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Research Article

Variations in the Urinary Iodine Concentration and Urinary Iodine/Creatinine Ratio among Preschool Children

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Variations in different urinary measurements for evaluating iodine status are concerning to clinicians and researchers. The present study aimed to analyze the interindividual and intraindividual variations in the urinary iodine concentration (UIC) and urinary iodine/creatinine (UI/Cr) ratio and evaluate their application in assessing the iodine nutrition of preschool children. Four repeated spot urine samples were collected from 163 children at different times within one day. The urinary iodine concentration (UIC) and urinary creatinine concentration (UCr) were measured, and the UI/Cr ratio was calculated. The UIC ($P < 0.001$) and urinary iodine/creatinine ratio ($P = 0.019$) of multiple measurements were significantly different. The UIC of morning urine was highest (99.83 μg/L) and then gradually decreased with collection time ($P < 0.001$). In contrast, the UI/Cr ratio of morning urine samples increased with collection time. By computing the mean intraindividual and interindividual coefficients of variance (CV), the intraindividual variation of the UI/Cr ratio (68%) was significantly lower than that of the UIC (86%). Nevertheless, the interindividual variation was lowest in the UIC (78.62%) of morning urine. In addition, the UIC and UI/Cr ratio showed moderate correlations ($r = 0.52$, $P < 0.001$), with kappa values of 0.42 in assessing iodine nutrition. The UIC of morning urine samples taken at 8:00–10:00 am was perhaps more stable and reliable in evaluating the iodine nutrition of preschool children at the population level. The UI/Cr ratio showed lower intraindividual variation and may be more suitable for assessing individual iodine nutrition.

1. Introduction

Normal thyroid gland function is critical for early neurocognitive development and growth and development [1]. As a result, more studies have demonstrated the need for early identification and treatment of thyroid disease in children and adolescents during the fetal period [2, 3]. Primary thyrotropin or thyroxine (T4) testing can efficiently screen for congenital hypothyroidism to ensure normal development and cognition [4]. Iodine is an essential component of the hormones produced by the thyroid gland. Therefore, thyroid hormones and iodine are vital for maintaining normal thyroid function [1]. Iodine prophylaxis and periodic monitoring of iodine nutrition in populations are cost-effective approaches to reduce adverse effects of iodine malnutrition across the lifespan [5]. Iodine is primarily obtained through diet and iodized salt and excreted in urine [6]. The 24-h urinary iodine excretion (UIE) is generally considered the most reliable measurement for assessing iodine nutritional status [7, 8]. However, since 24-h urine collection is far inferior to spot urine collection in time, cost, and feasibility, it is challenging to apply it to assess the iodine nutrition of the population. WHO recommends measuring the urinary iodine concentration (UIC) to evaluate population iodine nutrition [9]. The UIC in spot urine samples varies substantially due to variations in daily food and fluid intake [7]. Intraindividual variations in the UIC can considerably affect its reliability in estimating iodine nutritional

status [10–12]. It has been estimated that >10 repeated spot urine samples from an individual are needed to reliably assess individual iodine intake [10].

As a more accurate indicator of iodine levels than the UIC, the urinary iodine/creatinine (UI/Cr) ratio is often used [13–15]. Creatinine is a breakdown product of creatine and is steadily excreted through urine if fluid intake is regular [16]. The UI/Cr ratio in single spot urine samples quantifies individual urinary iodine, which has obvious advantages over the 24-h UIE in terms of time and cost [17, 18]. The intraindividual variation of the UIC has been monitored in adults [10], and the UI/Cr ratio in single spot urine samples has been applied to assess iodine nutrition in adults [11, 19–21].

However, little is known about the intraindividual variation in the UIC and the feasibility of the above evaluation methods for preschool children. Evaluating and comparing the reliability of the UIC and UI/Cr ratio in evaluating the iodine nutrition of preschool children could provide data support for clinicians to monitor the iodine nutritional status of preschool children using appropriate biological indicators. This study repeatedly collected spot urine samples from preschool children within one day, analyzed the intraindividual and interindividual variations in the UIC and UI/Cr ratio, and aimed to evaluate the application of the UIC and UI/Cr ratio in assessing the iodine nutrition of preschool children.

2. Materials and Methods

2.1. Study Design and Subjects. This cross-sectional study recruited children aged 3–6 years old who visited Tianjin Children's Hospital, Tianjin, China, from January to December 2021. All included children were admitted to the respiratory department of the hospital for pneumonia, bronchopneumonia, or bronchiectasis but were able to eat normally. The exclusion criteria were as follows: (1) a history of previous or current thyroid disease, autoimmune disease, endocrine-related disease, heart-related disease, genetic metabolic disease, etc.; (2) the use of iodine-containing drugs such as amiodarone or contrast agents before and during the investigation; and (3) chronic protein-energy malnutrition and particular dietary habits due to disease. Approximately 200 patients who met the eligibility criteria were approached to participate in the study within the proposed time frame, and those who declined did so mainly due to disinterest or being in a hurry. The sample size was estimated based on the number of potential participants who were available for recruitment and who could meet the inclusion criteria within the proposed study time. Written informed consent was obtained from parents or legal guardians, and assent was obtained from the study participants. The Medical Ethics Committee of Tianjin Medical University approved the research protocols.

2.2. Anthropometric Measurements. The height and weight of the subject children were measured using an electronic height and 82-weight meter (TCS-200 SuHeng). Measurements were rounded up to the nearest 0.1 kg for weight and the nearest 0.1 cm for height. Well-trained nurses performed all measurements. Body mass index (BMI) was calculated as body weight (kg)/height (m^2).

2.3. Collection and Determination of Urine Samples. Four repeated spot urine samples were collected from 163 children at different periods within one day. The four repeated urine samples were collected at 8:00 am~10:00 am, 10:00 am~12:00 pm, 12:00 pm~3:00 pm, and 3:00 pm~6:00 pm. All urine samples were stored in a polyethylene bottle and sent to the Tianjin Key Laboratory of Environmental Nutrition and Population for testing within two weeks.

The UIC was analyzed by inductively coupled plasma-mass spectrometry (ICP-MS; iCAP Q, Thermo Fisher Scientific). The UIC measurements' total inter-assay and intra-assay CV% were 1.4–3.2% and 0.6–1.8%, respectively. The urinary creatinine concentration (UCr) was measured by the national standard spectrophotometric method. Using this method, the CV for the UCr concentration was 0.2–3.2% in the laboratory. The UI/Cr ratio was calculated as follows: the spot urinary iodine concentration divided by the spot urinary creatinine concentration.

2.4. Categorization of Iodine Nutrition. As recommended by WHO [9], we evaluated the iodine status of preschool children using the UIC and UI/Cr ratio in the present study. Children with a UIC ≥300 μg/L were categorized as having excessive iodine nutrition, those with a UIC of 100–300 μg/L were categorized as having adequate iodine nutrition, and those with a UIC ≤100 μg/L were categorized as having insufficient iodine nutrition, as recommended by WHO [9]. There were no criteria for the use of the UI/Cr ratio in defining iodine status. Since the average UCr concentration in children's spot urine samples is approximately 0.3 g/L [22, 23], a UI/Cr ratio ≤300 μg/g was considered to indicate insufficient iodine nutrition, a UI/Cr ratio of 300–900 μg/g was considered to indicate adequate iodine nutrition, and a UI/Cr ratio ≥900 μg/g was considered to indicate excessive iodine nutrition.

2.5. Statistical Analysis. All data analyses were carried out using SPSS 19.0 (IBM, Armonk, New York, NY, USA), Microsoft Excel (XP 2007, Microsoft, Redmond, WA, USA), and GRAPH PRISM (version 8.0c, GraphPad Software Inc., La Jolla, CA, USA). The Shapiro–Wilk test was used to check the data distribution with a P value > 0.1, indicating that the data followed a normal distribution. For normally distributed data, values are presented as the means ± SDs, including age, weight, height, and protein intake. As the UIC, UCr, and UI/Cr ratio of spot urine samples were not normally distributed, the values are expressed as medians (interquartile ranges). The Friedman nonparametric hypothesis test examined the difference in urinary variables among the four time points. The CV% was the square root of the variance divided by the mean as a percentage. We applied the mean CV to evaluate the intraindividual variation of the urinary

variables. The mean CV was calculated by equation (1) [24]. Cohen's weighted kappa analysis assessed the degree of agreement between the two methods (UIC and UI/Cr ratio) to evaluate preschool children with different iodine statuses. A P value <0.05 was considered significant at a two-sided level.

$$\text{mean CV} = \left(\frac{\sum \text{CV}\%_n^2}{n}\right)^{1/2}. \quad (1)$$

3. Results

A total of 163 preschool-aged children participated in this study. The characteristics of the participants are presented in Table 1. The mean age was 4.5 ± 1.0 years old. The mean height was 108.7 ± 9.1 cm, the mean weight was 18.0 ± 4.6 kg, and the mean BMI was 15.0 ± 2.1 kg/m^2.

3.1. Differences in the UIC and UI/Cr Ratio among the Four Time Points within One Day. A total of 142 valid morning urine samples were collected from 163 children, while four repeated spot urine samples were collected from them within one day. Regarding morning urine, the median UIC was 84.79 μg/L and the median UI/Cr ratio was 287.74 μg/g. The UIC, UCr, and UI/Cr of spot urine at four collection times are shown in Table 2. The UIC ($P < 0.001$), UCr ($P < 0.001$), and UI/Cr ($P = 0.019$) of the four measurements were significantly different. As presented in Figure 1(a), we found that the UIC of morning urine was highest and then decreased with time, while the trend of UI/Cr was the opposite.

3.2. Intraindividual and Interindividual Variations in the UIC and UI/Cr Ratio. The interindividual variations in the UIC and UI/Cr ratio for the four time points are shown in Table 3. The mean CVs of the UIC and UI/Cr ratio at different collection time points were 112.13% and 322.80%, respectively, and the interindividual CV of the UI/Cr ratio at each time point was higher than that of the UIC. In addition, the interindividual variation CV of the UIC was lowest in the morning urine samples, at 78.62%. The intraindividual CV of the UIC and UI/Cr ratio within the same day was 86.39% and 68.35%, respectively. As presented in Figure 1(a), the interindividual variations in the UIC and UI/Cr ratio were higher than the intraindividual variations. In addition, compared with the UIC, for the UI/Cr ratio, the intraindividual variation was lower, while the interindividual variation was higher.

3.3. Correlation and Consistency of the UIC and UI/Cr Ratio in Defining Iodine Nutrition. The iodine status of children, defined by the spot UIC and UI/Cr ratio, is shown in Figure 2(a). Based on the spot UIC, 58.82% of the children were classified as iodine insufficient. A total of 38.97% and 2.21% of children were classified as iodine sufficient and iodine excessive, respectively. According to the spot UI/Cr ratio, 50.74% of the children were classified as iodine insufficient. A total of 39.71% and 9.56% of the children were defined as iodine sufficient and iodine excessive, respectively. When the UIC was used as the indicator, more children were classified as insufficient as when the UI/Cr ratio was used, and the number of children who were classed as iodine excessive was smaller. The kappa value was 0.42, demonstrating the consistency between the UIC and UI/Cr ratio of spot urine samples in defining iodine nutrition. As shown in Figure 2(b), the UIC was positively correlated with the UI/Cr ratio ($r = 0.52$, $P < 0.001$).

Table 1: Characteristics of the participants.

Variables	Boys ($n = 93$)	Girls ($n = 70$)	Total ($n = 163$)
Age (y)	4.3 ± 1.0	4.6 ± 1.1	4.5 ± 1.0
Height (cm)	108.0 ± 8.2	109.6 ± 10.1	108.7 ± 9.1
Weight (kg)	18.0 ± 4.1	18.0 ± 5.3	18.0 ± 4.6
BMI (kg/m^2)	15.1 ± 2.2	14.8 ± 2.1	15.0 ± 2.1

BMI, body mass index. Values are means ± SDs.

4. Discussion

As a more accurate indicator of iodine levels than the UIC, the urinary iodine/creatinine (UI/Cr) ratio is often used [13–15]. Creatinine is a breakdown product of creatine and is steadily excreted through urine with regular fluid intake [16], which is usually used as a simple measure to estimate other urinary biological analytes from the respective ratios. Due to significant variations in the UIC, the UI/Cr ratio is also used to evaluate iodine nutrition status [13–15] as a more accurate indicator in some studies. In contrast, few studies have investigated its applicability for preschool children. In our study, we provided a reference dataset comparing the reliability and stability of the UIC and UI/Cr ratio by calculating CVs. We analyzed the interindividual variations in the UIC and UI/Cr ratio at different collection times. We found that the interindividual variations in the UI/Cr ratio were higher than those in the UIC, which means that using the creatinine-corrected UIC to define iodine nutrition does not apply to all individuals and may even be counterproductive. Many previous studies have indicated that UCr can be affected by many factors, such as age, sex, and physical conditions [25, 26]. Based on observations in Chinese school-age children [27], UCr was not stable in repeated spot urine samples and increased with age; preschool children develop relatively rapidly, which may therefore lead to unstable creatinine levels.

We further analyzed the consistency of the UIC and UI/Cr ratio in evaluating the iodine nutrition status of preschool children. Positive correlations between the UIC and UI/Cr ratio were observed. With no criteria for the UI/Cr ratio in defining iodine nutrition, we estimated the reference urinary creatinine concentration for preschool children [22, 23]. We derived criteria for the UI/Cr ratio to evaluate iodine nutritional status. The kappa values (0.42) showed a fair agreement between the two methods in defining iodine nutrition status in preschool children. The criteria of the UI/Cr ratio to evaluate iodine nutrition in the population need to be further studied.

Table 2: UIC, UCr, and UI/Cr in preschool children according to collection time within one day.

Time	n	UIC (μg/L)	P	n	UCr (g/L)	P	n	UI/Cr ratio (μg/g)	P
8:00 am~10:00 am	142	84.79 (40.61, 136.45)	<0.001	136	0.30 (0.19, 0.43)	<0.001	136	287.74 (181.35, 515.23)	0.019
10:00 am~12:00 pm	142	21.49 (11.61, 57.29)		136	0.07 (0.03, 0.19)		136	332.58 (157.76, 511.84)	
12:00 pm~3:00 pm	148	27.51 (12.62, 59.92)		141	0.09 (0.04, 0.14)		141	347.67 (168.71, 635.06)	
3:00 pm~6:00 pm	142	41.22 (21.30, 83.62)		133	0.12 (0.05, 0.23)		133	394.72 (217.42, 670.50)	

UIC, urinary iodine concentration, UCr, urinary creatinine concentration, UI/Cr, urinary iodine/creatinine ratio. Values are medians (interquartile ranges). Differences between repeated spot urine collections were compared using the Friedman nonparametric hypothesis test.

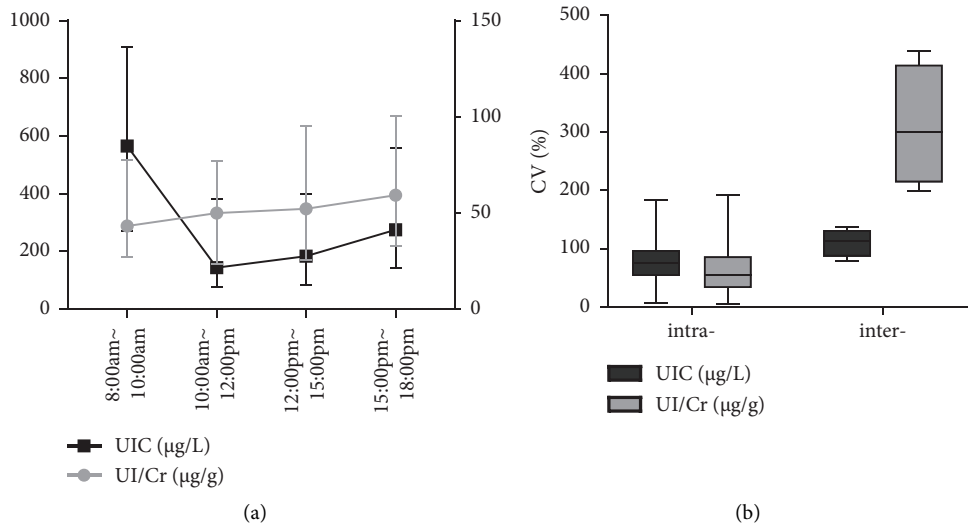

Figure 1: Variation in the UIC and UI/Cr ratio within one day. (a) The change in the UIC and UI/Cr ratio at different collection times. (b) Comparison of CV % on intraindividual and interindividual variations between the UIC and UI/Cr ratio.

Table 3: Descriptive and interindividual variations in the UIC and UI/Cr ratio in the population.

Time	UIC (μg/L)			UI/Cr ratio (μg/g)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
8:00 am~10:00 am	99.83	78.49	78.62	747.73	3281.53	438.87
10:00 am~12:00 pm	45.15	61.90	137.10	907.38	3131.45	345.10
12:00 pm~3:00 pm	45.28	52.36	115.64	638.63	1272.53	199.26
3:00 pm~g:00 pm	60.23	65.82	109.28	801.47	2050.04	255.78
Interindividual variations	62.62	70.22†	112.13‡	773.80	2497.92†	322.80‡
Intraindividual variations	60.59	52.34†	86.39‡	786.04	537.26†	68.35‡

UIC, urinary iodine concentration, UI/Cr ratio, urinary iodine/creatinine ratio, CVs, coefficients of variance. Intraindividual and interindividual variations at each time point. Intraindividual and interindividual variations of each subject within one day. †Calculations using the mean variance among individuals and using ANOVA techniques provided similar results. ‡Calculated as $(\sum \mathrm{CV}\%_n^2/n)^{1/2}$.

We also found significant variations in the UIC of spot urine samples collected at different times, with the UIC of morning urine samples being the highest and decreasing with time. In addition, the interindividual variation in morning urine (8:00 a.m.–10:00 a.m.) samples was relatively lower than that in casual urine samples collected at other time points. This may be why the UIC of morning urine samples is regarded as the ideal index to assess iodine nutrition, according to WHO [9]. Previous studies on healthy Swiss volunteers aged 4–60 years found that the UIC circadian rhythm of random urine samples increases from noon to midnight; therefore, collecting urine samples between 8:00 a.m. and 11:00 a.m. seems reasonable [28]. Some studies have pointed out that collecting the first void is not recommended due to the difficulty in collection [29]. Instead, fasting urine collection may impact the accuracy of the assessment of iodine nutritional status in morning urine samples [30, 31]. On the other hand, limiting fasting requirements for morning urine samples may impact their comparability with urine samples collected at different times due to their relatively higher concentration. This study did not require morning urine to be fasting void urine.

In addition, we found that the intraindividual variation of the UI/Cr ratio (68%) was lower than that of the UIC

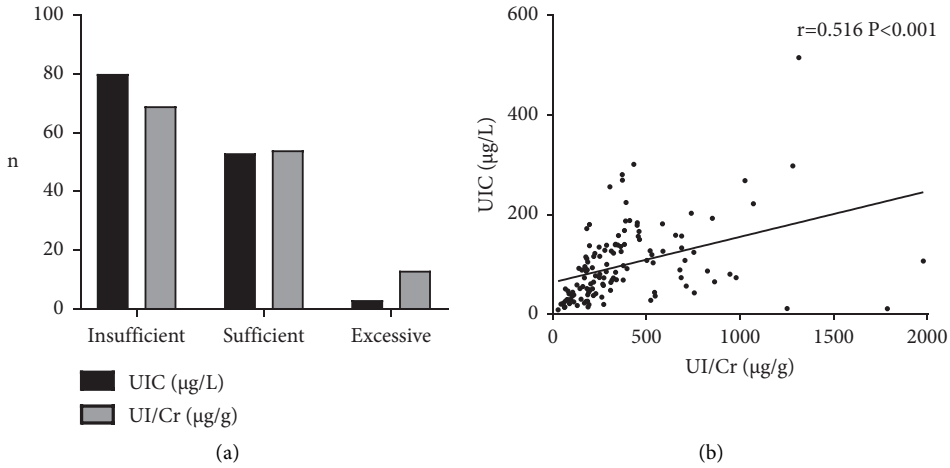

Figure 2: Correlation and consistency of the UIC and UI/Cr ratio in defining iodine nutrition. (a) Number of subjects with different iodine nutritional statuses. (b) Association between the UIC and UI/Cr ratio of spot urine samples.

(86%). For an individual, many factors contribute to the variation in the UIC, such as sex, age, and sociocultural and dietary influences [32]. A previous study showed that variation in iodine excretion in an individual may follow circadian rhythms [28]. As Figure 1(a) shows, the fluctuations were more pronounced at the four time points of the UIC. Intraindividual variation was higher in the UIC than in the UI/Cr ratio, which means that the UI/Cr ratio may be more stable for individual iodine nutrition evaluation.

In our study, the variations in the UIC and UI/Cr ratio in the population (interindividual) were higher than those in individuals (intraindividual). The same results were reported in a study of twenty-two healthy females performed in Switzerland, which reported that the interindividual CV % for the UIC was higher than the individual variation [10]. In the other study, participants were provided with the same diet for every measurement, which may have reduced the interindividual variation. Therefore, single random urine samples are more suitable for direct application to define iodine nutrition at the population level.

According to Andersen et al., the number of spot urine samples needed to determine the UIC to evaluate iodine nutrition in a population with 95% confidence within a precision range of ±5% is 500 [19]. However, their study focused on Caucasian adult men (CV = 57%), and the CV (78%) of preschool children in our study was relatively high. The estimated sample size with specified precisions was calculated by equation $N = (Z \times \text{CV } \%/D)^2$ [19]. The precision range (D) was used to estimate the precision of a set point in biochemical variables and was recommended for estimating the number of samples required for biochemical measurements. The 95% CI (Z) was 1.96 [24]. Based on the equation, the number of spot urine samples needed to determine the UIC to evaluate the iodine nutrition of preschool children with 95% confidence within a precision range of ±5% was 1000. However, a sample size of this magnitude makes estimating (with a 95% CI) the iodine status from spot urine samples within a precision range of ±7% possible.

The present study has several limitations. As the study was conducted in the hospital, the iodine nutrition of participating children may be affected by recent poor dietary intake, resulting in limited generalization of our results. However, the circadian rhythm of the UIC may not be affected since the included children were basically healthy.

Furthermore, although within one day, the intraindividual variation in the UI/Cr ratio was lower than that in the UIC, and exploring the suitability of the UI/Cr ratio for evaluating individual iodine nutrition still requires several days of intraindividual variation. Our study evaluated intraindividual and interindividual variations in the UIC and UI/Cr ratio by collecting repeated spot urine samples from individual children. Few studies have evaluated the reliability and variability of the UIC and UI/Cr ratio in assessing the iodine status of a population or an individual. In this instance, our study provided a reference dataset.

5. Conclusions

Our study shows that the UIC of morning urine at 8:00–10:00 am was perhaps more stable and reliable in evaluating iodine nutrition in preschool children at the population level; the UIC of morning urine samples may be a more reliable and cost-effective indicator for clinicians to assess iodine nutrition in preschool children. The UI/Cr ratio had lower intraindividual variation and may be more promising in evaluating the individual iodine nutrition of preschool children.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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