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The association between metabolic syndrome and hypothyroidism in school-aged obese children

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Abstract: Background: Subclinical hypothyroidism (SCH) is considered the most common hormonal disorder observed in obese children. SCH and metabolic syndrome (MS) are characterized by a set of common metabolic disorders such as visceral obesity, elevated TG (Triglycerides), T2DM (Type 2 diabetes mellitus), low HDL-C (High-density lipoprotein cholesterol), and therefore, undetected hypothyroidism may impair metabolic control and increase cardiovascular risk in patients with MS.

Objectives: The purpose of this study is to find out the association between having MS and the occurrence of SCH in overweight and obese Syrian children aged 5 - 14 years.

Methods: An observational cross - sectional analytic study was conducted on 90 overweight and obese patients aged 5-14 years (38 males 42.2% and 52 females 57.8%) who were followed up at the pediatric endocrine clinic at Tishreen University Hospital in Latakia from Aug'21 to July'22 and who met the eligibility criteria and had complete data.

Results: SCH is increased in the presence of MS and with a higher incidence in females compared to males. Also, SCH increased in obese children more than overweight children.

A positive correlation was observed between Thyroid-stimulating hormone (TSH) and TG levels, and a negative correlation was observed between TSH and HDL levels.

Conclusion: MS might increase the risk of SCH and the association between these two disorders may be bidirectional. Patients with MS and SCH should be monitored prospectively as an early intervention might play a role in reversing risk factors responsible for CVD (cardiovascular disease).

Keywords: metabolic syndrome, subclinical hypothyroidism, Children, Obesity, Syria.

العلاقة بين المتلازمة الاستقلابية وقصور الدرق عند الأطفال البدينين في عمر المدرسة

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المستخلص: يُعتَبَر قصور الدرق تحت السريري الأكْثر شُيوعًا بَيْن الاضْطرابات الهرْمونيَّة الملاحظة لَدى الأطْفال وتحْديدًا البدينين مِنْهم.

يَتَميَّز قُصُور الدَّرق والْمتلازمة الاسْتقْلابيَّة بِأَنَّهمَا يضمَّان مَجمُوعة مِن الاضْطرابات الاسْتقْلابيَّة المشْتركة كالْبدانة البطْنيَّة وارْتفاع الشُّحوم الثُّلاثيَّة والدَّاء السكريّ من النمط الثاني وانْخفاض HDL - C وَبذَلِك فَإن قُصُور الدَّرق غَيْر المكْتشف قد يُضْعِف ضَبْط الاسْتقْلاب ويضاعف الخطر اَلقلْبِي الوعائيّ عِنْد مَرضَى المتلازمة الاسْتقْلابيَّة.

يهدف البحث إلى تَقيِيم العلاقة بَيْن التَّعَرُّض لِلْمتلازمة الاسْتقْلابيّة وَحدُوث قُصُور الدَّرق عِنْد الأطْفال البدينين بِعمْر (5 - 14 سنة).

الطريقة: تم إجراء دراسة مقطعية عرضانية تحليلية على 90 طفلاً من الأطفال زَائدي الوزْن والْبدينين المتابعين في عِيادة أَمرَاض اَلغُدد الصُّمّ عِنْد الأطْفال في مَشفَى تِشْرين الجامعيّ في اللَّاذقيَّة خِلَال سنة البحْث (آب 2021 – تمُّوز 2022) مِمَّن حَققُوا مَعايِير الاشْتمال وكانتْ بياناتهم مُتكاملة.

النتائج: إن الإصابة بالمتلازمة الاستقلابيّة يزيد من خطر الإصابة بقصور الغدّة الدرقيّة تحت السريري عند الأطفال زائديّ الوزن والبدينين.

تزداد نسبة الإصابة بقصور الدرق تحت السريري عند الإناث مقارنةً بالذكور وبزيادة درجات البدانة.

وجدت هذه الدراسة علاقة ارتباط طردية ذات أهمية إحصائية بين قيم الـ TSH وقيم TG وعلاقة ارتباط عكسية بين قيم ال TSH وقيم الـ HDLc.

الخلاصة: نظراً لأن العلاقة بين المتلازمة الاستقلابيّة وقصور الدرق تحت السريري قد تكون ثنائيّة الاتجاه لذا نوصي بأهمية إجراء مسح روتيني للمتلازمة الاستقلابيّة وقصور الدرق عند الأطفال البدناء بمختلف الفئات العمريّة

كما يجب متابعة جمهرة الدراسة بشكل مستقبلي لتتبع التطورات السريريّة والبيولوجيّة لمرضى قصور الدرق المترافق مع المتلازمة الاستقلابيّة إذ أنّ التشخيص والتدخل الباكرين يلعبان دوراً هاماً في الوقاية من خطر الأمراض القلبية الوعائية.

الكلمات المفتاحية: المتلازمة الاستقلابية، قصور الغدة الدرقية، أطفال، البدانة، سوريا.

Introduction:

Hypothyroidism is considered one of the most common endocrine disorders. Its signs and symptoms are explained by inadequate production of thyroid hormones or lack of efficacy on target tissues [1].

The hypothalamic-pituitary axis regulates the release of TSH. TSH's primary target is the thyroid gland, where it stimulates the release of triiodothyronine (T3) and thyroxine (T4) from the follicular cells in the thyroid gland [2].

Thyroid hormones have an important role in lipid and glucose metabolism. Obesity, insulin resistance, hyperglycemia, dyslipidemia, and an increase in cardiovascular events are correlated with hypothyroidism [3].

SCH is classified based on clinical symptoms into subclinical hypothyroidism and overt hypothyroidism [4].

Subclinical hypothyroidism (SCH) is defined as a biochemical condition characterized by an elevated TSH level with a normal FT4 level. Recently, SCH has been classified as mild when the TSH level is between the upper limit of normal and 9.9 μiU/L or severe when the TSH level is greater than 10 μiU/L [5].

SCH is considered the most common hormonal disorder observed in obese children. Its prevalence in normal-weight children is 1.7% and increased in obese children to 10-23% [6].

Adipose tissue could be considered an endocrine gland, where it is responsible for the synthesis and secretion of several hormones, which may lead to many metabolic disorders such as increased blood insulin, type 2 diabetes mellitus, hyperlipidemia, and blood pressure (BP), related to cardiovascular diseases. Despite strong evidence that the process of atherosclerosis begins in childhood, the clinical features of cardiovascular diseases do not appear till early adulthood, these disorders are referred to as metabolic syndrome [7].

Metabolic syndrome refers to the association of several known cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension [8].

Noubiap JJ et al. estimated the proportion of MS as 3% among children and 5% among adolescents in 2020 [9], while it increased with Kharbotly D et al to 32.6% among obese children and 23% among obese adolescents in local studies [10].

The diagnosis of MS in children and adolescents lacks a consensus [11]

Throughout the years, there were a lot of criteria to diagnose MS, however, the most used definition is National Cholesterol Education Program Adult Treatment Panel Third (NCEP-ATP III) definition [12].

SCH and MS are characterized by a set of common metabolic disorders such as visceral obesity, elevated triglycerides (TG), T2DM, and low HDL-C, and therefore, undetected hypothyroidism may impair metabolic control and increase cardiovascular risk in patients with MS.

Therefore, it is necessary to study this relationship due to the lack of research correlated to children, and the controversial results of these research.

This study aims to:

1. Find out the relationship between having MS and the occurrence of hypothyroidism in overweight and obese school-aged children.
2. Study the relationship between TSH values and various MS components.
3. Study the relationship between SCH and the degree of obesity.

1- Patients and Methods:

An ethics approval was obtained from the Scientific Research Directorate at Tishreen University according to Decision No. 3347, after that, an observational cross- sectional analytic study was conducted on 90 overweight and obese patients aged 5-14 years (38 males 42.2% and 52 females 57.8%) who were followed up at the pediatric endocrine clinic at Tishreen University Hospital in Latakia from Aug'21 to Sep'22 and met the eligibility criteria and had complete data.

eligibility criteria:

A. Inclusion criteria: overweight and obese children aged 5-14 years who were observed in the pediatric endocrine clinic in children.

B. Exclusion criteria:

1. Past medical history for thyroids treatment.
2. Patients with familial hypercholesterolemia
3. Genetic syndromes associated with obesity (Prader-willi, Laurence-moon-Biedl, Turner)

Upon obtaining the informed consent from the children's parents, the following steps were taken:

a. Taking the clinical history

b. Measurement of weight, height, body mass index (BMI), and waist circumference (WC) were obtained.

c. BP (Blood pressure) was measured after 5 minutes of rest as per usual practice, it was considered high if systolic or diastolic pressure ≥ 90th percentile using American Academy of pediatric' (AAP) tables.

d. The samples of glycemia, TC (Total cholesterol), HDL and TG were obtained after fasting for 12 hours.

The definition of obesity was adopted according to the Centers for Disease Control and Prevention, where children are classified as overweight when 85> BMI> 95th percentile, while the BMI for obesity is greater than 95th percentile.

MS was diagnosed based on the National Cholesterol Education Program (NCEP) criteria, which require the presence of three out of five of the following criteria:

1. A WC is equal to or above the 90th percentile for the children's age and gender.
2. A BP measurement equal to or above the 90th percentile for the Children's age, gender, and height.
3. Fasting glycemia greater than or equal to 100 mg/dL or type 2 diabetes diagnosis.
4. Triglyceride level greater than or equal to 110 mg/dL
5. HDL (mg/dL) is less than or equal to 40 mg/dL.

Thyroid function test: TSH was performed as a primary screening test by using AYA360 machine in the laboratory of Tishreen University Hospital. Normal TSH values are considered between 0.38-4.31 µiU/l.

The statistical analysis included both descriptive and inferential statistics based on the tests of statistics. Descriptive statistics were used for quantitative variables and qualitative variables with frequencies and percentages. Inferential statistics were conducted using the following methods:

Chi-square test to study the relationship between qualitative variables.

Pearson Correlation to study the relationship between quantitative variables.

Z-test to examine the difference between the percentages of two groups.

Confidence intervals (CIs) at the level of 95%.

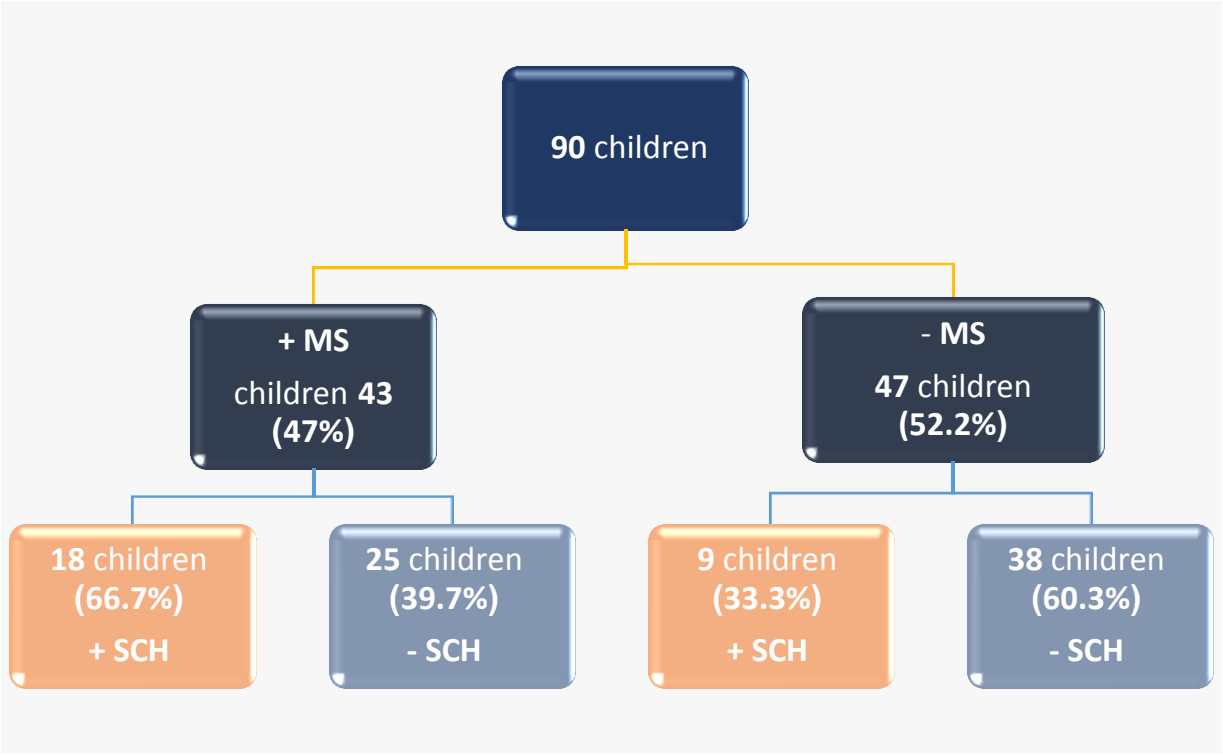
The results were considered statistically significant with a p-value ≤ 5%. The IBM SPSS statistics (version 19) program was used to calculate statistical coefficients and analyze results.

2- Results

The data of 90 overweight and obese children in our setting were analyzed, the patients' ages ranged from 5 to 14 years, with a mean age of 10.41±2.9 years, as the highest percentage was (48.9%) for the children aged 11-14 years.

The total number of patients included 52 females (57.8%) and 38 males (42.2%), 26 children (28.9%) were overweight and 64 children (71.1%) were obese, 43 (47%) children had MS, and 27 (30%) children had SCH.

Chart (1) displays the relationship between SCH and MS, where we found 18 Children (66.7%) with SCH and MS, and 9 children (33.3%) without MS, and it is displaying 25 Children (39.7%) with MS but without SCH, and 38 Children (60.3%) without both SCH and MS.



SCH: subclinical Hypothyroidism, MS: Metabolic syndrome

Chart (1): The relationship between MS and SCH.

The finding: SCH increased in presence of MS with a significant statistical difference (P-value = 0.001).

Table (1) displays the percentage of SCH according to the gender and degree of obesity. Out of the 27 children who had SCH ,7 children were males (25.9%), and 20 children were females (74.1%), 5 of these children (18.5%) were overweight and 22 Children (81.5%) were obese.

Table (1): the percentage of SCH according to the gender and degree of obesity.

	SCH		
	Positive	Negative	P Value
Gender			
Male	7 (25.9%)	31 (49.2%)	0.04
Female	20 (74.1%)	32 (50.8%)	
BMI			
Overweight	5 (18.5%)	21 (33.3%)	0.03
Obesity	22 (81.5%)	42 (66.7%)	

SCH: subclinical Hypothyroidism, BMI: Body Mass Index

The finding: SCH is higher in females with statistical difference (P-value = 0.04), and the proportion of SCH increased with higher BMI values (P-value = 0.03)

Table (2) displays the distribution of SCH cases according to the criteria of MS.

Table (2) Distribution of study participants by incidence of SCH and MS criteria:

Dx Criteria of MS	SCH	
	Positive	Negative
TG	24(88.9%)	37(58.7%)
BP	16(59.2%)	9(14.3%)
GLU	13(48.1%)	4(6.3%)
WC	10(37%)	2(3.2%)
HDL	23(85.2%)	34(54%)

SCH: subclinical Hypothyroidism, TG: Triglycerides, GLU: glucose, HDL high-density lipoprotein,

BP: blood pressure, Dx Criteria: Differential diagnosis, MS: Metabolic syndrome. WC: waist circumference

The finding: The SCH was accompanied by an increase in TG, BP, GLU, and WC, and decrease in HDL.

Table (3) displays the correlation between TSH and the criteria of MS.

Table (3) correlation between TSH levels and MS components:

Dx Criteria of MS	Pearson Correlation	P-value
WC	0.27	0.02
TG	0.38	0.005*
HDL	- 0.42	0.0001*
GLU	0.31	0.01
BP	0.22	0.04

TG: Triglycerides, GLU: glucose, HDL high-density lipoprotein, BP: blood pressure, Dx Criteria: Differential diagnosis, MS: Metabolic syndrome, TSH: thyroid stimulating hormone.

The finding: There is a significant positive correlation between TSH and TG and significant negative correlation between TSH and HDL.

3- Discussion:

This study included 90 overweight and obese children who met the eligibility criteria, 48.8% were with MS according to the NCEP criteria and 30% were with SCH.

SCH was observed in 66.7% of patients with MS compared to 33.3% without MS. We found a significant increase in SCH incidence with elevated TG levels, WC, BP and GLU, and decreased HDL levels.

The dysfunction of the pituitary gland, thyroid gland, and adipose tissue is a key part of the pathogenic mechanism.

The relationship between thyroid function and MS has been evaluated extensively in adults, while studies conducted in children are still controversial [13].

Our study and Zhang J et al. found that TSH levels were significantly higher in children with MS compared to those without, while Lee MK et al. indicated that there was no difference in TSH levels in obese children with or without MS, this is because Lee et al used a different definition according to the International Diabetes Federation (IDF) age category (10-18 years old) [14,15].

The mechanism by which thyroid hormones affect fat metabolism is well known. They decrease intestinal cholesterol absorption and increase hepatic fat synthesis. They also affect the composition and transport of fatty proteins, where SCH is associated with decreased lipoprotein lipase activity and lower cholesterol receptors, as well as decreased metabolism of fatty proteins. An association has been found between pro-atherogenic abnormalities and long-term SCH, due to dyslipidemia [16].

Jin HY. reported that TG levels were higher in patients with SCH compared to those with normal thyroid function, with no relationship to HDL cholesterol. In contrast, we and Kara O. found that HDL cholesterol levels were lower in the SCH group compared to the control group, with a positive correlationship between TSH levels and TG levels. This was interpreted as low levels of HDL cholesterol being associated with high levels of TG, especially in individuals with insulin resistance, as HDL particles are more easily metabolized in the presence of high TG levels [13,16].

Thyroid hormones influence the heart and blood vessels through their direct effect on the heart muscle, the sympathetic nervous system, and the peripheral blood vessels. Hypothyroidism decreases cardiac output, and sensitivity of the sympathetic nervous system and increases peripheral vascular resistance, which leads to an increase in cholesterol levels in the blood and the risk of atherosclerosis [17].

We found a weak correlation between SCH and BP, which is consistent with Cai Y et al whereas Cerbone et al did not observe the same results. This was explained by other factors that control BP regulation [18,19].

Insulin resistance is the primary mechanism responsible for the development of MS and type 2 diabetes. Hypothyroidism is associated with decreased glucose transport into muscle cells and decreased hepatic glucose production, where TSH is a stimulator for the basal expression of glucose transporters on cell surfaces. Hypothyroidism is also associated with insulin resistance in muscles and adipose tissues [20].

Rong F et al. indicated that the relationship between diabetes and the thyroid gland can be bidirectional. Elevated insulin levels in early type 2 diabetes can stimulate thyroid tissue hypertrophy, leading to thyroid enlargement and nodule formation [21].

Both Takaya R et al., and Kara O. found a positive correlation between TSH levels and insulin resistance, while we and JIN HY. found a weak correlation, this may be due to the use of fasting glycemia as a diagnostic tool for type 2 diabetes being less sensitive in children than the glucose tolerance test, insulin level, and HOMA-IR insulin resistance index used in previous studies [13,16,22].

MS develops primarily due to obesity that causes functional impairment resulting from the accumulation of excessive adipose cells. The secretion of leptin from adipose cells modifies the hypothalamic-pituitary-thyroid axis by bringing about certain changes in the production of thyrotropin-releasing hormone (TRH) [23].

Both Zhang J et al., and Salereno M et al. showed that SCH had insignificant effect on BMI in adolescents during follow-up years and that children with SCH had increased visceral obesity even if their BMI was normal. we could not compare this result with our study because our patients were overweight and obese children [3,15].

JIN HY, Takaya R et al, and we found a positive relationship between the TSH levels and the degree of obesity. This might be due to the role of TSH in energy conservation process [16,22].

Lee MK et al. reported a positive association between WC and SCH, but we and Takaya R et al. did not. This is because Lee et al used a different definition according to the IDF' criteria, which considers visceral obesity as a pre-requisite for diagnosing MS [14,22].

Assessing thyroid function in obese children is important to answer the question of whether SCH is a cause or a consequence of obesity. We need additional studies to confirm this. Krude H et al. found that giving thyroid hormone to obese children did not affect their weight status or body fat distribution [24], while Reinehr et al. suggested the positive role of weight loss programs on TSH homeostasis [25].

4- Conclusion:

MS might increase the risk of SCH and the association between these disorders might be bidirectional, but it is difficult to prove these associations in cross-sectional studies. Patients with MS and SCH should be monitored prospectively as an early intervention might play a role in reversing risk factors responsible for CVD.

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