Testicular Dysfunction Biomarkers in Reproductive Biochemistry Research

Omowumi T Kayode1*, Damilare E Rotimi1, Afolayan Olubisola Arike2 and Abolanle A A Kayode3

1Department of Biochemistry, College of Pure and Applied Sciences, Landmark University, Omu Aran, Kwara State, Nigeria
2Department of Science Laboratory Technology, Federal Polytechnic Ilaro, Ilaro, Ogun State, Nigeria
3Department of Biochemistry, School of Basic Medical Sciences, Babcock University, Ilishan-Remo, Ogun, Nigeria

*Corresponding Author: Omowumi T Kayode, Department of Biochemistry, College of Pure and Applied Sciences, Landmark University, Omu Aran, Kwara State, Nigeria.

Received: June 16, 2020; Published: November 28, 2020

Abstract

Currently reproductive function of men is usually monitored by semen and hormones analysis, which are insensitive and highly variable indicators of testicular functions. Testicular protein, glycogen, sialic acid and cholesterol play an important role in spermatogenesis and fertilizing capacity of spermatozoa. Therefore, measuring these biomarkers provides insight into testicular response to occupational and environmental exposures. This study has developed a predictive tool to measure altered testicular functions following exposure to occupational and environmental exposure. It will allow the physicians to monitor the reproductive capacity of patients and help them to better counsels their patients about their fertility.

Keywords: Testicular Dysfunction Biomarkers; Hormones; Semen; Fertility

Introduction

Sperm is produce and released by male reproductive system, which fertilize ovum that ultimate result in offspring production. The reproductive system of male adult consists of two testes both of which are connected to epididymis that joined with penis through vas deference. In testes, germ cells are produced, that move to epididymis (caput to cauda) where maturation take place i.e. gain of motility [1]. Vas deference is next to epididymis, where seminal vesicles join with it at the site of ejaculatory ducts. From here the sperm travel to urethra for ejaculation [2]. Final stages of maturation (capacitation) occur in female reproductive tract, where the sperm is released as semen during sexual intercourse. In this stage sperm is now ready for fertilization. Prostatic fluid and seminal vesicle fluid protects the sperm during its journey from epididymis to female genital tract. These three are collectively known as semen [3].

In male reproductive tract, epididymis and testes are present in scrotum that lies outside the body. The role of scrotum is to provide feasible temperature for spermatogenesis and regulate the temperature i.e. 2 - 7°C cooler than rest of the body [4].

Hormones

Hormones are organic materials, produced in little quantity by particular tissues (glands). They are usually released into blood to control biological and metabolic functions of specific cells [5]. Hormones are also involved in transmission of information from one cell or tissues to another cell or tissues respectively and thus considered as a chemical messenger [6]. They carry out this specific function via diverse mechanisms and control processes like sexual function, reproduction, growth and development, metabolism and mood. Hormonal
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Concentration in each organ or target cell are estimated through studies which identifies endocrine disease syndromes due to hormone imbalance and to apply effective therapy [7]. The hormones studied includes Follicle Stimulating Hormones (FSH), Luteinizing Hormone (LH) and Testosterone.

For the evaluation of testicular damage, investigation of plasma hormone levels of testosterone, FSH, LH, inhibin and InsI3 is usually done [8]. However, due to its invasive nature (repeated blood sampling is required), and inability to detect the initial toxic effects (like effects of HD treatment on Sertoli cells) this is not generally done [4,9].

**Testosterone**

In male, testosterone is the main sex hormone and steroid in nature [10] belong to class androstane and containing hydroxyl and keto groups at position number seventeen and thirteen respectively. It is synthesized form cholesterol precursor and converted to inactive metabolites in liver. It acts after binding to an androgen receptor [11].

It plays a major part in the development of male reproductive organs like prostate and testis. It also promotes secondary sexual character of male like increased growth of body hair, bone and muscle mass [10]. Moreover, it is helpful for health and well-being and has a key role in osteoporosis prevention [12]. Decreased level of testosterone lead to frailty and bone loss.

Testosterone, in most of the vertebrates and especially in humans is produced mainly by testes in males whereas small amount is also produced in females by ovaries. Levels of testosterone in male are seven to eight times higher as compare to females [13] and also the daily production is also higher in males (20 times more) as compare to females [14]. However, females are more sensitive to this hormone [13].

Testosterone, in addition to its role in sex, it is also used in medication therapy i.e. in males to treat low testosterone level while in females it is used to treat breast cancer (BC). In men during their old age, level of testosterone is decreased, and to overcome this deficiency, testosterone is used. Athletes also use this to enhance their performance and physique [15].

Androgen like testosterone usually has anabolic effect on protein synthesis and thus participates in tissues growth that has androgen receptors [16].

Generally, testosterone is known for its anabolic and virilization effects (however, these reports are arbitrary to some extent, as there a mutual overlap exists between them) [17].

Androgenic affects leads to maturation of sex organs. In fetus, it result in the formation of scrotum and maturation of penis whereas after birth and especially during puberty it results in hair growth on different body parts like face (beard) axilla (underarm) and pubic area. It also causes deepening of voice. These are also known as male secondary characteristics.

Anabolic affects stimulate linear growth and mature the bones. It also increases bone strength and density and increased muscle mass.

Effects of testosterone can also be categorized by the age of natural occurrence. Duration and level of free testosterone in circulation usually affects females and males in postnatal life [18].

**Follicle-stimulating hormone (FSH)**

FSH like thyroprotein, is a glycoprotein and belongs to gonadotropin family. It regulates the activity of sex organs or gonads that may be an endocrine gland or a source of sperms and eggs [19]. In female mammals, FSH stimulates the development of graafian follicle (small vesicle having egg) in ovary. In males, it stimulate the growth of seminiferous tubules and helps in differentiation of sperm [19] and main-
tenance of spermatogenesis. It is produced by gonadotrophic cells in pituitary gland [20].

Follicle-stimulating hormone (FSH) is produced in the pituitary gland by the go FSH also enhances the synthesis of Sertoli cells which increases sperm cell maturation. Decrease in this hormonal secretion leads to malfunctioning of the gonad (hypogonadism) and it eventually results in reduced production of sperm [21].

**Luteinizing hormone (Interstitial-cell-stimulating hormone)**

Luteinizing hormone (LH) is also known as interstitial cell stimulating hormone (ICSH) is another gonadotropin. It is glycoprotein in nature, having a molecular weight of 26,000 in humans [25]. It is produced by anterior pituitary gland and like FSH it is important for male reproductive functions. Decreased or increased level of LH show impaired testicular function or hypothalamic/pituitary function [23]. LH activates leydig cells of testis to produce testosterone. The level of LH is regulated by stimulation and inhibition by GnRH and testosterone (T) at the hypothalamic-pituitary-gonadal axis. Thus, when testosterone levels are low, the hypothalamus is stimulated to increase production of GnRH. This increase in GnRH in turn stimulates LH production. Thus, high LH levels can be an indicator of low testosterone [24].

In female’s mammals, it supports transformation of graafian follicle to corpus luteum (an endocrine gland) after ovulation (release of egg) [25].

Decreased secretion of FSH and LH leads to gonadal dysfunction (hypogonadism). In male it is manifested as low number of sperm [22]. Both LH and FSH are glycoprotein in nature, and their interrelationship makes them difficult to establish their presence as two separate hormones [25].

In mammals this is well established fact but in lower vertebrates this is not clear yet. Although all vertebrates have gonadotrophic activity in their pituitary glands, and LH and FSH like effects are also present but presences of two separate hormones is yet not clear [24]. An unexpected property of mammalian FSH and LH is that both have a thyrotropic action (i.e. stimulate secretion of thyroid hormones) in lower vertebrates. This effect (heterothyrotropic) has led to an assumption that thyrotropin, LH and FSH have a common ancestor (glycoprotein) that result in characteristics overlaps [26].

**Sperm analysis**

The assessment of human testicular function and male gamete quality currently relies on hormone measurements and semen parameters (sperm counts, motility and morphology). Semen analyses are highly variable both within and between individuals, which demonstrates their lack of sensitivity. Meanwhile, hormone measurements are generally unreliable at detecting mild testicular injury, so that only severe, potentially irreversible, injuries can be detected. A more sensitive approach is needed that allows for translation of findings in preclinical species to humans, and for monitoring of occupationally and environmentally induced testicular dysfunction at an early, reversible stage of injury.

**Testicular function indices**

Testicular function indices are used to evaluate the functional capability of the testes (Sharpe, 1984). The testicular function indices studied includes protein, glycogen, sialic acid and cholesterol.
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Testicular proteins

Proteins are the most abundant substances in nearly all cells. Testicular proteins are one of the constituents that are required for spermatogenesis and maturation of spermatozoa. Previous studies have indicated that increased protein concentration enhance sperm maturation in the testis thereby increasing testicular function indices [27].

Testicular glycogen

Glycogen is the main storage polysaccharide in animal and human cells. Glycogen is produced predominantly by the liver and muscles and can also be made through glycogenesis in the brain and stomach. It is a readily mobilized fuel store and provides energy if blood glucose level reduces. In the testis, the glycogen reserve is the sertoli cells and spermatogonia, providing carbohydrate and energy during the development of the male gonad and for seminiferous tubular cells [28]. Increased testicular glycogen enhances energy release which is important for spermatogenesis.

Testicular sialic acid

Sialic acid can be found in different tissues and fluids of the body including the testis, kidney, brain, serum, saliva, urine and breast milk. Sialic acid perform the function of a lubricant which aid the motility of the sperm and reduces friction among sperm cell and in a process facilitate their upward movement within the lumen of the testes as well as during their transfer through the epididymis and the vagina. Increase in testicular sialic acid positively affect the structural integrity of acrosomal membrane which ultimately may affect the metabolism, motility and fertilizing capacity of spermatozoa.

Testicular cholesterol

Cholesterol serves as precursor to steroid hormone especially those involved in steroidogenesis which is required for increased testicular function. Androgen(testosterone), an example of steroid hormones stimulates the growth of secondary sexual characteristics. Increased cholesterol level is credited to increase in androgen concentration, resulting in stimulation spermatogenesis. Cholesterol is normally produced by the prostate and deposited into the seminal plasma. One of the functions of cholesterol to the testis is to protect the sperm cell against environmental shock.

Conclusion and Future Directions

The ultimate goal of this project is to develop a predictive tool that will improve the detection of altered testicular function following exposure to a range of chemicals that include environmental contaminants and pharmaceutical compounds. We can leverage our current rat model to further develop and refine the biomarker panel by screening germ and Sertoli cell-specific toxicants.

Clinically, the biomarker panel will be used in screening human samples to uncover potential testicular dysfunction. Currently, over 450 semen samples from men presenting to the Division of Urology at Rhode Island Hospital have had traditional semen analyses performed, and the samples have been further processed for RNA and DNA. A subset of ~250 of these men have answered a detailed questionnaire regarding their lifestyle habits (i.e. smoking status, alcohol intake and body mass index) and pharmaceutical drug prescriptions and have a range of exposures and semen parameters typical for a young male population.

The sensitivity of our panel will be tested to see if it can identify alterations in the molecular biomarkers that are associated with these lifestyle and exposure scenarios. Of particular interest are men diagnosed with either lymphoma or leukemia who will undergo treatment with cytotoxic chemotherapeutic agents. There is evidence suggesting that chemotherapeutics can induce epigenetic changes in rodent sperm that have the potential for transgenerational impact, warranting further investigation in human populations.

Bibliography


Volume 9 Issue 12 December 2020
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