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Homeostatic model assessment (HOMA) index cut-off values to identify the metabolic syndrome in children

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The aim of the study was to establish the best cut-off value for the homeostatic model assessment (HOMA) index in identifying children and adolescents with the metabolic syndrome. The study included 72 non-obese and 68 obese children aged 7 to 16 years. Obesity is defined using the criteria proposed by Cole *et al.*, being included as metabolic syndrome variables waist circumference, systolic blood pressure, diastolic blood pressure and seric values of glucose, uric acid, fasting insulin, leptin, triglycerides and HDL-cholesterol. Children were considered as having the metabolic syndrome when four or more characteristics showed abnormal values. The HOMA index was calculated as the product of the fasting plasma insulin level (μU/mL) and the fasting plasma glucose level (mmol/L), divided by 22.5. HOMA index cut-offs from the 5^{th} to the 95^{th} percentile were used. A receiver operating characteristic (ROC) curve was generated using the different HOMA cut-offs for the screening of the metabolic syndrome. The areas under the ROC curve, 95% confidence intervals, and the point to the ROC curve closest to 1, were calculated. The area under the ROC curve was 0.863 (95% C.I.: 0.797, 0.930). The point closest to 1 corresponds to the 60^{th} percentile of the HOMA index distribution in our sample. HOMA index value at the 60^{th} percentile was 2.28. Cut-off values corresponding to a range of HOMA index from the 50 to the 75 percentile, showed similar distances to 1. HOMA index values for percentiles 50 to 75 ranged from 2.07 to 2.83. In conclusion, HOMA index could be a useful tool to detect children and adolescents with the metabolic syndrome. HOMA cut-off values need to be defined in the paediatric population; however, values near to 3 seem to be adequate.

Key words: Insulin resistance, Type 2 diabetes, Nutrition, Children, Obesity, Metabolic syndrome.

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Obesity, especially central body fatness, is associated with coronary heart disease morbidity and mortality (25, 26) and coronary disease risk factors, including dyslipidaemia, hyperinsulinemia/insulin resistance and hypertension (12, 24). The metabolic syndrome is characterized by clustering of metabolic abnormalities that leads to increased cardiovascular disease and mortality (31). The five most commonly noted features of the metabolic syndrome are obesity, insulin resistance-hyperinsulinemia, dyslipidaemia (high triglycerides and low HDL-cholesterol serum concentrations), impaired glucose tolerance and/or type 2 diabetes, and hypertension (10). Obesity prevalence has strongly increased in the last decades (23). This has also been observed in children and adolescents (14, 20). Overweight adolescents appear to have an increased risk of obesity-related morbidities later in life, regardless of their adult weight status (22). The persistence of obesity from childhood into adulthood also may favour an early onset of diabetes, as suggested by the recent trend of the early onset of type 2 diabetes in individuals who suffered from obesity since childhood. In children, it has been observed that cardiovascular risk factors tend to cluster (4, 6), and that in obese children (defined as a body weight for height greater than 20%, and body fat content higher than 25% in males and 30% in females); 8.9% of the study children had the metabolic syndrome (four risk factors) (2).

It has been observed (15) that children with a waist circumference greater than the 90^{th} percentile are more likely to have multiple risk factors than children with a waist circumference of less than or equal to the 90^{th} percentile. Other authors (28) also observed that waist circumference is a better indicator of cardiovascular disease risk factors than body mass index (BMI). Since insulin resistance appears central to the development of the metabolic syndrome (8), accurate quantification of insulin *in vivo* action, secretion, and disposal is necessary. For epidemiologic and clinical studies, several indices estimating insulin sensitivity, secretion and disposal, and based on fasting blood samples, have been developed mainly in adults. The homeostatic model assessment (HOMA) index is among the best validated and most widely used (16). The aim of this study was to establish the best cut-off value of the homeostatic model assessment (HOMA) index to identify children and adolescents with metabolic syndrome.

Patients and methods

The study included 140 children: 72 non-obese children (41 M, 33F, mean age 11.02 ± 2.11 y) selected from a school that is representative of the health area covered by the University Hospital of Zaragoza; and 68 patients with exogenous obesity (32 M and 36 F, mean age 10.99 ± 2.18 y), from the Department of Paediatrics, University Hospital of Zaragoza. Obesity was defined using the criteria proposed by COLE *et al.* (1). In the non-obese group we have only included those children with a BMI lower than the value equivalent to 25 kg/m^2 in adults. Obese children identified at school were not included in the obese group.

The main characteristics of these children are described in Table I. For statistical analysis, all the children were considered as a whole group. With the exception of obesity, the children have not apparent disease and were no taking any kind of medication. None of obese children had a history of endocrine, nutritional, growth,

Table I. *Main characteristics of the 140 studied children and cut-off values (75th percentile) for the definition of the metabolic syndrome. HDL-C: high density lipoprotein cholesterol. *25th percentile.*

	Mean	SD	75th percentile
Age (years)	11.01	2.13	
Waist circumference (cm)	76.18	12.95	
Systolic blood pressure (mm Hg)	106.31	12.50	115.0
Diastolic blood pressure (mm Hg)	60.78	9.36	70.0
Fasting insulin (pmol/L)	71.74	47.78	81.95
Glucose (mmol/L)	5.14	0.33	5.3
Triglycerides (mmol/L)	0.77	0.30	0.9
HDL-C (mmol/L)	1.46	0.33	1.2*
Uric acid (μmol/L)	283.7	61.9	315.2
Leptin (ng/mL)	11.79	10.51	16.0

or renal problems. Patients with other causes of secondary obesity were excluded. Parents, or the children's guardians, were informed by letter about the nature and purpose of the study. After receiving their written consent, the children were considered for inclusion in the study. The study was approved by the Ethics Committee of the University Hospital, Zaragoza, Spain.

Anthropometric measurements were taken by the same person. Height and weight were obtained for all individuals. BMI was calculated as weight in kilograms by the height in square metres. Waist circumference was measured with an unelastic tape, the subject being in a standing position; the tape was applied horizontally midway between the lowest rib margin and the iliac crest (18, 19).

Blood pressure was measured three times by the same examiner, using a mercury sphygmomanometer. The first, fourth and fifth Korotkoff phases were recorded each time. Finally, we considered the mean of the three measurements for each child.

Laboratory methods

After overnight fasting, blood was obtained by vein puncture between 08.00 and 09.30 on the same day that we obtained the anthropometric measurements. All the assays were performed at the Department of Biochemistry, University Hospital of Zaragoza. Glucose, uric acid, triglycerides and high-density lipoprotein-cholesterol (HDL-C) serum concentration were determined by an enzymatic colorimetric assay on a Roche/Hitachi MODULAR P analyser. Insulin was determined by immunometric assay with an Immulite analyser. Fasting serum samples were also freshly frozen at –70 °C until assayed for leptin concentration. The circulating serum leptin concentrations were determined with a commercially available human leptin RIA kit (Mediagnost, Tübingen, Germany). The HOMA index was calculated as the product of the fasting plasma insulin level (μU/ml) and the fasting plasma glucose level (mmol/l), divided by 22.5.

Statistical analysis

All statistical analyses were performed with the SPSS for Windows (Language System Corp, Chicago). As metabolic syndrome variables we included waist circumference, systolic blood pressure, diastolic blood pressure, glucose, uric acid, fasting insulin, leptin, triglycerides and HDL-cholesterol. Gender, age and pubertal status did not show a significant effect on the metabolic syndrome variables (regression analysis), which is why we did not adjust for them in the analysis. We considered it an abnormal value when systolic blood pressure, diastolic blood pressure, glucose, uric acid, fasting insulin, leptin or triglycerides were higher than the 75th percentile of the distribution in our own sample, in order to have a reasonable prevalence of elevated metabolic syndrome values to perform the ROC analysis. We also considered an abnormal HDL-C value when its serum concentration was lower than the 25th percentile. Children were considered as having the metabolic syndrome when four or more characteristics showed abnormal values.

HOMA index cut-offs from the 5th to the 95th percentile were used for estimating the sensitivity (the true-positive rate) and specificity (the true-negative rate) of each cut-off. The 95th confidence intervals for sensitivity and specificity were calculated for an exact binomial distribution. The ROC curve is a plot of true-positive rates against false-positive rates, obtained over a range of cut-off points from the screening measure. A perfect test has a true positive rate of 1 and a false-positive rate of 0, but this is almost never attained in practice. The closest point to the upper left corner of the ROC curve is the one that is often selected as the best combination of true-positive rate and false-positive rate, because this is the closest point to the perfect test.

The areas under each ROC curve (AUC) and 95% confidence intervals were calculated using a non parametric approach. Values for each AUC can be between 0 and 1. A value of 0 indicates that the screening measure does not perform well, whereas a value of 1 implies a perfect performance. The AUC has been described as the probability that a test will correctly identify a pair of patients with and without a disease who were randomly selected from the population. An AUC of 0.5 means that the diagnostic test is not better than a random assignement. Obviously, values >0.5 are more desirable.

Results

The sensitivities and specificities (with 95% CIs) at each screening cut-off point for HOMA index are listed in Table II. The ROC curve prepared from the data showed in Table II is presented in Fig.1. The area under the ROC curve was 0.863 (95% C.I: 0.797, 0.930). The point closest to 1 corresponds to the 60th percentile of the HOMA index distribution in our sample (Table III). HOMA index value at the 60th percentile was 2.28 (illustrating a sensitivity of 81% and a specificity of 76%). Cut-off values corresponding to a range of HOMA index from the 50 to 75 percentile, showed similar distances to 1. HOMA index values for percentiles 50 to 75 ranged from 2.07 to 2.83 (Table III).

Discussion

In order to establish which is the best marker of metabolic syndrome in children, we studied a clinical sample of non-syndromal obese children pooled with a

Table II. *Sensitivity and specificity for the metabolic syndrome at various HOMA cut-off points. 95% confidence intervals in parentheses.*

Percentile (cut-off)	Sensitivity	Specificity
5	1.00 (0.90-1.00)	0.06 (0.02-0.13)
10	1.00 (0.90-1.00)	0.13 (0.07-0.22)
15	1.00 (0.90-1.00)	0.20 (0.13-0.30)
20	0.97 (0.86-1.00)	0.27 (0.18-0.36)
25	0.97 (0.86-1.00)	0.34 (0.24-0.44)
30	0.97 (0.86-1.00)	0.40 (0.30-0.50)
35	0.97 (0.86-1.00)	0.47 (0.37-0.57)
40	0.95 (0.82-0.99)	0.53 (0.43-0.63)
45	0.92 (0.78-0.98)	0.59 (0.49-0.69)
50	0.87 (0.71-0.95)	0.64 (0.54-0.74)
55	0.84 (0.68-0.94)	0.69 (0.59-0.78)
60	0.81 (0.65-0.92)	0.76 (0.66-0.84)
65	0.73 (0.56-0.86)	0.80 (0.70-0.87)
70	0.68 (0.50-0.82)	0.85 (0.76-0.91)
75	0.65 (0.48-0.80)	0.91 (0.83-0.96)
80	0.51 (0.34-0.68)	0.92 (0.85-0.96)
85	0.41 (0.25-0.58)	0.95 (0.89-0.98)
90	0.32 (0.18-0.50)	0.99 (0.94-1.00)
95	0.14 (0.05-0.29)	0.99 (0.94-1.00)

Table III. *Values of the HOMA index and distance to 1 (the upper left corner of the ROC curve) at each HOMA percentile.*

Percentile (cut-off)	HOMA	Distance to 1
5	0.756	0.94
10	0.972	0.87
15	1.173	0.80
20	1.310	0.74
25	1.507	0.66
30	1.612	0.60
35	1.747	0.53
40	1.855	0.47
45	1.951	0.42
50	2.069	0.38
55	2.182	0.35
60	2.275	0.31
65	2.396	0.34
70	2.557	0.36
75	2.827	0.36
80	3.141	0.49
85	3.605	0.60
90	4.105	0.68
95	4.849	0.87

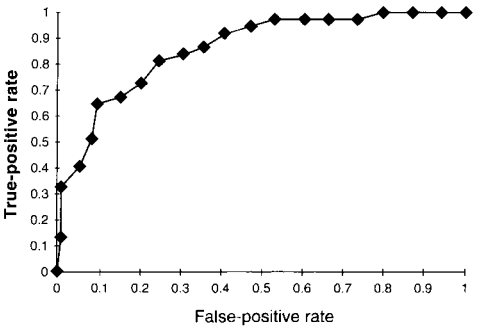

Fig. 1. *Receiver operating characteristic (ROC) curve for the screening of the metabolic syndrome in children and adolescents.*
Diagnostic test: Homeostatic Model Assessment (HOMA) index.

similar group of non-obese healthy children. We analysed the data of the two groups together in order to have a population with a range of variables wide enough to assess screening performances in order to detect the metabolic syndrome. The total population studied is similar to the population attending a paediatric nutrition clinic; therefore, our results could be extrapolated to a paediatric clinical setting, where we need simple tools to identify children at risk of having the different features of the metabolic syndrome. However, the results of the study cannot be extrapolated to the general population.

Nowadays there is no consensus on the diagnosis of the metabolic syndrome in either adults or children (17). Moreover, for the moment, we cannot say whether

the syndrome is one disease or simply a cluster of many ageing-or maturity-related risk factors, because causal links and underlying mechanism are as yet unknown (22, 23). In order to define the metabolic syndrome, we used a criterion similar to that used by CSÁBI *et al.* (24): the presence of four or more risk factors in the same children, and we also included leptin and uric acid concentrations, which are considered to play a part in this syndrome (11, 13).

A large waist circumference reflects high total body fatness and is also recognized as a good measure of abdominal fat, particularly the most metabolically active intra-abdominal fat, in both adults (29) and children (3, 9). Simple waist circumference measurements appear to have a similar performance to that of BMI in screening for the metabolic syndrome (21). Moreover, a single measurement, not a ratio, reduces the chance of error. Waist circumference cut-off points close to 70th age-and gender-specific percentiles should be used. MAFFEIS *et al.* (15) observed that children with a waist circumference greater than the 90th percentile are more likely to have multiple risk factors than children with a waist circumference less than or equal to the 90th percentile. SAVVA *et al.* (28) reported that waist circumference is a better indicator of cardiovascular disease risk factors than BMI. It has been also observed that waist circumference is a good tool for the screening of excess body fat percentage in children and adolescents (27). As in adults, waist circumference could be used to identify children with the metabolic syndrome, especially if we consider that reference values are available in the literature (18).

Type 2 diabetes mellitus is strongly associated with 2 additional cardiovascular disease risk factors: obesity and hyperinsulinemia (30). Hyperinsulinemia has been postulated as the critical component of the metabolic syndrome, including insulin resistance, hypertension, hypertrigliceridemia, low high density lipoprotein cholesterol, abnormal blood clotting tendency and chronic inflammation. This syndrome may be present in children before and during puberty (32). While a combination of hyperglycemic and euglycemic clamp studies supplies the gold standard for quantifying insulin *in vivo* action, secretion, and disposal, clamp studies are expensive and difficult to perform and require highly trained personnel (32).

The euglycemic clamp study involves a continuous infusion of regular insulin at a rate greater than 40 $\mu U \times m^{-2}$ body surface area x min^{-1} during 180 min. This rate was chosen to achieve sustained plasma insulin levels above 1,500 pmol/L, in order to completely suppress endogenous hepatic glucose output. Plasma glucose during the study must be maintained within the "normal" range of 5.5-5.8 mmol/L using a continuous infusion of variable amounts of 20% dextrose (5). Infusion adjustments are made every 5 min and steady–state hyperinsulinemia (plasma insulin > 1,500 pmol/L) with coincident euglycemia (plasma glucose between 5.3 and 5.8 mmol/L) must be achieved for the subject in the study between 120 to 180 min periods of the test. The difficulties with obtaining sequential clamp studies are even more pronounced for young children who may have more difficulty with clamp procedure requirements. HOMA-IR is a index based on fasting blood that estimate insulin sensitivity, secretion and disposal, which correlate closely with clamp studies (5, 32).

ROC analysis is a way of evaluating the accuracy of a diagnostic test by summa-

rizing the potential to discriminate between the absence and presence of a health condition. In the context of the present study, this diagnostic accuracy refers to the ability of the HOMA index to identify children with the metabolic syndrome. In conclusion, we found that HOMA index is a useful tool to detect children and adolescents with the metabolic syndrome. To the best of our knowledge, no papers on ROC curves for the screening of the metabolic syndrome in either adults or children have been published. From our results it seems that HOMA cut-off values need to be defined near to 3 in the paediatric population. Applications of the data in this study should be restricted to paediatric clinical settings in which there are a large number of children at risk for the metabolic syndrome.

B. TRESACO, G. BUENO, I. PINEDA, L.A. MORENO, J. M. GARAGORRI Y M. BUENO. *Puntos de corte del índice HOMA (Homeostatic Model Assessment) para la identificación de niños con síndrome metabólico.* J. Physiol. Biochem., 60 (2), 381-388, 2005.

El objetivo del estudio era establecer el mejor punto de corte del índice HOMA (Homeostatic Model Assessment) para la identificación de niños y adolescentes con el síndrome metabólico. Se incluyeron 72 niños no-obesos y 68 obesos, con edades entre 7 y 16 años. Se definió obesidad según los criterios propuestos por Cole y cols. Las variables utilizadas para describir el síndrome metabólico fueron las siguientes: Perímetro de la cintura, tensión arterial sistólica y diastólica, glucosa, ácido úrico, insulina en ayunas, leptina, triglicéridos y HDL-colesterol. Se consideraba que un niño tenía el síndrome metabólico cuando presentaba cuatro o más de estas características con valores anormales. El índice HOMA se calculó como el producto de las concentraciones de insulina en ayunas (μU/mL) y la glucosa plasmática en ayunas (mmol/L), dividido por 22.5. Se calcularon puntos de corte del índice HOMA correspondientes a los percentiles entre 5 y 95. Se elaboró una curva ROC (Receiver Operating Characteristics) tomando los diferentes puntos de corte del índice HOMA para la identificación del síndrome metabólico. Se calculó el área bajo la curva ROC, los intervalos de confianza al 95% y el punto de la curva ROC más cercano a 1. El área bajo la curva fue 0.863 (IC 95%: 0.797, 0.930). El punto más cercano a 1 correspondía al percentil 60 del índice HOMA en nuestra muestra. El valor del índice HOMA para el percentil 60 era 2.28. Puntos de corte del índice HOMA correspondientes a los percentiles comprendidos entre 50 y 75, mostraban distancias similares a 1. Los valores de índice HOMA correspondientes a estos percentiles oscilaban entre 2.07 y 2.83. En conclusión, el índice HOMA puede ser un buen instrumento para detectar el síndrome metabólico en niños y adolescentes. Es necesario definir mejor el punto de corte a utilizar en la población pediátrica; sin embargo, valores cercanos a 3 parecen ser los más adecuados.

Palabras clave: Resistencia a la insulina, Diabetes tipo 2, Nutrición, Niño, Obesidad, Síndrome metabólico.

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