

# Thyroid

## Patients diagnosed with fatigue experienced significantly increased energy levels after supplementing thyroid hormone

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**Structured Abstract:**

Patients diagnosed with fatigue experienced significantly increased energy levels after supplementing thyroid hormone

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*Objective:* This study sought to find if supplement preparations containing a combination of T3 and T4 are effective in alleviating symptoms of fatigue, and if so, also discover what type of preparation works best. Correlations between thyroid hormone parameters and changes in energy level ratings were also examined.

*Design:* A retrospective chart analysis was conducted on patients with low T3 and normal TSH levels, who were diagnosed with fatigue and prescribed thyroid hormone supplements (N=73). Energy levels were rated and serum thyroid hormone levels evaluated at 3-6 months (N=63) and 7-12 months (N=47).

*Main Outcome:* On average, patients experienced significantly increased energy levels, total T3 (TT3), free T3 (fT3), and free and total T3/T4 ratios by 7-12 months after taking thyroid hormone supplements. A significant correlation between fT3 and energy levels was present by 3-6 months ( $P=0.042$ ) and fT3/fT4 was correlated with energy levels throughout the study ( $P=0.047$ ). There was not a significant difference in fT3 or energy levels between patients taking Compound or Armour thyroid hormones.

*Conclusions:* Thyroid hormone supplements effectively regulate thyroid hormone parameters and increase energy levels by 7-12 months.

## **Patients diagnosed with fatigue experienced significantly increased energy levels after supplementing thyroid hormone**

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### **Introduction**

Thyroid hormones, triiodothyronine (T3) and thyroxine (T4), serve a wide variety of functions in the human body, controlling fetal development, growth, lipid and carbohydrate metabolism, heat production, and oxygen consumption, among others (1). Thyroid hormones also affect the body's cardiovascular, sympathetic, pulmonary, gastrointestinal, skeletal, and neuromuscular systems. The focus of this study is to examine the effect of thyroid hormone serum concentrations on energy levels in patients diagnosed with chronic fatigue.

The production of T3 and T4 is controlled by the hypothalamic-pituitary-thyroid axis (2). When low levels of T3 and T4 are sensed, the hypothalamus produces Thyroid-Hormone-Releasing Hormone (TRH), which signals the anterior pituitary to release Thyroid-Stimulating Hormone (TSH). The TSH then travels in the blood and eventually reaches the thyroid gland where it stimulates the release of T4 and T3. The thyroid gland normally secretes T4 in amount approximately 20-fold that of T3 (3). However, T4 is converted to T3 in the periphery by deiodinase enzymes. The affinity of T3 for nuclear thyroid hormone receptors is 10 to 15-fold that of T4. Therefore, the deiodinases convert T4 to T3, a more potent form at the cellular level. As a result, the state of an individual's thyroid hormone health not only resides on the level of signals to the thyroid gland and

thyroid hormone production, but also how effectively he or she converts the hormone to a more potent form and uses it at the cellular level.

A previous study by Davids, Witterick et al. (2006), studied the impact of T4 withdrawal by using a Quality of Life (QOL) survey in patients with residual/recurrent well-differentiated thyroid cancer who had total thyroidectomies (4). Their study found a “very small, though statistically significant, reduction...in the four domains of QOL defined by the QOL-thyroid survey from baseline values to 3 weeks after T4 withdrawal.” This study by Davids, Witterick et al. demonstrated the effect of thyroid hormone levels on fatigue and quality of life after inducing a hypothyroid state.

The patients in the present study initially had normal to low-normal thyroid hormone levels and were diagnosed with fatigue. Their thyroid hormone levels, along with energy level ratings, as assessed by the patients, were then tracked throughout the year as they received thyroid hormone supplementation. This study sought to answer three main questions: Is thyroid hormone supplementation effective in alleviating symptoms of fatigue? If so, what type of T3/T4 preparation does this the best, Compound or Armour thyroid hormones? Finally, what thyroid hormone parameters seem to change in correlation to changes in energy level ratings?

### **Materials and Methods**

A retrospective chart analysis was conducted to track levels of TSH, total T4 (TT4), free T4 (fT4), total T3 (TT3), and free T3 (fT3) from the time of the initial diagnosis of fatigue (73 subjects) to approximately 12 months after starting either Compound or Armour thyroid hormone supplementation. Serum levels of these hormones were measured by Radio Immuno Assay using Diagnostic Products

Corporation © “Coat-a-Count” kit and Iodine-125. Compounded thyroid hormone preparations consist of 10µg T3: 40µg T4 per 60mg (1 grain). Armour thyroid hormone preparations use a 1:4.22 ratio of T3:T4, from porcine sources which also contains some amount of thyroglobulin and mono-iodotyrosine. The commonly used medication Levothyroxine, which consists only of T4, was used in a few cases in this study. The prescribing of Armour and Compound thyroid hormone supplements was preferred over Levothyroxine because the patients in this study demonstrated low levels of conversion of T4 to T3. This decision to prescribe T3/T4 combination preparations is supported by the work of Bunevičius et al (1999) who found that patients who received T3/T4 combination supplements experienced significant mood and neuropsychological improvements compared to when they were using higher doses of thyroxine (5).

Patients included in this study had the diagnosis of fatigue, but were not taking any hormone replacement therapies other than thyroid hormone. The patients were 7 men and 67 women, who were 35 years old on average. They received various thyroid hormone medications at different dosages, and thyroid parameters were then recorded within 3-6 months (63 subjects) and once more between 7-12 months (47 subjects). At each of these visits, the patients were asked to rate their energy levels (1= low, 10 = high) and report heart palpitations or abnormal sleep, if present. The patients’ blood pressures and pulse readings were recorded. Scheffe tests were then performed on the data to evaluate significance.

## **Results**

On average, the patients in this study had significantly increased energy, TT3, and fT3 levels as well as significantly decreased levels of TSH by 7-12 months after starting

thyroid hormone supplementation. Free and Total T3/T4 ratios also significantly increased by 7-12 months.

#### *Energy Level Ratings*

Average energy level ratings increased throughout this study, as can be viewed on Figure 1. The increase in average energy ratings from the initial time period to 3-6 months was found to be significant ( $P=0.0001$ ), as was the increase from initial to 7-12 months ( $P=0.0001$ ).

#### *Total T3*

Figure 2 presents data for average TT3 levels throughout the study. The normal range for TT3 concentration is 100-190ng/dL. Therefore, the average initial levels of TT3 were on the low end of the normal range, but increased to the mid-normal range by 7-12 months. The increase in average TT3 levels from the initial time period to 7-12 months was found to be significant ( $P=0.003$ ).

#### *Free T3*

The normal range of fT3 is from 3-6pg/mL. Therefore, as seen in Figure 3, at the initial time period the average patient in this study was borderline-deficient in fT3, but by 7-12 months average fT3 levels had significantly increased to within the normal range ( $P=0.001$ ).

#### *Energy and Free T3*

Because fT3 is the form of thyroid hormone that is most available and active at the cellular level, the effect of fT3 levels on energy level ratings was analyzed. By 3-6 months, the correlation between fT3 levels and energy levels was significant ( $P=0.042$ ).

However, by 7-12 months the correlation between fT3 and energy levels was not found to be significant.

Interestingly enough, the change in energy level ratings from the initial time period to 3-6 months was indeed correlated to the change in fT3 during that same time period ( $P=0.012$ ). Yet by 7-12 months this correlation was no longer found to be significant.

#### *TT3/TT4 Ratios*

The ratio of T3 to T4 represents not only how thyroid hormone supplementation had a direct effect on serum levels of each hormone, but also the ratio depicts the work of deiodinases in the body's periphery. Changes from the initial T3/T4 ratio could suggest that deiodinases are working at a different rate after supplementation. The normal ratio of TT3/TT4 is approximately 0.0175ug/dL (6). The ratio of TT3/TT4 increased significantly from the initial time period to 3-6 months ( $P=0.003$ ) and the initial time period to 7-12 months ( $P=0.002$ ). By 3-6 months and 7-12 months, the average TT3/TT4 ratios were above what is considered the normal value. However the TT3/TT4 ratio did not change significantly between 3-6 and 7-12 months. This trend can be seen in Figure 4.

#### *fT3/fT4 Ratios*

The normal value for fT3/fT4 ratio is 0.2625ug/dL (6). Figure 5 shows trends in the fT3/fT4 ratio which changed significantly from the initial time to 7-12 months ( $P=0.014$ ). Once again, the average fT3/fT4 ratios were above what is considered the normal value by 3-6 and 7-12 months.

### *fT3/fT4 Ratios and Energy*

Using all of the fT3/fT4 data from the study along with all of the energy ratings, a significant correlation was found ( $P=0.047$ ) meaning as the fT3/fT4 ratio increased there seemed to be a correlated increase in energy level ratings. However, when this data was analyzed just within the initial, 3-6 month, or 7-12 month time periods, a significant correlation between fT3/fT4 ratios and energy levels could not be detected.

### *TSH*

The normal range for TSH levels is 0.54-3.7uIU/mL. As can be seen in Figure 6, during this study average TSH levels went from mid-normal range to low-normal range by 7-12 months after receiving thyroid hormone supplementation. Average TSH levels decreased significantly from the initial visit to 3-6 months ( $P=0.0001$ ), and from the initial visit to 7-12 months ( $P=0.0001$ ), but did not change significantly from 3-6 months to 7-12 months.

### *Total T4*

Initially, the average TT4 serum concentration was  $7.678 \pm 0.252$ ug/dL, which then decreased to  $7.080 \pm 0.201$ ug/dL by 3-6 months and increased to  $7.565 \pm 0.262$ ug/dL by 7-12 months after receiving thyroid hormone supplementation. The normal range for TT4 serum concentrations is 5-12ug/dL. Average levels of TT4 did not change significantly throughout this study, but remained within the normal range.

### *Free T4*

The normal range for fT4 is 0.8-2.5ng/dL. Initially, average fT4 levels were  $1.299 \pm 0.060$ ng/dL, which then were found to be  $1.244 \pm 0.048$ ng/dL by 3-6 months and  $1.385 \pm 0.093$ ng/dL by 7-12 months after thyroid hormone supplementation. Average

levels of fT4 were within the normal range and did not change significantly throughout the study.

#### *Blood Pressure, Pulse, and Weight*

On average, there were no significant changes in blood pressure, pulse, or weight measurements throughout this study. The average blood pressure measurement at the initial time period was 123/77±3/2mmHg, whereas by 3-6 months it was 122/75±3/2mmHg, and by 7-12 months it was 127/76±3/2mmHg. The average pulse measurement at the initial time period was 80±3bpm, by 3-6 months it was 82±2bpm, and by 7-12 months it was 84±2bpm. At the initial time period, the average patient weighed 191±2lbs, and at 3-6 months and 7-12 months the average weight was 194±2lbs and 195±2lbs respectively.

#### *Sleep*

Reports of abnormal sleep: excessive daytime sleepiness or insomnia, decreased throughout the study with a significance value of P=0.008, as can be seen in Figure 7.

#### *Heart Palpitations*

However, reports of heart palpitations did not change significantly throughout the study. Initially 8.5% of patients reported experiencing heart palpitations as opposed to 10.9% and 2.7% by 3-6 months and 7-12 months respectively.

#### *Types of Thyroid Supplements and Dosages*

Overall, two main types of thyroid medications were utilized in this study, Armour and Compound thyroid hormones. One should take notice that some people switched the type of supplement they were taking during the study and almost all patients increased their dosage (mg/day). The average dosage of Armour by 3-6 months was

74mg/day (range= 20-180mg/day), at which time the average dosage of Compound was 90mg/day (range=15-240mg/day). By 7-12 months the average dosage of Armour was 142mg/day (range= 30-360mg/day) and the average dosage of Compound was 145mg/day (range=15-300mg/day).

The effect of Armour and Compound thyroid hormones on fT3 levels was not significantly different. By 3-6 months the average fT3 level of those patients using Armour (N=18) was  $3.169 \pm 0.252$  pg/mL whereas those patients using Compound (N=41) had an average fT3 level of  $3.514 \pm 0.226$  pg/mL. Likewise, by 7-12 months patients using Armour (N=22) had an average fT3 level of  $3.983 \pm 0.365$  pg/mL and those patients using Compound (N=24) had an average fT3 level of  $3.823 \pm 0.299$  pg/mL.

In the same way, neither drug had an effect on energy level ratings that was significantly different from the other. Those patients using Armour had average energy level ratings of  $7.913 \pm 0.015$  by 3-6 months and  $7.490 \pm 0.006$  by 7-12 months. Patients taking Compound had average energy level ratings of  $7.192 \pm 0.003$  by 3-6 months and  $7.045 \pm 0.002$  by 7-12 months.

However, dosages of Compound and Armour thyroid hormone supplements affected fT3/fT4 ratios differently by 3-6 months. Using the 3-6 month data, as milligram dosage of Compound increased there was a significant increase in fT3/fT4 ( $P=0.004$ ). However, the correlation between Armour dosage and fT3/fT4 was not found to be significant. Yet, using the data collected at 7-12 months, neither drug's dosage had significant correlations to fT3/fT4 ratios.

*Discussion*

Patients who were diagnosed with fatigue and had low to low-normal thyroid hormone parameters significantly improved from using thyroid hormone supplements. Their rise in energy was accompanied by significant increases in TT3, fT3, TT3/TT4, and fT3/fT4 within a year of beginning thyroid hormone supplementation. Energy levels were found to be significantly correlated to fT3/fT4 ratios, using all the data from the study, disregarding time period.

In this study, it was not surprising that as thyroid hormone levels increased, TSH levels decreased. From the initial time period, TSH levels significantly decreased by 3-6 months and 7-12 months. It was also found that reports of abnormal sleep became significantly less frequent throughout the study, most likely contributing to increased energy level ratings by 3-6 and 7-12 months. Interestingly enough, Armour and Compound thyroid supplements had the same effect on fT3 and energy levels. Yet by 3-6 months, dosages of Compound were significantly correlated to fT3/fT4 ratios whereas Armour dosages were not.

From these results, one could reason that T3 plays an important role in increasing energy levels and thyroid hormone supplementation successfully aided in this process. The action of T3 is not only at the nuclear level, increasing the transcription of proteins involved in metabolism, but also at the mitochondrial level (7). St. Germain reports that T3 has direct influences on mitochondrial gene expression, which increases energy production within cells.

Because T3/T4 ratios increased with Compound and Armour thyroid hormone supplementations, one could also reason that not only does the supplementation directly

increase serum T3, but it also stimulates deiodinases to work at a higher level, therefore increasing the T3/T4 ratio. Thyroid hormone supplementation could increase the conversion of T4 to T3 just by making T4 more available to deiodinases. This hypothesis could also explain why the rate of change in T3/T4 and energy level seemed to decrease from 3-6 to 7-12 months. As, more deiodinases were stimulated over time, some down regulation of the deiodinases could have occurred.

There are three known types of deiodinases in the body, D1, D2, and D3 (8). D1 iso-enzymes are found in the liver, kidney, and thyroid and produce T3 and reverse T3 (rT3), a byproduct for clearance from the body. D2 iso-enzymes are found in the brain, anterior pituitary, placenta, thyroid, and skeletal muscle and only produce T3. D3 iso-enzymes are found in the brain, placenta, pregnant uterus, and fetus and exclusively produce rT3. Bianco (2004) reported that all of the deiodinases contain the same structural motif at the active site which requires selenium for its action (9). He also states that D2 iso-enzymes are most rapid in their conversion of T4 to T3. Yet St.Germain reports that while D1 enzymes are relatively inefficient in their action, they contribute a significant proportion of T3 because of their distribution throughout the liver and kidneys (10).

Interestingly enough, in a D2 knock-out study, mice experienced impaired hearing, thermogenesis, and neurocognition along with high TSH levels and reduced T4 feedback (10). However in a D1 knock-out study performed by the same researchers, mice had slightly elevated T4 levels, but T3 and TSH levels were unaltered. This experiment seemed to suggest that T3 production and degradation could have been impaired. These D1 knock-out mice were viable with normal growth and fertility. The

results of the knock-out studies could be applicable to the patients included in the present study. The patients in the present study at the initial time period had TSH and T4 levels well within the normal range, yet T3 levels that were borderline low. These results do not necessarily support faulty thyroid gland function, but instead suggest deiodinase hindrances.

Many commonly used medications can hinder the action of deiodinases such as glucocorticoids, propranolol, amiodarone, and clomipramine among others (11). The patients in this study were not screened for these medications. In addition, Sarne (2004) reported that cadmium, fasting, and low carbohydrate diets also reduce conversion of T4 to T3 (12).

The impact of selenium levels on thyroid health is still debatable. Sarne speculates that selenium deficiencies could predispose the thyroid to oxidative stress, because selenium is used as a cofactor by important enzymes that protect against free radicals (12). Yet a study by St.Germain (2001) showed that in experimental animals, selenium deprivation lead to a decrease in D1 translation in the liver and kidney, but selenium was better preserved in the thyroid gland and brain (13). However, Kohrle found that normal selenium levels and deiodinase expression are maintained throughout most of the body during a selenium deficiency, providing adequate T3 levels (14). Nonetheless, selenium deficiencies are highly unlikely because the element is contained in plants, meat, seafood, bread, and nuts as common sources (15). However selenium deficiencies could occur if there is low selenium in the soil where the plants are grown or food animals are grazing. Also severe gastrointestinal disorders could obstruct absorption of selenium from the diet. There are many possible causes of reduced

deiodinase efficiency in the patients included in the study, but more research would have to be performed to find the definite source of deiodinase hindrance.

It is important to recognize that energy level ratings are subjective measurements. In addition, patients could inflate energy level ratings at the 3-6 month office visit because they easily remember how they initially felt before thyroid hormone treatment. Yet by the 7-12 month time period, patients could have underestimated their energy levels relative to their initial diagnosis with fatigue. In future studies, it would be helpful to use more standard measurements of energy levels such as the previously mentioned Quality of Life survey used in the Davids, Witterick et al study.

Few men were used as subjects, so this study's results may not be as applicable to the male sex. Data analysis was not conducted in men and women separately and some discrepancies in data between the sexes could be present. This scenario is likely because estrogens tend to increase concentrations of thyroid hormone binding globulin, while androgens tend to decrease them (16). Perhaps if the men had been excluded from this study some of the correlations in the data could have been more significant. In the future, if more men could be included in a study like this one, researchers could examine the difference in thyroid hormone parameters and energy levels between the sexes.

When supplementing thyroid hormone levels, it is important for physicians to monitor patients for serious side effects. The side effects of thyroid hormone supplementation are characteristic of hyperthyroidism including "chest pain, increased pulse rate, palpitations, excessive sweating, heat intolerance, and nervousness" (17). In addition, Bauer et al (2001) found that women over the age of 65 who had low TSH levels, because of higher than normal levels of thyroid hormone, were more likely to

suffer from vertebral and hip fractures than women with normal TSH levels (18). Therefore, there is concern that supplementing thyroid hormone to excess may increase one's chance of developing osteoporosis later in life. As a preventative measure, physicians should also monitor patients' bone densities.

Measuring TSH levels is a common method used to screen for thyroid dysfunction. Yet, as we revealed in this study, what happens in the hypothalamic-pituitary-thyroid axis at the level of the pituitary, where D2 iso-enzymes are present, might not be indicative of thyroid hormone production or the ability of the peripheral D1 iso-enzymes to convert T4 to the more active form. It is possible that these patients' intrapituitary-Type 2 deiodinases functioned well, causing TSH levels to be normal, so that TSH levels did not reflect peripheral deiodinase activity. The patients in this study did not have primary hypothyroidism, but they experienced deiodinase hindrances in the periphery causing a "hypothyroid-like" state at the cellular level which resulted in fatigue. In addition, in future research, it would be interesting to measure the T4 to T3 turnover in these types of patients to definitively find out if the problem truly does lie in the deiodinases. If these patients do have deiodinase hindrances, it would be important to identify what is actually inhibiting their action. Whether the main reason the patients in this study initially experienced fatigue is genetic, environmental, or a mixture of both, it will be important in future research to identify the cause(s) to gain understanding into thyroid hormone health, and aid in treating these patients.

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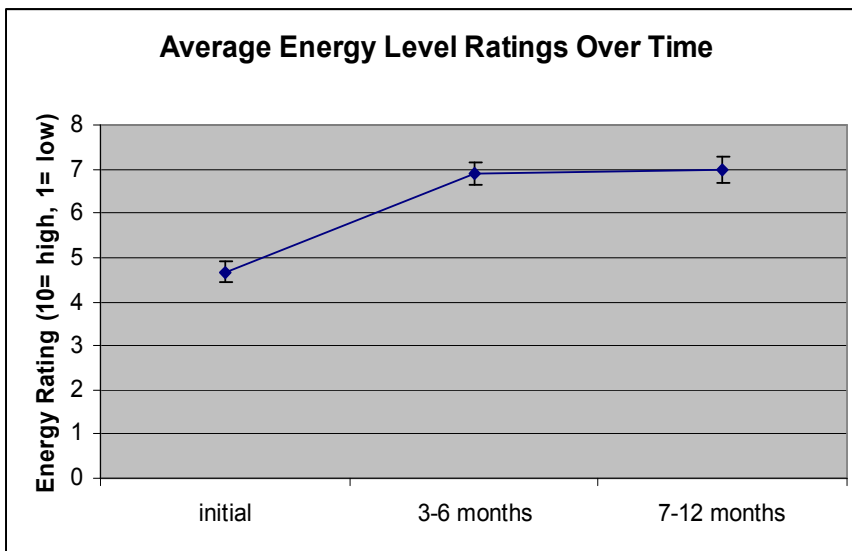
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For Peer Review

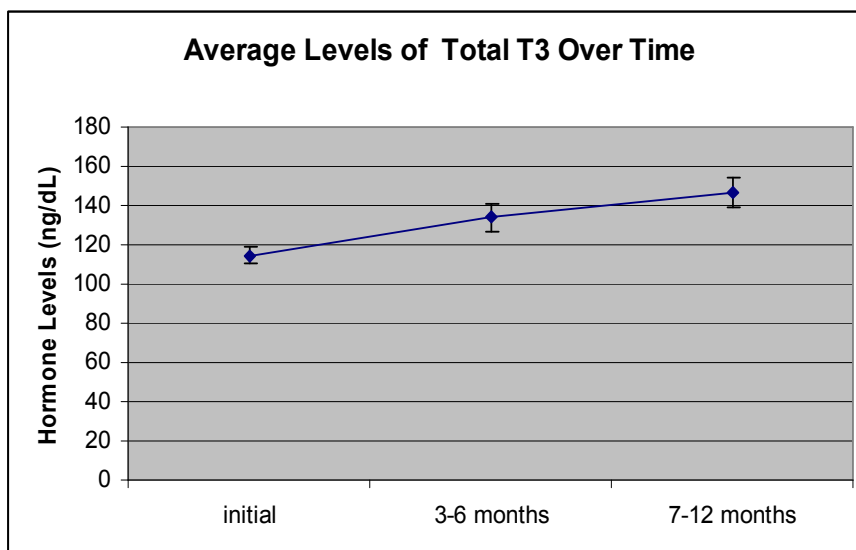
Figures

Figure 1



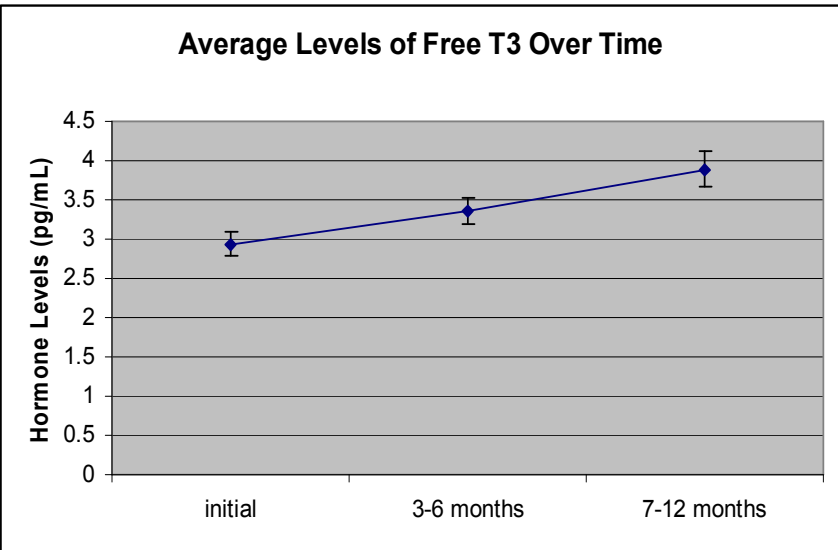
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Figure 2



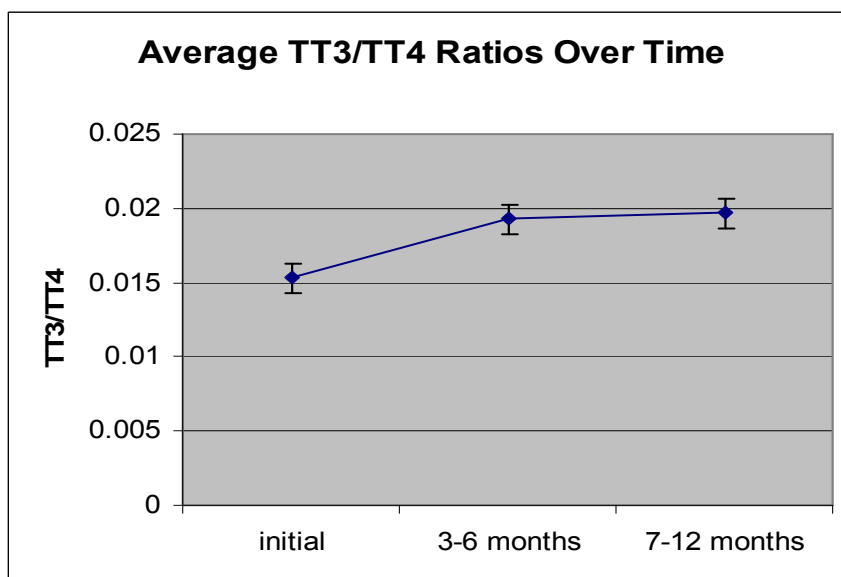
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Figure 3



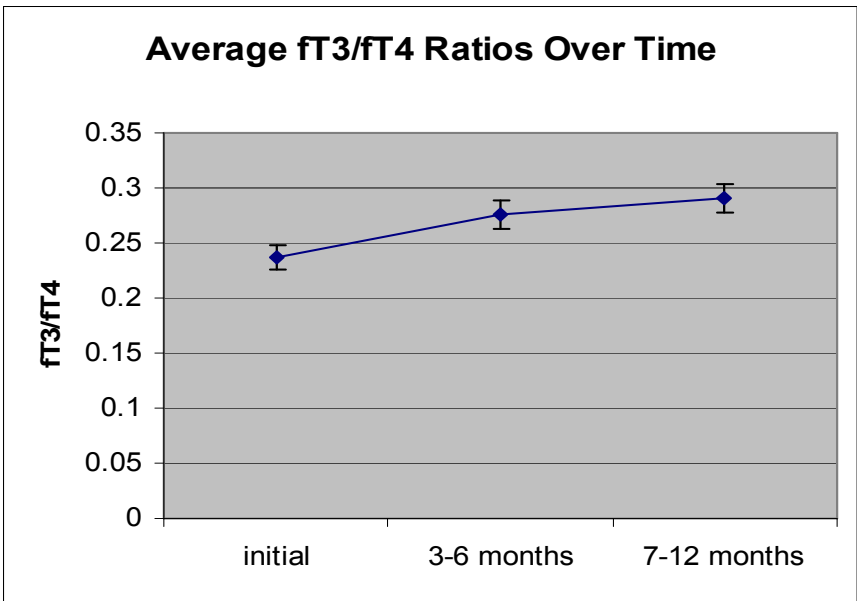
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Figure 4



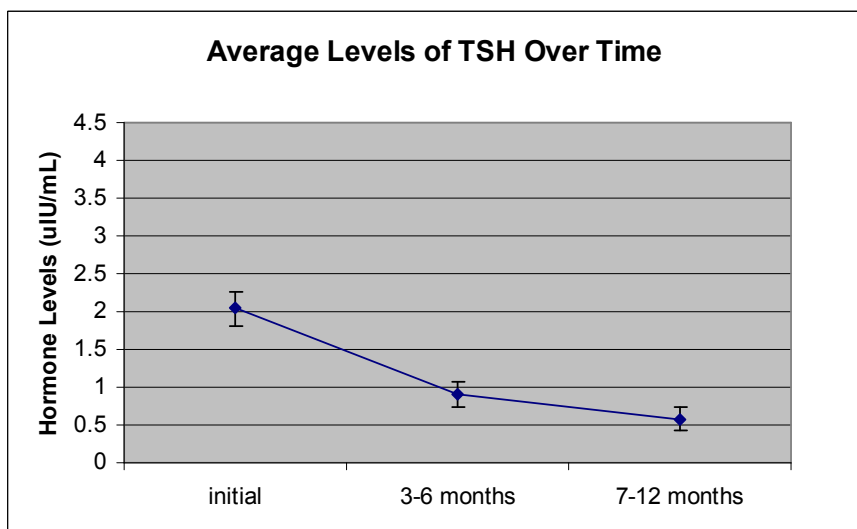
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Figure 5



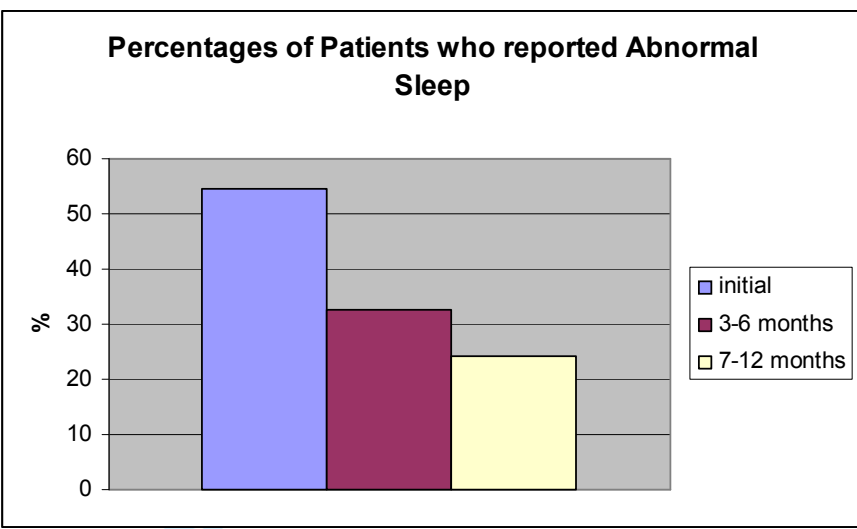
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Figure 6



Peer Review

Figure 7



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**Legends**

**FIG. 1.** Average energy ratings over time with thyroid hormone supplementation after the initial time period. The average energy level rating was initially  $4.671 \pm 0.222$  ( $\pm$ SEM),  $6.891 \pm 0.251$  by 3-6 months, and  $6.976 \pm 0.307$  by 7-12 months.

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**FIG. 2.** Average levels of TT3 over time after beginning thyroid hormone supplementation during the initial time period. Average TT3 levels were initially  $114.749 \pm 4.550$  ng/dL, which increased to  $133.823 \pm 7.209$  ng/dL by 3-6 months, and  $146.535 \pm 7.714$  ng/dL by 7-12 months.

For Peer Review

**FIG. 3.** Average levels of fT3 over time after receiving thyroid hormone supplementation during the initial time period. Average fT3 levels were initially  $2.938 \pm 0.146$  pg/mL,  $3.359 \pm 0.169$  pg/mL by 3-6 months, and  $3.889 \pm 0.227$  pg/mL by 7-12 months.

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**FIG. 4.** Average TT3/TT4 ratios over time after thyroid hormone supplementation during the initial time period. The initial TT3/TT4 ratio was  $0.0153 \pm 0.001$  which then increased to  $0.0193 \pm 0.001$  by 3-6 months and  $0.0197 \pm 0.001$  by 7-12 months.

For Peer Review

**FIG. 5.** Average fT3/fT4 ratios over time after thyroid hormone supplementation during the initial time period. The initial fT3/fT4 ratio was  $0.238 \pm 0.011$ , which increased to  $0.276 \pm 0.013$  by 3-6 months and  $0.291 \pm 0.013$  by 7-12 months.

For Peer Review

**FIG. 6.** Average levels of TSH over time after being supplemented with thyroid hormone following the initial visit. Initially the mean serum concentration of TSH was  $2.04 \pm 0.219 \text{ uIU/mL}$  which then decreased to  $0.910 \pm 0.168 \text{ uIU/mL}$  by 3-6 months and  $0.580 \pm 0.157 \text{ uIU/mL}$  by 7-12 months.

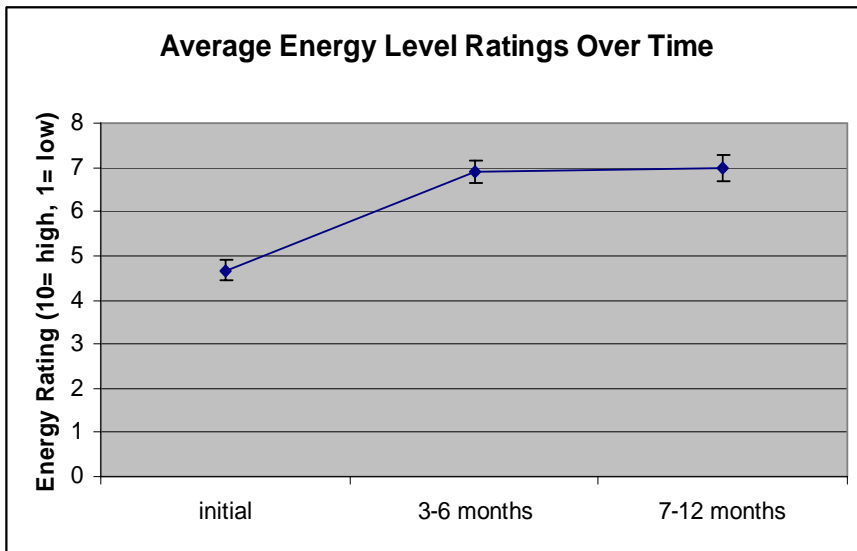
For Peer Review

**FIG. 7.** Percentages of patients who reported abnormal sleep after being treated with thyroid hormone supplements after the initial time period. Initially 54.4% of patients reported abnormal sleep compared to 32.7% and 24.3% by 3-6 months and 7-12 months, respectively.

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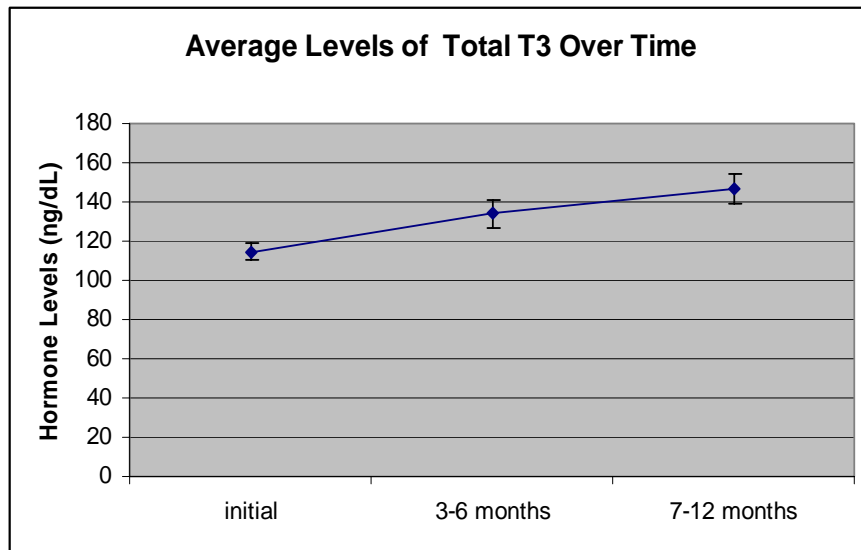
**Figures**

Figure 1



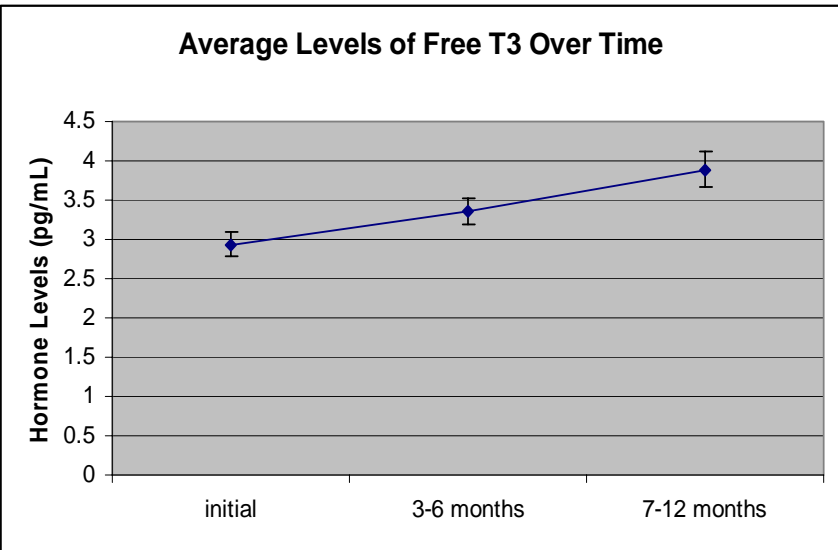
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Figure 2



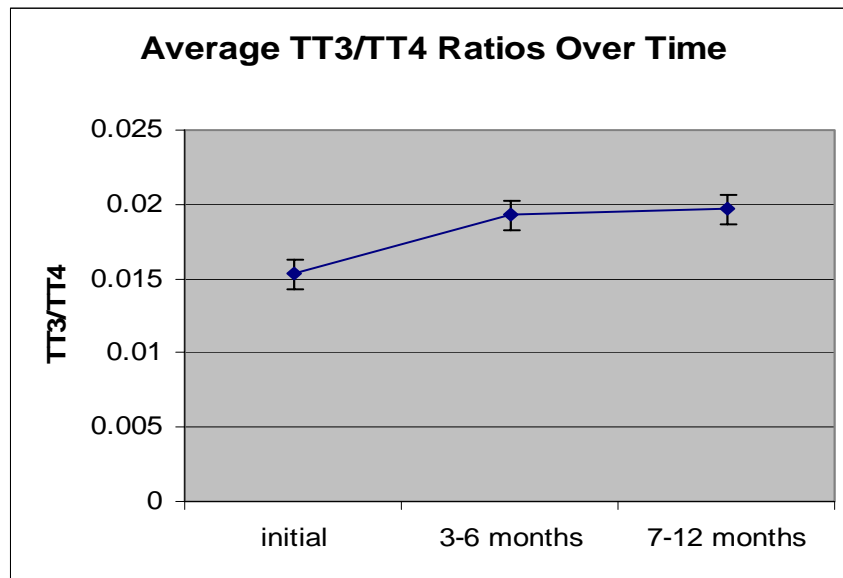
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Figure 3



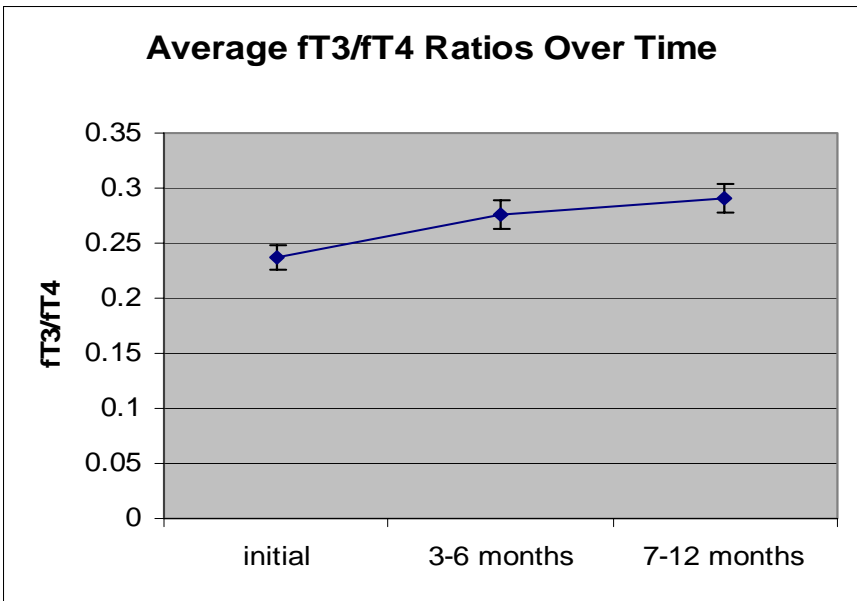
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Figure 4



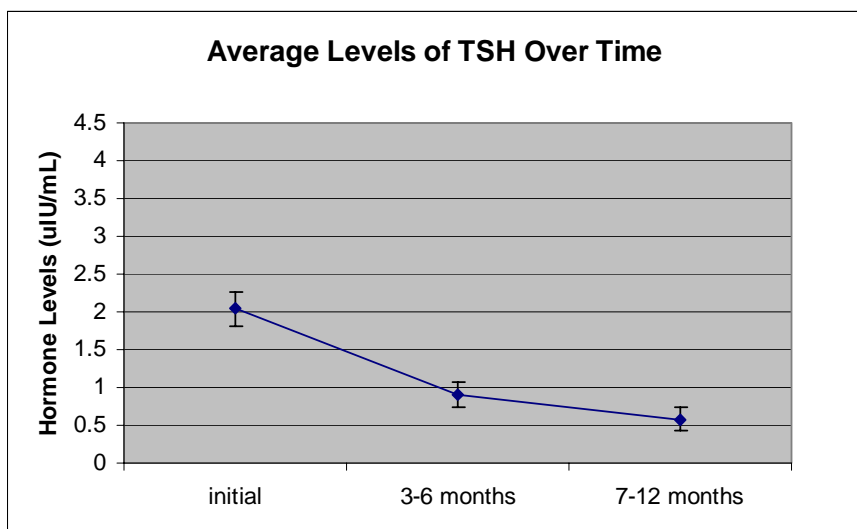
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Figure 5



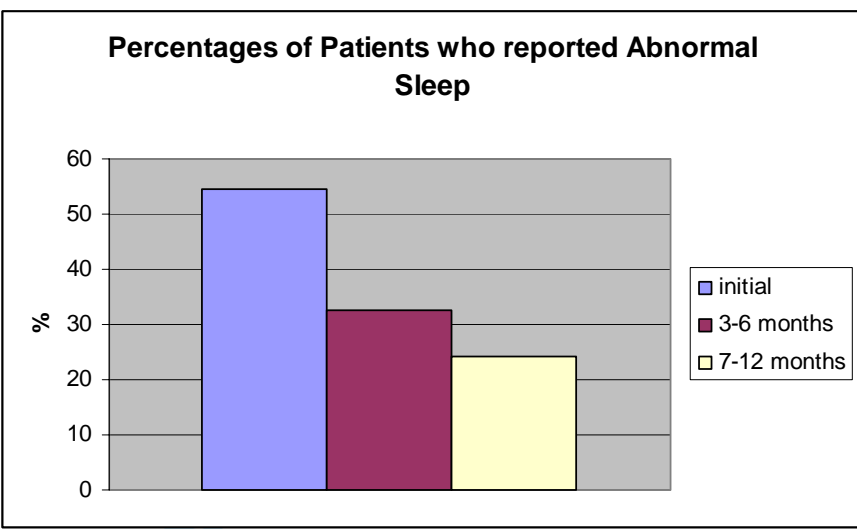
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Figure 6



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Figure 7



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**Legends**

**FIG. 1.** Average energy ratings over time with thyroid hormone supplementation after the initial time period. The average energy level rating was initially  $4.671 \pm 0.222$  ( $\pm$ SEM),  $6.891 \pm 0.251$  by 3-6 months, and  $6.976 \pm 0.307$  by 7-12 months.

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**FIG. 2.** Average levels of TT3 over time after beginning thyroid hormone supplementation during the initial time period. Average TT3 levels were initially  $114.749 \pm 4.550$  ng/dL, which increased to  $133.823 \pm 7.209$  ng/dL by 3-6 months, and  $146.535 \pm 7.714$  ng/dL by 7-12 months.

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