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Short Insulin Tolerance Test Can Determine the Effects of Thiazolidinediones Treatment in Type 2 Diabetes

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Purpose: The short insulin tolerance test is a simple and reliable method of estimating insulin sensitivity. This study was designed to compare the insulin sensitizing effects of thiazolidinediones (TZDs) on the degree of insulin resistance, determined by a short insulin tolerance test (Kitt) in type 2 diabetic patients. **Patients and Methods:** Eighty-three subjects (mean age = 57.87 ± 10.78) with type 2 diabetes mellitus were enrolled and received daily one dose of rosiglitazone (4 mg) or pioglitazone (15 mg). The mean follow-up duration was 25.39 ± 9.66 months. We assessed insulin sensitivity using HOMA-IR and the short insulin tolerance test before and after TZDs treatment. **Results:** When we compared patients' characteristics before and after TZDs treatment, the mean fasting glucose level was significantly decreased (183.27 ± 55.04 to 137.35 ± 36.42 mg/dL, $p < 0.001$) and the mean HbA1C level was significantly decreased (9.24 ± 1.96 to 8.11 ± 1.39%, $p < 0.001$). Also, Kitt values were significantly increased (2.03 ± 1.14 to 2.67 ± 0.97%/min, $p = 0.003$), whereas HOMA-IR was significantly decreased (2.98 ± 0.68 to 1.04 ± 0.24, $p < 0.05$). When classifying insulin resistance by Kitt values, insulin resistant subjects' values were increased (< 2.5 %/min; 1.51 ± 0.53%/min to 2.63 ± 0.88, $p < 0.001$), whereas the values decreased in insulin sensitive subjects (≥ 2.5%/min; 3.50 ± 0.75%/min to 2.75 ± 1.12%/min, $p = 0.002$). **Conclusion:** The glucose lowering effects of TZDs by improving insulin resistance could be determined by using Kitt. However, Kitt may be a beneficial tool to determine TZDs' effects only when patients' Kitt values are less than 2.5%/min.

Key Words: Thiazolidinediones, insulin sensitivity, short insulin tolerance test, type 2 diabetes

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INTRODUCTION

Insulin resistance is the main pathologic mechanism of type 2 diabetes mellitus and cardiovascular disease.[1-3] For evaluation of insulin sensitivity, the euglycemic hyperinsulinemic clamp is the gold standard method in both animal and human.[4] However, this technique is very difficult and complex and has been replaced by other simple and rapid methods such as the Homeostatic Model Assessment (HOMA) and the short insulin tolerance test (Kitt).[5] Kitt was shown to have a close correlation with glucose clamp studies and could be suitable for estimating insulin sensitivity over a long period.[6]

Thiazolidinediones (TZDs) are a more recently discovered antidiabetic agents thought to increase peripheral glucose utilization or inhibit hepatic gluconeogenesis by binding the nuclear peroxisome proliferators-activated receptors gamma (PPAR-γ).[7-9] The beneficial effects of TZDs on glycemic control by improving the insulin resistance in type 2 diabetic patients are already known, but no data are available to determine the effects of TZDs by Kitt.[10,11]

In this study, we investigated the insulin sensitizing effects of TZDs in Korean type 2 diabetic patients by using Kitt.

PATIENTS AND METHODS

Subjects

Eighty-three subjects (mean age = 57.87 ± 10.78)

who visited the diabetes clinic at Wonju Christian Hospital, South Korea from January 2004 to December 2006 were enrolled. Patients with type 2 diabetes who were inadequately treated with sulfonylurea or metformin (glimepiride, 50/83; gliclazide, 15/83; metformin, 18/83) were included in this study. Patients daily received either 4 mg of rosiglitazone or 15 mg of pioglitazone in a single dose regimen (rosiglitazone, 60/83; pioglitazone, 23/83), and medication was not changed throughout the study. Mean follow-up duration was 25.39 ± 9.66 months.

Assessment of insulin resistance

Insulin resistance was evaluated by means of Kitt and HOMA-IR. Insulin resistance was determined in all subjects at baseline and after 2 years. Plasma glucose disposal rate (Kitt; %/min) was calculated as previously described[6]: Kitt was the ratio between 0.693 and t1/2, where t1/2 is the time necessary to reduce the basal glucose level by one half. The t1/2 value was calculated from the slope of least square analysis of the glycemic concentrations, starting at the 3rd minute until the 15th minute after intravenous regular insulin injection (0.1 U/kg). We set our definition of insulin resistant state as a Kitt value below 2.5%/min, according to a previous study.[12] HOMA-IR was calculated using fasting serum insulin (pmol/L) and fasting plasma glucose (mmol/L; fasting insulin x fasting glucose ÷ 22.5).[13]

Clinical and biochemical measurements

Height, weight, waist circumference, hip circumference, waist-hip ratio (WHR), and body mass index (BMI) were measured in all subjects. BMI was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured with soft tape at midway between the lowest rib and the iliac crest. The hip circumference was measured at the widest part of the gluteus region. The waist-to-hip ratio was then calculated. Systolic and diastolic blood pressure (SBP and DBP) was taken after 5 minutes rest and cessation of smoking by an automatic sphygmomanometer. Blood samples for fasting glucose, fasting insulin (RIA, Cobra II, Packard, MI, USA), HbA1C (high performance liquid chromatography, variant II, Bio-Rad, Richmond, CA, USA), total cholesterol (TBA-200FR, Hitachi 7170, Tokyo, Japan), triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were collected after more than 10 hours of overnight fasting.

Statistical analysis

Data are expressed as means ± standard deviations unless stated otherwise. We used the Student's t test to compare characteristics between men and women and the values between insulin resistance and insulin sensitive states, as defined by Kitt. Paired t-test was used to compare values obtained before and after TZDs administration. A chi-square test was performed to validate differences in insulin resistance when variables were stratified. Pearson's correlation coefficient was used to establish the association between Kitt and clinical and laboratory parameters of subjects. All analyses were performed using the Windows-based SPSS statistical package (ver. 12.0, Chicago, IL, USA), and $p < 0.05$ were considered significant.

RESULTS

Clinical and biochemical characteristics of subjects

The main characteristics of study subjects are shown in Table 1. Male subjects were characterized by greater weight, waist circumference, waist-hip-ratio, and lower HDL cholesterol levels. Average BMI was 23.16 ± 2.51 kg/m^2 (males 23.17 ± 2.51 kg/m^2, females 23.14 ± 2.56 kg/m^2), and waist circumference was 81.97 ± 7.04 cm (males 83.49 ± 6.90 cm, females 78.98 ± 6.43). Insulin sensitivity markers were not different between males and females.

Parameter changes

Subjects showed improved glycemic control after the addition of TZDs to their oral hypoglycemic drugs. As shown in Table 2, there were significant changes in fasting glucose (183.28 ± 55.04 mg/dL to 137.34 ± 36.4 mg/dL, $p < 0.001$) and HbA1C levels (9.24 ± 1.96% to 8.11 ± 1.39%, p

Table 1. Clinical and Biochemical Characteristics of Subjects

	Total	Male (n = 45)	Female (n = 38)	*p* value
Age (yrs)	57.87 ± 10.78	58.01 ± 10.83	57.60 ± 10.86	0.871
Duration (yrs)	8.30 ± 7.41	8.04 ± 7.63	8.84 ± 7.06	0.658
Height (cm)	163.25 ± 8.27	167.75 ± 5.07	154.40 ± 5.82	< 0.001
Weight (kg)	61.95 ± 9.45	65.37 ± 8.55	55.23 ± 7.37	< 0.001
BMI (kg/m^2)	23.16 ± 2.51	23.17 ± 2.51	23.14 ± 2.56	0.960
Waist circumference (cm)	81.97 ± 7.04	83.49 ± 6.90	78.98 ± 6.43	0.005
Hip circumference (cm)	92.21 ± 5.79	92.97 ± 5.39	90.71 ± 6.35	0.114
Waist-hip-ratio	0.89 ± 0.05	0.90 ± 0.05	0.87 ± 0.04	0.012
SBP (mmHg)	129.84 ± 14.85	128.42 ± 13.72	133.46 ± 17.46	0.363
DBP (mmHg)	74.67 ± 11.94	74.30 ± 11.89	75.61 ± 12.50	0.748
Total cholesterol (mg/dL)	186.84 ± 34.66	184.69 ± 32.33	191.07 ± 39.12	0.461
Triglyceride (mg/dL)	146.10 ± 75.72	150.91 ± 79.04	136.67 ± 69.14	0.402
HDL-cholesterol (mg/dL)	44.11 ± 11.12	42.31 ± 10.66	47.64 ± 11.35	0.044
LDL-cholesterol (mg/dL)	114.04 ± 30.01	112.20 ± 26.93	117.66 ± 35.57	0.436
Fasting glucose (mg/dL)	183.28 ± 55.04	188.32 ± 56.41	173.36 ± 51.78	0.244
HbA1C (%)	9.20 ± 1.96	9.73 ± 2.22	8.92 ± 1.77	0.100
Kitt (%/min)	2.03 ± 1.14	2.04 ± 1.18	2.00 ± 1.04	0.240
HOMA-IR	3.62 ± 2.98	3.11 ± 1.56	5.05 ± 5.36	0.222

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; Kitt, rate constant for glucose disappearance in the insulin tolerance test; HOMA-IR, homeostasis assessment method for insulin resistance.
Values are presented as mean ± standard deviation.

< 0.001) after 2-year treatment with TZDs. Both body weight and BMI were significantly increased when compared with baseline values. Also, both waist and hip circumference increased significantly. No significant changes were observed in total cholesterol, LDL-cholesterol, and triglyceride levels. However, HDL-cholesterol levels significantly increased at 24 months when compared with baseline values (44.04 ± 11.17 mg/dL to 49.69 ± 14.97 mg/dL, $p < 0.001$; Table 2).

TZDs-induced improvement in insulin sensitivity measured by both Kitt and HOMA-IR was statistically significant (2.03 ± 1.14%/min to 2.67 ± 0.97%/min, $p = 0.003$ and 3.62 ± 2.98 to 1.61 ± 1.04, $p = 0.012$; Table 2). When the subjects were divided into insulin sensitive and resistant groups by baseline Kitt values, the changes of fasting glucose, HbA1C, and lipid profile were consistent with total subjects (Table 3). However, Kitt values were increased in insulin resistant subjects (1.51 ± 0.53%/min to 2.63 ± 0.88, $p < 0.001$) and decreased in insulin sensitive subjects (3.50 ± 0.75%/min to 2.75 ± 1.12%/min, $p = 0.002$; Table 3 and Fig. 1). In contrast, HOMA-IR was significantly decreased in both insulin resistance and sensitive subjects, defined by baseline Kitt values (Table 2).

DISCUSSION

It is well known that TZDs were efficacious in improving glycemic control and reducing HbA1C

Table 2. Anthropometric Data and Biochemical Characteristics at both Baseline and Follow-up

	Total (n = 83)		
	Baseline	Follow-up	*p* value
Weight (kg)	61.95 ± 9.45	63.11 ± 9.60	0.020
BMI (kg/m^2)	23.16 ± 2.51	23.74 ± 2.63	< 0.001
Waist circumference (cm)	81.97 ± 7.04	82.21 ± 7.63	0.048
Hip circumference (cm)	92.21 ± 5.79	93.36 ± 5.17	0.016
Waist-hip-ratio	0.89 ± 0.04	0.87 ± 0.05	0.090
SBP (mmHg)	129.84 ± 14.85	126.89 ± 12.52	0.086
DBP(mmHg)	74.67 ± 11.94	72.39 ± 9.72	0.207
Total cholesterol (mg/dL)	186.78 ± 34.87	187.67 ± 39.94	0.857
Triglyceride (mg/dL)	146.90 ± 75.84	144.77 ± 77.44	0.803
HDL-cholesterol (mg/dL)	44.04 ± 11.17	49.69 ± 14.97	< 0.001
LDL-cholesterol (mg/dL)	108.37 ± 35.79	114.04 ± 30.01	0.219
Fasting glucose (mg/dL)	183.28 ± 55.04	137.34 ± 36.42	< 0.001
HbA1C (%)	9.24 ± 1.96	8.11 ± 1.39	< 0.001
Kitt (%/min)	2.03 ± 1.14	2.67 ± 0.97	0.003
HOMA-IR	3.62 ± 2.98	1.61 ± 1.04	0.012

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; Kitt, rate constant for glucose disappearance in the insulin tolerance test; HOMA-IR, homeostasis assessment method for insulin resistance.
Values are presented as mean ± standard deviation.

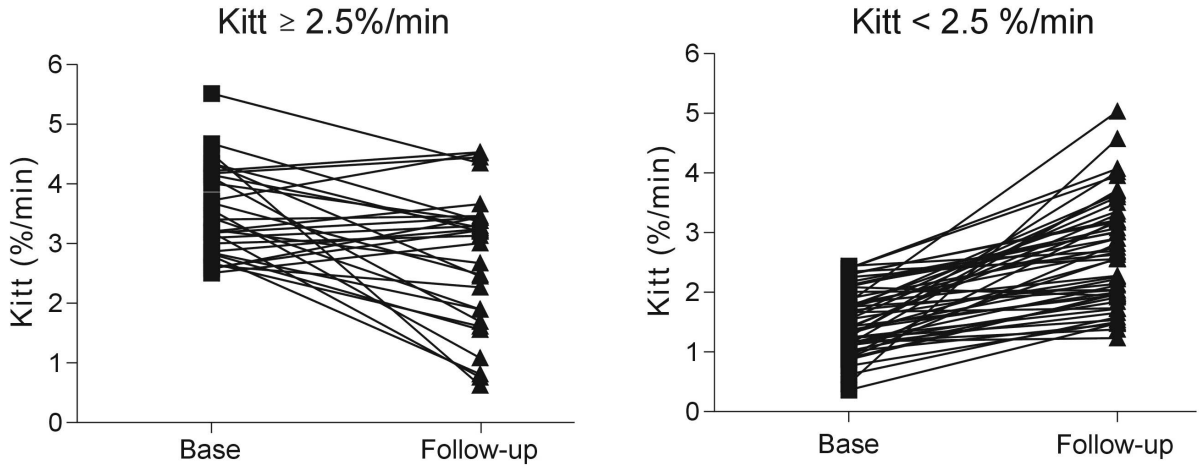

Fig. 1. The changes of Kitt values according to insulin resistant status defined by baseline Kitt values. Kitt values were significantly improved in subjects with insulin resistance. However, the Kitt values did not improve in subjects without insulin resistance.

Table 3. Parameter Changes according to Insulin Resistance as Defined by Baseline Kitt Values

	Subjects of baseline Kitt < 2.5 (n = 48)			Subjects of baseline Kitt ≥ 2.5 (n = 35)		
	Baseline	Follow-up	*p* value	Baseline	Follow-up	*p* value
Weight (kg)	62.26 ± 9.06	63.31 ± 9.48	0.005	61.46 ± 10.23	62.76 ± 9.97	0.027
BMI (kg/m^2)	23.56 ± 2.53	24.00 ± 2.73	0.001	22.45 ± 2.35	23.28 ± 2.42	0.003
Waist circumference (cm)	82.62 ± 6.29	82.36 ± 7.47	0.729	80.83 ± 8.20	81.97 ± 8.01	0.320
Hip circumference (cm)	92.71 ± 5.36	93.32 ± 4.99	0.210	91.33 ± 6.48	93.43 ± 5.56	0.037
Waist-hip-ratio	0.89 ± 0.04	0.88 ± 0.05	0.129	0.88 ± 0.05	0.87 ± 0.05	0.358
SBP (mmHg)	129.10 ± 12.27	123.95 ± 12.41	0.018	130.42 ± 16.78	129.15 ± 12.36	0.622
DBP (mmHg)	76.15 ± 11.12	71.00 ± 11.11	0.075	73.53 ± 12.63	73.46 ± 8.58	0.974
Total cholesterol (mg/dL)	190.17 ± 36.27	192.83 ± 43.59	0.713	180.90 ± 32.04	178.73 ± 31.37	0.687
Triglyceride (mg/dL)	153.48 ± 74.23	147.65 ± 82.97	0.608	135.50 ± 78.50	139.77 ± 67.81	0.741
HDL-cholesterol (mg/dL)	42.94 ± 9.98	48.36 ± 14.55	0.003	45.97 ± 12.95	52.00 ± 15.66	0.028
LDL-cholesterol (mg/dL)	116.72 ± 30.74	112.76 ± 38.16	0.542	109.30 ± 28.56	100.61 ± 30.23	0.134
Fasting glucose (mg/dL)	181.42 ± 54.50	134.11 ± 34.10	< 0.001	186.56 ± 56.76	153.06 ± 40.17	0.002
HbA1C (%)	9.36 ± 2.15	8.09 ± 1.62	< 0.001	9.04 ± 1.61	8.13 ± 0.89	0.004
Kitt (%/min)	1.51 ± 0.53	2.63 ± 0.88	< 0.001	3.50 ± 0.75	2.75 ± 1.12	0.002
HOMA-IR	5.11 ± 1.56	1.38 ± 1.01	0.011	3.07 ± 1.86	1.62 ± 1.07	0.007

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; Kitt, rate constant for glucose disappearance in the insulin tolerance test; HOMA-IR, homeostasis assessment method for insulin resistance.
Values are presented as mean ± standard deviation.

by insulin sensitizing action on muscle, adipose tissue, and liver.[10,11,14-17] Our data showed that TZDs treatment improved insulin sensitivity approved by both Kitt and HOMA-IR methods in type 2 diabetic patients who had been inadequately treated with sulfonylurea or metformin.

It was reported that metformin or sulfonylurea combined with either pioglitazone or rosiglitazone significantly improve glycemic control.[18,19] However, the combination of metformin or sulfonylurea with pioglitazone is associated with significant improvement in lipid and lipoprotein levels, whereas the rosiglitazone combination does not show a significant effect on lipid metabolism. In this study, we did not compare the effects between pioglitazone and rosiglitazone. However, fasting glucose and HbA1C levels were significantly improved, and lipid profiles except for HDL cholesterol levels were not changed after treatment with both pioglitazone and rosiglitazone compared with baseline values. We think that TZDs' effects on lipid metabolism should further be assessed in prospective trials.

Although several studies have provided strong evidence that TZDs may improve β-cell function,[20-22] the major effects of TZDs are mediated via their insulin sensitizing effects on muscle and liver by binding to PPAR-γ.[7,8,14-17] Previously, the insulin sensitizing effects of TZDs have been assessed by either euglycemic hyperinsulinemic clamp[16,23-25] or HOMA index.[18,19,26,27] Although the euglycemic hyperinsulinemic clamp is often referred to as the gold standard test, this technique is time-consuming and difficult to perform.[28] Consequently, vari-

ous simpler methods similar to the euglycemic hyperinsulinemic clamp method have been proposed in recent years. HOMA-IR is easily calculated from fasting glucose and insulin concentration, and relates closely with euglycemic hyperinsulinemic clamp.[13,29] However, because insulin secretion is pulsatile and HOMA-IR is not a dynamic test, a single sample needs to be carefully interpreted.[30] On the other hand, Kitt is a reproducible, inexpensive, and rapid method, allowing easy measurement of insulin sensitivity.[5,6,31-33] In this study, we performed HOMA-IR and Kitt to estimate insulin sensitivity. As expected, both measurements for insulin sensitivity were improved after TZDs treatments. However, when we performed subgroup analysis with baseline Kitt values, Kitt values decreased in patients who showed Kitt values above 2.5%/min at baseline, while fasting glucose and HbA1C levels improved consistently in all subjects. HOMA-IR was equally improved regardless of baseline Kitt values. We could not exactly explain the reason of why Kitt values were not consistently changed by the treatment of TZDs. Nevertheless, we speculate various possibilities. First, Kitt may fail to estimate insulin sensitivity in insulin sensitive subjects. The amount of insulin used for Kitt (0.1 U/kg) is a supraphysiological dose and suppresses hepatic gluconeogenesis.[31] After insulin injection during Kitt measurement, disappearance of glucose is mainly due to glucose uptake by muscles or adipose tissue. Consequently, Kitt may possibly underestimate the insulin sensitivity when patients have hepatic insulin resistance or show weak insulin resistance. In our study, insulin sensitivity may be improved in insulin sensitive subjects (Kitt > 2.5%/min) in a manner similar to insulin resistant subjects, although Kitt values did not change because of this reason. Second, TZDs may affect glycemic control in insulin sensitive subjects by an another mechanism rather than recovery of insulin resistance. It is well known that both beta cell function and insulin action are lessened in chronic hyperglycemic states[34,35] and reversed by improved glycemic control.[36,37] As mentioned above, since TZDs have an additional effect of preserving β-cell function,[20-22] TZDs may improve the glycemic control by improving glucose toxicity even if Kitt values did not improve. Therefore, it is highly likely that the Kitt rate did not improve when the baseline was above 2.5%/min. However, it is highly desirable to perform clamp studies to clarify why Kitt is not consistently changed, and this is the limitation of the study.

In conclusion, Kitt could be a reliable method to estimate the insulin sensitizing effects of TZDs when Kitt values are less than 2.5%/min.

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