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The Evaluation of Subclinical Hypothyroidism in Children with Morbid Obesity

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***Abstract*—**Cardiovascular (CV) pathology is one of the expected consequences of excessive fat gain. The role of zinc (Zn) in thyroid hormone metabolism (THM) is a matter of debate. Both thyroid stimulating hormone (TSH) and Zn levels are subject to variation in obese individuals. Zn participates in THM. It is closely related to TSH. Since thyroid hormones are required for Zn absorption, hypothyroidism can lead to Zn deficiency and vice versa. Zn exhibits protective effects on CV health and it is inversely correlated with CV markers in childhood obesity. The association between subclinical hypothyroidism (SCHT) and metabolic disorders is under investigation due to its clinical importance. SCHT is defined as the elevated serum TSH levels in the presence of normal free thyroxin (T_4) concentrations. The aim of this study is to evaluate the associations between TSH levels and Zn concentrations in SCHT cases detected in morbid obese (MO) children with and without metabolic syndrome (MetS) [(MOMetS+ and MOMetS-)], respectively. 42 children were present in each study group. Informed consent forms were obtained. Tekrdag Namik Kemal University Faculty of Medicine Non-Interventional Clinical Investigations Ethical Committee approved the study protocol. World Health Organization criteria were used for obesity classification. Children with age and sex-dependent body mass index percentile values above 99 were defined as MO. Children exhibiting at least two of MetS criteria were included in MOMetS+ group. Elevated fasting blood glucose, elevated triglycerides (TRG)/decreased high density lipoprotein-cholesterol (HDL-C) concentrations, elevated blood pressure values in addition to central obesity were listed as MetS criteria. Anthropometric measures were recorded. Routine biochemical analyses were performed. In MOMetS- group 13, in MOMetS+ group 15 children were with SCHT. Statistical analyses were performed. $p < 0.05$ was accepted as statistically significant. In MOMetS- and MOMetS+ groups, TSH levels were 4.1 ± 2.9 mU/L and 4.6 ± 3.1 mU/L, respectively. Corresponding values for SCHT cases were 7.3 ± 3.1 mU/L and 8.0 ± 2.7 mU/L. Free T_4 levels were within normal limits. Zn concentrations were negatively correlated with TSH levels in both groups. Significant negative correlation calculated in MOMetS+ group ($r = -0.909$; $p < 0.001$) was much stronger than that found in MOMetS- group ($r = -0.706$; $p < 0.05$). This strong correlation ($r = -0.909$; $p < 0.001$) calculated for cases with SCHT in MOMetS+ group was much lower in the same group ($r = -0.793$; $p < 0.001$) when all cases were considered. In conclusion, the presence of strong correlations between TSH and Zn in SCHT in both MOMetS- and MOMetS+ groups have pointed out that MO children were under the threat of CV pathologies. The detection of the much stronger correlation in MOMetS+ group in comparison with the correlation found in MOMetS- group was the indicator of greater CV risk due to the presence of MetS. In MOMetS+ group, correlation in SCHT cases found higher than correlation calculated for all cases confirmed much higher CV risk due to the contribution of SCHT.

***Keywords*—**Cardiovascular risk, child morbid obesity, subclinical hypothyroidism, zinc.

I. Introduction

THYROID hormones are associated with energy regulation, thermogenesis and many other metabolic pathways. They regulate basal metabolism. Thyroxin and triiodothyronine (T4 and T3, respectively) are known as thyroid hormones. They are under the regulation of TSH (thyrotropin) regulated by thyroid releasing hormone (TRH). Thyroid metabolism is highly affected by the status of trace elements such as zinc. These hormones stimulate basal metabolic rate and exert significant impact on body weight [1]-[3].

TSH limited by the negative feedback from the thyroid hormones shows an increasing trend with increasing body mass index (BMI). This hormone is positively associated with general and abdominal obesity in children [4]-[7]. Besides, the higher the TSH level, the lower the basal metabolic rate (BMR) [1]. The close associations between obesity and BMI as well as obesity and BMR make TSH important during the evaluation of obesity types. This parameter also gains importance during the course of some obesity-associated diseases such as diabetes mellitus, MetS and cardiovascular diseases (CVD) [8]-[15].

Hypothyroidism is associated with CV risk and may lead to atherosclerosis [16], [17]. The association between SCHT and MetS was also reported [18]. SCHT can be summarized as elevated TSH levels (4.5-10 mIU/L) in the presence of normal thyroid hormone concentrations [16], [19]-[21]. It was reported that about 4.3-9% of the general population was affected with SCHT [14], [16], [22]. In overweight and obese children, its prevalence varies between 7% and 23% [8], [23].

The aim of this study was to find out the effect of SCHT on metabolic parameters potentially associated with CV risk. Within this context, associations of TSH with lipid parameters including HDL-C, TRG, TRG/HDL-C and also, due to its cardioprotective effects, correlations between zinc and TSH, were investigated in MO children with and without MetS.

II. Patients and Methods

A. Patients

42 children with morbid obesity (MO) (Group 1) and 42 MO children with MetS (Group 2) were considered. Two groups constituted were investigated from the SCHT point of view.

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The number of children with SCHT was 13 in the MO-SCHT group (Group 3) and 15 in the MetS-SCHT group (Group 4). TSH concentrations between 4.5 mU/L and 10 mU/L were defined as mild form, of which their management was a still a matter of debate. The levels above 10 mU/L were subjected to treatment. In Group 1 there were three and in Group 2 there were six children with TSH levels higher than 10 mU/L.

Informed consent forms were obtained from parents. The Helsinki Declaration was applied, and ethical approvals were obtained. Ethics committee of the University approved the study protocol.

Body weight and height measurements were taken. Circumferences of waist, hip, head and neck of children were measured. BMI was calculated.

B. Obesity and MetS Criteria

Obesity and MetS criteria followed in this study can be summarized in the following manner:

MO children were those with BMI percentiles above 99 according to World Health Organization [24] age- and gender-dependent BMI percentile tables.

MO children with elevated systolic and diastolic blood pressure, high blood glucose, increased TRG and/or decreased HDL-C levels were MetS components considered [25]. These children were included in Group 2.

C. Laboratory Measurements

Routine laboratory tests including fasting blood glucose, TRG, HDL-C, thyroxin, triiodothyronine, TSH were performed by autoanalyzer. Zinc concentrations were determined.

D. Statistical Analysis

The statistics software SPSS was used for the evaluation of the data. Correlation coefficients and the degree of significance were calculated. Linear regression plots with 95% mean prediction interval were drawn.

III. Results

Groups were matched for age and gender ratios ($p > 0.05$). Table I showed thyroid hormone profile and zinc status of groups. Statistically significant differences between the groups were also shown in the table.

In SCHT cases, fT4 levels varied between 0.90-1.50 ng/dL against TSH levels, which varied between 4.83 and 15.22 in the MO group. The corresponding pattern in MetS group was 0.93-1.33 for fT4 and 4.53-11.36 for TSH.

TABLE I
THE CONCENTRATIONS OF ZINC, THYROXIN, TRIIODOTHYRONINE AND TSH OF THE GROUPS (MEAN ± SD)

Parameter		Group 1 MO	Group 2 MetS	Group 3 MO (SCHT)	Group 4 MetS (SCHT)
Zn*	µg/dL	76.5 ± 25.5	76.6 ± 26.7	63.3 ± 31.2	58.4 ± 28.9
T4 NS	ng/dL	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.2	1.1 ± 0.1
T3 NS	pg/mL	4.4 ± 0.8	4.1 ± 0.6	4.6 ± 0.4	4.3 ± 0.5
TSH *	mU/L	4.1 ± 2.9	4.6 ± 3.1	7.3 ± 3.1	8.0 ± 2.7

Zn = zinc, T4 = thyroxine, T3 = triiodothyronine, NS = not significant. [* 1-3, 2-4 $p < 0.05$]

Serum zinc concentrations did not differ between the MO (Group 1) and MetS (Group 2) groups. These values were almost the same.

In Group 3 and Group 4, the effect of SCHT was observed. Significantly decreased zinc concentrations were determined.

Statistically significant negative correlations were found between zinc and TSH concentrations both in Group 3 ($r = -0.706$; $p = 0.015$) and Group 4 ($r = -0.909$; $p = 0.001$). The related linear regression lines with 95.0% mean prediction interval were shown in Figs. 1 and 2, respectively.

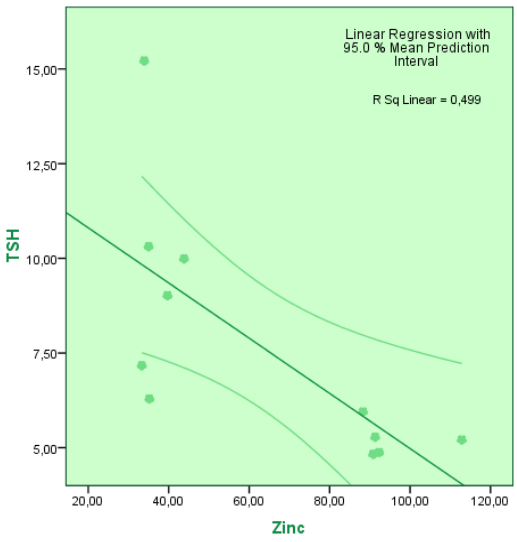

Fig. 1 Negative correlation between serum TSH levels and zinc concentrations among SCHT cases in MO group

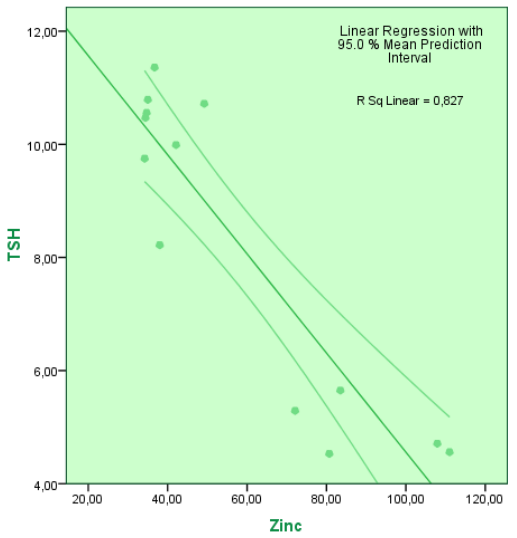

Fig. 2 Negative correlation between serum TSH levels and zinc concentrations among SCHT cases in MetS group

In terms of T4 and T3, almost the same values were observed in all four groups. TSH levels were increased in MetS group in groups encompassing all cases as well as SCHT groups.

Significantly increased TSH values were detected in SCHT groups of both MO and MetS cases.

IV. Discussion

SCHT is generally investigated in the elderly, however, it is also a common disorder in the pediatric age group. The diagnosis and treatment of SCHT particularly in obese children are problematic [26]. Children with serum TSH levels greater than 10 mU/L must be treated, however, there is a lack of consensus on the treatment of mild forms. It is suggested that the treatment should be individualized [27]-[30].

Obesity is a risk factor for SCHT. Obese subjects had higher TSH and a higher prevalence of SCHT than subjects in the normal group [31]. Obesity is also an important cause of SCHT in children. Studies indicate that SCHT may be detected in around 10-23% of children with obesity [29], [30], [32].

Thyroid hormones have multiple effects on the heart and CV system. Hypothyroidism including SCHT, also known as mild hypothyroidism, is associated with an increased risk for developing heart failure [20], [33], [34].

SCHT usually does not cause symptoms. However, it is particularly important in individuals with CV risk [27]. It is important to understand the interaction between thyroid hormone sensitivity and metabolic diseases in SCHT [35]. The presence of SCHT may be an additional risk factor for CV risk [15]. Both overt hypothyroidism and SCHT can have varied but profound effects on cardiac hemodynamics and physiology contributing to cardiac related morbidities [33]. SCHT may be associated with an increased risk of coronary artery disease events, heart failure and mortality from coronary heart diseases [28], [36].

Mild hypothyroidism may be associated with increased risk of metabolic abnormalities and CVD in adults. However, whether it is a CV risk factor among children is a matter of debate [34], [37].

SCHT and overt hypothyroidism may develop from an early age in overweight and obese pediatric individuals [12], [19], [37]. Mild SCHT may be associated with early changes in body composition parameters such as fat masses [38]. Elevated serum TSH concentrations are associated with higher BMI-z scores in children and adolescents [9]. SCHT was identified in obese children and adolescents. A clear association was observed among SCHT, insulin resistance and dyslipidemia in obese children [39]. SCHT in obese children may cause dyslipidemia carrying a high CVD risk [40].

In our study, although it was a small sample group for making prevalence estimation, of 84 children in MO as well as MetS groups, about 33% of the cases were defined as SCHT. This finding was consistent with the findings of a previous report [32].

Although HDL-C was subjected to decrease in MetS group compared to MO cases (46.7 ± 9.9 vs 51.5 ± 8.5) as TSH levels increase (4.1 ± 2.9 for MO; 4.6 ± 3.1 for MetS) and TRG/HDL-C values were calculated as 1.7 ± 0.9 and 3.6 ± 2.2 for MO and MetS groups, respectively, upon examination of correlations of TSH with these markers as of CV property, any association between TSH and HDL-C as well as TRG/HDL-C was not detected.

It was reported that further investigations about the role of zinc in the regulation of thyroid hormones metabolism was important [3].

Zinc deficiency was suggested as a contributing factor for developing CVDs. Zinc was introduced as a biomarker of CV health [41].

In a study performed by our team in 2021, about the association of zinc with new generation markers in childhood obesity, inverse correlations found between zinc and troponin T as well as cardiac myosin binding protein-C (cardiac markers used to evaluate the status of CV health and diseases) in MetS group pointed out that zinc may be a potential biomarker for CV health [42].

The correlation of TSH with zinc, another CV marker, showed that strong negative associations were valid in both MO and MetS groups. These correlations were compared with those calculated in SCHT cases. Similar values were obtained ($r = -0.718$; $p = 0.015$ and $r = -0.706$; $p = 0.015$) for all MO children and for SCHT MO children, respectively in MO group. However, correlations were much stronger in MetS group. This point is important from two aspects:

- First, in MetS group the correlation observed between TSH and zinc was $r = -0.909$; $p = 0.000$ in comparison with the correlation in MO group ($r = -0.706$; $p = 0.015$). This showed that cardiometabolic risk increases in MetS compared to MO.
- Second, in MetS group a striking difference was noted between correlations calculated for all MetS cases ($r = -0.793$; 0.000) and SCHT MetS cases ($r = -0.909$; 0.000).

These two findings have shown that children with MetS were more subjected to proceed with CV problems compared to MO children without MetS findings. Also, in MetS group, it was detected that SCHT makes great contribution to cardiometabolic risk considering that zinc is a valuable marker for CV status and zinc possesses protective feature against the development of CV problem.

V. Conclusion

In this study, the possible relations between SCHT and CV as well as MetS risks were investigated. For this purpose, the associations between TSH levels and concentrations of zinc, as the well-defined parameter for CV risk, were determined in MO children with and without MetS findings.

The results pointed out the clear relation between elevated TSH in the presence of normal fT4 levels and the depressed zinc concentrations. This relation was much higher in MO+MetS+ group. Both findings led to the conclusion that SCHT was closely associated with both CV risk and MetS also in pediatric age group.

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