Intratesticular, Seminal and Serum Testosterone in Sexual and Reproductive Disorders

Thesis

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Aim of work

In order to study whether there is a concentration gradient of serum testosterone, seminal testosterone and testicular tissue testosterone in patients with sexo-reproductive disorders.

List of Abbreviations

5-α DHT	5α-dihydrotestosterone.
ABG	Androgen-binding globulin.
ACTH	Adrenocorticotropic hormone.
AR	Androgen receptor.
BMI	Body mass index.
CMV	Cytomegalovirus.
CNS	The central nervous system.
COPD	Chronic obstructive pulmonary disease.
CT	Computed tomography.
CYP	Side chain cleavage enzyme.
DAX-1	Dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1.
DHT	Dihydrotestosterone.
DM1	Myotonic dystrophy protein kinase type 1.
DM2	Myotonic dystrophy protein kinase type 2.
DNA	Deoxyribonucleic acid.
ED	Erectile dysfunction.
FGF8	Fibroblast growth factor 8.
FGFR1	Fibroblast growth factor receptor 1.
FSH	Follicle-stimulating hormone.
GnRH	Gonadotropin-releasing hormone.
HAART	Highly active antiretroviral therapy.
HDL	High-density lipoprotein.
HH	Hereditary hemochromatosis.
HIV	Human immunodeficiency virus.

IHH	Idiopathic hypogonadotropic hypogonadism.
IL-1	Interleukin 1.
IL-2	Interleukin 2.
INSL3	Insulin-like factor 3.
IQR	Interquartile range
ITT	Intratesticular testosterone.
K Da	Kilo Dalton.
KAL1	Kallmann syndrome 1 sequence.
LCM	lymphocytic choriomeningitis virus.
LDL	Low-density lipoprotein.
LH	Luteinizing hormone.
m RNA	Messenger ribonucleic acid.
MAPK	Map-kinase pathway.
mGy	Milligray.
MRI	Magnetic Resonance Imaging.
NO	Nitric oxide.
NPT	Nocturnal penile tumescence.
PKA	Protein kinase A.
PKC	Protein kinase C.
PRL	Prolactin hormone.
PROK2	prokineticin 2.
PROKR2	Prokineticin receptor 2.
PWS	Prader-Willi syndrome.
rad	Absorbed radiation dose.
RIA	Radioimmunoassay.
RNA	Ribonucleic acid.
SHBG	Sex hormone-binding globulin.

SNRPN	Small nuclear ribonucleoprotein polypeptide N.
StAR	Steroidogenesis acute regulatory protein.
T	Testosterone.
TB	Tuberculosis.
TSH	Thyroid-stimulating hormone.

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Introduction

TESTOSTERONE (T) PRODUCTION and spermatogenesis are the two primary functions of the testis in man. Normal testicular function is dependent on the intratesticular activity of the pituitary gonadotropins, LH and FSH. LH stimulates Leydig cells to produce T within the testis. Intratesticular T (ITT) is an absolute prerequisite for normal spermatogenesis. Spermatogenesis is thought to critically depend on the high intratesticular testosterone (T) levels induced by gonadotropic hormones.**(Matsumoto and Bremner,1989)** FSH is also vital for normal testicular function and is necessary for quantitatively normal spermatogenesis in man.**(Matsumoto et al;1986)** Specifically,FSH is thought to play an important role early in spermatogenesis during spermatogonial maturation as well as late in the process during spermiation. The relative roles of intratesticular androgens and FSH are not fully understood in man. **(McLachlan et al;2002a)**

Control of the intratesticular hormonal environment is in large part regulated through negative feedback of T at the level of the hypothalamus and the pituitary.**(Sheckter et al;1989)** Exogenous T has been shown to dramatically suppress gonadotropin release when administered at supraphysiological as well as physiological doses. **(Anderson et al;1996)** Administration of T alone has been shown to reduce sperm production in the majority of men to levels acceptable for contraception.**(WHO research in 1996)** Gonadotropin withdrawal has also been shown to dramatically reduce ITT , which, in turn,decreases sperm production.**(McLachlan et al;2002b)** However, suppression of spermatogenesis is not uniform, and why some men are non responders is not clear.Possibilities include incomplete gonadotropin suppression, particularly with regard to FSH as well as inconsistencies in ITT suppression**(Wallace et al;1993)** so, It remains a dogma that the high intratesticular level of T is indispensable for the onset, maintenance, and completion of spermatogenesis in the adult

testis and for its restoration after experimentally induced azoospermia. **(Zhang et al;2003)**

The production of an appropriate number of spermatozoa is considered to depend critically on stimulation of the testes by the two pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). **(Sharpe,1994)** Numerous studies have reported that both FSH and T are required for quantitatively and qualitatively normal spermatogenesis in a variety of mammalian species and for the initiation of this process at puberty. The current contention is that FSH stimulates the early events in spermatogenesis, including spermatogonial proliferation and meiosis, but only T is able to sustain complete spermatid differentiation. **(Plant and Marshall,2001)**

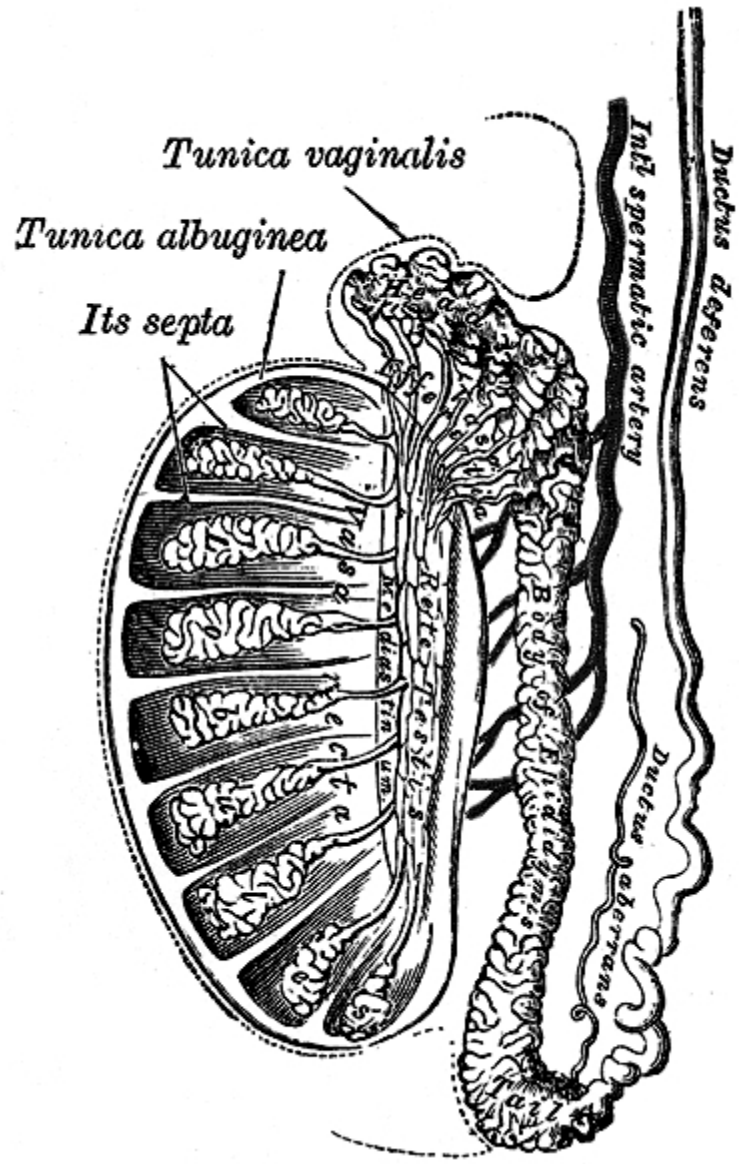
To understand better the hormonal regulation of spermatogenesis, it is essential to identify the specific effects of the hormones involved,so greater knowledge about measuring testosterone according to its level from its different sites of existance as testis,semen and blood and getting information upon comparison among their measures.may lead to know which level of testosterone in which site of existance that affects spermatogenesis mainly ,so it probably in the future will guide us to make a drug for patients suffering from sexo-reproductive disorders has effect with needed level of testosterone and is given with mode resembling the effective testosterone accoding to its level and its site of existance.

Testosterone anatomical and biophysiological view

Anatomical consideration:

Structure of the testis:

The testis is a firm, mobile organ lying within the scrotum.The left testis usually lies at a lower level than the right. Each testis is surrounded by a tough fibrous capsule, the tunica albuginea. Extending from the inner surface of the capsule is a series of fibrous septa that divide the interior of the organ into lobules. **(Fig. 1)** Lying within each lobule are one to three coiled seminiferous tubules. The tubules open into a network of channels called the rete testis. Small efferent ductules connect the rete testis to the upper end of the epididymis. **(Snell, 2012)** Seminiferous tubules contain epithelium consisting of sertoli cells that envelop and support germ cells undergoing progressive differentiation and development into mature spermatozoa. Once released into the lumen, mature spermatozoa are transported within seminiferous tubules, which measure up to 70 cm in length and are tightly coiled within lobules of the testis, to the rete testis, the efferent ducts, the epididymis, and, finally, the vas deferens for



(Fig. 1)

Vertical section of the testis, to show the arrangement of the ducts

ultimiate ejaculation. The seminiferous tubules are surrounded by a basal lamina composed of extracellular matrix that serves to separate them from the interstitial compartment, provides structural integrity to the tubules, and regulates the function of cells in contact with it. Histologic examination of a testis biopsy specimen in cross-section lobules . **(Fig. 2)** reveals many different seminiferous tubules surrounded by basal lamina and clusters of leydig cells in the interstitial compartment between each tubule. **(Matsumoto and Bremner, 2011).**

Spermatogenesis is the sequence of events in the seminiferous tubules of the testes that leads to the production of spermatozoa. The germ cells that migrate from the yolk sac to the testes during early embryonic development become stem cells, or spermatogonia, within the outer region of the seminiferous tubules. Spermatogonia are diploid (2*n*) cells (with 46 chromosomes) that give rise to mature haploid (1*n*) gametes by a process of reductive cell division called meiosis. Meiosis occurs within the testes of males who have gone through puberty and involves two nuclear divisions. During the first part of this process, the DNA duplicates (prophase I) and homologous chromosomes are separated (during