

Original Article

Relation between Delayed Superfluous Insulin Secretion during An Oral Glucose Tolerance Test and Metabolic Disorders in Obese Japanese Children

Hidetoshi Sato^{1,2}, Toru Kikuchi², Waka Harada¹, Hiroshi Yoshida¹, Sueshi Ito¹, and Makoto Uchiyama²

¹Department of Pediatrics, Shonai Hospital, Tsuruoka, Japan

²Division of Pediatrics, Department of Homeostatic Regulation and Development, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Abstract. The aim of this study was to clarify the relation between postprandial hyperinsulinemia and metabolic disorders in obese children. Twenty-eight obese Japanese children (8.8–16.2 yr) were divided into four groups: without impaired liver function and dyslipidemia (Group A), with impaired liver function (Group B), with dyslipidemia (Group C), and with impaired liver function and dyslipidemia (Group D). The levels of PG, serum immunoreactive insulin (IRI) and serum C-peptide (CPR) were measured during an oral glucose tolerance test (OGTT). The subjects had delayed superfluous insulin and CPR secretion during the OGTT compared with healthy references. In regard to the insulin secretion pattern, Group A's response peaked at 60 min and then decreased gradually until 120 min, Group B's response peaked at 60 min, remained at the peak until 120 min and then decreased gradually until 180 min, Group C's response peaked at 120 min and then decreased gradually until 180 min, and Group D's response peaked at 120 min and remained at the peak until 180 min. These results suggest that delayed superfluous insulin secretion during an OGTT is related to metabolic disorders in obese Japanese children and that these patients will experience a vicious cycle of postprandial hyperinsulinemia and metabolic disorders. It is important to prevent healthy children from becoming obese and to improve management of childhood obesity.

Key words: postprandial hyperinsulinemia, delayed superfluous insulin secretion, oral glucose tolerance test, obese children

Introduction

Postprandial hyperinsulinemia causes various metabolic disorders, more so than fasting hyperinsulinemia, in early or mild obesity or metabolic syndrome. Many studies have reported that the postprandial delayed superfluous insulin secretion is related to arteriosclerosis in adulthood obesity (1, 2). Kendorick *et al.* argued that insulin resistance appears to be a causal factor for the development of early occlusive atherosclerosis

Received: October 19, 2010

Accepted: November 26, 2010

Correspondence: Dr. Hidetoshi Sato, Division of Pediatrics, Department of Homeostatic Regulation and Development, Niigata University Graduate School of Medical and Dental Sciences, Niigata 950-2181, Japan

E-mail: totsutotsu118@hotmail.co.jp

and proposed that postprandial insulin resistance, in association with raised levels of cortisol and catecholamines, plays a major role, and may even be the primary causative factor (3). Kawamori *et al.* reported that the intimal plus medial thickness was found to be increased in hyperinsulinemic individuals with impaired glucose tolerance compared with control individuals with normal glucose tolerance. These studies argue in favor of a link between insulin resistance and arteriosclerosis, as fasting and postprandial hyperinsulinemia are largely determined by the severity of insulin resistance in nondiabetic obese adults (4).

In regard to childhood obesity, Burrows reported that low insulin sensitivity in prepubescent and pubescent obese children is associated with central obesity and a higher cardiovascular risk (5). However, few studies have reported on the relation between postprandial hyperinsulinemia and metabolic disorders in obese children.

Thus, the present study sought to clarify the relation between postprandial hyperinsulinemia and metabolic disorders in obese children. Using the oral glucose tolerance test (OGTT), we investigated how insulin secretion patterns are related to metabolic disorders in obese Japanese children with the hope that the results of this study would contribute to understanding the role that postprandial hyperinsulinemia plays in metabolic disorders of childhood obesity.

Subjects and Methods

This study examined 28 obese Japanese children (16 boys, 12 girls; aged 8.8–16.2 yr) who visited the Department of Pediatrics, Shonai Hospital. No subjects had known endocrine disorders or diabetes. Body height and weight were measured with a portable stadiometer and a digital scale to the nearest 1 mm and 0.1 kg, respectively. Percentage of overweight (POW) was calculated by using age- and sex-specific body weight for height of Japanese children (6);

$POW = [\text{measured body weight} - \text{standard body weight}] / \text{standard body weight}$.

An OGTT (glucose load of 1.75 g/kg, maximum 75 g) was carried out for all subjects. The levels of PG, serum immune-reactive insulin (IRI) and serum C-peptide (CPR) at preloading (0) and at 60, 120 and 180 min after loading were measured, and areas under the concentration-time curves from 0 to 180 min were calculated. The levels of alanine aminotransferase (ALT), total cholesterol (Tchol), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and hemoglobin A1c (HbA1c) were also measured.

We then compared the PG, IRI and CPR levels during the OGTT of the subjects with those of healthy children (7, 8). The subjects were divided into four groups: Group A, which was comprised of subjects without impaired liver function and dyslipidemia; Group B, which was comprised of subjects with only impaired liver function; Group C, which was comprised of subjects with only dyslipidemia; and Group D, which was comprised of subjects with both impaired liver function and dyslipidemia. Impaired liver function was defined as an ALT level >31 IU/L, and dyslipidemia was defined as a TG level >120 IU/L and/or a HDL-C level <40 mg/dl.

Informed consent was obtained from the parents and guardians of all subjects. The Ethics Committee of the Shonai Hospital approved the study protocol.

Statistical analysis was performed by Mann-Whitney's U-test to determine differences between two groups and by the Kruskal-Wallis test to determine differences between the four groups. P values less than 0.05 were considered significant. Stat View for Windows (version 5.0; Abacus Concepts, Berkeley, CA, USA) was used for data analysis.

Results

The clinical characteristics of the obese subjects in this study are shown in Table 1. The mean ALT level was significantly higher for boys

Table 1 Physical characteristics and biochemical parameters by sex in 28 obese children

	all subjects, n=28			boys, n=16			girls, n=12			
	Means \pm SD	min	max	Means \pm SD	min	max	Means \pm SD	min	max	
Age (yr)	13.0 \pm 2.2	8.8	16.2	12.3 \pm 1.9	8.9	15.9	13.8 \pm 2.5	8.8	16.2	
POW(%)	60.6 \pm 14.5	42.7	98.2	61.3 \pm 12.0	42.7	81.9	59.7 \pm 17.9	45.1	98.2	
BMI (kg/m ²)	30.8 \pm 4.0	24.7	40.0	30.5 \pm 3.4	25.2	36.7	31.3 \pm 4.8	24.7	40.0	
ALT (IU/l)	49.1 \pm 52.8	9.0	246.0	64.1 \pm 58.4	17.0	246.0	29.3 \pm 37.8	9.0	146.0	
Tchol (mg/dl)	171.8 \pm 30.7	120.0	250.0	170.7 \pm 28.9	120.0	215.0	173.2 \pm 34.1	125.0	250.0	
TG (mg/dl)	115.8 \pm 82.4	41.0	419.0	108.3 \pm 72.4	41.0	329.0	125.9 \pm 96.6	52.0	419.0	
HDLC (mg/dl)	53.1 \pm 9.8	36.0	78.0	52.8 \pm 10.9	36.0	78.0	53.6 \pm 8.6	40.0	68.0	
HbA1c (JDS) (%)	4.9 \pm 0.4	3.8	5.4	4.9 \pm 0.4	4.2	5.4	4.9 \pm 0.5	3.8	5.4	
HOMA-R	5.9 \pm 3.4	1.3	15.0	6.2 \pm 4.2	1.3	15.0	5.4 \pm 1.8	2.4	7.7	
PG										
0 (mg/dl)	92.6 \pm 5.9	82.0	104.0	92.8 \pm 6.3	82.0	104.0	92.4 \pm 5.6	83.0	104.0	
60 (mg/dl)	136.1 \pm 27.4	96.0	222.0	138.1 \pm 25.1	100.0	204.0	133.3 \pm 31.0	96.0	222.0	
120 (mg/dl)	129.0 \pm 17.4	101.0	182.0	129.8 \pm 16.1	107.0	182.0	128.0 \pm 19.7	101.0	167.0	
180 (mg/dl)	100.3 \pm 16.9	61.0	133.0	100.7 \pm 18.6	61.0	133.0	99.8 \pm 15.2	77.0	131.0	
Σ PG	180 (mg/dl)	458.0 \pm 45.6	369.0	624.0	461.4 \pm 31.7	421.0	539.0	453.5 \pm 60.9	369.0	624.0
IRI										
0 (μ U/ml)	25.4 \pm 13.9	5.3	59.4	26.5 \pm 17.1	5.3	59.4	24.0 \pm 8.3	10.3	37.0	
60 (μ U/ml)	155.3 \pm 122.2	23.5	698.0	167.9 \pm 150.0	66.5	698.0	138.4 \pm 73.7	23.5	249.0	
120 (μ U/ml)	171.2 \pm 150.0	29.0	787.0	177.4 \pm 174.8	32.5	787.0	163.0 \pm 115.8	29.0	344.0	
180 (μ U/ml)	80.5 \pm 63.0	3.7	250.0	84.0 \pm 70.1	3.7	250.0	75.9 \pm 54.7	24.7	179.0	
Σ IRI	180 (μ U/ml)	432.4 \pm 308.5	143.4	1,695.4	455.8 \pm 364.5	201.9	1,695.4	401.2 \pm 224.8	143.4	788.1
CPR										
0 (ng/ml)	3.3 \pm 1.2	1.9	6.1	3.5 \pm 1.4	1.9	6.1	3.1 \pm 0.9	1.9	4.6	
60 (ng/ml)	11.1 \pm 3.9	4.4	25.5	11.8 \pm 4.2	7.5	25.5	10.2 \pm 3.5	4.4	15.0	
120 (ng/ml)	12.3 \pm 5.2	4.5	28.9	12.7 \pm 5.6	7.6	28.9	11.7 \pm 4.9	4.5	18.9	
180 (ng/ml)	8.0 \pm 3.6	2.0	19.0	8.3 \pm 4.1	2.0	19.0	7.6 \pm 3.0	3.8	12.5	
Σ CPR	180 (ng/ml)	34.7 \pm 12.1	17.0	71.0	36.3 \pm 12.9	22.7	71.0	32.5 \pm 11.1	17.0	48.0

POW; percent of overweight, BMI; body mass index, ALT; alanine aminotransferase, Tchol; total cholesterol, TG; triglyceride, HDLC; high density lipoprotein cholesterol, HbA1c; glycohemoglobin A1c, HOMA-R; homeostasis model assessment insulin resistance, IRI; immuno-reactive insulin, CPR; C-peptide.

than girls ($p=0.0071$), but there were no significant differences in other laboratory findings between the two groups. The mean fasting PG level of the obese subjects was 92.6 ± 5.9 mg/dl, and the mean PG level and range for 120 min were 129.0 ± 17.4 mg/dl and 101–182 mg/dl, respectively. None of the obese children showed impaired fasting glucose (IFG) or diabetes. Their mean fasting insulin level was 25.4 ± 13.9 μ U/ml, which was higher than the reference value (15 μ U/ml) for Japanese children (9).

Comparison of PG, IRI and CPR levels during the OGTT between obese and healthy children

The levels of PG, IRI and CPR during the OGTT are shown in Fig. 1 (7, 8). The PG levels at preloading and 120 min were significantly higher in the obese children than in the healthy children. Levels of IRI and CPR at preloading and at 60, 120 and 180 min were also significantly higher in the obese children than in the healthy children. Furthermore, the IRI and CPR levels both peaked at 60 min in the healthy children but at 120 min in the obese children. Thus, obese children had superfluous insulin secretion during the OGTT.

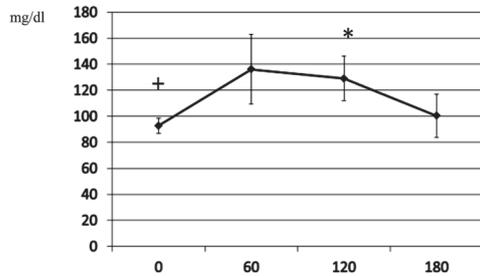
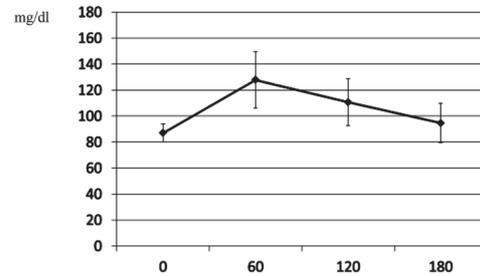
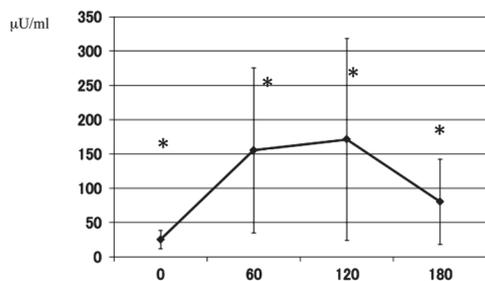
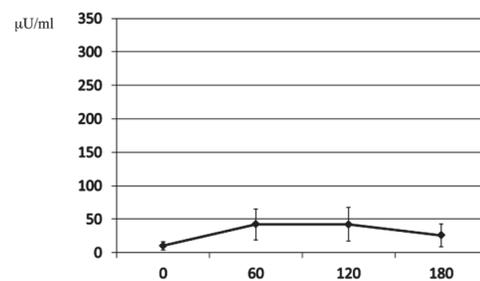
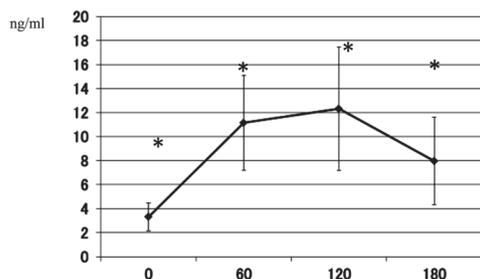
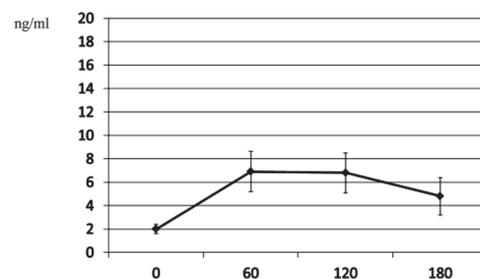
A. Obese children, PGD. Healthy children, PGB. Obese children, IRIE. Healthy children, IRIC. Obese children, CPRF. Healthy children, CPR

Fig. 1 PG, IRI, and CPR responses during an OGTT in obese children (A, B, and C) and healthy children (D, E, and F). The data for the healthy children were taken from Ohki *et al.* (6) and Tsunoda *et al.* (7). The plus signs and asterisks indicate significant differences ($p < 0.05$ and $p < 0.01$, respectively).

Comparison of PG, IRI and CPR levels during the OGTT between the four groups divided by metabolic disorder

The clinical characteristics of each group are summarized in Table 2, and the PG, IRI, and CPR levels during the OGTT are shown in Fig. 2. The pattern of PG response in each group was similar, and each group showed hypersecretion of IRI and CPR. However, the patterns of IRI and CPR response differed in each group as follows: Group A's response peaked at 60 min

and then decreased gradually until 120 min; Group B's response peaked at 60 min, remained at the peak until 120 min and then decreased gradually until 180 min; Group C's peaked at 120 min and then decreased gradually until 180 min; and Group D's peaked at 120 min and remained at the peak until 180 min.

Discussion

The differences of insulin levels between

Table 2 Physical characteristics and biochemical parameters by metabolic disorder in 28 obese children

	no complication, n=11			impaired liver function only, n=6			hyperlipidemia only, n=5			impaired liver function & hyperlipidemia, n=6			
	Means \pm SD	min	max	Means \pm SD	min	max	Means \pm SD	min	max	Means \pm SD	min	max	
Age (yr)	12.6 \pm 3.0	8.8	16.2	12.6 \pm 1.2	10.8	14.4	13.3 \pm 2.1	10.6	15.8	13.7 \pm 1.8	10.5	15.8	
POW (%)	58.6 \pm 15.6	45.1	98.2	56.5 \pm 12.9	42.7	77.5	60.9 \pm 15.1	45.6	77.8	68.3 \pm 14.4	46.8	82.8	
BMI (kg/m ²)	30.2 \pm 4.2	24.7	40.0	29.5 \pm 3.7	25.2	34.9	31.2 \pm 4.6	24.7	35.8	32.9 \pm 3.5	28.2	36.8	
ALT (IU/l)	18.7 \pm 7.9	9.0	29.0	103.0 \pm 76.3	45.0	246.0	21.2 \pm 7.3	12.0	30.0	74.3 \pm 44.7	31.0	146.0	
Tchol (mg/dl)	166.0 \pm 21.9	125.0	192.0	156.8 \pm 30.6	120.0	213.0	177.4 \pm 35.7	142.0	217.0	192.5 \pm 35.7	154.0	250.0	
TG (mg/dl)	82.4 \pm 22.8	52.0	118.0	59.5 \pm 13.1	41.0	73.0	226.4 \pm 138.6	122.0	419.0	141.3 \pm 28.5	124.0	198.0	
HDLc (mg/dl)	56.0 \pm 7.3	45.0	64.0	55.0 \pm 14.0	40.0	78.0	45.8 \pm 8.1	36.0	56.0	52.0 \pm 9.4	44.0	68.0	
HbA1c (JDS) (%)	4.9 \pm 0.5	3.8	5.4	4.9 \pm 0.3	4.4	5.2	4.9 \pm 0.4	4.2	5.3	5.0 \pm 0.4	4.5	5.4	
HOMA-R	5.1 \pm 2.8	1.5	11.4	4.7 \pm 3.2	1.3	9.3	5.2 \pm 1.6	3.4	6.9	9.1 \pm 4.3	3.4	15.0	
PG													
0 (mg/dl)	92.8 \pm 5.8	83.0	104.0	91.2 \pm 4.6	85.0	97.0	92.4 \pm 5.3	85.0	98.0	94.0 \pm 8.6	82.0	104.0	
60 (mg/dl)	127.8 \pm 22.3	96.0	167.0	127.7 \pm 13.0	110	150.0	129.2 \pm 3.3	124.0	132.0	165.3 \pm 39.5	128.0	222.0	
120 (mg/dl)	119.5 \pm 11.9	101.0	141.0	127.3 \pm 6.9	118	137.0	134.6 \pm 15.6	119.0	158.0	143.5 \pm 25.0	120.0	182.0	
180 (mg/dl)	99.8 \pm 12.6	77.0	120.0	97.2 \pm 12.6	78.0	112.0	100.2 \pm 12.1	89.0	119.0	104.3 \pm 30.3	61.0	133.0	
Σ PG	180 (mg/dl)	440.0 \pm 32.9	369.0	495.0	443.3 \pm 20.8	421.0	474.0	456.4 \pm 22.5	421.0	480.0	507.2 \pm 66.1	441.0	624.0
IRI													
0 (μ U/ml)	21.9 \pm 11.5	6.7	44.3	21.2 \pm 14.1	5.3	42.4	22.6 \pm 6.6	14.1	29.5	38.4 \pm 17.0	17.0	59.4	
60 (μ U/ml)	129.6 \pm 68.5	23.5	246.0	123.3 \pm 58.1	66.5	228.0	133.4 \pm 40.9	86.0	180.0	252.5 \pm 228.1	90.0	698.0	
120 (μ U/ml)	119.2 \pm 101.0	29.0	344.0	145.8 \pm 80.0	91.0	301.0	207.5 \pm 101.4	73.4	340.0	261.8 \pm 261.8	91.0	787.0	
180 (μ U/ml)	68.9 \pm 55.7	3.7	179.0	58.8 \pm 34.5	9.0	103.0	64.1 \pm 45.2	24.7	140.0	137.2 \pm 86.0	19.0	250.0	
Σ IRI	180 (μ U/ml)	339.7 \pm 217.1	143.4	788.1	349.0 \pm 152.9	236.3	625.6	427.5 \pm 168.4	198.2	589.0	689.9 \pm 516.4	217.0	1,695.4
CPR													
0 (ng/ml)	2.8 \pm 0.9	1.9	4.5	3.1 \pm 1.2	1.9	4.8	3.2 \pm 0.6	2.7	4.1	4.7 \pm 1.1	2.9	6.1	
60 (ng/ml)	9.7 \pm 3.5	4.4	15.0	9.9 \pm 2.4	7.5	14.1	11.4 \pm 2.0	9.0	14.0	14.5 \pm 5.5	10.6	25.5	
120 (ng/ml)	9.8 \pm 4.1	4.5	17.0	11.4 \pm 4.4	8.5	20.0	14.9 \pm 4.1	10.2	18.9	15.3 \pm 6.9	10.3	28.9	
180 (ng/ml)	6.8 \pm 3.0	2.0	12.0	7.0 \pm 2.7	2.4	9.9	8.2 \pm 3.0	5.8	13.0	11.0 \pm 4.7	5.4	19.0	
Σ CPR	180 (ng/ml)	29.1 \pm 10.2	17.0	48.0	31.4 \pm 9.3	22.7	47.3	37.8 \pm 8.7	28.8	49.1	45.5 \pm 14.2	32.3	71.0

POW; percent of overweight, BMI; body mass index, ALT; alanine aminotransferase, Tchol; total cholesterol, TG; triglyceride, HDLC; high density lipoprotein cholesterol, HbA1c; glycohemoglobin A1c, HOMA-R; homeostasis model assessment insulin resistance, IRI; immuno-reactive insulin, CPR; C-peptide. There was a significant difference in CPR0 ($p=0.0207$) and SCPR180 ($p=0.0408$) using Kruskal-Wallis test. There were no differences in Age, POW, and BMI between each group using Kruskal-Wallis test.

obese and healthy persons are greater in postprandial states than those in fasting states. Therefore, postprandial hyperinsulinemia is associated with disorders of obesity more than with fasting hyperinsulinemia. In regard to delayed superfluous insulin secretion in obese adults, Kawamori *et al.* reported that hyperglycemia and arteriosclerosis are mutually related to the quantity and pattern of insulin secretion in adulthood obesity. Furthermore, they concluded that an abnormal transient rise of the postprandial glucose level brought about the delayed superfluous insulin secretion, and that it was important to stop the vicious circle of the

hyperglycemia obesity (10). The results of the present study suggest that postprandial hyperinsulinemia is related to metabolic disorders in obese children as well as in obese adults.

Delayed superfluous insulin secretion and impaired liver function

A tendency for persistent superfluous insulin secretion was observed in obese children with impaired liver function. This is because the liver plays a major role in glucose metabolism: impairment of liver function might directly impact insulin secretion.

Abe *et al.* investigated the relation between

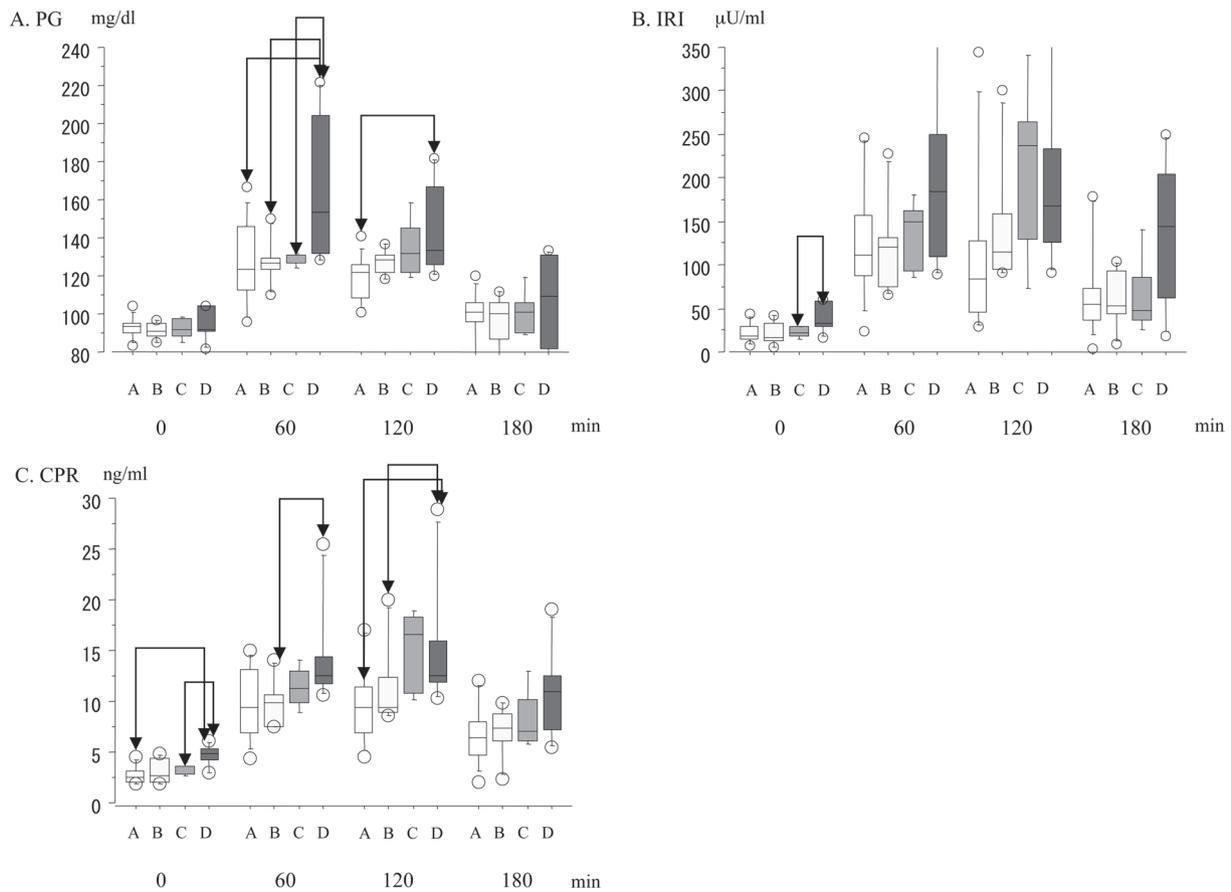


Fig. 2 PG, IRI and CPR responses during an OGTT for groups A, B, C and D. PG, IRI and CPR levels were compared at each time point between the four groups by using the Mann-Whitney U test. Arrows indicate significant differences ($p < 0.05$). Open circles show maximum and minimum values.

ALT level upsurge and insulin resistance in obese children and concluded that the ALT level was superior to the fasting glucose level as an index of child metabolic syndrome (11). Moreover, Wasada *et al.* reported that fatty liver was associated with insulin resistance regardless of adipocytokine secretion (12). In addition, Semple *et al.* reported that patients with mutant insulin receptors in the liver had extreme delayed superfluous insulin secretion during an OGTT (13).

In glucose metabolism, the main role of the liver is glucose uptake by the hepatic portal vein during postprandial states and glucose discharge by gluconeogenesis during fasting states. Insulin

reduces the liver's glucose discharge rate and increases its glucose uptake rate. In healthy children, but not obese children, gluconeogenesis is controlled by low-concentration insulin. However, when glucose is not taken into liver because of impaired liver function, redundant glucose is taken up across the plasma membranes of pancreatic beta cells by glucose transporter protein 2 (GLUT2). This vicious cycle eventually increases insulin secretion further.

In addition, overaccumulation of triglyceride in the liver produces fatty liver. Fatty liver prevents storage of glycogen and control of gluconeogenesis. Thus, the rate of hepatic glucose uptake is decreased by impaired liver

function. Also, due to decreases in insulin sensitivity in the liver, gluconeogenesis is not suppressed. These phenomena prevent a drop in PG level and cause persistent hyperglycemia. Furthermore, persistent hyperglycemia brings about continuation of insulin secretion and this results in hyperinsulinemia. Therefore, as shown in this study, superfluous insulin secretion might continue, and the insulin level might fluctuate at a high value near the maximal peak.

Delayed superfluous insulin secretion and dyslipidemia

In obese children with dyslipidemia, the peak insulin response to glucose loading tended to be delayed. Dyslipidemia is associated with impaired insulin secretion, and the impairment of early insulin response contributes to postprandial hyperglycemia. Therefore, because the hyperglycemia is caused by the impairment of early insulin response, superfluous insulin secretion occurs, and delayed superfluous insulin secretion arises in obese children with dyslipidemia.

Yamada *et al.* reported on the relationship between dyslipidemia and PG and insulin levels during an OGTT in many obese adults. Subjects with dyslipidemia had delayed maximal peaks of PG and insulin levels, respectively, and the levels of PG and insulin fluctuated at significantly high values compared with those of subjects without dyslipidemia (14). Boden *et al.* reported that in healthy adults, persistent hypersecretion of insulin compensated for fat infusion-induced insulin resistance within approximately 24 h (15). Tushuizen *et al.* reported that pancreatic lipid content might contribute to the dysfunction of pancreatic beta cells and possibly to the subsequent development of type 2 diabetes in susceptible adults (16).

When insulin action is reduced by insulin resistance, the discharge of free fatty acids (FFA) from adipose tissue increases, and very low-density lipoprotein (VLDL) catabolism or chylomicron catabolism is impaired. Moreover,

since production of VLDL in the liver increases, low-density lipoprotein (LDL) production also increases. In addition, a reduction in insulin action brings about a compensatory increase in insulin secretion, and promotes hyperinsulinemia. Superfluous insulin secretion leads to dyslipidemia by inhibiting hormone-sensitive lipase (HSL), which disassembles neutral fat, or by increasing glucose uptake from GLUT4 on adipose cells. Persistent dyslipidemia leads to fat accumulation on hepatic cells or pancreatic beta cells. As a result, these vicious cycles are formed (17, 18).

In our study, the results showed a remarkable tendency in Group D for delayed superfluous insulin secretion. At 180 min, superfluous insulin secretion was still occurring in Group D compared with Group C. In Group D, the subjects were hyperglycemic due to both impairment of the early insulin response caused by dyslipidemia and uncontrolled gluconeogenesis caused by impaired liver function. Their superfluous insulin secretion continued at 180 min in order to compensate for these hyperglycemic responses. Thus, Group D showed delayed insulin secretion compared with Group C.

As already reported in a number of studies on adulthood obesity, postprandial hyperinsulinemia is related to arteriosclerosis and dyslipidemia, and each of these metabolic disorders of obesity worsens the other. Furthermore, these phenomena arise not only in adulthood, but can also arise in childhood (19). In the present study, we showed changes in the insulin secretion pattern of nondiabetic obese children, and the relation between insulin secretion pattern and metabolic disorders of obesity. Obese children with metabolic disorders showed delayed superfluous insulin secretion during the OGTT. Therefore, they might already have the same pathological condition as obese adults. However, because our study included only a small number of patients, further studies of OGTT with larger numbers of Japanese obese children are needed to confirm our findings.

Conclusion

Obese Japanese children will experience a vicious cycle of postprandial hyperinsulinemia and metabolic disorders. Therefore, it is important to prevent healthy children from becoming obese and to improve the management of childhood obesity.

References

- Fontbonne A, Charles MA, Thibault N, Richard JL, Claude JR, Warnet JM, *et al.* Hyperinsulinemia as a predictor of coronary heart disease mortality in a healthy population: the Paris Prospective Study, 15-year follow-up. *Diabetologia* 1991;34:356–61.
- Despres JP, Lamarche B, Mauriege P, Cantin B, Dagenais GR, Moorjani S, *et al.* Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med* 1996;334:952–7.
- Kendrick M. Does insulin resistance cause atherosclerosis in the postprandial period? *Med Hypotheses* 2003;60:6–11.
- Kawamori R. Asymptomatic hyperglycaemia and early atherosclerotic changes. *Diabetes Res Clin Pract* 1998;40:S35–S42.
- Burrows R, Burgueno M, Leiva L, Ceballos X, Guillier I, Gattas V, *et al.* Cardiovascular risk and metabolic profile in obese children and adolescents with low insulin sensitivity. *Rev Med Chil* 2005;133:795–804.
- Murata M. Practical method for assessment of childhood obesity, Growth curve and percent overweight, *Japanese Journal of Pediatrics* 2003;56:2315–26.
- Ohki Y, Tsunoda M, Mineda T, Hosoi H, Teshirogi T. Insulin secretion and clearance in obese and diabetic adolescents —investigation in terms of CPR/IRI molar ratio during O-GTT. *Pediatrics International* 1991;95:1647–56.
- Tsunoda M, Ohki Y, Mineda T, Teshirogi T. Studies on insulin secretion and clearance in obese and diabetic children (7~11 years old) and adolescents (12~16 years old) – investigation by oral glucose tolerance tests (O-GTT). *J Nippon Med Sch* 1992;59:9–19.
- Araki S, Dobashi K, Asayama K. Diagnostic criteria of childhood obesity. *Japanese Journal of Pediatric Medicine* 2006;38:1523–7.
- Kawamori R. Metabolic syndrome. Main symptoms of metabolic syndrome and features. Glucose tolerance abnormality. *Japanese Journal of Clinical and Experimental Medicine* 2004;81:1759–63.
- Abe Y, Kikuchi T, Nagasaki K, Hiura M, Tanaka Y, Ogawa Y, *et al.* Usefulness of GPT for diagnosis of metabolic syndrome in obese Japanese children. *J Atheroscler Thromb* 2009;16:902–9.
- Wasada T, Kasahara T, Wada J, Jimba S, Fujimaki R, Nakagami T, *et al.* Hepatic steatosis rather than visceral adiposity is more closely associated with insulin resistance in the early stage of obesity. *Metabolism* 2008;57:980–5.
- Semple RK, Sleigh A, Murgatroyd PR, Adams CA, Bluck L, Jackson S, *et al.* Postreceptor insulin resistance contributes to human dyslipidemia and hepatic steatosis. *J Clin Invest* 2009;119:315–21.
- Yamada N, Yoshinaga H, Sakurai N, Shimano H, Gotoda T, Ohashi Y, *et al.* Increased risk factors for coronary artery disease in Japanese subjects with hyperinsulinemia or glucose intolerance. *Diabetes Care* 1994;17:107–14.
- Boden G, Chen X, Rosner J, Barton M. Effects of a 48-h fat infusion on insulin secretion and glucose utilization. *Diabetes* 1995;44:1239–42.
- Tushuizen ME, Bunck MC, Pouwels PJ, Bontemps S, Waesberghe JH, Schindhelm RK, *et al.* Pancreatic fat content and β -cell function in men with and without type 2 diabetes. *Diabetes Care* 2007;30:2916–21.
- Shimabukuro M. Free fatty acids as mechanism of the metabolic syndrome. *Adiposience* 2006;3:64–9.
- McGarry JD, Dobbins RL. Fatty acids, lipotoxicity and insulin secretion. *Diabetologia* 1999;42:128–38.
- Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, *et al.* Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004;350:2362–74.