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Associations between thyroid-stimulating hormone, blood pressure and adiponectin are attenuated in children and adolescents with overweight or obesity

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Abstract

Background: The association between thyroid-stimulating hormone (TSH) concentrations and blood pressure is well described in adults, but only studied to a limited extent in children and adolescents and almost entirely in population-based cohorts. The present study investigates the association between TSH and blood pressure, and the influence of leptin and adiponectin, in a cohort of children and adolescents enrolled in obesity treatment compared with a population-based cohort.

Methods: We studied 4154 children and adolescents aged 6–18 years from an obesity clinic cohort and a population-based cohort from The Danish Childhood Obesity Data- and Biobank. Anthropometrics, blood pressure and biochemical markers, including TSH, leptin and adiponectin concentrations, were collected. Adjusted correlation and interaction analyses were performed.

Results: Patients from the obesity clinic cohort exhibited higher concentrations of TSH and higher blood pressure than participants from the population-based cohort. TSH standard deviation scores (SDS) were significantly associated with all blood pressure-related variables in the population-based cohort, but only with systolic blood pressure SDS and hypertension in the obesity clinic cohort. The interaction between TSH SDS and adiponectin was found to be independently associated with systolic blood pressure and hypertension in the population-based cohort only.

Conclusions: The significant associations between TSH, adiponectin and blood pressure, observed in children and adolescents from a population-based cohort, are attenuated or absent in children and adolescents with overweight or obesity, suggesting that childhood obesity distorts the healthy interplay between the thyroid axis, thyroid-adipokine interaction and blood pressure.

Keywords: adiponectin; blood pressure; childhood obesity; leptin; paediatric endocrinology; thyroid-stimulating hormone.

Introduction

Childhood obesity has reached epidemic proportions and is now considered one of the most serious public health concerns [1]. Children with overweight or obesity are likely to carry their excess weight into adulthood [2], thus facing a higher risk of developing obesity-related cardiovascular and metabolic diseases [1]. It is well known that obesity affects both thyroid and cardiovascular functions, and that even mild changes in thyroid function have adverse
influence on the cardiovascular system [3]. The effects of thyroid dysfunction on the cardiovascular system are reviewed in depth in several recent papers, that all call for further research on the topic [3–5].

Childhood obesity is associated with increased prevalence of subclinical hypothyroidism, characterized by elevated serum concentration of TSH combined with normal thyroxine (T4) and normal or slightly increased triiodothyronine (T3) concentrations [6]. We have recently confirmed this in Danish children and adolescents with overweight or obesity compared with normal weight peers [7]. Subclinical hypothyroidism is associated with impaired endothelial vasodilation, increased arterial stiffness and left ventricular systolic and diastolic dysfunction [5]. These abnormalities contribute to the development of hypertension and serve as risk factors for cardiovascular morbidity and mortality [8].

Childhood obesity, independent of thyroid function, is a risk factor for increased systolic and diastolic blood pressure and hypertension [9, 10]. The pathophysiology of obesity-related hypertension in children and adolescents is complex. A contributory mechanism is activation of the sympathetic nervous system, mediated by hyperleptinaemia and hyperinsulinemia, resulting in increased sodium reabsorption in the kidneys [11, 12]. Furthermore, other contributing factors have been suggested: over activity of the renin-angiotensin-aldosterone system due to both increased sympathetic stimulation of renin release and increased angiotensinogen release directly from the adipocytes [13]; and increased systemic vascular resistance due to obesity-related low-grade inflammation and endothelial dysfunction [14].

The obesity-related systemic low-grade inflammation is characterized by increased concentrations of pro-inflammatory cytokines, including leptin, and decreased concentration of adiponectin [15]. Adiponectin is an anti-inflammatory hormone produced exclusively by adipocytes and the concentration is inversely related to the degree of obesity [16]. Low adiponectin concentrations in conjunction with obesity-related low-grade inflammation is associated with cardiovascular disease [17]. Leptin is another adipocyte-derived hormone which, in contrast to adiponectin, increases with the degree of obesity. Besides regulating energy balance, leptin increases sympathetic activity [18] and exerts direct effects on vascular tone and sodium reabsorption [19], suggesting an influencing role on blood pressure regulation. Furthermore, leptin regulates the hypothalamic-pituitary-thyroid axis and is positively correlated with TSH independently of body mass index (BMI) [20, 21]. Thus, leptin is a promising link between obesity and TSH.

The link between TSH and blood pressure has been extensively investigated in adults, where serum TSH is associated with both systolic and diastolic blood pressure [22, 23]. However, in children and adolescents this is only investigated in a few studies, which found associations between TSH and hypertension in populations-based cohorts of children and adolescents [24, 25], and between TSH and systolic blood pressure in a paediatric cohort where 60% had overweight or obesity [26]. Consequently, further research is needed to determine whether TSH may serve as a potential risk marker for the development of hypertension in children and adolescents with and without obesity. The present study investigates the associations between TSH, blood pressure, leptin and adiponectin in a large homogenous cohort of Danish/North-European white children and adolescents with overweight or obesity and in a population-based cohort.

Materials and methods

Study design and participants

This cross-sectional study included an obesity clinic cohort and a population-based cohort to serve as control, both from The Danish Childhood Obesity Data- and Biobank.

The obesity clinic cohort consisted of children and adolescents with overweight or obesity recruited between January 2009 and June 2018 at inclusion into an obesity treatment program at The Children’s Obesity Clinic, Holbæk Hospital, after referral by their own general practitioner or community nurse. The population-based cohort consisted of children and adolescents recruited between October 2010 and February 2016 from schools in the same geographical area as The Children’s Obesity Clinic, as previously described [27, 28]. Inclusion criteria for both cohorts were: (1) age between 6.0 and 18.9 years and (2) available data on anthropometry, TSH and blood pressure with no more than 30 days between anthropometric measurements and blood samples.

The exclusion criteria were: (1) self-reported ethnicity other than Danish/North-European white, (2) known thyroid disease, (3) medication known to affect thyroid function [29] and (4) a serum TSH concentration above 10 mIU/L or below 0.45 mIU/L, interpreted as possible overt thyroid disease [30, 31].

Ethics

Informed oral and written consent were obtained from all parents or legal guardians of participants under 18 years of age, and from the participants themselves if 18 years. The study was approved by the Scientific Ethics Committee of Region Zealand, Denmark (protocol no. SJ-104) and the Danish Data Protection Agency. The study is a part of The Danish Childhood Obesity Data- and Biobank, registered at ClinicalTrials.gov ID no.: NCT00928473.
Anthropometry

Anthropometric measurements were obtained by trained medical staff. The study participants wore light indoor clothing and no shoes. The height was measured to the nearest 0.1 cm using a stadiometer and weight was measured to the nearest 0.1 kg using a Tanita Digital Medical Scale (WB-100 MA, Tanita Corp., Tokyo, Japan). The body mass index was calculated as the weight in kilograms divided by the height in meters squared (kg/m²). BMI SDS was calculated by use of the Lambda-Mu-Sigma (LMS) method [32] according to Danish reference values [33], and overweight was defined as a BMI above the 90th percentile (BMI SDS >1.28).

Blood pressure measurements

Clinic brachial blood pressure was measured using the oscillometric device Omron 705IT (Omron Corp., Kyoto, Japan), validated in children and adolescents [34], using cuff sizes as recommended by the manufacturer: small (arm circumference <22 cm), medium (22–32 cm) and large (≥32 cm). Three measurements were taken and the mean of the last two was used to calculate SDS values [35]. Hypertension was defined as systolic and/or diastolic blood pressure above the 95th percentile of age, height and sex (SDS >1.65) of American reference values [35].

Biochemical measurements

Venous blood samples were collected between 07:00 and 09:00 AM following an overnight fast. A local anaesthetic cream was applied an hour before if requested (lidocaine/prilocaine mixture, Emla®, Astra Zeneca, Stockholm, Sweden). Blood samples were collected and analysed within 8 h at the Department of Clinical Biochemistry, Copenhagen University Hospital Holbæk. Analyses of serum concentrations of TSH were performed using immunologic chemiluminescent assays as previously described [36].

Subclinical hypothyroidism was defined by a serum TSH concentration above 4.5 mU/L combined with a normal serum free $T_3$ concentration (reference area 10.3–25.7 pmol/L) [7, 31]. Serum concentrations of leptin and adiponectin were quantitated using commercial enzyme-linked immunosorbent assay (ELISA) assays as previously described [27, 37].

Statistical analysis

Statistical analyses were performed in R statistical software (v.3.5.2) [38]. Data were evaluated for normality by visual inspection of histograms and qq-plots. TSH SDS were calculated based on a recent published population-based reference material from our own group [36]. As this reference study found no sex difference in TSH [36], the sexes were not segregated in this study. To investigate possible variation in the associations between TSH and blood pressure across the paediatric age range, the study participants were divided into three age groups: children (age 6.0–9.9 years), young adolescents (age 10.0–14.9 years) and old adolescents (age 15.0–18.9 years). The age intervals were chosen to approximate periods of pre-puberty, puberty and post-puberty in the Danish population [20]. Differences between the two cohorts were investigated using Student’s t-test, Wilcoxon rank-sum test, or chi-squared ($\chi^2$) test. Differences across age groups within each cohort were investigated using one-way analysis of variance (ANOVA), Kruskal-Wallis test or $\chi^2$ test.

Associations between blood pressure-related variables and TSH SDS were investigated by multivariable linear regression models adjusted for age, sex, BMI SDS and smoking status. In a second model, further adjustments were made for serum leptin and adiponectin, and possible interactions between these two biomarkers and TSH SDS were examined and visualized by three-dimensional scatterplots. A p < 0.05 was considered statistically significant.

Results

In total, 4673 children and adolescents met the inclusion criteria, 2011 from the obesity clinic cohort and 2662 from the population-based cohort. Three hundred and fourteen participants were excluded from the obesity clinic cohort ($n=290$ on ethnicity; $n=15$ on known thyroid disease; and $n=9$ on abnormal TSH levels) and 205 were excluded from the population-based cohort ($n=198$ on ethnicity and $n=7$ on known thyroid disease). The remaining eligible study cohort consisted of 1697 (921 girls) children and adolescents from the obesity clinic cohort and 2457 (1455 girls) from the population-based cohort.

Overall, the obesity clinic cohort had a median age of 11.9 years (interquartile range [IQR] 9.7; 14.2) and a median BMI SDS of 2.83 (IQR 2.43; 3.26). The population-based cohort had a median age of 11.3 years (IQR 8.6; 14.4) and a median BMI SDS of 0.25 (IQR −0.44; 0.99). Characteristics of the study participants stratified by cohort and age group are shown in Table 1.

The obesity clinic cohort had significantly higher BMI SDS, TSH, systolic and diastolic blood pressure and prevalence of hypertension compared with the population-based cohort (Table 1). Boys in the obesity clinic cohort had higher BMI SDS than girls (p < 0.001). BMI SDS, systolic and diastolic blood pressure increased significantly with age in both cohorts, and serum TSH decreased with age in the obesity clinic cohort. The difference in blood pressure between the two cohorts became more predominant with increasing age.

Multivariable regression analyses revealed significant associations between TSH SDS and all blood pressure-related variables in the population-based cohort (Table 2). In the obesity clinic cohort, TSH SDS was only significantly correlated with systolic blood pressure SDS and hypertension, and these associations were weaker than the ones found in the population-based cohort.
Additional analyses were performed on a subgroup consisting of study participants with defined subclinical hypothyroidism [31]. These analyses revealed no significant associations between TSH SDS and blood pressure-related variables.

Further adjusting the regression model for leptin and adiponectin only revealed significant associations between TSH SDS and systolic blood pressure in the population-based cohort (Table 3), and TSH SDS and hypertension in the obesity clinic cohort (Table 4).

Significant interactions were identified between adiponectin and TSH SDS in the population-based cohort, such that absolute systolic blood pressure increased with 0.21 mmHg per TSH SDS per μg/mL adiponectin; systolic blood pressure SDS increased with 0.02 per TSH SDS per μg/mL adiponectin; and the prevalence of hypertension increased with 0.07 per TSH SDS per μg/mL adiponectin.

Visual inspection of the interaction between adiponectin and TSH SDS for hypertension revealed that a high concentration of adiponectin was associated with a correlation between TSH SDS and hypertension (Figure 1). No interactions were found between adiponectin and TSH SDS in the obesity clinic cohort, or between leptin and TSH SDS in any of the two cohorts.

**Discussion**

The present study investigated the association of TSH and blood pressure, and the influence of leptin and adiponectin, in a large cohort of children and adolescents with overweight or obesity compared to a large population-based cohort of the same ethnicity and from the same geographical area. We found that TSH SDS was significantly associated with all blood pressure-related variables.
variables and hypertension in a population-based cohort, but only weakly with systolic blood pressure SDS and hypertension in an obesity clinic cohort. Furthermore, in the population-based cohort the associations between TSH SDS and blood pressure were attenuated with decreasing adiponectin concentration. Together this indicates that the observed associations in a population-based sample of children and adolescents are attenuated or absent in paediatric patients with obesity, suggesting that childhood obesity distorts the natural physiological interplay between the thyroid axis and blood pressure.

The associations between TSH and systolic and diastolic blood pressure as well as hypertension in the population-based cohort, presented in this study, are in accordance with results from previous paediatric studies [24–26]. The mechanisms behind these associations are uncertain, but leptin has been suggested as a possible link [39].

TSH is secreted by the pituitary gland when stimulated by thyrotropin-releasing hormone (TRH) from the hypothalamus, and leads to an increased production and secretion of thyroid hormones, T₃ and T₄ [40]. The thyroid hormones exert negative feedback on both TSH and TRH. Thus, high concentrations of thyroid hormones inhibit the production of TSH both directly and indirectly.

Leptin and TSH both influence blood pressure, and animal studies have found that leptin indirectly stimulates the production of TSH via TRH [40]. Furthermore, TSH stimulates leptin secretion by adipocytes in humans, indicating a cross-talk between the two hormones [41]. The mechanism by which leptin increases TRH synthesis in the paraventricular nucleus in the hypothalamus is both direct by activating leptin receptors and indirect through afferents from neurons in the arcuate nucleus, thus increasing TSH and T₃/T₄ secretion [40]. Studies in humans show a synchronicity between leptin and TSH secretion [42], but further research on the effect of leptin on TSH secretion is needed.

Leptin is an adipocyte-derived hormone that regulates long-term food intake and energy expenditure and thus overall energy status in the body. Leptin is associated with BMI, but there is evidence that individuals with overweight or obesity may become resistant to leptin’s satiety and weight-reducing effects, while other neuroendocrine and physiological effects of the hormone remain intact [43]. Recent studies have shown that leptin resistance can be classified into several forms underlain by various mechanisms, among these disorders of the blood-brain barrier and impairment of the leptin cellular signalling [44]. In analogy to obesity-related leptin resistance, our results suggest that the mechanisms behind the

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<th>Table 3: Associations between TSH SDS and blood pressure-related variables in the population-based cohort.</th>
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Data are β-values and confidence intervals from multivariable linear regressions adjusted for BMI SDS, smoking status and either leptin, adiponectin or both, in a subgroup (n = 949). Systolic BP and diastolic BP are further adjusted for age and sex. BP, blood pressure; SDS, standard deviation score. *p < 0.05.

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<th>Table 4: Associations between TSH SDS and blood pressure-related variables in the obesity clinic cohort.</th>
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Data are β-values and confidence intervals from multivariable linear regressions adjusted for BMI SDS, smoking status and either leptin, adiponectin or both, in a subgroup (n = 884). Systolic BP and diastolic BP are further adjusted for age and sex. BP, blood pressure; SDS, standard deviation score. *p < 0.05.
association between TSH and blood pressure are impaired in children and adolescents with overweight or obesity. This supports the hypothesis that leptin plays a role in obesity-related increases in TSH and blood pressure.

Another potential link between TSH and blood pressure is obesity-related low-grade inflammation. Consistent evidence show that obesity promotes a state of chronic low-grade inflammation characterized by increased concentrations of cytokines and proinflammatory adipokines [15] combined with decreased concentrations of the anti-inflammatory adipocyte-derived hormone adiponectin [16]. This obesity-induced inflammation is associated with endothelial dysfunction, which increases the risk of hypertension and atherosclerosis [15]. Recent studies find that patients with obesity and mildly increased serum TSH concentrations have more severe low-grade inflammation than patients with obesity and normal TSH concentrations [45, 46]. Another study reports that reductions in proinflammatory markers following weight loss could predict changes in TSH in children with overweight or obesity [47]. Together, this indicates that increased TSH in obesity reflects an even higher risk of developing cardiovascular disease. Further studies are warranted to elucidate these associations, and Mendelian randomization might prove an important future tool in exposing the causal direction between thyroid function, cardiovascular disease and inflammation.

We found that in the population-based cohort the prevalence of hypertension increased with increasing TSH in participants with high adiponectin concentrations, while this association was absent in those with low adiponectin concentrations (Figure 1). Given that adiponectin decreases with increasing BMI, these observations support our finding that overweight and obesity distort the normal physiological association between TSH and blood pressure in children and adolescents.

Strengths of the study include the inclusion of two large paediatric cohorts recruited from the same geographical area. This allowed for the creation and use of TSH SDS values in the analysis, thereby correcting for age- and sex-specific variations. Furthermore, all fasting blood samples were collected in adherence to a strict protocol, drawn at a narrow time point in the morning, and analysed in the same laboratory in a standardized manner.

Limitations include the cross-sectional study design, which limits the establishment of causality. Furthermore, there were relatively fewer girls in the obesity clinic cohort compared to the population-based cohort, the median age in the obesity clinic cohort was slightly higher than in the population-based cohort, and within the obesity clinic cohort, the boys had a higher median BMI SDS than the girls. However, these differences were adjusted for by the use of SDS values and by adjusting for BMI SDS and sex in all models.

In conclusion, this study shows that TSH is significantly associated with systolic blood pressure, diastolic blood pressure and hypertension in a population-based cohort of children and adolescents, and that the majority of these homeostatic associations are impaired in children and adolescents with overweight or obesity. The importance of adiponectin for the TSH SDS association with blood pressure is also only apparent in the population-based cohort, suggesting a broader weakening of homeostatic physiological functions in obesity. These results contribute with knowledge on how obesity causes imbalance in several biological systems of the body. Thus, instead of treating individual obesity-related health complications such as elevated blood pressure, we should focus on treating the common underlying factor, obesity.

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Author contributions: AD, MAVL, PLH, TJ, MC, TH and JH designed the research. AD, MAVL and JH conducted the data collection. AD and MAVL performed the literature search, analysed the data and generated the tables and figures and wrote the paper draft. All authors contributed to the interpretation of data and critical revision of the manuscript, and approved the final manuscript.

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Conflict of interest: JH received lecture fees from Novo Nordisk and is the owner of Dr Holm Ltd, which provides medical services, training and supervision. All other authors have nothing to disclose.

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