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The Prevalence of Subclinical Hypothyroidism and its Effect after Bariatric Surgery: A Review

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Abstract
One major cause of morbidity and mortality is obesity in this 21st Century obesity. Evidence has shown that obesity is related to comorbidities as subclinical hypothyroidism, type 2 diabetes, hypertension, polycystic ovarian syndrome, hyperlipidemia sleep apnea and coronary heart disease. Although the exact mechanism is unclear, the recent studies have shown the relation between obesity and metabolic disorders. It is seen that weight loss after surgery improves the metabolic disorders which were seen in morbidly obese patients. Other associated comorbidities like secondary angiopathy significantly improved after bariatric surgery. A significantly decreased Thyroid stimulating Hormones (TSH) and Glucose and glycated hemoglobin level were also seen in such patients. The bariatric surgery may have additional benefits including the long-term stable change in TSH level caused by weight reduction in all patients and deserve further study. In this review; we have focused on bariatric surgery as effective treatment modalities for subclinical Hypothyroidism. We have also including lifestyle changes such as diet modification, exercise regimens and medical therapy as usual regimen in the management of morbidly obese patients.
Keywords: Bariatric surgery, subclinical hypothyroidism, cardiovascular risk, metabolic syndrome, autoimmune diseases.

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Introduction

Obesity has become a major cause of morbidity and mortality in the 21st Century [1]. It is preventable causes of mortality worldwide. As per Institute of Health Metric & Evaluation (IHME), about 30% of the population i.e. 2.1 billion are either obese or overweight. Obesity is associated with comorbidities such as subclinical hypothyroidism comorbidities as type 2 diabetes, hypertension, polycystic ovarian syndrome, hyperlipidemia sleep apnea and coronary heart disease. Evidence has shown that bariatric surgery can control obesity and its related metabolic comorbidities. Although, the exact mechanism isunclear. It is considered that only therapeutic option for morbidly obese patients is bariatric surgery. A dysregulate endocrine loop in between the hypothalamic-pituitary unit and adipose tissue is thought to alter thyroid hormones in obese patients. It is reported that excess weight gain may contribute to SCH (Sub-Clinical Hypothyroidism) with the incidence varying between 4 and 10 % depending on the gender, age and population studies [2, 3] and up to 21% among 74-year-old women. The current treatment of subclinical hypothyroidism includes lifestyle modification i.e. diet, behavior changes including physical activity as well as pharmacotherapy i.e. levothyroxine and other similar drugs. Treating obesity, especially morbid obesity, with pharmaceutical agents is not overly effective. Studies have shown that the effective treatment for patients with subclinical hypothyroidism is bariatric surgery. The other risk factors associated with SCH such as atherosclerosis, cardiovascular risk, hyperglycemia, diabetes mellitus and secondary macro-microangiopathy is significantly improved after bariatric surgery. The mechanisms by which Bariatric surgery relieves SCH and cardiovascular risk are not clear. In this article, we have discussed the relation between obesity and SCH and recent concepts on SCH. We have explored weight loss diets and its effect on energy expenditure, body weight and the role of bariatric surgery for effective treatment of SCH associated cardiovascular risk and metabolic abnormalities.

Relation between obesity and subclinical hypothyroidism

Subclinical Hypothyroidism is an endocrine disorder in obesity subject. The main mechanism of subclinical hypothyroidism is altered thyroid hormones synthesis with feedback regulation mechanism leading to a lower limit of normal T3 [Triiodothyronine], T4 [Thyroxine] FT3, FT4 Levels and increased TSH which may be the primary event that induces an alteration in energy expenditure with a subsequent increase in weight and BMI. This consequent increased in fat with TSH value may raise the serum leptin levels. The pathophysiological relations between thyroid hormones and morbid obesity is still not clearly understood. It may be the effect the adipose tissue on hypothalamic pituitary endocrine axis. The above possible mechanism could perhaps be attributed to adipocyte secretion. There are several explanations indicating that TSH directly induced adipogenesis and adipokines [4-6]. Which independently influence thyroid hormones on energy balance. Some human and animal experiments have reported TSH can induce the differentiation of preadipocytes into adipocytes, which affect TSH receptor [7]. The TSH receptor expressions increased on the reduction of adipose tissue with weight loss. Therefore, the synthesis of thyroid hormones may be affected by adipose tissue and caloric intake. Adipocytes themselves considered as an active endocrine organ producing leptin. Leptin regulates energy homeostasis physiologically by informing the central nervous system about adipose tissues reserve. It also modulated behavioral responses to overfeeding and neuroendocrine effects by regulating foods intake with energy expenditures [8]. Leptin stimulates the hypothalamic Pituitary Thyroid axis by regulation TRH gene expressions on Para ventricular nucleus and increases TSH level [9-11]. Thus, increased TSH level may reflect pituitary adaption to increased adiposity through adipokines and perhaps adipocytes may stimulate TSH for leptin productions. [12,13]. Leptin also influences in thyroid deiodinase activity and conversion of T4 toT3 [14,15]. In-patient with obesity the rate of conversion of T4 to T3 is high due to deiodinase activity as a compensatory mechanism for fat accumulation to improve energy expenditure [16]. On the other hand, the obese subject has increased TSH, FT3 and Leptin levels. Weight loss causes a decrease of TSH, FT3 with Leptin levels. The above hypothesis supports an idea that thyroid functions are altered in obese patients and is reversible after bariatric surgery [20]. Hence, the concept of an inverse relationship between thyroid and leptin is supported by the above evidence. When the plasma level of TSH is higher, TSH receptor appears less on the fat cell of obese than non-obese subjects. The reduced receptor of TSH may induce down-regulation of thyroid Hormones receptor with the action of thyroid hormones resulting in an increase of plasma TSH & FT3 concentration with peripheral thyroid hormones resistance. This outcome is reverse with restores the function of mature adipocytes after weight loss [17]. Abnormal TSH Level & thyroid Function usually normalized after weight loss whether consequent to bariatric surgery or diet [15-18]. Weight loss results in significant reductions in TSH and FT3, due to decrease 5'-deiodination of the T3 receptor [16-19]. Weight loss surgery decreases T3 levels and continued caloric deprivation reduce energy expenditure. Therefore, if further weight loss occurs there may be difficulty maintaining T3 levels [19].

Evaluation of moderate increase in TSH for obese children and adults show increased thyroid volume with hypoechogenicity on ultrasound, suggestive of Hashimoto thyroiditis, with absence at thyroid autoantibodies [21,22]. In obese subjects, increase of hypoechogenicity linked to cytokines and inflammatory marker produced by adipose tissues. These cytokines can increase TSH level, increase the permeability of thyroid vessel with vasodilation and increase parenchymal swelling of the thyroid gland which might be related to the hypoechogenicity at ultrasound [21]. This hypoechogenicity suggestive of Hashimoto thyroiditis along with anti-thyroid peroxidase antibody (TPOAb) is expected to be autoimmune thyroid disease. But TPOAb could not detected more than 20% of obesity subject with ultrasound evidence of thyroid autoimmunity [23]. The prevalence of AITD (autoimmune thyroid dysfunction) in the obese subject is seen in 12.4% in children, between 10 and 60 % in adults [24]. AITD risk link between obesity shows main cause of hypothyroidism in adults. Marzullo et al. [25] reported an intriguing hypothesis linking obesity, autoimmunity, leptin and hypothyroidism. They evaluated of prevalence and characteristic thyroid autoimmunity in a population of premenopausal obese females and obese men have found that leptin increases susceptibility to AITD by regulating immune. According to recent studies, higher BMI is also associated with increasing the risk of thyroid cancer, and the serum TSH is considered as in independent predictor of presence thyroid cancer in thyroid nodules [26,27].

Recent concepts of subclinical hypothyroidism

Primary hypothyroidism does not require routine screening as recommended by ASMBS guidelines. However, the NIH guidelines programs require preoperative screening of obesity to ensure there are no organic causes. Yet the prevalence of SCH is higher in obese patients. According to the Framingham cohort study, the incidence in US of SCH is 13% in women, 5.7% in men [28]. In the UK, the Wickham prospective study reported an incidence of 7.5% in women and 2.8% in men. According to a report from the china Medical University, 2.8% males and 3,2% females have SCH in rural communities [29]. At present multiplies guidelines for SCH have been introduced. According to ETA (2013) the diagnostic criteria based on serum TSH, SCH has classified into two categories: mild elevated of TSH (4.0 ~ 10.0 mIU / L) with significantly elevated when TSH is increased (> 10.0mIU/L)[30]. In 2012, the endocrine society and the perinatal medicine branch of the Chinese Medical Association provide important clinical guidance for diagnosis and management of thyroid disease in pregnancy and postpartum. At present TSH measurement methods are different for different countries, they rely on the reagent used and upper limits of normal TSH levels are different. In 2012 the American association of clinical endocrine doctors (AACE) and American thyroid association (ATA) jointly issued the TSH normal upper reference value of 4.12 mIU/L.

SCH has atypical clinical symptoms and is usually diverse. Every year a certain percentage of patients developed clinical thyroid dysfunction, antithyroid peroxidase (TPO) antibodies are detected only in about 4.3% of clinical hypothyroidism patients, while rest have no detectable TPO antibodies. About 30% of patients may exhibit certain symptoms, such as dry skin, muscle weakness, and eyelid edema. Due to varying clinical symptoms, it is difficult to diagnose SCH on the time. If SCH is not treated timely it easily can convert to atypical hypothyroidism. Young patients with SCH show a mild decline in memory and emotional effect. Several studies have revealed SCH patients to have high cholesterol levels and insulin resistance, leading to heart dysfunction, atherosclerosis and other diseases, which are closely related to increased risk of cardiovascular disease. [31,32]. For asymptomatic hypothyroidism, TSH levels are higher in adult patients (<65years old, TSH>10mIu/L), 2013 (ETA) "adult subclinical hypothyroidism Guidelines" recommended L-Levthyroxine-T4 therapy. Medication is not recommended for sustained SCH, and thyroid function test should be repeated at the six-month interval. At present, whether subclinical hypothyroidism needs thyroid hormone replacement therapy or not is still controversial as excess hormones can cause subclinical hyperthyroidism. These patients may develop abnormal cardiac function and bone mineral density. There is still a lack of evidence-based medical information in support of it [33]. Large multicenter, prospective, placebo-controlled and systematic study are lacking for subclinical hyperthyroidism. Although studies report high TSH levels in obese patients there a few studies reporting that post-operative weight loss improved thyroid functions in obese subjects. Therefore, diagnosis and treatment of subclinical hypothyroidism in obese patients are getting more attention. The rapid development of surgical techniques for treatment of morbid obesity has led to a new concept in the field, especially minimally invasive laparoscopic Sleeve gastrectomy.

Bariatric surgery as a treatment of SCH

Bariatric surgery is effective, safe and durable for the treatment of obesity and associated comorbidities. Lifestyle interventions, Diet modification, exercise regimens and medical therapy (Levothyroxine drug) are usual regimens in overweight subjects. The principle of weight loss in elderly patients is to improve the quality of life and maintain physical function to enable these individuals to sustain independent life lives. Studies have reported that lifestyle intervention achieves health benefits equally in younger and older male and female subject [34]. However, studies have mainly focused at SCH associated with other metabolic consequences of obesity. A Few studies have concentrated on the physical consequences that are more relevant to older obese patients. A program of conventional exercise and diet contribute to modest weight loss of 5-10kg (-10%), generates a relatively large reduction in abdominal fat and improvement of metabolic syndrome. The Weight management program should be customized according to the individual requirements in order to provide optimal physical activity, balanced diet, and appropriate calories intake. The clinical benefits, i.e. improvement in mobility, bone health, improved arthralgia, dyspnea and memory power should be monitored routinely and therapeutic adjustment should be applied as needed. Guidelines in the US and the UK recommend a gradual increase of aerobic physical activity (brisk walking) to reach a goal of more than 150 minutes

per week. This indicates that a greater amount of physical activity is needed in the long term to prevent obesity and maintenance of weight [35].

Thousands of weight loss diets have been developed and appear in the lay literature with media on a regular basis. In fact, that there are many continuous new diet concepts available which suggest that, to date, no one diet plan has been universally satisfactory at inducing and maintain weight loss. However, dietary interventions in hyporthyroidism have some scientific evidence. Chronic deficiencies of iodine increase SCH. The world Health Organization (WHO) recommends a daily dietary intake of 150ug of iodine for adults, 50-120 ug for children and 200ug for pregnant and lactating women. Foods rich in antioxidants and vegetable, tyrosine amino acid contain food and eating selenium rich food can improve thyroid gland health with autoimmune disease. A scientific study reported that THS levels improved significantly when a group of obese pediatric patients were on a diet of green vegetable, beef, full-fat milk and butter for 3 months. Supplementation of (subclinical) immunomodulation or micronutrient deficiency improvement by a different component of the diet is a plausible concept. It is meaningful to underline that the diet is not an intensive treatment, but an everyday diet consisting of natural whole foods is easily available and has no side effects. However, diet alone is still not good alternative therapy, it is cost effective treatment for children with SCH [36]. The evidence and common sense both indicate that initial point for effective, long term, weight management should be low -fat, nutrient-rich diet and regular Physical activity based on individual ability. Weight management optimizes the quality of life and decreases CVD risk factors, and improves insulin sensitivity associated subclinical hypothyroidism.

Levothyroxine (LT4) is a monotherapy, which is, remains the current standard for management of primary, as well as central, hypothyroidism. The benefits and risk of drugs therapy should be weighed carefully when taking medication. Levothyroxine has a long half-life, approximately seven days. It is partially converted to T3 in the body, resulting in a constant physiologic blood level of both T4 and T3 in daily single dose, therefore treatment should be initiated at a low dose in an elderly patient, patients with long -standing severe hypothyroidism and coronary artery disease. TSH measurement should be repeated after 6-8 week of initial dose to guide adjustment of levothyroxine dosage. In Primary hypothyroidism serum TSH monitored with a target of 0.5 -2.0miU/L and in patients with central hypothyroidism, treatment is tailored according to free or total T4 level, which should be maintained up to the upper half of normal range for age. Those patients with persistently elevated TSH despite an apparently adequate replacement dose of LT4, malabsorption, poor complication and presence of drug interactions should be checked and corrected. Over-replacement is common in clinical practice, which is related to increased risk of osteoporosis and atrial fibrillation, and hence should be avoided [37].

SCH is associated with cardiovascular risk, diabetes and sleep apnea. All these may contribute to increased cardiovascular morbidity and mortality. Coronary arterial calcifications are most likely found in an obese subject with rapid progression than the non-obese subject. Moreover, obesity is associated other vascular disease such impaired endothelia–dependent vasodilation and increased carotid intima-medial thickness [39-43]. It has been studied that liposuction has no beneficial effect on cardiovascular risk factors as liposuction selectively removes subcutaneous rather than visceral fat studies [44]. The studies reported that total and LDL cholesterol is increased by hypothyroidism and SCH patient taking levothyroxine had no significant effect on the circulating level of triglycerides or HDL cholesterol [45,46]. Improvement in cardiac risk factors is generally proportional to the amount of weight lost. Cardiac function and structure have shown consistent benefit after surgically –induced weight loss. The different type of bariatric procedures results in a varied degree of weight loss. It has been estimated that progression of atherosclerosis could be slowed in 50% of patients after undergoing bariatric surgery. Similarly, cardiac geometry and structure were also improved. The significant improvements of the cardiac risk factor, especially decreased progression of atherosclerosis led to a reduction in the total and cardiovascular mortality over 10 years. [38]. Acknowledged for more than 40 years, some obese patients have normal serum cholesterol but remain at high cardiovascular risk [47]. A recent study has reported that total and LDL cholesterol level remained elevated after sleeve gastrectomy, regardless of whether a significant weight reduction was achieved or not. Which suggest that serum cholesterol is not an accurate indicator of body fat accumulation but weight loss is associated with a reduction of cardiovascular risk. The ratio of triglyceride and cholesterol describe a strong predictor of heart attack and other cardiovascular

complication. There was a significant association between TSH decrease and serum triglyceride reduction after surgery as well as a reduced triglyceride and cholesterol ratio. Hence, the decrease in lipid profiles should be attributed to weight loss and not change in thyrotropin levels [48].

Bariatric surgery causes sustained weight loss and dramatic clinical remission of insulin-resistant states. Animal experiments have shown that bariatric surgery's effects on insulin sensitivity and glucose homeostasis are not the consequence of reduction of food intake mechanism or energy absorption but variety of physiological mechanism, Recent randomized clinical trials have shown that bariatric surgery is a better treatment of Types 2 diabetic and helping in reducing cardiovascular risk factors with variety of lifestyle change and medical therapies combined [49]. According to the mounting clinical evidence, bariatric intervention is increasingly being proposed not only for the surgical management of obesity but also a valuable approach in treating Type 2 Diabetes. In general, practice this surgery is also referred as metabolic surgery [50].

Batsis et.al reported that after bariatric surgery metabolic syndrome (Mets) prevalence rate dropped from 87% to 29% [51]. An increasing number of reports shown that bariatric surgery is an involved in the intrinsic factor of the body's energy balance and regulation of metabolism. As it is well known that obesity has a higher risk of having diabetes, hypertension, dyslipidemia and other metabolic syndromes (Mets). However, further study found that the prevalence of SCH in patients with morbid obesity is getting higher and higher. It has been estimated that every fifth person in the world has Mets. The Mets prevalence in Europe is approximately 15% -35% [52]. But the global prevalence of Mets is difficult to determine as the definition of Mets varies [53]. Avantika et al. [48] and other studies have found aggregation in the patients with multiple Mets. The Increase of TSH level significantly increases the incidence of Mets, thus SCH has an obvious correlation with Mets. Surgery is the treatment of choice in Mets with a positive effect on TSH. Unfortunately, there are few published studies analyzing the effect of weight loss surgery in thyroid function. Roux-en–Y gastric bypass surgery induces weight loss, a improve SCH patients. In the Previous study, Tovar et al. [54] concluded that the patients with morbid obesity appear to have SCH that may be caused by obesity as a secondary phenomenon and after bariatric surgery SCH is often corrected. Therefore, it is unclear whether there is a need for such patients to receive intervention and treatment. The pathophysiologic relationship between SCH and Dyslipidemia show cardiovascular risk that may have the consequence of cardiac dysfunction, atherosclerotic diseases, and insulin resistance, however, these results are still controversial [16,55,56]. According to Reinehr and Andler, the serums TSH of obese children were increased as compared to non-obese children and similar findings were found in obese adults as well [57,58]. In the modern times, laparoscopic sleeve gastrectomy is popular throughout the world with the alternating bariatric procedure to LRYGB. Patients undergoing weight loss surgery have an extra benefit with improved subclinical hypothyroidism but correlations between them have not been studied widely and reported, However, in patients whose thyroid disease is autoimmune in nature, benefit satisfactorily with bariatric treatment. The bariatric surgery improves the immune dysfunction and metabolic syndrome seen in morbidly obese patients. A significantly decreased TSH and glucose and glycated hemoglobin levels were also seen in such patients. Many reports nevertheless suggest that this biochemical abnormality is secondary to obesity and not a real hypothyroid state and occurs as a consequence of abnormal fat deposited on the body. Whether such patients need treatment or not is still unclear. The evaluation of thyroid autoimmunity is important after surgery.

Conclusion

Obesity has been a major contributor to different cardiovascular and metabolic diseases recently. The role of bariatric surgery has been very important for managing the complications associated with morbid obesity. SCH in morbidly obese patients is just a consequence of the abnormal fat accumulation. The studies suggest that bariatric surgery corrects SCH. Other associated comorbidities like atherosclerosis, cardiovascular risk, hyperglycemia, diabetes mellitus, and secondary macro–microangiopathy significantly improved after bariatric surgery. The decrease of BMI and TSH as an outcome of Bariatric surgery may have additional benefits including long–term stable change in TSH levels caused by weight reduction in all patients and deserves further study. It is likely that bariatric surgery in future will have the major role in metabolic and cardiovascular diseases.

Declaration

All authors have disclosed no conflicts of interest.

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