JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Family history of diabetes in both parents is strongly associated with impaired residual β-cell function in Japanese type 2 diabetes patients

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Keywords
β-Cell function, Family history of diabetes, Type 2 diabetes

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J Diabetes Investig 2020; 11: 564–572

doi: 10.1111/jdi.13176

ABSTRACT

Aims/Introduction: The objective of the present study was to clarify the association of the type and number of first-degree family history of diabetes (FHD) with the clinical characteristics, especially with residual β-cell function, in type 2 diabetes patients.

Materials and Methods: A total of 1,131 type 2 diabetes patients were recruited and divided into four groups according to FHD information as follows: (i) patients without FHD (FHD–); (ii) those with at least one sibling who had diabetes without parental diabetes (FHD+); (iii) those with one parent (FHD++); or (iv) those with both parents (FHD+++) who had diabetes with or without a sibling with diabetes.

Results: The percentages of the FHD–, FHD+, FHD++ and FHD+++ groups were 49.4%, 13.4%, 34.0% and 3.2%, respectively. Patients in the FHD++ and FHD+++ groups were significantly younger at the time of diabetes diagnosis ($P < 0.001$) than those in the FHD– and FHD+ groups, even after adjusting for confounding factors. In addition, the levels of insulin secretion were significantly lower in the patients in the FHD+, FHD++ and FHD+++ groups than those in the FHD– group ($P < 0.05$) after adjusting for confounding factors, and the patients in the FHD+++ group presented with the lowest levels of insulin secretion among the four groups.

Conclusions: Our results showed that in type 2 diabetes patients, the degree of the associations between FHD and clinical characteristics differs according to the number and the type of FHD. In particular, FHD in both parents is most strongly associated with impaired residual β-cell function.

INTRODUCTION

Type 2 diabetes is a progressive disease, and a deterioration in pancreatic β-cell function might play a crucial role during the course of its progression[1,2]. A previous study showed a heterogeneous course of β-cell dysfunction in type 2 diabetes patients, who showed various rates of ongoing reductions in β-cell function[3]. Although this heterogeneous deterioration in β-cell dysfunction was speculated to have been caused by genetic factors and long-term poor glycemic control, the exact mechanism is not fully understood.

A family history of diabetes (FHD) is known to be a major risk factor for the development of diabetes[4]. To elucidate the mechanism responsible for this risk, several studies have

Received 6 February 2019; revised 5 November 2019; accepted 6 November 2019

examined the influence of FHD among first-degree relatives on insulin secretion and action in non-diabetic individuals[5–7]. For example, in previous studies examining the effect of FHD in detail, insulin secretion was reported to be impaired in non-diabetic relatives with parental diabetes, and such defects seemed to have been inherited, although insulin resistance was not impaired[5,7]. However, as FHD is not often considered after the onset of diabetes, only a few studies have evaluated the effects of FHD on residual β-cell function in type 2 diabetes patients with longer durations of diabetes, and these studies have reported conflicting conclusions[8–10]. One study reported that the level of fasting serum C-peptide immunoreactivity (F-CPR) was significantly lower in patients with FHD than in those without FHD[9]. In contrast, two other studies showed that the presence/absence of FHD had little influence on the level of F-CPR[8,10]. Furthermore, it has been reported that in non-diabetic individuals, the degree of association between FHD and the risk of type 2 diabetes and insulin secretion might differ according to the number and type of first-degree relatives with diabetes[7,11]. For example, Bennet *et al.* showed that FHD, with a positive history in three or more siblings plus parents is the most strongly associated with a high risk of diabetes and lower insulin secretion among various types of family history; for example, diabetes in only sibling(s), diabetes in only one parent and so on[7]. However, there have been no reports examining the association of the detailed information regarding FHD with the clinical characteristics, including residual β-cell function, in patients with type 2 diabetes.

With the above-described background in mind, the present study aimed to determine how the number and type of affected family members with diabetes is related to the clinical characteristics, especially to residual β-cell function, in type 2 diabetes patients.

METHODS

Participants

We enrolled a study cohort between January 2008 and March 2016; this cohort consisted of 1,131 patients with type 2 diabetes who had participated in our previous studies including a genome-wide association study examining genetic loci associated with type 2 diabetes in the Japanese population[12–14].

The exclusion criteria were individuals with diabetes caused by: (i) liver dysfunction; (ii) steroids and other drugs that might increase glucose levels; (iii) malignancy; (iv) monogenic disorders known to cause diabetes, essentially diagnosed on the basis of the clinical diagnosis[15,16]; (v) individuals who tested positive for anti-glutamic acid decarboxylase antibody; and (vi) individuals with renal impairment (serum creatinine level >1.5 mg/dL), as previously described[12,13].

Diabetes was diagnosed based on the 1998 American Diabetes Association Criteria[17].

The clinical characteristics of the participants in the present study are shown in Table 1.

Table 1 | Clinical characteristics of the study participants

n	1,131
Age (years)	64.6 ± 11.7
Male (%)	61.1
BMI (kg/m^2)	25.0 ± 4.4
Waist circumference (cm)	88.4 ± 11.5
Duration of diabetes (years)	13.3 ± 9.6
Age at diabetes diagnosis (years)	51.3 ± 12.1
Lifetime maximum BMI (kg/m^2)	27.9 ± 4.6
Family history of diabetes in the first-degree relatives (%)	50.6
FPG (mg/dL)	137.0 ± 35.8
HbA1c (%)	7.73 ± 1.48
sCre (mg/dL)	0.81 ± 0.33
Beta-cell function-related indices	
F-CPR (ng/mL)	1.73 ± 0.92
CPI	1.31 ± 0.75
Complications	
Diabetic nephropathy (%)	38.2
Diabetic retinopathy (%)	38.3
Treatment	
Lifestyle modification (%)	13.0
OHA and/or GLP-1 analog (%)	55.6
Insulin (%)	12.5
Insulin + OHA and/or GLP-1 analog (%)	18.9
Using insulin (%)	31.3
Insulin secretagogue[†] (%)	52.9
Presence of hypertension[‡] (%)	66.9
Systolic blood pressure (mmHg)	130.3 ± 15.7
Diastolic blood pressure (mmHg)	75.0 ± 11.5
Presence of dyslipidemia[§] (%)	70.3
Total cholesterol (mg/dL)	186.3 ± 33.4
Triglycerides (mg/dL)	125.6 ± 77.9
HDL cholesterol (mg/dL)	53.5 ± 17.1
LDL cholesterol (mg/dL)	111.2 ± 27.2

Continuous data values are expressed as the mean ± standard deviation. Categorical data are expressed as a percentage. [†]Insulin secretagogue include sulfonylureas, dipeptidyl peptidase-4 inhibitors, glinide and glucagon-like peptide-1 (GLP-1) analog. [‡]Determination of hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or having been treated for hypertension. [§]Determination of dyslipidemia was defined as serum low-density lipoprotein (LDL) cholesterol ≥140 mg/dL, serum triglycerides ≥150 mg/dL or high-density lipoprotein (HDL) cholesterol <40 mg/dL or having been treated for dyslipidemia. BMI, body mass index; CPI, C-peptide immunoreactivity index; F-CPR, fasting serum C-peptide immunoreactivity; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; OHA, oral hypoglycemic agents; sCre, serum levels of creatinine.

Collection of clinical information

We obtained clinical information including current body mass index (BMI), current waist circumference, lifetime maximum BMI (max BMI), blood pressure (BP), FHD, age at diabetes diagnosis, diabetic complications, and use of antidiabetic drugs, antihypertensive agents and lipid-lowering drugs from the

patients' medical records and self-reported questionnaires. In addition, we measured blood chemistry parameters including plasma glucose, glycated hemoglobin (HbA1c), and serum levels of C-peptide, creatinine, triglyceride, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol (HDL-c) after overnight fasting without taking antidiabetic drugs.

A detailed description of the methods used to determine FHD follows. FHD was considered as the presence of diabetes in first-degree relatives, such as biological parents and/or siblings, except for children. We examined not only the presence of parents and siblings with diabetes, but also the number of parents (mother only, father only or both parents) and siblings affected by diabetes in as much detail as possible. Unfortunately, we could not collect information on whether the relatives had type 1 diabetes or type 2 diabetes. However, as the majority of adult diabetes patients are thought to have type 2 diabetes[18], we simply considered the diabetes of the relatives as type 2 diabetes. Overall, 15.2% had a father and 18.8% had a mother with diabetes, irrespective of the presence of siblings with diabetes (Table 2). We referred to several previous studies[7,8,19], and the diabetes patients in the present study were divided into four groups according to the type and number of FHD: (i) patients without a FHD (FHD–); (ii) those with at least one sibling who had diabetes without parental diabetes (FHD+); (iii) those with one parent (father or mother) who had diabetes with or without a sibling affected by diabetes (FHD++); and (iv) those with both parents who had diabetes with or without a sibling affected by diabetes (FHD+++; Table 3).

The CPR index (CPI), which was recently reported to be useful for evaluating residual pancreatic β-cell function and insulin requirement[14,20,21], was calculated as follows: F-CPR (ng/mL) / FPG (mg/dL) × 100[14]. The homeostasis model assessment of insulin resistance was calculated as previously reported[22]. The HbAlc level was measured using high-performance liquid chromatography and was expressed as the international standard value; that is, HbA1c (1.02 × Japan Diabetes Society [%] + 0.25%), as defined by the Japan Diabetes Society[23]. The F-CPR level was measured using an electrochemiluminescence immunoassay (C-peptide Kit®; Roche Diagnostics, Tokyo, Japan). The serum insulin level was measured using a chemiluminescent enzyme immunoassay (Insulin Kit®; Roche Diagnostics).

All the study procedures were approved by the ethics committee of the University of Toyama, and written informed consent was obtained from all the study participants.

Definitions of insulin requirement and diabetic complications

Patients who were required to inject >10 units of insulin a day continuously were regarded as undergoing insulin therapy, as previously described[12,14].

Diabetic nephropathy and diabetic retinopathy were defined as previously described[12,14].

Statistical analysis

Categorical data were expressed as a percentage, whereas continuous data values were expressed as the mean ± standard deviation. The statistical analyses were carried out using JMP for Windows, Version 11.0 (SAS Institute, Cary, NC, USA). The normality of the distributions was checked using the skewed score, and variables with skewed distributions were logarithmically (naturally) transformed in subsequent analyses. The χ^2-test was used for testing the difference in frequency (Tables 2,3). Differences in clinical features between the four groups were determined using ANOVA and a multiple regression analysis after adjustments for related covariables (Table 3). The associations of individual groups having FHD (i.e., the FHD+, FH++ and FHD+++ groups) with age at diabetes diagnosis, insulin secretory capacity and insulin requirement were examined by calculating the β-values using a multivariate linear regression analysis adjusted for related covariables using the FHD– group as the reference (Table 4). When examining the association of FHD with insulin secretory capacity using multiple regression analysis (Tables 3,4), as age, sex, BMI, duration of diabetes, FPG and serum creatinine level were reported to affect the insulin secretory capacity[24], we used these factors as explanatory variables. In addition, we also used the intake of insulin secretagogue and the presence of microvascular complications as explanatory variables, as the former variables, such as sulfonylureas, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 analog, might promote endogenous insulin secretion, resulting in the increment of F-CPR and CPI, and the latter variables could reflect chronic hyperglycemia, which might cause impaired β-cell function. Results with *P*-values <0.05 were considered statistically significant.

RESULTS

Participant characteristics

The mean age of the participants in the present study was 64.6 ± 11.7 years; the diabetes duration and HbA1c levels were 13.3 ± 9.6 years and 7.7 ± 1.5%, respectively (Table 1). The percentage of male sex was 61.1%. The mean BMI was 25.0 ± 4.4 kg/m^2, and the mean concentrations of F-CPR and CPI were 1.73 ± 0.92 ng/mL and 1.31 ± 0.75, respectively (Table 1). A total of 50.6% of the participants had a family history of diabetes in a first-degree relative(s) (Table 1), which was almost identical to the frequency reported in previous studies carried out with Japanese type 2 diabetes patients[19,25,26].

Comparison of the clinical characteristics among the groups divided by the information regarding family history of diabetes

When the clinical characteristics were compared between patients with paternal diabetes and those with maternal diabetes, no significant differences were found (Table 2), as previously reported[8]. Therefore, we combined them together and treated them as a group consisting of patients with one parent having diabetes; that is, FH++. The FHD–, FHD+, FHD++ and

Table 2 | Comparison of clinical characteristics between the patients with paternal diabetes and those with maternal diabetes

	Father	Mother	*P*-value
n	172	213	
Age (years)	60.0 ± 12.6	62.3 ± 11.8	0.06
Male (%)	65.1	62.0	0.60†
BMI (kg/m^2)	25.1 ± 5.0	25.0 ± 4.8	0.91
Waist circumference (cm)	89.0 ± 12.5	88.3 ± 11.9	0.61
Duration of diabetes (years)	13.5 ± 9.7	13.6 ± 8.6	0.90
Age at diabetes diagnosis (years)	46.4 ± 11.8	48.8 ± 11.6	0.06
Lifetime maximum BMI (kg/m^2)	28.3 ± 5.5	28.4 ± 5.3	0.89
FPG (mg/dL)	140.5 ± 31.8	140.0 ± 38.5	0.90
HbA1c (%)	7.85 ± 1.56	7.79 ± 1.48	0.71
sCre (mg/dL)	0.79 ± 0.33	0.80 ± 0.36	0.73
Beta-cell function-related indices			
F-CPR (ng/mL)	1.63 ± 0.77	1.66 ± 0.92	0.76
CPI	1.20 ± 0.61	1.22 ± 0.68	0.83
Insulin resistance-related index			
HOMA-IR‡	2.63 ± 3.59	2.40 ± 1.91	0.962
Complications			
Diabetic nephropathy (%)	34.3	41.4	0.53†
Diabetic retinopathy (%)	47.9	36.9	0.14†
Treatment			
Lifestyle modification (%)	11.1	8.9	0.06†
OHA and/or GLP-1 analog (%)	48.3	58.7	
Insulin (%)	16.9	11.7	
Insulin + OHA and/or GLP-1 analog (%)	23.8	20.7	
Using insulin (%)	40.7	32.4	0.08†
Insulin secretagogue§ (%)	47.1	52.6	0.37†
Presence of hypertension¶ (%)	59.3	66.2	0.08†
Systolic blood pressure (mmHg)	130.7 ± 16.5	131.6 ± 16.1	0.56
Diastolic blood pressure (mmHg)	75.9 ± 12.1	76.2 ± 11.2	0.82
Presence of dyslipidemia†† (%)	69.2	72.2	0.88†
Total cholesterol (mg/dL)	186.3 ± 32.0	188.8 ± 35.2	0.56
Triglyceride (mg/dL)	123.0 ± 67.1	129.8 ± 93.4	0.40
HDL cholesterol (mg/dL)	54.6 ± 16.1	55.3 ± 19.4	0.70
LDL cholesterol (mg/dL)	111.4 ± 26.5	111.8 ± 28.1	0.88

Continuous data values were expressed as the mean ± standard deviation. Categorical data were expressed as a percentage. Between the patients with paternal diabetes and those with maternal diabetes, the *P*-values were calculated using Student's *t*-test for differences between means, and using the χ^2-test for differences between frequencies. †Pearson's χ^2-test. ‡Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated in the study participants who were not receiving insulin therapy. §Insulin secretagogue include sulfonylureas, dipeptidyl peptidase-4 inhibitors, glinide and glucagon-like peptide-1 (GLP-1) analog. ¶Determination of hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or having been treated for hypertension. ††Determination of dyslipidemia was defined as serum low-density lipoprotein (LDL) cholesterol ≥140 mg/dL, serum triglycerides ≥150 mg/dL or high-density lipoprotein (HDL) cholesterol < 40 mg/dL, or having been treated for dyslipidemia. BMI, body mass index; CPI, C-peptide immunoreactivity index; F-CPR, fasting serum C-peptide immunoreactivity; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; OHA, oral hypoglycemic agents; sCre, serum levels of creatinine.

FHD+++ groups accounted for 49.4%, 13.4%, 34.0% and 3.2% of the patient cohort, respectively (Table 3). When the clinical characteristics of the four groups were compared, significant differences in the following variables were observed: age, percentage of male sex, BMI, diastolic BP, age at diabetes diagnosis, duration of diabetes, levels of F-CPR, CPI and HDL-c, and percentage of participants requiring insulin therapy (Table 3). However, in a multiple logistic regression model with related covariables, the significant difference in diastolic BP and the serum HDL-c level among the four groups disappeared (*P*-values for diastolic BP = 0.839, *P*-values for HDL-c = 0.096; Table 3). In contrast, the age at diabetes diagnosis remained significantly different among the four groups after adjusting for sex and log-transformed max BMI ($P < 0.001$). In addition, the levels of F-CPR and CPI also remained significantly different among the four groups after adjusting for related covariables, as mentioned in

Table 3 | Comparison of clinical characteristics among the four groups divided according to the information of the family history of diabetes

	FHD–	FHD+	FHD++	FHD+++	*P* (ANOVA)	*P** (multivariate)
n	559	151	385	36		
Age (years)	65.8 ± 11.3	69.1 ± 9.5	61.2 ± 12.2	62.0 ± 11.4	<0.001	
Male (%)	63.5	48.3	63.4	55.6	<0.01†	
BMI (kg/m^2)	25.1 ± 4.1	24.1 ± 3.9	25.0 ± 4.9	24.5 ± 4.4	<0.05	
Waist circumference (cm)	88.8 ± 10.9	86.5 ± 11.4	88.6 ± 12.2	88.0 ± 11.9	0.28	
Duration of diabetes (years)	12.4 ± 9.6	15.5 ± 10.3	13.6 ± 9.1	15.2 ± 11.1	<0.01	
Age at diabetes diagnosis (years)	53.5 ± 11.7	53.7 ± 12.1	47.7 ± 11.8	47.0 ± 12.5	<0.001	<0.001
Lifetime maximum BMI (kg/m^2)	27.9 ± 4.2	27.4 ± 4.1	28.3 ± 5.3	27.1 ± 4.8	0.21	
FPG (mg/dL)	135.6 ± 35.2	133.3 ± 37.7	140.2 ± 35.6	134.7 ± 38.3	0.17	
HbA1c (%)	7.75 ± 1.51	7.49 ± 1.21	7.82 ± 1.51	7.54 ± 1.59	0.12	
sCre (mg/dL)	0.82 ± 0.32	0.80 ± 0.31	0.79 ± 0.35	0.79 ± 0.23	0.71	
Beta-cell function-related indices						
F-CPR (ng/mL)	1.85 ± 0.93	1.57 ± 1.03	1.65 ± 0.86	1.32 ± 0.64	<0.001	<0.01
CPI	1.41 ± 0.76	1.24 ± 0.95	1.21 ± 0.65	1.04 ± 0.56	<0.001	<0.01
Insulin resistance-related index						
HOMA-IR‡	2.44 ± 1.85	2.04 ± 1.67	2.50 ± 2.76	1.70 ± 1.09	0.159	
Complications						
Diabetic nephropathy (%)	37.2	42.3	38.3	34.3	0.68†	
Diabetic retinopathy (%)	34.2	42.9	41.8	41.2	0.13†	
Treatment						
Lifestyle modification (%)	15.7	11.9	9.9	8.3	<0.05†	
OHA and/or GLP-1 analog (%)	57.8	52.3	54.0	52.8		
Insulin (%)	10.2	15.2	14.1	19.4		
Insulin + OHA and/or GLP-1 analog (%)	16.3	20.5	22.1	19.4		
Using insulin (%)	26.5	35.7	36.2	38.9	<0.01†	<0.05
Insulin secretagogue§ (%)	54.9	51.0	50.1	58.3	0.43†	
Presence of hypertension¶ (%)	69.2	69.5	63.1	61.1	0.18†	
Systolic blood pressure (mmHg)	129.9 ± 15.8	130.0 ± 14.1	131.2 ± 16.2	131.0 ± 15.4	0.63	
Diastolic blood pressure (mmHg)	75.1 ± 11.5	71.9 ± 10.8	76.0 ± 11.6	75.1 ± 12.1	<0.01	0.84
Presence of dyslipidemia†† (%)	69.4	72.9	70.8	66.7	0.81†	
Total cholesterol (mg/dL)	186.2 ± 33.7	184.3 ± 30.3	187.4 ± 33.8	185.5 ± 39.5	0.80	
Triglyceride (mg/dL)	126.5 ± 77.3	118.8 ± 626	126.7 ± 82.6	128.5 ± 95.5	0.80	
HDL cholesterol (mg/dL)	51.9 ± 16.2	55.7 ± 17.0	55.0 ± 18.0	54.2 ± 18.2	<0.05	0.10
LDL cholesterol (mg/dL)	112.1 ± 27.1	107.6 ± 25.4	111.6 ± 27.4	107.7 ± 31.6	0.11	

Continuous data values were expressed as the mean ± standard deviation. Categorical data were expressed as a percentage. *P-value for comparison of adjusted data. Age at diabetes diagnosis was adjusted for sex and log-transformed (ln) lifetime maximum body mass index (BMI). Fasting serum C-peptide immunoreactivity (F-CPR) and C-peptide immunoreactivity index (CPI) were adjusted for age, sex, ln BMI, duration of diabetes, intake of insulin secretagogue, fasting plasma glucose (FPG), serum levels of creatinine (sCre), the presence of diabetic nephropathy and the presence of diabetic retinopathy. The ratio of insulin therapy was adjusted for age, sex, ln BMI, duration of diabetes, class of antihyperglycemic drug and glycated hemoglobin (HbA1c) level. Diastolic blood pressure and the level of high-density lipoprotein (HDL) cholesterol were adjusted for intake of antihypertensive drug and intake of lipid-lowering drugs, respectively, in addition to age, sex, ln BMI and waist circumference. †Pearson's χ^2-test. ‡Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated in the study participants who were not receiving insulin therapy. §Insulin secretagogue include sulfonylureas, dipeptidyl peptidase-4 inhibitors, glinide and glucagon-like peptide-1 (GLP-1) analog. ¶Determination of hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or having been treated for hypertension. ††Determination of dyslipidemia was defined as serum low-density lipoprotein (LDL) cholesterol ≥140 mg/dL, serum triglycerides ≥150 mg/dL or HDL-c < 40 mg/dL, or having been treated for dyslipidemia. FHD–, patient without family history of diabetes; FHD+, patients with at least one sibling who had diabetes without parental diabetes; FHD++, patients with one parent who had diabetes with or without diabetic siblings; FHD+++, patient with both parents who had diabetes with or without diabetic siblings. Between the four groups, the *P*-values were calculated using ANOVA for difference between means and using. FHD, family history of diabetes; OHA, oral hypoglycemic agents.

the Methods section ($P < 0.01$). Furthermore, the percentage of individuals receiving insulin therapy also remained significantly different among the four groups ($P < 0.05$) after adjustments for related covariables. Among the four groups, the patients in the FHD+++ group presented with the youngest age at diabetes diagnosis (age at diabetes diagnosis [years] for FHD–, FHD+,

Table 4 | Association of individual groups having a family history of diabetes with age at diabetes diagnosis, β-cell function-related parameters and insulin requirement

FHD–	FHD+			FHD++			FHD+++		
	β	SE	*P*	β	SE	*P*	β	SE	*P*
Age at diabetes diagnosis									
Ref.	−0.19	0.54	0.73	−2.78	0.38	<0.001	−3.53	1.00	<0.001
F-CPR									
Ref.	−0.06	0.02	<0.05	−0.05	0.02	<0.01	−0.12	0.05	<0.01
CPI									
Ref.	−0.05	0.03	<0.05	−0.06	0.02	<0.01	−0.11	0.05	<0.05
Insulin requirement									
Ref.	0.23	0.12	0.07	0.19	0.09	<0.05	0.41	0.24	0.09

Data show the the β coefficients with standard error (SE) when using multivariate linear regression to examine the associations of individual groups having a family history of diabetes (FHD; i.e., the patients with at least 1 sibling who had diabetes without parental diabetes [FHD+], patients with one parent who had diabetes with or without diabetic sibling [FHD++] and patient with both parents who had diabetes with or without diabetic sibling [FHD+++] groups) with age at diabetes diagnosis, insulin secretory capacity and insulin requirement using the patient without family history of diabetes (FHD–) group as the reference (Ref.). In this analysis, the following variables were used as explanatory variables: age at diabetes diagnosis was adjusted for sex and log-transformed (ln) maximum lifetime body mass index; fasting serum C-peptide immunoreactivity (F-CPR) and C-peptide immunoreactivity index (CPI) were adjusted for age, sex, log-transformed body mass index, duration of diabetes, intake of insulin secretagogue, FPG, sCre, the presence of diabetic nephropathy, and the presence of diabetic retinopathy; insulin requirement was adjusted for age, sex, log-transformed body mass index, duration of diabetes, class of antihyperglycemic drug and glycated hemoglobin level.

FHD++ and FHD+++ was 53.5 ± 11.7, 53.7 ± 12.1, 47.7 ± 11.8 and 47.0 ± 12.4, respectively), the lowest levels of insulin secretion (F-CPR [ng/mL] for FHD–, FHD+, FHD++ and FHD+++ was 1.85 ± 0.93, 1.57 ± 1.03, 1.65 ± 0.86 and 1.32 ± 0.64, respectively; CPI for FHD–, FHD+, FHD++ and FHD+++ was 1.41 ± 0.76, 1.24 ± 0.95, 1.21 ± 0.65 and 1.04 ± 0.56, respectively) and the highest percentage of insulin requirement (% of insulin requirement for FHD–, FHD+, FHD++ and FHD+++ was 26.5%, 35.7%, 36.2% and 38.9%, respectively; Table 3).

Investigation of the association of individual groups having FHD with age at diabetes diagnosis, β-cell function-related parameters and insulin requirement

The age at diabetes diagnosis was significantly and inversely associated with the FHD++ group and the FHD+++ group ($P < 0.001$), but not with the FHD+ group ($P = 0.73$; Table 4). In addition, we observed a higher beta coefficient for the FHD+++ group, compared with that for the FHD++ group (β for FHD+++ −3.53 vs β for FHD++ −2.78; Table 4). Regarding the insulin secretory capacity, there was a significant and inverse relationship between β-cell function-related parameters and individual groups with FHD, with higher beta coefficients for the FHD+++ group (β for F-CPR in FHD+++ = −0.12, $P < 0.01$; β for CPI in FHD+++ = −0.11, $P < 0.05$) compared with the FHD+ group (β for F-CPR in FHD+ = −0.06, $P < 0.05$; β for CPI in FHD+ = −0.05, $P < 0.05$) and the FHD++ group (β for F-CPR in FHD++ = −0.05, $P < 0.01$; β for CPI in FHD++ = −0.06, $P < 0.01$; Table 4). Regarding the percentage of insulin requirement, we observed a positive and significant association only between the FHD++ group and the percentage of insulin requirement (β = 0.09, $P < 0.05$), whereas there was a trend, although not significant, toward positive associations between the percentage of insulin requirement and the FHD+ (β = 0.23, $P = 0.07$) and FHD+++ groups (β = 0.41, $P = 0.09$; Table 4).

DISCUSSION

In the present study, we found that the degree of the association between FHD and age at diabetes diagnosis and residual β-cell function differed according to the number and the type of first-degree relatives with diabetes. Furthermore, we showed that among the various types of FHD, the presence of diabetes in both parents was most strongly associated with impaired residual β-cell function.

Until now, numerous studies have reported that FHD is a major risk factor for the development of type 2 diabetes in non-diabetic individuals[4–7,27–30]. In contrast, in type 2 diabetes patients, only a few studies have evaluated the association of FHD with clinical characteristics including residual β-cell function[8–10]. These studies have been carried out in type 2 diabetes patients with a diabetes duration of approximately 10 years in Korea and other countries[8–10]. However, the results were conflicting, as mentioned in the Introduction section. Furthermore, in non-diabetic individuals, although several studies have examined information on FHD in first-degree and second-degree relatives in detail, and have investigated the association between this information and clinical parameters including insulin secretion and resistance[7,28,29], to the best of our knowledge, such analyses have not been carried out in type 2 diabetes patients to date. Therefore, the present study

is the first to investigate the correlations between the detailed FHD in first-degree relatives and clinical characteristics, especially residual β-cell function and insulin requirement, in type 2 diabetes patients, and to show that among the various types of FHD, FHD in both parents was significantly and most strongly associated with a lower residual β-cell function, and tended to be associated with a higher percentage of requiring insulin therapy. These findings suggest that, similar to non-diabetic individuals, a detailed examination of FHD in type 2 diabetes patients might be important and useful for predicting β-cell function and insulin requirement long after the onset of diabetes.

Family history of diabetes is a reflection of both genetic components and environmental components, such as behavior and lifestyle (e.g., diet and exercise), that are shared, to some extent, by a family[31]. Regarding genetic factors, recent advances in genetic technologies have revealed a growing number of genes that are related to type 2 diabetes; to date, >120 distinct genetic loci, with >150 variants, with potential involvement in the pathogenesis of type 2 diabetes have been identified[32,33]. Almost all these variants (e.g., *SLC30A8*, *TCF7L2*, *KCNQ1*, *UBE2E2* and *C2CD4A/B*, etc.) regulate insulin secretion, and only a few variants (e.g., *IRS1* and *FTO*, etc.) regulate insulin sensitivity. A genetic risk score (GRS) was mainly calculated by the summation of the number of risk alleles of the above-mentioned variants, and relationships between the GRS and clinical characteristics, including diabetes risk, insulin secretion and sensitivity, have been reported[27,34–38]. Previous studies have shown that the GRS is more strongly associated with defective insulin secretion, rather than insulin resistance [27,34–38]. In addition, the GRS has been reported to be significantly associated with FHD information[27,28,39]. For example, Vassy *et al.*[39] examined 33 single-nucleotide polymorphisms associated with type 2 diabetes and calculated an additive 33-single-nucleotide polymorphism-weighted GRS; they showed that the mean GRS increased significantly according to the number of parents with diabetes (GRS = 16.8, 16.9 and 17.1 in participants with 0, 1 and 2 parents with diabetes, respectively), suggesting that the FHD in the parent can reflect the genetic factors of diabetes. Although we have not examined the GRS for type 2 diabetes in the present study, based on the above-mentioned previous reports, we speculated that the patients in the FH+++ group might have a greater GRS than those in other groups; as a result, their residual β-cell function might be impaired through the inverse effect of GRS on insulin secretion.

The anticipation phenomenon is a genetic disorder that is passed on to the next generation, and the symptoms of the genetic disorder become apparent at an earlier age with each generation[40]. As a previous study had reported that genetic anticipation might also be observed in patients with type 2 diabetes[41,42], we considered that the younger age at diagnosis of diabetes in patients with a history of diabetes in both parents could be attributable to this anticipation phenomenon.

We obtained information regarding first-degree relatives with diabetes, but not information regarding relatives more distant than first-degree, as information regarding second- and third-degree relatives with diabetes might not be accurate, and the inclusion of such information can lead to incorrect results. In addition, regarding the FHD in siblings, we recruited information on the presence of diabetic siblings, but not the number of siblings with diabetes, because the number, not the ratio, of siblings affected by diabetes might be influenced by the number of siblings in each family. Furthermore, to minimize the inclusion of type 1 diabetes in FHD, we purposely excluded participants who reported children with diabetes, as the FHD in these cases was likely to have been linked to type 1 diabetes, rather than type 2 diabetes.

The major strength of the present study was that it examined the difference in clinical characteristics among four groups divided according to the types and number of FHD, and showed that among the various types of FHD, FHD in both parents is more strongly associated with lower β-cell function than other types of FHD. These findings are novel. Nevertheless, the present study had some limitations. First, the information on first-degree FHD was obtained using a self-reported questionnaire based on patient recall; therefore, this information might not have been sufficiently accurate and might have skewed the present findings. However, in a sample of Caucasians and Hispanics, a complete agreement between self-reported FHD by the patients, and the prevalence of diabetes in their family members has been reported[43]. Furthermore, this method has been used in several studies to date[7–10,44]. In addition, as much as possible, we made an effort to obtain accurate FHD information by examining the information in the medical records of the participants. Therefore, we believe that the information on first-degree FHD might be considered accurate.

Second, we could not examine the association between the FHD and clinical characteristics in age-, sex-, BMI- and diabetes duration-matched participants among the four groups. As these factors could influence β-cell function, as previously reported[24], the differences among the four groups might have affected the present findings. However, in the present study, we evaluated the relationship between the FHD and the β-cell function-related indices using not only an ANOVA, but also a multiple logistic regression analysis with adjustments for the above variables, and a significant difference was observed. Third, because the present study was a cross-sectional analysis, we could not establish a temporal relationship between the FHD and β-cell function. Fourth, according to our method for determining the FHD in this study, participants without a sibling(s) were treated as individuals without a FHD in the sibling(s), similar to individuals having a sibling(s), but not having diabetes. This method might not entirely be valid, but it has been used in several studies to date[7,8,19]. Unfortunately, we did not examine the number of siblings that each participant had, and did not know the percentage of patients in this study who did not have a sibling(s). However, the white paper on health and welfare published in 2003 by the

Ministry of Health, Labor and Welfare in Japan[45] indicated that the percentage of persons without a sibling(s) among persons born in the 1950s in the Japanese general population was only approximately 6–7%. Therefore, although we could not confirm whether the above finding was applicable to our participants or not, the percentage of patients without sibling(s) in the present study was estimated to be very small, as the mean age of the participants in our study was approximately 65 years (they were born in the 1950s), and we speculated that although our method for determining the FHD in the siblings might have been slightly problematic, it is unlikely to have had a significant effect our conclusion.

In conclusion, we showed that the degree in the association of FHD with residual β-cell function differs according to the number and type of FHD. This finding might partly account for the heterogeneous progression in β-cell dysfunction among individual type 2 diabetes patients that is seen after the onset of the disease. In addition, among the various types of FHD, we showed that FHD in both parents was the most strongly associated with impaired β-cell function. In other words, we should explain to type 2 diabetes patients with a family history of both parents having diabetes that they might have a greater risk of a reduction in their ability to secrete insulin, compared with patients without diabetic relatives, and that they might be more likely to require insulin therapy in the future; more aggressive β-cell preserving therapy, such as the use of glucagon-like peptide 1 receptor agonists or medications that ameliorate insulin resistance, should be recommended for such patients. However, the present study was a cross-sectional analysis carried out in a relatively small sample size. A prospective study involving a larger number of participants is required to clarify the present findings.

ACKNOWLEDGMENTS

We are grateful to all the individuals who participated in this study.

DISCLOSURE

The authors declare no conflict of interest.

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