Impaired adaptation of first-phase insulin secretion in postmenopausal women with glucose intolerance

BO AHRÉN1 AND GIOVANNI PACINI2

1Department of Medicine, Lund University, S-205 02 Malmö, Sweden; and 2Institute of Systems Science and Biomedical Engineering (LADSEB-Consiglio Nazionale delle Ricerche), I-35127 Padua, Italy

Ahren, Bo, and Giovanni Pacini. Impaired adaptation of first-phase insulin secretion in postmenopausal women with glucose intolerance. Am. J. Physiol. 273 (Endocrinol. Metab. 36): E701–E707, 1997.—This study examined whether insulin secretion, insulin sensitivity, glucose effectiveness, and hepatic extraction of insulin are altered in subjects with impaired glucose tolerance (IGT). The frequently sampled intravenous glucose tolerance test was performed in postmenopausal women (age 63 yr, body mass index range 21.6–28.9 kg/m²) with IGT (n = 10) or normal glucose tolerance (NGT; n = 10). Insulin sensitivity (Si) was significantly lower in IGT than in NGT (P = 0.030). In contrast, insulin secretion was not significantly different between the two groups as determined by area under the curve for insulin and C-peptide, acute insulin response to glucose (AIRG), and glucose effectiveness of first-phase (ΔS1) or of second-phase (ΔS2) insulin secretion. In NGT (r = −0.68, P = 0.029) but not in IGT (r = −0.05, not significant), S1 correlated negatively with ΔS2. The B-cell “adaptation index” (S1 × ΔS2) was lower in IGT than in NGT [83 ± 25 vs. 171 ± 29 min⁻²(mmol/l), P = 0.042]. Also, the B-cell “disposition index” (S1 times AIRG) was lower in IGT (83 ± 25 10⁻⁴ min⁻¹) than in NGT (196 ± 30 10⁻⁴ min⁻¹, P = 0.011). In contrast, glucose effectiveness or hepatic extraction of insulin was not different between IGT and NGT. We conclude that postmenopausal women with IGT fail to adequately adapt to lowered Si by increasing first-phase insulin secretion.

insulin sensitivity; glucose effectiveness; C-peptide; mathematical modeling; minimal model

NON-INSULIN-DEPENDENT diabetes mellitus (NIDDM) is accompanied by a combination of reduced insulin secretion and reduced insulin sensitivity (12, 30). To study the temporal relation between these two derangements, subjects with impaired glucose tolerance (IGT) are of interest, because IGT is associated with an increased risk for developing NIDDM, and, furthermore, IGT often precedes the disease (1). Studies on the pathophysiology of NIDDM and IGT are, however, complicated by the intimate relation between insulin secretion and insulin sensitivity; the two parameters displaying a hyperbolic relation with compensatory increased insulin secretion when insulin sensitivity is reduced (4, 16, 19). Interpretations of pathophysiological studies are therefore sometimes difficult. Nevertheless, by using the insulin response to intravenous arginine at different glucose concentrations as a measure of insulin secretion, we recently concluded that in both obese and nonobese IGT, insulin secretion is impaired (20, 22). Furthermore, by analyzing insulin secretion in relation to insulin sensitivity, as determined by the hyperinsulinemic-euglycemic clamp technique, we showed an inadequate compensation in insulin secretion when insulin sensitivity is reduced in IGT (19). Other studies have arrived at similar conclusions. For example, one study in lean Japanese subjects showed that subjects with IGT who exhibited normal insulin sensitivity displayed a reduced insulin secretion when compared with a group of subjects with normal glucose tolerance (NGT) (32), and a study in Caucasian individuals—60 yr old showed impaired first-phase insulin secretion after intravenous glucose in IGT (11). Moreover, a recent epidemiologic study demonstrated that islet dysfunction rather than insulin resistance determines the development of NIDDM in a high-risk Caucasian population (26). In contrast, results of other studies have suggested that NIDDM is preceded mainly by reduced insulin sensitivity (13, 24). Other studies have also suggested that the glucose effectiveness, i.e., the ability of glucose to stimulate its own disposal (6), is impaired in IGT (18, 32). Hence, the underlying mechanism for IGT is far from clear.

In general, however, interpretation of the results from studies on the mechanisms of glucose intolerance is usually difficult, since studied groups may not be matched for age, gender, or degree of obesity. For example, in one report, the age of the studied individuals was higher in those with IGT than in those with NGT (32), and in another study, subjects of both genders were included (18). This is important because insulin sensitivity can be reduced by age (8) and because there is a gender-dependent difference in gastric emptying (14) that might influence the outcome of the oral glucose tolerance test. Therefore, whether B-cell function is altered in IGT has not been established in controlled groups. The purpose of this study was therefore to explore whether insulin secretion, insulin sensitivity, glucose effectiveness, and hepatic extraction of insulin are altered in IGT when we control for influences by age, gender, body mass index, and ethnic origin. To that end, groups with IGT and NGT were standardized for these confounding factors, and a frequently sampled intravenous glucose tolerance test (FSIGT) was performed (4, 10).

METHODS

Subjects. We studied 20 postmenopausal women aged 63 yr (mean ± SD, 63 yr ± 3 mo ± 3 mo) with a body mass index of 25.5 ± 2.2 kg/m² (range 21.6–28.9 kg/m²). According to a 75-g oral glucose tolerance test (OGTT) using World Health Organization (WHO) criteria, 10 of the subjects had NGT, whereas 10 subjects had IGT. Table 1 shows some clinical characteristics of the subjects. All subjects had normal liver and thyroid function tests, none were taking any medication known to
Table 1. Characteristics of two study groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IGT (n=10)</th>
<th>NGT (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>63.3±0.3</td>
<td>63.3±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.9±2.4</td>
<td>26.2±1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Waist-to-height ratio</td>
<td>0.80±0.05</td>
<td>0.77±0.06</td>
<td>NS</td>
</tr>
<tr>
<td>2-h Blood glucose, mmol/l</td>
<td>5.0±0.2</td>
<td>4.5±0.4</td>
<td>0.043</td>
</tr>
<tr>
<td>Fasting plasma HDL-cholesterol, mmol/l</td>
<td>8.8±0.9</td>
<td>6.4±0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting plasma LDL-cholesterol, mmol/l</td>
<td>1.43±0.48</td>
<td>1.56±0.53</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma triglyceride, mmol/l</td>
<td>4.40±1.02</td>
<td>4.12±0.99</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>132±1.54</td>
<td>128±15.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>86±7.6</td>
<td>82±5.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SD. OGTT, oral glucose tolerance test; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; NS, not significant; n, no. of subjects. P value indicates probability level of random difference between groups.

RESULTS

Baseline plasma glucose was slightly higher in the IGT group than in the NGT group, whereas basal insulin and C-peptide concentrations did not differ significantly between the two groups (Table 2).

FSIGT. Immediately after the glucose injection, serum insulin and plasma C-peptide rose rapidly with peak levels after 3 min, whereafter the levels declined (Fig. 1). The levels did not differ significantly between the groups, as analyzed by ANOVA for repeated measurements. Similarly, AUC for insulin, AUC for C-peptide, and AIRG did not differ significantly between the groups (Table 2). Plasma glucose was higher in...
The aim of this study was to establish whether insulin secretion, insulin sensitivity, glucose effectiveness, and hepatic extraction of insulin are altered in subjects with IGT vs. NGT. To allow reliable conclusions from the results, we exercised care when selecting our groups. First, we selected subjects with the age of 63 yr, which is an age group in which the annual transition from IGT to NIDDM is high (1, 3), and we chose postmenopausal women from a population of Caucasian subjects with a high prevalence of IGT in this age group (21). Second, to eliminate possible influence within the study group of age on the studied parameters, which may occur for insulin secretion and insulin sensitivity (8), we selected women with a range of age of only a few months. Third, we selected women with a body mass index that was not different between the two groups. Fourth, we selected individuals without any family history of NIDDM. Finally, we restricted our study to women to avoid gender-dependent confounding effects. These create problems in studies on IGT subjects with IGT than in subjects with NGT at all individual time points during the first 30 min after glucose injection (P < 0.05).

The subjects with IGT had a significantly lower $S_i$ than the subjects with NGT, whereas $S_G$ was not different between the two groups (Table 2). The other model-derived metabolic parameters did not differ between the two groups (Table 2). The disposition index ($S_i \times A_{IRG}$) was lower in subjects with IGT ($83 \pm 25 10^{-4} \text{min}^{-1}$) than in subjects with NGT ($196 \pm 30 10^{-4} \text{min}^{-1}$, $P = 0.011$; Fig. 2A). Furthermore, the disposition index correlated negatively to the 2-h glucose value, as obtained from the OGGT ($r = 0.50$, $P = 0.026$).

Table 2. Fasting levels of glucose, insulin, and C-peptide and parameters calculated from FSIGT for postmenopausal women with IGT or NGT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IGT (n = 10)</th>
<th>NGT (n = 10)</th>
<th>P</th>
<th>P when NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose, mmol/l</td>
<td>5.5 ± 0.3</td>
<td>4.9 ± 0.1</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Fasting serum insulin, pmol/l</td>
<td>70.7 ± 10.4</td>
<td>63.8 ± 8.6</td>
<td>NS</td>
<td>0.573</td>
</tr>
<tr>
<td>Fasting plasma C-peptide, nmol/l</td>
<td>0.84 ± 0.10</td>
<td>0.67 ± 0.07</td>
<td>NS</td>
<td>0.172</td>
</tr>
<tr>
<td>$S_i, 10^{-4} \text{min}^{-1}$</td>
<td>0.62 ± 0.09</td>
<td>1.16 ± 0.20</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>$S_G, \text{min}^{-1}$</td>
<td>0.019 ± 0.003</td>
<td>0.020 ± 0.003</td>
<td>NS</td>
<td>0.760</td>
</tr>
<tr>
<td>AUC insulin, nmol/l in 3 h</td>
<td>20.5 ± 2.4</td>
<td>18.3 ± 1.8</td>
<td>NS</td>
<td>0.484</td>
</tr>
<tr>
<td>AUC C-peptide, nmol/l in 3 h</td>
<td>295 ± 41</td>
<td>226 ± 22</td>
<td>NS</td>
<td>0.109</td>
</tr>
<tr>
<td>$A_{IRG}$, pmol/l</td>
<td>134 ± 33</td>
<td>197 ± 45</td>
<td>NS</td>
<td>0.192</td>
</tr>
<tr>
<td>BSR, (pmol/l)/min $\phi_1$ (nmol/l)</td>
<td>64.5 ± 11.6</td>
<td>48.2 ± 7.7</td>
<td>NS</td>
<td>0.258</td>
</tr>
<tr>
<td>BSR, (pmol/l)/min $\phi_2$ (pmol/l)</td>
<td>1.39 ± 0.39</td>
<td>1.93 ± 0.42</td>
<td>NS</td>
<td>0.364</td>
</tr>
<tr>
<td>Total insulin secretion, nmol/l</td>
<td>21.1 ± 3.7</td>
<td>14.2 ± 1.6</td>
<td>NS</td>
<td>0.112</td>
</tr>
<tr>
<td>Hepatic insulin extraction, %</td>
<td>79.3 ± 3.4</td>
<td>80.9 ± 3.0</td>
<td>NS</td>
<td>0.730</td>
</tr>
</tbody>
</table>

Values are means ± SE. $S_i$, insulin sensitivity; $S_G$, glucose effectiveness; $A_{IRG}$, area under curve $A_{IRG}$, acute insulin response to glucose; BSR, basal B-cell secretion rate; $\phi_1$, glucose sensitivity of first-phase insulin secretion; and $\phi_2$, glucose sensitivity of second-phase insulin secretion, respectively.

DISCUSSION

Plotting $A_{IRG}$ vs. $S_i$ in all subjects, we obtained the characteristic hyperbolic function (Fig. 3A). Also, the B-cell adaptation index, i.e., $S_i \times \phi_1$, was significantly lower in IGT ($85 \pm 26 10^{-4} \text{mmol/l}$) than in NGT ($171 \pm 29 10^{-4} \text{mmol/l}$, $P = 0.042$; Fig. 2B). In subjects with NGT, there was a significant negative correlation between $S_i$ and $\phi_1$ ($r = -0.68$, $P = 0.029$), whereas in subjects with IGT, this correlation was not significant ($r = -0.05$; Fig. 3B). This indicates that the normal compensation to increase first-phase insulin secretion in response to reduced $S_i$ was impaired in IGT. In contrast, the product of $S_i \times \phi_2$ was not significantly different between the groups ($0.40 \pm 0.08 10^{-4} \text{mmol/l}$ in IGT vs. $0.26 \pm 0.05 10^{-4} \text{mmol/l}$ in NGT), suggesting that the second phase of insulin secretion was not impaired in IGT. Finally, mean hepatic extraction of insulin was of the same magnitude in the two groups (Table 2).

Fig. 1. Concentrations of plasma glucose (A), serum insulin (B), and plasma C-peptide (C) during intravenous glucose tolerance test (300 mg/kg) in healthy postmenopausal women with normal glucose tolerance (NGT; ○, n = 10 subjects) and impaired glucose tolerance (IGT; ●, n = 10 subjects).
when the classification is based on OGTT, because gastric emptying is different in males and females (14). Therefore, our study group was highly selected and homogeneous, increasing the validity of the conclusions. The only difference we detected in the clinical parameters, except the glucose intolerance, was an elevated level of triglycerides in the subjects with IGT. This is a well-known characteristic of this group of subjects and has been discussed in relation to increased risk for cardiovascular diseases (1). Furthermore, we used the FSIGT to determine the studied parameters, since this technique has been previously shown to reliably document insulin sensitivity, insulin secretion, glucose effectiveness, and hepatic extraction (4, 29).

We found that insulin sensitivity was lower in the subjects with IGT than in those with NGT. It has also previously been demonstrated that in obese Caucasian subjects, IGT is associated with reduced insulin sensitivity, as determined during an FSIGT (18). Similarly, reduced insulin sensitivity, as determined by the hyperinsulinemic-euglycemic clamp technique, has been shown in other studies on subjects with IGT of Caucasian, Pima Indian, and Mexican American origin (1, 13, 24). In contrast, a study in nonobese Japanese subjects (mean body mass index 22 kg/m²) showed an insulin sensitivity in IGT subjects that was not significantly different from that in NGT subjects (32). Altogether, these results indicate that in most populations, regard-

less of degree of obesity, IGT is associated with reduced insulin sensitivity, irrespective of the technique used to determine it.

Under normal conditions, a reduction in insulin sensitivity is compensated with increased insulin secretion to preserve normoglycemia, as demonstrated both under experimental conditions (2, 15) and when insulin sensitivity and insulin secretion are compared in larger groups (4, 9, 19). A figure for insulin secretion in a subject or a group of subjects has to be interpreted, therefore, in the light of the ambient insulin sensitivity, as discussed by Bergman (4). We found that, in the group with IGT, absolute levels for basal insulin and C-peptide as well as other insulin secretion parameters were not significantly different compared with the group with NGT, yet insulin sensitivity was significantly reduced. To interpret these findings, we related the parameters for insulin secretion to the ambient insulin sensitivity. A mathematical relationship between insulin sensitivity and B-cell function was first introduced by Bergman (4) and recently exploited in depth by Kahn et al. (16), who demonstrated a hyper-
The disposition index relates insulin sensitivity to insulin by considering peripheral insulin concentration. This is of value to understand the relationship between circulating insulin and insulin sensitivity, particularly when dealing with a large number of subjects, since it avoids the burden of measuring C-peptide. However, the most appropriate descriptor characterizing the relationship between B-cell insulin secretion and insulin sensitivity would require a parameter directly related to insulin secretion rather than peripheral insulin concentrations. Therefore, in this study, we introduce the B-cell adaptation index to characterize the relationship between insulin sensitivity and direct B-cell function as determined by the B-cell sensitivity to glucose obtained by C-peptide data. The disposition index (insulin sensitivity times AIRC) weighs insulin sensitivity with the ambient peripheral insulin during the first phase. It is, however, a peripheral measurement and does not necessarily reflect pancreatic secretion of insulin. The adaptation index (insulin sensitivity times \( \phi_1 \)), on the other hand, relates insulin sensitivity directly to a descriptor of B-cell function, since \( \phi_1 \) is a direct prehepatic variable that derives from C-peptide and involves an active mechanism, such as the ability of the B cells to release insulin under a glucose stimulation. The adaptation index therefore tells us how the pancreas reacts to a possible alteration in insulin sensitivity. It has to be emphasized that a high \( \phi_1 \) does not necessarily yield a high AIRC. In fact, hepatic extraction of insulin may alter the insulin pattern that reaches the periphery, or, despite a high glucose sensitivity in the B cells, the pancreas may not be able to release sufficient amount of hormone to elicit a clear overt first phase. Therefore, both the disposition and the adaptation indexes relate insulin sensitivity with insulin but are not describing the same contingency, although both of them describe a possible compensation of insulin sensitivity to the peripheral insulin levels and to the B-cell ability to secrete insulin, respectively. Thus they integrate each other to provide a more complete metabolic picture.

We found that the adaptation index was reduced in subjects with IGT, suggesting that these subjects failed to respond to the reduced insulin sensitivity with an adequately increased B-cell response. It is worth noticing that the adaptation index seems to be a sensitive parameter, since it was significantly reduced in IGT despite nonsignificant differences between the two groups in other parameters of insulin secretion, like AIRG, \( \phi_2 \), and AUC. The impaired B-cell function adaptation is most likely the reason why, in the basal state, no hyperinsulinemia was seen in IGT despite low insulin sensitivity, which probably accounts for the slight basal hyperglycemia that was evident in these subjects. In a recent study, we demonstrated an inadequate insulin secretory response to arginine in subjects with IGT and reduced insulin sensitivity by using the glucose-dependent arginine injection technique (19). Although this technique of injecting arginine at different glucose levels enables calculations of basal and maximal insulin secretion as well as the glucose dependency of the B cells (33), it does not distinguish between the first and second phase of insulin secretion. This is, however, possible with the use of the minimal model analyses as used in the present study. Thus our present results show that subjects with NGT exhibit a strong negative correlation between insulin sensitivity and \( \phi_1 \), whereas no such correlation is seen in IGT, and that the B-cell adaptation index is lowered in IGT. This indicates that subjects with IGT have a disturbed first-phase insulin adaptation to low insulin sensitivity. The importance of impairment of first-phase insulin secretion for NIDDM was first emphasized by Cerisi and Luft (7) and later supported by other studies (4, 7, 11, 17, 19, 20, 22, 23, 27, 28, 30). We thus also show this for subjects with IGT.

In contrast, the second-phase insulin secretion appears normal in the subjects with IGT, since the AUC for insulin during the 3 h of the test as well as \( \phi_2 \) and the product insulin sensitivity times \( \phi_2 \) were not significantly different between the groups. In fact, mean values for these parameters were higher in IGT than in NGT subjects. Also, there was no correlation between insulin sensitivity and \( \phi_2 \) in subjects with NGT. This shows that the second-phase insulin secretion is not adapted to low insulin sensitivity as is first-phase insulin secretion and that IGT is not associated with disturbed second-phase insulin secretion. This suggests that the first and second phases of insulin secretion are regulated differently and these phases might also have different physiological implications. For example, it has been shown that the first- but not the second-phase insulin secretion is of major importance for hepatic glucose production (25). Also from that view, it is interesting that our study of a well-defined group of postmenopausal women indicates that mainly the first phase of glucose-stimulated insulin secretion is impaired in IGT.
Besides the importance of insulin sensitivity and insulin secretion, glucose disposal is also regulated by glucose effectiveness, i.e., the effect of glucose per se to stimulate its own peripheral uptake and to inhibit hepatic glucose production (6). We found that the two groups had the same glucose effectiveness. Previously, glucose effectiveness in glucose-intolerant subjects has been examined in ~40-yr-old obese subjects (18) and in young Japanese subjects with a low body mass index (32). In both these studies, glucose effectiveness was slightly reduced in IGT compared with NGT subjects. Our finding that glucose effectiveness was not different between subjects with IGT and NGT in postmenopausal women indicates that reductions in insulin sensitivity and first-phase insulin secretion are the main causes of IGT in this group. Whether the difference regarding glucose effectiveness between our study and the two mentioned studies (18, 32) depends on the different age groups remains to be examined directly. Possibly, insulin sensitivity and insulin secretion are of greater relative importance for glucose tolerance in older age groups than in younger age groups, in whom glucose effectiveness might play a more important role.

Our study also permitted conclusions on the possible influence of changes in hepatic extraction of insulin on glucose intolerance. Insulin and C-peptide are secreted equimolarly, and because insulin but not C-peptide is extracted to a large extent in the passage through the liver, quantification of this process is possible by using the dynamic changes of peripheral insulin and C-peptide (10). Changes in hepatic extraction of insulin might theoretically underlie glucose intolerance if the peripheral delivery of insulin is inadequate, despite an adequate compensation of insulin secretion. We found, however, that the two groups under study had the same hepatic extraction rate of insulin, indicating that the liver handling of insulin is not altered in subjects with IGT. This fits a previous study in obese subjects, in which the hyperinsulinemia both in subjects with NGT and in those with IGT was due to exaggerated secretion of insulin and not to altered hepatic extraction of the hormone (18).

On the basis of these results, we conclude that in carefully selected postmenopausal women belonging to a population and age group with a high prevalence of IGT, glucose intolerance is associated with reduced insulin sensitivity and impaired adaptation in the first-phase insulin secretion, whereas second-phase insulin secretion, glucose effectiveness, and hepatic insulin extraction are not altered. We suggest that the inadequate compensation to reduced insulin sensitivity of the first-phase insulin secretion is an early sign for the development of NIDDM, preceding the onset of the disease.

We are grateful to Lilian Bengtsson, Ulrika Gustavsson, Eva Holmström, and Margaretha Persson for expert technical assistance. This study was supported by the Swedish Medical Research Council Grant 14X-6834, Ernhold Lundström, Albert Pålsson, Craford and Novo Nordic Foundations, Swedish Diabetes Association, Malmö University Hospital, and the Faculty of Medicine, Lund University.

Address for reprint requests: B. Ahren, Dept. of Medicine, Malmö Univ. Hospital, S-205 02 Malmö, Sweden.

Received 13 March 1997; accepted in final form 6 June 1997.

REFERENCES

18. Kautzky-Willer, A., G. Pacini, B. Ludvik, G. Schernthaner, and R. Prage. β-Cell hypersecretion and not reduced hepatic...
insulin extraction is the main cause of hyperinsulinemia in obese nondiabetic subjects. Metabolism 41: 1304–1312, 1992.


