Managing Subclinical Hypothyroid Using Resting Metabolic Rate and Brachioradialis Reflexometry

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Abstract

Objective

This study looks at the risks associated with subclinical hypothyroidism and a new management paradigm that optimizes thyroid function based on Resting Metabolic Rate (RMR) and Brachioradialis Reflexometry (BR).

Main Outcome

Brachioradialis Reflexometry (BR) correlates the best with RMR measurements and, in this population, seems to be the best parameter to titrate thyroid dose. Using any form of thyroid therapy, RMR must increase approximately 383 kcalories above baseline values to achieve thyroid adequacy and resolution of symptoms. However, TSH values fall below 0.3 mU/L when RMR is increased only about 139 kcalories above baseline values.

Design

In 563 patient interactions, volunteers were evaluated by measuring:Thyroid symptoms, age, gender, height, weight, body mass index, calculated RMR, measured RMR, measured brachioradialis reflex intervals, and serum measurements of: TSH, T3U, T4, T7, cholesterol, LDL, HDL, and triglycerides. Some patients also had free T3, free T4, Microsomal (TPO) autoantibody, thyroglobulin autoantibody, ACTH, and prolactin measurements.

Patients that were on thyroid medication received a dosage increase of the same medication. People on no medications were given a choice of thyroid treatments. All patients were evaluated at 30 day intervals and dosages were increased until the BR parameter of: Fire Interval – Pre-fire Interval < 66 msec. was achieved.

Conclusion

Volunteers became functionally normal and thyroid symptoms resolved when their medication doses were titrated using RMR and BR as the primary endpoints. Only 14 of over 800 patient interactions (1.7%) noted symptoms of nervousness, tachycardia, palpitations or insomnia although TSH levels became <0.01mU/L. ACTH and prolactin levels remained normal in patients with low TSH, indicating no suppression of pituitary function.

Key Words: Subclinical Hypothyroid, Brachioradialis Reflex, Management, Thyroid Medication Dosage

INTRODUCTION

Subclinical Hypothyroid and Risk Literature reviews from searches done on MedLine until 5/1/05 revealed:

Cardiovascular Risk

Several investigators have shown an increase in dyslipidemia, homocysteine, C-reactive protein, coronary artery disease, hypertension, and ischemic heart disease in people with subclinical hypothyroid. [1-11]
Several investigators have also found hypercoaguability, endothelial dysfunction, and peripheral arterial disease. [12-16]. Ripoli measured decreased cardiac preload and increased afterload resulting in decreased stroke volume and cardiac output. [17]

Diabetes Risk

McCluskey showed that disruption of GLP-1 signalling affected corticosteroid and thyroid responses to stress in mice. Schultes demonstrated that in humans hypoglycemic episodes caused a decrease in TSH, free T3 and free T4 which lasted over eighteen hours after the hypoglycemia. Dessein showed that HOMA score and Triglyceride/HDL ratios increased and that subclinical hypothyroidism was associated with insulin resistance. Dimitriadis, et al showed that in hyperthyroid states post-absorptive plasma glucose and insulin increased, plasma insulin responses increased, insulin receptor binding increased due to increased receptor affinity, insulin clearance increased and maximal insulin induced glucose uptake and oxidation increased[18-22]. Risk of dysglycemia seems to be reduced with slightly hyper-thyroid function.

Arthritis and Inflammatory Risk.

Dessein showed that in rheumatoid arthritis patients, subclinical hypothyroid patients had dysfunctions of glucose metabolism and insulin resistance. Innocencio showed that 52% of systemic sclerosis and 32% of rheumatoid arthritis patients also had anti-thyroglobulin and/or anti-thyroperoxidase antibodies. This finding of silent autoimmune thyroiditis may contribute to the euthyroid sick syndrome seen in people with autoimmune diseases.[20, 23]

Neurological Risk

Klein showed that Hoffman's syndrome (increased muscle mass, stiffness and weakness) was associated with hypothyroidism. Cakir showed that there was an increased frequency of Dupuytren's contracture, carpal tunnel syndrome and decreased joint mobility in people who were sub-clinically hypothyroid. Madriaga showed a polymyositis-like syndrome in hypothyroid patients. Tandeter showed an increased incidence of subclinical hypothyroidism in Parkinson's patients. Brucker-Davis showed increased hearing loss in thyroid resistant patients. Dolu showed abnormal EEG in subclinical hypothyroid patients with lower skin conductance, lower fluctuation rates and prolonged onset latencies. Several investigators have shown an association between anxiety and depression and subclinical hypothyroidism. Valpato demonstrated that in 628 women older than 65 years there was a 1.97 relative risk of cognitive decline in subclinical hypothyroid women[24, 25{Finsterer, 1999 #49, 26-29}30-34

Bone
Engler showed that in subclinical hyperthyroidism there were increases in bone resorption and bone formation parameters and an increased frequency of higher urinary pyridinoline and deoxypyrodinoline excretion. Meier, et al demonstrated that in subclinical hypothyroid patients who were given L-thyroxine to restore serum thyroid measurements to the euthyroid range, there was an increase in bone resorption. Kisakol showed that in subclinical hypothyroidism there was no disturbance in calcium metabolism, but in subclinical hyperthyroidism there was increased urinary calcium excretion, increased serum osteocalcin, and increased urinary deoxypyridinoline.[35, 36]

Pregnancy
Casey recently reported a three fold increase in placenta previa and a two fold increase in premature delivery in pregnant women with subclinical hypothyroidism [95]

Factors Affecting Thyroid Function

Peripheral Conversion of T4 to T3
Thyroid hormones are metabolized in peripheral tissues by deiodination, conjugation, deamination and decarboxylation enzyme reactions. Hepatic and renal pathology as well as stress states impact peripheral enzyme pathways. Toxic metals, chemical poisons, several drugs and nutrients may impact peripheral conversion. Vondra showed that there was a relationship between thyroid function and enzymes involved in glycolysis and cytoplasmic H2 transport from NADH2.
[37]

Mitochondrial Proton Leakage
Porter showed that mitochondrial proton leakage was related to uncoupling protein 3 (UCP3). de LP, et al showed that UCP3 is regulated by T3 and causes mitochondrial uncoupling affecting RMR. Reitman showed that free fatty acids appear to regulate UCP3 expression. Yu demonstrated that in euthyroid sick syndrome there is a decrease in activity of type 1 iodothyronine-5'-deiodinase (5'D-I) hepatic enzyme conversion of T4 to T3. This is believed to be a competitive inhibition by cytokines (IL-1 and IL-6). Hoch demonstrated that thyroid states regulate each cardiolipin property, and are permissive, via the proton antenna, for proton leaks. Slow leakage in liposomes may be due to insufficient cardiolipin proton antennas.[38-42]

Stressed States and Euthyroid Sick Syndrome
Schultes found that after a single episode of hypoglycemia, free T3 and free T4 were diminished and TSH increased up to 18 hours. Several investigators have found that in the Euthyroid Sick Syndrome and other stress states, that thyroid function is severely decreased. [22, 43-48]

Cytokines
Yu demonstrated that Interleukins 1 and 6 competitively inhibit the T3 induction of 5'deiodinase RNA and enzyme activity in rat hepatocytes. Nagaya, et al showed that activation of NF-kappa-B by TNF-alpha (which is

elaborated in stress states) impairs T3 dependent induction of 5'deiodinase gene expression, which contributes to the Euthyroid Sick Syndrome. Rasmussen demonstrated that IL-1 alpha/beta in moderate and high concentrations reversibly inhibit thyroid cell function; while iL-1 beta in small doses stimulates thyroid cell function. This may contribute to the Euthyroid Sick Syndrome and/or autoimmune disease. The earliest stages involve antigen presenting cells interacting with the thyroid. In the later stages antigen specific and non-antigen specific immune cells are recruited to the thyroid and an inflammatory infiltrate is built. During this process cytokines, free nitric and oxygen radicals are released. Ren showed that Leukemia inhibitory factor (LIF), a neuroimmune pleiotropic cytokine is produced in the thyroid gland. TSH, IL-6, and glucocorticoid influence thyroid cell LIF expression. Kimur showed that IL-6 and IL-10 significantly correlated with TSH in acute MI patients that developed Euthyroid Sick Syndrome. Bagriacik demonstrated that serum T3 and T4 levels are sharply and transiently reduced during the first 24 hrs following systemic antigen exposure. These findings suggest that during the early phase of antigen exposure the immune system directly participates in the regulatory control of thyroid hormone activity.[49-55]

Nutrients

Barrows showed that very low carbohydrate diets caused decreases in RMR, T3, and RT3 without affecting T4. Mathieson found that although dietary carbohydrate content had an influence on the magnitude of fall of serum T3, RMR declined similarly in both high and low CHO diets. Poehlman showed that there was a slight, but insignificant decline in T3 in vegetarians versus non-vegetarians. Dubois and Goldman could demonstrate no effect of hypothyroid on gastric secretion and emptying. Poehlman showed that acute exercise and caffeine ingestion had no effect on thyroid function. Berger, et al showed that selenium supplementation had moderate effects on thyroid function with a quicker recovery in Euthyroid Sick patients although zinc and alpha tocopherol had no effect. Iron supplementation seems to increase RMR and thyroxine levels, as does zinc in iron/zinc deficient individuals but had no effect in iron/zinc sufficient. Clark showed that administration of kelp caused a significant and dose related increase in TSH and decrease in T3 and T4. Other sources of iodine performed similarly. In iodine deficient populations, supplementation of iodine improved thyroid function, but it reduces thyroid function in people who have adequate iodine. Benvenga showed that l-carnitine decreases thyroid function by preventing its entry into the nucleus of cells, which improves bone resorption in hyperthyroid individuals.[11, 56-66]

Environmental Toxins

Rat studies by several investigators showed that PCB exposure resulted in severely decreased serum T4 and moderate decreases in serum T3. Tomasi showed that in rats exposed to fungicides there was a decrease in thyroid hormone and that there was a corresponding increase in T3 turn-over. Pelletier proposed that organochlorine pesticide residues residing in adipose tissue would be released and cause a decrease in thyroid function in obese individuals during weight loss programs. Garry studied pesticide applicators and found subclinical hypothyroidism in 5/144. Guven found that 31.8% of

patients who had been poisoned by organochlorines had Euthyroid Sick Syndrome. [67-75]

Medications
Several authors have shown that seizure medications and lithium reduce thyroid function. Amiodorone has been implicated in thyroid dysfunction. Wang showed that a single dose of salsalate caused a decrease of T3 and T4 as well as an increase in reverse T3 which lasted up to 96 hrs. It was concluded that there was an acute release of T4 and T3 from circulatory transport proteins induced by an inhibitor of binding. This resulted in a large and rapid redistribution of T4 and T3 into tissue compartments associated with transiently reduced peripheral tissue 5'monodeiodination and deranged TSH regulation.[76]

Physiological Measurements Related to Thyroid Function
Many investigators have used either estimations of resting energy expenditure such as the Harris-Benedict equation or direct measurements of resting metabolic rate to look at energy expenditure and energy requirements in a variety of populations. Many authors have demonstrated decrease in RMR with age and decreased thyroid function. Vondra showed the relationship between thyroid function and enzymes involved in glycolysis and hydrogen transport from NADH2, correlating achilles tendon reflexes and thyroid function. Khurana, Carel, Goodman and others have demonstrated statistically significant correlations between achilles tendon reflexes and thyroid function. Goulis demonstrated a similar effect using stapedial reflex. Findings have been consistent in a slowing of the firing interval of the reflex with decrease in thyroid function and a corresponding return to normal with treatment by thyroid medication. Body mass index and other physical markers seem to correlate. Being female and increasing age have shown correlations with thyroid dysfunction.[40, 77-87]

Serum Thyroid Tests
Scobbo showed great variability in serum TSH depending on time of day samples were drawn and if the subject was fasted. Stockigt, et al showed that there was no current methodology that accurately reflects the free T4 in undiluted serum [88-90]

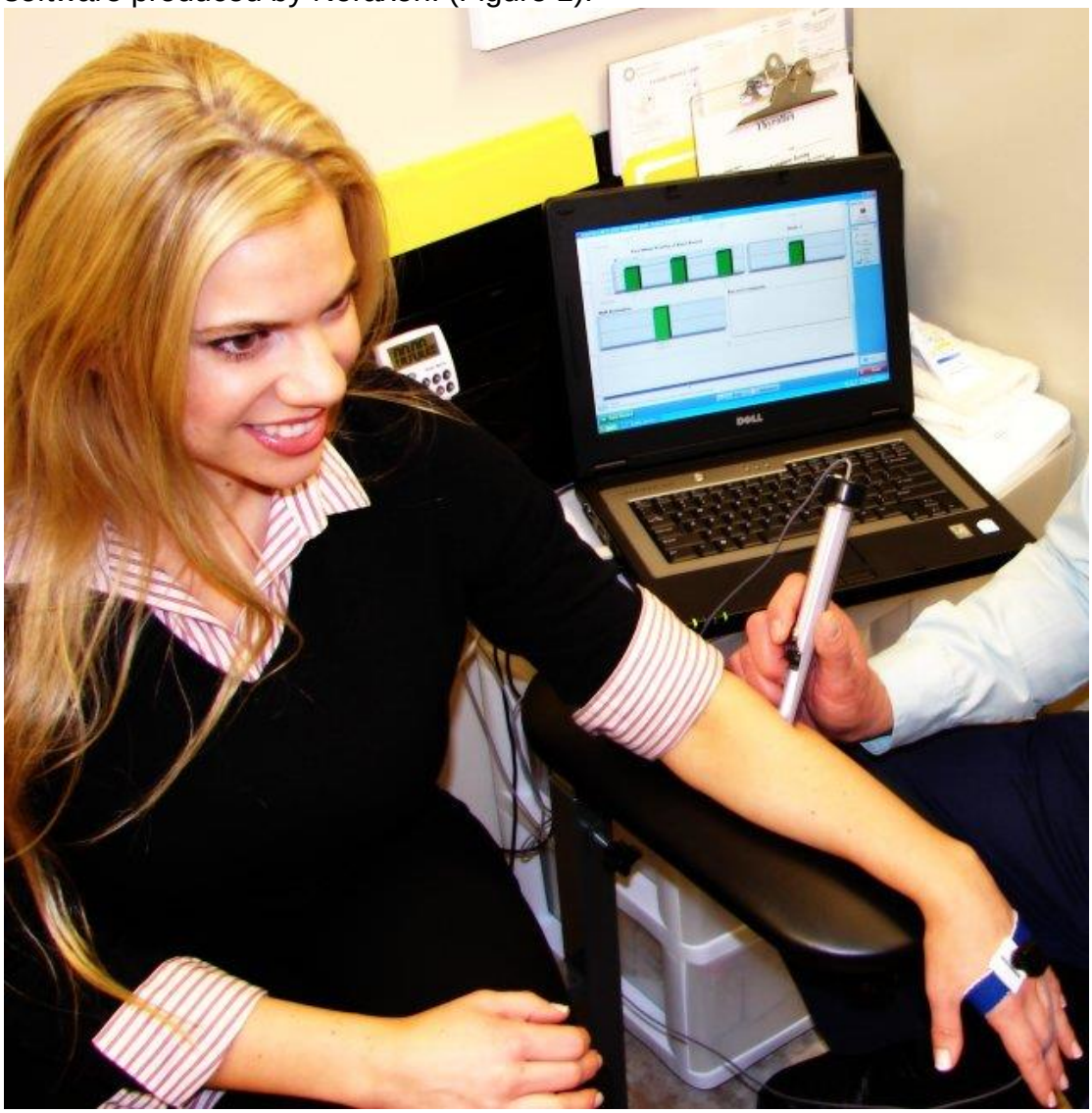
Risk Associated with Hyperthyroidism
Gussakoo found no correlation between plasma thyrotropin and free thyroxine in elderly patients with depression or cognitive dysfunction, but found that increased thyrotropin was correlated with increased longevity. Kisakol and others found that subclinical hyperthyroidism was associated with increased bone resorption, increased quality of life, increased lean body mass, increased functionality and increased longevity. [91, 92]

Materials and Methods

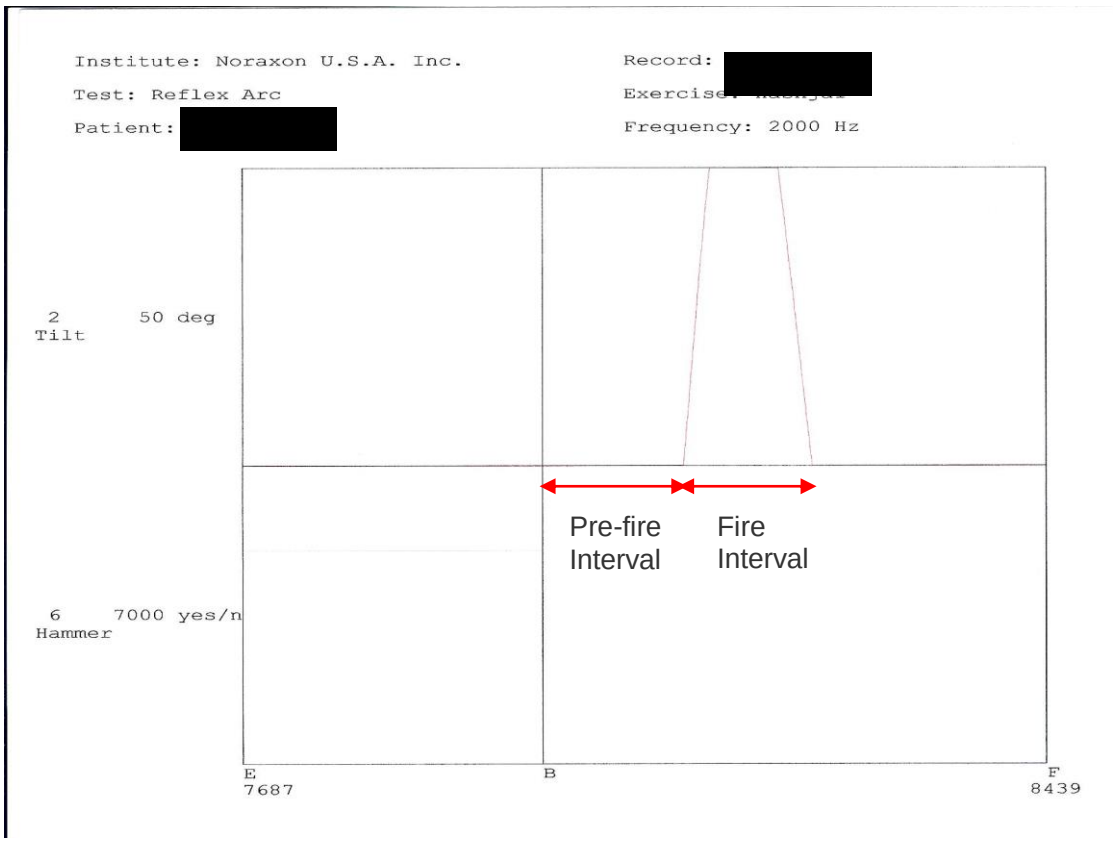
After suitable informed consent, volunteers were evaluated for thyroid status using:
A standardized Thyroid Symptom Questionnaire
Height and weight were measured on a standard clinic scale.

RMR was predicted using the Harris-Benedict Equation.
RMR was measured using the MedGem oxygen consumption device, which compared favourably to the Douglas Bag in clinical trials [93-94]

Brachioradialis reflex was measured using a prototype reflexometer designed by Noraxon Corporation, manufacturers of electromyogram equipment. The device was interfaced with a standard IBM compatible PC and proprietary software produced by Noraxon. (Figure 1).



Reflex measurements included:
Pre-Firing Interval defined as the number of milliseconds from hammer strike to initiation of the reflex response; Firing Interval defined as the number of milliseconds from initiation of the reflex firing until return to baseline; and Fire-PreFire which is the difference in milliseconds between those intervals (Figure 2).



Fasting serum specimens were collected for TSH, T3U, T4, T7 Cholesterol, LDL, HDL, and Triglycerides. Some volunteers received free T3, free T4, RT3, TRH, Thyroid Microsomal (TPO) auto-antibody, Thyroglobulin auto-antibody, ACTH and Prolactin measurements. All serum measurements were collected in our clinic and processed at Sonora-Quest laboratories. All serum measurements reflect their technique and norms.

All measurements were made at baseline and 30 day intervals. Volunteers already on thyroid medication continued it. Volunteers on no medication were given the choice between :
Homeopathic Thyroid Formula
Thyroid nutritional co-factors without tissue
Thyroid Tissue OTC
Prescription natural thyroid (Armour, Westhroid, Naturethroid)
Prescription Synthetic Thyroid (Cytomel, Liothyronine, L-thyroxine, Synthroid)

Doses of thyroid medication were increased until the reflex parameter of:
Fire –PreFire < 66 msecs. was achieved. If auto-immune disease (Hashimoto's) was identified, those volunteers had their medication switched (tissue to synthetic or visa versa).

Results

Focusing on which factors are the best predictors of the dependent variable Resting Metabolic Rate (RMR), a step-wise Multiple Linear Regression Analysis (MLRA) was the analytical method used on a population of 563 patient encounters (N=563). After analysis of the independent variables with

MLRA, it was determined that Patient Height (CM), Patient Weight (KG), Body Mass Index (BMI), PREFIRE, FIRE, and FIRE-PREFI (Fire minus Prefire) were the best predictors of the dependent variable (RMR). Note: Refer to text on how PREFIRE and FIRE was computed.

An acceptable Multiple R value indicates approximated 65% of all variation is accounted for with the predictive equation being:

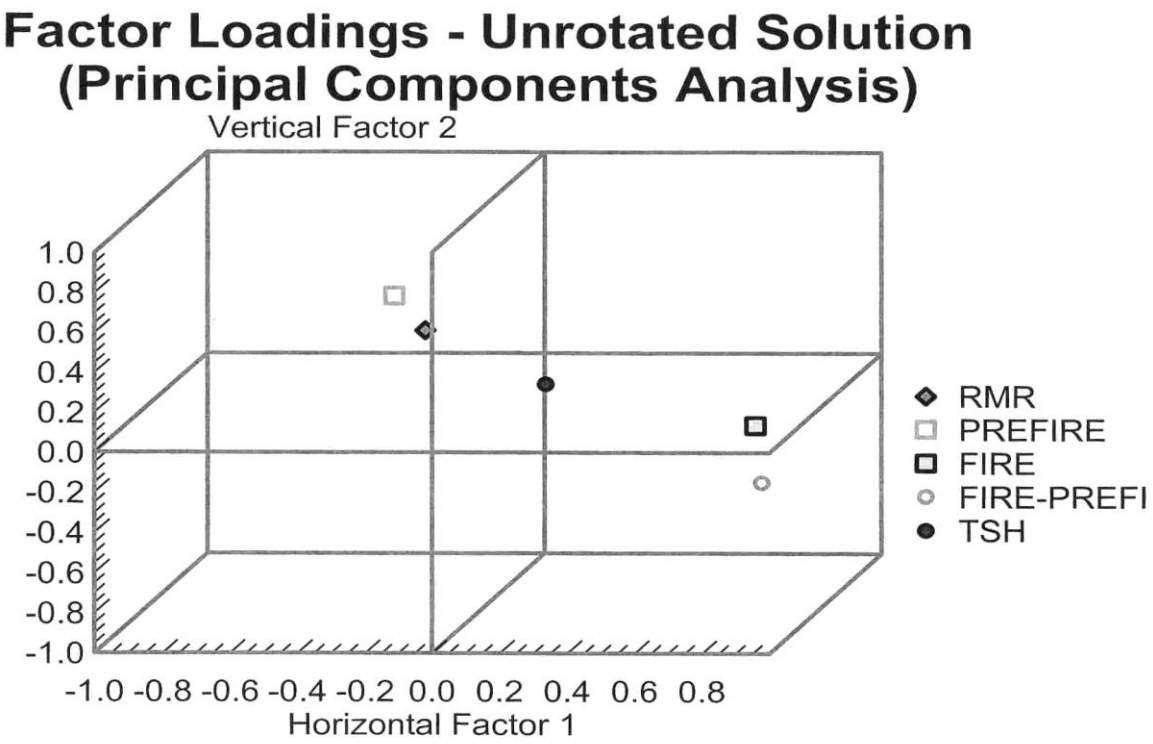
RMR = 2307.62 + [-7.53(CM)] + [27.09(KG)] + [-42.59(BMI)] + [-45.47(PREFIRE)] + [45.85(FIRE)] + [-46.27(FIRE-PREFI)]

Verification of the predictability of the equation was checked by computing a CRMR (Computed RMR) with the equation for all patient encounters, and statistically comparing CRMR with RMR using a Student t-test with a pooled variance. Ho: $u1 = u2$ and Ha: $u1 \neq u2$

Based on the t-value of .0019, the Ho is accepted with $u1 = u2$ or the mean of CRMR is statistically the same as the mean of RMR with a non-significant 2-tailed probability of $p = .9985$ giving relatively high credibility to the predictive equation.

Analysis of Thyroid Stimulating Hormone (TSH) with RMR, PREFIRE, FIRE, FIRE-PREFIRE

A common medical practice is to use quantitative serum TSH levels as a basis for the treatment of thyroid pathologies. This supposition may not be correct. Using a Factor Analysis (Principal Components Analysis), it appears that TSH may not be as closely associated with RMR as might be expected. The following data suggest that TSH has relatively independent variation compared to the other selected variables in this study. (Figure 3.)

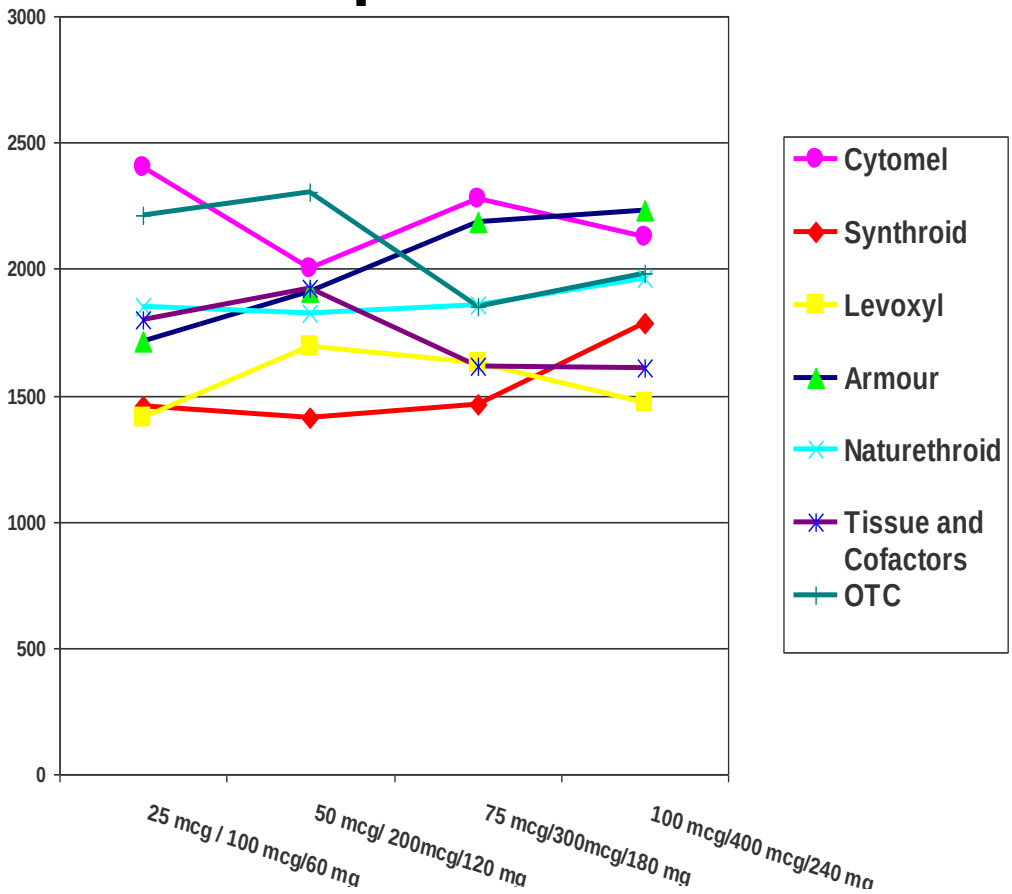


Response to Treatment

Symptoms and Physiologic Measurements

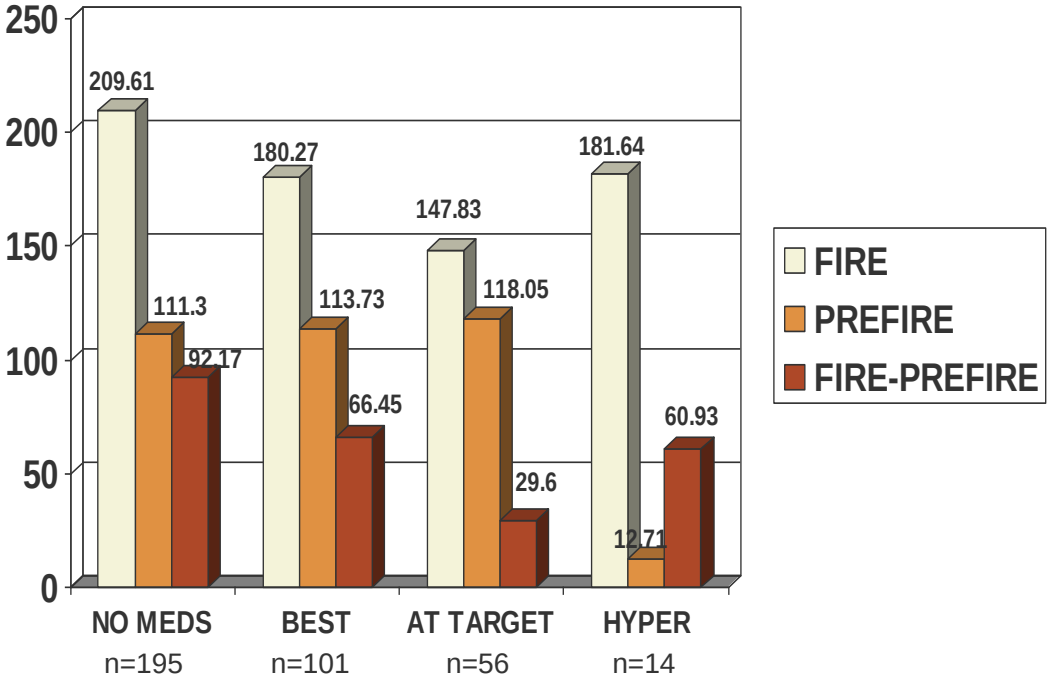
Thyroid symptoms decreased as thyroid function improved. Physiologic measurements responded to treatment as expected. BMI decreased, BBT increased as thyroid function improved. All therapeutic regimens raised RMR, except the preparation containing kelp. (Figure 4)

RMR Response to Medication



All therapeutic regimens improved BR measurements showing that as thyroid function improved, the PREFIRE interval became longer and the FIRE interval and PREFIRE-FIRE became shorter. BR treatment target was FIRE-PREFIRE @ 66 milliseconds. (Figure 5)

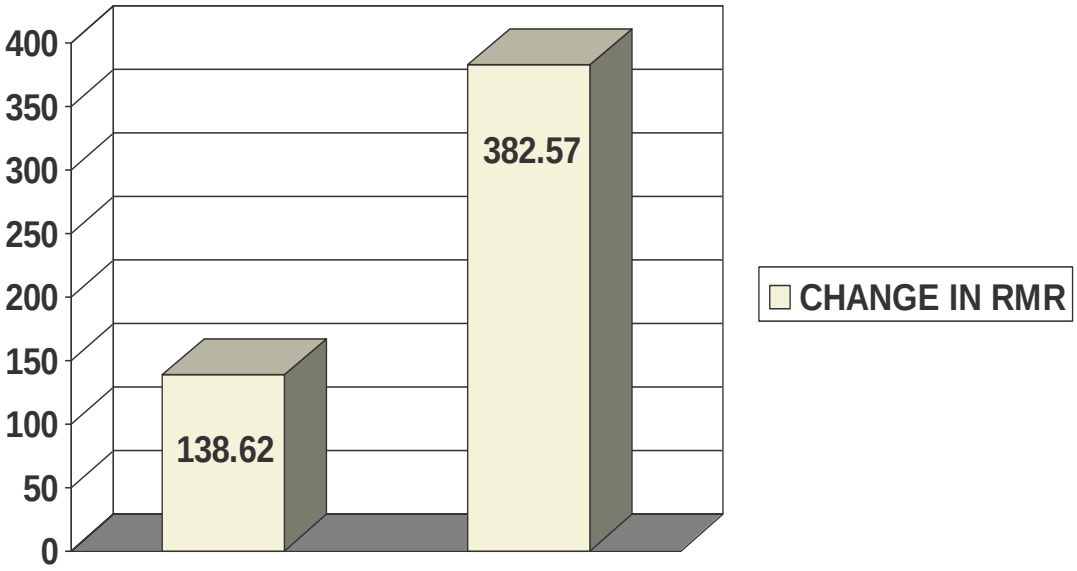
REFLEX PARAMETERS



Serum Measurements

TSH became small (<0.3 mU/L), when RMR increased only 138.62 calories above baseline values. Symptoms normalized when BR reached target level (FIRE-PREFIRE < 66 msecs). At that point RMR was 382.57 kcal above baseline values(Figure 6).

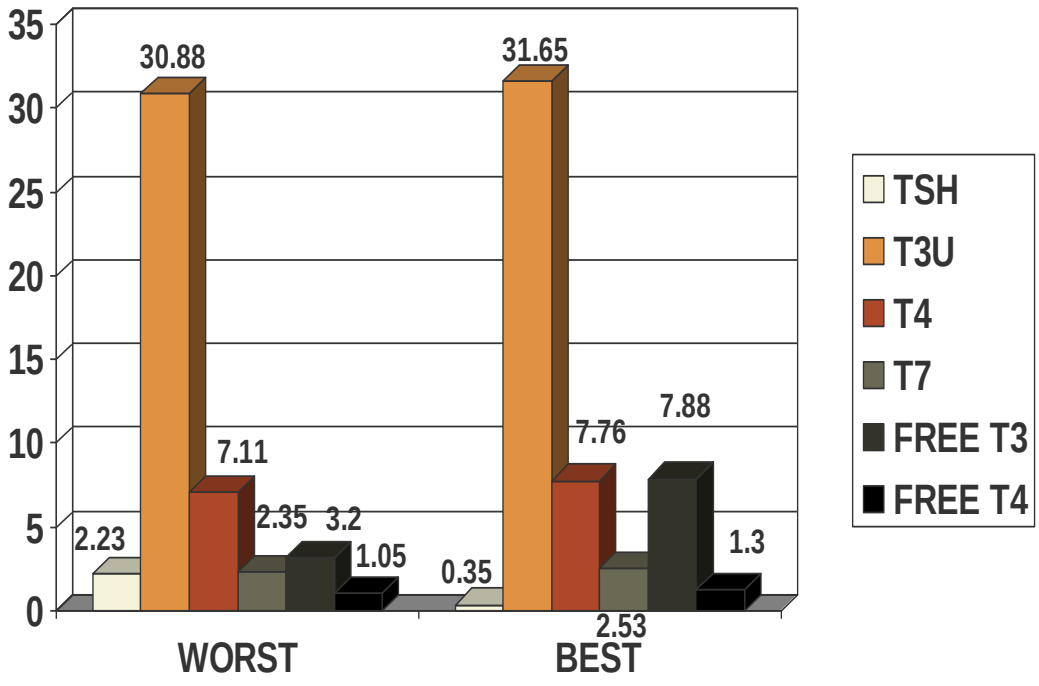
TSH BECOMES LOW BEFORE EFFECT



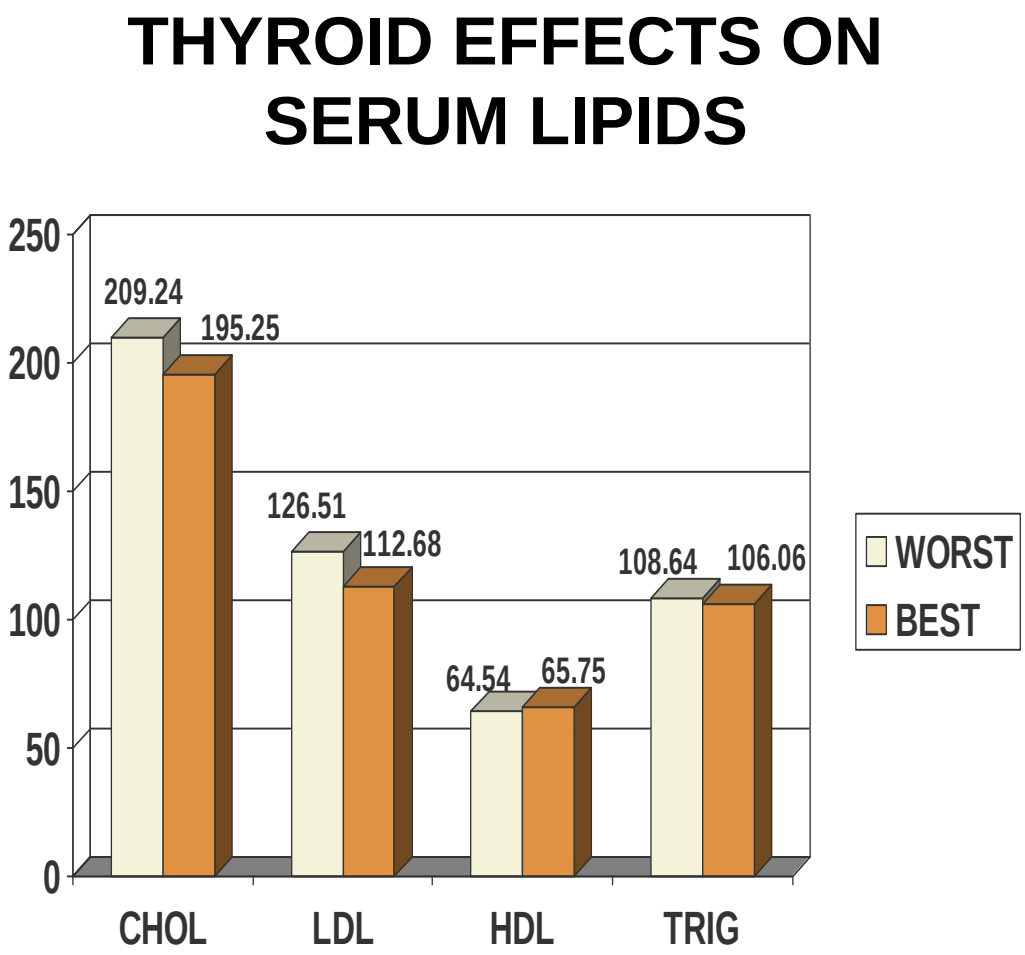
TSH <0.3 FIRE-PREFIRE<66

Free T3 became high, but other serum thyroid measurements remained normal. (Figure 7)

WORST TO BEST



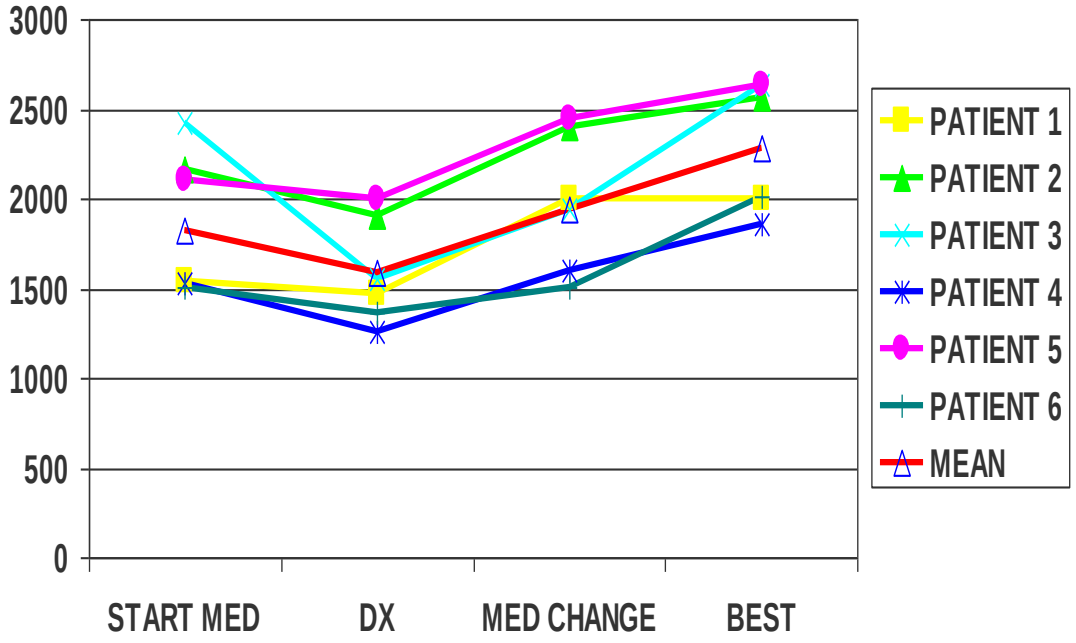
Serum cholesterol, LDL, and triglycerides were reduced by treatment with thyroid medication compared to baseline values. HDL increased. (Figure 8).



Serum ACTH and prolactin levels remained normal in the population that reached the reflex target of Fire-PreFire < 66 msecs; although serum TSH levels were <0.3 mU/L.

Hashimoto's Disease and Thyroid Treatment
Six patients in the database were discovered to have Hashimoto's. This was suspected if Symptoms, RMR and BR measurements regressed in spite of increasing thyroid medication dosage. In every case, when microsomal (TPO), and/or thyroglobulin antibodies, were found, the medication was switched from natural tissue to synthetic or visa versa. In every case, at the next measurement interval, Symptoms, RMR and BR increased, (showing more activity), although the antibodies remained high. This was seen as an indication that the antibodies did not recognize and bind with the new medication, thereby increasing receptor response. (Figure 9)

HASHIMOTO'S AND RMR



Discussion

Clinical investigators have long recognized that there was a discrepancy in reconciling patient's symptoms and serum measurements of thyroid function. We started this case series to find out which parameters were the best clinical markers to use in identifying and managing subclinically hypothyroid patients. Our hypothesis was that physiological measurements of thyroid function were better indicators of functional status than serum measurements, and that many subclinically hypothyroid patients were not receiving adequate treatment, which may increase their health risk. Statistics on the collected data support the hypothesis. We believe that the unaccounted variance comes from stress events that occurred between measurement intervals that affected thyroid function.

Conclusions

Subclinical Hypothyroidism appears to greatly affect the patient's health risk of many chronic degenerative diseases. We believe that it is essential to treat this syndrome. In this population, the evidence supports the hypothesis that physiologic measurements of thyroid function are more accurate at identifying the subclinical hypothyroid state than serum measurements. Volunteers became functionally normal and thyroid symptoms resolved when their medication doses were titrated using RMR and BR as the primary endpoints. Only 14 of over 800 patient interactions (1.7%) noted symptoms of

nervousness, tachycardia, palpitations or insomnia although TSH levels became <0.01mU/L in many volunteers. (Figure 10)

HYPERTHYROID SIGNS

PALPITATIONS	6:815	0.7%
TACHYCARDIA	4:815	0.4%
SHAKEY/HYPER	2:815	0.2%
HAIR LOSS	1:815	0.1%
HYPERTENSION	1:815	0.1%
TOTAL	14:815	1.7%

Looking at one chronic disease indicator, serum lipids; short term changes showed a reduction in serum lipids (increase in HDL) which suggested a reduction in risk was achieved with adequate treatment of subclinical hypothyroid. An incidental finding was that in Hashimoto's thyroiditis patients, thyroid activity appeared to increase if medication was changed from natural to synthetic or visa versa in spite of high antibody levels. This would indicate that the auto-antibodies did not "recognize" the new medication.

It appears that being slightly hyperthyroid has advantages in terms of increased longevity and decreased risk of several chronic degenerative diseases. Calcium supplementation of 1000-1500 mg/day as well as ipriflavone 900 mg/day to reduce bone resorption is important in patients whose TSH is less than 0.3 mU/L.

Competing interests

Dr. Kail is the Medical Director of Western Research Laboratories, Inc. Manufacturer of Naturethroid™, Westhroid™, and ThyroCare Hypo™.
Dr Kail is Medical Director and part owner of Non-invasive Medical Devices Inc. DBA Thyroflex™.

Authors' contributions

Dr. Kail designed and carried out the clinical trial. The data was statistically evaluated and reported by Dr. Waters.

Acknowledgements

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