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Role of the Change in BMI Classification as a Prognostic Factor for the Spontaneous Healing of Subclinical Hypothyroidism in Children Aged from 2 to 14 Years

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Abstract

Background: Subclinical hypothyroidism (SCH) is a biochemical disorder characterized by elevated serum thyroid-stimulating hormone (TSH) with normal free thyroxine (FT4) levels, in the absence of clinical symptoms. The prevalence of SCH is approximately 1.7% in the pediatric population. Several prognostic factors influence the progression to overt hypothyroidism (OH), which requires lifelong therapy and follow-up. These factors include goiter, elevated TSH levels, positive thyroid antibodies, and obesity. Obesity may also contribute to the development of SCH, making weight loss and monitoring of TSH levels important.The study aimed to assess the role of the change in BMI classification as a prognostic factor for the spontaneous healing of SCH.

Methods and patients: Patients aged 2-14 years, diagnosed for the first time with SCH without palpable goiter or any anterior hormonal therapy, were referred to the Department of Pediatrics, Endocrinology clinic at Latakia University Hospital, Syria (2021-2022).

Results: 104 children with SCH were included, 49 (47.1%) were females and 55 (52.9%) were males. The spontaneous healing rate was 71.2% of patients, with a higher rate among females, 54.1%. The change in BMI classification was a good prognostic factor for the spontaneous healing of SCH.

Conclusion: SCH is a common disorder in children. It may lead to cardiovascular diseases or metabolic disorders, so it must be followed long-term to monitor for healing or progression to overt hypothyroidism. The study found that the change in BMI classification was the main prognostic factor for spontaneous healing, while no statistical significance was found in the other factors.

Keywords: Body mass index; children; prognostic factors; spontaneous healing; subclinical hypothyroidism; thyroid-stimulating hormone

Background

Hypothyroidism is the most common endocrine hormonal deficiency in pediatrics [1]. Hypothyroidism is classified into overt hypothyroidism (OH) with an increase in the serum thyroid-stimulating hormone (TSH) and a decrease in the serum free thyroxine (FT4) [2], while Subclinical hypothyroidism (SCH) is a biochemical disorder characterized by an elevated of serum thyroid-stimulating hormone (TSH) with serum FT4 within normal limits without any clinical manifestation [3]. The estimated prevalence of SCH is around 1.7% in the pediatric population. The diagnosis of SCH depends on two tests of elevated TSH [4]. SCH is classified as mild TSH (4.5-10 mIU/L) or as severe TSH (> 10 mIU/L) [5]. The causes of SCH might be prolonged iodine deficiency, Hashimoto's disease (HT), especially in older children and adolescents (8-18 years), and obesity which may play a role in the pathogenesis of SCH as the estimation of SCH is 23.33% and 30% in overweight and obese children respectively [6-8]. SCH may lead to a lipid metabolism disorder. Unal E et Al. found that patients with SCH had increased total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C), while Habib A et Al. did not find that in their study [9-11]. Wasniewska M et al., found that the main prognostic factors for the progression to OH are goiter, elevated TSH levels, and positive thyroid antibodies [12]. Szeliga et al. found that elevated serum TSH values and elevated body mass index (BMI) were the prognostic factors for the progression to OH [13]. Reinehr et Al. found a positive correlation between elevated TSH with elevated BMI, so the change in BMI due to decreased TSH values [14].

Knowledge gape: In the absence of anterior data in our region and the actual situation of economic status due to the crisis in Syria with the unpublished data of the Ministry of Health in Syria indicating the presence of iodine insufficiency in the Syrian pediatric population we conducted this study to determine the main prognostic factors of spontaneous healing of SCH in our pediatric population and because most prognostic factors are not modifiable, the focus was on weight loss and monitoring the change in BMI classification and its role in the spontaneous healing of SCH.

Methods and Patients

Study Design

An observational prospective prognostic Study was conducted in the Department of Pediatrics, Endocrinology clinic at Latakia University Hospital, Latakia, Syria for two years (2021-2022). Informed consent was taken from the parents of all patients.

Study Population

The study included all patients aged 2-14 years, diagnosed for the first time with SCH based on elevated serum TSH values and normal serum FT4 values depending on age [15] without palpable goiter or any anterior hormonal therapy. The total sample size was 109 children. 5 of them dropped out, which is less than 5%.

The following prognostic factors were studied: age, gender, baseline body mass index classification, and the final BMI [classified as overweight (BMI ≥ 85%, < 95%), obesity (BMI ≥ 95%, < 99%), or severe obesity (BMI > 99%)], BMI is a measure used to assess weight relative to height and it is calculated by dividing weight by the square of height (Kg/m^2) [16], serum TSH was measured by using chemiluminescence assay, anti-thyroid peroxidase antibody (TPOAb), normal value is less than 35 IU/mL, family history of hypothyroidism or obesity. The duration of inclusion was one year, then the follow-up period was another year. The patients were followed up clinically and hormonally every 6 months.

Study limitations the sample consisted of only 109 children, all consecutively seen in the hospital's outpatient clinics and meeting the inclusion criteria. Three TSH tests were performed on them. We were unable to perform anti-thyroid peroxidase antibody (TPOAb) on all patients because it was not always available in the hospital.

Statistical Analysis

Descriptive statistics included Quantitative variables were summarized into measures of central tendency and measures of dispersion, and categorical variables in frequencies and percentages. Inferential statistics included the Chi-square test (χ^2) used to compare the relationship between categorical variables (as a Univariate analysis). Statistically significant variables with Univariate analysis were entered into the Multivariate analysis equation (logistic regression). P-values <0.05 were considered statistically significant. All analyses were performed on IBM SPSS Statistics (version 25).

Results

104 children with SCH were included, 49 (47.1%) were females, and 55 (52.9%) were males. The demographic characteristics and the hormonal work-up characteristics of the patients of SCH are shown in Table 1.

Table 1: The demographic characteristics and the hormonal work-up characteristics of the patients of SCH

	N	%	Healing	Non-healing	P value
Gender					
Male	55	52.9%	34(45.9%)	21(70%)	0.02
Female	49	47.1%	40(54.1%)	9 (30%)	0.02
Age (Years)					
2-9	57	54.8%	39(52.7%)	18(60%)	0.4
10-18	47	45.2%	35(47.3%)	12(40%)	0.4
Family History of Hypothyroidism	22	21.2%	14(18.9%)	8 (26.7%)	0.3
Family History of Obesity	29	27.9%	17(23%)	12(40%)	0.07
Baseline TSH					
≥ 10	3	2.9%	1 (1.4%)	2 (6.7%)	0.1
< 10	101	97.1%	73(98.6%)	28(93.3%)	0.1

TSH – thyroid-stimulating hormone

Spontaneous healing was considered to be the return of TSH values to normal. The overall spontaneous healing rate was 71.2% of patients, with a higher rate among females, 54.1% versus 45.9% in males, with a statistical significance. There was no statistical significance concerning the age, family history of Hypothyroidism or obesity, baseline TSH, and spontaneous healing.

TPOAb titers were performed only for 57 patients; they were positive in only 4 patients (7%).

The relationship between the change in the BMI classification and the spontaneous healing of SCH is shown in Table 2.

Table 2: The relationship between the change in the BMI classification and the spontaneous healing of SCH:

BMI					
Baseline			**Final**		
	N (%)	**N (%)**	**Healing**	**Non-healing**	**P value**
Underweight	12 (11.5%)	8 (7.7%)	6 (8.1%)	2 (6.7%)	0.04
Normal	40 (38.5%)	57 (54.8%)	44 (59.5%)	13(43.3%)	0.04

Overweight	18 (17.3%)	12 (11.5%)	7 (9.5%)	5 (16.7%)	0.04
Obesity	21 (20.2%)	6 (5.8%)	6 (8.1%)	———	0.04
Severe obesity	13 (12.5%)	21 (20.2%)	11 (14.9%)	10(33.3%)	0.04

BMI – body mass index.

According to Table 2, the highest spontaneous healing rate was in patients with normal baseline BMI compared to obese patients.

By the multivariate analysis, the change in BMI classification was found to be the only prognostic factor for spontaneous healing of SCH, with P <0.04.

Discussion

SCH is a common disorder that requires early diagnosis and follow-up; it might progress to an OH. SCH is estimated in the pediatric population to be around 1.7% [4]; it increases in obese children to 22.2% [17]. The study found that the spontaneous healing rate of SCH was 71.2%, mostly in females. Out of the eight variables studied and tested in Univariate analysis, we found only two prognostic factors were associated with the spontaneous healing rate of SCH were the female sex and the change in BMI classification. The study found that spontaneous healing was highest among patients classified as having normal baseline BMI.

Murrillo-vallés M et al., found that the spontaneous healing rate was 67.6% [18], and Wasniewska M et al., found that the spontaneous healing rate was 88% [12]. Szeliga et al. found that the majority of patients with SCH were of the female sex and that sex played a role in the spontaneous healing [13]. Baş et Al., noticed a positive correlation between the change in BMI classification and the improvement of serum TSH values [19], while Hari Kumar et al., did not find any association between the change in BMI classification and TSH values [20]; which could be explained by the small sample size of the population and the high rate of dropout in his study. Szeliga et al. found that the overweight and obese patients with SCH were higher than those of normal weight [13]. Murrillo-vallés M et al., found that the high baseline TSH, female sex, and the presence of thyroid antibodies (TPOAb), Antithyroglobulin thyroid antibody (TgAb)) were associated with the progression to OH [19]. Wasniewska M et al., found that the female sex with Hashimoto's was a main factor for the progression to OH [21].

Hashimoto's remains the most common cause of SCH, which is characterized by the presence of thyroid autoantibodies (TPOAb, TgAb) with or without goiter [22]. Genetic mutations in the TSH-receptor or dual oxidase 2 (DUOX2) [23, 24] and nutritional factors may play a role in the pathology of SCH as low iodine intake for a long time due to SCH but it is associated with goiter, Gökdeniz et al., found that 16.6% of children with iron deficiency anemia had SCH, sever iron deficiency may lead to decrease in the thyroid peroxidase activity which probably lead to a decrease in the production of thyroid hormones, which might lead to SCH or overt hypothyroidism [25-27]. Kuiper and van der Gaag showed improvement in 74% of cases with the supplementation of iodine, iron, and vitamin A for three months [28].

Obesity might also play an important role in the occurrence of SCH; it leads to an increase in the production of leptin, which stimulates the release of the hormone prothyrotropin. leptin leads to a decrease in the central and peripheral deiodinase activity [29]. Ortiga-Carvalho et al. found that leptin stimulates the release of TSH. On the other hand, TSH stimulates the release of leptin through a direct effect on adipocytes [30, 31]. Unpublished data from the Ministry of Health in Syria in 2021 on 5320 children to evaluate the level of iodine concentration in urine indicated an iodine deficiency. In our self-funded study, neither nutritional factors nor iodine concentration in urine were studied to evaluate their impact on the clinical course of the SCH.

The absence of TPOAb was performed only for 57 of the patients; it was normal in 53 (93%) patients, which might suggest that it has no statistical significance in our study.

Because multi-factorial nutritional deficiency may play a role in the development of the SCH, a nutritional survey could be necessary in the assessment in our patients. It is important to evaluate the role of iodine supplementation in patients with SCH in a randomized clinical trial to determine the effect of iodine supplementation on the clinical course of SCH.

Long-term assessment is necessary to determine the spontaneous healing or the progression to OH, which requires hormonal replacement.

The question that remains is whether the return of the serum TSH value to normal values always means definitive healing of SCH?

Conclusion

SCH is a common disorder in children. It may lead to cardiovascular diseases or metabolic disorders, so it must be followed long-term to monitor for healing or progression to overt hypothyroidism. The study found that the change in BMI classification was the main prognostic factor for spontaneous healing, while no statistical significance was found in the other factors.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical Approval

This case report did not require review by the Ethics Committee of Latakia University Hospital, Latakia, Syria

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Conflicts of Interest

All of the authors declare that they have no competing interests

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