

Thyroid stimulating hormone isn't a sensitive indicator of iodine nutritional status in schoolchildren

Hormônio tireoestimulante não é um indicador sensível do status nutricional de iodo em escolares

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Abstract

Introduction: iodine deficiency disorders (IDD) are most common cause of preventable brain damage, mental retardation and stunted growth in children worldwide. Several indicators are complementary to urinary iodine concentration (UIC) for assessing iodine nutritional status, as thyroid size, thyroglobulin (Tg) and thyroid stimulating hormone (TSH) concentrations in the blood. **Objective:** analyze TSH in filter paper blood values and correlate with UIC in schoolchildren from public school at state of Bahia, Brazil. **Methodology:** cross-sectional study was conducted in 880 schoolchildren aged 6-14 years, randomly selected, of public schools in five cities of four micro-regions of Bahia between October 2013 and September 2014. TSH was analyzed in filter-paper blood and UIC were measured by adapted Sandell-Kolthoff reaction. **Results:** 880 blood samples on filter-paper were analyzed for TSH. The reference range previously established is 0.72 to 6.0 $\mu\text{UI/mL}$. Results of this research TSH dosage ranged from 0.24 $\mu\text{UI/L}$ to 7.71 $\mu\text{UI/L}$, with a mean of $1.01 \pm 0.55 \mu\text{UI/L}$ and median 0.89 $\mu\text{UI/L}$. Only one child presented TSH greater than 6.0 (7.71 $\mu\text{UI/L}$); however, results of urinary iodine were consistent with a more than adequate nutrition iodine (243.70 $\mu\text{g/L}$). There' no correlation between TSH and UIC ($r = 0.115$; $p = 0.002$). **Conclusion:** in the present study, schoolchildren showed low values of TSH, but the mean UIC was indicative of adequate iodine nutrition.

Keywords: Iodine Deficiency. Thyroid Functions Tests. Thyroid Stimulating Hormone.

Resumo

Introdução: distúrbios por deficiência de iodo (DDI) é a causa mais comum de lesão cerebral evitável, retardo mental e atraso no crescimento infantil em todo o mundo. Vários indicadores são complementares à concentração de iodo urinário (CIU) na avaliação do estado nutricional de iodo, como o volume da tireoide, tireoglobulina (Tg) e concentrações séricas de hormônio tireoestimulante (TSH). **Objetivo:** analisar os valores de TSH em papel filtro e correlacionar com CIU em escolares de escolas públicas no estado da Bahia, Brasil. **Metodologia:** estudo transversal realizado em 880 escolares de 6 a 14 anos, selecionados aleatoriamente, de escolas públicas em cinco municípios de quatro microrregiões da Bahia, entre Outubro de 2013 a Setembro de 2014. O TSH foi analisado nas amostras de sangue em papel filtro e a CIU foi mensurada através da reação de Sandell-Kolthoff adaptada. **Resultados:** o TSH foi dosado em 880 amostras de sangue em papel filtro. O intervalo de referência para normalidade previamente estabelecido foi de 0,72 a 6,0 $\mu\text{UI/mL}$. Os resultados da dosagem do TSH desta pesquisa variaram entre 0,24 $\mu\text{UI/L}$ a 7,71 $\mu\text{UI/L}$, com uma média de $1,01 \pm 0,55 \mu\text{UI/L}$ e mediana 0,89 $\mu\text{UI/L}$. Apenas um escolar apresentou valor de TSH superior a 6,0 (7,71 $\mu\text{UI/L}$); no entanto, o resultado da CIU foi condizente com uma nutrição mais que adequada de iodo (243,70 $\mu\text{g/L}$). Não houve correlação entre TSH e CIU ($r = 0,115$; $p = 0,002$). **Conclusão:** no presente estudo, os escolares apresentaram valores baixos de TSH; contudo, a média de CIU foi indicativa de nutrição adequada de iodo.

Palavras-chave: Deficiência de iodo. Testes de função da tireoide. Hormônio tireoestimulante.

INTRODUCTION

Iodine deficiency disorders (IDD) is the most common cause of preventable brain damage, mental retardation and stunted growth in children worldwide (BERNAL, 1999; BATH et al., 2013). Fortunately, through salt iodization,

IDD is among the simplest and least expensive of nutrient deficiencies to prevent (ZIMMERMANN; ANDERSSON, 2012; ANDERSSON; BENOIST; ROGERS, 2010). Nutritional iodine status is routinely assessed by measuring UIC, considered a reliable biomarker of recent iodine intake in populations at all levels of chronic iodine intake; in positive iodine balance, more than 90% of ingested iodine is excreted in the urine (VEJBJERG et al., 2009a; KÖNIG et al., 2011).

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Although the measurement of UIC is most commonly employed method of assessing population iodine status, other methods are more sensitive to identify an iodine inappropriate chronic consumption (WHO, 2001). Moreover, UIC not is suitable for use as an individual test to diagnose IDD, but can yield an indication of overall population iodine status (WHO, 2001; ZIMMERMAN, 2008). Some indicators are complementary for assessing iodine nutritional status, as thyroid size, thyroglobulin (Tg) and thyroid stimulating hormone (TSH) concentrations in the blood (DELANGE, 1997; WHO, 2001; ZIMMERMAN et al., 2005; ZIMMERMAN, 2008; RISTIC-MEDIC et al., 2009; VEJBJERG et al., 2009b; EVANS et al., 2014).

TSH is determined mainly by the level of circulating thyroid hormone, which in turn reflects iodine intake; therefore, TSH could be used as an indicator of iodine nutrition (DELANGE, 1997). However, in adults and older children, although serum TSH may be slightly increased by IDD, values often remain within the normal range. TSH is therefore a relatively insensitive indicator of iodine nutrition of these individuals (DELANGE, 1997; EASTMAN, 2012). In contrast, TSH is a sensitive indicator of iodine status in the newborn period (BURNS et al., 2008; EHRENKRANZ et al., 2011; YAMAN et al., 2013). Compared to the adult, the newborn thyroid contains less iodine but has higher rates of iodine turnover. Particularly when iodine supply is low, maintaining high iodine turnover requires increased TSH stimulation (PISAREV et al., 1970).

Elevated serum TSH constitutes an indicator of the potential risk of iodine deficiency (DE LUCA et al., 2010). However, the difference is not great and large overlap occurs between individual TSH values, suggesting that the blood TSH concentration in schoolchildren is not a practical marker for iodine deficiency (BHATTACHARJEE et al., 2013). Therefore, this article aims to analyze the TSH levels and correlate with UIC of schoolchildren of five cities of four micro-regions of Bahia, Brazil.

METHODOLOGY

Subjects

In the present cross-sectional study, a multi-stage cluster sampling technique was employed. The study sample included healthy 6 to 14 year primary public schoolchildren living in four micro-regions in Bahia, Brazil (Alagoinhas, Salvador, Santo Antonio de Jesus and Santa Maria da Vitoria). Recruitment was from elementary public schools between October 2013 and September 2014. Exclusion criteria were: 1) age <6 or >14 years, 2) chronic diseases, 3) use of chronic medications or iodine supplements, and 4) in females, pregnancy.

Seventeen schools were randomly selected to represent specific geographic areas of the state (coast, northeast and west region), including urban and rural areas. In all municipalities, the sources of dietary iodine were local foods and variable amounts of iodized salt. A sample size of 1,314 children was determined using single population proportion formula. The following assumptions

were made: $Z = 1.96$ (90% level of confidence interval); $p = 0.15$ (the estimate of extended proportion) extracted from the last meta-analysis (ALVES et al., 2005); $DEFF = 1.5$ (the estimated design effect for small population) and $d = 0.2$ (the degree of precision).

At the schools, height and weight were measured using standard anthropometric technique (WHO, 1995). For Z score calculation, we used the software ANTHRO PLUS (WHO, Geneva, 2009). All participants voluntarily took part in the study and written consent was obtained from at least one parent or guardian. The study was approved by the Federal University of Bahia Ethical Committee for Research Projects.

Urinary iodine concentration analysis

Spot urine samples were obtained in universal collector and transferred to monovettes tubes for transport and storage at -20°C until analysis. The adapted Sandell-Kolthoff reaction was used for UIC determination. A spectrophotometer (Uv-Vis) was used to examine the reduction of ceric ammonium sulphate. A standard iodine solution using a potassium iodate was used in order to extrapolate the iodine concentrations. For each schoolchild, sample analysis was repeated. The iodine nutrition status classification was based on the criteria established by the WHO (WHO, 2001).

TSH in filter paper

Patients selected for the study was voluntary participation in the collection, on filter paper, type SS 903, whole blood for measurement of TSH. Blood was collected with lancet digital children, after obtaining the anthropometric data. TSH was measured by immunofluorometric assay – Luminex. For TSH in filter paper dosage, it uses a capture monoclonal antibody bound to solid phase and monoclonal antibody recognition. This method has sensitivity 0.1 mUI/L and intra and interassay coefficients of variation of 5% and 10%, respectively. In the state of Bahia, there is a structured system of screening for congenital hypothyroidism, accredited by the Ministry of Health, based at the Associação de Pais e Amigos dos Excepcionais (APAE), where measurements were done. Participated in this stage of the study only students who consented to the collection. The cutoff was 0.72-6.0 $\mu\text{UI}/\text{mL}$. The samples were stored under refrigeration and transport to the laboratory of APAE was conducted with the samples at room temperature.

Statistical analysis

Data processing and statistical analyses were performed using the statistical software packages SPSS version 22.0 (SPSS Inc., Chicago, IL, USA, 2013). A significance level of 5% (< 0.05) was considered. Statistical models adopted were: arithmetic mean, standard deviation, calculation of percentages, parametric collection of Pearson, test t, Pearson's Chi-square test and Fisher exact test. Differences in children's median UIC by age, sex and different groups classified on the basis of sociodemogra-

phic and geographic characteristics were tested with the Mann–Whitney test.

RESULTS AND DISCUSSION

We analyzed 880 blood samples on filter paper for TSH. The average value for TSH was found to be 1.01 ± 0.55 $\mu\text{UI/mL}$ and the median 0.89 $\mu\text{UI/mL}$. The reference range previously established is 0.72 to 6.0 $\mu\text{UI/mL}$. The results of this research TSH dosage ranged from 0.24 $\mu\text{UI/L}$ to 7.71 $\mu\text{UI/L}$, with a mean of 1.01 ± 0.55 $\mu\text{UI/L}$ and median 0.89 $\mu\text{UI/L}$. Most of the schoolchildren (67.5%) ($N=594$) had TSH values between 0.72 - 2.5 $\mu\text{UI/L}$, however, the UIC revealed proper nutrition of iodine (Table 1). Only one child has TSH greater than 6.0 (7.71 $\mu\text{UI/L}$). Nonetheless, the results of UIC were consistent with more than adequate nutrition iodine (243.70 $\mu\text{g/L}$). Interestingly, in this study, the average UIC increased as the TSH values elevated.

Table 1 – TSH reference values, clinical significance, distribution of 880 samples analyzed and compared to the average values of UIC.

Value ($\mu\text{UI/L}$)	Diagnose	(N)	%	TSH mean ($\mu\text{UI/L}$)	UIC mean ($\mu\text{g/L}$)
<0.72	Very low	272	30.9	0.55 ± 0.11	166.59
0.72-2.5	Adequate	594	67.5	1.18 ± 0.40	191.89
2.5-6.0	Adequate	13	1.4	2.99 ± 0.44	216.23
≥ 6.0	High	1	0.1	7.71	243.70

TSH: Thyroid Stimulating Hormone

Given that short stature and/or low growth rate in children and adolescents may reflect risk of thyroid dysfunction (WHO, 1995; DE LUCA et al., 2010; CERBONE et al., 2011; BHATTACHARJEE et al., 2013), we compared the mean values of BMI/A, TSH and UIC of school children diagnosed with low or very low height for age. However, the average TSH values were low, the average values of BMI/A Z-score showed normal weight and the UIC mean was conducive to proper nutrition iodine (Table 2).

Table 2 – Representation of BMI/A, TSH and UIC of schoolchildren with low HAZ according to gender

Height for age	Medium values			
	(N)	BMI/A (Z score)	TSH ($\mu\text{UI/L}$)	UIC ($\mu\text{g/L}$)
Boys				
Very low height for age	8	-0.24	0.87	188.06
Low height for age	14	-0.70	0.98	177.00
Girls				
Very low height for age	5	1.01	0.88	239.09
Low height for age	21	-0.91	0.99	174.25

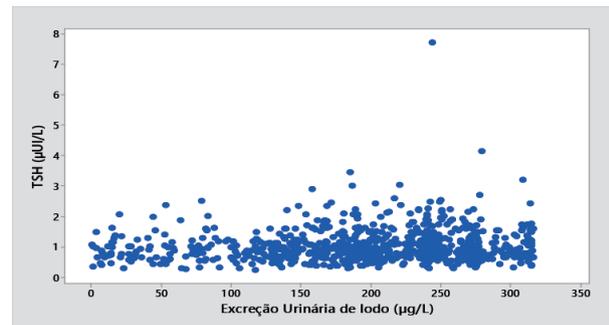
BMI /A: Body Mass Index for Age, TSH: Thyroid Stimulating Hormone, HAZ: Height for age Z score, UIC: Urinary Iodine Concentration.

Establishing cutoff for TSH values in healthy children is complex and there is no consensus in Brazil. In this monitoring, was adopted reference values for normality between 0.72 to 6.0 $\mu\text{UI/L}$ based on the study in Jerusalem, which is set in a iodine intake sufficient area (STRICH; EDRI; GILLIS, 2012).

According to Carvalho, Perez and Ward (2013), it is difficult to establish a universal reference value, since the circulating levels of TSH are heterogeneous with respect to glycosylation and biological activity. Another important determinant is considered the reference area has sufficient consumption or iodine deficient. TSH dosage is a reliable test for diagnosing the primary forms of hypothyroidism and hyperthyroidism, but is not constituted as the most appropriate marker for assessing the nutritional status of iodine. Several studies have used the TSH, especially in the neonatal period, as an indicator of nutritional iodine supply situation in populations (MCELDUFF et al., 2002; ALVES et al., 2005; GUAN et al., 2008; HASHEMPOUR et al., 2010; YAMAN et al., 2013; EVANS et al., 2014).

Indeed, we don't found correlation between TSH and UIC ($r = 0.115$; $p = 0.002$) (Figure 1), suggesting that TSH may not be a good marker of iodine nutritional status in children. Moreover, Ristic-Medic et al. (2009) state that, in general, TSH levels when using immunoradiometric or immunofluorimetric tests are better indicators of the nutritional status of iodine in pregnant and lactating women, but have limited utility in evaluating children and adolescents.

Figure 1 – Correlation between TSH and Urinary Iodine Concentration



Strich, Edri e Gillis (2012) in measuring TSH levels in more than 11,000 blood samples from newborns, children and adolescents up to 18 years in Jerusalem, found that the upper limit of normal for TSH is increased by about 1 $\mu\text{UI/L}$ in this population. In this study were observed below the reference values, even in schoolchildren with iodine intake deficient. Importantly, TSH has been measured in filter paper at the expense of serum TSH, because the collection is more practical, safe and convenient to transport the collection point of the samples to the laboratory for analysis.

Omar and Desouky (2015) to assess iodine deficiency and the prevalence of goiter in school in the city of Taif, Saudi Arabia, found a significant negative correlation between the average value of the UIC and the average value of TSH. The average value in participants with TSH level 0 goiter was 5.6 $\mu\text{U/L}$, compared to 5.9 $\mu\text{U/L}$ in those with grade 1 goiter ($p < 0.05$).

Bhattacharjee et al. (2013) investigated the serum TSH in 140 goitrous schoolchildren living in sub-Himalayan tarai region, an area with moderate IDD. The results show that overall 10% population has TSH level above 6.1 $\mu\text{U/ml}$, indicating that they had biochemical hypothyroidism. In 56.4% population TSH level was 3.2 to 6.1 $\mu\text{U/L}$, showing the tendency to be biochemically hypothyroid, while rest of the children had TSH level within normal ranges. The serum levels of TSH are in the normal range in most of the children with different grades of goiter, suggesting that these are relatively less sensitive marker for IDD.

In our study, we could not perform ultrasound of the thyroid gland in schoolchildren, as observed in other studies conducted in Brazil (ALVES et al., 2010; DUARTE et al., 2009). We opted for evaluate urinary iodine in casual samples, and TSH in blood samples on filter paper, to thereby investigate different parameters commonly used in the analysis of acute exposure and/or the chronic lack or excess of iodine. The choice of collection isolated urine samples showed relatively more feasible and fewer costs.

CONCLUSION

In the present study, schoolchildren showed average value for TSH of $1.01 \pm 0.55 \mu\text{U/ml}$ and median $0.89 \mu\text{U/ml}$. Levels of TSH are in normal range in most of the schoolchildren with different values of UIC, pointing that the TSH is a less sensitive indicator of iodine nutritional status.

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