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PROGNOSTIC FACTORS AND OUTCOMES IN OBESE AND OVERWEIGHT CHILDREN WITH SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT

Objectives: Subclinical hypothyroidism (SH) is known as high concentrations of serum thyroid stimulating hormone (TSH) above the upper limits with normal concentrations of free Thyroxine (F T4). Its prevalence rates have increased in children, especially with obesity. This study was conducted to evaluate the most important prognostic factors associated with the clinical course of (SH) in obese and overweight children. **Methods:** A prospective Analytical prognostic study was carried out on 52 overweight and obese children, aged between (3-14) years, diagnosed with (SH) in the pediatric endocrinology clinic in Lattakia, starting in June 2021 and, lasted for 18 months. Demographic, clinical, anthropometric, and, thyroid function parameters were evaluated every 6 months for all participants, and they received healthy lifestyle modifications. **Results:** Of the 52 obese and overweight children, TSH values returned to normal in 35 children (67.3%). By the univariate analysis, the following prognostic factors were associated with the normalization of TSH values: A Decrease in body mass index (BMI) with (p-value= 0.03), and lower initial TSH valuewith (p-value= 0.001), and in females with (p-value =0.03). Multivariate regression analysis revealed reduction BMI as the independent predictor for healing of TSH values, with an odds ratio of 3.2(95% confidence interval [CI] 1.4-7.3) (p-value 0.001). Of the 29 children tested for thyroid antibodies, only 3 (10.3%) were positive. **Conclusion:** The majority of cases of subclinical hypothyroidism in obese children resolve spontaneously and reducing the body mass index is considered the most important factor in improving TSH values.

KEYWORDS: body mass index; obesity; subclinical hypothyroidism; weight loss.

INTRODUCTION

Thyroid hormone (TH) plays a vital role in normal growth and development by regulating metabolic processes, and it correlates with energy expenditure and body weight.[1] Subclinical hypothyroidism (SH) is a common biochemical condition, defined as an increase in serum TSH values above the upper limits of the reference range, with normal concentrations of free Thyroxine (FT4).[2] The etiology of SH may be nonspecific (idiopathic SH), or secondary to many causes: Hashimoto's thyroiditis (HT), celiac disease, cystic fibrosis, chronic renal failure, chromosomal syndromes (Turner, Down), and obesity. obesity is a common chronic disorder that may often be associated with SH.[2] the prevalence of SH in overweight and obese children has been reported to range between (7-23) %[3], while its incidence in children generally is about 2%.[4] the underlying mechanism of SH in obese children is still unclear, it might be an adaptive process to increase energy expenditure, an increase in the level of leptin which stimulates the production of pro-TSH-releasing hormone, chronic low-grade inflammation, or related to resistance to thyroid hormones.[5] Although the clinical effects have not been clarified, studies indicate that these alterations in thyroid function in obese children may contribute to worsening of metabolic complications, and development of thyroid disorders in adulthood.[5,6] So, regular monitoring is necessary for these patients. Despite most cases of this disorder reversing after weight loss, this finding is sometimes controversial.[7,8] This study aims to evaluate the most important prognostic factors associated with the clinical course of SH in obese and overweight children.

MATERIALS AND METHODS

Study Population

After approval by the local research ethics committee and the consent of the participants 'parents, an analytic prognostic study was conducted on 52 overweight and obese (3-14) children and adolescents diagnosed with SH seen at the Endocrinology Pediatric Clinic of Tishreen University Hospital in Latakia in Syria between June 2021 and December 2022. Inclusion Criteria were as follows:

1. Children diagnosed with SH aged (3-18) years with body mass index BMI ≥ 85 percentile.
2. Children diagnosed with SH: TSH value ≥ 4.31µIU/ml with a normal FT4 value.

Non-Inclusion Criteria
1. Systemic or chromosomal disease.
2. Presence of overt hypothyroidism symptoms.
3. Children on thyroid hormone replacement at the time of assessment.
4. Treated with drugs that may interfere with thyroid function (e.g. antiepileptic drugs, lithium, glucocorticoids, or iodinated drugs).

Within 18 months all participants were followed up periodically every 6 months for evaluation: (clinical examination, anthropometric characteristics, and thyroid function investigation), and they received healthy lifestyle modifications by following a suitable diet, increasing physical activity, and limiting sedentary activities. Children's weight will be measured lightly dressed and without shoes to the nearest 100 g, while Height will be measured to the nearest 1 mm. Children were classified according to their BMI percentile (%) according to the CDC as follows: Overweight with BMI ≥ 85% and < 95%, obese with BMI ≥ 95% and < 99%, severely obese with BMI ≥ 99 %.

Laboratory investigations
Thyroid functions (TSH, FT4) were investigated using the Aya360 Machine by immunofluorescence method, The reference level for TSH, FT4 is (0.38-4.31) µIU/ml and (0.82-1.63) µIU/ml, respectively. Due to self-financing and cost, only 29 children were tested for anti-thyroid peroxidase antibody (anti-TPO Ab). Titer of (anti-TPO Ab) using an enzyme-labeled chemiluminescent sequential immunometric assay. The reference range for (anti-TPO Ab) was less than 35 IU/mL.

Statistical Analysis
The quantitative variables were presented as (mean, and standard deviation) and the qualitative variables as (frequency, and percentage). The Chi-square test was used to study the relationships between qualitative variables, and the Independent T-student test was used to compare the differences in means between the two independent groups. Testing all variables according to Univariate regression. Statistically significant variables were entered into the Multivariate analysis to establish independent predictions of the normalization of TSH values at the end of the follow-up period. The Relative Risk (RR) was measured and confidence intervals were found. The *p*-value < 0.05 was considered significant. All statistical analyses were conducted with the use of the Statistical Package for Social Sciences (SPSS) Version 25.

RESULTS
The study included 52 children and adolescents; their mean age was (8.96 ± 2.8) years (3-14) years. Both genders were equally presented. The number of overweight children was 18(34.6%), obese 21(40.4%), and severe obese 13(25%). At the baseline, the average values for each (TSH, FT4) were 6.04±1.6 (µUI/mL), and 1.14±0.1(ng/dL), respectively. The mean rate of BMI was 95.61±4.1 (85 – 99.90). A positive family history of thyroid disease was found in 22 children (42.3%), and a Positive family history of obesity was found in 16 children (30.8%). Immune thyroid antibodies were performed only on 29 children, and they were positive in 3 children (10.3%). As shown in (Table 1).

Table (1): Demographic, clinical, and laboratory characteristics at baseline.

n: 52	
Female (%)	26(50%)
Age at baseline(year)	8.96±2.8
Family History of (thyroid disease)	22(42.3%)
Family history of obesity	16(30.8%)
Obesity grades Overweight Obese I Obese II	 18(34.6%) 21(40.4%) 13(25%)
BMI at baseline (%)	95.61±4.1
TSH (µUI/mL)	6.04±1.6
Free thyroxin (ng/dL)	1.14±0.1

BMI, body mass index; TSH, thyroid-stimulating hormone, Ab: antibody.

Data are expressed as mean ± standard deviation or percentage (%)

After an average follow-up period of 18 months, TSH values returned to normal in 35 children (67.3%), while TSH values continued to rise in 17 children (32.7%).

The results of the univariate analysis showed that the healing of TSH values was with a higher percentage of girls (60% vs 29.4%) with (P=0.03), and with a greater decrease in the BMI percentile from (95.38±4.5) to (88.1±12.8) with (p=0.03), in addition associated with a lower average of baseline TSH values (5.61±1.5) vs (6.91±1.5) with (p=0.006). At the same time, we did not find an effect regarding the degree of obesity, age at diagnosis, family history of (thyroid disease, obesity), and FT4 values on follow-up outcomes. As shown in Table (2,3,4).

Table (2): Comparison between healing and non-healing of TSH values regarding demographic and family history variables.

variables	TSH-Healing	TSH-Non healing	p-value
Age at baseline(years) 2-9 10-18	 18(51.4%) 17(48.6%)	 9(52.9%) 8(47.1%)	0.9
Gender Male Female	 14(40%) to 21(60%)	 12(70.6%) 5(29.4%)	0.03
Family History of (thyroid disease)	14(40%)	8(47.1%)	0.6
Family history of obesity	9(25.7%)	7(41.2%)	0.2

p<0.05 is statistically significant, X2 Chi-square test

Table (3): Comparison between healing and non-healing of TSH values regarding anthropometrical variables.

Variables	TSH- Healing	TSH-Non healing	p-value
Obesity degree Overweight Obese I Obese II	 12(34.3%) 14(40%) ` 9(25.7%)	 6(35.3%) 7(41.2%) 4(23.5%)	0.9
BMI1	95.38±4.5	96.10±3.4	0.5
BMI2	88.1±12.8	92.01±12.6	0.2
ΔBMI	- 7.35±10.1	- 4.08±10.7	0.03

p<0.05 is statistically significant.

Table (4): Comparison between healing and non-healing of TSH values regarding to laboratory variables.

Variables	TSH- Healing	TSH-nonhealing	p-value
TSH at baseline	5.61±1.5	6.91±1.5	0.006
FT4	1.14±0.1	1.15±0.1	0.7
TPO positivity(n=29)	1(2.9%)	2(11.8%)	0.3

p<0.05 is statistically significant.

By the Multivariate regression analysis, it is noted that BMI reduction is the independent predictor for the healing of TSH values with (RR 3.2;95% CI 1.4-7.3).

DISCUSSION

It is important to clarify the health of thyroid function in obese children. However, an isolated increase in TSH values known as subclinical hypothyroidism (SH) constitutes the most common disorder in thyroid function.[5] A positive relationship between SH and the presence of dyslipidemia and insulin resistance has been observed in obese children.[6] To our knowledge, this is the first study to identify the most relevant prognostic factors in the clinical course of SH in obese children. In this context, TSH values returned to normal in 35 (67.3%) overweight and obese children with SH during approximately 18 months of follow-up. The decrease in BMI was associated significantly with the normalization of TSH values, this has often been explained by the role of weight loss in modifying the composition of the body's components, as a decrease in fat mass leads to a decrease in inflammatory elements and cytokines secreted from them, especially the leptin hormone.[7,9] To our review of the medical literature, several studies showed similar results of normalization of TSH values after weight loss and without hormonal therapy, but there is a difference in healing rates, for example, the normalization rate of TSH values in the Matusic study in Germany was 80%, in the Maria study in Italy 85%, and in the Mona study in Egypt, 65%.[10,11,12] This difference is probably due to the difference in research methods (age group, different TSH cut-off limits, sample size) in addition to lifestyle-related factors of diet, particularly dietary iodine intake, in addition to the difference in average BMI and fat distribution. Until now, adding LT-4 therapy to a healthy lifestyle did not have a significant effect on improving TSH values versus following only healthy lifestyle modifications. So that, we can just start hormonal treatment if clinical and laboratory signs of hypothyroidism occur.[10,13] Positive immune thyroid

disease was not the preferred prognostic factor in the SH disorder.[14] However, in cases of obesity, autoimmune thyroiditis is rarely considered a cause of SH cases, for example, the incidence of autoimmune thyroiditis did not exceed 7% out of 938 obese children in a Grandones's study,[15] likely in our study of the 29 obese and overweight children, only 10.3% had positive thyroid antibodies, without any warning effect. Because of the small sample size, we were unable to determine the cut-off values of TSH, which predicts the progression of SH cases towards improvement, in our series, normalization of TSH values was accompanied by lower basal TSH values, this is consistent with Marta's study on the development of SH in children in general.[16] Neither a family history of thyroid disease nor a family history of obesity had an impact on the follow-up results as shown in table (2), perhaps due to the acquired basis of the disorder and its being an adaptive process to increase energy expenditure.[5] Different results have been found about the role of gender, as Lazar's study and Marta's study have found a tendency for deterioration of TSH values in girls,[16,17] while Kamilia's study has not found an effect of gender.[18] Otherwise, in our research, girls had a greater rate of improvement. In Kamilia 's study on the course of SH in obese and non-obese children, both high BMI values and high baseline TSH values were the most important factors of concern after conducting the multivariate analysis, while in our study we found that the decrease in BMI is the most important prognostic factor in improving SH cases in obese and overweight children.[18]

The current study has its limitations. For example, the small size of the sample, the inability to administer thyroid antibodies to all participants due to their high cost, and a thyroid ultrasound were not performed to observe echogenic changes during monitoring.

CONCLUSION

The majority of cases of subclinical hypothyroidism in obese children resolve spontaneously and reducing the body mass index is considered the most important factor in the improvement of TSH values.

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Research ethics

Ethical approval was obtained from the Scientific Research Directorate at Tishreen University according to Decision No.3388**.**

Competing interests

All the authors do not have any possible conflicts of interest.

Author contributions

All authors performed the measurements and wrote the manuscript. Literature review was done by Dr. Hazar Mounef. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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REFERENCES

1. MULLUR, Rashmi; LIU, Yan-Yun; BRENT, Gregory A. Thyroid hormone regulation of metabolism. Physiological reviews, 2014.
2. MONZANI, Alice, et al. Subclinical hypothyroidism. Thyroid Diseases in Childhood: Recent Advances from Basic Science to Clinical Practice, 2015; 195-202.
3. NIRANJAN, Usha; WRIGHT, Neil P. Should we treat subclinical hypothyroidism in obese children? *Bmj*, 2016; 352.
4. WU, Tiejian, et al. Subclinical thyroid disorders and cognitive performance among adolescents in the United States. *BMC Pediatrics*, 2006; 6: 1-6.
5. FONTENELLE, L. C., et al. Thyroid function in human obesity: underlying mechanisms. Hormone and Metabolic Research, 2016; 48.12: 787-794.
6. KARA, Ozlem. Influence of subclinical hypothyroidism on metabolic parameters in obese children and adolescents. Clinical and experimental pediatrics, 2020; 63.3: 110.
7. REINEHR, Thomas; DE SOUSA, Gideon; ANDLER, Werner. Hyperthyrotropinemia in obese children is reversible after weight loss and is not related to lipids. The Journal of Clinical Endocrinology & Metabolism, 2006; 91.8: 3088-3091.
8. SHALITIN, S.; YACKOBOVITCH-GAVAN, M.; PHILLIP, M. Prevalence of thyroid dysfunction in obese children and adolescents before and after weight reduction and its relation to other metabolic parameters. Hormone Research in Paediatrics, 2009; 71.3: 155-161.
9. CAMBULI, Valentina M., et al. Assessment of adiponectin and leptin as biomarkers of positive metabolic outcomes after lifestyle intervention in overweight and obese children. The Journal of Clinical Endocrinology & Metabolism, 2008; 93.8: 3051-3057.
10. MATUSIK, Pawel, et al. Isolated subclinical hyperthyrotropinemia in obese children: does levothyroxine (LT4) Improve weight reduction during combined behavioral therapy?. International journal of endocrinology, 2015; 2015.1: 792509.
11. LICENZIATI, Maria Rosaria, et al. Altered thyroid function and structure in overweight and obese children and adolescents: reversal after weight loss. The Journal of Clinical Endocrinology & Metabolism.
12. AMIN, Mona Karem; ALI, Ahmed Ibrahim; ELSAYED, Hesham. Impact of weight reduction on

thyroid function and nonalcoholic fatty liver among Egyptian adolescents with obesity. International Journal of Endocrinology, 2022; 2022.1: 7738328.
13. KUMAR, Sugantha, et al. Levothyroxine supplementation for obesity-associated thyroid dysfunction in children: a prospective, randomized, case control study. Pediatric Endocrinology Diabetes and Metabolism, 2019; 25.3: 107-113.
14. AVERSA, Tommaso, et al. Five-year prospective evaluation of thyroid function test evolution in children with Hashimoto's thyroiditis presenting with either euthyroidism or subclinical hypothyroidism. Thyroid, 2016; 26.10: 1450-1456.
15. GRANDONE, Anna, et al. Thyroid function derangement and childhood obesity: an Italian experience. BMC Endocrine Disorders, 2010; 10: 1-7.
16. MURILLO-VALLÉS, Marta, et al. Subclinical hypothyroidism in childhood, treatment or only follow-up?. BMC Pediatrics, 2020; 20: 1-6.
17. LAZAR, Liora, et al. Natural history of thyroid function tests over 5 years in a large pediatric cohort. The Journal of Clinical Endocrinology & Metabolism, 2009; 94.5: 1678-1682.
18. SZELIGA, Kamila, et al. Subclinical hypothyroidism in children and adolescents as mild dysfunction of the thyroid gland: a single-center study. Pediatric Endocrinology Diabetes and Metabolism, 2023; 2.