Serum zinc level and its relation to insulin resistance and lipid profile in childhood and adolescent obesity

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Background
Obesity is considered to be a worldwide health problem. Obese individuals are at a high risk of developing dyslipidemia, hypertension, impaired glucose tolerance, insulin resistance, and consequent increase of the risk of metabolic and cardiovascular diseases. In obesity, elevated insulin resistance is observed, which may be associated with disturbances in zinc status in the body. The few studies concerning the status of zinc and its relationship with insulin resistance in obese children and adolescents have brought inconclusive results.
Aims
The aims of this work were to study the level of serum zinc in obese children and adolescents and to evaluate its potential relation to obesity, insulin resistance, and lipid profile.
Patients and methods
Thirty obese children and adolescents and 30 healthy controls aged 5–19 years were recruited for the study. Lipid profile, serum zinc, fasting plasma glucose, and fasting insulin were measured. Insulin resistance was calculated according to the homeostatic model of assessment for insulin resistance and quantitative insulin-sensitivity check index.
Results
Obese individuals had significantly higher serum triglycerides, total cholesterol, low-density lipoprotein cholesterol, fasting plasma glucose, fasting blood insulin, and homeostatic model of assessment for insulin resistance, whereas high-density lipoprotein cholesterol and quantitative insulin-sensitivity check index were significantly lower in obese children than in healthy controls (all $P<0.05$). The serum concentration of zinc was significantly lower in obese individuals compared with control. There was a positive significant correlation between serum zinc level and high-density lipoprotein ($r=0.511$, $P<0.05$).
Conclusion
Obese children and adolescents have a poorer zinc status than children and adolescents of normal weight, which may affect lipid profile.

Keywords:
adolescents, children, insulin resistance, lipid, obesity, zinc

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Introduction

The alarming worldwide development of pediatric overweight and obesity has become a major public health concern, negatively affecting national health systems [1]. The WHO states that childhood obesity is one of the most serious public health challenges of the 21st century [2]. Childhood obesity is associated with a wide range of negative health consequences such as psychosocial problems, obstructive sleep apnea, increased cardiometabolic risk, impaired glucose tolerance, type 2 diabetes, and adult obesity [3,4].

Zinc is an important micronutrient in DNA synthesis, gene expression, and activity of various enzymes involved in the metabolism of carbohydrates, proteins, and lipids, as well as in the maintenance of normal growth [5] and several body functions such as vision, taste perception, cognition, cell reproduction, and immunity [6]; as a result, zinc deficiency affects children's physical growth and may deteriorate health status [7].

As regards the possible factors contributing to changes in zinc homeostasis in obesity, chronic inflammation changes the expression of metallothionein and Zip-14 zinc transporter protein, which promotes the redistribution of plasma mineral content in the fat, liver, and muscle, contributing to zinc deficiency in obese individuals [8,9].

Zinc plays a major role in the stabilization of insulin hexamers and the storage of hormone in the pancreas [10], and its deficiency seems to impair release of insulin [11]. Furthermore, zinc may have an indirect insulin-like effect, as human pancreatic β cells have exceptionally high zinc content, which is present in insulin secretory granules, from which it is cosecreted with the hormone. Uptake of zinc into secretory granules is mainly mediated by zinc transporter 8. Therefore, zinc is essential for insulin processing, storage, secretion, and action [12,13].

Some studies have shown that obese individuals have zinc deficiency and it is associated with alterations in the metabolism of the adipose tissue of these patients. It may also be associated with insulin resistance, hyperglycemia, and impaired glucose tolerance [14–17].

On the contrary, other studies showed that no differences were observed in zinc concentrations between obese and nonobese individuals [18–20].

The objectives of this study were to detect the level of serum zinc in obese children and adolescents, and to evaluate its potential relation to obesity, insulin resistance, and lipid profile.

Patients and methods

This case–control study was conducted in obesity outpatient clinic in Alexandria University Children's Hospital. Thirty obese children and adolescents (BMI ≥95th percentile for age and sex) with an age range from 5 to 19 years were included and they were compared with 30 apparently healthy nonobese individuals matched for age and sex as a control group. Exclusion criteria were children with syndromic obesity or endocrine diseases or disorders that affect serum zinc levels, such as kidney disorders, diabetes, cancer, and acute infections, or those with a history of mineral and/or vitamin supplement use or medication that alters glucose and lipid metabolism.

A detailed medical and family history was obtained from all participants. At enrollment, obese and control underwent physical examination including weight, standing height, calculation of BMI, and looking for acanthosis nigricans (AN).

Anthropometric measurements

Height was measured using weight and height scale with a fixed stadiometer with a movable head piece. It was measured in standing position and without shoes with head in the Frankfort plane (head aligned so that an imaginary line from the ear canal to the lower border of the orbit of the eyes is parallel to the floor) with feet together, back and heels against the upright bar of the stature scale. Height was measured to the nearest 0.1 cm. Weight was measured to the nearest 0.1 kg on a standard beam scale with the participant dressed only in light underwear and without shoes.

The waist circumference was measured at a level midway between the lower rib margin and superior border of the iliac crest using a flexible tape all around the body in horizontal positions at the end of gentle expiration. Children with a waist circumference more than 90th percentile were detected according to waist circumference percentile values in the USA for children and adolescents according to sex [21], because of unavailability of Egyptian-specific reference growth curves for waist circumference.

The weight status was recorded as the BMI, which was calculated as follows.

BMI=weight (kg)/square of the body height 2 and expressed in units of kg/m^2. Because the BMI varies according to age and sex, we standardized the value for age and sex by calculating BMI *Z* score, which was calculated as follows: BMI-SDS=(individual measurement-population mean)/population SD and also by plotting the BMI on percentile curves; obesity was defined as BMI more than or equal to 95th percentile using the BMI for age and sex Centers for Disease Control (CDC) growth charts. Nonobese individuals were defined as having a BMI less than the 85th percentile using the BMI for age and sex CDC growth charts [22].

All the participants were examined for the presence of AN as a clinical marker of insulin resistance. The severity grading of AN was carried out using a standard scale of 0–4. According to this scale, grading at the neck was described as follows:

Grade 0: if it is not visible on close inspection.
Grade 1: clearly present on close visual inspection, extent not measurable.
Grade 2: limited to the base of the skull, does not extend to the lateral margins of the neck.
Grade 3: extending to the lateral margins of the neck, but not visible from the front.
Grade 4: extending anteriorly [23].

Biochemical analysis

Venous blood samples were withdrawn from every participant after an overnight fast (at least 12 h). Patients were subjected to the following laboratory investigations:

Serum zinc level was measured by the commercially available kit from Dialab (Wiener Neudorf, Austria). The cutoff levels of zinc deficiency were determined according to age [24].

Total cholesterol (TC), serum triglycerides (TGs), high-density lipoprotein-cholesterol (HDL-C), and fasting plasma glucose (FPG) were measured by Cobas Automated Analyzer (Roche Diagnostics, Mannheim, Germany). An estimated low-density lipoprotein (LDL) was obtained using the Friedewald equation [25]: LDL (mg/dl)=TC–HDL–TGs/5.

Diabetes is diagnosed when FPG is greater than or equal to 126 mg/dl. Impaired fasting glucose (IFG) was as follows: FPG=(100–126 mg/dl). Fasting insulin levels were determined by using enzyme immunometric assays intended for use on the IMMULITE Immunoassay Analyzer (Siemens Healthcare Diagnostics, Flanders, New Jersey, USA) [26].

Calculation of the insulin resistance was evaluated using the following formulas – homeostatic model of assessment for insulin resistance (HOMA-IR)= fasting insulin (μU/ml)×fasting glucose (mg/dl)/405 [27], and quantitative insulin-sensitivity check index (QUICKI)=1/log[fasting insulin (μU/ml)]+log [fasting glucose (mg/dl)].

The cutoff points for diagnosis of insulin resistance were greater than 2.7 for HOMA-IR and less than 0.328 for QUICKI [28].

Ethics

Informed parental consent was obtained to be eligible for enrollment into the study. The study was conducted after approval of Medical Ethics Committee of Alexandria Faculty of Medicine.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package, version 20.0 (Armonk, NY: IBM Corp)) [29]. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, SD, and median. Significance of the obtained results was judged at the 5% level.

The following tests were used: χ^2-test for categorical variables, to compare between different groups; Fisher's exact or Monte Carlo correction, to correct for χ^2 when more than 20% of the cells have expected count less than 5; Student's *t*-test for normally quantitative variables, to compare between two studied groups; and Mann–Whitney test for abnormally quantitative variables, to compare between two studied groups.

Results

Our study included 30 obese children (18 male and 12 female), with a mean age of 8.96±2.69 years, and 30 nonobese control (16 male and 14 female), with a mean age of 9±2.74 years. Clinical and biochemical characteristics are listed in Table 1. The obese children and control groups showed no significant differences in terms of age or sex, which denotes that both groups are comparable to each other. Compared with the control group, serum TGs, TC, and low-density lipoprotein-cholesterol (LDL-C) were significantly higher in obese children, whereas serum HDL-C was significantly lower (all $P<0.05$) (Table 1). Eight (26.7%) obese children compared with three (10%) children in the control group had zinc deficiency. FPG was significantly higher in obese children compared with controls. Eight (26.66%) obese children had IFG. Zinc was significantly lower in obese children compared with the control group ($P=0.04$). Fasting blood insulin and HOMA-IR were significantly higher and QUICKI was significantly lower in obese children compared with the control group. Insulin resistance was found in 20 (66.7%) obese children as defined by HOMA-IR greater than 2.7 and was present in 19 (63.3%) obese children as defined by QUICKI of less than 0.328, and was absent in the control group.

There was a positive significant correlation between serum zinc level and HDL ($r=0.511$, $P<0.05$) (Table 2).

The correlation between AN severity grading and insulin resistance was assessed. There was a significant correlation between AN severity grading with fasting insulin levels, HOMA-IR, and QUICKI (Table 3).

Discussion

Recent studies showed that obesity is associated with disturbances in the metabolism of zinc [5,28]. This association could be explained by the effect of zinc-α2-

Table 1 Comparison between the two studied groups according to clinical and biochemical characteristics parameters

	Cases (*n*=30)	Control (*n*=30)	*P*
Weight (kg)	56.3±19	32.4±10.4	<0.001*
Weight *Z* score	2.6±0.5	0.3±0.5	<0.001*
Height	135.6±15.06	134.3±14.7	0.730
Height *Z* score	0.5±0.8	0.2±0.8	0.133
Waist circumference	89.03±11.2	58.3±4.5	<0.001*
BMI	29.7±5	17.4±2	<0.001*
BMI percentile	1 (98–100)	66.5 (16–83)	<0.001*
<85	0 (0)	30 (100)	<0.001*
85–95	0 (0)	0 (0)	
≥95	30 (100)	0 (0)	
BMI *Z* score	2.6 (2.02–3.7)	0.4 (−1.01–1)	<0.001*
−1 to <0	0 (0)	7 (23.3)	<0.001*
0 to <1	0 (0)	23 (76.7)	
1 to <2	0 (0)	0 (0)	
≥2	30 (100)	0 (0)	
Cholesterol	162.2±32.9	127.3±18.3	<0.001*
<170	18 (60)	28 (93.3)	0.008*
170–199	9 (30)	2 (6.7)	
≥200	3 (10)	0 (0)	
Triglycerides	83 (50–200)	65.5 (40–104)	0.001*
<150	27 (90)	30 (100)	0.237
≥150	3 (10)	0 (0)	
HDL	43.2±12.6	52±9.9	0.004*
<40	16 (53.3)	3 (10)	0.001*
40–<45	4 (13.3)	1 (3.34)	
≥45	10 (33.3)	26 (86.66)	
LDL	98.2±24.1	61.6±14.9	<0.001*
<110	17 (56.7)	30 (100)	0.001*
110–129	10 (33.3)	0 (0)	
≥130	3 (10)	0 (0)	
FPG (mg/dl)	94.2±8.4	87.2±8.5	0.002*
<100 (normal)	22 (73.3)	30 (100)	<0.001*
100–126 (IFG)	8 (26.7)	0 (0)	
≥126 (DM)	0 (0)	0 (0)	
Fasting insulin (μU/ml)	14.5 (7.9–31.9)	7.5 (5.1–8.6)	<0.001*
HOMA-IR	3.7±1.5	1.6±0.26	<0.001*
≤2.7	10 (33.3)	30 (100)	<0.001*
>2.7	20 (66.7)	0 (0)	
QUICKI	0.3±0.02	0.4±0.01	<0.001*
<0.328	19 (63.3)	0 (0)	<0.001*
≥0.328	11 (36.7)	30 (100)	
Serum zinc level (μg/dl)	79.3 (27.8–161)	82.4 (65–160)	0.04*
Deficient	8 (26.7)	3 (10)	0.095
Nondeficient	22 (73.3)	27 (90)	

Qualitative data were described using number and percent and was compared using χ^2 test, whereas normally quantitative data were expressed in mean±SD and were compared using Student's *t*-test; abnormally distributed data were expressed in median (minimum–maximum) and were compared using Mann–Whitney test. DM, diabetes mellitus; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of assessment for insulin resistance; IFG, impaired fasting glucose; LDL, low-density lipoprotein; QUICKI, quantitative insulin-sensitivity check index. *Statistically significant at $P \leq 0.05$.

glycoprotein (ZAG) on leptin concentrations. ZAG is an adipokine involved in lipolysis in the adipocyte that is downregulated in obesity. In obese individuals, low ZAG gene expression is associated with low serum adiponectin and high plasma leptin levels, and may play an important role in the pathogenesis of obesity [30].

Our study revealed that median serum zinc was significantly lower in obese children compared with controls (79.3 vs. 82.4 μg/dl) ($P<0.005$). This finding is in agreement with that of others [5,12–15,28]. In addition, Marreiro *et al.* [31] reported that zinc concentrations in plasma were significantly lower in the obese women. However, Tascilar *et al.* [18] found

Table 2 Correlation between serum zinc level (μg/dl) and different parameters

Cases	Serum zinc level (μg/dl)	
	r	*P*
BMI	−0.097	0.609
Waist circumference	−0.213	0.259
HDL-cholesterol (mg/dl)	0.511*	0.004*
LDL-cholesterol (mg/dl)	−0.88	0.645
Serum cholesterol level (mg/dl)	0.13	0.944
Serum triglyceride level (mg/dl)	−0.899	0.289
FPG (mg/dl)	−0.076	0.689
Fasting insulin (μU/ml)	−0.0.059	0.759
HOMA-IR	−0.066	0.729
QUICKI	0.159	0.4

FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA-IR, homeostatic model of assessment for insulin resistance; LDL, low-density lipoprotein; QUICKI, quantitative insulin-sensitivity check index; *r*, Pearson's coefficient. *Statistically significant at $P \leq 0.05$.

Table 3 Correlation between acanthosis nigricans and different parameters

Cases	Acanthosis nigricans	
	r	*P*
Fasting insulin (μU/ml)	0.711	<0.001*
HOMA-IR	0.822	<0.001*
QUICKI	−0.826	<0.001*

HOMA-IR, homeostatic model of assessment for insulin resistance; QUICKI, quantitative insulin-sensitivity check index; *r*, Pearson's coefficient. *Statistically significant at $P \leq 0.05$.

that serum level of zinc tended to be lower in obese children; however, the difference was statistically insignificant. They explained this by the low number of participants enrolled in the study and the high prevalence of iron deficiency. In contrast to our results, Weisstaub *et al.* [19] reported that the serum zinc levels in preschool children were not associated with body weight. Moreover, Ennes Dourado Ferro *et al.* [20] also did not find any significant difference in plasma zinc concentration between the obese and the control groups. García *et al.* [32] reported zinc deficiency in 24.9% of Mexican school-aged children. Similarly, in the present study, eight (26.7%) obese children compared with three (10%) children had zinc deficiency in the control group.

In our study, obese children have significantly higher TGs, TC, and LDL-C, whereas HDL-C was significantly lower compared with nonobese peers ($P<0.05$). In contrast, Woo *et al.* [33] studied a cohort of obese individuals of Chinese ethnicity who did not show elevated cholesterol levels compared with a control group. Regarding the TC and LDL levels, our findings are in agreement with those of Reinehr *et al.* [34] and Nasreddine *et al.* [35], who observed higher TG and LDL-C and lower HDL-C in obese children compared with children with normal weight. In addition, Habib *et al.* [17] reported significant elevated levels of TC and LDL-C in all studied obesity groups and significantly elevated TG level was found in obese boys. High cholesterol and LDL-C levels have been detected in obese individuals as compared with controls [36,37].

In the current study, we observed that a significant positive correlation existed between serum zinc and HDL-C levels ($r=0.511$, $P<0.05$) in the obese children and adolescents. These results are in agreement with those of Habib *et al.* [17], who found a positive correlation between zinc and HDL-C levels ($r=0.29$, $P<0.01$). This is in agreement with the study by Azab *et al.* [38], but they also reported that serum zinc showed significant negative correlations with serum TC levels. In addition, Al-Sabaawy [39] reported a significant negative correlation between serum zinc and TC, LDL, and TG.

These findings indicate the possible effect of zinc level on serum lipid profile, and this effect may be because of the role of zinc as an antioxidant. Thus, the decrease in zinc level in obese children may lead to increased lipid peroxidation, thus leading to increased levels of TC, TG, and LDL-C [40]. Furthermore, zinc can act as a protective factor against atherosclerosis by inhibiting the oxidation of LDL-C [39].

Kelishadi *et al.* [41] documented a significant decrease of total and LDL-C after receiving 20 mg/day of elemental zinc for 8 weeks in obese Iranian children. In obese adults, Payahoo *et al.* [42] reported that zinc supplementation improves BMI, body weight, and TG concentration without considerable effects on other lipid profiles in obese adults. However, Kim and Lee [43] reported that zinc supplementation at 30 mg daily for 8 weeks increased serum zinc by 15%, but no significant difference was found with respect to TG and HDL-C after zinc supplementation in obese Korean women. Therefore, researches on the effect of zinc supplementation on the lipid profile and the metabolic risks in obesity should be performed in children.

In the present study, there was a significant difference between obese and control groups as regards FPG, as the obese children recorded higher levels of FPG than the control group.

Eight (26.66%) obese children had IFG. Furthermore, the fasting insulin level in obese children was significantly higher than in nonobese children; this would raise the possibility of insulin resistance in

those children. Rotteveel *et al.* [44] reported that 12.4% of the obese boys and 11.6% of obese girls had IFG.

In the present work, HOMA-IR was significantly higher and QUICKI was significantly lower in obese children compared with the control group. Insulin resistance was found in 20 (66.7%) cases among obese children as defined by HOMA-IR greater than 2.7 and was present in 19 (63.3%) cases among obese children as defined by QUICKI of less than 0.328, and was absent in the control group.

In the present work, we found significant insulin resistance in obese children, as represented by increased HOMA-IR, serum insulin, and glucose concentrations and decreased QUICKI. The association of obesity with insulin resistance has been recognized in studies for decades. In other studies, it has been observed that excess body fat, especially visceral fat, contributes to decreased insulin sensitivity in tissues [16].

In the present study, there was no significant correlation between serum zinc level and fasting glucose, fasting insulin, HOMA-IR index, and QUICKI index. These results are in agreement with those of Tascilar *et al.* [18], who reported no correlation between serum zinc level and HOMA-IR. In contrast, Ortega *et al.* [45] revealed an inverse correlation between serum zinc level and that of insulin (r=–0.1793) and the HOMA-IR index values (r=–0.149, P<0.05 in all cases). Moreover, Sulibursk*a et al.* [16] and Azab *et al.* [38] reported that serum zinc levels were negatively correlated with fasting glucose levels and HOMA-IR values.

Kelishadi *et al.* [41] reported a significant decrease of serum concentrations of FPG, insulin, and HOMA-IR index values after zinc supplementation in obese Iranian children. However, Payahoo *et al.* [42] reported that zinc supplementation had no significant difference on FPG, and serum lipid profiles except TG in obese adults. However, Kim and Lee [43] reported improvement in insulin resistance after zinc supplementation.

In the present work, AN was present in all the obese children. These results are in agreement with those of Zambon *et al.* [46], who found that 58% of a sample of obese children and adolescents had AN. There was a significant positive correlation between AN severity grading with the fasting insulin levels and HOMA-IR and significant negative correlation with QUICKI; therefore, AN should be looked for in all obese children and adolescents. This finding was supported by the finding reported by Valdes Rodriguez *et al.* [47], who found a relationship between the presence of AN with higher insulin resistance. In contrast, these findings are not in agreement with those reported by Shalitin *et al.* [48], who concluded that although 56.6% of the obese individuals had AN it was not a reliable marker for abnormal HOMA-IR or QUICKI values.

The present study has several limitations. First, we used only serum zinc as the only indicator of a zinc status and the small sample size. Therefore, we suggest that multicenter approaches may be necessary to attain larger sample size.

Conclusion

From the study we concluded that zinc serum level was lower in obese children and adolescents as compared with children and adolescents with normal weight. We suggest that further randomized controlled trial studies are needed to study the effect of zinc supplementation in obese children and adolescents on obesity, lipid profile, and insulin resistance.

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Conflicts of interest

There are no conflicts of interest.

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