Insulin Sensitivity, Insulin Secretion, and Glucose Effectiveness in Obese Subjects: A Minimal Model Analysis

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The aim of the present study was to estimate insulin sensitivity (SI), insulin secretion, and glucose effectiveness in 14 obese subjects who were further divided into two groups: one with normal glucose tolerance and the other with impaired glucose tolerance (IGT). Glucose tolerance was determined by criteria of the World Health Organization. All subjects were Japanese. They underwent a modified frequently sampled intravenous glucose tolerance test: glucose (300 mg/kg body weight) was administered, and insulin (20 mU/kg body weight given over 5 minutes) was infused from 20 to 25 minutes after administration of glucose. SI and glucose effectiveness at basal insulin (SG) were estimated by Bergman's minimal model method. Body mass index (33.0 ± 1.8 *v* 30.9 ± 1.5 kg/m^2, $P > .05$) and fasting insulin level (127.9 ± 30.0 *v* 107.4 ± 14.4 pmol/L, $P > .05$) were higher in obese IGT subjects than in normal obese subjects, but were not statistically significant. With regard to fasting glucose level, obese subjects with IGT (5.9 ± 0.3 mmol/L) had significantly higher levels than those with normal glucose tolerance (5.1 ± 0.2 mmol/L, $P < .01$). There was no significant difference in SI between the two groups (0.53 ± 0.10 *v* 0.56 ± 0.13 × 10^{-4} · min^{-1} · pmol/L^{-1}, $P > .05$). Pancreatic insulin secretion expressed as the integrated area of plasma insulin above the basal level during the first 19 minutes was significantly lower in obese subjects with IGT (3,366 ± 1,495 pmol/L · min) than in those with normal glucose tolerance (16,400 ± 4,509 pmol/L · min, $P < .05$). Glucose disappearance rate ([K_G] 1.03 ± 0.12 min^{-1}), SG (0.013 ± 0.002 min^{-1}), and glucose effectiveness at zero insulin ([GEZI] 0.007 ± 0.002 min^{-1}) were significantly lower in obese subjects with IGT than in those with normal glucose tolerance (K_G, 2.11 ± 0.25 min^{-1}, $P < .01$; SG, 0.022 ± 0.003 min^{-1}, $P < .01$; GEZI, 0.017 ± 0.003 min^{-1}, $P < .01$). Thus, the risk factor for worsening glucose tolerance in obese subjects is partially explained by the derangements in SG and GEZI and the impairment in β-cell function to adapt to insulin resistance. This is the first description that the impairments in both insulin secretion and glucose effectiveness but not insulin resistance may worsen glucose tolerance in obese subjects.

ALTHOUGH IT IS well recognized that obese subjects have an impairment in insulin action,[1-3] not all obese subjects are glucose-intolerant. The mechanism underlying glucose intolerance in obese subjects is not fully clarified. One of the approaches to clarify this mechanism is to study obese individuals with non–insulin-dependent diabetes mellitus (NIDDM). However, interpretation of the findings observed in NIDDM is complicated by the fact that hyperglycemia per se impairs insulin sensitivity (SI) and insulin secretion.[4] One way to overcome this difficulty is to investigate obese subjects with impaired glucose tolerance (IGT).

Only one report studying obese individuals with IGT is available. Using the insulin clamp technique, Golay et al[5] previously demonstrated that insulin-stimulated glucose uptake is markedly reduced in obese subjects with IGT as compared with those with normal glucose tolerance matched for age and body mass index, and concluded that insulin resistance appears to be related to the state of abnormal carbohydrate tolerance, not to the presence of obesity per se. This idea is supported by the previous study reported by Reaven et al,[6] who used the insulin clamp method and found that resistance to insulin-stimulated glucose uptake is a basic characteristic of lean subjects with IGT. However, not all IGT subjects are insulin-resistant. Using the minimal model approach shown by Bergman et al,[7-28] we recently reported on non-obese IGT subjects who were characterized by normal SI, decreased glucose effectiveness (SG), and mild impairments in pancreatic insulin secretion.[7] Therefore, it may be hypothesized that not only reduced SI but also derangements in SG and β-cell function are responsible for the evolution of IGT in non-obese subjects. However, to the best of our knowledge, it has not been studied extensively yet whether SG and β-cell function are impaired in obese IGT subjects, although Bergman et al[17] previously reported obese subjects with reduced SG and normal pancreatic insulin secretion. SI, SG, and β-cell function can be measured simultaneously by a minimal model approach.[7-28] We therefore recruited obese subjects (body mass index > 27.0 kg/m^2) and divided them into two groups, normal glucose tolerance and IGT, and investigated glucose kinetics using the minimal model approach.

SUBJECTS AND METHODS

The study population consisted of seven obese subjects with normal glucose tolerance and seven obese subjects with IGT. Obese subjects had a body mass index greater than 27.0 kg/m^2. Glucose tolerance was determined by criteria of the World Health Organization.[29] Subjects were all normotensive and had normal renal, hepatic, and thyroid function. They had no family history of

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type II diabetes and no previous history of gestational diabetes mellitus, and did not take any medications known to alter carbohydrate metabolism. None of the participants consumed alcohol or performed heavy exercise for at least 1 week before the test. For at least 3 days before the test, body weights and daily diets were stable. Their ages ranged from 20 to 45 years. Obese subjects with IGT (31.1 ± 3.8 years) were older than obese controls (25.1 ± 1.8 years), but this was not statistically significant. Women were studied in the follicular phase of the menstrual cycle. Before their participation, the nature, purpose, and risks of the study were explained to all subjects and informed written consent was obtained.

After an overnight fast, butterfly needles were inserted into the antecubital veins and were maintained by a slow drip of physiological saline. Subjects were allowed to rest quietly for at least 15 minutes before blood sampling was begun. Baseline samples for glucose and insulin determination were obtained at −20, −10, and −3 minutes. Glucose (300 mg/kg body weight) was administered intravenously within 2 minutes, and insulin (20 mU/kg over 5 minutes) was infused into an antecubital vein from 20 to 25 minutes after administration of glucose.[13] Blood samples were drawn frequently from the contralateral antecubital vein as described previously.[13]

Plasma glucose level was measured in duplicate with an automatic analyzer (Kyoto-Daiichi-Kagaku, Kyoto, Japan) by the glucose oxidase method. Immunoreactive insulin level was measured in duplicate using a radioimmunoassay Phadeseph insulin kit (Shionogi, Osaka, Japan). Coefficients of variation were 4% for insulin levels greater than 180 pmol/L and 7% for insulin levels less than 180 pmol/L, respectively.

The glucose disappearance rate (K_G) was calculated as the slope of the least-square regression line relating the natural logarithm of glucose concentration to time from more than four samples drawn between 10 and 19 minutes.

SI and SG were estimated by the minimal model approach.[7-28] In this analysis, fluctuations in circulating glucose levels over time are described by the following differential equations: $dG(t)/dt = -p1[G(t) - Gb] - X(t)G(t)$ and $dX(t)/dt = -p2X(t) + p3[I(t) - Ib]$, where $G(t)$ is plasma glucose concentration, $I(t)$ is plasma insulin concentration, and Gb and Ib are baseline concentrations. $X(t)$ represents the time course of the peripheral insulin effect. Parameter p1 represents the effect of glucose at basal insulin to normalize its own concentration in plasma independent of increased insulin. This parameter is known as SG and has been verified through comparison with studies in which the insulin secretory response was suppressed.[22] The ratio between p3 and p1 defines the index SI, which represents the insulin-dependent increase in net K_G. SI has been validated by comparison with a direct measure of SI from glucose clamp experiments in humans.[23,24] The basal insulin effect (BIE) can be calculated as the product of basal insulin (Ib) and SI: BIE = Ib × SI. Glucose effectiveness at zero insulin (GEZI) is the difference between SG and BIE, ie, GEZI = SG − (Ib × SI). This measure is analogous to tissue glucose sensitivity.[25,26]

The minimal model program was written in Pascal (Borland International, Scotts Valley, CA) on a Macintosh IIcx (Apple Computer, Cupertino, CA) as described previously.[13]

Endogenous plasma insulin responses were expressed as the area under the insulin curve between 0 and 19 minutes after administration of glucose.[12] The integrated area of plasma insulin above the basal level was calculated using the trapezoidal method.[30]

Data are expressed as the mean ± SEM. To evaluate differences between the two groups, data were analyzed by the Mann-Whitney *U* test. When more than two groups were compared, the significance of differences between any two groups was determined using Duncan's multiple-range test.[31] A P level of .05 was taken to establish statistical significance.

RESULTS

Obese subjects with IGT were older than those with normal glucose tolerance, but this was not statistically significant. Body mass index was greater in obese IGT subjects than in normal obese subjects, but it also was not statistically significant (Table 1). Fasting (5.9 ± 0.3 *v* 5.1 ± 0.2 mmol/L, $P < .01$) and 2-hour (8.9 ± 0.4 *v* 5.7 ± 0.2 mmol/L, $P < .01$) plasma glucose levels during a 75-g oral glucose tolerance test were significantly higher in obese subjects with IGT than in those with normal glucose tolerance.

Metabolic parameters of obese subjects with IGT or normal glucose tolerance are listed in Table 1 along with our previous data in normal-tolerance lean subjects.[13] The pancreatic insulin response to intravenous glucose stimuli (insulin area) was significantly lower in obese subjects with IGT than in those with normal tolerance. SI was similarly decreased in individual obese subjects as compared with lean controls. On the other hand, K_G, SG, and GEZI were significantly lower in obese subjects with IGT than in those with normal glucose tolerance, whose parameters were similar to those of lean controls. There was no significant difference in BIE among the three groups.

DISCUSSION

In the present study, we investigated carbohydrate metabolism in obese subjects. Our normal-tolerance obese subjects were already insulin-resistant, indicating some abnormality of carbohydrate metabolism in obese individuals. Of particular interest is that obese IGT subjects had a similar SI but a significantly lower insulin response to intravenous glucose stimuli as compared with normal-tolerance obese subjects. This is not in agreement with data reported by Golay et al,[5] who used the insulin clamp technique and found severe impairment in SI in obese IGT subjects. Bergman et al[17] also previously showed that obese subjects with low K_G had insulin resistance and normal pancreatic insulin response to intravenous glucose. The reason for the discrepant results between their data and ours remains to be clarified, but it may be due to a difference in the study population or dietary nutrition. Lovejoy and DiGirolamo[32] recently reported that an habitually low dietary fiber intake along with elevated dietary fat correlates with diminished SI in obese individuals. Alternatively, the discrepant results may be explained by other factors such as the different method to assess SI, the degree of body fat distribution, or the difference in the genetic background of the subjects studied,[3] although we did not measure body fat distribution in the present study.

The current understanding is that NIDDM is a genetic disorder, probably of a heterogenous nature, and that insulin secretion and SI both must be defective to produce

Table 1. Clinical Characteristics and Minimal Model Analysis of the Study Groups

Subject No.	Sex/Age (yr)	BMI (kg/m²)	Fasting Glucose (mmol/L)	Fasting Insulin (pmol/L)	Insulin Area (pmol/L · min)‖	SI × 10⁴ (min⁻¹ · pmol/L⁻¹)	K_G (%/min)	SG (min⁻¹)	GEZI (min⁻¹)	BIE (min⁻¹)
Obese IGT										
1	M/21	28.9	4.8	50	3,250	1.03	1.17	0.007	0.002	0.005
2	M/22	27.7	7.6	274	160	0.49	0.75	0.018	0.005	0.013
3	F/23	34.3	5.6	148	12,590	0.14	1.49	0.018	0.012	0.006
4	M/25	36.5	6.7	206	1,480	0.28	0.81	0.016	0.010	0.006
5	M/38	27.0	5.2	76	3,870	0.59	1.50	0.020	0.015	0.005
6	F/44	39.3	5.7	92	1,280	0.70	0.80	0.010	0.004	0.006
7	F/45	37.0	5.5	49	933	0.48	0.70	0.001	0	0.001
Mean ±SEM	31.1 ± 3.8‡	33.0 ± 1.8‡	5.9 ± 0.3‡	128 ± 30‡	3,366 ± 1,495†	0.53 ± 0.10§	1.03 ± 0.12*‡	0.013 ± 0.002*‡	0.007 ± 0.002*‡	0.006 ± 0.001
Obese normal										
1	F/20	32.5	5.3	124	8,010	0.35	1.17	0.012	0.008	0.004
2	F/20	34.5	4.5	161	20,200	0.47	2.16	0.023	0.015	0.008
3	M/22	27.0	5.8	86	11,324	0.32	1.52	0.018	0.015	0.003
4	M/22	27.3	4.9	71	5,165	0.59	1.58	0.018	0.014	0.004
5	M/30	27.0	5.1	48	3,505	1.28	2.59	0.017	0.011	0.006
6	F/30	38.3	4.6	149	30,000	0.17	3.10	0.028	0.025	0.003
7	F/32	29.4	5.3	113	36,600	0.73	2.65	0.038	0.030	0.008
Mean ± SEM	25.1 ± 1.8§	30.9 ± 1.5‡	5.1 ± 0.2	107 ± 14‡	16,400 ± 4,509§	0.56 ± 0.13§	2.11 ± 0.25	0.022 ± 0.003	0.017 ± 0.003	0.005 ± 0.001
Lean normal[13] (5M/6F)										
Mean ± SEM	21.9 ± 0.4	20.9 ± 0.4	5.1 ± 0.1	42 ± 4	4,643 ± 885	1.27 ± 0.18	2.19 ± 0.19	0.024 ± 0.003	0.018 ± 0.003	0.005 ± 0.001

Abbreviations: M, male; F, female; BMI, body mass index.
*$P < .01$ *v* obese normal.
†$P < .05$ *v* obese normal.
‡$P < .01$ *v* lean normal.
§$P < .05$ *v* lean normal.
‖Insulin area between 0 and 19 minutes after glucose administration.

full phenotypic expression.[33] No convincing data have yet proved whether one type of defect predates the other, and it remains to be determined whether both are genetically mediated or one causes the other. In some glucose-intolerant obese subjects, the primary defect starts as an impairment in tissue sensitivity to insulin; these individuals may be represented by the obese subjects reported by Golay et al[5] and Bergman et al.[17] In other glucose-intolerant obese subjects, the primary defect starts at the level of the β cell. These individuals may be represented by the obese subjects in our present experiment, since in our obese IGT subjects, absolute insulin response was not increased despite insulin resistance, suggesting an impairment in the β cell to adapt to insulin resistance.[34]

There are some data supporting the idea that insulin secretory dysfunction but not insulin resistance mainly worsens glucose tolerance in humans. Banerji and Lebovitz[35] reported on NIDDM patients with normal SI and severe impairment in insulin secretion. We also previously reported on lean NIDDM and lean IGT subjects who were both characterized by normal SI and derangements in β-cell function. Interestingly, impairment in β-cell function was more severe in lean NIDDM patients (214 ± 112 pmol/L · min) than in lean IGT subjects (2,556 ± 572 pmol/L · min, $P < .01$).[7,13] Therefore, it may be suggested that the derangement in β-cell function could partially explain the worsening of glucose tolerance in human subjects.

However, of particular interest is the observation that obese IGT subjects had decreased SG also. This result is consistent with findings reported by Bergman et al[17] that obese subjects with low K_G were characterized by diminished SG. Interestingly, SG in our obese IGT subjects (0.013 ± 0.002 min^{-1}) was similar to that reported in lean IGT patients (0.013 ± 0.002 min^{-1})[7] or NIDDM patients (0.014 ± 0.001 min^{-1}[19,12] and 0.011 ± 0.002 min^{-1} [13]). IGT is the classic risk factor for NIDDM.[36-38] Thus, decreased SG may play an important and permissive role in the development of NIDDM. This idea is supported by results reported by Martin et al[28] that the development of NIDDM is partially preceded by defects in SG.

It may be argued that the dietary condition per se affects SG, since it is reported that a low-carbohydrate diet or very–low-calorie diet (420 kcal) decreases SG, and since anorectic patients with dietary restriction had reduced SG.[14,20,21] However, it seems unlikely, since the subjects in our study ate a similar diet containing enough carbohydrate.

In summary, our present study demonstrates that obese IGT subjects had a significantly lower pancreatic insulin response to intravenous glucose and decreased SG and GEZI as compared with normal-tolerance obese subjects. Whether the impairment is one of the risk factors for worsening to IGT in normal-tolerance obese subjects requires further study.

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