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ORIGINAL ARTICLE

Basal insulin requirement in patients with type 1 diabetes depends on the age and body mass index

Yukari Mitsui[1], Akio Kuroda[2]*, Masashi Ishizu[2], Hiroyasu Mori[2], Kiyoe Kurahashi[1], Takeshi Kondo[3], Sumiko Yoshida[1], Yuko Akehi[2], Ken-ichi Aihara[4], Itsuro Endo[5], Masahiro Abe[1], Munehide Matsuhisa[2]

[1]Department of Hematology, Endocrinology and Metabolism Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan, [2]Diabetes Therapeutics and Research Center, Tokushima University, Tokushima, Japan, [3]Department of Endocrinology and Metabolism, Tokushima Red Cross Hospital, Komatsushima, Japan, [4]Department of Community Medicine and Medical Science, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan, and [5]Department of Bioregulatory Sciences, Tokushima University Graduate School of Medical Sciences, Tokushima, Japan

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***Correspondence**
Akio Kuroda
Tel.: +81-88-633-7587
Fax: +81-88-633-7589
E-mail address:
kurodaakio@tokushima-u.ac.jp

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ABSTRACT

Aims/Introduction: To investigate the basal insulin requirement in patients with type 1 diabetes who are on multiple daily injections (MDI) and to assess the patient characteristics that affect the percent of total daily basal insulin dose to the total daily insulin dose (%TBD/TDD).

Materials and Methods: The subjects of this study were 67 inpatients with type 1 diabetes who were served diabetic meals of 25–30 kcal/kg standard body weight during several weeks of hospitalization. The basal insulin requirement was adjusted to keep the blood glucose level from bedtime to before breakfast within a 30 mg/dL difference. The bolus insulin dose before the meal was adjusted to keep the blood glucose level below 140 and 200 mg/dL before and 2 h after each meal, respectively. The total daily insulin dose (TDD), the percent of total daily basal insulin dose (TBD) to TDD (%TBD/TDD), and clinical characteristics were collected.

Results: The median (Q1, Q3) of TDD was 33.0 (26.0, 49.0) units, and the %TBD/TDD was 24.1 ± 9.8%. The %TBD/TDD was positively correlated with the body mass index (BMI) and negatively correlated with the age at the onset and at the examination according to a univariate analysis. However, the %TBD/TDD was dependent on the BMI ($\beta = 0.340$, $P = 0.004$) and the age at examination ($\beta = -0.288$, $P = 0.012$) according to the multiple regression analysis.

Conclusions: The average %TBD/TDD in patients with type 1 diabetes on MDI was approximately 24% under inpatient conditions. The basal insulin requirement was dependent on the BMI and the age at examination.

INTRODUCTION

Type 1 diabetes is the result of the autoimmune destruction of insulin-producing beta cells in the pancreas, which results in insulin deficiency and high blood glucose[1,2]. Type 1 diabetes develops over years before the diagnosis in general[3]. To compensate for insulin deficiency, intensive insulin therapy is prescribed to mimic physiological insulin secretion. Such insulin therapy involves multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII).

Continuous subcutaneous insulin infusion provides a fine-tuning program of insulin doses every hour to achieve intensive glycemic control. However, it is associated with several disadvantages, such as difficulty in handling equipment and high medical costs. For these reasons, patients who choose CSII tend to have a longer duration of disease, a higher level of education, more diabetes-related knowledge, and a more stable financial background[4]. However, over 90% of patients with type 1 diabetes are on MDI in Japan. The MDI approach is easier than insulin pump therapy for patients who are unfamiliar with device handling, who are elderly, and who have low motivation for treatment[5,6]. The majority of patients with type 1 diabetes,

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therefore, are treated with MDI, and it is necessary to establish an adequate insulin algorithm that takes individual characteristics into account.

The MDI approach involves a basal insulin amount to maintain a stable blood glucose level not only during the night but also during the day, and bolus insulin is administered to control postprandial hyperglycemia and to correct instances of hyperglycemia. An excessive or short dose of basal insulin may result in a loss of blood glucose control early in the morning. The bolus insulin dose is expected to be adjusted by the patient according to the blood glucose level determined by self-measurement[7]. Physicians provide guidance on carbohydrate counting and set an appropriate insulin sensitivity factor (ISF) and carbohydrate-to-insulin ratio (CIR). The ISF refers to the amount by which 1 unit of insulin lowers the blood glucose, and the CIR refers to the amount of carbohydrate that 1 unit of insulin covers[8].

The basal insulin requirement was recommended to be 50% of the total daily insulin dose (TDD) in patients with type 1 diabetes; however, this was based on empirical data and was not investigated in subjects receiving recommended diabetic meals[9–10]. The percentage of the total daily basal insulin dose (TBD) in TDD (%TBD/TDD) in patients with type 1 diabetes has been reported under treatment with CSII[11,12], but it has not been reported in detail for patients with type 1 diabetes on MDI under a strict diabetic diet during hospitalization. In addition, few reports have described the patient background characteristics that influence the %TBD/TDD in adult patients with type 1 diabetes[13].

Most patients with type 1 diabetes are thought to be insulin-deficient, but there are some who are still positive for serum C-peptide because of a short duration of diabetes. There are also some patients with long-standing type 1 diabetes who maintain some residual insulin secretion ability. These patients also have positive serum or urine C-peptide levels[14].

The present study investigated the basal insulin requirement in patients with type 1 diabetes receiving MDI and assessed the patient characteristics that influenced the %TBD/TDD.

METHODS

Study design and population

Sixty-seven patients were consecutively selected who met the inclusion and exclusion criteria and gave their signed informed consent. The inclusion criterion of this study was patients with type 1 diabetes diagnosed by a diabetes specialist. The patients were admitted to the hospital to improve an optimal glycemic control with MDI. Only adult cases were eligible for the study, and children under 18 years of age were excluded from the study. We also excluded individuals who were using an insulin pump; who had eating disorders, concomitant dietary restrictions, unstable retinopathy, renal failure, liver dysfunction; who were pregnant; who were using other antidiabetic agents or steroids; and who were otherwise not eligible for this study. The present study was approved by the ethics committee of Tokushima University Hospital (approval #2319-1). It was conducted from April 2010 to September 2018.

According to the guidelines of the Japanese Diabetes Society, the diabetic meals in all patients were 25–30 kcal/kg standard body weight, consisting of 50–60% carbohydrates, 15–20% protein, and 20–25% fat and were prepared by dietitians. No additional food or drink was consumed unless required to treat hypoglycemia. The patients' physical activity varied from sedentary to a mildly active state, and moderate to marked activity was limited. The participants used insulin aspart, lispro, glulisine, or regular insulin for bolus insulin and insulin glargine U-100, detemir, glargine U-300, or degludec for basal insulin.

During hospitalization, self-monitoring of blood glucose was performed at least four times and up to seven times daily (before and 2 h after each meal and before going to sleep) to optimize the insulin requirement. The basal insulin dose was titrated to keep the blood glucose readings from bedtime to early morning to an approximately 30 mg/dL difference. To prevent the onset and progression of diabetic microangiopathy, the target fasting plasma glucose levels were set at <140 mg/dL, and the target 2 h post-meal plasma glucose level was set at <200 mg/dL[15]. The TDD, %TBD/TDD, and total daily bolus insulin dose were collected after the target blood glucose level had been achieved for at least 3 days. Diurnal variation of the sensor glucose level was assessed using continuous glucose monitoring (CGM) during hospitalization in 37 out of 67 patients (CGM: Gold: two patients/CGM: iPro: 21 patients/Intermittent CGM: Freestyle Libre: 14 patients). The average of 7 point glucose testing for the final 3 days of the study period was collected. The fasting serum C-peptide level was measured using an enzyme immunoassay kit (ST AIA-PACK C-peptide; Tosoh, Tokyo, Japan).

Of the eligible cases, 27 had their GAD antibody titer measured before 1 December 2015 with a radioimmunoassay, and 40 had it measured after that date with an enzyme-linked immunosorbent assay.

Statistical analyses

The Shapiro-Wilk test was performed to evaluate the normality of continuous variables. Data were described as the mean ± standard deviation (SD), median (Q1, Q3), or n (%). Pearson's correlation coefficient or Spearman's rank correlation coefficient were calculated to examine the correlation between the %TBD/TDD and eight clinical variables: age at examination, gender, age at onset, duration of diabetes, BMI, serum C-peptide level, GAD antibody, and stage of retinopathy. A multiple regression analysis was used to identify significant predictors of the %TBD/TDD. Clinical variables with $P < 0.1$ in the correlation analysis were included in the multiple regression analysis. Variables that were not normally distributed were bisected by the median, and the group with the lowest value was used as a reference.

The SPSS Statistics 26 software program (IBM Japan, Tokyo, Japan) was used for the statistical analyses. Statistical tests were 2-sided, and the threshold for significance was a P value <0.05.

RESULTS

A total of 67 Japanese patients with type 1 diabetes finished this study. These subjects' characteristics are shown in Table 1. Insulin secretion was preserved in some cases, and the median fasting serum C-peptide level was 0.0 (0.0, 0.4) ng/mL, while the median urinary C-peptide level was 2.3 (0.0, 19.8) μg/day. The types of basal insulin used were insulin degludec (n = 36), glargine U-100 (n = 24), detemir (n = 4), and glargine U-300 (n = 2), with one not using basal insulin. The basal insulin requirement was not markedly different among the basal insulin types (data not shown).

The 7 point blood glucose profile (after 3 days of achieving glycemic control goals) is shown in Figure 1. The pre-meal blood glucose levels were 127.0 ± 30.7 mg/dL, and the average 2 h value after meals was 160.1 ± 45.1 mg/dL, which was within the set target blood glucose range. The mean difference between bedtime and early-morning blood glucose levels was <30 mg/dL in 30 of 67 patients, with a mean difference of 17.5 mg/dL and an absolute difference of 37.0 mg/dL. A total of 1,334 blood glucose measurements were performed over 3 days, of which 50 showed hypoglycemia, with a level below 70 mg/dL. In addition, a few patients required a small dose of insulin to correct high blood glucose levels before sleep; however, it had no marked effect on the TDD. The CGM raw data for 16 patients were collected during the 3 days of evaluation. These raw data are shown as a supplementary figure.

Table 1 | Patient characteristics

	n = 67
Males/females	28/39 (41.8/58.2%)
Age at examination (years)	51.6 ± 15.8
Duration of diabetes (year)	8.0 (2.0, 16.0)
Age of onset (years)	40.2 ± 19.3
Body mass index (kg/m^2)	22.0 (19.6, 25.0)
Length of hospital stay (days)	16.0 (12.0, 22.0)
HbA1c (%)	9.3 (8.0, 10.5)
Serum C-peptide levels (ng/mL)	0.0 (0.0, 0.4)
Urine C-peptide levels (μg/day)	2.3 (0.0, 19.8)
GAD antibody (U/mL)	6.4 (0.0, 113.2)
Basal insulin type, n (%)	
Degludec	36 (53.7%)
Glargine U-100	24 (35.8%)
Detemir	4 (6.0%)
Glargine U-300	2 (3.0%)
Not in use	1 (1.5%)
Bolus insulin type, n (%)	
Aspart	37 (55.2%)
Glulisine	13 (19.4%)
Lispro	11 (16.4%)
Regular	6 (9.0%)
Retinopathy, n (%)	
None	43 (64.2%)
Background	13 (19.4%)
Proliferative	11 (16.4%)
Nephropathy, n (%)	
None	54 (80.6%)
Microalbminurea	7 (10.4%)
Macroalbuminurea	6 (9.0%)
Serum creatinine	0.63 (0.54, 0.78)
eGFR	80.0 (68.4, 97.6)
CCr (Cockcroft-Gault)	90.0 (76.4, 125.3)
CVR-R (%)	2.1 (1.5, 3.0)
CVR-R with deep breathing (%)	3.6 (2.4, 5.5)
Orthostatic hypotension, n (%)	11 (16.4%)
Absence of ATR, n (%)	17 (25.4%)

Data are presented as the mean ± standard deviation, median (Q1, Q3) or n (%). ATR, achilles tendon reflex, CCr, creatinine clearance; CVR-R, coefficient of variation R-R.

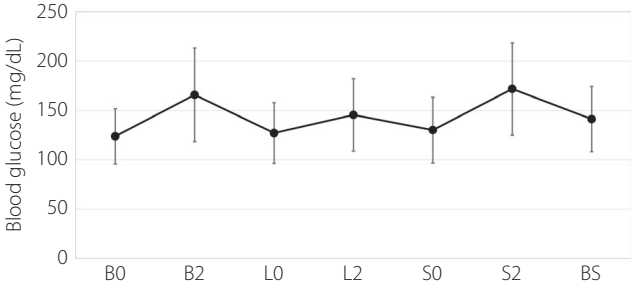

Figure 1 | Daily variation in blood glucose levels. Seven-point blood glucose profile during the final 3 days of hospitalization in type 1 diabetes patients: B0, before breakfast; B2, 2 h after breakfast; L0, before lunch; L2, 2 h after lunch; S0, before supper; S2, 2 h after supper; BS, before sleep. Data are shown as the mean ± SD.

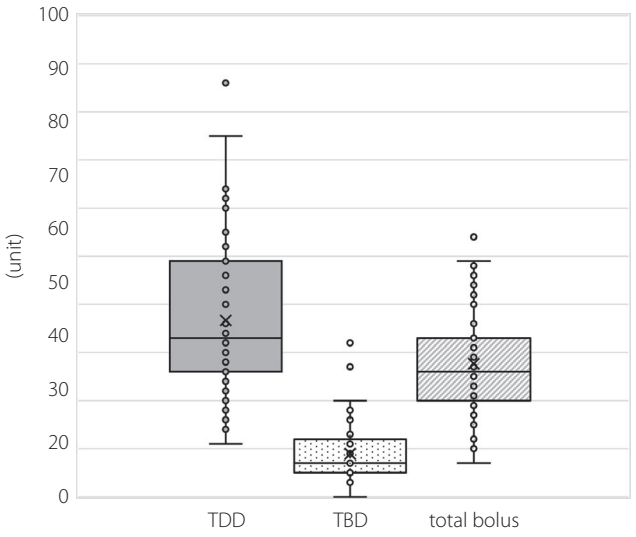

Figure 2 | TDD, TBD, and total bolus insulin. TBD, total daily basal insulin dose; TDD, total daily insulin dose; total bolus, total daily bolus insulin dose.

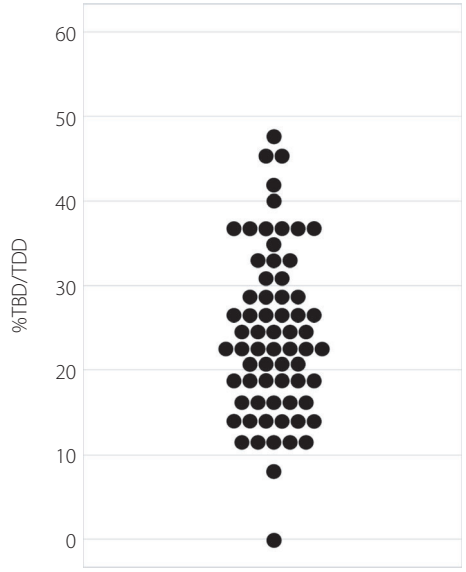

Figure 3 | The %TBD/TDD. Closed circles indicate patient data. TBD, total daily basal insulin dose; TDD, total daily insulin dose.

Table 2 | The correlation between %TBD/TDD and eight clinical variables

Variable	Correlation analysis	
	r	*P*-value
Sex ($F = 0$)‡	–0.038	0.763
Body mass index (kg/m^2)‡	0.489	<0.001
Age at examination (years)†	–0.270	0.027
Duration of diabetes (years)‡	0.239	0.052
Age at onset (years)†	–0.370	0.002
Urine C-peptide levels (μg/day)	–0.189	0.128
Serum C-peptide levels (ng/mL)‡	–0.211	0.087
GAD antibody (U/mL)‡	–0.080	0.534
Severity of retinopathy‡	0.156	0.207

TBD, total daily basal insulin dose; TDD, total daily insulin dose. †Pearson's correlation coefficient analysis. ‡Spearman's rank correlation coefficient analysis.

Table 3 | The independent factors accounting for %TBD/TDD

Variable	Multiple regression analysis	
	β	*P*-value
Body mass index (kg/m^2)	0.340	0.004
Age at examination (years)	–0.288	0.012
Duration of diabetes (years)	0.114	0.358
Serum C-peptide levels (ng/mL)	–0.118	0.325

TBD, total daily basal insulin dose; TDD, total daily insulin dose.

The 3 day insulin requirement was evaluated. The TDD was 33.0 (26.0, 49.0) units, the TBD was 7.0 (5.0, 12.0) units, and the total bolus insulin dose was 26.0 (20.0, 33.0) units (Figure 2). The %TBD/TDD was 24.1 ± 9.8% (Figure 3).

Pearson's correlation coefficient and Spearman's rank correlation coefficient between the %TBD/TDD and clinical characteristics are shown in Table 2. The %TBD/TDD was significantly correlated with the BMI ($r = 0.489$, $P < 0.001$), age at the examination ($r = –0.270$, $P = 0.027$), and age at the onset of diabetes ($r = –0.370$, $P = 0.002$; Table 2). Among these values, the BMI ($\beta = 0.340$, $P = 0.004$) and age at the examination ($\beta = –0.288$, $P = 0.012$) were shown to be independent factors influencing the %TBD/TDD, and the duration of diabetes and serum C-peptide levels were not selected in the multiple regression analysis (Table 3).

DISCUSSION

We investigated the basal insulin requirement in patients with type 1 diabetes who were treated with MDI under hospitalized conditions. The %TBD/TDD was 24.1 ± 9.8%, which was found to be related to the BMI and age at examination.

The majority of Japanese type 1 diabetes patients are treated with MDI, and smaller numbers of patients are treated with CSII than in the United States and European countries[5,6,16,17]. To our knowledge, there are fewer published reports describing the basal insulin requirements in patients with type 1 diabetes treated with MDI under hospitalized conditions than in those treated with CSII[18].

Many studies and guidelines in Europe and the United States have reported that the %TBD/TDD of adult type 1 diabetes patients is approximately 50%[9–10]; however, it was recently reported that this value is approximately 30–40%[18,19]. Two reports from Japan evaluating the %TBD/TDD in hospitalized adult type 1 diabetes patients under insulin pump treatment showed that the %TBD/TDD was 27.7 ± 6.9%[11] and 27.3 ± 6.7%[12], respectively. In the present study, the %TBD/TDD of type 1 diabetes patients treated with MDI was 24.1 ± 9.8%, which was slightly lower than that reported for CSII, and the variability (SD) among patients was higher than among those treated with CSII. Kuroda *et al.*[11] reported that patients who used CSII were all deficient in serum C-peptide. The present study included patients with varied durations of diabetes; some patients with a short duration of diabetes had high serum C-peptide levels, and vice versa. This might be why the SD of %TBD/TDD was larger than in previous CSII reports. Neither the duration of diabetes nor the serum C-peptide levels were selected as determinants of %TBD/TDD in this study; however, we found that the age and BMI at the time of the evaluation were determinants of the %TBD/TDD according to the multivariate regression analysis.

The age at the time of the evaluation and %TBD/TDD were negatively correlated, i.e. the proportion of basal insulin tended to be lower in older patients and higher in younger patients.

There have been some reports of the relationship between age and basal insulin requirements in pediatric patients with type 1 diabetes[20–22], but few studies dealing with adults have been reported. Scheiner and Boyer reported that type 1 diabetes patients had the highest %TBD/TDD among teens, with a 33% reduction in the elderly group over 60 years old compared with the group that was 20–60 years old[13]. They also reported that the basal insulin requirements and circadian variability were influenced by growth hormone (GH) and cortisol, both of which deteriorate glucose metabolism. In general, GH secretion peaks in puberty (12–16 years old) and decreases with age thereafter[23], this is also observed in type 1 diabetes patients[24]. GH secretion has been reported to be associated with the dawn phenomenon[25]. The reduction in GH secretion with age may be the mechanism underlying the reduction in the dawn phenomenon, which in turn may reduce the basal insulin requirements. Compared with a previous CSII study[11], the age at the examination was significantly higher in the present study ($P < 0.001$), which might be one reason for the basal insulin requirement being slightly low.

The BMI was found to be positively correlated with %TBD/TDD, i.e. obesity tended to increase the proportion of basal insulin. Although several studies have examined this trend, no clear trend has been obtained, and the mechanism responsible is unknown[26–30]. Because an increase in hepatic glucose production plays a major role in the regulation of fasting hyperglycemia[31], insulin resistance in the liver due to obesity may be involved[32–35]. Obesity-induced circulating and hepatic lipids may contribute to hepatic insulin resistance via the activation of isoforms of protein kinase C[35].

The types of basal insulin and target glucose levels at fasting and pre-meal state and 2 h after a meal might affect the % TBD/TDD in this study. However, the target glucose levels (less than 140 in the fasting state and before a meal, and less than 200 mg/dL 2 h after a meal) were close to the recent recommendation of Time in Range (70–180 mg/dL)[36]. In addition, we compared the %TBD/TDD according to properties of basal insulin, but we could not find any difference in the %TBD/TDD according to the properties of basal insulin. Therefore, we believe that the present observations could be adapted in the clinical setting.

Several limitations associated with the present study warrant mention. First, this was a retrospective observational study with a limited small number of patients. The further study will need a prospective design with a larger sample size. Second, the data reported here were collected from a single center in Japan; therefore, our conclusions cannot be automatically extended to other races. Finally, since the daily blood glucose profile was performed only by fixed-point observation using a portable blood glucose meter, the blood glucose profile from night to dawn could not be observed. However, 58 of the 67 patients were monitored for nocturnal blood glucose trends with blood glucose monitoring at 3:00 a.m. or continuous glucose monitoring in order to avoid late-night instances of hypoglycemia.

The strength of our study is that all patients were strictly controlled with a special diabetic diet provided while they were hospitalized, and their insulin requirements were evaluated until they achieved values in the target blood glucose range.

In conclusion, the %TBD/TDD of type 1 diabetes patients during MDI was approximately 24%. It is important to set the %TBD/TDD on an individual basis while considering the patient background characteristics, such as the BMI and age.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | CGM data of each 3 days for 16 participants.