Original Article

Community and individual iodine status assessment in premenopausal women in Shanxi, China: Repeated spot urine versus 24-hour urine

Xiaomin Jia MM[1†], Jie Liu MM[1†], Wenwen Gu MM[1], Peng Zhang MM[1], Wendi Liu MM[1], Hong Zhu PhD[1], Xiaotong Liu BSM[2], Maocheng Sang DSM[3], Jiawen Ding BSM[3], Zhongna Sang PhD[1]

[1]*Department of Nutrition and Food Hygiene, Tianjin Key Laboratory of Environmental Nutrition and Population Health, School of Public Health, Tianjin Medical University, Tianjin, China*
[2]*School of Nursing, Tianjin Medical University, Tianjin, China*
[3]*School of Clinical Medicine, Tianjin Medical University, Tianjin, China*
[†]*Both authors contributed equally to this manuscript*

Background and Objectives: Urinary iodine is an essential index of iodine nutrition evaluation. To establish the number of repeated spot urine collections necessary to reflect individual iodine status over 2 months and assess its feasibility to serve as an independent indicator of individual iodine status. **Methods and Study Design:** We performed a longitudinal, 2-months study from May to June in 2015 of 23 apparently healthy Chinese women aged 18 to 44 (32±9) y. Spot urine samples were collected on any two days of the week, and 24-h urine samples were collected once every 6 days. **Results:** 368 spot urine and 230 24-h urine samples were analysed. The median urinary iodine concentration (UIC) was 140.5 (75.2, 246.9) μg/L. The estimated 24-h urinary iodine excretion (24-h UIE) values from spot urine samples and measured 24-h UIE values from 24-h urine samples were 348±240 μg/24h and 330±216 μg/24h (p=0.003), respectively. Irrespective of the urinary iodine method, the intra-individual coefficient of variation (CV%) was lower than the inter-individual CV%. Bland-Altman analysis revealed differences between spot urine and 24-h urine. When the precision ranges with 95% confidence were ±15%, ±20%, ±25% or 30%, the number of an individual's spot urine samples required were 30, 16, 11 or 8, respectively. **Conclusions:** Repeated spot urine is not a feasible way to assess recent individual iodine intake. The development of a multi-indicator system could provide an acceptable individual evaluation index of iodine status.

Key Words: iodine intake, repeated spot urine samples, UIC, 24h-UIE, individual iodine assessment

INTRODUCTION

Iodine is one of the essential trace elements for humans. The main function is to participate in the synthesis of thyroid hormones. Thyroid hormones (TH) can promote protein synthesis, regulate fat and glucose and water-electrolyte metabolism. It is necessary for neurological development and growth of the fetus and infant.[1]

Iodine excess and deficiency can lead to thyroid dysfunction.[2,3] Biomarkers to monitor population iodine status include goiter rates, urinary iodine concentration (UIC), thyroglobulin (Tg) and thyroid hormones for short-term and long-term changes of iodine status.[4,5] World Health Organization(WHO), United Nations International Children's Emergency Fund (UNICEF) and International Council for Control of Iodine Deficiency Disorders (ICCIDD) proposed an indicator, median UIC, to report and evaluate population iodine nutritional status,[6] and defined thresholds based on the population median UIC for school-aged children: <100 μg/L, iodine insufficient; 100-199 μg/L, iodine appropriate; 200-299 μg/L, iodine sufficient; >300 μg/L, iodine excessive. 24-hour UIE is often considered the "reference" standard for assessing individual iodine intake.[7,8] Rather than a single spot urine, repeated 24-hour UIE has been considered more adequate and accurate in the evaluation of iodine status. Meanwhile, Cria G[7] has argued that median UICs from spot samples provide unbiased estimates of 24-hour UIC, and that spot urinary iodine samples could be a proxy for 24-hour iodine in monitoring population iodine status. Although the population median UIC may be a good indicator of the iodine status in a population, it is not suitable for individual iodine status because of the

Corresponding Author: Dr Zhongna Sang, Department of Nutrition and Food Hygiene, Tianjin Key Laboratory of Environmental Nutrition and Population Health, School of Public Health, Tianjin Medical University, No.22 Qixiangtai Road, Heping District, Tianjin 300070, China.
Tel: +86 022-83336615; Fax: +86 022-83336608
Email: sangzhongna@tmu.edu.cn
Manuscript received 28 May 2020. Initial review completed 28 June 2020. Revision accepted 23 August 2020.
doi: 10.6133/apjcn.202012_29(4).0013

wide variation in daily dietary iodine intake, liquid intake and hydration status.[7] Moreover, complete 24-hour urine samples are usually burdensome and not easy to collect.[8]

There are two reports of repeat spot urines over a year. Konig[9] showed that ten repeat collections for urinary iodine from spot or 24-hour samples can reliably estimate individual iodine status in women with 20% precision in a prospective, longitudinal, 15-mo study. Andersen[10] performed a longitudinal study of sixteen healthy men whose spot urine samples collected monthly for 13 months and calculated that more than ten spot urine samples avoided misleading evaluation. Although these two extended studies supported spot urine sampling, collection over shorter time frames would be an advantage in clinical management of iodine status and thyroid function. Our study sought to establish the number of repeated spot urine samples necessary to character rise individual iodine status in Chinese women of childbearing age over 2 months and assess its feasibility as an independent indicator of individual iodine status.

METHODS

Based on data from the Shanxi Provincial Center for Disease Control and Prevention and the Chinese Center for Disease Control and Prevention's survey of iodine nutrition in Shanxi Province in recent years, twenty-three apparently healthy and fertile women aged 18 to 44 (32±9) y were recruited from Shanxi Province where iodized salt was the main source of dietary iodine intake. The inclusion criteria were that participants were healthy, not pregnant, non-lactating, non-smoking, living locally for a full five years, did not use iodine-containing supplements or drugs and had not undergone an X-ray or Computed Tomography (CT) examination in the previous six months.

Sample collection

Spot urine samples Spot urines of 5 mL, not including the morning urine, were provided by each participant, and collected on any two days of the week in a 5 mL polyethylene bottle.

24-h urine samples 24-h urine samples were collected once every 6 days into a 2.5 L polyethylene bottle. All participants were instructed to collect their urine for 24 hours, starting with an empty bladder first thing in the morning, until the same time the following day when they again emptied their bladder. Investigators were trained to assist each participant with sample collections. Participants were instructed to inform investigators if they forgot or spilled urine samples, and if so to repeat the 24-h urine sample collection. Investigators asked about missed urine samples. The 24-h urine samples reported to be incomplete collections were excluded. After measuring the volume of 24-h urine samples, two aliquots containing 5 ml were taken from each sample.

All urine samples were kept at 4°C if analyzed within a month or stored at -20°C until analysis.

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and all procedures approved by the Ethics Committee of the Tianjin Medical University. Written informed consent was obtained from all participants.

Determination of UIC

UIC was determined using the Sandell-Kolthoff method,[11] with inter-assay and intra-assay CVs of 3.6% and 4.2%, respectively.

Determination of urinary creatinine and calculation of daily estimated UIE

Urinary creatinine was determined by a national spectrophotometric standard method, namely the alkaline picric acid method,[12] and the inter-assay and intra-assay coefficient of variations for urine creatinine concentration were 2.5% and 3.2%, respectively.

The estimated 24-hour UIE was calculated as follows: iodine (μg/L)/creatinine (g/L)* expected daily creatinine (g/day). Expected daily creatinine are calculated by following the equation:[13] expected daily creatinine (g/day) = 0.00163 x [140 - age (years)] x [weight (kg) 1.5 x height (cm) 0.5] x [1 + 0.18 x (blank = 1, nonblack = 0)] x [1.429 - 0.0198 x BMI (kg/m^2)] / 1000.

Statistical analysis

All analyses and statistics were carried out using SPSS 20.0 software (SPSS Inc, Chicago, IL, USA). The 24-h UIE was calculated by multiplying the 24-h UIC of the samples by the urine volume: UIE (μg/24h) = UIC (μg/L) × 24-h urine volume (L).[4] The normality of the data was checked with the Kolmogorov-Smirnov test. Values were expressed as mean±SD for normally distributed data, and presented as median (interquartile range) if not normally distributed. CVs for intra-individual and inter-individual variation were calculated from the mean and Standard Deviation (SD) of urinary iodine measurements: CV% = SD/mean. The overall (average) CV% is calculated as the square root of the sum of the squares of the individual CV% divided by the number of participants. Intra-individual variation for repeated measurements was calculated and expressed as CV% of the per individual mean of the respective urinary iodine measurements, while inter-individual variation (CV%) was calculated by treating all measurements as individual samples.[9,10] The number of urine samples needed to assess the UIE was calculated using $n=(Z\times CV\%/D)^2$, where Z is 1.96 for a confidence interval (CI) of 95%, CV% is the coefficient of variation of intra-individual, and the precision range (D) are the biochemical variables. Differences between means were compared using the paired t test. Significance was set at $p<0.05$.

RESULTS

Basic characteristics of healthy Chinese women

Twenty-three volunteers were recruited in this longitudinal study. Sixteen repeated spot urine samples and ten 24-h urine samples were collected per participant in the 2 months, so we collected 368 spot urine samples and 230 24-h urine samples in the final analysis. The baseline characteristics of 23 healthy Chinese women are shown in Table 1. The median UIC of spot urine samples was 140.5 (75.2, 246.9) μg/L. The spot UIC between individuals were 197±113 μg/L, and estimated 24-h UIE values from spot urine samples and measured 24-h UIE values from 24-h urine samples between individuals were

Table 1. Baseline characteristics of twenty-three healthy Chinese women

	Value	
N=23	Mean	SD†
Age (years)	32	9
Weight (kg)	56.1	7.2
Height (cm)	161.7	3.3
BMI (kg/m^2)	21.4	2.4
Spot UIC (μg/L)	197	113
24-h U-vol (L)	1.9	0.1
24-h UIC (μg/L)	178	115
Estimated 24-h UIE (μg/24h)	348	240
Measured 24-h UIE (μg/24h)	330	216

SD: standard deviation; BMI: body mass index (weight/height^2); UIC: urinary iodine concentration; U-vol: urine volume; UIE: urinary iodine excretion.

348±240 μg/24h and 330±216 μg/24h (t=3.289, p=0.003), respectively.

Coefficient of variations for intra-individual and inter-individual assessments

The mean and standard deviation of UIC per individual and CV% are shown in Table 2. The mean UIC of total spot urine samples (n=368) varied from 117 to 327 μg/L. The mean UIC of total 24h urine samples (n=230) varied from 112 to 336 μg/L. Irrespective of the urinary iodine method, the intra-individual CV% was lower than the inter-individual CV%. For mean UIC of total spot urine samples, the inter-individual CV% (67.6) was 1.3-fold higher than intra-individual CV% (45.3). For 24h UIC, the ratio of inter-individual CV% (64.5) to intra-individual CV% (46.8) was 1.4. This result is consistent with that of König[9] et al.

Consistency analysis of the two methods

Figure 1 and Figure 2 show the Bland–Altman results. In Figure 1, the mean difference was -24.48 (95% CI: -49.99, 4.43) on the log scale, and the LOA were -154.15 μg/L and 105.19 μg/L. And the Bland-Altman index was 8.7%. Through further analysis, in Figure 2, the mean difference was -24.33 (95% CI: -41.14, 6.00) on the log scale and the LOA were -289.96 μg/L and -221.31 μg/L. The Bland-Altman index was 5.8%. So it could be considered that there are differences between the two methods.

Minimum sample number necessary to achieve repeat collection values

According to the formula: $n = (Z \times CV\% / D)^2$, the number of spot samples needed to repeat collection was calculated when precision range from ±1% to ±50%, Z is 1.96 with 95% confidence and CV% is 41.8% for the median variation (Table 3).

Table 2. Mean of UIC and variation from two methods in individuals

	In an individual^2 (n) of spot urine			In an individual^2 (n) of 24h urine		
Participant	Mean	SD	CV%	Mean	SD	CV%
1	145	51	35.1	336	159	47.2
2	298	126	42.2	125	42	33.2
3	181	73	40.5	125	42	33.2
4	168	87	51.8	151	58	38.6
5	140	36	25.5	112	29	26.3
6	244	141	57.6	200	164	81.8
7	150	79	52.7	119	31	25.8
8	298	207	69.5	234	95	40.7
9	184	65	35.5	152	39	25.5
10	260	130	49.9	294	190	64.6
11	146	53	36.0	157	55	35.2
12	200	88	43.8	168	50	29.8
13	187	102	54.3	161	19	12.1
14	229	155	67.9	165	49	29.7
15	323	141	43.7	205	170	82.9
16	140	53	37.9	140	38	27.5
17	168	74	43.8	197	171	86.8
18	256	108	42.3	196	89	45.2
19	137	44	32.1	143	49	34.2
20	141	51	36.1	148	65	43.7
21	139	27	19.6	118	32	27.3
22	187	62	32.9	113	29	25.3
23	309	166	53.8	308	220	71.5
Mean			45.3			46.8

SD: standard deviation; CV%: coefficient of variation of intra-individual.

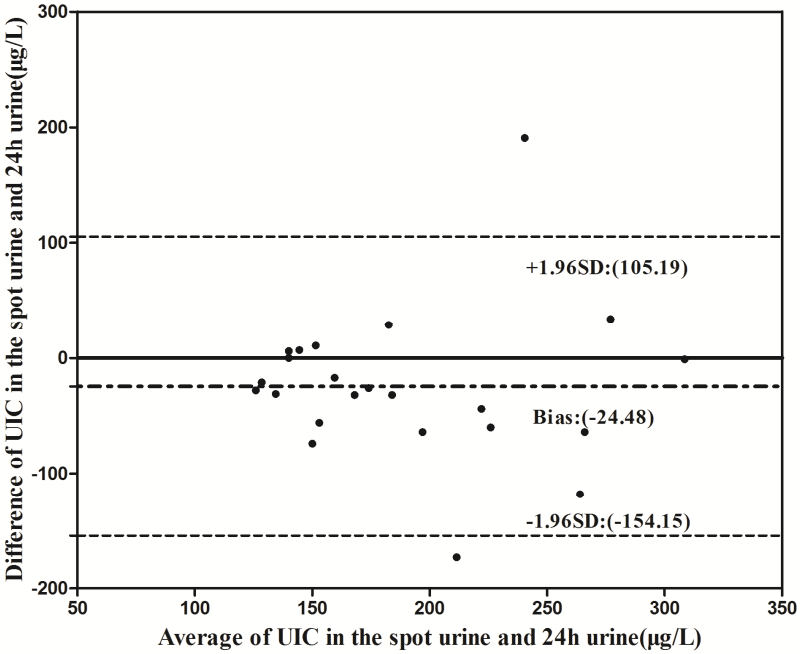

Figure 1. Bland-Altman plot showing the level of agreement between a UIC of spot urine and UIC of 24h urine from the individual means. The black line shows the overall mean difference between two methods UIC, and dashed lines represent the 95% limits of agreement of the individual mean values.

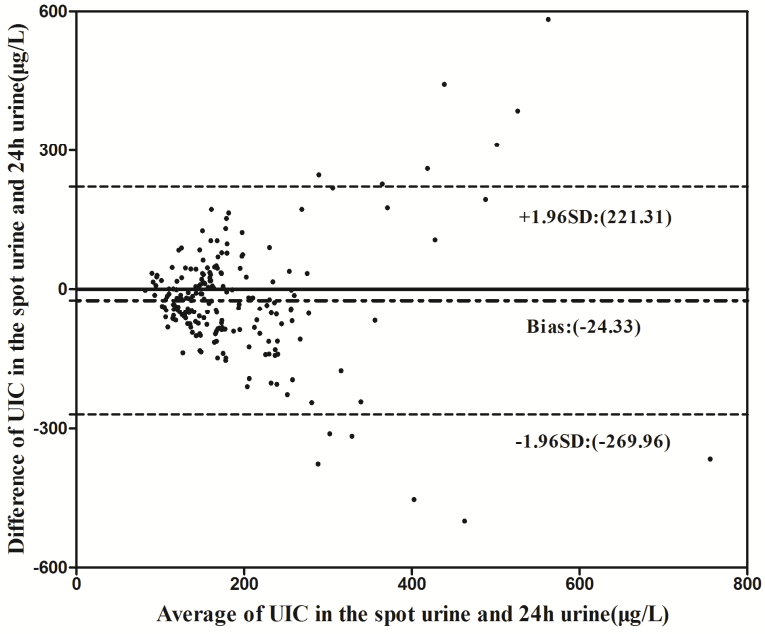

Figure 2. Bland-Altman plot showing the level of agreement between UIC of spot urine and UIC of 24h urine from all paired 24-h and spot urine collections. The black line shows the overall mean difference between two methods UIC, and the dashed lines describe the 95% limits of agreement for all measurements.

Table 3 shows the precision range is ±15%, ±20%, ±25% and 30% respectively, when the number of an individual's spot urine samples is 30, 16, 11 and 8, respectively. Since the purpose of this study is to find the minimum sample number that would necessitate repeated spot urine sampling, the data of an individual's lowest variation was chosen and the precision range was further determined between ±10% to ±20%. Based on the precision range, we determined the minimum number of repeated sampling ranged between 4~14. Therefore, if the per participant crude data was in the range of 4 to 14 in a unit, this necessitated secondary sampling to form 11 new subsamples, following the principle of sampling.

DISCUSSION

Since 1990, WHO and ICCIDD have recommended universal salt iodization (USI) to eliminate Iodine Deficiency Disorders (IDD),[14] with meaningful improvements in

Table 3. Number of spot urinary samples needed for 95% confidence within a specified range in individuals

	In an individual (n) †‡
Precision range	Median CV%
±1%	6712
±5%	269
±10%	67
±15%	30
±20%	16
±25%	11
±30%	8
±35%	6
±40%	4
±45%	3
±50%	2

†The number of samples was calculated by the equation: $n = (Z \times CV\% / D)^2$, where Z is 1.96 for a CI of 95%, CV% is coefficient of variation of intra-individual, and the precision range (D) are the biochemical variables.
‡The number of samples needed to sample in an individual were calculated based on the median variation in an individual.

population iodine nutrition status. By 2013, 111 countries had acceptable iodine status; 30 countries remained iodine deficient; and more than 10 countries had excessive levels of iodine.[15] In 1995, China began to supply iodized salt nationwide, in accordance with the USI. China eliminated IDD at the national level by 2000. In recent years, the iodized salt concentration range has been decreased to 18-33 mg/kg from 20-50 mg/kg in order to achieve more acceptable iodine levels.[16] The iodine nutrition status has improved among children in China with an MUIC of 38.6 μg/L in the sixth National IDD Survey.[17] Our study has found an acceptable iodine status with an MUIC of 140.5 μg/L, the provincial average for children being 237 μg/L in Shanxi province.[18]

The iodine nutritional status of the population is usually evaluated by urinary iodine and thyroid function, reflected in urinary iodine concentration, thyroid size, thyroid stimulating hormone (TSH), thyroid hormone (T3, T4) and Tg.[5] Urinary iodine can be expressed as 24h-UIE, spot UIC, or creatinine ratio (UIC/creatinine, μg/g).[4] Dietary survey methods sometimes assess individual iodine intake, such as by weighed food records, 24h dietary record or food frequency questionnaires (FFQ).[19,20] However, assessment of iodine intake by dietary survey is challenging because the iodine content of foods is influenced by many factors, including fertilizers, irrigation, season and location,[21] and the accuracy of individual food intake memory is difficult to determine.[19,20] Moreover, FFQ must be designed with appropriate iodine-related questions, dependent on a knowledge of local iodine-rich foods, usual foods and food patterns.[22]

Although the iodine nutrition status has improved globally, it is generally difficult to assess individual iodine nutrition status.[23] Consequently, individuals are unable to adjust their dietary iodine intake according to their own iodine nutrition status. Compared with other biological indicators, 24-hour urinary iodine data provides some reliability for the evaluation of individual iodine nutrition status. However, 24-h urine sample collection is unfeasible, which limits 24h-UIE estimation of individual iodine intake. Therefore, a convenient and effective way to assess iodine nutrition in individuals is needed. Women of childbearing age are sensitive to changes in iodine nutrition, putting their possible offspring at risk. They have been the focus of the present study. In view of the day-to-day variation (intra-CV%) of iodine intake and UIE,[8] a number of repeat spot urine samples would make it more possible to reliably estimate iodine intake in individuals.[9,10]

In this study, the mean lowest, median and highest intra-CV% of UIC in individuals were 19.6%, 42.3% and 69.5%, respectively, and less than the corresponding mean intra-individual variations (21.8%, 38.0%, 85.9%) of Anderson's study.[10] The intra-CV% of UIC in individuals is contributed not only by daily differences in iodine intake 24 but also by variations in daily U-vol.[25,26] In China, iodized salt is the major dietary sources of iodine and contributes to more than 90% of daily iodine intake.[27,28] The main salt sources are processed foods contributing approximately 60%-80% of the total salt intake in many countries.[29,30] The total amount of dietary iodine from salt varies depending on the type of foods[31,32] and the iodine concentration in fortified food,[33,34] which may be the main reasons for having high intra-CV% of spot urine in individuals. The U-vol of this study (1.85 L) and Konig's study (2.11 L) may also be different, which may account for some of the differences of intra-CV%.[25,35]

Andersen et al[10] calculated the number of repeat spot urine samples by precision range to be ±1%~±50% and it was ±20% in the Konig study.[9] In our study, the precision ranged from ±1% to ±50%. To find the optimal number of repeated spot urine samples, we considered the repeat sampling range for median variance level and found that the number of repeat samples for individuals needed to range from 8 to 30. Konig showed that 10 repeat collections for urinary iodine from spot samples were needed to reliably assess the individual iodine status in women with a 20% precision. At the same precision: of 20%, Andersen found that to guide iodine intake reliably required 14 spot urine samples. In the study, the number of repeated spot urine samples of individuals to reflect recent iodine intake of individuals in Chinese women was 16 with a ±20% precision range, which is more than repeated spot urine samples found desirable in Andersen's and Konig's studies. However, in contrast to the long-term studies, short-term surveys are more meaningful reflections of iodine intake by individuals. And 8 repeat collections for urinary iodine spot samples are acceptable (Table 3).

Compared with Andersen's and König's study, with ±30% precision ranges, the number of repeated spot urine samples of this study is also more than repeated spot urine samples in Andersen's study (8 vs 6).

Although our study has endeavoured to establish an approach to short-term iodine nutrition assessment of individuals, it is understandably inconvenient to collect 8 repeat spot urine samples in real life. Moreover, the Bland-Altman analysis indicates that this method cannot accurately represent the iodine nutritional status of women of childbearing age. Future work might be able to develop a multi-indicator system which, combined with urinary iodine, water iodine content, food iodine content, salt iodine intake and individual physiological status, would integrate the evaluation process for greater accuracy, precision and feasibility Individuals would then have more confidence in their purported iodine nutrition status and be able to adjust their iodine intake so as to avoid both iodine deficiency and iodine excess.

Conclusions

Repeat spot urine sampling is not sufficiently convenient, effective or accurate to assess recent individual iodine intake in premenopausal women. The development of a multi-indicator system might provide an acceptable individual evaluation index.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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