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Sensitivity, Specificity, and Predictive Values Measurement of Serum Thyroglobulin Considering Urinary Iodine Status as Gold Standard

Dr. Muhammad Abdul Halim Khan[1*], Prof. Md. Farid Uddin[2], Prof. M. A. Hasanat[3], Dr. Zubaida Naznin[4], Dr. Ashim Dhar[5]

[1]Assistant Professor, Department of Endocrinology, Shaheed Suharawardy Medical College & Hospital, Dhaka, Bangladesh
[2]Professor, Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[3]Professor, Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[4]Assistant Professor, Department of Endocrinology, Shaheed Suharawardy Medical College & Hospital, Dhaka, Bangladesh
[5]Medical Officer, Department of Endocrinology, Shaheed Suharawardy Medical College & Hospital, Dhaka, Bangladesh

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***Corresponding Author:** Dr. Muhammad Abdul Halim Khan
Assistant Professor, Department of Endocrinology, Shaheed Suharawardy Medical College & Hospital, Dhaka, Bangladesh
E-Mail ID: dr.mahalimkhan@gmail.com

Abstract

Background: Iodine is a necessary element of the hormones produced by the thyroid gland. Basically, thyroglobulin (Tg), a thyroid-specific protein, that reflects the size of the thyroid gland, is usually considered a biomarker of urinary iodine status of several patients. But in Bangladesh, we do have not enough information regarding the sensitivity, specificity, and predictive value of thyroglobulin in determining iodine deficiency among simple diffuse goiter patients. ***Aim of the study*:** The aim of this study was to evaluate the sensitivity, specificity, and predictive values of thyroglobulin in determining iodine deficiency among simple diffuse goiter patients. ***Methods:*** This cross-sectional observational study was conducted at the Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU), and Dhaka Bangladesh. The study was conducted during the period from May 2014 to March 2016. The targeted sample size of this study was between 39 and 90 and the final sample size was finalized as 87. A purposive sampling technique was used to select 87 patients with simple diffuse goiter attending the outpatient department of the mentioned hospital. ***Results:*** In this study, we did not find any statistically significant difference in urinary iodine between the different cut-off values of serum thyroglobulin at 14.46 (ng/ml). Similarly, there was not any statistically significant difference in urinary iodine levels at different cut-off values of thyroglobulin. Thyroglobulin had a high negative predictive value and comparatively low positive predictive value in determining iodine deficiency, at 98.51% and 30% respectively. Serum thyroglobulin had 85.71% sensitivity and 82.50% specificity. Thyroglobulin also had a high negative predictive value at 98.51%, but a low positive predictive value at 30%. The overall accuracy of thyroglobulin as an indicator for iodine deficiency was 82.76%. ***Conclusion:*** Thyroglobulin seems to have an inverse association in iodine deficiency state and a positive association in over sufficient state with UI. The overall sensitivity of thyroglobulin was satisfactory but the specificity was found very low. Considering the urinary iodine as the gold standard, basically, the positive predictive value of thyroglobulin was found very low but the negative predictive value was found very high.

Keywords: Iodine, Thyroglobulin, Sensitivity, Specificity, Predictive values, Goiter.

INTRODUCTION

In many countries including Bangladesh, thyroid disorder is one of the major health problems [1]. By iodine intake, the spectrum and the prevalence of thyroid disorders are influenced [2]. In all age groups, iodine deficiency may cause goiter [3]. Enlargement of the thyroid gland is termed goiter. Palpable thyroid enlargement is common, affecting about 5% of the global population [4]. Simple diffuse goiter (SDG) is common and appears endemically in areas with a low iodine intake [5]. The index of choice for evaluating the degree of iodine deficiency and of its correction therefore urinary iodine excretion is a good marker of dietary intake of iodine [6]. The value of thyroglobulin as an indicator of global IDD status has not yet been fully explored (WHO, 2004), but the results from population studies show that thyroglobulin seems to be a valuable indicator of thyroid status with respect to its sensitivity to recent changes in iodine nutrition [7].

Simple diffuse goiter or diffuse nontoxic or colloid goiter is soft, symmetrical and the gland is enlarged two to three times its normal size. According to WHO, UNICEF (United Nations International Children's Emergency Fund), and ICCIDD (International council for control of iodine deficiency disorders) the total goiter rate decreased to 20.4% in 1995 and to 8.8% in 1999 [2]. The spectrum of iodine deficiency disorders encompasses goiter, hypothyroidism, increased susceptibility to radiation, and impaired mental function in all ages. But pregnant women, lactating mothers, and neonates are considered the most vulnerable groups. A meta-analysis of Chinese studies, 2005 comparing the intelligence quotient (IQ) of children living in naturally iodine-sufficient areas to children living in severely iodine-deficient areas found that the 12.45 points were on average higher IQ of iodine-sufficient children [8]. In the United States, the IQ scores of 7- to 9-year-old children of mothers with subclinical hypothyroidism during pregnancy (an increased TSH during the second trimester) were 7 points lower compared to children of mothers with normal thyroid function [9]. The most critical period of iodine nutrition is from the second trimester of pregnancy to the third year after birth. A lack of thyroid hormone for more than a few weeks during brain development in utero or the first year of life may permanently harm brain function [10].

OBJECTIVE

The general objective of this study was to evaluate the sensitivity, specificity, and predictive values of thyroglobulin in determining iodine deficiency among simple diffuse goiter patients.

METHODS AND MATERIALS

This cross-sectional analytical study was conducted at the Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU), and Dhaka, Bangladesh during the period from May 2014 to March 2016. The targeted sample size of this study was between 39-and 90 and the final sample size was finalized as 87. A purposive sampling technique was used to select 87 patients with simple diffuse goiter attending the outpatient department of the study hospital. After completely explaining the procedure, purpose, risk, and utility of the study, proper written informed consent was taken from all the patients. The certificate of approval of the study was taken from the Institutional Review Board (IRB) of the mentioned institute. From each of the patients, a 5 ml blood sample was collected. After separation of serum, it was sent to the laboratory of NINMAS, BSMMU for analysis of serum thyroglobulin.

Inclusion Criteria

- Subjects who had diffusely enlarged thyroid gland and clinically, biochemically in the euthyroid state.
- Age range was 12-35 years.

Exclusion Criteria

- Patients with suspected differentiated thyroid cancer.
- Patients with acute and chronic illness.
- Pregnant and lactating mothers.
- Patient taking drug interfering in thyroid function test.
- Patients with Thyroiditis or Graves' disease.
- Patients with unilateral goiter.
- Patients with nodular goiter.

A predesigned questionnaire was used in data collection. All data were processed, analyzed, and disseminated by using MS Office and SPSS version 23 programs as per need.

RESULTS

In the present study, 33.3% of the participants were from the age group of 17-21 years, 16.1% from 22-26 years of age group, 18.4% from the age group of 27-31 years, 12.6% were aged between 12-16 years, and 19.5% were older than 31 years. The Mean ± SD age was 23.97 ± 6.83 years. Among the participants, 93% were female and only 7% were male. The male: female ratio was 1:13.5. Urinary iodine status was categorized into groups as>300, 200-299, 100-199, 50-99, and <50 µg/L with the concentration of thyroglobulin among the groups as: 12.89±2.26, 9.50±1.70, 6.88±2.44, 11.92±160, and 13.61±8.52 respectively without any statistical difference among the groups (p = 0.617). There was no statistical difference in urinary iodine (302.45±22.39 vs. 326.74±23.43, p = 0.589) between the different cut-off values of serum thyroglobulin at 14.46 (ng/ml). There was no statistical difference in serum thyroglobulin (11.12 ± 1.51vs. 12.64 ± 3.34, p = 0.772) between the different cut-off values of urinary iodine at 100 (µg/L). Cross-referencing the findings based on serum thyroglobulin levels and urinary iodine levels to determine iodine deficiency among the participants, Urinary iodine levels determined only 7 cases with iodine deficiency, while the remaining 80 were iodine sufficient. On the other hand, serum thyroglobulin levels determined 20 iodine-deficient cases and 67 iodine sufficient cases. Holding the urinary iodine status as a gold standard for determining iodine deficiency, we found 6 True Positive (TP), 66 True Negative (TN), 14 False Positive (FP), and 1 False Negative (FN) cases according to serum thyroglobulin findings. The sensitivity, specificity, and predictive value were determined by implementing mathematical formulas using TP, TN, FP, and FN cases. Serum thyroglobulin had 85.71% sensitivity and 82.50% specificity. Thyroglobulin also had a high negative predictive value at 98.51%, but a low positive predictive value at 30%. The overall accuracy of thyroglobulin as an indicator for iodine deficiency was 82.76%.

Table-1: Age distribution of the participants (N=87)

Age (years)	Frequency (n)	Percentage (%)
12-16	11	12.6%
17-21	29	33.3%
22-26	14	16.2%
27-31	16	18.4%
>31	17	19.5%
Mean ±SD	23.97 (± 6.83)	

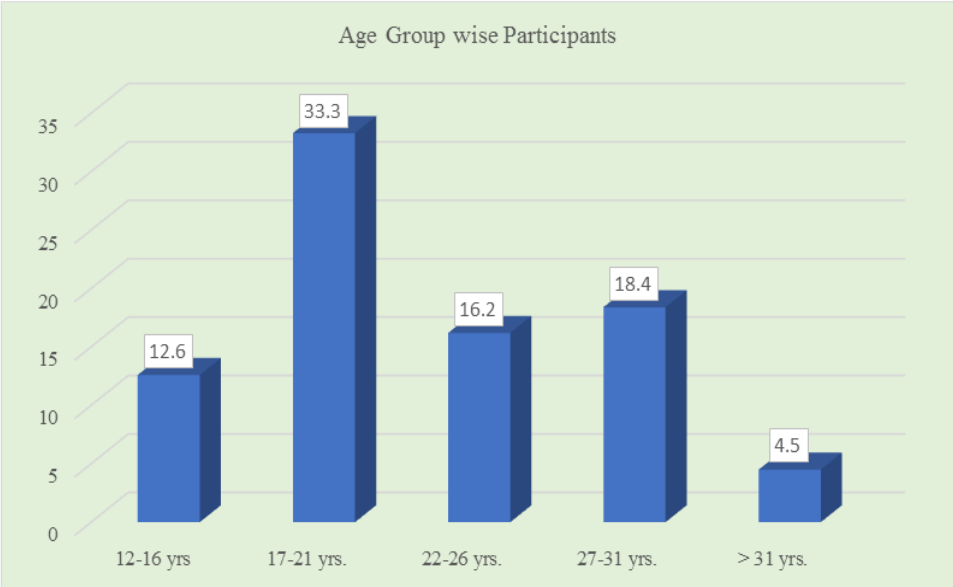

Fig-I: Age Group-wise distribution of participants (N=87)

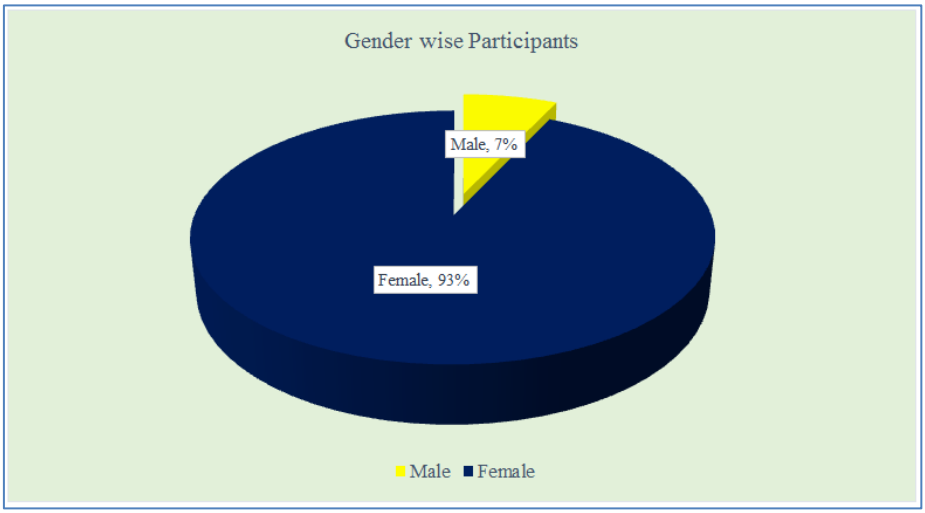

Fig-II: Gender distribution of participants (N=87)

Table-2: Mean Serum Thyroglobulin levels under various cut-off values of Urinary Iodine concentration (ng/ml)

Iodine Status (mg/L)	Serum Thyroglobulin (ng/mL, Mean ±SEM)	P-Value
UIC >300 (n=49)	12.89 ± 2.26	0.617
UIC 200-299 (n=17)	9.50 ± 1.70	
UIC 100-199 (n=14)	6.88 ± 2.44	
UIC 50-99 (n=4)	11.92 ± 1.60	
UIC < 50 (n=3)	13.61 ± 8.52	

Table-3: Mean Urinary Iodine (µg/L) in subjects divided by thyroglobulin cut-off 14.46 (ng/ml)

Thyroglobulin cut-off	Urinary iodine (mean ± SEM)	P-Value
Thyroglobulin > 14.46 ng/ml (n=20)	302.45 ± 22.39	0.589
Thyroglobulin < 14.46 ng/ml (n=67)	326.74 ± 23.43	

Table-4: Mean Serum thyroglobulin (ng/ml) in subjects divided by Urinary Iodine cut-off 100 (µg/L)

Urinary iodine cut-off	Thyroglobulin (ng/ml) (mean ± SEM)	P-Value
UI > 100 µg/L (n=80)	11.12 ± 1.51	0.772
UI < 100 µg/L (n=7)	12.64 ± 3.34	

Table-5: Cross-reference of serum thyroglobulin cut-off values with urinary iodine cut off values

Thyroglobulin	Urinary Iodine		Base
	Iodine deficiency Negative (UI > 100 µg/L)	Iodine deficiency Positive (UI < 100 µg/L)	
Iodine deficiency Negative (<14.46 ng/ml)	66 (TN)	1 (FN)	67
Iodine deficiency Positive (>14.46 ng/ml)	14 (FP)	6 (TP)	20
Base	80	7	87

Table-6: Sensitivity, specificity, and predictive value of Thyroglobulin for Iodine status holding Urinary Iodine cutoff as the gold standard

Characteristics	Percentage (%)
Sensitivity	85.71%
Specificity	82.5%
Positive Predictive Value	30.0%
Negative Predictive Value	98.51%
Accuracy	82.76%

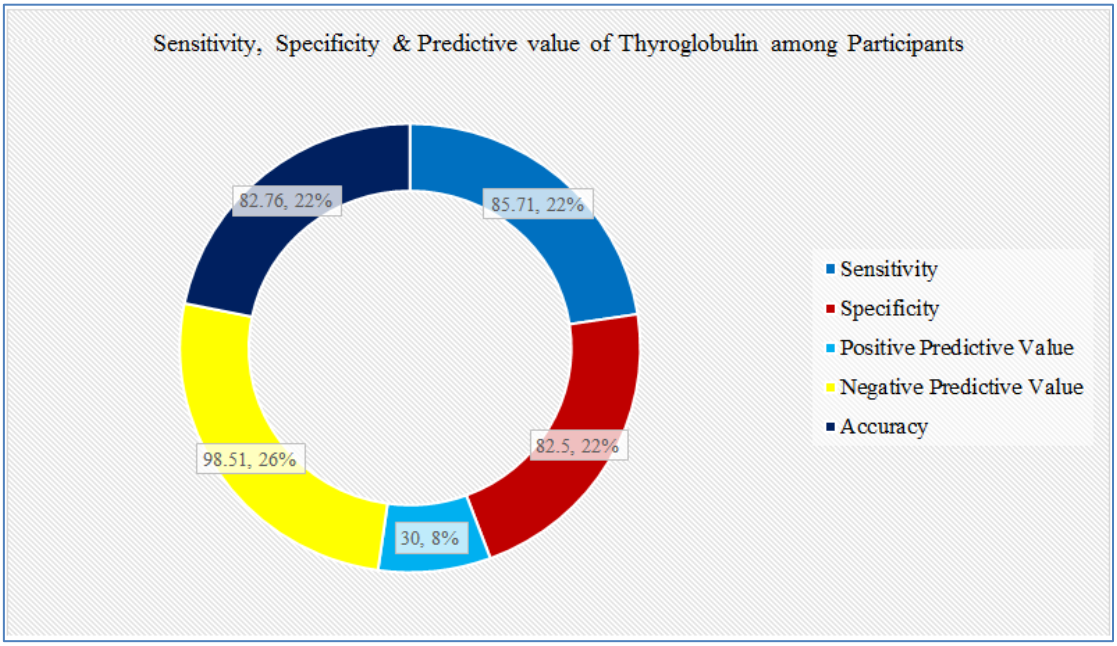

Fig-III: Sensitivity, Specificity, Predictive Value among the participants (N=87)

DISCUSSION

In the present study, we did not find any clear-cut observation to assume any predictive relationship of thyroglobulin over iodine nutritional status. Most of the subjects in the present study were iodine sufficient according to the defined criteria. Therefore, the link of thyroglobulin and deficient iodine status could not be properly apprehended by the data. However, as observed in some studies [3,11] where thyroglobulin

levels showed a trend of increased levels in both lower urinary iodine and higher urinary iodine concentration than that found with adequate iodine status. But it is wise to mention here that the sample size in the present study was very small; therefore, it may not be wise to make any inference in light of the present findings in this study. When subjects were divided into two groups by the reference cut-off value of thyroglobulin at 14.46 ng/ml, it did not show any statistically significant difference in urinary iodine concentration between the divided groups. Moreover, thyroglobulin levels showed no correlation with urinary iodine or duration of goiter or with TSH and FT4. In addition, in light of urinary iodine as the gold standard, sensitivity and specificity of thyroglobulin (dichotomized by the cut-off 14.46 ng/ml-as specified in the used kit) were 85.71% and 23.75% respectively with a positive predictive value of 8.95% and negative predictive value 95%. In our previous studies with simple diffuse goiter, we have observed that iodine nutrition status is more than adequate in most of the subjects [12]. Similarly, in the present study, only 7 participants showed iodine deficiency (<100µg/L); but the mean thyroglobulin status in them was below the proposed cut-off value of thyroglobulin. In agreement with the present finding some other authors abroad also failed to find any significant inverse relationship between thyroglobulin with urinary iodine [13]. It should be mentioned here that thyroglobulin level, though was found to be below the recommended cut-off in all the iodine nutrition sub-groups, showed a trend of higher values in iodine sub-groups with UI levels <100µg/L and >300µg/L with the lowest value in the subgroup of urinary iodine 100-199µg/L. This is in agreement with the findings of Zimmermann MB *et al*. [3] in regards to the trend of thyroglobulin level but not in context to the cut-off value used for thyroglobulin in discerning iodine nutrition status. As mentioned above, the sample size was too small and patients were collected from a tertiary care hospital. Therefore, the true reflection of thyroglobulin trend and iodine nutrition status might have not been reflected in this study. In our study, serum thyroglobulin level was found to be higher in females in regards to both the mean and median values. Conversely, urinary iodine (mean and median) was lower in females. Similar findings were observed by Bilek *et al*. [11] From the present finding of urinary iodine level in the different grades of goiter, it seems that subjects in the present study with grade-2 goiter have haveerienced such event longer time than that with grade-1 goiter; though in both cases the iodine level is far higher than the cut-off for the deficiency of the iodine. Accordingly, thyroglobulin was also found to be lower in grade-1 than grade-2 goiter, supporting an inverse relationship between thyroglobulin and urinary iodine as postulated by some authorities. Also, it reflects in another way that the larger the goiter increased is the level of thyroglobulin as observed by some other authorities [14]. In conclusion, thyroglobulin seems to have an inverse association in iodine deficiency state and a positive association in over sufficient state with urinary iodine. There was no statistically significant difference in thyroglobulin among the age groups and subgroups of various iodine statuses; but though non-significant relatively higher values of it were observed in the females and grade-2 diffuse goiter than that found in males and grade-1 goiter respectively. The sensitivity of thyroglobulin was 85.71% and specificity 23.75% holding a cut-off at 14.46 ng/ml and taking urinary iodine status as defined by UNICEF as the gold standard.

Limitations of the Study

Though the study was conducted in a single hospital with a small sample size, so, the results may not represent the whole community.

Funding: There was not any funding source.

Conflict of interest: None declared.

Ethical approval: The study was approved by the Institutional Ethics Committee.

CONCLUSION

Thyroglobulin seems to have an inverse association in iodine deficiency state and a positive association in over sufficient state with UI. The overall sensitivity of thyroglobulin was satisfactory but the specificity was found very low. Considering the urinary iodine as the gold standard, basically, the positive predictive value of thyroglobulin was found very low but the negative predictive value was found very high. For getting more reliable information regarding these issues we would like to recommend conducting similar studies in several places with larger-sized samples.

REFERENCES

1. Hossain, S.M., Fatema, B. (2008). Impact of Urinary Arsenic Level on Simple Diffuse Goiter. *Dhaka Univ. J. Pharma Sci*, 7; l61-168.
2. Delange, F., Bürgi, H., Chen, Z. P., & Dunn, J. T. (2002). World status of monitoring of iodine deficiency disorders control programs. *Thyroid*, *12*(10), 915-924.
3. Zimmermann, M. B., Aeberli, I., Andersson, M., Assey, V., Yorg, J. A. J., Jooste, P., ... & Timmer, A. (2013). Thyroglobulin is a sensitive measure of both deficient and excess iodine intakes in children and indicates no adverse effects on thyroid function in the UIC range of 100–299 µg/L: a UNICEF/ICCIDD study group report. *The Journal of Clinical Endocrinology & Metabolism*, *98*(3), 1271-1280.
4. WHO, 2001? 'Assessment of Iodine Deficiency Disorders and Monitoring for their Elimination' guide for program Managers. WHO Project TCP NUT, 005.

5. Bonnema, S. J., Nielsen, V. E., & Hegedus, L. (2004). Long-term effects of radioiodine on thyroid function, size and patient satisfaction in non-toxic diffuse goitre. *European journal of endocrinology*, *150*(4), 439-446.
6. Chandrasekaran, M., & Ramadevi, K. (2013). Thyromegaly and iodine nutritional status in a tertiary care hospital in South India. *Indian Journal of Endocrinology and Metabolism*, *17*(2), 260.
7. Knudsen, N., Bülow, I., Jørgensen, T., Perrild, H., Ovesen, L., & Laurberg, P. (2001). Serum Tg—a sensitive marker of thyroid abnormalities and iodine deficiency in epidemiological studies. *The Journal of Clinical Endocrinology & Metabolism*, *86*(8), 3599-3603.
8. Qian, M., Wang, D., Watkins, W. E., Gebski, V., Yan, Y. Q., Li, M., & Chen, Z. P. (2005). The effects of iodine on intelligence in children: a meta-analysis of studies conducted in China. *Asia Pacific journal of clinical nutrition*, *14*(1).
9. Klein, R. Z., Sargent, J. D., Larsen, P. R., Waisbren, S. E., Haddow, J. E., & Mitchell, M. L. (2001). Relation of severity of maternal hypothyroidism to cognitive development of offspring. *Journal of medical screening*, *8*(1), 18-20.
10. Bernal, J. (2000). Thyroid hormones in brain development and function.[updated 2015 Sep 2]. *Endotext [Internet]*. *South Dartmouth (MA): MDText. com, Inc*.
11. Bílek, R., Čeřovská, J., & Zamrazil, V. (2015). The relationship between iodine intake and serum thyroglobulin in the general population. *Physiological research*, *64*(3).
12. van den Briel, T., West, C. E., Hautvast, J. G., Vulsma, T., de Vijlder, J. J., & Ategbo, E. A. (2001). Serum thyroglobulin and urinary iodine concentration are the most appropriate indicators of iodine status and thyroid function under conditions of increasing iodine supply in schoolchildren in Benin. *The Journal of nutrition*, *131*(10), 2701-2706.
13. Teng, X., Shan, Z., Chen, Y., Lai, Y., Yu, J., Shan, L., ... & Teng, W. (2011). More than adequate iodine intake may increase subclinical hypothyroidism and autoimmune thyroiditis: a cross-sectional study based on two Chinese communities with different iodine intake levels. *European journal of endocrinology*, *164*(6), 943.
14. Vejbjerg, P., Knudsen, N., Perrild, H., Laurberg, P., Carlé, A., Pedersen, I. B., ... & Jørgensen, T. (2009). Thyroglobulin as a marker of iodine nutrition status in the general population. *European Journal of Endocrinology*, *161*(3), 475.