Research Article

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Investigation of ischemia modified albumin and coenzyme Q10 levels in obese children with metabolic syndrome

Metabolik sendromlu obez çocuklarda iskemi modifiye albumin ve koenzim Q10 düzeylerinin incelenmesi

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Abstract

Introduction: The aim of this study was to analyze serum ischemia modified albumin (IMA) and plasma CoQ10 levels and to evaluate their correlation with insulin resistance (homeostatic model assessment, HOMA) and lipid profile in obese children with and without metabolic syndrome (MS).

Methods: Thirty-one obese with MS, 30 obese without MS and 34 healthy children aged 6–18 years were included in the study. Serum IMA was measured by colorimetric method, plasma CoQ10 levels were measured by HPLC. Serum glucose, total cholesterol, triglyceride, high density lipoprotein cholesterol, low density lipoprotein cholesterol and insulin were analyzed.

Results: IMA levels were found to be significantly higher (\(p < 0.001\)) while the CoQ10 levels were significantly lower (\(p < 0.001\)) in obese children with and without MS compared to controls. IMA and CoQ10 significantly correlated with each other and metabolic parameters. Furthermore, IMA and CoQ10 levels did not significantly differ between obese children with and without MS, while glucose, insulin levels and HOMA were significantly higher (\(p < 0.001\)) in obese children with MS than obese without MS and controls.

Conclusions: Based on the high levels of IMA, low CoQ10 and association with HOMA and lipid profile; we suggest that obese children may have oxidative damage, lipid peroxidation and cardiometabolic risk.

Keywords: Ischemia modified albumin; Coenzyme Q10; Childhood obesity; Metabolic syndrome; Lipid profile.

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Özet

Amaç: Bu çalışmanın amacı; metabolik sendromu (MS) olan ve olmayan obez çocuklarda; serum iskemi modifiye albümin (İMA), plazma koenzim Q10 (CoQ10) düzeylerinin ölçülmemesi ve bu parametrelerin insülin direnci (homeostatic model assessment, HOMA) ve lipid profilinde ilişkisinin değerlendirilmesidir.

Yöntem: Yaşları 6 ile 15 arasında olan 31 MS’li obez, 30 metabolik sendromu olmayan obez ve 34 sağlıklı çocuk çalışmaya dahil edildi. Serum İMA kolorimetrik yöntemle, plazma CoQ10 seviyeleri HPLC ile ölçüldü. Serum glukoz, total kolesterol (TC), trigliserid (TG), yüksek dansiteli lipoprotein kolesterol (HDL-C), düşük dansiteli lipoprotein kolesterol (LDL-C) ve insülin düzeyleri analiz edildi.

Bulgular: Obez ve MS’li obez çocuklarda, kontrol grubuna göre İMA seviyeleri istatistiksel olarak anlamlı yüksek (\(p < 0.001\)), CoQ10 seviyeleri istatistiksel olarak anlamlı düşük (\(p < 0.001\)) bulundu. İMA ve CoQ10 birbirleriyile ve metabolik parametrelerle anlamlı korelasyon gösterdi. Ayrıca glukoz, insülin düzeyleri ve HOMA MS’li obez çocuklarda, MS’li olmayan obez ve kontrol grubuna göre
Introduction

Obesity is a chronic disease observed worldwide owing to its rapidly rising prevalence in not only developed, but developing countries as well; and it is connected with a number of metabolic complications [1]. Many of these complications frequently appear in childhood and display an inclination to be present during adulthood or progress further into metabolic syndrome (MS) [2] which also has relations with vascular dysfunction, cardiovascular disease (CVD) and type 2 diabetes (T2D) in children [3, 4]. In the literature, based on the relationship between obesity and adverse changes in lipid profiles, it is suggested that screening of children for obesity be conducted to prevent CVDs [5].

Bad eating habits and sedentary lifestyle worsen imbalance between free radicals and antioxidant defenses by aiding to the structural function changes in some proteins, for instance human serum albumin, playing a role in efficient antioxidant defense of the organism [6]. Overproduction of free radicals could modify N-terminal region of human serum albumin creating ischemia modified albumin (IMA), a sensitive marker of ischemia increasing in diseases related with obesity [7, 8]. Piva et al. [9] stated that a rise in IMA in obese patients and a connection with body mass index (BMI) shows a likely interplay of oxidative stress in obesity.

The studies conducted in recent years have supplied evidence of the potential value of coenzyme Q10 (CoQ10) for prophylaxis and therapy of different disorders associated with oxidative stress [10, 11]. It was stated that CoQ10 concentrations and redox status have connections with components of MS [12]. CoQ10 is an endogenously synthesized compound acting as an electron carrier in the mitochondrial respiratory chain [13]. Additionally, CoQ10 functions as an antioxidant, scavenging free radicals and inhibiting lipid peroxidation [14, 15].

Adipose tissue in obese individuals is poorly oxygenated and this hypoxia state is a potential risk factor for oxidative stress and development of obesity-connected diseases [16–18]. There are studies in which IMA and CoQ10 have been studied independently in patient groups [12, 19–22]. Both parameters, which have been investigated together in the same patient group, have exhibited that this study is different from other studies. The objective of this study was to analyze serum IMA and plasma CoQ10 levels and to assess their correlation with homeostatic model assessment (HOMA) and lipid profile in obese children with and without MS.

Materials and methods

Study design

The three study groups consisted of 30 obese children without MS, 31 obese children with MS and 34 controls (aged 6–15 applying to the Pediatric Endocrinology and Metabolism Department). The subjects were consecutively registered to the study. Informed parental consent was received to be eligible for registration to the study. The study was carried out in line with the Declaration of Helsinki and all its procedures were performed with sufficient understanding and written consent of the subjects. The study protocol was confirmed by the Scientific Research Evaluation Ethical Committee. The children that were receiving treatment for any reason, including syndromic and endocrinological diseases, were excluded from the study.

Data collection

The heights of the subjects were measured without shoes using a Harpenden stadiometer (Harpenden, Holtain Ltd., UK) to the nearest 0.1 cm. Their weights were measured to the nearest 0.1 kg on a standard beam scale with the subjects dressed solely in light underwear and without wearing shoes. BMI was calculated as kilograms of weight divided by square of the height in meters. We used specific BMI percentiles curves, prepared by Bundak et al. [23] and adjusted for different ages and sexes for Turkish children; and normal weight was described as BMI from the 15th to less than the 85th and obese as BMI of 95th percentile or more.

The obese children were divided into two groups as obese without MS (n = 30) and obese with MS (n = 31) in accordance with the International Diabetes Federation (IDF) consensus definition of MS in children and adolescents [24]. Based on the MS criteria suggested by the IDF, children were diagnosed as having MS when their waist circumference was ≥95th percentile for Turkish children.
Shortly, 200 binding analysis method developed by Bar-Or et al [25]. IMA level was measured by a colorimetric cobalt-albumin chromatograms were recorded by a UV-detector. Serum liquid chromatography (HPLC) reagent kit, Germany. The levels were measured using Immuchrom high performance and plasma samples were stored at –70°C. Blood specimens were centrifuged for 10 min at 2000 g were collected and allowed to clot for 30 min. Blood specimens without MS, c: obese without MS-obese with MS. Data were expressed as mean ± standard deviation. Statistical significance levels; p < 0.05 was considered to be statistically significant.

## Laboratory measurements

Using venipuncture technique, blood samples were drawn into Vacutainer tubes with EDTA or no anticoagulant. After an overnight (≥12 h) fasting, venous blood samples were collected and allowed to clot for 30 min. Blood specimens were centrifuged for 10 min at 2000 g and aliquots of serum and plasma samples were stored at –70°C. Plasma CoQ10 levels were measured using Immuchrom high performance liquid chromatography (HPLC) reagent kit, Germany. The chromatograms were recorded by a UV-detector. Serum IMA level was measured by a colorimetric cobalt-albumin binding analysis method developed by Bar-Or et al [25]. Shortly, 200 μL patient serum was added to 50 μL of 0.1% CoCl₂·6H₂O. After having been shaken, the mixture was incubated for 10 min to make sure the adequate cobalt albumin binding. Subsequently, 50 μL of 1.5 mg/mL dithiothreitol was added as a coloring agent. After 2 min, 1 mL of 0.9% NaCl was added to stop the binding between the cobalt and albumin. The absorbances were measured at 470 nm with a spectrophotometer and the results were expressed as absorbance units [25]. The intra- and inter-assay coefficient of variation (CV) were 4.1% and 5.3% for IMA; 3.1% and 3.9% for CoQ10, respectively.

The levels of serum glucose, TG, total cholesterol (TC), HDL-C and low-density lipoprotein cholesterol (LDL-C) were assayed using the Siemens Advia 1800 and serum insulin concentrations were analyzed with Centaur XP auto-analyzer. The data for insulin resistance were based on HOMA, and they were calculated from fasting plasma insulin with glucose levels by taking scores HOMA = 2.1 as the existence of insulin resistance in children and adolescents [26].

## Statistical analysis

The Shapiro-Wilk test and Q-Q graphics were performed to determine whether data distribution was normal. Descriptive statistics for numerical variables were presented as mean ± standard deviation. Study groups were compared using one-way analysis of variance (ANOVA). Tukey test was used for multiple comparisons. Pearson correlation test was employed to search the relationships between parameters displaying normal distribution. p < 0.05 was considered to be statistically significant.

## Results

As can be seen in Table 1, the anthropometric and metabolic features of the obese with and without MS and

| Table 1: Anthropometric and metabolic characteristics of the study population. |
|---------------------------------------------------------------|-----------------|------------------|-----------------|-----------------|
| **Age, year** | **Control (n=34)** | **Obese without MS (n=30)** | **Obese with MS (n=31)** | **p-Value** |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| 13.2 ± 2.1 | 11.1 ± 3.1 | 12.8 ± 2.3 | 0.106 |
| 162.4 ± 7.8 | 154.1 ± 14.4 | 162.0 ± 10 | <0.001<sup>a,b</sup> |
| 60.2 ± 5.9 | 71.7 ± 13.1 | 79.3 ± 9.1 | <0.001<sup>a,b</sup> |
| 22.9 ± 1.4 | 29.9 ± 1.1 | 30.2 ± 1.5 | <0.001<sup>a</sup> |
| 78.97 ± 16.4 | 82.3 ± 9.8 | 98.0 ± 8.8 | <0.001<sup>a</sup> |
| 11.1 ± 2.3 | 11.1 ± 2.2 | 17.1 ± 2.4 | <0.001<sup>a</sup> |
| 2.1 ± 0.6 | 2.2 ± 0.4 | 4.1 ± 0.4 | <0.001<sup>a</sup> |
| 91.2 ± 17.2 | 96.9 ± 14.2 | 127.2 ± 26.1 | <0.001<sup>a</sup> |
| 134.8 ± 9.6 | 161.2 ± 11.8 | 183.4 ± 12.7 | <0.001<sup>a,c</sup> |
| 62.9 ± 7.8 | 94.8 ± 11.5 | 111.8 ± 10.2 | <0.001<sup>a,c</sup> |
| 56.3 ± 6.4 | 47.0 ± 4.3 | 46.1 ± 5.5 | <0.001<sup>a</sup> |
| 1.11 ± 0.12 | 0.91 ± 0.10 | 0.86 ± 0.2 | <0.001<sup>a</sup> |
| 0.25±0.05 | 0.30±0.05 | 0.32±0.06 | <0.001<sup>a</sup> |

Data were expressed as mean ± standard deviation. Statistical significance levels; p < 0.001; a: control-obese with MS, b: control-obese without MS, c: obese without MS-obese with MS.
control groups are presented. The control, obese without MS and obese with MS groups did not exhibit any substantial differences in terms of age or gender. TC, LDL-C and BMI were significantly higher (p < 0.001), HDL-C was significantly lower (p < 0.001) in obese without MS than those of controls. However, no significant difference was found in glucose, insulin, TG levels and HOMA values between obese without MS and control groups. TC, TG, LDL-C, glucose, insulin and HOMA were significantly higher (p < 0.001) in obese with MS than in obese without MS and controls (Table 1).

When compared with the controls, the obese with and without MS possessed significantly higher IMA and lower CoQ10 levels (p < 0.001). Nevertheless, IMA and CoQ10 levels were similar between the obese with and without MS groups. In this study, the groups were assessed with regard to gender differences; and substantial differences were determined only in obese children in terms of CoQ10. The levels of CoQ10 were significantly lower in obese girls when compared to obese boys (0.85±0.10 vs. 0.96±0.11, respectively).

The correlation analyses revealed that IMA levels were significantly positively correlated with BMI, TC and LDL-C in the obese without MS group. CoQ10 levels were significantly negatively correlated with BMI, LDL-C and IMA; although CoQ10 levels showed significantly positive correlation with HDL-C in the obese without MS. In addition to this, IMA levels were significantly positively correlated with BMI (Figure 1A), HOMA (Figure 1B), glucose and insulin, but a significantly negative correlation was found between IMA and HDL-C in the obese with MS. CoQ10 levels demonstrated substantial negative correlation with IMA (Figure 1C), BMI (Figure 1D), glucose, insulin, HOMA, TC, LDL-C and TG in the obese with MS (Table 2).

**Discussion**

Obesity is a chronic and inflammatory condition which triggers free oxygen radicals [27]. Over-expression of oxidative stress harms cellular structures together with
under-production of anti-oxidant mechanisms, causing the development of obesity-related complications [28].

The oxidative modification of proteins plays an important role in pathogenesis and development of various metabolic disturbances [29]. In present study, we concentrated on IMA, reflecting oxidative stress-induced modifications of the albumin molecule; and we observed that IMA levels of obese children with and without MS were significantly higher than those of controls. These findings were compatible with the literature [20, 21]. In addition to this, some researchers reported increased IMA levels in obese adult subjects, and they also proposed that obesity and insulin were found to be independent determinants of IMA; and thus its formation seems to be associated with oxidative stress and atheromatous plaque development [7, 9, 19]. We may suggest that increased IMA levels may be an early indicator of oxidative stress in obese children before MS development. Furthermore, Valla Gottlieb et al. [8] have found out that serum IMA levels were significantly higher in adults with MS than controls. Zurawska-Płaksej et al. [30] pointed to significantly higher IMA levels in patients with a number of different MS features in comparison with the control group. In the present study, there were not any significant differences between the obese with and without MS in terms of IMA levels. This finding may be related with the numbers of MS risk factors in obese children.

It has been demonstrated that CoQ10 has antioxidant activity either by direct reaction with free radicals or by regenerating tocopherol and ascorbate from their oxidized state [31]. There are only two clinical studies on CoQ10 in obese children [11, 22], but there is no study about CoQ10 in obese children with MS. In this study, the obese children with and without MS had significantly lower CoQ10 levels than those of controls. Menke et al. [32] have informed that unadjusted plasma CoQ10 levels of the obese and normal weight children displayed no difference. Gvozdjakova et al. [22] declared that an increase in the ratios of lipid parameters to CoQ10 had an association with child obesity and could be used as biomarkers of early complications in the development of obesity in children. Then again, CoQ10 originates from endogenous synthesis as well as food intake [32]. So, the difference in lifestyle and nutritional patterns may arise from differences in plasma CoQ10 levels [33]. In present study, we were not able to investigate the obese children’s eating habits and lifestyle. We have confidence in the fact that the reason for the differences between these findings in obesity may be because of the usage of the lipid-adjusted or unadjusted CoQ10. In this study, the obese children with MS possessed lower CoQ10 levels than the obese without MS, but this difference was not significant because the number of subjects was small. We predict that obese children might be under higher oxidative stress, which has impact on their CoQ10 levels.

Predominant dyslipidemic pattern in childhood covers moderate-to-severe elevation in TG, no/mild elevation in LDL-C and reduced HDL-C. In pathological studies in children, adolescents and young adults; non-HDL-C and HDL-C levels were strongly related with atherosclerotic lesions. It has been declared that high TG and low HDL-C in youth are independent predictors of increased carotid intima-media thickness, particularly in those with full MS [34]. In a different study, HDL-C was significantly reduced; nevertheless, TG, TC, LDL-C, insulin levels and HOMA were significantly increased in obese children when compared with the control group [22, 35, 36]. In addition to all these, fasting glucose and triglycerides were significantly higher, while HDL-C was lower in MS patients [30]. In this study, as similar to literature, TC and LDL-C were significantly higher, whereas HDL-C was

| Groups                        | Parameters | IMAr | Parameters | CoQ10r |
|-------------------------------|------------|------|------------|--------|
| Control                       | BMI        | 0.244| BMI        | 0.055  |
|                               | Glucose    | 0.230| Glucose    | −0.111 |
|                               | Insulin    | 0.141| Insulin    | 0.074  |
|                               | HOMA       | 0.262| HOMA       | −0.033 |
|                               | TC         | 0.159| TC         | −0.390*|
|                               | HDL-C      | −0.136| HDL-C     | 0.519* |
|                               | LDL-C      | 0.253| LDL-C      | 0.092  |
|                               | TG         | 0.118| TG         | −0.085 |
|                               | CoQ10      | −0.146| IMA       | −0.146 |
| Obese without MS             | BMI        | 0.391*| BMI       | −0.402*|
|                               | Glucose    | 0.264| Glucose    | −0.285 |
|                               | Insulin    | 0.293| Insulin    | −0.078 |
|                               | HOMA       | 0.259| HOMA       | 0.012  |
|                               | TC         | 0.356*| TC        | −0.263 |
|                               | HDL-C      | −0.237| HDL-C     | 0.530* |
|                               | LDL-C      | 0.375*| LDL-C     | −0.468*|
|                               | TG         | 0.234| TG         | 0.326  |
|                               | CoQ10      | −0.301*| IMA      | −0.301*|
| Obese with MS                | BMI        | 0.546*| BMI       | −0.483*|
|                               | Glucose    | 0.397*| Glucose   | −0.468*|
|                               | Insulin    | 0.531*| Insulin   | −0.524*|
|                               | HOMA       | 0.470*| HOMA      | −0.568*|
|                               | TC         | 0.256| TC         | −0.409*|
|                               | HDL-C      | −0.372*| HDL-C    | 0.201  |
|                               | LDL-C      | 0.337| LDL-C      | −0.550*|
|                               | TG         | 0.216| TG         | −0.403*|
|                               | CoQ10      | −0.462*| IMA      | −0.462*|

Statistical significance levels; *p < 0.05, **p < 0.001. Significant correlation values between parameters were shown as bold.
significantly lower in the obese without MS than those of controls. In addition, TC, TG, LDL-C, glucose, insulin and HOMA were significantly higher in the obese with MS than those of the obese without MS and controls. These metabolic disturbances might be used to estimate the results of CVDs in the future.

In obesity, the significance of fat distribution in the context of oxidative stress was found out by the researchers who found the correlation of anthropometrical parameters with oxidative stress activation level [37, 38]. We discovered significant correlations between BMI and IMA as well as BMI and CoQ10 in both groups of obese children with and without MS groups. Likewise, an important positive correlation was found between IMA and BMI in obese adults [19]. We may recommend that increased IMA and decreased CoQ10 levels may be related to childhood obesity.

In the present study, IMA exhibited significant positive correlations with TC, LDL-C and negative correlation with CoQ10 in the obese without MS. Moreover, IMA levels were significantly positively correlated with glucose, insulin and HOMA, but substantial negative correlation was found between IMA and HDL-C in the obese with MS. In addition to this, CoQ10 levels showed a significant negative correlation with HOMA, TC, LDL-C, TG and IMA in the obese with MS. Accordingly, these results have made clear that increased IMA and decreased CoQ10 levels may be necessarily dependent on the metabolic disturbances giving rise to MS.

Despite the fact that the biological significances of these associations are far from being entirely understood, perhaps, due to the small number of subjects in each group, it surely necessitates further investigation; however, some speculations may be put forward on the bases of our findings. The levels of IMA may indicate a significant subclinical condition of an oxidative stress, and a successive change in serum albumin producing IMA in obese children with and without MS.

Endogenous CoQ10 synthesis might not compensate greater demand of lipophilic antioxidants in situations like obesity; and owing to the lower content of CoQ10 in most dairy products, vegetables, fruits and cereals [39], it is advisable to reinforce the diet of obese children with rich nutritional sources, for example meat, fish, nuts and some oils.

All in all, based on the high levels of IMA, low CoQ10 and association with HOMA and lipid profile; we put forward that obese children have oxidative damage, lipid peroxidation and cardiometabolic risk; and it is necessary to concentrate on obesity reduction in this population with high risk.

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Ethical issues: The subjects were consecutively registered into the study between January 2010 and April 2010. Informed parental consent was attained to be eligible for registration into the study. The study protocol was certified by the Ethics Committee of XXX, Scientific Research Evaluation Ethical Committee (Date: 08.10.2009/Decision No: 2009-73).

Conflict of interest: The authors declare that there is no conflict of interest in this work.

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