Hemoglobin A1c above Threshold Level is Associated with Decreased β-Cell Function in Overweight Latino Youth

Claudia M. Toledo-Corral, PhD, MPH[1], Lisa G. Vargas, MD[2], Michael I. Goran, PhD[1,3], and Marc J. Weigensberg, MD[2]

Objective To examine whether a hemoglobin A1c (HbA1c)-identified prediabetic state (HbA1c ≥6.0%-6.4%) is associated with decreased insulin sensitivity (SI) and β-cell dysfunction, known factors in the pathogenesis of type 2 diabetes, in an overweight pediatric population.

Study design A total of 206 healthy overweight Latino adolescents (124 males and 82 females; mean age, 13.1 ± 2.0 years) were divided into 2 groups: lower risk (n = 179), with HbA1c <6.0%, and higher risk (n = 27), with HbA1c 6.0%-6.4%. Measurements included HbA1c, oral glucose tolerance testing, fasting and 2-hour glucose and insulin, SI, acute insulin response, and disposition index (an index of β-cell function) by the frequently sampled intravenous glucose tolerance test with minimal modeling. Body fat was determined by dual-energy X-ray absorptiometry.

Results Compared with the lower risk group, the higher risk group had 21% lower SI (1.21 ± 0.06 vs 1.54 ± 0.13; $P < .05$), 30% lower acute insulin response (928 ± 102 vs 1342 ± 56; $P < .01$), and a 31% lower disposition index (1390 ± 146 vs 2023 ± 83; $P = .001$) after adjusting for age and total percent body fat.

Conclusion These data provide clear evidence of greater impairment of β-cell function in overweight Latino children with HbA1c 6.0%-6.4%, and thereby support the adoption of the International Expert Committee's HbA1c-determined definition of high-risk state for overweight children at risk for type 2 diabetes. *(J Pediatr 2012;160:751-6).*

M ore than 40% of the US population suffers from diabetes or prediabetes.[1] Identification of prediabetes allows clinicians to treat and delay its progression to type 2 diabetes.[2] Diagnostic criteria for prediabetes have been long established using plasma glucose cutoffs based on studies in adults demonstrating associated insulin resistance and other pathophysiological changes, including diminished insulin secretion and β-cell function.[3-5] An ∼15% decline in β-cell function has been reported in children with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).[6,7]

Until recently, hemoglobin A1c (HbA1c) level was used only to monitor individuals already diagnosed with diabetes, serving as the gold standard measure of glycemic level over a 3-month period. More recently, as with measures of glucose, HbA1c levels have been used to describe a continuum of risk for the development of diabetes and associated conditions. The DETECT-2 (Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance) study determined that the prevalence of nonproliferative diabetic retinopathy begins to rise with an HbA1c level >6.5%.[8,9] Other studies also found a relationship between HbA1c and the risk of other complications of diabetes and strongly suggest the use of HbA1c as a diagnostic tool.[10]

In 2008, the International Expert Committee (IEC) convened to review current and future methods of diagnosing type 2 diabetes using HbA1c measures.[11] The IEC recommended assigning a diagnosis of diabetes when HbA1c is ≥6.5% and confirming the diagnosis with a repeat HbA1c test. In addition, a subdiabetic "high-risk" state was defined as an HbA1c level below the threshold for diabetes but ≥6.0%, and a lower risk for type 2 diabetes was defined as an HbA1c level <6.0%. In 2010, the American Diabetes Association (ADA) released a separate set of recommendations, defining the prediabetic state as HbA1c ≥5.7% and <6.5%.[12] Both of these recommendations were intended for adults, but they could be extrapolated to pediatric populations if β-cell dysfunction is indeed shown to be associated with these newly proposed recommendations in children.

Current ADA guidelines for the diagnosis of prediabetes are based on glucose criteria established in adults, and generally have been adopted for the pediatric population without independent studies to validate their use in children. Our research group has reported impaired pancreatic β-cell function in prediabetic overweight Latino youth. IFG and IGT[6,7] were both associated with

ADA	American Diabetes Association	HR	Higher risk
AIR	Acute insulin response	IEC	International Expert Committee
BMI	Body mass index	IFG	Impaired fasting glucose
DI	Disposition index	IGT	Impaired glucose tolerance
DREAM	Diabetes Risk due to Ectopic Adiposity in Minority Youth	LR	Lower risk
		OGTT	Oral glucose tolerance test
FSIVGTT	Frequently sampled intravenous glucose tolerance test	SI	Insulin sensitivity
		SOLAR	Study of Overweight Latino Adolescents at Risk
HbA1c	Hemoglobin A1c		

an ~15% decline in β-cell function in these children. With the new HbA1c guidelines for diagnosing prediabetes, the question becomes whether these cutoffs similarly identify pediatric patients at risk for type 2 diabetes.

Our hypothesis is that in a pediatric Latino population at high risk for type 2 diabetes, both the IEC (HbA1c ≥6.0%-6.4%) and ADA (HbA1c ≥5.7%-6.4%) recommendations will be associated with lower insulin sensitivity (SI) and diminished β-cell function.

Methods

The current analysis includes data obtained from 2 separate studies of diabetes risk in overweight Latino youth: the Study of Overweight Latino Adolescents at Risk (SOLAR) and Diabetes Risk due to Ectopic Adiposity in Minority Youth (DREAM). The DREAM study is an ongoing cross-sectional investigation into relationships between ectopic fat distribution and diabetes risk in overweight minority adolescents. SOLAR is a longitudinal observational cohort study, and data included in this study represent baseline data at entry into the study. Further details of the SOLAR study have been published elsewhere.[7,13]

A total of 206 overweight but otherwise healthy Latino boys and girls (SOLAR, n =142; DREAM, n = 64) were included in the present analysis. Participants in the SOLAR and DREAM studies were recruited from the greater Los Angeles County area through community health clinics, health fairs, and word of mouth, and were required to meet the following inclusion criteria at baseline: (1) Latino ethnicity (all 4 grandparents of Latino descent); (2) age 8-17 years (SOLAR, 8-13 years; DREAM, 8-17 years); and (3) age and sex body mass index (BMI) ≥85th percentile based on the year 2000 standards of the Centers for Disease Control and Prevention. Participants in the SOLAR study also had to have a first-degree relative (parent, grandparent, or sibling) with type 2 diabetes. Although family history of diabetes was not an inclusion criterion for the DREAM study, 86% of the participants had a family history of type 2 diabetes by this definition. Children were excluded if they had a previous major illness, including type 1 or 2 diabetes, took medications, or had a condition known to influence body composition, insulin action, or insulin secretion. Participants and their parents provided written informed consent. Both studies were approved by the Institutional Review Board of the University of Southern California's Health Sciences Campus.

All Participants attended 2 visits at the University of Southern California's General Clinical Research Center at Los Angeles County General Hospital (or the Clinical Trials Unit at the University Hospital after 2008). On the first visit, participants underwent a comprehensive medical history and physical examination (including assessment of pubertal maturation stage using Tanner breast development stage for girls and Tanner pubic hair development for boys) by a licensed health care provider.[14,15] Clinical staff obtained vital signs, measured blood pressure in triplicate, and performed a 2-hour oral glucose tolerance test (OGTT). Within approxi-

mately 2 months after the outpatient visit, each participant was admitted for an inpatient visit at the General Clinical Research Center for their second visit. The participant was served dinner and a snack before 8:00 pm, which marked the beginning of an overnight fast. Water alone was permitted during this period. At ~7:30 the next morning, a 13-sample insulin-modified frequently sampled intravenous glucose tolerance test (FSIVGTT) was performed as follows. Intravenous catheters were placed in the antecubital fossa of each arm. After 2 fasting blood samples were obtained at −15 and −5 minutes, glucose (0.3 g/kg body weight) was administered at time 0 over a 1-minute period. Subsequent blood samples were collected at 2, 4, 8, and 19 minutes. Insulin (0.02 U/kg body weight; Humulin R; Eli Lilly, Indianapolis, Indiana) was administered intravenously at 20 minutes, followed by blood sample collection at 22, 30, 40, 50, 70, 100, and 180 minutes. Plasma was analyzed for glucose and insulin concentrations, and results were then entered into MINMOD MILLENNIUM 2003 version 5.16 (R.N. Bergman, Los Angeles, California) for calculation of whole-body SI, acute insulin response (AIR) to glucose (ie, the area under the plasma insulin curve between 0 and 10 minutes), and the disposition index (DI; the product of SI and AIR and a measure of the ability of the islet cells to secrete insulin normalized to the degree of insulin resistance).

Body composition measures were performed at either visit based on availability of the participant and staff. Total body composition was assessed by dual-energy x-ray absorptiometry using a Hologic QDR 4500 W unit (Hologic, Bedford, Massachusetts).

HbA1c was measured by high-pressure liquid chromatography (model 11c 2.2 HLC-723; Tosoh, Tokyo, Japan) in an assay approved by the International Federation of Clinical Chemistry Working Group on HbA1c standardization.[16] The interassay coefficients of variation were 0.76% for an HbA1c of 6.2% and 0.57% for an HbA1c of 10.3%. Glucose was assayed with an analyzer using a membrane-bound glucose oxidase technique (Yellow Springs Instruments, Yellow Springs, Ohio). In the SOLAR study, insulin was assayed using a specific human insulin enzyme-linked immunosorbent assay kit (Linco, St Charles, Missouri; intra-assay coefficient of variation, 4.7%-7.0%; interassay coefficient of variation, 9.1%-11.4%; cross-reaction with human proinsulin, 0%). In the DREAM study, insulin was measured by an automated enzyme immunoassay (Tosoh AIA 600 II analyzer; sensitivity, 0.31 μU/mL; intra-assay coefficient of variation, 2.9%; interassay coefficient of variation, 5.8%). The 2 insulin assay methods were confirmed to not differ significantly (correlation of 2 assays, r = 0.97; P < .0001). Homeostatic model assessment of insulin resistance was calculated using the following equation: [fasting glucose (mg/dL) × fasting insulin (μU/mL)]/405.

Statistical Analysis

Tests of normality (Q-Q plots; Shapiro-Wilks test) were used to assess the distribution of the outcome variables SI, AIR, and DI. All variables were nonnormal and thus were log-transformed to achieve a normal distribution. Analyses were conducted on

log-transformed variables, and the results were then back-transformed for figure presentation and ease of interpretation.

For the primary analysis, the 206 subjects were divided into 2 groups based on the recommendations of the IEC: a lower risk (LR group (n = 179), with HbA1c <6.0%, and a higher-risk (HR) group (n = 27), with HbA1c ≥6.0%-6.4%. For descriptive purposes, any differences in physical and metabolic characteristics between the LR and HR groups were assessed using the independent-samples t-test and χ^2 test. Data are reported as unadjusted mean ± SD. ANCOVA was performed to identify any differences in SI, AIR, and DI between in the LR and HR groups. Initially, these analyses were adjusted for covariates (age, sex, Tanner pubertal stage, and percent body fat) known from our previous studies to affect these outcomes. However, pubertal stage and sex were not significant in our models, and thus only age and percent body fat were used as covariates in the final analyses for SI and DI. For the analysis of AIR, the additional covariate of SI was used to assess the independent effects of insulin secretion on prediabetes. To assess any potential differences by study type, we also initially adjusted for study (SOLAR or DREAM) and for family history of type 2 diabetes; however, all results remained the same, and so these variables were not included in the final analyses. A separate ANCOVA analysis was used to identify any differences between 3 risk groups based on the ADA-recommended criteria: subjects with HbA1c <5.7%, subjects with HbA1c ≥5.7 and <6.0%, and subjects with HbA1c ≥6.0%-6.4%. For this analysis, the group previously identified as LR by IEC criteria (HbA1c <6.0%) was further divided into 2 subgroups, HbA1c <5.7% (n = 130) and HbA1c ≥5.7%-5.9% (n = 49), whereas the HR group (HbA1c ≥6.0%, n = 27) was left intact. A contrast analysis (post hoc analysis) was used to assess any intergroup differences. Data were analyzed using SPSS for Mac version 18.0 (SPSS Inc, Chicago, Illinois), with an a priori significance level of $P < .05$.

Results

The Table presents physical and metabolic characteristics of the LR and HR groups. There were no significant between-group differences in sex or Tanner stage. Compared with the LR group, the HR group were significantly older, heavier, taller, and had higher total fat, lean tissue mass, and percent body fat values ($P < .05$). BMI was significantly higher in the HR group ($P < .001$), yet the 2 groups did not differ in terms of BMI percentile ($P > .05$). By definition, the HR group had a significantly higher HbA1c than the LR group ($P < .001$). The HR group also had higher fasting and 2-hour glucose levels, homeostatic model assessment of insulin resistance, and fasting insulin levels, but the differences were not statistically significant ($P = .10$-.12). IGT was more prevalent in the HR group (40% vs 16%; $P = .02$), but IFG status did not differ between the groups. When prediabetes was defined as either IGT or IFG, the prevalence of prediabetes was higher in the HR group, but the difference was not statistically significant (36% vs 23%; $P = .09$). Assessment of unadjusted insulin dynamics revealed lower SI (1.31 ± 0.90 vs

Table. Physical and metabolic characteristics of the LR and HR groups (n = 206)

	LR (HbA1c <6.0) (n = 179)	HR (HbA1c ≥6.0) (n = 27)
Age, years	12.6 ± 2.2	13.6 ± 2.3*
Sex, male/female, n	106/73	18/9
Tanner stage, n		
1	39	3
2	38	5
3	13	2
4	40	5
5	49	12
Height, cm	156.8 ± 12.1	162.3 ± 10.5*
Weight, kg	74.1 ± 21.3	90.4 ± 24.0†
BMI, kg/m²	29.6 ± 5.6	33.9 ± 6.9†
BMI z-score	2.02 ± 0.44	2.30 ± 0.44‡
BMI percentile	96.3 ± 4.6	97.8 ± 3.5
Total lean tissue mass, kg	44.2 ± 12.3	52.4 ± 13.5‡
Total fat mass, kg	26.7 ± 10.3	34.6 ± 11.6†
Total percent fat	36.4 ± 6.9	39.1 ± 5.5*
Fasting glucose, mg/dL	90.4 ± 6.8	92.6 ± 7.3
2-hour glucose, mg/dL	124.1 ± 19.6	130.4 ± 27.4
Fasting insulin, μU/mL	16.4 ± 10.8	22.3 ± 17.9†
2-hour insulin	149.2 ± 132.0	186.8 ± 181.8
HOMA-IR	3.9 ± 4.1	7.7 ± 11.9
HbA1c, %	5.48 ± 0.28	6.07 ± 0.10†
IFG, n (%)	16 (9)	4 (16)
IGT status, n (%)	29 (16)	10 (40)*
Prediabetes (IFG and/or IGT), n (%)	40 (23)	10 (36)†
SI [× 10⁻⁴/min⁻¹)/(μU/mL)]§	1.91 ± 1.25	1.31 ± 0.90*
AIR, μU/mL§	1634 ± 1149	1554 ± 1428
DI§	2338 ± 1149	1631 ± 1225‡

HOMA-IR, homeostatic model assessment of insulin resistance.
Data expressed as mean ± SD except as indicated.
The independent-samples t-test and χ^2 test were used to compare differences between the LR and HR groups.
*$P < .05$.
†$P < .01$.
‡$P < .001$.
§Variables with a nonnormal distribution that were log-transformed for analyses. Nontransformed values are displayed for ease of interpretation.

1.91 ± 1.25 × 10⁻⁴ min⁻¹/[μU/mL]; $P = .02$) and lower DI (1631 ± 1225 vs 2338 ± 1149; $P < .01$) in the HR group, but no significant difference in AIR between the 2 groups ($P > .05$).

Figure 1 shows the estimated marginal means for SI, AIR, and DI in the LR and HR groups after adjustment for age and total percent body fat (and SI for AIR). The HR group had significantly lower SI (1.21 ± 0.13 vs 1.54 ± 0.06 × 10⁻⁴ min⁻¹/[μU/mL]), AIR (928 ± 102 vs 1342 ± 56 μU/mL; $P < .05$), and DI (1390 ± 146 vs 2023 ± 83; $P < .05$) than the LR group.

Repeating this analysis using the ADA-recommended cutoffs of HbA1c <5.7% for the LR group (n = 130) and HbA1c ≥5.7%-6.4% for the HR group (n = 76) revealed no significant between-group differences in SI (LR: 1.86 ± 0.86 vs HR: 1.74 ± 0.11 × 10⁻⁴ min⁻¹/(μU/mL), AIR (1614 ± 100 vs 1640 ± 130 μU/mL, $P < .05$), and DI (2300 ± 95 vs 2143 ± 124, $P > .05$). However, this analysis did not evaluate whether the children in the intermediary HbA1c range between 5.7% and 5.9% have insulin action that would most resemble a LR or HR for type 2 diabetes; thus, we then performed a 3-group analysis.

Figure 2 shows the estimated marginal means for SI, AIR, and DI by 3 risk groups: subjects with HbA1c <5.7%
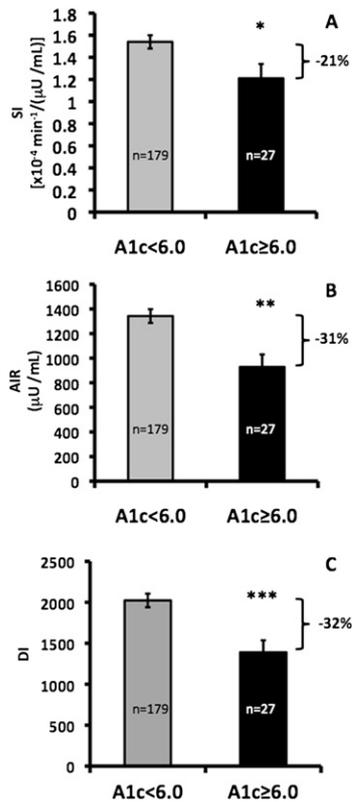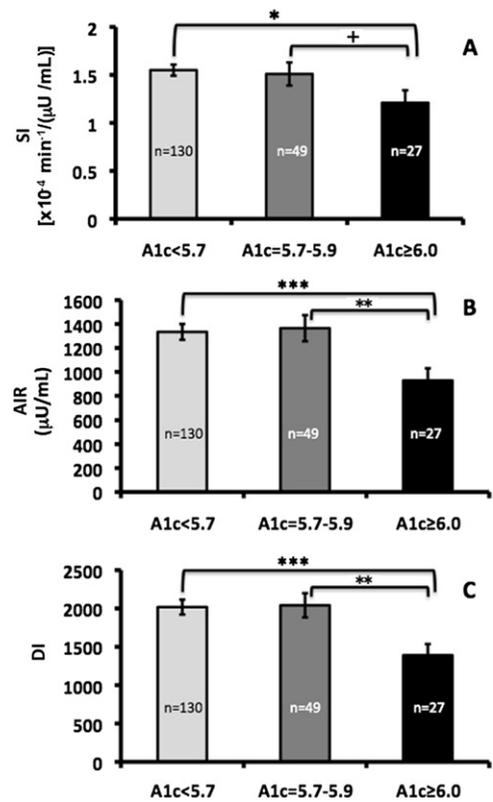
Figure 1. Estimated marginal means for SI, AIR, and DI in the LR and HR groups after adjustment for age and total percent body fat. **A**, SI **B**, AIR **C**, and DI. ANCOVA was performed on log-transformed data, and results were then back-transformed for presentation in the **Figure**. The SI and DI estimated marginal means (± SE) were adjusted for age and total percent body fat. The AIR estimated marginal mean was also adjusted for SI. *P < .05; **P < .01; ***P < .001.

Figure 2. Estimated marginal means for SI, AIR, and DI by 3 risk groups. **A**, SI **B**, AIR **C**, and DI. ANCOVA was performed on log-transformed data, and results were then back-transformed for presentation in the **Figure**. The SI and DI estimated marginal means (± SE) were adjusted for age and total percent body fat. The AIR estimated marginal mean was also adjusted for SI. *P < .05; **P < .01; ***P < .001.

(n = 130), those with HbA1c ≥5.7%-5.9% (n = 49), and those with HbA1c ≥6.0%-6.4% (n = 27). A decrease in SI was seen across the 3 HbA1c groups from lowest risk to highest risk, but this was not statistically significant (P = .10). Contrast analysis revealed no differences in SI between the 2 lowest-risk groups (P = .79). The subjects in the highest-risk group had a significantly lower SI than those with HbA1c <5.7% (P = .04) and a lower SI than those with HbA1c ≥5.7%-5.9%, but the latter difference was not statistically significant (P = .09). Significant decreasing trends in AIR and DI were seen across the 3 groups (P < .01). Contrast analysis revealed no significant differences in AIR and DI between the HbA1c <5.7% group and HbA1c ≥5.7%-5.9% group (P = .89), but significantly lower AIR and DI in the highest-risk group compared with both of those groups (both P < .01).

Discussion

Our primary result demonstrates that β- cell function (ie, DI) was significantly lower in the HR group compared with the LR group, independent of age and percent body fat. In addition, both SI and AIR were significantly lower in the HR group. In a separate analysis, we examined the recent ADA recommendation that uses a broader A1c range (≥5.7%-6.4%). We found no significant differences in SI, insulin secretion, or β-cell function between the lowest-risk group (HbA1c <5.7%) and the group with HbA1c ≥5.7%-5.9%, but did detect significant differences in AIR and DI between the HbA1c ≥5.7%-5.9% group and the highest-risk group. This finding suggests a distinct decline in β-cell function at an HbA1c value in the 6.0% range in overweight Latino adolescents.

This study addresses 2 recent recommendations of the IEC (high risk, HbA1c ≥6.0%) and the ADA (high risk, HbA1c ≥5.7%). Our post hoc analysis of 3 different HbA1c groups revealed no differences between the children with HbA1c <5.7% and those with HbA1c ≥5.7%-5.9%. In contrast, children with HbA1c ≥6.0%-6.4% had significantly lower insulin action than both of the LR groups. These results suggest no increased risk in the group with HbA1c ≥5.7%-5.9% compared with the lowest-risk group with HbA1c <5.7%. Based on these findings, we support the IEC's recommendation to use an HbA1c value

≥6.0%-6.4% as the cutoff for high risk for type 2 diabetes. It is important to note that we cannot generalize this conclusion beyond our study population of overweight Latino youth.

The clinical utility of using HbA1c value as a screen for diabetes and prediabetes could greatly improve the options for screening, which currently include diagnostic criteria for prediabetes and diabetes requiring either a fasting glucose or a 2-hour OGTT. Fasting blood draws and OGTTs may present logistical barriers, such as the need for an additional clinic visit to obtain a fasting sample and the inherent difficulties of multisample stimulation tests like the OGTT. The use of HbA1c allows medical providers to avoid delays in screening children at risk for asymptomatic type 2 diabetes at nonfasting visits.[17] The test is standardized, accessible, and easily performed and has low variability in day-to-day testing.[18,19] The disadvantages of using HbA1c instead of fasting glucose for screening includes higher cost and potential lack of standardization of HbA1c assays.

It should be noted that only 36% of our subjects with high-risk HbA1c values would have been identified as having prediabetes by glucose criteria alone, and that 23% of the subjects in the LR HbA1c group actually had prediabetes based on glucose criteria. Therefore, although the specificity of the HbA1c screen is high (89%), the sensitivity is very low (22%) when it comes to predicting which subjects have prediabetes based on glucose criteria. Despite its very low rate of false-positive results, the HbA1c test is not as reliable in detecting children who truly have prediabetes based on glucose criteria. However, determining the gold standard for identifying children at risk is difficult, requiring long-term longitudinal studies as have been performed in adults to see which test more accurately predicts progression to type 2 diabetes. For now, our data suggest that in overweight Latino adolescents, an HbA1c of 6.0%-6.4% is indicative of greater β-cell dysfunction ($\sim$30% lower DI) compared with a high fasting or 2-hour OGTT glucose value ($\sim$15% lower DI), and thus may identify a group at greater risk for progression to diabetes.[6,7] Ultimately, the advantage of screening for prediabetes in high-risk youth using HbA1c versus fasting glucose or the OGTT remains to be determined by prospective longitudinal studies demonstrating the sensitivity, specificity, and relative predictive value of HbA1c versus IFG or IGT in predicting progression of type 2 diabetes. Until such studies come to fruition, the HbA1c test offers the clinician a nonfasting method for detecting a population of children with significant β-cell dysfunction and likely at high risk to progress.

The strengths of the present study include a homogenous group of overweight Latino youth that are typically understudied, the evaluation of both the IEC and cross-comparison with the ADA recommendations, and the use of rigorous direct measures of insulin action and secretion by FSIVGTT with minimal modeling. Limitations include the lack of a lean group of children, which precluded testing children using FSIVGTT because of ethical considerations. Also, although we attempted to increase the power of our study by combining subjects from 2 separate studies, the relatively small

final size of the higher-risk group (n = 27) still may limit the study's power to detect some differences between HbA1c groups. For example, we were unable to achieve an adequate receiver operating characteristics curve to determine an HbA1c cutoff that can predict a decreased β-cell function, likely because of the small sample size. Finally, our results cannot be generalized beyond overweight Latino children. Studies in adults have shown that HbA1c cutoffs have varying impacts on different ethnic groups; thus, further research in a multiethnic cohort is clearly warranted.[20,21] ■

References

1. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, et al. Full accounting of diabetes and pre-diabetes in the US population in 1988-1994 and 2005-2006. Diabetes Care 2009;32:287-94.
2. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
3. Tripathy D, Carlsson M, Almgren P, Isomaa B, Taskinen MR, Tuomi T, et al. Insulin secretion and insulin sensitivity in relation to glucose tolerance: lessons from the Botnia Study. Diabetes 2000;49:975-80.
4. Kim DJ, Lee MS, Kim KW, Lee MK. Insulin secretory dysfunction and insulin resistance in the pathogenesis of Korean type 2 diabetes mellitus. Metabolism 2001;50:590-3.
5. Festa A, D'Agostino R Jr, Hanley AJ, Karter AJ, Saad MF, Haffner SM. Differences in insulin resistance in nondiabetic subjects with isolated impaired glucose tolerance or isolated impaired fasting glucose. Diabetes 2004;53:1549-55.
6. Weigensberg MJ, Ball GD, Shaibi GQ, Cruz ML, Goran MI. Decreased β-cell function in overweight Latino children with impaired fasting glucose. Diabetes Care 2005;28:2519-24.
7. Goran MI, Bergman RN, Avila Q, Watkins M, Ball GD, Shaibi GQ, et al. Impaired glucose tolerance and reduced β-cell function in overweight Latino children with a positive family history for type 2 diabetes. J Clin Endocrinol Metab 2004;89:207-12.
8. Colagiuri S. DETECT-2: early detection of type 2 diabetes and IGT. Diabetes Voice 2003;48:11-3.
9. Colagiuri S, Lee CM, Wong TY, Balkau B, Shaw JE, Borch-Johnsen K. Glycemic thresholds for diabetes-specific retinopathy: implications for diagnostic criteria for diabetes. Diabetes Care 2011;34:145-50.
10. Massin P, Lange C, Tichet J, Vol S, Erginay A, Cailleau M, et al. Hemoglobin A1c and fasting plasma glucose levels as predictors of retinopathy at 10 years: the French DESIR study. Arch Ophthalmol 2011; 129:188-95.
11. International Expert Committee report on the role of the HbA1c assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327-34.
12. Standards of medical care in diabetes—2010. Diabetes Care 2010; 33(Suppl 1):S11-61.
13. Weigensberg MJ, Cruz ML, Goran MI. Association between insulin sensitivity and post-glucose challenge plasma insulin values in overweight Latino youth. Diabetes Care 2003;26:2094-9.
14. Marshall WA, Tanner JM. Variations in pattern of pubertal pattern changes in girls. Arch Dis Child 1969;44:291-303.
15. Marshall WA, Tanner JM. Variations in pattern of pubertal pattern changes in boys. Arch Dis Child 1970;45:13-23.
16. Weykamp C, John WG, Mosca A, Hoshino T, Little R, Jeppsson JO, et al. The IFCC reference measurement system for HbA1c: a 6-year progress report. Clin Chem 2008;54:240-8.

17. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2000;23(Suppl 1):S32-42.
18. Little RR, Rohlfing CL, Wiedmeyer HM, Myers GL, Sacks DB, Goldstein DE. The National Glycohemoglobin Standardization Program: a five-year progress report. Clin Chem 2001;47:1985-92.
19. Sacks DB. HbA1c versus glucose testing: a comparison. Diabetes Care 2011;34:518-23.
20. Christensen DL, Witte DR, Kaduka L, Jorgensen ME, Borch-Johnsen K, Mohan V, et al. Moving to an HbA1c-based diagnosis of diabetes has a different impact on prevalence in different ethnic groups. Diabetes Care 2011;33:580-2.
21. Kramer CK, Araneta MR, Barrett-Connor E. HbA1c and diabetes diagnosis: the Rancho Bernardo Study. Diabetes Care 2011;33:101-3.

50 Years Ago in THE JOURNAL OF PEDIATRICS

A Decade with Agammaglobulinemia

Bruton OC. J Pediatr 1962;60:672-6

In 1952, Ogden Bruton reported the first case of a boy with X-linked agammaglobulinemia (XLA), now recognized as Bruton's XLA.[1] Fifty years ago in *The Journal*, he provided a progress report on the same child. Bruton described how gammaglobulin treatment allowed for normal growth, lack of serious illnesses, and how the boy was able to lead a normal life. This is followed by a summary of how study of these children advanced the young field of clinical immunology.

Intravenous preparations of gammaglobulin were not available. Children were given painful monthly intramuscular injections. Today, administration has been streamlined to intravenous or hyaluronidase-containing subcutaneous injections with equal effect and the same low-risk profile.

Two groups shaped the field of clinical immunology: the University of Minnesota, led by Robert Good, and the Boston group, led by Charles Janeway. A myriad of publications resulted, and the role of antibodies became apparent in host defense, pathophysiology of transplantation reactions, hemolytic disease of the newborn, idiopathic thrombocytopenia purpura, and systemic lupus. Medical conditions that led to secondary antibody deficiency were differentiated from the congenital forms, and the author warned against the indiscriminate use of gammaglobulin, a concern that remains relevant today.

The etiology of agammaglobulinemia was not known. A failure in gammaglobulin synthesis was proposed and believed to be the consequence of a defect in protein metabolism. The arrest in B lymphocyte development in these patients would not become clear until after Max Cooper's sentinel work on the bursa of Fabricius in chickens. Yet, it would take another 30 years to fully understand the genetic basis of XLA.[2,3]

This article provides a snapshot of pioneering work that has resulted in the characterization of >150 primary immunodeficiency diseases. The authors insightfully compared gamma globulin therapy for a patient with XLA to insulin therapy for a patient with diabetes mellitus. We may soon see the day in which recombinant gammaglobulin is administered on demand through a continuous subcutaneous pump.

Nathan R. York, MD, PhD
M. Teresa de la Morena, MD
Department of Pediatrics
UT Southwestern Medical Center Dallas
Dallas, Texas
10.1016/j.jpeds.2011.12.028

References

1. Bruton OC. Agammaglobulinemia. Pediatrics 1952;9:722-8.
2. Tsukada S, Saffran DC, Rawlings DJ, Parolini O, Allen RC, Klisak I, et al. Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. Cell 1993;72:279-90.
3. Vetrie D, Vorechovský I, Sideras P, Holland J, Davies A, Flinter F, et al. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature 1993;361:226-33.