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Review Article

Testicular Dysfunction Biomarkers in Reproductive Biochemistry Research

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Abstract

Biomarkers in biological research are key molecules that give important information about the state of an organ, tissue, or cell of interest. They are useful tools for predicting the state of health or otherwise of the subject as well as determining the rate of associated metabolic event deterioration or appreciation within the context of defined research. Several biomarkers exist in the form of proteins, enzymes, and other metabolites for in vivo research. Currently, the reproductive function of men is usually monitored by semen and hormones analysis, which are insufficient predictors of reproductive disorders because of wide variableness and sometimes false positive/negative results. It is therefore imperative to recommend further indicators and biomarkers of testicular functions for

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Introduction

The testis is a major part of the male reproductive system which coordinates the synthesis and release of sperm cells which is able to fertile the female ovum and form a new offspring [1, 2]. The male reproductive system consists of two testicles connected to the epididymis that joined the penis through the vas deferens. In the testes, germ cells are produced and moved to the epididymis (caput to cauda) where maturation takes place i.e. gain of motility [3, 4]. Vas deferens is next to the epididymis, where it joins with the seminal vesicles at the site of ejaculatory ducts. From here the sperm travel to the urethra for ejaculation [5]. The final stages of maturation (capacitation) occur in the 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 the epididymis to the female genital tract. These three are collectively known as semen [6]. In the male reproductive tract, epididymis and testis are present in the scrotum located outside the body. The role of the scrotum is to provide feasible temperature for spermatogenesis and regulate the temperature i.e. 2-70 C cooler than the rest of the body [7].

Male Sexual Dysfunction Biomarkers

Hormones

H Hormones are organic materials, produced in little quantity by particular tissues (glands). They are usually released into the blood to control the biological and metabolic functions of specific cells. Hormones are also involved in the transmission of information from one cell or tissues to another cell or tissues respectively and thus considered as a chemical messenger [8]. They carry out this specific function via diverse mechanisms and control processes like sexual function, reproduction, growth, and development, metabolism, and mood. Hormonal concentration in each organ or target cell is estimated through studies that identify endocrine disease syndromes due to hormone imbalance and to apply effective therapy [9]. The hormones studied include 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. 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 [10].

Testosterone

In the male, testosterone is the main sex hormone and steroid in nature [11] belong to class androstane and containing hydroxyl and keto groups at position number seventeen and thirteen respectively. It is synthesized from cholesterol precursor and converted to inactive metabolites in the liver. It acts after binding to an androgen receptor [12].

It plays a major part in the development of male reproductive organs like the prostate and testis. It also promotes the secondary male sexual characteristics like increased growth of body hair, bone, and muscle mass. Moreover, it is helpful for health and well-being and has a key role in the prevention of osteoporosis. Decreased level of testosterone leads to frailty and bone loss [13].

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

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, the level of testosterone is decreased, and to overcome this deficiency, testosterone is used. Athletes also use this to enhance their performance and physique [15, 16].

Androgen like testosterone usually has an anabolic effect on protein synthesis and thus participates in tissue growth that has androgen receptors [17].

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

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

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

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

Follicle-stimulating hormone (FSH)

FFSH like thyroprotein is a glycoprotein and belongs to the 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 the Graafian follicle (small vesicle having egg) in the ovary. In males, it stimulates the growth of seminiferous tubules and helps in the differentiation of sperm [19] and maintenance of spermatogenesis. It is produced by gonadotrophic cells in the pituitary gland [20].

Follicle-stimulating hormone (FSH) is produced in the pituitary gland by the gonadotropic cells. FSH also enhances the synthesis of Sertoli cells which increases sperm cell maturation. A 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) also known as interstitial cell-stimulating hormone (ICSH) is another gonadotropin. It is a glycoprotein in nature, having a molecular weight of 26,000 in humans [22]. It is produced by the anterior pituitary gland and like FSH, it is important for male reproductive functions. Decreased levels of LH show impaired testicular function or hypothalamic/pituitary function [23]. LH activates Leydig cells of the 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 the production of GnRH. This increase in GnRH in turn stimulates LH production. Thus, high LH levels can be an indicator of low testosterone [22].

In female mammals, it supports the transformation of the Graafian follicle to corpus luteum (an endocrine gland) after ovulation (release of the egg) [24]. Decreased secretion of FSH and LH leads to gonadal dysfunction (hypogonadism). In the male, it is manifested as a low number of sperm. Both LH and FSH are glycoprotein in nature, and their interrelationship makes it difficult to establish their presence as two separate hormones [25].

In mammals, this is a 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. 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 results 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 [27].

Recommended Testicular Function Biomarkers

Testicular function indices are used to evaluate the functional capability of the testes [4]. The testicular function indices proposed for male sexual function assessment in addition to sperm analysis and hormonal status includes protein, glycogen, sialic acid, and cholesterol.

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 enhances sperm maturation in the testis thereby improving testicular function [28].

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 the 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 [29]. 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 performs 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. An increase in testicular sialic acid positively affects the structural integrity of the acrosomal membrane which ultimately may affect the metabolism, motility, and fertilizing capacity of spermatozoa [20].

Testicular cholesterol

Cholesterol serves as a 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 an increase in androgen concentration, resulting in the stimulation of 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 [11].

Conclusion and Future Directions

The ultimate goal of this review 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 current successes with the rat model to further develop and refine the biomarker panel for human diagnosis by physicians and thus help improve human reproductive function.

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