Case of type 2 diabetes possibly caused by excessive accumulation of visceral fat in a child born small-for-gestational age

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INTRODUCTION
Small-for-gestational age (SGA) is defined in Japan as both birthweight and height less than the 10th percentile, and one of them <2 standard deviations for gestational age. SGA is one of the risk factors for metabolic syndrome, including hypertension, hyperlipidemia and type 2 diabetes, in adulthood1-4. The developmental origins of health and disease hypothesis proposed by Barker5 has shown that the risks of chronic disease in adulthood are associated with fetal growth restriction, which alter normal patterns of growth and development. Furthermore, it has been hypothesized that adverse prenatal environmental stimuli, such as overnutrition and high-protein and fat intakes, induce increased susceptibility to metabolic syndrome in adult life5. We encountered a 12-year-old boy with type 2 diabetes who was born SGA through the urine glucose screening program carried out in 2014. In the present report, we found that dominant accumulation of visceral fat in a case of SGA, as with a previous report6, resulted in developing type 2 diabetes. We aimed to describe his clinical characteristics during type 2 diabetes development and a possible etiological factor for the development of hyperglycemia in children born SGA.

CASE REPORT
A 12-year-old boy showed a positive result for urine glucose during urine glucose screening at school in the Tokyo Metropolitan Area in 2014. He was finally diagnosed with diabetes based on a 2-h plasma glucose level during an oral glucose tolerance test of 204 mg/dL and glycosylated hemoglobin (HbA1c) level of 6.9%. He was born SGA; his birthweight was 2,226 g, and birth height was 46.5 cm, both of which were <2 standard deviations and below the 10th percentile for gestational age. He developed well with sufficient nutrition and did not receive growth hormone therapy. He progressed to being overweight at 6 years-of-age as a result of a high-calorie, high-protein intake diet and a preference for sweet beverages. He tended to have a sedentary lifestyle and played video games for long time periods. He had a family history of type 2 diabetes (grandmother).

At the time of visiting Nihon University Hospital, Tokyo, Japan, his height was 141.5 cm (−1.4 standard deviation), bodyweight was 46.1 kg (percentage overweight for sex and age 31.2%, body mass index 23.0), waist circumference was 81.6 cm (waist circumference/height 0.55) and blood pressure was 86/42 mmHg. He had mild acanthosis nigricans on the neck; in terms of sexual development, he was Tanner stage 2.

He showed a diabetic pattern with a normal insulin response on an oral glucose tolerance test. The homeostasis model
assessments of insulin resistance and homeostasis model assessment of β-cell function were within the normal range. He showed a diabetic HbA1c level (6.7%), whereas serum lipid and liver enzyme levels were within the normal range. All autoantibodies against pancreatic β-cells were negative, and genetic tests for maturity-onset diabetes of the young were also negative. Accordingly, he was diagnosed with type 2 diabetes (Table 1).

Liver echography showed a fatty change, and he had a large total fat area of 239.4 cm²; in particular, his visceral fat area (VFA) was 103.0 cm²; computed tomography at the umbilical level showed a high ratio of VFA to subcutaneous fat area (0.76) (Aquilion CX; Toshiba, Tokyo, Japan; Figure 1). VFA >60 cm² and VFA/subcutaneous fat area ratio >0.3 were defined as excessive accumulation of VF based on the diagnostic criteria by the Japan Society for the Study of Obesity.

During the course of diabetes, after the diagnosis, the patient moderate-to-high fasting serum insulin levels between 8 and 23 µU/mL. He was initially treated with metformin 500 mg daily and shortly achieved optimal glycemic control with HbA1c levels <7.5%. However, his glycemic control gradually worsened, with HbA1c levels >8.0%, despite an increase in metformin dosage from 500 to 1,500 mg. Therefore, we started administering dapagliflozin, a sodium–glucose cotransporter 2 inhibitor, 5 mg daily after obtaining informed consent from him and his mother. Subsequently, his glycemic control improved, with HbA1c levels <7.5%, continued serum insulin levels between 7 and 12 µU/mL, and reduced bodyweight (Figure 2). No adverse events, such as ketoacidosis and urogenital infections, were associated with dapagliflozin use.

**DISCUSSION**

Some studies have shown an association between low birthweight including SGA and a subsequent increase in the risk of type 2 diabetes3,4, which supported the developmental origins of health and disease hypothesis1. Contrastingly, other studies have shown that both low birthweight and high birthweight were risk factors for type 2 diabetes in the future, which showed a U-shaped relationship between birthweight and subsequent risk of type 2 diabetes instead of a linear inverse relation5,6. Hofmann et al.7 reported intrauterine malnutrition as a causal factor for SGA that leads to insulin resistance and subsequent type 2 diabetes later in life. Low birthweight infants are likely to receive excessive neonatal feeding, leading to rapid neonatal weight gain, followed by overweight in later life; this might be a key etiological factor in addition to the association between low birthweight and risk of subsequent type 2 diabetes8.

Visceral obesity is known to be a significant risk factor of type 2 diabetes associated with insulin resistance. Both VF and SF have been reported to be correlated with insulin resistance; furthermore, VF was more strongly correlated to insulin resistance than SF in adults9. Metabolically unhealthy individuals have impaired adipose tissue function, which might result in great amounts of visceral adipose tissue, small amounts of subcutaneous adipose tissue and inflammation in visceral adipose

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**Table 1** | Laboratory data and results of the oral glucose tolerance test in the present patient

| Parameter                  | Value |
|----------------------------|-------|
| HbA1c (%)                  | 6.7   |
| Glycated albumin (%)       | 15.7  |
| TC (mg/dL)                 | 154   |
| HDL-C (mg/dL)              | 42    |
| LDL-C (mg/dL)              | 102   |
| Triglyceride (mg/dL)       | 35    |
| AST (IU/L)                 | 30    |
| ALT (IU/L)                 | 44    |
| Plasma glucose (mg/dL)     |       |
| 0 min                      | 92    |
| 30 min                     | 117   |
| 60 min                     | 173   |
| 90 min                     | 189   |
| 120 min                    | 204   |
| IRI (µU/mL)                |       |
| 0 min                      | 4.5   |
| 30 min                     | 10.9  |
| 60 min                     | 18.9  |
| 90 min                     | 21    |
| 120 min                    | 17.2  |
| HOMA-IR                    |       |
| HOMA-β                     | 55.9  |
| ΔRI/ΔPG                    | 0.3   |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, the homeostasis model assessment of β-cell function; IRI, immunoreactive insulin; LDL-C, low-density lipoprotein cholesterol; PG, plasma glucose; TC, total cholesterol.
tissue. Accordingly, accumulation of VF, rather than that of SF, can be more strongly attributed to the occurrence of type 2 diabetes. The present patient did not show elevated serum insulin resistance markers, such as serum insulin level and homeostasis model assessment of insulin resistance, but showed an expanded VFA and high VFA/SFA ratio at the time of diagnosis. During the course of diabetes after improving glycemic control without glucose toxicity, he showed moderate-to-high levels of serum insulin, suggesting insulin resistance. These results suggest that individuals born SGA might have impaired adipose tissue function and tend to accumulate a great amount of VF rather than accumulation of SF, which possibly causes insulin resistance leading to type 2 diabetes later in life. In contrast, a relative lower response of insulin observed on an oral glucose tolerance test could be attributed to later development of type 2 diabetes.

In conclusion, we first described a novel case born SGA developing type 2 diabetes with significant accumulation of visceral fat. Insulin resistance, possibly as a result of an accumulation of a great amount of VF, might be attributed to the pathogenesis of type 2 diabetes in children born SGA. Early diagnosis through the screening program carried out at schools, and early intervention by dietary management and physical exercise are necessary for controlling diabetes; if necessary, appropriate pharmacological treatment should be provided.

DISCLOSURE
The authors declare no conflict of interest.

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