STUDY OF THYROID FUNCTIONS AND LIPOPROTEIN PATTERN IN DIABETIC PATIENTS.

THESIS

submitted for partial fulfilment

for the Master Degree in general medicine.

Presented by

MOHAMED EL-SISY MOSTAFA

M. B., B. ch.

Supervised by

PROF. Dr. SAMIR SADEK
prof. of Internal Medicine

PROF. Dr. SAWSAN HOSNY
prof. of clinical pathology

Dr. ABDEL GHANY SHAWKAT
lect. of Internal Medicine

Faculty of Medicine

Ain Shams University

1983

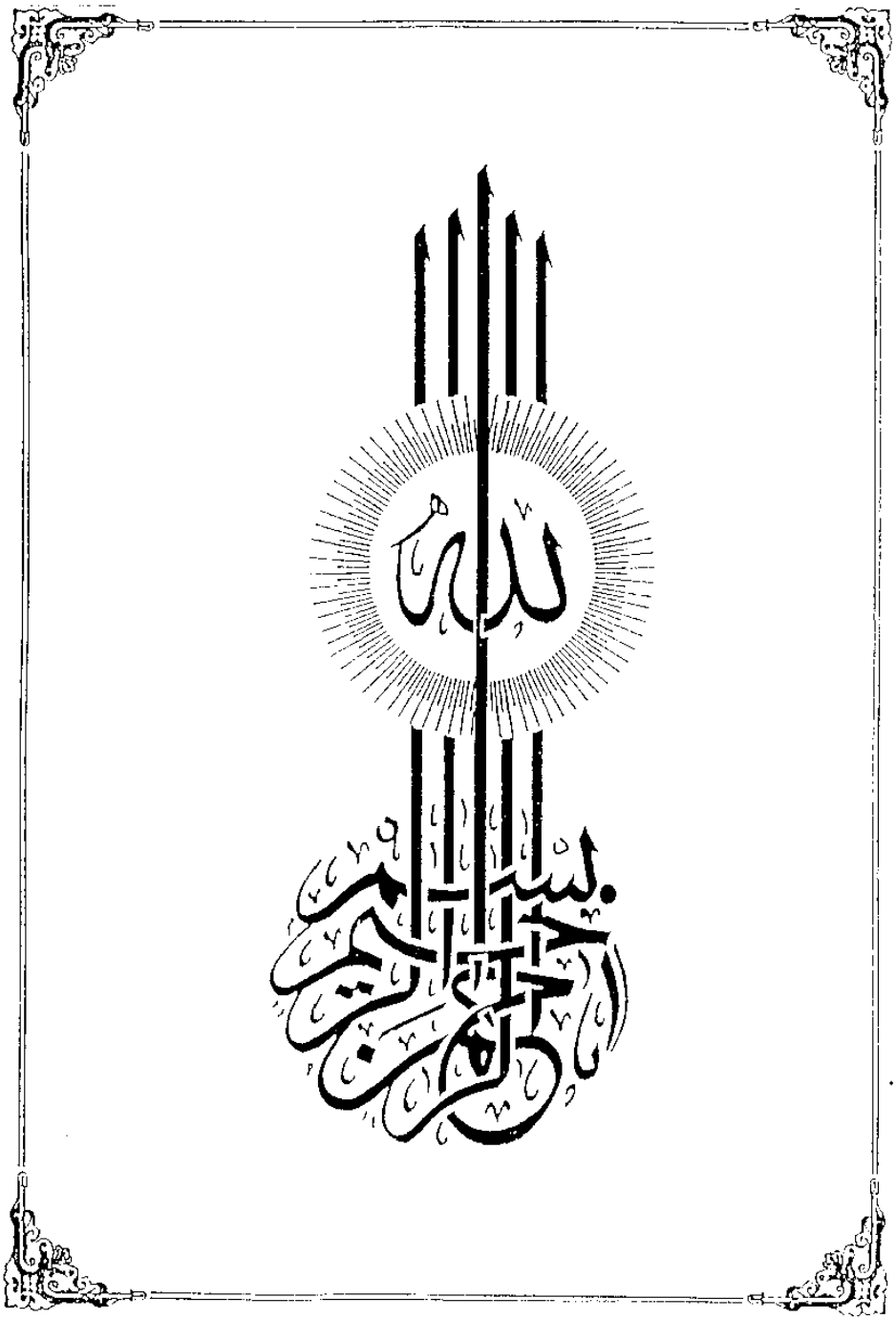
Acknowledgement

- I wish to express my deepest gratitude and sincerest thanks to professor Dr. Samir Mohamed Sadek, professor of general medicine, Ain Shams Medical Faculty for his very valuable supervision, fruitful guidance and kind help through out the ocurse of the work.

- I am also deeply indebted and cordially gratefull to professor Dr. Sawsan Mousny, professor of clinical pathology for her endless help.

  Also she has helped me so much in completion of statistical analysis of my data.

- In this context, I wish to express my deep gratitude and appreciation to Dr. Abdel Ghany Shawkat lecture of medicine for his helpfull instructions and facilities.



CONTENTS

INTRODUCTION — AIM OF THE WORK.

Introduction and aim of the work

The effect of thyroid hormones on carbohydrate metabolism is well established i.e. diabetogenic effect.

The association between diabetes and known autoimmune disease such as myxoedema has suggested that diabetes mellitus (D.M.) may have an autoimmune basis.

It was concluded that thyroid hormone parameters were not influenced by variations in serum glucose. (Alexander et al 1982). Also Pittman et al (1978) reported that no relationship was observed between elevations of serum glucose and T_3 and T_4 concentration.

But Saunderes et al (1978) and Naeije et al (1978) observed depressions of total serum T_3 and T_4 concentration, in untreated diabetes. However, the factors responsible for these aberrations have not been clearly defined.

The prevalence of clinical hypo-or hyperthyroidism in insulin dependent diabetics is reported to be between 5-8 % (Nabarro et al 1979).

Hunton et al (1955), Nikkila et al (1960) and skinner et al (1959) have found that sulphonylurea agents can exert clinically sigificant antithyroid action in certain diabetics.

The lipoproteins are classified by electrophoresis strip into: Alpha which corresponds to high density lipoprotein (HDL) prebeta (VLDL) and Beta lipoprotein (L D L).

In most surveys, the incidence of fasting hyperlipoproteinaemia in diabetes is 30-40%. Most commonly, fasting plasma triglyceride levels are elevated, but cholesterol conc. may be increased in diabetic population.

The most common abnormality in D.M. is elevation of serum triglyceride and (VLDL) levels, but thare is no general agreement on the significance of this change as a risk factor in coronary heart diseases.

The cholesterol and (L D L) conc. have been shown to be low, normal or high (Howard et al 1978).

The accumulated data have shown that the (H D L) conc. of diabetic patients may be low, normal or high depending mainly on the type and treatment of their disease (Kikkila 1981).

Recent studies in non-insulin dependent diabetics have demonstrated that the incidence and prevalence of coronary heart disease are inversely correlated with the plasma (H D L) conc. but this relationship has not been demonstrated in patients with insulin dependent diabetes (Calvert et al 1978 and Kennedy et al 1979).

The aim of this work is to study the protein - bound-iodine, serum cholesterol and lipoprotein pattern by electrophoresis strip method in diabetic patients.

Thyroid Functions in diabetic patients.

Macro and microscopic picture of thyroid gland:

It consists of 2 lobes which are connected by the thyroid isthmus and there is sometimes a pyramidal lobe arising from the isthmus. The gland is well vascularised. The thyroid is made up of multiple follicles. Each one is surrounded by a single layer of cells and filled with colloid. When the gland is inactive the colloid is abundant, the follicles are large and cells lining them are flat. When the gland is active, the follicles are small, the cells are cuboidal or columnar and the edge of colloid is scalloped forming small reabsorption lacunae.

Hormones:

The principal hormones secreted by the thyroid gland are thyroxine and triiodothyronine. The thyroid also secretes calcitonin, a calcium lowering hormone.

Biosynthesis and secretion:

Iodides are selectively trapped by the thyroid gland. In the follicles the iodide is oxidised to iodinate tyrosine (M I T) and (D I T). (M I T) and (D I T) underge oxidative condensation and by coupling reaction yield (T_3) and (T_4). These hormones are retained in the gland bound to thyroglobulin. The free hormone is released into the blood stream. During this

process any inactive MIT or DIT formed is deiodinated by iodotyrosine dehalogenase. The iodine released is recycled within the thyroid gland. About 80 ug/day of free thyroxine and up to 40 ug/day of triiodothyronine are secreted by the thyroid.

Control of thyroid hormone secretion:

The adenohypophysis secretes thyroid-stimulating hormone (TSH) under the influence of thyrotropin-releasing Hormone (TRH) formed in hypothalamus. High blood level of thyroid hormone inhibits TSH release, Whereas a low level stimulates it. This negative feed back mechanism acts mainly on pituitary and also on the hypothalamus.

Transport and metabolism:

T_4 is bound to (TBG). T_4 is also bound but less firmly to (TBPA) and also to albumin. T_3 is not bound to (TBPA) and it binds less firmly than T_4 to (TBG). There is eight to ten times more free T_3 in the blood than free T_4. T_3 is about three times as potent as T_4. so, the major functional thyroid hormone is T_3.

Most of T_3 in the plasma is formed by deiodination of T_4. T_4 is metabolically inert until it is deiodinated, to T_3. Deamination in the tissues produces pyruvic A. analogues of T_4 and T_3 and subsequent decarboxylation produces the acetic A. analogues Tetrac and triac. In

the liver, T_4 and T_3 are conjugated to form sulphates and glucoronides. These conjugates enter the bile and pass into the intestine. The thyroid conjugates are hydrolysed and some are reabsorbed but some are excreted in the stool.

Functions and mechanism of action:

Despite much research the mode of action is unknown. One possible explanation of the mechanism of action of T_4 and its analogues is that they decrease the efficiency of energy trnsduction by uncoupling phosphorylation from oxidation in the mitochondria.

Most of the effects of thyroid hormones are secondary to stimulation of O_2 consumption (calorigenic action). When metabolic rate is increased by T_3 , T_4, nitrogen excretion is increased, weight is lost. The catabolic response in skeletal muscle is sometimes so severe that creatinuria is marked. K^+ appears in urine and increases in uric acid excretion. The mobilization of bone protein leads to hyrer-calciuria and osteoporosis, thyroxine causes extra heat production. Cardiac cutput is increased so that cardiac rate is increased and circulation time is shortened.

In absence of thyroid hormones, moderate anaemia occurs. Also vitamin deficiency syndrome may be precipitated when M.R. is increased. Thyroid hormones are necessary for hepatic conversion of carotene to vit. A.

Milk secretion is decreased in hypothyroidism.

Large doses cause rapid mentation, irritability and restlessness. Thyroid hormones increase the rate of absorption of carbohydrate from G.I.T., also stimulate cholesterol synthesis and the hepatic mechanisms that remove cholesterol from the circulation, the drop in plasma cholesterol levels may occur because the rate of latter process exceeds that of the former.

There is some inhibition of the calorigenic effect of thyroxine when sympathetic flow is blocked. The effects of thyroid hormones especially on c.v.s. and nervous system are partly due to adrenergic nervous activity. It is clear that T_3 , T_4 potentiate the effects of catecholamine and vice versa. The thyroid hormones increase the amount of catecholamines in the tissues.

They are essential for normal growth and skeletal maturation. In absence of thyroid H. , growth hormone secretion may be depressed and it potentiates the effect of growth H. on the tissues.

Thyroid fuction tests:

Direct tests of thyroid function:

The thyroid radioactive iodine uptake, $(I)^{131}$; an increased

uptake is found in thyrotoxicosis.

Thyroid hormone levels in the blood:

(PBI) conc. is commonly used as a method of estimating serum T_4. PBI is raised in thyrotoxcosis and lowered in hypothyrcidism. The serum T_4 conc. Known as T_4 (D) can be measured by assessing the ability of T_4 extracted from patient's serum to displace labelled T_4 from protein mixture containing TBG. The serum T_3 conc. Can be measured by radio-immunoassay. Both these measurement include the bound hormone.

Measurement of free hormone ($F T_3$, $F T_4$) can be made but the techniques are difficult. Measurements of bound hormone are complicated. The resin T_3 uptake ($R T_3 U$) is a useful, simple test which indirectly measures free hormone.

Metabolic measurements:

Measurement of B.M.R. were used. Many errors in practice had occured. It is non specific test. Serum cholesterol level is non specific test as variation in blood cholesterol may occur in fat over-feeding and diabetes mellitus. It decreases in hyperthyroidism.

Tests of homeostatic control:

TSH can be measured by radio immunoassay methods. The level is high in myxoedema of thyroid origin, but

low in hypothyroidism of hypothalamic or pituitary origin.

TSH stimulation test:

Measures the ability of thyroid to respond to the hormone.

The thyrotropin-releasing hormone (TRH) stimulation test:

Is performed by estimating the serum TSH levels following a dose of TRH.

The Werner suppression test:

Is of value in diagnosing thyrotoxicosis.

Other tests:

The identification of antithyroid antibodies. Radio active scanning is a useful aid in the diagnosis of nodules in the thyroid.

Carbohydrate metabolism:

The principal product of carbohydrate digestion is glucose. Once it enters the cells, glucose is normally phosphorylated to form glucose -6- phosphate. The enzyme that catalyzes this reaction is hexokinase. In the liver is glucokinase, which is increased by insulin and decreased in starvation and diabetes. The glucose -6- phosphate is either polymerized into glycogen or catabolized. The major supplies of glycogen are present in the liver and skeletal muscle. The breakdown of glucose to pyruvic or lactic acid is called glycolysis which proceeds in 2 ways: via cleavage to trioses or via

oxidation and decarboxylation to pentoses. Pyruvic acid is converted to acetyl coA. interconversion between carbohydrate, protein and fat include the conversion of the glycerol from fats to dihydroxy acetone phosphate and the conversion of number of amino acids with carbon skeletons resembling intermediates in citric acid cycle to these intermediates by deamination. In this way, and by conversion of lactate to glucose, nonglucose molecules can be converted to glucose (gluconeogenesis). Glucose can be converted to fats through acetyl co A. The citric acid cycle (krebs cycle) is a sequence of reactions in which acetyl coA is metabolised to CO_2 and HC_2. The citric acid cycle is the common pathway for oxidation to CC_2 and H_2O of carbohydrate, fat and some amino acids. Glycolysis to pyruvate occurs outside the mitochondria. Pyruvic acid then enters the mitochondria and is metabolized. The citric acid cycle requires O_2 and does not function under anaerobic conditions.

During aerobic glycolysis the production of ATP is 19 times as great as it is under anaerobic conditions. Glycogen is synthesized from glucose -1- phosphate via uridine diphosphoglucose with the enzyme glycogen synthetase.

Because the liver contains the enzyme glucose -6-