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Factors Associated With Oxidative Stress in the Testes and the Mitigating Role of Antioxidants: A Review

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Abstract: Present day's reports have increased on relation to infertility of males associated with decreasing semen quality by the oxidative stress causing factors. Numerous external and internal factors were responsible for the ROS (reactive oxygen species) production, excessive ROS further effects on cellular antioxidant capacity in consequence leads to oxidative tension. The exogenous factors like, high testicular temperature, diabetes, Present life style and food habits, Declined testicular antioxidants, exposure of toxicants, exposure of radiation (X-ray) responsible for the imbalance production of hormones and antioxidants. However, under normal condition, the body has the ability to synthesize antioxidant defense enzymes for prohibiting the undesirable oxidative stress effects. But chronic exposure to environmental toxicants (endocrine disrupters, pesticides, xenobiotics) ionizing radiation and heat stress the body's antioxidants cannot stabilize the free radicals for prevention of deleterious oxidative stress in the testis. The impaired antioxidant system is associated with declining levels of antioxidant enzymes, increased levels of stress markers and probably affects the hormonal mechanism. This leads to abnormal sperm production and testicular morphological changes occur, finally leading to infertility in males. Exogenous antioxidant therapy (zinc, selenium, vitamins, and plant related compounds) can chelate the oxidative stress reaction and play an important role in improving the body's ability to fight against free radicals induced oxidative stress factors, and therefore betterment in the course of spermatogenesis.
Keywords: External factors, ROS, oxidative stress, antioxidant therapy, spermatogenesis.

Introduction

Testes are the chief reproductive organs in the males; they perform the two functions; spermatogenesis and steriodogenesis. Spermatogenesis occurs in the germinal epithelium of the seminiferous tubules and steriodogenesis is done by interstitial cells (Leydig cells), which are controlled by gonadotropins [1]. Spermatogenesis is an active replication process in which immature germ cells undergo division and produce 1000 primary spermatocytes per second. Primary spermatocytes differentiate into secondary spermatocytes, these undergo meiotic division produce haploid elongated spermatids [2].

The process of spermatogenesis in testis is regulated by a negative feedback loop of the hypothalamus and pituitary hormones. Imbalance of hormone homeostasis (gonadotropins and testosterone) is responsible for impaired sperm production in males and it leads to decrease of sperm count, sperm motility and morphology of spermatozoa [3].

Aberrant sperm production causes infertility, they by will not to be able to conceive the female partner. Oxidative stress is the major factor for the infertility, generation of oxidative tension in the testes.Several factors like; exposure to endocrine disruptors, physiological stress, temperature or pH imbalance and present life style are also major reasons for infertility in males [4, 5].

However the testes have a rich group of antioxidant enzymes and they scavenge the free radicals during oxidative stress condition to ensure that the twin spermatogenic and steroidogenic functions are not impacted. But prolonged, stress conditions the antioxidant enzyme levels decline leading to the impaired defense system, then predominantly internal testicular environment homeostasis gets disrupted causing abnormal sperm production by the testes [2].

Oxidative stress and factors associated with testicular oxidative stress

In the last 5 decades several studies have reported about the quality of semen and its impact on the fertility of males. They also discussed the impact of various environmental conditions and lifestyle factors on the male reproductive capacity [6]. Due to the result of various metabolic activities in the body, different reactive oxygen species (Superoxide radicals, Hydrogen peroxide and hydroxyl radicals) are released as by-products [7]. In general procedure the biological system has the capacity to nullify the impact of Reactive oxygen species in the body. The phenomenon of oxidative stress at cell and tissues level is raised due to the loss balance between the production and accumulation [7]. Western life style (alcohol consumption, cigarettes, smoking, tobacco chewing or drug addiction and fast food habits), exposure to escalating levels of pollutants, xenobiotics, technological advancements and physical stress are among the major exogenous factors causing of reactive oxygen species (ROS) production [8, 4].However, endogenous factors; various mechanisms participating cell membrane metabolization, endoplasmic reticulum, mitochondria and peroxisomes cell organelles also can produce endogenous ROS [9].

Factors causes' oxidative stress

Declined testicular antioxidants

The endogenous antioxidant system plays a prominent function in protection against the oxidative pressure in testicles, because the testes contained rich source of antioxidant enzymes. They are Glutathione S-transferases (GSTs), Catalases, Superoxide dismutases (SOD), Glutathione peroxidase (GPx) and Glutathione reductase (GR). These enzymes maintain the constant environment for proper spermatogenesis in seminiferous tubules as well as androgenic hormone production by interstitial cells [10]. Several reports have reported on the antioxidant enzyme status in testicular tissue, declined antioxidant levels associated with a decline of sperm parameters(count, motility &viability) and morphological changes in animals and humans also [2,4,10, 11].

Imbalance of reproductive hormones

Reproductive hormones are essential for the proper synthesis of semen and sperms in testes and associated glands. Generally two major gonadotropic hormones (FSH-Follicle stimulating Hormone & LH-Luteinizing Hormone) which are glycoprotein in nature and are responsible for the growth and development of the testicles, tubules and maturation of spermatozoa [12]. LH plays a prominent role in production androgenic hormone (testosterone) via stimulation of Leydig cells in between the seminiferous tubules [13].

Decreased levels of steroidogenic hormone and glycoprotein gonadotropins are associated with declined production, sperm quality and quantity [12]. Insufficient hormones are associated with abnormal function of the reproductive organs by the generation of free radicals. These free radicals impair the internal homeostasis condition and thus lead to oxidative stress [4]. Previously, several researchers reported that declined hormones are associated with reduction in antioxidant enzyme levels [2, 4, 10].

Current life, fashion and food habits

Modern life style and food habits are the major factors for oxidative stress in the testis [14]. Present days people are competing with work pressure, late night sleep, most of the time spent in mechanize instruments (mobiles, lab tabs, computers) are responsible for disturbing the biological cycle (circadian).Most of the people are taking too much high fat - high protein contained food in their daily activities. There is a contrary link among the dietary food intake and the incidence of oxidative

stress [15]. Men who consume the fast foods (high dietary fat content) like fried meat (processed meat), pizza, burger, fried rice (Gobi, egg, chicken), red meat, carbonated drinks and diet with high percentage of sweet are some of the factors responsible for declined sperm production, abnormality in sperm morphology and also sperm count. However, men who are consume antioxidant rich food showed normal sperm parameters [16-17, 4]. Intake of over fat and proteins diets stimulates the high quantity of reactive oxygen species, following oxidative pressure that impairs the mitochondrial metabolism and declines antioxidants. This might have negatively effects on the quality and quantity of semen via alteration of hormonal levels [4].

High testicular temperature

In males, testes are present outside the body in a scrotum pouch to facilitate the temperature (2 to 4^{o}C) which should be lower than body temperature [18]. Scrotum always keeps testicular heat at optimum level (below to body temperature) which helps for proper spermatogenesis process [19]. Various factors that are causing abnormal increased testicular temperature are associated with heat stress in testis. Several reports have documented that factors associated with heat stress in testicles, such as sleeping posture, peoples working in the steam rooms, using electronic gadgets on the lap, heavy metal exposure, long time driving and long time sitting leads to increase in the scrotal temperature than usual and eventually spermatogenesis [4]. Cryptorchidism, varicocele, and acute febrile illness, clinical disorders associated with increasing heat stress in testicles and suppress spermatogenesis. Heat stress may enhance the production of reactive oxygen species and decline the activity of antioxidant enzymes, promote the lipid peroxidation levels and H_2O_2 content in disrupting mitochondrial homeostasis [2, 4, 10, 11].

Toxins affect

Present days, most of the people used heavy metal coating products, pesticides, inorganic fertilizers, cosmetics, shampoos, galvanized pipes in their daily life. Most of these products are associated with endocrine disruption chemicals, over exposure of endocrine disruptors associated with infertility by impaired functions of reproductive organs [5]. Numerous studies have documented on experimental animals, rats treatment with lead (Pb), cadmium, arsenic found abnormal sperm morphology, sperm parameters (count, motility, viability) and decreased levels of steroid marker enzymes hydroxyl steroid dehydrogenase activities (3β HSD, 17βHSD), androgenic hormone (testosterone), and gonadotropic hormones (FSH, LH). Exposure of these metals associated with reduced levels of antioxidants and elevated levels of lipid peroxidation [20-23]. Exposure to Bisphenol and mercury also causes the impaired reproductive functions in rats. Over exposure to pesticides, xenobiotics and fertilizers effects on sperm physiology, morphology in male rats and structural modifications in Leydig cells, seminiferous tubules, spermatozoa [2, 4, 10]. In the modern lifestyle most of the youth are fascinated and addicted to cigarette smoking.. Nicotine consumption (smoking, chewing, snorting and orally) reported as neurological and endocrine toxicants by several reports. Experimental works on animal model (rat) also revealed reproductive related toxic findings. Cigarette smoke causes the over free radical generation by the elevated content of lipid peroxidation (LPO) content in the testicular tissue. The excessive LPO content in the testis is responsible for the production of oxidative pressure and effect on the spermatogenesis and semen parameters by declining of antioxidant defense mechanism. Therefore, tobacco related products interrupt normal male reproductive hormonal balance through their disturbing influence ahead of the endocrine and reproductive organs and also inquisitive in the crosstalk with various endocrine alignments. [2, 4, 24].

Diabetes

Diabetes is a metabolic disorder that occurs due to insulin imbalance production. Some of the physiological or developmental factor effect pancreatic beta cells and cause hormonal imbalance probably diabetes [25].Diabetes is a metabolic disorder associated with multiple organ function effects, elevated levels of glucose, free fatty acid sources for the accumulation of excessive lipid profile levels in testicular tissue, this excessive lipid content in those particular organs causes the

inhibition of spermatogenesis by generation of reactive oxygen species and oxidative stress causes DNA breakdown [26, 10].

Extra lipid content triggers the androgenic hormone levels through suppress in of LH- Leydig cell correlation pathway in testis [27]. Declined testosterone levels are associated with impaired sperm production and increase in fetal mortality. Experimentally diabetes induction in animal model studies report impaired testicular function and decreased male fertility. Streptozotocin (STZ) injected rats showed that hyperglycemia condition, enhances free radical generation and leads to ROS, oxidative stress and induce both lipid peroxidation and protein carbonyl expression in the testes [28, 10]. These adverse effects successfully repaired by supplementation of certain exogenous antioxidants such as zinc, vitamin-C, vitamin-E, selenium, melatonin, taurine and curcumin [29-32, 2, 4, 10]. Men suffering with diabetes have abnormal sperm morphology and increased levels of DNA damaged in spermatozoa when compared to normal men [10].

Testicular torsion, hyperthyroidism, vericoele, infection, exposure to ionizing radiation, physiological stress, infection of diseases and ageing are also exogenous factors associated with generation of oxidative stress in the testis [2, 4,10].

Antioxidant therapy repairs oxidative stress in the testes.

Antioxidants (endogenous & exogenous) play a prominent role in reducing oxidative stress in diseased conditions. Most of the trace elements and plant based foods used exogenous antioxidants for cure for any of the stress condition [33]. Biological trace elements such as zinc, selenium; vitamins; vitamin C, retinol, vitamin E and other compounds melatonin, cytochrome C, curcumin are used to reduce of free radicals by toxic substance generated oxidative stress. Most of these exogenous antioxidant therapies improve the hormonal levels and sperm production in experimental animals as well as humans. Primarily these compounds enhance the endogenous antioxidants such as SOD, CAT, GPX and GR levels in the seminal fluid in the testis, elevated levels of antioxidants consume overproduction lipid peroxidation [20, 34-40].SOD with a comparably higher amount than other antioxidant enzymes leads to conversion of superoxide (NO_2) anion into O_2 and H_2O_2. Furthermore, this enzyme protects the spermatozoa against O_2 toxicity and lipid membrane against peroxidation [10].

Catalase decomposes H_2O_2 into O_2 and H_2O. This enzyme also separates the superoxide anion produced by NADPH oxidase from neutrophils and protects spermatozoids against oxidative damage. In addition to containing enzymatic antioxidants, semen has a number of non-enzymatic antioxidants such as vitamins E and A, ascorbate, pyruvate, ubiquinole, glutathione, albumin, ureate, taurine, and hypotaurine, each of which play a vital part in fighting oxidative stress SOD with a comparably higher amount than other antioxidant enzymes leading to conversion of superoxide (NO_2) anion into O_2 and H_2O_2 [41]. Furthermore, this enzyme protects the spermatozoa against O_2 toxicity and lipid membrane against peroxidation. Catalase decomposes H_2O_2 into O_2 and H_2O. This enzyme also separates the superoxide anion produced by NADPH oxidase from neutrophils and protects spermatozoids against oxidative damage [42]. In addition to containing enzymatic antioxidants, semen has a number of non-enzymatic antioxidants such as vitamins E and A, ascorbate, pyruvate, ubiquinole, glutathione, albumin, ureate, taurine, and hypotaurine, each of which plays a vital part in fighting oxidative stress [2, 4, & 10]. In the light of such results it reveals that frequent supplementation of antioxidants improves the quality and quantity of cement profile in males.

Conclusion

In this review, we describe the factors (external and a few internal) are responsible for the ROS production in reproductive organs relative to abnormal spermatogenesis. Free radicals' life-threatening attacks to the body's different organs can cause arterial occlusion and induction of oxidative stress and subsequently causing serious damage to tissues. High production of oxidative

tension markers in the testis leads to necrosis or disturb the normal regulatory mechanisms (high cell division, cell contest for oxygen rate, and low oxygen pressure). These conditions lead to destabilized vessels in the testis and excessive production of cholesterol and fatty acids. So, an adverse effect of oxidative stress causes inability to neutralize the antioxidant system, this leads to infertility in males as well as females. Antioxidant supplementation is recommended to fight against oxidative stress, enhance of spermatogenesis and enhance fertility rate.

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