Prevalence of Diabetes Complications in Adolescents With Type 2 Compared With Type 1 Diabetes

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OBJECTIVE — To compare the prevalence of diabetes complications and their risk factors in youth with type 1 versus type 2 diabetes.

RESEARCH DESIGN AND METHODS — We performed a comparative clinic-based study of 1,433 patients with type 1 diabetes and 68 patients with type 2 diabetes aged <18 years from New South Wales, Australia. Retinopathy was assessed by seven-field stereoscopic retinal photography; albumin excretion rate from three consecutive, timed, overnight urine collections; peripheral neuropathy by thermal and vibration threshold; and autonomic neuropathy by pupillometry. HbA_{1c} (A1C) and lipids were measured in all patients and C-peptide in patients with type 2 diabetes.

RESULTS — In patients with type 1 versus type 2 diabetes, median (interquartile range) age was 15.7 years (13.9–17.0) and 15.3 years (13.6–16.4), respectively ($P = 0.2$), whereas median diabetes duration was 6.8 years (4.7–9.6) and 1.3 years (0.6–3.1), respectively ($P < 0.0001$). Retinopathy was significantly more common in patients with type 1 diabetes (20 vs. 4%, $P = 0.04$), while microalbuminuria and hypertension were significantly less common (6 and 16% in type 1 diabetes vs. 28 and 36% in type 2 diabetes). Rates of peripheral and autonomic neuropathy were similar (27 and 61% in type 1 diabetes vs. 21 and 57% in type 2 diabetes). In multivariate analyses, microalbuminuria was significantly associated with older age (odds ratio 1.3 [95% CI 1.2–1.5], $P < 0.001$) and systolic hypertension (3.63 [2.0–6.3], $P < 0.001$) in type 1 diabetes, while only higher A1C (1.7 [1.3–2.9], $P = 0.002$) was significant in patients with type 2 diabetes.

CONCLUSIONS — Youth with type 2 diabetes have significantly higher rates of microalbuminuria and hypertension than their peers with type 1 diabetes, despite shorter diabetes duration and lower A1C. The results of this study support recommendations for early complications screening and aggressive targeting of glycemic control in patients with type 2 diabetes.

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Reports of increasing incidence of type 2 diabetes in youth highlight a burgeoning caseload in both developed and developing nations (1). The incidence among children from Tokyo was 2.8 per 100,000 population (2) and 6.5 per 100,000 from Taiwan (3), while the prevalence among American children aged 15–19 years ranged from 2.3 to 50.9 per 100,000 (4). A population-based incidence estimate from Western Australia demonstrated a 27% increase over 12 years from the early 1990s (5), and data from New South Wales indicate that ~1 in 10 adolescents with new-onset diabetes has type 2 diabetes (6). The majority of recent studies of youth-onset type 2 diabetes have addressed its epidemiology and etiology, and a strong association with the increase in childhood obesity is now widely recognized (3,7); however, few studies have addressed the prevalence and risk factors for microvascular complications in this age-group (8–11).

In a recently published study (11) of 26 American youth with type 2 diabetes, microalbuminuria was found in 40% after a mean diabetes duration of 1.5 years. Among Pima Indians with type 2 diabetes diagnosed during childhood, 22% had microalbuminuria at diagnosis (10), while 35% of adolescents and young adults (aged <30 years) from New Zealand had microalbuminuria after a mean duration of 10 years (8). Apart from these data, little is known about complication rates in youth with type 2 diabetes.

We have recently reported a reduction in nephropathy and retinopathy in youth with type 1 diabetes from 1990 to 2002, although there was a concomitant increase in peripheral neuropathy over this period (12). HbA_{1c} (A1C) did not change, but more patients were treated with a multiple injection regimen, suggesting that more "intensive" management may have contributed to the reduction in microvascular complications. The aims of the present study were to assess the prevalence of diabetes complications in youth with type 2 compared with type 1 diabetes from 1996 to 2005 and to investigate factors associated with the development of complications in both groups.

RESEARCH DESIGN AND METHODS

— This was a comparative clinic-based study of complications in youth with type 1 and type 2 diabetes. Patients aged <18 years attending the Diabetes Complications Assessment service at the Children's Hospital at Westmead were included in the analysis. Assessment results were included for those attending between 1996 and July 2005, and results

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Abbreviations: ABS, Australian Bureau of Statistics; AER, albumin excretion rate; GEE, generalized estimating equation.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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from multiple visits were included for all patients who had attended more than once. The definitions of type 1 and type 2 diabetes were based on critera for registration in the Australasian Pediatric Endocrine Group diabetes register (6,13) and national guidelines (14). For type 2 diabetes, criteria included negative diabetes-associated antibodies, elevated fasting insulin or C-peptide, or presence of acanthosis nigricans (14). The study was approved by the ethics committee of the Children's Hospital at Westmead. Patients and their parents gave informed consent for the results of their complication assessment to be analyzed.

Assessment of complications was undertaken during a 2-h visit, which consisted of clinical assessment by the endocrinologist; anthropometry; biochemistry; measurement of blood pressure, pubertal stage, and A1C; and screening for retinopathy, microalbuminuria, and neuropathy. Retinopathy was assessed using stereoscopic fundal photography of seven fields. Before September 2004, the stereo photographs were taken with a Topcon Fundus camera (TRC 50-VT; Tokyo Optical) as previously described (15–19). From September 2004, the IMAGEnet 2000 Lite system was used to digitalize images. The photographs were graded by the same ophthalmologist (S.H.) according to the modified Airlie House classification of diabetic retinopathy (20).

Microalbuminuria was assessed by measurement of mean albumin excretion rate (AER) on three consecutive, timed, overnight urine collections. Albumin was measured using a polyclonal radioimmunoassay (Pharmacia RIA; Beckman Coulter, Gladesville, NSW, Australia). Microalbuminuria was defined as AER $\geq$20 μg/min in at least two of the three timed overnight urine collections or an albumin-to-creatinine ratio $\geq$2.5 mg/mmol.

Autonomic neuropathy was assessed by measuring the pupil size before and 3 s after a light stimulus was delivered using an infrared pupillometer (Pupilscan; Fairvill Medical Optics). Peripheral nerve function was assessed by thermal threshold testing for hot and cold at the left foot (Thermal Threshold Tester; Medelec, Old Woking, Surrey, U.K.) and vibration threshold at the left medial malleolus and left great toe (Biothesiometer; Biomedical Instrument, Newbury, OH) (12,21). Pupillary abnormalities and peripheral nerve abnormalities were defined as <5% of the normal range in a nondiabetic adolescent control group previously tested in our laboratory (22,23).

Glycemic control was assessed by measurement of A1C using the Bio-Rad Diamat analyzer (Bio-Rad, Herculus, CA). The nondiabetic range for A1C is 4–6%. DCA 2000 values were included at interim clinic visits, and all available A1C measurements were included to calculate the individual mean A1C.

Thyroid-stimulating hormone, total cholesterol, and triglyceride levels were measured in all patients, with the addition of C-peptide and liver function tests in those with type 2 diabetes. Dyslipidemia was defined as total cholesterol >5.2 mmol/l and triglyceride >1.7 mmol/l (24). C-peptide was measured by chemiluminescent enzyme immunoassay using the Immulite analyzer (Diagnostic Products, Los Angeles, CA) with normal levels between 0.30 and 0.80 nmol/l. Thyroid function was assessed by measuring thyroid-stimulating hormone (normal <5 μU/ml) and Free T_4 (normal range 10–20 pmol/l).

Height and weight were measured, and BMI was calculated as kilograms divided by the square of height in meters. Overweight and obesity were defined by the age- and sex-specified cutoffs by Cole et al. (25). Blood pressure percentiles for age and sex were determined using the U.S. Task Force Report (26), and hypertension was defined as systolic or diastolic blood pressure >95th percentile. Pubertal stage was assessed by the endocrinologist according to the standards of Tanner and Whitehouse (27). Treatment including insulin therapy (number of insulin injections and total daily insulin dose), oral hypoglycemic agents, or diet and exercise were recorded.

The Australian Bureau of Statistics (ABS) standard for classifying the ethnic and cultural composition of the Australian population was used to define ethnicity (28). Urban/rural status was determined by postcode using ABS data (29). A locality-based social disadvantage risk score was used as a measure of social disadvantage (30). The score ranged from −5.21484 (most social disadvantage) to +1.83241 (least social disadvantage).

Statistical analysis

Descriptive statistics are reported as median (range or interquartile range). The individual mean A1C from all clinic visits was used to compare glycemic control in patients with type 1 and type 2 diabetes, whereas results from their most recent complications assessment clinic visit were used to compare rates of microalbuminuria, retinopathy, and neuropathy. Clinical characteristics and complication rates were compared using χ^2 tests for categorical variables, *t* tests for normally distributed continuous data, and Mann-Whitney *U* tests for skewed data. Multivariate analysis of predictors of glycemic control and microalbuminuria was performed using generalized estimating equations (GEEs) (31) using all available time points. This method of analysis allows for differing length of follow-up and enables patients with only one assessment to be analyzed, along with those for whom longitudinal data are available. Complications were assessed on more than one occasion in 58% of type 1 diabetic patients and 55% of type 2 diabetic patients. The significance of explanatory variables in the final multivariate models are expressed as odds ratios (ORs) and 95% CIs. Clinically relevant interaction terms were examined in the models but were not significant, and models were assessed for goodness of fit. Data were analyzed using SPSS (version 13; Chicago, IL) and STATA (version 8; College Station, TX).

RESULTS

Patient characteristics

There were 1,433 patients with type 1 diabetes (47% male) and 68 with type 2 diabetes (50% male) aged ≤18 years assessed between 1996 and 2005. The patients with type 1 diabetes attended 3,109 assessments (median 2 assessments per patient, range 1–12). Of the patients with type 2 diabetes, 36 had complications assessment (median 2, range 1–4), all had measurement of AER, 25 had gradable retinal photographs, 24 had peripheral nerve function testing, and 23 had autonomic nerve function testing. Data from clinical visits, including anthropometry, blood pressure, details of treatment, biochemical results, and A1C, were available for a further 32 patients. The patients with type 2 diabetes who attended the complications assessment clinic were more likely to come from an urban than a rural area (91 vs. 9%, $P = 0.0001$), whereas there were no differences in age, socioeconomic disadvantage risk score, and A1C between attendees and nonattendees.

Patient characteristics and complication rates at the most recent clinic visit are shown in Table 1 and Fig. 1. There was no difference in age between patients with

Table 1—*Comparison of clinical characteristics and complication rates in youth with type 1 and type 2 diabetes in New South Wales from 1996 to 2005*

	Type 1 diabetes	Type 2 diabetes	*P* value
n	1,433	68	
Age at last assessment (years)	15.7 (13.9–17.0)	15.3 (13.6–16.4)	0.23
Age at diagnosis (years)	8.1 (4.8–10.8)	13.2 (11.6–15.0)	<0.0001
Sex (male/female)	674/759	34/34	0.63
Duration (years)	6.8 (4.7–9.6)	1.3 (0.6–3.1)	<0.0001
A1C (%)	8.5 (7.8–9.5)	7.3 (6.0–8.3)	<0.0001
A1C <7.5%	230/1,393 (17)	42/66 (64)	<0.0001
Insulin/weight	1.15 (0.96–1.39)	0.89 (0.51–1.31) (*n* = 9)	0.063
BMI SD score	0.80 (0.25–1.27)	1.86 (1.28–2.40)	<0.0001
Social disadvantage risk score	0.23 (−0.17–0.80)	0.14 (−0.47–0.56	0.058
From urban area	957/1,419 (67)	46/63 (73)	0.56
Microalbuminuria	81/1,325 (6)	10/36 (28)	<0.0001
Hypertension	223/1,393 (16)	21/58 (36)	<0.0001
Retinopathy	254/1,264 (20)	1/25 (4)	0.043
Peripheral nerve abnormality	375/1,376 (27)	5/24 (21)	0.48
Pupillary abnormality	568/928 (61)	13/23 (57)	0.65
Overweight	452/1,411 (32)	16/64 (25)	0.24
Obese	100/1,411 (7)	36/64 (56)	<0.0001

Data are median (interquartile range) or *n* (%) and are from last complications assessment

type 1 versus type 2 diabetes, but those with type 1 diabetes had significantly longer duration (6.8 vs. 1.3 years, $P < 0.0001$). Patients with type 1 diabetes had a higher median A1C (8.5 vs. 7.3%), and more patients with type 1 diabetes had an A1C level above the current recommended target of 7.5% (32,33). Significantly more patients with type 2 diabetes were obese, whereas there was no difference in the proportion of overweight in patients with type 1 versus type 2 diabetes. Additional medical problems were reported in 26 patients with type 2 diabetes (38%), and 12 patients (18%) had either a psychiatric disorder or developmental delay. Using the ABS classification of ethnicity (28), the majority of patients with type 1 diabetes were of Australian (Caucasian) background, whereas the ethnic background of patients with type 2 diabetes was more variable: Australian (Caucasian) 32%; Southern, Central, and North Asian 26%; Aboriginal/Torres Strait Islander 15%; North African/Middle Eastern 9%; Southern and Eastern European 9%; and Polynesian 6%.

Complications assessment

Retinopathy was significantly more common in patients with type 1 diabetes (20%), whereas early retinopathy was found in only one male patient with type 2 diabetes at his fourth complications assessment at age 20 years (diabetes duration 9.3 years). In contrast, microalbuminuria was significantly more common in patients with type 2 diabetes and was present in 28% at the last assessment compared with 6% of patients with type 1 diabetes. In the patients with type 2 diabetes, microalbuminuria was present in 31% of patients at any time point and in 7% within 3 months of diagnosis (in one of these patients, microalbuminuria had regressed at the follow-up visit 12 months later). Hypertension was also significantly more common in patients with type 2 diabetes (36 vs. 16%, $P < 0.0001$). The rates of peripheral or autonomic neuropathy did not differ between the two groups, but one in five patients with type 2 diabetes had peripheral nerve abnormalities and more than half had autonomic neuropathy after a median duration of only 1.3 years.

Biochemical measurements

In patients with type 2 diabetes, hypercholesterolemia was found in 32% and hypertryglyceridemia in 53% (24). Elevated C-peptide was observed in most patients (80%), and elevated liver enzymes were found in about half (49%). Thyroid function tests were normal in all patients with type 2 diabetes, and one patient had elevated anti-thyroid peroxidase antibodies. Results of diabetes-associated antibodies at diagnosis were available for 34 patients with type 2 diabetes, and all were negative.

Multivariate analyses

The significant predictors of microalbuminuria in patients with type 1 diabetes were older age and hypertension (Table 2). Higher A1C was also associated with microalbuminuria but did not reach statistical significance ($P = 0.06$). In contrast, the only significant predictor of microalbuminuria in patients with type 2 diabetes was higher A1C.

Factors associated with A1C >7.5% in patients with type 1 diabetes were older age and longer diabetes duration. In patients with type 2 diabetes, those with A1C >7.5% were less likely to be treated with oral hypoglycemic agents or diet/exercise than insulin and were more likely to be a resident in an urban area and have a lower social disadvantage risk score (where a lower score is associated with greater social disadvantage, Table 2). The same explanatory variables were obtained when A1C was used as a continuous outcome in the GEE models, with the addition of a lower BMI SD score having a small effect on higher A1C in patients with type 1 diabetes.

CONCLUSIONS — In this study comparing complication rates in youth with diabetes, microalbuminuria and hypertension were significantly more common in those with type 2 than type 1 diabetes. Despite shorter duration, microalbuminuria was found in >25% of patients with type 2 diabetes, compared with 6% of patients with type 1 diabetes. Higher A1C was the only significant risk factor for microalbuminuria in type 2 diabetes. Dsylipidemia was also frequent in type 2 diabetes, with hypercholesterolemia found in one-third and hypertryglyceridemia in more than one-half. While rates of peripheral and autonomic neuropathy were similar in both groups, only retinopathy was less common in type 2 diabetes.

The adolescents in this study were assessed using our established screening methods for adolescents with type 1 diabetes (15–19,34–37), enabling valid comparison of complication rates in type 2 diabetes. The study is limited, however, by the smaller numbers and short mean

Table 2—*Multivariate analyses (using GEEs) of microalbuminuria and glycemic control in youth with type 1 and type 2 diabetes*

Outcomes	OR*	95% CI	*P* value
Microalbuminuria			
Type 1 diabetes			
Age (years)	1.30	1.15–1.46	<0.001
A1C (%)	1.17	1.00–1.38	0.06
Systolic hypertension	3.63	2.01–6.30	<0.001
Type 2 diabetes			
A1C (%)	1.67	1.26–2.94	0.003
A1C >7.5%			
Type 1 diabetes			
Age (years)	0.94	0.90–0.98	0.005
Diabetes duration (years)	1.06	1.02–1.09	0.003
Type 2 diabetes			
Treatment with OHAs and diet/exercise vs. insulin	0.12	0.05–0.31	<0.001
Resident in urban area	22.78	4.06–127.89	<0.001
Aboriginal/Polynesian ethnic group	4.20	0.85–20.72	0.08
Social disadvantage risk score	0.41	0.21–0.79	0.03

*Explanatory variables from the multivariate GEE models are expressed as adjusted OR (95% CI). OHAs, oral hypoglycemic agents.

diabetes duration in those with type 2 diabetes, and many had undergone complications assessment only once. Therefore, although the use of GEE enabled all time points to be considered in the models, the conclusions are based on both cross-sectional and longitudinal data. For analysis of glycemic control, A1C was included for all visits, enabling evaluation over a longer time period, whereas inclusion of additional patients with type 2 diabetes who had not been assessed for other complications provided a larger sample size. While the study is clinic rather than population based, more than half of patients with type 2 diabetes diagnosed in New South Wales after 2001 were seen in the complications clinic (based on population-based incidence data from the Australasian Pediatric Endocrine Group diabetes register) (6). Furthermore, attendees did not differ in age or socioeconomic status from nonattendees, suggesting that the risk of selection bias was low.

Microalbuminuria was found in 28% of youth with type 2 diabetes after a relatively short duration of diabetes (median 1.3 years). This rate is much higher than in adolescents with type 1 diabetes in this study and in other reports (16,38–40) in which rates vary from 2 to 13% after comparable diabetes duration. Similarly, microalbuminuria was observed in 18% of Korean patients with youth-onset type 2 diabetes after a mean duration of 5.5 years compared with 11% in those with type 1 diabetes (duration 8.1 years) (9), and the incidence of nephropathy among Japanese type 2 diabetic patients diagnosed before the age of 30 years was twice as high than in type 1 diabetic patients (41). Poor glycemic control has been identified as a risk factor for microalbuminuria in youth with type 1 diabetes (38,42) and in young adults with type 1 or type 2 diabetes (43). Indeed, A1C was the only significant risk factor in patients with type 2 diabetes in the present study, despite a median A1C of 6.9%, but it may be that other potential explanatory variables for microalbuminuria in multivariate analysis did not reach statistical significance due to the small sample size.

In addition to microalbuminuria, features of the metabolic syndrome such as dyslipidemia and hypertension were common in adolescents with type 2 dia-

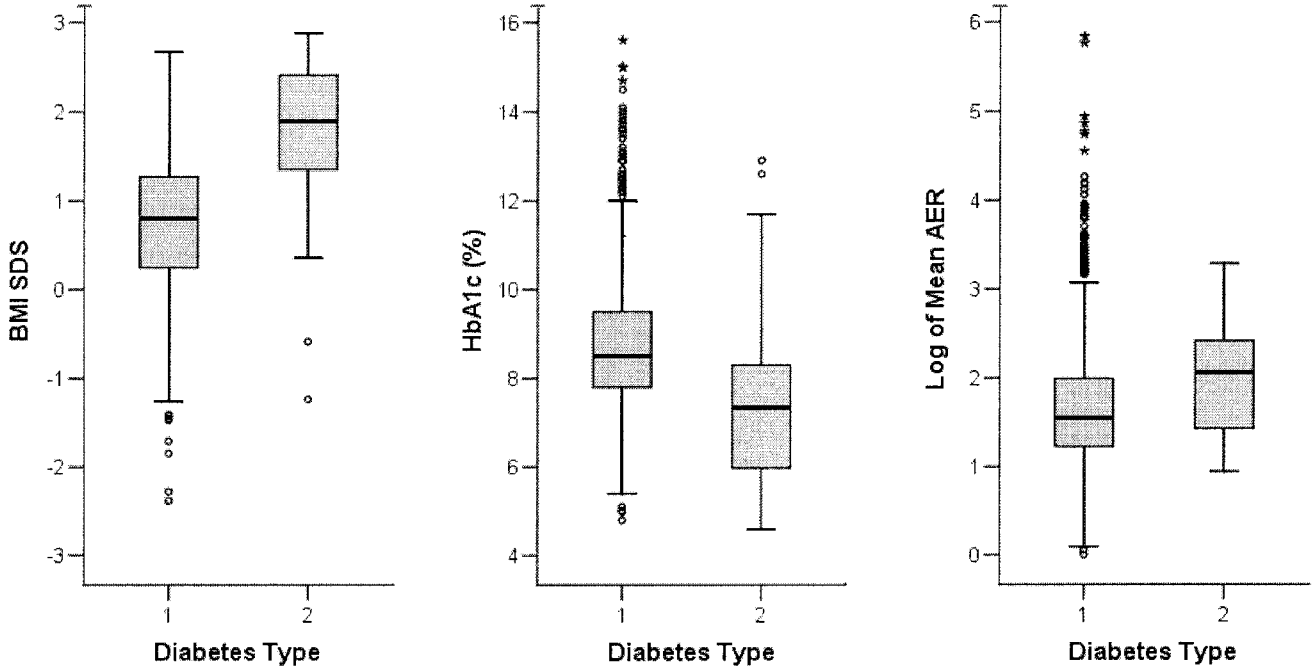

Figure 1—*Boxplots comparing BMI SD score, A1C, and log (mean AER) at last assessment in youth with type 1 and type 2 diabetes.*

betes, in keeping with a report of minority adolescents with recent-onset type 2 diabetes (11). Higher rates of urinary albumin excretion have been found in obese children with features of the metabolic syndrome (44), suggesting an association between early renal glomerular and tubular dysfunction and insulin resistance. Microalbuminuria is also associated with insulin resistance in adults without diabetes (45,46), and markers of insulin resistance are risk factors for microalbuminuria in youth and adults with diabetes (42,47). Hypertension is also associated with microalbuminuria, and although 36% of youth with type 2 diabetes were hypertensive in the current study, the lack of association between blood pressure and microalbuminuria in those with type 2 diabetes may be due to insufficient statistical power. Furthermore, the development of microalbuminuria in youth with type 2 diabetes is likely to have a multifactorial basis, with hypertension, dyslipidemia, obesity, insulin resistance, and genetic predisposition contributing to the risk.

Abnormalities in peripheral nerve function were common in patients with type 1 and type 2 diabetes (27 and 21%, respectively) based on quantitative sensory tests. The rate in type 1 diabetes is consistent with data from other authors (48,49) but is considerably lower than the rate of 63% in Danish patients screened in 1995 (38). In the latter study, risk factors for neuropathy included age, male sex, and elevated AER. Apart from a recent case report (50) of diabetic amyotrophy in an adolescent with type 2 diabetes, to the best of our knowledge, there are no other published reports of peripheral neuropathy in youth with type 2 diabetes. Longitudinal evaluation of larger cohorts will provide further information on the natural history of neuropathy in type 2 diabetes and may assist in identifying potential risk factors.

Duration of diabetes is difficult to determine in type 2 diabetes due to the long presymptomatic period. In adults, complications at presentation are not uncommon and may be the presenting feature, reflecting the long exposure of susceptible organs to damage from chronic asymptomatic hyperglycemia. Given the relatively short diabetes duration in this cohort, unrecognized microalbuminuria may have been present before the diagnosis of type 2 diabetes (51). Furthermore, the high rates of hypertension, microalbuminuria, and nerve abnormalities found in this study confirm that youth with type 2 diabetes should be screened for complications at diagnosis (32,52). These data also argue for screening of at-risk adolescents for type 2 diabetes because early treatment may reverse complications.

Many patients with type 2 diabetes in the current study had multiple conditions, including developmental and psychosocial problems in 12 patients (18%), consistent with a recent study (53) in which 19% of youth had neuropsychiatric disorders at diagnosis of type 2 diabetes. Psychotropic medications are recognized risk factors for the development of diabetes; however, the association between neuropsychiatric illness and diabetes is likely to be multifactorial and include depression, which contributes to overeating, hypothalamic obesity, other neuroendocrine disturbances, and poor impulse control associated with intellectual impairment. Management of type 2 diabetes is more complex in such cases, with patients often receiving multiple medications, including those known to cause weight gain. Motivation and ability to comply with lifestyle changes may also be more difficult for these patients.

The management of youth with type 2 diabetes provides a challenge for the health care team. Many patients had other medical problems and over half were obese. Patients with type 2 diabetes from minority groups (Aboriginal or Polynesian) and those with lower socioeconomic scores were more likely to have worse glycemic control; these are patients with greater need for health care resources (54). Rates of microalbuminuria, hypertension, and neuropathy were high, and microalbuminuria was significantly associated with higher A1C, indicating that aggressive treatment to improve glycemic control is required. Indeed, it may be that the target A1C of 7.5% for youth with type 1 diabetes (32,33) is too high for those with type 2 diabetes to prevent development of microvascular complications. Evaluation of additional risk factors for complications in youth with type 2 diabetes is imperative to assist in developing preventative strategies.

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