Comparison of Cynomel and Hypo Support Formula: Their Physiological Effects

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Abstract. This study compared the clinical effectiveness of a dietary organic natural desiccated thyroid product (Hypo Support Formula or HSF), to that of a synthetic T_3 product (Cynomel). **Methods:** A single-subject two-phase repeated-measures study design was used. Comparisons were made between two study phases: the Cynomel phase followed by the HSF phase. Clinical evaluations included four basal measures: metabolic rate (BMR), heart rate (BHR), axillary temperature (BAT), and blood pressure (BBP). Other measures were body composition, mean hypothyroid symptoms intensity, Zung's depression scale, and pain distribution. Study subjects were a female stable on 87.5 mcg of Cynomel for two years, and a male stable on 150 mcg of Cytomel or Cynomel for 24 years. In the Cynomel phase, the female remained on Cynomel through 10 evaluations on different days; the male subject remained on Cynomel through 12 evaluations. After the transition from Cynomel to HSF, she then had 10 more evaluations; the male subject had 12 more evaluations. **Results:** The female's temperature was the same in both phases. In the HSF phase, her heart rate was significantly lower and her basal metabolic rate significantly higher. A noteworthy improvement for her in the HSF phase was virtual elimination of lifelong, severe hyperhidrosis. This has persisted now for 3.5 months. The male subject's BMR and BAT were not different in the two phases. However, during the HSF phase, he had a significantly lower heart rate, diastolic blood pressure, pain distribution, pain intensity, and mean intensity of hypothyroid symptoms. **Conclusions:** Both Cynomel and HSF were effective. HSF, however, appears to have provided additional improvements. The physiological equivalency of HSF to Cynomel for the female was calculated to be 1 capsule to 14.4 mcg and for the male was 1 capsule to 15 mcg.

Key Words. Basal metabolic rate ● Basal temperature ● Cynomel ● Cytomel ● Desiccated thyroid ● Hypo Support Formula ● RLC Labs ● Triiodothyronine

Introduction

Dietary natural desiccated thyroid products have been available for purchase without a prescription in the U.S. since the 1994 Dietary Supplemental Health and Education Act.[1] The Act has enabled U.S. citizens to exercise considerable freedom in their choices of health care products, including dietary desiccated thyroid. This freedom has been extremely important to hypothyroid patients whose health has been adversely affected by the current conventional medical dictate that T_4 replacement is the only legitimate approach to thyroid hormone therapy.[25]

Despite the widespread use of dietary desiccated thyroid products, no studies appear to have been published in which researchers evaluated the efficacy of such products. The purpose of this study was to determine: (1) whether an organic dietary desiccated thyroid product (Hypo Support Formula[2] or HSF) was clinically effective compared to a synthetic T_3 product (Cynomel[3]); (2) the clinical equivalence of HSF to Cynomel; and (3) differences in clinical measurements while subjects took only HSF and only Cynomel.

Methods

Subjects. Two subjects took part in the study. One was a 49-year-old female with hypothyroidism, the other a 62-year-old male with partial peripheral resistance to thyroid hormone.

In 2006, the female subject had symptoms characteristic of hypothyroidism, a low basal body temperature, and the relaxation phase of her Achilles reflex was visibly slow. Because of her symptoms, she wanted to undergo a trial of thyroid hormone therapy.

In 2006, when she was 47-years-old, she underwent two basal metabolic rate (BMR) measurements. At the time, she was not taking exogenous thyroid hormone. On June 18, 2006, her BMR was 550 kcal/day. Her lean body weight (measured with 4-

electrode bioelectrical impedance) was high enough so that her predicted BMR (using the Sterling-Pasmore equation) was 807 kcal/day. Her measured BMR, then, was 32% lower than her BMR predicted by her lean body weight.

For her sex, age, height, and weight (using the Mifflin-St.Joer equation), her predicted BMR was 1115 kcal/day. Her measured BMR, therefore, was 51% lower than her predicted BMR using her sex, age, height, and weight.

The 308 kcal/day difference between the BMR predicted by her lean body weight and that predicted by her sex, age, height, and weight is unusual. In this case, the difference results from the subject having lower lean body weight than the average female of her age, height, and weight. Her lower lean body weight is evident in her slender body form, a physical feature she shares with a monozygotic sister.

The female subject's second BMR measurement was on September 29, 2006. Her measured BMR was 677 kcal/day. Her predicted BMR based on her lean body weight was 949 kcal/day. This BMR was 29% lower than that the BMR predicted by her lean body weight. The BMR predicted from her sex, age, height, and weight was 1120 kcal/day. Her measured BMR, then, was 40% lower than that predicted by her sex, age, height, and weight.

In metabolic clinical practice, if a patient has a low BMR and low lean body weight, it is appropriate for the patient to undergo a regimen of resistance exercise to increase his or her muscle and connective tissue mass. This is important because lean body weight is the strongest determinant of the BMR.[17-21] To determine whether resistance exercise, or more resistance exercise, is necessary for a patient, the lean body weight should be measured. The clinician should use the measurement in an equation such as the Sterling-Pasmore equation to obtain the predicted BMR by lean body weight. The patient's BMR should be measured with indirect calorimetry, and a calculation made to determine what percentage of the measure BMR is of the predicted BMR.

When this procedure was done for the female subject in 2006, she had enough lean body weight to have measured BMRs 29% higher on the first occasion and 32% higher on the second. It was clear from this outcome that low lean body weight was not the major mechanism of her low BMR, although perhaps a minor one. This was consistent with the fact that typically, she did resistance training at a gym seven days per week. She also was not restricting her calorie intake, which could have potentially lowered her measured BMR.[22] Because of these findings, she opted to increase her measured BMR by using Cynomel, starting with a single daily dose of 25 ì g.

The other subject, a 62-year-old male, had been stable on his optimal dose of synthetic T_3 for 23 years. He started treatment with Cytomel but for 8 years preceding this study, he had used Cynomel. His symptoms that were relieved by synthetic T_3 were intermittent suicidal depression, persistent cognitive dysfunction, and chronic pain referred from myofascial trigger points. After Synthroid and Jones desiccated thyroid failed to relieve his symptoms, Cytomel effectively relieved them. His effective dosage was 150 mcg.

His BMR, measured many times over the previous 5 years, was close to the predicted BMR by equations using both his lean body weight and his sex, age, height, and weight. As the Cynomel phase in Figure 2 shows, his measured BMR was closer to the BMR predicted by his lean body weight (green line with solid dots as predicted BMRs) and further away from the BMR predicted by his sex, age, height, and weight (brown line with square data points and yellow line with triangular data points).

Procedures. Upon waking from sleep and when comfortable with the temperature and bedding, each subject measured his or her basal metabolic rate with a hand-held indirect calorimeter (the MedGem®, Healthetech, Golden, Colorado). The subject then measured his or her basal axillary temperature of the left armpit with an electronic thermometer that gave a digital reading (Walgreens model VT-820W5T). The electronic thermometers were compared in a concurrent study to measurements with Galinstan-in-glass thermometers (Geratherm Medical AG, Fahrenheitstraße 1, D-98716 Geschwenda), which is equivalent to mercury thermometers. Measurements with the electronic and Galinstan thermometers strongly correlated and were highly consistent.[7] Each subject then took his or her basal pulse rate and blood pressure with an electronic sphygmomanometer (Omron Healthcare, Inc., Model HEM711-ACN, Bannockburn, IL.).

After arising from bed, the subjects measured the height and weight on a balance beam scale (Healthometer, Continental Scale Corp., Bridgeview, IL), drank approximately two 8-ounce glasses of water, and then measured their body composition by 4-electrode bioelectrical impedance (Biodynamics® Model 310, Seattle, WA).

Next the subjects filled out three sets of evaluation forms: (1) a questionnaire with visual analog scales for 12 major symptoms characteristic of

hypothyroidism;[6] (2) Zung's Self-rating Depression Scale (W.W.K. Zung © 1991); and (3) body drawings with 36 divisions for shading in the distribution of pain since the previous evaluation.[11]

After each evaluation, all measurements and scores were tabulated in an Excel spreadsheet in preparation for statistical analyses.

Study Design. An intrasubject replication study design (also termed a two-phase single-subject repeated measures design) was used.[8-16] The study actually involved three phases with repeated measurements in each, but comparisons were made only of the data from the first, the Cynomel phase, and the second, the HSF phase. The third phase was sandwiched between the Cynomel and the HSF phases. It was a transition phase during which the subjects progressively decreased their daily Cynomel intake and increased their HSF intake until their clinical measures were either acceptable or the same as in the Cynomel phase. For the female, the transition phase included 10 evaluations between November 8 and 24; for the male subject, the phase included 14 evaluations between November 1 and 25.

All phases occurred between October and December, 2008. In the first phase (the Cynomel-only phase), the female subject underwent 10 sets of measurements on different mornings between October 9 and November 5. The male subject underwent 12 sets of measurements between October 9 and 26. The mornings that the subjects chose to undergo evaluations were selected for convenience.

The subjects, both of whom were stable on their daily dosages of Cynomel[3], continued those dosages until all first-phase measurements were completed. The female subject's dose was 87.5 mcg and the male subject's dose was 150 mcg. Each took Cynomel on an empty stomach once per day.

As soon as each subject had stopped Cynomel altogether and was taking only HSF, the HSF phase began. During this phase, each subject underwent the same number of evaluations as in the Cynomel phase. The female subject underwent 10 evaluations between December 2 and 18, and the male subject 12 evaluations between November 26 and December 27.

After the subjects completed the HSF phase, they had electrocardiograms (ECGs).[15] The tracings were compared with ECGs performed before the study began. When the study began, the subjects filled out a sheet of visual analog scales containing common symptoms of thyrotoxicosis. The scores on the sheets were compared to subsequent sheets as indicators of possible symptoms of thyrotoxicosis.

Statistical Analyses. The t-test was used to test for differences between mean measurements. Levene's test for equality of variances was used to test for differences in the variance of measurements between the Cynomel and HSF phases. Bloom's probability table was used to statistically analyze any differences between Cynomel and HSF phases by the trend line method. The level of significance was set at $p \leq 0.05$. Statistical analyses were performed with SPSS for Windows® (SPSS, Inc., Chicago, IL), VassarStats: Website for Statistical Computation, and Microsoft® Excel 2002.

Results

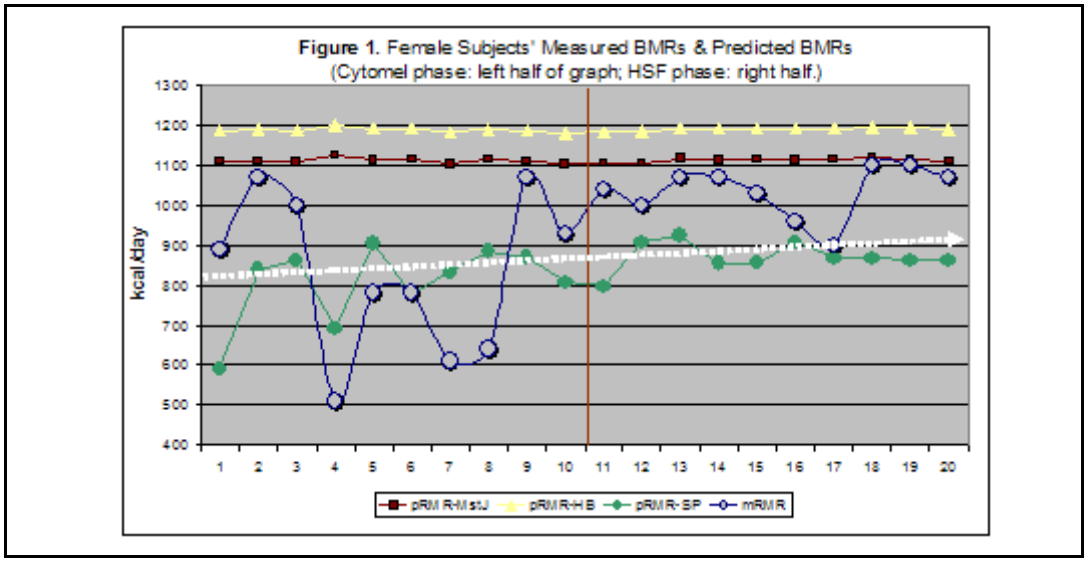
Basal Metabolic Rate. The female subject's mean measured BMR during the Cynomel phase was significantly lower than in the HSF phase (828 ± 197 kcal/day vs 1034 ± 64 kcal/day, $p = 0.006$). Variances of the BMR measurements within each phase also differed ($F = 12.668$, $p = 0.002$).

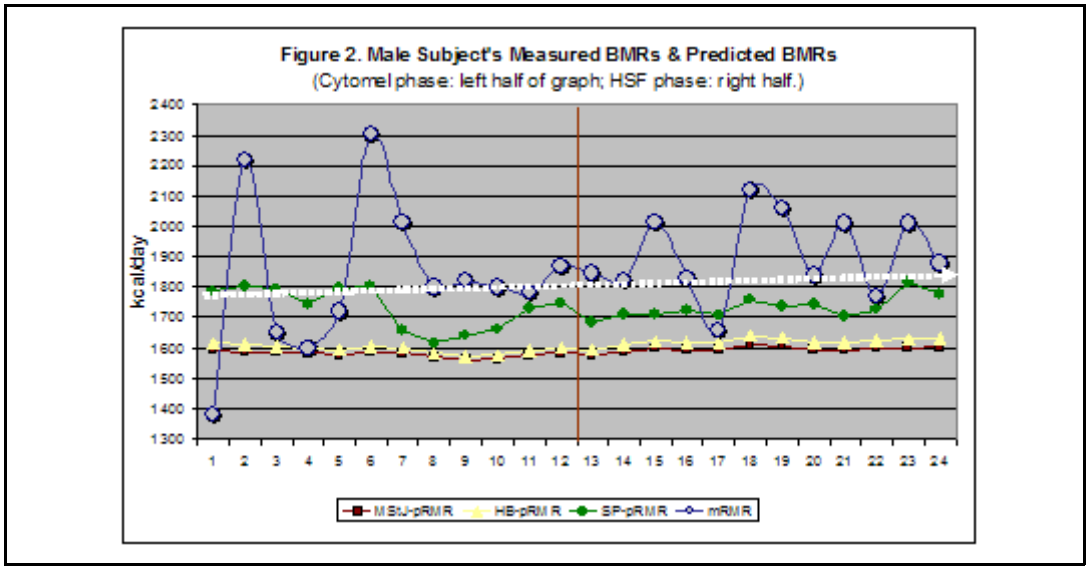
Figure 1 contains the measured BMRs for the female subject. Each BMR along the blue trend line is represented by an empty circle. The difference in BMRs between the Cynomel phase (left half of the graph) and the HSF phase (right half of the graph) are visibly obvious, with higher measured BMRs in the HSF phase of the study. According to Bloom's probability table,[5] because in the Cynomel phase (left half of graph), 5 measured BMRs are above and 5 below the trend line, and 10 BMRs are included in the HSF phase (right side of graph), 9 measured BMRs above the trend line in the HSF phase constitutes a statistically significant increase of BMRs at the 0.05 level.

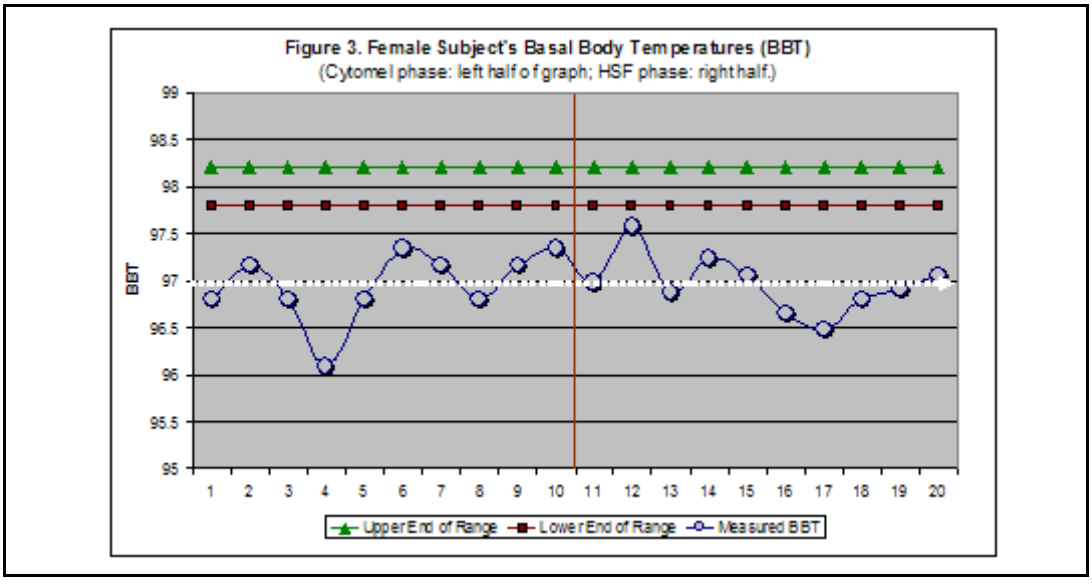
The male subject's mean measured BMR during the Cynomel phase did not significantly differ from that in the HSF phase (1830 ± 256 kcal/day vs 1905 ± 136 kcal/day, $p = 0.377$). Variances of the BMRs within reach phase also did not differ ($F = 1.609$, $p = 0.218$).

Figure 2 contains the male's measured BMRs (blue line with open circles representing each BMR). By Bloom's probability table,[5] with the baseline including 12 BMRs, and 5 below and 5 above the trend line for HSF-phase BMRs to be significantly different from those in the Cynomel phase. This criterion is not met. The lack of a significant difference is consistent with the lack of difference in the mean measured BMRs of the two phases.

Basal Axillary Temperatures. Both subjects were stable on Cynomel before this study, rarely experiencing mild symptoms characteristic of hypothyroidism. Despite this, both always had basal axillary temperatures below the lower end of the reference range reported by Barnes (97.8°F-to-98.2°F).[4]







trend line, 9 measured BMRs in the HSF phase (right half of graph) would have to be above or below the

In the Cynomel phase (left half of graph in Figure 3), the female's mean basal axillary temperature was 96.944 ± 0.378°F. During the HSF phase, the mean temperature was 96.960 ± 0.303°F. The mean temperatures in the two phases did not significantly differ, nor were their variances significantly different.

Figures 3 contains the female's basal temperature measurements represented as open circles on the blue line. Using the probability table of Bloom,[5] with 10 measurements in the Cynomel phase (left half of graph), with 5 above and 5 below the tend line, 9 data points would have to be above or below the trend line in the HSF phase (right half of the graph) for her temperature to have significantly changed. This criterion is not met, so the subject's temperatures in the two phases were not significantly different.

The female subject's mean temperature in September 2006, taken 20 times, was significantly lower than her mean temperature in both the Cynomel phase (96.118 ± 0.567 vs 96.9440 ± 0.378, p = 0.001) and HSF phase (96.118 ± 0.567 vs 96.959 ± 0.303, p = 0.001). When she was taking 25 mcg of Cynomel in September 2006, then, her temperature was significantly lower than when she was taking 87.5 mcg of Cynomel and when she was taking 6 capsules of HSF. Her mean temperatures during the Cynomel phase of the study, however, did not significantly differ from those in the HSF phase.

The male subject's mean temperature was 96.778 ± 0.673.°F during the Cynomel phase and 96.914 ± 0.548.°F during the HSF phase. These mean temperatures did not significantly differ, nor did the variances of the two sets of temperature measures.

Despite the male subject's use of 150 mcg of synthetic T_3, his temperature was low throughout his 23 years of using Cytomel and Cynomel, usually within the range of 96.5 to 97.0°F. His mean temperature while on HSF alone remained virtually the same.

Figure 4 contains the male's basal temperatures. Using Bloom's probability table,[5] with 12 measurements in the Cynomel phase and 5 of the BMRs above and 5 below the trend line, 10 BMRs in the HSF phase would have to be above or below the trend line for the BMRs to significantly differ from those in the Cynomel phase. That criterion is not met, so the BMRs in the two phases do not significantly differ.

Basal Heart Rates. A t-test showed that the female subject's mean basal heart rate was significantly lower during the HSF phase than in the Cynomel phase (62.50 ± 4.04 bpm vs 68.35 ± 5.11 bpm, p = 0.011). Bloom's probability table[5] also shows a significantly lower basal heart rate in the HSF phase. With 10 BHR measurements in the Cynomel phase (left half of the graph), and 4 BHRs above and 4 below the trend line, then 8 BHRs would have to be above or below the trend line in the HSF phase (right half of the graph) for the BHRs in the two phases to significantly differ. This criterion is met.

The female subject's mean systolic and diastolic pressures during Cynomel and HSF phases did not significantly differ.

The male's mean BHR was also significantly lower in the HSF phase than in the Cynomel phase (72.96 ± 8.24 vs 81.79 ± 7.51, p = 0.012). Bloom's probability table[5] also shows a significantly lower basal heart rate in the HSF phase: with 12 BHRs in the Cynomel phase (left side of graph), and 5 of these above and 5 below the trend line, then in the HSF phase (right side of graph), 9 BHRs would have to be below the trend line for the HSF-phase BHRs to be significantly lower at the 0.05 level. In fact, 10 BHRs were below the trend line. His heart rate was therefore significantly lower in the HSF phase.

The male subject's systolic pressure in the HSF phase was lower than in the Cynomel phase but did not quite reach statistical significance (123.08 ± 7.75 vs 129.27 ± 8.18, p = 0.07). His diastolic pressure, however, was significantly lower in the HSF phase than in the Cynomel phase (71.4167 ± 4.35 vs 77.14 ± 5.43, p = 01).

Weight and Fat Weight. Between the Cynomel and HSF phases, the female subject had no significant changes in weight, percentage body fat, fat or lean weight. For the male subject, however, weight was significantly higher during the HSF phase than in the Cynomel phase (174.93 ± 1.86 lbs vs 170.73 ± 2.13 lbs, $p < 0.0001$), and his fat weight was significantly higher during the HSF phase (49.24 ± 1.87 vs 45.33 ± 3.71, p = 0.005). His weight, or lean weight. For the male subject, however, weight was significantly higher during the HSF phase than in the Cynomel phase (174.93 ± 1.86 lbs vs 170.73 ± 2.13 lbs, $p < 0.0001$), and his fat weight was significantly higher during the HSF phase (49.24 ± 1.87 vs 45.33 ± 3.71, p = 0.005). His percentage body fat, however, was not significantly different in the two phases.

Mean Symptoms Intensity. For the female subject, the mean intensity of her symptoms characteristic of hypothyroidism did not significantly differ

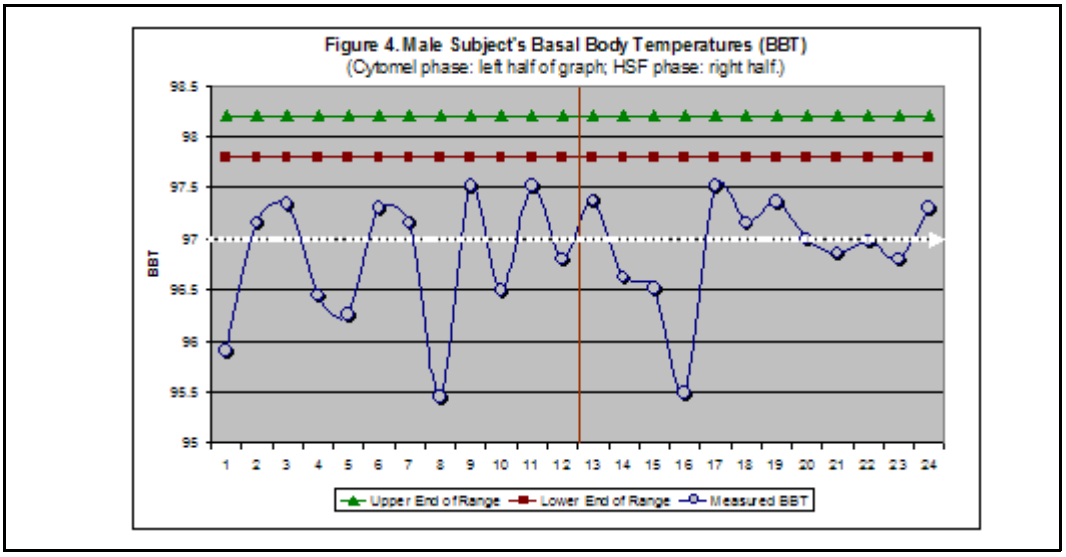


Figure 4. Male Subject's Basal Body Temperatures (BBT)
(Cytomel phase: left half of graph; HSF phase: right half.)
BBT
98.5
98
97.5
97
96.5
96
95.5
95
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Upper End of Range
Lower End of Range
Measured BBT

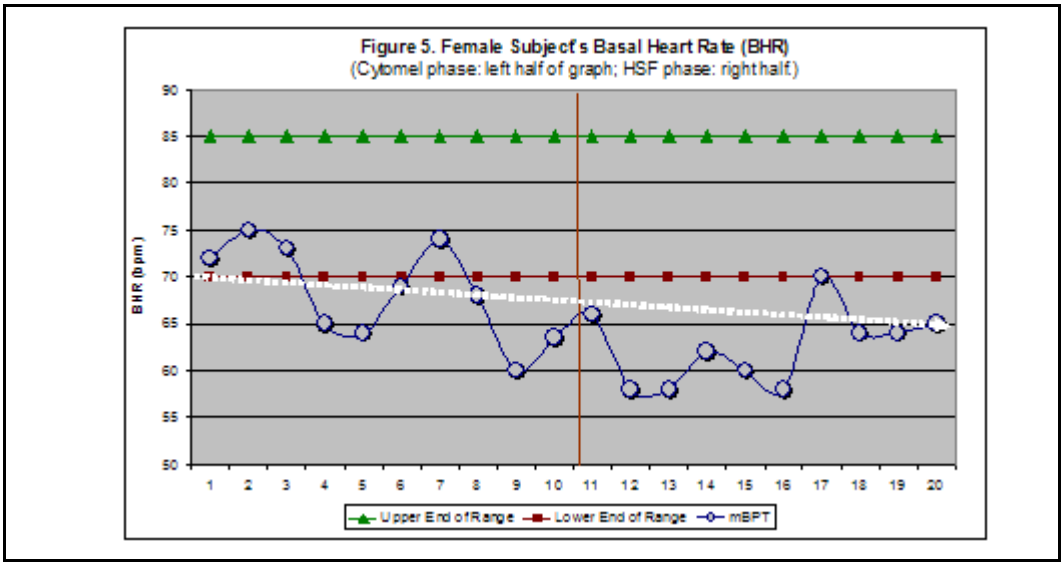


Figure 5. Female Subject's Basal Heart Rate (BHR)
(Cytomel phase: left half of graph; HSF phase: right half.)
BHR (bpm)
90
85
80
75
70
65
60
55
50
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Upper End of Range
Lower End of Range
mBPT

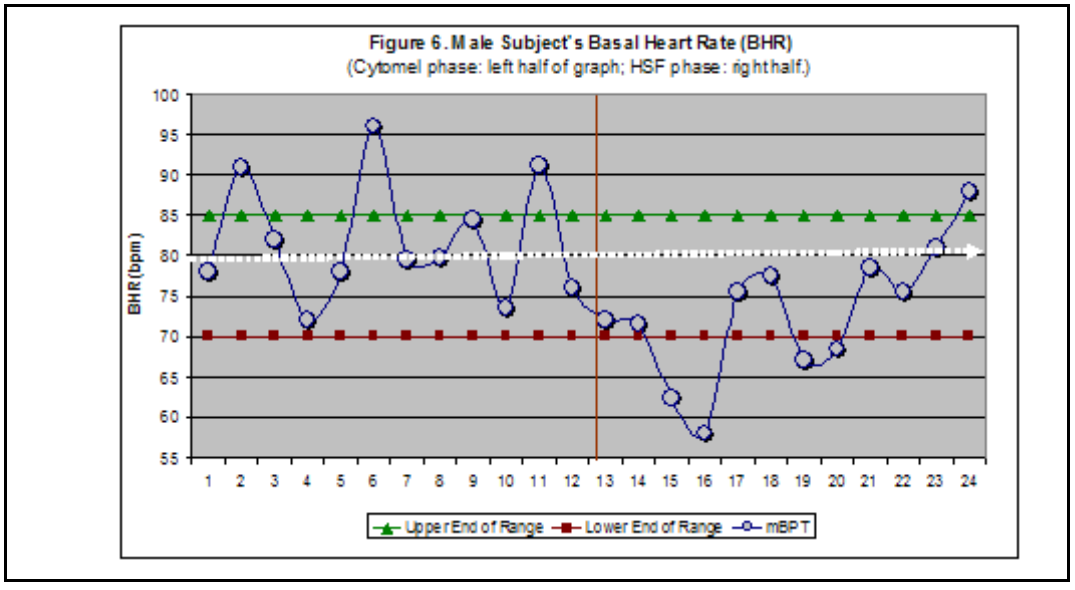


Figure 6. Male Subject's Basal Heart Rate (BHR)
(Cytomel phase: left half of graph; HSF phase: right half.)
BHR (bpm)
100
95
90
85
80
75
70
65
60
55
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Upper End of Range
Lower End of Range
mBPT

in the two phases. The mean intensity in the Cynomel phase was 3.68 (range from 0-to-10), and during the HSF phase was 2.68. Subjectively, however, she reported that as a global assessment, she felt better in the HSF phase.

In both phases, the male subject's mean symptoms intensity was low. However, the mean intensity of his symptoms was significantly lower in the HSF phase than in the Cynomel phase (1.09 ± 0.64 vs 2.18 ± 0.53, $p = 0.001$).

Zung's Self-rating Scale. During the Cynomel phase, the female subject had mild depression according to her mean Zung's score. In the HSF phase, however, her mean Zung's score was enough lower that it was significantly different from the mean scores in the Cynomel phase (1.67 ± 0.87 vs 1.00 ± 0.00, $p = 0.05$). The subject reported that the depression during the Cynomel phase was situational and uncharacteristic for her throughout her previous life, including her two years of Cynomel use.

For the male subject, the mean Zung's scores showed no depression in either of the two phases.

Pain Distribution. The female subject's pain distribution was not significantly different in the two phases. In the Cynomel phase, her mean pain distribution was 6.06% of 36 body divisions; in the HSF phase, the distribution was 5.81% of the 36 divisions.

The male subject's pain distribution was small in both phases, but it was highly significantly smaller in the HSF phase than in the Cynomel phase (0.22 ± 0.08 vs 1.98 ± 0.71, $p = 0.00003$).

Pain Intensity. The female subject's pain intensity did not significantly differ between the Cynomel and HSF phases. The male subject's pain intensity, however, was significantly lower in the HSF phase than in the Cynomel phase (0.22 ± 0.33 vs 1.68 ± 1.42, $p = 0.007$).

Discussion

Results of the clinical measures used in this study indicate that both Cynomel and HSF were effective. However, HSF provided some improvements in the subjects' clinical status that Cynomel did not provide. No symptoms of thyroid hormone overstimulation or ECG/EKG abnormalities were associated with the subjects' use of Cynomel or HSF.

Body Composition. Evaluation of the composition of an individual patient's body (a type of "clinico-anthropometric" analysis) is often essential to accurately diagnosing a disorder that afflicts him or her.[23] Similarly, a clinico-anthropometric analysis is often essential to finding a plausible explanation for an unexpected therapeutic effect. This is true for the female subject in this study: Her increased mean measured BMR when taking HSF was unexpected, and a likely mechanism for the increase becomes clear only through consideration of her body composition.

For two years prior to this study, the female subject had been free from symptoms characteristic of hypothyroidism by taking 87.5 mcg of Cynomel per day. Figure 1 shows visually that Cynomel maintained her BMRs closer to BMRs predicted by her lean body weight (green line in left half of the graph with solid dots as data points), and considerably lower than BMRs predicted by her sex, age, height, and weight (brown line in left half of graph with squares as data points and green line with triangles as data points). Her measured BMR being closer to her predicted BMR by lean body weight appears to have resulted from her ectomorphic body form. (The ectomorphic form is characterized by the relative prominence of structures derived from the embryonic ectoderm.[41][42]) The subject is more slender than other women of her age, height, and weight, as is her identical twin sister.

In the HSF phase, her BMRs were closer to those predicted by her sex, age, height, and weight, and further away from those predicted by her lean body weight. In looking for a plausible mechanism of her increased BMRs in the HSF phase (represented by data points 11 through 20 on the right side of the graph in Figure 1), lean body weight and thyroid hormone regulation of cell function are the two most important considerations. The reason is that among the determinants the BMR,[17-21] lean body weight is the most influential thyroid hormone is the second.

Her lean body weight was not higher in the HSF phase, and therefore could not have been the factor that raised her measured BMRs. In the U.S., the exact thyroid hormone content of dietary desiccated thyroid hormone products are not known. The FDA, however, does require that all but trace amounts of the T_4 be removed from the products. It is within the realm of possibility that thyroid hormones other than T_4 increased the subject's BMRs in the HSF phase.

It is also possible that one or more ingredients in the HSF capsules other than thyroid hormone increased her intracellular rate of oxidative metabolism. Such an increase in turn would have raised her oxygen consumption in the vegetative state during which she measured her BMR with a handheld calorimeter.

One would expect an increased rate of oxidative metabolism to increase the subject's calorie expenditure. This expectation is reasonable in that an increased BMR by definition is a higher calculated 24-

hour basal energy expenditure, which in turn is computed from oxygen consumption in a basal state. The increased energy expenditure is expected to change the body composition of the subject unless she also increases her calorie intake to compensate for the increased expenditure. However, the subject had virtually the same calorie consumption in the Cynomel and HSF phases. Because of this, one would expect that the subject would have had a lower weight and body fat measures during the HSF phase. This was not the case, however. The author knows of no explanation for this discrepancy.

In contrast to the female subject, the male has a mesomorphic body form; that is, the form is characterized by the prominence of structures derived from the embryonic mesoderm.[41][42] This appears to account for his BMRs, measured many times over the previous 5 years, most often being close to the BMR predicted from his lean body weight, and further away from the BMR predicted by his sex, age, height, and weight. This indicates that he had more lean body weight than the average male of his age, height, and weight. Figure 2 shows his measured BMRs (blue line with open circles in both halves of the graph) was generally closer to the BMRs predicted by his lean body weight (green line with closed dots) than they were to the BMRs predicted by his sex, age, height, and weight (brown line with square data points and yellow line with triangular data points).

Sympathetic Nervous System Activity. Several findings in this study during the subjects' HSF phases could be due to reduced sympathetic nervous system activity. In turn, theoretically, the putative reduced sympathetic activity could be due to decreased regulation of transcription of the adrenergic genes by thyroid hormone, resulting in a reduced number of stimulatory â-adrenergic receptors and an increase number of inhibitory á-adrenergic receptors.[40,pp.341-377] This mechanism could possibly account for five HSF-phase findings: for the female and male, reduced heart rates, subjective calmness, and a lower spread of BMR values around mean BMR values; for the female alone, improved hyperhidrosis; and for the male alone, lower blood pressure and increased weight.

Heart rate and blood pressure. Both subjects had significantly lower basal heart rates in the HSF phase. The female subject's systolic and diastolic pressures were not significantly different in the Cynomel and HSF phases. The male had reduced systolic pressure that approached statistical significance, and diastolic pressure that was significantly lower.

Hyperhidrosis. The virtual elimination of the female subject's life-long hyperhidrosis in the HSF phase and afterward might have involved any of several possible mechanisms.[26][27] One is a reduction in sympathetic activity, indicated by studies that show improved hyperhidrosis following surgical applications of clips above and below various thoracic sympathetic ganglia[28][29] and occasional effective adrenergic receptor blockade.[27]

Lower spread of BMRs from the mean BMR values. The lower variance of measured BMRs for the female subject in the HSF phase might also have resulted from lower sympathetic nervous system activity. The lower variance was significant ($F = 12.668$, $p = 0.002$). Two other descriptive data calculations show a wider distribution of BMRs during the Cynomel phase. In that phase, the range (the difference between lowest and highest BMRs) of BMR measurements (the difference between the minimum and maximum BMR) was 630 kcal/day. In the HSF phase, the range was only 230 kcal/day. And the respective standard deviations in the Cynomel and HSF phases were 213.58 kcal/day and 67.26 kcal/day, showing that the spread of BMR measurements around the mean were larger in the Cynomel phase.

For the male subject, the variances of BMRs did not significantly differ in the two phases ($F = 1.609$, $p = 0.218$). However, in the Cynomel phase, the range of BMR measurements was 925 kcal/day compared to only 460 kcal/day in the HSF phase. Similarly, in the Cynomel phase, the standard deviation was 255.4596 kcal/day compared to 135.979 kcal/day in the HSF phase.

For both subjects, then, BMRs in the HSF phase were less widely distributed than in the Cynomel phase. This may have resulted from lower sympathetic nervous system responsiveness in the HSF phase.

Subjective calmness. Toward the end of the transition phase, just before stopping Cynomel altogether and reaching their apparent optimal dosages of HSF, the subjects reported feeling a persistent and distinct subjective sense of calm. The female reported feeling "a more steady, stabilized sense of well-being, and less warmth after eating" (postprandial thermogensis). The male subject recorded feeling "calmer, less anxious except situationally, and mildly sedate without sleepiness." Both subjects recorded that these subjective feelings had persisted long enough so that they appeared to be associated with the HSF.

Weight. The significant increase in the male subject's total weight and fat weight could be argued

to have resulted from HSF decreasing his sympathetic activity. Decreased sympathetic nervous system activity, with consequently decreased secretion of adrenaline and noradrenaline, could have decreased the mobilization of fatty acids from adipose tissue. The resulting higher triglyceride content of the adipose tissues could account for weight gain and higher fat measurements. But this mechanism is unlikely. If this mechanism was operative in the male subject, it is likely that it would also have been operative in the female subject. However, she did not have a significant increase in her total weight or fat weight. In addition, the male subject, who has a lifelong commitment to fitness, was uncharacteristically sedentary through the study due to compelling work responsibilities. It is far more likely, then, that his weight gain of 4.2 lbs resulted from reduced calorie expenditure from a lower than usual level of physical activity.

If HSF were less potent than Cynomel in maintaining the â- and á-adrenergic balance expected from effective thyroid hormone therapy, then reduced sympathetically-mediated phenomena would be expected. These would include several found in the HSF phase of the study: reduced mean heart rate, improved hyperhidrosis, reduced diastolic pressure, and the subjective sense of calm. Other findings in the HSF phase, however, are inconsistent with reduced sympathetic activity. These are the lack of a significant difference between the male's mean BMRs in the Cynomel and HSF phases, and the increase in the female's mean BMR during the HSF phase. At the moment, the seemingly contradictory findings in regard to sympathetic function are inexplicable to the author.

Pain Reduction. The female subject's pain distribution and intensity were not significantly different in the two phases. In that her metabolic and clinical status were actually improved in the HSF phase, her pain most likely has a mechanism unrelated to her thyroid hormone status.

The male subject's lower pain distribution and intensity in the HSF phase constituted improved clinical status for him. Thyroid hormone therapy can reduce or alleviate pain by lowering substance P, a compound that amplifies neural signals that give rise to the perception of pain. Thyroid hormone normally inhibits the synthesis and secretion of substance P in many CNS cells. It does so by repressing transcription of the preprotachykinin-A gene. Preprotachykinin-A is the precursor of substance P and its cognate substance P receptor.[31,32] In studies, lowering thyroid hormone levels by thyroidectomy increased the substance P level in astrocytes,[32] anterior pituitary,[33,34,35] many brain nuclei,[38] and, most relevant to pain, the dorsal horns of the lumbar spinal cord. The increase in dorsal horn substance P was extreme (100%)[36,37] as in FMS patients.[30] Thyroid hormone treatment lowered the substance P level in the anterior pituitary,[34] brain nuclei,[39] and the dorsal horns.[37] Administering excessive amounts of thyroid hormone reduced substance P to subnormal levels.[35] Reduction of the substance P level is probably the mechanism for the relief of the chronic pain of fibromyalgia when patients are effectively treated with thyroid hormone therapy.[40,43-50]

Reduced substance P, however, seems like an unlikely mechanism of the male subjects improved pain measures in the HSF phase. Synthetic T_3 had effectively reduced his chronic myofascial pain and other somatic discomforts for years, the symptoms returning only during times when he had purchased subpotent Cytomel.

The pain reducing effect for him during the HSF phase may not be related to the thyroid hormone. Instead, the tyrosine in HSF may have had an analgesic effect. This is possible because tyrosine is the NH_2 terminal that is absolutely necessary for enkephalins to exert analgesic effects when they bind to opiate receptors.[24]

Effectiveness of HSF and Cynomel. The male subject's mean BMR did not differ between the Cynomel and HSF phases. The female subject's mean BMR during the HSF phase was significantly higher than in the Cynomel phase. However, she was not hypermetabolic in the HSF phase: her BMRs in this phase were between the BMRs predicted from her lean body weight and and those predicted from her sex, age, height, and weight (see Figure 1). In addition, she had no signs or symptoms characteristic of thyrotoxicosis, did not have hyperreflexia, she was satisfied subjectively with the effects of 6 capsules of HSF, and her measurements overall indicate a somewhat improved clinical status.

Safety. The subjects had no symptoms of thyrotoxicosis in any phase of the study. This was partly determined by comparing the intensity ratings of symptoms of thyrotoxicosis on visual analog scales that they filled out before the study and at intervals during the two phases. Neither subject had hyperreflexia. After the study, their ECGs/EKG tracings were no different from those performed before the study began. The thyrotoxicity symptom assessment, normal Achilles reflexes, and unchanged normal ECGs/EKGs indicate that neither Cynomel nor HSF in the dosages the subjects used had adverse effects.

Limitations. This study was unblinded, which raises the possibility of observer bias. However, the number of repeated measurements during the two analyzed phases diminishes the likelihood that the outcome was influenced by subtle biases.

In general, the clinical research community nowadays considers the only useful study method to be the randomized double-blind placebo-controlled design. An argument that the design of the study reported here is limited because it is not the randomized method is not truly a limitation of the study; rather, it is a limitation of the appreciation of the rich and fruitful use of study designs other than the randomized double-blind placebo-control procedure.

The single-subject A-B repeated measures design used in this study has merits lacking in the randomized design. For example, the subject who serves as the patient in one study phase also serves as the control in another. This eliminates the need for randomization in that the patient and the control could not be more perfectly matched. Also, repeated measures under systematically varied conditions not only provides data for traditional group statistical analyses, but also allows for clear visual assessment of functional relationships between independent and dependent variables.

Conclusion

In this study, both Cynomel and HSF, a dietary organic desiccated thyroid product, were physiologically effective. HSF, however, appears to have provided some improvements in the subjects' physiological status that Cynomel did not provide. The female subject's axillary temperatures did not differ in the two phases. In the HSF phase, however, her heart rate was significantly lower and her mean basal metabolic rate was significantly higher. A noteworthy benefit for her was the virtual elimination of previous life-long hyperhidrosis of her palms and soles; the reduced perspiration at this time has lasted 3.5 months.

The male subject's basal metabolic rates and basal axillary temperatures did not differ in the Cynomel and HSF phases. However, in the HSF phase, five measures were significantly lower: his heart rate, diastolic blood pressure, pain distribution, pain intensity, and mean hypothyroid symptoms intensity.

The physiological equivalence of HSF to Cynomel was calculated from the patients' dosages of HSF in their HSF phases that maintained measurements equivalent to or better than those in the Cynomel phase. The physiological equivalence of HSF to Cynomel was 1 capsule of HSF to 14.58 mcg of Cynomel for the female subject, and 1 capsule to 15 mcg for the male.

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