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The Cooperation among Insulin, Cortisol and Thyroid Hormones in Morbid Obese Children and Metabolic Syndrome

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***Abstract*—**Obesity, a disease associated with a low-grade inflammation, is a risk factor for the development of metabolic syndrome (MetS). So far, MetS risk factors such as parameters related to glucose and lipid metabolisms as well as blood pressure were considered for the evaluation of this disease. There are still some ambiguities related to the characteristic features of MetS observed particularly in pediatric population. Hormonal imbalance is also important, and quite a lot information exists about the behaviour of some hormones in adults. However, the hormonal profiles in pediatric metabolism have not been cleared yet. The aim of this study is to investigate the profiles of cortisol, insulin, and thyroid hormones in children with MetS. The study population was composed of morbid obese (MO) children without (Group 1) and with (Group 2) MetS components. WHO BMI-for age and sex percentiles were used for the classification of obesity. The values above 99 percentile were defined as morbid obesity. Components of MetS (central obesity, glucose intolerance, high blood pressure, high triacylglycerol levels, low levels of high density lipoprotein cholesterol) were determined. Anthropometric measurements were performed. Ratios as well as obesity indices were calculated. Insulin, cortisol, thyroid stimulating hormone (TSH), free T_3 and free T_4 analyses were performed by electrochemiluminescence immunoassay. Data were evaluated by statistical package for social sciences program. $p<0.05$ was accepted as the degree for statistical significance. The mean ages±SD values of Group 1 and Group 2 were 9.9±3.1 years and 10.8±3.2 years, respectively. Body mass index (BMI) values were calculated as 27.4±5.9 kg/m^2 and 30.6±8.1 kg/m^2, successively. There were no statistically significant differences between the ages and BMI values of the groups. Insulin levels were statistically significantly increased in MetS in comparison with the levels measured in MO children. There was not any difference between MO children and those with MetS in terms of cortisol, T_3, T_4 and TSH. However, T_4 levels were positively correlated with cortisol and negatively correlated with insulin. None of these correlations were observed in MO children. Cortisol levels in both MO as well as MetS group were significantly correlated. Cortisol, insulin, and thyroid hormones are essential for life. Cortisol, called the control system for hormones, orchestrates the performance of other key hormones. It seems to establish a connection between hormone imbalance and inflammation. During an inflammatory state, more cortisol is produced to fight inflammation. High cortisol levels prevent the conversion of the inactive form of the thyroid hormone T_4 into active form T_3. Insulin is reduced due to low thyroid hormone. T_3, which is essential for blood sugar control-requires cortisol levels within the normal range. Positive association of T_4 with cortisol and negative association of it with insulin are the indicators of such a delicate balance among these hormones also in children with MetS.

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I. Introduction

OBESITY is a disease, which may lead to the development of many severe and chronic health problems such as diabetes, cancer, cardiovascular diseases, and MetS. So far, parameters related to glucose and lipid metabolisms as well as blood pressure as the risk factors of MetS were considered in studies performed on the individuals with this disease. Besides well-known cardiovascular risk factors including hypertension, dyslipidemia, impaired glucose tolerance, there is growing evidence suggesting that hormonal alterations in various endocrine diseases also affect cardiac performance. Insulin resistance, hypothyroid state, or hypercortisolism are clinically important hormonal imbalances and strongly associated with overweight, obesity, and MetS [1], [2].

There are still some problems concerning the evaluation of MetS in pediatric population, particularly in prepubertal age. The interpretation of the members of the endocrine system is also difficult, and still the understanding on the behaviour of some hormones is far from being complete even in adults. The hormonal profiles and the cooperation among some hormones in pediatric metabolism have not been cleared yet.

Insulin analysis was included in MetS diagnosis for serving as a predictor of the diagnosis [2], [3]. The findings of a very recent report confirmed the relation between being overweight and the thyroid hormones [4]. Basal cortisol levels were found to be elevated in patients with MetS [5].

Fig. 1 shows how complicated the network among the above mentioned topics is.

The aim of this study is to overview the effects of hormones, including insulin, cortisol and thyroid hormones, to investigate the profiles of them and the cooperation among all MO children and those with MetS.

II. Patients and Methods

A. Patients

A study was organized on MO children divided into two groups, those without and with MetS findings; Group 1 and Group 2, respectively. A total of 128 informed consent forms were taken from the participants and their parents. Ethical Committee approval was obtained.

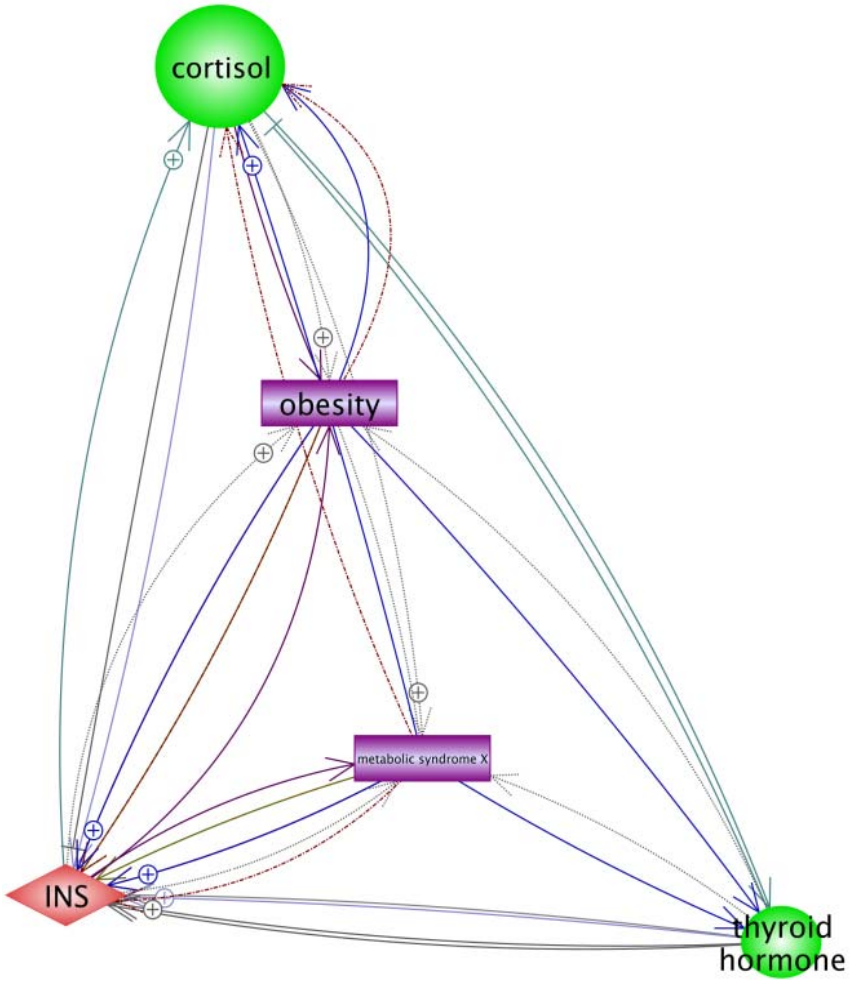

Fig. 1 Relations of the network composed of insulin, cortisol and thyroid hormones with obesity and MetS

B. Anthropometric Measurements

Weight, height as well as waist, hip, head, neck circumferences (Cs) were measured within the scope of anthropometric measurements.

C. Obesity and MetS Criteria

World Health Organization age and sex-adjusted BMI percentile tables were used for the classification of obesity. Children, whose percentiles were above 99th were defined as morbid obesity [6].

MetS criteria were defined [7]. Fasting blood glucose, triacylglycerol, high density lipoprotein cholesterol concentrations related to the components of MetS (central obesity, glucose intolerance, high blood pressure, high triacylglycerol levels, low levels of high density lipoprotein cholesterol) were determined.

D. Laboratory Methods

Electrochemiluminescence immunoassay technic was used to determine the concentrations of insulin, cortisol, TSH, free triiodothyronin (fT_3) and free thyroxine (T_4).

E. Ratio Calculations

Ratios such as BMI as well as obesity indices such as waist-to-hip, head-to-neck ratios were calculated.

F. Statistical Evaluations

Data were evaluated by SPSS program. Mean ±SD values were calculated. Correlation analyses were performed. The degree for statistical significance was accepted as $p<0.05$.

III. Results

One hundred and twenty-eight children were participated into the scope of the study. All the children were MO. The study population was divided into two groups. Group 1 was composed of 92 MO children without MetS parameters. Group 2 comprised 36 MO children with MetS. The mean age±SD of Group 1 was 9.9±3.1 years. The corresponding value for Group 2 was 10.8±3.2 years. BMI values (mean±SD) were calculated as 27.4±5.9 kg/m^2, and 30.6±8.1 kg/m^2 kg/m^2 for Group 1 and Group 2, respectively. The groups did not differ from one another in terms of their ages and BMI values.

Cortisol, fT_3, fT_4 and TSH concentrations did not differ

between the groups (p>0.05) (Table I).

TABLE I
INSULIN, CORTISOL, FREE TRIIODOTHYRONIN (fT_3), FREE THYROXIN (fT_4) AND TSH LEVELS IN MO CHILDREN AND METS

Parameters \ Groups	Group 1 (MO) (x±SD)	Group 2 (MetS) (x±SD)
Insulin (μIU/ml)	20.5 ± 19.2	24.3 ± 12.4
Cortisol (μg/dl)	9.8 ± 5.1	11.6 ± 6.2
fT3 (pg/ml)	4.3 ± 0.6	4.3 ± 0.6
fT4 (ng/ml)	1.3 ± 0.2	1.3 ± 0.2
TSH (mIU/ml)	3.2 ± 1.8	3.5 ± 1.5

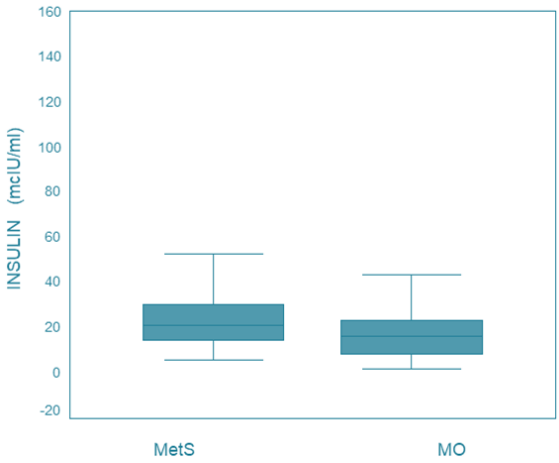

Fig. 2 Box plots for insulin levels in MetS and MO children

Statistically significantly elevated insulin levels were determined in children with MetS in comparison with the levels measured in MO children (p<0.05) (Fig. 2). However, fT_4 levels were negatively correlated with insulin (r= - 0.330; p≤0.05) and positively correlated with cortisol (r= 0.479; p≤0.01) (Fig. 3). These correlations did not exist in MO children.

Cortisol levels measured in MO group were significantly correlated with the levels determined in MetS group (r=0.383; p≤0.05).

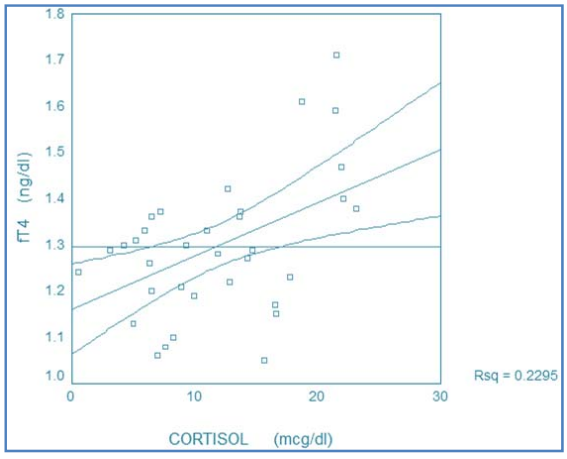

Fig. 3 Correlation between fT4 and cortisol in children with MetS

IV. DISCUSSION

Hypothalamic-pituitary-adrenal axis hyperactivity increases cortisol resulting in abdominal obesity, insulin resistance and MetS [8], [9].

Features of MetS include obesity, elevated glucose, insulin, triacylglycerol, blood pressure levels and reduced high density lipoprotein cholesterol levels [10], [11]. Aside from increased insulin levels, increased cortisol levels were also found to be associated with obesity and MetS [12]. Children and adolescents with obesity and MetS have high circulating cortisol levels [13], [14]. Within this context, inhibition of cortisol biosynthesis may promise hope for the treatment of MetS [15].

In our study cortisol levels were higher in MetS group, however, this elevation was not statistically significant. In a similar manner, fT3, fT4 and TSH levels also exhibit almost the same values.

In many recent studies, the profiles of thyroid hormones as well as TSH, TSH were found to be elevated in overweight and obese individuals. Positive associations between TSH levels and BMI were reported [16]-[21].

The optimum levels of cortisol, insulin, and thyroid hormones are essential for healthy life. Cortisol, as the main member of glucocorticoids, affects almost all systems of the body. It is in close association with the performances of the other hormones. Cortisol exhibits a contradictory secretion profile in children. This makes the interpretation of the behaviour of this hormone difficult. There may be a link between hormonal imbalance and inflammation. Cortisol is a regulator of inflammatory responses. Cortisol levels elevated during inflammation fight against inflammation. Cortisol decreases TSH and by this way lowers active thyroid hormone production. The conversion of inactive T_4 into active T_3 is inhibited. Insulin is lowered because of insufficient amount of active thyroid hormone. Active form of thyroid hormone, T_3, is one of the blood glucose controlling hormones, like cortisol. Low thyroid hormone concentrations are associated with high BMI. In children with MetS, a sensitive and critical balance among cortisol, insulin and thyroid hormones was introduced by positive correlation between T_4 and cortisol and negative one with insulin.

In this study, the cooperation among insulin, cortisol, a major stress hormone acting as a potent functional antagonist of insulin action [22], thyroxine, which is expected to modify insulin levels [23], was investigated in MO children and those with MetS. Significantly increased insulin levels in MetS compared to MO group suggest the dominance of this hormone. The characteristic features of the correlations between fT4 and cortisol as well as insulin showed that fT4 may be the centre of attraction in this discussion. On the other hand, correlation existed between cortisol levels of children with morbid obesity and MetS confirms the persistent link to dyslipidemia as well as increased insulin during abdominal adiposity.

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