Clinical and Laboratory Features of Youth Onset Type 2 Diabetes in Jamaica
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ABSTRACT

Objectives: To assess the frequency of youth onset Type 2 diabetes mellitus (T2D) in Jamaica and the characteristics of youth with this form of diabetes.

Methods: Patients from two major referral hospitals, diagnosed with diabetes before age 25 years and < 6 years prior to the study, were evaluated. Classification was based on the presence of GAD-65 and IA-2 diabetes autoantibodies (AB), fasting (FCP) and stimulated C-peptide (SCP) measurements, serum leptin and clinical phenotype as follows: (i) Type 1A diabetes – AB+, (ii) Type 1B diabetes – AB- and FCP < 230 pmol/l and/or SCP < 660 pmol/l, (iii) Type 2 diabetes – AB- and FCP > 500 pmol/l and/or SCP ≥ 1160 pmol/l (iv) Untypeable diabetes – AB- and FCP 230–500 pmol/l and/or SCP 660–1160 pmol/l and (v) Lipoatrophic diabetes – clinical phenotype and serum leptin.

Results: Fifty-eight participants (21M, 37F, age 20 ± 8 years, duration of diabetes 2.6 ± 2 years) were enrolled in the study. Using the classification criteria, Type 1 diabetes was the most common form of diabetes: 18(31%) Type 1A, 18(31%) Type 1B. Overall 22% (13 patients) had T2D. Patients with T2D were more likely to be female, older at diagnosis, obese and have a higher blood pressure when compared to those with Type 1 diabetes. In logistic regression analysis, age of diabetes onset, gender, BMI, systolic and diastolic blood pressure were significantly associated with T2D. Obesity measured by BMI was the strongest predictor of T2D.

Conclusions: While Type 1 diabetes was the predominant form of diabetes in this study, a significant proportion of Jamaicans with youth onset diabetes may have T2D. Obesity is the strongest clinical predictor of Type 2 diabetes in the young diabetic patient.

Keywords: Adolescent, Caribbean, classification, diabetes mellitus, young adult

Características Clínicas y de Laboratorios en la Aparición de la Diabetes de Tipo 2 en los Jóvenes de Jamaica
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RESUMEN

Objetivos: Evaluar la frecuencia de la aparición de la diabetes mellitus tipo 2 (DT2) en los jóvenes de (T2D) en Jamaica y las características de los jóvenes con esta forma de diabetes.

Métodos: Pacientes de dos importantes hospitales de remisión, fueron evaluados y diagnosticados con diabetes antes de los 25 años de edad y < 6 años antes del estudio. La clasificación se basó en la presencia de auto-anticuerpos (AC) GAD-65 e IA-2 de la diabetes, mediciones de péptido C en ayunas (PCA) y péptido C estimulado (PCE), leptina sérica y fenotipo clínico como sigue: (i) diabetes tipo A1 – AB+; (ii) diabetes tipo B1 – AB– y PCE < 230 pmol/l y/o PCE < 660 pmol/l; (iii) diabetes tipo 2 – AB– y PCE > 500 pmol/l y/o PCE ≥ 1160 pmol/l; (iv) diabetes no tipificable – AB– y PCE 230–500 pmol/l y/o PCE 660–1160 pmol/l; y (v) diabetes lipoatrófica – fenotipo clínico y leptina sérica.

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The prevalence of diabetes in Jamaican adults is estimated to be between 13 and 18% with a female predominance of the disease (11, 12). In a study of Jamaican adolescents 11–12 years old, the prevalence of overweight or obesity (Body Mass Index [BMI] > 85th percentile) was 19.3% (13). The 2000 Ministry of Health Lifestyle Survey found that approximately 16% of youth 15–24 years old were overweight and 9% were obese putting them at increased risk for developing Type 2 diabetes. While national data on the prevalence of gestational diabetes in Jamaica are available, in a study of women in the University Hospital of the West Indies Antenatal Clinic, the prevalence of gestational diabetes was 12.5% in those with a family history of early onset diabetes and 1.5% in those who had no family history of this disease (14).

The aim of this study was to determine whether a significant proportion of patients with recently diagnosed youth onset diabetes had Type 2 diabetes, to assess how well physicians were able to identify patients with youth onset Type 2 diabetes and to examine the clinical characteristics of these patients that might allow the practitioner to identify cases of the disease.

SUBJECTS AND METHODS
The study was conducted in Jamaica, a multi-ethnic, predominantly black, middle income developing country in the Caribbean. A list of hospital admissions and clinic records for diabetes at the island’s two largest referral hospitals over a 5-year period 1999–2004 was obtained. Patients diagnosed with diabetes mellitus after January 1, 1998, 25 years old or younger at the time of diagnosis and living in the Southeast region of the island, where approximately 50% of the island’s population reside (within two hours commute of the Tropical Medicine Research Institute) were invited to participate in this study. Additional patients who met the inclusion criteria were referred at the time of diagnosis or admission to hospital.
while the study was being conducted (September 2004 to May 2006). Patients with gestational diabetes (diabetes that resolved after pregnancy) who were pregnant or less than 10 years old at the time the study (as they were unlikely to have Type 2 diabetes) were excluded. The study was approved by The University of the West Indies and the Kingston Public Hospital Ethics Committees and informed consent was obtained from each participant prior to enrolment.

Medical History

Each study participant was invited to attend a research clinic at the Tropical Medicine Research Institute. During the visit, the participants (and, for participants less than 12 years old, their parents/guardians) completed an interviewer administered questionnaire to determine details about their history such as symptoms of diabetes at diagnosis, hospitalizations, diabetes related complications, medications, co-morbid illnesses, social habits and family medical history.

Hospital records were also requested for each participant and data abstracted by one investigator (MTR) on the symptoms and laboratory results at presentation, co-morbid illnesses and the treatment administered.

Anthropometric Measurements

Height, weight and waist circumference were measured using a standardized protocol by trained investigators. Height was measured to the nearest centimetre using a portable stadiometer and weight was measured to the nearest 0.1 kg with an electronic digital scale. The body mass index was calculated as the weight in kilograms divided by the square of the height in metres. Participants under 18 years old were classified according to their age and gender specific BMI percentiles using the CDC growth standards (15). Those in the 85–94th percentile were classified as overweight while those in the 95th and higher centiles were considered obese (16). Participants over 18 years old with a BMI between 25 and 29.8 kg/m² were classified as overweight and those with a BMI > 30kg/m² were obese (17). Waist circumference was measured midway between the anterior-superior iliac spine and the lowest rib. Sitting blood pressure was measured with a mercury sphygmomanometer to the nearest 2 mm Hg using the first (systolic) and fifth (diastolic) Korotkoff phases (18). Three measurements were taken at one-minute intervals after the participant had been seated for five minutes. The mean of the last two readings was used for the analysis. A focused physical examination was performed by one investigator (MTR) on all the patients.

Laboratory Measurements

After verifying an overnight fast of at least 8 hours and determining the time of the last insulin dose, a fasting blood sample was obtained. A C-peptide stimulation test was performed using Boost (7 mls/kg up to maximum of 400 mls) given at 0 minutes. Blood samples for glucose and C-peptide were collected from an indwelling catheter every 30 minutes for two hours. Samples were stored in ice where appropriate and all specimens were processed at the Institute’s laboratory within four hours of collection and stored at -70°C. Specimens that were sent to an overseas laboratory were shipped by courier using a cold pack.

Serum glucose was measured using a glucose oxidase enzymatic method. Serum C-peptide concentration was measured using commercially prepared reagents with a lower detection limit of 165 pmol/L (IMMULITE Diagnostic Products Cooperation, Los Angeles, CA). Glutamic acid decarboxylase (GAD65) and tyrosine phosphate IA-2 autoantibodies were measured at Northwest Lipid Laboratory (University of Washington, Seattle, WA) using a radioligand binding assay (19). Patients with a GAD65 Index > 0.085 or an IA-2 Index > 0.017 were considered diabetes antibody positive. Serum leptin levels were determined by immunoassays with the use of a commercial kit (Linco Research, St Charles, MO).

Diabetes Classification

Subjects were classified into five groups by two endocrinologists (MTR and MSB) using the following criteria:

(i) Type 1A diabetes – GAD65 or IA-2 positive
(ii) Type 1B diabetes – GAD65 and IA-2 negative and fasting C-peptide < 230 pmol/L and/or stimulated C-peptide < 660 pmol/L
(iii) Type 2 diabetes – GAD65 and IA-2 negative and fasting C-peptide > 500 pmol/L and or stimulated C-peptide ≥1160 pmol/L
(iv) Lipoatrophic diabetes (a rare form of diabetes associated with loss of subcutaneous fat and severe insulin resistance) – distribution of subcutaneous fat with or without a low serum leptin (< 5 ng/ml)
(v) Untypeable diabetes – GAD65 and IA-2 negative with fasting C-peptide between 230–500 pmol/L and/or stimulated C-peptide 660–1160 pmol/L

Statistical Methods

For continuous variables, comparisons were made between patients according to diabetes type using the Wilcoxon Rank Sum Test and the Kruskal Wallis Test while comparisons between dichotomous variables were made using the Fisher’s Exact Test. Multivariable logistic regression was used to assess the association between clinical characteristics and the likelihood of youth onset Type 2 diabetes. The kappa statistic was used to assess agreement between physician and investigator assigned diabetes classification. Results were considered significant if p < 0.05. Analysis was performed using Stata 8.0 (Stata Corporation, College Station, TX).

RESULTS

Of the 65 patients identified, two refused to participate in the study, two could not be located, two had died and one, on repeat testing was not found to have diabetes. The charac-
participants evaluated were classified as having Type 2 diabetes. Type 1 diabetes was the most common form of diabetes in the sample (62%). Lipoatrophic diabetes was found in three female participants and six patients remained unclassified at the end of the study.

Sixteen percent of the patients studied under 18-years old had Type 2 diabetes, while 30% (8/27) of those over 18 years old had the disease ($p = 0.18$). Approximately half of the subjects with Type 2 diabetes had the disease onset before age 18 years (mean age of onset 19 ± 5 years). The youngest patient was 13 years old at diagnosis. The majority of the participants classified as having Type 2 diabetes were female (12F, 1M) compared to those with Type 1 diabetes (21F, 15M).

As there were few subjects in the other diabetes groups (lipoatrophic and unclassified) further analysis was restricted to the participants classified as having Type 1 (Type 1A and 1B combined) and Type 2 diabetes. Participants with Type 2 diabetes were more likely to be female ($p = < 0.01$) and diagnosed at an older age compared to those with Type 1 diabetes ($19 ± 5 \text{ vs } 15 ± 5 \text{ years}; p = 0.01$). The prevalence of diabetes in the parents or siblings of participants with Type 1 and Type 2 diabetes was not different. Participants with both these forms of diabetes were equally likely to have been admitted to hospital at diagnosis and treated for diabetic ketoacidosis. Participants with Type 2 diabetes reported more treatment with oral agents for diabetes (Table 2).

Participants with Type 2 diabetes had a higher waist circumference ($p < 0.01$), BMI ($p < 0.01$) and mean systolic blood pressures ($p < 0.01$) and diastolic blood pressures ($p = 0.02$). Acanthosis nigricans was a common examination finding in the patients with Type 2 diabetes ($p = 0.02$). Female participants with Type 2 diabetes were equally likely to have hirsutism compared with those with Type 1 diabetes.

Table 3 presents logistic regression models used to examine factors that might help to differentiate Type 1 from Type 2 diabetes in youth. An older age of onset of diabetes, being female, and higher BMI, systolic and diastolic blood pressure readings were significantly associated with Type 2 diabetes. After adjustment for BMI, none of the other factors remained significantly associated with the presence of Type 2 diabetes suggesting that this was the most important predictor of this type of diabetes (Table 3).

Finally, we compared physician diabetes classification from patient records with that obtained from our laboratory testing (Table 3). Almost a third of patients (21/58) had no diabetes type stated in their medical records. Of those with investigator defined Type 1 diabetes a little over half (20/36) were classified as having Type 1 diabetes by physicians while over one third of the patients with investigator determined Type 2 diabetes (5/13) were similarly classified by their physicians. Four of the 36 patients with Type 1 diabetes were thought to have Type 2 diabetes by their clinicians and for a large proportion of these patients no attempts were made to determine their diabetes phenotype. The kappa statistic, comparing classification using both methods, was 0.26 when the entire sample was assessed but improved to 0.51 when those who had no diabetes classification type from their physicians were excluded.
DISCUSSION

While Type 1 diabetes was the most common form of diabetes in this study, 22% of the participants studied had Type 2 diabetes. The likelihood of Type 2 diabetes increased with age at diagnosis and was more common in the female patients. There were no significant differences in the clinical presentation of patients with Type 1 and Type 2 diabetes at the time of initial hospitalization for this disease or how they were initially treated at diagnosis. Obesity appeared to be the most important factor associated with youth onset Type 2 diabetes.

It is important for clinicians to be able to distinguish between Type 1 and Type 2 diabetes as there are differences...
in treatment. Patients with Type 1 diabetes develop ketoacidosis if insulin is withheld while those with Type 2 diabetes may be treated with oral agents only and have a lower risk of ketoacidosis. In addition Type 2 diabetes is usually associated with insulin resistance and treatments directed at reducing insulin resistance, such as weight loss and increased physical activity, are a critical aspect of the management of these patients. Additionally, oral therapy instead of insulin for diabetes management may be more acceptable to some patients.

The difficulty distinguishing between patients with the two most common forms of diabetes clinically has been demonstrated in this and other studies (20). While obesity was more common in those with Type 2 diabetes it was also present in some of the patients with Type 1 diabetes. Similarly acanthosis nigricans a marker of insulin resistance was sometimes present in those with Type 1 diabetes. Family history of diabetes in a first degree relative was also not a useful factor in distinguishing between the different forms of diabetes. Clinicians did a poor job in determining diabetes type when all the patients studied were considered (Kappa = 0.26) with a little over a half of those with investigator determined Type 1 diabetes and a third of patients with investigator determined Type 2 diabetes being classified similarly by their doctors based on the clinical information available. In a substantial number of the patient records (21/58) no attempts at patient classification of diabetes had been made.

Laboratory testing can assist tremendously in the classification process. While not 100% specific, the presence of diabetes autoantibodies is generally considered to confirm the presence of Type 1 diabetes (20). However in non-Caucasian patients there is a higher prevalence of non-autoimmune/autoantibody negative Type 1 diabetes (21). In this study only half of the patients with Type 1 diabetes had at least one diabetes autoantibody present. Because Type 1 diabetes is generally characterized by reduced insulin production, C-peptide measurement can be useful in the diagnostic process. Patients with Type 2 diabetes should have an elevated C-peptide at diagnosis but there are no generally accepted criteria as to what an elevated C-peptide level is. In addition, differences in the standardization of C-peptide assays do not allow for the values from one laboratory to be applied in another setting.

There are very few population-based prevalence and incidence studies of Type 2 diabetes in childhood and adolescence. In Japanese and Taiwanese children, where school-based urine screening for glucose is performed, Type 2 diabetes is more common than Type 1 diabetes in the young and the marked female predominance noted in the United States of America (USA) and the United Kingdom (UK) was not present (22, 23). In Japan, the incidence of Type 2 diabetes has increased significantly over the last 20 years and this has been related to increases in weight (22). Among the Pima Indians, Type 2 diabetes is the only type of diabetes that is present with many cases of this disease occurring prior to the onset of puberty (4). The SEARCH study for Diabetes in Youth, one of the largest to examine this phenomenon, estimated that the prevalence of diabetes in US residents less than 20 years old in 2001 was 1.82 per 1000 persons with 15% of the 10–19 year olds having Type 2 diabetes (24). In a study of Type 2 diabetes in children less than 17 years old in the UK between 2004–2005, the incidence of Type 2 diabetes was estimated to be 3.9 (95% CI: 2.1, 6.7) per 100 000 per year in black and 1.25 (95% CI: 0.6, 2.4) per 100 000 per year in South Asians – compared to 0.35 (95% CI: 0.2, 0.5) per 100 000 per year in whites with 41% of cases from minority populations (10).

The proportion of participants with Type 2 diabetes in this population was lower than one might have expected given the high prevalence of diabetes in adults, the significant number of overweight youth and the age of the study sample. In the SEARCH study where all participants were under 19 years old (24) the proportion of participants with Type 2 diabetes varied with ethnicity, from 6% in non-Hispanic white, 22% in Hispanic, 33% in Black, 40% in Asian Pacific Islanders and 76% in American Indian youth. In a review of all newly diagnosed cases of diabetes in children and adolescents in Florida from 1994–1998, Type 2 diabetes was present in 36% of the cases of diabetes that occurred in black children over this time period (25). In another series of patients seen at Montefiore Medical Centre in New York there was an increase from 12% in 1990 to nearly 50% of all newly diagnosed cases of diabetes in African-American and Caribbean-Hispanic Youth in 2000 (26). A larger population based study to estimate the prevalence of Type 2 diabetes might provide us with proportions that are more in keeping with what has been reported.

Apart from the SEARCH group, very few investigators have stated the criteria they have used for the identification of youth onset Type 2 diabetes (19). We used a modification of the SEARCH criteria in this study. In an unpublished analysis, we did not find that the original SEARCH criteria were useful in helping to identify Type 2 diabetes in this study population. Since their initial publication, these SEARCH criteria have been modified (27). The prevalence of obesity in those with Type 2 diabetes, the female predominance and the higher proportion of subjects on oral agents suggest that the criteria we used are valid. Our classification criteria can only be validated with time as the natural history of the disease in this group of participants is allowed to unfold.

Despite all efforts, 10% of the patients studied could not be classified. These patients were antibody negative and had C-peptide measurements that were intermediate. The difficulty in classification of diabetes in Jamaica has long been described with a series of patients who generally were not overweight, were resistant to ketosis and were not sensitive to insulin (28). The term J-Type diabetes or phasic insulin dependent diabetes was suggested for this group of patients (29). Whether some of the patients described in this
report might have had lipoatrophic diabetes (which we found in an unusual high proportion in this study) or might represent this group of patients which we could not classify, is of interest. Untypeable diabetes in black patients of Caribbean origin continues to be a phenomenon of interest (30).

The DIAMOND study has demonstrated a low incidence of Type 1 diabetes in Latin America and the Caribbean compared to Europe (31). No estimates of the incidence of Type 1 diabetes in Jamaica are available. While no cases of diabetes (Types 1 or 2) were detected by history or laboratory testing in an island-wide sample of Jamaican youth 15–24 years old conducted in 2000 (unpublished data), a nationally representative sample of youth 15–19 years old conducted in 2006 found a 2% prevalence of diabetes based on self-reporting and finger-stick glucose testing (32). Given the low prevalence of diabetes in this age-group, estimates of the incidence of the different forms of diabetes can best be determined through the creation of a registry to identify all newly diagnosed cases.

The sample in this study may not be representative of all patients with youth onset diabetes in Jamaica as we recruited patients from tertiary referral hospitals in Kingston who lived within a certain geographic radius of the Tropical Medicine Research Institute. Residents in this region may constitute up to 50% of the island’s population. In addition, patients were identified using hospital admissions data during the study period. So, asymptomatic patients, those not ill enough for admission, or who had been admitted to private institutions might not have been identified. From clinical experience, most young persons with newly diagnosed Type 1 diabetes are hospitalized within weeks of diagnosis. We may however have missed some patients with Type 2 diabetes who could have received outpatient treatment. At both hospitals, outpatient clinic visits were not coded and therefore we were not able to use this as a means of identifying eligible patients who may have been initially hospitalized elsewhere or were never hospitalized at diagnosis. However, as one of the main objectives of the study was to evaluate the clinical and laboratory characteristics at diagnosis, hospitalized patients were more likely to have this information available. We also had a very low refusal rate from potential participants for the study, so this would not be a significant contributor to selection bias.

In summary, Type 2 diabetes is present in Jamaicans with youth onset diabetes. Particular attention should be paid to obese young persons with diabetes as these are more likely to be Type 2 and the management approaches should be adjusted accordingly with appropriate safeguards as there are no pathognomonic features to differentiate the two most common types of diabetes.

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