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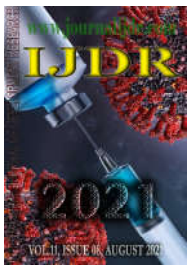

RESEARCH ARTICLE OPEN ACCESS

MAGNESIUM NUTRITIONAL STATUS AND ITS RELATIONSHIP TO METABOLISM OF THYROID HORMONES IN OBESE WOMEN

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ABSTRACT

Objective: To evaluate the magnesium nutritional status and its relationship to thyroid hormones in obese women. **Methods:** Cross-sectional study involving 177 women, aged between 20 and 50 years, distributed in two groups: obese women, n = 73, and normal weight women, n = 104. The analysis of magnesium intake was performed using the three-day food registry using Nutwin version 1.5. Plasma, erythrocyte and urinary magnesium concentrations were determined using the inductively coupled plasma optical emission spectrometry method. Serum concentrations of thyroid hormones were determined by chemiluminescence. Data were analyzed using the statistical software SPSS for Windows 25.0. **Results:** Obese women had reduced plasma and erythrocyte magnesium concentrations when compared to the control group ($p<0.05$). The urinary excretion of this mineral presented a significant difference between the groups ($p<0.05$). Serum concentrations of T3 and T3/T4 ratio showed a statistically significant difference between the groups ($p< 0.05$), with lower values in obese women. There was a negative correlation between erythrocyte magnesium and serum free T4 ($p<0.05$), between dietary magnesium and T3/T4 ratio ($p<0.05$), and positive correlation between plasma magnesium and serum TSH ($p<0.05$). **Conclusion:** Given the negative correlation between magnesium concentrations in erythrocytes and T4 levels, this study does not show a possible role of the mineral in the metabolism of this hormone. Thus, it is suggested a probable impairment in the action of magnesium on the absorption of iodine by thyroid cells, as well as the probable interference of other biochemical factors during the process of metabolizing its precursor, TSH, which reflects negatively on the synthesis of the T4 hormone.

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INTRODUCTION

Obesity is defined as excessive accumulation of body fat, resulting from increased food intake and reduced energy expenditure, being considered a serious public health problem, often associated with several comorbidities, an example of breast cancer, diabetes mellitus, cardiovascular diseases and endocrine changes (JEONG *et al*., 2018; GAJDA *et al*., 2019). In the context of the pathogenesis of obesity, the importance of thyroid dysfunction and its relationship with the hormonal abnormalities associated with the disease is highlighted. In this scenario, scientific evidence has shown changes in serum concentrations of thyrotrophin hormone (TSH), which are attributed to dysregulation of the hypothalamic-pituitary-thyroid axis, which contributes to increase the amount of this hormone in the serum, as well as to the emergence of complications metabolic disorders associated with obesity. Associated with this aspect, there is also an increase in the measurements of the hormone triiodothyronine (T3), as a response to an adaptive mechanism to excess weight (JIN *et al*., 2018; LUNDBACK *et al*., 2017; RAHBAR *et al*., 2017; MAHDAVI

et al. 2021). In order to identify the mechanisms involved in the regulation of the metabolism of the thyroid gland and its hormones, studies show the participation of some nutrients, such as magnesium. This mineral is involved in energy-generating reactions, in addition to being an important cofactor in enzymatic reactions, including most ion transporters coupled to ATPase enzymes, playing a direct role in mitochondrial oxidative metabolism (RABBANI *et al*., 2021; ALBUQUERQUE *et al*., 2018). In this regard, magnesium has been identified as an important substrate in the regulation of the thyroid gland, as it activates the adenylate-cyclase enzyme, stimulating the production of adenosine 3'5'-cyclic monophosphate (cAMP), responsible for the gland's hormonal signaling, as well as providing ATP molecules, necessary for energy-demanding processes, in particular iodine uptake (WANG *et al*., 2018; IGE *et al*., 2019; YANKO, 2018; NISA *et al*., 2013; HSU *et al*., 1984). In recent decades, some studies have shown that obese individuals are deficient in magnesium, which may contribute to reduced thyroid hormone synthesis, as this nutrient acts on iodine absorption by thyrocytes and, consequently, on thyroid hormone synthesis (JAYANTHI *et al*., 2017; CELIK *et al*., 2011). In this scenario, the objective of this study was to evaluate the magnesium nutritional status and its relationship to thyroid hormones in obese women.

METHODS

Cross-sectional study involving 177 women, aged between 20 and 50 years, distributed in two groups: case group (obese women, n = 73) and control group (normal weight women, n = 104). Participants were selected after interview and met the following inclusion criteria: not being pregnant or nursing; no participation in another clinical study; no diagnosis of diabetes mellitus, chronic kidney disease, cancer and/or inflammatory bowel disease; no use of vitamin-mineral supplements and/or medicines that may interfere with the nutritional status related to magnesium or with the metabolism of thyroid hormones. Such information was self-reported by the participants. The study was protocolized and approved by the Research Ethics Committee of the Federal University of Piauí, under the opinion number 3.774.163, according to Resolution 466/12 of the Brazilian National Health Council (CNS). All participants signed a free and informed consent form (BRASIL, 2012).

Nutritional Status Assessment: To evaluate the nutritional status, the body mass index was calculated from the weight divided by the height squared. Nutritional status classification was performed according to the recommendations of the World Health Organization (WHO).

Measurements of magnesium levels in plasma, erythrocytes, and urine: A volume of 12 mL of venous blood was collected between 7 and 9 AM after 12 h fasting, and the blood amount was distributed among different tubes: (1) polypropylene tube containing 30% sodium citrate as an anticoagulant for magnesium analysis (4 mL); (2) vacuum tube with clot activator for analysis of thyroid hormones and antibodies (7 mL). For plasma magnesium measurement, plasma was separated from whole blood by centrifugation (CIENTEC® 4K15, São Paulo, Brazil) at 1831 × g for 15 minutes at 4 °C. The plasma was aspirated with an automatic pipette, placed in polypropylene microtubes and stored at -20 °C. Erythrocyte separation was performed according to the methods proposed by Whitehouse *et al*. (1982). The erythrocyte mass was washed three times with 5 mL of isotonic saline (0.9% NaCl), carefully homogenized by inversion and centrifuged (CIENTEC® 4K15, São Paulo, Brazil) at 2493 × g for 10 minutes, and the supernatant was aspirated and discarded. After the last centrifugation, the saline solution was discarded, and the erythrocyte mass was carefully aspirated with an automatic pipette and transferred to microtubes, which were stored at -20 °C for measurement of magnesium levels. The described procedure was performed three times to remove any contaminants from erythrocytes (i.e., platelets and leukocytes). For 24-hour urine collection, demineralized containers were weighed before and after collection on a semi-analytic scale, for determination of urinary volume from the density. After this procedure, 20 mL of urine was removed, distributed among polypropylene microtubes and stored at -20 °C for later measurement of magnesium levels. Measurement of the magnesium concentration in the samples was performed using an inductively coupled plasma spectrometer (optical emission spectrometry) with an axial view configuration and a V-Groove nebulizer (720 ICP / OES, Varian Inc., California, United States). The reference values adopted were 0.65 - 1.05 mmol/L for plasma magnesium (TIETZ, 1995), 1.65 - 2.65 mmol/L for erythrocyte magnesium (TIETZ, 1995) and 3.00 - 5.00 mmol/24 h for urinary magnesium (TIETZ, 1995).

Determination of Thyroid Function: Serum TSH, fT3 and fT4 hormones, and the autoantibodies anti-thyroperoxidase (TPOAb) and anti-thyroglobin (TgAb) were determined via chemiluminescence using specific kits and following the manufacturer's instructions (Abbott®, USA). The women were considered euthyroid if they had TSH, fT3 and fT4 values in the following reference ranges, respectively: 0,40 - 5,0 µUI/mL, 1,71 - 5,27 pg/mL e 0,70 - 2,19 ng/dL. For thyroid antibodies, the result was considered negative when the participants had TPOAb concentrations between 1 and 16 IU/mL and TgAb between 5 and 100 IU/mL.

Statistical analysis: Data were analyzed using SPSS software for Windows® version 25.0. Data distribution was assessed by the Shapiro-Wilk test. For comparison between groups, Student's t-test was used for data with parametric distribution, and the Mann-Whitney test was used for data with non-parametric distribution. Spearman's correlation coefficient was used for data with non-parametric distribution, specifically for each group, and this test was partially applied, adjusted according to BMI and WC. It is noteworthy that a linear regression analysis was not conducted because the distribution was not homogeneous. In the perspective of identifying the magnesium concentration in the analyzed compartments according to body mass index, there was the distribution of obese women in both groups (Obese class II and Obese Grade III), leading comparison test between them selves and still compared to the control group. Therefore, the Kruskall Wallis test and the Bonferroni post-hoc test were performed, respectively, and for all tests performed, the difference was considered statistically significant when the value of $p<0.05$, adopting a confidence interval of 95%.

RESULTS

The mean values and standard deviations of age and anthropometric parameters used in the assessment of the nutritional status are presented in Table 1. Statistical difference was observed in all anthropometric parameters ($p <0.05$). It was possible to verify that there was a statistically significant difference for weight, body mass index and waist circumference ($p<0.001$), being higher in women with obesity.

Table 1. Mean values and standard deviations of age, body weight, height, body mass index and waist circumference of the control group and obese participants

Parameters	Control (n=104) Mean ± SD	Obese (n=73) Mean ± SD	p
Age (years)	33,36 ± 9,04	32,93 ± 7,29	0,937
Body weight (kg)	55,85 ± 5,96	107,50 ± 17,05*	<0,001
Height (m)	1,59 ± 0,07	1,61 ± 0,06	0,061
BMI (kg/m^2)	22,14 ± 1,72	41,67 ± 6,24*	<0,001
WC (cm)	73,85 ± 5,43	113,93 ± 13,13*	<0,001

*Significantly different values between obese patients and control group, Student's t-test or Mann-Whitney test ($p<0,05$). BMI = body mass index; WC = waist circumference

The mean values and standard deviations of the intake of energy, macronutrients and magnesium found in the diets consumed by the study participants are described in Table 2. It was found that there was a statistically significant difference between the groups in relation to the intake of carbohydrates, proteins and magnesium

(p<0.05). Table 3 shows magnesium concentrations in plasma, erythrocyte and urine in the control group and in obese participants. Statistically significant difference in all these levels was observed between the groups (p <0.05). Table 4 shows the mean values and standard deviations of the serum concentrations of thyroid hormones of the study participants. It was found that there was a statistically significant difference between the control group and obese women in terms of serum fT3 concentrations (p<0.001) and fT3/fT4 ratio (p=0.029).

Table 2. Mean values and standard deviations of energy intake, macronutrients and magnesium from the control group and obese participants

Parameters	Control (n=81) Mean ± SD	Obese (n=31) Mean ± SD	p
Energy (Kcal/day)	1563,57 ± 452,22	1701,34 ± 555,54	0,179
Carbohydrates (g/ day)	181,52 ± 24,14	197,79 ± 34,46*	0,020
Proteins (g/ day)	72,37 ± 15,55	47,17 ± 23,63*	<0,001
Lipids (g/ day)	47,57 ± 10,35	50,28 ± 8,50	0,197
Dietary magnesium (mg/day)	149,52 ± 44,41	173,19 ± 38,64*	0,002

Student's t-test or Mann-Whitney test (p<0,05). Reference Values: 45 to 65% carbohydrate, 10 to 35% protein, and 20 to 35% lipid. Dietary magnesium: EAR = 265 mg / day, age group between 19 and 50 years (female).

Table 3. Mean values and standard deviations of plasma, erythrocyte and urinary magnesium concentrations of the control group and obese participants

Parameters	Control (n = 104) Mean ± SD	Obese (n = 73) Mean ± SD	P
Plasma magnesium (mmol/L)	0,90 ± 0,10	0,60 ± 0,10*	<0,001
Erythrocyte magnesium (mmol/L)	2,21 ± 0,24	1,50 ± 0,21*	<0,001
Urinary magnesium (mmol/24 h)[#]	3,58 ± 1,76	6,25 ± 2,27*	<0,001

* Significantly different values between obese patients and control group, Mann-Whitney test (p <0.05). Reference values: Plasma magnesium = 0.65 - 1.05 mmol/L (TIETZ, 1995), Erythrocyte magnesium = 1.65 - 2.65 mmol/L (TIETZ, 1995), Urinary magnesium = 3.00 - 5.00 mmol/24 h (TIETZ, 1995). [#]Urinary Magnesium: control (n = 86), obese (n = 39).

Table 4. Mean values and standard deviations of serum concentrations of thyroid hormones in the control group and obese women

Parameters	Control (n = 104) Mean ± SD	Obese (n = 73) Mean ± SD	p
TSH (µIU/mL)	2,48 ± 1,37	2,69 ± 1,13	0,226
fT3 (pg/mL)	2,78 ± 0,85	2,33 ± 0,65*	<0,001
fT4 (ng/dL)	1,20 ± 0,36	1,12 ± 0,30	0,224
fT3/fT4	2,42 ± 0,79	2,18 ± 0,69*	0,029

*Significantly different values between obese patients and control group Mann-Whitney test (p <0.05). TSH = Thyrotrophin; T4 = Thyroxine; T3= Triiodothyronine. Reference values: TSH = 0.40 - 5.00 µIU/mL; fT3 = 1.71 - 5.27 pg/ml; fT4 = 0.70 - 2.19 ng/dL.

Table 5. Simple linear correlation analysis between magnesium biomarkers and serum thyroid hormone concentrations in obese women

Parameters	TSH		fT4		fT3		fT3/fT4	
	r	p	r	p	r	p	r	p
Dietary Magnesium	0,155	0,423	0,323	0,088	-0,286	0,132	-0,567	0,001*
Plasma magnesium	0,238	0,047*	0,069	0,572	-0,110	0,363	-0,081	0,507
Erythrocyte magnesium	0,201	0,095	-0,248	0,038*	-0,157	0,194	0,027	0,825
Urinary magnesium	-0,135	0,433	0,167	0,331	0,153	0,372	0,047	0,786

*Spearman rank correlation (p<0.05).

Table 5 shows the results of the correlation analysis between magnesium parameters and serum concentrations of thyroid hormones in obese women. There was a significant negative correlation between erythrocyte magnesium concentrations and serum fT4 (p<0.05), as well as between dietary magnesium and fT3/fT4 ratio (p<0.05), and a positive correlation between plasma concentrations of magnesium and TSH (p<0.05).

DISCUSSION

In this study, we evaluated the relationship between magnesium status and serum concentrations of thyroid hormones in obese women. On the magnesium content in the diet, it was observed that both groups had lower values intake of the mineral recommendation, and this finding similar to those demonstrated in studies conducted by Dominguez *et al*. (2021) and Lu *et al*. (2020) who also showed reduced levels of magnesium in diets consumed by individuals with obesity. This result may be due to the intake of reduced amounts of magnesium-rich foods, such as dark green vegetables, whole grains, nuts and seeds, both by obese women and by the participants who constituted the control group, which may also justify the low consumption of this mineral by this group (LIU *et al*., 2020; DE BAAIJ *et al*., 2015). It is reinforced that obese women consumed higher amounts than the control group, however, the amounts of this mineral in the blood compartments (plasma and erythrocytes) were lower. Some factors may have contributed to this result, such as the occurrence of changes during the magnesium absorption process in enterocytes in obese organisms, as the literature makes clear the existence of competition mechanisms between some minerals in the cells of the gastrointestinal tract, among them magnesium, calcium and sodium (SEVERO *et al*., 2015; UL HASSAN *et al*., 2017; DINICOLANTONIO *et al*., 2018). Another possible justification for the reduction in blood concentrations of magnesium among women with obesity concerns the probable influx of this mineral to

adipocytes, which consequently induces its reduction in blood compartments. This finding is in agreement with those already identified in other studies that also demonstrated reduced plasma concentrations of magnesium in obese individuals (THILLAN et al., 2021; BABAPOUR et al., 2021). Also in this discussion, the reduced concentrations of magnesium in erythrocytes are highlighted, particularly in participants with obesity, reinforcing the possibility that these women have chronic deficiency in this nutrient, considering that the concentration of magnesium in erythrocytes constitutes an evaluation biomarker from medium to long-term use of the nutrient in the body (ZEMVA et al., 2000; CORICA et al., 1997). With regard to urinary magnesium, the results show that obese participants excreted a higher amount of this nutrient when compared to the control group, with a statistical difference, similar to the results found in the study by Deng et al. (2017). This data emphasizes the existence of alterations in magnesium homeostasis in obese women, because even with reduced levels of the mineral in plasma and erythrocytes, they presented high excretion of the nutrient in the urine.

As for the results obtained from the analysis of thyroid hormones, the present study did not reveal a statistically significant difference in terms of serum TSH concentrations between the groups evaluated. This aspect can be explained due to the likely existence of a compensatory activation of the hypothalamic-pituitary-thyroid axis, with a view to maintaining serum TSH concentrations within the euthyroid range (ORTEGA et al., 2012; NANNIPIERI et al., 2009). On the other hand, data in the literature show high TSH values in obese individuals, which are justified by the reduction in the activity of the deiodinase 2 enzyme and possibly the thyroid hormone receptors, which is capable of compromising the negative feedback mechanism, and consequently, the regulation of the TSH hormone (MAHDAVI et al., 2021; ZHANG et al., 2019; BÉTRY et al., 2015). Differently from the literature, that is, high concentrations of fT3 in obese individuals, as a result of an adaptive thermogenic process, it was possible to verify that the obese women in this study had lower serum fT3 concentrations than the control group. This data can be explained by the probable reduction in the activity of deiodinase 1, the enzyme responsible for the conversion of T4 into T3, although it was not analyzed in this study (NIE et al., 2020; GOLDBERG et al., 1988; ASTRUP et al., 1996). Associated with this, the values of the fT3/fT4 ratio, a parameter used to assess the activity of thyroid hormones, were lower in obese women when compared to eutrophic women. This result suggests that there is, particularly among obese participants, inefficiency in the conversion of T4 to T3, although in this study, high concentrations of fT4 were not verified. Similarly, it can be seen in the data found in the study carried out by Hepsen et al. (2021). In the perspective of a better understanding of the role of magnesium in the homeostasis of thyroid hormones, a correlation analysis between mineral markers and serum concentrations of these hormones was conducted. It was possible to verify the existence of a negative correlation between erythrocyte magnesium and fT4 concentrations in obese women.

However, it should be noted that magnesium, as it acts on iodine absorption, would be expected that the greater its concentrations in erythrocytes, the greater would be the synthesis of fT4. However, this finding was not evidenced in this study, which is probably a result of the interference of other biochemical factors during the process of metabolizing its precursor, TSH. The correlation between dietary magnesium content and the fT3/fT4 ratio in obese women was negative, and this result is in line with the data in the literature, as it is expected that the increase in magnesium intake favors the conversion of T4 to T3. It is appropriate to draw attention to some aspects that can justify the impossibility of further discussion of the results, such as the fact that the record of food intake, particularly quantification of dietary magnesium content not constitute sensitive marker to express the actual amount intake of the mineral. Associated with this, the absence of analysis of iodine and deiodinase 1 and 2 enzymes, which participate in thyroid metabolism, also constitute limiting factors for further discussion. Thus, the perspective is to advance in obtaining knowledge about the role of magnesium in the metabolism of thyroid hormones, through the use of more robust molecular-based biomarkers, which can bring more effective responses, both with regard to its homeostasis in obese individuals, regarding the interaction in mechanisms involved in the metabolism of thyroid hormones.

CONCLUSIONS

From the results of this study it can be conclude that obese women presents changes in nutritional status relative to magnesium. In addition, shows changes in the metabolism of thyroid hormones, being this characterized by reduced serum free T3 concentrations in obese women. Given the negative correlation between magnesium concentrations in erythrocytes and T4 levels, this study does not show a possible role of the mineral in the metabolism of this hormone. Thus, it is suggested a probable impairment in the action of magnesium on the absorption of iodine by thyroid cells, as well as the probable interference of other biochemical factors during the process of metabolizing its precursor, TSH, which reflects negatively on the synthesis of the T4 hormone.

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