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Original Article

Utility of hemoglobin A1c to screen for impaired glucose tolerance

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Abstract

Background Childhood obesity is associated with an increased likelihood for having impaired glucose tolerance, dyslipidemia, and diabetes. Hemoglobin A1c (HbA1c) has emerged as a recommended diagnostic tool for identifying diabetes and persons at risk for the disease. This recommendation was based on data in adults, showing the relationship between HbA1C and the future development of diabetes. However, studies in the pediatric population have been limited and no standard values of HbA1c levels in children have been established.

Objective To evaluate HbA1c as a test for impaired glucose tolerance in obese children and adolescents and to identify the optimal HbA1c threshold level (cut off point).

Methods We studied 65 obese and 4 overweight children (BMI ≥ +2 SD for age and gender) aged 10-15 years in Palembang. All subjects underwent HbA1c and oral glucose tolerance tests.

Results Nineteen out of 69 subjects (28%) had impaired glucose tolerance. Based on the receiver operating characteristic curve, the optimal cut off point of HbA1c related to impaired glucose tolerance as diagnosed by oral glucose tolerance test was found to be 5.25%, with 63% sensitivity and 64% specificity, 40% positive predictive value, and 82% negative predictive value. The area under the receiver operating characteristic curve was 0.687 (95%CI 0.541–0.833; P < 0.001).

Conclusion A HbA1c cut off value of 5.25% may be used as a screening tool to identify children and adolescents with impaired glucose tolerance. **[Paediatr Indones. 2014;54:223-6.]**

Keywords: *HbA1c, glucose intolerance, obesity*

The prevalence of obesity in young people has increased dramatically. Obesity in children predisposes them to subsequent adult obesity and to metabolic co-morbidities including insulin resistance and type 2 diabetes.[1,2] Glucose intolerance is an early sign of diabetes mellitus (DM) type 2. This phase, with no clinical symptoms of diabetes, is called the asymptomatic phase.[3] The prevalence of glucose intolerance in obese children and adolescents is around 30-40%.[4-6] Oral glucose tolerance test (OGTT) is considered to be the gold standard for diagnosing impaired glucose tolerance (IGT). Hemoglobin A1c (HbA1C) has emerged as a recommended diagnostic tool for identifying diabetes and patients at risk for the disease. This recommendation was based on data in adults showing a relationship between HbA1C and the future development of diabetes. However, little is known about the use of the HbA1C test for the diagnosis of type 2 diabetes and pre-diabetes in childhood and adolescence. No standard values of HbA1c levels in children have been established.[7-9]

The aim of this study was to evaluate HbA1c

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as a test for glucose intolerance in obese children and adolescents and to identify the optimal HbA1c thresholds (cut off point).

Methods

This cross-sectional diagnostic study was conducted at junior high schools (Madrasah Tsanawiyah Negeri 1, SMP Negeri 3, SMP Xaverius 7, SMP Metodis) and a pediatric clinic in Palembang from January 2013 until May 2013.

Participants were recruited by purposive sampling. We included obese and overweight children and adolescents (BMI ≥ +2 SD for age and gender) aged 10 to 15 years. We excluded participants who were sick or diagnosed with diabetes. We estimated the minimum required sample size to be 63 subjects, based on $\alpha = 0.05$ and power = 70%. The total number of subjects was 69 children and adolescents.

The Ethics Committee of Sriwijaya University Medical School, Palembang, Indonesia approved this study. We explained all study procedures to participants and their parents prior to enrollment. Subjects' parents provided written informed consent. Data collected included history, physical examinations, and laboratory tests. Physical examinations were performed to measure body weights and heights. The results were plotted on BMI curves for age and gender.

All subjects underwent oral glucose tolerance tests (OGTT) and HbA1c measurements. Blood specimens were taken after fasting overnight (at least 8 hours) for HbA1c and fasting glucose measurements (first specimen). Subjects then drank a solution of 1.75g glucose/kg body weight in 300 mL of water, maximum 75g, within 5 minutes. Second blood specimens were taken 2 hours after ingesting the glucose solution for plasma glucose measurements.

Type 2 diabetes was defined as having a fasting glucose of ≥125 mg/dL or a 2-hr glucose of ≥ 200 mg/dL from OGTT. Glucose intolerance was defined as having a fasting glucose of 100-125 mg/dL or a 2-hr glucose of 140-199 mg/dL from OGTT.

Blood drawing and measurements of HbA1c and plasma glucose were performed at the Prodia Laboratory. The HbA1c measurement was done by high performance liquid chromatography (HPLC).

Descriptive analysis was used for characteristic data and reported in a distribution table. Diagnostic analysis was performed by receiver operating characteristic (ROC) curve analysis, calculation of the area under the curve (AUC), determination of the cut off point, as well as calculations of sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio. Data was processed using SPSS software for Windows version 15.

Results

We studied 69 obese children and adolescents. There were 46 males (66%) and 23 females (34%), with a ratio of 2:1. The subjects' median age was 13.7 (range 11-15) years. Their mean BMI was 30.7 (SD 4.8) kg/m^2. Baseline characteristics of subjects are shown in **Table 1**.

There were 19 children (28%) with impaired glucose tolerance and 50 children (72%) with normal glucose tolerance. No subjects had type 2 diabetes **(Table 2).**

Table 1. Baseline characteristics (n=69)

Characteristics	n	%
Gender		
Male	46	66
Female	23	34
Age		
10-12 years	10	14
13-15 years	59	86
Nutritional status		
Overweight	9	13
Obese	50	87

Table 2. Glucose tolerance status (n=69)

Glucose tolerance status	n	%
Normal	50	72
Impaired	19	28
Type 2 diabetes mellitus	0	0
Total	69	100

Table 3. Hemoglobin A1c levels (n=69)

HbA1c	n	%
<5.7%	60	87
5.7 - 6.4%	8	12
>6.4%	1	1
Total	69	100

There were 60 children (87%) with HbA1c levels <5.7%, 8 children (12%) with HbA1c levels of 5.7 to 6.4% and 1 child (1%) with HbA1c level >6.4%. The mean HbA1c was 5.26 (SD 0.39)% with a median of 5.20 (range 4.50-6.70)% **(Table 3).**

Based on the receiver operating characteristic curve (**Figure 1**), the optimal cut off point of HbA1c based on impaired glucose tolerance as diagnosed by OGTT was 5.25%, which had 63% sensitivity, 64% specificity, 40% positive predictive value, 82% negative predictive value, and an area under the receiver operating characteristic curve of 0.7 (95% CI 0.5 to 0.8; P< 0.001).

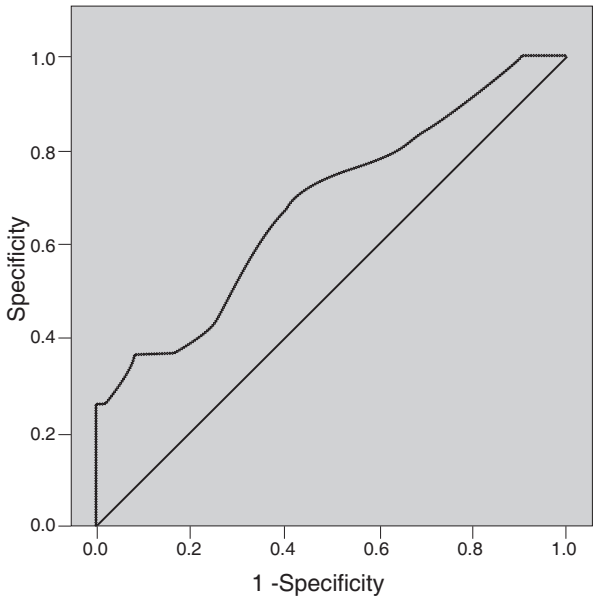

Figure 1. Receiver operating characteristic (ROC)

Discussion

In this study, 19 out of 69 participants (28%) had impaired glucose tolerance. A study in South Korea found that 27% of obese children and adolescents had impaired glucose tolerance.[10] Also, Arifin in Palembang, Indonesia found impaired glucose tolerance in 4.2% of normal weight children, 20.8% of overweight children, and 29.2% of obese children.[11] These results indicated an association between obesity and an increased risk of impaired glucose tolerance. The relationship between obesity and impaired glucose tolerance is due to a peripheral insulin resistance in obese children and adolescents, in which insulin sensitivity is very low. Individuals with impaired glucose tolerance were found to have reduced insulin secretion compared to individuals with normal glucose tolerance.[6]

Given the high state of impaired glucose tolerance in overweight and obese children and adolescents (28%), periodic OGTTs should be performed on these children for early detection of the condition, in order to prevent the progression to type 2 diabetes.

In this study, there were 60 children (87%) with HbA1c level <5.7%, 8 children (12%) with HbA1c levels of 5.7 to 6.4% and 1 child (1%) with HbA1c level >6.4%. The mean HbA1c was 5.26 (SD 0.39)% with a median of 5.2 (range 4.5-6.7)%. Another study found 77% of patients with HbA1c level <5.7%, 21% with HbA1c level of 5.7 to 6.4% and 1% with HbA1c level >6.4%.[12]

Based on the receiver operating characteristic curve, the optimal HbA1c concentration cut off point based on impaired glucose tolerance as diagnosed by OGTT was 5.3%, with 63% sensitivity, 64% specificity, 40% positive predictive value, 82% negative predictive value, and an area under the receiver operating characteristic curve of 0.7 (95% CI 0.5 to 0.8; P< 0.001). A study found this optimal cut off point to be 40 mmol/mol (5.8%), with 64.7% sensitivity, 61.6% specificity, and an area under the receiver operating characteristic curve of 0.7 (95% CI 0.5 to 0.8).[10] Another study found that the optimal threshold of HbA1c concentration was 5.8% for identifying type 2 diabetes, with a specificity of 87.6%, sensitivity of 67.7%. For identifying impaired glucose intolerance, that cut off point was 5.5%.[13]

The *American Diabetes Association* (ADA) published revised recommendations to use HbA1c level between >5.7 and 6.4% to identify subjects at risk for developing future diabetes.[13] However, we observed that using this HbA1c level would largely underestimate the prevalence of pre-diabetes in children and adolescents.

In conclusion, obesity is associated with an increased risk of impaired glucose tolerance. An HbA1c value of 5.25% may be used as a screening tool cut off point to identify children and adolescents with impaired glucose tolerance.

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