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Interpretation of Two Indices for the Prediction of Cardiovascular Risk in Pediatric Obesity

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***Abstract*—**Obesity and weight gain are associated with increased risk of developing cardiovascular diseases and the progression of liver fibrosis. Aspartate transaminase–to-platelet count ratio index (APRI) and fibrosis-4 (FIB-4) were primarily considered as the formulas capable of differentiating hepatitis from cirrhosis. However, to the best of our knowledge, their status in children is not clear. The aim of this study is to determine APRI and FIB-4 status in obese (OB) children and compare them with values found in children with normal body mass index (N-BMI). A total of 68 children examined in the outpatient clinics of the Pediatrics Department in Tekirdag Namik Kemal University Medical Faculty were included in the study. Two groups were constituted. In the first group, 35 children with N-BMI, whose age- and sex-dependent BMI indices vary between 15 and 85 percentiles, were evaluated. The second group comprised 33 OB children whose BMI percentile values were between 95 and 99. Anthropometric measurements and routine biochemical tests were performed. Using these parameters, values for the related indices, BMI, APRI, and FIB-4, were calculated. Appropriate statistical tests were used for the evaluation of the study data. The statistical significance degree was accepted as $p < 0.05$. In the OB group, values found for APRI and FIB-4 were higher than those calculated for the N-BMI group. However, there was no statistically significant difference between the N-BMI and OB groups in terms of APRI and FIB-4. A similar pattern was detected for triglyceride (TRG) values. The correlation coefficient and degree of significance between APRI and FIB-4 were $r = 0.336$ and $p = 0.065$ in the N-BMI group. On the other hand, they were $r = 0.707$ and $p = 0.001$ in the OB group. Associations of these two indices with TRG have shown that this parameter was strongly correlated ($p < 0.001$) both with APRI and FIB-4 in the OB group, whereas no correlation was calculated in children with N-BMI. TRG are associated with an increased risk of fatty liver, which can progress to severe clinical problems such as steatohepatitis, which can lead to liver fibrosis. TRG are also independent risk factors for cardiovascular disease. In conclusion, the lack of correlation between TRG and APRI as well as FIB-4 in children with N-BMI, along with the detection of strong correlations of TRG with these indices in OB children, was the indicator of the possible onset of the tendency towards the development of fatty liver in OB children. This finding also pointed out the potential risk for cardiovascular pathologies in OB children. The nature of the difference between APRI vs. FIB-4 correlations in N-BMI and OB groups (no correlation vs. high correlation), respectively, may be the indicator of the importance of involving age and alanine transaminase parameters in addition to AST and PLT in the formula designed for FIB-4.

***Keywords*—**APRI, FIB-4, obesity, triglycerides.

I. Introduction

BIOCHEMICAL parameters are subject to variation during various stages of obesity and the related chronic diseases. Aside from lipid metabolism, parameters related to glucose homeostasis are also affected. Hematologic parameters also participate in this process [1]-[7].

Insulin resistance (IR) is an important problem, which is closely associated with the severity of obesity. There are many ratios and indices, which are capable of giving considerable amount of valuable information about the matter. Homeostatic model assessment of insulin resistance (HOMA-IR), which is calculated from fasting blood glucose and insulin, is the most commonly used index. This index is apparently concerned with the status of glucose homeostasis. There are many others derived from carbohydrate metabolism parameters [8], [9].

However, there are also some other ratios, which are irrelevant. Transaminases as well as some blood count parameters are among them. In some reports, indices calculated by using aspartate transaminase, alanine transaminase and platelet count are in clinical use [3]-[6]. In these reports, the associations of these parameters with IR were introduced. The potential involvement of platelet indices in IR observed in MO children were evaluated. Increased PLT count, as a hemostasis marker, was observed both in MO and MetS groups. HOMA-IR showed significant correlation with PLT in MO group. The clinical utility of surrogate IR indices among OB children were compared. Transaminases were also considered. Alanine transaminase to aspartate transaminase ratio as well as alanine transaminase were examined [3]-[6].

The association of liver transaminases, AST and ALT, with cardiovascular diseases (CVDs) were reported [10]. Within this context, ratios derived from these parameters were considered for the evaluation of CVDs and liver fibrosis. Aspartate transaminase-to-platelet count ratio index (AST-to-PLT, APRI) and FIB-4 are introduced for the purpose and many studies [11]-[13] were performed to investigate their potential use for these health problems. However, the number of studies determining their performance for diagnostic use was limited. Particularly, those performed on the pediatric population was rare [11]-[14].

In this study, the aim was to determine the APRI and FIB-4 values in OB children and compare them with the values calculated for children with N-BMI and investigate possible associations of these two indices with the potential for

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cardiovascular (CV) and liver fibrosis risks.

II. Patients and Methods

A. Patients

68 children were recruited for the study. Two groups, Group 1 and Group 2, were constituted. The first group was composed of children with N-BMI. Their age- and gender-adjusted BMI percentiles were between 15 and 85 according to the tables prepared by World Health Organization (WHO) [15]. These figures varied between 85th and 95th percentiles for the children included in OB group, which is Group 2. The groups were composed of 35 and 33 children in Group 1 and Group 2, respectively. Parents were asked to fill out informed consent forms and to sign them. The Non-interventional Ethical Committee of Tekirdag Namik Kemal University Medical Faculty has allowed the scientific team to proceed with the proposed study.

B. Anthropometric Measurements

Body weight in kilograms and height in meters were measured for the calculation of BMI values. The circumferences of waist, hip, head and neck in centimeter were measured. The values obtained for the study population were recorded.

C. Laboratory Analysis

The complete blood cell count analysis including platelet count and biochemical tests including the levels of lipid profile (total cholesterol, TRG, high density lipoprotein cholesterol and low-density lipoprotein cholesterol) as well as the activities of transaminases (aspartate transaminase (AST) and alanine transaminase (ALT) were determined using autoanalyzers.

D. Calculation of Ratios

Two ratios, APRI and FIB-4, were calculated. In Table I, formulas of these two ratios were shown. The first ratio, APRI was calculated from PLT and AST. The second ratio, FIB-4 was calculated from age, PLT, AST and ALT.

E. Statistical Analysis

Descriptive tests using statistical package SPSS were performed. Mean ± standard deviation values were calculated. T-test was applied to data compiled in two different groups, Group 1 and Group 2; p values smaller than 0.05 were statistically significant. Bivariate correlations were calculated. Plots for statistically significant correlations were drawn.

III. Results

In N-BMI group, APRI and FIB-4 values were calculated as 0.0810 ± 0.0296 and 0.0999 ± 0.0661, respectively. The corresponding values for these two ratios in OB group were 2.295 ± 0.829 and 2.754 ± 1.281.

Correlations between APRI and FIB-4 were compared to check the possible differences between two groups if there is any. There was not any statistically significant correlation in Group 1. However, a strong correlation ($r = 0.707$; $p < 0.001$) was found in Group 2 (Fig. 1).

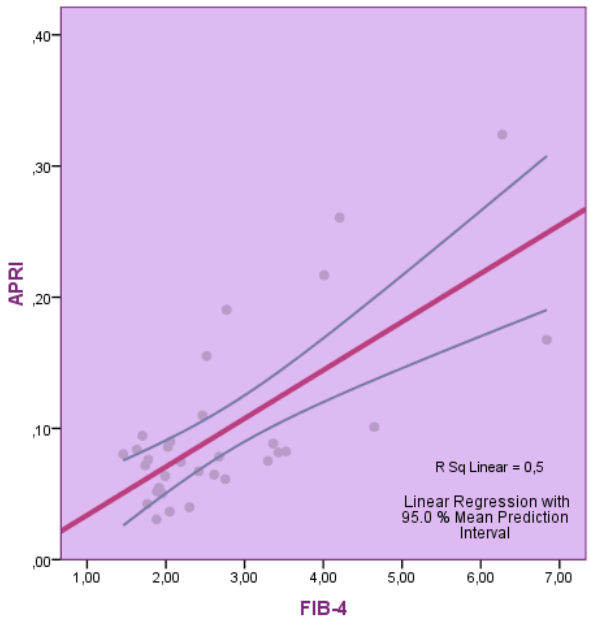

Fig. 1 Bivariate correlation between APRI and FIB-4 ratios in OB group

The correlations between BMI and APRI as well as FIB-4 were determined. In Group 1, BMI was correlated with FIB-4 ($r = 0.550$; $p < 0.01$). In the other group, no correlation was found between BMI and FIB-4.

TRG appears to be the most prominent lipid profile associated with these ratios. In the OB group, this lipid parameter was found to be strongly correlated with both APRI ($r = 0.687$; $p < 0.001$) and FIB-4 ($r = 0.773$; $p < 0.001$). These correlations were demonstrated in Figs. 2 and 3, respectively.

TABLE I
Formulas of APRI and Fib-4

Parameter	
APRI	(AST / PLT count) * 100
FIB-4	(age * AST) / (PLT count * √ ALT)

PLT = platelet

No correlation with WC, (WC+HC)/2, fat mass index was detected in groups.

IV. Discussion

This study was performed to check the clinical utility of two indices derived from routine biochemical parameters for the tendency towards liver fibrosis and CV problems in the future among children.

The interrelationship between fibrosis and CV risk has been a matter of concern. Actually, association of both alcoholic and non-alcoholic steatohepatitis with CV risk and liver fibrosis were noted [16]. It was reported that pediatric patients with high BMI values and severe liver steatosis are at risk for severe liver fibrosis [17]. Atherosclerotic CVD is the principal cause of death in patients with non-alcoholic fatty liver disease (NAFLD). The incidence of NAFLD rises with the increasing rates of obesity both in adults and children. NAFLD

identification is important for CV disease prevention [18].

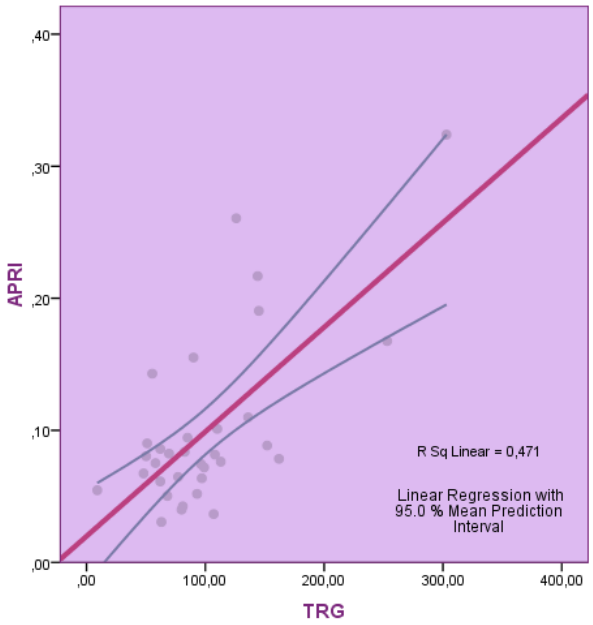

Fig. 2 Bivariate correlation between APRI and TRG in OB group

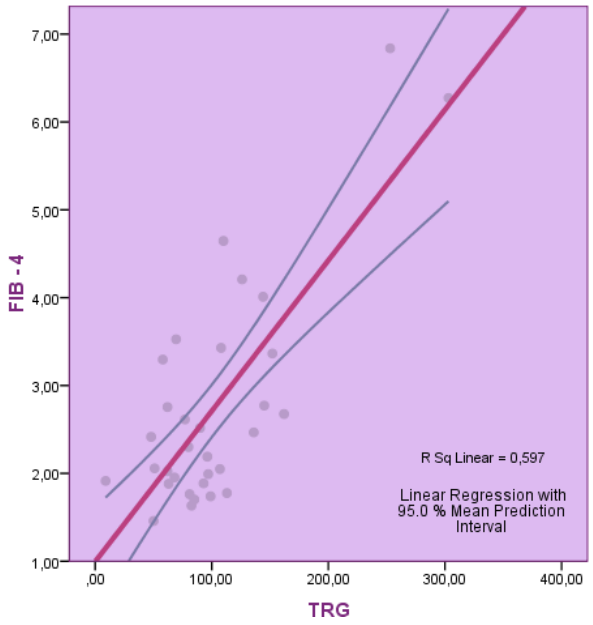

Fig. 3 Bivariate correlation between FIB-4 and TRG in OB group

The APRI and FIB-4 were introduced as the indices with the best performance to predict advanced fibrosis [19]. In OB adults, non-invasive tests, APRI and FIB-4, were capable of excluding 86% and 96% of clinically significant and advanced fibrosis, respectively [20].

The APRI index was reported as the best predictor of advanced liver diseases in severe obesity [21]. This index was capable of the recognition of fibrosis in OB individuals [22].

APRI score was the most specific biochemical diagnostic tool for steatosis in severely OB patients [23]. In a study, APRI was proved to be an accurate index in children with NAFLD in the estimation of the fibrosis risk [14]. APRI may be a non-invasive, simple and readily available method for medical practice to predict hepatic fibrosis of childhood NAFLD [24]. In a very recent study, APRI was introduced as a simple biochemical marker of liver injury rather than NAFLD/non-alcoholic steatohepatitis in severely OB children and adolescents. BMI, TRGs, HOMA-IR and APRI were introduced as positive predictors of NAFLD [25]. Another study reported that APRI significantly correlated with CV risk and played role as a predictor score for CV risk in metabolic subjects [13]. This index, being one of the non-invasive liver fibrosis serum markers, can predict CV risk in adults. Both APRI score and FIB-4 score were significantly higher in MetS patients than non-metabolic patients [13]. A significant relation existed between APRI and carotid intima-media thickness. Therefore, an increased APRI score in OB adolescents with NAFLD may predict a CV risk profile [26].

There is a controversy on the performance of FIB-4. In a report, it was stated that FIB-4 exhibited no utility for the evaluation of severe steatosis in severely OB patients [23]. A population study introduced FIB-4 as a marker exhibiting low accuracy for screening chronic liver diseases including liver fibrosis [27]. On the other hand, FIB-4 was reported as one of the best-performing fibrosis biomarkers in OB patients [28]. In a study performed on adults, FIB-4 was suggested as an accurate predictor of advanced fibrosis in NAFLD throughout all BMI stages [29]. In a similar manner, this index was introduced as the most accurate non-invasive score in predicting advanced cirrhosis among OB adults [30].

Obesity is associated with CV risk and the progression of liver fibrosis; therefore, non-invasive tests gain importance [13], [17], [31]-[33].

In our study, the APRI and FIB-4 profiles were determined in both OB and N-BMI children. This study was important because it was performed on pediatric age group. As the second point, the APRI and FIB-4 profiles were examined for their possible associations with CV risk in OB children without MetS findings and these results were compared with those found in N-BMI children for diagnostic use.

In conclusion, it was interesting to note that associations of APRI with CV risk reported in adult MetS patients were observed in OB children when compared to N-BMI children. Also, in our study, TRG levels, of which their deposition in the liver refers to hepatic steatosis, were highly correlated with both APRI and FIB-4 in OB children.

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