

CLINICAL STUDY

Variations in urinary iodine excretion and thyroid function. A 1-year study in healthy men

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Abstract

Objective: The iodine intake level in a population is determined in cross-sectional studies. A fraction of samples with iodine content below a certain level, e.g. 25 µg/l, may suggest iodine deficiency in part of the population. However, urinary iodine varies considerably from day to day and the fraction of low samples caused by dispersion remains unsettled.

Design: A longitudinal study of 16 healthy men living in an area of mild to moderate iodine deficiency.

Methods: We measured urinary iodine and creatinine concentrations, and serum TSH, total thyroxine (T₄), free T₄ index and total tri-iodothyronine (T₃) in samples collected monthly for 1 year.

Results: Average urinary iodine excretion was 57.0 µg/l (49.1 µg/24 h (corrected for creatinine excretion)) and varied from 29 to 81 µg/l (28 to 81 µg/24 h) between participants. Individual samples varied between 10 and 260 µg/l, and the variation around the mean was 2.4 times larger when calculated for the 180 individual samples compared with the 15 average annual values (1.7 times larger for estimated 24 h iodine excretion values). The fraction of individual samples below 25 µg/l was 6.7% (7.2% <25 µg/24 h), whereas none of the participants had average iodine excretion below 25 µg/l or 25 µg/24 h. Participants with average annual iodine excretion below 50 µg/24 h had a negative correlation between iodine excretion and TSH, whereas a positive correlation was observed when average annual iodine excretion was above this level.

Conclusions: Seven per cent of individual urine samples indicated severe iodine deficiency without this being present in the group studied. Dispersion was reduced by 24% when using estimated 24 h urinary iodine excretion rather than urinary iodine concentration. Participants with moderate iodine deficiency (average annual urinary iodine excretion 25–50 µg/24 h) showed clear signs of substrate deficiency for thyroid hormone synthesis while participants with mild iodine deficiency (50–100 µg/24 h) did not.

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Introduction

The iodine intake level has a marked influence on the incidence and prevalence of thyroid abnormalities in a population (1, 2) and iodine exerts a number of effects on the normal and the sick thyroid gland (3, 4). The most severe consequences of extremes in iodine intake, with developmental brain damage and endemic goitre, are seen in areas with a very low iodine intake (below 20 or 25 µg/day) (5–7). The iodine intake of a population is often assessed by measurements of iodine in urine in cross-sectional studies of selected cohorts (5, 6). This provides information on the average iodine intake and on the frequency of low iodine excretion values. However, in individual subjects urinary iodine excretion to a considerable extent reflects iodine intake over a short period prior to collection (8–10). On the other hand, the thyroid gland has the capacity to store considerable amounts of iodine in thyroglobulin (4, 6)

and a short period of low iodine intake is not necessarily an indicator of iodine deficiency in a subject.

In areas with severe iodine deficiency the thyroid gland lacks iodine, a main substrate for thyroid hormone synthesis, and an increase in iodine intake causes an increase in thyroid hormone levels in serum and a decrease in serum thyrotrophin (TSH) (11, 12). Conversely, in iodine replete areas, an increase in iodine intake causes a decrease in thyroid hormone levels in serum and an increase in serum TSH (13–15) due to autoregulatory iodine inhibition of the thyroid (4). In areas with mild or moderate iodine deficiency, iodine supplementation programmes have been initiated (16) or intensified (17). However, the exact level of iodine intake where the shift between these different mechanisms occur remains unsettled (5, 6).

We studied urinary iodine excretion in a group of healthy men living in an area with mild to moderate

iodine deficiency with monthly sampling for 1 year to approach an estimation of the true iodine excretion level. The aim was to evaluate the relationship between average annual iodine excretion and iodine excretion in single samples. Furthermore, we studied the association between urinary iodine and thyroid function in individual subjects and the importance of average annual iodine excretion for this association.

Subjects and methods

Sixteen healthy Caucasian men, age 24–52 years (median age 38 years) participated. Participant number 7 had subclinical hyperthyroidism with permanently suppressed serum TSH and normal thyroxine (T_4), tri-iodothyronine (T_3) and free T_4 index (FTI) in serum. He was excluded. Of the remaining 15, none had clinical goitre, and none had previous or present thyroid disorders. All had serum TSH, T_4 , T_3 and FTI within the laboratory reference range. None took regular medication or iodine-containing vitamin/mineral preparations. None had undergone examinations with contrast media within 6 months prior to or during the study. Five were non-smokers and 11 present smokers (5–25 cigarettes/day). The characteristics of the individual participants are listed in Table 1.

The participants lived in Jutland, Denmark, where the iodine intake is moderately low (18). We made no restrictions to their daily or yearly routines and sampling procedures were designed to copy the procedures used in cross-sectional studies of urinary iodine excretion to describe the dispersion included in such studies. The study period of 1 year was chosen to include also seasonal differences in the estimate of dispersion. Approval by the regional Ethics Committee was obtained prior to the commencement of this study.

Blood and urine samples were collected monthly for 12 months. A morning (0900 h to 1200 h) blood sample was taken from the cubital vein and a spot urine sample was collected simultaneously from each participant. Serum was promptly separated and samples were stored at -20°C until analyses. All samples from a subject were analysed in the same assay.

Analytical techniques

Serum TSH was measured using immunochemiluminometric technique and a third generation assay (Brahms, Berlin, Germany). Serum total T_3 and serum total T_4 were measured by RIAs (Amerlex-M T_3 RIA Kit and Amerlex-M T_4 RIA Kit, Johnson & Johnson, Cardiff, UK) and T_3 uptake for calculation of FTI using reagents from Farnos Diagnostica, Helsinki, Finland. Urinary creatinine was measured by a kinetic Jaffé method (19). Iodine was determined by the ceri/arsen method after alkaline ashing (20) as described previously (21) and urinary iodine excretion was expressed in $\mu\text{g/l}$ or as an estimate of 24 h urinary

Table 1 Baseline characteristics of individual participants.

Participant no.	Age (years)	BMI (kg/m^2)	Smoking (cigarettes/day)
1	35	27.8	None
2	28	21.5	5
3	38	24.7	20
4	38	26.2	25
5	38	29.0	None
6	53	26.0	None
7	51	29.4	10
8	53	21.4	None
9	31	22.9	10
10	37	23.9	20
11	26	24.5	10
12	53	26.4	10
13	24	21.3	20
14	32	26.2	20
15	43	30.9	15
16	48	24.2	None

iodine excretion. This estimate was based on measurement of creatinine concentration and the average 24 h urinary creatinine excretion in an age- and gender-matched group of Danes (1.52 g/24 h) (22) as suggested previously (23, 24).

Statistical analysis

Dispersion was evaluated by CV% and interquartile range. Pearson's coefficient of correlation was used to evaluate relations between estimated 24 h iodine excretion and serum TSH after logarithmic transformation because the distributions were moderately positively skewed, and ANOVA for comparing monthly means. Mann–Whitney U test or paired t -test were used for comparison of groups and Kendall's tau was used when testing for a trend in the association between estimated 24 h urinary iodine excretion and TSH. A P value of less than 0.05 was considered significant. All data were processed and analysed using Corel Quattro Pro 8 and the statistical package for the social sciences (SPSS), version 8.0.

Results

The average annual urinary iodine concentration (mean of 12 monthly samples) in the 15 participants varied from 29 to $81\text{ }\mu\text{g/l}$ (mean $57.0\text{ }\mu\text{g/l}$; median $50.0\text{ }\mu\text{g/l}$). Iodine concentration in individual urine samples varied from 10 to $260\text{ }\mu\text{g/l}$ and the estimated 24 h urinary iodine excretions in individual samples varied from 18 to $142\text{ }\mu\text{g/24 h}$. The 12 estimated 24 h urinary iodine excretions for each of the 15 participants are depicted in Fig. 1. They were, in general, low but with considerable individual differences in levels (from 28 to $81\text{ }\mu\text{g/24 h}$) and variability (CV% from 20.1 to 70.5). The average estimated 24 h

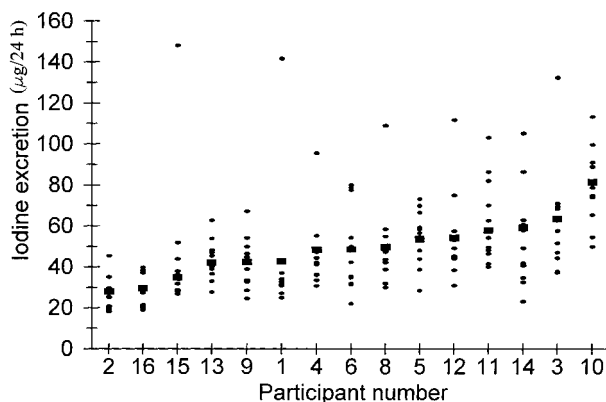


Figure 1 Estimated 24 h urinary iodine excretion in 12 consecutive monthly samples in each of 15 healthy men living in an area with mild to moderate iodine deficiency. Horizontal bars indicate the average estimated 24 h urinary iodine excretion and each dot represents a monthly estimated 24 h urinary iodine excretion (corrected for creatinine excretion from an age- and gender-matched group).

urinary iodine excretion was 49.1 µg/24 h (median 44.7 µg/24 h).

If iodine intake was evaluated from individual samples 6.7% were below 25 µg/l (indicating severe iodine deficiency) and 8.3% above 100 µg/l (indicating sufficient iodine intake). However, none of the participants had average annual iodine excretion below 25 µg/l or above 100 µg/l. A similar difference was observed between estimated 24 h urinary iodine excretion in individual samples and average annual estimated 24 h urinary iodine excretion: 7.2% of single samples <25 µg/24 h; 4.4% >100 µg/24 h; none of the average annual values were <25 or >100 µg/24 h.

Table 2 shows calculations of the spread of urinary iodine concentration and of estimated 24 h urinary iodine excretion for the individual samples and for the average of 12 monthly samples. The variation around the mean urinary iodine concentration was 2.4 times larger when calculated for the 180 individual samples

Table 2 Variation of urinary iodine concentrations and estimated 24 h urinary iodine excretions in individual samples and in average annual values over 1 year. For comparison they are expressed as both CV% and interquartile range.

	CV%	Interquartile range
Average annual urinary iodine concentration ($n = 15$)	23.6%	11.7 µg/l
Urinary iodine concentration in individual samples ($n = 180$)	57.3%	32.0 µg/l
Average annual estimated 24 h urinary iodine excretion ($n = 15$)	27.0%	13.8 µg/24 h
Estimated 24 h urinary iodine excretion in individual samples ($n = 180$)	45.0%	23.7 µg/24 h

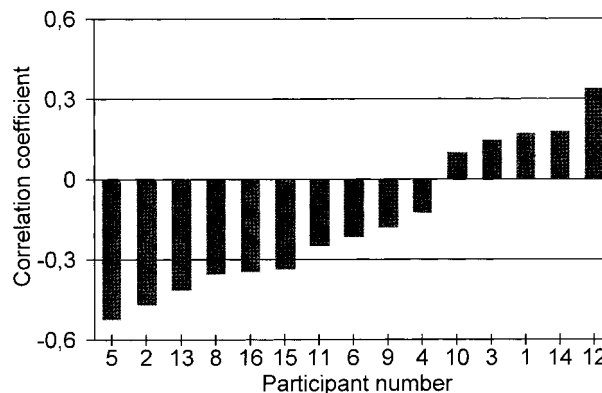


Figure 2 Correlation coefficients between estimated 24 h urinary iodine excretion and TSH in 15 healthy men with mild to moderate iodine deficiency. Serum and urine samples were collected simultaneously, monthly for 1 year. The 24 h urinary iodine excretion was calculated from the measured urinary iodine and creatinine in spot urine samples. Correlations are Pearson's correlation coefficients on ln-transformed data.

than when calculated for the 15 average annual values (1.7 times larger when estimated 24 h urinary iodine excretion was used). When using interquartile range, this difference was 2.7 times for urinary iodine concentrations (1.7 times for estimated 24 h urinary iodine excretion).

Figure 2 shows the coefficients of correlation between estimated 24 h urinary iodine excretion and thyroid function evaluated by serum TSH in the individual participants. In 10 participants a negative correlation was observed whereas it was positive in five. Samples from participants with a negative correlation showed significantly lower annual urinary iodine excretion (Mann-Whitney U test $P = 0.02$) and lower T_4 ($P = 0.02$) and T_3 , and a higher TSH in serum, though the latter did not reach significance (Table 3). This suggested a lower thyroid function in participants with a negative correlation. Furthermore, the correlation between estimated 24 h urinary iodine excretion and serum TSH showed a significant trend from negative towards positive ($P = 0.005$) when participants were evaluated according to average annual estimated 24 h iodine excretion. The level for change in this correlation was around 50 µg/24 h (Fig. 3).

When comparing monthly means of urinary iodine excretion, serum TSH and thyroid hormones, no statistically significant differences were observed. Between seasons, however, minor differences were observed (ANOVA for iodine excretion, $P = 0.077$; for TSH and thyroid hormones, not significant). Estimated 24 h iodine excretion was higher in spring and summer than in autumn (23% and 18%) (t -test, $P = 0.02$ and 0.01) and winter (17% and 12%) ($P = 0.08$ and 0.03). Serum total T_3 was 5% higher in autumn and winter than in summer; serum total T_4 was 4% higher in

Table 3 Laboratory features of participants with positive and with negative correlation between estimated 24 h urinary iodine excretion and serum TSH. Results are expressed as mean \pm S.D.

	Positive correlation (n = 5)	Negative correlation (n = 10)	P
Average annual urinary iodine excretion ($\mu\text{g}/24\text{ h}$)	60.3 \pm 14.1	43.6 \pm 10.0	0.02
Average annual free T_4 index (nmol/l)	119.3 \pm 12.9	93.9 \pm 12.8	0.02
Average annual total T_4 (nmol/l)	123.7 \pm 14.9	97.7 \pm 12.9	0.02
Average annual total T_3 (nmol/l)	1.78 \pm 0.27	1.57 \pm 0.26	NS ^a
Average annual TSH (mU/l)	1.12 \pm 0.55	1.35 \pm 0.46	NS ^a

^a NS = $P > 0.05$.

autumn and winter than in summer; serum free T_4 index showed the same pattern but differences were below 2%; serum TSH was 8% higher in autumn and winter than in spring and summer.

Discussion

The iodine intake of a population is usually evaluated by measuring urinary iodine excretion in a sample of the population. The most important value obtained is the median or mean urinary iodine concentration or 24 h urinary iodine excretion (5, 6). It has been suggested that not only mean urinary iodine concentration but also the fraction of samples below a certain value is important for evaluation of iodine intake in a population (7).

The results of the present study demonstrate that the distribution of iodine measured in single spot urine samples from a population is much broader than the distribution of average iodine excretion in urine in an individual over 1 year. This implies that a certain per

cent of individual values in the range of, for example, severe iodine deficiency does not necessarily indicate that a similar proportion of the population is severely iodine deficient. In this study 7% of individual samples were below 25 $\mu\text{g}/\text{l}$ while none of the participants had such low iodine excretion when evaluated over 1 year. Under the circumstances of the present study the distribution of average annual values as estimated by CV% and interquartile range was only 40% of the distribution of single values. It cannot be excluded, however, that more heterogeneous populations than this may include subgroups with severe iodine deficiency even if the median population iodine excretion is normal. A way to identify subgroups at risk is by evaluation of dietary habits or by repeated measurements of urinary iodine in subjects with low values.

Estimated 24 h urinary iodine excretion has been preferred to crude urinary iodine excretion by some authors (23, 24) as this was more precise in determining the 24-h urinary iodine excretion. In the present study, the use of estimated 24-h iodine excretion reduced the dispersion of measures of iodine excretion by 24% compared with crude urinary iodine. Such a reduction is especially important when the group investigated is small.

Iodine deficiency is often graded into mild and moderate by urinary iodine excretion above or below 50 $\mu\text{g}/24\text{ h}$ (5, 6). The results of this study imply that this is a reasonable level to use as a separator. The group of subjects investigated lived in an area with mild to moderate iodine deficiency and, by the definition indicated, seven subjects were mildly and eight were moderately iodine deficient. Participants with average annual urinary iodine excretions below 50 $\mu\text{g}/24\text{ h}$ (moderately iodine deficient) had signs of variation in thyroid function dependent on availability of the substrate iodine, as a distinct negative correlation between urinary iodine and serum TSH was observed. Conversely, subjects with an annual urinary iodine excretion above 50 $\mu\text{g}/24\text{ h}$ (mildly iodine deficient) had no correlation or a positive correlation between urinary iodine and TSH, suggesting no lack of substrate for thyroid hormone synthesis. Thus, the mechanism by which iodine influences thyroid function changes around 50 $\mu\text{g}/24\text{ h}$.

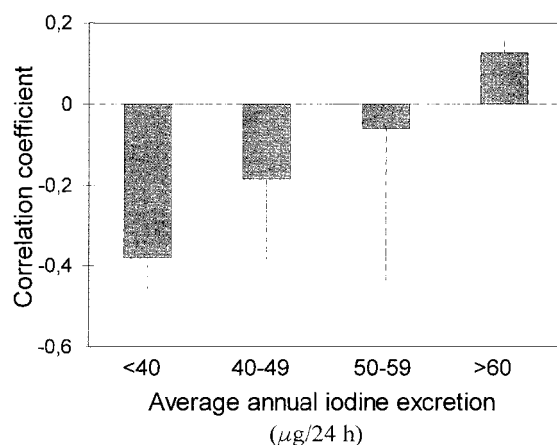


Figure 3 Average correlation coefficients (mean \pm S.E.) between estimated 24 h urinary iodine excretion and serum TSH in 15 healthy men with mild to moderate iodine deficiency. Participants were grouped according to average annual estimated 24 h urinary iodine excretion ($n = 3, 6, 4, 2$ in the four groups with increasing iodine excretion). Pearson's correlation coefficients on ln-transformed data were used.

In conclusion, variations in average levels of iodine intake between individuals is much more narrow than indicated by variations between samples obtained in cross-sectional studies. This is important for risk estimation in evaluation of population iodine intake. The present study supports the use of estimated 24 h urinary iodine excretion rather than measurements of urinary iodine concentration as dispersion was reduced by 24%. Subjects with moderate iodine deficiency evaluated over 1 year showed signs of substrate deficiency for thyroid hormone synthesis, whereas subjects with mild iodine deficiency did not.

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