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Associations among Fetuin A, Cortisol and Thyroid Hormones in Children with Morbid Obesity and Metabolic Syndrome

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***Abstract*—**Obesity is a disease with an ever-increasing prevalence throughout the world. The metabolic network associated with obesity is very complicated. In metabolic syndrome (MetS), it becomes even more difficult to understand. Within this context, hormones, cytokines, and many others participate in this complex matrix. The collaboration among all of these parameters is a matter of great wonder. Cortisol, as a stress hormone, is closely associated with obesity. Thyroid hormones are involved in the regulation of energy as well as glucose metabolism with all of its associates. Fetuin A has been known for years; however, the involvement of this parameter in obesity discussions is rather new. Recently, it has been defined as one of the new generation markers of obesity. In this study, the aim was to introduce complex interactions among all to be able to make clear comparisons, at least for a part of this complicated matter. Morbid obese (MO) children participated in the study. Two groups with 46 MO children and 43 with MetS were constituted. All children included in the study were above 99th age- and sex-adjusted body mass index (BMI) percentiles according to World Health Organization criteria. Forty-three morbid obese children in the second group also had MetS components. Informed consent forms were filled by the parents of the participants. The institutional ethics committee has given approval for the study protocol. Data as well as the findings of the study were evaluated from a statistical point of view. Two groups were matched for their age and gender compositions. Significantly higher body mass index (BMI), waist circumference, thyrotropin, and insulin values were observed in the MetS group. Triiodothyronine concentrations did not differ between the groups. Elevated levels for thyroxin, cortisol, and fetuin-A were detected in the MetS group compared to the first group ($p > 0.05$). In MO MetS- group, cortisol was correlated with thyroxin and fetuin-A ($p < 0.05$). In the MO MetS+ group, none of these correlations were present. Instead, a correlation between cortisol and thyrotropin was found ($p < 0.05$). In conclusion, findings have shown that cortisol was the key player in severely obese children. The association of this hormone with the participants of thyroid hormone metabolism was quite important. The lack of association with fetuin A in the morbid obese MetS+ group has suggested the possible interference of MetS components in the behavior of this new generation obesity marker. The most remarkable finding of the study was the unique correlation between cortisol and thyrotropin in the morbid obese MetS+ group, suggesting that thyrotropin may serve as a target along with cortisol in the morbid obese MetS+ group. This association may deserve specific attention during the development of remedies against MetS in the pediatric population.

***Keywords*—**Children, cortisol, fetuin A, morbid obesity, thyrotropin.

I. Introduction

THE advanced stages of obesity such as morbid obesity and metabolic syndrome (MetS) are life-threatening health problems because they are associated with severe metabolic derangements, metabolic disorders, hormonal dysfunctions and severe chronic diseases. In comparison with adults, children are more susceptible to developing obesity due to the consumption of junk foods, soft drinks, and the sedentary life style caused by the developments in electronic devices. Childhood obesity may prepare a basis for the development of severe health problems during the future life of the individual. It may increase the mortality and morbidity risk in adulthood [1]-[3]. Therefore, the analysis of particularly the advanced forms of obesity deserves attention. Within this context, cytokines and hormones particularly carry the weight of this matter.

Fetuin A is a multifunctional hepatokine involved in the pathology of many disorders and also may positively correlate with markers of early atherosclerosis, MetS, obesity, insulin resistance (IR) [4]-[7]. Fetuin A was correlated positively with homeostasis model of assessment-IR, thyroid hormones in patients with hyperthyroidism. It was reported that hypothyroidism as well as hyperthyroidism influence fetuin A levels [4], [8]-[11].

Altered hormonal regulation, including increased cortisol, is known to be a causative factor in central obesity and suggested as a mechanism linking adiposity to obesity-related disorders [12], [13]. Several measures of adiposity, such as leptin are associated with cortisol [13]. In obesity, cortisol accumulates in adipose tissue, possibly leading to adverse metabolic consequences [14]. However, a report did not support a cortisol driven obesity etiology in an older population and even point to an inverse association of body weight with cortisol [15] levels.

Metabolic disorders such as diabetes are generally linked with fluctuations in the levels of cortisol, which is a hormone triggering obesity, hyperglycemia, IR, hypertension, triglycerides and repressing high-density lipoprotein cholesterol [16], [17]. This fact points out the close association between cortisol and MetS. Diabetes also triggers differential cortisol levels during stress and depression, further increasing the risk of MetS.

The association between thyroid stimulating hormone (TSH, thyrotropin) and cortisol is generally evaluated as a pathological finding. However, a positive relationship

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between TSH and cortisol in apparently healthy young individuals was also reported [18].

Thyroid hormones, free triiodothyronine (fT_3) and free thyroxine (fT_4) are important regulators of energy expenditure, body weight, IR, and cardiac function [19]-[22]. Thyroid dysfunction may affect the endocrine products of adipose tissue [10], [23].

The aim of this study was to examine the complicated network among an important hepatokine fetuin A, thyroid hormones fT_3, fT_4, TSH and cortisol in morbid obese MetS- and MetS+ children. The potential differences, as well as associations between children with morbid obesity and MetS, were investigated.

II. Patients and Methods

A. Patients

Forty-six morbid obese (MO) children (Group I) and 43 MO children with MetS (Group II) participated in the study. Informed consent forms were filled out by the parents of the children. Tekirdag Namik Kemal University, Faculty of Medicine, Ethics Committee approved the study protocol.

B. Criteria for Morbid Obesity

Tables prepared by World Health Organization were used to evaluate the morbid obesity criteria [24]. Children with age- and sex-adjusted body mass index (BMI) percentiles above 99 were defined as MO.

C. Metabolic Syndrome Components

Metabolic syndrome was diagnosed according to the set of rules recommended by International Diabetes Federation [25]. Forty-three children in the second group also had MetS components aside from being MO.

In MO children, the presence of two criteria from the following list was the condition of being MO MetS+.

1. Systolic blood pressure above 130 mm Hg and/or diastolic blood pressure above 85 mm Hg.
2. Triacylglycerol levels above 150 mg/dl and/or high density lipoprotein cholesterol levels below 40 mg/dl.
3. Fasting blood glucose concentrations higher than 100 mg/dl.

D. Anthropometric Measurements for Obesity Description

Three anthropometric measurements commonly used for the description of obesity were performed: Weight, height, and waist circumference (WC). Body mass index values were calculated from the weight and height values of the individuals.

E. Laboratory Analyses

Routine hematologic and biochemical tests were performed. Insulin, cortisol, TSH, fT_3 and fT_4 concentrations were determined by electrochemiluminescence immunoassay technic. Enzyme-linked immunoassay technic was used to determine fetuin A levels.

F. Statistical Analyses

Statistical analyses were performed using SPSS program. The results were presented as mean±standard deviation for variables with a normal distribution, medians (interquartile ranges) for skewed variables. Variables such as cortisol, insulin, TSH, fetuin A concentrations were logarithmically transformed before the statistical analysis. Associations among anthropometric measurements, fetuin A, cortisol and thyroid measures were tested by bivariate correlations and linear regression analyses. A p-value of 0.05 was accepted as the statistical significance degree.

III. Results

The mean±SD values for age, BMI, and WC of MO children with MetS- and MetS+ were tabulated in Table I.

Table I also showed the concentrations of fetuin A, insulin, cortisol, thyroid hormones, fT_3 and fT_4 as well as TSH.

TABLE I
PARAMETERS MEASURED IN THE STUDY POPULATION

Groups	Group I MO-MetS- (x±SD)	Group II MO-MetS+ (x±SD)	p
Age (year)	10.7±3.3	12.1±3.2	NS
BMI (kg/m^2)	28.6±5.6	31.0±5.6	0.01
WC (cm)	89.6±15.9	95.0±14.8	0.01
T_3 (pg/ml)	4.30±0.51	4.29±0.55	NS
T_4 (ng/ml)	1.29±0.21	1.36±1.11	NS
TSH (mIU/ml)	2.88±1.51	3.39±1.83	0.05
Insulin ^{m} (µIU/ml)	17.9	30.4	0.01
Cortisol (µg/dl)	8.9±3.4	9.6±5.2	NS
Fetuin A ^{m} (mg/L)	367	451	NS

MO=morbid obese, MetS-metabolic syndrome, BMI=body mass index, WC=waist circumference, T_3=triiodothyronine, T_4=thyroxine, TSH= thyrotropin, thyroid stimulating hormone, NS= not significant, ^{m} median.

The difference between mean age±SD values of the groups was not significant. Significantly increased BMI as well as WC values were observed for MO MetS+ children. No significant difference was observed for fT_3 and fT_4 concentrations between the groups. Higher TSH concentrations were noted in Group II than those in Group I ($p<0.05$). Insulin levels were significantly increased in Group II ($p<0.01$). Elevated cortisol and fetuin A concentrations were found in Group II ($p>0.05$).

In both groups, BMI was strongly correlated with WC (MO MetS- and MetS+, $r=0.872$; $p<0.001$ and $r=0.899$; $p<0.001$, respectively). Body mass index as well as WC values were negatively correlated with T_3 ($p<0.05$) and T_4 levels ($p<0.01$) in both groups.

In MO MetS- group, cortisol was correlated with T_4 ($r=0.296$; $p<0.05$) as well as fetuin A ($r=0.339$; $p<0.05$). In the other group, such correlations were not found. Instead, a correlation between cortisol and TSH was calculated ($r=0.364$; $p<0.05$). In Fig. 1, bivariate correlation with linear regression between logarithmic transformations of cortisol and TSH was shown.

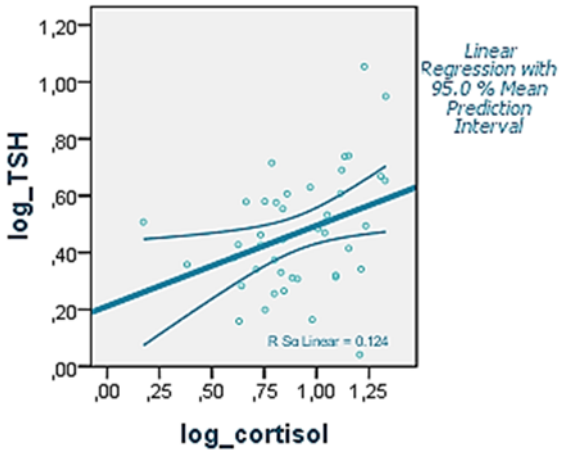

Fig. 1 Graph drawn for bivariate correlation between log [TSH] and log [cortisol] in MetS children

IV. Discussion

Fetuin A is a complex metabolic phase reactant in blood with a controversial role in MetS. Previous studies performed on the association between fetuin A and MetS found inconsistent results [26]-[28].

Elevated concentrations in obese diabetic patients were reported compared with non-obese patients and obese normal glucose tolerance subjects. It was suggested that this supports the hypothesis that fetuin A may be a link connecting obesity and obesity-related diabetes [29]. A recent meta-analysis of fetuin A on MetS has reported that there might be a relationship between fetuin A and MetS. Patients with MetS exhibiting significantly higher fetuin A concentrations than those in the control group, may exhibit an increased risk of developing MetS [26].

The interaction between thyroid hormones and components of MetS is complex and not fully understood [30]. Metabolic syndrome development and weight gain have been positively associated with TSH in several studies [31], [32]. Thyrotropin was reported to be higher in MetS [33].

A study suggests that hypothyroid subjects are at about 2- to 5-fold increased risk for MetS independent of age, gender, smoking status and alcohol intake. This may contribute to the increased risk of atherosclerotic disease in hypothyroidism [34]. The most common abnormality is hyperthyrotropinemia. Obesity is associated with elevations in TSH levels [35], [36].

Increased cortisol may promote the development of MetS [16], [37]. A report did not support a strong relationship between systemic cortisol or stress and obesity or metabolic syndrome [38]. Cortisol might play a role in the development of MetS at both a central and a peripheral level [39]. In a study performed on both MetS- and MetS+ groups in severely obese patients, cortisol was introduced as a contributing factor to the development of MetS in severely obese patients. Significantly increased baseline serum cortisol levels were measured in MetS+ group [40].

In this study, elevated cortisol levels were observed in MetS+ group compared to those measured in the MetS- group in MO children. Cortisol may be a potential biomarker for childhood MetS and may help in the early diagnosis of this clinical condition in MO children.

Fetuin A appears to be associated with the progression of MetS. In this study, higher fetuin A concentrations were observed in MetS in comparison with the values detected in morbid obesity. In MO group, a significant correlation was found between cortisol and fetuin A, whereas in the group with MetS, cortisol was found to be correlated with TSH. An association between cortisol and fetuin A was not detected in MO MetS+ group. The components of MetS may interfere with this association in this group.

Thyroid stimulating hormone regulates thyroid hormone synthesis. It was also indicated that TSH acts on adipose tissue. Adipocyte inflammatory responses may occur in disorders associated with elevated TSH levels [41]. In the present study, this is confirmed by the participation of TSH in the complex interactions detected in MO children with MetS.

In conclusion, the correlation between serum TSH and cortisol levels suggests the derangement of the cortisol axis in children with MetS. The existence of this relationship may predict a pathological disorder, because this has not been detected in the previous stages of obesity.

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