SHORT REPORT

Diurnal variation of carbohydrate insulin ratio in adult type 1 diabetic patients treated with continuous subcutaneous insulin infusion

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ABSTRACT

To estimate the carbohydrate-to-insulin ratio (CIR), a formula dividing a constant, usually 300–500, by the total daily dose (TDD) of insulin, is widely utilized. An appropriate CIR varies for each meal of the day, however. Here, we investigate diurnal variation of CIR in hospitalized Japanese type 1 diabetic patients treated with continuous subcutaneous insulin infusion. After optimization of the insulin dose, TDD and total basal insulin dose (TBD) were 34.9 ± 10.2 and 9.3 ± 2.8 units, respectively, with a percentage of TBD to TDD of $27.3 \pm 6.0\%$. The products of CIR and TDD at breakfast, lunch and dinner were 311 ± 63, 530 ± 161, and 396 ± 63, respectively, suggesting that in the formula estimating CIR using TDD, the constant should vary for each meal of the day, and that 300, 500, and 400 are appropriate for breakfast, lunch, and dinner, respectively.

INTRODUCTION

Type 1 diabetic patients treated with basal–bolus insulin therapy along with carbohydrate counting determine the dose of insulin before each meal according to the amount of carbohydrate they will intake. The ratio of insulin required for appropriate metabolism of carbohydrate to the amount of carbohydrate intake, known as the carbohydrate-to-insulin ratio (CIR), is influenced by the insulin sensitivity of each individual[1,2]. Although CIR should be adjusted by considering the various factors that affect insulin sensitivity of individuals, including physical constitution and age[1,2], several formulas to estimate CIR by the total daily dose of insulin (TDD) have been proposed, given that TDD reflects insulin sensitivity. A widely used formula is dividing a constant, usually 450 or 500, by TDD (units)[1–3], which is often referred as the 450-rule or 500-rule, respectively. More recent studies have proposed a lower constant (~300) in this formula[4,5]. However, the appropriate CIR is also known to vary for each meal of the day (i.e., breakfast, lunch and dinner)[5,6], likely as a result of diurnal alterations of insulin sensitivity. We evaluated the CIR of each meal of the day for Japanese type 1 diabetic patients treated with continuous subcutaneous insulin infusion (CSII).

MATERIALS AND METHODS

Japanese type 1 diabetic patients hospitalized for the start or the adjustment of CSII therapy (using Paradigm 712 or 722 pumps; Medtronic, CA, USA) in the Division of Diabetes and Endocrinology of Kobe University Hospital from March 2010 to September 2012 were studied. Patients were excluded if they were aged <20 years, manifested severe renal or liver dysfunction, were pregnant or their fasting serum C-peptide (CPR) levels were >0.2 ng/mL. All studied patients signed a written consent for analyzing and publishing their clinical data for scientific purpose. On administration, patients were provided meals consisting of a constant nutritional balance prepared by dietitians (25–30 kcal/kg ideal body mass, and consisting of 50–60% carbohydrate, 20–25% fat and 15–20% protein, divided equally into three portions and provided at 7:30, 12:00, and 18:00 h). We first optimized the basal dose of insulin to maintain blood glucose levels during fasting and sleeping time <130 mg/dL, and at relatively constant levels (within 30 mg/dL variance until the next meal) with the omission of meals as described previously[7]. After the optimization of the basal dose of insulin, the bolus insulin dose was then optimized to maintain postprandial glucose levels <180 mg/dL. After achieving the target blood glucose levels, the dose of insulin and CIR of each meal of the day were evaluated. The eight-point blood

glucose profile of the day of the evaluation was determined with blood samples obtained from the fingertips using glucose monitoring devices. Data are presented as mean ± standard deviation and were compared among groups by analysis of variance. Glycated hemoglobin values are expressed as National Glycohemoglobin Standardization Program values calculated from the Japan Diabetes Society value[8].

RESULTS

The characteristics of the study participants are shown in Table 1. The average of the eight-point blood glucose profile on the day of the evaluation is shown in Figure 1. The basal insulin infusion rate was relatively constant during the afternoon, whereas it gradually increased after midnight and reached maximal rates in the early morning (Figure 2a). TDD and total basal insulin dose (TBD) were 34.9 ± 10.2 and 9.3 ± 2.8 units, respectively, and the percentage of TBD to TDD (%TBD) was 27.3 ± 6.0%. The ratios of TDD and TBD to body mass were 0.61 ± 0.17 and 0.16 ± 0.04 units/kg, respectively. CIR at breakfast, lunch and dinner was 9.7 ± 3.3, 16.3 ± 6.2, and 12.6 ± 5.3, respectively (Figure 2b), and the average CIR of all three meals was 12.9 ± 4.5. The products of CIR and TDD at breakfast, lunch and dinner were 311 ± 63, 530 ± 161, and 396 ± 63, respectively, and the average product of CIR and TDD for all three meals was 412 ± 69 (Figure 2c).

DISCUSSION

We analyzed the insulin dose of type 1 diabetic patients treated with CSII after optimization of the insulin dosage during hospitalization. The value of %TBD observed in the present study (27.3 ± 6.0%) was much smaller than 50%, a widely cited value of %TBD[1,2]; however, it is similar to the value recently reported by Kuroda et al.[9] (27.7 ± 6.9%) from a study of Japanese adult type 1 diabetic patients. The lower of %TBD in the current study and in the study by Kuroda et al. might be attributable to meals that are relatively rich in carbohydrates (50–60% of total energy), which is recommended by the Japan Diabetes Society on the basis of the nutritional balance of the Japanese traditional daily diet[10]. It is also possible that, by monitoring sleeping time blood glucose levels with a continuous glucose monitoring system, we avoided overdosage of basal insulin while sleeping, which results in an increased of %TBD. Hashimoto et al.[11] recently reported that of %TBD for type 1
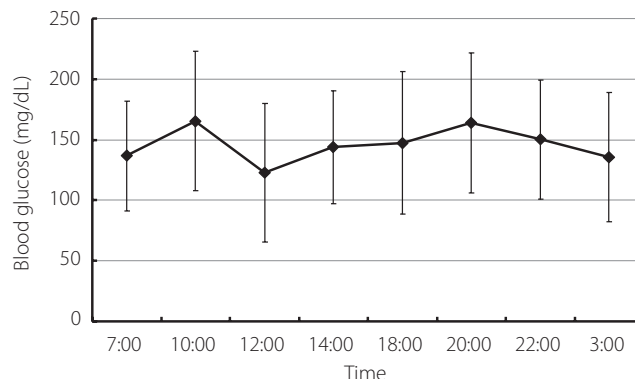
Table 1 | Clinical characteristics of the study participants

Age (years)	38.3 ± 13.5
Male/female	6/22
Body mass (kg)	58.1 ± 9.5
BMI (kg/m²)	22.8 ± 3.6
Duration of diabetes (years)	10.8 ± 9.6
HbA1c (%)	8.0 ± 1.1

Data are presented as mean ± standard deviation. BMI, body mass index; HbA1c, glycated hemoglobin.

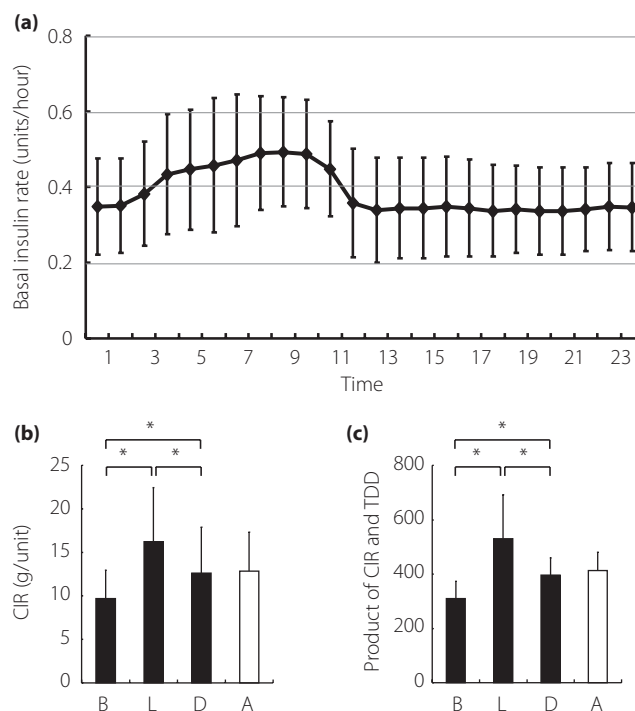**Figure 1** | Eight-point blood glucose profile on the day of evaluation.

Figure 2 | Daily profile of (a) basal insulin requirement, (b) carbohydrate-to-insulin ratio (CIR), and (c) the products of CIR and total daily dose (TDD) for breakfast (B), lunch (L) and dinner (D), respectively, and the average of the three meals (A). Data shown are mean ± standard deviation.

diabetic children and young adult outpatients (age 15.9 ± 16.1 years) treated with basal–bolus insulin therapy (including both CSII and multiple daily injections) was 35 ± 10%.

To estimate CIR, it is convenient to use a formula in which a constant is divided by TDD. Although the constants 450 and 500, and more recently 300, have been proposed[1–5], the present results suggest that the constant should vary for each meal of the day, and that 300, 500 and 400 appear to be appropriate for breakfast, lunch, and dinner, respectively. Recently, Kuroda et al.[5] investigated the insulin dose of CSII-treated Japanese type 1 diabetic patients, and proposed a lower constant (~300) for breakfast than for those at lunch and dinner (~400). The

lowest constant at breakfast accords well with the largest excursion of glycemic level often observed after breakfast in type 1 diabetic patients[12]. The basal insulin infusion rate was higher in the morning than at around noon or in the evening, as previously reported[7,13,14], which favors the notion that the formula for calculating CIR should be modified during the day. The circadian change of the levels of hormones that counteract with insulin appears to contribute to the diurnal variation of the basal insulin infusion rate[15–17]. Furthermore, evidence suggests that the length of fasting time before a meal modulates insulin sensitivity[18,19], which also likely influences the diurnal variation of CIR.

In conclusion, the products of CIR and TDD of type 1 diabetic patients treated with CSII varied for each meal of the day, and were approximately 300, 500 and 400 at breakfast, lunch, and dinner respectively. The limitations of the present study are the small number and the relatively homogenous characteristics of the participants, comprised mostly of non-obese Japanese adults. Further study is thus required to validate whether our proposal; that is, the 300–500–400 rule, is applicable to patients of different ages, physical constitutions and ethnicities.

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