Longitudinal trends in thyroid function in relation to iodine intake: ongoing changes of thyroid function despite adequate current iodine status

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Abstract

Objective: Several cross-sectional studies on populations with iodine deficiency showed that TSH-levels are negatively associated with age, while in populations with high iodine intake TSH is positively associated with age. The question is whether such an age-thyroid function relation is an ongoing process apparent also in longitudinal studies and whether it reflects an actual iodine deficiency or an iodine insufficiency in the past.

Methods: In an area with a borderline iodine status in the past, we studied 980 participants of the Nijmegen Biomedical Study. We measured serum TSH, free thyroxine (FT₄), total triiodothyronine (T₃), peroxidase antibodies, and the urine iodine and creatinine concentration 4 years after our initial survey of thyroid function, in which we reported a negative association between TSH and age.

Results: Within 4 years, TSH decreased by 5.4% (95% CI 2.5–8.3%) and FT₄ increased by 3.7% (95% CI 2.9–4.6%). Median urinary iodine concentration was 130 µg/l. Estimated 24-h iodine excretion was not associated with TSH, T₃, change of TSH, or FT₄ over time or with the presence of antibodies against thyroid peroxidase. Only FT₄ appeared to be somewhat higher at lower urine iodine levels: a 1.01% (95% CI 0.17–1.84%) higher FT₄ for each lower iodine quintile.

Conclusions: In this longitudinal study, we found an ongoing decrease in TSH and increase in FT₄ in a previously iodine insufficient population, despite the adequate iodine status at present. This suggests that low iodine intake at young age leads to thyroid autonomy (and a tendency to hyperthyroidism) that persists despite normal iodine intake later in life.

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Introduction

Iodine is an essential micronutrient and an important component of thyroid hormones. Iodine deficiency can cause thyroid dysfunction, goiter, and cretinism (1). Monitoring the iodine status and maintaining an optimal

iodine intake are very important to prevent brain damage in newborns and thyroid function disorders at all ages. Iodine deficiency remains a global public health problem (2). To assess the iodine status of a population, the median

iodine concentration of series of single urine samples is the most widely used measurement (1, 3). In large population studies, there is a leveling out of the day-to-day variation, and the median value of the urinary iodine concentration in samples can be used to assess whether a population is iodine sufficient (4). According to the World Health Organization (WHO) criteria, a population has an optimal iodine intake if its median urine iodine concentration is between 100 and 199 µg/l and no more than 20% of the population has an urinary iodine concentration of 50 µg/l or less (1, 3).

In the past, mild iodine deficiency was present in the eastern and southern part of The Netherlands (5, 6, 7). Iodine supplements were instituted as of 1935. Since then, several additional measures, like the compulsory use of iodized salt in bakeries, instituted in 1963, were taken to achieve a daily intake of iodine within the optimal range as recommended by the WHO (3). Currently, the iodine status of The Netherlands is considered to be adequate, based on studies regarding the iodine intake and urinary excretion in several regions in The Netherlands (2, 8, 9, 10, 11, 12). Owing to decrease in salt consumption and reduced bread consumption, regular monitoring of the iodine status in the population is necessary to verify the maintenance of adequate iodine status (13).

Previous cross-sectional population studies have shown that in populations with a history of mild or moderate iodine deficiency, the average serum level of thyroid-stimulating hormone (TSH) is negatively associated with age, and free thyroxine (FT₄) is positively associated with age, which is probably due to the gradual development of autonomous function of the thyroid gland (14, 15, 16). By contrast, in populations with high iodine intake, TSH is positively associated with age (17). In subjects of the Nijmegen Biomedical Study (NBS), a large population-based survey performed in Nijmegen, a municipality in the eastern part of The Netherlands, TSH is negatively associated with age and FT₄ is positively associated with age (14). These associations were found in cross-sectional surveys. The question is whether such an age–thyroid function relation is apparent also in longitudinal analyses and, if so, whether it reflects an actual iodine deficiency.

Subjects and methods

Subjects

The subjects of this study are a subset of the participants of the NBS, a large population-based survey performed in

Nijmegen, a town in the eastern part of The Netherlands. Details of this study have been described previously (14). Approval to conduct the study was obtained from the Institutional Review Board of the Radboud University Nijmegen Medical Centre (RUNMC). A total of 2253 respondents, aged 50–72 years, were invited to participate in a study of non-invasive measurements of atherosclerosis (NBS-NIMA), of whom 1517 gave their informed consent. In 1052 participants of this subgroup, the iodine concentration was measured in fasting morning urine samples in 2006. Serum TSH and FT₄ were measured twice with an interval of 4 years (2002 and 2006). The mean interval between the measurements was 4.1 years (range 2.8–5.4 years). Triiodothyronine (T₃) and antibodies against thyroid peroxidase (TPOAb) were measured in 2006. We excluded subjects with previously known thyroid disease, a medical history of thyroid surgery or iodine treatment, the use of thyromimetic and/or thyrostatic drugs, and the use of medication interfering with thyroid function or iodine status such as amiodarone, kelp, oral corticosteroids, dopamine agonists, and lithium. A total of 72 participants were excluded, so in total 980 participants were included in the current analysis.

Laboratory methods

Serum TSH and T₃ were measured by an immunoluminometric assay on a random-access analyzer (Architect; Abbott Laboratories). The reference interval for serum TSH used in our laboratory is 0.4–4.0 mIU/l. Serum FT₄ was measured with a luminescence enzyme immunoassay on a random-access assay system (Vitros ECI; Ortho Clinical Diagnostics, Rochester, NY, USA). Our laboratory reference interval is 8.0–22.0 pmol/l. TPOAbs were measured with a fluorescence immunoassay for the quantitative measurement of the IgG class of anti-TPOAbs (AxSYM, Abbott Laboratories). The reference interval was defined as <12 kIU/l (data provided by manufacturer). More details about these measurements are described elsewhere (14). In order to control a possible drift in assays between the two study periods, we repeated TSH and FT₄ measurements of pooled plasma with TSH and FT₄ in the lower, middle, and higher range. For TSH, the control samples showed a drift of –2.2, –6.0, and –9.6% for the lower, middle, and higher range respectively. For FT₄, the control samples showed a drift of –9.7, –5.7, and –1.8% for the lower, middle, and higher range respectively. We suspected that a bias was introduced during analysis of the control samples, perhaps by sample instability in the

freezer or some other unknown factor. Therefore, we choose to use the original results of the assays.

To assess the iodine status of our population, we calculated the median urinary iodine concentration, obtained from single urinary samples, as recommended by the WHO (1, 3). For the individual subjects, we used the estimated 24-h iodine excretion, adjusted for age and gender, as an indicator for the iodine status. The estimated 24-h urinary iodine excretion was calculated as follows: iodine ($\mu\text{g/l}$)/creatinine (g/l) $\times$ expected 24-h creatinine (g/day) (18, 19, 20). A large Belgian population study provides data on the expected creatinine excretion per individual, taking age and sex into account (21). The urine iodine concentration was measured with the Ammonium Persulfate Destruction Microplate (APDM) method, using a Peltier Thermal Cycler (PTC-200) for the heating and cooling process (22). The urinary creatinine concentration was measured by an enzymatic assay (Roche) on the Aeroset chemistry analyzer (Abbott Laboratories).

Statistical analysis

Because of a skewed distribution of the urinary iodine concentration, we used quintiles of the estimated 24-h urinary iodine excretion for stratification. We displayed geometric means of FT_4 and TSH with its 95% CIs. We expressed change over time of TSH and FT_4 as a percentage of change. We performed logarithmic transformation of FT_4 and TSH for regression analysis. Linear regression analysis was performed in order to investigate the relationship between thyroid function and iodine excretion. Each model included the estimated 24-h urine iodine excretion as the independent variable and a thyroid function parameter (either FT_4 , T_3 , TSH, or change of TSH or FT_4 over time) as the dependent variable. To control for possible confounding, we added age, gender, BMI, and current smoking status to the models. We analysed the data with STATA, version 11.0 (StataCorp., College Station, TX, USA).

Results

The characteristics of the population are shown in Table 1. The median urinary iodine concentration was $130 \mu\text{g/l}$. The median urinary iodine concentration was higher in men in comparison with women, 156 vs $104 \mu\text{g/l}$ respectively. The urinary iodine concentration was $<50 \mu\text{g/l}$ in 15% of the participants. The urinary iodine concentration was $<50 \mu\text{g/l}$ in 9% of the men and in 20% of the women. Owing to a higher urinary creatinine concentration, men had a lower urinary iodine:creatinine

ratio (I:C ratio) in comparison with women (135 vs $171 \mu\text{g/g}$ respectively). However, the median estimated 24-h urinary iodine excretion, taking age and gender into account, was higher in men in comparison with women (208 vs $186 \mu\text{g/day}$ respectively).

During the follow-up period of 4 years, the average TSH decreased with 5.4% (95% CI 2.5–8.3%, P value <0.001) and FT_4 increased with 3.7% (95% CI 2.9–4.6%, P value <0.001) (Table 1).

A lower quintile of estimated 24-h iodine excretion was associated with a 1.01% higher FT_4 (95% CI 0.17–1.84%, P for trend along quintiles 0.02, adjusted for age, gender, BMI, and current smoking status). There was no significant association between the TSH level and the estimated 24-h iodine excretion after adjustment for age, gender, BMI, and current smoking status: a lower quintile of urinary iodine excretion resulted in a 0.17% higher serum TSH (95% CI -3.0 to 3.2% , P for trend along quintiles 0.92). There was no association between T_3 and the estimated 24-h iodine excretion.

There was no association between iodine excretion and the percentage of decrease in TSH or increase in FT_4 : a higher quintile of the estimated 24-h iodine excretion resulted in a 1.4% stronger decrease in TSH over time (95% CI -1.0 to 3.6% , P for trend along quintiles 0.25 after adjustment for age, gender, BMI, and current smoking status) and a lower quintile of the estimated 24-h iodine excretion resulted in a 0.4% stronger increase of FT_4 over time (95% CI -0.3 to 1.0% , P for trend along quintiles 0.26 after adjustment for age, gender, BMI, and current smoking status).

There was no relationship between the presence of TPOAb and estimated 24-h urinary iodine excretion (data not shown). After exclusion of subjects with TPOAb, the analyses of TSH, FT_4 , and T_3 gave similar results (data not shown). Analyses with TSH or FT_4 and iodine as (log transformed) continuous variables gave similar results (data not shown).

Discussion

Despite the fact that our population has an optimal iodine intake at this moment, we found an ongoing decrease in TSH and increase in FT_4 over time. The decrease in TSH and the increase in FT_4 in the 4-year follow-up period were even larger than we expected, based on the cross-sectional data in 2002. Iodine excretion was in the recommended range and was not associated with a change in TSH or FT_4 . One might speculate that the decrease in TSH and increase in FT_4 with age in our population is caused by mild iodine

Table 1 Population characteristics.

	Total	Men	Women
<i>n</i>	980	492	488
Mean age (range) (years)	61 (50 to 72)	62 (50 to 72)	61 (50 to 71)
Serum TSH in 2002 (mIU/l) ^a	1.35 (1.30 to 1.41)	1.35 (1.28 to 1.42)	1.35 (1.27 to 1.43)
Serum TSH in 2006 (mIU/l) ^a	1.29 (1.24 to 1.34)	1.30 (1.24 to 1.36)	1.28 (1.20 to 1.36)
Change in TSH over time ^b	−5.4% (−8.3 to −2.5%)	−5.5% (−8.6 to −2.4%)	−5.3% (−10.0 to 0.3%)
Serum FT ₄ in 2002 (pmol/l) ^a	13.0 (12.9 to 13.1)	13.0 (12.8 to 13.2)	12.9 (12.8 to 13.1)
Serum FT ₄ in 2006 (pmol/l) ^a	13.5 (13.3 to 13.6)	13.4 (13.2 to 13.6)	13.5 (13.3 to 13.8)
Change in FT ₄ over time ^b	3.7% (2.9 to 4.6%)	2.9% (1.7 to 4.2%)	4.5% (3.3 to 5.8%)
Serum T ₃ (nmol/l) ^a	1.61 (1.59 to 1.62)	1.61 (1.59 to 1.63)	1.60 (1.58 to 1.62)
Presence of TPOAb (%) ^c	115 (11.9%)	27 (5.6%)	88 (18.2%)
Urinary iodine conc. (μg/l) ^d	130 (70 to 211)	156 (91 to 238)	104 (55 to 176)
Urinary creatinine conc. (g/l) ^d	0.89 (0.4 to 1.5)	1.2 (0.7 to 1.8)	0.6 (0.3 to 1.0)
Iodine:creatinine ratio (μg/g) ^d	154 (109 to 212)	135 (101 to 186)	171 (120 to 241)
Estimated 24-h urinary iodine excretion (μg/day) ^d	199 (145 to 274)	208 (151 to 287)	186 (134 to 262)

TSH, thyroid-stimulating hormone; FT₄, free thyroxine; TPOAb, antibodies against thyroid peroxidase; Conc., concentration.

^aGeometric means (95% CI).

^bPercentage change of TSH and FT₄ from 2002 until 2006, geometric means (95% CI).

^cTPOAb missing in 14 subjects.

^dMedian (interquartile range).

deficiency in the past and not by iodine deficiency in the present. Iodine deficiency in the past may have led to autonomous thyroid function, which at present causes an ongoing increase in FT₄ and decrease in TSH over time.

The mechanism by which mild iodine insufficiency leads to thyroid autonomy is only partially understood. In case of mild iodine deficiency, low iodine intake might lead to a reduced T₄ and T₃ production. In order to prevent this, several TSH-independent autoregulatory mechanisms are triggered, such as an increase in vascularity, an increase in iodine uptake, and increased T₃ production and secretion, at the expense of T₄ (23). If these mechanisms fail, TSH levels will rise as a response to a lower thyroid hormone production. TSH stimulates follicular cell replication and due to the higher replication rate, the chance of activating mutations in the TSH-receptor gene leading to TSH-independent growth and function is increased (24). This and other mechanisms lead to autonomous function of the thyroid and, especially when iodine intake is supplemented, to hyperthyroidism.

We found that a lower estimated 24-h iodine excretion was associated with a somewhat higher serum FT₄. However, we found no relationship between TSH and the estimated 24-h urinary iodine excretion. Previous studies reported conflicting results on the relationship between urinary iodine excretion and thyroid function. Haddow *et al.* (25) found no relationship between urine iodine concentration and thyroid function and only a weak positive association between the urinary I:C ratio and TSH. Their study was performed in an iodine sufficient

population, where TSH increases with age (17). Hwang *et al.* (26) found that the urinary I:C ratio had a negative correlation with FT₄ and showed a positive trend with TSH in a Korean population, with a high iodine intake. In this Korean study, creatinine adjustment of urine iodine measurements was done without taking gender and age into account.

We used the estimated 24-h iodine excretion, adjusted for age and gender, as an indicator for the iodine status of individuals. Assessing the iodine status of individuals is difficult. The within-day and day-to-day variation in urinary iodine excretion are large (27). Therefore, repeated 24-h urine samples are considered to be the best measure (28). However, 24-h collections are not very practical to perform when large numbers of persons have to be investigated. To minimize the variation in urinary iodine concentration caused by a variable urinary volume, the I:C ratio has also been used to assess the iodine status. However, creatinine excretion varies with sex, age, cultural, and genetic background. That is the reason why adjustment for age and sex is recommended (18, 19, 27, 28). This can be done by estimating the 24-h iodine excretion, using the expected 24-h creatinine. A large Belgian population study provides data on the expected creatinine excretion per individual, taking age and sex into account (21).

Our study has a few limitations. Our study is a subset of a large epidemiological study, the NBS-NIMA study. Because of the nature of the NBS-NIMA survey, urinary iodine measurements were only performed in subjects

aged between 50 and 72 years old. Second, as already mentioned, assessing the iodine status of an individual is difficult due to variation in iodine intake and excretion. Owing to the variation in iodine excretion, the relationship between iodine excretion and thyroid function parameters might be underestimated as a result of regression dilution bias (29, 30, 31). Third, the fact that sera from 2002 and 2006 were assayed several years apart introduced a potential bias. Although this potential bias by variation in assay is inescapable in every large population study using biochemical analyses at different moments, this problem is not always recognized and addressed. Finally, although previous population studies have shown an iodine insufficiency in the past in this part of The Netherlands, we have no historical data on iodine excretion of this cohort to support our hypothesis that the current changes in thyroid function are due to iodine insufficiency in the past (5, 6, 7).

In conclusion, in this longitudinal study, we found an ongoing decrease in TSH and increase in FT₄ in a previously iodine insufficient population, despite the adequate iodine status at present. This suggests that low iodine intake at young age leads to thyroid autonomy (and a tendency to hyperthyroidism) that persists despite normal iodine intake later in life.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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