The Role of Haemoglobin A1c in Screening Obese Children and Adolescents for Glucose Intolerance and Type 2 Diabetes

O Papel da Hemoglobina A1c no Rastreio de Intolerância à Glicose e da Diabetes Tipo 2 em Crianças e Adolescentes Obesos

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ABSTRACT

Introduction: In 2012, an international expert committee in diabetes wrote in favor of screening adult and paediatric patients for glucose intolerance and type 2 diabetes using glycated haemoglobin. The aim of this study was to evaluate glycated haemoglobin utility as a screening tool in a young obese mainly Caucasian population.

Material and Methods: Children [(n = 266), body mass index z-score 3.35 ± 0.59, 90% Caucasian 90%, 55% female, median age 12.3 (range: 8.9 - 17.6) years old] recently referred to a tertiary hospital-based obesity clinic underwent a routine oral glicose tolerance test and glycated haemoglobin measurement. Exclusion criteria: abnormal forms of haemoglobin and conditions linked to increased erythrocyte turnover.

Results: The oral glicose tolerance test diagnosed 13 (4.9%) subjects as prediabetic but none as diabetic. According to glycated haemoglobin, 32 would be prediabetic (29 false positives) and one would be diabetic (when he was only glucose intolerant). On the other hand, 10 prediabetic patients would not have been identified (false negatives). Glycated haemoglobin receiver operator characteristic analysis area under the curve was 0.59 (CI 95% 0.40 - 0.78), confirming its reduced capacity to identify prediabetes. Better results were achieved when calculating receiver operator characteristic analysis area under the curve for fasting glucose (0.76; CI 95% 0.66 - 0.87), homeostasis model assessment for insulin resistance (0.77; CI 95% 0.64 - 0.90) and triglycerides:HDL cholesterol ratio (0.81; CI 95% 0.66 - 0.96).

Discussion: In Paediatric populations, especially when mainly Caucasian, glycated haemoglobin does not seem to be a useful screening tool for prediabetes.

Conclusion: For this reason, it would appear premature to advise it as a diagnostic tool until significantly more data is available. Homeostasis model assessment for insulin resistance and triglycerides: HDL cholesterol have higher precision and can be calculated using a fasting blood sample.

Keywords: Adolescent; Child; Diabetes Mellitus, Type 2; Glucose Intolerance; Haemoglobin A, Glycosylated; Mass Screening; Obesity; Pediatric Obesity.

RESUMO

Introdução: Em 2012, um comité internacional de peritos em diabetes aconselhou a hemoglobina glicada como teste de rastreio de intolerância à glicose e diabetes mellitus tipo 2 no adulto e em idade pediátrica. O objetivo deste estudo foi avaliar a utilidade deste exame numa população de crianças e adolescentes obesos, maioritariamente de etnia caucasiana.

Material e Métodos: Foram recrutados 226 doentes [índice de massa corporal *z-score* 3,35 ± 0,59, 90% caucasianos, 55% do sexo feminino, idade mediana de 12,3 (âmbito: 8,9 – 17,6) anos] referenciados à consulta de obesidade pediátrica de um hospital terciário, com critérios para rastreio de diabetes mellitus tipo 2. Situações de hemoglobinopatia ou de alteração da sobrevida eritrocitária foram excluídas. Todos os indivíduos foram submetidos a uma prova de tolerância à glicose oral e à medição da hemoglobina glicada.

Resultados: Segundo a prova de tolerância à glicose oral, 13 (4,9%) eram pré-diabéticos e nenhum diabético. De acordo com a hemoglobina glicada, 32 seriam pré-diabéticos (29 falsos-positivos) e um diabético (falso positivo, sendo este, na realidade, apenas intolerante à glicose). Por outro lado, 10 pré-diabéticos não seriam identificados (falsos-negativos). A área sob a curva *receiver operator characteristic analysis* da hemoglobina glicada foi 0,59 (IC 95% 0,40 - 0,78), confirmando a sua reduzida capacidade de discriminação para pré-diabetes. Mais promissoras foram as áreas sob as curvas *receiver operator characteristic analysis* da glicemia em jejum (0,76; IC 95% 0,66 - 0,87), *homeostasis model assessment for insulin resistance* (0,77; IC 95% 0,64 - 0,90) e razão triglicerídeos:colesterol HDL (0,81; IC 95% 0,66 - 0,96).

Discussão: Em Pediatria, particularmente em populações maioritariamente caucasianas, a hemoglobina glicada parece ser uma má ferramenta para diagnóstico de pré-diabetes.

Conclusão: Pelo exposto, parece-nos prematura a utilização da hemoglobina glicada com fins diagnósticos até um maior número de estudos estar disponível. O *homeostasis model assessment for insulin resistance* e a razão triglicerídeos:colesterol HDL demonstraram uma maior exatidão diagnóstica, podendo ser calculados com base numa amostra única em jejum.

Palavras-chave: Adolescente; Criança; Diabetes Mellitus Tipo 2; Hemoglobina A Glicosilada; Intolerância à Glucose; Obesidade; Obesidade Pediátrica; Rastreio.

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INTRODUCTION

Worldwide, paediatric obesity has reached epidemic proportions over the last decade. Several studies have shown that in Europe, overweight affects about 22% of children aged 5 to 9 (6% of whom are obese) and 16% of adolescents (4% of whom are obese).[1-3] In addition, there has been a steady annual rise and it has been calculated that six million obese and 26 million overweight young people existed in 2010 in the European Union.[4]

As in the adult, visceral adiposity is directly associated to hyperinsulinemia and to insulin resistance in this age group and is a major risk factor for young-onset type-2 diabetes mellitus (DM_2).[5] In fact, it is estimated that 20 thousand obese European young people have DM_2 (incidence of approximately 0.2 to 0.5/100,000/year) and that 400 thousand present with impaired glucose tolerance (IGT).[6] In addition, it is known that comorbidity situations occur earlier in children (approximately two years after diagnosis) than in adults. Therefore, a reviewed capacity for earlier prevention, diagnosis and treatment of obesity and DM_2 is fundamental both in healthcare centres and in Paediatrics departments, in order to allow for the prevention of a considerable increase in cardiovascular diseases and subsequent early death in the young adult, over the next decades.[7]

Patients with DM_2 may have no symptoms, with no polyuria or polydipsia and therefore its identification requires laboratory screening. As such, the American Diabetes Association (ADA) recommends the determination of fasting blood glucose levels and an oral glucose tolerance test (OGTT) in every obese in-risk young patient.[5] These tests, beyond requiring fasting (frequently preventing a timely assessment), are also affected by acute fluctuations in glucose levels as well as by recent changes in lifestyle.

In July 2009, for these reasons, and upon reviewing several studies showing a strong correlation between HbA1c levels and the emergence of retinopathy, an international diabetes expert committee (members of the ADA, the European Association for the Study of Diabetes and the International Diabetes Federation) suggested a change to screening using the HbA1c measurement in isolation. Nevertheless, this was a deliberation with level E of evidence and only based on studies carried out in adults. Apart from the abovementioned disadvantages, the HbA1c level is better standardized, with a lower biological variability and lower pre-analytical instability and is still a better index of overall glycaemic exposure and therefore a better predictor of the risk of future complications.[8] It is however not very useful in every potential clinical situation that may affect haemoglobin glycosylation and/or erythrocyte survival, namely pregnancy, haemoglobinopathies, anaemia, recent blood transfusion and certain drugs. The presence of a considerable ethnic and age-related heterogeneity should also be considered.[9-11]

In accordance, the same committee issued new guidelines in early 2012, in which the use of HbA1c was formally included. This screening is therefore currently recommended in every patient aged above 10, with Body Mass Index (BMI) above the P85 for the patient's gender and at least two of the following family risk factors: 1st or 2nd degree family member with DM_2, mother with gestational diabetes occurring during patient's pregnancy, non-Caucasian ethnicity or signs / conditions associated to insulin resistance (low weight for gestational age, acanthosis nigricans, high blood pressure, dyslipidaemia or polycystic ovary syndrome [POS]). The HbA1c, fasting blood glucose or OGTT measurement may be used and the test should be repeated every three years in case of normality. Pre-diabetes should be considered with HbA1c levels between 5.7 and 6.4% and diabetes when ≥ 6.5%.[12]

Several studies were published since these guidelines were pre-announced, based on populations with different origins. The different conclusions that were obtained have been conflicting, possibly due to the demographic heterogeneity and use of different cut-off HbA1c levels, when compared to several tests regarded as gold-standard.[13-20]

To our knowledge, only four studies (all American) have been published so far. From these, two studies supported the usefulness of the HbA1c screening and included Hispanic and Afro-American patients (around three quarters of the group of participants), who admittedly present a higher risk of dysglycemia.[21,22] The other two found that HbA1c has a low power of discrimination and also the use of the recommended cut-off values in children clearly underestimated the prevalence of pre-diabetes and diabetes in this age group.[23,24]

Therefore, considering the scarce available data regarding the role of this test in pre-diabetes and diabetes diagnosis in obese children, as well as the importance of ethnicity on the levels of glycosylation of haemoglobin, these results seem unsuitable for extrapolation to European countries mostly Caucasian.

Aims

Our study aimed to assess HbA1c as a screening tool for pre-diabetes and DM_2 in high-risk obese children from a country with mostly Caucasian ethnicity. The diagnostic usefulness of fasting blood glucose level, HOMA-IR and triglyceride (TG): HDL-C ratio was also assessed.

MATERIAL AND METHODS

This was a cross-sectional study designed in a tertiary-level British Paediatric Hospital. Over the first semester of 2012, all new patients referred to the Children Obesity (BMI > P_{98}) outpatient department meeting the currently recommended criteria were recruited for DM_2 screening.[13] Exclusion criteria included: pregnancy; known intolerance to glucose or diabetes; chronic medication, namely hypoglycaemic; haemoglobinopathy or other condition associated to any change in erythrocyte survival. The

protocol for the study was approved by the United Bristol Hospitals Trust Research Ethics Committee (Reference: 04/Q2006/9). An informed consent was signed by the adolescents or, in the case of small children, by their parents.

Clinical and laboratory assessment

Patients were examined in an outpatient setting after a 12-hour fast. Patient's weight (kg) and height (cm) were measured to one decimal using a SECA (United Kingdom) scale and stadiometer. Body fat percentage was measured using Tanita Bioimpedance Monitor Model BC-418 MA (Japan).

Upon clinical examination, a peripheral venous line was inserted and blood glucose, insulin and lipid profile were obtained. Thereafter, patients were asked to drink a glucose standard solution (1.75 g/Kg, 75 g maximum) and blood samples for glucose level were obtained every 30 min, for two hours.

Glucose levels were obtained using the hexokinase/glucose-6-phosphate dehydrogenase method. Plasma insulin levels were obtained by immunoassay. HbA1c levels were obtained through a NGSP assay, using human anti-HbA1c monoclonal antibody. These three biochemical parameters as well as lipid assays were obtained with a Roche Cobas Mira Plus Chemistry Analyser (Switzerland).

Definitions and calculations

OGTT test was adopted as the gold standard: pre-diabetes was diagnosed with a 2-hour blood glucose level between 7.8 mmol/L (140 mg/dL) and 11.0 mmol/L (199 mg/dL), while DM_2 was defined with values ≥ 11.1 mmol/L (200 mg/dL). Pre-diabetes was defined with the use of HbA1c level as diagnostic test at levels between 5.7% and 6.4% and diabetes at levels ≥ 6.5%. As regards fasting blood glucose, pre-diabetes was established at levels of 5.6 mmol/L (100 mg/dL) to 6.9 mmol/L (125 mg/dL) and diabetes at levels ≥ 7.0 mmol/L (126 mg/dL).[13] The blood glucose area under the curve (AUC) was calculated using the trapezoidal rule: AUC = 0.25 × [fasting blood glucose + 2 × (blood glucose at 30 min) + 2 × (blood glucose at 60 min) + 2 × (blood glucose at 90 min) + blood glucose at 120 min]. The insulin resistance index was calculated as HOMA-IR = [fasting insulin level (μIU/mL) x fasting blood glucose (mg/dL)] / 405 and was considered as significant when ≥ 4.5. The TG: HDL-C ratio was considered elevated when ≥ 3.0.

Sensitivity (proportion of patients with disease who test positive), specificity (proportion of patients without disease who test negative), predictive value of a positive test (proportion of patients with positive tests who have disease) and of a negative test (proportion of patients with negative tests who do not have disease) and positive likelihood ratio (ratio between sensitivity and 1 – specificity) were calculated for different HbA1c cut-offs and the ROC curve was analysed. Diagnostic usefulness of fasting blood glucose, HOMA-IR and TG: HDL-C ratio was also assessed using the same parameters.

Statistical analysis

The SPSS 14.0 software for Windows was used for the statistical analysis. The variables with positive deviation (HbA1c, insulin, HOMA-IR, triglyceride, cholesterol and TG: HDL-C ratio) were log transformed (log10) using the geometric mean and its range for variable description. The remaining results were described as mean ± standard deviation. After patients were ranked and according to the OGTT results, variables were compared using chi-square and Student's t-test. Bivariate correlations were assessed using Pearson's correlation coefficient. A 5% significance level was used for all tests.

RESULTS

In total, 266 patients with 12.3 median age (range: 8.9 to 17.6 years of age) were assessed, from which 147 (55.3%) were female. Regarding patient's ethnicity, 240 (90.2%) were Caucasian, 22 (8.3%) Black and the remaining were of a mixed ethnicity: As regards family history, 215 (80.8%) patients had obese members in the family and 74 (27.8%) had 1st or 2nd-degree family members with DM_2. The mothers of 15 patients (5.6%) developed gestational diabetes and 11 (4.1%) patients were born small for their gestational age. BMI average z-scores were 3.35 ± 0.59 while average z-scores of body fat percentage were 2.84 ± 0.61. A 36.51 ± 8.06% average central fat percentage was found. According to Tanner's classification, 106 (39.9%) patients were classified as pre-pubertal, 108 (40.6%) as pubertal and the remaining as post-pubertal. The presence of acanthosis nigricans was found in 77 (28.9%) patients and, according to the HOMA-IR, 71 (26.7%) were resistant to insulin (both situations coexisted in 32 patients). High blood pressure was found in 25 patients (9.4%) and 87 (32.7%) presented with dyslipidaemia (37 with hypercholesterolemia, 22 with hypertriglyceridemia and 28 with both). POS was found in two patients (0.01%). Total median HbA1c level was 5.2% (range: 4.1 - 6.9%), a statistically significant difference (p = 0.026, 95% CI 0.002 – 0.024) having been found between Caucasian (5.25%; range: 4.10 - 6.30%) and non-Caucasian geometric means (5.43%; range: 4.70 - 6.90%).

According to the OGTT result, 253 (95.1%) patients were normoglycaemic, 13 (4.9%) had pre-diabetes and no patient was diagnosed with DM_2. The demographic, auxological and laboratorial characteristics of both groups of patients is shown in Table 1; no significant differences were found between the groups as regards patient's age, ethnicity, pubertal status, BMI and central fat percentage.

As expected, levels of glycated haemoglobin correlated positively with the AUC for glucose (R^2 = 0.158, p < 0.001, 95% CI 0.046 - 0.081), with OGTT (R^2 = 0.064, p < 0.001, 95% CI 0.003 - 0.010) and with fasting blood glucose levels (R^2 = 0.021, p = 0.017, 95% CI 0.002-0.017) (Fig. 1).

Table 1 - Demographic. auxological and laboratorial data according to the glycaemic classification obtained by the OGTT

		Normal n = 253 (95.1%)	Pré-diabetes n = 13 (4.9%)	*p-value*	$_{95\%}$CI
Age (years) (median, range)		12.23 (8.92 - 17.63)	13.16 (9.05 - 17.46)	0.18	-2.94 - 0.56
Female		136 (53.8%)	11 (84.6%)	0.04	0.03 - 0.44
Caucasian		228 (90.1%)	12 (92.3%)	0.62	-0.24 - 0.10
Family history of DM_2		67 (26.5%)	7 (53.8%)	0.04	0.02 - 0.51
History of gestational diabetes		7 (2.8%)	8 (61.5%)	< 0.001	0.33 - 0.80
Small for gestational age		5 (2.0%)	7 (53.8%)	< 0.001	0.27 - 0.75
Pubertal status	**Pre-pubertal**	103 (40.7%)	3 (23.1%)		
	Pubertal	101 (39.9%)	7 (53.8%)	0.48	-0.42 - 0.54
	Post-pubertal	49 (19.4%)	3 (23.1%)		
Acanthosis nigricans		73 (28.9%)	4 (30.8%)	0.59	-0.17 - 0.29
BMI z-score (mean ± SD)		3.35 ± 0.60	3.37 ± 0.45	0.91	-0.35 - 0.31
Central fat (%) (mean ± SD)		36.43 ± 8.16	38.26 ± 5.64	0.48	-6.99 - 3.32
Blood glucose (mean ± SD)	**Fasting** (mmol/L)	4.59 ± 0.42	4.98 ± 0.41	0.001	0.16 - 0.63
	2h (mmol/L)	5.91 ± 0.92	8.42 ± 0.43	<.0.001	2.34 - 2.80
	AUC (mmol/L x min)	13.17± 1.92	16.88 ± 2.01	<.0.001	2.63 - 4.79
Insulin (geometric mean, range)	**Fasting** (µUI/mL)	14.72 (0.60 - 14.93)	28.37 (5.0 - 71.0)	0.008	0.08 - 0.49*
	30 min (µUI/mL)	75.23 (3.41 - 86.62)	137.84 (54.10 - 368.0)	0.015	0.19 - 1.74*
HOMA-IR (geometric mean, range)		2.99 (0.12 - 10.68)	6.26 (1.07 - 11.0)	0.003	0.11 - 0.53*
	≥ 4.5	80 (31.6%)	10 (76.9%)	0.001	0.17 - 0.61
Hb A1c (%) (geometric mean, range)		5.25 (4.10 - 6.30)	5.43 (4.70 - 6.90)	0.06	-0.03 - 0.01*
	≥ 5.7	29 (11.7%)	3 (23.1%)**	0.21	-0.04 - 0.39
Triglyceride (mmol/L) (geometric mean, range)		1.08 (0.30 - 3.20)	1.78 (0.80 - 3.90)	< 0.001	0.10 - 0.33*
Cholesterol (geometric mean, range)	**Chol : HDL-C ratio**	3.46 (1.60 - 6.30)	4.19 (2.50 - 6.70)	0.005	0.02 - 0.14*
	LDL-C (mmol/L)	2.38 (1.0 - 4.70)	2.21 (1.10 - 3.40)	0.42	-0.04 - 0.11*
TG : HDL-C ratio (geometric mean, range)		0.92 (0.17 - 2.70)	1.75 (0.47 - 4.33)	< 0.001	0.13 - 0.44*
	≥ 3.0	4 (1.6%)	2 (15.4%)	0.027	0.02 - 0.41

SD – standard deviation; * Means and $_{95}$% CI were calculated upon value's log transformation; ** One patient would be incorrectly classified as diabetic according to the value of HbA1c.

Nevertheless, we did not find any statistically significant difference between HbA1c geometric means both in normoglycaemic or pre-diabetic patients (p = 0.06, 95% CI – 0.03 - 0.01) (Table 1). In addition, when the HbA1c level was used for pre-diabetes classification, we found 29 false positive and 10 false negative (and one patient with pre-diabetes incorrectly classified as diabetes).

HbA1c's sensitivity, specificity, positive and negative predictive values and positive likelihood ratio for diagnosis of pre-diabetes, with a 5.7% cut-off value, were respectively 23.08%, 88.54%, 9.38%, 95.73% and 2.01. For this test, the area under the ROC curve was 0.59 (95% CI 0.40 - 0.78), showing its lack of discrimination power (Fig. 2).

In addition, fasting blood glucose level (R^2 = 0.192, p < 0.001, 95% CI 0.068-0.112), HOMA-IR (R^2 = 0.042, p = 0.001, 95% CI 0.016-0.060) and TG: HDL-C ratio (R^2 = 0.024, p = 0.017, 95% CI 0.001-0.013) also correlated positively with glucose's AUC. Finally, unlike what was found regarding glycated haemoglobin, a statistically significant difference was found between the mean values of these three parameters in normoglycaemic *vs.* pre-diabetic group of patients (Table 1), as well as a higher power of diagnostic discrimination shown by their ROC curves (Fig. 2). Sensitivity, specificity, positive and negative predictive values and positive likelihood ratio of the various tests, for the different cut-offs are shown in Table 2.

DISCUSSION

One of the major barriers to a timely screening of glucose intolerance in asymptomatic risk populations has been the need to obtain blood fasting sample for glucose measurement or for OGTT.[25,26] The HbA1c determination, which can be obtained at any time of the day, was a seemingly simple and efficient alternative, especially promising in an age group in which fasting samples are more difficult to obtain.[12] In fact, a survey made with American paediatricians and GPs showed an increased number of screenings carried out in primary healthcare upon the ADA recommendation.[27]

As described above, no studies in children or in adolescents were considered in the design of these new guidelines and cut-off values were extrapolated from studies carried out in adults. As it is known, a screening test, beyond involving a simple, timely and non-expensive procedure, should be sensitive, in order to include as many patients as possible. However, the need for a diabetes diagnostic value lower than recommended (6.5%, between 5.8 and 6.3%) is underlined in the studies by Lee *et al*. and Nowicka *et al*., in order to allow for an acceptable sensitivity to be obtained regarding a screening test and to minimize the number of false negatives.[23,24]

The ROC curve of our study (AUC 0.59, 95% CI 0.40-0.78) has confirmed that for pre-diabetes detection the sensitivity of the recommended value (5.7%) is even worse, in line with the results found in those two studies: AUC 0.53, 95% CI 0.39-0.67 and AUC 0.60, 95% CI 0.56-0.65. In order to obtain an acceptable sensitivity, a 5.3% minimum cut-off would be necessary, which is even lower to the 5.5% proposed in the same studies.[23,24] This reduction in the thresholds of HbA1c may correspond to (1) a higher risk of complications associated to high blood glucose in young age (shown by its earlier onset compared to the adult) and (2) to a higher physiological variability in this age group (for instance, according to the levels of haemoglobin, the glycosylation rate or the pubertal status).[28]

In addition, the sensitivity of a diagnostic test will be positively correlated to the prevalence of the disease in the target population. This may explain the disparity in HbA1c's behaviour as a screening tool for studies involving groups of patients mostly from Hispanic and Afro-American

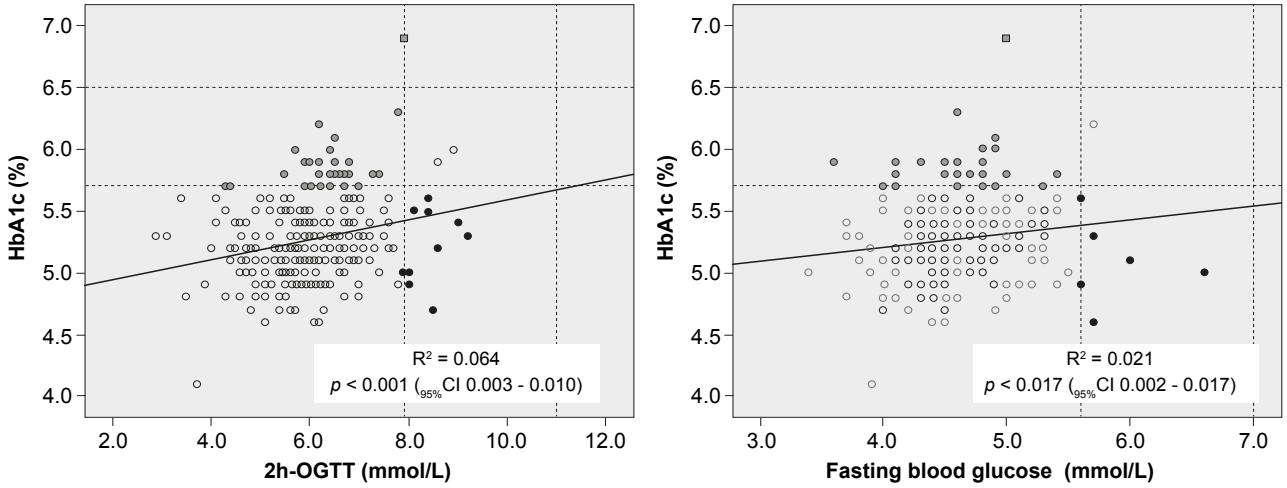

Figure 1 - HbA1c distribution according to the OGTT and fasting glucose level – linear regression analysis obtained upon log transformation (log10) of the HbA1c values.

Dotted lines correspond to the recommended cut-offs for pre-diabetes and DM_2 diagnosis. • False positive for pre-diabetes; ▪ False diabetes; • False negative for pre-diabetes.

Table 2 - Characteristics of the different tests regarding the diagnosis of pre-diabetes for different cut-offs

	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Positive Likelihood Ratio
HbA1c (%)					
3.1	100	0	5	----------	1.00
4.4	100	1	5	100	1.01
4.8	92	4	5	90	0.96
5.0	85	15	5	95	1.00
*5.3	62	53	6	96	1.32
•5.7	23	89	9	96	2.01
5.9	23	96	23	96	5.75
6.1	8	99	30	95	8.00
6.3	8	100	100	95	----------
Fasting blood glucose (mmol/L)					
2.4	100	0	5	----------	1.00
3.7	100	1	5	100	1.01
4.0	100	4	5	100	1.04
4.5	100	39	8	100	1.64
*4.7	77	61	9	98	1.97
5.0	46	84	13	97	2.88
5.3	31	93	19	96	4.43
•5.6	8	98	17	95	4.00
5.7	8	99	30	95	8.00
7.6	0	100	----------	95	----------
HOMA-IR					
0.1	100	0	5	----------	1.00
1.1	100	11	6	100	1.12
3.5	92	53	9	99	1.96
4.0	85	61	10	99	2.18
*•4.5	77	67	11	98	2.33
5.0	69	75	13	98	2.76
5.8	54	80	12	97	2.70
7.6	46	88	17	97	3.83
8.2	39	90	17	97	3.90
9.5	31	96	29	96	7.75
11.0	0	100	----------	95	----------
TG:HDL-C ratio					
0.2	100	0	5	----------	1.00
0.5	91	11	5	96	1.02
1.0	82	61	10	98	2.10
1.3	73	74	13	98	2.81
2.0	64	92	30	98	8.00
*2.3	27	96	26	96	6.75
•3.0	18	98	32	96	9.00
3.4	9	98	19	95	4.50
3.7	9	99	32	95	9.00
4.2	0	100	----------	95	----------

• Recommended cut-off; * Optimized cut-off.

ethnicity (with higher prevalence of glucose intolerance and DM_2) when compared to other studies, like ours, based on predominantly Caucasian patients.[21-24]

The screening strategies will also consider the economic weight of the tests that were used. On this subject, a recent American study involving 2.5 million children and adolescent aged 10 to 17, showed that the use of HbA1c, with the cut-offs recommended by the ADA, is not only not very effective (only about 33% of patients were identified) but is also the less efficient (cost per each identified patient: $938 for pre-diabetes and $571,344 for diabetes *vs.* $390 and $312,224 for OGTT, respectively).[29]

Due to the high cardio-metabolic risk involved, the insulin resistance and lipid profile should be initially obtained in the patients with extreme obesity (BMI > 3 z-score).[30] In our study, the HOMA-IR and the TG : HDL-C ratio, beyond showing a statistically significant difference between the averages of the normoglycaemic and pre-diabetic groups, also showed more promising ROC curves than those from HbA1c and fasting blood glucose levels: AUC 0.77, 95% CI 0.64 – 0.90 and AUC 0.81, 95% CI 0.66 – 0.96, respectively. Despite a requirement for fasting, the different parameters may be obtained with only one sample, without the disadvantages of the OGTT and adding the advantage of metabolic syndrome exclusion.

Strong and weak aspects of our study

As far as we know, this is the first European study in children assessing the usefulness of HbA1c in a group of patients that, despite being a convenience group, showed the relative ethnic prevalence of the population involved. Among other positive aspects, the reasonable number of patients studied and the systematic and simultaneous assessment of HbA1c and OGTT should be mentioned.

The fact that no single case of diabetes was diagnosed was the major limitation to our study. However, considering that in the USA the study SEARCH for Diabetes in Youth used the same gold standard and found a 0.02% prevalence, our result in not unexpected.[31] In addition, according to the ADA, two positive tests are required for the diagnosis of diabetes or pre-diabetes. However, we were unable to obtain two OGTTs for each patient due to the inconvenience it would have brought for patients and financial impact. Other studies, including the Diabetes Prevention Program

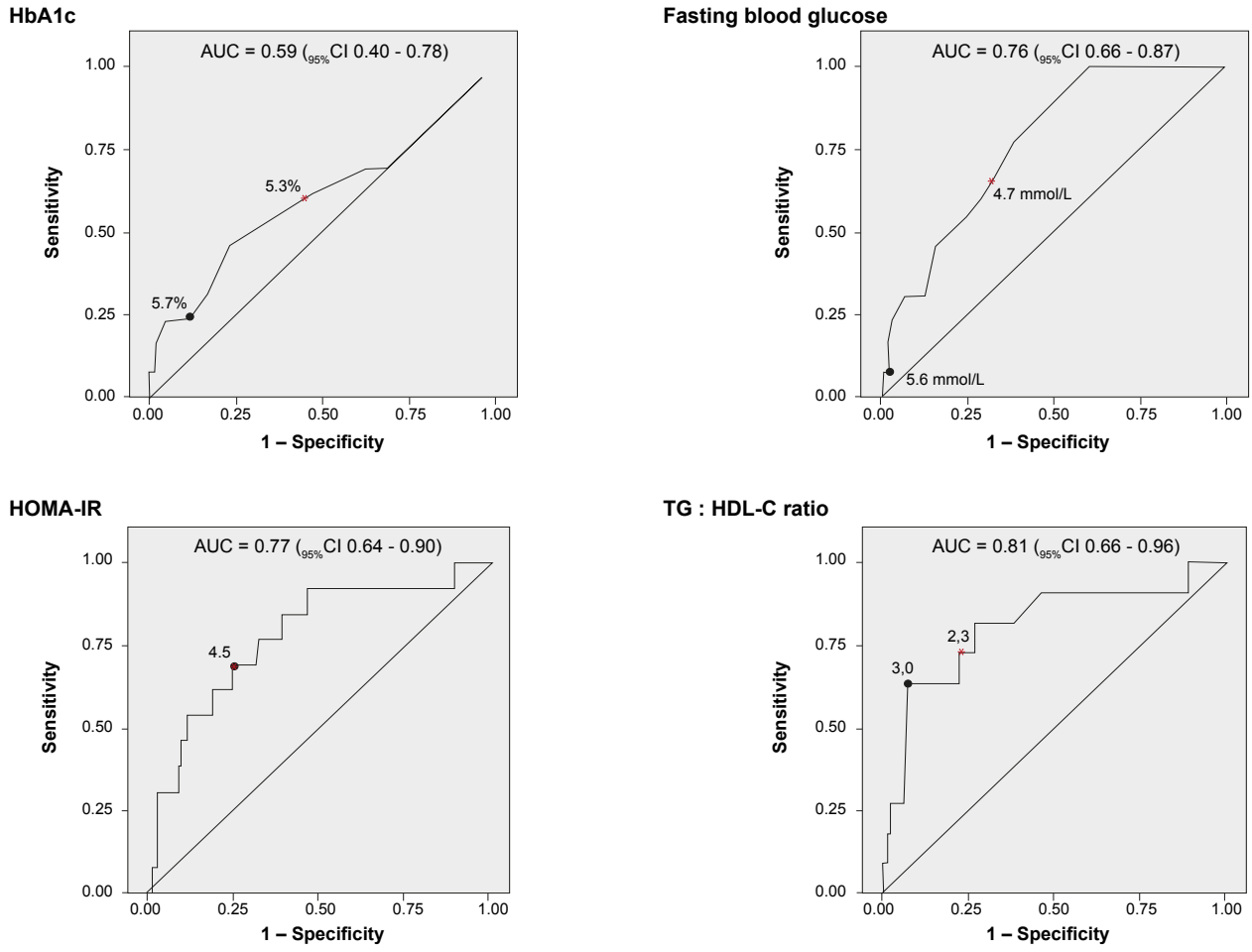

Figure 2 - ROC curves of HbA1c, fasting blood glucose, HOMA-IR and TG : HDL-C ratio for pre-diabetes diagnosis, using the OGTT as gold standard. Sensitivity represents the proportion of real positive, while (1-Specificity) means the proportion of false positive.

• Recommended cut-off; * Optimized cut-off (lower distance at the left upper corner). These two values overlap in the distribution curve of HOMA-IR

and the Screening for Impaired Glucose Tolerance have also classified the patient's glycaemic status based on a single test.[32,33]

CONCLUSION

A global use of HbA1c levels as major screening method in children seems premature and dangerous, at least with the cut-off values currently proposed for the adult, as it will delay the detection of children and adolescent already pre-diabetic, reducing and wasting the opportunity of an early intervention and exposing them to the risk of a chronic hyperglycaemia status, which has been shown to be more hazardous in the child than in the adult. Further prospective studies are therefore needed allowing for the optimization of the cut-off values in different ages and ethnic origins as well as for a better understanding of the role of HbA1c in diabetic comorbidity prediction in the young obese.

Until then, we suggest the use of the HOMA-IR and the TG: HDL-C ratio on a first approach for the exclusion of patients with an adequate blood glucose level. The patient's glycaemic status may be confirmed using the OGTT in the remaining patients.

HUMAN AND ANIMAL PROTECTION / DATA CONFIDENTIALITY

The authors declare that the protocol of the study was reviewed and approved by the United Bristol Hospitals Trust Research Ethics Committee (UK National Research Ethics Service, Reference: 04/Q2006/9). All clinical data was coded and kept in a database at the Bristol University, protected by access codes.

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CONFLICTS OF INTEREST

The authors declare there were no conflicts of interest in writing this manuscript.

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