

Iodine for Greatest Mental and Physical Health- Dr Guy Abraham M.D., Dr. Jorge D Flechas M.D.

For the sake of clarity, the element iodine in all its forms will be identified in this manuscript with the letter I, whereas the name iodine will be reserved for the oxidized state I₂. According to a recent editorial of the Journal of Clinical Endocrinology and Metabolism (1), one third of the world's population lives in areas of I deficiency, which is the world's leading cause of intellectual deficiency (2). I is an essential element and its essentiality is believed to be due to its requirement for the synthesis of the thyroid hormones thyroxine (T₄) and triiodothyronine (T₃). The recommended daily intake of I for adults of both sexes in North America and Western Europe varies from 150 to 300 ug (1). I deficiency results in goiter (enlarged thyroid gland) and hypothyroidism. The recommended levels for daily I intake were chosen with the goal of preventing and correcting endemic goiter and hypothyroidism, assuming that the only role of I in health maintenance is in its essentiality for the synthesis of T₄ and T₃.

Considering the importance of this element for overall wellbeing, it is most amazing that no study so far has attempted to answer the very important question: What is the optimal amount of daily I intake that will result in the greatest mental and physical levels of wellbeing in the majority of a population with a minimal degree of negative effects? In the studies designed to answer this question, consideration should be given to the possibility that I, at levels higher than those required to achieve normal thyroid function tests and absence of simple goiter, may have some very important thyroidal and extrathyroidal non T₃-T₄ related roles in overall wellbeing.

Some eighty years ago, D. Marine reported the results of his landmark study on the effect of I supplementation in the prevention and treatment of iodine-deficiency goiter. Based on extensive studies of goiter in farm animals, he estimated the amount of I that would be required for human subjects. He chose a population of adolescent school girls from the 5th to 12th grade between the ages of 10 and 18 years residing in Akron, Ohio, a city with a 56% incidence of goiter (3). His choice was based on the observation that the incidence of goiter was highest at puberty, and 6 times more common in girls than in boys (4). He studied two groups of pupils devoid of goiter (thyroid enlargement by palpation) at the beginning of the project. The control group consisted of 2305 pupils who did not receive I supplementation; and 2190 pupils received a total of 4 gm of sodium iodide per year for a period of 2 & 1/2 years. The amount of I was spread out in 2 doses of 2 gm each during the spring and during the fall. This 2 gm dose was administered in daily amounts of 0.2 gm of sodium iodide over 10 days. At 4000 mg of sodium iodide per 365 days, the daily amount is 12 mg, equivalent to 9 mg I. After 2 & 1/2 years of observation, 495 pupils in the

control group developed thyroid enlargement (22%). Only 5 cases of goiter occurred in the I-supplementation group (0.2%). Iodism was observed in 0.5% of the pupils receiving I supplementation. In an area of Switzerland with an extremely high incidence of goiter (82 to 95%), Klinger, as reported by Marine (3), administered 10-15 mg of iodine weekly to 760 pupils of the same age group. The daily I intake in this group was 1.4-2 mg. The initial examination revealed 90% of them had enlarged thyroid. After 15 months of this program, only 28.3% of them still had an enlarged gland. None experienced iodism. In response to these studies, the Swiss Goiter Commission advised the use of I supplementation in all cantons. Iodized fat in tablet form containing 3 to 5 mg I per tablet was used for I supplementation.

Due to the large consumption of seaweeds in the Japanese diet, this population ingests several milligrams of I daily without ill effects and in fact with some very good results evidenced by the very low incidence of fibrocystic disease of breast (5) and of the low mortality rates for cancers of the female reproductive organs (6). According to the Japanese Ministry of Health and Welfare, the average daily intake of seaweed is 4.6 gm. At an average of 0.3% I content (range = 0.08-0.45%), that is an estimated daily I intake of 13.8 mg (7). Japanese living in the coastal areas consume more than 13.8 mg (7). Studies performed in some of the subjects living in the coastal areas, revealed that the thyroid glands exposed to those levels of I, organify more I than they secrete as T3 and T4 and the levels of T3 and T4 are maintained within a narrow range. The excess I is secreted as non hormonal I of unknown chemical composition, mostly as inorganic I (7). The intake of I in the non-coastal areas of Japan is less. A recent study of 2956 men and 1182 women residing in the non-coastal city of Sapporo, Japan (8), revealed a urine concentration of I in spot urine samples, with a mean value of 3.4 mg/L, corresponding to an estimated daily intake averaging 5.3 mg (5). This relatively low I intake by Japanese standard, is more than 30 times the recommended daily amount of I in North America and Europe (1).

B.V. Stadel, from the National Institute of Health, proposed in 1976 to test the hypothesis that the lower incidence and prevalence of breast dysfunctions and breast Ca; and the lower mortality rate from breast, endometrial and ovarian cancers observed in Japanese women living in Japan versus those women living in Hawaii and the continental US, was due their I intake (6). He suggested a prospective study with 2 groups of subjects recruited from the same population with a high incidence of the above pathologies: one control group on intakes of I from a Western diet at RDA levels, and the other intervention group, receiving I in amounts equivalent to that consumed by Japanese women living in Japan. So far, data from this type of prospective epidemiological research are not available in the published literature, regarding the incidence of cancer of the female reproductive organs in women receiving several mg of I daily as the only

known variable, compared to women whose diet supplies RDA levels of I. Data are available, however, regarding the effects of I, ingested in daily amounts of several mg on subjective and objective improvements of fibrocystic disease of the breast (FDB). In 1966, two Russian scientists (9) published their results regarding the effect of oral administration of potassium iodide in daily amounts equivalent to 10-20 mg I, on 200 patients with "dys hormonal hyperphasia of mammary glands". They postulated that this form of mastopathy was due to excess estrogens from ovarian follicular cysts which were caused by insufficient consumption of I. The duration of I supplementation of their patients varied from 6 months to 3 years. Within 3 months, there was significant reduction of swelling, pain, diffuse induration and nodularity of the breast. Out of 167 patients who completed the program, a positive therapeutic effect was observed in 72% of them. In five patients with ovarian follicular cysts, there was a regression of the cystic ovaries following 5 months to one year of I supplementation. No side effects of I supplementation was reported in those patients.

Ghent et al (10) extended the Russian study further, using different amounts of different forms of I in women with FDB. Beginning in 1975, these Canadian investigators tested various amounts of various forms of I in three open trials. Lugol 5% solution was used in 233 patients for 2 years in daily amounts ranging from 31 to 62 mg I. They achieved clinical improvement in 70% of the patients. Thyroid function tests were affected in 4% of the patients and iodism was present in 3% of them. In 588 patients, using iodine caseinate at 10 mg/day for 5 years, only 40% success rate was achieved. In 1365 patients, using an aqueous saturated solution of iodine in daily amount based on body weight, estimated at 3-6 mg I/day, 74% of the patients had clinical improvements both subjectively from breast pain and objectively, from breast induration and nodularity. Iodism was present in only 0.1% in this last group. In a double blind study of 23 patients ingesting aqueous solution of iodine in amounts of 3 to 6 mg/day for a mean of 191 days, 65% showed objective and subjective improvement whereas in 33 patients on a placebo, 3% experienced worsening of objective signs and 35% experienced improvement in subjective breast pain. These data are summarized in Table I. Although the percent of subjects reporting side effects in Ghent's studies appear high ranging from 7% to 10.9%, the authors stated that the incidence of iodism was relatively low and most complaints were minor such as increased breast pain at the onset of I supplementation, and complaint about the unpleasant taste of iodine. When the data from Marine's, Klinger's and Ghent's studies (3,10) were evaluated regarding the incidence of iodism in relation to the daily amount of I ingested, a positive correlation was found between those 2 parameters: zero percent iodism at a daily amount of 1.4-2 mg; 0.1% iodism with 3-6 mg daily; 0.5% with 9 mg and 3% with 31-62 mg (Table II).

In the 19th Edition of Remington's Science and Practice of Pharmacy,

published in 1995 (11), the recommended daily oral intake of Lugol 5% solution for I supplementation was between 0.1 and 0.3 ml. This time-tested Lugol solution has been available since 1829, when it was introduced by French physician Jean Lugol. The 5% Lugol solution contains 50 mg iodine and 100 mg potassium iodide per ml, with a total of 125 mg I/ml. The suggested daily amount of 0.1 ml is equivalent to 12.5 mg of I, with 5 mg iodine and 7.5 mg of iodide as the potassium salt. This amount of I is very close to 13.8 mg, the estimated daily intake of I in Japanese subjects living in Japan, based on seaweed consumption (7). Obviously, this quantity of I present in 4.6 gm of seaweed would have to be consumed daily to maintain the I intake at this level. As quoted by Ghent et al (10), in 1928 an autopsy series reported a 3% incidence of FDB, whereas in a 1973 autopsy report, the incidence of FDB increased markedly to 89% (10,12,13). Is it possible that the very low 3% incidence of FDB reported in the pre-RDA early 1900's (12) was due to the widespread use of the Lugol solution available then from local apothecaries; and the recently reported 89% incidence of FDB (13) is due to a trend of decreasing I consumption (2) with such decreased levels still within RDA limits for I, therefore giving a false sense of I sufficiency? This lengthy introduction could be justified in the present context by stating that this background information was necessary to set the stage for the present study. If indeed, as suggested by Ghent et al, the amount of I required for breast normality is much higher than the RDA for I which is based on thyroid function tests and thyroid volume (10), then the next question is: What is the optimal amount of I that will restore and maintain normal breast function and histology, without any significant side effects and negative impact on thyroid functions? From the studies referred to (9,10) and Table I, the range of daily I intake in the management of FDB was between 3 and 62 mg. From Table II, we observe that the incidence of iodism increased progressively from zero % at 2 mg to 3% at 31-62 mg. Our goal was to assess the effect of a standardized fixed amount of I within the range of daily amount of I previously used in FDB, on blood chemistry, hematology, thyroid volume and function tests in clinically euthyroid women with normal thyroid volume by ultrasonometry; and subsequently trying the same in women with FDB if there was no evidence of toxicity and adverse effects on the thyroid gland. The equivalent of 0.1 ml of a 5% Lugol solution, that is 12.5 mg I was chosen, a value close to the average intake of 13.8 mg consumed in Japan (7), a country with a very low incidence of FDB (5); slightly higher than the 9 mg amount used in Marine's original study (3) of adolescents, with a very low 0.5% incidence of iodism following this level of I supplementation; also within the range of the 10 to 20 mg amount used in the Russian study of FDB, without any side effects reported (8); and five times less than the largest amount of 62 mg used in Ghent's studies with a 3% iodism reported (10).

Because administration of I in liquid solution is not very accurate, may stain

clothing, has an unpleasant taste and causes gastric irritation, we decided to use a precisely quantified tablet form containing 5 mg iodine and 7.5 mg iodide as the potassium salt. To prevent gastric irritation, the iodine/iodide preparation was absorbed unto a colloidal silica excipient; and to eliminate the unpleasant taste of iodine, the tablets were coated with a thin film of pharmaceutical glaze. Ten clinically euthyroid caucasian women were evaluated before and 3 months after ingesting a tablet daily. The evaluation included thyroid function tests and assessments of thyroid volume by ultrasonometry. The results suggest that this form and amount of I administered daily for 3 months to euthyroid women had no detrimental effect on thyroid volume and functions. Some statistically significant changes were observed in the mean values of certain tests of urine analysis, thyroid function, hematology and blood chemistry following I supplementation. These mean values were within the reference range, except for mean platelet volume (MPV) with a mean value below the reference range prior to supplementation, but the mean MPV value increased to reach a level within the normal range following I supplementation. In 2 subjects, baseline TSH levels were above 5.6 mIU/L, the upper limit for the reference range of the clinical laboratory used in this study. In both subjects, I supplementation markedly suppressed TSH levels.

II. Subjects and Methods

The female subjects were recruited from the private patients of one of us (JDF) and staff members of a medical clinic. They were ambulatory, without any serious medical problem, clinically euthyroid and on no medication known to affect thyroid functions. Informed consent was obtained on all subjects. Of 12 subjects recruited, 2 subjects were dropped from the data analyzed. One subject had a diffusely enlarged thyroid with a volume of 43 ml by ultrasonometry (14), significantly higher than the upper normal of 18 ml (14,15). Even though the thyroid function tests were within the normal limits for this subject, we decided to exclude her from this study, but she was placed on the same I supplementation and reevaluated every 3 months. The other subject did not return for follow-up. The clinical information on the 10 women selected are displayed in Table III. Mastodynia (breast pain) was initially the only symptom evaluated pre- and post-I supplementation. However, some of the subjects volunteered information regarding improvement of restless leg and tremor while on the program, so we included these 2 symptoms also.

The tablets containing 5 mg iodine and 7.5 mg of iodide as the potassium salt were prepared by one of us (JCH). A 5% Lugol solution prepared with USP grade iodine crystals and potassium iodide powder in purified water, was added to a colloidal silica excipient under mixing and the preparation was calibrated to contain the above amounts per tablet. The excess water was evaporated under low heat and the resulting dried preparation compressed into tablets which were coated with a thin film of pharmaceutical

glaze. There was no loss of I due to evaporation since triplicate analysis by a commercial laboratory (Weber Laboratories, New Port Beach, CA) of tablets taken from the batch used in the present study, revealed quantitative recovery, with I concentrations of 12.5, 12.5 and 12.6 mg per tablet. After initial evaluation, each subject was supplied with a bottle of 90 tablets*, with instruction to ingest one tablet a day for 90 days and to report any adverse effects.

The following laboratory evaluations were performed prior to and after 3 months of I supplementation: Complete blood count (CBC), was obtained from a Abbott Cell-Dyn[®] 1200; the metabolic panel and thyroid profile were performed by Lab Corporation of America; urine analysis was processed at the clinic with Multistix 10SG Reagent Strips, read on a Clinitek 100 that was calibrated daily. Measurement of thyroid volume by ultrasonometry was performed at the clinic by a registered sonographer using a portable Biosound Esaote Megas System unit with a frequency of 7.5 megaHertz, according to the procedure described by Brunn et al (14). The volume of each lobe of the thyroid gland was calculated according to the formula: $V \text{ (mL)} = W(\text{cm}) \times D(\text{cm}) \times L(\text{cm}) \times 0.479$ (14). The thyroid volume was the sum of the volumes of both lobes, taking 18 ml as the upper limit for normal thyroid volume in women living in a non-endemic goiter area (16). Body compositional analysis was performed at the clinic by near infrared technology (17), using a Futrex 5000: muscle mass, fat mass, % fat and total body water. The body mass index (BMI) is the ratio of body weight divided by height squared, using the metric units of kilogram (kg) for weight and meter (m) for height (18). Based on the classification of overweight and obesity by BMI, the normal range is 18.5-24.9 kg/m², with less than 18.5 as underweight; between 25-29.9 as overweight, and 30 and above as obesity. The latest NHANES III study (1988-1994) revealed that 25% of American women are overweight and 25% obese (18). Based on this classification, 5 subjects were within the normal range, 2 were overweight; and 3 were obese (Table III). Therefore these subjects are a good representation of our "normal" population. Statistical analysis of the data, comparing pre- and post-I supplementation values within patients, was done by paired data analysis (19).

III. Results

Clinically, (Table III) there were significant improvements of mastodynia ($p = 0.004$), tremor ($p = 0.048$) and restless leg (0.009). There was no statistical significant effect of I supplementation on blood pressure, body temperature and body composition (Table IV). Percent body fat reached a near significant drop ($p = 0.075$).

Regarding laboratory evaluation of the subjects, results of urine analysis were normal in all subjects pre- and post-I supplementation. The only statistically significant effect of I was on urine pH ($p = 0.012$) with pre- and post-I values (mean $\pm$ S.D.) respectively of 6.05 ± 0.69 and 7.00 ± 0.85 .

(Reference Range: 5.0-8.5). Out of 17 different measurements performed on blood chemistry, 9 were affected significantly by I supplementation: a drop in creatinine ($p < 0.01$), calcium ($p = 0.04$), albumin ($p < 0.01$), A/G ratio ($p < 0.01$), alkaline phosphatase ($p < 0.01$); and a rise in sodium ($p = 0.01$), carbon dioxide ($p = 0.02$), globulin ($p = 0.01$), and SGPT levels ($p < 0.01$). However, all those values remained well within the reference ranges for these parameters (Table V). Three hematological measurements out of 13 assessed were significantly altered by the intervention: a drop in mean corpuscular volume (MCV) ($p < 0.01$), mean corpuscular hemoglobin (MCH) ($p < 0.01$) and a rise in mean platelet volume (MPV) ($p = 0.04$). Although the above differences were statistically significant, they represented a small percentage of the mean values compared. (Table VI). The values for MCH and MCV were within the reference ranges both pre- and post-I supplementation. However, the mean value for MPV ($\pm$ SD) was below the normal range of 8.2-10.3 μ m prior to intervention (7.5 ± 1.3 μ m) and increased to reach the normal range following I supplementation (8.2 ± 1.3 μ m). Although MPV below 4 μ m is an indication of a compromised immune system, this slightly low mean value prior to I supplementation may not be of clinical significance. Nevertheless, the effect of I supplementation was beneficial on this parameter.

The data on thyroid function tests and thyroid volume are displayed in Table VII. Thyroid volume in all the subjects were below 18 ml, the upper limit of normal values reported (14,15), suggesting that their intake of I prior to this study was adequate to prevent enlargement of the thyroid gland, and to maintain normal thyroid hormones, since all these values were within normal limits. Serum T4 levels dropped significantly ($p < 0.01$) from a mean of 8.8 (SD = 1.3) to 7.2 μ g/dL (SD = 1.1). However, all individual values remained within the reference range (Table VII). Mean serum TSH levels decreased following I intake from 4.4 mIU/L to 3.2 mIU/L. This non significant decrease was due to the marked fall in subjects #1 and #10, with 16 mIU/L decrease between these 2 subjects contributing 1.6 mIU/ml less to the mean value. Using the classification of subclinical hypothyroidism as clinical euthyroidism with normal levels of thyroid hormones but elevated TSH above 6 mIU/L (20-22), subjects #1 and #10 would be classified as subclinical hypothyroid before I supplementation.

V. Discussion

The goal of this pilot study was to evaluate the effect of I supplementation in caucasian american women, a population with a high incidence of FDB and breast cancer (23,24,25), using daily I intake comparable to average daily I consumption in Japanese women living in Japan, a country with a very low incidence of FDB and breast cancer (25,26). The parameters evaluated were: thyroid volume by ultrasonometry; thyroid function tests; and evidence of toxicity based on urine analysis, hematology and blood chemistry.

The mean thyroid volume ($\pm$ SD) in our 10 subjects (7.7 ± 3.6 ml) is comparable to the mean thyroid volumes measured using the same method, in normal euthyroid women from Sweden (7.7 ml), Holland (8.7 ml) and Hong Kong (8.9 ml); but 60% of the mean thyroid volume from Ireland (12.9 ml): and 47% of the mean thyroid volume from Germany (16.5 ml) (15,16,27). The high mean thyroid volumes observed in Irish and German women could be due to their low I intake and high prevalence of goiter (15,16). Two subjects (#1 and #10) had an elevated TSH level prior to intervention and in both cases, I supplementation suppressed markedly TSH levels; in subject #1, from 7.8 to 1.4 mIU/L; and in subject #10, from 21.5 to 11.9 mIU/L (Table VII). Subclinical hypothyroidism is defined as clinical euthyroidism with normal levels of thyroid hormones, but with elevated TSH levels above 6 mIU/L (20-22). By this classification, subject #1 would be classified as subclinical hypothyroid before I supplementation, and reclassified as normal 3 months after starting the ingestion of I in daily amount of 12.5 mg, 80 times RDA levels. It is likely that subject #10, if continued on this program, would have reached TSH levels within the normal range. It is estimated that close to 8 million american women suffer from subclinical hypothyroidism (21), which is a risk factor for coronary heart disease and possibly peripheral arterial diseases (21). If the above findings can be confirmed in a larger group of subjects with subclinical hypothyroidism, the solution to this problem could be very simple: increase daily I intake using I supplement in these individuals to levels consumed from seaweed by Japanese women living in Japan. At the least, a therapeutic trial of I supplementation could identify a subgroup of subclinical hypothyroid subjects who would be responsive to such an approach. We have reviewed published studies in Russia and Canada showing a beneficial effect of I intake at several mg a day on FDB both subjectively in terms of mastodynia and objectively on breast cysts nodularity and induration (9,10). In the present study, there was a significant improvement in the mean score of mastodynia in 7 subjects experiencing this symptom following 3 months of I supplementation. Of interest is the observation that 3 months after termination of I intake, the beneficial effect on mastodynia was still present in those subjects. Based on an extensive review of breast cancer epidemiological studies, R.A. Wiseman (28) came to the following conclusions: 92-96% of breast cancer cases are sporadic; There is a single cause for the majority of cases; The causative agent is deficiency of a micronutrient that is depleted by a high fat diet; If such an agent is detected, intervention studies with supplementation should lead to a decline in the incidence of breast cancer. Several authors have proposed that this protective micronutrient is the essential element I (5,6,10,29,30). Some of the mechanisms by which I could prevent breast cancer are: the antioxidant properties of iodides (31); the ability of I to markedly enhance the excited singlet to triplet radiationless transition (32). Reactive oxygen species

causing oxidative damage to DNA are usually excited singlet with a high energy content released rapidly and characterized by fluorescence whereas the corresponding triplet state releases its lower energy at a slower rate expressed as phosphorescence. Such an effect of I would depend on its concentration in the intra- and extracellular fluids. Other possible mechanisms involved were reviewed by Derry (29): the apoptotic properties of I and its ability to trigger differentiation, moving the cell cycle away from the undifferentiated characteristic of breast cancer, for that matter, of all cancers. The above properties of I are totally independent of thyroid hormones. A recent study in female rats (33) has demonstrated an effect of I deficiency independent of thyroid hormones, on the response of the hypothalamo-pituitary-adrenal axis to stress. There was an attenuation of this axis to stress, following I deficiency, and this attenuation persisted after functional recovery of the thyroid axis.

The significant increase in urine pH following I-supplementation, with mean ($\pm$ SD) values of 6.05 ± 0.69 and 7.00 ± 0.85 for pre- and post-intervention respectively, is suggestive of increased reducing equivalents in biological fluids. This effect could be due to the 7.5 mg of iodide ingested daily (31). However, an effect of I on the enhancement of singlet $\rightarrow$ triplet transition (32) would decrease the oxydative burden of the body and such an effect would result also in an increase of urine pH. To our knowledge, this effect of I supplementation on urine pH has not been previously reported. Although several extrathyroidal organs and tissues have the capability to concentrate and organify

I (34-36), the most compelling evidence for an extra thyroidal function of I is its effects on the mammary gland. Eskin et al have published the results of their extensive and excellent studies on the rat model of FDB and breast cancer and the importance of iodine as an essential element for breast normality and for protection against FDB and breast cancer (30,37,38). The amount of I required for breast normality in the female rats was equivalent based on body weight, to the amounts required clinically to improve signs and symptoms of FDB (9,10). Eskin's findings on the protective effect of iodine against breast cancer in the rat model were recently confirmed by Japanese workers (39).

Of interest is the findings of Eskin et al (40) that the thyroid gland preferentially concentrate iodide whereas the mammary gland favors iodine. In the I-deficient female rats, histological abnormalities of the mammary gland were corrected more completely and in a larger number of rats treated with iodine than iodide given orally at equivalent doses. Recent textbooks of endocrinology continue the tradition of the past, reaffirming that iodine is reduced to iodide prior to absorption in the intestinal tract, referring to a study by Cohn (41), published in 1932, using segments of the gastrointestinal tract of dogs, washed clean of all food particles prior to the application of I in the lumen. However, Thrall and Bull (42) observed that in

both fasted and fed rats, the thyroid gland and the skin contained significantly more I when rats were fed with iodide than with iodine; whereas the stomach walls and stomach contents had a significantly greater level of I in iodine-fed rats than iodide-fed animals. Peripheral levels of inorganic I were different with different patterns, when rats were fed with these 2 forms of I. The authors concluded: "These data lead us to question the view that iodide and iodine are essentially interchangeable". Based on the above findings, I supplementation should contain both iodine and iodide.

Regarding the potential adverse effects of I supplementation at the levels used in the present study, they are threefold: iodism, I-induced hyperthyroidism (IIH) and I-induced goiter (IIG). Iodism is dose-related and the symptoms are: unpleasant brassy taste, increased salivation, coryza, sneezing, and headache originating in frontal sinuses. Skin lesions are mildly acneiform and distributed in the seborrheic areas (11,43). Those symptoms disappear spontaneously within a few days after stopping the administration of I. As of this writing, no iodism and for that matter, no side effect has been reported in more than 150 subjects who underwent I supplementation at 12.5 mg/day. It has been suggested 100 years ago that iodism may be due to small amounts of bromine contaminant in the iodine preparations and trace amount of iodate and iodic acid in the iodide solutions (43). With greater purity of USP grade materials now available, iodism may no longer be a problem at the level of I used in the present study.

The next potential complication is IIH, which occurs predominately in population with I-deficiency during the early period of I replacement (45). In the 8th Edition of Werner and Ingbar's *The Thyroid*, published in 2000, Delange (46) stated: "The possible reason for the development of IIH after iodine supplementation has now been identified: iodine deficiency increases thyrocyte proliferation and mutation rates. Possible consequences are the development of hyperfunctioning autonomous nodules in the thyroid, ... and hyperthyroidism after iodine supplementation. Therefore, IIH is an IDD (Iodine Deficiency Disorder)." The prevalence of goiter in the United States is about 3.1% (46). In non-endemic goiter areas, IIH occurs predominantly in elderly subjects with nodular goiter, which could be detected by ultrasonography.

The last of the 3 adverse effects of I supplementation is I-induced goiter (IIG) and hypothyroidism. Most patients with IIG have received large amounts of I (up to 2 gm per day) for prolonged period of time, usually as an expectorant for asthma, chronic bronchitis and emphysema (11,47). In the 10th Edition of Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, published in 2001, Farwell and Braverman wrote: "In euthyroid individuals, the administration of doses of I from 1.5 to 150 mg daily results in small decreases in plasma thyroxine and triiodothyronine concentrations and small compensatory increases in serum TSH values, with all values remaining in the normal range" (48). However, in patients with

underlying thyroid disorders, IIG with hypothyroidism could be induced, mainly by I-containing drugs. Predisposing factors to I-induced hypothyroidism are: treated Graves' disease, Hashimoto's thyroiditis, post-partum lymphocytic thyroiditis, subacute painful thyroiditis, and lobectomy for benign nodules (47). Needless to stress the importance of medical supervision during the implementation of I supplementation for FDB and other conditions. A careful history should reveal previous and current thyroid disorders. Ultrasonography, although not required, is highly recommended prior to I-supplementation to detect abnormal echopatterns. Serum thyroid autoantibodies would supplement finding from history and physical examination. Reevaluation is recommended every 3 months to assess response to I-supplementation and to monitor possible side effects. The significant decrease in serum T4 observed in the present study, concomitant with the absence of significant changes in the mean values for TSH, FT3 and FT4, following I supplementation at 12.5 mg/day (Table VII), could be due to either a decreased secretion of T4 by the thyroid gland; or it could be due to lower levels of thyroxine binding globulin (TBG). The synthesis of TBG occurs in the liver and this synthesis is stimulated by estrogens (48). In the female rat, I-deficiency increases the sensitivity of mammary tissue to estrogens (37). I-supplementation to these female rats in amounts equivalent, based on body weight, to amounts of I required in women with FDB for subjective and objective improvement of FDB (10), had an attenuating effect on estrogen stimulation of the mammary tissue in those female rats, decreasing their response to estrogens (41). Therefore, the decreased T4 levels following I-supplementation could be due to a similar mechanism on hepatic synthesis of TBG, by decreasing the sensitivity of hepatic receptors to estrogens, resulting in decreased synthesis and release of TBG by the liver and decreased T4 levels. Since we did not include serum TBG levels in our thyroid profile, the explanation for this decrease of serum T4 levels must await future research.

The amount of I used in the present study would be considered physiological by Japanese standard. In the United States, there is a dichotomy regarding the physician's attitude toward I: Iodophobia in the physiological range (49), requiring a leap of faith to move up from RDA ug amounts to the mg amounts ingested by Japanese with a very low incidence of FDB, and breast cancer (25,26); and iodophylia in the therapeutic range, prescribing excessively large amounts of I in gm amounts for long periods of time (11,48) as an expectorant in patients with asthma, chronic bronchitis and emphysema, at least up to 1995.

The ranges of I ingested by human subjects for physiological and therapeutic purposes in different countries are displayed in Figure 1. From the lowest amount observed in areas with severe endemic goiter to the highest amount prescribed, a millionfold range. Based on the most recently published literature, we have made an attempt in Figure 1 to display the physiological

and therapeutic ranges on the right side of the graph. Within the physiological range, we have displayed first the levels of I necessary for normal thyroid functions, and control of endemic goiter under all physiological conditions (1,2). Thyroid sufficiency for I is defined according to Saxena et al (50) as the minimal effective daily dose of I required for either maximal suppression of radioactive I uptake by the normal thyroid gland or for a decrease of radioactive I uptake to approximately 5% of the total dose of radioactive I administered. A daily amount of I from 1.5 to 2 mg/m²/day was required to achieve the 5% goal. These authors state: "Thus, for the adult, the minimal effective daily dose of iodide becomes 3 to 4 mg." We have chosen this level of I daily for I sufficiency of the thyroid gland. However, Sternthal et al (51) were able to reduce this mean percent uptake below 5% with higher daily dose of I given for 12 days: 4% at 10 mg; 1.9% at 15 mg; 1.6% at 30 mg; 1.2% at 50 mg; and 0.6% at 100 mg. For breast sufficiency, the average daily consumption of I by Japanese women living in Japan was chosen, a population with the lowest prevalence of FDB and breast cancer (25,26). This value is also within the range of I supplementation used in published studies of FDB (9,10), with the limitation that the number of subjects in these studies were relatively small compared to the Japanese female population. The therapeutic range was divided into two parts based on Farwell and Braverman (47), as quoted in this text: up to 150 mg of I, a range without adverse effects on the normal thyroid gland, and above that quantity, there is a risk for IIG and hypothyroidism, mainly in the presence of thyroid disorders. The benefits of I supplementation within the range used in FDB outweigh the risks, if implemented under medical supervision. We plan to expand this pilot study in order to build a database that could be used to develop a protocol for the implementation of I supplementation in FDB and other conditions such as subclinical hypothyroidism, by interested physicians. There is a need for assays of serum inorganic I levels, to complement urine I levels. Not one of the clinical laboratories contacted offered this service.

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Table I

Summary of results obtained by Vishnyakova et al (Vestn Akad Med Navk SSSR, 21:19-22, 1966) and Ghent et al (Can. J. Surg. 36:453-460, 1993) for objective and subjective improvements of fibrocystic disease of the breast in response to various dosages of various forms of I.

Study Design	# pts	Duration	Form of I	Daily Dosage	% of pts with clin. improvement	% of pts with side effects
Open Trial	200	3 years	Potassium Iodide	10-20 mg	72%	none reported
Open Trial	233	2 years	Lugol 5%*	5-10 drops (31-62 mg I)	70%	7%
Open Trial	588	5 years	Iodine Caseinate	10 mg	40%	9.5 %

Open Trial	136 5	18 mont hs	Aqueo us Soluti on of Iodine	0.08 mg/Kg BW	74%		10.9 %
Double Blind	$P_L = 33$ $I_2 = 23$	mea n of 191 days	Aqueo us Soluti on of Iodine	0.08 mg/Kg BW	<u>Obj</u> <u>ect.</u> $P_L =$ $\equiv$ -3% $I_2 =$ 65%	<u>Su</u> <u>bje</u> <u>ct.</u> $\frac{33}{\%}$ $\frac{65}{\%}$	N / A

5% Lugol solution contains 5% iodine and 10% potassium iodide with a total I of 125 mg/ml, consisting of 50 mg iodine and 75 mg iodide. At 20 drops per ml, 5-10 drops represent .25-.5 ml, or 31-62 mg I.

Table II

Relationship between the amount of I ingested and the percent of students/patients with Iodism

Autho r(s)	Popul ation	#	Form of I	Daily Amou nt (mg)	Durati on	% of stud/ pts with iodis m
Marine (1)	studen ts	760	iodin e	1.4 - 2	15 mos.	0

Ghent (2)	patient s	1368	iodin e	3 - 6	9.9 mos.	0.1
Marine (1)	student s	2190	sodiu m iodid e	9	30 mos.	0.5
Ghent (2)	patient s	233	Lugol (5%)	31 - 62	24 mos.	3.0

(1) = Marine, Alt. Med. J 26:437-442, 1923 (2) = Ghent et al, Can J. Surg 36:453-460, 1993

Table III

Clinical data on the 10 subjects.

Su bj ect s	A g e	H ei gh t	w t	B M I	menst rual status	medi catio ns	Symptoms assessed in response to I supplementation° (pre-I / post-I)		
							Mastody nia	Trem or	Restless legs
#	(y e a r)	(in ch es)	(l b s .)	(k g/ m ²)					
1	31	68	152	23.2	Pre Meno pausal	O.C.	1/.5	1/.5	1/.5
2	49	70	216	30.9	Pre Meno pausal	Diure tics	0/0	0/0	1/0

3	4 9	63	1 6 1	28 .5	Post Meno pausal	Anti- Anx.	1/0	1/0	0/0
4	4 9	66	2 0 2	32 .5	Pre Meno pausal	Anti- Dep.	1/0	1/1	1/1
5	4 3	65	1 4 6	24 .3	Pre Meno pausal	None	1/5	0/0	0/0
6	3 5	67	1 4 9	23 .4	Pre Meno pausal	Ritali n (AD D)	1/1	1/0	0/0
7	4 4	62	1 1 5	21 .2	Pre Meno pausal	None	0/0	0/0	1/0
8	4 7	69	1 6 8	24 .9	Pre Meno pausal	None	1/0	0/0	0/0
9	5 9	69	1 9 6	29	Post Meno pausal	Anti- Hista mine	0/0	0/0	1/0
10	5 3	66	2 1 9	35 .2	Post Meno pausal	ERT	1/0	0/0	1/0
$\bar{x}$	4 5. 9	66 .50	1 7 2	27 .3		$\bar{x}$	0.70/.020	0.4/0. 15	0.6/0.15

S D	8. 2	2. 64	3 4 .3	4. 6		p value	0.004	0.048	0.009
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*1=present; 0=absent; 0.5=improved

Table IV

Effect of I supplementation in daily amount of 12.5 mg for 3 consecutive months on blood pressure, body temperature, weight and composition.

	Units	Refer ence	Pre- 		Post- 		p value
		Rang e	$\bar{x}$	SD	$\bar{x}$	S D	
Temp (p.o)	°F	—	97.5	0.99	97.3	1.1	0.20
Body weight	kg	—	78	15.4	78.3	15.1	0.46
Height	m	—	1.7	0.1	1.7	0.1	—
BMI	kg/ m ²	18.5-24.9	27.3	4.6	27.1	4.2	0.31
SBP	mm Hg	<140	127	21	124.2	13.5	0.23

DBP	mm Hg	<90	8 0. 4	12	78 .2	8. 6	0.24
Muscle mass	kg	–	5 3. 1	7.8	53 .5	7. 3	0.24
Fat	kg	–	2 5. 1	8.8	24 .3	8. 5	0.45
% Fat	%	–	3 1. 3	5.9	30 .6	6. 0	0.075
Water	liters	–	4 0. 9	6.2	40 .8	5. 9	0.43

Table V

Effect of I supplementation in daily amount of 12.5 mg for 3 consecutive months on blood chemistry.

	Units	Refere nce	Pre- 		Post- 		p value
		Range	$\bar{X}$	S D	$\bar{X}$	S D	
Glu	mg/dL	65-109	76 .6	19	78 .4	20 .4	0.41

BUN	mg/dL	5-26	12 .8	4. 2	11 .9	2. 9	0.18
Creat	mg/dL	0.5-1.5	0. 85	0. 12	0. 73	0. 07	<0.01
BUN/Creat	—	—	14 .6	4. 7	15 .9	3. 9	0.13
Na	mMole /L	135-14 8	14 0	3. 8	14 4	2. 6	0.01
K	mMole /L	3.5-5.5	4. 7	0. 54	4. 7	0. 58	0.46
CL	mMole /L	96-109	10 1	3. 6	10 2	2. 9	0.08
CO₂	mMole /L	20-32	23 .2	4. 2	26 .1	4. 2	0.02
C_A	mg/dL	8.5-10. 6	9. 6	0. 45	9. 2	0. 32	0.04
Prot	gm/L	6-8.5	7. 1	0. 42	7. 1	0. 32	0.47
Alb	gm/L	3.5-5.5	4. 5	0. 16	4. 1	0. 17	<0.01
Glob	gm/L	1.5-4.5	2. 6	0. 41	2. 9	0. 19	0.01
A/G ratio	—	1.1-2.5	1. 7	0. 29	1. 38	0. 08	<0.01

Total BiL	mg/dL	0.1-1.2	0. 58	0. 37	0. 59	0. 5	0.43
ALK. Phos	I.U/L	25-165	84 .8	24 .7	77 .5	21 .9	<0.01
SGOT	I.U/L	0-40	18 .5	3. 4	21 .3	6. 9	0.08
SGPT	I.U/L	0-40	13 .8	2. 5	19 .9	4. 6	<0.01

Table VI

Effect of I supplementation in daily amount of 12.5 mg for 3 consecutive months on Hematology.

	Units	Refere nce	Pre- R		Post- R		p value
		Range	$\bar{X}$	S D	$\bar{X}$	S D	
WBC	10³/uL	4.6-10. 2	6. 04	1. 7	6. 05	1. 7 2	0.49
Lymph	—	12-51	33 .4	8. 5	32 .4	6	0.23
Mid	—	0-12	6. 3	1. 2	6. 1	1. 9	0.33
Gran	—	43-85	60 .3	7. 8	61 .6	5	0.22

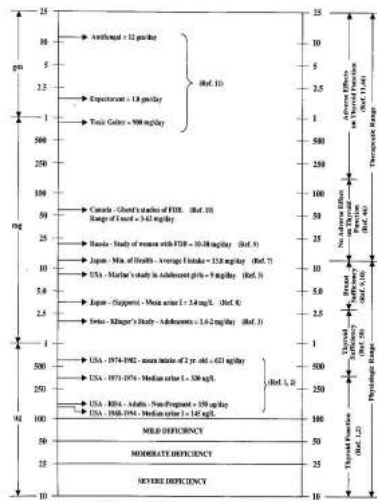
RBC	10⁶/uL	3.8-6.5	4. 35	0. 3 3	4. 53	0. 2 5	0.09
Hb	g/dL	11.5-1 8	13 .5	0. 8 3	13 .7	0. 9 6	0.35
Hct	—	37-54	38	2. 2	38 .8	2. 6	0.23
MCV	∣ L	80-100	87 .4	4. 2	85 .7	3. 9	<0.01
MCH	pg	27-32	31 .2	2. 2	30 .1	1. 7	<0.01
MCHC	g/dL	31-36	35 .6	1. 3	35 .1	0. 6	0.05
RWD	—	11.5-1 4.5	11 .4	0. 4 8	11 .4	0. 6	0.35
PLAT	10³/uL	150-40 0	28 2	4 7	27 4	7 7	0.33
MPV	∣ L	8.2-10. 0	7. 5	1. 0 3	8. 2	1. 3	0.04

Table VII

**Effect of I supplementation in daily amount of 12.5 mg for
3 consecutive months on thyroid volume and thyroid function tests**

Subjects #	Thyr. Vol. (mL)		TSH (mIU/L)		T ₄ (ug/dL)		FT ₄ (ng/dL)		FT ₃ (pg/mL)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	4.35	3.6	7.8	1.4	9.2	7.9	0.85	1.3	2.9	2.5
2	5.5	5.5	2.0	2.2	10.7	8.9	1.1	1.1	2.5	2.5
3	4.7	5.6	3.4	5.1	9.6	6.4	1.1	1.1	2.7	2.8
4	5.9	12	2.7	6.1	8.7	8.0	1.2	1.2	3.0	3.2
5	5.7	8.9	1.4	1.1	6.3	6.3	1.0	1.2	2.9	2.9
6	11.6	9.5	1.0	0.34	7.5	6.9	1.2	1.1	2.9	2.7
7	7.0	6.1	1.4	2.3	8.2	6	1.0	0.84	2.9	2.7

8	6. 7	7.5	2. 3	1.3	9. 4	7.4	1. 0	1.1 5	2. 7	3.1
9	15 .8	14. 7	0. 76	0.5 3	9. 7	8	1. 2	1.3	3. 1	3.4
10	9. 2	7.7	21 .5	11. 9	8. 3	5.4	1. 2	0.9	2. 8	2.6
$\bar{x}$	7. 7	8.1	4. 4	3.2	8. 8	7.1	1. 1	1.1	2. 8	2.8
SD	3. 6	3.3	6. 34	3.6	1. 3	1.1	0. 12	.16	. 1 7	.31
p value	.29		0.18		< .01		0.34		0.50	
Ref. Range	<18		0.35-5.5		4.5-12		0.61-1.7 6		2.3-4.2	



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