CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Premature Mortality and Comorbidities in Young-onset Diabetes: A 7-Year Prospective Analysis

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ABSTRACT

BACKGROUND: There is an increasing prevalence of young-onset diabetes, especially in developing areas. We compared the clinical outcomes and predictors for cardiovascular-renal events between Chinese patients with type 2 diabetes with young- or late-onset of disease diagnosed before or after the age of 40 years, respectively.

METHODS: The Hong Kong Diabetes Registry was established in 1995 as an ongoing quality improvement initiative with consecutive enrollment of diabetic patients from ambulatory settings for documentation of risk factors, microvascular and macrovascular complications, and clinical outcomes using a structured protocol.

RESULTS: In 9509 Chinese patients with type 2 diabetes with a median (interquartile range) follow-up period of 7.5 (3.9-10.8) years, 21.3% (n = 2066) had young-onset diabetes. Despite 20 years difference in age, patients with young-onset diabetes (mean age, 41.3 years) had a similar or worse risk profile than those with late-onset disease (mean age, 61.9 years). Compared with the patients with late-onset diabetes, those with young-onset diabetes had lower rates of cardiovascular disease and chronic kidney disease for the same disease duration but a higher cumulative incidence of clinical events at any given age. With the use of stepwise Cox proportional hazard analysis, patients with young-onset diabetes had higher risks for cardiovascular and renal events when adjusted by age, but no difference in risks than in the patients with late-onset diabetes when further adjusted by disease duration.

CONCLUSIONS: Patients with young-onset diabetes had a similar or worse metabolic risk profile compared with those with late-onset disease. This group had higher risks for cardiovascular-renal complications at any given age, driven by longer disease duration.

 • *The American Journal of Medicine (2014) 127, 616-624*

KEYWORDS: Cardiovascular-renal events; Mortality; Young-onset diabetes

Type 2 diabetes in youth is an emerging public health problem especially in developing areas, such as Asia, which is undergoing rapid socioeconomic and lifestyle changes.[1,2] In a recent national survey conducted in China, the prevalence of diabetes and pre-diabetes in the age group of 18 to 39 years was approximately 45%, with the majority being previously undiagnosed.[3] Young adults with type 2 diabetes are as susceptible to the development of vascular

Funding: The study is partially supported by the Hong Kong Foundation for Research and Development and Liao Wun Yuk Memorial Diabetes Research Fund of the Chinese University of Hong Kong.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2014.03.018

complications as their older counterparts. In Pima Indians, at any given age, the cumulative incidence of nephropathy was 5-fold higher in those with young-onset type 2 diabetes than in those with late-onset type 2 diabetes.[4] In Caucasians, compared with the normal age-matched population, the risk for any macrovascular complications was 2-fold higher in young than in older patients with diabetes.[5]

We hypothesize that apart from long disease duration, other risk factors may influence the clinical course of patients with young-onset diabetes compared with patients with late-onset diabetes. By using a prospective cohort established through the Hong Kong Diabetes Registry,[6] we compared the clinical outcomes and their predictors between young- and late-onset diabetes, stratified by an age of diagnosis of 40 years.

CLINICAL SIGNIFICANCE

- Patients with young-onset type 2 diabetes had worse or similar metabolic control compared with the group with late-onset diabetes but were less likely to receive high-impact treatment, such as statins and renin-angiotensin system blockers, despite clinical indication.
- At any given age, the group with young-onset type 2 diabetes had a higher cumulative incidence of cardiovascular-renal disease.
- Our results highlight the high risks of premature morbidity and mortality in those who are diagnosed with diabetes at a young age.

METHODS

Patients

The Prince of Wales Hospital is the teaching hospital of the Chinese University of Hong Kong and serves a catchment of 1.2 million, representing one sixth of the population in Hong Kong. The Hong Kong Diabetes Registry, established since 1995 as a quality improvement program, consecutively enrolled patients who were referred to the hospital for comprehensive assessment of metabolic control and diabetes complications. Referral sources included regional public community clinics, hospital-based clinics, and patients discharged from the Prince of Wales Hospital. Once a patient is enrolled, he or she is followed to the time of death. Patients were excluded if they were non-Chinese in ethnicity or had type 1 diabetes as defined by acute presentation with diabetic ketoacidosis, heavy ketonuria or continuous requirement of insulin within 1 year of diagnosis, or unknown diabetes type. Young-onset diabetes was defined by age of diagnosis less than 40 years, and late-onset diabetes was defined by age of diabetes diagnosis at $\geq$40 years. The selection of 40 years as a cutoff was based on the use of similar age strata (20-39 years, 40-59 years, and 60-79 years) in the latest International Diabetes Federation estimates of world diabetes prevalence.[7] Previous studies that examined the clinical features of patients with young-onset diabetes also have used 40 years as an age threshold.[8] Ethical approval was obtained from the Chinese University of Hong Kong Clinical Research Ethics Committee. All patients gave written informed consent for data analysis and research purpose at the time of assessment.

Baseline Clinical and Laboratory Measurement

All patients attended after an overnight 8-hour fast and underwent structured comprehensive assessments, including eye, feet, urine, and blood examinations. Eye examination included visual acuity and fundoscopy through dilated pupils or retinal photography. Retinopathy was defined by typical changes due to diabetes, laser scars, or a history of vitrectomy. Doppler ultrasound scan and monofilament and graduated tuning fork were used for foot examination. Peripheral artery disease was defined by absent foot pulses with an ankle:brachial ratio $<$0.90. All assessments and examinations were performed by nurses with training in diabetes and diabetes education, and eye examinations and interpretation of retinal photos were performed by endocrinologists. All laboratory assays were performed at the Prince of Wales Hospital using externally audited assays with precision within the manufacturer's specification. We used the Chinese-calibrated Modification of Diet in Renal Disease Study formula for estimated glomerular filtration rate (eGFR) expressed in mL/min/1.73 m^2: $eGFR = 186 \times [SCR \times 0.011]^{-1.154} \times [age]^{-0.203} \times [0.742 \text{ if female}] \times 1.233$, where SCR is serum creatinine (μmol/L) and 1.233 is the adjusting coefficient.[9] A sterile, random spot urine sample was used to measure the albumin-to-creatinine ratio. Microalbuminuria was defined as a urine albumin-to-creatinine ratio of 2.5 to 30 mg/mmol in female patients and 3.5 to 30 mg/mmol in male patients. Macroalbuminuria was defined as a urine albumin-to-creatinine ratio $>$30 mg/mmol.

Definition of Clinical Events

Hong Kong has a heavily subsidized health care system that provides 95% of chronic care. It has a territory-wide electronic medical record system including a death registry, which can be matched to a unique Hong Kong identity number, held by all citizens. Outcome data were retrieved from the Hong Kong Death Registry and Hong Kong Hospital Authority Central Computer System using the International Classification of Diseases, Ninth Revision (ICD-9). Of note, events treated in the private sector or outside of Hong Kong would not be captured and based on data captured by the Hospital Authority, this would be less than 15% of the total hospitalization during follow-up after initial assessment.[10] Because private medical insurance is not compulsory in Hong Kong, many patients with serious events were being followed up in the public sector.

Table 1 Comparison of Baseline Clinical Profile and Biochemical Characteristics Between Chinese Patients with Young- and Late-onset Type 2 Diabetes

	Young-onset Diabetes (n = 2066)	Late-onset Diabetes (n = 7440)	*P* Value	Adjusted *P* Value*
Age (y)	41.3 ± 9.8	61.9 ± 10.3	<.001	/
Male gender (%)	44.0	47.5	.005	/
Duration of diabetes (y)	6 (1-13)	5 (1-10)	<.001	/
Current or ex-smoker (%)	24.7	30.7	<.001	/
Family history of diabetes (%)	57.7	40.1	<.001	/
BMI (kg/m^2)	25.7 ± 4.7	25.1 ± 3.8	<.001	.02
Waist circumference				
Male (cm)	88.4 ± 11.3	88.7 ± 9.4	.47	.29
Female (cm)	82.4 ± 11.1	84.2 ± 9.7	<.001	.042
Systolic BP (mm Hg)	125.7 ± 17.8	137.5 ± 20.8	<.001	.49
Diastolic BP (mm Hg)	75.0 ± 10.5	75.5 ± 11.1	.06	<.001
Laboratory results				
Hemoglobin A_{1c} (%)	7.8 ± 2.0	7.6 ± 1.7	<.001	<.001
Fasting plasma glucose (mmol/L)	9.0 ± 3.6	8.5 ± 3.1	<.001	<.001
LDL cholesterol (mmol/L)	3.1 ± 1.0	3.1 ± 1.0	.95	.49
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	<.001	.104
Triglyceride (mmol/L)	1.4 (0.9-2.1)	1.4 (1.0-2.1)	.009	.51
Blood hemoglobin (g/dL)	14.0 ± 1.7	13.6 ± 1.7	<.001	<.001
Red blood cell count ($\times 10^9$/L)	4.8 ± 0.6	4.6 ± 0.6	<.001	<.001
Urinary ACR (mg/mmol)	1.6 (0.7-7.2)	2.3 (0.8-12.3)	<.001	<.001
eGFR ($mL/min/1.73\ m^2$)	125.1 ± 36.7	96.9 ± 32.0	<.001	<.001
Microvascular complications at baseline				
Microalbuminuria (%)	23.0	26.9	.001	/
Macroalbuminuria (%)	13.4	17.8	<.001	/
Chronic kidney disease† (%)	4.5	12.9	<.001	/
End-stage renal failure (%)	0.6	0.9	.23	/
Retinopathy (%)	22.9	28.1	<.001	/
Sensory neuropathy (%)	16.1	23.6	<.001	/
Macrovascular complications at baseline				
Coronary heart disease (%)	2.9	9.2	<.001	/
Congestive heart failure (%)	0.7	2.5	<.001	/
Stroke (%)	1.0	3.1	<.001	/
Peripheral vascular disease (%)	3.4	6.6	<.001	/
Use of medications				
Antihypertensive drugs (%)	26.6	52.9	<.001	/
ACEI or ARB (%)	15.7	24.1	<.001	/
Lipid-lowering drugs (%)	10.9	21.0	.001	/
Oral antidiabetic drugs (%)	56.1	69.2	<.001	/
Insulin (%)	19.5	16.4	<.001	/

Mean ± standard deviation or median (IQR).

ACEI = angiotensin-converting enzyme inhibitor; ACR = albumin-to-creatinine ratio; ARB = angiotensin II receptor blocker; BP = blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

*Adjusted by age using linear regression.

†Inclusive of end-stage renal disease defined as eGFR <15 $mL/min/1.73\ m^2$ or dialysis.

Discharge coding was performed by trained personnel at the hospital. The censor date of the analysis was the date of first clinical outcome or January 31, 2009, whichever came first. Coronary heart disease was defined as myocardial infarction (ICD-9 code 410), ischemic heart disease (ICD-9 code 411-414), or death due to coronary heart disease (ICD-9 code 410-414). Congestive heart failure was defined as nonfatal and fatal heart failure (ICD-9 code 428). Stroke was defined as nonfatal (ICD-9 code 432-434, 436) or fatal ischemic stroke (ICD-9 code 432-438), or hemorrhagic stroke as defined by fatal and nonfatal subarachnoid hemorrhage (ICD-9 code 430), intracerebral hemorrhage (ICD-9 code 431), or other/unspecified intracranial hemorrhage (ICD-9 code 432). Transient ischemic attack was not included in the definition of stroke in the present analysis. Peripheral vascular disease was defined as diabetes with peripheral circulatory disorders (ICD-9 code 250.7), gangrene (ICD-9 code 785.4), angiopathy in diseases classified elsewhere (ICD-9 code 443.81), peripheral vascular disease unspecified (ICD-9 code 443.9), other peripheral vascular shunt or

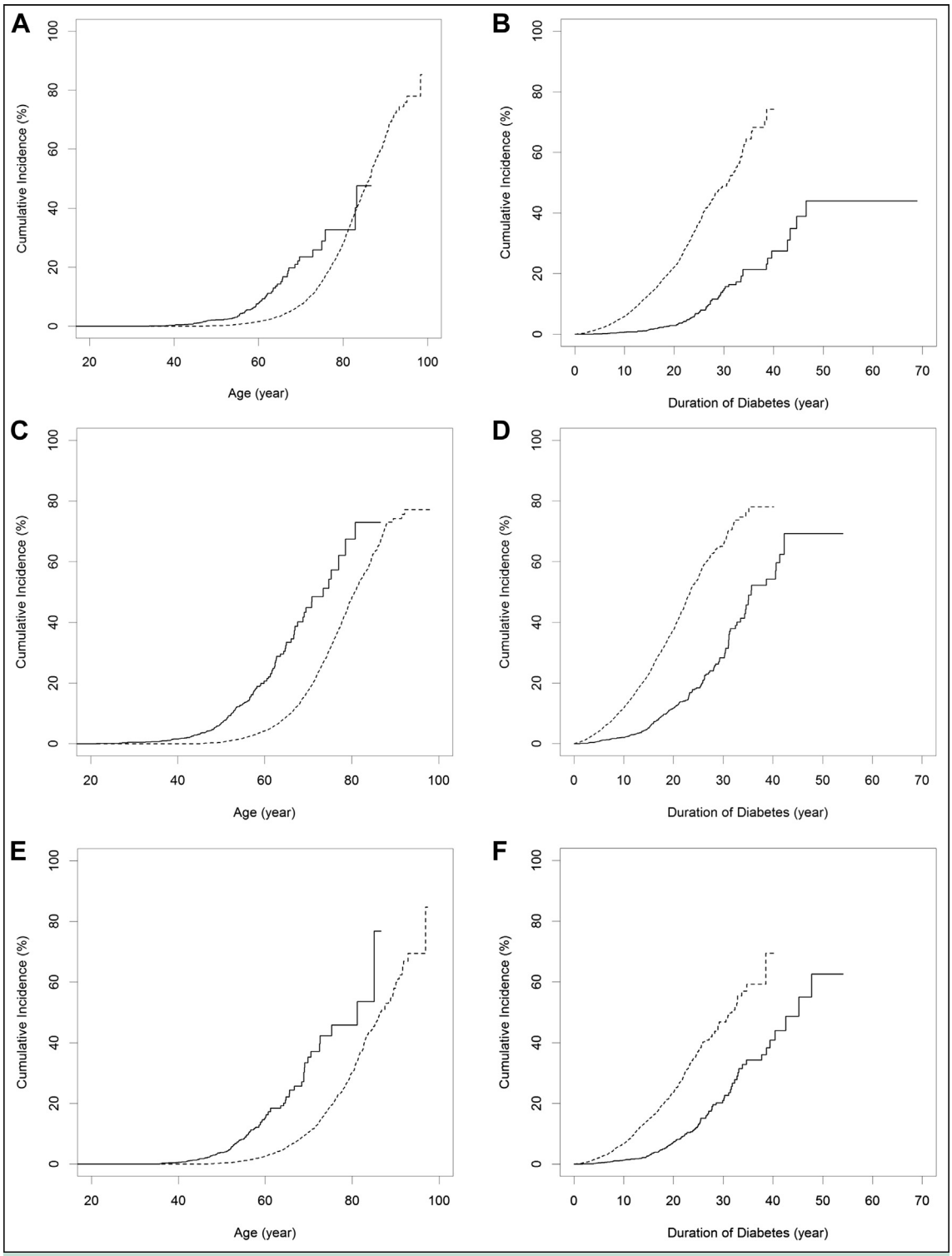

Figure 1 (**A**) Kaplan-Meier plot of cumulative incidences of all-cause death stratified by attained age: young-onset diabetes (*solid line*) and late-onset diabetes (*dotted line*). (**B**) Kaplan-Meier plot of cumulative incidences of all-cause death stratified by duration of disease: young-onset diabetes (*solid line*) and late-onset diabetes (*dotted line*). (**C**) Kaplan-Meier plot of cumulative incidences of chronic kidney disease stratified by attained age: young-onset diabetes (*solid line*) and late-onset diabetes (*dotted line*). (**D**) Kaplan-Meier plot of cumulative incidences of chronic kidney disease stratified by duration of disease: young-onset diabetes (*solid line*) and late-onset diabetes (*dotted line*). (**E**) Kaplan-Meier plot of cumulative incidences of cardiovascular disease stratified by attained age: young-onset diabetes (*solid line*) and late-onset diabetes (*dotted line*). (**F**) Kaplan-Meier plot of cumulative incidences of cardiovascular disease stratified by duration of disease: young-onset diabetes (*solid line*) and late-onset diabetes (*dotted line*).

bypass (procedure code 39.29), insertion of non-drug-eluting peripheral vessel stents (procedure code 39.90), or amputation of lower limb (procedure code 84.1) without a traumatic amputation diagnosis code (ICD-9 code 895-897). In this analysis, cardiovascular disease as an outcome included coronary heart disease, congestive heart failure, stroke, and peripheral vascular disease.

We retrieved all serum creatinine measurements during the observation period to identify the first event of chronic kidney disease as defined by eGFR <60 mL/min/1.73 m^2. End-stage renal disease was defined by eGFR <15 mL/min/1.73 m^2 or first hospital discharge diagnosis of renal manifestation with renal failure (ICD-9 code 250.4), fatal or nonfatal renal failure (ICD-9 code 585 and 586), or requirement of dialysis (ICD-9 procedure code 39.95 or 54.98).

Statistical Analysis

Statistical analysis was performed using SPSS version 15 (SPSS Inc, Chicago, Ill) package and R version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria). Data were expressed as mean ± standard deviation, median (interquartile range [IQR]), or percentages as appropriate. Triglyceride and urinary albumin-to-creatinine ratio were logarithmically transformed because of skewed distributions. Student *t* test, Wilcoxon rank-sum test, or chi-square tests were used to compare baseline data between patients with young- and late-onset diabetes. Kaplan-Meier analysis was used to plot the cumulative incidences of cardiovascular disease, chronic kidney disease, and all-cause death against duration of diabetes and attained age. Incidences of these end points were further compared between the young- and late-onset groups stratified by baseline age strata from 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years.

To address the question of whether young-onset diabetes, when adjusted for age, with and without adjustment for disease duration, modifies the risks for major clinical outcomes, Cox proportional hazard regression for separate end points of cardiovascular disease, chronic kidney disease, and all-cause death was performed to include clinical variables in the following manner: Model 1 contained age, gender, and young-onset diabetes; model 2 contained variables in model 1 and disease duration; model 3 contained variables in model 2 and metabolic risk factors, including smoking, body mass index (BMI), systolic blood pressures, glycated hemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, urine albumin-to-creatinine ratio, and eGFR (for end point of cardiovascular event); model 4 included variables in model 3 and interactive term of young-onset diabetes × disease duration. The interactive term of young-onset diabetes with disease duration was to evaluate whether disease duration had a greater or lesser impact in young-onset diabetes on clinical outcomes. We excluded patients with a history of cardiovascular disease and chronic kidney disease in developing the cardiovascular and renal event models, respectively. Because of multicollinearity, we included BMI and systolic blood pressures and excluded waist circumference and diastolic blood pressures. A *P* value <.05 (2-tailed) was considered significant.

RESULTS

Baseline Patient Characteristics

Among 10,129 enrolled patients, 374 with type 1 diabetes, 38 with unknown type of diabetes, and 211 with non-Chinese ethnicity were excluded. In the remaining 9506 patients with type 2 diabetes, 2066 (21.3%) were diagnosed before the age of 40 years: 87 (0.9%) before the age of 20 years, 392 (4.0%) between the age of 20 to 29 years, and 1587 (16.3%) between the age of 30 to 39 years. There was a female preponderance in the young-onset group who were more likely to have positive family history, longer disease duration, and insulin treatment, but were less likely to receive cardiovascular drugs. After age adjustment, compared with patients with late-onset diabetes, those with young-onset disease had lower diastolic blood pressures and urinary albumin-to-creatinine ratio, and higher glycated hemoglobin, BMI, eGFR, and hematocrit (**Table 1**). Hypertension was prevalent in 54.8% and 81.1%, and dyslipidemia was prevalent in 74.0% and 79.5% in the young- and late-onset groups, respectively. Within the young-onset group, 48.5% of those with hypertension were treated with antihypertensive agents, and 27.6% of those with dyslipidemia received lipid-lowering drugs. Pharmacotherapy was prescribed to 65.3% of patients with hypertension and 53.8% with dyslipidemia in the late-onset group.

Incidence Rates of Major Clinical Events in Young- Versus Late-onset Diabetes

Over a median follow-up of 7.1 years (IQR, 3.7-10.6 years) (median follow-up 9.2 [IQR 6.1-11.5] years in the young-onset group and 6.4 [IQR 3.4-10.2] years in the late-onset group), 7653 clinical events were accrued. **Figure 1** shows the Kaplan-Meier plots for the cumulative incidences of major clinical events against attained age and disease duration. After excluding patients with a history of cardiovascular disease or chronic kidney disease, compared with the late-onset group, patients with young-onset diabetes had lower event rates for the same disease duration but higher cumulative incidence of major events at any given age. At any given age at baseline, patients with young-onset diabetes had a higher incidence of both cardiovascular and renal events compared with those with late-onset diabetes (**Table 2**).

Risks of Clinical Events in Young-onset Diabetes

With the use of Cox regression analysis (**Table 3**, model 1), young-onset diabetes increased the age- and gender-adjusted hazard ratio of cardiovascular disease by 1.48 (95% confidence interval, 1.17-1.88) and chronic kidney disease by

Table 2 Incidence Rates of Cardiovascular-renal Events and Death in Patients with Young- and Late-onset Diabetes Stratified by Baseline Age at Enrollment

Age at Enrollment (y)	Young-onset Diabetes (95% CI)	Late-onset Diabetes (95% CI)	*P* Value
Cardiovascular disease			
40-44	7.0 (4.6-10.6)	3.6 (2.0-6.7)	.08
45-49	14.7 (10.4-20.9)	8.9 (6.6-12.0)	.030
50-54	24.3 (16.4-36.1)	10.6 (8.3-13.5)	<.001
55-59	34.2 (20.5-57.4)	15.7 (12.9-19.1)	.005
Chronic kidney disease			
40-44	12.6 (9.2-17.1)	4.6 (2.7-7.9)	.001
45-49	19.5 (14.4-26.3)	15.0 (12.0-18.8)	.18
50-54	31.0 (21.7-44.6)	18.5 (15.4-22.3)	.012
55-59	63.4 (42.7-94.3)	27.6 (23.9-32.0)	<.001
All-cause death			
40-44	3.5 (2.0-6.2)	2.4 (1.2-4.9)	.40
45-49	5.4 (3.7-7.7)	6.2 (3.8-10.2)	.64
50-54	14.9 (9.6-23.2)	7.3 (5.6-9.6)	.007
55-59	20.4 (11.8-35.7)	14.7 (12.2-17.6)	.27

Incidence rates are expressed per 1000 person-year.
CI = confidence interval.

1.35 (95% confidence interval, 1.11-1.62). Further adjustment for disease duration (**Table 3**, model 2) rendered the association of young-onset diabetes with cardiovascular or renal events statistically insignificant. The addition of cardiometabolic risk factors (**Table 3**, model 3) did not affect the relationship of young-onset diabetes with clinical events. The interactive term of young-onset diabetes × disease duration was borderline statistically significant for cardiovascular disease with a positive correlation, suggesting that disease duration may have a greater effect in young-onset diabetes for this outcome. Young-onset diabetes was not associated with all-cause death.

DISCUSSION

Despite the increasing prevalence of young-onset type 2 diabetes worldwide,[11] there are relatively few reports on the natural history of this form of diabetes.[4,5,12,13] To the best of our knowledge, this is the largest prospective cohort of patients with young-onset diabetes, which accounted for 20% of the entire cohort. Despite being younger by 20 years, the young-onset group had similar or worse risk profiles than the late-onset group. With a mean age of 40 years and mean disease duration of 6 years, as many as 5% of patients with young-onset diabetes had cardiovascular or chronic kidney disease at enrollment. At any given age, the young-onset group had higher incidences of developing cardiovascular-renal complications.

Premature Mortality and Comorbidities in Young-Onset Diabetes

In the Emerging Risk Factor Collaboration Study of >820,000 people from Europe and North America, diabetes increased all-cause deaths by 1.3- to 3-fold with loss of 6 years of life in a 40-year-old person.[14] In a prospective analysis of Pima Indians with type 2 diabetes, the age- and sex-adjusted incidence of end-stage renal disease was 25.0 cases per 1000 person-years in patients diagnosed before the age of 20 years, compared with 5.4 cases per 1000 person-years in patients diagnosed after the age of 20 years.[4] The respective rates of death from natural causes were 15.4 versus 7.3 cases per 1000 person-years. The increased risk ratios for these outcomes were explained mainly by the longer disease duration in the young cases at baseline, because on adjustment for disease duration, the cumulative incidences of both these outcomes were lower in the young-onset group.

In the current analysis, cumulative incidences of cardiovascular-renal events were similarly lower in patients with young-onset diabetes when plotted against disease duration but higher when examined against attained age. The independent effects of age and disease duration in driving diabetes outcomes in young-onset diabetes were examined in Cox proportional hazards regression. When adjusted by age only, patients with young-onset diabetes were at 30% to 50% increased risks for cardiovascular-renal events compared with those with late-onset diabetes. Further adjustment for disease duration eliminated the risk association of young-onset diabetes with diabetes complications, indicating that the high risk of cardiovascular-renal outcome in this young group was largely explained by the long disease duration.

Glycemic Control in Young-onset Diabetes

Given the importance of disease duration in patients with young-onset diabetes, it follows that sustained control of metabolic risk factors may have an even greater impact in this group compared with older individuals. In our cohort, the young-onset group had lower blood pressure but higher glycated hemoglobin, greater BMI, and similar low-density lipoprotein cholesterol relative to the late-onset group. Worse glycemic control in younger patients has been reported.[15] In a recent analysis of data from the National Health and Nutrition Examination Survey in the United States, younger adults aged 18 to 44 years had consistently lower rates of reaching glycated hemoglobin targets compared with older adults.[15] Particularly alarming was the observation that rates of target attainment in the younger group have not improved over the 12-year observation period.

Although clinical inertia and poor motivation for self-management may explain the higher glycated hemoglobin in young-onset diabetes, it has been proposed that the pathophysiology underlying the development of type 2 diabetes in younger individuals may be more aggressive. In support of this, we found that the young-onset group was more likely to have positive family history and be treated with insulin. Among Caucasians, patients with young-onset disease were 80% more likely to require insulin than their late-onset peers despite a similar duration of diabetes.[5] In the Treat Type 2 Diabetes Early and Aggressively in Young study evaluating

Table 3 Hazard Ratios with 95% Confidence Intervals of Risk Factors for Predicting Cardiovascular-renal Events in Chinese Patients with Type 2 Diabetes and Their Comparisons Between Young-onset and Late-onset Diabetes with Explained Variance

	Cardiovascular Disease	Chronic Kidney Disease	All-cause Death
Model 1			
Young-onset diabetes	1.48 (1.17-1.88)	1.35 (1.12-1.62)	1.09 (0.82-1.43)
Age	1.07 (1.06-1.08)	1.07 (1.07-1.08)	1.09 (1.08-1.10)
Model 2			
Young-onset diabetes	1.02 (0.79-1.32)	0.87 (0.71-1.06)	0.80 (0.59-1.07)
Age	1.06 (1.05-1.07)	1.06 (1.05-1.06)	1.08 (1.07-1.09)
Disease duration	1.03 (1.03-1.04)	1.04 (1.03-1.05)	1.02 (1.02-1.03)
Model 3			
Young-onset diabetes	0.99 (0.77-1.28)	0.88 (0.72-1.08)	0.88 (0.66-1.19)
Age	1.05 (1.04-1.06)	1.05 (1.04-1.06)	1.06 (1.05-1.07)
Disease duration	1.02 (1.00-1.03)	1.02 (1.02-1.03)	1.00 (0.99-1.01)
Model 4			
Young-onset diabetes	0.76 (0.52-1.12)	0.82 (0.61-1.10)	0.71 (0.44-1.14)
Age	1.05 (1.04-1.06)	1.05 (1.04-1.05)	1.06 (1.05-1.07)
Disease duration	1.01 (1.00-1.02)	1.02 (1.01-1.03)	1.00 (0.99-1.01)
Interactive term (young-onset diabetes × disease duration)	1.02 (1.00-1.04)	1.01 (0.99-1.02)	1.01 (0.99-1.04)

Independent variables included in different models using stepwise Cox proportional hazard analysis: model 1: young-onset diabetes, age, gender; model 2: variables in model 1 + disease duration; model 3: variables in model 2 + smoking, BMI, systolic blood pressures, glycated hemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, urine albumin-to-creatinine ratio, and eGFR (for cardiovascular event); model 4: variables in model 3 + interactive term (young-onset diabetes × disease duration).

durability of glycemic control in 700 adolescents aged 10 to 17 years with recently diagnosed type 2 diabetes, more than 50% of patients on metformin monotherapy reached the primary end point of glycemic failure under 4 years of follow-up.[16] Moreover, patients with glycemic failure had a more rapid decline in beta-cell function compared with those without glycemic failure.[17] The hereditary nature of type 2 diabetes is well established, and the majority of the identified genetic variants for type 2 diabetes have been shown to affect beta-cell biology.[18] The contribution of insulin deficiency to dysglycemia is particularly pertinent among lean Asian subjects.[19,20] In a subset of young Chinese patients with type 2 diabetes, we have previously reported on the association of family history with low BMI, low C-peptide, and high glycated hemoglobin.[21] These data underline the need of early insulin supplement in patients with young-onset diabetes, in addition to keeping high vigilance on lifestyle factors, to maintain optimal glycemic control.

Cardiometabolic Risk Factors in Young-onset Diabetes

At a mean age of 40 years, more than half of the young patients had hypertension and three quarters were dyslipidemic. High rates of adverse metabolic profile have been similarly reported in other studies. In the SEARCH for Diabetes in Youth Study surveying diabetic children and adolescents across the United States, high blood pressure was documented in approximately 30% and high low-density lipoprotein cholesterol was documented in half of the non-Hispanic white youth with type 2 diabetes.[22] In our cohort, only 48% of the young-onset group with hypertension was receiving antihypertensive drugs, and lipid-lowering agents were prescribed to only 28% of those with dyslipidemia. In contrast, up to 65% of the late-onset group with hypertension and 54% with dyslipidemia were treated. Our results indicated that suboptimal medical attention was given to younger patients, in part because of the absence of clinical guidelines targeted to this age group and possibly the misconception of low risks of life-threatening complications in these patients. Although there have been many studies in the middle-aged and elderly population to evaluate the effect of treatment to multiple targets,[23] there is a scarcity of similar randomized clinical trials in these vulnerable subjects.

Renal Insufficiency in Young-onset Diabetes

At enrollment, 37% of patients in the young-onset group had micro/macroalbuminuria and 4% had chronic kidney disease. In Japan, 40% of young type 2 diabetic patients developed overt proteinuria compared with 20% in type 1 diabetic patients after 30 years.[13] In Caucasians, patients with young-onset type 2 diabetes had a 20% increased hazard ratio for microalbuminuria compared with the late-onset group.[5] Apart from genetic factors,[24] endemic low-grade infections such as chronic hepatitis B infection might contribute to the earlier age of onset of diabetes and renal disease in Asian subjects.[25] In addition, prolonged exposure to hyperglycemia, dyslipidemia, and oxidative stress may cause epigenetic changes, contributing to microvascular complications.[26] All of these factors may be of particular relevance to patients with young-onset diabetes

who face long disease duration. In agreement with other reports,[27] there was inadequate prescription of disease-modifying drugs in young-onset diabetes, with only 15% of patients treated with renin-angiotensin inhibitors.

Public Health Implications of Young-onset Diabetes

Rapid lifestyle and nutritional transition may lead to biological mismatching through epigenetic factors, resulting in young-onset diabetes and chronic diseases.[28] Compared with the West where major increase in diabetes prevalence occurs in the elderly, in most developing areas, the main increase occurs in the young- to-middle aged group.[1] During the 1994-2000 period, there was an 88% increase in the prevalence of diabetes in the age group of 35 to 44 years in China.[29] Together with the increasing prevalence of childhood obesity, this trend of suboptimal treatment and noncompliance in young patients heralds a looming epidemic of premature chronic disease with major personal, family, and societal implications.[2]

Study Limitations

In this ongoing registry, we did not systematically evaluate the impacts of interventions and control of risk factors on clinical events because of the nonstructured nature of data collection. We also did not examine autoantibodies, genetic variants, and C-peptide levels that were not part of our routine clinical service, although epidemiologic reports from Asia suggested that some of them might have autoimmune antibodies or monogenic diabetes.[30,31] We acknowledge that the use of ICD-9 code as a method to identify events is limited by potential misclassification. Finally, we may have underestimated the number of hospital events because events presented to the private sector were not able to be captured. However, incomplete ascertainment of clinical events would affect both the young- and late-onset groups.

CONCLUSIONS

In this large prospective cohort, 1 in 5 patients had young-onset diabetes characterized by strong family history and suboptimal risk factor control. Given the long disease duration faced by these patients, their lifetime risk for complications becomes considerably higher than in the late-onset group given the same age. An integrated program combining detection, treatment, and prevention is urgently needed to monitor disease trend, improve care, and evaluate the cost-effectiveness of intensified treatment in these high-risk patients.

ACKNOWLEDGMENTS

The authors thank all the patients for being part of this prospective cohort. Special thanks are extended to our medical and nursing staff at the Chinese University of Hong Kong, Prince of Wales Hospital Diabetes and Endocrine Centre, an International Diabetes Federation Centre of Education.

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