

HbA_{1c} Diagnostic Categories and β -Cell Function Relative to Insulin Sensitivity in Overweight/Obese Adolescents

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OBJECTIVE—The recommended HbA_{1c} diagnostic categories remain controversial and their utility in doubt in pediatrics. We hypothesized that alterations in the pathophysiologic mechanisms of type 2 diabetes may be evident in the American Diabetes Association recommended at-risk/prediabetes category (HbA_{1c} 5.7 to <6.5%).

RESEARCH DESIGN AND METHODS—We compared in vivo hepatic and peripheral insulin sensitivity by [6,6-²H₂] glucose and a 3-h hyperinsulinemic-euglycemic clamp and β -cell function by a 2-h hyperglycemic clamp (~225 mg/dL) in overweight/obese (BMI \geq 85th percentile) adolescents with prediabetes (HbA_{1c} 5.7 to <6.5%) ($n = 160$) to those with normal HbA_{1c} (<5.7%) ($n = 44$). β -Cell function was expressed relative to insulin sensitivity (i.e., the disposition index = insulin sensitivity \times first-phase insulin).

RESULTS—In the prediabetes versus normal HbA_{1c} category, fasting glucose, insulin, and oral glucose tolerance test (OGTT) area under the curve for glucose and insulin were significantly higher; hepatic and peripheral insulin sensitivity were lower; and β -cell function relative to insulin sensitivity was lower (366 ± 48 vs. 524 ± 25 mg/kg/min; $P = 0.005$). A total of 27% of youth in the normal HbA_{1c} category and 41% in the prediabetes HbA_{1c} category had dysglycemia (impaired fasting glucose and/or impaired glucose tolerance) by a 2-h OGTT.

CONCLUSIONS—Overweight/obese adolescents with HbA_{1c} in the at-risk/prediabetes category demonstrate impaired β -cell function relative to insulin sensitivity, a metabolic marker for heightened risk of type 2 diabetes. Thus, HbA_{1c} may be a suitable screening tool in large-scale epidemiological observational and/or interventional studies examining the progression or reversal of type 2 diabetes risk.

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Glycated hemoglobin (HbA_{1c}) is used to monitor diabetes control in diagnosed patients (1). In 2009, an international expert committee recommended that HbA_{1c} also be used for diagnosis of diabetes and risk of diabetes (1). Subsequently, HbA_{1c} diagnostic cutoffs were incorporated into the 2010 American Diabetes Association (ADA) guidelines for diabetes (HbA_{1c} \geq 6.5%) and prediabetes (HbA_{1c} 5.7 to <6.5%)

(2). Unlike glycemic measures (e.g., fasting glucose, oral glucose tolerance test [OGTT]), the HbA_{1c} may be performed in the nonfasting state (2). However, adoption of these proposed criteria continues to be debated (3–8). In cross-sectional studies of adults, the HbA_{1c} criteria had lower sensitivity for diabetes diagnosis compared with OGTT (6) or a single fasting plasma glucose (9). But, the sensitivity of the HbA_{1c} criteria improved

when compared with repeated fasting plasma glucose samples (3 years apart), and the combination of fasting glucose and HbA_{1c} provided the greatest predictive value for 10-year diabetes risk compared with fasting glucose alone (single or repeated) (9). Furthermore, in a longitudinal study, HbA_{1c} identified fewer cases of prediabetes at baseline, but had similar predictive value for progression to diabetes as fasting glucose (~5-year follow-up) (10). Accordingly, recent pediatric studies indicate that HbA_{1c} identifies fewer adolescents with diabetes/prediabetes compared with glycemic measures (4,5,11). However, similar to adults, HbA_{1c} improved the predictive value of glycemic measures alone after a 2-year follow-up in adolescents (5). Because glycemic measures of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are linked to impaired insulin secretion relative to insulin sensitivity, conferring an increased risk of type 2 diabetes (12,13), we hypothesized that alterations in the pathophysiologic mechanisms of type 2 diabetes could be detected in the ADA recommended at-risk/prediabetes category (HbA_{1c} 5.7 to <6.5%). Therefore, we aimed to evaluate in vivo insulin sensitivity and β -cell function in overweight/obese youth categorized according to the 2010 ADA HbA_{1c} criteria (2) as normal versus prediabetes.

RESEARCH DESIGN AND METHODS

Approval by the Institutional Review Board of the University of Pittsburgh, parental consent and child assent were obtained prior to any research procedure. A total of 204 overweight/obese youth (according to age- and sex-specific BMI percentiles [14]) (89 African Americans and 115 Caucasians; 88 males and 116 females; ages 9 to <20 years old; Tanner stage II–V) (15) who had complete hyperinsulinemic-euglycemic and hyperglycemic clamp data obtained while participating in our ongoing studies of National Institutes of Health grants “Childhood Metabolic Markers of Adult Morbidity in Blacks” and “Childhood Insulin Resistance” were included. Some of

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these participants' data have been reported along with details of our recruitment and screening procedures (13,16–18). Tests were conducted at the Pediatric Clinical and Translational Research Center of the Children's Hospital of Pittsburgh.

Experimental procedures

A 3-h hyperinsulinemic (80 $\mu\text{U}/\text{m}^2/\text{min}$)-euglycemic (100 mg/dL) clamp was performed after a 10–12-h overnight fast (13,19). Fasting endogenous/hepatic glucose production (HGP) was measured in 164 participants using a primed (2.2 $\mu\text{mol}/\text{kg}$)-constant rate infusion of [6,6-²H₂] glucose (Isotech, Miamisburg, OH) at 0.22 $\mu\text{mol}/\text{kg}/\text{min}$ for 2 h (–120 to 0 min) (20,21). Four baseline blood samples were collected (–30 to 0 min) for determination of glucose, insulin, and isotopic enrichment of glucose prior to the initiation (0 min) of the clamp. On a separate occasion, 1 to 3 weeks apart, and in random order, a 2-h hyperglycemic clamp (~225 mg/dL) was performed (12,13,22). Either the day preceding one of the clamp procedures or on a separate visit within a 1- to 3-week period, a 2-h OGTT (1.75 g/kg glucola, maximum 75 g) was performed in 142 participants (23,24). Normal versus impaired glycemia was defined according to standards for fasting or 2-h OGTT glucose (2).

Percent body fat was measured with dual energy X-ray absorptiometry and abdominal visceral adipose tissue (VAT) with computed tomography in 154 subjects and magnetic resonance imaging in 50 subjects (17,21).

Biochemical analyses

Plasma glucose was measured by the glucose oxidase method (Yellow Springs Instrument Co., Yellow Springs, OH), and insulin by a commercial radioimmunoassay (catalog number 1011; LINCO Research, St. Charles, MO) (13). HbA_{1c} was measured by high-performance liquid chromatography (Tosoh Medics), and “normal” was defined as HbA_{1c} <5.7% and “prediabetes” as HbA_{1c} \geq 5.7% to <6.5% according to ADA criteria (2). Deuterium enrichment of glucose in the plasma was determined on a Hewlett-Packard 5971 mass spectrometer coupled to a 5890 series II gas chromatograph (Hewlett-Packard) (20,21).

Calculations

Fasting HGP was measured during the last 30 min of the 2-h baseline isotope infusion and hepatic insulin sensitivity (HIS) was calculated as 1,000/(HGP \times fasting insulin) (12,20). Peripheral insulin sensitivity (mg/kg/min per $\mu\text{U}/\text{mL}$) was calculated during the last 30 min (150–180 min) of the hyperinsulinemic-euglycemic

clamp (12,13,19,22). First-phase insulin ($\mu\text{U}/\text{mL}$) was calculated as the mean insulin concentration at times 2.5, 5, 7.5, 10, and 12.5 min during the hyperglycemic clamp (21,25). β -Cell function relative to insulin sensitivity, the disposition index (DI; mg/kg/min), was calculated as the product of insulin sensitivity and first-phase insulin (13,16). In the subset of 142 participants with OGTT, area under the curve (AUC) for glucose and insulin was calculated by the trapezoidal rule and the insulinogenic index ($\Delta\text{I}_{30}/\Delta\text{G}_{30}$) and the oral DI (oDI) as before (24–26).

Statistical analyses

Differences in categorical variables were determined by χ^2 analysis, and differences in continuous variables were determined by two-tailed *t* test or by ANCOVA adjusting for race. Differences in insulin sensitivity, first-phase insulin, and DI across HbA_{1c} categories (normal versus prediabetes) were determined by two-tailed *t* test and also by ANCOVA adjusting for race and adiposity (BMI, percent body fat, or VAT). Overall differences across subgroups of NGT versus dysglycemia by OGTT and normal versus prediabetes by HbA_{1c} were determined using ANCOVA, adjusting for race and VAT in SPSS (PASW 18; SPSS Inc., Chicago, IL). Data are presented as mean \pm SE.

Table 1—Subjects' physical and metabolic characteristics according to HbA_{1c} category (normal, HbA_{1c} <5.7% and prediabetes, HbA_{1c} \geq 5.7 to <6.5%)

	HbA _{1c} <5.7% (N = 160)	HbA _{1c} \geq 5.7 to <6.5% (N = 44)	Unadjusted P	Adjusted P
Physical characteristics				
Age	14.2 \pm 0.2	14.2 \pm 0.3	0.96	—
Sex, M/F (%)	44/56	41/59	0.74	—
Race, AA/C (%)	37/63	68/32	<0.001	—
Tanner stage, IV to V (%)	71	70	0.98	—
HbA _{1c} (%)	5.2 \pm 0.03	5.9 \pm 0.03	<0.001	<0.001
BMI (kg/m ²)	33.7 \pm 0.5	37.4 \pm 0.8	<0.001	0.001
BMI percentile	97.5 \pm 0.2	98.8 \pm 0.1	0.003	0.01
Body fat (%)	41.9 \pm 0.6	44.7 \pm 0.8	0.02	0.01
VAT (cm ²)	68.8 \pm 2.8	78.0 \pm 5.3	0.13	0.003
Metabolic characteristics				
Fasting glucose (mg/dL)	95.7 \pm 0.5	98.3 \pm 1.1	0.01	0.03
Fasting insulin ($\mu\text{U}/\text{mL}$)	35.7 \pm 1.4	49.8 \pm 4.4	<0.001	<0.001
HGP (mg/kg/min)	2.3 \pm 0.1	2.1 \pm 0.1	0.12	0.19
HIS (mg/kg/min per $\mu\text{U}/\text{mL}$) ⁻¹	15.4 \pm 0.7	12.6 \pm 1.2	0.05	0.03
Glucose AUC (mg \cdot min/dL)	14,722 \pm 290	15,860 \pm 375	0.05	0.004
Insulin AUC ($\mu\text{U} \cdot \text{min}/\text{mL}$)	20,249 \pm 1,106	28,519 \pm 3,170	0.002	0.001

Adjusted *P* value is the significance after adjusting for race. AA, African American; C, Caucasian.

A *P* value of ≤ 0.05 was considered statistically significant, and $P \leq 0.10$ was considered a trend.

RESULTS

Subject characteristics

Age, sex, and Tanner stage distributions were not different between participants divided according to HbA_{1c} category (normal versus prediabetes) (Table 1). There were more Caucasians in the normal HbA_{1c} category and more African Americans in the prediabetes category. Adiposity measures (BMI, BMI percentile, percent body fat, and VAT) were significantly higher in the prediabetes HbA_{1c} category than normal HbA_{1c}, before and after adjustment for race.

Metabolic characteristics by HbA_{1c} categories

Fasting glucose, insulin, OGTT glucose AUC, and insulin AUC were higher, and HIS was lower, in the prediabetes versus normal HbA_{1c} category (Table 1). These

differences persisted after adjusting for race and percent body fat. Peripheral insulin sensitivity was lower in the prediabetes versus normal HbA_{1c} category before and after adjustment for race ($P = 0.004$; data not shown), but was not different after additional adjustment for adiposity (Fig. 1A). First-phase insulin was not different between the two groups; however, DI, β -cell function relative to insulin sensitivity, was significantly lower in the prediabetes versus normal HbA_{1c} category after adjusting for race and adiposity (BMI, percent body fat, or VAT; Fig. 1A). In the subset of participants with OGTT-derived indices (Fig. 1B), results of insulin sensitivity ($1/I_F$) and oDI mirrored the results observed with the clamps.

HbA_{1c} categories and glycemic measures from OGTT

In the normal HbA_{1c} category, 27% had dysglycemia, and in the prediabetes HbA_{1c} category, 41% had dysglycemia ($P = 0.09$). Within each HbA_{1c} category, DI was lower by $\sim 35\%$ in dysglycemia

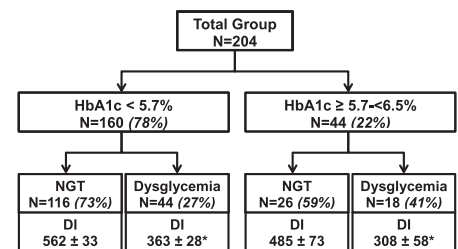


Figure 2—Flow chart illustrating the distribution of NGT vs. dysglycemia (IFG and/or IGT) within each HbA_{1c} category and their DI (mg/kg/min). * $P < 0.05$: NGT vs. dysglycemia within each HbA_{1c} category analyzed by one-tailed *t* test based on previous findings of lower DI in dysglycemia compared with NGT (12,13).

versus NGT groups. After adjustment for race and VAT, there were significant differences in DI among the four groups ($P < 0.001$), with the highest value in NGT in the normal HbA_{1c} category (562 ± 33 mg/kg/min) and the lowest value in the dysglycemia group in the prediabetes HbA_{1c} category (308 ± 58 mg/kg/min) (Fig. 2).

CONCLUSIONS—The current study demonstrates that overweight/obese adolescents meeting the ADA HbA_{1c} diagnostic criteria (2) for prediabetes have evidence of impaired β -cell function relative to insulin sensitivity, a metabolic signal for heightened risk of type 2 diabetes (27). This finding persisted after adjustment for race and for the greater adiposity in the youth with elevated HbA_{1c}. These data support our hypothesis that alterations in the pathophysiologic mechanisms of type 2 diabetes are evident in the ADA-recommended at-risk/prediabetes category (HbA_{1c} 5.7 to $< 6.5\%$).

Since the release of the HbA_{1c}-based diagnostic criteria for prediabetes/diabetes by the ADA in 2010 (2), reports of adults and some in pediatrics have concluded that HbA_{1c} is inferior to glycemic measures for diagnostic purposes (4–6,11). These studies evaluated the diagnostic sensitivity and specificity of HbA_{1c} compared with glycemic measures, treating the latter as the gold standard. One such study determined that the inferior sensitivity of the recommended HbA_{1c} cutoff compared with OGTT was worse for adolescents than for adults (4). However, although these studies evaluated equivalence of the new HbA_{1c} criteria compared with glycemic criteria, they did not evaluate metabolic characteristics linked to future diabetes risk. Moreover, as noted in a Comment published in

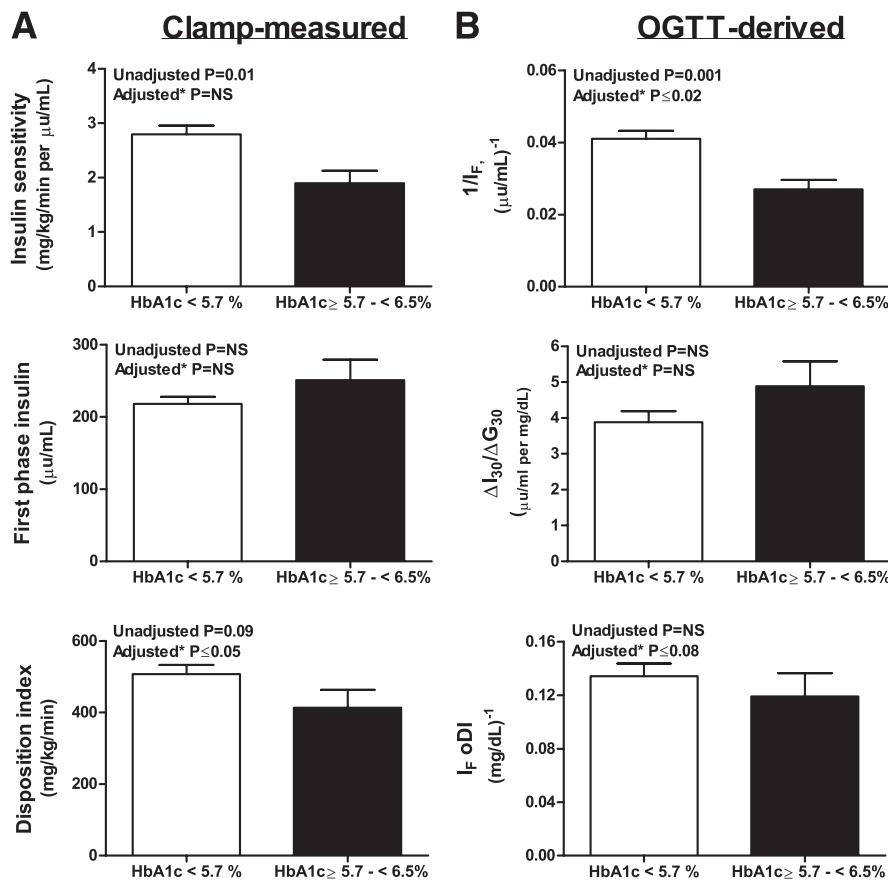


Figure 1—Clamp-measured insulin sensitivity, first-phase insulin, and DI (A) and OGTT-derived measures of insulin sensitivity, insulinogenic index ($\Delta I_{30}/\Delta G_{30}$), and oDI (B) in normal ($< 5.7\%$) versus prediabetes (5.7 to $< 6.5\%$) HbA_{1c} categories. Adjusted *P* is the significance after adjusting for race and adiposity (BMI, percent body fat, or VAT).

Diabetes Care, “it is a fallacy that the OGTT is a gold standard. . . if you define one test as a gold standard, all comparators will be inferior” (28). Indeed, in longitudinal studies, HbA_{1c} criteria predicted a similar rate of progression to diabetes as did IFG, and the combination of fasting glucose and HbA_{1c} provided the greatest predictive value of diabetes incidence (9,10).

The DI, which expresses β -cell function relative to insulin sensitivity, is an established metabolic predictor of progression to diabetes (12,13,29–31). Numerous longitudinal studies in adults have demonstrated the predictive value of DI (including oral DI) for the future development of diabetes (27,29,32,33). In addition, we (12,13) and others (30,31) have reported progressively declining DI across the spectrum of glycemia from normal to IFG and/or IGT to type 2 diabetes in youth. Therefore, even though the ADA HbA_{1c} diagnostic criteria have a lower sensitivity for diagnosis of prediabetes when compared with glycemic measures, we show in this study that these criteria are consistent with greater metabolic risk (lower clamp DI, oral DI, and insulinogenic index) using sensitive metabolic assessments.

Evaluating HbA_{1c} and glycemia together, youth with normal HbA_{1c} combined with normoglycemia had the highest DI compared with the other groups, and DI seemed to be lowest overall in the group with both elevated HbA_{1c} and dysglycemia (Fig. 2). Moreover, rates of dysglycemia were higher in the prediabetes (41%) versus normal HbA_{1c} category (27%) (Fig. 2). Overall, these data support the use of HbA_{1c} to identify youth with lower β -cell function for epidemiological observational and/or interventional studies of overweight/obese youth and progression to type 2 diabetes. However, the independent use of HbA_{1c} for clinical diagnostic purposes may be premature. Collectively, these observations indicate that the combination of HbA_{1c} and a glycemic measure may best pinpoint subjects at lowest or greatest risk of eventual diabetes (9,10). Longitudinal studies will be necessary to determine whether there are differences in rates of the development of diabetes between youth with normal HbA_{1c} and dysglycemia versus those with elevated HbA_{1c} and dysglycemia.

A potential challenge in the application of the HbA_{1c} is the higher HbA_{1c} in African Americans than Caucasians, present in our study and reported by others

(5,34). Racial differences in HbA_{1c} result in more African Americans and fewer Caucasians being identified as having prediabetes using HbA_{1c} compared with glycemic criteria (6,7). Potentially, the ADA-recommended cut points may not be appropriate for all racial groups, and exploration of cut points customized for race/ethnicity in larger scale studies may be warranted. Regardless, in this study, we report impaired β -cell function as well as lower peripheral and hepatic insulin sensitivity in youth with elevated versus normal HbA_{1c}, independent of the effects of race.

Strengths of the current investigation include the simultaneous assessment of HbA_{1c}, clamp-measured *in vivo* insulin sensitivity and β -cell function, and an OGTT in a large group of adolescents. A limitation of this report is that we included only overweight/obese adolescents, and our population does not represent other minority groups (e.g., Hispanics) in which the utility of HbA_{1c} may vary (34). Lastly, the number of youth with elevated HbA_{1c} and dysglycemia is somewhat limited.

In conclusion, the recently recommended HbA_{1c} criteria coincide with lower peripheral and hepatic insulin sensitivity and lower β -cell function relative to insulin sensitivity in overweight/obese adolescents. Larger and longitudinal studies are required to more thoroughly investigate the interplay of race within categories of dysglycemia and HbA_{1c} in relation to metabolic risk factors for diabetes (e.g., DI). Although controversy is likely to continue surrounding the adoption of HbA_{1c}-based criteria for the diagnosis of prediabetes and diabetes in youth, these data support that the ADA HbA_{1c} criteria for prediabetes correspond to impaired β -cell function in overweight/obese youth, a metabolic marker of heightened type 2 diabetes risk.

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L.A.S. analyzed the data and first-authored the manuscript. S.F.M. provided technical support for data analysis, editing, and review of the manuscript. S.L., H.T., and F.B. contributed

research participants and data. L.F. managed the data entry and database maintenance. S.A.A. provided the study concept and design; acquired data; obtained funding; provided administrative, technical, and material support; supervised the study; and critically reviewed and edited the manuscript. S.A.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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