Poor Prognosis of Young Adults With Type 1 Diabetes

A longitudinal study

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OBJECTIVE — To determine the role of early behavioral and psychological factors on later outcomes in young adults with childhood- or adolescent-onset type 1 diabetes.

RESEARCH DESIGN AND METHODS — We conducted a longitudinal cohort study of patients recruited from the register of the young adult outpatient diabetes clinic, Oxford, U.K. A total of 113 individuals (51 male subjects) aged 17–25 years completed assessments, and 87 (77%) were reinterviewed as older adults (aged 28–37 years). Longitudinal assessments were made of glycemic control (HbA_{1c}) and complications. Psychological state at baseline was assessed using the Present State Examination and self-report Symptom Checklist, with corresponding interview schedules administered at follow-up.

RESULTS — There was no significant improvement between baseline and follow-up in mean HbA_{1c} levels (8.5 vs. 8.6% in men, 9.3 vs. 8.7% in women). The proportion of individuals with serious complications (preproliferative or laser-treated retinopathy, proteinuria or more severe renal disease, peripheral neuropathy, and autonomic neuropathy) increased from 3–37% during the 11-year period. Women were more likely than men to have multiple complications (23 vs. 6%, difference 17%, 95% CI 4–29%, $P = 0.02$). Psychiatric disorders increased from 16 to 28% (20% in men, 36% in women at follow-up, difference NS), and 8% had psychiatric disorders at both assessments. Baseline psychiatric symptom scores predicted follow-up scores ($\beta = 0.32$, SE [β] 0.12, $P = 0.008$, 95% CI 0.09–0.56) and recurrent admissions with diabetic ketoacidosis (odds ratio 9.1, 95% CI 2.9–28.6, $P < 0.0001$).

CONCLUSIONS — The clinical and psychiatric outcome in this cohort was poor. Psychiatric symptoms in later adolescence and young adulthood appeared to predict later psychiatric problems.

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Psychiatric disorders, subthreshold psychological distress, and behavioral problems in patients with type 1 diabetes are common during the transition from adolescence to young adulthood (1–7) and result in variable adherence to insulin treatment (2,3,7–9), contribute to poor glycemic control (5) and to an increased incidence of diabetic ketoacidosis and later microvascular complications (5–7). The most common psychiatric symptoms are depression and low self-esteem, but eating disorders and subclinically disordered eating attitudes and behaviors are also common (3,7). These problems have been extensively documented (1–8) but may be much more protracted than previously recognized, persisting well into adulthood. The resulting longer-term clinical and psychiatric morbidity may have been underestimated.

Longitudinal studies are needed to define the prognosis and to explore causal relationships among psychosocial factors, regimen adherence, and metabolic control (10). Prospective studies have focused on younger age groups, and the prognosis for type 1 patients in their late twenties and thirties remains poorly defined. Our aim was to examine the prognosis in a representative population-based cohort of young adults and to assess how behavioral and psychological factors in early adulthood are related to later psychological health, glycemic control, and the risk of diabetic complications.

RESEARCH DESIGN AND METHODS

— The index group of patients was identified from the case register of the young adult diabetic clinic in Oxford between 1987 and 1988. The clinic provides specialist treatment by a multidisciplinary team of doctors, nurses, and dieticians. It is the only clinic specifically serving adolescents and young adults aged 17–25 years with type 1 diabetes living within the defined geographic area of the Oxfordshire Health Authority (population 610,000). After excluding pregnant patients and students resident only during the academic term, we identified a total of 127 patients (all Caucasian) with diabetes diagnosed for at least 1 year. Eligible patients were invited to participate in a study of self-care behavior, psychiatric state, and eating habits. Of these patients, 5 declined to participate and 9 could not be contacted, but the remaining 113 (89%) were interviewed. Of these, 53 (47%) had been diagnosed at age <12 years.

Follow-up assessments were undertaken in 1999–2000. Patients consenting

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Abbreviations: GSI, Global Severity Index; UAC, urinary albumin-to-creatinine.

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

to participate were interviewed wherever they lived in the U.K. Patients not residing in Oxfordshire were traced through general practitioners, district health authority computerized records, or the National Health Service Central Register, which also provided a copy of the death certificate for deceased patients. The cohort was followed for 1,261 person-years, with a duration (mean ± SD) of 11.2 ± 2.5 years. The vital status for 111 (98%) of the 113 index patients was known and included 4 who had died. The clinical case notes were audited for 105 patients (93%), and 87 (77%) agreed to a second interview, including 22 (25%) who lived outside Oxfordshire. The distribution of occupational classes among patients interviewed was similar to the general population of England and Wales (data not shown).

Baseline assessment in 1987–1988

A detailed interview was conducted, and demographic and clinical data were recorded. Self-care behavior and disordered eating behavior, such as self-induced vomiting and/or laxative misuse, were assessed by interview, which included questions about deliberate insulin omission or under-use for the purposes of weight control. Psychiatric morbidity was assessed using *1*) the Present State Examination (a diagnostic interview yielding categorical diagnoses) (11) and *2*) the self-report Symptom Checklist (SCL-90), which measures severity of mood and other symptoms (12). From the latter, the Global Severity Index (GSI) was derived, which gives a continuous score of increasing severity of symptoms. The results of the baseline assessments have been reported in detail previously (1,2,8).

Follow-up assessment (1999–2000)

The research assessment was conducted in the homes of participants by a research nurse blind to the results of the baseline assessment. Psychiatric state was assessed using the Revised Clinical Interview Schedule (a diagnostic interview yielding a categorical psychiatric diagnosis, defined as a score ≥11) (13) and the self-report Brief Symptom Inventory (a shortened version of the Symptom Check List) (14). From the latter, the GSI was derived. Glycemic control was assessed by measurement of HbA_{1c}. For subjects attending Oxford adult diabetic clinics, the HbA_{1c} measured nearest to the time of the research interview was used as an indicator of current glycemic control. For other patients, a capillary blood sample was taken during the interview and measured by the Oxford laboratory. Assessment of renal function was made by collection of three consecutive early-morning urine specimens for measurement of the urinary albumin-to-creatinine (UAC) ratio. Height and weight were obtained from the clinic visit nearest to the interview date or from measurements made in the homes of participants, using Seca model 888 electronic scales (Seca, Birmingham, U.K.) and a Leicester stadiometer.

Available case notes were reviewed after completion of the follow-up assessment, which ensured blinding of the research nurse. The details recorded included clinic attendance, diabetic complications, hospital admissions with diabetic ketoacidosis, and psychiatric referrals. Serial measurements of HbA_{1c} were documented and, to ensure comparability, only samples measured by the central laboratory were included in the subsequent analyses. Serious complications were defined as preproliferative or laser-treated retinopathy, proteinuria or more severe renal disease, peripheral neuropathy, and autonomic neuropathy. The diagnostic criteria for preproliferative retinopathy, peripheral neuropathy, and autonomic neuropathy were not prespecified but were based on the clinical diagnoses recorded in the case notes. Ethical committee approval was obtained from the Central Oxford Research Ethics Committee.

Laboratory assays

HbA_1 was measured from 1987 to 1991 by a Glytrac electroendosmosis method (Ciba Corning Diagnostics, Halstead, U.K.). From 1991 onwards, HbA_{1c} was measured by a high-performance liquid chromatography method (normal range 4.3–6.1%), using a Biorad Diamat automated HbA_{1c} analyzer (Biorad Laboratories, Hemel Hempstead, Hertfordshire, U.K.). The changeover between the two methods was carefully documented, and appropriate regression equations were available for conversion of the earlier data to the current method and are documented in detail elsewhere (15).

Albumin was measured by a double-antibody enzyme-linked immunosorbent assay method (15). Creatinine was measured using the modified Jaffe method (Unimate 7) on a Cobas Mira automated spectrophotometer (Roche Diagnostic Systems, Basel). Details of intra- and interassay variability of the HbA_{1c} assays and of the albumin and creatinine assays are documented elsewhere (15). Microalbuminuria was defined as a UAC ratio ≥3.5 mg/mmol in male subjects or ≥4.0 mg/mmol in female subjects in the absence of proteinuria, which was defined as an albumin excretion rate >200 μg/min or UAC ratio >35 mg/mmol in two of three consecutive samples.

Statistical methods

SPSS 10.05 for Windows (SPSS, Chicago, IL) was used for statistical analysis. Parametric data were analyzed using *t* tests, and nonparametric data were analyzed using Mann-Whitney *U* tests. Associations between assessments were compared using Wilcoxon matched-pairs tests, and association between variables was tested using Spearman's correlation. Categorical data were analyzed using χ^2 or Fisher's exact test. Multiple and logistic regression analyses were used to explore the contribution of baseline variables with the following outcomes as dependent variables: psychiatric referral, recurrent admissions over the study period for diabetic ketoacidosis, any serious diabetic complication, HbA_{1c}, and psychiatric symptoms (GSI) at follow-up. Independent variables entered into the model at baseline were sex, psychiatric symptoms (GSI), HbA_{1c}, duration of diabetes, BMI, number of injections daily, and marital status. Sex and baseline psychiatric symptoms were forced into the model, but other covariates that were not statistically significant at the 10% level were excluded from the final models.

RESULTS — Characteristics of patients interviewed at each assessment are shown in Table 1. Among those not reinterviewed, there were 4 deaths (all women), 1 man and 1 woman were too ill to participate, 9 declined to take part (1 man, 8 women), and we were unable to contact 11 others (4 men, 7 women). There was no difference in age or diabetes duration between interviewed patients and those not reinterviewed. The proportion of unemployed was similar at each assessment (3 vs. 5%) and was comparable with age-related general population data (16).

Table 1—*Demographic and clinical characteristics of interviewed patients*

	Men		Women	
	Baseline	Follow-up	Baseline	Follow-up
n	51	45	62	42
Age (years)	22.4 ± 2.5	34.8 ± 2.7	21.5 ± 2.9	33.6 ± 3.0
Duration of diabetes (years)	10.1 ± 5.2	22.1 ± 4.9	9.2 ± 5.3	21.3 ± 5.5
Marital status				
Single	43 (84)	14 (31)	48 (77)	12 (29)
Married/cohabiting	8 (16)	29 (64)	13 (20)	27 (64)
Divorced/separated	0	2 (4)	1 (2)	3 (7)
Children	0	26 (58)	0	25 (60)
Insulin regimen				
Once daily	7 (14)	1 (2)	10 (16)	1 (2)
Twice daily	36 (71)	13 (29)	42 (68)	9 (21)
Multiple injections	6 (12)	30 (67)	10 (16)	31 (74)
Infusion	2 (4)	1 (2)	0	1 (2)
Units/kg	0.82 ± 0.25	0.75 ± 0.17	0.83 ± 0.31	0.74 ± 0.22
BMI	23.1 ± 2.6	25.9 ± 3.6	24.5 ± 4.6	27.1 ± 5.0
Overweight (BMI >25 kg/m^2)	12 (25)	21 (47)	15 (25)	15 (36)
Obese (BMI >30 kg/m^2)	0	4 (9)	4 (7)	9 (21)
HbA_{1c} (%)	8.5 ± 1.7	8.6 ± 1.2	9.3 ± 2.4	8.7 ± 1.6

Data are *n*, means ± SD, or *n* (%).

Self-care

A total of 65 patients (75%) were attending specialist adult diabetes clinics at follow-up, 3 (3%) did not attend any clinic, and the remaining 19 (22%) were cared for exclusively by their general practitioner. Use of multiple injection regimens increased in frequency (Table 1), as did blood glucose self-monitoring (median 20 tests/month at baseline vs. 36 tests/month; $z = 3.8$, $P < 0.0001$). At follow-up, 53 (65%) patients performed more frequent blood glucose tests and 24 (30%) performed fewer tests, and those patients who performed more blood glucose tests per month had lower current HbA_{1c} (Spearman's r −0.35, $P = 0.001$). Hypoglycemic symptoms in the month before interview were reported by 48 (43%) patients at baseline vs. 74 (85%) at follow-up ($z = 6.2$, $P < 0.0001$). The proportion of smokers was similar at each assessment (25 vs. 21%).

In both sexes, the mean BMI increased significantly (Table 1, men $z = 5.3$, $P < 0.0001$; women $z = 2.9$, $P = 0.004$). In comparison to age-related general population data (17), the proportion of overweight men at follow-up was similar (48 vs. 40–48%), but the proportion of obese men was lower (9 vs. 16–17%). By contrast, the proportion of overweight women was greater (39 vs. 27–30%), as was the proportion of obese women (24 vs. 16–21%). During the study period, 3 women received treatment for bulimia nervosa, and a further 12 (21%) had a history of self-induced vomiting and/or laxative misuse. A total of 21 patients (37%), all women, reported a history of insulin omission or reduction for the purpose of weight control, although none admitted to insulin misuse at follow-up.

Glycemic control and diabetes outcomes

There was no significant difference between mean HbA_{1c} at baseline and follow-up (Table 1), by which time the percentages of patients with an HbA_{1c} level ≤7.0, ≤7.5, and ≤ 8.0% were 9.4, 26.0, and 40.6%, respectively. Longitudinal data (Fig. 1) showed a decrease after late adolescence in both sexes.

The overall mortality was 3.6% (4 of 111, 95% CI 1.0–9.0%). Two of the four female deaths were from diabetic renal failure, one from suicide, and one from congenital heart disease. Two women had received renal transplants, one man and

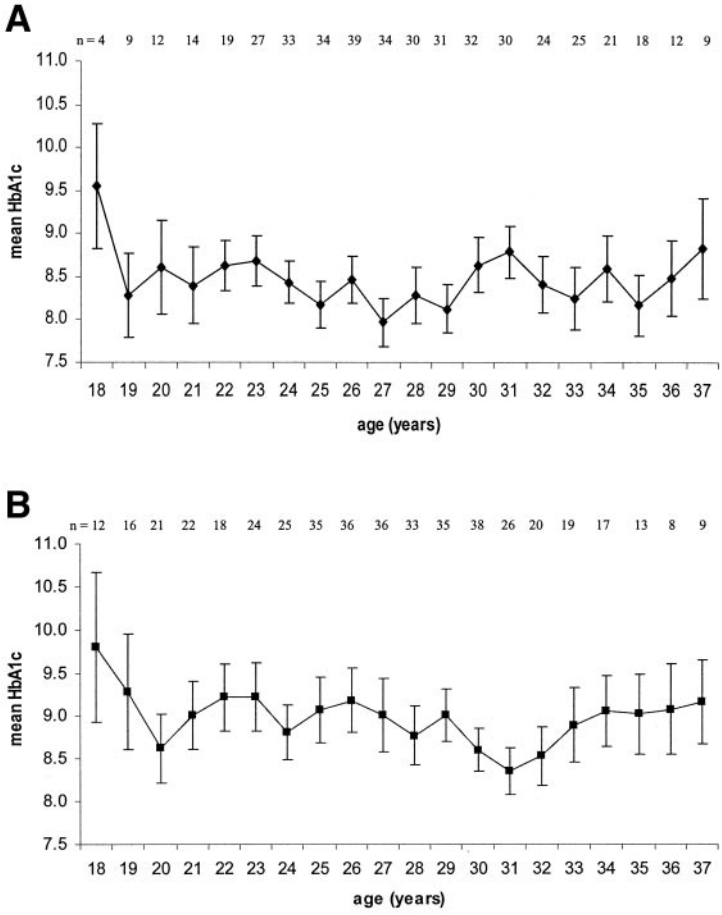

Figure 1—*Mean HbA_{1c} (and SE) for men* (A) *and women* (B) *by age. Bars, SE.*

Table 2—*Prevalence of complications at baseline and follow-up*

	Men		Women	
	Baseline	Follow-up	Baseline	Follow-up
n	51	48	62	57
Retinopathy				
Background	8 (16)	17 (36)	8 (13)	19 (33)
Preproliferative	0	5 (11)	0	3 (5)
Laser-treated	0	10 (21)	1 (2)	16 (28)
Nephropathy				
Microalbuminuria	0	2 (4)	1 (2)	4 (7)
Proteinuria	0	2 (4)	1 (2)	3 (5)
Receiving dialysis	0	1 (2)	0	1 (2)
Transplant	0	0	0	2 (4)
Died from renal failure	0	0	0	2 (4)
Peripheral neuropathy	0	1 (2)	0	11 (19)
Required toe amputation	0	1 (2)	0	1 (2)
Autonomic neuropathy	0	4 (8)	0	6 (11)
One serious complication*	0	16 (33)	2 (3)	7 (12)
Two serious complications	0	2 (4)	0	6 (11)
Three or more serious complications	0	1 (2)	0	7 (12)

Data are *n* or *n* (%). *Defined as any one of the following: preproliferative or laser-treated retinopathy, proteinuria or more severe renal disease, peripheral neuropathy, or autonomic neuropathy.

one woman were undergoing dialysis, and a total of five other patients were registered as disabled, including four due to diabetic complications. The prevalence of serious complications increased from 3% at baseline to 37% at follow-up (Table 2), and women were more likely than men to have multiple complications (23 vs. 6%, difference 17%, 95% CI 4–29%, $P = 0.02$). Mean HbA_{1c} over the follow-up period was significantly worse in patients who developed complications (9.9% [1.2] vs. 8.0% [1.0], $t = 7.3$, $df = 70$, $P < 0.0001$). Of the patients, 9% (four men, six women) had two or more admissions for diabetic ketoacidosis and were significantly more likely to have developed complications (18 vs. 5%, difference 13%, 95% CI 0.4–27%, $P = 0.04$). There was no significant difference in mean duration of diabetes between patients who developed serious complications and those who did not.

Psychological outcomes

The cross-sectional prevalence of psychiatric cases based on Present State Examination at baseline and the Revised Clinical Interview Schedule at follow-up increased from 16 to 28% (9 men and 15 women) and included 7 patients with a psychiatric disorder at both assessments. We performed a sensitivity analysis to examine the effect of a nonresponse bias at follow-up, using the extreme assumption that none or all of the patients declining to be interviewed was a case subject. The overall prevalence of psychiatric disorders was then shown to be 25% (24 of 96) and 34% (33 of 96), respectively. The proportion of psychiatric case subjects did not differ between patients with and without serious complications, although median GSI symptom scores were nonsignificantly higher among patients with serious complications (0.5, interquartile range 0.3–1.2 vs. 0.3, 0.1–0.7). During the follow-up period, 18% of patients had undergone a hospital psychiatric assessment (6 men, 13 women), including 1 man and 7 women (8%) who had taken overdoses or attempted self-harm. A higher proportion of women than men had committed or attempted suicide or self-harm (8 of 57 [14.0%] vs. 1 of 48 [2.1%], difference 12.0%, 95% CI 2.1–21.8%). As a result of a psychiatric assessment, four women had been admitted as inpatients. Two of these women had severe psychiatric problems, including bulimia nervosa, and multiple admissions for diabetic ketoacidosis, and both patients died from diabetic nephropathy: one aged 31 years during the follow-up period and one aged 36 years shortly after completing the follow-up assessment. The 35-year-old woman who committed suicide had not been referred for psychiatric assessment.

Baseline predictors

In multivariate analysis, baseline psychiatric symptoms (GSI score) predicted psychiatric referrals (odds ratio 7.2, 95% CI 2.6–19.7, $P < 0.0001$) and recurrent admissions with diabetic ketoacidosis (odds ratio 9.1, 95% CI 2.9–28.6, $P < 0.0001$). Female sex and baseline HbA_{1c} predicted diabetic complications (Table 3). Follow-up HbA_{1c} was predicted by baseline HbA_{1c} ($\beta = 0.22$, 95% CI 1.08–0.36, $t = 3.1$, $P = 0.003$) and baseline BMI ($\beta = 0.14$, 95% CI 0.06–0.23, $t = 3.3$, $P = 0.002$). Psychiatric symptoms at follow-up (GSI score) were predicted by baseline psychiatric symptoms (GSI score) and recurrent admissions with diabetic ketoacidosis (Table 3).

CONCLUSIONS— The principal finding of this prospective cohort study was the poor outcome of many young adults with type 1 diabetes in their late 20s and 30s. Although self-care behavior improved over the period of follow-up, this was overshadowed by the development of psychiatric morbidity in about one-quarter of patients and serious diabetic complications in over one-third. The study provides further evidence of the special needs of younger adults with type 1 diabetes, as identified in our earlier adolescent cohort, which followed patients to a mean age of 23 years (5). This is the first study to assess prospectively their later psychiatric outcome using validated measures in a representative community-based cohort, and it has the advantage of a high participation rate, increasing the generalizability of the results. Its limitations are the relatively small sample size, a probable underestimate of the prevalence of those complications ascertained by case note review, and the failure to reinterview the entire cohort at follow-up, although 98% of patients were traced and 77% interviewed.

The overall mortality of 3.6% was consistent with earlier studies, which have reported mortality rates ranging from 3.1 to 5.5% at 20 years' duration of diabetes (18). The outcome was similar to the British Diabetic Association cohort of 23,753 insulin-treated patients diagnosed at age <30 years, identified from 1972 to 1993 and followed until 1997, in which all-causes mortality in men and women aged 30–39 years was increased, respectively, by 3.7- and 4.9-fold compared with the general population (19). Some

Table 3—*Regression analysis with dependent variables of diabetic complications (logistic regression) and psychiatric symptoms (multiple regression)*

Independent variables	β	SE (β)	*t*	*P*	Odds ratio (95% CI)	95% CI of β
Diabetic complications						
Sex	−1.46	0.63	—	0.02	0.23 (0.07–0.80)	—
Baseline psychiatric symptoms	0.23	0.58	—	0.69	1.26 (0.41–3.88)	—
Baseline HbA_{1c}	0.74	0.18	—	<0.0001	2.10 (1.48–2.96)	—
Baseline BMI	0.16	0.09	—	0.09	1.17 (0.97–1.40)	—
Baseline injection regimen	0.54	0.34	—	0.10	1.72 (0.88–3.37)	—
Psychiatric symptoms						
Sex	0.12	0.10	1.20	0.24	—	−0.08 to 0.32
Baseline psychiatric symptoms	0.32	0.12	2.71	0.008	—	0.09 to 0.56
DKA recurrent admissions	0.73	0.22	3.40	0.001	—	0.30 to 1.16

DKA, diabetic ketoacidosis.

caution, however, is necessary in interpreting our results because the small number of deaths observed resulted in wide confidence intervals around the estimated mortality rate.

The prevalence of serious complications in the cohort increased from 3% at baseline to 37% 11 years later. Although the prevalence of microalbuminuria at follow-up was lower than that observed among 2,205 type 1 patients (20) with a similar mean age of 33 years who were recruited from 31 diabetes clinics in 16 European countries by the EURODIAB type 1 diabetes complications study (5.7 vs. 21.7%), the prevalence of macroalbuminuria was similar (10.5 vs. 7.8%). The overall prevalence of retinopathy at follow-up was higher in our cohort (66.6 vs. 46.2%), as was the prevalence of laser-treated proliferative retinopathy when compared with proliferative retinopathy assessed by retinal photography (24.8 vs. 10.6%) (21). These differences are explained in part by the inclusion in EURODIAB of patients aged up to 60 years, a 5-year-shorter duration of disease, and a mean age of onset that was 8 years later. They emphasize, however, the poor prognosis in adulthood for many patients with childhood and adolescent-onset type 1 diabetes.

A disturbing finding was the poor psychiatric outcome in many patients, particularly in women. At follow-up, the prevalence of psychiatric cases based on the Revised Clinical Interview Schedule was >40% higher than in the general population (22), and a high proportion of patients had needed hospital referral for psychiatric assessment. Several patients required protracted inpatient psychiatric care, and concomitant eating disorders appeared to result in an especially poor outcome in a small number of women. Eating disorders have previously been shown to be highly predictive of poor metabolic control and subsequent complications (7), but we earlier found no higher prevalence of these disorders in young adult patients than in a control population. (2) Existing evidence of an increased incidence of suicide is restricted to young men (23), although in our cohort one woman had committed suicide and a significantly higher proportion of women than men had committed or attempted suicide or self-harm. By contrast, at follow-up many patients appeared better adjusted to diabetes, as evidenced by improved self-care behavior with an increased frequency of blood glucose self-monitoring and no reported insulin misuse to control weight. The results provide some insight into the causal relationships between psychological factors, regimen adherence, and metabolic control. Depression is recognized to be associated with hyperglycemia (24), and this study provides some evidence of the directional nature of the relationship. Although higher levels of psychological distress were associated with worse glycemic control at baseline (1), HbA_{1c} did not predict psychiatric symptoms at follow-up, which were associated only with baseline psychiatric symptoms and recurrent hospital admissions for ketoacidosis.

Implications of the study

This longitudinal study demonstrated worse-than-expected clinical and psychiatric outcomes in about one-third of all young adult patients. The high prevalence of microvascular complications may relate partly to the widespread use of once-daily insulin regimens in pediatric practice before clinical trial evidence demonstrated that intensive treatment with multiple injection therapy substantially reduced the risk of longer-term complications (25). Most patients continued to attend specialist adult diabetes clinics throughout the follow-up period, receiving individualized care and support from the diabetes team and, when required, psychiatric referral, but usually without access to formal psychological support. However, because psychiatric outcomes were predicted by psychiatric symptoms in late adolescence and young adulthood, much earlier identification and treatment of at-risk patients is probably needed. Intensive educational and behavioral treatments seem to have limited efficacy (26), and individualized therapy using cognitive behavioral principles dealing with specific misconceptions and inappropriate beliefs about diabetes and its treatment may be more effective in changing attitudes and behavior (27,28). In summary, without early identification and treatment of at-risk patients, our results suggest that psychiatric disorders, subthreshold psychological distress, and behavioral problems may persist well into adulthood and predict later psychiatric symptoms in many patients with childhood and adolescent-onset type 1 diabetes.

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