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Oxidative DNA damage and subclinical hypothyroidism in children with obesity

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Abstract

Background: Obesity-related oxidation stress plays a key role in obesity complications; however, its relation to thyroid status is an area for further research. The study aimed to assess thyroid function in obese children and its relation to oxidative deoxyribonucleic acid (DNA) damage.

Results: Fifty obese and 40 normal weight children were included. Anthropometric measurement, lipid profile, thyroid function, anti-thyroglobulin antibody, thyroid peroxidase antibody, and 8-hydroxydeoxyguanosine serum level as marker of oxidative DNA damage were measured. Thirty-six percent of children with obesity have subclinical hypothyroidism. Central obesity but not oxidative DNA damage and lipid profile was significantly associated with subclinical hypothyroidism. Waist circumference > 97th centile increases the risk for subclinical hypothyroidism (odd ratio 10.82; confidence interval 95% 2.75–42.409; *p*-value<0.001).

Conclusion: Central obesity represents a risk factor for subclinical hypothyroidism in obese children. Oxidation DNA damage did not show significant association with subclinical hypothyroidism.

Keywords: Thyroid function, Obesity, Oxidative stress, Children

What is already known on this topic?

Obesity-related oxidation stress plays a key role in obesity complications.

What this study adds?

Subclinical hypothyroidism is not uncommon in children with obesity. However, the underlying mechanisms are not fully explored. This study aimed to assess thyroid function status in obese children and its relation to oxidative DNA damage and found that central obesity represents a major risk factor for subclinical hypothyroidism in obese children while oxidation DNA damage, serum cholesterol, and triglyceride did not show significant association with subclinical hypothyroidism.

Background

Obesity is a global health problem associated with several metabolic complications that may extend into adult life. Most of these complications start early in childhood and are strongly linked to dyslipidemia and insulin resistance. Early identification and understanding of the underlying mechanism of such complications is an important step in management to allow early intervention and decrease long-term obesity-related morbidities and mortality [1].

Thyroid hormones represent key regulators of basal metabolism, thermogenesis, appetite, and energy balance. There is a strong negative association between body weight and thyroid hormones. Hypothyroidism is one of the suggested causes of childhood obesity; however, there is emerging evidences revealed that thyroid dysfunction may be a consequence rather than a cause of obesity as suggested by normalization of thyroid hormone levels in response to weight reduction [2].

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Subclinical hypothyroidism is characterized by mildly elevated TSH (>4.5 mIU/L but <10 mIU/L) with normal total and free T4 level in absence of thyroid antibodies or goiter. Subjects with subclinical hypothyroidism have no clinical manifestation. Several reports demonstrated that progression of subclinical hypothyroidism to overt hypothyroidism is uncommon [3]. The prevalence of subclinical hypothyroidism is low accounting for 2% in pediatric age group, but higher frequency of 10–23% was reported in children with obesity [4].

Experimental studies on thyroid showed that on exposure to oxidative stress, thyroid nuclear and mitochondrial DNA have greater sensitivity than membrane lipids to oxidative damage. 8-Hydroxy-2deoxyyguanosine (8-OHdG) is generated in response to increased reactive oxygen species and is widely used as marker of oxidative DNA damage [5].

The underlying mechanisms of obesity-associated thyroid dysfunction are not fully explored. Several factors have been studied with controversial reports [6]. Obesity-related oxidation stress plays a key role in obesity complications; however, its relation to thyroid status is an area for further research [7]. This study aims to assess thyroid function status in obese children and its relation to oxidative DNA damage.

Methods

This case control study included 50 obese children and 40 matched age and sex normal weight healthy children as controls. Participants were recruited consecutively from outpatient clinic of pediatric and endocrinology department. Inclusion criteria was prepubertal age 6–8 years with BMI > 95th percentile for obese group and BMI between 5th and 85th percentiles for normal weight control group based on WHO definition for obesity [8]. Children were excluded if they have any endocrinal disorders, short stature, goiter, acute or chronic medical illness (e.g., metabolic, cardiac, respiratory, hematological, liver, renal diseases), genetic or syndromic cause for obesity, or those who received medication that may affect thyroid function as antiepileptic drugs. Study was approved by local ethics Committee, and informed consent was taken from all parents of included children.

Medical history and examination

Participating children were subjected to full history taking including age, sex, nutritional history, lifestyle, physical activity, and medication history. Complete detailed general and systemic clinical examination was performed. Puberty was evaluated based on Tanner's criteria [9].

Anthropometric measurements

Anthropometric measures for weight (kg) while the child is wearing light clothes, height (cm) of standing child with stretched knees and bare feet, hip (HC) and waist (WC) circumference (cm) were measured according to WHO guideline in standing posture using flexible non-stretchable measuring tape. HC was assessed at the level of the greater trochanters while WC was assessed midway between the lower rib margin and iliac crest at the end of normal expiration. Hip/waist ratio was estimated by dividing WC by HC [10]. BMI was estimated according to equation weight in kilograms divided by squared height in meters. All measurements were recorded to the nearest 0.1 value and were plotted on age- and sex-specific Egyptian growth chart [11].

Laboratory investigations

Thyroid function test

Serum samples were collected for chemical analysis of TSH, total T3, and T4 using Cobas e411 Hitachi Roche chemiluminescence technique. Reference ranges for TSH are 0.45–4.5 mIU/L. In pediatric as in adults, thyrotropin >10 mIU/L is potentially indicative of overt hypothyroidism. Subclinical hypothyroidism is identified as isolated raised TSH (>4.5 mIU/L but <10 mIU/L) without clinical symptoms, thyroid antibodies, goiter, or associated thyroidal illness [12]. Obese children were classified according to the level of TSH into obese children with and without subclinical hypothyroidism.

Thyroid antibody detection

In serum samples, thyroid peroxidase antibody and antithyroglobulin antibodies were detected using enzyme-linked immunosorbent assay (ELISA) kit. A human thyroid peroxidase solid-phase sandwich ELISA was used to assess thyroid peroxidase antibodies (thermoscientifical/ELISA kit). In the wells of the micro plate supplied, a target-specific antibody was pre-coated. These wells are then fitted with samples, standards, or controls, and attached to immobilized (capture) antibody. The sandwich is made up of the second antibody (detector), which is a substratum solution which reacts to the complex enzyme-antibody-objective in order to produce a measurable signal. The signal intensity is directly proportionate to the target concentration in the original specimen. A point-to-point curve fit was used with measured absorption on an ELISA plate reader of 450 nm and 550 nm. In each sample, determining the amount of thyroid peroxidase was done by interpolating the concentration of thyroid peroxidase from the X axis to the absorbent Y axis.

Lipid profile assessment

Blood samples were obtained after overnight 8-h fasting. We assess serum total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) by enzyme colorimetric method.

Oxidative DNA damage

Serum level of 8-hydroxydeoxyguanosine (8-OHdG) was measured as marker of oxidative DNA damage by ELISA kit for human (Enzo Life Sciences, Inc., USA) using a monoclonal antibody 8-OHdG to bind 8-OHdG competitively into the sample of the wells of the 96-well immunoassay plate, as standard or pre-bonded with the wells. Anti-8-OHdG is tightly linked to 8-OHdeG in a sample, or conventional anti-8-OHdG is removed while the caught ones are identified by a secondary antibody. The test is performed with a tetramethylbenzidine substratum, and the absorption is measured by a 450-nm micro-plate reader. Yellow color frequency is in reverse proportion to the 8-OHdG concentration. The concentration of 8-OHdG in samples was then determined by comparing the optical density of the samples to the standard curve.

Statistical analysis

Statistical package for social science (IBM-SPSS), version 22 IBM Chicago, USA, was used for data statistical analysis. Data were expressed as mean ± standard deviation (SD) for quantitative data, number and percentage for non-numerical data. Student *t*-test, Mann-Whitney test, and Chi-square test were used to compare the mean between 2 groups. Pearson correlation test was used to assess correlations between variables. Odds ratio was used to determine risk factors of subclinical hypothyroidism in children with obesity. Significance was considered when p value <0.05.

Results

This study included 50 children with obesity (23 males, 27 females); their age ranged between 6 and 10 years with mean of 7.24 ± 0.797 years. Another 40 healthy normal weight children were included as control group (19 males and 21 females) with main age of 7.17 ± 1.77 years. There was no significant difference between cases and control regarding age and sex (p=0.262 and p= 0.887, respectively). Eighteen out of 50 children with obesity have subclinical hypothyroidism (36%).

Table 1 shows significantly higher level of TSH in obese children in comparison to normal weight children. Despite that T3 and T4 levels were within normal range for age for both groups, obese children showed significantly lower level of T3 and T4 than normal weight children. 8-Hydroxydeoxyguanosine was higher in the obese group; however, this difference has no statistical significance.

Table 2 demonstrates that anthropometric indices of central obesity (WC, hip/waist ratio) were significantly higher in children with subclinical hypothyroidism than those without subclinical hypothyroidism.

Table 3 revealed significant positive correlation between anthropometric indices of central obesity (WC, hip/waist ratio) and TSH level in children with obesity.

Table 4 showed that increase in the waist circumference > 97th percentile for age and sex was significantly associated with increase in the risk of subclinical hypothyroidism in children with obesity by 10 folds.

Discussion

The current study revealed higher incidence of subclinical hypothyroidism in children with obesity (36%) with significant association between TSH level and BMI. Despite of the significant increased frequency of subclinical hypothyroidism in children with obesity, there is variation in the prevalence between studies which ranged from 7 to 36% [12]. This variation could attribute to different ethnic groups and the contributing effect of

Table 1 Comparison of thyroid function, lipid profile, and oxidative DNA damage between children with obesity and healthy controls

	Healthy children *N*=40	Obese children *N*=50	Independent *t* test/Mann-Whitney test	
	Mean±SD	Mean±SD	*t*	*p*-value
TSH (μIU/ml)	2.125±1.405	5.426±2.978	−6.931	<0.0001*
T4 (μg/dl)	7.810±2.771	5.418±1.796	4.722	<0.0001*
T3 (μg/dl)	1.377±0.502	0.962±0.521	3.834	<0.0001*
TPO AB (IU/ml)	79.435±18.691	72.689±11.810	1.987	0.055
TG AB (IU/ml)	23.562±11.015	26.992±9.835	−1.539	0.128
8-OHdG (pg/ml)	1732.01±1083.67	1968.32±1390.62	−0.906	0.367

TSH thyroid-stimulating hormone, *TPO* thyroid peroxidase antibody, *TG* anti-thyroglobulin antibodies, *8-OHdG* 8-hydroxydeoxyguanosine
*Significant (*p*-value <0.05)

Table 2 Comparison of clinical data, thyroid function, lipid profile, and oxidative DNA damage in relation to subclinical hypothyroidism in children with obesity

	Obese children with subclinical hypothyroidism *N*=17	Obese children without subclinical hypothyroidism *N*=33	Independent *t* test/Mann-Whitney test	
	Mean±SD	Mean±SD	*t*	*p*-value
Age (year)	7.294±0.848	7.212±.0781	0.332	0.742
Weight (kg)	53.058±10.346	45.666±9.771	2.438	0.021*
Height (cm)	135.352±9.212	129.666±9.681	2.032	0.052
BMI	28.619±2.768	26.777±2.514	2.298	0.029*
HC (cm)	101.205±10.410	97.048±5.204	1.550	0.137
WC (cm)	89.529±9.663	80.272±7.446	3.456	0.002*
Hip/waist ratio	0.874±0.041	0.833±0.067	2.708	0.009*
Triglyceride (mg/dl)	94.00±7.558	89.606±6.777	2.016	0.053
Cholesterol (mg/dl)	147.352±22.312	147.545±23.285	−0.028	0.977
HDL (mg/dl)	52.529±14.820	48.272±7.045	1.121	0.276
TSH (μIU/ml)	8.911±0.572	3.630±1.908	14.671	0.0001*
T4 (μg/dl)	4.917±1.308	5.675±1.970	−1.622	0.112
T3 (μg/dl)	0.876±0.562	1.006±0.501	−0.800	0.430
TPO AB (IU/ml)	67.553±15.937	75.334±8.083	−1.892	0.073
TG AB (IU/ml)	25.388±11.048	27.818±9.221	−0.778	0.443
8-OHdG (pg/ml)	1652.97±1185.96	2130.772±1475.766	−1.239	0.223

HC hip circumference, *WC* waist circumference, *HDL* high-density lipoprotein, *TPO* thyroid peroxidase antibody, *TG* anti-thyroglobulin antibodies, *8-OHdG* 8-hydroxydeoxyguanosine
*Significant (*p*-value < 0.05)

Table 3 Correlation of clinical data, thyroid function, lipid profile, oxidative DNA damage, and thyroid-stimulating hormone level in children with obesity

	TSH	
	r	*p*-value
Age (year)	0.102	0.482
Weight (kg)	0.282	0.047*
BMI	0.667	0.0001*
HC (cm)	0.267	0.061
WC (cm)	0.479	0.0001*
Hip/waist ratio	0.380	0.006*
Triglyceride (mg/dl)	0.220	0.125
Cholesterol (mg/dl)	−0.078	0.592
HDL (mg/dl)	0.163	0.259
T4 (μg/dl)	−0.277	0.052
T3 (μg/dl)	−0.101	0.484
TPO AB (IU/ml)	−0.312	0.027
TG AB (IU/ml)	0.034	0.817
8-OHdG (pg/ml)	−0.166	0.249

HC hip circumference, *WC* waist circumference, *BMI* body mass index, *TSH* thyroid-stimulating hormone, *HDL* high-density lipoprotein, *TPO* thyroid peroxidase antibody, *TG* anti-thyroglobulin antibodies, *8-OHdG* 8-hydroxydeoxyguanosine
*Significant (*p*-value<0.05)

hyperlipidemia and metabolic syndrome on the development of subclinical hypothyroidism.

Several mechanisms have been suggested to explain the association between obesity and thyroid dysfunction. Leptin is one of the hormones secreted by adipose tissue. Increased leptin production adversely affects thyroid function, inhibits thyroid hormone secretion by hypothalamic-pituitary-thyroid axis in addition to induce thyroid hormones resistance leading to more increase in body weight [13]. This increase in pituitary and peripheral tissue resistance to thyroid hormones in obese children leads to impairment of the negative feedback on the TSH production [14]. Some studies explained the isolated elevated TSH as an adaptive response against obesity to increase the metabolic rate and energy expenditure rather than a cause of obesity. The previous explanation was supported by normalization of TSH level after weight reduction without receiving any medications [15], while other studies linked subclinical hypothyroidism to the obesity-associated increased inflammatory status [16].

Our study revealed a significant association between anthropometric indices of central obesity and the development of subclinical hypothyroidism. Central obesity was associated with 10-folds risk for subclinical hypothyroidism. In agreement with our findings,

Table 4 The association between central obesity and subclinical hypothyroidism

	WC>97th centile *N* =18	WC<97th centile *N* =32	Chi-square test	Odds ratio CI 95%
Subclinical hypothyroidism	12 (66.67%)	5 (6.2%)	*F*= 13.375 *p*-value= <0.0001*	10.800 (2.750–42.409)
No subclinical hypothyroidism	6 (33.33%)	27 (93.8%)		

WC waist circumference, *CI* confidence interval
*Significant (*p*-value<0.05)

Răcătăianu et al. [17] reported significant association between waist-hip ratio and elevated TSH suggesting that central obesity may contribute to altered thyroid function. In a large cohort study, Mamtani et al. [18] demonstrated that increased waist circumference independently associates with higher risk of subclinical hypothyroidism. However, this association was not detected in normal weight subjects [19]. Central obesity was associated with increased leptin level [20] and proinflammatory cytokines [21] that could explain the strong association between central obesity and subclinical hypothyroidism in children with obesity.

Metabolic syndrome, insulin resistance, and dyslipidemia have been studied as risk factors for obesity-associated subclinical hypothyroidism with controversial results [22, 23].. Our study did not show significant association between lipid profile and thyroid function in children with obesity. This could be explained as lipid profile of all included children was within the normal limits and none of the included children with obesity have hyperlipidemia.

Oxidative stress is strongly linked to inflammation with several reports demonstrated significant increase in oxidation stress in children with obesity that plays a key role in the development of obesity complications [24]. Several studies reported higher oxidative stress in subjects with subclinical hypothyroidism [25]. However, our study showed no significant difference in oxidative DNA damage between obese and normal weight children with no significant association between 8-hydroxydeoxyguanosine and subclinical hypothyroidism. This may indicate multifactorial contribution of DNA damage other than obesity and altered thyroid function that might lead to oxidative DNA damage in both groups.

The major limitations of our study including the cross-sectional study design limited the ability to detect cause-and-effect relationships and lack of follow-up of those children so further longitudinal large scale studies are required to demonstrate the long-term impact of subclinical hypothyroidism in obese children.

Conclusion

Subclinical hypothyroidism occurs frequently in children with obesity. Central obesity represents a major risk factor for subclinical hypothyroidism in obese children. Oxidation DNA damage did not show significant association with subclinical hypothyroidism.

Abbreviations

DNA: Deoxyribonucleic acid; TSH: Thyroid-stimulating hormone; TPO: Thyroid peroxidase antibody; TG: Anti-thyroglobulin antibodies; 8-OHdG: 8-Hydroxydeoxyguanosine; HC: Hip circumference; WC: Waist circumference; TC: Total cholesterol; HDL: High-density lipoprotein; BMI: Body mass index; ELISA: Enzyme-linked immunosorbent assay

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Authors' contributions

MEE, IHA, ME: collected the data, searched for literature, performed data analysis, and prepared the manuscript. IHA, MK: performed the study design and supervised the clinical work. MK, MA: perform the laboratory analysis. MA, ME: performed editing of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This article was approved by the ethics committee at faculty of medicine for girls, Al-Azhar University (IRP: 202007297). A written informed consent was obtained from all patients' caregivers.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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