Ten Repeat Collections for Urinary Iodine from Spot Samples or 24-Hour Samples Are Needed to Reliably Estimate Individual Iodine Status in Women[1–4]

Franziska König,[5] Maria Andersson,[5,7]* Karin Hotz,[5] Isabelle Aeberli,[5,6] and Michael B. Zimmermann[5,7,8]

[5]Human Nutrition Laboratory, Institute of Food, Nutrition, and Health, ETH Zurich, Zurich, Switzerland; [6]Clinic for Endocrinology, Diabetes and Clinical Nutrition, University Hospital Zurich, Zurich, Switzerland; [7]International Council for the Control of Iodine Deficiency Disorders, Zurich, Switzerland; and [8]Human Nutrition Division, Wageningen University, Wageningen, The Netherlands

Abstract

Although the median urinary iodine concentration (UIC) is a good indicator of iodine status in populations, there is no established biomarker for individual iodine status. If the UIC were to be used to assess individuals, it is unclear how many repeat urine collections would be needed and if the collections should be spot samples or 24-h samples. In a prospective, longitudinal, 15-mo study, healthy Swiss women (n = 22) aged 52–77 y collected repeated 24-h urine samples (total n = 341) and corresponding fasting, second-void, morning spot urine samples (n = 177). From the UIC in spot samples, 24-h urinary iodine excretion (UIE) was extrapolated based on the age- and sex-adjusted iodine:creatinine ratio. Measured UIE in 24-h samples, estimated 24-h UIE, and UIC in spot samples were (geometric mean ± SD) 103 ± 28 μg/24 h, 86 ± 33 μg/24 h, and 68 ± 28 μg/L, respectively, with no seasonal differences. Intra-individual variation (mean CV) was comparable for measured UIE (32%) and estimated UIE (33%). The CV tended to be higher for the spot UIC (38%) than for the estimated 24-h UIE (33%) (P = 0.12). In this population, 10 spot urine samples or 24-h urine samples were needed to assess individual iodine status with 20% precision. Spot samples would likely be preferable because of their ease of collection. However, the large number of repeated urine samples needed to estimate individual iodine status is a major limitation and emphasizes the need for further investigation of more practical biomarkers of individual iodine status. J. Nutr. 141: 2049–2054, 2011.

Introduction

Iodine in the urine is a reliable biomarker of iodine status of populations (1), but defining iodine status at the individual level remains challenging. A biomarker of individual iodine status would be useful to assess iodine intake to reduce risk of thyroid dysfunction due to iodine deficiency or excess. Dietary iodine is well absorbed (92% bioavailability) (2) and plasma iodine is taken up by the thyroid to be incorporated in thyroid hormones (3). The excess is excreted in the urine at a renal plasma clearance rate of ~12%/h together with a small amount of iodine from deiodinated thyroid hormones (4). Most of the ingested iodine (90%) is excreted in the urine within 24 h (5) and urinary iodine thus reflects recent iodine intake.

The iodine content in urine can be measured in spot samples or in 24-h collections and expressed as a urinary iodine concentration (UIC, in μg/L) or as the amount daily excreted (μg/24 h). UIC from spot samples is the recommended indicator for population assessment and monitoring of iodine interventions globally (1,6). Adequate iodine status is indicated by a population median UIC ≥100 μg/L; below this cutoff the iodine intake is considered inadequate. Although UIC as a population indicator of iodine status is well established, there is no consensus on the method to use for urinary iodine as a biomarker of individual iodine intake (3,7–9). UIC in spot samples varies substantially between days and seasons (10–12), as a consequence of a circadian rhythm of iodine excretion (13,14), and due to differences in fluid intake (15). Therefore, a single spot UIC is not a suitable indicator for individual assessment (8). Urinary iodine excretion (UIE) in 24-h collections is regarded as a better method, because urinary iodine determined from pooled 24-h urine samples reflects an individual's true daily excretion (8). However, the UIE over 24 h also varies considerably from day to day due to daily and seasonal variations in iodine intake

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(10–12) and differences in renal clearance (16). The challenges of obtaining complete 24-h urine collections may limit the use of this method.

An alternative method to assess individual iodine status is to use the age- and sex-adjusted iodine:creatinine ratio to estimate daily UIE from spot samples (7,12,17,18). The estimated UIE corrects for differences in urine volume and dilution of samples and has been suggested to be more reliable than UIC alone (8). However, few studies have examined the validity of estimated UIE as an indicator of individual iodine status and assessed its strength as a biomarker of iodine deficiency in different populations. Therefore, our objective was to compare the relative utility of repeated spot samples compared to 24-h collections for urinary iodine to assess individual iodine status in adults living in a borderline iodine-sufficient area where most iodine intake comes from iodized salt. We measured UIC in spot samples and 24-h samples collected longitudinally over 15 mo and compared the estimated UIE with the measured UIE.

Materials and Methods

Study population. This article presents secondary analysis from a prospective longitudinal study of ^{41}Ca bone excretion. Twenty-two women aged 52–77 y (mean 64 y) living in Zurich, Switzerland, participated in the present study. The inclusion criteria were healthy women, nonsmoking, no vegetarian or other unusual diets, no use of iodine-containing multivitamin supplements or algae products, and with a BMI between 18 and 30 kg/m^2. In the latest national iodine study in Switzerland in 2009, school children and pregnant women were iodine sufficient (19) and >80% of households were using adequately iodized salt. However, because salt iodization is not compulsory, both iodized (20 ppm) and noniodized salts are available (20). The study was conducted between September 2009 and November 2010. Written informed consent was obtained from the participants, and the study was approved by the Ethics Committee of the Canton of Zurich. The Ethics Committee of the ETH Zurich (Zurich, Switzerland) was informed.

Methods. The study was divided into 2 periods as defined by the principal study protocol. In the first period, between September 2009 and March 2010, each woman provided 24-h urine samples according to a defined schedule of 2 and 8 wk interval. In the second period, from March 2009 to November 2010, 24-h urine samples were collected biweekly by the same women on specified days (weekend and weekdays). During the vacation season, participants were allowed to shift collection days (±3 d) after consultation with the study leader. Participants were instructed to collect 24-h urine samples in preweighed polyethylene bottles containing 10 mL 1 mol/L HCl. The 24-h samples were collected by discarding the first morning urine and adding the morning urine of the consecutive day. Samples were either kept at 5°C if analyzed within 24 h or stored as 500-mL subsamples in acid-washed polyethylene containers at −20°C until analysis. The stored 500-mL samples were defrosted in random order at room temperature and divided into aliquots. The aliquots were either directly measured or stored at −20°C until analysis.

Spot urine samples were collected on weekdays every 4 wk in the second study period, within ±2 d of the 24-h urine collections. Spot samples were collected as fasting second morning urine samples, dictated by the overall study protocol. Spot samples were either kept at 5°C if analyzed within 24 h or stored at −20°C until analysis. All 24-h samples and spot urine samples were analyzed for UIC (*n* = 341 24-h urine samples and *n* = 177 spot urine samples).

Laboratory analysis. UIC was determined in duplicate at ETH Zurich by using a modification of the Sandell-Kolthoff reaction with spectrophotometric detection (21). With this method, the CV for UIC (± SD) in our laboratory was 10.2% at 33 ± 3 μg/L and 3.6% at 214 ± 8 μg/L. The urinary creatinine concentration was determined for all spot samples by the Jaffé method (rate-blanked with compensation) (22) at the

Institute of Clinical Chemistry at the University Hospital Zurich, Zurich, Switzerland.

Data and statistical analysis. Data processing and statistics were done with EXCEL (2010; Microsoft), SPSS 17.0, and the R statistical software version 2.12.1 including the MethComp package (23,24).

UIE in 24-h samples (as μg/24 h) was calculated by multiplying the UIC of the samples (μg/L) by the volume of the corresponding 24-h urine samples. The iodine content of spot samples was expressed as concentration (UIC) (μg/L), iodine:creatinine ratio (μg iodine/g creatinine), and estimated 24-h UIE (μg/24 h)[9]. The latter was calculated by multiplying the iodine:creatinine ratio by the expected 24-h creatinine excretion to correct for age and gender variations, as suggested by Knudsen et al. (17) based on data from a study in 4008 Belgian adults (25). Creatinine excretion values used were 1.15 g for women aged between 50 and 59 y, 1.07 g for women aged between 60 and 69 y, and 1.00 g for study participants who were 70 y and older. Where the category changed during the duration of the study, the category during which the majority of the samples was provided was used.

The normality of data was checked with the Kolmogorov-Smirnoff test. Indicators were expressed as means ± SD for normally distributed data, geometric means ± SD for normal distribution after Ln-transformation (natural logarithm function), and medians (95% CI, obtained by 1000 bootstrap samples) for non-normally distributed data. UIC, iodine:creatinine ratio, and estimated and measured 24-h UIE for individuals were all normally distributed after Ln-transformation (close to normal distribution after Ln-transformation for UIC). Variation (CV) per participant and inter-individual variation were calculated from the SD of the Ln-transformed urinary iodine measurements (26). Overall (mean) intra-individual CV for the different urinary iodine methods was computed as square root of the sum of squared individual CV divided by the number of participants. Intra-individual variation of repeated measurements was calculated and expressed as CV% of the overall individual mean of respective urinary iodine measurements. Inter-individual variation (CV%) was calculated by treating all measurements as individual samples.

The agreement between the estimated UIE and measured UIE (standard method) was assessed by a Bland-Altman plot (27). The differences between the estimated and measured UIE were plotted against the mean of the 2 methods. The 95% limits of agreement were estimated for the individual mean values (27), and for all data points by using mixed effect model analysis of all individual repeated measurements (28).

Sample size and precision range calculations were conducted by using a modification of a formula for the SEM (7,29). The number of samples was calculated as $n = (Z \cdot CV/D)^{1/2}$, where Z is 1.96 for a CI of 95%, CV is the intra- or inter-individual variation, and D is the precision range for biochemical variables. The precision range D for individuals was calculated as $D = Z \cdot CV/(n^{1/2})$.

Differences between means were analyzed by *t* test for independent samples. Homogeneity of variances was analyzed by Bartlett's test. Correlations were evaluated by Pearson correlation for normally distributed data and by Spearman correlation for non-normally distributed data. $P < 0.05$ was considered significant.

Results

Measured 24-h UIE. The characteristics of the individual participating women as well as their urine volumes and urinary iodine measurements with the 4 different methods are available online (**Supplemental Table 1**). The 22 study participants collected 16 (range, 14–17) repeated 24-h urine samples each over the 15-mo study period (*n* = 341). Individual measured UIE (geometric mean ± SD, all such values) ranged from 54 ± 13 to 167 ± 33 μg/24 h (overall group, 103 ± 28 μg/24 h) (**Table 1**).

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[9] To convert μg iodine/24 h into μmol iodine/24 h, and μg iodine/L into μmol iodine/L, multiply by 0.0079. To convert μg iodine/g creatinine into μmol iodine/mmol creatinine, multiply by 0.00089. To convert g creatine/L into mmol creatine/L, values are multiplied by 8.84.

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Figure 1 shows the geometric mean ± SD of the measured 24-h UIE for each individual and illustrates the spread of data. The CV for the individual UIE ranged from 18 to 46%. Measured 24-h UIE was not correlated with urine volumes ($r = 0.07$, $P = 0.19$), whereas UIC measured in 24-h samples (results not shown) were correlated with urine volume ($r = 0.66$; $P < 0.001$). There was no correlation between urine volume and BMI ($r = 0.10$; $P = 0.16$). The 24-h UIE in individuals did not vary between summer and winter. The individual mean UIE in 24-h samples collected in parallel with spot samples (5–9 per individual, $n = 190$) ranged from $52 ± 13$ to $164 ± 48$ μg/24 h and the overall group mean was in agreement with the pooled results of all 24-h collections ($P = 0.80$) (Table 1). The CV of the individual mean measured UIE ranged from 16 to 51%.

Estimated 24-h UIE from spot samples. The participants collected 8 (range, 5–9) spot urine samples in parallel with the 24-h collections ($n = 177$). The mean UIC in the spot samples was $68 ± 28$ μg/L. The mean creatinine concentration was $0.82 ± 0.5$ g/L with no seasonal variation and the corresponding iodine:creatinine ratio was $80 ± 31$ μg iodine/g creatinine. The mean estimated UIE was $86 ± 33$ μg/24 h, adjusted for age and sex. The estimated UIE from spot samples was 16% lower than the measured 24-h UIE ($P < 0.001$). A Bland-Altman analysis comparing all paired UIE measurements (**Fig. 2**) showed that the estimated UIE was 16 μg/24 h lower than the measured UIE. The 95% limits of agreement (±1.96 SD) were −57 and 24 μg/24 h of the individual means and −125 and 93 μg/24 h of the individual means.

Intra- and inter-individual variation of urinary iodine methods. The variations (mean CV%) per participant for UIC in spot samples, estimated 24-h UIE, and measured 24-h UIE are shown in **Figure 3**. Irrespective of the urinary iodine method, the intra-individual CV was lower than the inter-

FIGURE 1 Measured 24-h UIE for each participant. Values are geometric mean ± SD, $n = 14$–17. UIE, urinary iodine excretion.

individual CV. For measured 24-h UIE ($n = 190$), the inter-individual CV (41%) was 1.3-fold higher than intra-individual CV (32%). For UIC, the inter-individual CV (55%) was 1.4-fold higher than the intra-individual CV (38%) and for estimated 24-h UIE, the ratio of inter-individual CV (46%) to intra-individual CV (33%) was 1.4. Intra-individual variation was highest for crude UIC (38%) and decreased for estimated 24-h UIE (33%) ($P = 0.12$) and measured 24-h UIE (32%) ($P < 0.05$). The magnitude of the intra-individual CV for UIE was not associated with the daily amount of iodine excreted ($P = 0.14$ for estimated UIE, $P = 0.21$ for measured UIE).

Sample size calculation and precision ranges. Based on the mean intra-individual variation for the different urinary iodine methods, the number of samples needed to assess an individual's iodine status with set precision and CI requirements was calculated (**Table 2**). For a precision of 10%, 56, 41 and 40 urine samples are needed to assess UIC, estimated UIE and measured 24-h UIE, respectively. If 10 repeat samples are collected, the precision is 24% for crude UIC, 20% for estimated 24-h UIE, and 20% for measured 24-h UIE.

The precision range for our participants, based on the total number of 24-h samples collected per individual, varied between 9 and 22% (mean = 15%). The number of spot samples needed for a population survey (CI = 95%, D = 5%) is 473 if using UIC and 328 if using estimated 24-h UIE (based on a population CV of 55% for UIC and 46% for estimated 24 UIE).

Discussion

In this longitudinal study of women living in a borderline iodine-sufficient area, we showed that repeated casual spot urine samples can be used to estimate UIE and assess individual iodine status as a reliable alternative to 24-h urine collections. Although the UIE varied considerably between individuals, the mean intra-individual variation was lower for UIE than for UIC and was not associated with the amount of iodine excreted. We showed that the intra-individual variation of estimated UIE (CV 33%) was comparable with that of the measured UIE (CV 32%; $P = 0.63$) over 15 mo. The obtained day-to-day variation in UIE is consistent with earlier studies of estimated UIE in European adults (7,12,30–32) and with short-term studies of measured UIE (12,33). An individual UIE variation of 33% can thus be considered representative for Western populations with diverse food choices but is likely lower in populations with a more monotonous diet.

In our study area, where most of the iodine intake comes from iodized salt, the intra-individual variability is mainly determined by day-to-day variations in iodized salt consumption

TABLE 1 General characteristics, urine volume, individual mean UIE, UIC, and iodine:creatinine ratio from 24-h or spot urine collections in the 22 healthy women[1]

Characteristics	n	CV (%)[2]
General characteristics		
Age, y	22	$64 ± 7$	—
BMI, kg/m^2	22	22.8 (21.0, 24.3)	—
24-h collection		
Urine volume,[3] L	341	2.11 (2.04, 2.21)	—
Measured 24-h UIE,[3,4] $μg/24 h$	341	$103 ± 28$	32
Measured 24-h UIE,[5] $μg/24 h$	190	$102 ± 29$	32
Spot samples		
UIC, $μg/L$	177	$68 ± 28$	38
Iodine:creatinine ratio, $μg/g$	177	$80 ± 31$	33
Estimated 24-h UIE, $μg/24 h$	177	$86 ± 33$[6,7]	33

[1] Values are geometric mean ± SD, median (95% CI by bootstrapping), or percent. UIC, urinary iodine concentration; UIE, urinary iodine excretion.
[2] Mean CV calculated as $CV_{mean} = (\sum CV\%^2_{1-22}/n)^{1/2}$ (7).
[3] Values are based on the total number of 24-h urine samples collected ($n = 341$).
[4] To convert μg iodine/24 h into μmol iodine/24 h and μg iodine/L into μmol iodine/L multiply by 0.0079. To convert μg iodine/g creatinine into μmol iodine/mmol creatinine multiply by 0.00089.
[5] Values are based on the 24-h urine samples collected in parallel with spot samples ($n = 190$).
[6] 95% CI for estimated 24-h UIE: 77, 89 μg/24 h.
[7] Different from measured 24-h UIE, $P < 0.001$ (t test for independent samples). The group comparison included only 24-h samples collected in parallel with spot samples.

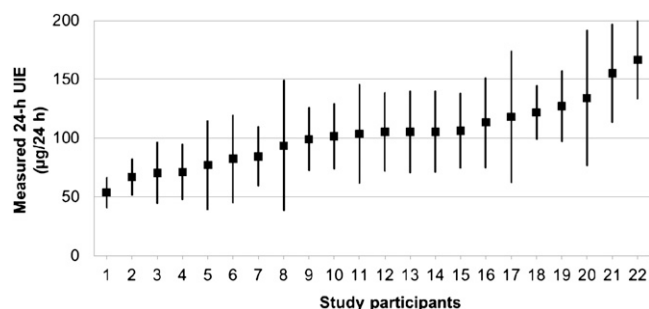Assessment of individual iodine status 2051

FIGURE 2 Bland-Altman plot showing the level of agreement between estimated and measured UIE from all paired 24-h and spot urine collections. The black line shows the overall mean difference between estimated and measured UIE, bold dashed lines represent the 95% limits of agreement of the individual mean values, and the thin dashed lines describe the 95% limits of agreement for all measurements. UIE, urinary iodine excretion.
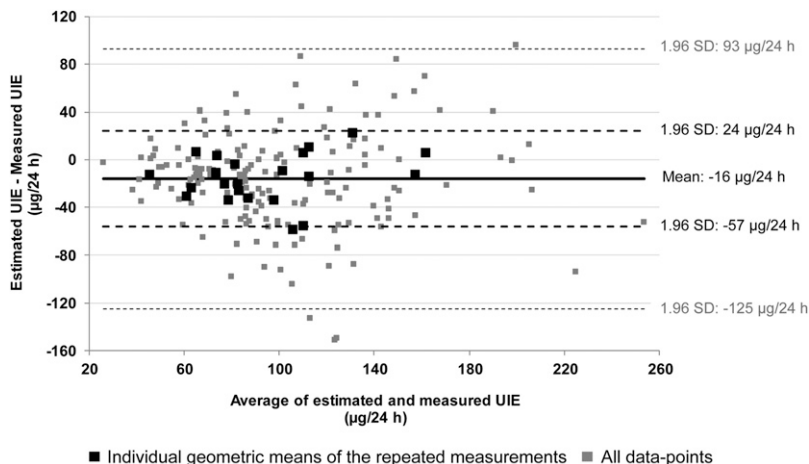
(34). But because the majority of salt consumed in Switzerland comes from processed foods and not household use of salt, the variability is mainly attributed to the use of iodized salt in processed foods. In addition, the natural iodine content of regularly consumed iodine-containing foods and food items is also highly variable (35,36). Therefore, the daily iodine consumption by Western populations, even with apparently constant dietary patterns, is likely to vary considerably. However, we found no seasonal variation in UIE during the study and thus no influence of seasonal food choices on iodine status.

We show that it takes 10 repeated spot urine samples or 24-h urine collections to determine an individual's iodine status at a precision of 20%. The number of required repeated measurements is in agreement with earlier findings for estimated UIE (7). The large number of repeated samples is not surprising considering the extensive day-to-day variation observed for sodium intake and sodium urine excretion (37,38). Studies investigating sodium intake show that at least five 24-h collections are needed to obtain a representative estimate of individual sodium excretion (39–41).
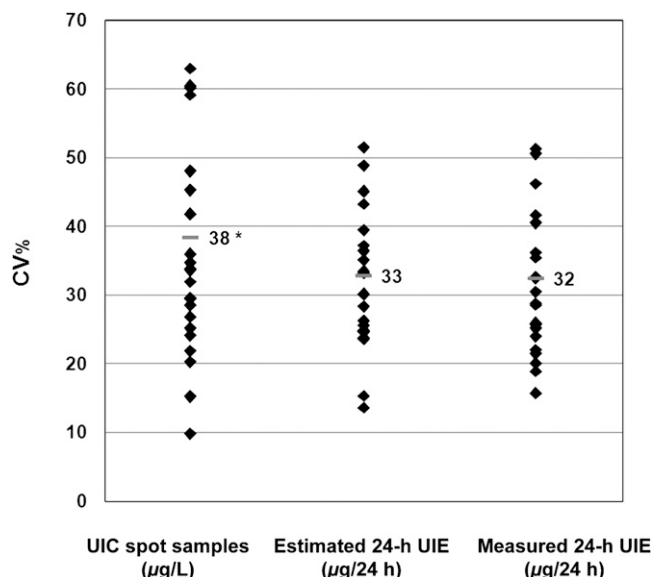

FIGURE 3 Variation (mean CV%) per participant (n = 22) for UIC in spot samples, estimated 24-h UIE and measured 24-h UIE. Mean CV % for each method is indicated with a bar. *Different from measured 24-h UIE, P < 0.05. UIC, urinary iodine concentration; UIE, urinary iodine excretion.

The Bland-Altman analysis (Fig. 2) showed satisfactory agreement between estimated and measured UIE for the overall individual mean of all repeated measurements, in agreement with previous studies (12,17,18). However, in our study, the estimated UIE was significantly lower (16%) than the measured UIE, possibly due to the time of sampling. The spot samples were fasting second void samples. UIC follows a circadian rhythm and the spot urine samples collected as morning fasting urine generally tend to underestimate the iodine status (12–14). Spot urine samples collected to estimate UIE should therefore be nonfasting samples or samples taken at random at any time during the day.

The estimated UIE of 86 μg/24 h corresponds to a daily iodine intake of 104 μg/24 h (assuming 92% bioavailability and 90% excretion). The daily iodine intake can also be calculated from UIC, using the formula: daily iodine intake = UIC (μg · L^{-1})/0.92 · (0.0009 L · h^{-1} · kg^{-1} · 24 h · d^{-1}) · weight (kg) (42), where 0.92 refers to 92% bioavailability and 0.0009 L · h^{-1} · kg^{-1} refers to urine volume. Applying the formula to the geometric mean UIC of 68 μg/L derives an estimated iodine intake of 98 μg/24 h, which is in agreement with the intake extrapolated from the estimated UIE (P = 0.47). However, as an indicator of iodine status, UIC may underestimate the UIE (8,10,12,15). UIC of 24-h samples was correlated with 24-h urinary volume (r = 0.66; P < 0.001), whereas measured 24-h UIE was not (r = 0.07; P = 0.19). Daily UIE, estimated from UIC and corrected for age- and sex-adjusted creatinine excretion, is thus more reliable than UIC alone, because creatinine accounts

TABLE 2 Number of urine samples to be collected from an individual to assess UIC/UIE with a defined precision range[1]

	Precision range, %					
Type of method	5	10	20	30	40	50
24-h collection						
Measured 24-h UIE, μg/24 h	161	40	10	4	3	2
Spot samples						
UIC spot samples, μg/L	226	56	14	6	4	2
Iodine:creatinine ratio, μg/g	165	41	10	5	3	2
Estimated 24-h UIE, μg/24 h	165	41	10	5	3	2

[1] Based on mean intra-individual CV. Calculated from $n = (Z \cdot CV/D)^{1/2}$. n = number of samples needed; Z = number of standard deviates (calculated assuming a CI of 95%, Z = 1.96); CV = mean intra-individual CV; D = precision range. UIC, urinary iodine concentration; UIE, urinary iodine excretion.

for individual hydration status. Other confounders of UIC are circadian differences in iodine excretion (13,14) and seasonal variation (10,11). Moreover, taking creatinine into account also reduces the intra-individual variation compared to UIC (Fig. 3) (7,8). The creatinine excretion in our study population was fairly constant and did not vary between seasons. The day-to-day variation for estimated UIE was 13% lower than for UIC, although not significantly different ($P = 0.12$). Estimated UIE has not been evaluated in children, but data on age-specific creatinine excretion in children is available (43), making estimated UIE a potential method also for children. A caveat to the method is that it cannot be used in malnourished individuals in whom the creatinine concentration is low and creatinine excretion is unreliable (44).

We show that the individual UIE derived from repeated spot samples provides a rough estimate of iodine status that can distinguish a mean intake in the range from low to high (Fig. 1). The recommended daily iodine intake in adult women is 150 μg/24 h (1), which roughly corresponds to an estimated UIE of 124 μg/24 h (assuming 92% bioavailability and 90% excretion, as above). However, for UIE to be used as a diagnostic tool for iodine deficiency, reference ranges for UIE derived from populations in iodine balance are needed. The WHO reference ranges for defining optimal iodine status are based on UIC for population medians and are not intended for individuals (1).

Thyroid hormones are well-established clinical indicators of thyroid function, but estimated UIE may be a useful biomarker of iodine nutrition that can detect low iodine intake and identify mild iodine deficiency in an individual before it adversely affects thyroid function. Estimated UIE predicts thyroid dysfunction in iodine-deficient populations (31,45,46). In contrast, no association between UIC from spot samples and thyroid stimulating hormone or total thyroxine was observed in adult U.S. women, likely due to the overall sufficient iodine status (47).

A possible limitation to the generalization of our results to the general population is the homogeneous study population of female seniors. Age may influence iodine status in adults, but studies in adult populations are inconsistent and report both increasing (18,48,49) and decreasing (50,51) UIC with age. Women tend to have lower iodine status than men (48–51), but the day-to-day variation of UIC and UIE in our group of women was similar to the variation observed in adult men (7,31) and was not correlated with the daily amount of excreted iodine. The present results are thus likely representative of the overall mixed-gender adult population, but more data are needed for children. A further limitation is that we did not use para-aminobenzoic acid to control for complete 24-h collections (8,52). However, the participants carefully followed instructions, making the urine collections reliable.

In conclusion, estimated UIE from 10 spot samples can be used to assess individual iodine status and is preferred over measured UIE from 24-h urine collections because of their ease of collection. The spot samples may be collected at any time of the day, except the first morning samples and should be spread over a time frame that covers potential seasonal variations in iodine intake. However, the large number of repeated samples may limit the practical application of estimated UIE and warrants further investigation of more feasible biomarkers of individual iodine status.

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