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ORIGINAL ARTICLE

ANALYSIS OF GLYCEMIC VARIABILITY AND INSULIN RESISTANCE IN PATIENTS WITH PANCREATIC DIABETES USING A CONTINUOUS GLUCOSE MONITORING SYSTEM

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Abstract The purpose of this study was to analyze glycemic variability and insulin resistance of different types of diabetes, emphasizing mainly pancreatic diabetes, using Continuous Glucose Monitoring System (CGMS). The study involved a total of 59 patients receiving care at our department: 11 with pancreatic diabetes, 37 with type 2 diabetes, and 11 with type 1 diabetes. The CGMS data and several markers of insulin resistance were compared among the 3 groups and correlations were analyzed statistically. Standard deviation (SD_{CGMS}) measured with CGMS and high molecular weight (HMW) adiponectin (Ad) as parameters of insulin resistance were identified as factors strongly affecting glycemic variability and insulin resistance. The magnitude of glycemic variability in patients with pancreatic diabetes was as large as that in patients with type 1 diabetes. Insulin resistance in patients with pancreatic diabetes was comparable to that in patients with type 1 diabetes. Our results suggest that CGMS data allow evaluation of both glycemic variability and insulin resistance in patients with pancreatic diabetes. HMW-Ad also appears to be a useful parameter of insulin resistance in patients with pancreatic diabetes.

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Key words: pancreatic diabetes; continuous glucose monitoring system (CGMS); insulin resistance; adiponectin; glycemic variability.

原　著

持続血糖モニタリングシステムによる膵性糖尿病の血糖変動解析とインスリン抵抗性

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抄録　我々はCGMS(Continuous Glucose Monitoring System)を用いて病態の異なる糖尿病の特徴(インスリン抵抗性を含む)について，特に膵性糖尿病を中心に検討したので報告する．当科通院中の膵性糖尿患者11名，2型糖尿病患者37名，1型糖尿病患者11名の59症例についてCGMSから得られたデータといくつかのインスリン抵抗性評価指標を求めそれらの比較・相関の統計学的な検討を行った．CGMSから得られたStandard deviation (SD_{CGMS})，インスリン抵抗性指標として求めたHigh molecular weight (HMW) adiponectin (Ad)は血糖変動，インスリン抵抗性を評価する因子として強い影響をもつ因子であった．膵性糖尿病患者の血糖変動は1型糖尿病患者と同程度に大きかった．またインスリン抵抗性も1型糖尿病と同程度であった．膵性糖尿病患者のCGMSから得られたデータは血糖変動もインスリン抵抗性も評価できるものであった．またHMW-Adも膵性糖尿病患者のインスリン抵抗性評価指標として有用だと考えられた．

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キーワード：膵性糖尿病；持続血糖モニタリングシステム；インスリン抵抗性；アディポネクチン；血糖変動．

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I. Introduction

Pancreatic diabetes is defined as diabetes associated with other pancreatic disorders like pancreatitis, pancreatic trauma, pancreatectomy, pancreatic tumor, pancreatic hemochromatosis, autoimmune pancreatitis, and pancreatic hypoplasia[1]. Its pathophysiology is considered to be mainly due to loss of pancreatic endocrine function evoked by morphological alterations of pancreas ; however, its clinical manifestation is not well clarified. Diabetes represents a group of metabolic disease characterized by chronic hyperglycemia due to deficiency of insulin effect. The deficiency of insulin effect involves a combination of decreased insulin secretion and increased insulin resistance (insulin sensitivity)[2]. In cases with pancreatic diabetes, patients show not only decreased insulin secretion but also increased insulin resistance to a greater or lesser degree. There is no consensus on insulin resistance in patients with pancreatic diabetes, with some investigators reporting higher insulin sensitivity them in to healthy controls[3] and others reporting lower insulin sensitivity[4]. However, to achieve stable glycemic control, it is necessary to evaluate both insulin secretion and insulin resistance. The glucose clamp method based on the glucose insulin infusion rate (GIR)[5] is the gold standard for evaluation of insulin resistance. This technique is rarely used in clinical practice, as it is costly and complex. As simple parameters for evaluation of insulin resistance, quantitative insulin sensitivity check index (QUICKI = (1/[log (insulin) + log (glucose)])[6] and homeostatic model assessment of insulin resistance (HOMA-R)[7] are used in routine clinical practice, and a report is also available on use of the estimated glucose infusion rate (EGIR) which correlates closely with GIR[8].

Glucagon, one of the counterregulatory hormones, promotes hepatic glucogenesis and glycogenolysis to elevate blood glucose levels under hypoglycemic conditions. In patients with pancreatic diabetes, due to loss of glucagon producing cells "α-cells", hypoglycemia easily occurs before meals or at night with insulin therapy. Blood glucose level also easily changes because of underlying disorders of digestion and malabsorption due to exocrine pancreatic insufficiency[9].

Recently, Continuous glucose monitoring system (CGMS®), capable of serially measuring glycemic profile, is available for clinical use in Japan[10]. In this system, a sensor inserted into subcutaneous tissue measure the glucose level in interstitial fluid by reaction with glucose oxidase (GOD) in the sensor, followed by conversion to electrical signals. Measurement is conducted every ten seconds and the average for each five-minute period is recorded. Two hundred eighty eight measurements are conducted and recorded daily, providing sufficient information to understand circadian glycemic patterns. In cases showing a pattern of intense glycemic variability, the reason involved in such changes can be explored using this system[11]. CGMS® measures the glucose level in interstitial fluid, not blood glucose. However, since CGMS® data are corrected by self-monitoring of blood glucose (SMBG) data, the CGMS® data usually correspond to blood glucose values. We report the glycemic profile in pancreatic diabetes (chronic pancreatitis with decompensated stage or diabetes after pancreatectomy) comparing with the features of type 1 or 2 diabetes using CGMS® and analyzed their features. Furthermore, we sought to determine whether CGMS® data could provide a parameter for evaluation of insulin resistance.

II. Subjects and Methods

Subjects

Glycemic profiles were serially recorded

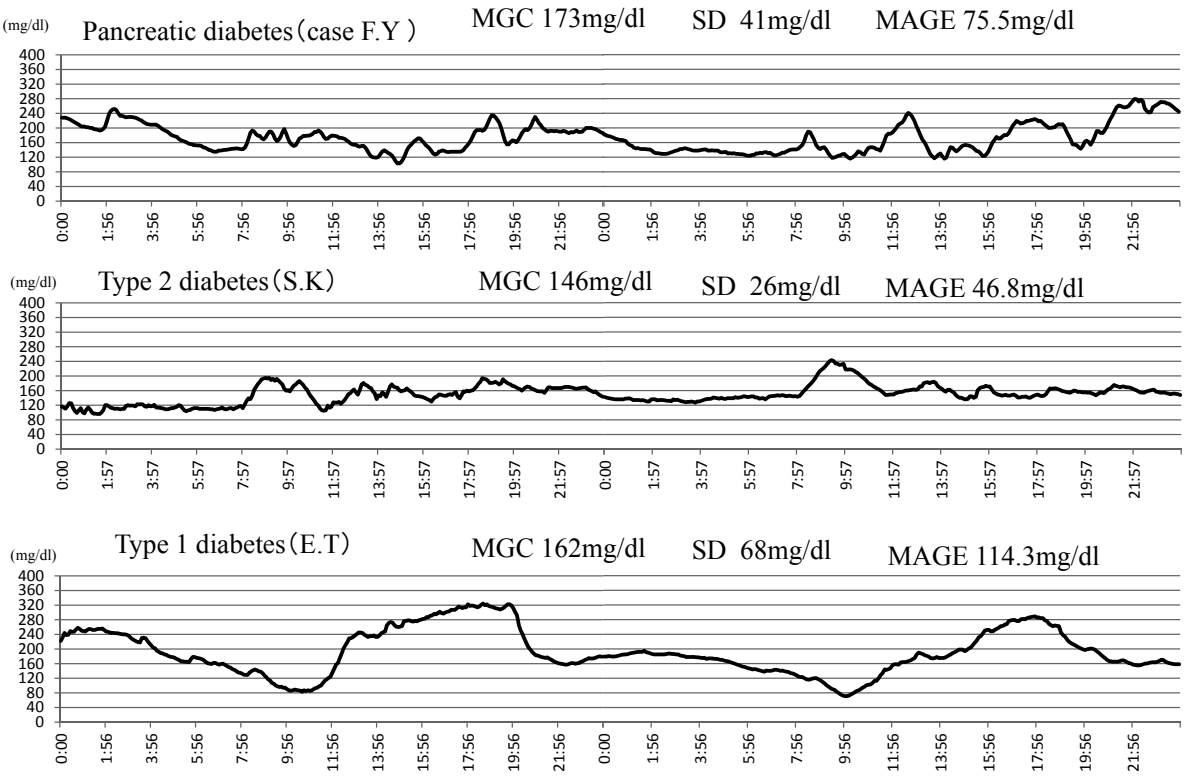


Fig 1 Figure showing temporal profiles of CGMS in a case of patient with Pancreatic diabetes, Type 2 diabetes and Type 1 diabetes.

for 3 days using CGMS® in 59 patients at our department, including 11 with pancreatic diabetes (Group A), 37 with type 2 diabetes (Group B) and 11 with type 1 diabetes (Group C). The glycemic variability of the patients with Pancreatic diabetes, Type 2 diabetes and Type 1 diabetes are shown in Fig 1.

Each patient gave an informed consent before the start of the study which was approved in advance by our institution's ethics committee.

Apparatus and Evaluation Methods

Glycemic variability were measured with CGMS® System Gold™ (Medtronic, Japan). The CGM device approved in Japan is CGMS® System Gold™ which was first marketed in 1999 in Europe/USA by Medtronic. For SMBG, One Touch Ultra™ (Johnson & Johnson, Japan) was used. The followings were analyzed as CGMS® parameters: (1) mean glucose concentration (MGC), (2) standard deviation (SD_{CGMS}) in blood glucose values, (3) mean amplitude of glycemic excursions ($MAGE_{CGMS}$), an parameter of variation in blood glucose[12, 13], and (4) the slope of glycemic variability per 5 minutes, an parameter of the magnitude of elevation or reduction in blood glucose per unit time. For the fourth parameter, blood glucose was measured with CGMS® for 72 hours at maximum, and the data during the intermediate 48-hour period were adopted to avoid influences of unstable monitoring immediately after the start of CGMS® measurement. In addition, the data during the intermediate 48-hour was divided by 24-hour. Average of the slope of glycemic variability per 5 minutes at first and second 24-hour was calculated. This parameter was calculated using the following equation: positive glucose slope (PGS) or negative glucose slope

(NGS) = [(pre-value – post-value) / 5 (min) – (first blood glucose reading – last blood glucose reading) / 1440 (min)].

The following were analyzed as parameters of insulin resistance: body mass index (BMI), waist circumference (WC), serum C-peptide (S-CPR), total-adiponectin (Total-Ad), high molecular weight adiponectin (HMW-Ad), the ratio of HMW-Ad to Total-Ad (HMWR), and EGIR. We did not adopt HOMA-R as an parameter of insulin resistance since it does not correlate with GIR under the limitation in cases with low BMI, compromised pancreaticβ-cell function, high fasting blood glucose levels, and/or pancreatic diabetes or type 1 or 2 diabetes receiving insulin replacement because of insufficient insulin secretion[14].

Measurements

S-CPR was measured with electrochemiluminescence immunoassay (ECLIA). HbA1c level was measured by high performance liquid chromatography (HPLC) using ADAMS™ A1c HA 8180. JDS results were converted into National Glycohemoglobin Standardization Program (NGSP) values by adding 0.4% based on the equation : NGSP value (%)=JDS value (%) +0.4%. Capillary blood glucose level was measured with One-Touch Ultra™ (Johnson & Johnson). Total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) levels were measured by enzymatic methods, using BioMajesty JCA-BM 6070 (JEOL).

T-Ad and HMW-Ad were measured with a human multimeric adiponectin fractional measurement kit (SEKISUI MEDICAL CO., LTD, Japan).

Statistical Analysis

Unpaired analysis of variance (ANOVA) was used for statistical comparison of parametric data among the 3 groups. If this analysis revealed significant differences, the Tukey-Kramer test was employed for multiple comparisons. The Chi-square test was used for non-parametric data. Canonical correlation analysis was used for analysis of correlations between CGMS® parameters and parameters of insulin resistance. Canonical correlation extracts principal components (i.e., canonical variates) from sets of variables in a manner that maximizes shared variance between the sets. The canonical variate explaining the greatest proportion of variance is selected first, and additional orthogonal variates are selected in descending order of importance (i.e., amount of shared variance explained). Standardized canonical coefficients (SC) indicate how the canonical variable is calculated by weighting individual variables, whereas correlations between individual and canonical variables provide a description of the nature of the canonical variables. The ratio of canonical weights (R) is the ratio of the contribution of the variable to the given canonical correlation, controlling for other variables in the equation. The results of canonical correlation analysis were subjected to multivariate analysis using stepwise regression analysis, to calculate standardized partial regression coefficients and to test the significance of differences. Values were expressed as means ± SD. All analyses were conducted using Statcel version 2 (OMS, Japan). $P < 0.05$ was regarded statistically significant.

III. Results

Characteristics of Each Subject Group

Background variables of patients are summarized in Table 1. Age was significantly lower in Group C than in Groups A and B. There was no significant difference in illness duration between any 2 of the 3 groups. HbA1c (Japan Diabetes Society level: JDS) was significantly

Table 1 Clinical and biological characteristics of subjects and Indices obtained from CGMS and Indices of insulin resistance

	Pancreatic Group A (n=11)	Type 2 Group B (n=37)	Type 1 Group C (n=11)	p
Men/Women	6/5	20/17	4/7	0.29
Age (year)	71.5 ± 10.5^{bc}	58.1 ± 11.9	47.4 ± 13.2^{b}	<0.05
Duration (year)	13.2 ± 7.8	10.3 ± 7.6	9.6 ± 8.8	0.5
Family history +/-	3/8	9/28	2/9	0.33
HbA1c (JDS) (%)	7.4 ± 0.9^{b}	9.1 ± 2.0	8.4 ± 2.0	<0.05
LDL (mg/dl)	93.6 ± 31.4	103.2 ± 35.1	107.7 ± 31.0	0.6
HDL (mg/dl)	57.9 ± 23.3	51.2 ± 27.9	69.1 ± 13.4	0.11
TG (mg/dl)	100.4 ± 68.1	119.2 ± 56.0	76.5 ± 26.6	0.07
Total daily insulin dose (U) (Bfter CGM)	25.8 ± 14.4^{c}	29.7 ± 14.8	48.4 ± 16.8^{b}	<0.05
Total daily insulin dose (U) (After CGM)	24.0 ± 12.2^{c}	27.8 ± 13.0	46.5 ± 17.6^{b}	<0.05
Diabetic neuropathy +/-	7/4	18/19	1/10	0.29
Diabetic retinopathy NDR/SDR/PPDR/PDR	4/4/0/3	19/10/1/7	9/1/0/1	0.23
Diabetic nephropathy Stage 1/2/3A/3B/4/5	5/6/0/0/0/0	26/5/1/3/2/0	10/1/0/0/0/0	0.43
Indices obtained from CGMS				
MGC (mg/dl)	175.4 ± 31.2^{b}	143.4 ± 24.9	174.6 ± 37.9^{b}	p<0.05
SD (mg/dl)	54.5 ± 19.4^{b}	30.4 ± 11.8	63.8 ± 12.0^{b}	p<0.05
MAGE (mg/dl)	93.5 ± 32.1^{b}	60.1 ± 27.4	98.5 ± 22.0^{b}	p<0.05
PGS (mg/dl/5min)	0.92 ± 0.27^{b}	0.69 ± 0.28	0.87 ± 0.24	p<0.05
NGS (mg/dl/5min)	-0.77 ± 0.24	-0.63 ± 0.25	-0.80 ± 0.23	0.07
Indices of insulin resistance				
BMI (kg/m^2)	21.9 ± 3.7^{b}	27.2 ± 6.2	22.0 ± 3.4^{b}	p<0.05
WC (cm)	79.5 ± 13.0^{b}	94.7 ± 14.3	83.2 ± 9.8^{b}	p<0.05
S-CPR (ng/ml)	0.8 ± 0.5^{b}	2.1 ± 2.1	0.02 ± 0.06^{b}	p<0.05
HMW-Ad (μg/ml)	4.9 ± 4.3^{b}	2.5 ± 2.0	4.9 ± 3.3^{b}	p<0.05
HMWR (HMW-Ad/Total-Ad)	0.54 ± 0.19	0.49 ± 0.17	0.59 ± 0.15	0.22
EGIR	7.1 ± 3.0^{b}	4.6 ± 2.4	7.8 ± 1.8^{b}	p<0.05

Values are means ± SD
$a^{p<0.05}$ compared to the group A.
$b^{p<0.05}$ compared to the group B.
$c^{p<0.05}$ compared to the group C.

Data are means ± SD. One-way ANOVA or v2-test was used for statistical analysis. Significant difference (P <0.05). MGC, the mean glucose concentrations in CGM equaled; SD, standard deviation; MAGE, the mean amplitude of glycemic excursions; PGS, positive glucose slope; NGS, negative glucose slope; BMI, Body mass index; WC, Waist Circumference; S-CPR, SerumC-peptide; Total-Ad, Total-adiponectin; HMW-Ad, High molecular weight adiponectin; HMWR, Ratio of high molecular weight adiponectin to total adiponectin; EGIR, Estimated glucose infusion rate;

higher in Group B than in Group A. There were no significant inter-group differences in LDL, HDL or TG levels. Insulin doses before and after CGMS® were significantly higher in Group C than in Groups A and B. Only patients from the type 2 diabetes group were using oral hypoglycemic agents (metformin in 9 cases, sulfonylurea in 2, thiazolidinedione in 2, α-glucosidase inhibitors in 5, glinide in 1, and a DDP-4 inhibitor in 1). There were no significant inter-group differences in microvascular complications of diabetes.

CGMS® parameters

Table 1 shows the data on CGMS® parameters and parameters of insulin resistance. MGC (mg/dL) was 175.4 ± 31.2 in Group A, 143.4 ± 24.9 in Group B, and 174.6 ± 37.9 in Group C, differing significantly between Group B and Groups A or Group C. SD_{CGMS} (mg/dL) was 54.5 ± 19.4 in Group A, 30.4 ± 11.8 in Group B, and 63.8 ± 12.0 in Group C, differing significantly low in Group

Table 2 Standardized Canonical Coefficients and Correlations With Canonical Variables from the Canonical Correlation Analyses of the Association Between the indices obtained from CGMS and indices of insulin resistance resistance

	subjects(n=59) First Variate	
Variable	SC	R
Indices obtained from CGM		
Mean glucose concentration (MGC)	-0.07	0.61
Mean amplitude of glycemic excursions (MAGE)	-0.05	0.64
Standard deviation (SD_{CGMS})	1.29	0.90
Positive glucose slope (PGS)	-0.39	0.17
Negative glucose slope (NGS)	0.16	-0.12
Indices of insulin resistance		
Body mass index (BMI)	-0.10	-0.60
Waist circumference (WC)	0.29	-0.56
Estimated glucose infusion rate (EGIR)	0.41	0.78
Serum C-peptide (S-CPR)	-0.41	-0.72
High molecular weight adiponectin (HMW-Ad)	0.68	0.86
The ratio of HMW-Ad to Total-Ad (HMWR)	-0.17	0.61

SC=Standardized canonical coefficient.
R=Canonical weights

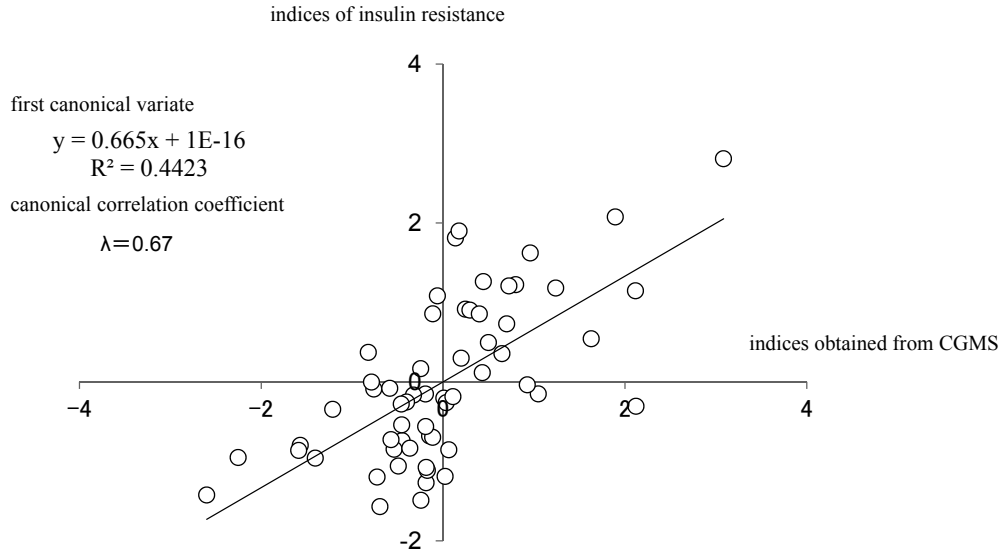
B and Groups A or Group C. $MAGE_{CGMS}$ (mg/dL) was 93.5 ± 32.1 in Group A, 60.1 ± 27.4 in Group B, and 98.5 ± 22.0 in Group C, differing significantly low in Group B and Groups A or Group C. PGS (mg/dL/5 min) was 0.92 ± 0.27 in Group A, 0.69 ± 0.28 in Group B, and 0.87 ± 0.24 in Group C, differing significantly between Group A and Group B. NGS (mg/dL/5 min) was not statistically significant -0.77 ± 0.24 in Group A, -0.63 ± 0.25 in Group B, and -0.80 ± 0.23 in Group C.

Parameters of insulin resistance

Table 1 also shows the data on parameters of insulin resistance. BMI (kg/m^2) was 21.9 ± 3.7 in Group A, 27.2 ± 6.2 in Group B, and 22.0 ± 3.4 in Group C, differing significantly between Group B and Groups A or Group C. WC was significantly larger in Group B than in Groups A and C. S-CPR (ng/mL) was 0.8 ± 0.5 in Group A, 2.1 ± 2.1 in Group B, and 0.02 ± 0.06 in Group C, differing significantly between Group B and Groups A or Group C. HMW-Ad (μg/mL) was 4.9 ± 4.3 in Group A, 2.5 ± 2.0 in Group B, and 4.9 ± 3.3 in Group C, differing significantly between Group B and Groups A or Group C. HMWR (HMW-Ad/Total-Ad) was 0.54 ± 0.19 in Group A, 0.49 ± 0.17 in Group B, and 0.59 ± 0.15 in Group C. EGIR was 7.1 ± 3.0 in Group A, 4.6 ± 2.4 in Group B, and 7.8 ± 1.8 in Group C, thus indicating significantly higher insulin resistance in Group B.

In canonical correlation analysis, the coefficient of correlation between canonical variables (between CGMS® parameters and parameters of insulin resistance) was 0.67. SD_{CGMS} was identified as parameter of insulin resistance, and HMW-Ad was shown to be a factor determining CGMS® parameters (Table 2). In analysis of canonical weights (coefficients of correlation between canonical variables and their component variables), the absolute SD_{CGMS} was large for CGMS® parameters and was shown to be associated with these parameters (Table 2). In analysis of the parameters of insulin resistance, absolute HMW-Ad was large and was shown to be associated with the parameters of insulin resistance (Table 2). In addition, parameters of CGMS® and insulin resistance showed significantly positive correlation (Fig 2).

In stepwise regression analysis with SD_{CGMS} serving as a dependent variable and the other parameters of insulin resistance and CGMS®



Indices of insulin resistance ＝-0.10BMI+0.29WC+0.41EGIR-0.41S-CPR-0.69HMW-Ad+0.12HMWR

Indices obtained from CGMS ＝-0.07MGC-0.05MAGE+1.29SD-0.39PGS+0.16NGS

Fig 2 Standardized coefficients of canonical variate between indices obtained from CGMS and indices of insulin resistance Formula was written based on SC values calculated by canonical analysis. SC=Standardized canonical coefficient

Table 3 Correlations among SD, and HMW-Ad data of the indices obtained from CGMS and indices of insulin resistance

objective variable SD	Simple correlation		Stepwisestepwise multivariate regression	objective variable HMW-Ad	Simple correlation		Stepwisestepwise multivariate regression
explanatory variable	r	p	β	explanatory variable	r	p	β
BMI	-0.38	<0.05		BMI	-0.49	<0.05	
WC	-0.3	<0.05		WC	-0.44	<0.05	
EGIR	0.45	<0.05		EGIR	0.54	<0.05	
S-CPR	-0.48	<0.05	-0.17	S-CPR	-0.38	<0.05	
HMWR	0.29	<0.05		HMWR	0.72	<0.05	0.55
HMW-Ad	0.46	<0.05		MGC	0.35	<0.05	
MGC	0.66	<0.05	0.26	MAGE	0.34	<0.05	
MAGE	0.84	<0.05	0.53	SD	0.46	<0.05	
PGS	0.58	<0.05		PGS	-0.04	n.s	
NGS	-0.51	<0.05		NGS	0.007	n.s	
			R^2=0.91				R^2=0.80

parameters serving as independent variables, S-CPR, MGC, and $MAGE_{CGMS}$ were identified as significant explanatory variables (determinants) (Table 3). In stepwise regression analysis with HMW-Ad serving as a dependent variable and the other parameters of insulin resistance and CGMS® parameters as independent variables, HMWR was identified as a significant explanatory variable (Table 3).

IV. Discussion

1. Relationship of SD_{CGMS} to glycemic profiles and insulin resistance.

Canonical correlation analysis revealed SD_{CGMS} to be a factor strongly determining glycemic variability. SD_{CGMS} was additionally shown to serve as a factor strongly determining insulin resistance. SD_{CGMS} was thus shown to determine both glycemic variability and insulin resistance. In stepwise regression analysis revealed $MAGE_{CGMS}$, S-CPR, and MGC to be determinants of SD_{CGMS}. Some reports have shown SD_{CGMS} to be a determinant of glycemic variability[15, 16]. $MAGE_{CGMS}$ reportedly correlates closely with SD_{CGMS} [13]. $MAGE_{CGMS}$ also had a significant positive correlation with SD_{CGMS} in this study, suggesting it to be a significant determinant of SD_{CGMS}. However, our literature search yielded no reports demonstrating SD_{CGMS} to determine insulin sensitivity or resistance. The concept "insulin resistance" is: "a condition characterized by reduced sensitivity to insulin activity, requiring insulin doses higher than usual for expression of insulin activity at the cell, organ, and individual levels." Past evaluation of insulin resistance used: 1) a closed-loop model allowing free interference by insulin and blood glucose values, 2) a mathematical model, and 3) an open-loop model involving measurement of insulin and blood glucose values in a fixed state [17]. SD_{CGMS} explains glycemic variability but does not directly reflect insulin secretion. In the present study, however, S-CPR had a significant negative correlation with SD_{CGMS}, suggesting that insulin secretion explains SD_{CGMS}. In cases with sufficient insulin secretion reserves, blood glucose is kept normal range by secreted insulin. In normal subjects, MGC is 100 mg/dL and SD_{CGMS} is 15 mg/dL[18, 19, 20]. Blood glucose levels can elevate due to insulin resistance, but it should be noted that there are also insulin-resistant cases where blood glucose remains normal through compensatory endogenous insulin secretion. In this report, there was no significant correlation between SD_{CGMS} and S-CPR ($r = 0.3$, $P = 0.08$) when the insulin secretion was preserved (fasting S-CPR ≥ 1.0[21]). When insulin secretion fails to compensate for insulin resistance, glycemic control becomes unstable[22]. This probably accounts for the negative correlation between SD_{CGMS} and S-CPR, observed in the present study. As to glycemic variability, it becomes difficult to judge from SD_{CGMS} data alone whether SD_{CGMS} is small because blood glucose remains high or SD_{CGMS} is small when blood glucose is within the optimum range. To make this judgment, we need to check MGC data obtained from CGMS®. Classification into the following types is possible: 1) Both MGC and SD_{CGMS} are high ($SD_{CGMS} \geq 40$)[23]; 2) MGC is high and SD_{CGMS} is 15 to 40 [23]; 3) MGC is within optimal range and SD_{CGMS} is high (≥ 40); and 4) MGC is within optimal range and SD_{CGMS} is 15 to 40. We therefore thought that evaluation of S-CPR and MGC and checking of SD_{CGMS} allow explanation of insulin secretion potential and insulin resistance in each cases.

2. Relationship of HMW-Ad to glycemic profiles and insulin resistance

Canonical correlation analysis revealed that among the parameters of insulin resistance, HMW-Ad strongly determines changes in blood glucose as well as insulin resistance. HMWR was identified as a factor determining HMW-Ad. Adiponectin levels have recently been reported to correlate negatively with insulin resistance calculated by the insulin clamp method[24] and adiponectin known to be closely involved in insulin resistance in organs and muscles[25]. It has been revealed that HMW-Ad such as 12-mer (4 × 3 mer) and 18-mer (6 × 3 mer), but not the monomer or trimer, have activities, playing critical roles in diabetes pathogenesis and metabolism[26, 27]. HMWR was identified as a

significant explanatory variable (determinant) for HMW-Ad in the present study. HMWR indicates the percentage of HMW-Ad relative to Total-Ad and has been reported as an parameter more sensitively reflecting and predicting insulin resistance than Total-Ad[28]. In the present study, HMWR correlated significantly with HMW-Ad. HMW-Ad reportedly correlates negatively with insulin secretion and HOMA-R[29] and HMW-Ad decreases markedly in states of obesity or insulin resistance[30]. Our results suggest HMW-Ad to be useful as a parameter of insulin resistance in patients with pancreatic diabetes.

3. Characteristics of patients with pancreatic diabetes

The magnitude of blood glucose change in this group was as large as that in the type 1 diabetes group (Table 1). Patients with pancreatic diabetes are impaired insulin secretion in response to postprandial glycemic elevation[4] as well as the type 1 diabetes .However, because malabsorption of carbohydrates due to the diminished secretion of amylase (arising from exocrine pancreatic insufficiency) makes postprandial glycemic elevation slow, severe and persistent hypoglycemia[9] could caused patients with pancreatic diabetes receiving insulin therapy who were easily influenced the content of meals and the amount of food intake on.

For these reason, glycemic profile of a patient with pancreatic diabetes could have been random pattern compared to a patient with type 1 diabetes(Fig 1).

There is a report that insulin resistance, as measured by the glucose clamp method, was low in patients with pancreatic diabetes, allowing glycemic control with low-dose insulin therapy[4]. BMI, WC, HMW-Ad, HMWR and EGIR, which were analyzed as parameters of insulin resistance in the present study, differed little between the pancreatic diabetes group and the type 1 diabetes group. However, the total daily insulin dose was significantly lower in the pancreatic diabetes group.

This findings might be attributable to fewer counterregulatory factors in the pancreatic diabetes group where insulin resistance is low, as suggested by the BMI, HMW-Ad and EGIR data, glucagon secretion is low[4], because of pancreatic insufficiency[9] and so on.

In the results of SD_{CGMS} correlating negatively with S-CPR, as well as S-CPR secretion being lower in the type 1 diabetes than in the pancreatic diabetes group, we can reasonably assume that SD_{CGMS} was larger in the former than in the latter group.

V. Conclusions

Our results suggest that CGMS® data allow evaluation of insulin resistance and that among CGMS® parameters, SD_{CGMS} and MGC (an explanatory variable for SD_{CGMS}) can serve as parameter determining insulin resistance and glycemic variability. Furthermore, determining HMW-Ad and S-CPR appears to be useful for evaluating glycemic variability and insulin resistance. The magnitude of glycemic variability and the intensity of insulin resistance differed little between the pancreatic diabetes and type 1 diabetes groups, while the insulin dose needed was significantly lower in the former. What seems to be essential for optimal glycemic control of patients with pancreatic diabetes is comprehensive evaluation of glycemic variability and insulin resistance on the basis of: 1) performing CGMS® in poorly controlled patients, 2) evaluating SD_{CGMS} and the mean blood glucose values obtained by CGMS®, and 3) checking BMI, WC and S-CPR which can easily be measured during routine clinical practice.

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