THYROID STIMULATING HORMONE (TSH) IN GRAVES' DISEASE AND IN TOXIC NODULAR GOITRE BEFORE AND AFTER MEDICAL CONTROL

THESIS

SUBMITTED FOR FULFIL MENT

OF MASTER DEGREE IN

(CLINICAL PATHOLOGY)

BY

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1988

ACKNOWLEDGEMENT

I wish to express my deep appreciation and sincere gratitude to Professor Dr. **AIDA ABD EL-AZEIM**, Professor of Clinical Pathology, Ain Shams University who offered much of her experience and support for providing me with advice, suggestion and planning of this work.

I am deeply indebted to Dr. **AMANI IBRAHIM SALEH**, Assistant Professor of Clinical Pathology, Ain Shams University for her kind advice and guidance, her meticulous supervision and revision of this thesis and for her continuous and enthusiastic stimulation throughout the whole work.

I would also like to thank Dr. **SOHEIR GAMAL EL-DIN**, Assistant Professor of General Medicine, Ain Shams University for her supportive advice, generous help and revision of this work.

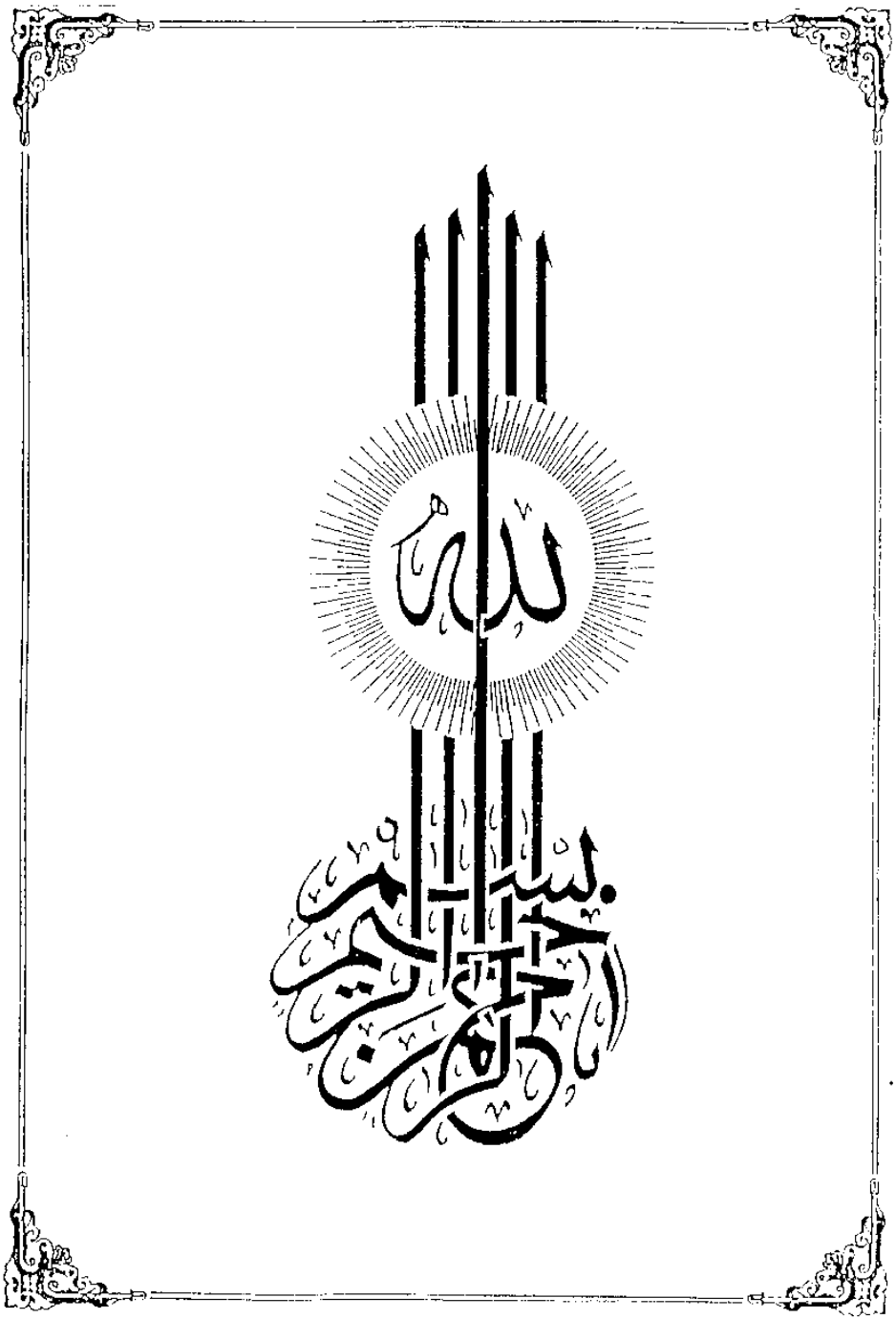
Last but not least, these persons can not be forgotten who save a lot

My Parents

and My Husband

The Candidate

Nahla



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Introduction:

Growth and function of the thyroid gland are mainly controlled by the level of thyrotropin (TSH) (Dumont, 1971). Concentrations of TSH in the circulation should reflect thyroid status and pituitary function, because the secretion of TSH from the pituitary is regulated by the concentrations of thyroid hormones. Thus low concentrations of TSH are found in thyrotoxicosis and hypopituitary patients and increased concentrations are found in hypothyroidism (Adams et al., 1969).

The measurement of TSH in serum has traditionally been applied to the initial diagnosis and subsequent therapeutic monitoring of patients with primary hypothyroidism. Because several rapid turnaround assays capable of measuring low TSH concentrations are now available, the potential exists to significantly expand the utility of TSH measurements in clinical practice. Since 1984, many new TSH assay methods have been introduced. These assays are claimed to be capable of distinguishing normal from subnormal serum TSH levels (Klee and Hay, 1987).

Aim of the Work:

The aim of this work is to study the level of TSH in patients with Graves' disease and toxic nodular goitre before and after medical control by "neomercazole", to clarify the role of TSH measurement in diagnosis of hyperthyroidism and to determine our normal range to be a reference in subsequent analysis.

PART I

REVIEW OF LITERATURE

PHYSIOLOGY OF THYROID GLAND

The thyroid gland secretes two hormones, thyroxine (3,5,$\bar{3}$,$\bar{5}$ L-tetraiodothyronine) and triiodothyronine (3,5,$\bar{3}$ L-triiodothyronine) that are commonly known as T_4 and T_3 respectively. In addition, the thyroid gland secretes minute amounts of biologically inactive 3,$\bar{3}$,$\bar{5}$ L-triiodothyronine (reverse T_3 or rT_3). (Nagasaka et al., 1971).

Synthesis of Thyroid Hormones:

Thyroid hormone formation requires the coincident presence of peroxidase, H_2O_2, iodide and acceptor protein at one anatomic locus in the cell (DeGroot and Niepomniszcze, 1977). Iodide ingested in food and water is actively concentrated by the thyroid gland, converted to organic iodine by peroxidase and incorporated into tyrosine in the thyroglobulin. The tyrosines are iodinated at either one (monoiodotyrosine, MIT) or two (diiodotyrosine, DIT) sites and then coupled to form the active hormones (diiodotyrosine + diiodotyrosine $\longrightarrow$ tetraiodothyronine = T_4) or (diiodotyrosine + monoiodotyrosine$\rightarrow$triiodothyronine = T_3) (Berkow, 1982). Synthesis of T_3, T_4, DIT and MIT in the thyroglobulin molecules occurs mainly at the follicular cell/colloid interface and also within the colloid (DeGroot, et al., 1972). About 15% of circulating T_3 is produced

by the thyroid. The remainder is produced by monodeiodination of the outer ring of T_4, mainly in the liver. Monodeiodination of inner ring of T_4 also occur possibly in extrahepatic sites to yield reverse T_3. This compound has minimal metabolic activity but is present in normal human serum and thyroglobulin (Berkow, 1982).

Acute or chronic stress or illness will cause shift in the direction of this deiodination, favouring formation of rT_3 rather than T_3, whereas the T_4 level remains essentially unchanged, this could be considered as protection of the tissues against the highly potent T_3 (Ghareeb et al., 1984).

T_3 and T_4 in the circulation are reversibly bound to carrier proteins. These carrier proteins (thyroxine-binding globulin, thyroxine-binding prealbumin and albumin) bind approximately 99.97% of T_4 and 99.7% of T_3. This means that only a very small fraction of each hormone is free for biological activity (Greenspan and Rapoport, 1986).

It has become increasingly clear that T_3 provides most, if not all, of the thyromimetic activity of thyroid secretion. Although T_4 is normally secreted at eight to 10 times the rate of T_3, T_3 is three to four times

more potent. One explanation for the fact that T_3 is the active thyroid hormone is that the receptor protein for thyroid hormone within the cell nucleus has about a 10-fold higher affinity for T_3 than for T_4. Furthermore, the high affinity binding proteins in the plasma restrict the enterance of T_4 into the cell much more than they do that for T_3, which is less strongly bound to these proteins (Larsen, 1982).

Throid Hormone Secretion:

The thyroid gland secretes, mainly in the venous outflow, thyroid hormones and some iodide. The secretion of thyroid hormones involves at least two consequative processes: the endocytosis of colloid by phagocytosis resulting in the formation of intracellular colloid droplets and the digestion of colloid thyroglobulin by lysosomal enzymes with the release of thyroid hormone. The digestion of thyroglobulin also releases iodotyrosines which are deiodinated requiring deiodinase, part of the iodide derived from iodotyrosines is reorganified while another part is "spilled out" of the cell (Dumont, 1971).

Metabolism:

In the liver T_3 and T_4 are conjugated to form sulfates and glucuronides. These conjugates enter the

bile and pass into the intestine. The thyroid hormone conjugates are hydrolysed, some are reabsorbed through the enterohepatic circulation, and some are excreted in the stool (Ingbar and Woeber, 1981).

Physiological Effects of Thyroid Hormones:

Although thyroid hormones have many actions, the primary one is to increase energy expenditure in many tissues as indicated by O_2 consumption. Thyroid hormones are indispensible for growth, development and sexual maturation. Other actions include stimulation of heart contractions, maintenance of body weight, stimulation of protein synthesis and carbohydrate metabolism, increase in the synthesis and degradation of cholesterol and triglycerides, increase in vitamin requirements and enhancement of sensitivity of the B-receptors to catecholamines (Sterling, 1979).

Table(1): Current estimates of kinetic parameters for thyroxine and triiodothyronine (Larsen, 1972a).

	Serum concentration µg/Liter	Distribution volume (Liter)	Turnover rate (day-1)	Total extra-thyroidal hormone (µg)	Metabolic clearance (µg day-1)	Free hormone Percent	Free hormone ng/100ml
Thyroxine	84.2	9.4	0.100	790	79	0.024	0.7-1.9 *
Triiodothyronine	1.20	37.3	0.726	45	33	0.36	0.23-0.66 *

* (Ingbar et al., 1965).

PHYSIOLOGY OF THYROID STIMULATING HORMONE (TSH)

Structure:

TSH is a glycoprotein secreted by the thyrotropic cells of the anterior pituitary. The glycoprotein hormones of pituitary (Luteinsing hormone, follicle stimulating hormone and TSH) and placenta (human chorionic gonadotrophin) are composed of two non identical, non covalently bound subunits, ∝ and B, each with a carbohydrate substituent group attached. The carbohydrate moeity, accounting for 15-31% of the molecular weight, includes fucose, mannose, galactose, glucosamine, galactosamine and sialic acid (Chattoraj and Watts, 1987). The alpha subunits of the glycoprotein hormones are immunologically indistinguishable, whereas the beta subunits are unique and confer immunologic and biologic specificity to each hormone (Pierce and Eli Lilly, 1971).

Secretion and Metabolism:

If labeled TSH is injected it will be distributed in a space only slightly larger than plasma volume. Because of its glycoprotein nature, it disappears from plasma with a half life of about 50 minutes. The secretion rate is normally between 50-200 µg/day (Daughaday, 1985).

Mode of Action:

TSH binds to a specific receptor on the outer side of the follicular cell plasma membrane. This binding activates adenyl cyclase catalyzing adenosine triphosphate (ATP) transformation to cyclic adenosine monophosphate (cAMP). Intracellular cAMP activates various enzymes and thus elicits, more or less directly, the hormonal effects (Dumont, 1971).

Actions:

TSH exerts profound effects on many aspects of thyroid function. The size and vascularity of the gland increase, the height of the follicular epithelium is increased, and the amount of colloid is reduced. Iodide transport, thyroglobulin synthesis, iodotyrosine and iodothyronine formation, thyroglobulin proteolysis and T_4 and T_3 release are increased (Daughaday, 1985).

Regulation:

Thyrotrophin-releasing hormone (TRH) stimulates TSH release after attachment to high affinity receptors on the thyrotrope, activation of adenyl cyclase and subsequent generation of cAMP (Hershman, 1974). The secretion of TSH is primarily regulated by the negative feedback suppression of thyroid hormone at the level