Med. J. Cairo Univ., Vol. 62, No. 2, June (Suppl.) : 1-7, 1994.

Effect of Thyroid Hormones (T_3 & T_4) on Insulin Secretion

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Abstract

The effect of thyroid hormones on the blood glucose level and its role on insulin secretion in the fasting state and after glucose loading in hyper- and hypothyroid rats has been studied. Increase in T_3 and T_4 levels resulted in glucose intolerance even in the fasting state which did not affect the levels of insulin. This can lead to the belief that insulin resistance must have resulted. However, after glucose loading, there was prompt insulin response, yielding higher rates of insulin secretion compared to the control. The peak of rise of serum insulin was reached at 30 minutes, which was earlier than the control group. Then the level declined, yet remaining elevated at 120 minutes. Decreased levels of T_3 & T_4 showed no characteristic changes in the blood glucose levels or in its pattern, whether in the fasting state or after glucose load. However, there was an increased serum insulin level, even in the fasting state, which suggests a decrease in the rate of insulin degradation or a peripheral sensitivity to insulin.

Introduction

IMPAIRMENT of glucose tolerance is a common phenomenon occurring in as many as 44-57% of hyperthyroid patients [1]. Despite this high frequency; the mechanisms underlying the diabetogenic effects of thyroid hormones are uncertain and not clearly established. The role of insulin in this decreased glucose tolerance has been studied by several workers with inconsistent results.

The aim of the present study was to investigate the effect of thyroid hormones on the blood glucose level and its role on insulin secretion in the fasting state and after glucose loading in hyper- and hypothyroid rats.

Material and Methods

The work was carried out on thirty (30) adult albino rats of either sex, of

approximately the same body weight, ranging from 200-250 gms. They were fed on a diet consisting of bread and milk. They were divided into three groups :

Group I : This consisted of ten animals, which were considered as a control group.

Group II : In this group comprising 10 rats, thyrotoxicosis was induced by daily subcutaneous injection of 200 g of L. thyroxine (E-troxine) for five days[2].

Group III : In this group, 10 rats were subjected to the same procedure as group II and then left for 7 days. This group of rats were considered as the hypothyroid group, since stopping the subcutaneous injection of the high dose of thyroxine led to decreased level of TSH which resulted in inhibition of thyroid gland activity. This was according to a modification of the technique of Friedman[3].

In all groups, serum T_3 and T_4 were assessed using the ELISA principle, blood glucose was estimated using a «Bio-Mericux Kit» and serum insulin was measured by the radio-immuno-assay technique. In all groups, before any procedure, the rats were allowed to fast for 12-14 hours, only given water, after which blood samples were withdrawn.

The following blood samples were taken retroorbitally :

1. Fasting samples.
2. Samples after 30, 60, 90 and 120 minutes after giving an intraperitoneal glucose load in a dose of 0.5 gm/kg body weight (D glucose) over a period of 10-15 seconds.

Blood samples were taken for immediate estimation of blood glucose. The serum was kept in plastic tubes, frozen at -20°C to be later used for assaying T_3, T_4 and insulin levels.

Results

Tables 1 & 2 compare the data of the various parameters obtained in the control, hypo- and hyperthyroid groups of rats with each other.

Table (1) revealed the mean values of serum T_3 (ng/dL), T_4 (g/dL), blood glucose (mg%) and serum insulin (U/ml) in the control, hyperthyroid and hypothyroid groups.

In the hyperthyroid group, serum T_3 and T_4 levels (65.1 ± 4.5 ng/dL and 5.1 ± 0.3 g/dL) respectively were significantly higher than the control group (45.5 ± 5.6 ng/dL and 3.0 ± 0.4 g/dL) which lead to a significant increase in the fasting blood glucose (79.0 ± 3.9 mg%) compared to the control group (56.0 ± 4.7 mg%) and insignificant change in the fasting serum insulin (10.2 ± 1.7 U/ml) in comparison to the control group (9.3 ± 1.6 U/ml).

In the hypothyroid group, serum T_3 and T_4 levels (31.8 ± 2.0 ng/dL and 1.8 ± 0.2 g/dL) respectively were significantly lower than the control group, which resulted in no significant change in the fasting blood glucose level (53.5 ± 5.0 mg%) compared to the control group. However, there was a significant increase

in the fasting serum insulin (15.4 ± U/ml) when compared with the control group.

Table (2) and Figs. (1, 2, 3 & 4) demonstrated the mean values of blood glucose in mg% and the corresponding mean values of serum insulin in μ U/ml before and after glucose loading in the control, hyperthyroid and hypothyroid groups.

Table (1) : Mean Values of Fasting Blood Glucose in mg/100 ml and Fasting Serum insulin in U/ml in the Control, Hyperthyroid and Hypothyroid Groups, Reflected by Serum T_3 (ng/dL) & T_4 (g/dL).

	Control	Hyperthyroid	Hypothyroid
T_3 (ng/dL)	45.5 ± 5.6	65.1 ± 4.5**	31.8 ± 2.0**
T_4 (μg/dL)	3.0 ± 0.4	5.1 ± 0.3**	1.8 ± 0.2**
Fasting blood glucose (mg%)	56.0 ± 4.7	79.0 ± 3.9**	53.5 ± 5.0
Fasting serum insulin (μU/ml)	9.3 ± 1.6	10.2 ± 1.7	15.4 ± 3.0**

** Highly significant increase compared to the control group. ($P < 0.001$).
** Highly significant decrease compared to the control group. ($P < 0.001$).
Insignificant change in comparison to the control group. ($P > 0.05$).

Table (2) : Mean Values and Standard Deviations of Blood Glucose (mg%), Serum Insulin (μU/ml) in the Control, Hyperthyroid and Hypothyroid Groups Before and After Glucose Loading.

Analytical Items		Fasting value	After glucose load 30'	60'	90'	120'
1) Blood glucose (mg%)	Control	56.0 ± 4.7	11.4** ± 4.6	99.3** ± 4.2	85.6** ± 5.6	66.0* ± 5.0
	Hyper-thyroid	79.0 ± 3.9	123.1** ± 4.3	117.8** ± 3.6	104.5** ± 6.5	91.8** ± 4.8
	Hypo-thyroid	53.5 ± 5.0	103.7** ± 5.5	87.7** ± 3.4	79.2** ± 2.3	65.0** ± 2.2
2) Serum insulin (μU/ml)	Control	9.3 ± 1.6	20.1* ± 1.6	27.6* ± 2.6	23.8* ± 3.2	14.7* ± 5.0
	Hyper-thyroid	10.2 ± 1.7	37.1** ± 4.5	29.9** ± 2.5	31.9** ± 1.7	18.2** ± 2.2
	Hypo-thyroid	15.4 ± 3.0	29.2** ± 2.2	43.2** ± 6.3	37.6** ± 2.6	31.0** ± 9.0

** Highly significant increase compared to the fasting value ($P < 0.001$).
* Significant increase compared to the fasting value ($P < 0.005$).

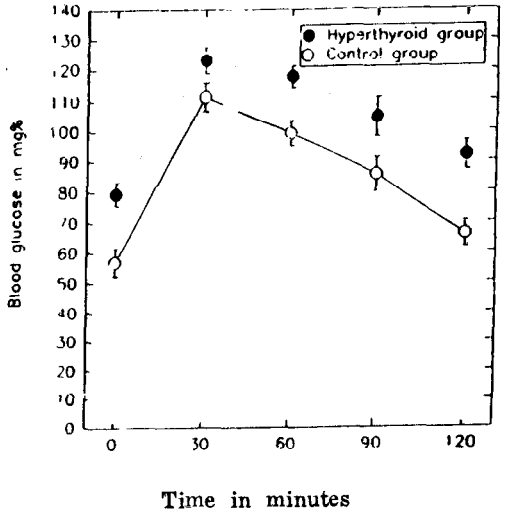

Fig. 1. Mean values of blood glucose levels in mg% before and after glucose load in the control and hyperthyroid groups.

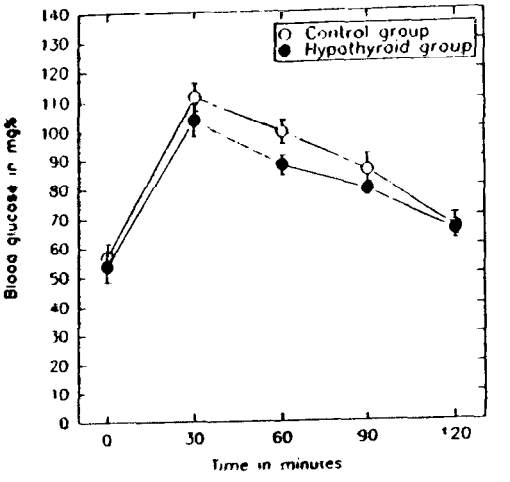

Fig. 3. Mean values of blood glucose levels in mg% before and after glucose load in control and hypothyroid groups.

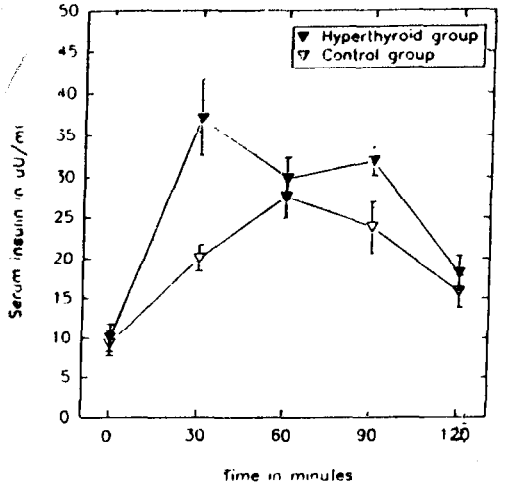

Fig. 2. Mean values of serum insulin levels in μ U/ml before and after glucose load in the control and hyperthyroid groups.

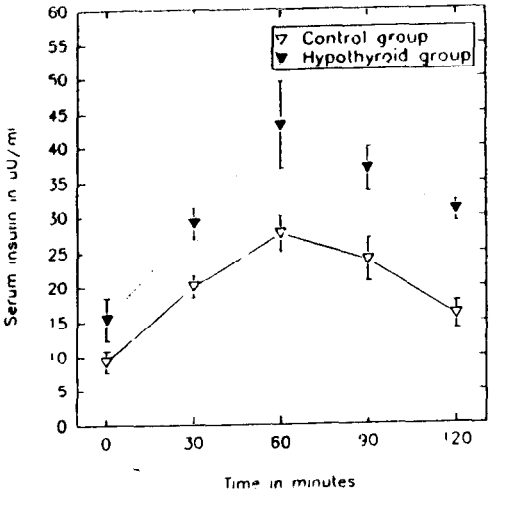

Fig. 4. Mean values of serum insulin levels in μ U/ml before and after glucose load in the control and hypothyroid groups.

It is eviden that after glucose loading in the hyperthyroid group, blood glucose showed a significant increase in its levels specially at 30 minutes (123.1 ± 4.3 mg%) followed by a decline but the levels remained higher than the corresponding control values throughout the whole experiment.

Regarding serum insulin level in he same group, there was prompt insulin response, yielding higher rates of insulin secretion, compared to the control group. The peak of rise was reached at 30 minutes (37.1 ± 4.5 U/ml) which was earlier than in the control group which occurred at 60 minutes (27.6 ± 2.6 U/ml), then the level declined yet remaining elevated at 120 minutes.

In the hypothyroid group, after glucose load, the blood glucose level showed a significant increase in its values, but the pattern of increase was similar to that of the control group with the levels almost reaching control values after 120 minutes. Insulin response to glucose load showed the same pattern of increase as the control group and the peak of rise was reached at 60 minutes (43.2 ± 6.3 U/ml). However, the decline was extremely slow, and the values at 120 minutes remained significantly higher than the fasting state as compared to the control group.

Discussion

The important role of thyroid hormones (T_3 and T_4) in the regulation of glucose homeostasis and insulin secretion has been the subject of many studies. In the present work, induction of hyperthyroidism in adult rats (serum T_3, T_4 levels 65.1 ± 4.5 ng/dL and 5.1 ± 0.3 g/dL respectively compared to 45.5 ± 5.6 ng/dL and 3.0 ± 0.4 μg/dL in control rats) leads to a significant increase in the mean fasting blood glucose (79.0 ± 3.9 mg%) compared to (56.0 ± 4.7 mg%) in the control animals (Table 1). The most likely suggestion is an impairment in glucose tolerance; one of the factors proposed is the enhanced gastric emptying and increased intestinal absorption[4]. Furthermore, these hormones were found to regulate the abundance of glucose transporter protein and mRNA[5].

Blood insulin, when assessed in hyperthyroid cases, yielded conflicting results. Reports suggested decreased[6], normal[7] and even increased[8] concentrations of serum insulin in the fasting state and after glucose challenge.

The data in the present study demonstrated that the mean fasting serum insulin in hyperthyroid rats showed an insignificant increase in its value (10.2 ± 1.7 μU/ml) compared to (9.3 ± 1.6 μU/ml) in the control group (Table 1).

In the present work, the glucose intolerance was even more pronounced in the hyperthyroid rats after glucose loading (the mean value of blood glucose was 123.1 ± 4.3 mg% versus a mean control value of 11.4 ± 4.6 mg% 30 minutes after glucose injection). This significant increase in the mean blood glucose continued throughout the test, although it yielded successive reduced levels (Fig. 1).

The prompt insulin response after glucose administration in the hyperthyroid rats yielded higher rates of insulin secretion compared to the control (Table 2 and Fig. 2). Blood insulin reached a peak of 37.1 ± 4.5 μ U/ml after 30 minutes from the glucose loading in contrast to 27.6 ± 2.6 μ U/ml after 60 minutes in the control group. Another increase of serum insulin was observed 90 minutes from glucose loading (31.9 ± 1.7 μ U/ml), whereas the corresponding control mean value continued to show a reduction at this stage (23.8 ± 3.2 μ U/ml) (Fig. 2).

The present results seem to agree with Wennlund and his co-worker[**9**], who concluded that the glucose intolerance observed with hyperthyroidism could be explained by a diminished suppression of hepatic glucose production by the endogenous insulin. Muller and his collegues[**10**] confirmed that the plasma concentrations of gluconeogenic precursors mainly lactate, pyruvate and alanine are elevated in the hyperthyroid state. Another study by Nolte et al.[**11**] revealed a decrease in the glycogen synthesis due to a decline in the activity of the enzymes involved in glycogenesis as glucokinase and phosphoglucomutase during hyperthyroid state.

The hepatic resistance to insulin in thyroid hormone excess may serve a beneficial effect in preventing the development of hypoglycaemia, since increased energy demands in hyperthyroidism necessitates an increase in the substrate availability[**12**].

Decreased levels of T_3 and T_4 as in hypothyroidism showed no characteristic changes in the blood glucose level, whether in the fasting state or after glucose load (Table 2) (Fig. 3). However, there was an increased serum insulin level (Fig. 4) even in the fasting state which suggests a decrease in the rate of insulin degradation or a decreased peripheral insulin sensitivity[**13**].

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