Urinary iodine, thyroid function, and thyroglobulin as biomarkers of iodine status[1–3]

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ABSTRACT

The accurate assessment of population iodine status is necessary to inform public health policies and clinical research on iodine nutrition, particularly the role of iodine adequacy in normal neurodevelopment. Urinary iodine concentration (UIC) directly reflects dietary iodine intake and is the most common indicator used worldwide to assess population iodine status. The CDC established the Ensuring the Quality of Iodine Procedures program in 2001 to provide laboratories that measure urinary iodine with an independent assessment of their analytic performance; this program fosters improvement in the assessment of UIC. Clinical laboratory tests of thyroid function (including serum concentrations of the pituitary hormone thyrotropin and the thyroid hormones thyroxine and triiodothyronine) are sometimes used as indicators of iodine status, although such use is often problematic. Even in severely iodine-deficient regions, there is a great deal of intraindividual variation in the ability of the thyroid to adapt. In most settings and in most population subgroups other than newborns, thyroid function tests are not considered sensitive indicators of population iodine status. However, the thyroid-derived protein thyroglobulin is increasingly being used for this purpose. Thyroglobulin can be measured in either serum or dried blood spot (DBS) samples. The use of DBS samples is advantageous in resource-poor regions. Improved methodologies for ascertaining maternal iodine status are needed to facilitate research on developmental correlates of iodine status. Thyroglobulin may prove to be a useful biomarker for both maternal and neonatal iodine status, but validated assay-specific reference ranges are needed for the determination of iodine sufficiency in both pregnant women and neonates, and trimester-specific ranges are possibly needed for pregnant women. UIC is currently a well-validated population biomarker, but individual biomarkers that could be used for research, patient care, and public health are lacking. *Am J Clin Nutr* 2016;104(Suppl):898S–901S.

Keywords: clinical laboratory tests, dried blood spots, iodine status, thyroid function tests, urinary iodine

INTRODUCTION

Adequate iodine nutrition is essential for the production of thyroid hormones. Pregnant women, infants, and young children are particularly vulnerable to the effects of iodine deficiency because of the importance of thyroid hormone for normal neurodevelopment. The accurate assessment of population iodine status is necessary to inform public health policies and clinical research on the effects of iodine nutrition. We briefly describe the biomarkers currently available to assess iodine nutrition and discuss areas in which additional research is needed.

URINARY IODINE AS A BIOMARKER

Approximately 90% of iodine is excreted in the urine (1). Urinary iodine concentration (UIC)[6] directly reflects dietary iodine intake and is the most common indicator used worldwide to assess iodine status. The very high day-to-day variability in the dietary iodine intake of individuals results in very high day-to-day variation in UIC (2). The large daily flux in UIC limits the usefulness of this measure for assessing the iodine status of individuals. It has been estimated that 10 UIC measurements from spot samples or 24-h collections are required to establish an individual's iodine status with 20% precision (3). However, when evaluated at a population level, UIC from spot samples has been shown to be a reliable biomarker of recent iodine intake for the population as a whole (4). Because the 24-h excretion of creatinine is fairly constant, creatinine adjustment of UIC to correct for urine volume has been advocated by some authors.

A recent study assessed 4 variables calculated from spot urine data with respect to their correlations with the observed 24-h urinary iodine excretion (UIE) and the observed 24-h UIC. Participants were asked to collect all urine over a 24-h period, with each void in a separate container. A 24-h urine sample was prepared by taking a proportional aliquot from each void, taking

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[6] Abbreviations used: DBS, dried blood spot; EQUIP, Ensuring the Quality of Iodine Procedures; FT4, free thyroxine; hCG, human chorionic gonadotropin; TBG, thyroxine binding globulin; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; UIC, urinary iodine concentration; UIE, urinary iodine excretion.

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into account individual and total void volumes, to determine the 24-h UIE. Four timed spot urine specimens covering specific intervals within the 24-h period were selected. Each of the 4 timed spot specimens was analyzed, yielding spot UIC. The 24-h UIC was calculated as the spot UIC averaged across the 24-h period. The 4 variables calculated from spot urine data were the spot UIC, the iodine-to-creatinine ratio, and 2 measures of the estimated 24-h UIE (iodine:creatinine × 24-h creatinine), each calculated by a different method for predicting 24-h creatinine excretion (5). The authors concluded that the 24-h UIC estimate based on average spot UIC did not differ from the observed 24-h UIC. Estimated 24-h UIE, when calculated by using predicted 24-h creatinine values based on age, sex, ethnicity, and anthropometric measurements, was most comparable to the observed 24-h UIE. The results of this study suggest that the threshold values established for population iodine status, which currently are based on UIC, reflect population-estimated 24-h UIE values.

UIC is typically sampled in school-aged children to determine population iodine status. Median UIC values of 100–199 μg/L are consistent with optimal iodine nutrition in schoolchildren (6). Pregnant and lactating women have the highest dietary iodine requirements. In pregnant women, median UIC values of 150–249 μg/L are considered consistent with population iodine sufficiency (6). In women who are lactating, because some ingested iodine is excreted in breast milk and therefore less is excreted in urine, median UIC values >100 μg/L are considered optimal (6). Recent studies suggest that UIC measured in US schoolchildren may not be an appropriate proxy for iodine status in pregnant women in all regions (7). For example, the United States has been iodine sufficient overall for decades, but the most recent NHANES UIC data suggest that US pregnant women have become mildly iodine deficient, whereas school-aged children have iodine intake that is more than adequate (8, 9).

UIC QUALITY CONTROL: THE EQUIP PROGRAM

Accurate and precise UIC measurement is important to accurately assess the status of iodine nutrition in the United States and around the world. Erroneous laboratory data can lead to suboptimal—and potentially harmful—public health interventions. For example, a low estimate of the population median UIC might prompt inappropriate salt iodization that could result in excessive fortification, a problem that carries its own risks.

The CDC established the Ensuring the Quality of Iodine Procedures (EQUIP) program in 2001 to provide laboratories that measure urinary iodine with an independent assessment of their analytic performance; the program also provides reference materials as well as technical support for improving laboratory practices. EQUIP sends participating laboratories 3–5 urine samples of different concentrations to analyze. The laboratories submit their results to the EQUIP program staff and receive detailed reports from the CDC on how well they performed the analyses. EQUIP results are not used for accreditation or certification; however, the program does enable laboratories to improve the precision and accuracy of urinary iodine analyses (10). EQUIP accuracy is based on National Institute of Standards and Technology Standard Reference Material 3668. Providing quality-assurance materials is a service that the CDC provides free of charge. The program currently works with >180 iodine laboratories in >70 countries.

VARIATION IN THYROID FUNCTION TESTS IN SPECIAL POPULATIONS

Clinical laboratory tests of thyroid function are sometimes used as indicators of iodine status, although such use is often problematic for the reasons described in this section and the following section. The thyroid gland secretes the thyroid hormones triiodothyronine (T3) and thyroxine (T4) in response to thyrotropin [also known as thyroid-stimulating hormone (TSH)], which is produced by the pituitary gland. The vast majority of T4 (99.97%) and T3 (99.70%) is tightly bound to thyroxine binding globulin (TBG) and other plasma proteins, and it is only the unbound or free thyroid hormones that are bioactive. Serum TSH is the most sensitive early indicator of thyroid dysfunction (11). Subclinical hypothyroidism is defined as elevated serum TSH in the setting of normal serum free thyroxine (FT4). In overt hypothyroidism, serum TSH is elevated and serum FT4 is low. Serum free and total T3 concentrations usually do not decline until hypothyroidism is quite advanced, because elevated TSH stimulates the release of T3 from the thyroid.

The usual reference ranges for thyroid function tests do not apply to all populations. Thyroid hormone production increases by ~50% starting in early gestation. Human chorionic gonadotropin (hCG), a hormone associated with pregnancy, is an activator of the thyroidal TSH receptor (12). In the first trimester, when hCG concentrations are highest, hCG activation of the TSH receptor leads to a transient increase in serum FT4, which, in turn, causes a decrease in serum TSH to concentrations that may be below the reference range for nonpregnant women (12). After the first trimester, when hCG concentrations fall, serum FT4 typically decreases.

In addition, high concentrations of circulating estrogen during pregnancy increase the circulating concentrations of TBG, which increases serum total T3 and T4 (13). Severe nonthyroidal illnesses can also cause alterations in serum thyroid hormone and TSH concentrations, even in individuals with normal underlying thyroid function. Serum TSH and T3 typically decrease during the acute phase of illness, and T4 may also become low as illness progresses (14). During the recovery phase, serum TSH may transiently increase above the normal range before thyroid function tests normalize. In infants, serum free and total T4 and T3 concentrations normally increase in the first 24 h of life in response to a physiologic surge in TSH that occurs shortly after birth. Therefore, age-normative values are needed for the interpretation of thyroid function in newborns (15).

THE RELIABILITY OF THYROID FUNCTION TESTS FOR ASSESSING IODINE DEFICIENCY

The thyroid gland may adapt to iodine deficiency in several ways (16). Iodine deficiency will cause an increase in serum TSH, which, in turn, will trigger increased avidity of the thyroid gland for available iodine, an increase in the ratio of T3 to T4 production (17), increased T4 to T3 conversion in peripheral tissues, and thyroid gland enlargement (18). In severe iodine deficiency, these compensatory responses may prove inadequate, and hypothyroidism can result.

In moderately to severely iodine-deficient regions, serum TSH concentrations may be elevated compared with those seen in iodine-sufficient regions, serum T4 concentrations may be slightly low, and serum T3 concentrations may be slightly high (19). After

successful iodine fortification programs in severely deficient regions, these changes may reverse (20–22). However, even in severely iodine-deficient regions, there is a great deal of intra-individual variation in the ability of the thyroid to adapt (23); therefore, thyroid function tests (including serum TSH, T3, and T4) are not considered sensitive indicators of population iodine status in most settings (4). In some regions of mild-to-moderate iodine deficiency, paradoxically, average serum TSH values may be lower than in iodine-sufficient areas, particularly among older individuals. This is attributable to the increased prevalence of hyperthyroidism from autonomously functioning nodular goiter in areas with insufficient iodine intakes (24). Finally, excessive iodine exposure can lead to thyroid dysfunction; average serum TSH values may be slightly elevated in regions with excessively high iodine intakes (25, 26).

The neonatal period is the only setting in which thyroid function can provide a reliable index of population iodine status. In most of the developed world, universal TSH screening is carried out in newborns to detect congenital hypothyroidism. Neonatal serum TSH is a sensitive marker for population iodine deficiency; the prevalence of neonatal TSH concentrations >5.0 mIU/L should be <3% in iodine-sufficient regions (6). Although neonatal T4 concentrations have been reported to be higher in iodine-sufficient regions than in iodine-deficient regions, normative values for iodine-sufficient populations have not been established.

THYROGLOBULIN AS A MARKER FOR IODINE STATUS

Thyroglobulin, a protein synthesized and secreted by the thyroid gland, is increasingly being used as an index of population iodine status (27). Thyroglobulin can be measured in serum or dried blood spots (DBSs). The use of DBS specimens is advantageous in resource-poor regions because they do not require refrigeration and can be transported easily. Serum thyroglobulin concentrations are positively correlated with thyroid volume in iodine-deficient regions, and mean thyroglobulin concentrations are typically elevated in regions of both iodine deficiency and excess (28). Thyroglobulin concentrations change more rapidly than goiter rates and thus may be a better tool for gauging population responses to alterations in iodine intake (29).

Reference ranges for DBS thyroglobulin values were recently established in an international cohort of iodine-sufficient schoolchildren (30). On the basis of the findings for this cohort, a median thyroglobulin concentration <13 μg/L with <3% of thyroglobulin values >40 μg/L indicates iodine sufficiency in school-aged children. Similar thyroglobulin reference ranges for population iodine sufficiency have not, to date, been established in other age groups. It is known that serum thyroglobulin concentrations normally increase after birth in response to the neonatal TSH surge (31) and that neonatal values are higher in iodine-deficient regions than in areas of iodine sufficiency (32). Serum thyroglobulin concentrations are increased by hCG; therefore, serum thyroglobulin may be elevated in pregnancy at times when hCG concentrations are high (12). No normative thyroglobulin reference ranges currently exist for pregnant women.

One drawback to the use of thyroglobulin as a marker for iodine status is the fact that it cannot be reliably measured in people with detectable anti-thyroglobulin antibodies, who comprise ~10% of the adult population (33, 34). Anti-thyroglobulin antibodies are more frequent in women than in men and are more prevalent with increasing age. In addition, despite the development of a National Institute of Standards and Technology Standard Reference Material for serum thyroglobulin, laboratory assays for this biomarker remain highly method dependent (35).

AREAS FOR FURTHER RESEARCH

Median UIC values can be used to assess population iodine status as long as quality-control programs such as EQUIP are used to ensure the accuracy of laboratory UIC measurements. Serum or DBS thyroglobulin values can be used as population biomarkers of iodine status in school-aged children, whereas TSH values can be used in neonates. However, currently there is no validated biomarker that allows the determination of the iodine status of individual patients. This lack has important implications for public health monitoring, routine patient care, and study development.

Pregnant women and their offspring are especially vulnerable to the effects of iodine deficiency disorders. Therefore, the accurate assessment of the iodine sufficiency of pregnant women is particularly critical. Many research efforts currently are focusing on the examination of associations between maternal iodine status and child developmental outcomes. Improved methodologies for ascertaining maternal iodine status are needed to facilitate this research. In many regions, median UIC values are available for school-aged children but not for pregnant populations. National surveys of pregnant populations would be informative for public health recommendations in many areas. Changes in maternal UIC over the course of gestation are not well understood. Thyroglobulin may prove to be a useful biomarker for both maternal and neonatal iodine status, but validated assay-specific and possibly trimester-specific reference ranges are needed for the determination of iodine sufficiency in these groups.

Alternative individual and population iodine biomarkers have been suggested, including hair and toenail iodine content. The authors of a recent population study of hair iodine content proposed a reference range for adequate long-term iodine status (36). However, it is unclear whether hair might be contaminated by exposures to iodine-containing dyes and other hair products. To date, no methods for measurement of hair iodine content have been validated. Toenails have frequently been used as a source of biomarkers for other nutrients such as selenium (37). Validation studies for toenail iodine content are lacking, and it is unclear whether nail polishes might contain iodine or interfering substances.

Many cohort studies collect, freeze, and store serum samples for potential future analysis; it would be appealing to be able to use such samples for the analysis of plasma or serum iodine content as a nutritional biomarker. However, despite some recent advances (38), plasma and serum iodine measurements are currently limited by the lack of reliable, well-characterized reference intervals.

In conclusion, UIC is currently a well-validated population biomarker, but individual biomarkers that could be used for research, patient care, and public health are lacking. Such biomarkers, particularly for pregnant women and other population groups who are the most vulnerable to the effects of iodine deficiency, would be of great value.

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