± 0.07	0.59 ± 0.07	0.65 ± 0.05

Se, selenium; TSH, thyroid stimulating hormone; T_4L, free thyroxin; T_3, total triiodothyronine; T_3L, free triiodothyronine; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio.
The variables were presented as mean ± SD. The groups were divided into tertiles according to plasma Se concentrations. To compare the groups, we used the Kruskal-Wallis test due to the abnormal distribution of variables. We used the Mann-Whitney test for analysis between two groups in a post-hoc comparison.
*P < 0.05: 2nd tertile versus 3rd tertile. † P < 0.05: 1st tertile versus 3rd tertile.‡ P < 0.05: 1st tertile versus 2nd tertile.

The medications used for treating dyslipidemia are presented in table II. It is noteworthy that most of the patients were taking statins.

Se intake associated positively with T3L/T4L ratio ($r = 0.273$; $P = 0.03$), BMI ($r = 0.257$, $P = 0.04$) and WC ($r = 0.299$, $P = 0.02$).

The differences between the tertiles of plasma Se concentrations and the serum thyroid hormone levels and anthropometric variables are presented in table III.

No differences in TSH concentrations, thyroid hormones or T3L/T4L ratio were found between the groups according to plasma Se concentrations (Table III).

Patients belonging to the group with the highest plasma Se concentrations were found to have the highest BMI (P=0.02), WC ($P < 0.001$) and WHtR ($P=0.003$) when compared to those with intermediate concentrations. Moreover, the patients in the 1st plasma Se tertile too had a higher WC compared to the group with the intermediate concentrations ($P = 0.03$), despite the patients belonging to the 1st tertile showing a lower WC when compared to those of the 3rd tertile ($P=0.04$) (Table III).

Figure 2 features the prevalence of increased WC by plasma Se-concentration tertiles.

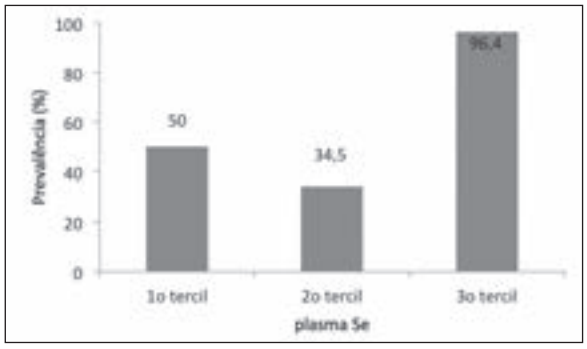

Fig. 2.—Prevalences of increases (%) in Waist Circumference (WC) according to tertiles of plasma Se concentrations. The prevalence of increased WC was least in the group with intermediate Se concentrations (P = 0.001).

Discussion

In this cross-sectional study, we found plasma Se concentrations were low, given how 95 to 150 μg/L[14] was considered to be the optimal range for plasma Se concentrations in the dyslipidemic and hypertensive patients. This can be explained by the low dietary intake of Se. Furthermore, the increase in oxidative stress inherent in dyslipidemia[22], which causes a rise in demand for glutathione peroxidase and other antioxidant selenoproteins[23], may possibly have a role in this finding. There are some studies in dyslipidemic patients that show low plasma Se concentrations, between 55 and 88 μg/L[24,25]. Another significant aspect comes from a cross-sectional study by Arnaud et al. (2008)[26], they found the use of statin treatment in dyslipidemic patients takes to a lower plasma Se concentrations than those taking fibrates, theaverage plasma Se concentrations being 75.8 and 87.7 μg/L, respectively. However, no difference in plasma Se values was found between the groups that were given statins, fibrates or who didn't take oral lipid-lowering medication after nine years of accompaniment[26]. Statin treatment appears to have a negative impact on selenoprotein synthesis[27].

Dietary Se intake undergoes great variability in worldwide because of its content in the soil and the diversity of eating habits[28]. Maihara et al. (2004)[29] demonstrated that in Brazil dietary Se intake varies from 19 to 94.5 μg per day, depending on the region.

The positive associations between Se intake, BMI, WC and higher BMI, WC and WHtR values in the group of patients with higher plasma Se concentrations can be attributed to the alterations induced in energy metabolism, as demonstrated by Pinto et al. (2012)[30] in their study on animals. In this study, a rise in plasma Se resulted in an increase in GP (x) activity and a decrease in the genetic expression of enzymes involved in energy metabolism, such as AMP-activated kinase and the glycolytic enzyme pyruvate kinase. Thus, Se supplementation would tend to block the oxidation of glucose while increasing the oxidation of fatty acids, altering the source of energy and the physiological metabolism of the individual, which could lead to an increase in body weight. A study on

Table III
Study-participant drug therapy for treating dyslipidemia, hypertension, diabetes and other disorders

Drug therapy – no		*Combination of medications – no**
Lipid-lowering drugs		38
Statins	66	
Ezetimibe	33	
Fibrates	29	

*Number of patients using a combination of two or more oral medications.

humans by Hawkes et al. (2003)[31] reports an increase in body weight after 64 days of a diet rich in Se. On the other hand, we found in our study that individuals belonging to the 1st tertile, with the lowest concentrations of plasma Se, had increased WC values as well, indicating that low plasma Se levels do not associate with benefits to health, as increased visceral fat leads to an increase in cytokines, which likely reduces plasma Se concentrations[32].

In this study we found no association between plasma Se concentrations and thyroid hormones, which may be explained by the fact that the group studied was found to have low plasma Se levels and, furthermore, because the thyroid gland, which holds the highest Se content of the entire human body, was less affected by insufficient consumption of the mineral[33]. We can thus formulate the hypothesis that, in euthyroid individuals, the metabolism of these hormones is less affected by Se deficiency, considering how the plasma concentrations needed to achieve peak selenoenzyme deiodinase activity are above 65 μg/L, well below what is needed for Gpx and SePP[34]. On the other hand, the positive association we found between Se intake and T3L/T4L ratio affirms the important role the mineral has in the conversion of T4 into its most metabolically active form, T3, for the fact that the activity of some deiodinase enzymes is Se dependent[6].

Conclusion

From our results, we can conclude that dyslipidemic patients has low selenium intake and a high prevalence of obesity. Se intake associates positively with the proportion of the most metabolically active form of thyroid hormones, evincing the important role the mineral plays in the metabolizing of these hormones.

Conflict of interest

The authors declare that there is no conflict of interest.

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