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Subclinical hypothyroidism in childhood obesity and its correlation with lipoproteins.

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Abstract

Background/Objective: There is an ongoing debate regarding the influence of subclinical hypothyroidism on body mass index. The objectives of the study were (i) to determine whether levels of thyroid stimulating hormone (TSH) are elevated in obese children, (ii)to compare the serum levels of triiodothyronine (T_3) and thyroxine (T_4) in obese with non-obese and (iii) to examine the association of subclinical hypothyroidism with lipoproteins and body mass index.

Methods: Fifty six obese children/adolescent girls aged 10.5±4.3years, BMI 31.2±2.2kg/m^2 and apparently healthy children aged 11.2±5.2 years, BMI 21.0±2.1kg/m^2 were evaluated. Serum T_3, T_4 and TSH were measured using ELECSYS 1010 autoanalyzer while serum triglyceride, total cholesterol, LDL cholesterol, HDL cholesterol and glucose were measured using enzyme catalyzed colorimetric techniques.

Results: Subclinical hypothyroidism was observed in 10.7% of obese subjects. Significantly increase levels of T_3 ($p<0.02$), TSH ($p<0.01$) and all lipoprotein fractions ($p<0.001$) except HDL cholesterol which was lower ($p<0.001$) were observed in obese than control subjects. TSH and triglyceride correlated positively with body mass index.

Conclusion: Subclinical hypothyroidism was present in 10.7% of obese children. TSH and triglyceride correlated positively with body mass index in childhood/ adolescent obesity. There is need for this group of subjects to be evaluated for thyroid hormones so that those requiring therapy can be diagnosed and treated.

Keywords: *Obesity, subclinical hypothyroidism, thyroid hormones, body mass index,lipoproteins.*

Résumé

Il y a un débat continue sur l'influence de l'hypothyroïdisme subclinique sur l'indexe de masse corporelle. Les objectifs de cette étude étaient (i) de déterminer si les taux de stimulants d'hormones thyroïdiens (TSH) sont élevés chez les enfants obeses, (ii) de comparaitre les taux d'hormones thyroïdiens dans le sérum thiiodothyronine (T_3) et thyroxine (T_4) chez les obeses et non obeses et (ii) d'examiner l'association de l'hypothyroïdisme subclinique avec lipoprotéines et l'indexe de masse corporelle. Cinquante six enfants et adolescent filles obeses âgées de 10.5±4.3ans, IPC 31.2±2.2kg/m^2 et les enfants apparemment sain âgées 11.2±5.2 ans, IPC 21.0±2.1kg/m^2 étaient évaluées. Les taux de sérum T_3, T_4 et TSH étaient mesures en utilisant l'auto analyseur ELECSYS 1010 cependant les taux de sérum triglycéride, cholestérol total, LDL cholestérol, cholestérol HDL et glucose étaient mesurés utilisant les techniques de colorimétriques catalysés par des enzymes. Hypothyroïdisme subclinique était observé chez 10.7% des sujets obese. Les taux significatifs augmentaient T_3 ($p<0.02$), TSH ($p<0.01$) et toutes les fractions de lipoprotéines ($p<0.001$) exception cholestérol HDL qui était faible ($p<0.001$) étaient observé chez les sujets obeses que les sujets sains. TSH et triglycéride corrélaient positivement avec l'indexe de masse corporelle en obésité infantile et à l'adolescence. L'hypothyroïdisme subclinique était présent chez 10.7% des enfants obeses. Il est nécessaire pour ces sujets d'évaluer les hormones thyroïdiennes afin que ceux malades puissent être diagnostiqués et traités.

Introduction

Subclinical hypothyroidism (SCH) is defined as elevated serum levels of thyroid stimulating hormone (TSH) >4.2μIU/mL (range: 0.27-4.2μIU/mL) with normal levels of triiodothyronine (T_3) and thyroxine (T_4) and is often encountered in an endocrine practice[1-2]. There is an ongoing debate regarding the influence of SCH on body mass index (BMI) [1]. Overt thyroid disorder has been recognized to influence weight, but data demonstrating effects of relatively minor defects in thyroid hormones on weight are few and conflicting. Studies elsewhere of thyroid function in obesity have shown that TSH is higher in

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obese than individuals with normal BMI [3], but the proportion of obese Nigerian children with SCH is not known. It is assumed that elevated TSH levels in patients with SCH do not reflect pituitary compensation to maintain euthyroidism but may represents a state of mild tissue hypothyroidism. Some of the subjects with this condition may experience subtle symptoms of hypothyroidism, mild abnormalities of serum lipoproteins that may provoke atherosclerosis and cardiac dysfunction. There is also the risk of progression of SCH to overt hypothyroidism and risk of neuropsychiatric effects[1,4]. It is for these reasons that scientists are now screening obese subjects for SCH. Obesity is now frequently observed all over the world in both developed and developing countries [5-7]. Obesity is defined as body mass index for age of >30kg/m^2. Studies have shown positive correlation between TSH and BMI in Asians[7] and European countries[8] but there seems to be no consistency in the relationship of thyroid hormones with obesity in most studies [1,9]. Data in the literature on status of thyroid function in obese are not consistent, some indicating no change[9], others show elevated TSH, free triiodothyronine (fT3) and free thyroxine (fT4) levels[8] and yet others indicated TSH in the upper normal range and fT4 in the lower normal[10]. Considering the increasing incidence of obesity and its associated consequences, the association between hypothyroidism, BMI and lipoprotein is of importance to researchers. There is no report as at now to the best of our knowledge on SCH in childhood/adolescents obese Nigerians. The aims of this study were (i) to determine whether the levels of TSH are elevated in obese children (ii) to compare the levels of serum T_3 and T_4 in obese with non-obese children/adolescents and (iii) to examine the association of SCH with lipoproteins and BMI in the study group.

Materials and methods

The study was conducted at Aminu Kano Teaching hospital, Kano. It is a retrospective analysis of records of 56 childhood/adolescents girls, mean aged 10.5±4.3 years referred for evaluation because of obesity from 2004-2008. They had a mean BMI 31.2±2.2 kg/m^2. The control population consisted of 20 non obese apparently healthy adolescent girls of similar age 11.2±5.2 years, BMI 21.0±2.1kg/m^2. These were subjects who reported for routine medical check for the purpose of obtaining certificate of fitness. The clinical and demographic findings were obtained from the medical record of the individual patient. Obesity is defined by a body mass index for age (BMI) >30kg/m^2. BMI levels were calculated by weight (kg) divided by height in metres squared (m^2). The subjects were evaluated clinically and sent to the Chemical Pathology laboratory for thyroid evaluation. Five millilitres of venous blood was collected in a fasting state into plain container and allowed to clot for 30 minutes. The blood was centrifuged at 3000rpm for 10 minutes and serum obtained. Triiodothyronine (T_3), thyroxine (T_4) and thyroid stimulating hormone (TSH) were measured using ELECSYS 1010 autoanalyzer, Roche Diagnostics, Germany. The technique employed the principle of chemiluminescence immunoassay. Triglyceride, total cholesterol and high density lipoprotein cholesterol (HDL cholesterol) were determined using enzyme catalyzed colorimetric technique (Randox laboratories, UK). Low density lipoprotein cholesterol (LDL cholesterol) was calculated using Friedewald formula [11]. Glucose was measured using glucose oxidase method (Randox laboratories, UK). Statistical analysis was done using SPSS 14 version and Students't-test was used to compared the concentrations of studied parameters in obese with non-obese subjects and Pearson correlation coefficient was used to test the association of SCH with TSH, lipoproteins and BMI in the study group. Values of $p<0.05$ was considered statistically significant.

Results

Table 1 shows thyroid hormones and anthropometric variables in obese and control subjects. The weight and BMI of the obese subjects were significantly higher ($p<0.001$) than the controls while the mean height of the control was significantly higher ($p<0.005$) than the obese subjects. The mean levels of T_3 and TSH were significantly higher in the obese than the control while the T_4 was not significantly different in the obese and control subjects. Six out of 56 obese subjects (10.7%) had TSH level above the upper limit of the reference limit. A proportion of 10.7% subclinical hypothyroidism was observed in the obese subjects. The TSH in the obese subjects correlated with BMI ($p<0.005$).

Table 1: Thyroid hormones and anthropometric variables in obese and control subjects.

Variables No of subjects	Control 20	Obese 56	p-value
Age (Years)	11.2±5.2	10.5±4.3	NS
Weight (kg)	46.1±9.6	66.5±4.7	P<0.001
Height (cm)	148±5.2	146±5.0	P<0.005
BMI (kg/m^2)	21.0±2.1	31.2±2.2	P<0.001
T_3 (nmol/L)	1.86±1.2	2.24±1.0	P<0.02
T_4 (nmol/L)	98.6±30	95.7±42	NS
TSH (μIU/mL)	2.12±1.4	3.1±2.7	P<0.01

Table 2: Lipoproteins and glucose levels in obese and control subjects (mean±SEM).

Variables	Control	Obese	p-value
Triglyceride (mmol/L)	1.0±0.08	1.2±0.06	P<0.001
T.cholesterol (mmol/L)	4.0±0.14	4.4±0.05	P<0.001
HDL cholesterol (mmol/L)	1.31±0.03	1.01±0.02	P<0.001
LDL cholesterol (mmol/L)	2.28±0.04	2.45±0.06	P<0.001
VLDL cholesterol(mmol/L)	0.44±0.02	0.52±0.04	P<0.001
Glucose (mmol/L)	4.2±0.5	4.8±0.5	P<0.001

Table 2 shows mean levels of lipoproteins and glucose in obese and control subjects. All lipoprotein fractions except HDL cholesterol were significantly higher ($p<0.001$) in obese than control subjects while HDL cholesterol was significantly lower ($p<0.001$) in obese than control subjects. Serum triglyceride correlated ($p<0.05$) positively with BMI in obese subjects and shows no association with serum TSH levels.

Table 3: Thyroid hormone profile of the obese subjects with sub-clinical hypothyroidism.

Obese subjects	T_3 (nmol/L)	T_4 (nmol/L)	TSH (μIU/mL)
Subject 1	2.03	100.6	4.79
Subject 2	2.50	148	4.89
Subject 3	3.05	113	4.88
Subject 4	2.14	88	4.73
Subject 5	1.45	68	4.80
Subject 6	2.67	79.8	5.14
Mean	2.31	99.6	4.87
SD	±0.53	±26.0	±0.13

Table 3 shows T_3, T_4 and TSH levels of the six obese subjects with SCH. They had TSH levels above the upper limit of the reference range.

Discussion

The results demonstrated that SCH was present in 10.7% of obese subjects and the mean levels of serum TSH and T_3 were significantly increased in obese than non-obese children. There was an association between TSH and BMI; triglyceride and BMI but no association was observed between TSH and other lipoproteins. The mean levels of TSH, total cholesterol and LDL cholesterol were also significantly higher while HDL cholesterol was significantly lower in obese subjects with SCH than obese with normal TSH levels. The observation of 10.7% subclinical hypothyroidism in obese subjects in this study is consistent with other studies[8,12,13]. SCH of 11.7% was observed in a group of Korean adolescents[12], while Grandone *et al* [13] reported that 12.8% of children with obesity in Italy had SCH.

SCH has been reported to be common in obese children but it is not clear whether such condition may lead to increase cardiovascular risk factors [13]. Rodoni *et al* [14], in a systematic review of SCH and risk of coronary disease indicated that SCH was associated with an increased risk of coronary heart disease. In the Italian study [13], it was observed that thyroid function was reversed to normal after weight loss. It is important to know that the presence of obesity in at least one parent increases the risk of persistence of obesity into adulthood in children[15]. An association between TSH and BMI ($p<0.005$) was observed in this study which is in agreement with other studies[16-17]. This observation suggests that excess fat may exert considerable influence on thyroid tissue modification. Deficit in thyroid hormone actions lead to modulation of calorigenesis and oxygen consumption in most tissues of the body. Increased TSH in obesity has been reported to correlate with resting energy expenditure (REE) [18]. A prolonged decrease in REE might lead to increase body weight in situation of excess food intake and physical inactivity. It was suggested that obesity may lead to a state of thyroid hormone resistance in peripheral tissues[19]. De Moraes *et al*[3] reported that obesity leads to increased thyroid hormone requirements, which may induce or worsen an existing thyroid insufficiency. Leptin was observed to modulate TRH-gene expression in the paraventricular nucleus of the hypothalamus[20]. Leptin is synthesized by the adipose tissue and binds to specific receptors in the hypothalamus, regulating appetite and energy. Its concentrations are proportional to the amount of total adipose tissue [21]. A reduction in plasma leptin levels after treatment of hypothyroidism was observed by Pinkney *et al* [22]. But Rosenbaum *et al* [23] shown that the influence of leptin on hypothalamic-pituitary-thyroid axis was that of stimulatory since the injection of leptin reversed the effect of weight loss on the thyroid hormone levels. There is however no agreement on the influence of leptin on thyroid hormone as other studies did not find relationship between leptin and thyroid function [24-25].The manifestation of hypothyroidism could be explained at the molecular level thus: inability to stimulate the growth hormone gene in pituitary somatotrophs causes short stature in pre-pubertal children; a deficit in expression of the hepatic LDL receptor gene mediated by thyroid hormone regulated sterol regulatory element binding transcription factor-2 (SREBP2), decreases the rate of LDL-cholesterol clearance which could results in hyperlipidaemia. It can also lead to decreased expression of myocardial sarcoplasmic reticulum ATPase and á-myosin heavy

chain may impair diastolic and systolic ventricular performance[16].

The relationship between obesity and thyroid dysfunction has been of interest in recent years due to the increasing incidence of childhood obesity in both developed and developing world. It is well known that hypothyroidism may lead to obesity and obesity is a conventional risk factor for cardiovascular disease. The association between obesity, lipid and thyroid dysfunction is of interest to scientists, hence studies are being done to link up these three aspects [11]. Unfortunately, there is lack of consistency in the observations [9,10,12]. Our result shows that TSH was significantly increased ($p<0.01$) in obese than control subjects. The mechanism of elevated TSH levels in obese children is not clear, but iodine deficiency in childhood is common in our population [26]. It could be as a result of non responding receptors of target cells to TSH, a situation similar to the insulin resistant state observed in obesity [27]. The merit of this suggestion is that T_3 receptors are decreased in obesity, leading to a relative pituitary resistance to thyroid hormone [28] despite significantly increase levels of T_3 in the circulation as observed in this study. Total thyroxine (T_4) was not significantly different in obese compared with controls but T_3 was significantly higher ($p<0.02$) in obese than controls. This observed increase may be a regulating response to changes in the TSH levels. The limitation of this study is that we did not evaluate free T_3 (fT_3) levels because only the fT_3 is biologically active, the estimation is of immense help to compensate for variation in binding proteins. A thyrotropin releasing hormone stimulation test could also help to decide whether pituitary response is altered or not in obese subjects.

Statistically significant differences ($p<0.001$) in lipoproteins were observed in obese than control subjects. Triglyceride correlated positively with BMI in obese children. This result is also consistent with other studies[7,29]. This is however different from that of Grandone *et al*[13] which reported that obese children with SCH do not have an increase in their metabolic risk factor and therefore did not demonstrate significant relationship between SCH and lipid levels.

Conclusion

Subclinical hypothyroidism was present in 10.7% of obese subjects. The mean TSH level is significantly higher in obese than non-obese children. TSH and triglyceride correlated positively with BMI in childhood/adolescent obesity. There is need for this group of subjects to be evaluated for thyroid hormones so that those requiring therapy can be diagnosed and treated.

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