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SHORT ARTICLE

Correlation between insulin resistance score and daily total insulin dosage in patient with type 1 diabetes mellitus: a pilot study

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Abstract

Purpose of the study Although insulin resistance is the pathogenic basis of type 2 diabetes mellitus (T2DM), it can also affect patients with type 1 diabetes mellitus (T1DM). In this clinical study, we investigated the relationship between insulin resistance grade and daily insulin dosage in order to clarify whether the approach to improving insulin resistance along with insulin therapy should be considered to treat T1DM and T2DM.

Methods As the means of insulin resistance estimation, we selected the insulin resistance score because patients use insulin therapy and homeostatic model assessment insulin resistance (HOMA-IR) is not appropriate for those patients. The insulin resistance score was calculated as 24.31 – (12.22 × WHR) – (3.29 × HT) – (0.57 × HbA1c), where WHR is the waist-to-hip ratio, HT is hypertension, and HbA1c is glycated hemoglobin (%).

Results The insulin resistance score was negatively correlated with the body mass index (BMI; r = –0.511) and the WHR (r = –0.773). The total insulin dosage was positively correlated with the BMI (r = 0.734) but negatively correlated with the insulin resistance score (r = –0.540).

Conclusion Insulin resistance estimation is necessary for T1DM treatment, and the insulin resistance score is a useful tool for estimating insulin resistance in patients with T1DM accompanied with insulin resistance.

Keywords Insulin resistance · Insulin resistance score · Type 1 diabetes mellitus · Insulin therapy

Introduction

Type 1 diabetes mellitus (T1DM) results from primary loss of β-cell mass due to complex autoimmune processes with consecutive insulin deficiency. For long the presence of insulin resistance in T1DM has been unclear. However, recent clinical and experimental evidence suggests that insulin resistance can indeed be present in T1DM [1]. In this clinical study, we studied the relationship between insulin resistance (IR) grade and daily insulin dosage in order to clarify whether the approach to improving IR along with insulin therapy should be considered to treat T1DM.

Materials and methods

Subjects

The study protocol used was reviewed and approved by the review boards of Hidaka Hospital (Takasaki City, Gunma

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Prefecture, Japan; #335) and the Saku Central Hospital Advanced Care Center (Saku City, Nagano Prefecture, Japan; R201811-03) in accordance with the Declaration of Helsinki.

In this two-center retrospective study, we used the electronic records of 32 patients who visited Hidaka Hospital and the Saku Central Hospital Advanced Care Center every month between 2020 and 2021 for T1DM treatment.

The exclusion criteria were as follows: patients treated with glucocorticoids, those who were anemic (hematocrit < 39% in men and < 36% in women), and those with compromised glucose levels (such as pregnant women). In addition, patients with cancer were also excluded.

T1DM was diagnosed if there was history of ketoacidosis or fasting C-peptide <0.3 PMol/mL and stimulated C-peptide <0.6 PMol/mL or if insulin treatment was required from the time of diagnosis [2].

Blood examination

Venous blood samples were collected into tubes containing EDTA and fluoride. Plasma was separated from whole blood within 1 h after collection. The casual plasma glucose (PG) and glycated hemoglobin (HbA1c; %) were measured according to the hexokinase method using a Synchro CX4/CX5 glucose analyzer (Beckman Coulter Inc., Fullerton, CA, USA) and Glycohemoglobin Analyzer RC20 (Sekisui Medical Co., Ltd, Tokyo, Japan), respectively. Both intra- and inter-assay coefficients of variation were ≤ 2% at PG values of < 126 mg/dL.

Estimation of the IR score

The IR score (estimated glucose disposal rate (eGDR), a validated, inverse measure of insulin resistance derived from hyperinsulinemic-euglycemic clamp studies) was calculated as 24.395 – (12.971 × WHR) – (3.388 × HT) – (0.601 × HbA1c), where WHR is the waist-to-hip ratio and HT is hypertension [3]. Hypertension is blood pressure ≥140/90 mmHg or use of blood pressure lowering medication (0= no, 1 = yes) [3]. The IR score was presented in milligrams per kilogram per minute [3].

Statistical analysis

All statistical data were analyzed using SPSS software version 10.0 (SPSS Inc., Chicago, IL, USA). To estimate the linear correlation between variables, we calculated Pearson's correlation coefficient.

Results

Characteristics of subjects at baseline measurements

Table 1 presents the patients' characteristics at baseline measurements. The median duration with T1DM was 20 years (range ~ 5–42). The patients' median age was 59 (range ~ 29–85) years. The median body height (BH) was 161.2 (range ~ 151.6–175.0) cm, the median body weight (BW) was 57.1 (range ~ 45.9–123.0) kg, and the median body mass index (BMI) was 23.4 (range ~ 17.9–40.2) kg/m^2. The median estimated glomerular filtration rate (eGFR) of the patients was 68.0 (range ~ 32.0–128.0) mL/min/1.73 m^2. The median systolic blood pressure (SBP) was 124.0 (range ~ 92–198) mmHg, the median diastolic blood pressure (DBP) was 69.0 (range ~ 47–95) mmHg, and the median HbA1c was 7.65 (range ~ 5.5–12.7) %. The median total insulin dosage was

Table 1 Patient characteristics

	Median	Min.	Max.
Duration with T1DM (year)	20	5	42
Age (years old)	59	29	85
BH (cm)	161.2	151.6	175
BW (kg)	57.1	45.9	123
BMI (kg/cm^2)	23.4	17.9	40.2
WHR	0.91	0.68	1.04
SBP (mmHg)	124	92	198
DBP (mmHg)	69	47	95
GOT (IU/L)	20	9	33
GPT (IU/L)	18	7	23
SCr (mg/dL)	0.74	0.53	1.46
eGFR (mL/Min/1.73m^2)	68	32	128
HDL (mg/dL)	59.5	30	103
LDL (mg/dL)	103	60	146
TG (mg/dL)	110	51	326
PG (mg/dL)	167	77	375
HbA1c (%)	7.65	5.5	12.7
Total insulin dosage (unit/day)	28	8.4	99
IR score (mg/kg/min)	6.09	1.85	11.78
Sex (F/M)	16/16		
Antihyperlipidemic drugs (Y/N)	8/32		
Antihypertensive drugs (Y/N)	17/32		

The characteristics of the participants at baseline measurements were summarized

BH, body height; *BW*, body weight; *BMI*, body mass index; *WHR*, waist-to-hip ratio; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *GOT*, glutamic oxaloacetic transaminase; *GPT*, glutamic pyruvic transaminase; *SCr*, serum creatine; *eGFR*, estimated glomerular filtration rate; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *TG*, triglyceride; *PG*, plasma glucose; *HbA1c*, glycated hemoglobin

28.0 (range ~ 8.4–99) units/day, and the median IR score was 6.09 (range ~ 1.85–11.78) mg/kg/min.

Relationship between IR score and BMI, and WHR in patients with T1DM

Figure 1 illustrates the regression coefficients of the univariate linear regression between the IR score and the BMI (Fig. 1A) and the WHR (Fig. 1B). The IR score was negatively correlated with the BMI (r = –0.511) and the WHR (r = –0.773).

Relationship between total insulin dosage and BMI, and IR score in patients with T1DM

Figure 2 illustrates the regression coefficients of the univariate linear regression between the total insulin dosage and the BMI (Fig. 2A) and the IR score (Fig. 2B). The total insulin dosage was positively correlated with the BMI (r = 0.734) but negatively correlated with the IR score (r = –0.540).

Discussion

The euglycemic-hyperinsulinemic clamp is a gold standard method to estimate insulin resistance [4]. However, the euglycemic-hyperinsulinemic clamp is a costly and invasive procedure, and sample size is limited [4]. Therefore, based on the clinical characteristics of hypertension, WHR, triglyceride and HDL cholesterol levels, family history of type 2 diabetes, and glycemic control, an IR score was developed and validated using the euglycemic-hyperinsulinemic clamp in a subset (n = 24) of the Pittsburgh Epidemiology of Diabetes Complications (EDC) population [4]. The results from the IR score and estimated glucose disposal rate (GDR) are remarkably consistent [4]. Alternatively, the frequently sampled intravenous glucose tolerance test could have been used to assess insulin resistance [5]. In type 1 diabetes, this testing would have also required an overnight hospital admission for discontinuation of long-acting insulin and stabilization of glucose levels, a practice that could also limit sample size. Thus, the IR score is a validated clinical tool for estimating insulin sensitivity in T1DM [3, 4].

Several studies have assessed IR score cutoffs. Tam et al. found that patients with an IR score of < 5.6 mg/kg/min are insulin resistant [6]. Epstein et al. found that most patients with IR have an IR score of < 5.39 mg/kg/min [7]. Šimonienė et al. estimated that the IR score cutoff that reflects IR is < 6.4 mg/kg/min [8]. In this study, the median IR score was 6.09 (range ~1.85–11.78), suggesting that some of the patients had IR.

Obesity is related to IR. Low-grade inflammatory cells (e.g., adiponectins, tumor necrosis factor) in adipose tissue cause IR [9]. Although the frequency of T1DM with obesity is rare compared to that of T2DM with obesity, obesity in T1DM has become a clinical problem [10, 11]. Obesity in T1DM might be explained, in part, by intensive insulin therapy, which causes insulin-induced IR. The distribution of the BMI in our study was ~17.9–40.2 kg/m^2, suggesting that some of the patients were obese. Importantly, we found a strong negative correlation between the IR score and the BMI (Fig. 1A) and the WHR (Fig. 1B). Thus, consistent with previous studies [6–8], the IR score showed a good negative correlation with representative indicators of obesity, suggesting that the IR score is a good indicator of IR and is affected by obesity.

We discovered that the daily total insulin dosage is significantly positively correlated with the BMI (Fig. 2A) and significantly negatively correlated with the IR score (Fig. 2B). Thus, overweight patients tend to be prescribed more insulin, and patients with severe IR also tend to use more insulin. Over-insulinization induces overweight [9, 10], and there seems to be a vicious circle between overweight and over-insulinization, which can be avoided with appropriate insulin dosage. As our current data indicated that the IR score is significantly negatively correlated with the daily total insulin dosage, a reduction in IR is required for treating patients with T1DM. This approach will increase the treatment efficacy of insulin therapy and reduce the risk of hypoglycemia and inappropriate weight gain. In addition, conventional risk factors

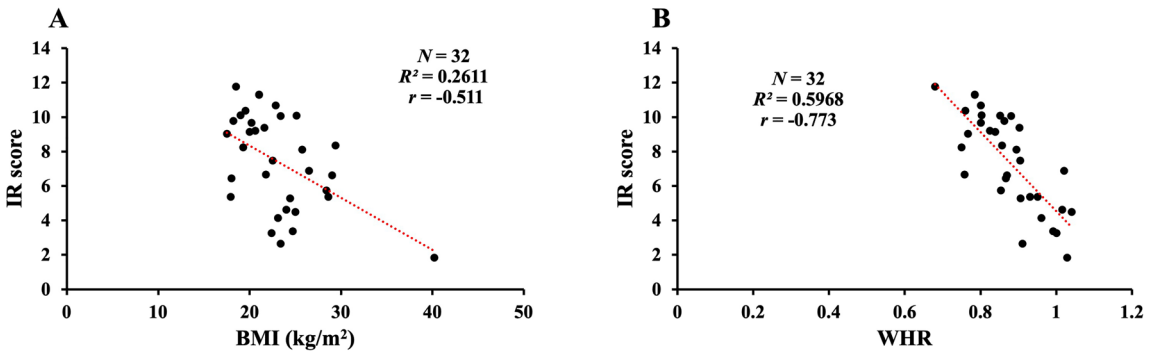

Fig. 1 Correlation between the IR score and the BMI and the WHR in patients with T1DM. The regression coefficients of the univariate linear regression between the IR score demonstrated a negative correlation with **A** the BMI (r = –0.511) and **B** the WHR (r = – 0.773). T1DM, type 1 diabetes mellitus; IR score, insulin resistance score; BMI, body mass index; WHR, waist-to-hip ratio

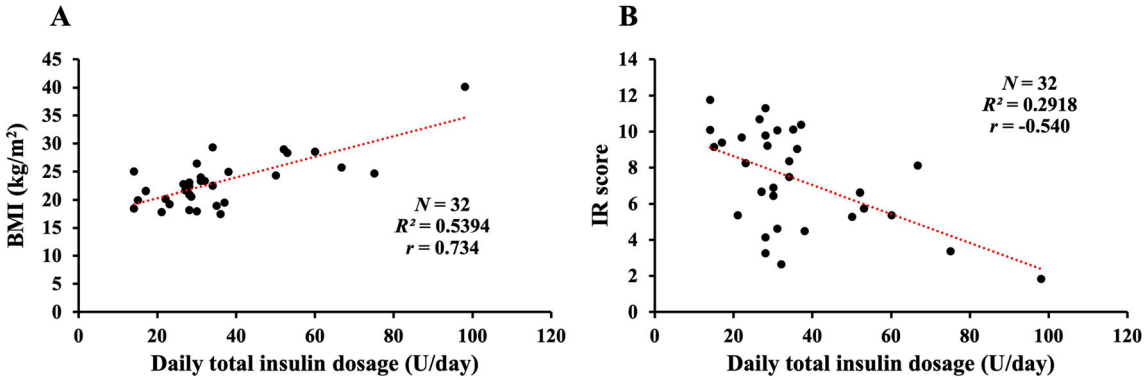

Fig. 2 Correlation between the total insulin dosage and the BMI and the IR score in patients with T1DM. The regression coefficients of the univariate linear regression between the total insulin dosage demonstrated **A** a positive correlation with the BMI (r = 0.734) and **B** a negative correlation with the IR score (r = –0.540). T1DM, type 1 diabetes mellitus; BMI, body mass index; IR score, insulin resistance score

(e.g., HT, overweight, dyslipidemia) generally predict adverse cardiovascular disease (CVD) outcomes, and the IR score or IR is the strongest independent factor for CVD [12]. Therefore, the estimation of IR is important and the IR score is a validated clinical tool for patients with T1DM.

How do we improve IR in patients with T1DM? Numerous small trials on people with T1DM have evaluated metformin, with the hope that its insulin-sensitizing properties would improve glycemic management or reduce CVD risk [13, 14]. The largest study to date assessed the use of 1 g of metformin, twice daily, in 428 patients with T1DM who were treated for 3 years, with the primary end point being changes in the mean carotid intima–media thickness, a marker of CVD risk. The study ultimately found no difference in the primary end point, minimal and nonsustained effects on HbA1c, minimal effects on weight (~1-kg reduction), and no change in the total daily insulin dose [15]. Thus, we need to focus on appropriate diet therapy and physical exercise to avoid obesity and improve IR. In addition, new medicine to improve IR in patients with TIDM needs to be developed.

The limitation of this study was the relatively small sample size, which could decrease the probability to detect real differences between groups.

Conclusion

IR estimation is necessary for T1DM treatment, and the IR score is a useful tool for estimating IR in patients with T1DM accompanied with IR.

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Author contribution TW and SO collected the data. EY, KO (Okada), KK, KO (Ohshima), and SO analyzed the data. JO and SO prepared the manuscript.

Data availability The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Ethics approval The ethics committees at Hidaka Hospital and Saku Central Hospital Advanced Care Center approved our study, which conformed to the Declaration of Helsinki (as #355 and R201811-03, respectively).

Informed consent All patients provided written informed consent to analyze and present their clinical laboratory data.

Consent for publication All of the authors have also agreed to submit our manuscript to your journal.

Conflict of interest The authors declare no competing interests.

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