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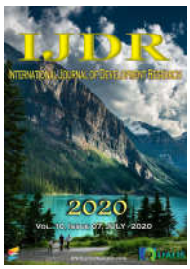

RESEARCH ARTICLE OPEN ACCESS

THE BEHAVIOR OF THYROID HORMONES IN A POPULATION EXPOSED TO MERCURY AND SELENIUM, WHICH INHABIT A MUNICIPALITY LOCATED IN THE WESTERN AMAZON, IN BRAZIL

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ABSTRACT

Objective: To investigate the behavior of thyroid hormones in a population exposed to mercury and selenium, which lives in a municipality located in the Western Amazon, in Brazil. **Methodology:** Observational, descriptive, cross-sectional study, conducted with 141 people, distributed by neighborhoods based on the epidemiological study of clusters that occurred randomly in 21 neighborhoods. Blood was the material used to analyze total Hg, total Se and TSH and free T4. In addition, hair was used only for the analysis of total Hg.**Results:** The researched population shows average levels of total Hg in blood and hair samples above the biological limits of normality recommended by the WHO. In addition, the Se deficiency was not identified in the population sample of the studied municipality, that is, there is availability of the mineral in the region. The results of the free T4 hormone in the blood, in comparison with the concentrations of total Hg and total Se, do not seem to have produced changes in the averages of the studied sample, this finding suggests that the studied population may be exposed to the mineral in a recent or acute form. **Conclusion:** high levels of total Hg in the blood and hair in the population sample confirm human exposure. In addition, this study acutely identified the population's health risk in relation to the presence of Hg in the body and the thyroid gland was impaired in relation to the synthesis of free T4 hormone in prolonged exposure to the metal, even in the face of the high presence of Se in the diet of the studied population.

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INTRODUCTION

The contamination of soils and water by heavy metals represents a serious environmental problem, especially in regions where anthropological activities are carried out, since soil and water are used to feed the population. Among the metals that most contaminate these environments is mercury (Hg), a chemical element capable of combining with macromolecules and accumulating in organisms such as fish and, consequently, bioaccumulation can occur in the food networks of aquatic environments and reach humans (Souza; Batista and Bernstein, 2014).

The Hg is a mineral used on a large scale in gold mining, as this element is capable of amalgam. However, Hg is quickly transported through the atmosphere, a process that allows the dispersion of this element in the environment, that is, the population that lives in or near mines is vulnerable to metallic vapors and also to methylmercury found in rivers and contaminated fish (Jesus *et al*., 2018). This element, in organic form, is soluble in fat and, therefore, extremely toxic, so that Hg can cross the blood-brain and placental barriers and cause damage to the neurological development of newborns. Among the main organic systems most affected by Hg toxicity, the central nervous system and the renal system stand out (PAHO, 2011). In addition, epidemiological studies relate changes in the endocrine system in relation to exposure to Hg, through

the hypothalamic-pituitary axis (Cunha, 2008). The endocrine system, especially the pituitary gland, produces the thyroid stimulating hormone (TSH) that regulates the activity of the thyroid gland (Ganong, 2007). Stimulation induces the production of free T4 (thyroxine) in large quantities, while T3 (triiodothyronine) is relatively low and T3 inverts even less, which are later released into the bloodstream (Vartanian, 2013). In addition, the thyroid gland has the highest concentration of selenium (Se) in the body (Rayman, 2012). Therefore, the absence of this element can lead to a deficit of hormones in the thyroid gland and, consequently, trigger hypothyroidism, and its excess can cause hyperthyroidism, when not treated correctly, leads to the appearance of functional changes (Vartanian, 2013). In continuity, in the Amazon region there are fish, a food considered an important source of Se, whose essential characteristic is its antioxidant function related to the presence of selenoproteins P and glutadione peroxidase (GPx) (Raymond and Ralston, 2004). These proteins are found in all mammalian tissues where oxidative processes exist, whose action is to reduce the production of Reactive Oxygen Species (ROS) (Gonzaga *et al*., 2005). Thus, Se can exert its protective effect due to its antagonistic function to methylmercury, protecting the organism from the populations that live in these Amazonian regions (Ralston *et al*., 2008). In addition, the North region is considered the richest in Se, whose animal foods, such as meat, chicken, eggs and fish, have significant concentrations of this mineral (Martens *et al*., 2012). It is also important to note that products of plant origin have the best sources of Se due to their high bioavailability, mainly Brazil nuts (*Bertholletiaexcelsa*) (Rocha *et al*., 2014). From this, despite the laboratory mechanisms, still not being properly clarified, studies suggest that Se may be actively involved in the demethylation of methylmercury and, in turn, interfere in the production of thyroid hormones (Yang *et al*., 2008).

Objective: To investigate the behavior of thyroid hormones in a population exposed to mercury and selenium, which lives in a municipality located in the Western Amazon, in Brazil.

MATERIALS AND METHOD

Type of study: Cross-sectional, observational and descriptive study.

Participants: The study included 141 people, distributed by neighborhood based on the epidemiological study of clusters that occurred randomly in 21 neighborhoods. On each street, five families were visited, up to the limit of 24 members, regardless of age. All participants signed the Free and Informed Consent Form (ICF).

Ethical aspects: This study was approved by the Ethics Committee in Research with Human Beings of the Evandro Chagas Institute (IEC), protocol nº 141.519, CAAE: 10114212.1.0000.0019 / 2012.

Methodological procedures

Study Scenario: The study was carried out in June 2019, in the municipality of SenaMadureira, in the state of Acre, located in the southwest of the northern region of Brazil and on the border with Bolivia and Peru. This municipality is bathed by large rivers such as Purus and Acre.

Laboratory analysis: Blood was the material used to analyze total mercury (total Hg), total selenium (if total) and thyroid stimulating hormone (TSH) and Thyroid hormones Thyroxine (Free T4). In addition, hair was used only for the analysis of total Hg. The blood samples were stored in 10 mL tubes with 10% ethylenediamine tetraacetic acid (EDTA) and the hair samples collected in the occipital region of the head were stored in white envelopes for analysis. In addition, the determinations of total Hg and total Se were carried out from the acidic opening and analyzed by Atomic Absorption Spectrometry with the Cold Steam Generation System (CV-AAS) (Mercury Analyzer, Hg-201, Sanso Inc), according to the method proposed by Akagi (2004) and the atomic absorption spectrometer with hydride generation system (HG-AAS), brand VARIAN, model AA 220, respectively (Vogel *et al*., 2002). The normal reference values for humans with total Hg in the blood are in the range of 5 to 10 $\mu g.L^{-1}$, while the biological tolerance limit is 30 $\mu g.L^{-1}$. As for the reference values for hair, there are 1 to 2 $\mu g.g^{-1}$ and the Biological Tolerance Limit of 6 $\mu g.g^{-1}$ (WHO, 2008). In addition, it is accepted as a daily requirement to eat 50-70 $\mu g.L^{-1}$ of the total Se to maintain the proper functioning of the organism (Alexander, 2015). As the TSH and T4 determinations were performed by the ELFA method (Enzyme Fluorescent Assay), using the BioMérieux kit in the VIDAS® system, model GRAY 30. In addition, normal TSH values from 0.4 - 4.5 Ul/L and free T4 values from 10.6 to 19.4 pmol/L, these values were recommended according to the manufacturer's guidelines (Carayon *et al*., 2002).

Statistical analysis: A statistical analysis and related studies were performed using Microsoft Excel 10 and Statistical Science, version 3. In the distribution of data by matrices, the upper limit of the 95% confidence interval was considered. For univariate and bivariate analysis, between continuous variables from two or more groups, parametric and nonparametric tests were used, when indicated. In the analysis of categorical variables, the Mann-Whitney test was used and in the multivariate analyzes of the Generalized Linear Models and Spearman's Correlation, when used as quantitative variables (Dawson, 2004). Finally, the Multivariate Additive Models (GAM) were used to obtain the occurrence of a statistical relationship of the rates analyzed (Sothe *et al*., 2017).

RESULTS

In the studied population, the average levels of total Hg in blood and hair were 28.7 (8.2-176.9) $\mu g.L^{-1}$ and 8.1 (0.7-55.4) $\mu g.g^{-1}$, respectively.The Spearman correlation ($r = 0.8256$; $t = 32.1215$; $p < 0.0001$) was positive and significant among the biological matrices investigated, while the levels of total Se in the blood were 122.1 (46.7 -370.6) $\mu g.L^{-1}$. In addition, in relation to gender, the levels of total Hg and total Se in the blood were found in men, which were 33.0 (8.5-176.9) $\mu g.L^{-1}$ and 121.4 (46.7 -298.3) $\mu g.L^{-1}$, respectively, while in hair, the total Hg levels were 9.66 (1.6-55.4) $\mu g.g^{-1}$. Among women, total Hg rates of 25.5 (8.2-142.6) $\mu g.L^{-1}$ and total Se of 122.8 (58.8-370.6) $\mu g.L^{-1}$ were observed, while in hair the levels of total Hg were 7.0 (0.7-45.0) $\mu g.g^{-1}$. Among the participants who reported consuming fish in their diet, the average level of total Se was 122.4 ± 49.8 $\mu g.L^{-1}$ and the total Hg of 30.0 ± 30.9 $\mu g.L^{-1}$ and the correlation was $r = 0.24$; $p = 0.006$, while individuals who denied consuming this food, total Se levels of 120.9 ± 28.8 $\mu g.L^{-1}$ and total Hg levels of 14.9 ± 9.4 $\mu g.L^{-1}$

Table 1. Rates of total Hg and total Se in blood, total Hg in hair, correlation with gender, age and fish consumption

n = 141 participants	Total Hg in the blood	Total Hg in the	Total Se in the blood
	Average (μg.L-1)	Average (μg.g-1)	Average (μg.g-1)
Total	28.7 (8.2-176,9)	8.1 (0.001-55.40)	122.1 (46.7-370,6)
Genre			
Men (55)	33.0(8.5-176,9)	9.6 (1.6-55,4)	121.4 (46.7-298.3)
Women (86)	25.5(8.2-142.6)	7.0 (0,7-45,0)	122.8 (58.8-370.6)
Age range			
04-15	31.8 (8.2-176,9)	9.1 (0.001-55.40)	105.8 (46.7-370,6)
16-29	28.3 (8.2-176,9)	6.4 (0.001-55.40)	120.9 (46.7-370,6)
30-59	27.5 (8.2-176,9)	8.3 (0.001-55.40)	126.2 (46.7-370,6)
≥60	29.3 (8.2-176,9)	8.3 (0.001-55.40)	127.5 (46.7-370,6)
Fish consumption			
Yes	30.0 (8.2-176,9)	-	122.4 (46.7-370,6)
No	14.9 (8.2-176,9)	-	120.9 (46.7-370,6)

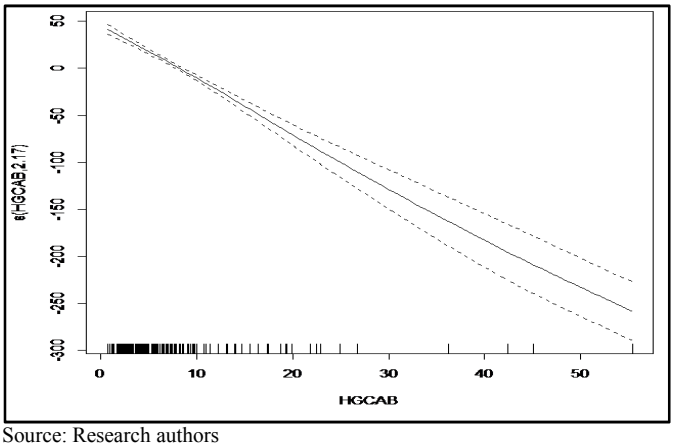
Source: Research authors

Table 2. Results of the multivariate model of GAM associated with serum T4 concentration and total Hg hair in 141 individuals

Variables	Coefficient	Std error	Z value	*p* -value
Intercept	44.0	3.1	14.4	< 0.01
Total Hg concentration in hair	5.2	0.3	13.8	< 0.01

Source: Research authors

and the correlation was r = 0.24; p = 0.040. Mann-Whitney tests showed that there was no statistically significant difference between the means of total Se (p = 0.19) and total Hg (p = 0.02) in the blood. Regarding serum levels of thyroid hormones among men, the mean found for TSH and free T4 was 3.6 Ul / L (0.5 - 60.0 IU / L) and 13.9 pmol / L (3, 9 - 30.0 pmol / L), respectively. These values, among women, were 2.2 Ul / L (0.3 - 8.2 IU / L) for TSH and 13.3 pmol / L (3.9 - 122.6 pmol / L) for T4 free. Table 02 and Figure 01 show the results of the association of free T4 in the blood and total Hg in the hair, using the Generalized Additive Model (GAM) applied to the population sample of the studied municipality. Therefore, there is a positive statistical relationship.



Source: Research authors

Figure 2. Association between free T4 and total Hg in the hair through the GAM

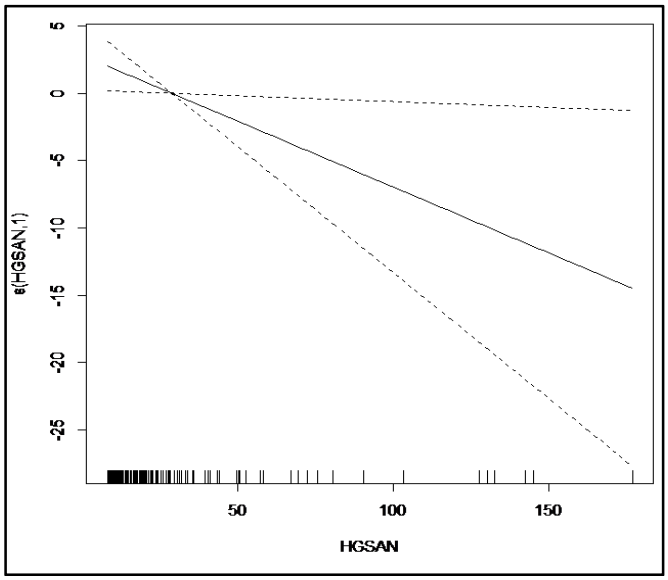
In heredity, Table 03 and Figure 03 express the results of the association of free T4 and total Hg in the blood, using the GAM model in the population sample. It is observed that the occurrence of a statistical relationship was not significant.

Table 3. Results of multivariate GAM model associating concentration of serum T4 with concentration of blood Hg total

Variables	Coefficient	Std error	t value	*p* -value
Intercept	47.4	0.9	49.8	< 0.01
Hg total concentration in blood	1.4	0.0	45.2	0.02

Source: Research authors

In addition, Table 04 and Figure 04 express the results of the association of free T4 in serum and total Se in blood, using the GAM model in the population sample. In this case, a non-significant statistical relationship was observed.



Source: Research authors

Figure 3. Association of T4 free of Hg in the blood by means of GAM

Table 4. Results of multivariate GAM model associating concentration of serum T4 with concentration of blood Se total

Variables	Coefficient	Std error	t value	*p* -value
Intercept	88.7	3.6	24.0	< 0.01
Se total concentration in blood	0.0	0.0	0.1	0.88

Source: Research authors

DISCUSSION

The researched population shows average levels of total Hg in blood and hair samples above the biological limits of normality recommended by the World Health Organization (WHO) (PAHO, 2011; WHO, 2008).

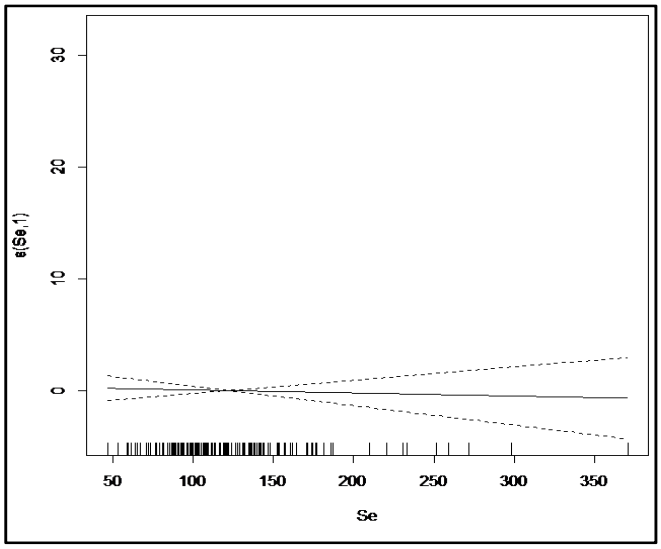


Figure 4. Association of free T4 and total Se in the blood through GAM

These levels are also higher than other studies that analyzed the mean Hg concentration (Cryderman et al., 2016; Jesus et al., 2018). This condition observed in this research indicates a recent and long-standing environmental exposure, whose statistical relationship is positive among the evaluated matrices.Therefore, other studies carried out in the Amazon indicate that Hg has great circulation in the environment and in the populations of the region (Passos et al., 2008; Hacon et al., 2006). The correlation between the levels of Hg in the blood and in the hair is indicative that there is a flow of accumulation of this metal in the body of the researched population, a situation that corroborates the findings of Amaro (2014), when affirming that the individuals close to the mining regions of handmade gold present high levels of total Hg in the body, due to the high consumption of fish and other foods in the food chain. Fish are primarily responsible for the accumulation and transport of Hg in the Amazon region, which can be found far from the site of environmental exposure (Roach et al., 2013).The circulation in the body through the consumption of fish depends on the species and the frequency of ingestion, conditions that interfere with the distribution of the metal between the gender and the age groups of the population (Santos et al., 2002). In addition, the average blood and hair values of total Hg, for men and women surveyed, are above normal limits, with predominance among men, whose metal level suggests greater exposure, these findings can be justified due to cultural, economic specificities , social and nutritional aspects of this community in the Amazon.However, the consumption of fish in the diet is not the main source of food for the population studied, therefore, the consumption of fish does not seem to interfere in the proportion of Hg and Se in this population.

The high rate of total Hg in some women suggests the possibility of vertical transmission, exposing the vulnerability to which children are subjected in the region (Gibicar et al., 2006).In addition, another study in the Amazon region corroborates these findings, identifying that among 1,510 women surveyed and their newborns, in the Tapajós river basin, in the State of Pará, the correlation of Hg contamination by the mother and her children was highly significant (r = 0.8019; p = 0.000), as 11.53 µg.L-1 (0.38-117.62 mg.L-1) were identified in the mothers' peripheral blood and 16.68 in the umbilical cord blood µg.L-1 (0.35-135.04 µg .L-1), that is, the passage of metal through the placental barrier was evidenced (Santos et al., 2007). The Pan Amazon region is considered an important risk area for exposure to Hg due to natural and artificial processes (Rocha et al., 2014).This region also has the richest selenium soils, in this case, fish are important sources of this mineral, whose antioxidant function establishes the body's balance (Khan; Wang, 2009). The concentration of Se in the population's body is directly associated with soil availability and mineral food intake, whose age, physical state and lifestyle interfere with body absorption (Esteves et al., 2012), mainly in the North and Northeast regions from Brazil, where the rates of this mineral are high (Cozzolino, 2007). In this study, the Se deficiency was not identified in the population sample of the studied municipality, that is, there is availability of the mineral in the region.It is noteworthy, therefore, that the Pan-Amazonian region is one of the places of greatest human exposure to Hg in the world and, in turn, its soil is recognized as the richest in Se, therefore, there is a molecular balance between the element aggressor and protector in the exposed population.

The interaction between Hg and Se involves a variety of biochemical and toxicological processes that are still unknown.In vitro research suggests that the protective effect of Se in relation to the toxic effects of Hg is due to the formation of an inert Hg-Se (1: 1) complex linked to selenoprotein P in the blood (Chen et al., 2006). The coexistence of the population of the municipality surveyed with high levels of Hg in the blood and hair, for several decades, gives this population an important risk of developing diseases.On the other hand, the availability of Se in the population, can influence the promotion of adverse effects to the metal, however, it does not exclude an action of the mechanism of aggression to the various systems of the organism. In continuity, the normal thyroid gland has high concentrations of Se, important for the body's antioxidant mechanism and homeostasis (Dean, 2012).In addition, the biological activity of free T4 is fundamental in the assessment of glandular function, whose alteration in its concentrations results in a high or decreased production of these hormones, through negative feedback from the pituitary-thyroid axis (Cozzolino, 2009). Due to the affinity between the chemical element mercury and selenium, the formation of the molecular complex [Hg-Se] occurs, whose toxic action of the metal is minimized by the mineral.Therefore, the advance of Hg inactivation in the body results in a marked decrease in aggression in the cells of the most vulnerable tissues, such as the central nervous system.In addition, the GAM mathematical model revealed a positive statistical relationship between free T4 in the blood and Hg in the hair of the studied population.The difficulty in the production of the hormone suggests a lower bioavailability of Se in the thyroid gland, due to the need of the mineral in the formation of the molecular complex [Hg-Se] to exert its protective effect.

In the blood matrix, the results of the free T4 hormone in the blood, compared to the concentrations of total Hg and total Se, do not seem to have produced changes in the averages of the studied sample, probably because they represent the entry of elements in the body, presenting a recent environmental exposure or acute.In chronic or long-term exposure, the formation of the [Hg-Se] complex occurs actively according to its bioavailability until the process is exhausted, allowing the harmful action of the metal in the body, especially in the

thyroid gland. In addition, a randomized study in elderly people with Se deficiency with mineral supplementation did not show changes in thyroid function or in the concentrations of their hormones (Rayman et al., 2012).However, low levels of this mineral in the body are associated with the incidence of goiter and neoplasm in the thyroid (Stockigt, 2001).Another study, this time with children from the Amazon region, suggests that Se deficiency may be related to the diagnosis of hypothyroidism and an increased risk of thyroid cancer (Drutel et al., 2013). In addition, this research identified in the capillary matrix of the investigated population an inverse relationship of Hg in relation to the production of free thyroid hormone T4 in individuals from the Amazon region.Therefore, this fact imposes on the health system the need for special attention in the investigation of the thyroid gland, due to the possibility of producing changes in its function. The health surveillance system generally does not associate tropical conditions with exposure to Hg and Se in the studied region.However, the epidemiological, clinical and toxicological investigation of populations exposed to Hg contributes to the identification of the natural history of diseases in the region.

Conclusion

The high rates of total Hg in the blood and hair in the population sample confirm human exposure.Artisanal gold mining developed in the border region may be transposing the metal from international rivers to areas with no record of this activity.In addition, the nutritional status of the studied population allows to affirm the absence of total Se deficiency, whose probable source of this mineral is the diet.Although fish is an important source of Se in the respondents' bodies, this food is not the only option for the availability of the mineral in the studied region. This study indicates the health risk of the population in relation to the presence of Hg in the body in an acute way.The thyroid gland was impaired in relation to the synthesis of free T4 hormone in prolonged exposure to the metal, despite the high presence of Se in the diet of the population studied.

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