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Controversies in urinary iodine determinations

Offie Porat Soldin^{a,b,*}

^aSoldin Research and Consultants, Inc., Bethesda, MD

^bMotherisk, Division of Clinical Pharmacology, The Hospital for Sick Children, Toronto

Abstract

Iodine deficiency (ID) is associated with increased prevalence of goiter, increased risk for neurodevelopmental disorders, and is the world's leading cause of intellectual deficits. Iodine nutritional status of a population is assessed by measurements of urinary iodine concentrations which are also used to define, indicate, survey and monitor iodine deficiency and consequently its treatment. Several methods are available for urinary iodine determination. Discussed here are some of the limitations and controversies related to urinary iodine determinations, and recent findings with emphasis on measurements of urinary iodine concentrations in children and during pregnancy.

Keywords

Urinary iodide measurement; Iodine deficiency; Environmental; Thyroid diseases; Epidemiology; Thyroid hormones; Pregnancy; Review

1. Introduction

Iodine is an essential micronutrient and an integral component of thyroid hormones. Iodine is obtained only through the diet and is mainly absorbed by the gastrointestinal tract as the inorganic anion, iodide. The status of iodine nutrition of a population is determined by measurements of iodine as urinary iodide (UI) concentration since it is considered an indicator of the adequacy of the iodine intake of that population. In general, it is assumed that most ingested iodine, such as sodium or potassium iodide, is excreted in the urine, and that equilibrium is established between dietary iodine intake and UI excretion. The assessment is of urinary iodide anion concentration; nevertheless, it is common to refer to the laboratory tests as urinary iodine tests.

Daily iodine intake can be estimated by measuring daily excretion, or by random spot urine sampling calculated either in relation to urinary creatinine excretion or as UI concentration per liter. The choice among methods depends on the intended application, the number of samples, technical capability and cost. Epidemiologic field studies are large by default and therefore demand simple, reliable, rapid and cost-effective methods for determining the iodine status of the population.

Iodine nutritional status is most closely estimated by the amount of iodine excreted in the urine in 24-h. Often 24-h urine samples for UI determination are impractical to obtain, and can be unreliable because of incorrect or incomplete collection [1,2]. When the nutrition is adequate, the creatinine concentration has been used to adjust for adequacy of sample

collection. The UI to creatinine ratio (UI/Cr) in random single voided urine samples is considered a reliable and practical laboratory technique available to quantify UI in individuals and has obvious advantages in terms of time, cost and patient's convenience [3,4]. UI/Cr is considered a more reliable measure of iodine excretion than random spot UI concentration measurement since there is a great day-to-day variability in iodine intake, in water consumption for any individual, and in the amount of time it takes for iodine exposure to equilibrate. In the effort to eliminate ID simple and appropriate methods are being developed to improve monitoring and surveillance [5,6].

2. Urinary iodine determination

2.1. Correlation of dietary iodine intake with UI

The measurement of urine iodine excretion provides the best single measurement of the iodine nutritional status of a population [7–9]. Dietary iodine intake was positively correlated with the urinary excretion of iodine in an iodine-replete area [10]. Rasmussen et al. [11] found that in a mildly iodine deficient area, the iodine intake (mean $89 \pm 6.5 \mu\text{g/day}$) also correlated well with iodine excretion measurements (mean UI $95 \pm 5.3 \mu\text{g/day}$) [11].

2.2. Methods in UI determination

The available methods for UI determination have been reviewed by Dunn et al. [6,12]. The most practical and simple method involved mild acid digestion and timed colorimetric procedures. This procedure is less time consuming than the more traditional method of dry ashing [12]. Various methods are available using different procedures for the removal of chromogens and other substances such as thiocyanate which interfere with the sensitive colorimetry of the Sandell-Koltoff reaction, in which urine is first acid digested under mild conditions and iodide then determined from its catalytic reduction of cerium ammonium sulfate in the presence of arsenic acid. For the National Health and Nutrition Examination Survey (NHANES) I (1971–1974) ($n = 18,617$) and NHANES III (1988–1994) ($n = 22,070$) surveys UI concentrations were determined using the Sandell-Koltoff reaction [13].

In conducting large epidemiologic studies it is important to have close agreement among the methods for UI determination used in the participating laboratories. One large comparison of six different methods for UI measurement found that no method showed a bias or inconsistency and good inter-method comparison for individual samples was indicated by the high correlation coefficient ($r = 0.9$) [14]. UI concentrations determined by inductively coupled plasma mass spectrometry had a lower limit of detection for the assay ($2 \mu\text{g/L}$), and the reproducibility of the assay was good. Comparison with the colorimetric/Sandell-Koltkoff reaction method showed a highly significant correlation ($P < 0.001$) and no systematic bias at low iodine concentrations [14].

Several simple methods are available and suitable for UI concentration measurements in developing countries. A rapid test based on the iodide-catalyzed oxidation of 3,3',5,5'-tetramethylbenzidine by peracetic acid/ H_2O_2 to yield colored products has been developed [15]. The samples are put into ranges rather than absolute concentrations for individuals making this method simpler to execute. This grouping by ranges is satisfactory for many epidemiologic purposes and is considerably more rapid than other approaches.

3. Creatinine and UI/Cr in UI measurements

Creatinine, is endogenously produced as a breakdown product of creatine normally appearing in urine at a relatively constant rate over a 24-h period when liquid consumption is regular. For this reason, urinary creatinine has been used as an indicator for assessment of the adequacy of a 24-h urine collection. A greater than normal intake of water will increase

the urine volume, leading to lower urinary creatinine and lower iodide concentrations, but usually will not reduce the amount of creatinine excreted daily.

Creatinine can be viewed as a relative marker for an individual, based on their lean body mass, age and other characteristics of metabolism. Urinary creatinine concentrations are somewhat variable between individuals, depending on their general nutritional status; poor nutrition leads to loss of muscle mass and hence will lower daily urinary creatinine excretion, contributing an independent source of variation, which may invalidate the ratio [8,16,17]. Similarly, advancing age or sedentary lifestyle are associated with progressively lower daily creatinine excretion as lean body mass declines [18]. A low daily creatinine excretion usually suggests an incompletely collected specimen. Urinary creatinine is somewhat unstable and needs to be stored appropriately until analyzed; it may decompose after three days if left without refrigeration. Urinary iodide is relatively more stable than creatinine.

Additional problems may arise when the population is iodine deficient [17]. In a study of healthy volunteers in an iodine deficient area fed on a diet of average 230 $\mu\text{gI/day}$, 24-h UI collection detected that only 16% to 18% of the dietary iodine was excreted [19]. In this case the iodine balance in iodine deficient areas was not well represented by the UI/Cr ratio since the creatinine was normal but there was increased uptake of iodine by the thyroid [16,20]. Andersen et al. [21] reported that 7% of individual UI/Cr concentrations of healthy men indicated severe ID without iodine deficiency being clinically present in the group studied, while a 24-h UI excretion gave a better assessment of the iodine nutritional status.

Although some studies note no significant age or gender differences in UI concentrations [10], others have reported age and/or gender differences [22–24]. In children 3 to 18 yr of age the UI/Cr ratio calculated with consideration of body surface area allows an age-independent assessment of iodine status during growth [25].

4. Urinary spot iodine concentration measurement in populations

Random spot UI concentration, and no longer the UI/Cr, is the most widely used biochemical measurement for UI. UI concentrations can be expressed as a range with a median or by the proportions at a series of cut off points ($<25 \mu\text{g/L}$, $<50 \mu\text{g/L}$). Spot UI concentrations collected from a population are currently the internationally accepted criteria for assessing and monitoring the iodine status of that population. According to World Health Organization (WHO) criteria, median iodine concentrations should be greater than $100 \mu\text{g/L}$ in “iodine sufficient” populations, and no more than 20% of the population should have UI concentrations $<50 \mu\text{g/L}$ [26]. Despite the drawbacks of spot urine laboratory measurements’ validity in reflecting the iodine status of individuals, and of populations, when populations are surveyed UI spot concentrations have been found to be an adequate measurement in reflecting their iodine status. Thyroid size and serum concentrations of thyroid stimulating hormone (TSH) and thyroid hormones are useful, but secondary in the assessment of iodine deficiency [26].

5. Day-to-day, within-day variation and circadian rhythmicity in UI excretion

Variation in UI concentrations is to be expected when there is day-to-day and within-day variation in iodine intake, especially in iodine-sufficient areas [27]. In an area of mild to moderate ID, Andersen et al. [21] found UI concentrations varied considerably from day-to-day.

Due to diurnal variations random spot UI concentration measurement is unlikely to precisely determine the proportion of a population that has a UI median concentration $<50 \mu\text{g/L}$

indicating iodine deficiency; the data can only be used to describe the central tendency and the dispersion of UI concentrations for a particular population.

Circadian rhythms are biologic processes that take about 24 h to complete from start to finish. Various hormones display circadian rhythms, notably thyroid hormones of which iodine is an essential component. Intra-day rhythmicity in UI concentrations was found in a prospective study of 3,023 urine spots (3–5 samples/month) collected at any time of the day [28]. The circadian rhythmicity of UI concentrations in adults and in children was found to be independent of the individual subject, age, gender, and season. The lowest UI concentrations were found between 08:00 to 11:00 h increasing progressively between 12:00 to 24:00 h. UI peaks occurred 4 to 5 h after main meals. UI returned to base-line concentrations between 21:00 to 22:00 h in children only, and the concentrations peaked in adults earlier. Although the existence of a circadian rhythm of UI is probably universal, its profile depends on dietary iodine intake. In view of the circadian rhythmicity of UI excretion, studies with restriction of sampling time to morning hours, for example, may not be directly comparable with studies in which urine is sampled at all times of day.

Fasting morning urine samples gave significantly lower iodine intake estimates in healthy subjects compared to the 24-h UI excretion [11]. On the other hand, iodine status calculated as UI/Cr determined from the first sample after the morning sample and the last sample before retiring to bed were not significantly different from actual 24-h iodide excretions. These studies demonstrate that a casual single UI measurement is not representative of an individual's iodine nutritional status, and that the time of the testing is important. Thompson et al. claim that it is the fasting urine samples and not casual urines that may give a reasonable estimate of UI concentrations [29]. In the NHANES I and NHANES III surveys ($n = 40,687$), fasting morning urine samples were used for the determinations of UI concentrations [1]. When used in cross-sectional epidemiologic surveys random spot UI concentration measurements retain their value in population samples of appropriate size.

6. Urinary iodine measurements in pregnancy

ID can lead to an impaired production of thyroid hormones since iodine is essential for thyroid hormone synthesis. Exposure of the developing fetus to inadequate thyroid hormone concentrations can lead to irreversible neurodevelopmental and intellectual deficits [30] therefore, determination of UI concentrations in women of child-bearing age in iodine deficient areas is especially important, as are efforts undertaken to promote their adequate intake of iodine.

Renal iodide clearance depends principally on glomerular filtration rate (GFR), there being no evidence of tubular secretion or of active transport with a transfer maximum [31]. Reabsorption of iodide is partial, passive, and depressed by an osmotic diuresis. It is normal for the GFR to be as much as 50% higher during pregnancy [32]. Hypothyroidism may decrease and hyperthyroidism may increase renal iodide clearance [33]. A wide variability in plasma and UI concentrations was noted during and after pregnancy. [34] UI concentrations increased during pregnancy in iodine replete areas [35–38] and in marginally sufficient areas [35,39,40]. UI concentrations of pregnant women were greater than those of nonpregnant women in both of the US NHANES I and NHANES III surveys [1]. The percentage of women with low UI concentrations (<0.4 mmol/L i.e., moderate to severe ID) decreased from 11.3% during the first trimester to 4.7% near term (mean UI concentration of $132 \mu\text{g/L}$ SEM 6.8) [35,40]. Higher UI concentrations (increased iodine loss) during pregnancy can be perceived as a “normal” level of iodine intake resulting in an under-estimation of the prevalence of ID during pregnancy if the assessments are based on UI concentrations alone. It is not clear whether the apparently higher UI concentrations in

pregnant women are pregnancy related or, in fact, masked iodine deficiency in pregnancy. However, UI concentrations slightly decreased during pregnancy in moderately ID areas [29,37,38,41–45] possibly reflecting marginally low iodine intake.

A higher GFR during pregnancy results in decreased circulating creatinine and a possible trend toward lower urinary creatinine concentrations but not in daily creatinine excretion. At the same time, increased goiter during pregnancy [46], and a higher requirement for iodine during pregnancy (due to an increase in demand for maternal thyroid hormones by the fetus and newborn) might lead to a lower UI/Cr ratio [39]. In mild ID the correlation between UI concentrations and UI/Cr ratio was lower for pregnant women ($r = 0.419$; $P < 0.001$) than for nonpregnant women ($r = 0.969$; $P < 0.001$) [47].

7. Discussion

Iodine deficiency disorders (IDDs) are a global health problem. According to the WHO over two billion people are at risk worldwide [48]. Among the consequences of IDD are goiter, hypothyroxinemia, neurodevelopmental disorders, cretinism, stillbirth, and increased perinatal mortality [49,50]. Worldwide, at least 50 million people are affected by some degree of IDD-related brain damage.

UI analysis is the recommended and most common method used to assess iodine status. Various methods for assessment of UI concentrations are available [6,51]. Some practical and simple methods involve mild acid digestion and colorimetric procedures. A more sophisticated measurement method, such as the UI reference method used by the Centers for Disease Control and Prevention (CDC), uses inductively coupled plasma mass spectrometry (ICP-MS). In an effort to reduce global IDD, the CDC established an international program to increase the level of confidence in the UI analytical work.

For the determination of the iodine nutritional status of an individual, daily UI excretion is the most reliable measurement of iodine excretion. More than one 24-h UI sample should be collected for most reliable assessment. Random spot UI concentration measurements present a problem because of diurnal and day-to-day variations in iodide excretion in both UI/Cr and UI concentration determinations. The UI/Cr of spot urine samples is a more reliable measure of iodine status than UI concentration per liter, and is a usable measure of iodine status more so if corrected for the age- and sex. Pregnancy is a special case because of lower circulating plasma creatinine concentrations and higher UI excretion due to a higher GFR, higher demand for iodine by the fetus and other thyroid hormone metabolism considerations due to the pregnancy.

For epidemiologic studies a population distribution is required rather than individual UI concentrations. There is no need for the more difficult 24-h urine collections since less precision is needed provided the sample size is large enough [52]. The fluctuations in UI concentrations in a population reflect changes in iodine nutritional status resulting from changes in societal and commercial practices that in the US are largely unrecognized and unregulated. The urinary iodide reference ranges have recently been calculated [53]. The fluctuations within individuals can be the result of differences in daily iodine intake or in higher or lower water consumption.

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