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The impact of thyroid function on the occurrence of metabolic syndrome in obese children and adolescents

Wpływ czynności tarczycy na wystąpienie zespołu metabolicznego w grupie otyłych dzieci i młodzieży

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Abstract
Introduction: Thyroid axis abnormalities are common in obese patients. Their contribution in the development of metabolic obesity complications remains unclear.
Aim of study: To assess the influence of thyroid axis dysfunction on the occurrence of metabolic obesity complications.
Material and methods: A cross-sectional review of the thyroid function in 100 obese patients (59 girls and 41 boys, mean age 13.5 years) with alimentary obesity (mean standardised body mass index [BMI SDS] in boys 4.175 and girls 4.723) complicated by metabolic syndrome (MS) diagnosed on the basis of the IDF 2006 criteria (MS, 25 patients) and uncomplicated (75 patients). TSH, fT4, fT3 thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TGAb) were assessed in a single fasting blood sample.
Results: There was no case of overt thyroid disease within the whole analysed group. There were no significant differences in mean TSH, fT4, and fT3 levels in patients with and without MS (2.7 μIU/ml vs. 3.0 μIU/ml, 14.5 vs. 14.0 pmol/l, and 5.6 vs. 6.2, respectively; $p > 0.05$). In the MS group only two patients (8%) presented with a TSH level above the upper limit of the normal range; in the group without MS elevated TSH was noticed in 18 (24%) patients. The maximal value of TSH (10.44 μIU/ml) was noticed in one boy without MS. Positive TPOAb and/or TGAb were present in 11% of all patients: two patients (8%) with MS and nine (12%) without MS.
Conclusions: Isolated increased TSH level is common in obese adolescents, although there is no correlation between TSH, fT3, and fT4 levels and BMI SDS value. Isolated increased TSH level is not associated with the occurrence of MS in obese adolescents. The occurrence of asymptomatic autoimmune thyroiditis (AITD) in obese adolescents is more common than in the general population.
Key words:
obesity, metabolic syndrome, thyroid.

Streszczenie
Wstęp: Zaburzenia funkcji osi tarczycowej są częste u pacjentów otyłych. Ich znaczenie w rozwoju metabolicznych powikłań otyłości pozostaje niejasny.
Cel badania: Ocena wpływu zaburzeń funkcji tarczycy u pacjentów otyłych na wystąpienie u nich powikłań metabolicznych.
Materiały i metody: Ocena funkcji tarczycy w grupie 100 pacjentów (59 dziewcząt, 41 chłopców; średni wiek 13,5 roku) z otyłością prostą (średni BMI SDS u chłopców 4,175 i u dziewcząt 4,723) z zespołem metabolicznym rozpoznanym na podstawie kryteriów IDF 2007 ZM (ZM, 25 pacjentów) i bez. U wszystkich wykonano oznaczenie stężeń TSH, fT4, fT3 przeciwciał przeciw tyreoperoksydazie tarczycowej (TPOAb) i przeciwciał przeciwko tyreoglobulinie (TGAb) w pojedynczej próbce krwi.
Wyniki: W analizowanej grupie nie stwierdzono przypadku jawnej niedoczynności tarczycy. Nie było istotnych statystycznie różnic ($p > 0,05$) średniej wartości TSH, fT4 i fT3 u pacjentów z ZM i bez ZM (odpowiednio: 2,7 μIU/ml *vs* 3,0 μIU/ml, 14,5 *vs* 14,0 pmol/l i 5,6 *vs* 6,2 pmol/l). W grupie spełniającej kryteria ZM ($n = 25$) tylko dwie osoby (2/25; 8%) miały stężenie TSH powyżej górnej granicy normy (N: 0,3–4,0 μIU/ml). W grupie bez ZM zwiększone stężenie TSH stwierdzono u 18 (18/75; 24%) pacjentów. Maksymalną wartość TSH (10,44 μIU/ml) odnotowano u chłopca bez ZM. Dodatnie miano przeciwciał przeciwtarczycowych (TPOAb i/lub TGAb) było obecne u 11% pacjentów: 2 pacjentów (2/25; 8%) z ZM i u 9 (9/75; 12%) bez ZM.
Wnioski: Izolowane zwiększenie stężenia TSH jest częste u otyłych nastolatków, chociaż nie występuje zależność pomiędzy stężeniem TSH, fT3 ani fT4 a wartością BMI SDS. Izolowane zwiększenie stężenia TSH nie ma związku z występowaniem ZM u młodzieży.
Słowa kluczowe:
otyłość, zespół metaboliczny, tarczyca.

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Introduction

Obesity and its consequences have become a significant health problem nowadays. By 2030 an estimated 38% of the world's adult population will be overweight, and another 20% will be obese [1]. This phenomenon is associated with increased morbidity because excessive fat tissue is a source of many regulatory factors. Fat tissue hormones and cytokines can directly and indirectly affect many of the body's functions. One of them is the thyroid axis. Obese people are often found to present increased thyrotropin (TSH) concentration levels and changes in the ratio between the thyroid hormones: triiodothyronine and thyroxine, although both levels are usually within the normal range [2-4]. The aetiology of these processes is still unclear. It is hypothesised that at least four mechanisms are involved in this phenomenon: 1) an adaptive process to increased leptin production by fat tissue, 2) insulin resistance and concomitant chronic low-grade inflammation leading to abnormal mitochondrial function and abnormal pattern of energy expenditure, 3) abnormal activity of deiodinases and relative thyroid hormone resistance, and 3) development of autoimmune thyroid disease (AITD) [2-6]. The first three mentioned effects seem to be reversible after weight reduction, leading to normalisation of free triiodothyronine (fT3) and free thyroxine (fT4) ratio. The effect of weight reduction on normalisation of TSH remains controversial [7, 8]. Although the clinical implications of thyroid axis dysfunction in obesity are not well investigated, some studies suggest that they may contribute to the worsening of metabolic complications [2]. According to some studies, thyroid dysfunction can be an additional risk factor that should be taken into consideration when calculating individual cardiometabolic risk [9].

The aim of the study was to assess the influence of thyroid axis dysfunction on the occurrence of metabolic obesity complications. For this purpose, we compared the thyroid axis function in adolescents with uncomplicated nutritional obesity and obesity complicated by the occurrence of metabolic syndrome (MS).

Material and methods

The study included 100 patients (59 girls and 41 boys) between five and 18 years of age (mean age 13.5 years) with alimentary obesity (mean standardised body mass index [BMI SDS] in boys 4.175 and in girls 4.723) and without history of thyroid diseases. Patients were recruited from the Clinic of Paediatric and Adolescent Endocrinology University Children's Hospital in Krakow, Poland. In all patients, evaluation was performed before starting the process of weight reduction. BMI was calculated from the following equation: BMI = body weight (kg)/body height (m)^2. Obesity was defined by BMI above the 95th percentile for sex and age [10]. Hypertension was diagnosed when systolic and/or diastolic value was above the 95th percentile according to sex and height [10]. MS was diagnosed on the basis of the IDF 2006 criteria [10]. Glucose, HDL-cholesterol, and triglyceride concentrations were measured in blood samples collected after eight hours of fasting. TSH, fT4, fT3, thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TGAb) were determined in a single fasting blood sample. Normal ranges were defined as: TSH 0.3-4.0 μIU/ml, fT4 10-25 pmol/l, fT3 3.0-8.1 pmol/l, TPOAb $<$ 30 IU/ml, and TGAb $<$ 30 IU/ml. TSH, fT3, and fT4 were measured using immunochemistry method with an Advia Centaur machine, and TPOAb and TGAb using radioimmunoassay (RIA) method with a Brams machine.

Statistical analysis

To compare the two sets of data, Student's t-test or two-sided Mann-Whitney U test was used. For a correlation analysis, the correlation coefficient (R) and regression analysis were used. Statistically significant results were assumed for which the probability value was less than 0.05.

Results

There was no case of overt hypothyroidism within the whole analysed group. We did not notice abnormal values of fT3 or fT4. There were no significant differences in mean TSH, fT4, and fT3 levels in patients with and without MS (2.7 μIU/ml vs. 3.0 μIU/ml, 14.5 vs. 14.0 pmol/l, and 5.6 vs. 6.0 pmol/l, respectively; $p > 0.05$) (Fig. 1). There was no significant correlation between BMI SDS and TSH, fT4, or fT3 levels (R = 0.008; –0.04; –0.03, respectively; $p > 0.05$) (Fig. 2). In the group that met IDF criteria of MS ($n = 25$) only two (2/25, 8%) presented with TSH above the upper limit of the normal range. For comparison, in the group without MS elevated TSH was noticed in 18 (18/75, 24%) patients. Sub analysis performed for girls and boys revealed that among girls with MS two (2/14, 14%) presented with elevated TSH value vs. 11 (11/4524%) in the group without MS. In boys with MS no one presented with elevated TSH value vs. seven (7/30, 23%) in the group without MS. The differences were not significant. The maximal value of TSH (10.44 uIU/ml) was noticed in one boy without MS. Positive antithyroid autoantibodies (TPOAb and/or TGAb) were present in 11% of all patients: 2 patients (2/25, 8%) with MS (both girls, both with normal TSH) and 9 (9/75, 12%) without MS (2 with elevated TSH [boys only], seven with normal TSH [5 girls]). Elevated TSH was not associated with autoimmunity, and only two patients with higher TSH were positive for antithyroid antibodies.

Discussion

Thyroid axis function in obese patients has been investigated widely in recent years. It has been shown that TSH level above upper laboratory normal range is more prevalent in obese patients than in healthy pears. According to literature data, 10-24% of obese children and adolescents present with elevated TSH in the absence of thyroid disease [3, 13], similarly

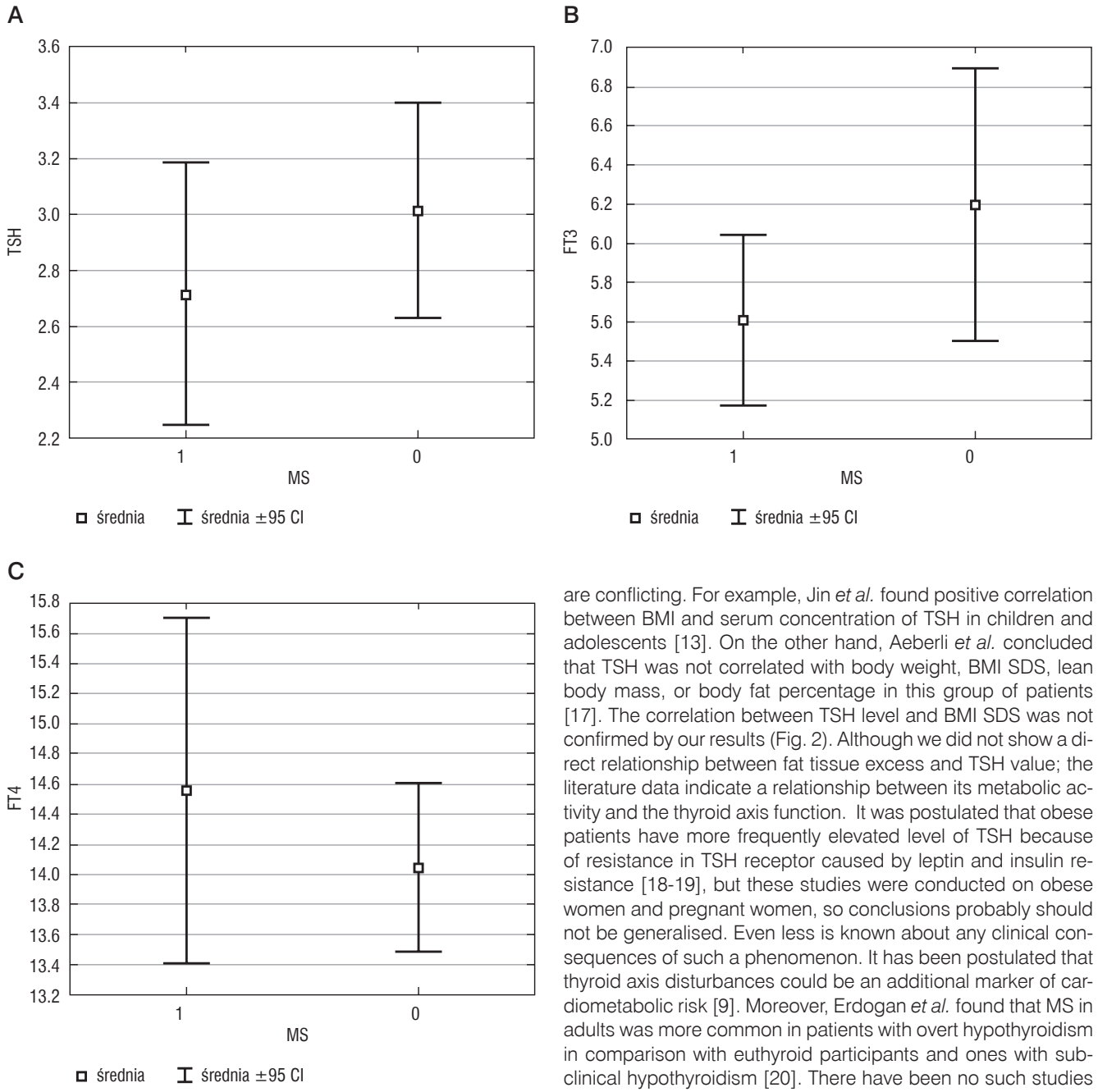

Figure 1. TSH (A), fT3 (B), and fT4 (C) values in patients without MS (0) and with MS (1)

as in the present study (20%). Although the mechanism of such an increase in TSH level in obese patients remains unclear, it is usually not caused by primary thyroid dysfunction (as in subclinical/overt hypothyroidism). In adults the TSH value increases proportionally to the degree of obesity [14-16]. Such a correlation is uncertain in children because the literature data are conflicting. For example, Jin *et al.* found positive correlation between BMI and serum concentration of TSH in children and adolescents [13]. On the other hand, Aeberli *et al.* concluded that TSH was not correlated with body weight, BMI SDS, lean body mass, or body fat percentage in this group of patients [17]. The correlation between TSH level and BMI SDS was not confirmed by our results (Fig. 2). Although we did not show a direct relationship between fat tissue excess and TSH value; the literature data indicate a relationship between its metabolic activity and the thyroid axis function. It was postulated that obese patients have more frequently elevated level of TSH because of resistance in TSH receptor caused by leptin and insulin resistance [18-19], but these studies were conducted on obese women and pregnant women, so conclusions probably should not be generalised. Even less is known about any clinical consequences of such a phenomenon. It has been postulated that thyroid axis disturbances could be an additional marker of cardiometabolic risk [9]. Moreover, Erdogan *et al.* found that MS in adults was more common in patients with overt hypothyroidism in comparison with euthyroid participants and ones with subclinical hypothyroidism [20]. There have been no such studies in children and adolescents to date. The results of the present study do not confirm any association between abnormal thyroid axis function (measured as TSH, fT3, and fT4 levels) and the presence of MS in adolescents. No frequent occurrence of overt thyroid diseases was confirmed in that group either. Such an increased incidence reported by research carried out on adults pointed to a potential association between elevated TSH and insulin sensitivity [21]. On the basis of the results of newer publications, the direction of this dependence seems to be the opposite: the insulin resistance in obesity seems to lead to tissue hypothyroidism and subsequent increase in TSH synthesis [2].

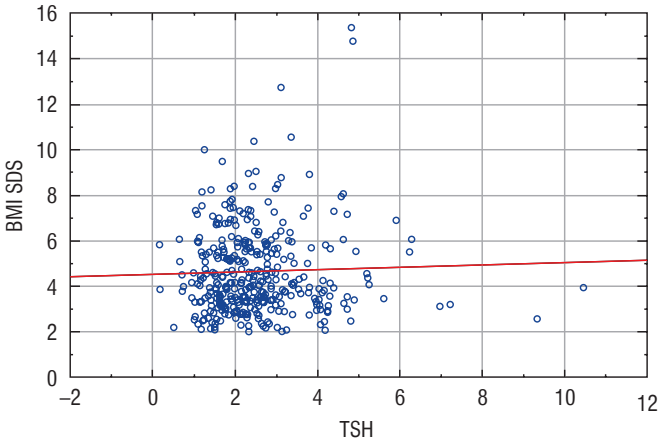

Figure 2. Correlation between BMI SDS and TSH level [μIU/ml], $r = 0.008$; $p > 0.05$

The relationship between thyroid function and components of MS has been discussed in a few articles only, with conflicting conclusions [22-24]. Ruhla *et al.* reported that even a high normal TSH level is associated with greater susceptibility to MS [22]. Other studies, conversely, revealed no association between TSH fT4 and fT3 levels and MS occurrence, similarly to our observation [23-24]. Another aspect analysed in our study was the association of obesity and its metabolic complications with AITD. Some studies point to a potential role of obesity as an environmental factor contributing to the onset and progression of AITD [25]. For example, Hashimoto thyroiditis seems to be more prevalent in patients with polycystic ovary syndrome, in which the development of basic motions has insulin resistance [26]. Adipokines, such as leptin and adiponectin, seem to play roles in regulating immunity and be links between obesity and autoimmunity [25, 27-34]. Moreover, some authors suggest that a hypoechogenic thyroid ultrasound image, frequently observed in obese patients, may be the early sign of a seronegative AITD and could precede the generation of antithyroid antibodies [3]. On the other hand, many studies deny increased incidence of AITD in obese patients with elevated TSH [34-38]. In the study by Gherghere-hchi *et al.* among patients with obesity and increased TSH levels, only 10.7% were positive for antithyroid antibodies [39]. In our group 11% of patients presented with positive antithyroid autoantibodies, which is more than previously reported for an obese Italian population (7% of obese adolescents in the paper by Grandone *et al.*) and almost 10 times more often than reported for the normal weight population (1.2%) [5, 40]. The main limitation of our study is its small sample size. All components of MS can be influenced by different factors, e.g. genetic and environmental factors, not only TSH, so it is hard to be sure about its causality. Also, we did not interview our patients about their daily habits (diet, exercise), and these factors could also influence the results. Further clinical, longitudinal studies should be performed to investigate whether thyroid status plays a role in the occurrence of MS or not.

Conclusions

Isolated, increased TSH levels can be found in a significant percentage of obese adolescents. There is no correlation between TSH, fT3, and fT4 levels and BMI SDS value. Isolated, increased TSH level is not associated with the occurrence of MS in obese adolescents.

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