REVIEW ARTICLE

Thyro-weight: Unlocking the Link between Thyroid Disorders and Weight

Shashank R Joshi

Abstract

Thyroid hormone is an important determinant of energy expenditure and contributes to appetite regulation, while hormones and cytokines from the adipose tissue act on the CNS to inform on the quantity of energy stores. A continuous interaction between the thyroid hormone and regulatory mechanisms localized in adipose tissue and brain is important for human body weight control and maintenance of optimal energy balance. Direct effects on ATP utilization are a result of thyroid hormone's actions on metabolic cycles and increased cell membrane ion permeability. However, the majority of thyroid hormone induced energy expenditure is thought to be a result of indirect effects, which, in turn, increase capacity for energy expenditure. This review discusses the direct actions of thyroid hormone on energy expenditure, and places special emphasis on the indirect actions of thyroid hormone, which include mitochondrial biogenesis and reduced metabolic efficiency through mitochondrial uncoupling mechanisms.

Introduction

It is well defined that Thyroid Hormone regulates energy balance, body weight, lipid metabolism and cardiovascular function.[1] Excessive thyroid hormone levels (hyperthyroidism) lead to hypermetabolic state characterized by increased energy expenditure and weight loss despite increased appetite. Decreased thyroid hormone levels (hypothyroidism), by contrast, is associated with decreased metabolic rate and weight gain.[2] Most of these effects are due to the direct action of thyroid hormones on target tissues, such as liver, white and brown adipose tissues (WAT and BAT, respectively), heart and skeletal muscle via modulation of adrenergic nervous system and direct actions on genes expression.[3] However, there is increasing body of evidence for a direct central action of thyroid hormone modulating metabolic processes and energy expenditure.

Thyroid Hormone and Energy Expenditure

Thyroid hormone plays a role in the determination of energy expenditure in humans. Thyroid hormone has been demonstrated to modulate the behaviour of many metabolic pathways potentially relevant for the basal metabolic rate (BMR) and REE. Major mechanisms include uncoupling of cellular metabolism from adenosine triphosphate (ATP) synthesis, or changes in the efficiency of metabolic processes downstream from the mitochondria. The latter category includes ''futile cycles,'' which occur when single reversible steps in metabolism proceed simultaneously, or ''substrate cycles'' such as when opposing energy-requiring pathways of metabolism proceed simultaneously, for example, glycolysis simultaneous with gluconeogenesis (Figure 1).[4] The critical role of thyroid hormone in energy expenditure modulation has been known for more than a century, starting with the ground-breaking work of Magnus-Levy in 1895. However, each specific mechanism, and in particular their regulatory systems, have yet to be fully elucidated.

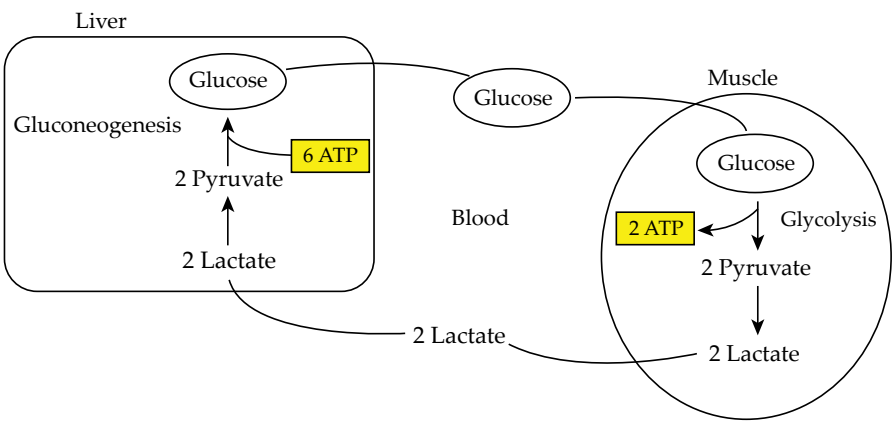

Fig. 1: Glycolysis simultaneous with gluconeogenesis

Direct Effects

Direct effects refer to TH actions that inherently cause an increase in ATP utilization. In general, these actions can be further classified into those that are related to metabolic cycles, and those that are related to ion leaks.

Metabolic Cycles

Metabolic cycles, also referred to as substrate or futile cycles, are the combination of two or more reactions which act in a cyclical manner; for a two reaction cycle, the reactions operate in reverse under the control of separate enzymes. Broadly then, futile cycles include such processes as glycolysis/gluconeogenesis, lipolysis

Department of Endocrinology, Lilavati Hospital, Mumbai, Maharashtra
Received: 13.10.2017; Accepted: 20.10.2017

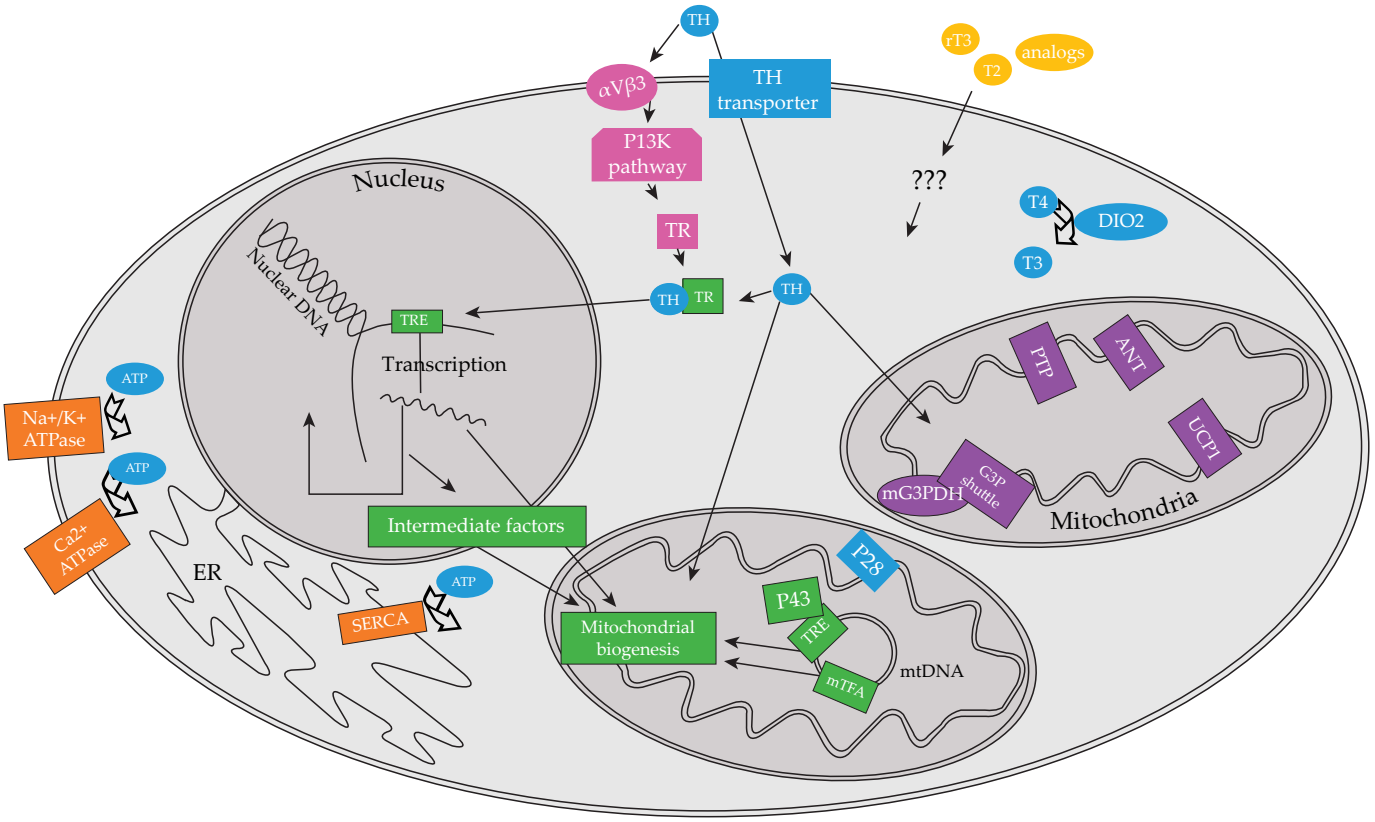

Fig. 2: Mechanisms by which thyroid hormone modulates energy expenditure on the cellular level. Adapted from: Vaitkus JA et al. Thyroid Hormone Mediated Modulation of Energy Expenditure. Int J Mol Sci. 2015 Jul 16;16(7):16158-75.

(also referred to as fatty acid oxidation)/ lipogenesis, and protein turnover, among others.[5] Thyroid hormone action promotes substrate cycling. Interestingly, Grant and colleagues demonstrated that this increase in cycling results in a reduction in reactive oxygen species (ROS) formation in states of over nutrition. Therefore, thyroid hormones, by promoting "futile" cycles, plays an important role as an antioxidant in addition to increasing energy expenditure.[6]

Ion Leaks

A similar yet distinct target of thyroid hormone activity is an increase in ion leakage, resulting from thyroid hormone -induced increased cellular membrane permeability to ions. Consequently, a new ion gradient is established, and cells act to re-establish the desired ion concentrations across the membrane of interest at the cost of increased ATP utilization. Two of the most widely studied and understood ion leaks which are induced by thyroid hormone and lead to futile ion cycling are the Na+/K+ ATPase and the sarco/ endoplasmic reticulum Ca2+ ATPase (SERCA) (Figure 2). TH action increases both Na+ influx and K+ efflux into/ out of cell plasma membranes, which not only results in increased Na+/K+ ATPase activity[7] but also increased expression and insertion of these Na+/ K+ ATPases into the plasma membrane.[8] TH also mediates leakage of Ca2+ from the sarcoplasmic/endoplasmic reticulum (SR/ER) into the cytosol,[9] and induces increased expression of ryanodine receptors, which in turn further increase Ca2+ efflux out of the SR/ER into the cytosol.[10] Since Ca2+ is an extremely important signaling ion and second messenger used by cells, its leakage has the potential to undermine cell survival. In order to restore homeostasis, the cell compensates by increasing Ca2+ influx back into the SR/ER via TH-induced expression of SERCA.[11]

Indirect Effects

Thermogenic effect

While direct effects have been demonstrated to be important in thyroid hormone -induced energy expenditure, the majority of the thermogenesis induced by thyroid hormone can be attributed to indirect effects.[5] Indirect effects result in an increased capacity for EE through non-genomic pathways and mitochondrial biogenesis, and also a reduction in metabolic efficiency at the stage of ATP production, by activating uncoupling mechanisms.

Non-Genomic Pathways

thyroid hormone participates in diverse non-genomic actions which can be initiated at the plasma membrane, in the cytoplasm, or in the mitochondria. These recently discovered non-genomic actions of TH are important for the coordination of normal growth and metabolism, and include regulation of ion channels and oxidative phosphorylation. The principal mediators of non-genomic thyroid hormone actions on metabolism are the protein kinase signalling cascades.[12,13]

Mitochondrial Biogenesis Thyroid hormone exerts some of its thermogenic effects by stimulating mitochondrial biogenesis, which has substantial energy expenditure implications. Of note, the elevated oxidative capacity due to an increase in the number of mitochondria is not synonymous with an increase in baseline energy expenditure, but rather reflects the

potential for expansion of respiration in response to an increased demand (such as muscle contraction or adaptive thermogenic response activation).[14]

TH-dependent mitochondrial biogenesis occurs via three mechanisms:

1. action on nuclear thyroid hormone receptors;
2. activation of mitochondrial transcription; and
3. expression and activation of intermediate factors that span both the nucleus and the mitochondria

Alternatively, changes in ion fluxes linked to ATP utilization or kinase activities may lead to increased metabolic inefficiency and heat generation, as could increases in protein turnover and perhaps bone turnover. Data exist to support the concept that thyroid hormone acts in each of these ways, at least in pathologic states of thyroid hormone excess or deficiency, but it still remains to be determined which are most physiologically relevant in euthyroid subjects. The example of thyroid hormone–dependent thermogenesis is not strictly related to the basal metabolic rate, but rather adaptive thermogenesis, with uncoupling of oxidative phosphorylation in cold-exposed brown adipose tissue (BAT) being dependent on locally generated thyroid hormone. In small mammals, sympathetic adrenergic stimulation of BAT induces uncoupling protein-1 (UCP-1), a protein that uncouples the mitochondrial proton gradient from ATP production promoting the generation of heat. A critical element in this pathway is the type 2 deiodinase (D2), which increases local, intracellular T3 production from T4 to such an extent that thyroid hormone receptor (TR) saturation increases from 70% to near 100% upon cold exposure, while serum T3 levels do not appear to be affected.[15] The increased cyclic adenosine monophosphate (cAMP) synergistically combines with the increased, locally produced T3 such that UCP-1 is upregulated. This mechanism also illustrates the molecular links between the adrenergic signalling cascade/sympathetic innervation and thyroid hormone action, a relationship that has been shown to be important for both thermogenic and nonthermogenic roles of thyroid hormone.[9,16]

The modulation of thyroid hormone's actions is critical in the delivery of time and tissue specific signalling. The effects of thyroid hormone in increasing energy expenditure via modulation of the adaptive thermogenesis response, coupled with the ability of increasing respiratory capacity by regulating mitochondrial biogenesis, are augmented by the increase in thyroid hormone's non-mitochondrial effects on futile cycles and ion transport.[17]

Thyroid Function in Obese patients

TSH levels are at the upper limit of the normal range or slightly increased in obese children, adolescents, and adults and are positively correlated with BMI.[18] Low fT4 with a moderate increase in T3 or free T3 (fT3) levels has been reported in obese subjects.[19] Progressive fat accumulation was associated with a parallel increase in TSH, and fT3 levels irrespective of insulin sensitivity and metabolic parameters and a positive association has been reported between the fT3 to fT4 ratio and both waist circumference and BMI in obese patients.[20]

The causes underlying these alterations in thyroid functions are not known. One theory suggests an increased deiodinase activity leading to a high conversion rate of T4 to T3. This is interpreted as a defense mechanism in obese subjects capable of counteracting the accumulation of fat by increasing energy expenditure.[21] Another probable mechanism is the compensatory increase in secretion of TSH and fT3 in an attempt to overcome decreased tissue responsiveness to circulating thyroid hormones due to the reduced expressions of both TSH and thyroid hormones in adipocytes of obese subjects.[22] High levels of leptin, found in obese subjects, is another potential cause. The main action of leptin is to report centrally the amount of fat, leading to a decrease in appetite and food intake. Leptin has also been shown to stimulate centrally the transcription of pro-thyrotropin-releasing hormone (TRH) and consequently also that of TRH and TSH. Leptin also enhances the activity of deiodinases. Further explanation is that inflammatory cytokines secreted from adipose tissue such as tumor necrosis factor alpha, interleukin (IL)-1 and IL-6, inhibit sodium/iodide symporter mRNA expression and iodide uptake activity.

Hypothyroidism and Weight Gain

Thyroid hormones and body fat appear to be closely related. In humans, overt hypothyroidism is associated with variable degrees of weight gain of 3 to 6 kg.[23] Thyroid hormones play an important role in regulating basal metabolism, thermogenesis and play an important role in various metabolic processes like lipid and glucose metabolism, food intake and fat oxidation.[24] Thyroid dysfunction undoubtedly is associated with changes in body weight and composition, body temperature and total and resting energy expenditure (REE) independent of physical activity.

Hypothyroidism is associated with decreased thermogenesis, decreased metabolic rate, and has also been shown to correlate with a higher body mass index (BMI) and a higher prevalence of obesity.[25] There is clinical evidence suggesting that even mild thyroid dysfunction in the form of subclinical hypothyroidism is linked to significant changes in body weight and represents a risk factor for overweight and obesity.

In humans, overt hypothyroidism is associated with variable degrees of weight gain. While being a frequent complaint (weight excess was reported in 54% patients with overt hypothyroidism), weight gain is usually of limited extent. In line with this concept, the BMI was not found to be greater in elderly women with subclinical hypothyroidism compared with euthyroid controls.[26-28] The alterations in body weight associated with hypothyroidism may reflect both the accumulation of body fat, due to decreased REE and reduced physical activity, and the increased water content of the body, consequent to a reduced capacity of excreting free water. Hypothyroid subjects also have increased amounts of glycosaminoglycans that are responsible for the greater water-binding capacity, a condition that results in the typical 'myxedema' of hypothyroidism.[29]

From a clinical perspective, obesity and mild thyroid failure are common diseases and frequently coexist. An Indian study showed that among the obese, 33% had overt, and 11%

had subclinical hypothyroidism. It further showed that obesity was more common (46% vs. 34%) in overt than in subclinical hypothyroidism.[30]

Hyperthyroidism and Weight Loss

Despite increased appetite, hyperthyroidism is usually associated with a variable decrease in body weight, due to a decline in both lean and fat mass, associated with an increase in total energy expenditure.[31,32] The latter phenomenon results from a reduced thermodynamic efficiency of the biologic machine with increased heat production.[33] As a consequence, accelerated protein catabolism and skeletal muscle atrophy has been observed in experimental thyrotoxicosis.[34] Furthermore, hyperthyroidism causes a negative calcium balance and reduced bone mineral density.[35] The extent of these phenomena depends on the severity of the thyrotoxic state and the length of exposure. Occasionally, a paradoxical weight gain is observed in some thyrotoxic patients because, due to a greatly increased appetite, their caloric intake exceeds the augmented energy expenditure.

Pearls for Clinical practice

Clinicians should be particularly alert to the possibility of thyroid dysfunction in obese patients. The problem lies in identifying obese subjects who are affected by mild thyroid hormone deficiency. On one hand, raised TSH may be a just a functional consequence of obesity. On the other hand, thyroid failure, especially the subclinical form, may go undiagnosed in obese patients. These patients will continue to increase in weight and will develop a deranged lipid profile, thereby bringing the thyroid/obesity and cardiovascular link association to a full circle. The question that emerges is whether an obese patient should be diagnosed as having subclinical hypothyroidism based on an elevated serum TSH level alone. Data suggest that just an elevated serum TSH might not be enough for diagnosing subclinical hypothyroidism in patients with morbid obesity. Thus, it would seem reasonable to measure circulating plasma levels of thyroid hormones and thyroid autoantibodies in these patients to support a diagnosis of autoimmune thyroid failure.[36]

References

1. Brent GA. Mechanisms of thyroid hormone action. *J Clin Invest* 2012; 122:3035-3043.
2. Kim B. Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. *Thyroid* 2008; 18:141-144.
3. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. *Physiol Rev* 2014; 94:355-382.
4. Bianco AC, Maia AL et al. Adaptive Activation of Thyroid Hormone and Energy Expenditure. *Biosci Rep* 2005; 25:198-208.
5. Yehuda-Shnaidman E., Kalderon B., Bar-Tana J. Thyroid hormone, thyromimetics, and metabolic efficiency. *Endocr Rev* 2014; 35:35–58.
6. Grant N. The role of triiodothyronine-induced substrate cycles in the hepatic response to overnutrition: Thyroid hormone as an antioxidant. *Med Hypotheses* 2007; 68:641–649.
7. Haber RS, Ismail-Beigi F, Loeb JN. Time course of Na, K transport and other metabolic responses to thyroid hormone in clone 9 cells. *Endocrinology* 1988; 123:238–247.
8. Gick G.G., Ismail-Beigi F. Thyroid hormone induction of Na+-K+-ATPase and its mRNAs in a rat liver cell line. *Am J Physiol* 1990; 258:C544–C551.
9. Silva J.E. Thermogenic mechanisms and their hormonal regulation. *Physiol Rev* 2006; 86:435–464.
10. Jiang M, Xu A, Tokmakejian S, Narayanan N. Thyroid hormone-induced overexpression of functional ryanodine receptors in the rabbit heart. *Am J Physiol Heart Circ Physiol* 2000; 278:H1429–H1438.
11. Kahaly GJ, Dillmann WH. Thyroid hormone action in the heart. *Endocr Rev* 2005; 26:704–728.
12. Weitzel JM, Iwen KA. Coordination of mitochondrial biogenesis by thyroid hormone. *Mol Cell Endocrinol* 2011; 342:1–7.
13. Bassett JH, Harvey CB, Williams GR. Mechanisms of thyroid hormone receptor-specific nuclear and extra nuclear actions. *Mol Cell Endocrinol* 2003; 213:1–11.
14. Holloszy JO. Skeletal muscle "mitochondrial deficiency" does not mediate insulin resistance. *Am J Clin Nutr* 2009; 89:463S–466S.
15. Bianco AC, Silva JE. Nuclear 3,5,30-triiodothyronine (T3) in brown adipose tissue: receptor occupancy and sources of T3 as determined by in vivo techniques. *Endocrinology* 1987; 120:55–62.
16. Ojamaa K, Klein I, Sabet A, Steinberg SF. Changes in adenylyl cyclase isoforms as a mechanism for thyroid hormone modulation of cardiac beta-adrenergic receptor responsiveness. *Metabolism* 2000; 49:275–279.
17. Vaitkus JA, Farrar JS, Celi FS. Thyroid Hormone Mediated Modulation of Energy Expenditure. Ross JM, Coppotelli G, eds. *International Journal of Molecular Sciences* 2015; 16:16158-16175. doi:10.3390/ijms160716158.
18. Biondi B. Thyroid and obesity: An intriguing relationship. *J Clin Endocrinol Metab* 2010; 95:3614–7
19. Tagliaferri M, Berselli ME, Calò G, Minocci A, Savia G, Petroni ML, et al. Subclinical hypothyroidism in obese patients: Relation to resting energy expenditure, serum leptin, body composition, and lipid profile. *Obes Res* 2001; 9:196–201
20. Chomard P, Vernhes G, Autissier N, Debry G. Serum concentrations of total T4, T3, reverse T3 and free T4, T3 in moderately obese patients. *Hum Nutr Clin Nutr* 1985; 39:371–8
21. Longhi S, Radetti G. Thyroid function and obesity. *J Clin Res Pediatr Endocrinol* 2013; 5(Suppl 1):40–4.
22. Nannipieri M, Cecchetti F, Anselmino M, Camastra S, Niccolini P, Lamacchia M, et al. Expression of thyrotropin and thyroid hormone receptors in adipose tissue of patients with morbid obesity and/or type 2 diabetes: Effects of weight loss. *Int J Obes (Lond)* 2009; 33:1001–6.
23. I Kostoglou-Athanassiou, K Ntalles. Hypothyroidism - new aspects of an old disease. *Hippokratia* 2010; 14:82–87.
24. Rosenbaum M, Hirsch J, Murphy E, Leibel RL. Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function. *Am J Clin Nutr* 2000; 71:1421–32.
25. Danforth E, Jr, Horton ES, O'Connell M, Sims EA, Burger AG, Ingbar SH, et al. Dietary-induced alterations in thyroid hormone metabolism during overnutrition. *J Clin Invest* 1979; 64:1336–47.
26. Zulewski H, Müller B, Exer P, Miserez AR, Staub JJ. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. *Journal of Clinical Endocrinology and Metabolism* 1997; 82:771–776.
27. Carlé A, Bülow Pedersen I, Knudsen N, Perrild H, Ovesen L, Banke Rasmussen L, Jørgensen T, Laurberg P. Smoking cessation is followed by a sharp but transient rise in the incidence of overt autoimmune hypothyroidism – a population-based, case–control study. *Clinical Endocrinology* 2012; 77:764–772.
28. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam study. *Annals of Internal Medicine* 2000; 132:270–278.
29. Skowsky WR & Kikuchi TA. The role of vasopressin in the impaired water excretion of myxedema. *American Journal of Medicine* 1978; 64:613–621.
30. Verma A, Jayaraman M, Kumar HK, Modi KD. Hypothyroidism and obesity? Cause or effect. *Saudi Med J* 2008; 29:1135–8.
31. Ramsay ID. Muscle dysfunction in hyperthyroidism. Lancet 1966 2 931–934. Hoogwerf BJ & Nuttall FQ. Long-term weight regulation in treated hyperthyroid and hypothyroid subjects. *American Journal of Medicine* 1984; 76:963–970.
32. Seppel T, Kosel A & Schlaghecke R. Bioelectrical impedance assessment of body composition in thyroid disease. *European Journal of Endocrinology* 1997; 136:493–498.
33. Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. *Annals of Internal Medicine* 2003; 139:205–213.
34. Martin WH III, Spina RJ, Korte E, Yarasheski KE, Angelopoulos TJ, Nemeth PM, Saffitz JE. Mechanisms of impaired exercise capacity in short duration experimental hyperthyroidism. *Journal of Clinical Investigation* 1991; 88:2047–2053.
35. Cohn SH, Roginsky MS, Aloia JF, Ellis KJ, Shukla KK. Alteration in elemental body composition in thyroid disorders. *Journal of Clinical Endocrinology and Metabolism* 1973; 36:742–749.
36. Rotondi M, Leporati P, La Manna A, Pirali B, Mondello T, Fonte R, et al. Raised serum TSH levels in patients with morbid obesity: Is it enough to diagnose subclinical hypothyroidism? *Eur J Endocrinol* 2009; 160:403–8.