Abstract. The relationship between insulin sensitivity and oral glucose tolerance was studied in 8 conventionally treated type 1 diabetic patients (age 34 ± 4 years, relative body weight (RBW) 113 ± 5%) and in 11 healthy subjects (age 35 ± 3 years, RBW 114 ± 2%). In each subject and patient, oral glucose tolerance (75 g glucose) and in vivo sensitivity to insulin (euglycaemic clamp technique, 1 mU/kg/min insulin infusion) were measured. The response to oral glucose in the diabetic patients was measured during maintenance of similar peripheral plasma free insulin levels as in the normal subjects during the oral glucose tolerance test (OGTT). During the OGTT, the post-glucose plasma glucose values in the diabetic patients were markedly higher (P < 0.001) than in the normal subjects. During the clamp study, the rate of glucose metabolism in the diabetic patients (4.53 ± 0.58 mg/kg/min) was 37% lower than in the normal subjects (7.19 ± 0.67 mg/kg/min, P < 0.02). The area under the glucose curve was inversely related to the rate of glucose metabolism in both the diabetic (r = −0.72, P < 0.02) and the normal (r = −0.69, P < 0.02) subjects. The slope of the curve was substantially steeper in the diabetic than the control subjects. Thus, peripheral insulin sensitivity contributes to oral glucose tolerance both in healthy man, and even to a greater extent, in type 1 diabetic patients.

In normal man, a majority of oral glucose is taken up by peripheral tissues (mainly muscle) whereas only 20 to 30% is retained in the liver (Ferrannini et al. 1985). Since most of peripheral glucose uptake is insulin-mediated (Katz et al. 1983), a normal peripheral insulin action should be important for maintenance of normal glucose tolerance. So far, however, the relationship between oral glucose tolerance and peripheral insulin action has not been studied in healthy man.

Type 1 diabetic patients are characterized not only by lack of endogenous insulin but also by reduced peripheral insulin sensitivity (DeFronzo et al. 1982; Yki-Järvinen et al. 1984). It is not known to what extent in these patients insulin resistance contributes to impaired glucose tolerance. Consequently, in the present study we wanted to examine, if, and to what extent, peripheral insulin sensitivity contributes to glucose tolerance in normal subjects and in type 1 diabetic patients.

Material and Methods

Subjects and experimental protocol

Eight type 1 diabetic patients and 11 matched normal subjects participated in the study (Table 1). None of the subjects had any disease other than diabetes, and none was taking any medication in addition to insulin. For 2 days before each study, the subjects ingested a weight-maintaining diet with the proportion of carbohydrate (45–50%), fat (30–35%) and protein (15–20%) similar in diabetic and control subjects. In each subject oral glucose tolerance and insulin sensitivity were measured as described below. The studies were performed after an overnight (10–12 h) fast at 1 to 2 weeks intervals. The diabetic patients received no sc insulin on the morning of the study.
Table 1.
Characteristics of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>RBW* (%)</th>
<th>Serum C-peptide** (µg/l)</th>
<th>HbA1** (%)</th>
<th>Insulin dose (U/kg)</th>
<th>Duration of diabetes (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 diabetic patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>34</td>
<td>67</td>
<td>99</td>
<td>0.15</td>
<td>10.8</td>
<td>0.88</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>25</td>
<td>76</td>
<td>131</td>
<td>0.11</td>
<td>8.9</td>
<td>0.62</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>20</td>
<td>55</td>
<td>101</td>
<td>0.10</td>
<td>10.0</td>
<td>0.84</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>24</td>
<td>75</td>
<td>135</td>
<td>0.18</td>
<td>15.1</td>
<td>0.61</td>
<td>3</td>
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<tr>
<td>5</td>
<td>M</td>
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<td>61</td>
<td>98</td>
<td>0.17</td>
<td>11.2</td>
<td>0.56</td>
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</tr>
<tr>
<td>6</td>
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<td>38</td>
<td>76</td>
<td>124</td>
<td>0.10</td>
<td>9.2</td>
<td>0.54</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>54</td>
<td>66</td>
<td>110</td>
<td>0.10</td>
<td>9.4</td>
<td>0.37</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>31</td>
<td>79</td>
<td>104</td>
<td>0.26</td>
<td>10.1</td>
<td>0.51</td>
<td>6</td>
</tr>
<tr>
<td><strong>Mean ± SEM</strong></td>
<td>4/4</td>
<td>34 ± 4</td>
<td>69 ± 3</td>
<td>113 ± 5</td>
<td>0.15 ± 0.02</td>
<td>10.6 ± 0.7</td>
<td>0.62 ± 0.06</td>
<td>8 ± 2</td>
</tr>
</tbody>
</table>

** 11 normal subjects**

Mean ± SEM 5/6 35 ± 3 72 ± 5 114 ± 2 1.8 ± 0.2


** Reference values: HbA1 5.9–8.0% (women), 6.0–9.0% (men); C-peptide 1.0–2.5 µg/l.

The purpose, nature, and potential risks of the study were explained to all subjects, and informed consent was obtained before their participation. The experimental protocol was approved by the Ethical Committee of the Helsinki University Hospital.

**Oral glucose tolerance tests**

In normal subjects, the oral glucose (75 g) tolerance test was performed according to WHO recommendations (WHO 1980). Blood samples for the determination of plasma glucose and insulin concentrations were withdrawn at 0, 30, 60 and 120 min after the glucose load. In type 1 diabetic patients 75 g of glucose was given orally. A variable rate insulin infusion was begun into a forearm vein simultaneously with glucose ingestion to simulate the peripheral insulin patterns spontaneously exhibited by the normal subjects after the glucose load. The primed continuous infusion during 0 to 45 min was similar to that used in the euglycaemic clamp study (see below). Thereafter (45 to 120 min), the rate of the insulin infusion was reduced to 0.5 mU/kg/min. Plasma glucose and insulin levels were measured similarly as in the normal subjects.

**In vivo sensitivity to insulin**

In both the normal subjects and diabetic patients, the sensitivity to insulin in vivo was measured by the euglycaemic clamp technique (DeFronzo et al. 1982; Yki-Järvinen et al. 1984). The subjects were studied at 08.00 h after a 10- to 12-h overnight fast. An indwelling catheter was inserted in an antecubital vein for glucose and insulin infusions. A second catheter was inserted retrograde into a hand vein for blood sampling. The hand was then kept in a heated chamber in which the air temperature was maintained at 60°C to ensure arterIALIZATION of venous blood (DeFronzo et al. 1982). Before glucose or insulin infusions, blood samples were withdrawn for the determination of plasma glucose, free insulin, serum C-peptide and glycosylated haemoglobin (HbA1) concentrations. Thereafter, a priming plus continuous infusion of porcine insulin (Actrapid®, Novo) was given. The priming dose was infused in a logarithmically falling manner for 10 min to reach the hyperinsulinaemic level. The continuous steady-state insulin infusion of insulin was begun at 10 min and continued for 110 min to maintain stable hyperinsulinaemia. The rate of continuous insulin infusion was 1 mU/kg/min in all subjects. In normal subjects the plasma glucose concentration was maintained at the fasting level by constant (4 mg/kg/min from 4 min to 10–13 min) and variable (from 10–13 min to 120 min) infusions of 20% glucose. In the diabetic patients, the variable infusion of glucose was begun after the plasma glucose level had declined to 5.0 mmol/l during infusion of insulin. The time to reach the 5.0 mmol/l averaged 33 ± 9 min (SEM). The rate of glucose metabolism during hyperinsulinaemia was determined during the period 20–100 min in the normal subjects, and during the subsequent 100 min after reaching the 5.0 mmol/l level in the diabetic patients.
Analytical procedures

Plasma glucose was measured with the glucose oxidase method (Kadish et al. 1968) using Beckman Glucose Analyzer II (Beckman Instruments Corp., Fullerton, CA). Plasma free insulin was determined using the Phadeseph™ Insulin RIA kit (Pharmacia, Uppsala, Sweden) after precipitation with polyethylene glycol (Desbuquois & Aurbach 1971). Serum C-peptide was measured using the Byk Mallinckrodt kit (Byk Mallinckrodt, Dietzenbach, FRG) (Kuzuya et al. 1977). HbA₁ was measured by microcolumn chromatography (Isolab, Inc., Akron, OH) (Welch & Boucher 1978). Statistical comparisons within and between the two groups were made using Student’s paired and unpaired t-test, respectively. Analysis of data distribution and correlation studies were made using BMDP-computer programs (Dixon 1981) for detailed data description (2D) and Spearman’s correlation coefficient (8D), respectively. Results are expressed as mean ± SEM.

Results

Oral glucose tolerance

Fasting plasma glucose levels were comparable in the diabetic and the normal subjects (Fig. 1). The highest plasma glucose levels in the normal subjects in the fasting state and 30, 60 and 120 min after oral glucose were 5.0, 8.5, 7.5 and 5.4 mmol/l, respectively. Thus, all subjects had normal glucose tolerance according to standard criteria (WHO 1980). In the diabetic patients, plasma glucose levels after oral glucose were significantly higher than in the normal subjects (Fig. 1). Peripheral plasma insulin levels were comparable in the normal subjects and the diabetic patients both in the fasting state and following glucose ingestion (Fig. 1).
**Insulin sensitivity**

During the insulin clamp study, the mean plasma insulin level rose from $5.4 \pm 1.1$ mU/l and $8.9 \pm 2.0$ (NS) to $79 \pm 3$ and $70 \pm 6$ mU/l (NS) in the normal subjects and diabetic patients, respectively. The coefficients of variation of the plasma insulin level was $9 \pm 1\%$ in the normal subjects and $14 \pm 5\%$ (NS) in the diabetic subjects. During hyperinsulinaemia, the plasma glucose concentration was maintained at $4.8 \pm 0.1$ and $4.8 \pm 0.1$ mmol/l with coefficients of variation of $6 \pm 1\%$ and $5 \pm 1\%$ in the normal and diabetic subjects, respectively.

The rate of glucose metabolism in the diabetic patients ($4.53 \pm 0.58$ mg/kg/min) was $37\%$ lower than in the normal subjects ($7.19 \pm 0.67$ mg/kg/min, $P < 0.02$, Fig. 2).

**Relationships between oral glucose tolerance and insulin sensitivity**

In the normal subjects, the rate of insulin mediated glucose disposal was inversely related to the area under the glucose curve in the OGTT ($r = -0.69$, $P < 0.02$, Fig. 3). In the diabetic patients,

![Graph showing relationships between glucose metabolism and area under the glucose curve](image)

*Fig. 3.*

Relationships between the rate of glucose metabolism and the area under the glucose curve during the oral glucose tolerance test in the diabetic patients ($\bullet$, $r = -0.72$, $P < 0.02$) and the normal subjects ($\circ$, $r = -0.69$, $P < 0.02$).
the correlation coefficient between the rate of glucose metabolism and area under the glucose curve was $-0.72$ ($P < 0.02$, Fig. 3). The slope of the curve, however, was markedly steeper in diabetic than the control subjects.

**Relationships between clinical parameters, oral glucose tolerance and insulin sensitivity**

No significant relationship was found between the area under the glucose curve and the insulin dose (U/kg, $r = 0.13$, NS) or the HBA$_1$ level ($r = 0.16$, NS). The HBA$_1$ level was inversely related to the rate of glucose metabolism in the diabetic patients ($r = -0.62$, $P < 0.05$) whereas no significant relationship was found between the insulin dose and the rate of glucose disposal (U/kg, $r = 0.02$, NS).

**Discussion**

The lack of an adequate insulin response to glucose challenge has invalidated comparisons of oral glucose tolerance between type 1 diabetic patients and healthy subjects. In the present study, we simulated the insulin response to glucose load in diabetic patients by using an exogenous insulin infusion, and achieved comparable peripheral insulin levels in the diabetic and control subjects. Yet the oral glucose tolerance in the diabetic patients was significantly impaired.

Previous findings in normal man have demonstrated that a major proportion of oral glucose is taken up by peripheral tissues rather than the liver (Ferrannini et al. 1985; Katz et al. 1983). An inverse correlation between plasma glucose response and the rate of glucose disposal in our normal subjects is in keeping with the quantitative importance of extrahepatic tissues in the uptake of glucose after both oral and iv (DeFronzo et al. 1981) administration. Moreover, these data suggest that the sensitivity of peripheral tissues to insulin determines, at least in part, oral glucose tolerance.

As expected, in the diabetic patients both oral glucose tolerance and peripheral insulin sensitivity were subnormal. Glucose intolerance occurred in the face of normal peripheral insulin levels. In addition, the slope of the curve between glucose area and the glucose utilization rate was steeper in the diabetic patients as compared to healthy controls. Regarding the causes for these differences, several factors should be considered. First, a difference in gastric emptying and glucose absorption are unlikely explanations. None of the patients had any signs of autonomic neuropathy and even if present, it would delay rather than accelerate gastric emptying. Secondly, defective suppression of hepatic glucose production could have contributed to the excessive rise in plasma glucose. In normal man, insulin levels in the basal state are 2 to 3-fold higher in the portal than in the peripheral circulation (Blackard & Nelson 1970), and this difference may become even greater after a glucose load. Our patients, in spite of their normal peripheral insulin levels, may have had portal hypoinsulinaemia and an augmented hepatic release delays oral glucose disposal augmenting postprandial hyperglycaemia as indicated by the correlation between plasma glucose response and insulin resistance.

The contribution of peripheral insulin resistance to glucose intolerance was markedly greater in the diabetic than the normal subjects. Based on the correlation curves one can estimate that a comparable decline in the rate of glucose uptake would result in a 5-fold greater impairment in glucose tolerance in diabetic compared to normal man. This difference might have been even greater, had the plasma glucose levels been followed longer after an oral load. In Pima Indians, Bogardus et al. (1984) reported a similar relationship between changes in the rate of glucose disposal and fasting plasma glucose levels. Thus, in diabetic patients even a small decline in peripheral insulin action increases either the fasting glucose level or the postprandial glucose response substantially more than in healthy man.

Regarding the causal relationship between insulin resistance and glucose intolerance, the present study suggests that insulin resistance was one of the reasons for glucose intolerance. However, there is increasing evidence in favour of the notion that also chronic hyperglycaemia may lead to insulin resistance which then can be ameliorated by intensive therapy and normoglycaemia (Lager et al. 1983; Yki-Järvinen & Koivisto 1984; Beck-Nielsen et al. 1984). In keeping with this was the inverse relationship between HbA$_1$ and insulin sensitivity in our patients. Provided this hypothesis is correct, a circulus vitiosus between hyperglycaemia and insulin resistance may exist in diabetes worsening the condition of the patient.
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References


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