

IODINE TESTING IN DRIED URINE

Iodine deficiency is a Global Health Problem

Approximately 2 billion of the world's population is iodine deficient^{1,2}. According to the most recent NHANES surveys^{3,4}, urinary iodine levels have dropped in the U.S. by half since the 1970s, and nearly 10% of the population has some degree of iodine deficiency. Iodine deficiency is resurfacing in developed countries like the U.S. and Western Europe as efforts are made to reduce the consumption of iodine-containing salt and foods (eggs and dairy) to lower blood pressure and blood lipids^{4,5}.

Adequate Iodine is Essential at All Stages of Life

In the developing fetus, an adequate iodine supply from the mother is essential for thyroid hormone production, which is vital for proper neurological development^{6,7}. In those areas of the world with severe iodine deficiency, pregnant women are at increased risk of miscarriage, stillbirths, or giving birth to children with cretinism and severe neurological and developmental defects². Even in areas of the world with mild to moderate iodine deficiency, which includes some regions of the U.S., children born to mothers who are iodine deficient during pregnancy can have impaired intellectual development⁸ and are at increased risk for developing attention deficit and hyperactivity disorders^{7,9}.

In children and adults, iodine deficiency can lead to lower thyroid hormone synthesis and consequent symptoms and conditions of hypothyroidism^{1,2}. When iodine levels drop below a critical threshold, consequent low thyroid hormone levels signal the brain to increase TSH production. Excessive stimulation of the thyroid gland by TSH, caused by iodine deficiency, leads to overgrowth (goiter) in an effort to maintain steady-state thyroid hormone synthesis. Areas of the world with low iodine usually have a much higher incidence of goiter.

High Iodine Levels can be Problematic

High iodine levels, resulting from consumption of high iodine containing foods (e.g., seaweed) or iodine medications or supplements, can also disrupt normal thyroid function, causing goiter and both hyperthyroidism or hypothyroidism^{2,10}. Hyperthyroidism is more likely to occur in the elderly who have been exposed acutely to high iodine after living for years in a low iodine environment. Chronic low iodine can lead to the development of autonomous thyroid nodules that produce excessive amounts of thyroid hormones (hyperthyroidism) when acutely exposed to high levels of iodine^{11,12}. Although rare, hyperthyroidism and associated thyrotoxicosis caused by excessive iodine consumption can cause arrhythmias and precipitate adverse cardiovascular events¹².

In some people, acute high iodine exposure can paradoxically suppress thyroid hormone synthesis (Wolff-Chaikoff effect) and lead to goiter and hypothyroidism¹³. Formation of iodolipids within the thyroid gland following high iodine exposure, and their inhibition of TSH-activated thyroid hormone synthesis, is thought to underlie the Wolff-Chaikoff effect. Ultimately, this results in lower synthesis of T4 and T3 and consequent increase in TSH. Most people with normal thyroid glands escape from the Wolff-Chaikoff effect within about 2 days. However a small percentage of people, particularly those with underlying subclinical hypothyroidism (normal T4 and T3, but elevated TSH) or with thyroid glands compromised by autoimmune problems (e.g., Hashimoto's), are less likely to recover from the suppressive effects of high iodine, and progress to a more severe and permanent hypothyroid state that requires thyroid medication^{2,14}.

Dried Urine Testing.

Non-invasive home test kit.

How Much Iodine is Needed for Optimal Thyroid Health?

Maintaining optimal iodine levels through consumption of iodine containing foods, salt, or supplements is essential for optimal thyroid hormone production. The World Health Organization (WHO), Centers for Disease Control (CDC), and other international organizations that study iodine nutritional status of world populations, unanimously agree and recommend, for non pregnant adults, consumption of 150 μg of iodine daily for optimal thyroid function and have set 1,100 μg as the upper level of tolerance^{2,15}. In Japan, where a much higher amount of iodine is consumed in the form of seaweed and fish, the Japanese Ministry of Health has set the upper limit at 3,000 μg .

Iodine's Role in Extrathyroidal Tissues

While iodine's role in thyroid hormone synthesis is well recognized, its other and equally important roles in maintaining health are less well appreciated, but well researched¹⁶⁻²⁹. Iodine serves many different and protective roles in the body including those of an antioxidant, antimicrobial, anti-proliferative, and anti-carcinogen. Tissues other than the thyroid gland that utilize iodine, concentrate it by one or more of the three known cellular iodine transport mechanisms (NIS, Pendrin, and Apical Iodide Transporter)³⁰. These tissues include white blood cells, salivary and lacrimal glands, ciliary body of the eye, renal cortex, pancreas, liver, stomach, small and large intestinal mucosa, nasopharynx, choroid plexus, skin, adrenal cortex, mammary gland, placenta, uterus and ovary^{16-19, 25, 29, 30}.

One of iodine's unique properties is its ability to form multiple oxidation states and serve as both an oxidant and antioxidant¹⁶. Iodine also forms bioactive conjugates with lipids and proteins. By interacting with double bonds of unsaturated fatty acids, iodine protects against toxic reactive oxygen species (ROS) that would otherwise convert the unsaturated lipids to highly reactive peroxy lipids that damage tissues of the body, particularly the cardiovascular system^{16,20,26}. Molecular

iodine (I_2) reacts with unsaturated double bonds of several highly reactive lipids, including arachidonic and docosahexaenoic acids to form iodolactones and plasmalogens to form 2-iodohexadecanal^{31,32}.

Iodine's ability to form iodolipids also underlies its capacity to serve as an antiproliferative and prevent abnormal benign growths (e.g., thyroid nodules, fibrocystic breasts, uterine fibroids) as well as cancers of these and other tissues (listed above)^{27,29}. The iodinated lipids that form in tissues such as the breast, interact with the steroid family of PPAR receptors to inhibit proliferation and induce apoptosis. These mechanisms are thought to underlie the anticarcinogenic effects of iodine in the breast and tissues of the lower reproductive tract¹⁶⁻²⁹. In the rodent uterus, progesterone increases the uptake of iodine¹⁷. Through this mechanism of increasing intracellular iodine levels, progesterone may also help to protect the breast and other progesterone responsive tissues from excessive stimulation by estrogens^{16-18,21-25}. Further research on the protective actions of both progesterone and iodine, and their possible synergy in preventing benign cysts and cancer in the breast and other progesterone sensitive tissues, is warranted.

Iodine Helps Prevent Infection

Iodine's effectiveness as an antimicrobial has been known for over a hundred years as it has been used for preoperative surgical skin preparation to prevent infection. As an antimicrobial, it is of relevance that iodine from the bloodstream concentrates in a broad spectrum of tissues that are repeatedly exposed to infectious organisms (e.g., skin, eyes, gastrointestinal tract, salivary gland, nasal and oral mucosa, breast ducts, uterine lining, prostate). Uptake of iodide by these tissues and enzymatic formation of reactive iodine compounds (e.g., hypoiodous acid) would serve the role of a protective antimicrobial, working in concert with the immune system. It is also of interest that like the thyroid, many of these iodine-concentrating tissues (e.g., skin, eyes, gastrointestinal tract) are the most sensitive to the adverse effects of iodine excess^{2,14}.

Iodine Sufficiency is Likely Different in the Thyroid Gland than in Other Tissues

Controversy exists as to how much iodine consumption is optimal. Sufficiency for the thyroid (about 150-300 μg daily consumption of iodine)^{2,15} is likely much lower than sufficiency for other tissues that are known to concentrate iodine such as the breast^{16,24,26,27,29}. Studies in humans have shown that for iodine to be protective (prevent benign breast disease such as fibrocysts), a minimum of 3,000 μg and optimally 6,000 μg or more of daily iodine consumption are required^{24,27,28,29}, far exceeding the CDC and WHO recommendations of 150-300 μg daily consumption of iodine-containing foods, salts, or supplements. The higher iodine levels found to be breast-protective are more consistent with the amounts of iodine consumed in countries like Japan, where the breast cancer rate is only about one-fifth that of the U.S. and other countries with much lower iodine consumption^{16,19,22}.

Development of a Patient-Convenient Test to Measure Iodine Levels in Dried Urine

With iodine playing so many different roles in optimizing health and preventing disease in the thyroid and other tissues, it is essential that adequate iodine intake is maintained and problems associated with low or excessive iodine intake are identified and treated appropriately.

To this end, ZRT has developed a simple and convenient test to measure an individual's iodine level in urine dried on a filter strip. This method was developed to circumvent the more cumbersome collection of all urine over a 24 hour period.

Collecting and Testing Urinary Iodine

Iodine is collected twice during the day (first morning and last night void) on filter strips either by dipping the strip in urine collected in a cup, or by urinating directly on the strip. The urine-saturated filter strips are allowed to dry overnight and then sent to the laboratory for iodine and creatinine testing. The iodine content of

the dried filter strips is determined following extraction and measurement by inductively coupled plasma mass spectrometry (ICP-MS). Creatinine is measured in the same urine extract by a modification of the Jaffe method³³. Iodine is measured in μg per liter of urine and the average of morning and night levels is taken. The creatinine level is used to correct for hydration status of the individual, because it is dependent on urine dilution. Results are therefore expressed in μg of iodine per g of creatinine.

Assay Validation

Iodine levels determined in extracts of urine dried on filter paper are quantitatively equivalent to measurements in wet urine ($r^2=0.99$). Moreover, in individuals not supplementing with iodine, or eating iodine rich foods, the average iodine level from first morning and last night voids is equivalent to 24 hr collections, making the urine collection procedure much more patient convenient. ZRT Laboratory participates in the CDC-sponsored EQUIP (Ensuring the Quality of Iodine Procedures) iodine standardization program where multiple urine samples are tested for iodine content and compared with values generated by ICP-MS at CDC and other laboratories performing iodine testing around the world (results available on request).

Advantages of Dried Urine for Iodine Testing

- Urine collection and shipment of the dried filter strips are simple and convenient for the patient and practitioner.
- Dual collections of urine directly on a filter strip, upon awakening and just before bed, are far more convenient and less subject to the inherent inaccuracies of a 24 hr urine collection.
- Iodine and creatinine in dried urine are exceptionally stable for weeks at room temperature allowing more flexibility in collection, shipment, testing, and storage.
- Iodine results expressed in μg iodine per g creatinine helps to normalize results when problems exist with urine that is very concentrated or dilute.
- Iodine testing allows for determination of iodine status based on CDC and WHO guidelines for thyroid sufficiency, as well as extra-thyroidal sufficiency.

References

1. Eastman CJ, Zimmermann MB. Chapter 20. The Iodine Deficiency Disorders. 2009. Available at: <http://www.thyroidmanager.org/chapter/the-iodine-deficiency-disorders/>.
2. Zimmermann MB. Iodine deficiency. *Endocr Rev* 2009;30:376-408.
3. Haddow JE, McClain MR, Palomaki GE, Hollowell JG. Urine iodine measurements, creatinine adjustment, and thyroid deficiency in an adult United States population. *J Clin Endocrinol Metab* 2007;92:1019-22.
4. Hollowell JG, Staehling NW, Hannon WH, et al. Iodine nutrition in the United States. Trends and public health implications; iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971-1974 and 1988-1994). *J Clin Endocrinol Metab* 1998;83:3401-8.
5. Hopton Cann SA. Hypothesis: dietary iodine intake in the etiology of cardiovascular disease. *J Am Coll Nutr* 2006;25:1-11.
6. Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. *Eur J Endocrinol* 2004;151:U25-37.
7. Sethi V, Kapil U. Iodine deficiency and development of brain. *Indian J Pediatr* 2004;71:325-9.
8. Bleichrodt N, Born MP. A meta-analysis of research on iodine and its relationship to cognitive development. In: Stanbury JB, ed. *The damaged brain of iodine deficiency*. New York, NY: Cognizant Communications, 1994:195-200.
9. Vermiglio F, Lo Presti VP, Moleti M, et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. *J Clin Endocrinol Metab* 2004;89:6054-60.
10. Zhao J, Wang P, Shang L, et al. Endemic goiter associated with high iodine uptake. *Am J Public Health* 2000;90:1633-5.
11. Delange F, de Benoist B, Alnwick D. Risks of iodine-induced hyperthyroidism following correction of iodine deficiency by iodized salt. *Thyroid* 1999;9:545-6.
12. Dunn JT, Semigran MJ, Delange F. The prevention and management of iodine-induced hyperthyroidism and its cardiac features. *Thyroid* 1998;8:101-6.
13. Wolff J. Iodide goiter and the pharmacologic effects of excess iodide. *Am J Med* 1969;47:101-24.
14. Braverman LE. Iodine and the thyroid: 33 years of study. *Thyroid* 1994;4:351-6.
15. Als C, Minder C, Willems D, et al. Quantification of urinary iodine: a need for revised thresholds. *Eur J Clin Nutr* 2003;57:1181-8.
16. Venturi S, Donati FM, Venturi A, et al. Role of iodine in evolution and carcinogenesis of thyroid, breast, and stomach. *Adv Clin Path* 2000;4:11-17.
17. Brown-Grant K, Rogers AW. The sites of iodide concentration in the oviduct and the uterus of the rat. *J Endocrinol*. 1972;53:355-62.
18. Miller DW. Extrathyroidal benefits of iodine. *J Am Physicians Surgeons* 2006;11:106-10.
19. Pizzorno L, Melitis CD. Iodine: the next vitamin D? Part II. *Longevity Medicine Review* 2010. Available at: www.lmreview.com/articles/print/iodine-the-next-vitamin-d-part-ii/
20. Winkler R, Griebenow S, Wonisch W. Effect of iodide on total antioxidant status of human serum. *Cell Biochem Funct* 2000;18:143-6.
21. Aceves C, Anguiano B, Delgado G. Is iodine a gatekeeper of the integrity of the mammary gland? *J Mammary Gland Biol Neoplasia* 2005;10:189-96.
22. Kato N, Funahashi H, Ando K, Takagi H. Suppressive effect of iodine preparations on proliferation of DMBA-induced breast cancer in rat. *J Jpn Soc Cancer Ther* 1994;29:582-8.
23. Eskin BA, Bartuska DG, Dunn MR, et al. Mammary gland dysplasia in iodine deficiency. Studies in rats. *JAMA* 1967;200:691-5.
24. Funahashi H, Imai T, Tanaka Y, et al. Suppressive effect of iodine on DMBA-induced breast tumor growth in the rat. *J Surg Oncol* 1996;61:209-13.
25. Eskin BA, Grotkowski CE, Connolly CP, Ghent WR. Different tissue responses for iodine and iodide in rat thyroid and mammary glands. *Biol Trace Elem Res* 1995;49:9-19.
26. Cann SA, van Netten JP, van Netten C. Hypothesis: Iodine, selenium and the development of breast cancer. *Cancer Causes Control* 2000;11:121-7.
27. Smyth PP. Role of iodine in antioxidant defence in thyroid and breast disease. *Biofactors* 2003;19:121-30.
28. Ghent WR, Eskin BA, Low DA, Hill LP. Iodine replacement in fibrocystic disease of the breast. *Can J Surg* 1993;36:453-60.
29. Kessler JH. The effect of suprathysiologic levels of iodine on patients with cyclic mastalgia. *Breast J* 2004;10:328-36.
30. Shen DH, Kloos RT, Mazzaferrri EL, Jhian SM. Sodium iodide symporter in health and disease. *Thyroid* 2001;11:415-25.
31. Panneels V, Van Sande J, Van den Bergen H, et al. Inhibition of human thyroid adenyl cyclase by 2-iodoacetyldehydro. *Mol Cell Endocrinol* 1994;106:41-50.
32. Boeynaems JM, Watson JT, Oates JA, Hubbard WC. Iodination of docosahexaenoic acid by lactoperoxidase and thyroid gland in vitro: formation of an iodolactone. *Lipids* 1981;16:323-7.
33. Bartels H, Böhmer M. Micro-determination of creatinine. *Clin Chim Acta* 1971;32:81-5.