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Review Article

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Effect of Levothyroxine Therapy on Body Mass and Obesity in Overt and Subclinical Hypothyroidism

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ABSTRACT

Obesity has been defined as a body mass index (BMI) greater than 30 kg/m2 and is becoming a leading cause of preventable death. A significant cause of obesity development is an imbalance between energy intake and expenditure. Cellular respiration and thermogenesis modulate resting metabolic rate, and thyroid hormones impact energy expenditure. Thyroid hormones affect appetite regulation and modulate lipid turnover in adipocytes. Many health disorders have been linked to obesity, which causes a burden on the individual as well as the community. Preventable diseases such as type 2 diabetes, hypertension, hypercholesterolemia, hypertriglyceridemia, and nonalcoholic fatty liver disease are associated with overweight and obesity. Moreover, obesity can influence thyroid function in various clinical presentations, such as subclinical Hypothyroidism, which may cause alterations in basal metabolic rate with a consequent increase in BMI, and overt Hypothyroidism, in which obesity may be a presenting feature. This review focuses on the effect of Thyroxine treatment for overt and subclinical Hypothyroidism on body mass and obesity.

Key words: *Obesity, Body mass, Subclinical, Overt, Hypothyroidism*

INTRODUCTION

Continuously, there has been a significant increase in the prevalence of obesity and overweight. Sedentary lifestyles and high-calorie diets are the key behavioral factors contributing to obesity [1]. Previous studies have suggested that abnormalities in food metabolism resulting in hypothyroidism can lead to the accumulation of fat and subsequent thyroid-related obesity. However, recent research focuses on the idea that obesity may contribute to thyroid dysfunction. Structural changes and altered thyroid activity commonly observed in obese children prove this connection. These studies demonstrate a significant correlation between body mass index (BMI) and thyroid hormone levels and the impact of increased body fat on thyroid structure. Furthermore, thyroid functions tend to normalize after weight loss. There is no conclusive evidence regarding transforming childhood thyroid dysfunction into chronic thyroid diseases in adulthood [2].

While most adult studies have explored the relationship between BMI and abnormal thyroid function, low thyroid hormone levels are associated with decreased energy expenditure [3] and fluid retention [4] in individuals with overt hypothyroidism. In the case of obese children, many studies pay particular attention to thyroid function, as it is believed that hypothyroidism can be one of the causes of obesity [5]. Thus, thyroid function tests are commonly conducted in this group of patients. Numerous studies have shown that obese children have higher thyroid-stimulating hormone (TSH) levels than non-obese children. Some studies have also demonstrated that weight loss is associated with reduced TSH levels [6].

In studies focusing on thyroid adults with obesity, higher levels of TSH [7] and triiodothyronine (T3), as well as slightly decreased levels of free thyroxine (FT4) [8], have been associated with increased adiposity. However, the results are inconsistent, as other studies have yet to find a relationship between measures of adiposity and TSH, T3, or FT4 [6, 9, 10]. Research in the pediatric population is relatively limited, often with small sample sizes and conflicting findings. Most studies have shown an association between TSH and BMI, as well as T3 and BMI, while others have not observed this association. In contrast to adults, most pediatric studies have not found a relationship between FT4 and BMI [11-13].

Whether levothyroxine (LT4) treatment alone can lead to significant weight loss or whether obese patients with hypothyroidism need additional weight management strategies has triggered several studies. This report summarizes the literature on the effect of LT4 treatment for Overt and Subclinical Hypothyroidism on body mass and obesity.

Thyroid hormones and body mass

Independent of physical activity, thyroid dysfunction is linked to alterations in body weight and composition, core body temperature, and total and resting energy expenditure (REE). Furthermore, weight gain frequently occurs after thyroid dysfunction treatment [14]. Weight gain, reduced thermogenesis, and slowed metabolism are frequently seen in both subclinical and overt hypothyroidism [14-16]. Subclinical and overt hypothyroidism is associated with a higher BMI and a higher prevalence of obesity in smokers and nonsmokers, according to a recent cross-sectional population-based study of 27,097 adults over 40 with a BMI of at least 30.0 kg/m2 [15]. It has been noted that in hypothyroid patients, slight variations in serum TSH brought on by tiny adjustments to the LT4 dosage during replacement therapy are linked to noticeably altered REE [17]. These studies confirm the clinical findings that a small amount of thyroid dysfunction is associated with significant weight changes and may be a risk factor for obesity and overweight people [18].

Thyroid hormones abnormalities in the obese population

Notably, obese individuals have a mild rise in total T3 or free T3 (FT3) levels [19, 20]. FT3 to free (FT4) ratio has been linked positively to both waist circumference and BMI in obese patients, and progressive fat accumulation has been linked to a parallel increase in TSH and FT3 levels regardless of insulin sensitivity and metabolic characteristics [21]. This observation shows that enhanced deiodinase activity, a compensatory strategy for fat accumulation to increase energy expenditure, results in high conversion of T4 to T3 in patients with central fat obesity [21].

Moreover, TSH levels were reported to be metabolic risk factors in obese children [20, 22] and adults [23]. However, disparities exist among studies, as one study demonstrated [20] that serum TSH levels affect lipid profiles in obese children and adolescents. At the same time, others [23] reported no significant differences between TSH levels and serum triglyceride (TG), total cholesterol (TC), and high-density lipoprotein-cholesterol (HDL-C) concentrations in adults. A conflicting result was observed between TSH concentration and BMI and fat mass in obese adults [24-26] and the pediatric population [27-29].

After losing weight, whether due to a diet or bariatric surgery, abnormal thyroid function and TSH levels typically return to normal [20-28, 30-32]. Losing weight causes a considerable drop in TSH and FT3 [20, 21, 31, 32], which raises reverse T3 because of reduced 5′-deiodination. When people continue to restrict calories while losing weight, their T3 levels fall, which lowers their energy usage. Therefore, challenges in maintaining or further reducing weight loss may be brought on by decreased T3 levels [32]. The observation that obesity causes an increase in TSH, FT3, and leptin levels and that weight loss causes a decrease in these levels supports the idea that the altered thyroid function seen in obese people can be reversed by decreasing weight [33].

Effect of levothyroxine therapy on body weight/ BMI in SCH

Recent evidence did not support a causal relationship between obesity and SCH since TSH levels reverted to normal upon weight reduction. Moreover, the current European Thyroid Association guidelines proposed that there is no evidence in favor of levothyroxine's beneficial effects on body weight in obese subjects having SCH with TSH <10 mIU/l [34]. Many studies evaluated the effect of LT4 on weight or BMI on subclinical hypothyroidism **(Table 1)**.

A systematic review included four studies looked at the effect of LT4 therapy on either weight or BMI with a total of 305 SCH subjects and a period ranging from 5-12 months in which none found any significant change in either weight or BMI after five months, 24 weeks, six months, or one year [35]. A study examined the

relationship between SCH, weight change, and body composition in elderly individuals. The authors concluded that there is a clinically insignificant impact of subclinical hypothyroidism on weight status in the elderly [36].
A relationship of LT4 to fat mass was explored in one study [37] and concluded that epicardial adipose tissue (EAT) thickness due to SCH improved with L-thyroxine treatment in predominantly old male subjects with more excellent baseline EAT thickness.
A study carried out an investigation exploring the role of LT4 replacement in subclinical hypothyroidism. No significant changes were observed from baseline till the end of the investigation in the thyroxine and placebo group, and it was concluded that no relevant clinical benefits were observed from six months of LT4 treatment in women with mild subclinical hypothyroidism [38]. Although there is a lack of prospective studies in the pediatric population, a study demonstrated no significant changes in weight and body mass detected during follow-up of children with subclinical hypothyroidism [39, 40].

Table 1. LT4 therapy effect on Weight (kg)/body mass index (BMI) (kg/m2) in subclinical hypothyroidism

Study, (Year)	Study design	Target population	Study Duration	Study Measures	Conclusion
Garin *et al*., 2014 [36]	Cross-sectional prospective study	Elderly	6 years	Weight/body composition	NS
Sayin *et al*., 2015 [37]	Prospective study	Older men	3 months	Fat mass/EAT thickness	Significant effect
Kong *et al*., 2002 [38]	Randomized controlled trial	Women	6 months	body weight and REE	NS
Caraccio, (2005) [41]	double-blind study	Adults	6 months	BMI	NS
Iqbal *et al.* (2006) [42]	double-blind intervention study	Adults	1year	BMI	NS
Rasvi *et al*. (2007) [43]	Randomized controlled trial	Adults	3 months	weight	NS

Abbreviations: BMI=body mass index; NS=not significant. EAT=epicardial adipose tissue. REE=resting energy expenditure

Effect of LT4 therapy on body weight/ BMI in overt hypothyroidism
Variable studies examined the weight change in hypothyroid patients after initiating LT4 therapy **Table 2**. One study [44] aimed to investigate weight change for primary hypothyroidism with a TSH level ≥ 10 mIU/L. The authors concluded that only 52% of patients lost weight, meaning no significant weight change occurred after LT4 treatment. Of interesting note, many patients post total thyroidectomy complained of weight gain and changes in body composition. A study [45] evaluated the effect of LT4 replacement on BMI and body composition following total thyroidectomy for benign multinodular goiter. The results showed no effect on the body composition; however, age was found to be an essential factor for weight gain and change in BMI during the midterm follow-up period.
Another study [46] aimed to evaluate mechanisms involved in body weight changes associated with a newly diagnosed hypothyroid patient. Their results demonstrated a significant decrease in body weight due to a change in the lean mass compartment but no change in fat mass and an increase in REE, in which authors concluded that the weight loss observed was due to the excretion of excess body water associated with untreated myxedema.
A retrospective study on children with acquired hypothyroidism and LT4 found that treatment of hypothyroidism did not significantly alter weight or BMI percentiles from baseline up to 4 years of follow-up. Their conclusion was consistent with previous studies in adults and did not support the notion of hypothyroidism as a cause of obesity [47].
Further literature review [48], sought to estimate concentration changes of serum lipoprotein in patients treated with LT4 in mild thyroid failure. The authors concluded that there was a better decrease in lipoprotein levels after LT4 therapy compared to untreated individuals.
In a recent prospective, randomized, case-control research, the impact of LT4 supplementation on thyroid dysfunction in children who are obese was investigated. It concluded that children should not be given levothyroxine as part of weight-management therapies because it has no positive impact on parameters of lipid and thyroid profiles or BMI reduction [49].

Following treatment in animals, a significant decrease in body weight, leptin, and adiponectin, but an increase in butyrylcholinesterase (BChE) and Hp. The successful treatment of hypothyroidism reduces circulating adiponectin and leptin levels while increasing BChE activity in dogs. The mean increase in Hp values and decrease in serum amyloid A (SAA) for some dogs after treatment warrants further investigation [50].

Table 2. Studies on levothyroxine effect on Weight (kg)/body mass index (BMI) (kg/m2) in overt hypothyroidism

Study, (Year)	Study design	Target population	Study Duration	Study Measures	Conclusion
Lee *et al.*, (2014) [44]	Retrospective cohort study	Adults	24 months	Weight changes	NS
Ozdemir *et al.*, (2010) [45]	Prospective study	Adults	6-month	BMI and body composition	
Karmisholt *et al.*, (2011) [46]	Prospective study	Adults	12 months	Weight changes and body composition	significant decrease in BW
Lomenick *et al.*, (2008) [47]	Retrospective	Children	4 years	weight or BMI percentiles	NS
Kumar *et al.*, (2019) [49]	Prospective, randomized, case-control study	Children	6 months	BMI in thyroxine versus weight management group	NS
Tvarijonaviciute *et al.* (2013) [50]	Prospective, randomized study	Animal study (dogs)	6 weeks	BW, insulin resistance, and lipid profile	Significant decrease in BW, leptin, and adiponectin.

Abbreviations: BMI=body mass index; NS=not significant; BW= bodyweight

CONCLUSION

Clinicians should be aware of the potential for thyroid dysfunction in obese patients because obesity and thyroid dysfunction are frequent illnesses. Contrary to popular belief that thyroxine replacement can cause weight loss, many studies showed no significant changes after the initiation of levothyroxine in both adults and children, although concurrent lifestyle changes such as diet and exercise were not assessed in these studies.

Future studies are needed to elucidate the relationship between weight changes and treatment of hypothyroidism with standardization of concurrent lifestyle changes, gender, race, education levels, initial TSH and initial weight levels, and how much weight patients gained with the onset of hypothyroidism. Follow-up data is also needed to know if those who did lose weight are the ones who needed to lose weight the most. Consequently, practitioners should not expect a significant decrease in weight after treatment. Advice on diet modification and exercise is essential, and patients should be educated that they should not have high expectations of weight loss if no lifestyle modifications are done.

Studies are also needed to determine whether having high levels of leptin makes a person more susceptible to thyroid autoimmunity, increasing the likelihood of overt or subclinical hypothyroidism.

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