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Associations between Surrogate Insulin Resistance Indices and the Risk of Metabolic Syndrome in Children

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Abstract**—**A well-defined insulin resistance (IR) is one of the requirements for the good understanding and evaluation of metabolic syndrome (MetS). However, underlying causes for the development of IR are not clear. Endothelial dysfunction also participates in the pathogenesis of this disease. IR indices are being determined in various obesity groups and also in diagnosing MetS. Components of MetS have been well established and used in adult studies. However, there are some ambiguities particularly in the field of pediatrics. The aims of this study were to compare the performance of fasting blood glucose (FBG), one of MetS components, with some other IR indices and check whether FBG may be replaced by some other parameter or ratio for a better evaluation of pediatric MetS. Five-hundred and forty-nine children were involved in the study. Five groups were constituted. Groups 109, 40, 100, 166, 110, 24 children were included in normal-body mass index (N-BMI), overweight (OW), obese (OB), morbid obese (MO), MetS with two components (MetS2) and MetS with three components (MetS3) groups, respectively. Age and sex-adjusted BMI percentiles tabulated by World Health Organization were used for the classification of obesity groups. MetS components were determined. Aside from one of the MetS components-FBG, eight measures of IR [homeostatic model assessment of IR (HOMA-IR), homeostatic model assessment of beta cell function (HOMA-%β), alanine transaminase-to-aspartate transaminase ratio (ALT/AST), alanine transaminase (ALT), insulin (INS), insulin-to-FBG ratio (INS/FBG), the product of fasting triglyceride and glucose (TyG) index, McAuley index] were evaluated. Statistical analyses were performed. A p value less than 0.05 was accepted as the statistically significance degree. Mean values for BMI of the groups were 15.7 kg/m^2, 21.0 kg/m^2, 24.7 kg/m^2, 27.1 kg/m^2, 28.7 kg/m^2, 30.4 kg/m^2 for N-BMI, OW, OB, MO, MetS2, MetS3, respectively. Differences between the groups were significant ($p < 0.001$). The only exception was MetS2-MetS3 couple, in spite of an increase detected in MetS3 group. Waist-to-hip circumference ratios significantly differed only for N-BMI vs, OB, MO, MetS2; OW *vs* MO; OB *vs* MO, MetS2 couples. ALT and ALT/AST did not differ significantly among MO-MetS2-MetS3. HOMA-%β differed only between MO and MetS2. INS/FBG, McAuley index and TyG were not significant between MetS2 and MetS3. HOMA-IR and FBG were not significant between MO and MetS2. INS was the only parameter, which showed statistically significant differences between MO-MetS2, MO-MetS3, and MetS2-MetS3. In conclusion, these findings have suggested that FBG presently considered as one of the five MetS components, may be replaced by INS during the evaluation of pediatric morbid obesity and MetS.

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I. Introduction

WHILE there has been a remarkable rise in obesity, any consensus has not been reached on the diagnostic criteria for IR in the pediatric population. There are also some controversies related to the evaluation of MetS in children. Despite a considerable amount of investigations have been performed in children and adolescents with IR, many questions have not been cleared yet [1]-[7].

The hyperinsulinemic euglycemic clamp technique is the gold measurement of IR. However, the clinical applicability of this technique is limited. Due to the complex nature of the glucose clamp method, some problems exist related to its clinical usefulness [6]. There are a number of clinically useful surrogate measures of IR including HOMA-IR, HOMA-%β, INS, INS/FBG, the product of fasting triglyceride and glucose (TyG) index, McAuley index, in addition to recently introduced ALT, ALT/AST. As a result, multiple surrogate markers for IR have been developed and are being tested [8]-[14].

The INS is commonly used as surrogate marker of INS sensitivity by characterizing INS levels during a fasting state. However, in some reports, it has not been considered an adequate method for the evaluation of INS sensitivity. Also, there is a need for the universal INS assay standardization. Alterations, which occur in β-cell function over time, are considered as the main disadvantages of HOMA-IR [7].

Liver enzyme levels were positively correlated with MetS risk in adults. Elevated ALT was found to be positively associated with MetS prevalence in the elderly. ALT/AST ratio was introduced as the best reliable surrogate marker for IR in Japanese adults [15]-[17].

This study was conducted to evaluate and interpret FBG, one of the components of MetS evaluation criteria, compare the effectiveness of this MetS component with some other surrogate measures, and suggest the possibility of the replacements of this parameter with some other biochemical parameter in children with MetS.

II. Patients and Methods

A. Study Population and Groups

Five-hundred and forty-nine children participated in the study. One hundred and nine children with N-BMI, 40 OW,

100 OB, 166 MO, and 134 children with MetS comprised the study groups. Informed consent forms were obtained.

B. Obesity Classification

BMI percentiles prepared according to ages as well as sexes of participants, and tabulated by World Health Organization were used for the classification of groups [18].

C. MetS Criteria

MetS components based upon the degree of central obesity, concentrations of FBG, triglycerides, high density lipoprotein cholesterol, and blood pressure values were determined [19]. MetS group were divided into two, the first with two components (MetS2) and the other group with three components (MetS3).

D. Biochemical Analyses

Aside from FBG; one of the MetS components, eight measures of IR were considered (Table I). HOMA-IR, HOMA-%β, ALT/AST, ALT, INS, INS/FBG, TyG index, McAuley index were either determined in the laboratory or calculated from the previously measured concentrations.

E. Statistical Evaluation

Statistical package for social sciences for Windows was used for statistical analyses. The p values below 0.05 were accepted as the degree for statistical significance.

TABLE I
MAIN SURROGATE INDICES OF IR IN CHILDREN AND ADOLESCENTS

Method	Parameters	Formula/Equation
HOMA-IR	FBG, INS	FBG*INS/22.5
HOMA-%β	FBG, INS	(20*INS)/(FBG-3.5)
INS	INS	INS
INS/FBG	INS, FBG	INS/FBG
McAuley index	INS, TRG	2.63-0.28 ln(INS) - 0.31 ln (TRG)
ALT	ALT	ALT
ALT/AST	ALT, AST	ALT/AST
TyG	TRG, FBG	TRG*FBG
FBG	FBG	FBG

TRG = triglycerides.

III. RESULTS

Mean ± SD(SEM) BMI values of the groups were 15.7 ± 1.1 (0.1) kg/m^2 for N-BMI, 21.0 ± 2.7 (0.4) kg/m^2 for OW, 24.7 ± 2.7 (0.3) kg/m^2 for OB, 27.1 ± 3.8 (0.3) kg/m^2 for MO, 28.7 ± 5.3 (0.5) kg/m^2 for MetS2, and 30.4 ± 5.4 (1.1) kg/m^2 for MetS3. Groups were significantly differed from one another ($p < 0.001$) except MetS2-MetS3 couple, although much more elevated values were obtained in MetS3 than MetS2 group.

Waist-to-hip circumference ratios were calculated as 0.86 ± 0.06 (0.01), 0.89 ± 0.07 (0.01), 0.89 ± 0.06 (0.01), 0.93 ± 0.07 (0.01), 0.93 ± 0.07 (0.01), 0.91 ± 0.06 (0.01), successively. Values were significantly different between N-BMI and OB, N-BMI and MO, N-BMI and MetS2; OW and MO; OB and MO, OB and MetS2.

A strong correlation was detected between BMI and waist circumference values when the study population was considered (Fig. 1).

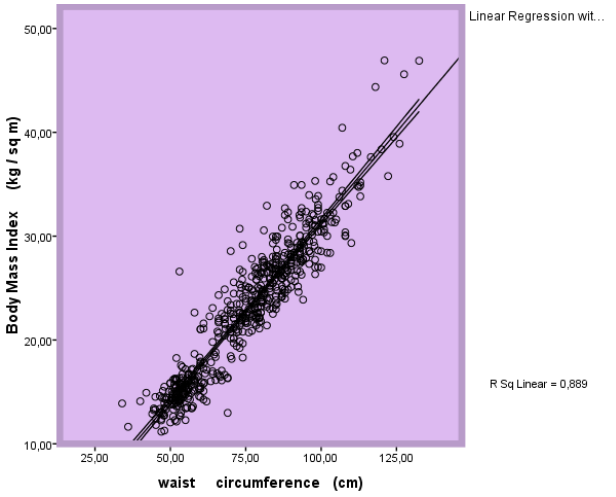

Fig. 1 Association between BMI and waist circumference values of the study population (Linear Regression wit… = Linear Regression with 95.0% Mean Prediction Interval)

Differences between MO and MetS2, MO and MetS3, MetS2 and MetS3 were not statistically significant for ALT activities and ALT/AST values. HOMA-%β was different between MO and MetS2. INS/FBG, McAuley index and TyG did not exhibit any difference between MetS2 and MetS3. HOMA-IR and FBG did not differ significantly between MO and MetS2 groups. INS was unique among all parameters, because it showed statistically significant differences between MO-MetS2, MO-MetS3, and MetS2-MetS3. INS levels in MO, MetS2 and MetS3 were 12.6 ± 9.5(0.8) mU/L, 17.8 ± 13.7(1.3) mU/L and 30.5 ± 34.2 (7.1) mU/L, respectively (Fig. 2).

Linear regression lines concerning correlations between HOMA-IR and FBG ($r= 0.383$; $p>0.05$) as well as INS ($r = 0,982$; $p < 0.001$) were shown in Figs. 3 (a) and (b), respectively.

IV. DISCUSSION

The management of IR is difficult and requires the collaboration of the members in a multidisciplinary team. The clinical presentation of this problem varies depending on its etiology and severity. The responsible mechanisms for its different signs and symptoms are still under investigation. Beta-cell dysfunction, which occurs in OB children and adolescents may be one of the explanations related to the pathogenesis of the correlation between IR and MetS [6], [7].

The gold standard technique is the hyperinsulinemic euglycemic clamp during the evaluation of IR. However, it is expensive and difficult to perform. Therefore, several surrogate markers have been proposed [7], [9]-[11], [15].

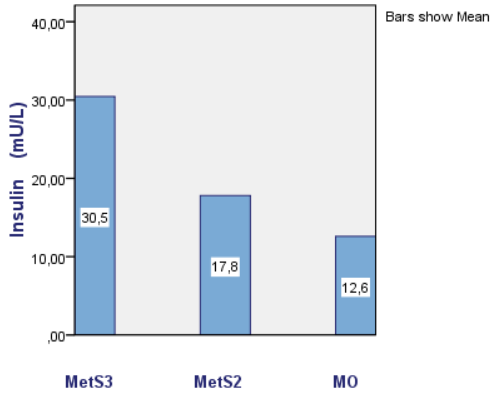

Fig. 2 INS concentrations in MO groups

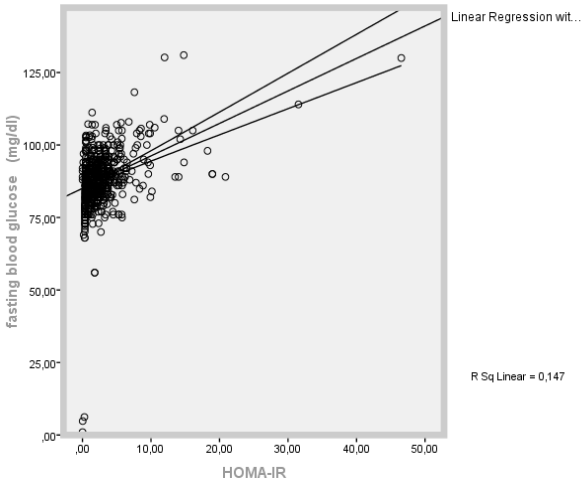

Fig. 3 (a) Association between FBG and HOMA-IR values of the study population (Linear Regression wit… = Linear Regression with 95.0% Mean Prediction Interval)

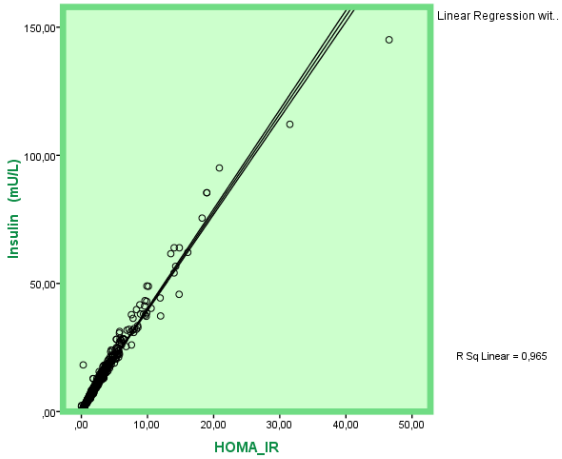

Fig. 3 (b) Association between INS and HOMA-IR values of the study population (Linear Regression wit… = Linear Regression with 95.0% Mean Prediction Interval)

HOMA-IR displays a correlation with the hyperinsulinemic-euglycemic clamp; however, it is not recommended as a valid test for the evaluation of IR. Therefore, in the clinical practice the diagnosis of IR in OB patients is based on clinical features such as abdominal obesity, hyperglycemia, dyslipidemia, and hypertension [7], [8]. In our study, any significant difference was not detected between MO and MetS2 groups when HOMA-IR or FBG values were considered.

In adults, McAuley and TyG indices had higher sensitivity and specificity for MetS than HOMA-IR. Both indices include triglycerides, the main component of MetS. The McAuley index was reported as one presenting the strongest correlation with IR and showed the best accuracy in the diagnosis of MetS as a surrogate marker of IR [12], [20]. We have also observed that both indices behaved in a similar manner. Both did not exhibit any difference between MetS2 and MetS3. However, significant differences were observed between MO and MetS groups when these indices were evaluated.

Increased ALT within normal range was associated with an increased MetS risk. Two or more MetS components were associated with elevated ALT. By elevation of ALT, the prevalence of MetS increased in both OB and normal weight adolescents as well. It was suggested that serum ALT levels along with BMI might be accepted as a surrogate marker for MetS [10], [21].

ALT/AST ratio has recently been introduced as one of the best markers of IR in Chinese as well as Korean adults. Whether ALT/AST ratio may be suggested as an additional MetS component needs further investiga

tion [11], [22]. In our study, differences among MO groups (MO- MetS2- MetS3) were not significant for ALT activities and ALT/AST values.

MO children may be with or without MetS. Those exhibiting two or three out of five MetS components are considered as children with MetS. Aside from obesity and hypertension, dyslipidemia characterized by elevated triglycerides and reduced high density lipoprotein-cholesterol concentrations is also considered. Our findings have pointed out that INS was in a better coordination with HOMA-IR, a well-accepted and commonly used marker for IR, than FBG. And also, INS was the only parameter discriminating between MO children and those with MetS2 as well as MetS3, and between MetS2 and MetS3.

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