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Original Article

Clinical characteristics in children with maturity-onset diabetes of the young detected by urine glucose screening at schools in the Tokyo Metropolitan Area

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Highlights

- Genetic testing should be conducted to distinguish between children with non-obese type 2 diabetes and those with MODY to provide appropriate treatment.
- Urine glucose screening at schools is one of the best opportunities to detect not only children with type 2 diabetes but also those with MODY before disease progression.

Abstract. This study aimed to examine the clinical characteristics of young children diagnosed with maturity-onset diabetes (MODY) using urine glucose screening at schools. The study participants were 70 non-obese children who were clinically diagnosed with type 2 diabetes through urine glucose screening at schools in Tokyo between 1974 and 2020. Of these children, 55 underwent genetic testing, and 21 were finally diagnosed with MODY: MODY2 in eight, MODY3 in eight, MODY1 in four and MODY5 in one. A family history of diabetes was found in 76.2% of the patients. Fasting plasma glucose levels did not differ between the different MODY subtypes, while patients with MODY 3, 1, and 5 had significantly higher levels of glycosylated hemoglobin and 2-hour glucose in an oral glucose tolerance test than those with MODY2. In contrast, most patients exhibit mild insulin resistance and sustained β-cell function. In the initial treatment, all patients with MODY2 were well controlled with diet and exercise, whereas the majority of those with MODY3, 1, and 5 required pharmacological treatment within one month of diagnosis. In conclusion, urine glucose screening in schools appears to be one of the best opportunities for early detection of the disease and providing appropriate treatment to patients.

Key words: children, maturity onset diabetes of the young, non-obesity, urine glucose screening at schools

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Introduction

The clinical criteria for the diagnosis of maturity-onset diabetes of the young (MODY) are classically defined as follows: autosomal dominant inheritance, onset before 45 yr of age, absence of insulin resistance, sustained pancreatic β-cell function, and lack of β-cell autoimmunity evidence (1, 2). Meanwhile, the Practice Guideline for MODY in 2008 includes: onset before 25 yr of age in one family member, presence of diabetes in two consecutive generations, maintained endogenous insulin secretion after 3 yr of diabetes, and absence of β-cell autoantibodies within 3 yr of diabetes onset (3). The current Clinical Practice Consensus Guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) showed the diagnosis of MODY as follows: a family history of diabetes in a parent and first-degree relatives of the affected parent in persons with diabetes who lack the characteristics of type 1 and type 2 diabetes (4). MODY is the most common form of monogenic diabetes and is estimated to account for approximately 5% of diabetes cases identified before 45 yr of age (5, 6) and 1–6% of pediatric cases (4). However, several cases of MODY may be misdiagnosed as type 1 or type 2 diabetes with only clinical presentation and without genetic testing (4, 6). Genetic testing for the diagnosis of MODY was first performed in the 1990s. To date, mutations associated with MODY have been reported in at least 14 different genes, including the following six genes encoding major factors: hepatocyte nuclear factor (HNF) 4α (*HNF4A*), glucokinase (*GCK*), HNF1α (*HNF1A*), pancreatic and duodenal homeobox 1 (*PDX1*), HNF1β (*HNF1B*), and neurogenic differentiation 1 (*NEUROD1*), which correspond to MODY subtypes 1–6, respectively (4, 7, 8). Distinguishing MODY from type 1 and type 2 diabetes is crucial to provide appropriate treatment and improve prognosis. Therefore, selection of appropriate candidates for genetic testing and molecular analysis is strongly recommended for MODY diagnosis.

In contrast, a unique program to detect diabetes in children at an early disease stage using urine glucose screening is conducted annually for children attending government primary and junior high schools in all Japanese cities (9, 10). In the Tokyo Metropolitan Area, this screening program started in 1994, and many children with type 2 diabetes and a small number with type 1 diabetes have minimal or no symptoms of diabetes (11, 12). Most children with type 2 diabetes detected by the screening program were obese; however, some children were non-obese without any evidence of β-cell autoimmunity (13, 14). Some children with slowly progressive type 1 diabetes have been identified through screening programs (15, 16). They usually show mild symptoms of hyperglycemia without ketosis at diagnosis; majority of the patients have positive β-cell autoantibodies and maintain a certain degree of β-cell function within at least 3 years after diagnosis. This novel type of diabetes is often encountered in adults and is referred to as latent autoimmune diabetes in adults (17, 18). In Japan, there seems to be some heterogeneity in the clinical forms of diabetes; therefore, discrimination between type 1 and type 2 diabetes is sometimes difficult, with only clinical manifestations at the time of diagnosis. Moreover, some children with monogenic diabetes, mainly those with MODY, are diagnosed incidentally through a screening program and the diagnosis is confirmed only by specific genetic testing.

In the present study, we performed genetic testing for MODY in non-obese children clinically diagnosed with type 2 diabetes, in whom MODY was detected using urine glucose screening at schools. We studied the clinical characteristics and laboratory data at the time of diagnosis and suggested an appropriate therapeutic approach.

Materials and Methods

Study design and participants

The present study was a retrospective observational study on MODY conducted at Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo, Japan. We identified 414 patients, including 379 with diabetes and 35 with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), using a urine glucose screening program in schools in the Tokyo Metropolitan Area between 1974 and 2020. Of these 414 patients, 35 were diagnosed with type 1 diabetes based on deficient endogenous insulin secretion requiring insulin treatment and presence of β-cell autoantibodies (15, 16). Of the 344 patients who were clinically diagnosed with type 2 diabetes based on substantially maintained insulin release and absence of β-cell autoantibodies (9–12), 285 were obese and 59 were non-obese; whereas among the 35 patients with IFG or IGT, 24 were obese and 11 were non-obese. Overall, 70 non-obese patients, including 59 with clinical type 2 diabetes and 11 with IFG or IGT, were selected as candidates for genetic testing for MODY. Finally, the genetic testing was performed for 55 patients (male/female=16/39; age at screening, 13.4 ± 1.4 [range: 9–15] yr); informed consent was obtained from the parents (**Fig. 1**). Participants with obesity was defined as body mass index (BMI) exceeding the 90th centile for sex- and age-matched Japanese children (19). Patients who visited the hospital soon after positive results underwent urine glucose screening.

The procedure for urine glucose screening at schools was as follows: if a first-morning urine sample was positive for glucose in two consecutive tests, an OGTT with loading of 1.75 g/kg body weight of glucose (maximum of 75 g) was conducted to confirm the diagnosis of diabetes. Glycosylated hemoglobin (HbA1c) and serum levels of immunoreactive insulin (IRI), total cholesterol, and triglycerides were simultaneously examined. If the fasting plasma glucose (FPG) level was > 200 mg/dL, the OGTT was not performed. The diagnosis of diabetes was confirmed along with the HbA1c levels. Diabetes, IFG, and IGT were evaluated based on World Health Organization

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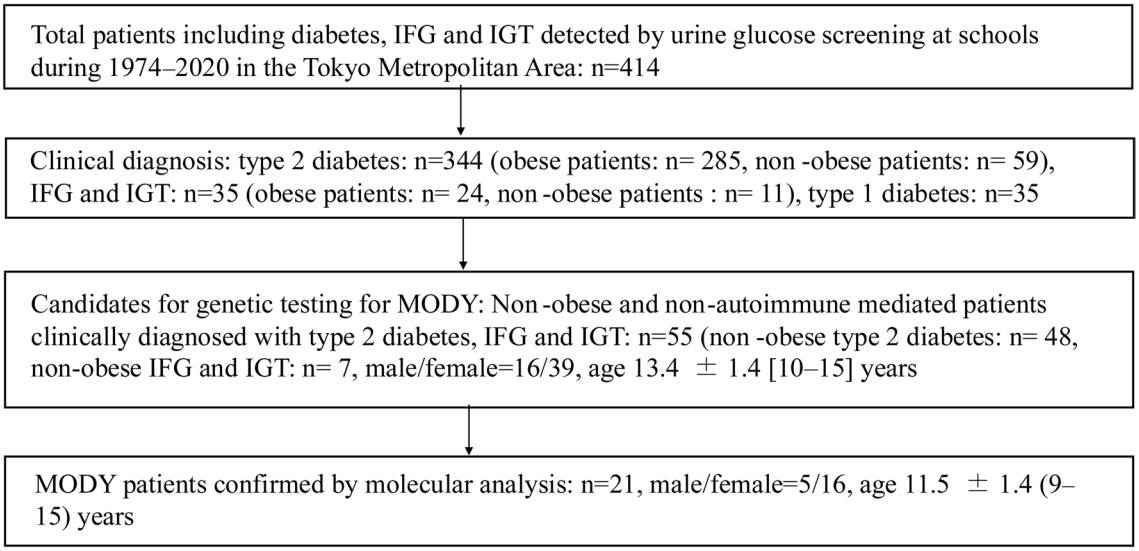

Fig. 1. Flow chart for selection of candidates with genetic testing for MODY. IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ACMG, American College of Medical Genetics and Genomics; ranges in parentheses. Diabetes, IFG, and IGT were determined based on the World Health Organization (WHO) criteria adopted each year (20).

(WHO) criteria adopted each year (20). Additionally, IRI levels were simultaneously examined with an OGTT, and indices for insulin resistance (the homeostasis model assessment-insulin resistance [HOMA-IR]) and insulin secretion capacity (the homeostatic model assessment of beta cell function [HOMA-β]) were also evaluated in the screening program. Additional follow-up examinations, such as testing of β-cell autoantibodies, including islet-cell antibody (ICA), and/or glutamic acid decarboxylase (GAD) antibody, and/or insulinoma-associated antigen-2 (IA-2) antibody, and/or zinc transporter 8 (ZnT8) antibody, were conducted along with genetic studies to classify the types of diabetes. All β-cell autoantibodies tested were negative for patients diagnosed with MODY although the numbers and kinds of the antibodies were different according to the time examined. In the screening program, plasma glucose (PG) and HbA1c levels were measured using the glucose oxidase and high-performance liquid chromatography methods, respectively. HbA1c levels, expressed in Japan Diabetes Society values, were converted to National Glycohemoglobin Standardization Program (NGSP) values (reference range for the NGSP value: 4.6–6.2%). HOMA-IR was calculated as FPG (mg/dL) × fasting IRI (μU/mL)/405, and insulin resistance was evaluated as HOMA-IR > 2.5. HOMA-β was calculated as fasting IRI (μU/mL) × 360/(FPG–63) mg/dL, and insulin secretory capacity was considered to be maintained in HOMA-β > 30 (21).

Analysis methods in MODY genes

Genomic DNA was extracted from peripheral blood leukocytes using the QIAamp DNA Blood Kit (QIAGEN, Hilden, Germany). The mitochondrial 3243A>G mutation was first excluded by polymerase chain reaction (PCR)-restriction fragment length polymorphism analysis, and patients who tested positive were excluded from further analysis. All coding exons and exon–intron boundaries of *HNF4A*, *GCK*, *HNF1A*, *HNF1B* genes were amplified from genomic DNA and directly sequenced using Sanger sequencing. The amplified products were purified using the Wizard PCR Preps DNA Purification Kit (Promega, Madison, WI, USA) or the Agencourt AMPure XP purification system (Beckman Coulter Genomics, Danvers, MA, USA), and directly sequenced using the BIGDYE TERMINATOR v3.1 Cycle Sequencing Kit (Roche, Basel, Switzerland). They were then analyzed using an ABI PRISM 3100xl automated sequencer (Applied Biosystems, Foster City, CA, USA). When negative, the sequencing of *HNF4A*, *HNF1A* and *HNF1B* was performed using targeted multigene panel analysis combined with multiplex ligation-dependent probe amplification (MLPA) analysis, as previously reported (22–24). Reactions were performed using the SALSA MLPA kit P241 (MRC-Holland, Amsterdam, Netherlands). Pathogenic/likely pathogenic variants were listed according to the 2015 American College of Medical Genetics and Genomics and Association for Molecular Pathology criteria. The nucleotide and protein changes are shown in **Table 1**.

Statistical analysis

The results were expressed as means ± SD. The Mann-Whitney U test was used to assess the significance of the differences between the two groups. The Kruskal-Wallis test was used to detect the significance of differences between three or more groups. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics (version 25.0; IBM Corp., Armonk, NY).

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Table 1. Mutations in the *GCK*, *HNF1A*, *HNF4A* and *HNF1B* genes in the patients

No.	Gene	Location	Nucleotide change	Protein change
1	*K*	Exon 8	c.895 G>C (hetero)*1	p.Gly299Arg
2	*GCK*	Exon 8	c.895 G>C (hetero)*1	p.Gly299Arg
3	*GCK*	Exon 6	c.617 C>T (hetero)	p.Thr206Met
4	*GCK*	Exon 8	c.873 G>C (hetero)	p.Lys291Asn
5	*GCK*	Exon 8	c.895 G>C (hetero)	p.Gly299Arg
6	*GCK*	Exon 5	c.572 G>A (hetero)	p.Arg191Gln
7	GCK	Exon 5	c.572 G>A (hetero)	p.Arg191Gln
8	*GCK*	Exon 7	c.836 837 del AG (hetero)	p.Glu279fs
9	*HNF1A*	Exon 4	c.752 C>T (hetero)	p.Ala251Val
10	*HNF1A*	Exon 7	c.1340 C>T (hetero)	p.Pro447Leu
11	*HNF1A*	Exon 2	c.392 G>A (hetero)	p.Arg131Gln
12	*HNF1A*	Exon 4	c.827 C>A (hetero)	p.Ala276Asp
13	*HNF1A*	Exon 2	c.493 T>C (hetero)	p.Trp165Arg
14	*HNF1A*	Exon 4	c.778 A>T (hetero)	p.Thr260Ser
15	*HNF1A*	Exon. 3	c.607 C>A (hetero)	p.Arg203Ser
16	*HNF1A*	Exon 5	c.1054 del T (hetero)	p.Ser352fs
17	*HNF4A*	Exon 8	c.874 C>T (hetero)	p.Gln292*
18	*HNF4A*	Exon 4	c.335 G>A (hetero)	p.Cys112Tyr
19	*HNF4A*	Exon 8	c.956_958 dup TGC (hetero)	p.Leu319dup
20	*HNF4A*	Intron 3	c.582+2_582+10 del TGAGGATGG (hetero)	p.? (aberrant splicing)
21	*HNF1B*	All exon	Deletion	

MODY, maturity onset diabetes of the young; genes for glucokinase, *GCK*; hepatocyte nuclear factor 1α, *HNF1A*; hepatocyte nuclear factor 4α, *HNF4A*; hepatocyte nuclear factor 1β, *HNF1B*; hetero, heterozygous. The nucleotide and protein changes were based on the following accession numbers: NM_000162.3 for *GCK*, NM_000545.5 for *HNF1A*, NM_175914.4 *HNF4A* and NM_000458.3 for *HNF1B*.

This study was approved by the Ethics Committee of Nihon University Hospital (No. 20220306, March 18, 2022) and performed in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments.

Results

Classification and clinical manifestations in patients with MODY at diagnosis

Of the 55 patients tested for MODY genes, the mutations for MODY were identified in 21 patients (male/female=5/16; screening age, 11.5 ± 1.4 [range: 9–15] yr) (**Fig. 1**). The mutations in MODY genes are shown in **Table 1**. Mutations in *GCK* (MODY2), *HNF1A* (MODY3), *HNF4A* (MODY1), and *HNF1B* (MODY5) were identified in eight, eight, four, and one patient, respectively. Patients 1 and 2 in **Table 1** were members of the same family but were diagnosed with diabetes in different years by urine glucose screening at schools.

The clinical features of patients with MODY at diagnosis are shown in **Table 2**. Female predominance was distinct in patients with MODY3 and 5. There was no statistically significant difference in age and standard deviation score of weight or height between the genetic causes of MODY. Most patients with MODY2 (7 out of 8), were diagnosed with IFG or IGT by OGTT, while most patients with MODY3, 1, and 5 (12 out of 13) were diagnosed with diabetes by OGTT. One patient with MODY3 showed ketonuria, with an FPG level of 320 mg/dL at the time of diagnosis. Patients with MODY5 did not have renal disease, genitourinary tract malformations, or pancreatic hypoplasia at the time of diagnosis.

Family history of diabetes in the first- and second-degree relatives in patients with MODY at diagnosis

A family history of diabetes or identification of hyperglycemia on physical examination in first- and second-degree relatives was found in 16 out of 21 patients (76.2%) at diagnosis: i.e., patients with MODY2: 7 in 8 (87.5%), MODY3: 6 in 8 (75.0%), MODY1: 2 in 4 (50.0%), and MODY5: 1 in 1 (100%). Genetic testing for MODY was performed in eight families. The same mutations were found in seven families: *GCK* in four out of five and *HNF1A* in three out of three families. One patient had a negative genetic testing result in the family.

Comparison of the results of an OGTT and HbA1c levels at diagnosis between patients with MODY2 and those with MODY3, 1, and 5

The patients were classified into two groups according to the genetic causes of MODY: eight patients with MODY2 (Group A) and 13 with MODY 3, 1, and 5 (Group B) because glucose abnormalities are known to be milder in patients with MODY2 than in those with MODY3, 1, and 5. Clinical data, including FPG, 2-hour PG on an OGTT, and HbA1c levels, were compared between the two patient groups: eight patients with

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MODY2 (Group A) and 13 with MODY3, 1, and 5 (Group B).

FPG: There was lack of a significant difference in FPG levels between Group A and Group B (131.9 ± 16.7 mg/dL vs. 175.6 ± 75.3 mg/dL, p = 0.125). Five of eight patients (62.5%) in Group A had an FPG level > 126 mg/dL (diagnostic criteria for diabetes) (20), while 9 out of 13 patients (69.2%) in Group B exceeded this FPG level (**Fig. 2-a**).

2-hour PG on an OGTT: Patients in Group B had significantly higher levels of 2-h PG with an OGTT than those in Group A (274.4 ± 55.7 mg/dL vs. 169.8 ± 18.8 mg/dL, p < 0.001). One (12.5%) out of eight patients in Group A had a 2-hour PG level > 200 mg/dL (diagnostic criteria for diabetes) (20), while four (80.0%) out of five patients in Group B exceeded this PG level. An OGTT was not conducted in eight patients in Group B because they already had FPG levels > 200 mg/dL (**Fig. 2-b**).

HbA1c: Patients in Group B showed significantly higher levels of HbA1c than those in Group A (8.5 ± 1.9% vs. 6.6 ± 0.3%, p = 0.010). Six out of eight patients (75.0%) in Group A had HbA1c levels above 6.5% (diagnostic criteria for diabetes) (20), while 12 out of 13 patients (92.3%) in Group B exceeded this HbA1c level (**Fig. 2-c**).

Comparison of HOMA-IR and HOMA-β with an OGTT examined at diagnosis between patients with MODY2 and those with MODY3, 1, and 5

There was lack of a significant difference in HOMA-IR (1.5 ± 0.7 vs. 2.5 ± 1.4, p = 0.094) and HOMA-β (30.3 ± 11.2 vs. 26.1 ± 13.0, p = 0.461) between Group A and Group B (**Fig. 3-a**, and **Fig. 3-b**). A total of 7 out of 21 patients (33.3%) with MODY, including 1 out of 8 patients (12.5%) in Group A and 6 out of 13 patients (46.2%) in Group B, had HOMA-IR > 2.5; these patients were evaluated as having insulin resistance (21). A total

Table 2. Clinical features in MODY patients at diagnosis

Genetic cause of MODY	N	Male/Female	Age at screening: yr	BMI SDS	Height SDS	Diabetes/IFG, IGT on an OGTT
GCK MODY2	8	3/5	10.4 ± 1.3 (7–12)	0.4 ± 0.5 (–0.3–1.0)	0.2 ± 0.8 (–0.8–1.1)	1/7
HNF1α MODY3	8	1/7	12.3 ± 1.5 (11–14)	0.1 ± 0.6 (–0.5–1.0)	–0.1 ± 0.8 (–1.2–0.8)	7/1
HNF4α MODY1	4	1/3	11.8 ± 1.1 (10–13)	0.4 ± 0.6 (–0.5–1.1)	–0.6 ± 1.1 (–2.2–1.1)	4/0
HNF1β MODY5	1	0/1	12.3	0.3	–1.3	1/0

BMI, body mass index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance. Rages in the parentheses.

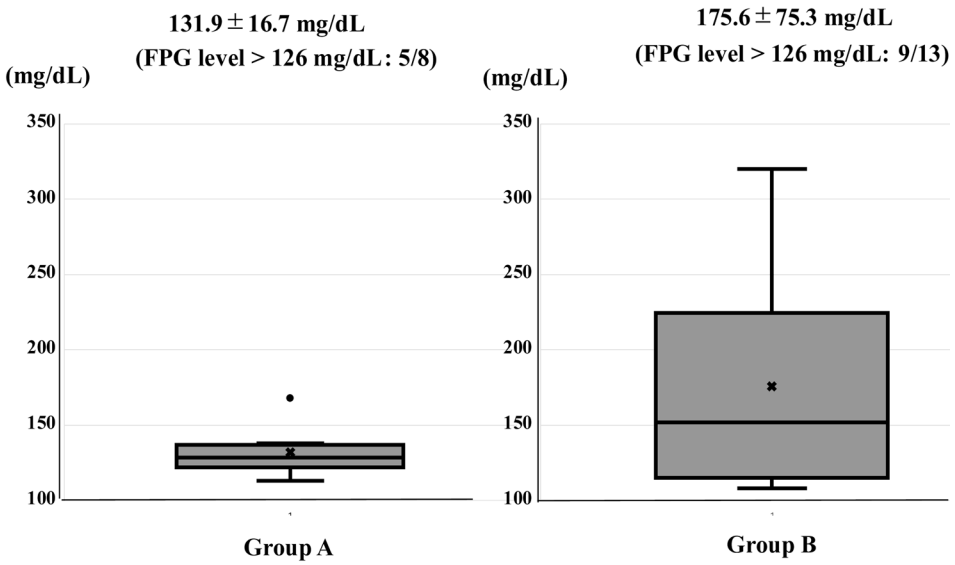

Fig. 2-a. Comparison of FPG levels between patients in Group A (MODY2) and Group B (MODY3, 1, and 5). FPG, fasting plasma glucose.

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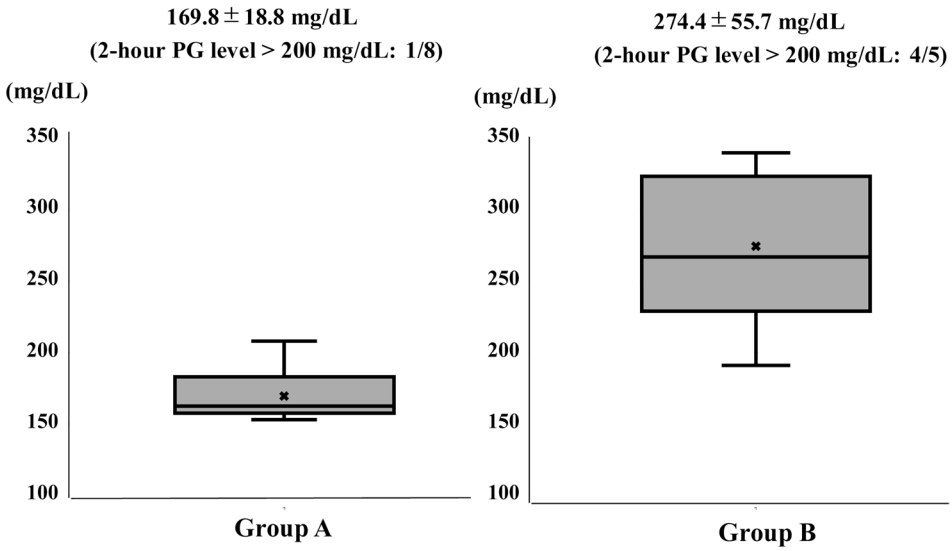

Fig. 2-b. Comparison of 2-hour PG levels on an OGTT between patients in Group A (MODY2) and Group B (MODY3, 1, and 5). PG, plasma glucose; OGTT, oral glucose tolerance test.

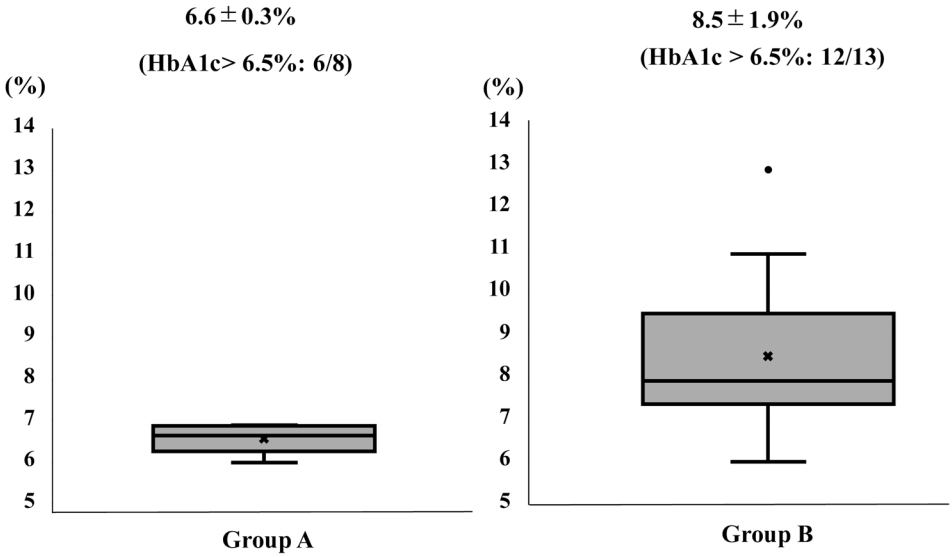

Fig. 2-c. Comparison of HbA1c levels between patients in Group A (MODY2) and Group B (MODY3, 1, and 5). HbA1c. glycosylated hemoglobin. HbA1c levels, expressed as the Japan Diabetes Society (JDS) value, were converted to the National Glycohemoglobin Standardization Program (NGSP) value (reference range for NGSP value: 4.6–6.2%).

of 13 out of 21 patients (61.9%) with MODY, including 4 of 8 patients (50.0%) in Group A and 9 of 13 patients (69.2%) in Group B, had HOMA-β > 30; these patients were evaluated as having sustained β-cell function (21).

Initial treatment

In terms of the initial treatment within one month after diagnosis, all patients in Group A were treated with dietary management (avoiding the intake of excessive calories and carbohydrates) and adequate physical activity without pharmacological treatment; they maintained optimal glycemic control with HbA1c < 7.0%. In contrast, in Group B, the majority of patients (11 out of 13) were treated with oral hypoglycemic drugs or insulin to improve hyperglycemia, i.e., among patients with MODY3, two patients each were treated with diet, exercise, and sulfonylurea (SU), one was treated with a glucagon-like peptide-1 (GLP-1) receptor agonist, and three with insulin. Among the patients with MODY1, one patient each was treated with metformin and a dipeptidyl peptidase-4 (DPP-4) inhibitor, and two with insulin. One patient with MODY5 was treated with insulin. Informed consent for drug use was obtained from all patients. No adverse events occurred following pharmacological treatment in any of the patients in Group B.

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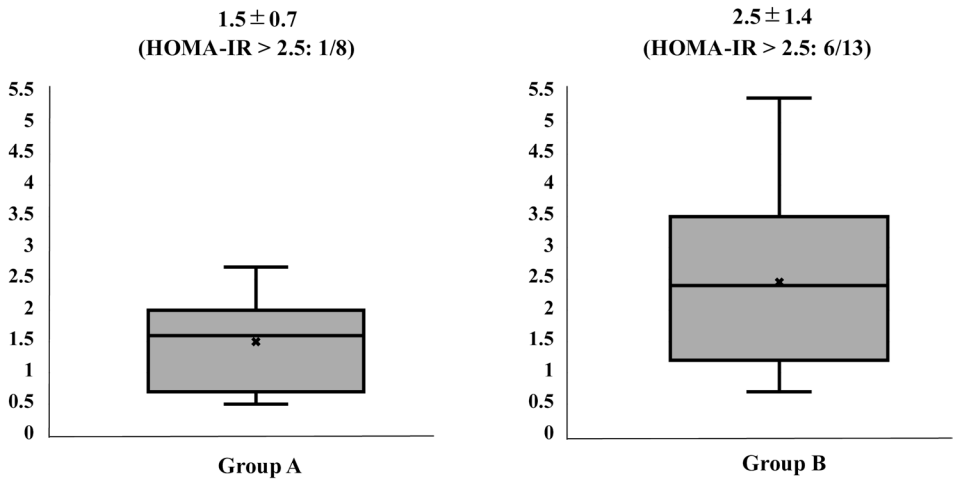

Fig. 3-a. Comparison of HOMA-IR between patients in Group A (MODY2) and Group B (MODY3, 1, and 5). HOMA-IR, the homeostasis model assessment-insulin resistance. HOMA-IR was calculated as FPG (mg/dL) × fasting IRI (μU/mL) / 405, and insulin resistance was evaluated HOMA-IR more than 2.5 (21).

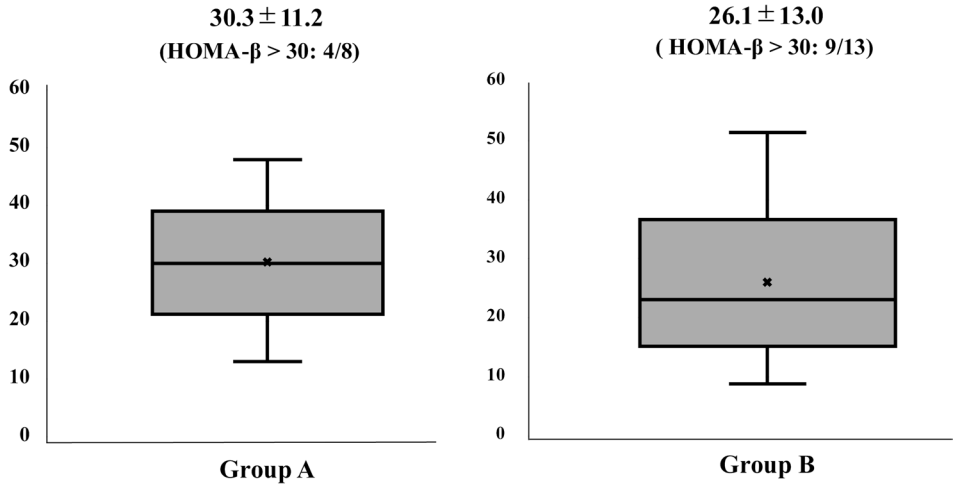

Fig. 3-b. Comparison of HOMA-β between patients in Group A (MODY2) and Group B (MODY3, 1, and 5). HOMA-β, the homeostatic model assessment of beta cell function. HOMA-β was calculated as fasting IRI (μU/mL) × 360 / (FPG–63) mg/dL, and insulin secretory capacity was considered to be maintained in HOMA-β exceeding 30 (21).

Discussion

Most children diagnosed with type 2 diabetes are obese; however, 10–20% are non-obese, which is a notable characteristic reported among Japanese children (13). The clinical features of MODY are similar to those of non-obese type 2 diabetes (7, 8). Accordingly, to confirm the diagnosis, it is necessary to exclude patients with MODY from non-obese patients clinically diagnosed with type 2 diabetes by genetic testing. In the present study, which was conducted on 55 non-obese children clinically diagnosed with type 2 diabetes, IGF, and IGT, 21 were identified as having MODY by genetic testing. This mutation identification rate (38.2%) was similar to that reported in previous studies conducted on Japanese children (22, 23). Urine glucose screening in schools can detect not only a large number of children with type 2 diabetes but also MODY before the progression of diabetes. Genetic testing is essential to distinguish children with non-obese type 2 diabetes from those with MODY in the screening system and could provide appropriate treatment to patients according to the subtypes of diabetes.

The most common type of MODY is reported to be MODY3, as evidenced by its detection in Europe, North America, and Asia (24, 25). In contrast, Yorifuji *et al.* (22, 23) reported that the most common type of MODY among Japanese children was MODY2, followed by MODY3. The present study also showed that the most common type was MODY2 with the same frequency as MODY3. Japanese studies included asymptomatic patients who were detected by chance through urine glucose screening in schools, whereas Caucasian studies mainly examined symptomatic patients for genetic testing, which may be a possible reason for the higher prevalence of MODY2 in Japanese studies. Children with MODY2 usually have

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normoglycemia in their regular lives, however, they sometimes show high FPG levels resulting in glucosuria at urine glucose screening at schools. Therefore, a school-based urine glucose screening system appears to be one of the best tools for identifying patients with MODY2. Most patients with MODY2 cannot be diagnosed without a screening system. On the other hand, MODY3 is likely to be detected by the screening program prior to the progression of diabetes because patients with MODY3 have a low renal threshold for glucose reabsorption due to impaired renal tubular transport of glucose and show a positive result for urine glucose at the screening program even if the PG level is not high (26).

Among the glycemic indicators, FPG did not differ between patients with MODY2 and those with MODY 3, 1, and 5; however, as expected, patients with MODY 3, 1, and 5 had significantly higher levels of 2-hour PG on OGTT and HbA1c than those with MODY2. It is well known that patients with MODY 3, 1, and 5 have more impaired β-cell function, and show higher levels of post glucose-loading PG and HbA1c than those with MODY2 (6–8). However, we showed that some patients with MODY2 had 2-h PG levels > 200 mg/dL and/or HbA1c levels > 6.5%. Kawakita *et al*. (27) also reported that some children with MODY2 had 2-h PG levels on an OGTT > 200 mg/dL, and 79.6% exceeded HbA1c levels by 6.5%. Patients with MODY2 are believed to have mildly elevated FPG levels but normoglycemia after glucose loading, which is compensated for by an increase in insulin secretion to a high PG level (4, 7, 8). However, some Japanese children with MODY2 have mild hyperglycemia under both fasting and postprandial conditions. This hyperglycemia might be caused by the impaired insulin secretion generally observed in Japanese people, in contrast to Caucasians with hypersecretion of insulin in response to increased PG levels (28, 29).

In the present study, 33.3% and 61.9% patients with MODY had overall frequencies of HOMA-IR > 2.5 and HOMA-β > 30, respectively. Yorifuji *et al*. (22) reported that 31.2% and 64.3% children with MODY had HOMA-IR > 2.0 and HOMA-β > 30, respectively, which is similar to our results. Glucose toxicity may have contributed to insulin resistance in these patients. On the other hand, of interest, we found that not only patients with MODY2 but those with MODY3, 1, and 5 relatively sustained β-cell function at screening, i.e., 4 out of 8 patients with MODY2 (50.0%) and 9 out 13 (69.2%) patients with MODY3, 1, and 5 exhibited HOMA-β > 30. Contrarily, it is reported that patients with MODY3 gradually develop β-cell failure, and diabetes is usually identified in adulthood, as they are normoglycemic during childhood (30). However, adolescents with MODY3, 1, and 5 may show elevated glucose levels during puberty due to impaired insulin action caused by an increase in growth and sex hormones (31). Urine glucose screening at schools could detect patients with MODY3, 1, and 5 at the early stage of diabetes before disease progression during adulthood.

Patients with MODY2 do not usually require pharmacological interventions for glycemic control, as demonstrated in the present study. However, Kawakita *et al*. (23) reported that 7 out of 55 patients with MODY2 were treated with oral hypoglycemic drugs: i.e., four with a SU, one with metformin, and two with an α-glucosidase inhibitor over time. In contrast, the present study demonstrated that 11 of 13 patients with MODY3, 1, and 5 required pharmacological treatment to control hyperglycemia within one month after diagnosis. SU is recommended as the first-line treatment for patients with MODY3 and 1; these patients can maintain optimal glycemic control with SU over a long period, although they eventually require insulin treatment (32–34). However, we used other hypoglycemic drugs, such as metformin, a GLP-1 receptor agonist, and a DPP-4 inhibitor, which seem to improve hyperglycemia, as the first-line treatment. We previously reported the efficacy and safety of a GLP-1 receptor agonist in patients with MODY3 (35) and a DPP-4 inhibitor in patients with MODY1 (36) to maintain optimal glycemic control over a long period without adverse events. Another double-blind randomized crossover trial revealed glucose-lowering effects and a low risk of hypoglycemia in patients with MODY3 treated with a GLP-1 receptor agonist (37). Incretin-associated drugs such as GLP-1 receptor agonists and DPP-4 inhibitors may be promising agents for improving hyperglycemia without causing hypoglycemia in patients with MODY 3 and 1. In contrast, patients with MODY5 usually do not respond to SU, and progress to insulin treatment earlier (38). In the present study, patients with MODY5 also required insulin treatment soon after diagnosis. Patients with MODY5 have exon deletions rather than point mutations (39, 40), which may lead to a more severe loss of function (39) and an earlier requirement for insulin treatment. Our patient with MODY5 also exhibited all-exon deletions, which might have resulted in severe hyperglycemia and an earlier requirement for insulin treatment. Correct determination of MODY subtype is important for providing appropriate treatment to patients.

This study had several strengths. First, some Japanese children with type 2 diabetes are non-obese, which is a notable characteristic of the Japanese population, and the clinical features of non-obese type 2 diabetes are similar to those observed in MODY (13, 14, 22, 23). It is difficult to diagnose non-obese type 2 diabetes based solely on clinical characteristics and laboratory data at diagnosis (22, 23). The present study emphasizes the importance of performing genetic testing to distinguish patients with MODY from those clinically diagnosed with type 2 diabetes and to determine the treatment strategy. Second, the identification of the MODY subtype is essential to provide appropriate treatment to patients. We emphasize the usefulness of urine glucose screening in schools to detect patients with MODY at an early stage of the disease and introduce interventions before the progression of diabetes (9–12).

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Third, we suggest a possible effect of incretin-associated drugs, a GLP-1 receptor agonist and a DPP-4 inhibitor, in patients with MODY3 and 1. These drugs can improve hyperglycemia with a low risk of hypoglycemia and might sustain residual β-cell function (35–37), as compared to SU. Large-scale double-blind studies are necessary to confirm the effectiveness and safety of these new drugs in patients with MODY3 and 1.

The present study has some limitations. First, we selected non-obese children clinically diagnosed with type 2 diabetes as candidates for genetic testing for MODY. However, Yorifuji *et al*. (41) reported that 35% of patients with MODY had a BMI above the average (BMI > 50th percentile) and 8.2% were overweight (BMI > 85th percentile). Therefore, genetic testing may be necessary, even for obese children with a strong family history of diabetes, to increase the MODY mutation identification rates. Second, clinical characteristics and laboratory data are influenced by other genetic or environmental factors such as eating habits and lifestyle. These factors may play important roles in determining the clinical manifestations of MODY. Finally, the treatment strategy for children with MODY has not yet been established. Patients clinically diagnosed with type 2 diabetes before 2000 were usually treated with insulin or sometimes with SU, whereas in recent years, we have tried to use a DPP-4 inhibitor and GLP-1 receptor agonist with informed consent. Therefore, treatment options differ according to the time of MODY diagnosis.

In conclusion, we identified some children with MODY at an early stage of diabetes by genetic testing and urine glucose screening at schools. In Japanese patients, it is important to distinguish patients with MODY from those clinically diagnosed with type 2 diabetes. Urine glucose screening in schools appears to be one of the best opportunities to detect MODY earlier and provide appropriate treatment to patients. Specific genetic testing is essential to confirm the diagnosis of MODY; however, the testing is expensive and can only be conducted in a limited number of medical centers and hospitals. Therefore, it is necessary to select appropriate candidates for testing to maximize cost-effectiveness through health economic assessments (3).

Conflict of interests: T.U. received honoraria from Novo Nordisk Pharma Ltd.; Eli Lilly Japan K.K.; Abbott Japan L.L.C.; Terumo Corp.; and JCR Pharmaceuticals Co., Ltd. I. M. received honoraria from MSD Co., Ltd. Novo Nordisk Pharma Ltd. and AbbVie L.L.C.. Other authors have no conflicts of interest to declare.

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