Factors Predicting the Age When Type 2 Diabetes Is Diagnosed in Hong Kong Chinese Subjects

SHAO C. LEE, PHD
GARY T.C. KO, MBCHB, FRCP
JUNE K.Y. LI, MBCHB, MRCP
CHUN C. CHOW MBBS, FRCP
VINCENT T.F. YEUNG, MD, FRCP
JULIAN A.J.H. CRITCHLEY, PHD, FRCP
CLIVE S. COCKRAM, MD, FRCP
JULIANA C.N. CHAN, MD, FRCP

OBJECTIVE — To examine the factors predicting age at diagnosis of type 2 diabetes in Hong Kong Chinese.

RESEARCH DESIGN AND METHODS — The relationships between age at diagnosis and parental history of diabetes as well as an array of clinical and metabolic factors were examined using a hospital clinic-based diabetes registry involving 3,414 index patients with type 2 diabetes. Patterns of age at diagnosis in successive generations were also examined using 21 affected child-parent pairs and 7 affected child-parent-grandparent trios.

RESULTS — Approximately 29% of the index patients were diagnosed with type 2 diabetes at ≤35 years of age (hereby defined as early-onset). Compared with the patients diagnosed at >35 years of age (hereby defined as late-onset), the early-onset patients had higher rates of positive paternal (16 vs. 5%) and maternal (22 vs. 12%) history of diabetes (both at $P < 0.01$) and had poorer metabolic profiles. In the overall index patients, male sex, higher HbA_{1c}, waist-to-hip ratio (WHR), and systolic blood pressure (sBP); lower HDL cholesterol level; and a positive paternal as well as maternal history of diabetes predicted younger age at diagnosis. More senior age and higher BMI and diastolic blood pressure predicted older age at diagnosis. Predictors for younger age at diagnosis in the male patients were higher HbA_{1c} and sBP and a positive paternal history of diabetes. Predictors for younger age at diagnosis in the female patients were higher HbA_{1c}, WHR, and sBP and a paternal as well as maternal history of diabetes. In the affected child-parent pairs and child-parent-grandparent trios, there was a decrease in age at diagnosis in successive generations.

CONCLUSIONS — Our data indicate that both familial (possibly genetic) and metabolic factors affect the age of onset of type 2 diabetes in the Chinese population. The results also suggest an onset and progression pattern of the disease that is compatible with the phenomenon of anticipation.

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Type 2 diabetes is one of the major noncommunicable diseases worldwide, and its complications have significant socioeconomic impacts. Classically, type 2 diabetes develops predominantly in older populations. However, there is increasing evidence for a high prevalence of type 2 diabetes in young people, particularly in non-Caucasians (1). Early onset of type 2 diabetes appears to be heterogeneous in etiologies. Maturity-onset diabetes of the young (MODY) is a monogenic disease inherited in an autosomal dominant manner, whereas autoimmune diabetes may have atypical presentations (2,3). In Hong Kong Chinese, MODY, typical type 1 diabetes, and atypical autoimmune diabetes do occur, but they only account for a small proportion of the overall type 2 diabetic population (2–4). In a recent segregation study involving 2,310 index patients, we observed the evidence for familial clustering, maternal influence, a male sex–specific paternal effect, and an association between younger age at diagnosis and a positive parental history of diabetes (5). Our data, together with those from Caucasian populations (6–8), implicate that parental diabetes may contribute to a younger onset of type 2 diabetes.

In the present study, we further investigated the influences of both parental and metabolic factors on onset age of type 2 diabetes. Patterns of onset age among successive generations in families segregating type 2 diabetes were also examined.

RESEARCH DESIGN AND METHODS

Subjects

Approval for the study was obtained from the Clinical Research Ethics Committee, the Chinese University of Hong Kong. Informed consent was obtained from each of the participants. All patients were recruited at the Diabetes Center, the Prince of Wales Hospital of the Hong Kong Special Administration Region. The hospital is a regional teaching hospital with a catchment population of ~1 million with typical demographic and social class distributions. Most of the inhabitants are southern Chinese in origin. Because of the lack of a long-term health care financing policy, the majority of people in Hong Kong do not have medical insurance for chronic diseases, such as diabetes and hypertension. As a result, most of these patients seek medical care at the public hospitals where only nominal fees are charged.

Patients involved in the study were

From the Department of Medicine and Therapeutics, the Prince of Wales Hospital, the Chinese University of Hong Kong, Shatin, Hong Kong SAR, China.

Address correspondence and reprint requests to Dr. Shao Lee, Department of Medicine and Therapeutics, The Prince of Wales Hospital, the Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR, China. E-mail: shaochin@citmail.com or b200387@mailserv.cuhk.edu.hk.

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Abbreviations: dBP, diastolic blood pressure; FPG, fasting plasma glucose; MODY, maturity-onset diabetes of the young; sBP, systolic blood pressure; WHR, waist-to-hip ratio.

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

recruited from our diabetes registry (5). Type 2 diabetes was diagnosed according to the 1985 World Health Organization criteria (9). For the study, 3,414 patients who attended our clinic between 1995 and 1999 were consecutively selected from the diabetes database. All the patients reported the diabetes status of both of their parents as well as their children if they had any. Patients who were diagnosed for 3 years or less by the time of their registration and had already been treated with insulin were not included. Although MODY and atypical autoimmune diabetes were not specifically excluded, they are uncommon in the Chinese population (2,3). Early- and late-onset were hereby defined as diagnosis at ≤35 and >35 years of age, respectively. Moreover, we invited the family members of 21 early-onset and 7 late-onset patients to undergo screening for diabetes using a 75-g oral glucose tolerance test following the previously described procedure (5,9). The overall ascertainment rate among the parents and siblings of the index patients was 85%. All the family members who were reported to have diabetes by the index patients were confirmed with type 2 diabetes in the ascertainment. The 21 early-onset index patients were randomly selected from the overall early-onset patients who reported at least an affected parent. The seven late-onset patients were randomly selected from the overall late-onset patients who reported at least an affected parent and at least an affected child.

Table 1—*Clinical and biochemical characteristics of 3,414 Chinese index patients with type 2 diabetes*

	Patients with type 2 diabetes		
	Total	Early-onset	Late-onset
n	3,414	973	2,441
Age (years)	56 ± 13	41 ± 8	61 ± 10*
Sex ratio (M:F)	1:1.4	1:1.5*	1:1.3
Age at diagnosis (years)	49 ± 12	34 ± 5	55 ± 9*
BMI (kg/m^2)	25.0 ± 3.7	25.5 ± 4.5	24.7 ± 3.5
WHR	0.88 ± 0.07	0.87 ± 0.07	0.89 ± 0.07
HbA_{1c} (%)	7.8 ± 1.9	7.7 ± 1.9	7.8 ± 1.8
FPG (mmol/l)	9.0 ± 3.4	8.9 ± 3.5	9.0 ± 3.4
sBP (mmHg)	136 ± 21	125 ± 17	140 ± 21*
dBP (mmHg)	78 ± 11	77 ± 10	79 ± 11*
Total cholesterol (mmol/l)	5.4 ± 1.2	5.2 ± 1.1	5.5 ± 1.2*
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.2 ± 0.4	1.3 ± 0.4
LDL cholesterol (mmol/l)	3.4 ± 1.0	3.3 ± 0.9	3.5 ± 1.0*
Triglyceride (mmol/l)	1.8 (0.3–84)	1.7 (0.3–28)	1.8 (0.3–84)
Albuminuria (%)	37	36	38
With a diabetic parent (%)	27	47	19*
With a diabetic father alone (%)	8	16	5*
With a diabetic mother alone (%)	15	22	12*
With diabetic father and mother (%)	4	9	2*

Data are means ± SD or medians (range) unless otherwise indicated. *$P < 0.01$ (with adjustments for significance for metabolic parameters).

Clinical and biochemical measurements

Patients had fasted at least 8 h before their clinical examination. Systolic blood pressure (sBP) and diastolic blood pressure (dBP) were measured after patients remained seated for at least 5 min. Body measurements were taken when patients were standing with light clothing and no shoes for calculations of BMI and waist-to-hip ratio (WHR). Waist circumference was the minimum circumference between the umbilicus and iliac crest, and the hip circumference was the widest circumference around the buttocks. Family history of diabetes was also taken. Fasting plasma glucose (FPG) and HbA_{1c} were measured using a glucose oxidase method (Diagnostic Chemicals) and an automated ion-exchange chromatographic method (BioRad, Hercules, CA; normal range 5.1–6.4%), respectively. Plasma levels of total cholesterol and triglyceride were assayed enzymatically using commercially available reagents (Centrichem chemistry system; Baker Instrument, Allentown, PA). HDL cholesterol was determined after fractional precipitation with dextran sulfate-$MgCl_2$ and LDL cholesterol, calculated using Friedewald's equation (10). Using an immunoturbidimetry method (11), 24-h urine samples were collected to measure albumin concentration. The lowest detection limit was 2.5 mg/l, and intra- and interassay coefficients of variation were <5%. Albuminuria was defined as a urinary albumin excretion rate ≥20 μg/min. We also attempted to measure the fasting plasma concentrations of insulin and C-peptide in the patients. However, we were unable to complete the measurements because of technical difficulties and were thus unable to examine whether there was a correlation between age at diagnosis and the levels of the two hormones.

Statistical analysis

All data for continuous variables are expressed as mean ± SD or median (range). The Student's *t* test and Mann-Whitney rank-sum test were used as appropriate when comparing the metabolic parameters between the early- and late-onset patients. The paired *t* test was used for comparing the age at diagnosis in successive generations of the 21 affected child-parent pairs. The χ^2 test was performed for analyzing proportions. Linear regression analyses were performed using age at diagnosis as a dependent factor. Age, sex, FPG, HbA_{1c}, BMI, WHR, sBP, dBP, lipids, and paternal as well as maternal history of diabetes were entered as independent factors, except sex was not entered when analyzing single-sex groups. The statistical analyses were performed using the Statistical Package for Social Sciences version 7.5 (SPSS, Chicago). A P value <0.05 was considered to be statistically significant.

RESULTS — Among the 3,414 index cases, 973 (29%) were early-onset patients. The late-onset patients were older and had higher WHR, sBP, and dBP as well as higher levels of total and LDL cholesterol ($P < 0.01$) than the early-onset patients. Although there was a female preponderance in our overall diabetes population, the early-onset patients had a higher male-to-female ratio and higher rates of parental history of diabetes than the late-onset patients (all at $P < 0.01$)

Table 2—*Linear regression analysis using age at diagnosis as a dependent factor*

	β	SEM	*P* value
Total index patients*			
Age	0.88	0.93	<0.01
Male sex	−0.64	0.23	0.04
HbA_{1c}	−0.50	0.08	<0.01
BMI	0.08	0.03	<0.01
WHR	−4.35	1.82	0.02
sDP	−0.08	0.01	<0.01
dBP	0.16	0.01	<0.01
HDL cholesterol	0.95	0.37	0.01
Paternal history of diabetes	−1.46	0.32	<0.01
Maternal history of diabetes	−0.58	0.26	0.03
Male index patients			
Age	0.89	0.01	<0.01
HbA_{1c}	−0.56	0.11	<0.01
BMI	0.09	0.04	0.04
sDP	−0.09	0.01	<0.01
dBP	0.18	0.017	<0.01
HDL cholesterol	0.84	0.45	0.07
Paternal history of diabetes	−1.36	0.43	<0.01
Female index patients‡			
Age	0.86	0.02	<0.01
HbA_{1c}	−0.42	0.05	<0.01
WHR	−6.9	3.1	<0.01
sBP	−0.08	0.01	<0.01
dBP	0.15	0.02	<0.01
Paternal history of diabetes	−1.45	0.47	<0.01
Maternal history of diabetes	−0.8	0.41	0.05

Age, sex, FPG, HbA_{1c}, BMI, WHR, blood pressure, and lipids as well as paternal and maternal history of diabetes were entered as independent factors. *R^2 = 0.8, $P < 0.01$; †R^2 = 0.8, $P < 0.01$; ‡R^2 = 0.8, $P <$ 0.01.

(Table 1). However, the early- and late-onset patients had comparable rates of albuminuria (Table 1).

Using linear regression analysis (Table 2), we found that male sex; higher HbA_{1c}, WHR, and sBP; and lower levels of HDL cholesterol, as well as a positive paternal and maternal history of diabetes, predicted younger age at diagnosis in the overall index patients. In the male group, factors predicting younger age at diagnosis were higher HbA_{1c} and sBP a positive paternal history of diabetes. In the female group, the predictors for younger age at diagnosis were higher HbA_{1c}, WHR, and sBP and paternal and maternal history of diabetes. On the other hand, higher BMI and dBP consistently predicted older age at diagnosis, except that BMI was not identified as a predictor in the female group.

Table 3—*Mean age at diagnosis of 21 affected pairs (early-onset index patient-affected parent)*

	Diabetic parents	Index patients
n	21	21
Sex ratio (F:M)	1:13	1:13
Age (years)	67 ± 11*	41 ± 10
Age at diagnosis (years)	56 ± 9*	35 ± 9

Data for age are means ± SD. The index patients were randomly selected from the early-onset group, who reported a diabetic parent. Paired *t* test was used for the statistical analysis. *$P < 0.01$.

In the 21 affected child-parent pairs, all the index patients were diagnosed with type 2 diabetes at a younger age (21 years on average) than their parents ($P < 0.01$) (Table 3). In the affected trios, a decrease in age at diagnosis in successive generations was noted, except in index patient-child in family 6 and index patient-parent in family 7 (Table 4).

Table 4—*Age at diagnosis of seven affected trios (parent-index patient-child)*

	Patients (sex/age/age at diagnosis)		
Family number	Diabetic parents	Index patients	Diabetic children
1	F/?/80	F/62/61	M/40/38
2	M/96/67	M/62/46	M/36/32
3	F/80/59	F/63/43	M/46/42
4	F/72/70	F/60/59	F/39/30
5	F/?/85	F/80/75	M/53/50
6	M/?/90	F/62/41	M/46/44
7	M/?/50	M/76/63	M/44/38

The index patients were randomly selected from the late-onset group, who reported at least a diabetic parent and at least a diabetic child. ?, Patients died after having been diagnosed with type 2 diabetes.

CONCLUSIONS — Our data demonstrate that an early occurrence of type 2 diabetes is common, and onset age of type 2 diabetes is under the influences of multiple factors in the Chinese population.

Currently, there is a lack of putative criteria to define early and late onset of the disease. A cutoff age of 35 or 40 years at diagnosis was commonly used to separate the two groups arbitrarily. In an early study involving Caucasian patients, Laakso and Pyorala (12) investigated the age at diagnosis and types of diabetes in Caucasians and proposed a cutoff age of ≤35 years for the early-onset group, which was adopted for the study. The difference is that early-onset Caucasian diabetic patients may include a large proportion of individuals with type 1 and atypical diabetes, whereas in the Chinese population, typical type 1, MODY, and atypical autoimmune diabetes are uncommon (2–4). In this study, we observed that the early-onset patients had a strong parental history of diabetes (Tables 1 and 3). In the male patients, the early occurrence of type 2 diabetes was associated with a positive paternal but not maternal history of diabetes (Table 2). These data are in keeping with our previous findings of familial clustering of diabetes and a male sex–specific paternal effect on the pathogenesis of type 2 diabetes in the Chinese population (5).

Moreover, age at diagnosis was found to be inversely correlated with a positive parental history of diabetes (Tables 1 and 2), indicating that familial (possibly genetic) factors may promote younger onset of the disease (6–8). The finding that younger age at diagnosis was also correlated with higher HbA_{1c} levels (Table 2) suggests that younger-onset patients had poorer glycemic control, implicating that they might have more severe clinical presentation of type 2 diabetes. Data from the family investigations (Tables 3 and 4) revealed a trend of decrease in age at diagnosis in successive generations. These observations, taken together, suggest an onset and progression pattern of the disease that is compatible with the concept of anticipation that describes younger-onset and/or more severe symptom(s) in successive generations of a disease with genetic susceptibility (13–15). At the molecular level, anticipation may be associated with genomic instability, such as trinucleotide repeat expansions (13,14). In Huntington's disease, anticipation may be inherited through the male line (15). In this respect, it is interesting that we have observed a paternal effect on the development of type 2 diabetes in this Chinese population (5).

In addition to parental history of diabetes, younger age of onset of type 2 diabetes was also found to be associated with male sex, higher WHR, and sBP and lower HDL cholesterol levels (Tables 1–4).

These data are in keeping with our previous findings that early-onset patients involve predominantly male subjects and commonly present clinical features of the metabolic syndrome (16) and suggest that metabolic factors may be implicated in an early occurrence of type 2 diabetes.

The prevalence of type 2 diabetes is increasing worldwide. In developing countries, the increase in diabetes prevalence occurs predominantly among people in and before middle age (1,17). This trend is also reflected in our diabetes registry by the high percentage of early-onset cases and a relatively young mean age at diagnosis (49 years) (Table 1). Changes in lifestyle because of Westernization may promote deterioration(s) in metabolic profiles, i.e., more central obesity, higher sBP, and lower HDL cholesterol. Poor metabolic profiles may interact with familial factors such as parental diabetes (possibly genetic) to promote younger onset of type 2 diabetes, resulting in the observed increasing prevalence of the disease in and before middle age (Table 1) (1,17). In this sense, metabolic factors might also contribute to the observed successive decrease in age at diagnosis in the family samples (Tables 3 and 4)—the possible anticipation.

We are also aware that possible bias may affect the analysis. Younger age at diagnosis may reflect an increased awareness of diabetes in younger generations, especially with the presence of family history of diabetes. Data from affected child-parent pairs may not be adequate for anticipation analysis because the natural age truncations among generations may cause bias (18). More studies using population-based samples and/or molecular approaches are required for more informative data about patterns of onset and progression of the disease, although a link between trinucleotide repeats and the development of type 2 diabetes was not established in a genome-wide scan involving Pima Indians (19). Some parameters (i.e., sBP and WHR) were found to be inversely associated with the age at diagnosis in patients (Table 2). These associations are less likely to be biased by age factor because they are positively associated with age in Hong Kong Chinese in general (20). However, possible effects of bias on the associations of some other metabolic parameters with younger or older age at diagnosis cannot be fully excluded in the regression analyses.

In conclusion, our data indicate that early onset of type 2 diabetes is common in the Chinese population and suggest that onset of type 2 diabetes may be influenced by familial (possibly genetic) and metabolic factors. The results also suggest a disease-onset and progression pattern that is compatible with the phenomenon of anticipation.

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