Racial and ethnic differences among children with new-onset autoimmune Type 1 diabetes

K. Gandhi1, M. Tosur1, R. Schaub1, M. W. Haymond2 and M. J. Redondo1

1Section of Diabetes and Endocrinology, Department of Pediatrics, Texas Children’s Hospital/Baylor College of Medicine and 2Children’s Nutrition Research Center, Baylor College of Medicine, Houston, TX, USA

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Abstract

Aim To compare demographic and clinical characteristics among children from ethnic minorities and non-Hispanic white children with new-onset autoimmune Type 1 diabetes.

Methods We analysed a single-centre series of 712 children with new-onset autoimmune Type 1 diabetes between January 2008 and March 2011. The median (range) age was 9.7 (0.3–18.1) years, the mean (SD) BMI percentile was 69.7 (25.4) and 48.3% of the cohort were girls. The cohort comprised 57.3% non-Hispanic white, 20.5% Hispanic and 14.8% African-American children, and 7.4% were of other, mixed or unknown race.

Results The Hispanic subgroup, compared with non-Hispanic white subgroup, had a higher mean (SD) C-peptide level [0.82 (1.62) vs 0.55 (0.47) ng/ml; \( P = 0.004 \)], and a greater proportion of children with elevated BMI (overweight or obesity; 49.6% vs 32.5%; \( P < 0.001 \)) and diabetic ketoacidosis (51.8% vs 38.2%; \( P = 0.006 \)). The African-American group had a higher mean (SD) glucose level [24.4 (12.8) vs 21.4 (10.7) mmol/l; \( P = 0.017 \)], a greater proportion of children with ketoacidosis (56.7% vs 38.2%; \( P = 0.001 \)), a greater proportion with elevated BMI (52.9% vs 32.5%; \( P < 0.001 \)), and a lower proportion of children at pre-pubertal stage (49.0% vs 61.6%; \( P = 0.01 \)), and tended to have higher C-peptide levels [0.65 (0.59) vs 0.55 (0.47) ng/ml; \( P = 0.079 \)] compared with the non-Hispanic white children. The differences in C-peptide levels compared with non-Hispanic white children persisted for Hispanic (\( P = 0.01 \)) but not African-American children (\( P = 0.29 \)) after adjustment for age, sex, BMI, ketoacidosis, glucose, Tanner stage and autoantibody number.

Conclusion At the onset of paediatric autoimmune Type 1 diabetes, Hispanic, but not African-American children had higher C-peptide levels, after adjustment for potential confounders, compared with non-Hispanic white children. These findings suggest that ethnicity may contribute to the heterogeneity of Type 1 diabetes pathogenesis, with possible implications for intervention.

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What’s new?

- At diagnosis of autoimmune Type 1 diabetes, Hispanic children, but not African-American children, had higher C-peptide levels compared with their non-Hispanic white counterparts, after adjustment for potential confounders.
- Ethnicity should be included in the phenotypic characterisation of subtypes of Type 1 diabetes, as it specifically contributes to heterogeneity in β-cell function at diagnosis.
- The design of intervention trials may need to consider ethnic differences among individuals with Type 1 diabetes.

obtained from the electronic health records of children who presented sequentially at the Texas Children’s Hospital with a clinical diagnosis of new-onset Type 1 diabetes (n=759). Essentially all children admitted to the Texas Children’s Hospital with a diagnosis of new-onset diabetes mellitus have biochemical islet autoantibodies [glutamic acid decarboxylase 65 (GAD65), islet cell autoantigen 512 (ICA512) and insulin autoantibodies (IAA)], and C-peptide tested at presentation. To ensure that only Type 1 diabetes cases were studied, the present study only included children with positivity for at least one islet autoantibody (excluded, n=47; final sample, n=712). The study was approved by the institutional review board at Baylor College of Medicine.

Data collection

Demographic information included dates of birth and diagnosis, gender and race/ethnicity (as recorded in the medical record system). Anthropometric information included weight and height at the first clinical visit (at a median of 1.2 months after diagnosis), and Tanner pubertal staging, carried out by a paediatric endocrinologist. Biochemical data included blood glucose, HbA1c, pH, bicarbonate, random C-peptide, and islet autoantibodies (GAD65, IAA and ICA512), all of which were measured simultaneously at diagnosis, on arrival at our facility. C-peptide and islet autoantibody concentrations were measured by the Quest Diagnostics Nichols Institute (San Juan Capistrano, CA, USA). C-peptide concentration was measured using a solid-phase, two-site chemiluminescent immunoassay, with total coefficient of variance: 7.73% for GAD65 (positivity > 1 U/mL); 6.79% for IAA (positivity > 0.4 U/mL); and 7.99% for ICA512 (positivity > 1 U/mL). BMI was calculated in children aged >2 years and was categorized using sex- and age-specific percentiles according to the Centers for Disease Control and Prevention criteria [12]. Overweight was defined as BMI between the 85th and 94th percentiles and obesity as BMI ≥95th percentile [12].

Statistical analysis

Statistical analyses were conducted with SPSS version 23.0 and STATA 12 (StataCorp., 2007, Stata Statistical Software: Release 12, StataCorp LP, College Station, TX, USA). To compare groups, chi-squared tests, t-tests or one-way ANOVA were used as appropriate. Multivariable linear regression was used to evaluate the relationship between C-peptide concentration and race/ethnicity, while controlling for confounding variables. P values <0.05 were taken to indicate statistical significance. All statistical data are presented as mean ± SD, except age which is reported as median (range).

Results

We studied the clinical characteristics of 712 children with newly diagnosed autoimmune Type 1 diabetes and a median (range) age of 9.7 (0.3–18.1) years (Table 1). Non-Hispanic white children comprised 57.3% (n=408) of the sample, with Hispanic and African-American children the next largest ethnic groups (20.5% and 14.8%, respectively). BMI, measured at the first clinical visit, was elevated in 38.4% of the children, with 19.4% classified as overweight and 19% classified as obese. Other characteristics of the sample are shown in Table 1.

The prevalence of elevated BMI (P<0.001), presence of ketoacidosis (P=0.002), positivity for insulin autoantibodies (P=0.02) and plasma C-peptide concentration (P=0.02) differed among the race/ethnic groups (non-Hispanic white, Hispanic, African-American, other /mixed/unknown race).

Compared with the non-Hispanic white group, the Hispanic group with new-onset Type 1 diabetes (Table 1) had a higher BMI (P=0.0006) and a higher proportion of obese or overweight children (P=0.001). Ketoacidosis was more frequent among Hispanic than non-Hispanic white children (P=0.006). Hispanic children had a higher C-peptide concentration than non-Hispanic white children (P=0.004). Multivariate analysis showed that C-peptide concentration at the onset of autoimmune Type 1 diabetes was higher in Hispanic than non-Hispanic white children (P=0.01, coefficient=0.30) after adjustment for sex, age, Tanner stage, BMI percentile, presence of ketoacidosis, glucose level and autoantibody number.

Compared with non-Hispanic white children (Table 1), African-American children had a higher BMI (P<0.0001), and a higher prevalence of overweight or obesity (P<0.001), and were less likely to be at the pre-pubertal Tanner stage (P=0.01). African-American children were more likely to have ketoacidosis (P=0.001) and had higher glucose levels (P=0.017) than non-Hispanic white children. There was a trend for African-American children to have a higher
Table 1 Characteristics of children with new-onset autoimmune Type 1 diabetes, stratified by race/ethnicity (n=712)

| Race/ethnicity          | Overall | Non-Hispanic white | Hispanic | African-American | Other | p* |
|-------------------------|---------|--------------------|----------|------------------|-------|----|
|                         | p1      | p2                 | p3       |                   |       |    |
| Sample size, n (%)      | 712 (100) | 408 (57.3)        | 146 (20.5) | 105 (14.8)   | 53 (7.4) | n/a | 0.10 | 0.99 | 0.01 |
| Tanner stage, n (%)     | 393 (59.3) | 236 (61.6)        | 81 (60)   | 48 (49)     | 28 (60.9) |       | 0.10 | 0.99 | 0.01 |
|                         | 74 (11.2) | 41 (10.7)         | 14 (10.4) | 11 (11.2)   | 8 (17.4)  |       | 0.10 | 0.99 | 0.01 |
|                         | 64 (9.7)  | 35 (9.1)          | 14 (10.4) | 10 (10.2)   | 5 (10.9)  |       | 0.10 | 0.99 | 0.01 |
|                         | 70 (10.6) | 42 (11)           | 15 (11.1) | 10 (10.2)   | 3 (6.5)   |       | 0.10 | 0.99 | 0.01 |
|                         | 61 (9.2)  | 29 (7.6)          | 11 (8.1)  | 19 (19.4)   | 2 (4.3)   |       | 0.10 | 0.99 | 0.01 |
| Missing, n              | 50       | 25                 | 11        | 7            | 7        |       | 0.10 | 0.99 | 0.01 |
| Median (range) age, years | 9.8 (0.3–18.1) | 9.7 (0.7–18.1) | 9.9 (0.3–18.0) | 10.4 (1.1–17.9) | 9.4 (1.6–17.5) | 0.45 | 0.48 | 0.23 |
|                         | 2        | 0                  | 0         | 2            | 0        |       | 0.45 | 0.48 | 0.23 |
| Girls, n (%)            | 344 (48.3) | 193 (47.3)        | 74 (50.7) | 50 (47.6)    | 27 (50.9) |       | 0.88 | 0.48 | 0.95 |
| Missing, n              | 0        | 0                  | 0         | 0            | 0        |       | 0.88 | 0.48 | 0.95 |
| Obese or overweight, n (%) | 237 (38.4) | 118 (32.5)       | 61 (49.6) | 46 (52.9)    | 12 (27.3) |       | <0.0001 | 0.001 | <0.0001 |
| Missing, n              | 95       | 45                 | 23        | 18           | 9        |       | <0.0001 | 0.0006 | <0.0001 |
| BMI percentile           | 69.7±25.4 | 66.1±26.0         | 75.4±25.0 | 78.5±21.6   | 65.9±22.2 |       | 0.63 | 0.58 | 0.33 |
|                         | 95       | 45                 | 23        | 18           | 9        |       | 0.63 | 0.58 | 0.33 |
| HbA1c, mmol/mol          | 104±25   | 104±26             | 103±26    | 106±25      | 105±19   |       | 0.02 | 0.096 | 0.079 |
|                         | 11.7±2.3 | 11.7±2.4           | 11.6±2.4  | 11.9±2.3    | 11.8±1.8 |       | 0.02 | 0.096 | 0.079 |
| Missing, n              | 18       | 12                 | 4         | 1            | 1        |       | 0.02 | 0.096 | 0.079 |
| Ketoadiabetes, n (%)     | 291 (43.8) | 146 (38.2)        | 70 (51.8) | 55 (56.7)    | 20 (40)  |       | 0.02 | 0.096 | 0.079 |
| Missing, n              | 48       | 26                 | 11        | 8            | 3        |       | 0.02 | 0.096 | 0.079 |
| Glucose, mmol/l          | 22.4±11.3 | 21.4±10.7         | 23.1±9.9  | 24.4±12.8   | 23.6±14.8 |       | 0.06 | 0.096 | 0.017 |
| Missing, n              | 11       | 5                  | 4         | 2            | 0        |       | 0.06 | 0.096 | 0.017 |
| C-peptide, ng/ml         | 0.63±0.88 | 0.55±0.47         | 0.82±1.62 | 0.65±0.59   | 0.62±0.81 |       | 0.023 | 0.004 | 0.079 |
| Missing, n              | 34       | 20                 | 6         | 1            | 7        |       | 0.023 | 0.004 | 0.079 |
| Positive diabetes antibodies, n (%) | 269 (38) | 139 (34.3)        | 61 (42.1) | 40 (38.1)    | 29 (54.7) |       | 0.02 | 0.096 | 0.47 |
| IAA                     | 4        | 3                  | 1         | 0            | 0        |       | 0.02 | 0.096 | 0.47 |
| Missing, n              | 577 (81.4) | 336 (83)         | 117 (80.1) | 82 (78.1)    | 42 (79.3) |       | 0.63 | 0.44 | 0.25 |
| ICAS12                  | 3        | 3                  | 0         | 0            | 0        |       | 0.63 | 0.44 | 0.25 |
| Missing, n              | 611 (86.1) | 345 (84.6)       | 126 (86.9) | 94 (89.5)    | 46 (88.5) |       | 0.54 | 0.50 | 0.20 |
| GAD65                   | 2        | 0                  | 1         | 0            | 1        |       | 0.54 | 0.50 | 0.20 |
| Missing, n              | 149 (21.2) | 88 (21.8)        | 30 (20.8) | 20 (19.1)    | 11 (21.2) |       | 0.94 | 0.80 | 0.53 |
| Single positive autoantibody, n (%) | 8        | 5                  | 2         | 0            | 1        |       | 0.94 | 0.80 | 0.53 |

GAD65, glutamic acid decarboxylase 65; ICAS12, islet cell autoantigen 512; IAA, insulin autoantibodies; n/a, not applicable.

Values are mean ± SD, except where otherwise indicated. Percentages do not include missing values. Missing values were not included in the statistical analysis.

*Comparisons between Hispanic and African-American children were all non-significant. ¹P value for overall comparison. ²P value for the comparison between non-Hispanic white and Hispanic children. ³P value for the comparison between non-Hispanic white and African-American children.
C-peptide concentration ($P=0.079$) than non-Hispanic white children. In the multivariable analysis, African-American race, compared with non-Hispanic white race, was not a significant factor ($P=0.29$) in C-peptide levels at the onset of paediatric Type 1 diabetes after adjusting for age, sex, BMI percentile, ketoacidosis, glucose level, Tanner stage or autoantibody number (model: $P<0.0001$). None of the variables studied were significantly different between Hispanic and African-American children.

Discussion

We compared the demographic, metabolic and clinical characteristics of a single-centre cohort of 712 racially diverse children with newly diagnosed autoimmune Type 1 diabetes. Hispanic children had higher C-peptide concentrations than non-Hispanic white children at the onset of paediatric autoimmune Type 1 diabetes, after adjusting for confounders including age, Tanner stage, BMI, glucose, ketoacidosis and autoantibody number.

These findings highlight the heterogeneity of Type 1 diabetes and point to race/ethnicity as an important contributor to this. The phenotypic identification of diabetes subtypes to inform individualized treatment decisions is a recognized need [8]. Understanding the drivers of differences in C-peptide levels at various stages of islet autoimmunity and Type 1 diabetes [13] is critical for the design of trials that aim to preserve β-cell function. Age has been recognized as a major factor in C-peptide decline and is therefore proposed as a criterion for prevention trials [14]. The present study shows that ethnicity influences β-cell function at the onset of Type 1 diabetes. The large sample size and data completeness allowed us to adjust for the potential confounders of the relationship between C-peptide concentration at Type 1 diabetes onset and race/ethnicity. The finding that Hispanic children had greater β-cell function than non-Hispanic white children warrants further investigation into differential patterns of C-peptide loss before and after onset according to ethnicity so that preventive and therapeutic strategies can be tailored accordingly.

Because diabetes develops when insulin secretion cannot maintain euglycaemia, the observation that Hispanic children present with new-onset Type 1 diabetes with higher β-cell function than non-Hispanic white children suggests that insulin resistance in the former subgroup is also higher, despite adjustment for BMI. It has been previously reported that BMI underestimates the degree of adiposity in Hispanic people compared with non-Hispanic white people [15]. It is possible that more than one mechanism of diabetes, namely, insulin resistance, in addition to autoimmune β-cell loss, plays a role in the development of autoimmune Type 1 diabetes in Hispanic people. The realization that several diabetogenic processes may co-exist in the same person has recently been emphasized as a critical concept in preventive and therapeutic interventions [8]. In addition, previous studies have suggested that greater β-cell function is associated with better diabetes outcomes [16] and thus longitudinal studies are needed to evaluate progression of Type 1 diabetes in those individuals with greater β-cell function at the onset. In the present study, 49.6% of Hispanic and 52.9% of African-American children had an elevated BMI compared with 32.5% of non-Hispanic white children. This high frequency of obesity and overweight, more extreme among minority children, is consistent with previous reports in children with new-onset or established Type 1 diabetes, as well as in the general population [1,11,17,18] and underscores the limitations of BMI as a criterion by which to discriminate Type 1 and Type 2 diabetes [9]. Furthermore, children with Type 1 diabetes and obesity often have additional cardiovascular risk factors [19] that warrant screening and treatment as appropriate [1,7].

The major strengths of the present study include the large sample size and diversity in a single-centre cohort with systematically collected data and a low proportion of missing data. These characteristics gave us the opportunity to compare race/ethnicity with regard to clinically important variables and to adjust comprehensively for potential confounders. While area-under-the-curve of C-peptide concentrations in a mixed-meal tolerance test is the ‘gold standard’ measure of β-cell function [20], many have previously used random C-peptide at the time of onset. This measurement, easily obtained in a real-world clinical setting, has demonstrated high correlation with clinically significant variables [11,21]. The cross-sectional nature of the present study limits its ability to investigate the longitudinal effects of preserved C-peptide function on long-term diabetes outcomes. The lack of significant differences between Hispanic and African-American children may have been attributable to the relatively small numbers in the subgroups.

In summary, race/ethnicity contributes to heterogeneity of Type 1 diabetes presentation. Analysis of race/ethnicity in prospective studies on the development and progression of Type 1 diabetes may lead to the inclusion of race/ethnicity in predictive models and subsequently preventive and therapeutic trials.

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Competing interests

None declared.

References

1. Lawrence JM, Mayer-Davis EJ, Reynolds K, Beyer J, Pettitt DJ, D’Agostino RB, Jr et al. Diabetes in Hispanic American youth: prevalence, incidence, demographics, and clinical characteristics:
the SEARCH for Diabetes in Youth Study. Diabetes Care 2009; 32 (Suppl. 2): S123–132.
2 Mayer-Davis EJ, Beyer J, Bell RA, Dabelea D, D’Agostino R, Jr, Imperatore G et al. Diabetes in African American youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009; 32 (Suppl. 2): S112–122.
3 Tosur M, Redondo MJ. Heterogeneity of Type 1 Diabetes: The Effect of Ethnicity. Curr Diabetes Res 2017; https://doi.org/10.2174/157339981366170502105402. [Epub ahead of print].
4 Jacobsen JJ, Black MH, Li BH, Reynolds K, Lawrence JM. Race/ethnicity and measures of glycaemia in the year after diagnosis among youth with type 1 and type 2 diabetes mellitus. J Diabetes Complications 2014; 28: 279–285.
5 Willi SM, Miller KM, DiMeglio LA, Klingensmith GJ, Simmons JH, Tamborlane WV et al. Racial-ethnic disparities in management and outcomes among children with type 1 diabetes. Pediatrics 2015; 135: 424–434.
6 Gallegos-Macias AR, Macias SR, Kaufman E, Skipper B, Kalishman N. Relationship between glycemic control, ethnicity and socioeconomic status in Hispanic and white non-Hispanic youths with type 1 diabetes mellitus. Pediatr Diabetes 2003; 4: 19–23.
7 Pettiti DB, Klingensmith GJ, Bell RA, Andrews JS, Dabelea D, Imperatore G et al. Glycemic control in youth with diabetes: the SEARCH for diabetes in Youth Study. J Pediatr 2009; 155: 668–672.
8 Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L et al. Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis. Diabetes 2017; 66: 241–255.
9 Klingensmith GJ, Connor CG, Ruedy KJ, Beck RW, Kollman C, Haro H et al. Presentation of youth with type 2 diabetes mellitus in the Pediatric Diabetes Consortium. Pediatr Diabetes 2016; 17: 266–273.
10 Valenzuela JM, Seid M, Waitzfelder B, Anderson AM, Beavers DP, Dabelea DM et al. Prevalence of and disparities in barriers to care experienced by youth with type 1 diabetes. Pediatr 2014; 164: 1369–1375.
11 Redondo MJ, Rodriguez LM, Escalante M, O’Brien Smith E, Balasubramanyam A, Haymond MW. Beta cell function and BMI in ethnically diverse children with newly diagnosed autoimmune type 1 diabetes. Pediatr Diabetes 2012; 13: 564–571.
12 Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA 2014; 311: 806–814.
13 Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care 2015; 38: 1964–1974.
14 Hao W, Gitelman S, DiMeglio LA, Boulware D, Greenbaum CJ. Type 1 Diabetes TrialNet Study Group. Fall in C-Peptide During First 4 Years From Diagnosis of Type 1 Diabetes: Variable Relation to Age, HbA1c, and Insulin Dose. Diabetes Care 2016; 39: 1664–1670.
15 Wong WW, Strizich G, Heo M, Heymsfield SB, Himes JH, Rock CL et al. Relationship between body fat and BMI in a US Hispanic population-based cohort study: Results from HCHS/SOL. Obesity 2016; 24: 1561–1571.
16 Stetges MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care 2003; 26: 832–836.
17 Liu LL, Lawrence JM, Davis C, Liese AD, Pettitt DJ, Pihoker C et al. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth study. Pediatr Diabetes 2010; 11: 4–11.
18 Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of Obesity Among Adults and Youth: United States, 2011-2014. NCHS Data Brief 2015; 219: 1–8.
19 Redondo MJ, Foster NC, Libman IM, Mehta SN, Hathaway JM, Bethin KE et al. Prevalence of cardiovascular risk factors in youth with type 1 diabetes and elevated body mass index. Acta Diabetol 2016; 53: 271–217.
20 Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H et al. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21-22 October 2001. Diabetes 2004; 53: 250–264.
21 Keenan HA, Sun JK, Levine J, Doria A, Aiello LP, Eisenbarth G et al. Residual insulin production and pancreatic ss-cell turnover after 50 years of diabetes: Joslin Medalist Study. Diabetes 2010; 59: 2846–2853.