



Weight Gain after Treatment of Thyroid Dysfunction and Thyroid Surgery

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Abstract

Thyroid surgery is generally recommended for malignant conditions and for some benign thyroid disorders. Many patients report weight gain after thyroidectomy especially during the first months following surgery. Studies on patients with Graves' disease treated either with antithyroid drugs or radioiodine confirm that these patients frequently gain weight after restoration of thyroid function. Other studies have also shown that there is considerable weight gain after thyroidectomy for both nodular goiter and thyroid cancer. Transient hypothyroidism during the postoperative period is often thought to be associated with weight gain after thyroidectomy. The role of a number of adipocytokines and their interaction with the thyroid function has been investigated in the pathogenesis of weight changes. Levothyroxine replacement or suppressive therapy after thyroidectomy has a different impact on the metabolic parameters independent of TSH levels. The long-term effects of the impaired T3/T4 ratio are not fully understood as there are no sensitive markers to assess the biological response of target organs and tissues. Future studies are needed to identify such parameters, provide new considerations for the treatment of patients after total thyroidectomy, and help determine individual target hormone levels to ensure a sustained euthyroid state.

Keywords

Graves' disease, levothyroxine, thyroid-stimulating hormone, thyroidectomy, weight gain

INTRODUCTION

Thyroid disorders are among the most common endocrine diseases. The main therapeutic approaches for different thyroid conditions include medication, radioiodine, and surgical treatment. Thyroid surgery is recommended for malignant conditions as well as for some benign thyroid disorders. Many patients report unintentional weight gain after thyroidectomy and most of them consider surgery to be the potential underlying cause. Weight changes are most pronounced during the first months following the intervention despite patients' efforts to diet and exercise.

Weight changes in patients after treatment of Graves' disease

Early studies have been focused on weight gain after treatment in patients with Graves' disease and the proposed effects of the treatment modality (antithyroid drugs, radioiodine or surgery) on the degree of weight changes.¹⁻⁵ Observational studies on patients with Graves' disease treated either with antithyroid drugs or radioiodine confirm the weight gain tendency after restoration of thyroid function.³⁻⁵ Pearce et al.³ demonstrated weight gain in all patients with Graves' disease one year after treatment initiation regardless of the treatment modality (antithyroid medications, radioiodine, or surgical treatment), the great-

est weight gain being observed over the first three months. Weight gain (mean 5.42 kg) was also found by Dale et al.² in patients with thyrotoxicosis after normalization of thyrotrophic hormone (TSH) proposing pre-existing obesity, weight loss during the active thyrotoxic phase and the duration of follow-up as risk factors. Of note, the established weight gain in this study was significantly greater in patients undergoing thyroidectomy than in those treated with radioiodine or antithyroid drugs (10.27 ± 2.56 vs. 4.75 ± 0.57 vs. 5.16 ± 0.63 kg, respectively, $p=0.007$).² In addition, the development of hypothyroidism while on levothyroxine treatment was associated with further weight gain.^{1,2} However, Schneider et al.⁶ demonstrated that compared to patients initially treated with radioiodine, patients undergoing thyroidectomy as a first choice treatment option were less likely to gain weight during the postoperative period.

The results of the aforementioned studies suggest that the observed weight gain is independent of the natural course of the disease¹⁻³ which leads to rapid weight re-gain after restoration of euthyroid state⁷. The fact that Graves' disease is currently being diagnosed at an earlier stage makes it less likely that considerable weight loss will occur prior to initiation of therapy.

Weight changes in euthyroid patients undergoing thyroid surgery

The effect of thyroid surgery on body weight in euthyroid patients is unclear. Low-quality evidence from a recent systematic review and meta-analysis suggests no significant impact of surgery for thyroid cancer or nodules on patients' body weight.⁸ Of interest are studies in patients undergoing thyroidectomy for non-toxic nodular goiter in whom weight gain after surgery is not related to thyroid hyperactivity and subsequent restoration of initial body weight.⁹ There was more pronounced weight gain in patients after thyroidectomy than in those with autoimmune hypothyroidism with the largest increase seen in postmenopausal women compared to premenopausal women (4.4 vs. 2.3 kg, $p=0.007$) or men (4.4 vs. 2.5 kg, $p=0.013$).⁹ In a retrospective study of 267 patients after thyroidectomy Rotondi et al.¹⁰ reported significant weight gain 9 months after the intervention in more than 50% of the cases irrespective of the surgical indication (non-toxic nodular goiter, Graves' disease, toxic nodular goiter, differentiated thyroid carcinoma). Other studies have also shown considerable weight gain after thyroidectomy for both nodular goiter⁹ and thyroid cancer^{11,12}. No relationship between TSH levels during the follow-up period and the risk of weight gain was found indicating that the only risk factor was the degree of initial weight gain in the early postoperative period (40-60 days after thyroidectomy).¹⁰ Moreover, Lang et al.¹³ found significant weight gain over the first year after thyroid surgery in patients with benign nodular goiter regardless of the extent of the resection. Changes in body weight were similar in both patients after total thyroidectomy and after lobectomy despite normal TSH levels. Significant weight gain

in euthyroid patients following hemithyroidectomy for benign goiter may be a clinical manifestation of permanently reduced metabolic activity.¹⁴

Early weight gain, in addition to being difficult to reverse, may also favour a tendency to further gain weight. This may be of particular importance in specific age groups such as perimenopausal women or children in whom even being overweight is a strong predictor of future obesity development.¹⁵ There are a number of studies that show weight gain in children with Graves' disease during the first months after treatment and subsequent increase over the following months.^{16,17}

Hormonal dysfunction during postoperative period as a risk factor

Another factor often thought to be associated with weight gain after thyroidectomy is transient hypothyroidism during the postoperative period.^{1,2} In several studies, patients with Graves' disease who developed hypothyroidism on levothyroxine replacement after therapeutic intervention showed the greatest weight gain. These data suggest that normalization of TSH levels only by levothyroxine substitution may lead to incomplete hormonal replacement.¹ Clinical observations indicate that weight gain in hypothyroidism is mainly caused by water retention and that normalization of TSH leads to rapid weight recovery.¹⁸ Despite the variations of TSH in the first months after thyroidectomy Rotondi et al.¹⁰ did not find a relationship between TSH values and the changes in body weight during the postoperative period. The increase in patients' body mass index (BMI) was independent of the underlying cause for thyroidectomy as well as of the thyroid function before and after the surgery assessed by serial TSH measurement.¹⁰ The 24-hour TSH secretion was stable and was not affected by BMI and age suggesting that the changes in body weight following thyroidectomy were not related to age and BMI prior to surgery.¹⁹

Role of adipocytokines in thyroid function and weight control

Based on the fact that leptin is involved in energy homeostasis, enhances the expression of the TSH gene and increases the conversion of thyroxine (T4) to triiodothyronine (T3) through deiodinases, the potential role of this hormone in body weight regulation in patients after thyroidectomy has been a subject of substantial interest.²⁰ Hsieh et al.²¹ investigated leptin levels in patients after surgery for differentiated thyroid cancer before and during the first 6 months following radioiodine ablation. They found a significant increase in BMI and leptin levels across the changing hormonal state from hypothyroidism to subclinical hyperthyroidism depending on the free thyroxine (FT4) levels.²¹ In addition, the state of transient hypothyroidism after levothyroxine discontinuation was associated with decreased resistin levels though its concentration did not correlate with TSH

and thyroid hormone levels.²² Kaplan et al.²³ investigated pre- and post-operative levels of a number of adipocytokines in women undergoing thyroidectomy for multinodular goiter. No significant changes were found in the leptin, adiponectin, and resistin levels during the hypothyroid phase following thyroidectomy despite the significant increases in body weight, BMI, adipose tissue, and serum lipids in those women.²³ Leptin levels in hypothyroid women after thyroidectomy did not differ from those in euthyroid controls and showed no correlation with thyroid hormone levels.^{23,24} Data from previous studies on adipocytokine levels in patients with thyroid dysfunction suggest that the state of hypo- or hyperthyroidism is associated with changes in adipocytokine levels which however are not affected by thyroid function restoration.^{25,26}

Impact of levothyroxine replacement or suppressive therapy

Some investigators assume that weight gain during the postoperative period may be due to inadequate levothyroxine replacement therapy.^{1,9} This concept is supported by the results of experimental studies showing that small variations in levothyroxine dosage cause significant fluctuations in basal metabolism rate even when TSH is maintained within the reference range.²⁷ This was observed also in population-based studies in which higher TSH levels even within the normal range were associated with an increased incidence of overweight/obesity.^{28,29}

In a number of studies, patients after thyroidectomy for differentiated thyroid cancer were found to experience weight gain being on suprathreshold suppressive levothyroxine treatment.^{10,11} The potential effect of inadequate substitution, if any, seems insignificant.^{11,12} In fact, patients after thyroidectomy receiving suppressive levothyroxine doses showed a significant increase by 3.2% in body weight during 3-to-5-year follow-up despite the suppressed TSH levels.¹¹ Sohn et al.³⁰ found a tendency for a significant increase in BMI after surgery in women but not among men with thyroid cancer during long-term follow-up. In women on levothyroxine, suppressive therapy treatment had no adverse effects on energy expenditure or body composition.³¹ Levothyroxine replacement therapy, however, is associated with lower basal metabolism at rest despite the normal TSH. This may be partially explained by the lower levels of free triiodothyronine (FT3) suggesting that relative tissue hypothyroidism contributes to impaired energy expenditure in levothyroxine replacement therapy.³¹ In a retrospective analysis by Gullo et al.³² of over 1800 patients after thyroidectomy, 15.2% of the patients were found to have lower levels of FT3 and 7.2% had higher values of FT4 compared to healthy individuals despite the similar normal TSH levels. These results probably reflect the inadequate peripheral deiodination and inability to compensate for the lack of T3 secretion leading to impaired pituitary feedback at TSH levels within the reference range.³² Comparison of some markers reflecting the biological activity of thyroid

hormones showed that patients after thyroidectomy were in a hypothyroid state compared to baseline even when TSH was maintained within normal ranges on levothyroxine treatment.³³ The metabolic profile of patients with mildly suppressed TSH values one year after thyroidectomy did not differ from that prior to surgery and was closest to euthyroid state.³³ In patients after thyroidectomy, higher suppressive doses of levothyroxine were required to maintain subnormal TSH values that provided FT3 levels and metabolic parameters similar to pre-surgical values.^{33,34}

CONCLUSIONS

The review of literature raises the question about the presence of unidentified factors associated with levothyroxine replacement therapy which lead to weight gain or whether weight changes are a result of the thyroidectomy itself especially during the early postoperative period. The possible additional factors might include perioperative stress, changes in the diet and lifestyle, sleep disorders, adherence to the levothyroxine therapy, pharmacokinetic features of the medication, and some psychological factors. The long-term effects of the impaired T3/T4 ratio are not fully understood as there are no sensitive markers to assess the biological response of target organs and tissues. Future studies are needed to identify such parameters, provide new considerations for the treatment of patients after total thyroidectomy and help determine individual target hormone levels to ensure a sustained euthyroid state. These data would be useful in the clinical approach for the treatment and follow-up of patients after thyroidectomy and the development of preventive weight-loss strategies especially in high-risk groups.

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Увеличение веса после лечения дисфункции щитовидной железы и операции на щитовидной железе

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Резюме

Операция на щитовидной железе обычно рекомендуется при злокачественных новообразованиях и некоторых доброкачественных заболеваниях щитовидной железы. Многие пациенты сообщают об увеличении веса после тиреоидэктомии, особенно в первые месяцы после операции. Исследования с участием пациентов с основным заболеванием, получавших либо антигипотиреоидные препараты, либо радиоактивный йод, подтверждают, что эти пациенты часто набирают вес после восстановления функции щитовидной железы. Другие исследования также показали, что после тиреоидэктомии наблюдается значительная прибавка в весе как при узловом зобе, так и при раке щитовидной железы. Считается, что транзиторный гипотиреоз в послеоперационном периоде часто связан с увеличением веса после тиреоидэктомии. Роль ряда адипоцитокинов и их взаимодействие с функцией щитовидной железы изучалась в патогенезе изменения веса.

Заместительная или подавляющая терапия левотироксином после тиреоидэктомии по-разному влияет на метаболические параметры, независимо от уровня тиреотропного гормона (ТТГ). Долгосрочные эффекты нарушенного соотношения Т3 / Т4 полностью не выяснены, поскольку нет чувствительных маркеров для оценки биологической реакции органов и тканей-мишеней. Необходимы дальнейшие исследования для определения таких параметров, чтобы предоставить новые предложения по лечению пациентов после тотальной тиреоидэктомии и помочь определить индивидуальные целевые уровни гормонов для обеспечения долгосрочного эутиреоидного статуса.

Ключевые слова

базедова болезнь, левотироксин, тиреотропный гормон, тиреоидэктомия, увеличение веса
