



METALS: MALE REPRODUCTIVE FUNCTION

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ABSTRACT

Reproductive hazards from metal exposure in males are one of the fastest growing areas of concern in toxicology today. Exposure to different heavy metals causes irreversible toxic insult to male reproductive system. Heavy metals produce cellular impairments at structural and functional level in male reproductive system. The effect of metals, such as lead, mercury, cadmium, chromium and arsenic on male reproduction has been studied in details in various experimental species. But data on humans are steadily building up and where metals, interfere with the gametogenic cells or Leydig cell or spermatozoa directly in semen. These effects may result in reduced fertility or associated with pregnancy wastage, congenital malformation associated with genetic diseases. Moreover, the features of heat stress protein (HSP), androgen-binding protein (ABP), Cadherin and many other stressor proteins along with reactive oxygen species (ROS) and neuro-endocrine mechanism are highly affected by these metals exposure. Still the data is inadequate and need confirmation.

Keywords: Metals, Reproduction, Testis, Sperm, Semen.

INTRODUCTION

Human fertility is complex, it depends upon synergy of male and female reproductive competence in which physiological, genetic, behavioral and environmental factors interact. The myriad of interacting factors has limited our understanding of the mechanisms of conception and fertility, and the problem is compounded by the diversity of reproductive physiology among mammals, which limits extrapolation from animal models. Historical interest and research in human fertility have been motivated by several goals, including diagnosis and treatment of infertility, improvements in contraceptive technology and, more recently, concerns of environmental and occupational exposure¹.

The rapid industrialization and overgrowing urbanization, the toxic effects of heavy metals on male reproduction system have become a major health concern in the globe^{2, 3}. The evidence of the past twenty years have shown disturbing trend in male reproductive health hazards due to careless use of these chemicals which caused detrimental effects on different organs. Therefore, broad-spectrum irreversible toxic actions at cellular and molecular level were observed mainly on reproductive system of human and experimental animals^{4, 5}.

The humans are exposed to various types of environmental contaminants at different stages of their life span, majority of them are harmful. In recent years, there has been growing concern about the deleterious effects of chemical on developing male reproductive system. Exposure of heavy metals during pregnancy has been associated with adverse effects on development of gonads. These substances may act as testicular toxicants and correspond to different compounds, which are

related to social habits, life conditions, working hazards or use of drugs and medicines⁶⁻⁸. Although, many studies have reported the toxic and carcinogenic effects of metals in human and animals, it is also well known that these metals form a crucial part in normal biological functioning of cells. Many heavy metals are classical testicular toxicants, though the mechanism of their action may differ.

SEMINAL-BASED BIOMARKERS

From a systematic perspective, there are three primary foci in the study of male reproduction.

- (i) The pituitary gland and the gonadotropic hormone secretions that signal spermatogenesis.
- (ii) The male reproductive tract which creates and supports the maturation of spermatozoa.
- (iii) The quantity and quality of spermatozoa themselves. So far, most of the studies on male fertility have focused mainly on parameters such as seminal quality and fecundity (time to pregnancy, TTP), very occasionally on hormonal effects and pregnancy outcome. Similarly, biomonitoring on the health effect of environmental and occupational exposure also tended to concentrate on seminal quality and fecundability. Investigations have rarely been conducted on the more long term endpoints such as hormonal changes or birth outcomes.

It is undeniable that good quality semen is essential for reproductive success. This quality appears to have been directly affected in recent years, and evidently there are now unfavorable trends in male reproductive health⁹. Since the 1970s various authors have reaffirmed the possible significant drop in sperm quality and consequently an increase in male infertility rates^{10, 11}. The



actual causes of increased infertility remain controversial^{11, 12} but research suggests that many substances to which men are exposed can affect their fertility may be work-related^{13, 14}.

SEMEN ANALYSIS

A normal semen sample should have a volume of 1.5-5.0 ml, with greater than 20 million sperm/ml. The number of abnormal sperm should be less than 40 percent, with greater than 30 percent of the sperm sample demonstrating proper motility. Unfortunately, conventional semen analysis is not a highly accurate predictor of fertility. Purvis et al reported, after surveying infertility clinics, that 52 percent of men with a sperm count below 20 million/ml were able to impregnate their partners and 40 percent of men with a sperm count below 10 million/ml were also able to conceive¹⁵. Conventional semen analysis often fails to identify infertile males with normal samples and conversely fails to identify fertile males with subnormal semen parameters¹⁶. Another confounding factor is variations in sperm density, motility, and morphology among multiple samples from the same subject.

Metals have the capacity to interfere in the functioning of the endocrine system, in the hormones' mechanism of action, and are called endocrine deregulators or endocrine disruptors¹⁷⁻¹⁹. Alterations caused by endocrine disruptors can be temporary or permanent^{18,20,21}. Endocrine disruptors can cause the following, reproductive anomalies (morphological and functional gonadal dysfunction, e.g., infertility and decreased libido) and congenital malformations (altered embryonic and fetal intrauterine development)^{18,22,23,24}. The principal effects of exposure to endocrine disruptors on male fertility are temporal reduction in sperm concentration and quality⁹, high incidence of cryptorchidism and hypospadias²⁵, and altered sex ratio^{26, 27}.

TESTIS

Testis is the major organ for male sexual development and fertility^{28, 29}. It secretes hormones to promote male-specific traits, produces sperm for reproduction. The key structural components in testes are seminiferous tubules, which provide physical barriers and nutrient supplies for the survival and maturation of sperm. Seminiferous tubules are formed from epithelial cells like Sertoli cells, along with associated myofibroblast-like peritubular myoid (PM) cells at the periphery. During testis development, Sertoli cells and PM cells secrete specific extracellular matrix proteins and assemble a layer of basement membrane (BM)³⁰, to separate particularly the seminiferous tubules from the interstitial space, where Leydig cells, endothelial cells and other unidentified mesenchymal cells reside.

The major gonads, testis or testicles, begin their development high in the abdominal cavity, near the kidney. During development testis got short after birth, they descend through into the scrotum, a pouch that

extends below the abdomen, posterior to the penis. Each testis is an oval structure about 5cm long and 3cm in diameter which outer surrounds by tunica albuginea. There are about 250 lobules in each testis. Each lobule contains 1 to 4 highly coiled seminiferous tubules. Toxicity is manifested in male reproductive system by deposition of lead in testes, epididymis, vas deferens and seminal vesicle. Lead has an adverse effect on sperm count and retarded the activity of live sperm reported by Chowdhury³¹. The potential toxicity of Metals, i.e., lead, cadmium, chromium, selenium and arsenic, caused alteration in sperm morphology, count, motility as well as biochemical disruptions of enzymes and hormones.

ADVERSE EFFECT OF METALS ON MALE REPRODUCTION

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Lead

Lead became popular because of its dense, ductile, malleable and corrosion resistant properties³². Lead is a ubiquitous environmental and industrial pollutant that has been detected in every facet of environmental and biological systems. Lead is a heavy soft metal, occurs in nature as an oxide or salts. Lead can be found in water pipes, insecticides, lining of equipment where corrosion resistance and pliability are required, in petroleum refining, in construction, bullets of gun, x-ray and atomic radiation protection and is a major industrial by product. Lead appears in homes in many forms as lead piping, lead-containing solders, paints, ceramic glazes, base metal utensils and fixtures. Also, cream powder, lipstick and hair colour have lead. Agricultural soil contamination may be responsible for lead found in many herbal medicines and cigarettes. On the contrary, their detrimental effects on physiological, biochemical, and behavioural dysfunctions have been documented in animals and humans by several investigators^{33, 34}.

Al-Omar, *et al.*,³⁵ reported that lead causes decrease in seminiferous tubules diameter in adult rats. Corpas, *et al.*,³⁶ showed that lead acetate causes decrease in the diameter and epithelial thickness of rat seminiferous tubules. Low activity of ATPase and AMPase at the basement membrane of seminiferous tubules was observed in rats exposed to lead at dose of 6mg/kg i.p over a period of 90 days reported by Chowdhury, *et al.*,³⁷.

The effects of lead on adult rat testis have been widely studied and observations demonstrate that Pb in particular alters those organs, as evidenced by testicular atrophy in rodents³⁸, reported that lead ingested by experimental pups, caused decrease in mean testis weight on postnatal days 21. Dorostghoal³⁹ study was designed to determine short- and long-term developmental effects of maternal exposure to different doses of lead acetate during lactation on testicular structure in offspring wistar rats. They that testicular



parameters decrease in offspring wistar rats following maternal exposures of lead acetate at doses above 100 mg/kg/day. These dose-related changes suggest that the effects of maternal lead exposure are expressed in offspring. Corpas, *et al.*,⁴⁰ was found that lead could disturb mitosis of spermatogenic cells and cause alterations in the proliferation of Sertoli cells, therefore an important decrease in the testis sperm count within testes of adult offspring, and subsequently reduction of epididymal sperm count.

Cadmium

Cadmium released from tannery, smelter, battery crushing unit. The action of cadmium is spermatogenic stage specific. High dose of cadmium chloride exposure caused rapid testicular edema, haemorrhage and necrosis. Cadmium exerted deleterious effect on the vascular structure of testis that may be the result of varying degrees of cadmium induced ischemia. Degeneration of testicular tissue after different doses of cadmium exposure caused rupture of blood vessels⁴¹. Cadmium can directly injure the testes. A testicular toxin and various derived compounds were shown to induce severe damage to the spermatogenic epithelium in an animal model⁴². The effect of cadmium on the testes appears to be manifested mainly in the sertoli cells, which present more morphological changes under scanning electron microscopy. Cadmium can also interfere with the normal functions of mitochondrial enzymes⁴³. Testicular lesion from cadmium is primarily vascular, and the vascular damage determines the degree of lesion in the germ cells and leydig cells. This lesion can generate leydig cell tumors, tubular degeneration (in highdose exposure), and atrophy⁴⁴; in addition to inducing tissue necrosis and deficient androgen production^{44, 45}.

In a study by the World Health Organization (WHO) on the effects of lead and cadmium in the blood of adult men, the overall results indicate that even low-level exposure to lead (400µg/l) and cadmium (10µg/l) can significantly reduce the quality of semen, although the study did not show conclusive evidence of male endocrine reproductive alterations^{46, 47}.

Mercury

Mercury is widely used in refinery, plastic and paints, antiseptic, scientific instruments, photography, fuel combustion and agriculture field. This metal is spermatogenic and fetotoxic agent. Mercury chloride exhibited structural alteration of testicular tissue along with biochemical change. Mercury can interfere in spermatogenesis and also affects the epididymis. It can also cause Young syndrome, associated with obstructive lesion of the upper epididymis⁴⁸. The prominent feature of Mercury induced toxicity are : (1) depletion and clogging of different spermatogenic cells, (2) presence of pyknotic or karyotectic pachytene nuclei, (3) absence of nuclear chromatin at stage XII in dividing cells, (4) absence of noticeable lumen and (5) presence of vacuolated early elongated spermatid along with

dispositioning of acrosome. The intensity of damage is directly proportional to the duration of exposure⁴⁹.

Arsenic

Arsenicals are widespread in the environment as a result of natural and anthropogenic occurrence. Ingestion of contaminated drinking water is the major routes for human exposure to arsenic². Arsenic exposure causes both acute and chronic toxicity in human. Human arsenic exposure is related to severe health problems such as skin cancer, diabetes, liver, kidney and CNS disorders³. It also causes many other toxic effects^{4, 5}. Male reproductive effect of arsenic was first studied in mice, then in fishes⁵⁰. Arsenic exposure in experimental rats has shown to produce steroidogenic dysfunction leading to impairment of spermatogenesis⁵¹. Sarkar *et al.*,⁵² revealed that arsenic effects mainly the processes of meiosis and post-meiotic stages of spermatogenesis and acute exposure to arsenic causes rapid and extensive disruption of spermatogenesis in mice⁵². Few recent investigations have shown that arsenic in drinking water is associated with oxidative stress⁵⁰, genotoxicity in testicular tissue of mice⁴¹. On the other hand recent study suggests that arsenic causes testicular toxicity probably by affecting the pituitary testicular axis⁵³.

Increased distribution of metals and metal compounds in the environment, especially through anthropogenic activities, raises increasing concern for ecotoxicological effects. The precise chemical basis of metal toxicology is inadequately understood but a uniform mechanism for all toxic metals is implausible because of the great variation in chemical properties and toxic endpoints. Chemically, metals in their ionic form can be very reactive and can interact with biological systems in a large variety of ways. In this regard, a cell presents numerous potential metal-binding ligands. Such adventitious binding is an important chemical mechanism by which exogenous metals exert toxic effects that can result in steric re-arrangement that impairs the function of biomolecules^{54, 55}.

Metals may operate through hormonal or genotoxic pathways to affect male reproduction. Metals may penetrate the blood testis barrier to potentially affect spermatogenesis, either by affecting genetic integrity or hormone production. Effects may be at different stages of the cell cycle such as during meiotic disjunction and such abnormalities can have deleterious effects on reproduction and offspring. Exposure to metals has been long associated with low sperm motility and density, increased morphological anomalies and male infertility.

CONCLUSION

The above findings from different scientific studies also indicated that the degree of toxic manifestation of different metals depends on dose, duration, route of administration and other physiological factors specially nutrition. The signs and symptoms of metal toxicity depend on the duration of exposure, type of metal, condition of workplace, socio-economic status and history



of disease. Metals may effect through hormonal or genotoxic pathways to effect the male reproduction. Metals may penetrate the blood testis barrier to affect spermatogenesis either by affecting genetic integrity or hormone production. Exposure to metals has been long associated with low sperm motility and density, increased morphological anomalies and male infertility. Further efforts should be made to widen our knowledge in this unmapped area of research.

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