GLUCOSE TOLERANCE AND INSULIN SECRETION IN HYPERTHYROIDISM

By

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ABSTRACT

To evaluate the glucose tolerance and insulin secretion in hyperthyroidism patients were examined in the toxic state and after they had been made euthyroid.

Fasting values: In 42 untreated patients the glucose- and insulin concentrations in serum were significantly elevated. In 24 treated patients the glucose concentrations became normal, while the insulin concentrations remained elevated.

Oral-glucose-tolerance test: In 20 untreated patients the glucose- and insulin responses were significantly increased. In 8 treated patients the glucose response became normal, while the insulin response remained unchanged.

Intravenous-glucose-tolerance test: In 28 untreated patients the K-values were significantly decreased and the insulin response increased. In 23 treated patients the K-values rose significantly, but the insulin response remained unchanged.

Intravenous-tolbutamide test: In 41 untreated patients the glucose concentration decreased significantly compared with the controls, and the insulin responses were significantly increased. In 23 treated patients the glucose concentrations decreased even more, while the insulin response remained unchanged.

The results indicate enhanced sensitivity or an increase in the mass of $\beta$-cells in hyperthyroidism. The glucose tolerance tests point to an increased peripheral insulin resistance. The normalized glucose tolerance and still enhanced insulin secretion during treatment support the assumption, that hyperthyroidism causes an increase in the $\beta$-cell mass.
The glucose tolerance in hyperthyroidism has attracted attention for many years. As early as in 1928 Jostin & Lahey (1928) in non-diabetics with hyperthyroidism found glucosuria in 38.6 per cent of patients with hyperthyroidism compared with 13.6 per cent in a large control sample. Sanger & Hun (1922), Andersen (1933), Soffer (1956), Elrich et al. (1961), Lamberg (1965) and Jacobsen (1972) found elevated fasting blood sugar in hyperthyroidism, whereas Hales & Hyams (1964), Woeber et al. (1966) and Holdsworth & Besser (1968) found normal values.

By using oral-glucose-tolerance test Hales & Hyams (1964), Kreines et al. (1965) and Doar et al. (1969) found diabetic patterns. Amatuzio et al. (1954), Hales & Hyams (1964), Woeber et al. (1966), Holdsworth & Besser (1968) and Lamberg (1969) showed a rapid rise followed by a steep fall in the glucose concentration, consistent with increased absorption rate of glucose from the intestine as shown by Althausen & Stockholm (1938) and Amatuzio et al. (1954) or an enhanced gastric emptying rate as shown by Holdsworth & Besser (1968) in hyperthyroidism. These factors make the evaluation of the oral glucose tolerance test difficult.

To avoid the influence of altered intestinal absorption some investigators have used the intravenous-glucose-tolerance test to examine the glucose tolerance in hyperthyroidism. The results obtained using this test, have also been conflicting, thus Amatuzio et al. (1954), Macho (1958), Elrich et al. (1961) and Andreani et al. (1970) found that the glucose utilization was normal. Lamberg (1965) found increased and Jacobsen (1972) significantly reduced K-values. Lamberg (1965) has also used the intravenous-tolbutamide test and found hyper-response with a steep fall in blood glucose after tolbutamide administration.

Only one or two parameters have mainly been used for the evaluation of the glucose tolerance. Only few investigators have examined the insulin secretion during tolerance tests and even fewer investigators have made a longitudinal study and tested patients before and after treatment.

The purpose of this investigation has been to evaluate the glucose tolerance and insulin secretion in fasting patients during oral- and intravenous-glucose-tolerance test and during intravenous-tolbutamide test in patients with hyperthyroidism, partly in untreated, and partly during, or after treatment in the euthyroid state.

**MATERIALS AND METHODS**

Forty-two patients with hyperthyroidism participated in the study. All patients were of normal weight. The mean age ± sd was 52 ± 18 years. Twenty-eight patients had a diffuse goitre, 7 patients a multinodular goitre and 7 patients had a toxic adenoma. The diagnosis was based on the clinical evaluation together with examination of the concentration of thyroxine in the serum, T₃-resin test, radio-iodine uptake in glandula

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thyreoidea and in the majority of patients on the technetium scanning of glandula thyreoidea.

Out of 42 patients 8 were examined with oral-glucose-tolerance test (OGTT), intravenous-glucose-tolerance test (IVGTT) and intravenous-tolbutamide test (IVTTT). Twelve patients were examined only with OGTT and IVTTT, 19 patients were examined only with IVGTT and IVTTT, 1 patient was examined with IVGTT and 2 patients with IVTTT alone. All the 22 controls were of normal weight and without any endocrine or gastro-intestinal diseases. The mean age ± sd was 47 ± 20 years. Fifty-four normal weight controls with a mean age ± sd of 38 ± 15 years were previously examined with IVGTT. The results of these examinations have kindly been placed at the authors' disposal by Dr. med. T. Deckert.

Out of 42 patients 24 were examined during (20) or after (4) treatment with anti-thyroid drugs. Eight patients with OGTT, 23 patients with IVGTT and 23 patients with IVTTT. The interval between the two examinations was 5–18 months, mean ± sd: 10 ± 4 months. At the second examination the patients had been euthyroid in 3–18 months, mean ± sd: 9 ± 4 months.

Methods

OGTT was carried out with examination of the serum glucose concentration in capillary blood from the ear with a glucose oxidase method before and 15, 30, 60, 120, 150 and 180 min after an oral glucose load of 1 g glucose per kg body weight (maximal 70 g). The coefficient of variation in the method was 3.6 per cent. Simultaneously the serum insulin concentration in venous blood was examined with the Wide solid phase technique. Fasting values in normal controls were found to be 14 ± 8 μU/ml, the coefficients of variations were 10 and 6 per cent of concentrations of 20 and 60 μU/ml, respectively.

The IVGTT was carried out by examination of serum glucose concentration and the serum insulin concentration as mentioned above before and after 10, 20, 30, 40, 50, 60 and 120 min following an intravenous glucose load of 25 g glucose. The glucose disappearance rate, K-value, was calculated.

The IVTTT was carried out by examination of the serum glucose concentration and the serum insulin concentration as mentioned above before and 5, 10, 20, 30, 60 and 90 min after an intravenous load of 1 g sodium tolbutamide.

Statistical evaluation

When comparing controls and patients the Wilcoxon test for two samples was used in the evaluation of the results in OGTT and IVTTT.

When evaluating the results in the IVGTT Student's t-test has been used.

When comparing the results in all three tolerance tests on patients before and during (or after) treatment the Wilcoxon test for pair differences was used.

Results

Fasting values

The serum glucose and insulin concentrations were found to be significantly elevated in patients with hyperthyroidism when compared with normal controls. During or after treatment the serum glucose concentrations normalized, while the serum insulin concentrations remained elevated (Table 1).

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Table 1.
Serum glucose concentration, serum insulin concentration and glucose disappearance rate (K-value) during OGTT, IVGTT and IVTTT in controls and in patients with hyperthyroidism untreated and treated.

<table>
<thead>
<tr>
<th></th>
<th>Oral-glucose-tolerance test</th>
<th>Intravenous-glucose-tolerance test</th>
<th>Intravenous-tolbutamide test</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Serum glucose mg/100 ml min</td>
<td>Insulin μU/ml min</td>
<td>K-value</td>
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</table>
Serum glucose concentration during oral-glucose-tolerance test in controls and in patients with hyperthyroidism, untreated and treated.

Oral-glucose-tolerance test

Figs. 1 and 2 together with Table 1 show the serum glucose concentration and serum insulin concentration in normal controls, and untreated and treated patients with hyperthyroidism, respectively. When compared with controls, patients with hyperthyroidism showed a more pronounced rise in serum glucose concentration. Two hours after glucose load the glucose concentration was the same in the two groups. Patients with hyperthyroidism showed a higher and more rapid insulin response than the controls, and a significantly elevated serum insulin concentration 30 min after glucose load, as well as a significantly lower serum insulin concentration 120 min after glucose load.

The treatment of patients resulted in significantly reduced response in the serum glucose concentration when compared with untreated patients. The
insulin response to glucose load was unchanged, significantly increased when compared with normal controls, and not different from the response in the untreated patients.

Intravenous-glucose-tolerance test

Fig. 3 and Table 1 show the K-values in the controls and in the untreated and treated patients with hyperthyroidism. It thus appears that patients with untreated hyperthyroidism had significantly lower K-values than the controls, 18 per cent had diabetic values and 21 per cent were borderline.

Fig. 4 and Table 1 show that the insulin response was slightly, though not significantly increased when compared with controls. During treatment, 19 out of 23 patients (83 per cent) showed increased K-values, when compared with untreated patients, the K-values being increased significantly, Fig. 3. The insulin response remained unchanged in the treated patients, Fig. 4.

Fig. 2.
Serum insulin concentration during oral-glucose-tolerance test in controls and in patients with hyperthyroidism, untreated and treated.
Glucose disappearance rate, K-value during intravenous-glucose-tolerance test in controls and in patients with hyperthyroidism, untreated and treated.

The K-values and the insulin responses were compared in two groups of treated patients who had been euthyroid for less than 9 months, or for more than 9 months, respectively. No differences in the above mentioned parameters were found between the two groups of patients.

**Intravenous-tolbutamide test**

Fig. 5 shows the serum glucose concentration after intravenous administration of tolbutamide. On an average the serum glucose decreased by 33 per cent in normal controls. In patients with hyperthyroidism the serum glucose decreased by 44 per cent, the difference being significant.

As shown in Fig. 6 the insulin response after tolbutamide administration was significantly greater in patients with hyperthyroidism when compared with the controls.
Treatment of patients resulted in an additional decrease in the serum glucose concentration. When compared with untreated patients the fall in glucose concentration was significantly enhanced, Fig. 5.

The insulin response in the treated patients was unchanged as compared to untreated patients as seen in Fig. 6 and significantly enhanced as compared with normal controls.

The fall in serum glucose concentration and the insulin response were compared in two groups of treated patients who had been euthyroid for less than 9 months or for more than 9 months respectively. No differences in the above mentioned parameters were found between the two groups of patients.

**DISCUSSION**

Numerous investigations on the carbohydrate tolerance in patients with hyperthyroidism have led to different conclusions. The present study confirms that patients with hyperthyroidism have a significantly increased fasting blood-glucose concentration.

**Fig. 4.**

Serum insulin concentration during intravenous-glucose-tolerance test in controls and in patients with hyperthyroidism, untreated and treated.
Elevated fasting blood-glucose could be the result of a diabetic state with reduced insulin secretion. Such a state has never been observed previously. On the contrary, Elrich et al. (1961), Holdsworth & Besser (1968) and Doar et al. (1969) in concordance with the observations in this study found an increased concentration of serum insulin in the fasting state. These observations may indicate an increased peripheral insulin resistance caused by the hyperthyroidism.

Levine (1953), Danowski (1962), Svednyr (1966), Freedland & Krebs (1967), Isaacs et al. (1969) and Sutherland & Robinson (1969) demonstrated enhanced gluconeogenesis in hyperthyroidism. This phenomenon may explain the increased fasting blood-glucose, in agreement with the increased sensitivity to catecholamines in hyperthyroidism as demonstrated by Harlan et al. (1963) and Waldstein (1966).

Sutherland & Robinson (1969) assumed that an increased activity of cyclic-AMP was responsible for an increased gluconeogenesis and for the increased insulin secretion. Tata (1964) and Waldstein (1966), too, were able to demonstrate an enhanced activity by cyclic AMP.
Serum insulin concentration during intravenous-tolbutamide test in controls and in patients with hyperthyroidism, untreated and treated.

In accordance with Amatuzio et al. (1954), Hales & Hyams (1964), Woeber et al. (1966), Holdsworth & Besser (1968) and Lamberg (1969), we found that during the oral-glucose-tolerance test, the serum glucose rapidly reached the peak concentration after the glucose load followed by a steep fall. This phenomenon could be explained by an enhanced absorption rate of glucose from the intestine (Althausen & Stockholm 1938) and an enhanced gastric emptying-rate (Holdsworth & Besser 1968). Contrary to Hales & Hyams (1964), Klink & Estrich (1964), Woeber et al. (1966) and Cavagnini et al. (1974) who found reduced insulin response in the oral glucose tolerance test, we found an increased insulin response during the tolerance test in agreement with Holdsworth & Besser (1968).

To avoid the influence of disturbances in the intestinal glucose absorption, we examined the glucose disappearance rate (K-value) after intravenous glucose administration. In accordance with Jacobsen (1972) we found a significantly reduced K-value in patients with hyperthyroidism. This finding does not agree with the observations by Lozner et al. (1941), Amatuzio et al. (1954), Macho
Althausen (1958), Elrich et al. (1961), Lamberg (1965) and Andreani et al. (1970). These investigators found that the glucose disappearance rate was unchanged as compared with the control.

Renauld et al. (1971) observed a reduced insulin response during intravenous glucose tolerance test in patients with hyperthyroidism. On the contrary, we found the insulin response enhanced, though not significantly.

During the intravenous-tolbutamide test in agreement with the findings of Lamberg (1965) we observed, that the fall in the serum glucose concentration was enhanced in patients with hyperthyroidism as compared with controls. This observation fits very well with a significantly enhanced insulin response.

Thus in patients with hyperthyroidism we found an enhanced insulin response to three different methods of stimulation; even in fasting state the insulin concentration was elevated. These observations favour the assertion that the sensitivity of the β-cells is enhanced or the β-cell mass is increased in the hyperthyroid state. Elevated fasting serum glucose, reduced tolerance in the glucose tolerance test furthermore also point to an increased peripheral insulin resistance.

In a number of patients the different tolerance tests were repeated during or after treatment with antithyroid drugs.

The fasting insulin concentration continued to be significantly elevated compared with normal controls and not different from the values in the hyperthyroid state. During stimulation the insulin response, too, continued to be unchanged as compared with the response in the hyperthyroid state, and significantly enhanced when compared with normal controls.

These observations are in contrast to the findings by Holdsworth & Besser (1968) and Cavagnini et al. (1974) using an oral glucose tolerance test.

Jacobsen (1972) found that patients rendered euthyroid showed normal fasting serum glucose and K-values in the intravenous-glucose-tolerance test. In agreement with that we found the fasting serum glucose became normal in patient made euthyroid. During stimulation tests glucose response showed a trend to be 'hypernormalized' possibly due to abolished peripheral resistance combined with an enhanced insulin secretion.

The unchanged hyperinsulinism during fasting and during stimulation in patients made euthyroid for 2½–18 months is in favour of the assumption that the enhanced insulin secretion in hyperthyroidism may be due to an increased β-cell mass.

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