Evidence of Defective Cellular Oxidation and Organification of Iodide in a Female with Fibromyalgia and Chronic Fatigue

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Introduction

Orthoiodosupplementation is the daily amount of the essential element iodine needed for whole body sufficiency and is assessed by an iodine/iodide loading test.[1,2] The test consists of ingesting four tablets of a solid dosage form of Lugol (Iodoral®), a total of 50 mg iodine/iodide. Then urinary iodide levels are measured in a subsequent 24-hour collection. During orthoiodosupplementation, a negative feedback mechanism is triggered that progressively adjusts the excretion of iodine to balance the intake. When whole body sufficiency for iodine is achieved, the absorbed iodine/iodide is quantitatively excreted as iodide in the urine, and 90% or more of the iodine load is recovered in the 24-hour collection. The body retains around 1.5 g of elemental iodine at sufficiency.[2] Baseline serum inorganic iodide levels 24 hours after the last dose of iodide in eight normal subjects with normal body weight who achieved whole body iodine sufficiency had a mean $\pm$ SD of 1.1 ± 0.18 mg/L.[3,4] We have defined whole body sufficiency for iodine and a normally functioning iodine retention mechanism as a baseline serum inorganic iodide level from 0.85 to 1.3 mg/L when the serum sample is obtained 24 hours after the last dose of 50 mg iodine in a subject who excretes 90% or more of the ingested iodine.[4]

In patients with normal gastrointestinal absorption of iodine but with a very defective iodine retention system, the absorbed iodine is quantitatively excreted in the urine with little or no retention.[5] In these cases, the loading test will suggest whole body iodine sufficiency (90% or more excreted), but the serum inorganic iodide levels 24 hours after the iodine load will remain low (less than 0.13 mg/L). The inefficient iodine retention mechanism could be due to either an inefficient cellular iodine transport system or to an inefficient oxidation and organification of the intracellular iodide, or possibly both.[6,7]

We previously evaluated one hypothyroid patient with pre-supplementation high urinary excretion of the iodine load.[5] The patient, a 52-year-old woman (height 64 inches; weight 140 lbs.), had a past history of hyperthyroidism followed by hypothyroidism and had taken Synthroid 50 µg/day for five years. She developed side effects to orthoiodosupplementation and could tolerate only half a Lugol tablet/day (6.25 mg iodine/day) due to the detoxification of elevated bromide levels by the iodine supplementation.

She was evaluated with serial serum samples for 11 hours post-load, before and after three months on a sustained-release form of vitamin C at 3 g/day. Pre-vitamin C loading test showed 90% of the load excreted in the urine, but her baseline serum iodide level was only 0.016 mg/L, compared to the expected levels of 0.85-1.3 mg/L in those with whole body iodine sufficiency. Prior to intervention with vitamin C, a sharp peak of serum iodide at 32 mg/L at one hour post-load was followed by a rapid drop. This suggested that the gastrointestinal absorption of iodine was very efficient, but the transfer of the serum iodide to the target cells was not efficient. After three months on vitamin C, the same test was repeated. The data revealed a normal profile of serum inorganic iodide levels. Her baseline serum inorganic iodide level increased from 0.016 mg/L to 0.42 mg/L, and she retained 50% of the iodine load, compared to 10% of the load prior to vitamin C supplementation.

To our knowledge, this was the first case report of a patient with evidence of a very defective retention mechanism for iodine who was studied with serial serum iodide levels prior to and following intervention. A combination of orthoiodosupplementation in amounts of iodine the patients could tolerate and administration of the antioxidant vitamin C via the oral route improved the performance of the iodine retention mechanism.

The milder forms of inefficient iodine retention and utilization, due either to inefficient cellular uptake of peripheral iodide or to inefficient oxidation and organification of intracellular iodide, will probably be overlooked until a more refined procedure is worked out to assess accurately the efficiency of the iodine transport and utilization mechanisms. Obviously, serial serum measurement of iodide would not be practical on a routine basis to evaluate patients with a high percentage of the iodine load excreted prior to supplementation. A simple test was needed for the combined assessment of whole body sufficiency for iodine with the assessment of the efficiency of the body to utilize peripheral iodide.

Assessing the Cellular Uptake and Utilization of Peripheral Iodide

Currently, radioiodide is used to assess the uptake of

Table 1—Some Clinical Data on the 6 Female Volunteers

SS#	Age	Height	Weight	SBP	DBP	COMMENT
1	48	67”	178 lbs	106	63	
2	47	62”	126 lbs	116	73	*CFS-FM
3	47	69”	170 lbs	123	81	
4	56	61”	148 lbs	132	79	**Mild Hypothyroidism
5	22	65”	125 lbs	122	88	
6	47	66”	130 lbs	130	89	

* Undiagnosed Fibromyalgial and chronic fatigue detected at the initial evaluation.
**Undiagnosed hypothyroidism detected at initial evaluation based on thyroid function tests.

iodide by the thyroid gland.[7] In conjunction with potassium perchlorate, radioiodide is used to evaluate the oxidation and organification of iodide by the thyroid gland. However, there is no available procedure to assess whole body iodine uptake and utilization. The salivary glands use a mechanism similar to the thyroid gland and the other target cells to concentrate peripheral iodide with subsequent oxidation and organification of iodide. Although the salivary glands can incorporate iodine in thyrosine to form mono- and di-iodothyrosine, they cannot couple iodinated thyrosine to form thyroid hormones.[1,3]

We previously reported a procedure to measure saliva and serum inorganic non-radioactive iodide levels 24 hours following ingestion of 50 mg of iodine in the form of Lugol tablets.[6] The saliva/serum iodide ratio measures the ability of the salivary glands to concentrate peripheral iodide. The assumption made is that the saliva/serum ratio of iodide is an index of iodide uptake and utilization by target cells throughout the whole body. Inefficient cellular uptake of iodide is associated with a low saliva/serum iodide ratio whereas inefficient organification of intracellular iodide with normal cellular iodide uptake is associated with an elevated ratio.[8] The normal range of saliva/serum ratios was 28-74 with a mean $\pm$ SD of 44.2$\pm$12.7 in 14 normal subjects. Low saliva/serum iodide ratios were observed in breast cancer patients with high serum bromide levels. Orthoiodosupplementation at 50-100 mg/day resulted in decreased serum bromide and increased saliva/serum ratio .[6]

Effect of the Daily Amounts of Lugol

After three months of supplementation with 50 mg iodine/iodide/day, most non-obese subjects with normal iodide retention mechanisms achieved whole body iodine sufficiency, defined as 90% or more of the iodine load excreted in the 24-hour urine collections and 24-hour post-load serum inorganic iodide level between 0.85 and 1.3 mg/L.[1,2] Adult subjects retained approximately 1.5 g of iodine when they reach sufficiency.[3]

We previously discussed the possibility of achieving whole body sufficiency for iodine in less than three months if greater amounts of iodine/iodide were ingested.[9] In balance studies of amiodarone, a sustained release form of iodine, whole body sufficiency for iodine was achieved at seven weeks when given orally at 112 mg iodine/day, and the patients retained 1.5 g of iodine at sufficiency. Based on these balance studies, we postulated that with a daily intake of Lugol tablets at 100 mg iodine, whole body sufficiency could be achieved in six weeks.

Quoting Abraham and Brownstein:[9] “The above comparison of the data obtained from amiodarone administration and orthoiodosupplementation is suggestive of an important role of inorganic iodine released from amiodarone in the therapeutic effect of this drug, and that whole body sufficiency for iodine is a requirement for optimal cardiac function. Since the amount of iodine used in the amiodarone study is twice the amount of iodine used in orthoiodosupplementation, the time required for whole body iodine sufficiency was only seven weeks for amiodarone and 12 weeks for orthoiodosupplementation. In order to achieve whole body sufficiency for iodine in six weeks using orthoiodosupplementation, the daily intake required would be 100 mg.”

To validate the above statement, one of us (JDF) recruited six female volunteers. This project was performed under contract at Flechas Family Practice and supported by a grant from Optimox Corporation. The

clinical data on these six subjects are displayed in Table 1. Following informed consent, the six volunteers received 100 mg of elemental iodine (two tablets of Iodoral® 50 mg daily) for six weeks. The iodine/iodide loading test was performed with two tablets of Iodoral® 50 mg for a total of 100 mg prior to; two weeks; four weeks; and six weeks following a daily ingestion of two tablets of Iodoral® (50 mg). At 24 hours post-load, serum and saliva samples were collected as previously described[7,8] to measure the saliva/serum inorganic iodide ratio. The subjects were asked to abstain from the iodine supplement for 48 hours prior to the loading test in order to prevent a carryover effect. Thyroid function tests were performed pre-intervention and after six weeks on Iodoral® at 100 mg/day. Pre-intervention thyroid function tests were normal in five of the subjects (Table 2). Volunteer #4 had mild hypothyroidism with a TSH level of 6.4 IU/L (normal: 0.35-5.5) and T4 value of 4.4 µg/dL (normal: 4.5-12).

Evidence for Inefficient Oxidation and Organification of Peripheral Iodide

One of the female volunteers (subject #2 in Table 1) suffered from fibromyalgia based on the American College of Rheumatology 1990 criteria[10] and also chronic fatigue. The diagnosis was made at the initial evaluation by one of us (JDF). This manuscript presents the data obtained in volunteer #2 pre- and post-intervention for markers of iodine metabolism and for the self-assessed severity of her symptoms. Data on the other five female volunteers will be published separately.

During the 6-week study, she reported significant improvement of her symptoms and she decided to continue orthoiodosupplementation at 50 mg iodine/day. Following 40 weeks at 50 mg/day, thyroid function tests were repeated again, and her daily intake was increased to 100 mg/day combined with 1,000 mg of vitamin B_3 (Inositol Hexanicotinate - Vitamin Research Product). The loading test and saliva/serum ratio of inorganic iodide was repeated after 40 weeks on Iodoral® at 50 mg/day and after eight weeks on Iodoral® at 100 mg/day combined with Vitamin B_3 at 1,000 mg/day. She was asked to score her symptoms on an analogue scale from 1 to 10; 1 being the worst she had ever felt, and 10 being the best (Table 3). From a pre-intervention score of 3 for myalgia, the score improved to 5 at six weeks post-Iodoral® 100 mg/day; 7 after 40 weeks at 50 mg iodine/day; and 6 following eight weeks on iodine 100 mg plus B_3 1,000 mg/day. However, the addition of vitamin B_3 resulted in a significant improvement of muscle pain post-exercise. The scores for this symptom were 2 pre-intervention; 6 after 46 weeks on iodine at 50-100 mg/day; and 9 after 8 weeks on 100 mg iodine plus 1,000 mg B_3/day. The score for fatigue was 2 pre-intervention and increased to 5 after six weeks at 100 mg iodine/day; to 8 after 40 weeks at 50 mg iodine/day; and to 9 following eight weeks on 100 mg iodine and 1,000 mg B_3/day.

Prior to intervention, the total score for the 24 symptoms was 121, that is 50% of the maximum overall wellbeing. Following six weeks at 100 mg iodine/day, her total score improved to reach 62% of maximum. Following 40 weeks at one tablet Iodoral® 50 mg/day, a marked improvement was observed, scoring 83% of the maximum. The addition of vitamin B_3 to iodine 100 mg/day for 8 weeks resulted in a further improvement with a total score of 87% of the maximum value. Out of 24 symptoms evaluated, the subject gave scores of 9 or 10 for 11 symptoms following 40 weeks on Iodoral® at 50-100 mg/day, compared to scores of 9 or 10 for 18 symptoms following 8 weeks on Iodoral® and vitamin B_3 1,000 mg/day. Overall, the addition of vitamin B_3

Table 2—Results of the Initial Thyroid Function Tests in the 6 Female Volunteers

SS#	TSH (IU/L)	T4 (µg/dl)	FT4 (ng/dl)	T3 (ng/dl)	FT3 (pg/ml)
1	2.4	7.4	1.1	83	2.5
2	4.0	7.7	1.09	120	3.2
3	1.8	6.6	1.19	118	3.6
4	6.4	4.4	0.83	81	2.6
5	1.1	6.9	1.05	109	2.9
6	4.0	7.2	0.99	119	3.3
Normal range	0.35-5.5	4.5-12.0	0.6-1.8	85-205	2.3-4.2

to orthoiodosupplementation resulted subjectively in a significant amelioration of her symptoms.

Pre-intervention TSH, T3, T4, free T3, and free T4 were within the normal range. TSH level increased above normal at six weeks of Iodoral® 100 mg/day. After 40 weeks at 50 mg/day, TSH decreased from 8.0 to 3.6 (Table 4). TPO antibodies were not detected.

The results of the loading tests and the saliva/serum iodide ratios are displayed in Table 5. Prior to supplementation with Iodoral®, the volunteer excreted 107% of the 100 mg ingested, and the original saliva/serum iodide ratio was elevated at 103, the normal range being 28-74.[6]

After two weeks ingesting 100 mg Iodoral®/day, the saliva/serum iodide ratios decreased to 43 and remained within the normal range during the rest of the study, fluctuating between 36 and 46. Pre-intervention, she excreted the total iodine load in the 24-hour urine collection. Following two weeks on Iodoral® at 100mg/day, a sharp drop in the percentage of the load excreted was observed — 18% of the 100 mg ingested. The percentage load excreted thereafter increased progressively to 66% at four weeks and to 88% at six weeks of supplementation with 100mg/day. She excreted 96% of the load after 40 weeks at 50 mg Iodoral®/day and 102% after eight weeks on 100 mg Iodoral® plus 1,000 mg B_3 daily.

Table 3—Self-Assessed Effects of Lugol Tablets (Iodoral®) at 50-100 mg/day with or without the Addition of Vitamin B_3 on Symptomatology in a Female Subject with Fibromyalgia and Chronic Fatigue

	Pre-Intervention	100 mg Iodoral®/day for 6 weeks	50 mg Iodoral®/day for 40 weeks	100 mg Iodoral® and 1,000 mg B_3 per day for 8 weeks
Muscle Pain	3	5	7	6
Pain w/Exercise	2	3	6	9
Joint pain	3	4	7	8
Joint swelling	2	4	8	9
Leg cramps	10	10	10	8
Restless legs	4	6	9	10
Stiffness	4	5	7	9
Fatigue	2	5	8	9
Insomnia	1	4	8	9
Brain fog	7	7	8	9
Dizziness	6	6	10	10
Headaches	9	9	4	6
Frequent urination	10	6	10	10
Burning urination	5	7	9	10
Abdomen cramping	7	7	9	10
Constipation	6	7	8	8
Nasal congestion	4	6	7	7
Anxiety	1	5	7	9
Irritability	8	9	10	10
Hostility	10	10	10	10
Depression	3	7	8	9
Panic attack	2	4	10	9
Flushing	6	6	10	10
Fever	6	6	10	10
Total Score	121	148	200	214
Percentage of Maximum Score	**50**	**62**	**83**	**87**

* Score from 1-10; 1 being the worst and 10 being the best; Maximum score for overall best response = 240

Discussion

Fibromyalgia is a common clinical syndrome of generalized musculoskeletal pain, stiffness, and chronic aching, characterized by reproducible tenderness on palpitation of specific anatomical sites, called tender points.[10] Fibromyalgia is nine times more common in middle-aged women (between the ages of 30 and 50 years) than in men. The association of fibromyalgia with chronic fatigue syndrome has been reported.[11] We previously proposed that fibromyalgia is caused by deficiencies of substances needed in ATP synthesis.[10] The role of iodine in ATP synthesis and in normal functions of striated muscles is presently unknown. In severely iodine-deficient individuals, the thyroid gland takes the lion's share (70-80%) of the total body iodine pool. However, in iodine-sufficient individuals, the maximum iodine content of the thyroid gland (50 mg) represents only 3% of the total body iodine of 1,500 mg at sufficiency.[3] Striated muscles contain 33% of the total body iodine in iodine sufficient individuals.[17]

The synthesis of ATP by intact respiring mitochondria requires the presence of oxygen, magnesium, ADP, inorganic phosphate, and the substrates from the metabolism of carbohydrates, lipids, and amino acids.[10] When all substances are present in optimal concentrations, the integrity of the mitochondrial membrane and the capacity of the enzymatic system in the respiratory chain become rate limiting. Defects in carbohydrate metabolism have been reported in fibromyalgia patients.[12,13] ATP levels are low in muscle tender points[14] and in the red blood cells of fibromyalgia patients.[15]

ATP is the universal currency of the energy used in biological systems to maintain an organism in a state that is far from thermodynamic equilibrium with the environment, that is far from death.[18] The active form of ATP is a complex of ATP with mainly magnesium, but also with manganese. In cases of manganese deficiency, magnesium can replace manganese. The turnover of ATP is extremely high. For example, a human at rest consumes one half of his/her weight of ATP daily. The synthesis of ATP from ADP plus a high energy phosphate group is called oxidative phosphorilation and is dependent on the electron flow through the electron transport chain via electron carriers. NADH and FAD H_2 are the major electron carriers in the synthesis of ATP. The B vitamins, niacin and riboflavin, are the precursors of the cofactors NADH and FAD H_2. These cofactors play an important role also in the oxidation and organification of iodide by generating hydrogen peroxide via the NADPH oxydase system.[1]

Iodine may play an important role in the protection of the cell and mitochondrial membranes against free radical damage by iodination of unsaturated lipids in the membranes.[16] The iodination of lipids of the cell membrane requires the oxidized form iodine, not iodide. The only plausible explanation for the elevated saliva/serum iodide ratio prior to intervention in the volunteer with fibromyalgia is a deficient oxidation and organification of intracellular iodide, combined with a normal cellular uptake of peripheral iodide.[7] Therefore, the enhancing effects of vitamin B_3 during iodine supplementation may be due to increased iodination of lipids and proteins involved in the synthesis of ATP and also in cell function and membrane integrity. The importance of magnesium and the vitamins B_2 and B_3 in ATP synthesis and overall well-being emphasizes the need for a complete nutritional approach[1] in the implementation of orthoiodosupplementation program for best results.We are planning to study patients with fibromyalgia following the same protocol but with a more extensive clinical evaluation pre- and post-supplementation.

Table 4—Results of Thyroid Function Tests Pre- and Post-Supplementation of 100 mg Iodine/day for 6 weeks and 50 mg iodine/day for 40 weeks in a Female Volunteer with Fibromyalgia and Chronic Fatigue

	Pre-Supplementation	After 6 weeks	After 46 weeks	Normal Range
TSH (IU/L)	4	8	3.6	0.35 – 5.5
T4 (µg/dl)	7.7	6.2	6.5	4.5 – 12.0
T3 (ng/dl)	120	98	120	85 – 205
FT4 (ng/dl)	1.1	0.86	0.9	0.6 – 1.76
FT3 (pg/ml)	3.2	2.2	2.5	2.3 – 4.2

Table 5—Effects of Iodine Supplementation and Vitamin B_3 on Some Parameters of Iodine Metabolism in a Female Subject with Fibromyalgia and Chronic Fatigue

	Percentage of Load Excreted*	Saliva/Serum Iodide Ratio **
Pre-Intervention	107	103
Iodoral® 100mg/day for 2 weeks	18	43
Iodoral® 100mg/day for 4 weeks	66	39
Iodoral® 100mg/day for 6 weeks	88	36
Iodoral® 50mg/day for 40 weeks	96	44
Iodoral® 100mg and B_3 1,000mg/day for 8 weeks	102	46

* Percent of 100mg iodine/iodide excreted in 24hr urine collection
** The ratio of inorganic non-radioactive iodide in mixed saliva over the serum level

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