SERUM TESTOSTERONE IN CHRONIC RENAL FAILURE

Thesis

Submitted for Partial Fulfilment of
Master Degree in Internal Medicine

By

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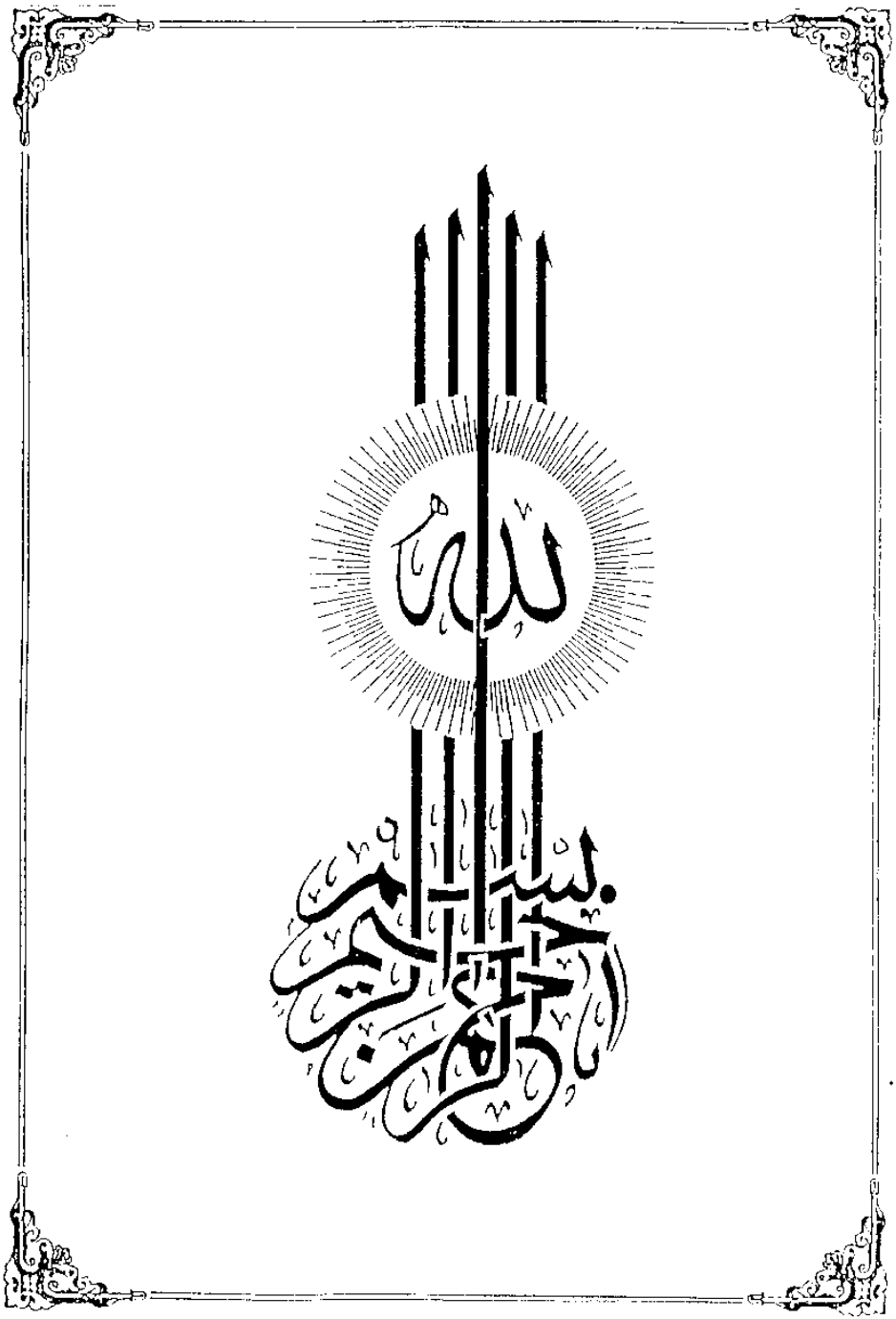
1990

TO MY DEAREST FATHER,
MOTHER AND BROTHERS
FOR THEIR SUPPORT AND
ENCOURAGEMENT



ACKNOWLEDGMENT

I wish to express my deepest gratitude to Prof. Dr. Moghazy Ali Mahgoub for his help, guidance and the support he constantly offered through out the period of preparation of this thesis.

My special thanks and appreciation for Dr. Mahmoud Abd El-Fattah, who so willingly offered me his precious time and continuous advice to complete this work in a proper manner.

I would also like to thank Dr. Mohamed Fahmy Abd El-Aziz for the tremendous effort he has exerted and for his sincere concern in every single step taken to accomplish this thesis.

I also wish to express my gratitude to Dr. Fadila Gad-Allah for her efforts and help.

I am also deeply thankful to Dr. Mohamed Saad for his guidance and care.

Last but not least, I would like to also thank all my colleagues, who helped me in the revision and organization of my work.

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INTRODUCTION
AND
AIM OF THE WORK

INTRODUCTION AND AIM OF THE WORK

Until the early 1960's chronic renal failure represented a terminal illness for which there was no treatment (*Abram et al, 1975*). The development of facilities for dialysis therapy has offered such patients an opportunity to return to a more useful life and often to productive work (*Elstein et al, 1969*). In this situation, the question of sexual potency became more relevant, especially to the patient who regards it as an important part of his return to a more normal life (*Elstein et al, 1969*).

Patients with chronic renal failure manifest a multitude of abnormalities in their sexual function (*Massry et al, 1983*). Dialysis may not improve these abnormalities and even frequently, some dialysis patients describe worsening of their sexual dysfunction after starting dialysis therapy (*Procci et al, 1981*).

The mechanisms responsible for the pathogenesis of sexual dysfunction in uremia are not fully elucidated and several potential factors have been implicated. These factors include zinc deficiency, autonomic neuropathy, depression, medication for hypertension as well as the state of

chronic illness itself (*Massry et al, 1983*). Hormonal abnormalities in chronic renal failure have also been implicated. These abnormalities include hyperparathyroidism and abnormalities in the hypothalamic-pituitary gonadal axis including follicle-stimulating hormone, luteinizing hormone, testosterone and prolactin (*Procci et al, 1981*).

From this wide range of potential factors, abnormalities in the testosterone hormone was chosen as the main topic for this thesis.

The aim of this work :- is to estimate serum level of testosterone in patients with chronic renal failure in a group before and another group after regular hemodialysis.

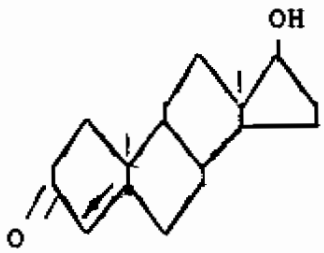
REVIEW OF LITERATURE

TESTOSTERONE

Chemistry :-

Testosterone, the principle hormone of the testes, is a C_{19} steroid with -OH group in the position 17. It is synthesized from cholesterol in the leydig cells. According to current concepts, the biosynthetic pathways in all endocrine which form steroid hormones are similar, the organs differing from one another only in the enzyme system they contain. In the leydig cells, 17∝-hydroxylase is present.

Pregnenolone is therefore hydroxylated in the 17 position then form 17-ketosteroid. These in turn are converted to testosterone (*Ganong, 1985*).



Testosterone

Secretion :-

The testes in adult men produce large amount of testosterone in the leydig cell (about 5-12 mg/day) plus very small amount of other steroids (*Kicklighter and Kulkarni, 1984*).

Testicular androgen biosynthesis :-

Testosterone is the major androgen produced in the testes and secreted into systemic circulation. Small amounts of other potent steroids such as dihydrotestosterone are secreted, but they contribute very little to over all androgen content of the blood in men. Androstendione, a testosterone precursor, is also secreted by the testes, but its only importance in man is as a plasma precursor for estrogen. Other testosterone precursors such as 17-hydroxy-progesterone and progesterone are also secreted by the testes but their biological function are not known (*Bardin, 1985*).

Leydig cells are the primary site of testosterone biosynthesis and the testes secrete 95% of the testosterone in the blood of normal men. In the leydig cells cholesterol is either synthesized from acetate or accumulated from the circulating cholesterol in low density lipoprotein (*Bardin, 1985*).

In leydig cells mitochondria cleave the cholesterol to produce pregnenolone. In the testes, pregnenolone is converted to testosterone by several microsomal enzymes (*Christensen, 1975*).

Regulation of testicular function :-

The testes produce both gametes and steroid hormones. The two activities spermatogenesis (sperm production) occurs in seminiferous tubules and androgen biosynthesis occurs in the leydig cells. The anterior pituitary controls these functions through its secretion of the gonadotropins as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (*Bardin, 1985*).

LH stimulates leydig cells synthesis of testosterone through cyclic-AMP (c.AMP) mediated processes. LH binding occurs in leydig cells membrane located in interstitial tissue of the testes. FSH stimulates spermatogenesis *(Kicklighter and Kulkarni, 1984).*

In addition to LH, fluoride ion, cholera toxin and guanyl nucleotides (GTP and analogues) stimulate c.AMP synthesis *(Bardin and Paulsen, 1981).*

Five components are involved in the mechanism of adenylate cyclase activation. These include :- a catalytic unit of adenylate cyclase which catalyzes the conversion of ATP to cAMP; a stimulatory and an inhibitory receptor; and a stimulatory and an inhibitory G protein that links the receptor to the catalytic unit. When the appropriate ligand binds to the stimulatory receptor, the α subunit of G_s activates adenylate cyclase. Conversely when the appropriate ligand binds to the inhibitory receptor, the α subunit of G_i inhibits adenylate cyclase. G_s mediates the excitatory effects of many different ligands on adenylate cyclase, yet the effects of chemical messengers are specific.

The specificity of responses depends on the receptors associated with the adenylate cyclase; in each cell, the receptor has a high degree of specificity for the substance or substances that normally stimulate it (*Ganong, 1989*).

Once cAMP is released into the cytoplasm of leydig cell it binds to regulatory subunit of protein kinase which dissociates and activates this enzyme. Then phosphorylation of leydig cells facilitates the conversion of cholesterol to pregnenolone and increases androgen synthesis (*Christensen, 1975 ; Bardin, 1985*).

Hormonal control of pituitary-leydig cell axis :-

The rate of testosterone synthesis and secretion by leydig cells is primarily dependent upon LH secreted into blood. Increase LH secretion results in leydig cell hypertrophy and increase testosterone secretion. Whereas lowered LH as in following hypophysectomy is associated with reduced activity of testicular leydig cells and decrease testosterone secretion. A fall in testosterone concentration results in increase release of LH into general circulation.

In response to increase LH leydig cells secrete testosterone which in turn inhibits LH secretion. In this manner the hypothalamus, the pituitary and leydig cell keep the testosterone blood level relatively constant from day to day and week to week. There is slight diurnal variation in blood testosterone with the levels at 8 a.m. being 20-25% higher than those at 6 p.m. (Baker et al, 1975). Some others demonstrated that the secretion of testosterone by testes is episodic, a circadian pattern can be demonstrated with maximum in the early morning (about 7 a.m.) and minimum 13 hours later and its amount is 6-12 mg/day (*Kicklighter and Kulkarni, 1984*).

Both testosterone and estradiol inhibit LH secretion. Each produces different effects on the LH release from the pituitary. An acute infusion of estradiol reduces the mean LH by decreasing the amplitude of each LH discharge. This is a direct effect of estrogen achieved partly by decreasing the sensitivity of the pituitary to the luteinizing hormone-releasing hormone (LHRH).

By contrast an acute testosterone infusion decreases the mean plasma LH level by reducing the frequency of each LH discharge and it is not associated with change in sensitivity of pituitary to LHRH.