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CD36 deficiency predisposing young children to fasting hypoglycemia

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Abstract

Fatty acid (FA) β-oxidation defects cause hypoglycemia. Our aim was to determine if CD36—a membrane transporter for long-chain FAs—deficiency predisposes children to hypoglycemia. After overnight fasting, we measured parameters for carbohydrate and FA metabolisms at 12-, 14-, and 16-hour fasting points in 51 preschool children with histories of episodic hypoglycemia and 49 age-matched healthy controls. Simultaneously, the expressions of CD36 on platelets and monocytes were examined to determine the phenotypes. Six of the 51 hypoglycemic children and none of the 49 control children were diagnosed as having type I CD36 deficiency. Four and 3 children were diagnosed as having type II CD36 deficiency, respectively. Hypoglycemia was often recurrent in the type I CD36 group. At any fasting point, the type I CD36 group showed significantly lower blood glucose and insulin concentrations than the other groups: glucose, $P < .001$ vs control group and $P < .01$ or $P < .001$ vs type II/wild-type CD36 hypoglycemic groups; insulin, $P < .001$ vs control group and $P < .01$ vs type II/wild-type CD36 hypoglycemic groups. Free FA concentration in the type I group was always 1.5- to 2.0-fold higher than that in the other groups, whereas the total ketone body concentration was consistently about two thirds of that in the other groups. Among the type II, wild-type, and control groups, there were no significant differences in the parameters except that the wild-type group showed significantly lower FFA concentration ($P < .05$). These results suggested that type I CD36 deficiency but not type II CD36 deficiency predisposes preschool children to hypoglycemia.

1. Introduction

CD36 is a multifunctional membrane-associated glycoprotein with a molecular weight of 88 kd [1-5]. CD36 is a receptor for collagen and thrombospondin on platelets and oxidized low-density lipoproteins on macrophages [1-4]. CD36 also plays an important role in the uptake of long-chain fatty acids (LCFAs) in the heart, skeletal muscle, adipose tissue, and small intestine [5].

Based on its expression patterns on platelets and monocytes, CD36 deficiency is classified into 2 subgroups: type I and II [6]. Type I CD36 deficiency lacks CD36 expression on

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both cell types, whereas type II CD36 deficiency lacks expression only on platelets. Most type I cases are either homozygous or compound heterozygous for CD36 gene mutations, whereas type II cases are often free of CD36 gene mutations [7-9]. CD36 deficiency is one of the common genetic disorders in Japan [9-10]. As the metabolic manifestations of CD36-deficient adult subjects, decreased insulin sensitivity and postprandial hypertriglyceridemia have been reported [10-13]. However, for children, its clinical manifestations and the prevalence have been scarcely studied [14,15].

Hypoglycemia is highly prevalent in children, but its underlying disease or condition cannot be identified in most cases [16-18]. Children with fatty acid (FA) β-oxidation defects often show profound hypoglycemia [19].

The present study aimed to elucidate whether CD36 deficiency is attributable to the development of hypoglycemia in young children as other FA β-oxidation defects. We examined the prevalence of CD36 deficiency among preschool children with histories of hypoglycemia and examined the glucose and FA metabolism in them with special reference to CD36 phenotype.

2. Subjects and methods

2.1. Subjects

From 2004 to 2008, we prospectively screened 198 consecutive preschool children brought to our local affiliated hospitals for unconsciousness and/or seizures in the morning (Fig. 1).

Fifty-three children (23 girls and 30 boys, aged 1.8-5.2 years) were found to have hypoglycemia. Their blood glucose (BG) concentrations were only 25 to 42 mg/dL. Blood gas analyses revealed that their base excess ranged from −2.7 to −6.1 mEq/L. All these children had bradycardia or tachycardia with excessive sweating, suggesting hypoglycemia-induced autonomic responses. Their symptoms disappeared immediately after intravenous glucose infusions.

The 53 children were referred to our institutions for further examinations at 1 to 3 months after their episodes of hypoglycemia. At the time of admission for an extended fasting test, their ages were 2.1 to 5.5 years; and they were free of symptoms suggestive of any disorders. As age-matched healthy controls, we enrolled 49 children (22 girls and 27 boys) aged 2.1 to 4.6 years.

Both hypoglycemic and control children had no medical problems during their newborn and infancy periods and had grown completely healthy. There were no significant differences in birth weight and gestational age between both children: hypoglycemic children—2673 to 3462 g and 37 to 41 weeks; control children—2790 to 3369 g and 38 to 40 weeks.

Informed consent was obtained from the parents before enrolling these children in this study. The protocol was approved by the medical ethics committees of the participating institutions.

2.2. Study design

Firstly, we excluded children with metabolic or hormonal diseases that cause hypoglycemia. To diagnose hyperinsulinemia; hyperthyroidism; growth hormone deficiency; FA β-oxidation disorders; organic acidemia; fructose-1,6-diphosphatase deficiency; and glycogen storage disease, we specifically examined the profiles of blood amino acids and acylcarnitine, and blood concentrations of ammonia, lactate, insulin, growth hormone, insulin-like growth factor–1, free thyroxine, free thyronine, thyroid-stimulating hormone, and cortisol. We also examined profiles of urinary organic acids.

Secondly, the children with histories of hypoglycemia were divided into 3 subgroups according to the CD36 expression patterns on the platelets and monocytes by flow cytometry: Type I CD36, type II CD36, and wild-type hypoglycemic groups. The CD36 expression patterns in the control children were also examined.

For the 3 hypoglycemic groups and the control group, extended fasting tests were performed. At 7:00 to 7:30 PM on the day before blood sampling, we provided the children with suppers containing one third of the daily required calories for children of these ages. Fasting blood samples were collected from cubital veins for biochemical assays 3 times in the morning (12, 14, and 16 hours after supper). Body weight and height SD scores were also recorded for all enrolled children.

2.3. Biochemical assays

Fasting BG and insulin concentrations were determined by an enzymatic method and an enzyme immunoassay using a commercial kit (TOSOH-II; Tosoh, Tokyo, Japan), respectively. Serum total cholesterol and triglycerides were measured enzymatically using an automated analyzer. Low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were determined by homogenous assays. Serum concentrations of free FA (FFA) and total ketone bodies (TKB) were measured by enzymatic methods using commercial kits (NEFA-SS kit EIKEN; Eiken Chemicals, Tokyo, Japan, and Total-ketone body kit; Kainos Laboratories, Tokyo, Japan, respectively). Acylcarnitine profiles were examined by tandem mass spectrometry as described previously [20].

2.4. CD36 phenotyping

Phenotypes of CD36 were determined by flow cytometry using platelets and monocytes as described previously [6]. Fasting venous blood was drawn into a tube containing EDTA-K_2 to prepare platelet-rich plasma (PRP). In monocyte assays, PRP was processed in a Multi-Q-Prep (Coulter, Miami, FL) for hemolysis and fixation. The prepared PRP was then mixed with a fluorescein isothiocyanate (FITC)–conjugated monoclonal antibody (Mab) (FA6-152; Immunotech, Miami, FL) [6]. To detect CD36 expressions on platelets or monocytes, the CD36 signal was gated with either a phycoerythrin-conjugated anti-CD42b Mab (AN51; Dako, Copenhagen, Denmark) using an EPICS Profile II flow cytometer (Coulter, Miami, FL) or an

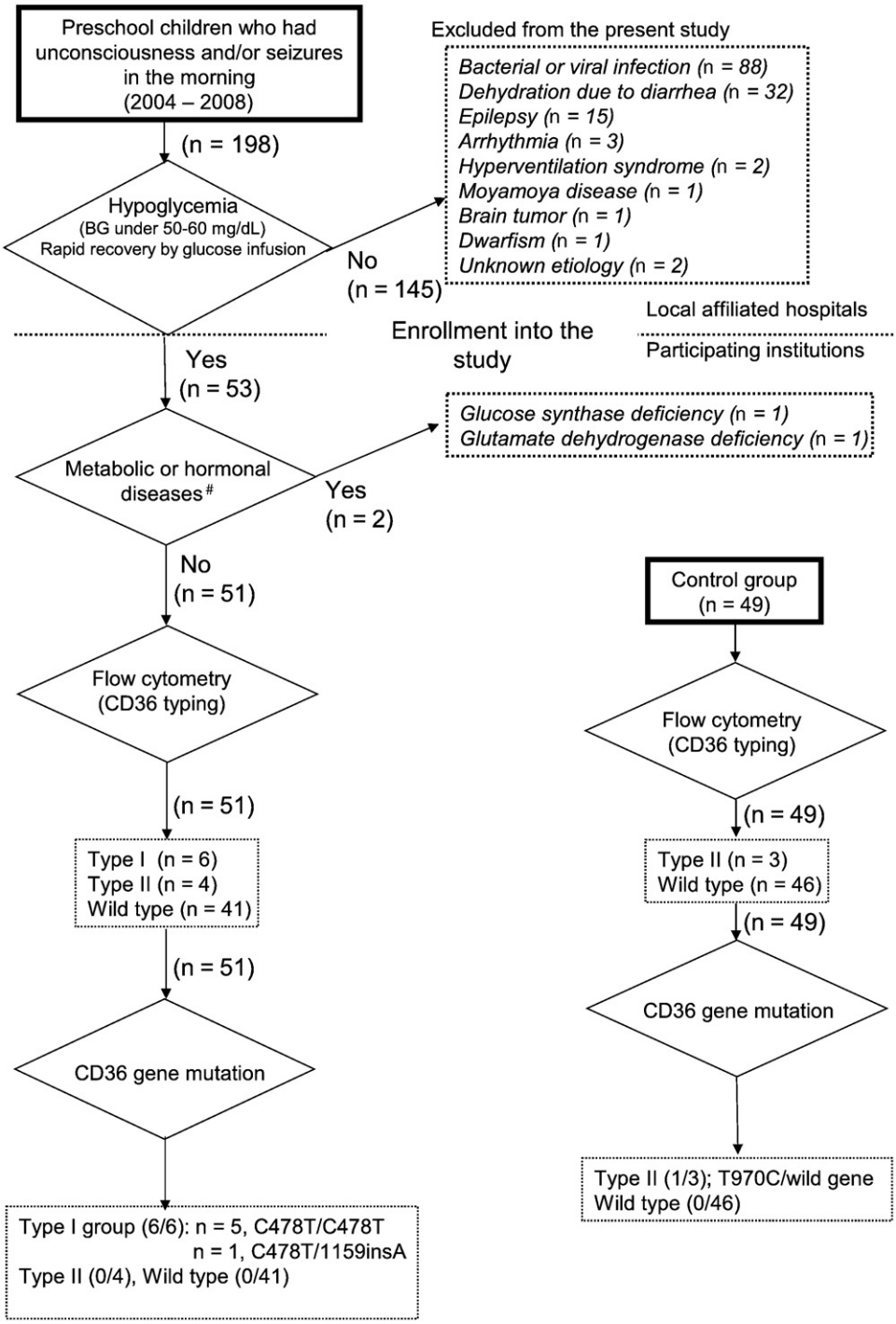

Fig. 1. Flowchart for classifying hypoglycemic children. #Profiles of blood amino acids and acylcarnitine, plasma ammonia, and lactate levels were measured. Insulin, growth hormone, insulin-like growth factor–1, free thyroxine, free thyronine, thyroid-stimulating hormone, and cortisol were also examined to detect endocrinologic disorders leading to hypoglycemia.

FITC-conjugated anti-CD14 Mab (MY4-FITC, Coulter) using an XL-MCL flow cytometer (Coulter).

2.5. CD36 gene analysis

In children with types I or II CD36 deficiencies, 3 common mutations of the CD36 gene, irrespective of histories with hypoglycemic episodes, were determined: (*a*) a substitution of T for C at nt 478 in exon 4 (C478T), (*b*) an AC deletion at nt 539 in exon 5 (539delAC), and (*c*) an A insertion at nt 1159 in exon 10 (1159insA) [7-9,14]. A previous study showed that 478T mutation impairs the maturation of the CD36 precursor, leading to CD36 defects on both platelets and macrophages [7]. Both

539delAC and 1159insA mutations cause a frame shift of the CD36 gene, resulting in the formation of a stop codon and a marked reduction in the CD36 messenger RNA level [8,21]. DNA was extracted from whole blood and amplified by polymerase chain reaction. The polymerase chain reaction products were digested with endonuclease, electrophoresed on a 4% NuSieve GTG agarose gel (FMC Bioproducts, Rockland, ME), and stained with ethidium bromide for restriction fragment length polymorphism analysis.

When these common mutations were not detected, we directly determined the sequences covering all exons and exon-intron boundaries [22].

2.6. Statistical analysis

Values between groups were compared using the Mann-Whitney *U* test. Values at 2 time points within the group were compared using the 1-factor analysis of variance test. Changes in parameters (Δ values) between 2 time points among the groups were compared using the Mann-Whitney *U* test. All *P* values < .05 were considered significant.

3. Results

3.1. Prevalence of CD36 deficiency

Of 53 children with histories of episodic hypoglycemia, 2 were diagnosed with glycogen synthase and glutamate dehydrogenase deficiencies, respectively, which were confirmed by gene analyses (Fig. 1). The parents of the child with glycogen synthase deficiency were first cousins.

The remaining 51 children without any abnormalities in hormones, metabolic profiles, and muscle enzymes such as creatine kinase and aldolase were divided into 3 hypoglycemic groups: type I, type II, and wild-type groups. The numbers of type I, type II, and wild-type among these children were 6 (2 girls and 4 boys), 4 (2 girls and 2 boys), and 41 (18 girls and 23 boys), respectively. Accordingly, the prevalence of type I and II deficiencies were 11.8% and 7.8%, respectively.

Of the 49 healthy control children, 3 children (2 girls and 1 boy) exhibited the expression pattern of type II CD36 deficiency (6.1%); but no one showed that of type I deficiency.

3.2. Gene mutations of CD36 deficiency

Of the 6 children with type I CD36 deficiency, 5 were homozygous for the C478T mutation and 1 was compound heterozygous for C478T/1159insA. Of the 7 children with type II CD36 deficiency, 1 girl in the control group had a heterozygous T970C mutation (a substitution of C for T at nt 970 in exon 9) in CD36 gene reported by Hanawa et al (Fig. 1) [22].

3.3. Comparisons of clinical features

In general, the clinical features of children with type I CD36 deficiency were similar to those of control children as well as to those of other children with episodic hypoglycemia. However, the number of hypoglycemic episodes in the type I group was significantly greater than that in the other groups. It should also be noted that the wild-type CD36 hypoglycemic group showed lower body weight SD scores than the other 3 groups (Table 1).

3.4. Effects of extended fasting on glucose and FA metabolism

Blood glucose concentrations were always significantly lower in the type I CD36 group than in the other 2 hypoglycemic groups (type II CD36 deficiency and wild-type groups) and the control group (Fig. 2A, left panel).

Table 1
Characteristics of the hypoglycemic and control groups

Group	Hypoglycemic group (n = 51)				Controls (n = 49)
	Type I[a] (n = 6)	Type II[a] (n = 4)	Wild type[a] (n = 41)	Total (n = 51)	
Age, y	3.2 ± 0.7	3.8 ± 1.0	3.7 ± 0.6	3.6 ± 0.7	3.3 ± 0.3
Sex, F/M	2/4	2/2	18/23	22/29	22/27
No. of episodes, ranges	1.9 ± 0.5† (1–4)	1.0 ± 0 (1)	1.2 ± 0.3 (1–2)	1.3 ± 0.4	0
BW SD score	−0.4 ± 0.5	−0.1 ± 0.7	−0.9 ± 0.5*	−0.6 ± 0.7	0.2 ± 0.6
Ht SD score	0.1 ± 0.6	−0.2 ± 0.6	0.3 ± 0.6	0.2 ± 0.6	0.4 ± 0.6
Total protein, g/dL	6.8 ± 0.2	6.9 ± 0.3	6.6 ± 0.2	6.7 ± 0.2	6.8 ± 0.3
Albumin, g/dL	3.9 ± 0.2	4.0 ± 0.2	3.9 ± 0.2	3.9 ± 0.2	4.1 ± 0.2
AST, IU/L	19 ± 3	17 ± 4	16 ± 3	17 ± 3	16 ± 5

Values are mean ± SD. BW indicates body weight; Ht, height; AST, aspartate aminotransferase.

[a] Hypoglycemic group was classified into 3 subgroups according to CD36 phenotypes: type I CD36 deficiency (type I), type II CD36 deficiency (type II), and wild-type groups.

* $P < .05$ vs controls (Mann-Whitney *U* test).

† $P < .001$ vs controls (Mann-Whitney *U* test).

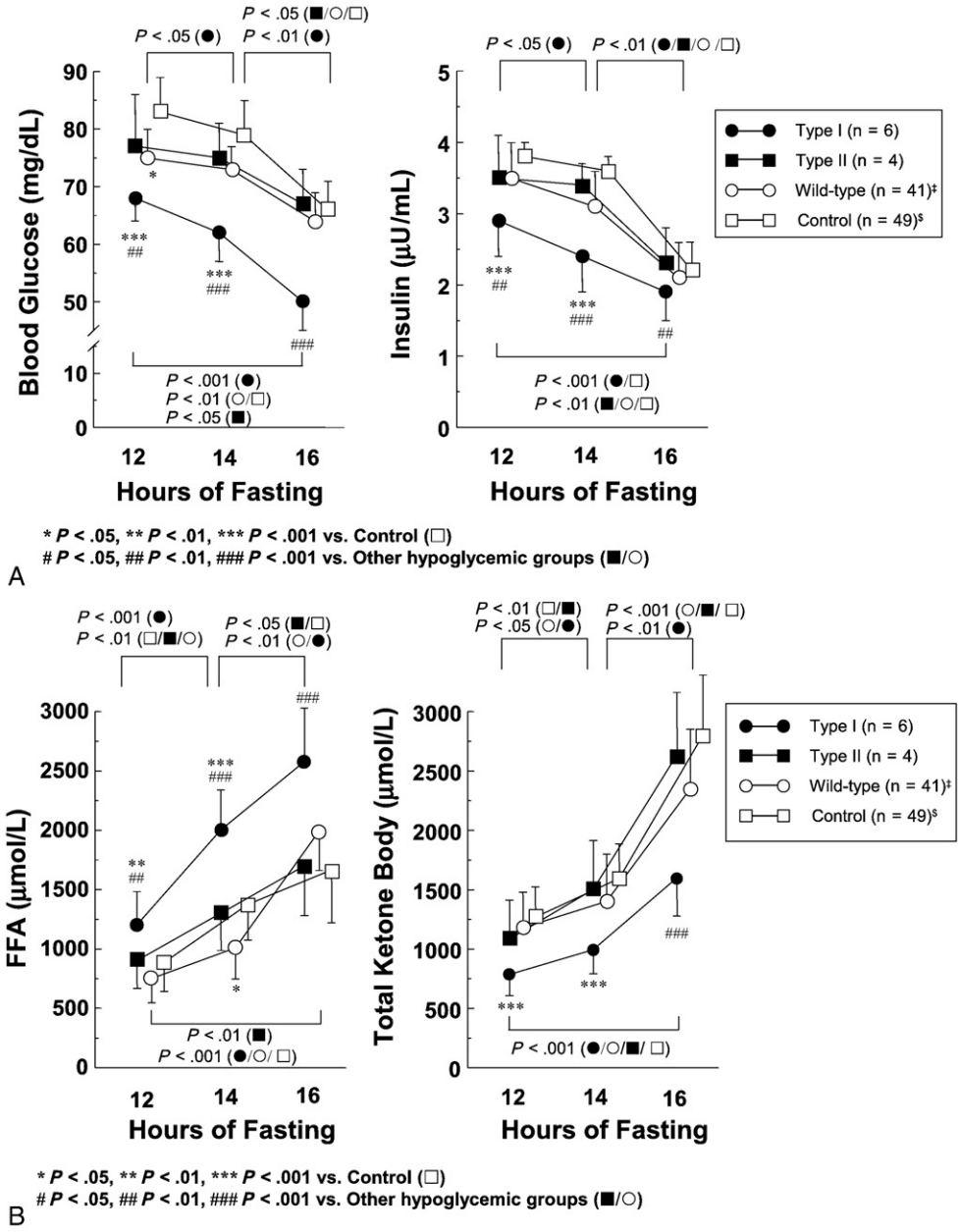

Fig. 2. Differences in BG, insulin, FFAs, and TKB concentrations at the 12-, 14-, and 16-hour fasting points. Children were not allowed to ingest any food or drink after supper on the day before blood sampling. [#]Data obtained from 24 of the 41 wild-type group children are presented. [$]Data obtained from 17 of the 49 control group children are presented.

After 16 hours of fasting, BG concentrations in the type I CD36 deficiency group were less than 50 mg/dL. Serum insulin concentrations showed results similar to those of BG concentrations (Fig. 2A, right panel).

The FFA concentrations were always significantly higher in the type I CD36 group than in the other 3 groups (Fig. 2B, left panel). The ΔFFA between 12 and 14 hours was larger in the type I CD36 deficiency group ($P < .001$) than in the other 3 groups ($P < .01$).

The TKB concentrations were always lower in the type I CD36 group than in the other 3 groups. The last 2 hours of fasting induced a great increase in TKB in all the groups. However, the ΔTKB was significantly smaller in the type I CD36 group ($P < .01$) than in the other groups ($P < .001$) (Fig. 2B, right panel).

Unlike type I CD36 group, these parameter levels in the type II CD36 group were consistently similar to those in the wild-type and control groups and did not show any significant differences.

At any fasting point, serum lipid concentrations were not significantly different among the groups. Triglyceride concentration but not other lipid concentrations exhibited

Table 2
Serum lipid concentrations at 12, 14, and 16 hours of fasting in the hypoglycemic and control groups

Group	Hypoglycemic group (n = 51)									Controls (n = 49)		
Subgroup	Type I (n = 6)			Type II (n = 4)			Wild type (n = 41)					
Hours of fasting	12	14	16	12	14	16	12	14	16[a]	12	14	16[b]
TC	152 ± 20	149 ± 22	144 ± 19	155 ± 17	151 ± 20	147 ± 22	142 ± 11	138 ± 12	137 ± 10	151 ± 13	149 ± 12	145 ± 8
TG	53 ± 15	49 ± 9	44 ± 12†	56 ± 17	49 ± 15	47 ± 15*	51 ± 12	47 ± 10	44 ± 10†	51 ± 10	47 ± 10	45 ± 8†
HDL-C	56 ± 12	56 ± 11	54 ± 9	55 ± 10	57 ± 9	55 ± 9	56 ± 10	55 ± 10	56 ± 11	56 ± 14	55 ± 13	55 ± 12
LDL-C	85 ± 13	82 ± 11	81 ± 11	89 ± 16	83 ± 14	81 ± 15	80 ± 19	77 ± 15	74 ± 15	80 ± 13	78 ± 11	77 ± 11

Values are mean ± SD (in milligrams per deciliter). At any fasting point, there were no significant differences in lipid concentrations between each 2 groups (Mann-Whitney *U* test). Triglyceride concentrations but not other lipid concentrations exhibited significant changes between the 12- and 16-hour fasting points in respective groups:*$P < .05$ and †$P < .01$ (1-factor analysis of variance test). There were no significant differences in changes in lipid concentrations (Δ values) between 2 fasting points among the groups (Mann-Whitney *U* test). TC indicates total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

[a] Data obtained from 24 of the 41 wild-type children were presented.

[b] Data obtained from 17 of the 49 controls were presented.

significant changes between the 12- and 16-hour fasting points in the respective groups (Table 2).

4. Discussion

The present study showed that fasting BG concentration was lower in preschool children of type I CD36 deficiency than in children of type II/wild-type CD36 hypoglycemic groups and control children.

Type I CD36 deficiency accounted for 11.8% of 51 children with histories of hypoglycemia but was not diagnosed in the 49 age-matched control children without histories of hypoglycemia. On the other hand, the prevalence of type II CD36 deficiency was not different between the hypoglycemic and control children. According to earlier reports, the prevalence of type I CD36 deficiency in the general Japanese population is 0.5% to 1.0% [9-10,15]. It is, therefore, plausible that this deficiency is highly prevalent among hypoglycemic children. However, the children groups enrolled in this study were too small to define the reliable prevalence. To gain more informative data, more extensive studies would be essential.

Besides fasting BG level, fasting insulin, TKB, and FFA concentrations in type I CD36 group were different from those in the other groups. We found that fasting insulin and TKB concentrations were significantly lower in the type I group than in the other groups, whereas the fasting FFA level was significantly higher in the type I group. These differences were more prominent as the fasting time was extended (Fig. 2A, B).

High FFA levels at the fasting state can probably be attributed to impaired FFA uptake by skeletal and heart muscles in type I CD36 deficiency. Free FA is used as an energy source in skeletal and heart muscles, as well as in the liver. Long-chain FAs enter cells either by passive diffusion or by transporter-dependent uptake. In humans, there are 3 transporters for LCFA: CD36, plasma membrane-associated FA binding protein (43 kd), and FA transport protein (FATP, 63 kd) [23–25]. Although plasma membrane-associated FA binding protein and FATP are expressed in the liver as well as skeletal and heart muscles, CD36 is expressed in skeletal and heart muscles, but not in the liver. Most serum LCFAs are bound to albumin. CD36 promotes the dissociation of LCFA from albumin, which results in increased passive diffusion of LCFA [24]. Furthermore, CD36 is coexpressed with FATP in skeletal and heart muscles [24]. This colocalization strongly suggests that the FATP-mediated uptake of LCFA is promoted by an interaction with CD36 in skeletal and heart muscles. In patients with type I CD36 deficiency, the radiolabeled LCFA analog ^{123}I-15-(*p*-idiophenyl)-(*R,S*)-methylpentadecanoic acid (BMIPP) does not accumulate in heart muscles; and BMIPP clearance from the circulation is delayed [5]. Furthermore, the oxidation rate of LCFA is reduced by 40% to 60% in the isolated hearts of CD36-deficient mice [25]. These observations agree well with our hypothesis.

In skeletal and heart muscles, impaired FA uptake in CD36 deficiency is probably compensated by shifting the energy supply from FA dominant to glucose dominant. In fact, CD36-deficient rats had high glucose oxidation rates and maintained normal myocardial functions [26]. If this is the case in humans, it would be a rationale for the increased susceptibility of CD36-deficient children to hypoglycemia in the fasting state. Similar to CD36-deficient children, CD36-deficient rats had higher serum FFA concentrations; and their BG concentrations were lower than those observed in control rats [27].

Nevertheless, the findings obtained from this study were not consistent with those in CD36-deficient adults described in earlier reports [10-13]. It has been shown that CD36 deficiency predisposes one to insulin resistance and the subsequent hyperglycemia. Most of the subjects described in such reports were older than 30 years, and young subjects have been scarcely examined. Yanai et al [14] previously reported increased insulin sensitivity in young adults with CD36 deficiency, suggesting different effects of CD36 deficiency on carbohydrate metabolism by age. To gain a

better understanding of the relationship between CD36 deficiency and insulin sensitivity, we will perform more extensive studies covering large groups of children and adolescents.

The energy demands of young children exhibiting rapid growth and development are quite high. Their glucose and FA metabolisms must be greatly activated. In fact, ketone body synthesis via FA β-oxidation is far greater in young children than in adults [19,28]. Therefore, impaired FA metabolism must have a more serious effect in children than in adults, although both have the same genetic disorder (CD36 deficiency).

The reason for the low TKB levels in type I CD36 deficiency remains to be elucidated. Ketone bodies are generated mainly in the liver and secreted into the blood circulation. The substrate of ketone bodies is acetyl–coenzyme A, which is a product of FA β-oxidation. From this context, we speculated that decreased FA β-oxidation in heart and muscles led to the limited synthesis of ketone body from acetyl–coenzyme A. In type I CD36 deficiency, hepatic uptake of BMIPP (an analog of LCFA) is nearly double [5], probably because CD36 is naturally absent in normal liver and the other transporters play significant roles in hepatic uptake of LCFA [23-25]. As a whole, ketone body synthesis along with FA β-oxidation in type I CD36 deficiency was substantially but not definitely reduced.

The results of this study suggested that type I CD36 deficiency predisposes preschool children to hypoglycemia. If this is true, affected children should avoid long-time fasting and excess exercise without sugar supplementation.

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