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Thyroidectomy and Thyroxine Replacement Caused Impaired Oral Glucose Tolerance in Rat

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Abstract: Thyroxine influences diverse metabolic pathways important in glucose metabolism and important mediators of glucose homeostasis. Thyroxine replacement therapy is usually given in cases of hypothyroidism thus this study was conducted to assess the effects of thyroxine replacement therapy and thyroidectomy on glucose tolerance. Forty rats were divided into four groups (n=10). Group 1(control) was sham operated, group 2 was thyroidectomised, group3 was sham operated and treated with 10mcg/100g bdwt for five weeks, Group 4was thyroidectomised and given 10mcg/100g bdwt T4 for five weeks. The rats were anaesthetized by injecting 0.2ml/100g/bdwt ketamine hydrochloride intraperitonially. The rats were weighed before and weekly after the surgery. Oral glucose tolerance test was performed on the rats after five weeks treatment period and total serum thyroxine was determined by chemi-immunoluminiscence. Results were presented as mean +SEM and P values less than or equal to 0.05 was taken as significant. There was fluctuating weight loss and gain in groups 3 and 4 while group 2 had significant steady weight gain compared with control. Fasting blood sugar at zero minute was significantly higher at groups 2, 3 and 4. At 30 mins, glucose level was significantly reduced in groups 2 and 3while group 4 was not significantly different from control. At 60 and 90 minutes, glucose level was markedly reduced in the three groups compared with control but at 120 min there was significant difference between glucose level in the groups and control. Based on the results in this study, hypothyroidism and hyperthyroidism cause impairment in glucose tolerance and a n elevated fasting blood glucose level while thyroxine replacement did not normalise the disturbances caused by thyroidectomy on glucose tolerance nor did it reduce the fasting blood sugar level as observed when compared to the control.

Key words: Thyroidectomy · Thyroxine · Oral Glucose Tolerance

INTRODUCTION

Thyroxine influences diverse metabolic pathways important in glucose metabolism and important mediators of glucose homeostasis [1]. For nearly a century, many publications focused on the relationship between diabetes and thyroid disease [2]. Essentially all aspects of metabolism are enhanced under the influence of thyroid hormone. Toshiki mano *et al*. [3] reported abnormal glucose tolerance in hyperthyroidism however glucose tolerance in hypothyroidism has not been reported. Hypothyroidism sometimes resulting from thyroidectomy has become an increasing trend in recent years. Thyroxine is taken to replace the deficiency which exists in hypothyroidism and therefore to probably completely restore normal metabolic activity. However thyroxine is a diabetogenic hormone. This study was conducted to evaluate the effect of exogenous thyroxine on glucose tolerance in other to understand how well thyroxine replacement therapy can compensate for the removal of the thyroid gland in relation to its role in glucose metabolism and to evaluate the relationship between exogenous thyroxine administration and body weight in the management of hypothyroidism.

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MATERIALS AND METHODS

40 rats of the Wister strain were bred at the central animal house, university of Ibadan, they were allowed to acclimatize for two weeks and then they were divided into four groups of ten rats each. Group 1 (Control) was sham operated; Group 2 was thyroidectomised; Group 3 was sham operated and given 10mcg/100g body weight Thyroxine (T4) for five weeks. Group 4 was thyroidectomised and given 10mcg/100g body weight T4 for five weeks.

Method of Thyroidectomy: The rats were anesthesized with 0.2ml/100g body weight ketamine hydrochloride injection intraperitoneally. After which an incision was made in the neck. The thyroid glands were then extirpated and the incision sutured for the thyroidectomised rats while the incision was closed with the thyroid intact in the sham operated rats.

Thyroxine Administration: One week after surgery groups 3 and 4 rats were given L-thyroxine daily before meals at a dose of 10mcg of L-thyroxine per 100g of their body weight for five weeks as a modification of the method of Mokuno *et al*. [4]. Thyroxine was diluted in distilled water at a concentration of 10mcg per 0.5ml of distilled water and was orally administered with the aid of an oral cannula for thirtyfive days. Groups 1 and 2 rats were given distilled water only.

Body Weights: The body weights of the rats in all the groups were measured before surgery and on a weekly basis after with the aid of an electronic weighing scale.

Oral Glucose Tolerance Test: The rats were fasted overnight but had access to water. Blood sugar was determined from a drop of blood from the tail vein using the Accu-check glucometer and strip. Each rat was then orally administered 0.175g of glucose D per 100g of body weight dissolved in distilled water at a concentration of 8.75g of glucose per 25mls of water. The blood sugar level was again determined after 30, 60, 90 and 120 minutes of oral ingestion of glucose.

Thyroxine Assay: The rats were sacrificed by cervical dislocation and blood was collected via cardiac puncture. The blood was allowed to cloth and centrifuged for 30 minutes at a speed of 3,000 rpm. The supernatant (Serum) was then collected into another bottle with the use of a mircropippete and frozen until the hormonal assay was done. The levels of total serum thyroxine for each rat was determined by chemi-immunoluminiscence with the aid of the authomated immunodiagnostic ECiQ and the thyroxine reagent kit products of Ortho-Clinical Diagnostics, a Johnson-Johnson Company, UK. Using the methods outlined by the kit manufacturer, a calibration curve was generated [5].

Statistical Analysis: Results are presented as mean ± *SEM* and data analysed using student t test. $P < 0.05$ was taken as significant.

RESULTS

The thyroxine replacement group had a mean thyroxine level slightly lower than that of the control ($P<0.05$) but markedly greater than that of the hypothyroid group ($P<0.001$) and lower than that of the hyperthyroid group ($P<0.01$) (Table 1).

The mean blood fasting sugars of groups 2, 3 and 4 when compared to the control group was significantly higher. The mean blood glucose after 30 mins of oral glucose ingestion of groups 2 and 4 was significantly lower than control but the mean glucose level of group 3 was not significantly different from the control group. After one hour of oral glucose ingestion, the mean blood glucose levels of the groups 2, 3 and 4 was significantly lower than control group, the same was observed after 1hr, 30 minutes of oral glucose ingestion. After 2 hours of oral glucose ingestion, there was no significant difference in the mean glucose levels of groups 2, 3 and 4 when compared with the control group. The mean fasting blood sugar of group 2 was significantly lower than that of group 4, the mean blood sugars 30 mins after oral ingestion of glucose were not significantly different, but 1 hour after the ingestion of glucose, the mean glucose level of group 2 was significantly higher than group 4. There was no significant difference across the groups in the mean glucose levels 1hr, 30 mins and 2 hrs after oral ingestion of glucose (Fig. 1).

Thyroxine replacement and hyperthyroid groups in Figure 2 shows fluctuations in weight. There was an initial rapid loss in weight in the thyroxine replacement group followed by brief weight gain in the third week and weight loss in the fourth and fifth week.

Table: Mean serum thyroxine levels in the rats after the five weeks period of thyroxine administration

GROUP1 (CONTROL)	GROUP 2 (Hypothyroid)	GROUP 3 (Hyperthyroid)	GROUP 4 (thyroxine replacement)
30.4 ± 1.2 nmol/l	17.4 ± 1.7*** nmol/l	49 ± 4.7** nmol/l	27.14 ± 1.2* nmol/l

*significantly different from control group with P<0.5

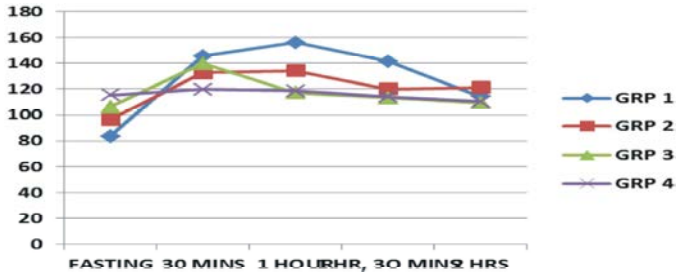

Fig. 1: Effect of thyroxine on oral glucose tolerance test
A plot of concentration of glucose in mg/dl against time

Fig. 2: Changes in weight observed in thyroxine treated and thyroidectomised rats

DISCUSSION

The elevated serum thyroxine in group 3confirmed hyperthyroidism and in the thyroxine replacement group, hypothyroidism was overcome significantly. Hexokinase promotes glucose phosphorylation in the liver and other body tissues which serves to capture the glucose in the cell. The elevated fasting blood glucose of the hypothyroid rats could be attributed to lower activities of hexokinase as was observed by Walter and Mclean [6] in hypothyroid rats. Hyperthyroidism results in altered glucose metabolism [7], therefore in hyperthyroid humans as well as in experimental thyrotoxicosis in animals, glucose turnover and hepatic glucose production are increased due to increased metabolic rate and peripheral glucose utilization [8]. This was reported by Dimitriadis *et al*. [9]. It is not well understood why thyroxine therapy administered to thyroidectomised rats did not normalize the fasting blood glucose level although Walter and Mclean observed that the level of hexokinase approached control values after administration of thyroxine to thyroidectomised rats.

The marked rise in blood glucose level in the hyperthyroid and control rats after 30 minutes of oral ingestion of glucose may be due to impaired glucose tolerance that resulted from glucose loading; a phenomenon termed oxyhyperglycaemia [4]. Overweight hyperthyroid women lose their first-phase response to hyperglycemia [7].

The effect of glucose loading on the blood glucose level wears out as was seen in all the groups. In the hypothyroid rats, the blood glucose falls minimally over the 120 minute period and did not return to the fasting blood glucose level within this period; this is in line with the findings of Sudipta *et al*. [10] in which blood glucose level remained elevated even after 24 hours after glucose loading. This may also be due to decreased activities of hexokinase observed by Walter and Mclean [6] in hypothyroid rats.There is conflicting reports regarding the glucose tolerance of hyperthyroid rats. According to Roubsanthisuk *et al*. [11], in hyperthyroid patients, thyroid hormone levels are inversely related to the rate of insulin release, suggesting a relationship between altered insulin secretion and severity of hyperthyroidism.

Oghuni *et al*. [7] also stated that insulin sensitivity is altered in hyperthyroid patients. The pattern observed in the hyperthyroid rats in which the blood glucose started to fall after 60 minutes of glucose loading and returned to the normal level after 120 minutes although in conflict with the above stated observations is in line with the findings of Mokuno *et al.* [4] and this could be as a result of increased insulin secretion to compensate hyperglycaemia after glucose load that was observed in hyperthyroid patients less than 30 years old by Komiya *et al*. [12]. The fall in blood glucose was also observed in the rats treated with thyroxine in which the blood glucose level returned to normal 90 minutes after oral glucose loading.

Thyroidectomy which led to hypothyroidism caused weight gain, an effect which was reversed by thyroxine therapy. On the other hand, hyperthyroidism led to weight loss.The weight gain in the hypothyroid rats is in line with the findings of Sudipta *et al*. [10] who reported that hypothyroidism is generally associated with some weight gain because of low Basal Metabolic Rate (BMR). It is well known that hyperthyroidism caused extensive weight loss despite normal or increased caloric intake [13]. This was observed in the hyperthyroid rats. Weight loss reflects not only a depletion of body adipose tissue stores but also a loss of muscle mass caused by accelerated catabolism and heat elimination [13]. The rats that were administered thyroxine showed no net gain in weight, this could be attributed to the effect of thyroxine administration in reversing the low metabolic rate that resulted in weight gain observed in hypothyroid rats.

Based on these results it can be concluded that hypothyroidism and hyperthyroidism may cause disturbances in glucose tolerance and an elevated fasting blood glucose level. Thyroxine replacement therapy used in thyroidectomy did not normalise the disturbances caused by hypothyroidism on glucose tolerance neither did it reduce the fasting blood sugar level although it inhibited hyperglycaemia in a non-synchronous manner as compared to the pattern of glucose tolerance curves in the hypothyroid rats.

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