Plasma insulin and C-peptide in relation to glucose intolerance in middle-aged men

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Abstract. The relation between glucose homeostasis and insulin secretion (immunoreactive insulin and C-peptide) was studied in middle-aged males matched for age and body weight. Subjects with mild type II diabetes mellitus were compared to normals and to individuals with impaired glucose tolerance (IGT). In addition, the diabetics were subdivided according to duration, some of the subjects having recently deteriorated from IGT status.
In the IGT individuals, there were no indications of a reduction in basal or glucose-induced insulin output. On the contrary, data indicate somewhat higher than normal secretion. Within the type II diabetics, those of short duration were largely similar to normals, whereas diabetes of longer duration was associated with some diminution in indices of B cell secretion.
The data support the notion that a deficient insulin output is not a primary pathophysiological event in the development of type II diabetes.

It is generally accepted that individuals with typical juvenile diabetes (type I) have a reduced insulin secretion (Parker et al. 1968). In typical adult onset diabetes (type II) and individuals with impaired glucose tolerance (IGT) the situation is less clear, and opinions differ on the importance of insulin resistance vs limitation of insulin release (Kipnis 1968; Reaven et al. 1976; Luft et al. 1981). A complete assessment demands that data on glucose tolerance be related not only to data on insulin secretion but to parameters of insulin sensitivity and hepatic insulin extraction as well.

Interpretation of plasma insulin values is hampered by uncertainty on the extent of hepatic insulin uptake. Simultaneous determinations of insulin and C-peptide in peripheral plasma afford an improved insight into true insulin secretion as well as into the extent of hepatic uptake of insulin, as C-peptide is not retained by the liver to any significant extent (Horwitz et al. 1975).
In the present study the above considerations have been applied in investigations on weight-matched middle-aged men, normal or with milder degrees of glucose intolerance.

Study Population

The individuals were grouped into diagnostic categories on the basis of blood glucose levels obtained during oral glucose tolerance test (OGTT). The categories were: normals (N), individuals with impaired glucose tolerance (IGT), mild type II diabetes of short duration (MOD-SD), and mild diabetes with longer duration (MOD-LD). IGT individuals were defined by two OGTTs. The MOD-SD subjects were known to have had IGT status when tested between 6 and 15 months earlier, whereas the MOD-LD had had their disease more than 2 years. In both MOD groups, the only treatment applied was dietary advice. The MOD-LD group was recruited from patients attending a diabetic out-patient department, whereas all other subjects were taken from a population health screening project.
Since all IGT and MOD individuals were found to be moderately overweight, normal individuals with relative body weight equal to or exceeding 1.10 were taken for this study. Relative body weight was defined as actual weight divided by ideal weight according to the tables of Lindberg et al. (1956).
The characteristics of the study groups are listed in Table 1.
Methods

All glucose tolerance tests (OGTT) were performed with the subjects having fasted over night. The glucose dose was 30 g/m² body surface area as a 10% solution. Venous samples for blood glucose, plasma immunoreactive insulin (IRI) and plasma C-peptide were taken at 0, 40, and 120 min.

Blood glucose was analyzed with a hexokinase method (Carrol et al. 1970). Plasma IRI was assayed according to Heding (1966) and plasma C-peptide according to Heding (1975), employing antiserum M1230.

Table 1.
Characteristics of study groups.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Age (range)</th>
<th>Relative body weight (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OGGT: BG O' and 120' &lt; 7.0</td>
<td>47–49</td>
<td>1.21</td>
</tr>
<tr>
<td>2 OGGT: BG O' &lt; 7.0 120' ≥ 7.0</td>
<td>47–49</td>
<td>1.21</td>
</tr>
<tr>
<td>BG O' ≥ 7.0</td>
<td>47–49</td>
<td>1.23</td>
</tr>
<tr>
<td>BG O' ≥ 7.0</td>
<td>38–57</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Calculations. Student's t-test was used for the evaluation of differences between groups. The test was applied to the various measurements at each time point, as well as to increments between 0 and 40 min levels, and to ratios formed between measurements.

Results

Blood glucose (Fig. 1)

There was no statistically significant difference in the degree of fasting hyperglycaemia between the MOD-SD and MOD-LD individuals. Likewise, the OGGT glucose increment 0–40 min was similar. As expected, the MOD groups differed in both respects from normal and IGT individuals, who were indistinguishable in this regard.

IRI and C-peptide (Fig. 2)

Basal levels of IRI and C-peptide were higher in the total glucose intolerant group (IGT + MOD-LD + MOD-SD) than in normals. With regard to basal insulin, both MOD groups were higher than the normal group, and in basal C-peptide the IGT and MOD-SD subjects were higher than the normals.

At 40 min, IRI levels were lower in MOD-LD than in normals, otherwise no differences were seen. With regard to 40 min C-peptide, the MOD-LD were lower than N and lower than IGT. In contrast, in neither measurement did the MOD-SD or the IGT differ from normals.

In increments 0–40 min, both IRI and C-peptide were lower in MOD-LD than in any of the other groups, which were similar to each other.

At 120 min, the IGT and MOD-SD had significantly higher levels of both IRI and C-peptide than the other groups.
Ratios IRI/glucose and C-peptide/glucose (Fig. 3)

These calculations were also performed with glucose concentration subtracted by 2.5, since 2.5 mM is the limiting blood glucose level below which no insulin secretion takes place.

In the basal state (data not shown), the main finding was made with C-peptide divided by (glucose – 2.5). Here, IGT individuals were higher than both MOD groups (2P < 0.05), whereas normals were only higher than MOD-LD (2P < 0.05).

At 40 min, C-peptide/glucose values were higher in normals than in both MOD groups, higher in IGT than in MOD-LD and higher in MOD-SD than in MOD-LD. Accordingly, the general trend was that this 40 min ratio was highest in normals and decreasing through IGT, MOD-SD and MOD-LD. The same relationship was observed for IRI/glucose at 40 min.

At 120 min, C-peptide/glucose was highest in the IGT group. MOD-SD did not differ from normals, whereas MOD-LD were clearly lower. In IRI/glucose IGT and MOD-SD were similar, followed by lower levels in the N and MOD-LD subjects.

The ratio IRI/C-peptide was similar in all groups at all time points.

Discussion

Investigations on insulin in relation to glucose tolerance require great attention with regard to possible confounding factors. The present study on groups of male individuals matched for age and

Fig. 2.
Plasma immunoreactive levels of insulin (IRI, open columns) and C-peptide (IRCP, hatched columns) during OGTT. ○ = normals; ● = IGT; □ = MOD-SD; ■ = MOD-LD. Significance of intergroup differences: * 2P < 0.05; ** 2P < 0.01; *** 2P < 0.001.

Fig. 3.
Ratios of C-peptide to glucose (IRCP/G) and insulin to glucose (IRI/G) during OGTT at 40 min (upper half) and 120 min (lower half). Group symbols and significance levels as in Fig. 2.
relative body weight affords some insight into the pathophysiology of impaired glucose tolerance and mild type II diabetes.

The IGT had high basal levels of IRI as well as C-peptide. The 120 min levels were elevated as well. Furthermore, it is to be noted that IGT subjects, in spite of being selected on the basis of higher than normal 120 min glucose, were higher than normals in C-peptide/glucose at 120 min as well as IRI/glucose at 120 min. Accordingly, in individuals with the most subtle deviation from normal in glucose tolerance, there was no evidence of deficiency in glucose induced insulin secretion. On the contrary, data indicate an enhanced output. This may be taken to indicate a state of decreased insulin sensitivity.

With regard to the MOD groups, it should be noticed that the short duration group (MOD-SD) did not display a low insulin secretion as evidenced by IRI and C-peptide values, whereas the longer duration MOD group (MOD-LD) had clearly lower levels. The results therefore indicate that in individuals with very mild type II diabetes, a decrease in insulin (and C-peptide) output is not to be found in those of short duration. This suggests that a diminution in insulin secretory capacity is a secondary phenomenon, appearing with time, and not a primary pathophysiological event.

Recent studies (Heding 1977) indicate that levels of proinsulin in plasma may be higher than heretofore thought, particularly in diabetics. Because of immunological cross-reaction, proinsulin may contribute a considerable part of plasma IRI. Cross-reaction with C-peptide is generally lower, this being clearly true with antiserum M1230 which was used in the present study (Heding 1975). It is quite evident that the role of an increased proportion of proinsulin in the pancreatic endocrine response in diabetes require much further investigation.

Simultaneous IRI and C-peptide measurements give a rough estimate of the extent of hepatic uptake of insulin, although again the possibility of elevated proinsulin levels is a confounding factor. In the present study comparisons of IRI/C-peptide ratios did not indicate differences in hepatic insulin extraction between normal and glucose intolerant groups. However, results of other studies (Sando et al. 1980; Malmquist et al., 1981) suggest that differences in this regard may well be a factor of pathophysiological importance.

References


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