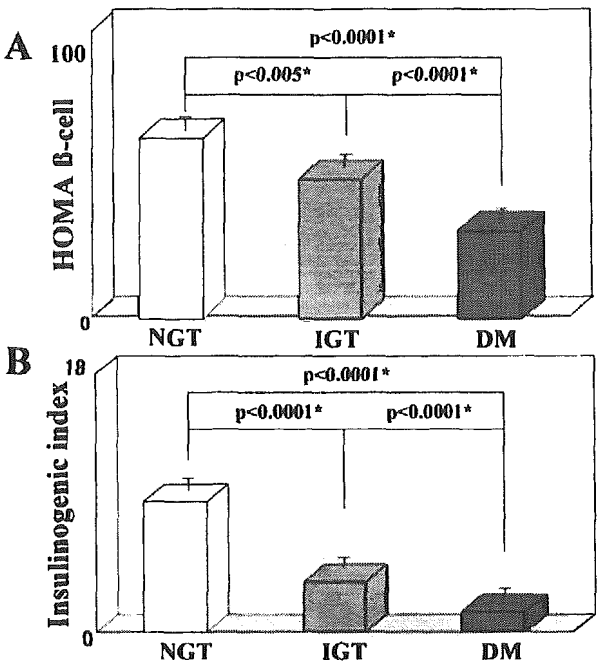

Fig 2. (A) Comparison of insulin secretion index in the basal state across the range of glucose tolerance. Insulin secretion decreases with increasing glucose intolerance. (B) Early-phase insulin secretion decreases remarkably with increasing glucose intolerance. *Significant differences assessed by analysis of variance.

correlation coefficients of these indices with G-AUC in simple regression analysis and β values and P values of multiple regression analysis are shown in Table 2. As estimates of basal insulin secretion and sensitivity, β value of HOMA β-cell was higher than HOMA-IR. As estimates of postchallenge insulin secretion and sensitivity, β value of insulinogenic index was considerably higher than ISI composite.

DISCUSSION

Indices of insulin secretion (HOMA β-cell) and insulin resistance (HOMA-IR) were evaluated from a fasting sample by HOMA.[16-18] These estimations correlated well with the insulin secretion and insulin sensitivity indices of minimal model analysis.[17] Matsuda and DeFronzo[19] have reported a new index of insulin sensitivity as an ISI composite, which has been validated by glucose clamp study. The insulinogenic index (30minutes) is a well-known measure of early-phase insulin secretion during OGTT.[20,21] Comparison of these 4 indexes across the range of glucose tolerance indicates that Japanese type 2 diabetic patients are characterized primarily by a decrease in insulin secretion and show less attribution of insulin resistance. BMI is a strong determinant of insulin resistance, and it is concordant with the evidence that the mean BMIs of representative epidemiologic studies of Japanese diabetic patients are from 23 to 25, lower than the studies of the other ethnic populations.[7-10]

These data indicate that the major factor in glucose intolerance that is characteristic of type 2 diabetes also differs in Japanese patients. Tripathy et al[11] found using OGTT in the Botnia study that the factors responsible for the development of glucose intolerance are decreased insulin secretion and sensitivity. Using HOMA-IR, insulin resistance increased nearly 2-fold from 1.7 as glucose intolerance increased from NGT to IGT and 3.6-fold in DM in that study. Using the same index, insulin resistance of Japanese subjects also increased from 1.2 to 1.5 as glucose intolerance increased from NGT to IGT and from 1.5 to 2.4 as glucose intolerance increased from IGT to DM, remarkably less than in the Botnia study. The difference of HOMA-IR in DM patients between Caucasian and Japanese becomes more than double as a number. Considering even the difference of insulin assay method and the existence of proinsulin, insulin resistance indices of Caucasian are remarkably higher than those of the Japanese. The HOMA-IR of Japanese subjects also is lower compared with that in other ethnic populations of previous studies.[23-27]

On the other hand, the reduction in insulin secretion in Japanese subjects is remarkable. The insulinogenic index (30minutes) of Japanese subjects decreased from 10.0 to 5.3 as glucose intolerance increases from NGT to IGT and from 5.3 to 1.7 as glucose intolerance increases from IGT to DM. In the Botnia study, insulin secretion decreased from 22 by half as glucose intolerance increased from NGT to IGT and by half as glucose intolerance increased from IGT to DM. The insulin secretion in Japanese subjects is considerably lower both than these and those reported in other populations.[28,29] These findings are in accord with those in the Japanese-American population, suggesting a common predisposition of Japanese populations.[30,31]). Multiple regression analysis revealed that HOMA-IR, HOMA β-cell, ISI composite, and insulinogenic index are independently associated with G-AUC. The correlation coefficients of insulinogenic index are considerably higher than the ISI composite (Table 2). In this study, the mean of all the subjects of fasting and 2-hour glucose levels were 6.8 mmol/L and 11.3 mmol/L, respectively, and their glucose intolerance was very mild. Compensately, increase in insulin secretion can make the fasting glucose levels stay near the normal range in these subjects. However, glucose intolerance, expressed as G-AUC during OGTT, appears after the challenge of glucose. Thus, indices using the results not only fasting levels, but after the glucose load, can detect a slight difference of glucose tolerance in subjects with mild glucose intolerance. Matsuda and DeFronzo[19] reported ISI composite is a good surrogate measure of whole body insulin sensitivity in comparison to clamp studies. We also have confirmed the validity of ISI composite using the minimal model analysis.[32]

The factors responsible for the ethnic differences in glucose tolerance are not yet fully clarified. Body fat distribution plays an important role in insulin resistance and glucose tolerance in some studies. We have reported not only visceral, but subcutaneous adiposity contributes to glucose intolerance suggesting the characteristic of Japanese patients.[33] Recently, the contribution of β-cell function to ethnic difference and genetic predisposition was described using precise estimation method of insulin secretion by simultaneous measurement of glucose, insulin, and C-peptide.[34,35] The analysis of body fat distribution and further estimation of insulin secretory capacity will give more explanations for ethnic differences in glucose tolerance.

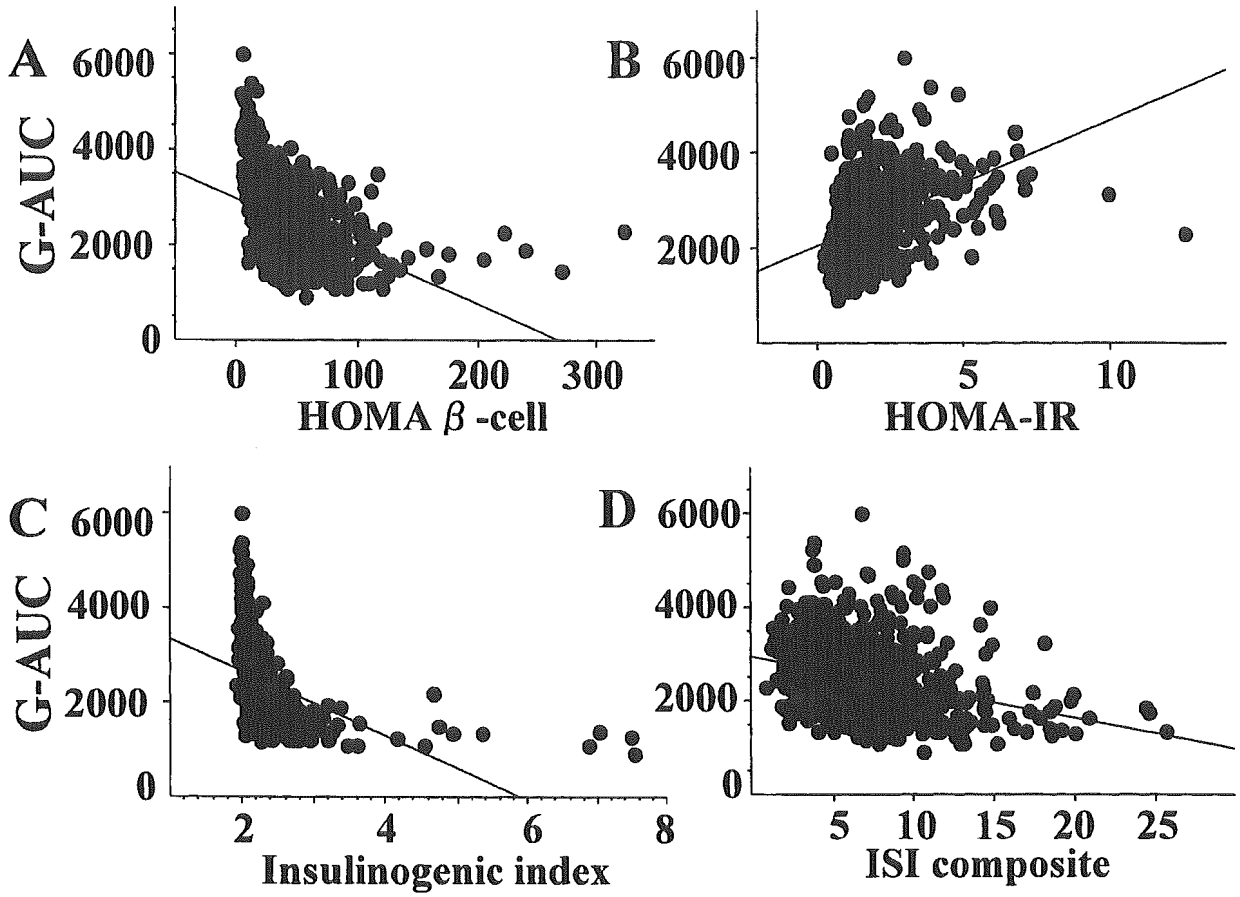

Fig 3. The relationship between G-AUC and the indices of insulin secretion and sensitivity. (A, B) As estimates of basal state, HOMA β-cell and HOMA-IR had significant relationships with G-AUC ($r = -0.45$, $P < .0001$, and $r = 0.41$, $P < .0001$, respectively). (C, D) As estimates of insulin secretion and sensitivy including postchallenge state, there were significant relationships between G-AUC and insulinogenic index ($r = -0.42$, $P < .0001$), and ISI composite ($r = -0.29$, $P < .0001$).

In addition, we compared the indices of insulin secretion and sensitivity between the subgroups of the prediabetic state to elucidate the profile of glucose tolerance (isolated IFG: 6.1 < FPG < 7 and 2-hour PG level < 7.8(n = 44) and isolated IGT: FPG level < 6.1 and 7.8 < 2-hour PG level < 11.1(n = 102)). Isolated IFG is characterized that they cannot keep fasting plasma glucose levels within normal limit at basal steady state, even if they have reserve capacity of insulin secretion after the glucose challenge. In these study subjects, we found HOMA β-cell of isolated IFG was significantly higher than that of isolated IGT (36.5 and 58.1, respectively, $P < .0001$), but there were no significant differences in other indices. It is considered that the difference between IFG and IGT is, at least in part, in the different disrupted balance of insulin secretion and sensitivity at the fasting state. We described the importance of early-phase insulin secretion for the elevation of 2-hour PG levels in Japanese subjects.[36] Further studies are necessary to clarify the different mechanisms of regulation between FPG and 2-hour PG levels.

Table 2. Relationship of the Indices of Insulin Secretion and Sensitivity With G-AUC

	Correlation Coefficients	Standardized β	P Value
HOMA β-cell	−0.45	−0.61	<.0001
HOMA-IR	0.41	0.53	<.0001
Insulinogenic index	−0.42	−0.20	<.0001
ISI composite	−0.29	−0.11	<.001

The incidence of type 2 diabetes has increased recently in Japan and is now comparable to that in other countries, but the causation of the glucose intolerance differs.[3,25,30,31] It is important in terms of prognosis and therapeutic strategy for each diabetic patient to consider the contribution of impaired insulin secretion and insulin resistance to glucose intolerance.[37] The present study clearly shows the clinical relevance of lower basal and impaired early-phase insulin secretion in type 2 diabetes in Japanese patients.

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IGT with fasting hyperglycemia is more strongly associated with microalbuminuria than IGT without fasting hyperglycemia

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Abstract

Previous studies have established that impaired glucose tolerance (IGT) patients with fasting hyperglycemia (IGT/FH: fasting plasma glucose (FPG) level 6.1–7.0 mmol/l and 2 h PG level of 7.8–11.1 mmol/l) exhibit higher insulin resistance than those with isolated IGT (FPG level <6.1 mmol/l and 2 h PG level of 7.8–11.1 mmol/l), but the association with microalbuminuria has not been determined. Here, we evaluate the prevalence of microalbuminuria in non-diabetic Japanese males 20–70 years of age. The subjects were classified into four groups based on the results of OGTT: normal glucose tolerance (NGT: $n = 71$), impaired fasting glucose (IFG: $n = 24$), isolated IGT ($n = 36$), and IGT/FH ($n = 23$). A urinary albumin-to-creatinine ratio (ACR) from 30 to 300 μg/mg creatinine was counted as microalbuminuria. The prevalence of microalbuminuria was higher in subjects with IGT/FH than in subjects with isolated IGT (26% versus 14%). Logistic regression analysis showed microalbuminuria to be more significantly associated with IGT/FH (OR = 3.82, 95% CI 1.09–13.36) than with isolated IGT (OR = 1.75, 95% CI 0.50–6.17). While insulin resistance (HOMA-IR) in isolated IGT was not significantly different from that in NGT, insulin resistance in IGT/FH was significantly higher ($P < 0.01$). Regression analysis of ACR in IGT showed a significant correlation with insulin resistance ($P = 0.012$). Accordingly, microalbuminuria is more strongly associated with IGT/FH than with isolated IGT, most likely due to the higher insulin resistance.

Keywords: Microalbuminuria; Impaired glucose tolerance; Fasting hyperglycemia; Type 2 diabetes; Insulin resistance

1. Introduction

Microalbuminuria reflects widespread vascular damage due to generalized endothelial dysfunction [1–3], and is a predictor of all-cause mortality and

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cardiovascular morbidity in diabetic patients as well as in non-diabetic subjects [4–7]. Microalbuminuria has a significant association with impaired glucose tolerance (IGT), and both increasing insulin resistance and hypertension are thought to be major factors in its development [8–11].

As impaired fasting glucose (IFG) has been identified as a pre-diabetic condition by 1998 WHO diagnostic criteria [12], IGT can be divided into IGT without fasting hyperglycemia (isolated IGT; FPG level: <6.1 mmol/l, 2 h PG level: 7.8–11.1 mmol/l) and IGT with fasting hyperglycemia (IGT/FH; fasting plasma glucose (FPG) level: 6.1–7.0 mmol/l, 2 h plasma glucose (PG) level: 7.8–11.1 mmol/l). Several studies have shown that subjects with IGT/FH have higher insulin resistance than those with isolated IGT [13–15]. However, the association between IGT/FH and microalbuminuria has not been determined. In the present cross-sectional study, we have evaluated the prevalence of microalbuminuria in Japanese males with varying degrees of glucose intolerance.

2. Material and methods

2.1. Subjects

We consecutively recruited Japanese male subjects undergoing 75 g OGTT for closer evaluation if they had a family history of diabetes, positive urine glucose test, or >5.5% of HbA_{1c} level at initial examination for regular medical check-up at Kyoto University Hospital and its affiliated hospitals between 1991 and 2001. OGTT was performed within 3 months of initial examination. Subjects with clinical proteinuria or occult blood in urine were excluded because of possible progressive diabetic nephropahty or other renal diseases. Subjects with FPG level higher than 11.0 mmol/l and those who had received any treatment for diabetes or hypertension also were excluded. The study was designed in compliance with the ethics regulations of the Helsinki Declaration.

Standard oral glucose tolerance test was administered according to National Diabetes Data Group recommendations [16], which require the subject to fast overnight for 10–16 h. Blood samples for the determination of blood glucose were drawn 0 and 120 min after oral administration of 75 g glucose. Blood samples for measurement of HbA_{1c}, insulin, total cholesterol, HDL-cholesterol, and triglyceride were drawn after an overnight fast.

Based on the results of 75 g OGTT, the subjects were classified into the following five groups: normal glucose tolerance (NGT), impaired fasting glucose (IFG), isolated IGT, IGT/FH, and DM. The NGT group included subjects with FPG level less than 6.1 mmol/l and 2 h PG level less than 7.8 mmol/l (n = 71). The IFG group included subjects with FPG level between 6.1 and 7.0 mmol and 2 h PG level less than 7.8 mmol/l (n = 24). The isolated IGT group included subjects with FPG level less than 6.1 mmol/l and 2 h PG level between 7.8 and 11.1 mmol/l (n = 36). Subjects with FPG level between 6.1 and 7.0 mmol/l and 2 h PG level between 7.8 and 11.1 mmol/l comprised the IGT/FH group (n = 23). Subjects with FPG level not less than 7.0 mmol/l and/or 2 h PG level not less than 11.1 mmol/l comprised the DM group (n = 149).

2.2. Measurements

Weight and height were measured in light clothing without shoes, and body mass index (BMI, kg/m^2) was calculated. Blood pressure was checked at the brachial artery in supine position after 10 min rest. Plasma glucose was measured by glucose oxidase method using a Hitachi Automatic Clinical Analyzer 7170 (Hitachi, Tokyo, Japan). Serum insulin was measured by radioimmmunoassay (Dainabot, Tokyo, Japan). Serum total cholesterol, HDL-cholesterol, and triglyceride level were measured on a Hitachi 7170 (Hitachi, Tokyo, Japan), as reported previously [17].

As the measure of insulin resistance, the index of insulin resistance by homeostasis model assessment (HOMA-IR) was used (FPG (mmol/l) × fasting insulin (mU/l)/22.5) [18]. HOMA-IR correlates well with measurements obtained by glucose clamp and minimal model studies [19,20].

Early morning first voided urine samples were collected. Urine albumin was measured by a commercial immunoprecipitation assay (LX2000, Eiken, Tokyo, Japan) with sensitivity of 3.0 μg/ml and intra- and inter-assay coefficients of variation of less than 10%. Urinary creatinine was determined

by enzyme assay (Hitachi, Tokyo, Japan). The urinary albumin-to-creatinine ratio (ACR) was calculated, and less than 30 μg/mg creatinine was counted as normoalbuminuria and ACR between 30 and 300 μg/mg creatinine as microalbuminuria, based on American Diabetes Association criteria [21]. Microalbuminuria in untimed specimens (30 μg/mg creatinine) corresponds to not less than 30mg albumin in 24 h urine collection and not less than 20 μg/min in timed specimens [22]. Subjects with ACR of more than 300 μg/mg creatinine were excluded from the study due to possible clinical proteinuria.

2.3. Statistical analyses

All analyses were performed using the Statistical Package for the Social Sciences version 10.0J (SPSS Inc., IL, USA). Age, BMI, systolic and diastolic blood pressure, FPG/2 h PG, HbA_{1c}, fasting insulin, insulin resistance, triglycerides, total cholesterol, and HDL-cholesterol were compared among NGT, IFG, isolated IGT, and IGT/FH by general analysis of variance (ANOVA; Table 1). Dunnett's procedure as post hoc analysis was applied to compare with the NGT group. The prevalence of microalbuminuria of each subgroup was evaluated by Chi-square test and was compared with that of the NGT group. In addition, in subjects with IGT, age, BMI, systolic and diastolic blood pressure, FPG, 2 h PG, HbA_{1c}, fasting insulin, insulin resistance, triglycerides, and total and HDL-cholesterol were compared according to the presence of microalbuminuria by unpaired Student's *t*-test (Table 2). In both of these analyses, the value of fasting insulin, insulin resistance (HOMA-IR), triglycelides, total cholesterol, and HDL-cholesterol were log-transformed before analysis so their distribution would be close to normal. Probability (*P*) values less than 0.05 were considered statistically significant. Data are expressed as mean ± S.E.

Multiple logistic regression analyses were performed to investigate the association between microalbuminuria and the various subgroups based on OGTT (Table 3). Microalbuminuria is the dependent variable and the independent variables are (1) glucose tolerance status, (2) glucose tolerance status and age, (3) glucose tolerance status, age, and hypertension, and (4) glucose tolerance status, age, hypertension, and insulin resistance. The Wald test was used to

Table 1
Demographic/metabolic characteristics and prevalence of microalbuminuria of all study subjects

	NGT	IFG	Isolated IGT	IGT/FH	DM	Total
n	71	24	36	23	149	303
Age (years)	45.3 ± 1.2	52.7 ± 1.9***	50.0 ± 1.3*	54.0 ± 1.3***	51.3 ± 0.6***	50.1 ± 0.5
BMI (kg/m^2)	24.1 ± 0.3	23.6 ± 0.6	23.4 ± 0.4	24.3 ± 0.5	24.4 ± 0.2	24.2 ± 0.2
Systolic BP (mmHg)	128 ± 2	132 ± 4	123 ± 3	130 ± 4	130 ± 1	129 ± 1
Diastolic BP (mmHg)	78 ± 2	79 ± 2	75 ± 2	78 ± 3	78 ± 1	77 ± 1
FPG (mmol/l)	5.3 ± 0.1	6.3 ± 0.0***	5.6 ± 0.1	6.5 ± 0.1***	7.8 ± 0.1***	6.7 ± 0.1
2 h glucose (mmol/l)	5.8 ± 0.2	6.2 ± 0.3	8.9 ± 0.2***	9.6 ± 0.2***	15.2 ± 0.3***	11.1 ± 0.3
HbA_{1c} (%)	5.5 ± 0.1	5.9 ± 0.1	5.9 ± 0.1	6.1 ± 0.1*	7.2 ± 0.1***	6.4 ± 0.1
Fasting insulin (pmol/l)[a]	23.8 ± 1.6	26.8 ± 3.1	28.8 ± 2.7	28.9 ± 3.5	27.3 ± 1.2	26.7 ± 0.9
Insulin resistance (mU mmol/l^2)[a,b]	0.9 ± 0.1	1.3 ± 0.2	1.2 ± 0.1	1.4 ± 0.2*	1.6 ± 0.1***	1.3 ± 0.2
Triglycerides (mmol/l)[a]	1.13 ± 0.09	1.01 ± 0.13	1.65 ± 0.17*	1.52 ± 0.20	1.54 ± 0.08***	1.40 ± 0.05
Total cholesterol (mmol/l)[a]	5.04 ± 0.11	5.06 ± 0.18	5.08 ± 0.15	5.18 ± 0.19	5.25 ± 0.08	5.16 ± 0.05
HDL-cholesterol (mmol/l)[a]	1.25 ± 0.04	1.37 ± 0.07	1.02 ± 0.04**	1.15 ± 0.06	1.16 ± 0.03	1.18 ± 0.02
Prevalence of microalbuminuria (%)	9 (6/71)	13 (3/24)	14 (5/36)	26 (6/23)†	26 (39/149)†	19 (59/303)

Data are means ± standard error. Microalbuminuria: urine albumin-to-creatinine ratio ≥30 μg/mg creatinine.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs. NGT.
[a] Data are adjusted for age and BMI.
[b] HOMA-IR = fasting insulin × fasting glucose/22.5.
† $P < 0.05$ vs. NGT by Chi-square test.

Table 2
Demographic/metabolic characteristics of IGT subjects in relation to the presence of microalbuminuria

	Microalbuminuria		
	No	Yes	*P*-value
n	48	11	
Age (years)	50.9 ± 1.1	54.6 ± 2.5	0.139
BMI (kg/m^2)	23.7 ± 0.4	24.1 ± 1.0	0.705
Systolic BP (mmHg)	124 ± 3	134 ± 6	0.115
Diastolic BP (mmHg)	75 ± 2	78 ± 4	0.509
FPG (mmol/l)	5.9 ± 0.1	6.1 ± 0.2	0.335
2 h glucose(mmol/l)	9.1 ± 0.1	9.7 ± 0.4	0.082
HbA_{1c} (%)	6.0 ± 0.1	5.9 ± 0.2	0.742
Fasting insulin (pmol/l)	26 ± 2	37 ± 7	0.048
Insulin sensitivity (mU mmol/l^2)[a]	1.2 ± 0.2	1.7 ± 0.3	0.041
Triglycerides (mmol/l)	1.57 ± 0.15	1.57 ± 0.36	1.000
Total cholesterol (mmol/l)	5.15 ± 0.13	5.02 ± 0.27	0.677
HDL-cholesterol (mmol/l)	1.09 ± 0.04	1.06 ± 0.13	0.716

[a] HOMA-IR = fasting insulin × fasting glucose/22.5.

determine the statistical significance of each coefficient. To quantify the proportion of variation due to dependent variables, Nagelkerke R^2-statistics were calculated on each model [23]. For these analyses, age was divided into four groups: <40, 40–50, 50–60, and >60 years. Hypertension was defined as systolic blood pressure more than 140 mmHg or diastolic blood pressure more than 90 mmHg [24]. HOMA-IR was used to measure insulin resistance, and was divided to create quartiles for analysis.

To evaluate the metabolic factors associated with microalbuminuria in IGT subjects (n = 59), linear regression analyses of ACR as the dependent variable and each of the metabolic variables as independent variables were performed (Table 4). A partial standardized regression coefficient (β) was used to show the magnitude of association between ACR and each independent variable. Age was included in all models as an independent variable. For analysis, ACR, HOMA-IR, fasting insulin, triglycerides, total cholesterol, and HDL-cholesterol were transformed to natural logarithms to satisfy statistical assumptions.

Table 4
Standardized partial regression coefficients of urine albumin-to-creatinine ratio and metabolic variables in IGT subjects (n = 59)

	Standardized β	*P*-value
Insulin resistance[a]	0.306	0.012
sBP	0.238	0.060
dBP	0.147	0.250
BMI	0.101	0.420
FPG	0.122	0.352
2 h glucose	0.148	0.235
Fasting insulin[b]	0.255	0.039
HbA_{1c}	−0.109	0.390
Triglycerides[b]	0.132	0.299
Total cholesterol[b]	0.008	0.950
HDL-cholesterol[b]	0.018	0.891

Partial correlation coefficients adjusted for age by linear regression.
[a] HOMA-IR = fasting insulin × fasting glucose/22.5.
[b] Log-transformed.

Table 3
Multiple logistic regression analysis of the presence of microalbuminuria across the subgroups based on OGTT

Adjusted for	Glucose tolerance status								R^2
	IFG		Isolated IGT		IGT/FH		DM		
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	
None	1.55	(0.36–6.74)	1.75	(0.50–6.17)	3.82	(1.09–13.36)*	3.84	(1.54–9.57)**	0.066
Age	1.68	(0.37–7.52)	1.86	(0.52–6.68)	4.39	(1.17–16.40)*	4.40	(1.67–11.58)**	0.072
Age, hypertension	1.62	(0.36–7.31)	1.85	(0.51–6.66)	4.41	(1.17–16.54)*	4.56	(1.73–11.99)**	0.090
Age, hypertension, insulin resistance	1.38	(0.30–6.30)	1.59	(0.43–5.83)	3.45	(0.89–13.41)	3.26	(1.18–9.02)*	0.126

Divided into three groups: <40, 40–50, 50–60 and >60 years. Hypertension: a systolic blood pressure of ≥140 mmHg, or a diastolic blood pressure of ≥90 mmHg. Quartile of HOMA-IR as a measurement of insulin sensitivity.
*$P < 0.05$; **$P < 0.01$ vs. NGT.

3. Results

Demographic and metabolic characteristics of the subjects are shown in Table 1. Three hundred three subjects were enrolled. The average age and BMI was 50.1 ± 0.5 and 24.2 ± 0.2, respectively. Altogether, 19% of the subjects were found to have microalbuminuria (ACR ≥ 0 μg/mg creatinine). There was no significant difference in BMI and blood pressure among the four groups. The IGT/FH group had significantly higher FPG, 2 h PG, and HbA_{1c} than the NGT group, while the isolated IGT group had only significantly higher 2 h PG level. Insulin resistance (HOMA-IR) in the IGT/FH group was significantly higher than in the NGT group ($P = 0.024$), but there was no significant difference between the isolated IGT and the NGT groups. The lipid profile of the isolated IGT group was similar to that of the IGT/FH group, and was deteriorated relative to the NGT group. The prevalence of microalbuminuria in the IGT/FH group (26%, $P = 0.028$ versus NGT by Chi-square test) was higher than in the isolated IGT group (14%, $P = 0.381$ versus NGT by Chi-square test). Mean ACR was 16.2 ± 3.6 μg/mg creatinine in the isolated IGT group and 42.2 ± 10.7 μg/mg creatinine in the IGT/FH group, while the mean ACR in the NGT group was 15.5 ± 2.6 μg/mg creatinine.

The demographic and metabolic characteristics of the IGT subjects according to the presence or absence of microalbuminuria are shown in Table 2. Subjects with microalbuminuria had significantly higher insulin resistance (higher HOMA-IR) and higher fasting plasma insulin than those without microalbuminuria ($P = 0.041$ and 0.048, respectively). The lipid profiles of both groups were similar.

The results of multiple logistic regression analysis with microalbuminuria as a dependent variable and glucose tolerance status as an independent variable are shown in Table 3. With no adjustment, microalbuminuria showed a significant association with IGT/FH ($P = 0.036$). After adjustment for age and hypertension, the odds ratio of microalbuminuria in the IGT/FH group was still significant (OR = 4.41, 95% CI 1.17-16.54; $P = 0.028$). There was no significant association of microalbuminuria with isolated IGT (OR = 1.85, 95% CI 0.51-6.66; $P = 0.348$). The R^2-values suggest that 9% of the variance was due to age, hypertension, and glucose tolerance status. The addition of insulin resistance to the analysis resulted in loss of significant association of microalbuminuria with IGT/FH, but increased the proportion of variation explained (R^2) by 3%.

Table 4 shows the partial correlation coefficients of urine albumin-to-creatinine ratio (ACR; log-transformed) with insulin resistance and other metabolic variables in subjects with IGT. After adjustment for age, there was a significant correlation between ACR and insulin resistance ($P = 0.012$). Fasting insulin also had a significant relation to ACR ($P = 0.039$), while systolic blood pressure had a marginal relation ($P = 0.060$) and there was no significant relation with the other variables. In all measured variables, insulin resistance was the strongest determinant of ACR (standardized $\beta = 0.306$).

4. Discussion

Microalbuminuria has been shown to be a predictor of renal dysfunction and cardiovascular diseases in both non-diabetic and type 2 DM subjects [4,5], and is significantly associated with IGT [8,9]. As previous studies have shown that isolated IGT and IGT/FH have different metabolic profiles [13–15], we compared the prevalence of microalbuminuria in the two subgroups. Our analyses clearly demonstrate that microalbuminuria in these subjects is more strongly associated with IGT/FH than with isolated IGT, which reflects the higher insulin resistance in IGT/FH.

In addition to higher insulin resistance, subjects with IGT/FH exhibit higher age, blood pressure, BMI, plasma glucose, cholesterol, and fasting insulin than those with isolated IGT and NGT, so these factors all might be related to the appearance of microalbuminuria in IGT/FH [10,11,25]. Regarding age and hypertension, the absolute differences between subjects with isolated IGT and IGT/FH are small, and the odds ratio of microalbuminuria in IGT/FH is high even after adjustment for age and hypertension. In addition, linear regression analysis of urine ACR shows insulin resistance to be the stronger determinant of microalbuminuria and fasting insulin the weaker determinant, and no significant correlation with other variables such as BMI, plasma glucose level, or cholesterol level. However, the link between insulin resistance and microalbuminuria is unclear.

Some studies report that hyperglycemia and/or hyperinsulinemia alters permeability of the glomerular membrane and increases intraglomerular pressure [26,27]. Epidemiological studies suggest that hyperglycemia or hyperinsulinemia itself is not the major cause of increased microalbuminuria among IGT subjects [8,10]. However, insulin resistance has been shown to produce changes in the amount and/or the effects of nitric oxide and other chemical mediators by causing endothelial dysfunction [28,29]. Dysfunction at the glomerular capillary wall might well induce increased leakage of albumin at the glomerulus that results in microalbuminuria [30,31]. Another possibility is that endothelial dysfunction causes parallel defects of microalbuminuria and insulin insensitivity, since several studies report that insulin resistance correlates with impaired peripheral vasodilation [32]. However, the role of blood flow in the modulation of insulin-mediated glucose utilization is controversial.

In conclusion, our results show an increased prevalence of microalbuminuria in IGT/FH subjects compared to isolated IGT subjects that is closely associated with increased insulin resistance. Because IGT/FH patients have heightened risk of cardiovascular and other diabetic complications requiring more intensive therapeutic approaches, the results of 75g OGTT should be clinically useful in pre-diabetic patients.

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2型糖尿病患者における糖尿病に関連した日常生活のストレス原因に対するコーピングと血糖コントロールの関連

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要約：通院中の2型糖尿病患者の188名を対象に，糖尿病に関連した日常生活のストレス原因に対するコーピングと血糖コントロールの関連について検討した．HbA1c≧8%を血糖コントロール不良群(n=48)とし，HbA1c<8%を血糖コントロール良好群(n=140)とした．コーピングはストレスコーピングインベントリーで測定し，ストラテジー配分(問題解決優位群・情動中心優位群)と，対処型から検討した．その結果，ストラテジー配分では，血糖コントロール不良群に情動中心優位型が多いことが明らかになった．対処型でみると，逃避型・離隔型・自己コントロール型の得点において，血糖コントロール不良群の得点が良好群に比し高かった．血糖コントロール不良群は，情動中心優位のストラテジーをとる傾向があり，それは逃避型・離隔型の対処型が用いられることに起因すると考えられた．

Key words：①2型糖尿病　②コーピング　③血糖コントロール
〔糖尿病47(11)：883～888, 2004〕

はじめに

2型糖尿病患者の血糖値の乱れ，治療中断にいたる要因のひとつに心理社会的ストレスが考えられる．糖尿病患者の心理社会的ストレスについての研究は，主に思春期から青年期の1型糖尿病を対象にしたものが多いが，我々はこれまで，日本人に比較的多い2型糖尿病を対象に研究を行ってきた[1,2]．

心理社会的ストレッサーを計量的に評価する方法は，大きく2つに分けることができる[3]．配偶者の死や転勤などの生活上の大きな出来事を中心とするライフイベント評価と，学校や職場，家族関係などにおける日々の細々とした煩わしい出来事を中心とする評価(以下daily hassles)の2つである．特に後者daily hasslesは糖尿病患者にとって，大きく関与している問題と捉えることができる．なぜなら，日々繰り返し続けなければならない食事療法や薬物療法(特にインスリン注射)が煩わしく，糖尿病患者特有のdaily hasslesが生じると考えられるからである．実際，我々のこれまでの成績では，63.2%の患者が何らかの糖尿病特有のdaily hasslesを常に感じていた[1]．

心理社会的ストレスモデルでは，心理社会的ストレッサーは，その種類や強度によって一定量のストレス反応がきまって生じるわけではなく，それらの間に介在するコーピングが重要な要因であるとする考えがあ

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る．コーピングの定義はさまざまであるが，困難な状況にある時に，その人がその不快な感情にうまく対応したり，苦痛の原因である問題にうまく対応するために，物事のとらえ方や行動を変化させることであるととらえられる[3]．これらのコーピングは，ストレッサーと血糖コントロールの調節要因として位置づけることができる[4]．

現在の研究では，コーピングの測定は，主に特性としての尺度と状況別尺度の二つの視点にもとづいて行われている．特性としての尺度は，コーピングを性格特性として捉えるものであり，どのような状況でもおおむね同じような対処行動をとると考えるものである．Peyrotら[5,6]は，このような特性としてとらえたコーピングと糖尿病マネジメントの関連についていくつかの研究を行っている．Fukaoら[7]や瀧井ら[8]も，コーピングを特性としてとらえ，血糖コントロールとの関連を検討している．これらにより，個々の患者の特性に合わせた対処の仕方を教育するという点において，有効な成果をもたらしたといえる．

しかし，このように特性としてコーピングをとらえた場合，各個人の性格は変化しにくいものであるため，ストレスを低減するために有用なコーピング方法を検討することは難しくなる可能性もある．Deweら[9]も，コーピングはプロセスであって，パーソナリティ特性とは区別すべきであるとしている．そこで今後は，状況別でコーピングをとらえること，すなわちストレッサーの種類によってコーピングの方法を自在に変えていくようにすすめていくことも，日常診療の場では有用になるであろう．特に，糖尿病の患者教育に生かすためには，糖尿病特有のdaily hasslesというストレッサーに対する有用なコーピングを検討する必要がある．

そこで，本研究では，daily hasslesに分類される糖尿病特有のストレッサーを「糖尿病に関連した日常生活のストレス原因」とし，それに対してどのようにコーピングしたかを評価し，それらと血糖コントロールの関連を検討した．

対象と方法

1）対　象

関西電力病院に通院中の，35歳以上の2型糖尿病患者を対象とした．自記式質問紙に回答する上で認知，知覚機能に問題がある患者は除外した．有効な回答が得られた188名の分析を行った．回収率は88.1%，有効回答率97.9%であった．

2）方　法

外来において，研究の趣旨を説明の上，研究協力の同意を得て調査用紙を手渡し，郵送で回収した．さらに，外来診療録から，HbA_{1c}，年齢，性別，糖尿病の罹病期間，合併症の有無，治療法について情報を得た．

調査用紙は，「糖尿病に関連した日常生活のストレス原因」，「糖尿病に関連した日常生活のストレス原因に対するコーピング」の2つの尺度で構成した．糖尿病に関連する日常生活のストレス原因は，通常一つとは考えにくいが，コーピングを特性としてではなく状況別にとらえるには，一つを具体的に想起しそれに対してとったコーピングを回答させる必要がある．そこで，まず，糖尿病に関することで最近体験した「困難な状況」を想起することを求め，そのうち最も困難だと感じたことはどれかを提示した糖尿病に関連したストレス原因(15項目，Table 2参照)の中から一つ選択させた．続けて，選択した項目について，どのように対処したか(糖尿病に関連した日常生活のストレス原因に対するコーピング)を，ストレスコーピングインベントリー[10](以下SCI)を用いて回答させた．

SCIは，64項目について「あてはまる」「少しあてはまる」「あてはまらない」の3段階で評定する尺度であり，「ストラテジー」と「対処型」の2つの視点から評価される．本研究では，まずSCIの「ストラテジー」評価により，認知的ストラテジー(32項目)と，情動的ストラテジー(32項目)の2つの下位尺度によるストラテジー評価を行い，それを用いて認知的ストラテジーの得点に比し，情動的ストラテジーの得点が低い群を「問題解決優位型」，高い群を「情動中心優位型」として分類した(以下，ストラテジー配分)．次に，SCIの「対処型」評価により，それぞれ8項目からなる8つの下位尺度(計画型，対決型，社会的支援模索型，責任受容型，自己コントロール型，逃避型，離隔型，肯定評価型)による対処型評価を行った．

血糖コントロールの評価は，調査用紙回答日に最も近い時点のHbA_{1c}値に基づき判定した．日本糖尿病学会の血糖コントロール指標[11]に従い，不可(HbA_{1c} ≧8%)に分類される群を血糖コントロール不良群，可，良，優(HbA_{1c} <8%)に分類される群を血糖コントロール良好群とした．血糖コントロール不良群は48名，血糖コントロール良好群は140名であった．

統計的分析は，統計パッケージSPSS Ver. 11 J for Windowsを用いて行った．カテゴリー間の比較にはχ^2検定を，平均値の比較にはt検定を用いた．両側検定を用い，有意水準は0.05以下とした．

結　果

1）対象の臨床像(Table 1)

血糖コントロール別の臨床像では，年齢，罹病期間に差はなかったが，良好群は不良群に比し，男性の割合が多かった(69.3% vs 45.8%)．治療では，良好群は

Table 1 対象の臨床像

	血糖コントロール 良好群	不良群	p
n	140	48	
年齢(歳)	60.7±10.2	62.0±10.2	0.449
男性(%)	69.3	45.8	<0.01
罹病期間(年)	10.1±8.4	12.1±8.1	0.146
治療			
食事療法と運動療法のみ(%)	42.9	8.3	<0.001
経口剤(%)	36.4	35.4	0.900
インスリン注射(%)	20.7	56.3	<0.001
HbA1c(%)	6.7±0.8	8.9±0.9	
合併症有り(%)	34.3	54.2	<0.05
網膜症(%)	12.9	29.2	<0.05
腎症(%)	15.0	27.1	0.061
神経障害(%)	18.6	33.3	<0.05

表中数値は，平均±標準偏差かパーセンテージである．
カテゴリー間の比較には χ^2 検定を，平均値の比較には t 検定を用いた．

Table 2 糖尿病に関連した日常生活のストレス原因の割合

糖尿病特有のストレッサー	全体(n=188)	血糖コントロール 良好群(n=140)	不良群(n=48)
食事療法に関すること	80(42.6)	62(44.3)	18(37.5)
自己管理がうまくいかないこと	28(14.9)	19(13.6)	9(18.8)
体重コントロールに関すること	17(9)	13(9.3)	4(8.3)
合併症に関すること	15(8)	13(9.3)	2(4.2)
運動療法に関すること	11(5.9)	9(6.4)	2(4.2)
日常生活をかえなければならないこと	10(5.3)	7(5.0)	3(6.3)
インスリン注射に関すること	8(4.3)	4(2.9)	4(8.3)
家族に負担をかけていること	6(3.2)	6(4.3)	0(0)
糖尿病が悪化していること	3(1.6)	1(0.7)	2(4.2)
糖尿病患者とみなされるのが恥ずかしい	3(1.6)	2(1.4)	1(2.1)
医療費のこと	2(1.1)	1(0.7)	1(2.1)
低血糖に関すること	1(0.5)	0(0)	1(2.1)
尿糖測定や血糖測定に関すること	1(0.5)	1(0.7)	0(0)
糖尿病の薬に関すること	1(0.5)	0(0)	1(2.1)
その他	2(1.1)	2(1.4)	0(0)

表中数値：n(%)
χ^2 検定(血糖コントロールと糖尿病に関連した日常生活のストレス原因の関連)：ns

不良群に比し，食事療法と運動療法のみの割合が多く(42.9% vs 8.3%)，インスリン注射の割合は少なかった(20.7% vs 56.3%)．また，良好群は不良群に比し，糖尿病の三大合併症を持つ割合が少なく(34.3% vs 54.2%)，合併症別では，網膜症(12.9% vs 29.2%)と神経障害(18.6% vs 33.3%)を持つ割合が少なかった．

2) 糖尿病に関連した日常生活のストレス原因

ストレス原因として最も回答の多かった項目は「食事療法に関すること」(188名中80名，42.6%)であり，続いて「自己管理がうまくいかないこと」(28名，14.9%)，「体重コントロールに関すること」(17名，9%)，「合併症に関すること」(15名，8%)などであった(Table 2)．血糖コントロールと日常生活のストレス原因の割合には，関連はなかった．

3) 血糖コントロール別にみた，糖尿病に関連した日常生活のストレス原因に対するコーピング

まず，血糖コントロールとストラテジー配分の関連を検討した(Table 3)．その結果，血糖コントロール

Table 3　血糖コントロールとストラテジー配分の関連

ストラテジー関係	血糖コントロール 良好群 ($n=140$)	不良群 ($n=48$)
問題解決優位型	72.1	56.3
情動中心優位型	27.9	43.8

χ^2 検定：$p<0.05$

Table 4　血糖コントロール別にみた対処型の得点

対処型	血糖コントロール 良好群 ($n=140$)	不良群 ($n=48$)	p^*
計画型	6.7(3.9)	6.3(4.0)	0.502
対決型	4.4(2.9)	5.0(3.1)	0.227
社会的支援模索型	4.0(3.4)	4.1(3.4)	0.913
責任受容型	7.5(4.3)	7.6(4.3)	0.883
自己コントロール型	5.3(3.7)	6.7(4.3)	<0.05
逃避型	3.9(3.1)	4.9(2.6)	<0.05
離隔型	5.2(3.3)	6.4(3.9)	<0.05
肯定評価型	7.7(4.3)	7.5(4.6)	0.756

表中数値：平均(標準偏差)

*：良好群と不良群の平均値の比較(t 検定)

不良群(48名中21名，43.8%)では，良好群(140名中39名，27.9%)に比べ情動中心優位型の割合が高かった($p<0.05$)．

続いて，血糖コントロール別(良好群 vs 不良群)に8つの対処型の得点を比較した(Table 4)．逃避型(3.9±3.1 vs 4.9±2.6, $p<0.05$)，離隔型(5.2±3.3 vs 6.4±3.9, $p<0.05$)，自己コントロール型(5.3±3.7 vs 6.7±4.3, $p<0.05$)で，血糖コントロール不良群の得点が良好群に比し，高かった．計画型，対決型，社会的支援模索型，責任受容型，肯定評価型では両群に有意差はなかった．

考　察

コーピングの機能は多種多様で，さまざまな分類が試みられている．中でも，ストレッサーをたくみに処理し変化させていく「問題解決型」と，感情の調整を図る「情動中心型」の2種類に分類する方法がよく用いられている[3]．今回用いたSCIでは，ストラテジー評価の「認知的ストラテジー」と「情動的ストラテジー」がそれぞれに対応している．

これまでの多くの研究では，「問題解決型」はストレス反応を低減し，逆に「情動中心型」はそれを増加させるという形で両者を二分して検討しており，糖尿病患者を対象にした研究においても同様である[12]．例えば，特性としてコーピングをとらえた研究では，「問題解決型」が良好な血糖コントロールに影響するとされている[6,7]．しかし実際には，あるストレスフルな状況に対しては「問題解決型」のみを用いるのではなく，同時に「情動中心型」も用いており，適応的か否かは対処の各タイプのバランスによる[13]．SCIを用いてカウンセリングを行う場合も，両者の配分で評価することが薦められている[10]．そこで，本調査では，糖尿病特有のストレッサーを想起させて，それに対してどのような行動をとったかを，「問題解決型」と「情動中心型」両者を含んだ質問項目から回答させ，そのどちらを多く用いたかによりコーピングを評価することを試みた．

その結果，血糖コントロール不良群は良好群に比し，情動中心優位の配分をとる患者が多いことが明らかになった．

2型糖尿病患者を対象に，今回のように糖尿病に関連した日常生活のストレス原因を想起させて，それに対してどのようなコーピングをしたかを定量的に検討した報告はない．しかし一般的には，「情動中心型」より「問題解決型」がやや優位な配分の方が，ストレスにうまく対応できると言われている[10]．我々は，糖尿病に関連した日常生活のストレス原因についても，一般的に言われていることと同様に[10]，「問題解決型」をやや優位にコーピングすることの方が，2型糖尿病患者を心理的に安定させ，過食や飲酒などの不適応行動が抑制され，良好な血糖コントロールが得られるのではないかと考えている．しかし，今回の結果からは，「問題解決型」を優位に用いる場合のその程度について言及することはできない．個々の事例を詳細に積み重ねることにより，その程度について今後検討する必要がある．

次にこの点を踏まえ，血糖コントロール別に各対処型の得点を比較した．その結果，血糖コントロール不良群は良好群に比し，逃避型・離隔型・自己コントロール型の得点が高いことが明らかになった．逃避型には，「その問題が好転する様子を空想した」「その状況が早く終わるように願った」といった項目が含まれ，問題から心理的に逃げ出すことを考える対処型である．離隔型は「そのことについてあまり考えすぎないようにした」「あとはなるようにしかならないと思った」などの項目からなり，問題を自分と切り離すようにする対処型である．自己コントロール型には，「自分の沈んだ気持ちが他のことに影響しないようにした」「気分に振り回されないようにした」などの項目が含まれ，自分の感情を制御し外に表さないようにする対処型である．

これらのことから，血糖コントロール不良群は，良好群に比し，自分の感情を抑え，問題から心理的に逃

げ出すことを考えたり，問題を忘れようとするといった傾向があると考えられた．

逃避型と離隔型は，SCIでは情動的ストラテジーの項目で構成される対処型である．一方自己コントロール型は，情動的ストラテジーと認知的ストラテジーそれぞれ4項目で構成されている．したがって，血糖コントロール不良群において情動中心優位のストラテジーをとる傾向が高いのは，逃避型・離隔型の対処型が用いられることに起因する可能性がある．

逃避型コーピングは，アドヒアランス不良に関連し[14]，将来糖尿病特有の合併症をもたらす可能性もある[15]と指摘されている．Sinzatoら[16]も，糖尿病患者を網膜症の重症度で分け，重度群は軽症群に比し，不安のレベルは低いものの，治療や食事療法に対して逃避する対処をすると報告した．また佐藤[17]は「あきらめ・逃避」コーピングは血糖コントロールに関連はなかったものの，網膜症や虚血性心疾患などの合併症との関連はあったと報告している．

このように，問題や苦しみを忘れようとするストレスからの逃避は一時的には感情の均衡を保つために有用であると思われるが，長期的には問題になると言えよう．特に，離隔型は，問題を自分と切り離すようにする対処型であり，これは失感情症に近い病態[18]に進展するとも考えられる．このようなことから，逃避型や離隔型は，daily hasslesに分類される糖尿病に関連した日常生活のストレス原因への対応としては不適であると考えられる．血糖コントロール良好群は，糖尿病に関連した日常生活のストレス原因に対して，逃げたり放り投げたりせずに積極的に対処している結果として，不良群との差が生じたと考えられる．

状況別でコーピングをとらえることの利点は，糖尿病に関連した日常生活のストレス原因によってコーピングの方法を自在に変えていくようにすすめていくアプローチができることにある．糖尿病に関連した日常生活のストレス原因別にみて，実行しやすいコーピングや血糖コントロールに有用なコーピングがあると考えられる．今後は，特に糖尿病患者の食事療法を中心に，糖尿病に関連した日常生活のストレス原因別にみた効果的なコーピング，さらにそれらを促進する要因などをあわせ検討していく必要がある．

本研究の限界として，まず，臨床像において良好群と不良群には，性別，治療別，合併症の有無に差があったことがあげられる．一般的にコーピングと性差の関連についての研究結果は一致していないが，ストレス原因のタイプやその評価の違いがコーピングに影響している可能性が指摘されている[19]．治療法や合併症の有無も，患者にとって日常生活への負担は大きいと考えられ，コーピングに影響を及ぼす可能性がある．同様に，これらの臨床像の違いは，糖尿病に関連した日常生活のストレス原因のタイプやその評価の違いを生じさせると考えられるため，ストレス原因の評価の違いにも焦点をあてた検討が必要である．2点目として，11.9%(26名)にのぼる質問紙の未回収者の分析を行っていないことがあげられる．血糖コントロール不良群は48名と少なく，未回収者26名が分析に加えられれば，今回の結果に大きな影響を及ぼした可能性を否定できない．本研究において，2型糖尿病患者のコーピングと血糖コントロールの関連があることを示したものの，これらの限界をふまえ，さらに検討する必要がある．

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Physiology of GIP – A Lesson from GIP Receptor Knockout Mice

Abstract

A much greater insulin response is observed after oral glucose load than after intravenous injection of glucose. The hormonal factor(s) implicated as transmitters of signals from the gut to pancreatic β-cells was referred to incretin; gastric inhibitory polypeptide or glucose-dependent insulinotropic polypeptide (GIP) is identified as one of the incretins. GIP exerts its effects by binding to its specific receptor, the GIP receptor, which is expressed in various tissues including pancreatic islets, adipose tissue, and brain. However, the physiological role of GIP has been generally thought to stimulate insulin secretion from pancreatic β-cells, and the other actions of GIP have received little attention. We have bred and characterized mice with a targeted mutation of the GIP receptor gene. From these studies, we now know that GIP not only mediates early insulin secretion by acting on pancreatic β-cells, but also links overnutrition to obesity by acting on adipocytes.

Key words
Diabetes · Obesity

Introduction

A much greater insulin response is observed after oral glucose load than after intravenous injection of glucose [1]. This effect is attributed to signals that arise from the gut following ingestion of glucose and stimulate insulin release from pancreatic β-cells. The hormonal factor(s) implicated as transmitters of signals from the gut to pancreatic β-cells are collectively referred to as incretins [2].

Two incretins have been identified – gastric inhibitory polypeptide or glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) (Fig. **1**). Both gut hormones are secreted in proportion to the quantity of meal ingested and potentiate insulin secretion. GIP was first isolated from porcine intestine on the basis of its ability to inhibit gastric acid secretion; this 42-amino-acid hormone is released from duodenal endocrine K cells after absorption of glucose or fat. Subsequent studies have revealed that GIP potentiates glucose-induced insulin secretion from pancreatic β-cells [3].

GIP exerts its effects by binding to its specific receptor, the GIP receptors, and activating adenylyl cyclase. We isolated the human GIP receptor (GIPR) gene and cDNA [4]. The GIPR has seven potential membrane-spanning domains, a feature characteristic of the vasoactive intestinal peptide (VIP)/glucagon/secretin receptor family of G protein-coupled receptors. The GIP receptor is expressed in various tissues including pancreatic islets, adi-

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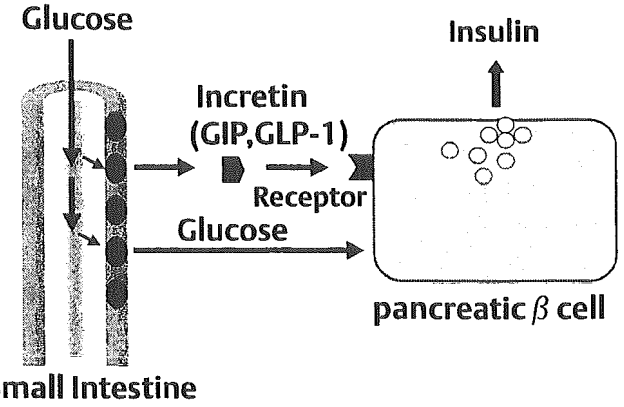

Fig. 1 Not only direct effect of glucose but also indirect effect of glucose via release of incretin such as GIP and GLP-1 stimulate insulin secretion from pancreatic β-cells.

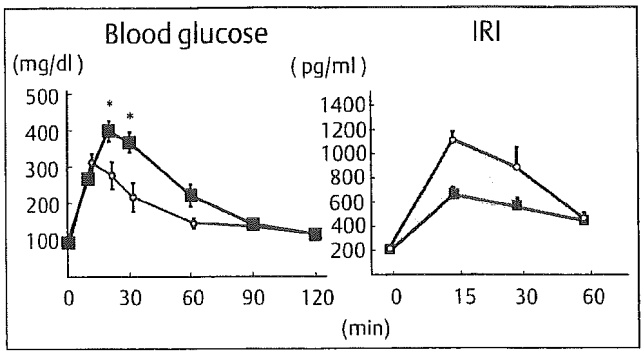

Fig. 2 Glucose tolerance test. Blood glucose levels (left) and plasma insulin levels (right) after oral glucose loading for the wild-type mice (open circle) and the GIP receptor KI mice (filled box). Estimated insulin secretion induced by GIP is shaded. From reference [6].

pose tissue, and brain [5]. However, the physiological role of GIP has generally been taken to be to stimulate insulin secretion from pancreatic β-cells; its other actions of GIP have received little attention.

We generated and characterized mice with a targeted mutation of the GIP receptor gene [6–11]. From these studies, we now know that GIP not only mediates early insulin secretion by acting on pancreatic β-cells, but also links overnutrition to obesity by acting on adipocytes.

GIP Receptor Knockout (KO) Mice

GIP receptor KO mice were generated as follows [6]. The 1.2-kb fragment containing exons 4 and 5 of the GIP receptor gene was replaced with a cassette containing the neomycin resistance gene. A negatively selectable marker gene, the herpes simplex virus thymidine kinase gene (HSV-TK), was placed external to the 3′ region of homology with the target locus. Embryonic stem (ES) cells were cultured without feeders in the presence of leukemia inhibitory factor, transfected with the targeting construct, and selected in the presence of G418 and gancyclovir. Colonies surviving positive and negative selection were isolated and screened to confirm that genuine homologous recombination had occurred on both sides of the gene. The chimeric mice were produced by microinjection of a targeted ES clone into blastocysts. Mice with the targeted allele were backcrossed to C57BL/6 mice before analysis of homozygous mice. The absence of GIP receptors was confirmed by batch-incubation studies using isolated pancreatic islets. GIP stimulated insulin secretion 2.9-fold from the islets of wild-type mice, but had no insulinotropic effect in the GIP receptor KO mice. The GIP receptor KO mice showed no gross abnormalities in general behavior or feeding or any histological abnormalities in pancreas, antrum, duodenum, or adrenal gland.

GIP as an Insulinotropic Peptide

In an intraperitoneal glucose tolerance test (IPGTT), blood glucose levels were not significantly different between wild-type or GIP receptor KO mice. However, in an oral glucose tolerance test (OGTT), the peak levels of blood glucose were delayed and significantly higher in GIP receptor KO mice compared to wild-type mice (Fig. 2). Fasting insulin levels in the GIP receptor KO mice were identical to those in the wild-type mice. In contrast, at 15 min after glucose challenge, insulin levels in the GIP receptor KO mice were significantly lower than in the wild-type mice. The islets isolated from the GIP receptor KO mice secret insulin responding to glucose in a dose-dependent manner, and *in vitro* perfusions were carried out to confirm that insulin secretions stimulated by glucose in the wild-type and the GIP receptor KO mice were comparable [8]. Therefore, the decrease of insulin secretion after oral glucose challenge is not caused by impaired glucose-induced insulin secretion, but by disruption of the GIP enteroinsular axis. These results show the physiological role of GIP as an incretin, and further demonstrate that insulin secretion from the pancreatic β-cells is regulated not only by glucose but also by GIP, especially in the early phase after glucose ingestion (Fig. 2).

Glucose-stimulated insulin secretion from pancreatic β-cells depends on glucose metabolism and electrical activity controlled by plasma membrane ion channels. The ATP-sensitive K (K_{ATP}) channel links glucose metabolism to membrane potentials. Recently, K_{ATP} channel-deficient mice were generated by genetic disruption of Kir6.2 [12]. The Kir6.2 KO mice still showed the insulin response after oral glucose loading *in vivo*, suggesting that elevation of intracellular cAMP concentration might induce insulin secretion even in the absence of the K_{ATP} channel. We generated mice that were deficient in both GIP receptor and K_{ATP} channel [11]. The GIP receptor and Kir6.2 double KO mice showed elevated blood glucose levels after oral glucose loading, and the insulin response was almost completely lost although insulin secretion from isolated islets was stimulated by GLP-1. Therefore, GIP is the major insulinotropic factor in the secretion of insulin in response to oral glucose loading in K_{ATP} channel-deficient mice.

Interaction of GIP and GLP-1 on Insulin Secretion

Perfusion and batch-incubation studies have demonstrated that the GIP receptor KO mice exhibit an increased insulin secretion in response to GLP-1 [8], which are consistent with the findings that GLP-1 produces higher intracellular cAMP levels in the GIP receptor KO mice than in the wild-type mice, implying that β-cell sensitivity to GLP-1 was increased. These results revealed upregulation of the compensatory mechanisms that take place within the enteroinsular axis.

We and the other group have generated and characterized the double incretin receptor KO mice with complete loss of both GIP and GLP-1 receptor action [9,10]. Double-incretin receptor KO mice showed impaired glucose tolerance and decreased insulin secretion after oral glucose loading. Furthermore, the glucose-lowering actions of dipeptidylpeptidase IV (DPP-IV) inhibitors were eliminated in the double-incretin receptor KO mice, suggesting that the GLP-1 and GIP signaling are the main targets for DPP-IV inhibitors, and that both incretins play a critical role in insulin release after meal ingestion.

GIP as an Obesity-promoting Factor

Plasma GIP concentrations have been reported as elevated in obese type 2 diabetic patients [13] and obese diabetic *ob/ob* mice [14], suggesting that GIP might induce obesity. Furthermore, functional GIP receptors was identified on adipocytes [15] and GIP has been shown to stimulate the synthesis and secretion of lipoprotein lipase in rat adipose tissue that hydrolyzes lipoprotein-associated triglycerides to produce free fatty acids available for local uptake [16]. However, the physiological significance of the anabolic effect of GIP was previously unclear. Using the GIP receptor KO mice, we have revealed that GIP directly links overnutrition to obesity [7].

The wild-type and the GIP receptor KO mice were fed either a control diet or a high-fat diet. On the control diet, which supplied 13% of calories as fat, 60% as carbohydrate and 27% as protein, with energy density of 3.57 kcal/g, body weights of the wild-type and the GIP receptor KO mice remained similar; on the high-fat diet, which supplied 45% of calories as fat, 35% as carbohydrate, and 20% as protein, with energy density of 3.57 kcal/g, the wild-type mice exhibited 35% body weight gain in the 50-week period. In contrast, there was no weight gain in the GIP receptor KO mice. Both visceral and subcutaneous fat mass was increased, and liver steatosis and hypertrophy of adipocytes was observed in high-fat-fed wild-type mice, but there was no such change in high-fat-fed GIP receptor KO mice. Insulin-tolerance test revealed that high-fat-fed wild-type mice had insulin resistance and that high-fat-fed GIP receptor KO mice remained as sensitive to insulin as controls, demonstrating that inhibition of the GIP signal prevents insulin resistance as well as obesity.

Obese *ob/ob* mice exhibit a marked increase in adipose tissue due to hyperphagia caused by mutation of the leptin gene. By crossbreeding the GIP receptor KO mice with *ob/ob* mice and generating double KO mice, we can show the role of the GIP signaling in adiposity, even in addition to leptin signaling.

The high-fat-fed GIP receptor KO mice showed the similar energy intake. We evaluated energy expenditure by measuring the respiratory quotient and oxygen consumption by indirect calorimetry. The respiratory quotient represents the proportion of fat and carbohydrate oxidation and the oxygen consumption represents the amount of energy combustion. After 3 weeks of high-fat feeding, the GIP receptor KO mice exhibited a significant reduction of respiratory quotient during the light phase, indicating that fat is utilized as preferred energy substrate in the GIP receptor KO mice and is not efficiently accumulated in adipocytes. After another 3 weeks on the high-fat diet, the wild-type mice consumed less oxygen than the GIP receptor KO mice during the light phase. These results clearly show that the resistance to obesity of the GIP receptor KO mice was due to higher energy expenditure rather than lower energy intake.

The GIP receptor is expressed in adipocytes and GIP stimulates cellular uptake of glucose and increases in heparin-releasable lipoprotein lipase (LPL) activity in 3T3-L1 adipocytes [7]. Therefore, GIP stimulates efficient uptake of nutrients into adipocytes; the loss of peripheral GIP actions in the GIP receptor KO mice may well have contributed to the increased fat oxidation without accumulating in adipocytes in these mice.

GIP has a physiological role on nutrient uptake into adipocytes, and is a key molecule linking overnutrition to obesity (Fig. **3**). Excessive fat intake induces hypersecretion of GIP. Hypersecretion of GIP increases nutrient uptake in the adipocytes that readily cause obesity and insulin resistance. Hyperinsulinemia could further increase nutrient uptake into the adipocytes, completing a vicious cycle of developing adiposity and insulin resistance. In the absence of GIP receptor, fat is not efficiently accumulated in adipocytes, but is used predominantly as the preferred energy source.

Here, we have shown that the GIP receptor expressed in pancreatic β-cells contributes to meal-induced insulin secretion, espe-

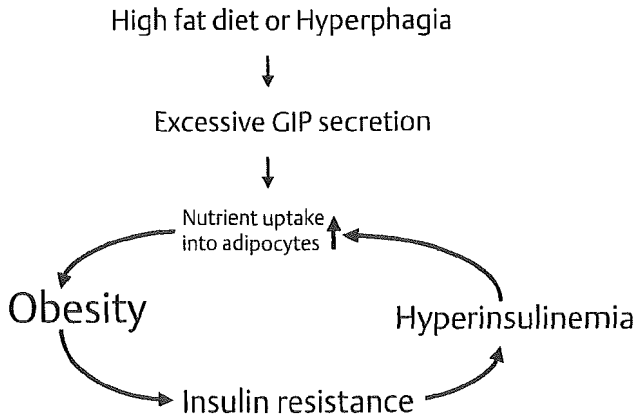

Fig. **3** GIP links excessive intake of nutrients to obesity. See text in detail.

cially in the early phase; we have also shown that the GIP receptor expressed in adipocytes contributes to nutrient uptake into adipocytes. Expression of GIP receptor other than in pancreatic β-cells and adipocytes has been demonstrated. The physiological significance of GIP will be uncovered after full characterization of the GIP receptor KO mice.

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