Prospective Study on the Incidences of Cardiovascular-Renal Complications in Chinese Patients With Young-Onset Type 1 and Type 2 Diabetes

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OBJECTIVE

We examined metabolic profiles and cardiovascular-renal outcomes in a prospective cohort of Chinese patients with young-onset diabetes defined by diagnosis age <40 years. Patients with type 1 diabetes and normal-weight (BMI <23 kg/m^2) and overweight (BMI ≥23 kg/m^2) patients with type 2 diabetes were compared.

RESEARCH DESIGN AND METHODS

Between 1995 and 2004, 2,323 patients (type 1 diabetes, *n* = 209; normal-weight type 2 diabetes, *n* = 636; and overweight type 2 diabetes, *n* = 1,478) underwent detailed clinical assessment. Incident cardiovascular disease (CVD) including coronary heart disease, stroke, and peripheral vascular disease were identified using hospital discharge diagnoses. End-stage renal disease (ESRD) was defined by glomerular filtration rate <15 mL/min/1.73 m^2 or dialysis.

RESULTS

Overweight patients with type 2 diabetes had the worst metabolic profile and highest prevalence of microvascular complications. Over a median follow-up of 9.3 years, incidences of CVD were 0.6, 5.1, and 9.6 per 1,000 person-years in patients with type 1 diabetes, normal-weight patients with type 2 diabetes, and overweight patients with type 2 diabetes. The respective figures for ESRD were 2.2, 6.4, and 8.4 per 1,000 person-years. Compared with type 1 diabetes, the overweight type 2 diabetes group had a greater hazard of progression to CVD (hazard ratio [HR] 15.3 [95% CI 2.1–112.4]) and ESRD (HR 5.4 [95% CI 1.8–15.9]), adjusted for age, sex, and disease duration. The association became nonsignificant upon additional adjustment for BMI, blood pressure, and lipid.

CONCLUSIONS

Young patients with type 2 diabetes had greater risks of developing cardiovascular-renal complications compared with patients with type 1 diabetes. The increased risk was driven primarily by accompanying metabolic risk factors.

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A slide set summarizing this article is available online.

Amid the current diabetes pandemic, the perpetual decline in the age of disease onset is a disturbing worldwide trend that has major public health ramifications (1). In susceptible ethnic groups including Asians, type 2 diabetes has emerged as the predominant form of dysglycemia in childhood and adolescence (2–5). The evolving epidemic of obesity in youth as a result of global industrialization favoring energy conservation over energy expenditure is the main culprit for the increasingly younger age of diabetes development. Consistent with the role of insulin resistance in type 2 diabetes, development of cardiometabolic risk factors precedes the diagnosis of diabetes in a large proportion of patients (3,4).

Relative to adult-onset diabetes, early development of disease imposes a longer exposure to the hazards of chronic hyperglycemia and increases the likelihood of progression to overt complications even before reaching middle age. In Pima Indians, the incidence of diabetic nephropathy was similar between patients with young- and adult-onset type 2 diabetes and at any given age, and the cumulative incidence of nephropathy was higher in those with young-onset disease (5). Furthermore, compared with age-matched members of the general population, young individuals with early diabetes have 30 times the risk of stroke and 14 times the risk of myocardial infraction, reinforcing the notion that young diabetic patients are not impervious to the life-threatening manifestations of atherosclerosis (6). While overwhelming evidences support the efficacy of global risk factor control on cardiovascular-renal protection among older patients with or without established comorbidities (7), data on the benefit of aggressive intervention with early use of adjunctive therapy such as statins and renin-angiotensin system blockade in younger patients are limited.

On a separate note, it has long been recognized that a proportion of Asian patients with type 2 diabetes have a low BMI, which deviates from their obese counterparts in terms of metabolic profile and early requirement for insulin (8). In a previous report, we have remarked on the heterogeneity of diabetic phenotypes in Chinese and showed the correlation of low BMI with insulin deficiency as measured using C-peptide (9). In another study of young lean Asian diabetic patients with detailed assessment of insulin sensitivity using hyperinsulinemic-euglycemic clamp, patients with type 2 diabetes were more insulin resistant than those with type 1 diabetes despite comparable anthropometric indices (10). Thus, lean type 2 diabetic individuals represent a special group in the Asian population who are more insulin deficient compared with their obese counterparts and more insulin resistant compared with the type 1 group.

Few reports have prospectively compared late vascular outcomes between type 1 and type 2 diabetes (11–13). To our knowledge, differences in the incidences of diabetes complications between normal-weight and overweight patients with type 2 diabetes have not been examined. In a consecutively recruited, prospective Chinese cohort of patients with young-onset diabetes, we compared the baseline clinical characteristics and incidences of cardiovascular-renal outcomes between patients with type 1 diabetes and normal-weight and overweight patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

The Hong Kong Diabetes Registry, established since 1995 at the Prince of Wales Hospital, consecutively enrolled patients referred to the hospital for comprehensive assessment of diabetes complications and metabolic control. Referral sources included hospital-based specialty clinics, community clinics, and general practitioners. All enrolled patients were followed until the time of death.

For this analysis, we included patients with young-onset type 1 or type 2 diabetes who entered the Registry from its inception until 31 December 2004. Young-onset diabetes was defined by age of disease onset $<$40 years. Patients were classified as type 1 diabetic if they presented with diabetic ketoacidosis or required continuous use of insulin within 1 year of diagnosis. Given the low prevalence of anti-GAD antibodies and anti–islet cell antigen antibodies among Chinese patients with type 1 diabetes (14), the presence of autoantibodies was not a prerequisite in defining type 1 diabetes in our cohort. The remaining patients were designated to have type 2 diabetes after exclusion of those in the category of "other diabetes type," which included secondary diabetes and gestational diabetes mellitus. The Declaration of Helsinki was adhered to, and written informed consent was obtained from all patients at the time of enrolment for data analysis and research purposes. Ethics approval was obtained from The Chinese University of Hong Kong Clinical Research Ethics Committee.

Baseline Clinical and Laboratory Measurements

Baseline clinical assessment was performed using a modified form of the European DiabCare protocol (15). Information including key demographics, past medical history, and current drug history were documented. Fasting blood samples were taken for measurement of fasting plasma glucose, glycated hemoglobin (HbA_{1c}), lipid profile (total cholesterol, HDL cholesterol, triglyceride, and LDL cholesterol), and renal function. The abbreviated Modification of Diet in Renal Disease Study formula recalibrated for the Chinese population was used to estimate glomerular filtration rate (GFR): estimated GFR = $186 \times (\text{serum creatinine } [\mu\text{mol/L}] \times 0.011)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times 1.233$, where 1.233 is the adjusting coefficient for Chinese (16). A random spot urine sample was obtained to measure the albumin-to-creatinine ratio (ACR). Microalbuminuria was defined as urine ACR of 2.5−30 mg/mmol in females and 3.5−30 mg/mmol in males. Macroalbuminuria was defined as urine ACR $>$30 mg/mmol. We defined hypertension by either blood pressure $\geq$130/80 mmHg or baseline use of antihypertensive medication. Dyslipidemia was defined by either LDL cholesterol $\geq$2.6 mmol/L or the use of lipid-lowering drugs. Anti-GAD was measured in a consecutive subset of patients (n = 605) using a

radioimmunoprecipitation assay where the upper-normal limit of 18 units defined positivity. Laboratory assays, except for anti-GAD antibodies, were performed at the Department of Chemical Pathology, the Prince of Wales Hospital, which is accredited by the Royal College of Pathologists of Australasia. Anti-GAD antibodies were measured at the laboratory at the University of Colorado.

Outcome Identification and Definition

Hong Kong has a heavily subsidized health care system. The Hospital Authority (HA) is the governing body of all public-funded hospitals and outpatient clinics and provides 95% of the total hospital bed days and 80% of the outpatient visits (17). Details of all medical admissions of the cohort were retrieved from the HA Central Computer System, which records admissions to all public hospitals. The databases were matched by a unique identification number, the Hong Kong Identity Card number, which is compulsory for all Hong Kong residents.

A trained team of personnel in the HA routinely coded all hospital discharge diagnoses according to the ICD-9. Coronary heart disease was defined as myocardial infarction (ICD-9 code 410), ischemic heart disease (ICD-9 code 411–414), or death owing to coronary heart disease (ICD-9 code 410–414). Congestive heart failure was defined as nonfatal or 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) or intracerebral hemorrhage (ICD-9 code 431). 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 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). Cardiovascular diseases (CVDs) included coronary heart disease, congestive heart failure, stroke, and peripheral vascular disease.

All measurements of serum creatinine performed during the follow-up period were retrieved from the HA Central Computer System. End-stage renal disease (ESRD) was defined as fatal or nonfatal renal failure (code 585 and 586), requirement of dialysis (procedure code 39.95 or 54.98), or estimated GFR $<$15 mL/min/1.73 m^2.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Science, version 13.0, for Windows software package. Follow-up time was calculated as the period from enrolment to the date of the first cardiovascular event, renal event, death, or censored date of 31 January 2009—whichever came first. For comparison of baseline clinical characteristics and incidences of diabetes complications, patients were separated into three groups: type 1 diabetic, normal-weight type 2 diabetic, and overweight type 2 diabetic. We defined overweight by the Asian-specific BMI cutoff of $\geq$23 kg/m^2 (18). Data are expressed as mean $\pm$ SD, median (interquartile range), or percentages. χ^2 test was used for between-group comparison of categorical variables, *t* test for normally distributed continuous variables, and Kruskal-Wallis test for continuous variables with skewed distribution. Kaplan-Meier analysis was used to plot cumulative incidences of cardiovascular and renal events, separated by the three patient groups.

Cox proportional regression was performed to obtain the hazards of normal-weight or overweight type 2 diabetes versus type 1 diabetes on incident CVD and ESRD. Four Cox models were constructed sequentially for each outcome: model 1, adjusted for age, sex, and time since diabetes diagnosis; model 2, adjusted for HbA_{1c} in addition to variables in model 1; model 3, adjusted for other metabolic indices including BMI, systolic blood pressure, LDL cholesterol, triglycerides, and HDL cholesterol, in addition to variables in model 2; and model 4, adjusted for baseline albuminuria status, estimated GFR, history of retinopathy, neuropathy (and history of CVD in the Cox model for ESRD), in addition to variables in Model 3. Patients with baseline ESRD were excluded in the analysis of renal end point, and patients with baseline CVD were excluded in the analysis of cardiovascular end point. Given the age difference between patients with type 1 and those with type 2 diabetes, Cox regression analysis was repeated using restricted cubic spline procedure for the adjustment of age. A two-sided *P* value of $<$0.05 was considered significant.

RESULTS

Of 10,129 patients enrolled into the registry, 7,762 patients with diabetes onset after 40 years of age, 50 patients with other or unknown types of diabetes, and 61 patients of non-Chinese ethnicity were excluded. Of the remaining 2,323 patients, 209 (9.0%) had type 1 diabetes, 636 (27.4%) had type 2 diabetes and were of normal weight, and 1,478 (63.6%) had type 2 diabetes and were overweight. Patients with type 2 diabetes were older, while those with type 1 diabetes had longer duration of diabetes (Table 1). Overweight type 2 diabetic patients had the worst lipid and blood pressure profile.

The prevalence of hypertension and dyslipidemia was 22.4 and 57.5% in type 1 diabetic patients, 40.9 and 70.1% in normal-weight patients with type 2 diabetes, and 60.1 and 75.7% in overweight patients, respectively. Of those with type 2 diabetes, 45.9% did not reach a blood pressure target of 130/80 mmHg, and only 48.1% of patients with hypertension were on pharmacotherapy. Similarly, 65.0% did not meet target LDL cholesterol of $<$2.6 mmol/L and just 14.4% of those identified as dyslipidemic were on lipid-lowering drugs. Overall, only 7.9% of young patients with type 2 diabetes attained all three targets of blood pressure $<$130/80 mmHg, LDL cholesterol $<$2.6 mmol/L, and HbA_{1c} $<$7%.

Table 1—Baseline patient characteristics of 2,323 Chinese patients with young-onset diabetes stratified by the type of diabetes

	Type 1 diabetes	Normal-weight type 2 diabetes	Overweight type 2 diabetes	*P*
n	209	636	1,478	
Age (years)	27.8 ± 11.5	41.9 ± 10.5	40.8 ± 9.5	<0.001
Male (%)	46.4	41.7	45.1	0.2850
Age at diabetes diagnosis (years)	19.5 ± 10.6	32.8 ± 6.2	33.0 ± 5.9	<0.0001
Time from diabetes diagnosis (years)	8 (2–12)	7 (1–14)	5 (1–12)	0.0060
Current or ex-smoker (%)	20.4	23.5	25.3	0.2553
Family history of diabetes (%)	22.0	54.1	59.7	<0.0001
BMI (kg/m^2)	21.7 ± 3.7	20.7 ± 1.8	27.8 ± 3.9	<0.0001
Waist circumference (cm)				
Male	76.0 ± 10.8	76.8 ± 5.9	92.9 ± 9.6	<0.0001
Female	70.8 ± 9.3	71.9 ± 6.2	86.9 ± 9.5	<0.0001
Systolic blood pressure (mmHg)	114.1 ± 15.1	120.3 ± 17.9	127.8 ± 17.2	<0.0001
HbA_{1c}				
NGSP (%)	8.6 ± 2.2	8.0 ± 2.2	7.8 ± 1.9	<0.0001
IFCC (mmol/mol)	66 ± 17	64 ± 18	62 ± 15	
LDL cholesterol (mmol/L)	2.8 ± 0.8	3.0 ± 1.0	3.1 ± 1.0	<0.0001
Triglyceride (mmol/L)	0.7 (0.5–1.0)	1.0 (0.7–1.4)	1.5 (1.1–2.4)	<0.0001
HDL cholesterol (mmol/L)	1.7 ± 0.5	1.5 ± 0.4	1.2 ± 0.3	<0.0001
Urine ACR (mg/mmol)	1.1 (0.6–2.3)	1.2 (0.6–3.6)	1.8 (0.7–8.8)	<0.0001
Estimated GFR (mL/min/1.73 m^2)	142.9 ± 42.6	126.7 ± 34.3	124.2 ± 36.4	<0.0001
Proportion with hypertension (%)	22.4	40.9	60.1	<0.0001
Proportion with dyslipidemia (%)	57.5	70.1	75.7	<0.0001
Baseline diabetes complications (%)				
Microalbuminuria	16.3	20.5	24.3	<0.0001
Macroalbuminuria	3.4	8.8	11.1	0.0050
Chronic kidney disease	0.5	3.1	4.9	0.0013
Retinopathy	14.8	23.3	22.9	0.0245
Peripheral neuropathy	10.5	17.9	15.4	0.0342
History of coronary heart disease	0.5	1.6	3.3	0.0069
History of stroke	0.0	0.6	0.9	0.4298
History of peripheral vascular disease	3.8	3.6	3.0	0.7105
Medication use at baseline (%)				
Insulin	100	22.0	19.0	<0.0001
Oral hypoglycemic drugs	4.8	45.9	59.0	<0.0001
Lipid-lowering drugs	1.9	6.6	12.4	<0.0001
Antihypertensive drugs	8.1	19.2	29.1	<0.0001
Renin-angiotensin system blockers	4.8	12.7	16.6	<0.0001

Data are means ± SD or median (interquartile range) unless otherwise indicated. IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; NGSP, National Glycohemoglobin Standardization Program.

Presence of family history was observed more frequently in patients with type 2 than type 1 diabetes. Anti-GAD was detected in 31.0% of patients with type 1 diabetes, 11.8% of normal-weight patients with type 2 diabetes and 2.9% of overweight patients with type 2 diabetes ($P < 0.001$).

Compared with patients with type 1 diabetes, those with type 2 diabetes, either normal- or overweight, had higher rates of micro-/macroalbuminuria, retinopathy and peripheral sensory neuropathy. Background frequencies of CVDs were overall low in this young cohort, and between-group comparison of rates of past macrovascular events did not reach statistical significance.

Over a median follow-up duration of 9.3 years (interquartile range 6.2–11.6), 138 patients (type 1 diabetes, *n* = 1; normal-weight type 2 diabetes, *n* = 26, and overweight type 2 diabetes, *n* = 111) developed CVD, while 141 patients (type 1 diabetes, *n* = 4; normal-weight type 2 diabetes, *n* = 34; and overweight type 2 diabetes, *n* = 103) developed ESRD. The Kaplan-Meier curves for the cumulative incidences of major clinical outcomes are shown in Fig. 1*A* and *B*. The incidence of CVD was highest in the overweight type 2 diabetic group and lowest in type 1 diabetes, with respective rates of 9.6 (95% CI 8.0–11.6), 5.1 (95% CI 3.5–7.5), and 0.6 (95% CI 0.1–3.2) per 1,000 person-years in overweight type 2 diabetes, normal-weight type 2 diabetes, and type 1 diabetes ($P < 0.01$ for all comparisons). A similar trend was observed in the incidences of ESRD, and the corresponding rates for overweight type 2 diabetes, normal-weight type 2 diabetes, and type 1 diabetes were 8.4 (95% CI 6.9–10.2), 6.4 (95% CI 4.6–9.0),

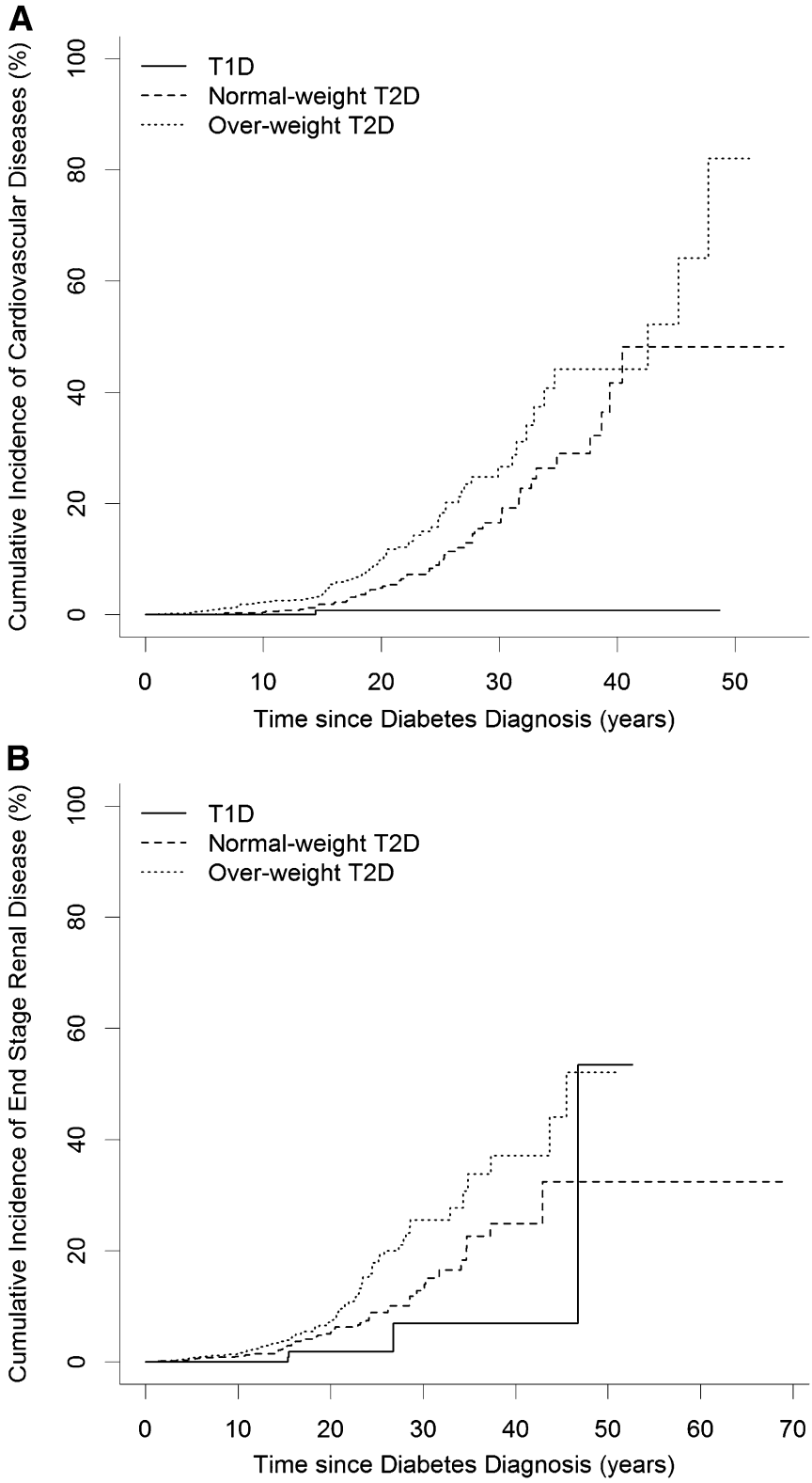

Figure 1—*A*: Kaplan-Meier plot of cumulative incidence of CVD in patients with type 1 diabetes (T1D), normal-weight patients with type 2 diabetes (T2D), and overweight patients with type 2 diabetes. *B*: Kaplan-Meier plot of cumulative incidence of ESRD in patients with type 1 diabetes, normal-weight patients with type 2 diabetes, and overweight patients with type 2 diabetes.

and 2.2 (95% CI 0.9–5.7) per 1,000 person-years (P = 0.035 for comparison between type 1 diabetes and normal-weight type 2 diabetes, P = 0.005 for comparison between type 1 diabetes and overweight type 2 diabetes, and P = 0.182 for comparison between normal-weight and overweight type 2 diabetes).

Cox regression analysis was performed to derive hazard ratios (HRs) of overweight or normal-weight type 2 versus type 1 diabetes for CVD and ESRD (Tables 2 and 3). Compared with patients with type 1 diabetes, overweight patients with type 2 diabetes had 15- and 5-fold greater hazards of developing CVD and ESRD, respectively, when adjusted for age, sex, and time from diagnosis. The association remained robust when adjustment was made for HbA_{1c} but became nonsignificant upon further adjustment for other metabolic indices and baseline complications. There was no difference in hazards between type 1 diabetes and normal-weight type 2 diabetes for either CVD or ESRD. Adjustment of age using restricted cubic spline analysis did not change the statistical significance of results from the regression model.

CONCLUSIONS

In this prospective Chinese young diabetic cohort, overweight patients with type 2 diabetes had the highest incidences of both CVD and ESRD, followed by normal-weight patients with type 2 diabetes. This is the first longitudinal study comparing macrovascular outcomes between young type 1 and type 2 diabetes and the only study examining diabetes outcomes in lean Chinese patients with type 2 diabetes. The increased risk ratio for cardiovascular-renal events in type 2 diabetes was driven primarily by obesity, hypertension, and dyslipidemia. Results from this study quantify the impact of young-onset diabetes on development of chronic complications and underscore the need for more effective intervention including global risk factor management in this young group.

Renal Complications

Microvascular complications were more prevalent in type 2 than type 1 diabetes, and the rates were highest in the group who were overweight. Close to 40% of the overweight patients with type 2 diabetes had albuminuria after a median time since diagnosis of 5 years, while only 19% of patients with type 1 diabetes had evidence of nephropathy against longer diabetes duration of 8 years. Our findings echoed those reported by others (11,19). In a recent prospective study by Dart et al. (11), albuminuria was noted in 14% of youths with type 1 diabetes after 6.2 years but has occurred in up to one-third of type 2 diabetic youth after just 1.6 years. Thus, diabetic nephropathy was not only more common in type 2 compared with type 1 diabetes but also developed sooner after diagnosis. Nonetheless, it should be noted that owing to the long asymptomatic phase of early hyperglycemia in type 2 diabetes, the precise onset of disease is difficult to ascertain and disease duration may be underestimated (20).

Consistent with higher prevalence of albuminuria in type 2 diabetes, the incidences of ESRD were significantly higher in both normal-weight and overweight patients with type 2 diabetes than type 1 diabetes. Compared with those with type 1 diabetes, the overweight group with type 2 diabetes had a fivefold increased risk of progressing to ESRD when adjusted for age, sex, and time from diagnosis. Of note, the risk association became nonsignificant upon further adjustment for BMI and other metabolic indices, suggesting that while glycemic control may be the most important factor in developing renal complications in type 1 diabetes, hypertension and additional components of insulin resistance including dyslipidemia, visceral obesity, and chronic low-grade inflammation contribute to accelerated progression to ESRD in type 2 diabetes. The heterogeneity of kidney disease in type 2 diabetes is also evident at a histological level (21). In addition to characteristic nodular glomerulosclerosis of type 1 diabetes, tubulointerstitial lesions, arteriolar hyalinosis, and arteriosclerosis in various magnitudes may be observed in type 2 diabetes (21). It is also conceivable that patients with type 2

Table 2—Cox proportional regression comparing the hazards of obese type 2 versus type 1 diabetes for incident CVD and ESRD

	HR (95% CI)	*P*
CVD		
Model 1	15.30 (2.08–112.41)	0.0073
Model 2	15.26 (2.07–112.29)	0.0075
Model 3	6.49 (0.83–50.69)	0.0744
Model 4	6.62 (0.84–52.37)	0.0734
ESRD		
Model 1	5.41 (1.84–15.88)	0.0021
Model 2	5.69 (1.93–16.79)	0.0017
Model 3	2.69 (0.69–10.54)	0.1555
Model 4	2.35 (0.59–9.46)	0.2280

Model 1 adjusted for age, sex, and time from diabetes diagnosis. Model 2 adjusted for age, sex, time from diabetes diagnosis, and HbA_{1c}. Model 3 adjusted for age, sex, time from diabetes diagnosis, HbA_{1c}, BMI, systolic blood pressure, diastolic blood pressure, LDL cholesterol, triglyceride, and HDL cholesterol. Model 4 adjusted for age, sex, time from diabetes diagnosis, HbA_{1c}, BMI, systolic blood pressure, diastolic blood pressure, LDL cholesterol, triglyceride, HDL cholesterol, estimated GFR, albuminuria status, history of retinopathy, history of neuropathy, and history of CVD in the analysis for ESRD.

Table 3—Cox proportional regression comparing the hazards of lean type 2 versus type 1 diabetes for incident CVD and ESRD

	HR (95% CI)	*P*
CVD		
Model 1	6.03 (0.76–48.31)	0.0909
Model 2	6.43 (0.79–52.51)	0.0822
Model 3	4.49 (0.47–43.43)	0.1941
Model 4	3.70 (0.36–37.80)	0.2693
ESRD		
Model 1	2.43 (0.76–7.80)	0.1356
Model 2	2.28 (0.71–7.28)	0.1660
Model 3	2.03 (0.51–8.06)	0.3158
Model 4	1.01 (0.23–4.46)	0.9891

Model 1 adjusted for age, sex, and time from diabetes diagnosis. Model 2 adjusted for age, sex, time from diabetes diagnosis, and HbA_{1c}. Model 3 adjusted for age, sex, time from diabetes diagnosis, HbA_{1c}, BMI, systolic blood pressure, diastolic blood pressure, LDL cholesterol, triglyceride, and HDL cholesterol. Model 4 adjusted for age, sex, time from diabetes diagnosis, HbA_{1c}, BMI, systolic blood pressure, diastolic blood pressure, LDL cholesterol, triglyceride, HDL cholesterol, estimated GFR, albuminuria status, history of retinopathy, history of neuropathy, and history of CVD in the analysis for ESRD.

diabetes derive less renal protection from renin-angiotensin system blockade than those with type 1 diabetes (11).

Cardiovascular Complications

Given the paucity of longitudinal data on cardiovascular events among diabetic youth, a salient finding from the current study is the increased rates of CVDs in young type 2 relative to type 1 diabetic patients. Overweight patients with type 2 diabetes were 15 times more likely to develop cardiovascular events compared with their type 1 counterparts. Adjustment for glycemic control had no impact on the statistical significance of the results, but additional adjustment for BMI, blood pressure, and lipid levels eliminated the risk. While controversies regarding the benefits of intensive glycemic control on macrovascular complications remain (22), the clinical impact of attaining multiple metabolic targets on reducing vascular events and death has been clearly demonstrated (7). Our results highlight the dominant contribution of cardiometabolic risk factors, and not exclusively hyperglycemia, in driving CVD in this young population. Increased arterial stiffness was demonstrated in adolescents with hyperglycemia, indicating that vascular changes have already occurred early on in life (23).

Heterogeneity of Type 2 Diabetes in Asia

Asian patients with type 2 diabetes represent a heterogeneous group in terms of age of onset, mode of presentation, metabolic phenotype, and insulin requirement. It is long recognized that a large proportion of Asian patients with type 2 diabetes are of normal body weight. In the current study, 40% of type 2 diabetic patients had normal weight. This is consistent with findings from the recent AsDiab study, which showed that up to 40% had BMI <23 kg/m^2 (4). In the current study, among the subset of patients with measurements of autoimmune antibodies, only 11.8% of the lean patients and 2.9% of the overweight ones with type 2 diabetes had anti-GAD, compared with 31% of patients with type 1 diabetes. On the other hand, it is quite clear that lean patients with type 2 diabetes have lower β-cell reserve with earlier insulin requirement compared with obese patients (9). We speculate that lean Chinese patients have a constitutional predisposition to β-cell dysfunction and that genetic factors rather than autoimmunity are involved in the pathogenesis of diabetes (8). In support of this, a significantly greater proportion of normal-weight type 2 (54.1%) compared with type 1 diabetic (22.0%) patients have a positive family history. Furthermore, recent genome-wide association studies have revealed that the majority of loci associated with type 2 diabetes are implicated in β-cell structure and biology (24).

Despite lower BMI, other metabolic indices of blood pressure and lipids were worse in the lean type 2 diabetic group compared with patients with type 1 diabetes. The incidences of CVD and ESRD were also higher among normal-weight type 2 diabetic patients, although there was no statistically significant increase in hazards of lean type 2 relative to type 1 diabetes for cardiovascular-renal outcomes when adjusted for age, sex, and time from diagnosis. The significant age disparity between the two groups may partly account for differences in baseline risk profile and complication rates. Underlying insulin resistance in type 2 diabetes, even in normal-weight patients, may also contribute to development of cardiometabolic risk factors. Herein, Hsu et al. (10) have demonstrated lower insulin sensitivity in lean patients with type 2 diabetes compared with type 1 diabetes, suggesting that insulin resistance is not exclusive to those who are obese.

Metabolic Control

In this cohort of patients with type 2 diabetes, 54.3% had hypertension and 73.9% had dyslipidemia. Our results agree with the SEARCH for Diabetes in Youth Study reporting obesity in 80%, hypertension in one-quarter, and elevated LDL cholesterol in one-half of young affected people in the U.S. (25). The early development of cardiometabolic risk factors is further highlighted in the recently published TODAY (Treat Type 2 Diabetes Early and Aggressively in Young) trial of adolescents with newly diagnosed type 2 diabetes (26,27). Despite the provision of intensive monitoring, lifestyle reinforcement, and medical support in a trial setting, the frequency of hypertension was increased threefold from 11.6 to 33.8% while the frequency of high-risk LDL cholesterol was increased twofold from 4.5 to 10.7% over an average follow-up time of 4 years. Importantly, among youth who were prescribed statins, only one-third achieved the prespecified LDL cholesterol goal. We observed gross underuse of lipid-lowering and antihypertensive drugs despite high prevalence of atherogenic risk factors. Likewise, the number of patients using renin-angiotensin system blockade fell short of the proportion with clinical nephropathy. A substantial percentage of our patients were not achieving international targets for blood pressures and lipids. Based on a longitudinal evaluation of care provision in the diabetic population in the U.S. (28), not only were young patients less able to reach treatment targets compared with older adults but the rates of target attainment in the young group have not changed over the past decade. The lack of evidence-based guideline on optimal risk factor management in young disease population and concerns over possible adverse effects are major reasons for clinical inertia and delay in initiation of high-impact therapy such as statins. It is also well recognized that young people with diabetes are more difficult to manage owing to greater level of diabetes-related distress, competing social demands, poor drug adherence, and high default rates.

Limitations

Our study has the following limitations. First, although we have set criteria for defining type 1 diabetes, it remains possible that some patients with type 2 diabetes were misclassified as type 1, given increasing recognition of overlap in clinical presentation of the two types. Recently, the SEARCH study group proposed an aetiological approach in characterizing diabetes among young people, using autoimmunity and insulin sensitivity as the two factors considered (29). However, in view of the low frequency of autoimmune positivity in Asians, we believe that this scheme may

not be applicable to our population. It is also possible that a very small proportion of the normal-weight group had mature-onset diabetes of the young. We have previously reported mutations in the glucokinase and hepatocyte nuclear factor 1-α genes in 3 and 5%, respectively, of Chinese diabetic patients with a positive family history (30). Second, as we have only used health records from public hospitals to identify cardiovascular and renal end points, events that were treated in the private sector were not captured. Based on government statistics, we estimated that this would be $<$15% of total hospitalization during follow-up, as there is a huge discrepancy in costs between private and public services, but this incomplete capture pertains to all three groups of patients examined. Third, the small number of events in our cohort, particularly in the type 1 diabetic group, limits interpretation of results from the Cox model, as evidenced by the wide CI. Lastly, we have studied only Chinese patients, and our results may not be generalizable to other Asian ethnic groups.

Conclusion

We have shown that among Chinese patients with young-onset diabetes, those with type 2 diabetes had higher rates of CVD and ESRD compared with type 1 diabetes. The increased risks of cardiovascular-renal complications in type 2 diabetes were attributable to attendant metabolic abnormalities of obesity, hypertension, and dyslipidemia. The high cardiometabolic burden notwithstanding, there was suboptimal provision of important ancillary treatment of these conditions, with underachievement of metabolic targets. Our results draw attention to existing shortfalls in effective reach and management of this challenging patient population and support the need for further studies to evaluate the long-term benefit of aggressive risk factor control in young individuals.

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