# Study of the Serum Thyroid Binding Globulin ( T B G ) Level in chronic Renal Failure Patients undergoing regular Haemodialysis and in Renal Transplanted patients

Thesis
submitted in
partial fulfillment of the
requirement for the Master Degree ( M. SC. )
Internal Medicine

Presented by

**Hisham Samir Riad**
**M.B. B. Ch.**

Supervised by
**Dr. Essam Mohamed Kheidr**
Assistant Professor of Internal Medicine & Nephrology
Ein Shams University

**Prof. Dr. Aly Khalifa Aly**
Professor of Biochemistry
Ein Shams University

**Dr. Mostafa Mohamed El Rassad**
Assistant Professor of Biochemistry
Ein Shams University

**Dr. Mohamed El Tayeb Nasser**
Lecturer of Internal Medicine & Nephrology
Ein Shams University

Faculty of Medicine
Ein Shams University

1992

# ACKNOWLEDGEMENT

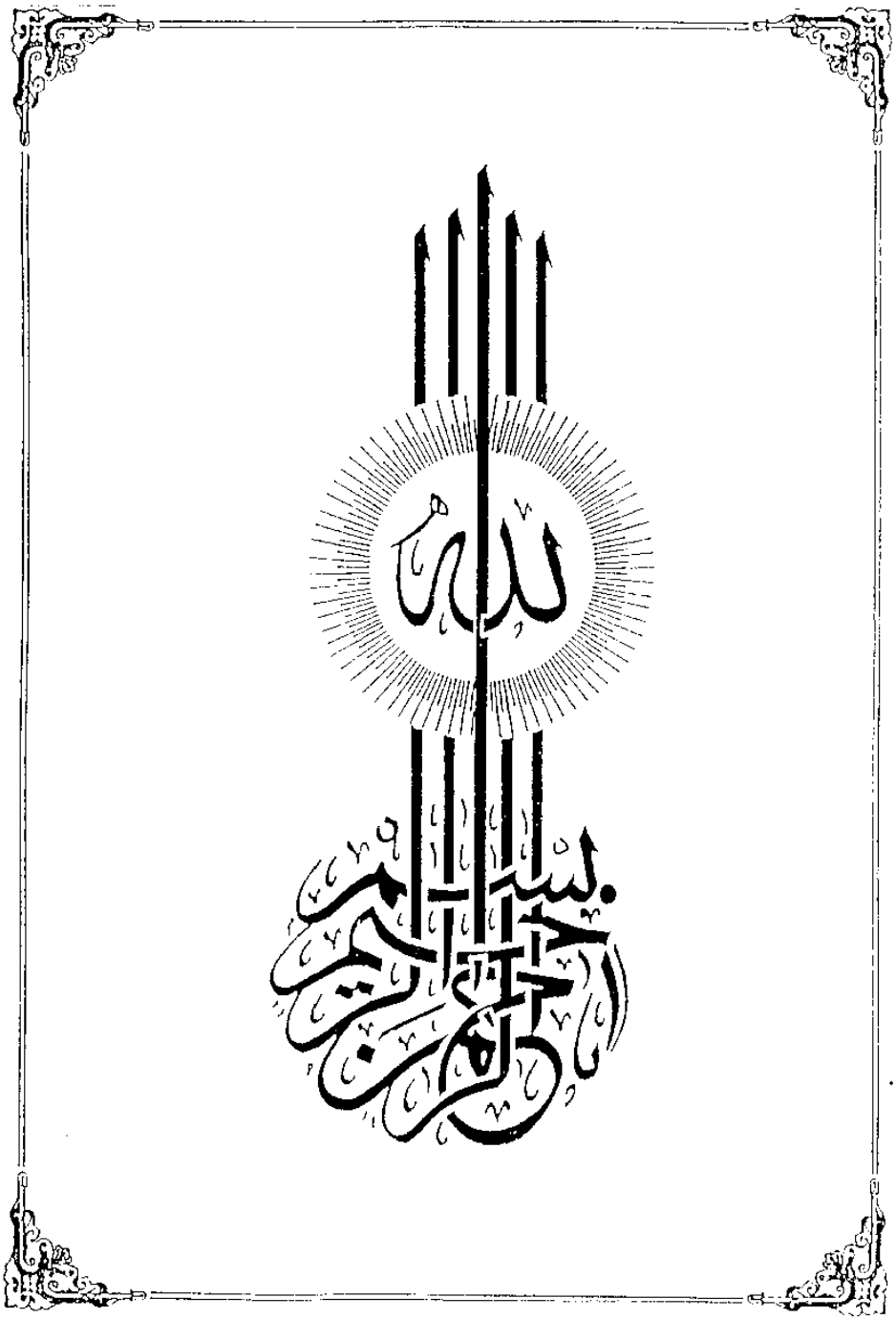
I am most greatful to professor Dr. Mohamed Essam kheidr Assistant Professor of Internal medicine and Nephrology, for his sincere and constant support and under whose supervision I had the honour to do this work.

I am greatly indebted to professor Dr. Aly Khalifa Aly Professor of Biochemistry, for his great effort and guidance that have been of utmost help in performing this work.

I wish to express my sincere thanks to Professor Dr. Mostafa Mohamed el Rassad Assistant Professor of Biochemistry, for his supervision, advice and practical help that made this thesis attain its shape.

I would like to thank Dr. Mohamed El-Tayeb Nasser Lecturer of internal medicin, for his enthusiastic cooperation during this work .

I would also like to thank Dr. Hady Gobran lecturer of internal medicin, for his statistical guidance that made the results meaningful.



# CONTENTS

# Introduction

Diverse abnormalities of thyroid function have been reported in patients with chronic renal failure during chronic therapy with haemodialysis . Serum level of thyroid hormones varies from significantly subnormal in some reports (Sennsael et al 1985, Pagliacci et al 1987) to generally normal in others (Neuhaus et al 1975). However it was established that euthyroid state is present in patients with chronic renal failure .

Joasoo et al 1974, Kaptein etal. 1988 reported that the circulating thyroid hormone changes subsided upon resumption of a normal kidney function .

The recently described low TBG syndrome in patients on chronic haemodialysis (Lambert 1989, Djurica 1989) led us to examine further the serum TBG changes in chronic haemodialysed patients as well as in renal transplanted recipients .

## Aim Of The Work :

The aim of the present work is to monitor the

serum TBG in patients with end stage renal failure undergoing regular haemodialysis, also estimating the serum TBG level after restoration of normal renal function following successful renal transplantation .

# The Thyroid Gland

The thyroid gland is one of the most important organs of the endocrine system. It produces, stores and secretes the thyroid hormones, the most important of which are thyroxin (T4) and triiodothyronine (T3), the action of the thyroid is mediated through other centers such as the hypothalamus and the anterior Pituitary gland. The physiological effects of thyroid hormones are widespread being mediated through their influence on cellular metabolism in all tissues. Skeletal growth, sexual maturation & mental development, all require a normal thyroid gland function. Complete lack of thyroid secretion usually cause the basal metabolic rate to fall about 40% below normal, and extreme increase of thyroid secetion can cause the BMR to rise as high as 60 to 100% above normal (Guyton 1981) . The heart rate and cardiac output are influenced by thyriod horomnes, which also increase the peripheral utilization of glucose and the conversion of liver glycogen to glucose.

## Thyroid Hormones And The Kidney

A reciprocal relationship exists between the kidney function and the thyroid hormones. The kidney plays an important role in the peripheral metabolism of thyroid hormones. So in renal diseases the thyroid function may be disturbed. Thyroid hormones, on the other hand, affect both renal morphology and function as they promote the growth and development of the kidney (katz et-al 1975) .

Role of the kidney in the degradation and excretion of thyroid hormones :

### A - Metabolism

The peripheral degradation of thyroid hormones proceeds through several metabolic pathways. The main pathways are deiodination, conjugation with sulphate or glucoronic acid and side chain metabolism, iodine released in the circulation is in part taken up by the thyroid gland and in part excreted as iodides in urine, the latter being the larger fraction .

In normal man, approximately 80% of metabolism of T4 and the various products derived from it proceeds by enzymatic monodeiodination. From kinetic studies, it has been estimated that approximately 35% of the T4 secreted in normal man is deiodinated to yield T3, and about 40% to yield rT3. Hence with a normal T4 production rate of 90 ug/day, about 26 ug of T3 & 30 ug of rT3 would be produced by peripheral deiodination. Since the dai ly production rate of T3 and rT3 are 30 mg of each of them, we can notice that peripheral deiodination accounts for about 80% of normal T3 production and all of the rT3 production, (Ingbar and woeber 1981). This pathway of deiodination has been demonstrated in numerous tissues including liver, kidney, muscle heart and brain. Conjugation of the phenolic hydroxyl group of T4 and T3 with glucoronic acid or sulphate occurs mainly in the liver, but it has also been demonstrated in the kidney and in eviscerated animals (Etting and barker 1969). Oxidative deamination and decarboxylation of the alanine side chain to their acetic acid derivatives is the predominant metabolic pathway of thyroid hormones in the kidney.

The liver and the kidney together account for most of the degradation and excretion of thyroid hormones . The kidney in addition to its ability to carry out all the major degenerative pathways, also stores more T4, T3 and inorganic iodide per unit mass than other extra-thyroidal tissues and is the most important route for the excretion of iodide (Pittman et-al 1977) .

## B-Excretion.

Urinary excretion of inorganic iodide occurs through a combination of glomerular filtration and partial tubular reabsorption of the plasma iodide, with a fraction of urine iodide possibly generated denovo in the kidney by local deiodination of iodo thyronines (shimodo and greer, 1972). Iodide clearance varies with thyroid status, being lower in hypothyroidsim and high in hyperthyroidism.

The average excretion of T4 is 8.3 ug/day in urine. Vrinary thyroxine represents only non protein bound hormone and therfore, independent of circulating thyroxine binding globulin. The daily T3 excretion range between 2 and 9 ug in euthyroid individuals (Shakespear, and Burke 1976).

# THYROID HORMONES

Iodine is essential for the formation of thyroid hormones.

Exogenous sources of iodine include food, water, dietary supplements and medications.

Iodine used for thyroid hormone synthesis is drawn from the inorganic iodide of the extracellular fluid. This iodine is compensated for by iodide lost from the thyroid into the blood, and by deiodination of thyroid hormones in peripheral tissues.

Iodine is removed from the extracellular fluid either by the kidney or the thyroid gland.

## BIOSYNTHESIS AND SECRETION OF THYROID HORMONES:

The thyroid undergoes the following steps in order to form the thyroid hormones:

1 - Active transport of iodide into the thyroid.

2 - Oxidation of iodide, and iodination by the oxidized form of tyrosyl residues within thyroglobin to yeild hormonally inactive iodotyrosines.

3 - Coupling of iodotyrosines to form To and T4.

## 1- Iodide transport :

For the synthesis of adequate quantities of thyroid hormones, the rate of iodide uptake by the thyroid must be more rapid than would be possible by simple diffusion .

There is a special transport mechanism by which the thyroid can get its optimum requirements of iodide .

Iodide transported into the gland is either oxidized and organified or is free to diffuse back into the extracellular fluid .

Under normal circumstances the rate of inward clearance of iodide exceeds the combined rates of organic binding to form iodotyrosine, and back diffusion, with the result that intrathyroid concentration gradients are maintained within the gland. Such gradients are often referred to as thyroid/plasma ratios.

The exact biochemical mechanism of active iodide transport is unknown, but it is known to be an energy requiring process highly dependent on continued generation of phosphate bond energy. This process is closely related to the function of

sodium, potassium dependent ATPase system (Ingbar and Woeber, 1981) .

The activity of the iodide transport mechanism is influenced by a variety of physiologic factors, the most important of which is the level of TSH stimulation. It is also influenced by an internal autoregulatory system through which the intrinsic activity of the iodide transport system and its responsiveness to TSH stimulation are caused to vary inversely with the glandular content of organic iodine (Ingbar, 1978) .

The thyroid mechanism for concentrating iodide is shared by other monovalent anions such as perchlorate and pertechnetate . These anions act as competitive inhibitors of iodide transport . Thiocyanate inhibits iodide transport possibly through uncoupling thyroid oxidative phosphorylation (Bastomsky, 1974).

The ability of the thyroid to concentrate iodide is shared by other tissues of endocrinal origin, mainly the salivary and gastric glands .

In addition to this way of iodide transport,

iodine is generated in the thyroid by the deiodination of iodotyrosines liberated during the hydrolysis of thyroglobulin .

## 2- Oxidation of Iodide and Organic Iodinations

After its transport into or regeneration within the thyroid, iodide enters into a series of reactions which ultimately lead to the synthesis of the active thyroid hormones .

The first of these reactions involves oxidation of iodide and incorporation of the resulting inter mediate into the hormonally inactive iodotyrosines monoiodotyrosine (MIT) and diiodotyrosine (DIT)

Oxidation of the thyroid is almost certainly mediated dy a peroxidase This reaction is inhibited both in vivo and in vitro by antithyroid agents and by high concentrations of iodide (Wolff_Chiakoff effect).

As judged from studies in vitro,soluble inhiditors of organic iodinations, principally ascorbic acid reduced glutathione, exist in thyroid tissue. These may inhibit iodinations by reducing either the oxidized form of iodine or hydrogen

peroxide itself (Taurog .1974).

Thus mitochondrial systems may provide a source of hydrogen peroxide and cell membrane the iodide _peroxidase. While the cytoplasmic fraction may contain regulatory inhibitors of organic iodinations

Organic iodinations are conditioned by the extent of thyroid stimulation by TSH. They are retarded in the hypophysectomized rat and are promptly increased by administration of TSH

Iodinations are susceptible to inhibition by a great number of pharmacolgic agents, including the usual antithyroid drugs, most of Which are inhibitors of peroxidase and also have intrinsic reducing activity. Iodinations are also inhibited by freezing, or cooling .

## 3 - Formation of Iodothyronines:

Synthesis of MIT and DIT is followed by the formation of the hormonally acive iodothyronines T4, and T3.

Thyroxine (T4) is formed by coupling of two