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## ABSTRACT

**Introduction:** The ketogenic diet reportedly improves metabolic disorders, such as obesity and diabetes. The objective of this study was to investigate effects of the Quick-Fat (QF) diet, which contains high-fat and high-sucrose, on the progression of diabetes in SDT rats.

**Materials and Methods:** SDT rats were divided into 2 groups at 5 weeks of age, which were fed a standard diet or the QF diet for 34 weeks. Body weight, calorie intake, and blood glucose and ketone body levels were measured every 2 weeks. The cumulative incidence of diabetes or cataract was also determined. Blood electrolyte levels, such as sodium and potassium, were measured at 25 and 30 weeks of age. **Results:** The SDT rats fed a QF (QF-SDT) showed an increase of body weight after 7 weeks of age and a decrease of calorie intake after 29 weeks of age. Blood glucose levels in the QF-SDT group decreased after 23 weeks of age, and blood ketone body levels in the QF-SDT group increased after 9 weeks of age. In addition, reduction in the incidence of diabetes or cataract was observed in the QF-SDT group. The changes in blood electrolyte levels were observed in the QF-SDT group at 25 weeks of age, but no changes were observed at 30 weeks of age. **Conclusion:** SDT rats fed a QF diet showed the delay of diabetic incidence, accompanied by an increase in blood ketone body levels.

**Keywords:** Diabetes, quick-fat diet, Spontaneously Diabetic Torii rat

## INTRODUCTION

Diabetes mellitus has become a global health problem, and the patient number is rapidly increasing all over the world.<sup>[1]</sup> Type 2 diabetes is brought on by genetic and environmental/behavioral factors such as a sedentary lifestyle and over rich nutrition.<sup>[2,3]</sup> Pharmacological and lifestyle interventions reportedly prevent or delay the development of type 2 diabetes.<sup>[4]</sup> Moreover, patients who develop Type 2 diabetes pass through a phase of prediabetes diagnosed by either impaired glucose tolerance or impaired fasting glucose.<sup>[5]</sup> The prevalence of prediabetes, as well as Type 2 diabetes, is increasing, and the burden of prediabetes and Type 2 diabetes on the health-care system will continue to grow.<sup>[6,7]</sup> Intervention in prediabetes stage is also important to prevent onset of diabetes or delay the progression.<sup>[5,8]</sup>

Spontaneously Diabetic Torii (SDT) rat is a model of non-obese Type 2 diabetes, which was developed by Torii Pharmaceutical Co., Ltd. (Tokyo, Japan).<sup>[9,10]</sup> Male SDT rats have normal body weight, blood glucose levels, insulin levels, and lipid levels until approximately 16 weeks of age and, thereafter, develop hyperglycemia and the diabetic complications.<sup>[11-14]</sup>

The quick-fat (QF) diet (CLEA Japan, Tokyo, Japan) is a new original diet to augment the severity of diabetes mellitus in Goto-Kakizaki type 2 diabetic rats. Since the rats fed fat- or sucrose-enriched diet reportedly induce abnormalities in glucose/lipid metabolism,<sup>[15,16]</sup> the QF diet contains higher concentrations of fat (14%, calorie ratio) and sucrose (25%, calorie ratio). On the other hand, the ketogenic diet containing a high-fat reportedly improves metabolic disorders.<sup>[17-19]</sup> Furthermore, a high-fat diet inhibits the development of diabetes in SDT rats.<sup>[20]</sup> In this study,

we speculated the effects of the QF diet on the progression of diabetes mellitus in SDT rats.

## MATERIALS AND METHODS

### Animals and Diets

This experiment was conducted in compliance with the Guidelines for Animal Experimentation of our institutes. All the experiments obtained the approval of the Animal Experiment Committee of CLEA Japan.

Male SDT rats at 5 weeks of age from our colonies were used (CLEA Japan, Tokyo, Japan). The rats were kept in plastic cages, with one animal/cage in a climate-controlled room with a temperature of  $23 \pm 3^\circ\text{C}$ , humidity of  $55 \pm 15\%$ , and a 12-h light cycle. The SDT rats were divided into two groups. One group ( $n = 15$ ) was fed a QF diet (13.83% fat, 24.98% protein, and 45.43% carbohydrate [25%-sucrose content] based on total calories, CLEA Japan, Tokyo, Japan) from 5 to 39 weeks of age, and the other group ( $n = 15$ ) was fed a standard diet (SD) (4.38% fat, 25.33% protein, 49.68% carbohydrate [non-sucrose content] based on percentage of total calories, CE-2, CLEA Japan, Tokyo, Japan). Table 1 present the ingredient composition of the diets. The energy contents of the standard and QF diets were 3.39 and 4.06 kcal/g, respectively. Water was provided by *ad libitum*.

### Biological Parameters

Body weight, calorie intake, plasma glucose level, and serum ketone body level in rats were evaluated every 2 weeks. Serum sodium and potassium levels were evaluated at 25 and 30 weeks of age. Blood samples were collected from the tail vein of rats. Plasma glucose level and serum ketone body, sodium, and potassium levels were measured by the automatic analyzer (BIOLIS 24i; TOKYO BOEKI MEDISYS INC., Tokyo, Japan).

### Incidence of Diabetes and Cataract

“Incidence of diabetes” is defined by 250 mg/dl or higher in plasma glucose level and “Incidence of cataract” is defined by cataract existence in both eyes. Both incidences were calculated to be the subject of the calculation.

### Statistical Analysis

The biological parameters, except for the incidence of diabetes and cataract, are expressed as the mean  $\pm$  standard deviation. Statistical analysis was performed to body weight, calorie intake, and serum biochemical parameters (glucose, ketone body, sodium, and potassium) between SDT rats with SD (SD-SDT) and QF diet (QF-SDT). The F-test was used for measuring the variance of the SD-SDT and the QF-SDT. If homoscedasticity was confirmed, Student's *t*-test was used. If not, Aspin-Welch's test was used. Differences were considered significant at  $P < 0.05$ .

## RESULTS

### Body Weight and Calorie Intake

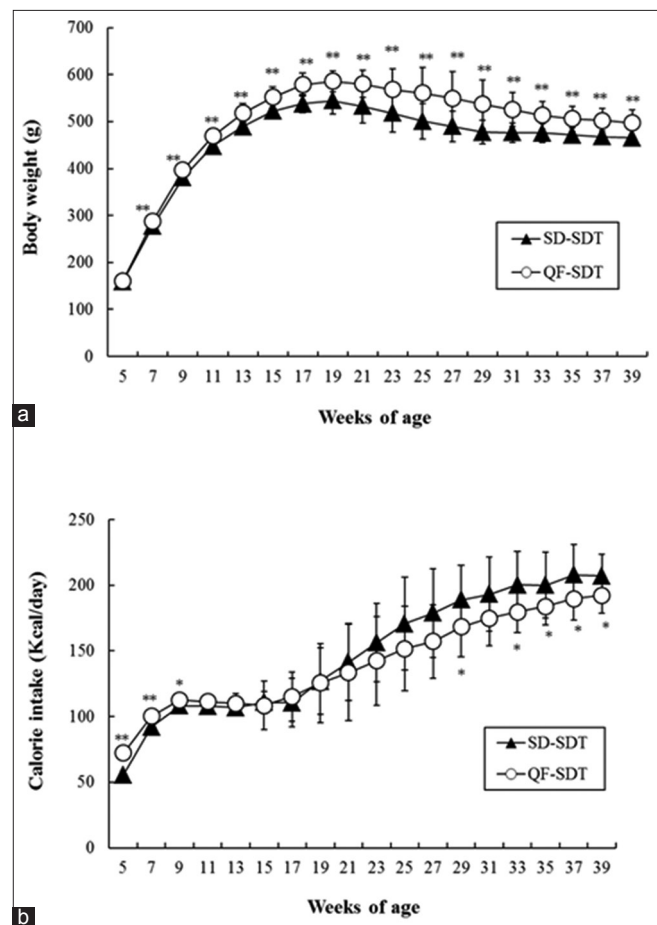
Figure 1 shows the change of body weight and calorie intake of the SD-SDT group and the QF-SDT group. Body weights in the SD-SDT group continued to increase until 19 weeks of age

( $159.6 \pm 2.2$  g, at 5 weeks and  $544.6 \pm 28.9$  g, at 19 weeks), and periodically decreased ( $465.6 \pm 16.8$  g, at 39 weeks) after 19 weeks of age. Body weights in the QF-SDT group increased after 7 weeks of age, as compared with those in the SD-SDT group (QF-SDT;  $287.7 \pm 9.3$  g, SD-SDT;  $277.6 \pm 5.3$  g, at 7 weeks), and the increase was maintained until 39 weeks of age (QF-SDT;  $497.5 \pm 27.2$  g, at 39 weeks). The calorie intake in the

**Table 1:** Ingredient composition of the experimental diets (CE-2 and QF diets)

| Ingredient                 | CE-2  | QF    |
|----------------------------|-------|-------|
| Moisture (%)               | 8.91  | 7.25  |
| Crude protein (%)          | 25.33 | 24.98 |
| Crude fat (%)              | 4.38  | 13.83 |
| Crude fiber (%)            | 4.88  | 3.15  |
| Crude ash (%)              | 6.83  | 5.38  |
| Nitrogen free extracts (%) | 49.68 | 45.43 |
| Total                      | 100.0 | 100.0 |

Both diets were supplied by CLEA Japan. QF: Quick-fat



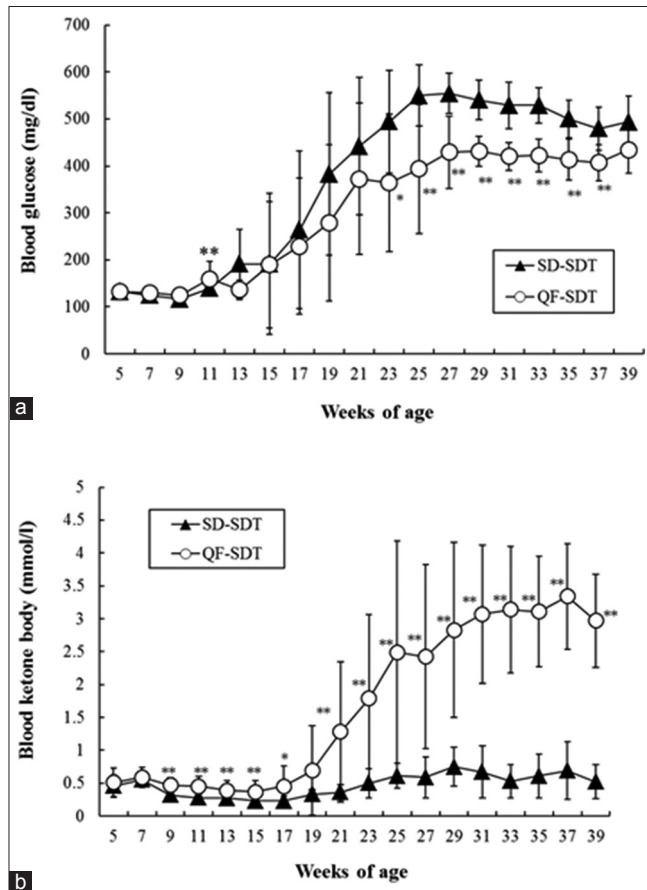
**Figure 1:** Changes in body weight (a) and calorie intake (b) in the standard diet-Spontaneously Diabetic Torii and the quick-fat-Spontaneously Diabetic Torii rats. The data are shown as the mean  $\pm$  standard deviation ( $n=15$ ). \* $P < 0.05$ ; \*\* $P < 0.01$ , significantly different compared with the SD-SDT rats at indicated time points

QF-SDT group increased from 5 to 9 weeks of age, as compared with those in the SD-SDT group, and it became no significant difference from 11 to 27 weeks of age. The calorie intake in the QF-SDT group decreased after 29 weeks of age [Figure 1b].

## Biochemical Parameters

Changes in plasma glucose, serum ketone body, sodium, and potassium levels were shown in Figures 2 and 3. Plasma glucose levels in the SD-SDT group began to be higher in a time-dependent manner from 13 to 25 weeks of age ( $191.1 \pm 73.2$  mg/dl at 13 weeks and  $549.8 \pm 65.1$  mg/dl at 25 weeks), and thereafter, the hyperglycemia maintained until 39 weeks of age. However, the elevation of glucose levels in the QF-SDT group was significantly lower from 23 to 37 weeks of age compared to the SD-SDT group [Figure 2a].

Serum ketone body levels in the SD-SDT group did not show any significant change in a time-dependent manner during the experimental period ( $0.46 \pm 0.16$  mmol/l at 5 weeks and  $0.71 \pm 0.26$  mmol/l at 39 weeks). On the other hand, serum ketone body levels in the QF-SDT group significantly increased from 9 to 39 weeks of age compared to the SD-SDT group (QF-SDT;  $2.97 \pm 0.71$  mmol/l at 39 weeks) [Figure 2b].

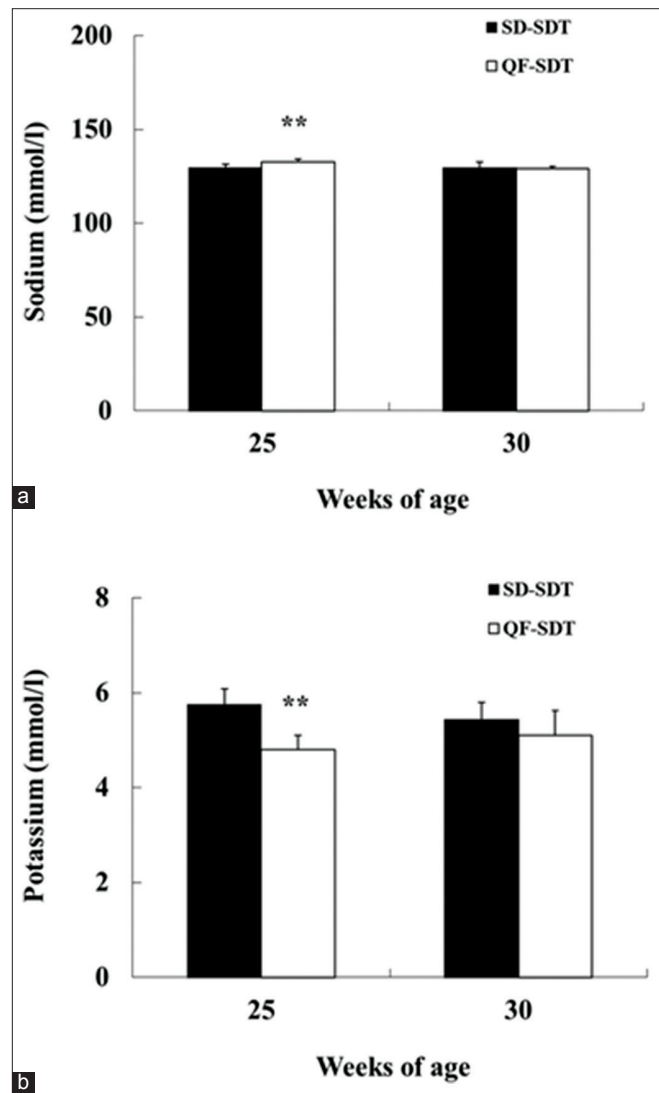


**Figure 2:** Changes in blood glucose (a) and ketone body (b) levels in the standard diet-Spontaneously Diabetic Torii (SD-SDT) and the quick-fat-Spontaneously Diabetic Torii rats. The data are shown as the mean  $\pm$  standard deviation ( $n=15$ ). \* $P<0.05$ ; \*\* $P<0.01$ , significantly different compared with SD-SDT rats at indicated time points

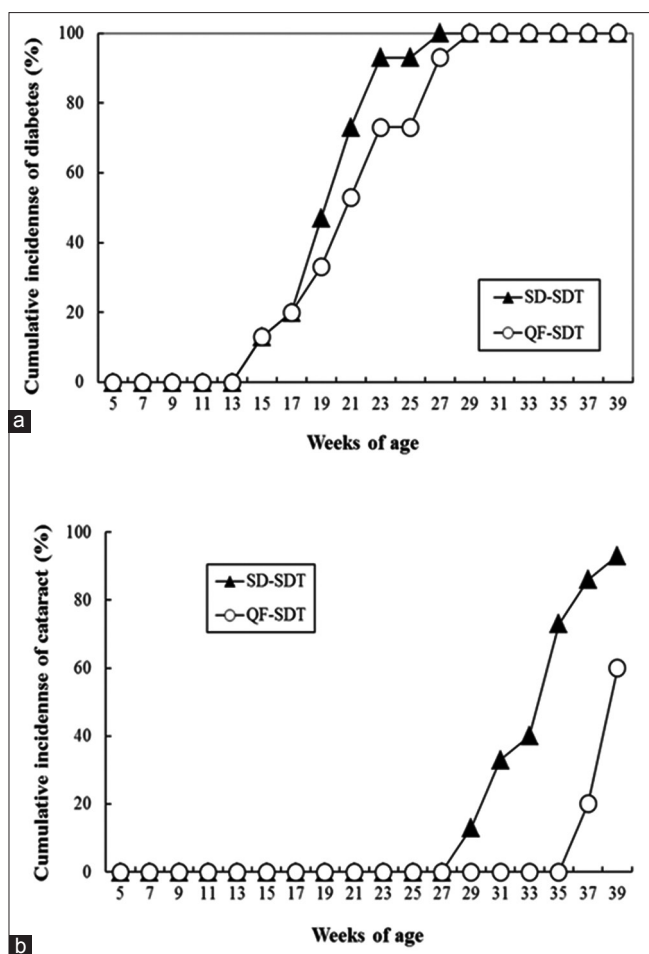
In the QF-SDT group at 25 weeks of age, serum sodium level significantly increased, and potassium level significantly decreased compared to the SD-SDT group [Figure 3]. The serum sodium and potassium levels at 30 weeks of age were comparable between the QF-SDT and SD-SDT groups.

## Incidence of Diabetes and Cataract

Figure 4 shows the cumulative incidence of diabetes and cataract in the QF-SDT group and the SD-SDT group. Cumulative incidence of diabetes in the SD-SDT group continued to increase after 13 weeks of age, and the incidence reached 100% at 27 weeks of age. In the incidence level of diabetes, the QF-SDT group represented lower than SD-SDT group from 19 to 27 weeks of age (QF-SDT; 33% vs. SD-SDT; 47% at 19 weeks and QF-SDT; 93% vs. SD-SDT; 100% at 27 weeks).



**Figure 3:** Changes in blood sodium (a) and potassium (b) levels in the standard diet-Spontaneously Diabetic Torii (SD-SDT) and the quick-fat-Spontaneously Diabetic Torii rats at 25 and 30 weeks of age. The data are shown as the mean  $\pm$  standard deviation ( $n=15$ ). \* $P<0.05$ ; \*\* $P<0.01$ , significantly different compared with SD-SDT rats



**Figure 4:** Changes in cumulative incidence of diabetes (a) and cataract (b) in the standard diet-Spontaneously Diabetic Torii and the quick-fat-Spontaneously Diabetic Torii rats

Cumulative incidence of cataract in the SD-SDT group increased after 27 weeks of age, and the incidence reached 93% at 39 weeks of age. On the other hand, the development of cataract in the QF-SDT group was not observed until 35 weeks of age, and the cumulative incidence at 37 and 39 weeks of age was 20% and 60%, respectively.

## DISCUSSION

Type 2 diabetes is a serious problem to health-care services, and the growing population of diabetic patients has resulted in an increase in the number of patients who have microvascular complications, such as nephropathy, neuropathy, and retinopathy.<sup>[21,22]</sup> In addition to the deterioration a quality of life, growing number of patients contributes to increase in medical costs.<sup>[23]</sup> Therefore, the preventing of the development of prediabetes and Type 2 diabetes is extremely important.

In this study, the QF diet induced an increase of blood ketone body levels in SDT rats from 9 weeks of age. Thereafter, the blood glucose levels in the QF-SDT rats decreased from 23 weeks of age. The incidence of diabetes in SDT rats was suppressed by feeding a QF diet, and the increase of blood ketone body levels may be related to an improvement of

glucose metabolism in the QF-SDT rats. Ketones have been proposed as super metabolic fuel because of their good effects on cellular metabolism in many tissues.<sup>[19,24]</sup> It is reported that ketones may induce proper cellular localization of glucose transporters recycling, and ketone bodies can attenuate certain inflammatory response by blocking specific cytokines.<sup>[25,26]</sup> Furthermore, plasma glucose level is reportedly reduced with the increased plasma ketones.<sup>[27]</sup>

Recently, ketogenic diet, which is a high-fat, adequate protein, and low carbohydrate that leads to nutritional ketosis, has shown promising results in neurological disorders, traumatic brain injury, cancer, and metabolic disorders.<sup>[19,24]</sup> In diabetic animal models, ketogenic diet reportedly prevents the development of diabetes.<sup>[17,18]</sup> On the other hand, long-term ketogenic diet causes glucose intolerance and insulin resistance,<sup>[28]</sup> and there is still room for argument about the effects of ketogenic diet. The QF diet contains higher sucrose and fat concentrations as compared with a standard diet. Sucrose- or fat-enriched diet reportedly induced glucose/lipid metabolic disorders including insulin resistance,<sup>[15,16]</sup> but the QF diet prevented the development of diabetes in SDT rats. The sustained high levels of blood ketone body may exceed the metabolic disorders by feeding the sucrose/fat-enriched diet. In a further study, it is necessary to determine the changes in lipid parameters, such as triglyceride, free fatty acid, and cholesterol, in the QF-SDT rats.

The reduction of cumulative incidence of cataract in the QF-SDT rats is considered to be related to the reduction of incidence of diabetes. Chronic hyperglycemia leads to the increase of incidence of cataract, and the improvement of hyperglycemia prevents the development of cataract.<sup>[29,30]</sup> The transient changes in blood sodium and potassium in the QF-SDT rats may be caused by an increase of insulin secretion due to the improvement of glucose metabolic disorders. Since the insulin levels were not determined in this study, it is necessary to investigate the relationship between blood insulin level and blood sodium or potassium level in the SDT rats fed a QF diet.

## CONCLUSIONS

SDT rats fed a QF diet showed the delay of diabetic incidence with an increase in blood ketone body levels. It suggests that inducing an elevation of blood ketones contributes to beneficial effects on diabetic therapy.

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