Adequacy of Iodine Nutrition in the United States*

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ABSTRACT—Concerns have been raised about the adequacy of iodine nutrition in the United States despite recent NHANES III data indicating that iodine intake remains generally adequate. Such concerns probably reflect misunderstanding of definitions of iodine deficiency. We review current criteria for iodine deficiency, the reasons for variability of urine iodine determinations, and their relation to interpretations of NHANES data. Although NHANES data indicate that iodine nutrition in the United States is adequate, the possibility remains that those who adhere to restricted diets may have reduced intake of iodine. Because of such possibilities, patients' diets and use of dietary supplements should be explicitly considered as a part of routine medical care.

THE adequacy of iodine nutrition in the United States has been evaluated periodically as one aspect of the National Health and Nutrition Examination Surveys (NHANES).[1–3] Designed to provide national normative estimates of the nutritional status of the civilian, non-institutionalized population of the United States, the NHANES surveys have measured fasting urinary iodine (UI) to evaluate the sufficiency of iodine nutrition. The importance of ensuring adequate iodine intake is generally well recognized; iodine deficiency disorders are the most common preventable cause of intellectual deficiency and mental retardation world-wide.[4,5] It has been estimated that more than 1.6 billion people worldwide are at risk of iodine deficiency, of whom 5.7 million suffer cretinism, 26 million suffer brain damage and 655 million suffer goiter.[4]

In 1998, Hollowell et al[3] analyzed UI data from the NHANES III (1988-1994) survey and compared them to corresponding data from the earlier (1971–1974) NHANES I survey. They found that dietary iodine levels had declined by about 50% from the earlier survey: median UI values in NHANES I were 320 ± 6 μg/L, but only 145 ± 3 μg/L in NHANES III. In addition, the proportion of participants with UI < 50 μg/L had increased: from 2.6% to 14.5% in the general population, from 3.9% to 14.9% in women of child-bearing age (15–44 years) and from 1.0% to 6.9% in pregnant women.

Such a trend raised concerns that the United States diet, historically regarded as iodine sufficient, might be heading towards insufficiency. Although NHANES III data indicated that iodine intake remained adequate in the US population, Hollowell et al cautioned that "should the intake of iodine continue to decrease in the US … a portion of the population could become iodine deficient."[3]

Despite efforts to distinguish between current iodine adequacy and possible future deficiency, the Hollowell et al report has been prone to misinterpretation. For example, recent articles in prominent internal medicine and endocrinology journals have proposed that Hollowell et al documented "endemias of variably treated iodine deficiency" in the United States[6] as well as "moderate iodine deficiency ... in a significant proportion of the US population."[7] Such conclusions, clearly at odds with the actual statements in the Hollowell et al report, suggest misunderstandings of current definitions of iodine deficiency and their application to NHANES data. The following discussion aims to address such confusions.

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WHO/UNICEF/ICCIDD Criteria for Iodine Deficiency

There exists a single set of consensus criteria for the determination of iodine deficiency. Those criteria, utilized by Hollowell et al to analyze the NHANES data, were developed collectively by the World Health Organization (WHO), United Nations International Children's Emergency Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) for the identification of populations at risk of iodine deficiency due to geographically- or culturally-determined dietary iodine insufficiency.[8] The WHO/UNICEF/ICCIDD criteria, which do not consider the diagnosis of iodine deficiency in individuals, have been cited (directly or by reference to the linked National Academy of Sciences recommendations[9]) and endorsed or adopted by an array of national and international medical and scientific organizations.

The criteria first categorize populations as adequate or deficient, and the latter category is further divided into three levels of deficiency: mild, moderate, and severe. Measurement of urinary iodine concentration is regarded as "the most practical biochemical marker of iodine nutrition" when performed by appropriate methods.[8] In evaluating the results of population-based studies of urine iodine, it is necessary to consider both the central tendency and dispersion of the data. Urinary iodine values from population studies are usually skewed, rather than normally distributed. Accordingly, the median is the preferred measure of central tendency and percentiles, rather than standard deviations, are the preferred measure of spread.[8]

The WHO/UNICEF/ICIDD criteria for using median urine iodine levels to determine the adequacy of iodine nutrition in populations are presented in Table 1. An additional criterion for adequacy is that not more than 20% of samples are below 50 μg/L.[8] Thus, the iodine intake and nutrition of a given population would be judged "adequate" if its median urine iodine was ≥100 μg/L and fewer than 20% of its urine samples were ≤50 μg/L.

It may seem confusing that populations can be judged "adequate" for iodine nutrition despite urinary iodine levels <50 μg/L in up to 20% of urine samples. Such confusion is the likely source of misinterpretations of NHANES data and the Hollowell et al report. The reason for such seemingly inconsistent criteria is the need to anticipate potentially large variability when iodine levels are measured in spot urine samples. Because of such variability, there is only limited statistical confidence that extreme values (very high and very low) correctly reflect the underlying state of iodine nutrition. Several aspects of variability in urine iodine measurements are discussed in the following section.

Variability of Urinary Iodine Measurements

At least four different sources of variability affect the accuracy and precision of urine iodine measurements: day-to-day variations; intra-day variations; analytical variations; and adequacy of urine collections. The NHANES survey employed spot samples and a standardized collection protocol, which addressed most concerns about collection adequacy and intra-day variability. However, day-to-day variability and analytical variations remain relevant concerns.

Day-to-Day Variation.—Urinary iodine levels reflect dietary iodine intake over a very limited time period, generally not more than the preceding 24 hours. Accordingly, variations in day-to-day dietary content lead to variations of day-to-day urine iodine levels. As described below, there is ample evidence of such effects. In addition, significant day-to-day variations have been documented in subjects under conditions of controlled iodine intake. For example, Vought et al studied six adults on the metabolism ward of the NIH Clinical Center.[10] Subjects were studied for 30 days while adhering to diets with fixed daily iodine contents. Following a six-day stabilization period, daily 24-hour urine specimens were collected for urinary iodine measurements. Day-to-day coefficients of variation (CV) for 24-hour iodine excretion were calculated for each of two successive 12-day periods. Among the individual

Table 1. Criteria for Adequacy of Iodine Nutrition *

Median urine iodine (mg/L)	Iodine Intake	Iodine Nutrition
< 20	Insufficient	Severe iodine deficiency
20-49	Insufficient	Moderate iodine deficiency
50-99	Insufficient	Mild iodine deficiency
100-199	Adequate/Sufficient	Sufficient / Optimal
200-299	More than adequate	More than adequate
>300	Excessive	Excessive risk of adverse health consequences

* Source: (8)

subjects, CVs ranged from 7%–24.1%. Thus, even under the controlled conditions of a metabolic research ward with constant diet and measurements of total iodine in 24-hour urine samples (rather than iodine levels in spot samples), iodine excretion demonstrated substantial day-to-day variability. More substantial variability has been reported in epidemiologic studies that did not restrict subjects' diets. In Denmark, Rasmussen et al[11] measured iodine excretion in 24-hour urine samples collected on four consecutive days from each of ten subjects whose daily food and drink were weighed and recorded, but not standardized. For individuals, day-to-day urinary iodine levels varied up to three-fold. In Switzerland, where salt iodization is almost universal, Bürgi et al[12] collected morning urine samples from eleven subjects on 21 consecutive days. Diets were not controlled or monitored. Among individual subjects, day-to-day CVs ranged from 15%–75%; the average day-to-day CV for the group was 39%. Results from individual subjects demonstrated hectic day-to-day variability, which was substantially reduced when day-to-day group averages were considered. The authors concluded: "it is probably wise to include 50–100 persons per site in a cross-sectional epidemiological survey to obtain a reliable estimate of the true mean."[12]

In a third study, Andersen et al[13] measured urinary iodine in 15 men sampled monthly for 12 months. Diets were not controlled or monitored. Iodine levels in individual urine samples ranged from 10–260 μg/L and 12-month-averaged urine levels for individual subjects ranged from 29–81 μg/L. The CVs calculated for each subject's 12 monthly samples ranged from 20.1%–70.5%, while the CV for annualized averages across all 15 subjects was 23.6%. The CV for mean urinary iodine concentration was 2.4 times larger when calculated from individual urine samples (57.3%) than when calculated from each subject's annual average (23.6%).

Because of such day-to-day variations in urine iodine excretion, even among individuals with stable iodine intake, cross-sectional studies report significantly greater dispersion for individual urine iodine levels than do studies that consider urine levels averaged over time or for groups. In other words, urinary iodine levels are relatively imprecise for individuals, while much greater statistical precision can be achieved when results are averaged across a population, especially when the sample includes an adequately large number of representative individuals. In that case, individual day-to-day fluctuations tend to off-set one another, yielding relatively stable aggregate results.

Analytical Variability.—Uncertainty in urinary iodine measurements also stems from the limits in precision of analytical methods. In most surveys including NHANES, urinary iodine is measured by the standardized Sandell-Kolthoff colorimetric method.[14] An analytical method's precision is generally evaluated in terms of its CV; the 95% confidence interval for a given analytical result can be estimated as [measured value ± 1.96 CV]. Assessments of the precision of the Sandell-Kolthoff method were recently published by the National Academy of Clinical Biochemistry,[15] which noted that the inter- and intra-assay CV for the colorimetric measurement of urinary iodine "should be <10%" and "in expert hands the reaction yields … CVs <5%."

Published results of recent population-based surveys of urine iodine are consistent with such laboratory practice guidelines. In a recent Danish study,[11]two urine samples were each tested 50 times and the results were evaluated statistically. The first sample (mean urine level = 34 μg/L) had a CV of 10%, indicating a 95% confidence interval of 27.3-40.7 µg/L. The second sample (mean urine level = 150 μg/L) had a CV of 4% and a 95% confidence interval 138.2-161.8 μg/L. Analytical precision was also reported in a study from Hong Kong.[16] For a sample with mean urine level of 29 μg/L, the intra-assay CV was 10.2%, while the CV was 5.5% for a sample with a mean urine level of 123 μg/L. Similar results have been reported for the urinary iodine analyses in the NHANES surveys.[3] Depending on urinary iodine levels, the CVs for urinary iodine measurements ranged from 3.8%–11.0% in NHANES I and from 2.7%–7.0% in NHANES III.

Such findings indicate better analytical precision at high urine levels, and less precision at lower iodine levels. It can be expected that urine levels at or below the lower limits of normal (e.g., 50 μg/L) will be less accurate (±20% or more), while those in the range of iodine sufficiency will be more accurate (±10% or less). Thus there is need for caution when interpreting urine iodine levels determined to be at or below lower limits of normal.

Discussion

Recent publications have misinterpreted NHANES III data and the Hollowell et al[3] report on iodine nutrition in the US. Such misinterpretations are probably due to misunderstanding of the imprecision of urine iodine measurements, which result from assay variability and day-to-day variations in iodine intake and excretion. As a consequence, there is considerable uncertainty about urine iodine levels measured at the extremes of a population's distribution. Moreover, because the standard colorimetric assay method is less precise at low concentrations, there is proportionately more uncertainty about low iodine concentrations. One implication of such uncertainty is that cross-sectional studies of urine iodine can be expected to find a number of individuals with very low iodine levels, relative to the sample population, even when the sampled population has sufficient iodine intake. That was apparently the case for NHANES III.

Table 2. Daily Iodine Excretion in Selected European Countries*

Country	Daily Iodine Excretion (μg/day)
Finland	>300
Norway	150–250
United Kingdom	70–130
France	60–170
Spain	30–110
Italy	10–130
Portugal	10–130
Germany	20–70
Poland	40–70
Belgium	50–60

* Source: (5;24)

The most important finding of the Hollowell et al[3] analysis of NHANES III data was an apparent downward trend toward iodine deficiency, one which required ongoing monitoring. If that trend continued, corrective actions might one day be needed to ensure the adequacy of US iodine intake. For perspective on the general adequacy of iodine nutrition in the US, Table 2 presents data on daily urinary iodine excretion in selected European countries. The data in Table 2 are presented in 'μg/day' units, while corresponding NHANES data are in units of 'μg/L'; as a first approximation, the median urine concentration in NHANES III, 145 ± 3 μg/L, corresponds to an excretion rate of about 290 μg/day.

In fact, such ongoing monitoring has been performed and the good news is that the downward trend apparently has not continued. The results of NHANES 2000, thus far available only in summary form,[2] indicate that the median value of urine iodine rose to 161 mg/L (95% CI 147–176), compared to 145 mg/L obtained from NHANES III. While this finding does not diminish the need for further monitoring, it should further allay concerns of those who have proposed that iodine nutrition in the US is not sufficient.

Nevertheless, clinicians and public health officials should not become complacent. Although sufficient iodine is found in "core foods" of the U.S. food supply,[17] those who adhere to atypical restricted diets (eg, vegans[18]) may have reduced intake of iodine and other nutrients.[19–23] Because of such possibilities, physicians and other health care providers should ensure that patients' diets and uses of dietary supplements are explicitly considered as a part of routine care.

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