

## The Clinical Characteristics of the Newly Diagnosed Early Onset (< 40 Years Old) Diabetes in Outpatients' Clinic

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**Background:** The prevalence of type 2 diabetes in young adults and adolescents has increased in the last decade according to the increasing obese population. The aim of this study was to examine the clinical characteristics of patients diagnosed with diabetes mellitus before the age of 40 years as compared with patients diagnosed at older ages.

**Methods:** This was a cross-sectional, retrospective study using data from 350 diabetic patients who were diagnosed with diabetes in an outpatient setting between January 2005 and December 2007. Patients were diagnosed according to the criteria set forth by the American Diabetes Association. We examined the clinical characteristics and laboratory data of the patients through review of medical records and compared the early-onset diabetic patients (< 40 years old) and the usual-onset diabetic patients (≥ 40 years old).

**Results:** The frequency of early-onset diabetes and usual-onset diabetes were 31.1% (n=109) and 68.9% (n=241), respectively. The early-onset diabetic patients more often had a positive family history of diabetes; higher HbA1c, fasting glucose, and postprandial glucose levels; experienced typical symptoms more frequently; had microalbuminuria more frequently; and required insulin therapy as initial treatment more frequently as compared to usual-onset diabetic patients, and these differences were significant. Conversely, hypertension was significantly more common in the usual-onset diabetic patients.

**Conclusion:** It could be concluded that we should control early onset diabetes more strictly to prevent its complication because early onset diabetic patients represented more severe hyperglycemia and had more prevalent microalbuminuria.

**Keywords:** Diabetes mellitus; Early-onset; Outpatient

### INTRODUCTION

Recently, the size of the aging population has increased with the increased life expectancy of the average individual, likely due to the westernization of many aspects of people's lives, and, consequently, the prevalence of diabetes has skyrocketed around the world [1,2]. The prevalence of diabetes in Korea, which was estimated to be less than 1% in 1970, increased dramatically to 7.6% of the total population in 2000 [3], and this trend is likely to continue. Additionally, the mortality rate of patients with

diabetes was reported to be only 3 per 100,000 persons in 1979, whereas, in 2002, it was the fourth overall cause of death at 25 per 100,000 persons, following cancer, cerebrovascular disease, and heart disease. Moreover, the fact that diabetes is the number one cause of loss of eyesight, foot amputation (notwithstanding car accidents), and chronic renal failure requiring dialysis, shows its seriousness [4].

In the past, diabetes was primarily regarded as a chronic disease most commonly affecting the elderly population, but, recently, the prevalence of early-onset (< 40 years of age) diabetes

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has increased with the growing rate of obesity [5-7]. Considering that the duration of diabetes onset is directly associated with its complications, the occurrence of diabetes in younger individuals has serious ramifications for the health of the population at large. However, it is well known that active blood sugar control through appropriate treatment can reduce the occurrence of the various diabetic complications, especially when the disease is detected early [8-10]. Additionally, the clinical characteristics of early-onset diabetic patients and those of usual-onset ( $\geq 40$  years of age) diabetic patients have been reported to be different [11-13]. Therefore, further elucidation of the unique clinical characteristics of young diabetic patients will provide vital information for a proper diabetes management for them.

However, there have been only a few researches on distributions of types and the clinical characteristics of early-onset diabetes, and studies comparing early-onset diabetes with usual-onset diabetic patients are lacking in the literature. Therefore, the aim of the present study was to investigate the clinical characteristics of diabetes patients diagnosed at less than 40 years of age and to compare their clinical manifestation with those of diabetes patients diagnosed at age of 40 or older.

## METHODS

### Subjects

Study subjects were 350 diabetes patients newly diagnosed based according to criteria recommended by American Diabetes Association [14], selected among the patients who visited the outpatient clinic at endocrinology department of Bundang CHA general hospital from January 2005 to December 2007. Patients were divided into two groups based upon the age at diagnosis: the young group ( $< 40$  years of age) and the older group ( $\geq 40$  years of age). Patients who had previously used insulin preparations, oral hypoglycemic agents, or steroids; those who had received anti-cancer chemotherapy for organ transplantation or a malignant tumor; and those who had undergone pancreatectomy were excluded from the study.

### Methods

Data were collected by retrospective review of medical records and included the age of onset of diabetes, gender, height, maximal body weight before diabetes onset, body weight at diagnosis, family history of diabetes, typical symptoms of diabetes upon visiting the hospital (polyphagia, polyuria, and weight loss), systolic and diastolic blood pressures, and treatment re-

ceived during the first three months after diagnosis. A positive family history of diabetes was defined as having at least one 1st-degree or 2nd-degree relative with diabetes. The presence of hypertension was defined as taking antihypertensive agents or a recorded systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg. Body mass index (BMI) ( $\text{kg}/\text{m}^2$ ) was calculated with patient's weight (kg) divided by height squared ( $\text{m}^2$ ). Maximal BMI was calculated using the maximal body weight before diagnosis. Upon diagnosis with diabetes mellitus, blood was drawn to determine the patient's fasting blood glucose (glucose oxidase method), HbA1c (high performance liquid chromatography, Bio-Rad Variant II; Bio-Rad Laboratories, Hercules, CA, USA), insulin (Roche Diagnostic GmbH, Mannheim, Germany), C-peptide (Roche Diagnostic GmbH), total cholesterol, triglycerides, and high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C). Furthermore, 2-hour postprandial serum glucose, insulin, and C-peptide were also measured. Random urine microalbumin and creatinine were measured, and the albumin-to-creatinine ratio (ACR) was calculated. Microalbuminuria was assessed and defined as the presence of 30 mg of albumin/g of creatinine or 30 mg of albumin on 24-hour urine collection. The homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of  $\beta$ -cell function (HOMA- $\beta$ ) were calculated by using the formula of Matthews et al. [15]:  $\text{HOMA-IR} = \text{fasting insulin } (\mu\text{U}/\text{mL}) \times \text{fasting blood glucose } (\text{mmol}/\text{L}) / 22.5$  and  $\text{HOMA-}\beta = 20 \times \text{fasting insulin } (\mu\text{U}/\text{mL}) / (\text{fasting blood glucose } [\text{mmol}/\text{L}] - 3.5)$ .

Type 1 diabetes was diagnosed when the fasting C-peptide level was  $\leq 0.6$  ng/mL or autoantibodies were demonstrated, and type 2 diabetes was diagnosed when the fasting C-peptide level was  $\geq 1.2$  ng/mL. Cases that could not be classified were defined as "unclassified."

### Statistical analysis

Statistical analysis was conducted using the SPSS software package (version 11.5; SPSS Inc., Chicago, IL, USA), and statistical values were presented as mean  $\pm$  standard deviation. Triglycerides, insulin, C-peptide, HOMA-IR, and HOMA- $\beta$  were shown with their medians (ranges). Because triglycerides, insulin, C-peptide, HOMA-IR, and HOMA- $\beta$  showed skewed distributions, they were analyzed after logarithmic transformation. Comparisons of the mean values of continuous variables between the two groups were analyzed by using the independent

sample *t*-test, and discontinuous variables using the chi-squared test. A *P*-value < 0.05 was considered to be statistically significant.

**Table 1.** Type of diabetes mellitus according to age at diagnosis

	Early onset <sup>a</sup> ( <i>n</i> = 109)	Usual onset <sup>b</sup> ( <i>n</i> = 241)	Total ( <i>n</i> = 350)
Type 1 DM	7 (6.4)	1 (0.4)	8 (2.3)
Type 2 DM	93 (85.3)	222 (92.1)	315 (90.0)
Unclassified	9 (8.3)	18 (7.5)	27 (7.7)

Data are expressed as number (%).

DM, diabetes mellitus.

<sup>a</sup> Early-onset, onset at < 40 years of age, <sup>b</sup> Usual-onset, onset at ≥ 40 years of age.

cant.

## RESULTS

### Types of diabetes

Fasting C-peptide levels of all subjects were measured. Of the 20 patients who had their autoantibody levels measured, only 4 were positive. The number of patients with type 1 diabetes, type 2 diabetes, and unclassified diabetes were 8 (2.3%), 315 (90.0%), and 27 (7.7%), respectively. Of the 109 patients (31.1%) who were diagnosed at less than 40 years, 6.4% were type 1 diabetes, 85.3% were type 2 diabetes, and 8.3% were unclassified diabetes (Table 1).

**Table 2.** Clinical characteristics according to age at diagnosis

	Total	Early onset <sup>a</sup>	Usual onset <sup>b</sup>	<i>P</i> value
No.	350	109	241	
Age, yr	47.5 ± 13.5	31.8 ± 6.4	54.6 ± 9.3	<0.001 <sup>c</sup>
Male	232 (66.3%)	82 (75.2%)	150 (62.2%)	0.017 <sup>c</sup>
Family history	151 (43.1%)	67 (61.5%)	84 (34.9%)	<0.001 <sup>c</sup>
BMI, kg/m <sup>2</sup>	25.1 ± 3.6	25.5 ± 4.6	25.0 ± 3.1	0.261
Maximal BMI, kg/m <sup>2d</sup>	27.0 ± 3.7	27.8 ± 4.1	26.6 ± 3.4	0.017 <sup>c</sup>
Hypertension	148 (42.3%)	37 (33.9%)	111 (46.1%)	0.034 <sup>c</sup>
Systolic BP, mm Hg	130.1 ± 15.9	126.5 ± 14.5	131.6 ± 16.3	0.006 <sup>c</sup>
Diastolic BP, mm Hg	84.2 ± 11.9	82.1 ± 13.0	85.1 ± 11.3	0.033 <sup>c</sup>
Fasting glucose, mg/dL	200.7 ± 89.2	233.9 ± 118.0	185.3 ± 67.0	<0.001 <sup>c</sup>
PP 2 hour glucose, mg/dL	309.8 ± 114.7	337.3 ± 132.0	298.5 ± 105.1	0.012 <sup>c</sup>
HbA1c, %	9.7 ± 2.5	10.6 ± 2.7	9.2 ± 2.3	<0.001 <sup>c</sup>
Fasting C-peptide, ng/mL	2.38 (0.28 to 16.72)	2.15 (0.28 to 16.00)	2.47 (0.49 to 16.72)	0.287
PP 2 hour C-peptide, ng/mL	6.11 (0.28 to 21.40)	5.64 (0.28 to 21.40)	6.26 (0.85 to 19.92)	0.012 <sup>c</sup>
Fasting insulin, μU/mL	5.3 (1.0 to 117.4)	5.7 (1.0 to 117.4)	5.1 (1.0 to 30.1)	0.300
PP 2 hour insulin, μU/mL	22.0 (1.9 to 216.0)	21.5 (2.0 to 216.0)	23.4 (1.9 to 179.0)	0.683
HOMA-IR	2.30 (0.41 to 37.39)	2.63 (0.43 to 37.39)	2.25 (0.41 to 19.40)	0.046 <sup>c</sup>
HOMA-β	17.68 (1.53 to 640.36)	18.87 (1.53 to 640.36)	17.20 (1.90 to 98.05)	0.912
Total cholesterol, mg/dL	199.4 ± 41.4	202.9 ± 40.2	197.8 ± 41.9	0.291
Triglyceride, mg/dL	152 (42 to 1,194)	154 (46 to 1,194)	151 (42 to 783)	0.305
HDL-C, mg/dL	45.3 ± 11.2	44.6 ± 9.6	45.5 ± 11.9	0.498
LDL-C, mg/dL	117.0 ± 36.2	117.0 ± 32.1	117.1 ± 38.1	0.984
Microalbuminuria <sup>e</sup>	58/241 (24.1%)	24/70 (34.3%)	34/171 (19.9%)	0.018 <sup>c</sup>

Data are expressed as mean ± standard deviation or number (%).

BMI, body mass index; BP, blood pressure; HDL-C, high density lipoprotein cholesterol; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; PP, postprandial.

<sup>a</sup> Early-onset, onset at < 40 years of age, <sup>b</sup> Usual-onset, onset at ≥ 40 years of age, <sup>c</sup> *P* < 0.05, early-onset vs usual-onset, <sup>d</sup> Maximal BMI, calculated using maximal weight, <sup>e</sup> Microalbuminuria, albumin/creatinine ratio, ACR ≥ 30 or 30 mg/g of creatinine or mg/day and data are expressed as positive microalbuminuria number/measured microalbuminuria number (%).

### Clinical characteristics of subjects

Of the total 350 subjects, the mean age of diabetes onset was  $47.5 \pm 13.5$  years, and the mean BMI was  $25.1 \pm 3.6$  kg/m<sup>2</sup>. Among them, 232 patients (66.3%) were male and 151 patients (43.1%) had a positive family history of diabetes (Table 2).

### Differences in clinical characteristics according to age of onset

The mean age of the young group and the older group was  $31.8 \pm 6.4$  years and  $54.6 \pm 9.3$  years, respectively. The rate of males was higher in the young group compared with the older group, and the young group showed more frequent positive

family history of diabetes, higher maximal BMI, higher fasting and postprandial glucose levels, higher HbA1c, and higher HOMA-IR compared with the older group. Although there were no differences in BMI, fasting C-peptide, fasting and postprandial insulin, HOMA- $\beta$ , total cholesterol, triglycerides, HDL-C, or LDL-C between the two groups, the older group had a higher frequency of hypertension, higher systolic and diastolic blood pressures, and higher postprandial C-peptide levels. Although urinary albumin excretion was not measured in all subjects, among the 241 patients who were tested for urine albumin, microalbuminuria was found more frequently in the young group compared with older group (Table 2).

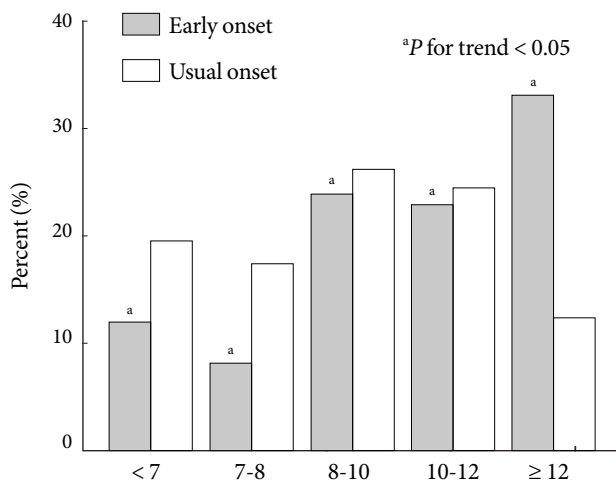


Fig. 1. Distribution of early-onset and usual-onset diabetes according to HbA1c level at diagnosis.

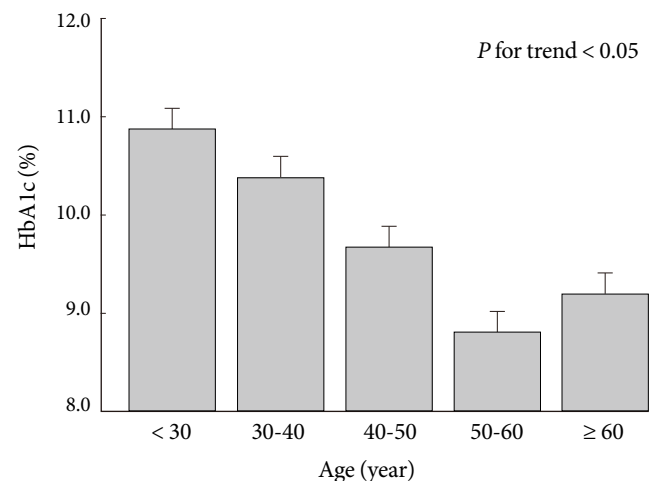


Fig. 2. HbA1c levels according to age at diagnosis.

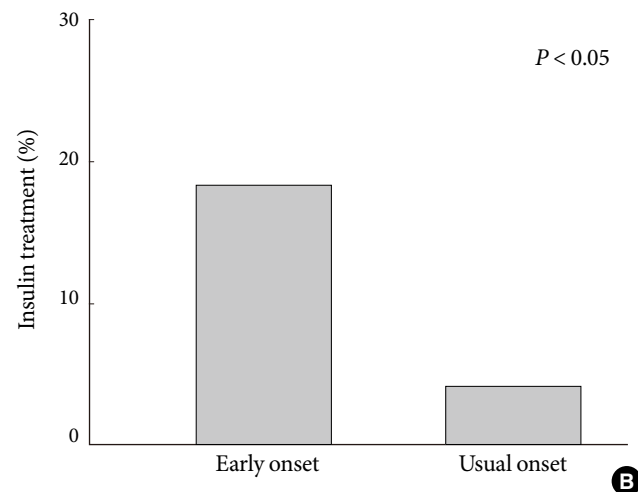
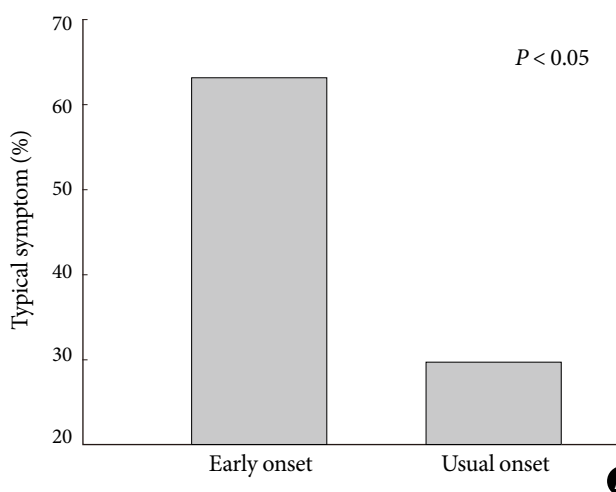


Fig. 3. Frequencies of typical symptoms (A) and insulin treatment (B) according to age at diagnosis.

Among the young group, 20.2% had their HbA1c at diagnosis less than 8%, and 33% had those over 12%. In contrast, 36.9% of patients in the older group had their HbA1c at diagnosis less than 8% and 12.4% of patients had those over 12%. Therefore, the average blood glucose tended to be higher in the young group ( $P$  for trend < 0.05; Fig. 1). In addition, the younger the age of diabetes onset was, the higher HbA1c at diagnosis was shown ( $P$  for trend < 0.05; Fig. 2).

### Differences in symptoms and treatments according to age of onset

Typical symptoms of diabetes due to hyperglycemia (polyphagia, polyuria, and weight loss) were found in 63.3% of the young group, while they were found only in 29.9% of the older group ( $P$  < 0.05). During the first three months after diagnosis, 18.3% of the young group required insulin treatment compared to only 4.1% of patients in the older group ( $P$  < 0.05; Fig. 3).

## DISCUSSION

As the prevalence and incidence of diabetes have skyrocketed around the world as well as in Korea due to lifestyle changes, concern about the disease is greater than ever. Moreover, diabetes, a disease which was previously considered to be a chronic disease frequently found in the elderly, occurs in young adults and even in adolescents with gradual increase of prevalence. Due to a known close correlation between the development of complications and the disease duration, and due to the fact that the HbA1c level will increase gradually despite intensive treatment, determining clinical characteristics of early-onset diabetes patients and treating their disease properly are critical to prevent its complications. However, there have been only a few studies on the investigation of clinical characteristics of diabetes occurring in young adults and adolescents, and comparing their characteristics with those in adults.

Researches performed in young diabetes patients have reported the prevalence of type 1 and 2 diabetes differently. According to a report published in Korea [16], when 235 diabetes patients diagnosed at less than 35 years of age were classified according to their C-peptide levels, the rates of type 1, type 2, and unclassified diabetes were 13.8%, 80.3%, and 5.9%, respectively. Another study [17] using data from 85 diabetes patients diagnosed at less than 30 years of age, reported that when the type of diabetes was classified according to the fasting C-peptide level, the existence of autoantibodies, and the causes of ke-

toacidosis, the frequencies of type 1, type 2, and unclassified diabetes were 45.9%, 23.5%, and 25.9%, respectively. The present study found that, among the 109 newly diagnosed patients at less than 40 years of age, the frequencies of type 1, type 2, and unclassified diabetes were 6.4%, 85.3%, and 8.3%, respectively. Possible reasons for this high rate of type 2 diabetes in this early-onset diabetes population could be, i) because this study investigated only outpatients, some patients having type 1 diabetes who initially presented with diabetic ketoacidosis could have been excluded, ii) because autoantibodies of all of the patients were not available, and iii) because the application of relatively higher age cutoff of early-onset diabetes could have led to higher prevalence of type 2 diabetes. The finding that most of the early-onset diabetes patients had type 2 diabetes, not type 1 diabetes, different from our expectation, may suggest that the increasing rate of obesity is having a significant effect on the metabolic status of the younger population.

Prevalence of diabetes diagnosed at young ages varies according to researchers and regions. A study by Chuang et al. [12] conducted in Asians, reported that the prevalence of diabetes diagnosed at less than 30 years of age varied from 0.4 to 5.6% according to countries, and another study performed in Mexicans showed that the prevalence of diabetes diagnosed at less than 40 years of age was 14% [18]. According to a study by Hillier and Pedula [11], the prevalence of diabetes diagnosed at less than 45 years of age was 11.4%. The present study employed an age cutoff for early-onset diabetes as 40 years of age because this is the age at which diabetes screening was conducted in Korea, and four representative cohort studies on diabetes in Korea reported that its prevalence increases significantly as patients reach the age of 40 and beyond [19]. The prevalence of diabetes diagnosed at less than 40 years of age observed in this study was 31.1%, which was relatively higher than those reported in previous studies, and this discrepancy could be due to the fact that this study examined patients diagnosed with diabetes by their voluntary visit to the hospital, did not use questionnaires or employ the patients' recollections, and excluded patients who had already taken oral hypoglycemic agents or insulin preparations. However, the findings of the present study were consistent with those of previous studies that reported that changes in diet and reduced physical activity have led to a fast-growing obese population and an increase in the prevalence and incidence of diabetes in younger persons [20-22].

Among persons with a positive family history of diabetes, the disease is known to occur earlier, and obesity has been re-

ported to play a key role in its early onset. Shim et al. [23] reported that diabetes occurred more earlier when persons had a family history of diabetes or a genetic predisposition to beta cell dysfunction along with associated insulin resistance, such as obesity. These results are concordant with those of the present study, which showed that the young group had a higher rate of positive family history of diabetes, higher maximal BMI, and higher HOMA-IR than the older group. However, the finding that no difference in BMI according to age of onset was observed, and that the maximal BMI was higher in the young group compared with the older group, suggests that efforts to reduce body weight and increase exercise to improve insulin sensitivity could decrease the occurrence of diabetes at younger ages because a rapid increase in body weight may lead to or aggravate insulin resistance, and higher insulin resistance could be a factor provoking the development of diabetes.

In addition, the young group was observed to have higher fasting and postprandial blood glucose levels at diagnosis, higher HbA1c, more typical symptoms of the disease, and more prevalent microalbuminuria than the usual-onset group. Chuang et al. [12] reported that, among type 2 diabetes patients diagnosed at less than 30 years of age, fasting blood glucose and HbA1c at diagnosis were higher than those of type 2 diabetic patients diagnosed at older ages. Park et al. [17] showed in their study performed in diabetes patients aged less than 30 years, that HbA1c levels at diagnosis and in 6.8-year follow-up, were higher than those of older patients with type 2 diabetes measured in other studies, and that the prevalence of complications was relatively higher in young diabetes patients with 32.9% of diabetic retinopathy, 22.4% of neuropathy and 16.4% of proteinuria. In line with the results with previous reports, the higher blood glucose levels in diabetes patients diagnosed at younger age compared with those in older group, could be considered because they had more possibility to visit a hospital due to dietary changes, decreased physical activity, increased work hours, and more confidence in their health. In addition, considering that young diabetes patients had lower postprandial C-peptide levels and higher HOMA-IR, their beta cell function might have been already declined with more serious degree of insulin resistance, causing higher HbA1c levels. Therefore, complications of diabetes could progress faster and more seriously in young diabetes patients, and more efforts for early detection of the disease and for strict blood glucose control are warranted to deal with the future burden of complications in these young patients.

This study has limitations as a cross-sectional and single center study. In addition, for microalbuminuria measured at diagnosis, there could be a possibility of false positive results caused by high blood sugar. However, our study is meaningful in that we compared various examination results and clinical characteristics at diagnosis according to the age of diabetes onset. Large-scaled, randomized, prospective studies are necessary to determine progressive clinical characteristics including the development of complications and the outcomes of intensive blood sugar control in this patient population.

These days, the prevalence of young diabetes patients has increased continuously. However, the rate of type 2 diabetes patients, different from our expectation, was high in this early-onset diabetes patients, and these young patients showed more frequent positive family history of diabetes, exhibited more typical symptoms associated with high blood sugar at diagnosis, and more prevalent microalbuminuria. Therefore, active and strict blood sugar control at its early stage is warranted to prevent future diabetic complications.

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