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Review Article

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Toxic effects of transition metals on male reproductive system: A review

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ABSTRACT

Transition metals are *d* block elements, which show multiple oxidation states. Transition metals have a wide variety of applications in the industrial world. Recent studies have shown a considerable increase in metal contamination all over the world due to extensive use of metals and anthropogenic activity. A significant amount of many metals including transition metals have been reported in semen and blood of occupationally exposed workers. In the biological system, transition metals are mostly conjugated to proteins, forming metalloproteins, which are part of the enzymatic system. These are an essential component of biological function, but at higher concentration they can be toxic. Transition metals can interact additively, synergistically or antagonistically and affect each other's absorption, distribution and excretion. Recent studies have shown that exposure to transition metals such as Cd, Cr, Hg, manganese, Ni, V and Zinc affects many body organs including the reproductive system. Transition metals may adversely affect male reproductive system in the terms of disruption of spermatogenesis, reduction in sperm count, motility, viability and increase in oxidative stress, inhibition of testicular steroidogenesis, serum testosterone, libido and decline in fertility. Various underlined mechanism have been proposed for such effects. The aim of this review is to provide a summary of the effects of transition metal exposure on male reproductive organs and functions.

KEY WORDS: Antioxidants, fertility, lipid peroxidation, sperm quality, testis, testosterone, transition metal

INTRODUCTION

Transition metals are those elements whose atom has an incomplete *d* sub-shell, or which can give rise to cations with an incomplete *d* sub-shell. Because of this physical characteristic, transition metals have a wide variety of applications in the industrial world. They are the key to making different alloys, colored paints, photo reactive eye glasses, mercury thermometers and in medicines. Transition metals are also used as a catalyst in fertilizers and chemical industries.

The characteristic property of transition metal is that they have many oxidation states, due to the relatively low reactivity of unpaired *d* electrons. The major role of transition metal ions is in oxidation-reduction reactions. In biological systems, transition metals are mostly conjugated or bound to proteins forming metalloproteins. Most of the metals in metalloproteins are part of enzymatic systems, have structural functions, or use the protein to be transported to their target site in the organism [1]. Transition metals include trace elements that are of significance for mammalian physiology like: (i) Cobalt (Co), a component of cobalamine, or vitamin B_{12}, (ii) molybdenum (Mo), an electron transfer agent in enzymes such as xanthineoxidase and sulphite reductase, (iii) vanadium (V), which is biochemically related to glucose and lipid metabolism, (iv) copper (Cu), responsible for the production of a wide range of neurotransmitters, also required for the proper function of vitamin C and iron absorption and (v) zinc (Zn), necessary for a healthy immune system [2].

Certain transition metals like Zn, Cu, manganese (Mn), gold (Au) and nickel (Ni) play a significant role in male reproductive functioning and deficiency of these trace metals have negative impact on spermatogenesis and semen quality. Zinc is essential for the maintenance of germ cells, the progression of spermatogenesis, stabilization of the cell membrane and regulation of capacitation, acrosome reaction and sperm motility [3]. Its deficiency leads to gonadal dysfunction, decreases testicular weight, and causes shrinkage of seminiferous tubules [4]. Mn is a potent stimulator of sperm motility through the stimulation of adenylate cyclase activity [5]. It also stimulates luteinizing hormone (LH) secretion and spermatogenesis in pre-pubertal male rats and its deficiency can impair fertility and cause birth defects [6]. Gold also has been claimed to have a beneficial effect on testicular function and sperm. "Swarna bhasma" (ash of gold) has been used with good results by Ayurvedic practitioners in the treatment of infertility [7]. The role of Cu in male reproductive capacity appears to be largely unknown, but this metal appears to be involved in spermatozoa motility and it may also act at the pituitary receptors which control the release of LH [8]. Nickel is also an activator of some enzymes (dehydrogenase and carboxylase). Nickel deficiency can have a negative impact on spermatogenesis and semen quality [9,10].

Table 1: Toxic effects of certain transition metals on male reproductive system

Transition metal	Animal model	Route of exposure	Dose	Duration	Effect	Reference
Spermatogenesis						
Cadmium (Cd)	Human	Occupational (inhalation)	-	-	Testicular tumors and necrosis was observed	[29]
	Mouse	Drinking water	30 ppm	7 weeks	Seminiferous tubules of testes showed complete absence of spermatogonia, primary spermatocytes, secondary spermatocytes, spermatids and spermatozoa and loss of spermatogenesis	[32]
	Culture of rat seminiferous tubules	-	0.1, 1 and 10 μg/L	Over a 2-week	Dose-and-time-dependent alterations of the meiotic process of spermatogenesis. Increase of total abnormalities of fragmented sertoli cells	[45]
Cadmium acetate ($Cd(CH_3COO)_2.2H_20$)	Mouse	Orally	20 mg/kg b.wt.	2 weeks	Disorganization of seminiferous epithelium was observed. Germ cells were sloughed off from the seminiferous epithelium and were located in the luminal region of the tubules. Seminiferous tubules devoid of spermatides in latest steps of differentiation	[46]
Cadmium chloride ($CdCl_2$)	Wistar rats	Orally	200 mg/kg b.wt.	Single dose	Testicular atrophy and necrosis was observed	[47]
	Pregnant Wistar rats	Orally	10/20 mg/kg b.wt.	On gestational days 18 and 21 and from lactation 1-7	Body weight, absolute weight of testis, epididymis, and seminal vesicle were decreased at the higher cadmium dose. Disrupted sexual behavior in male rats was also observed	[48]
	Pregnant Wistar rats	Orally	0 or 1 mg/kg	Single	Histological alterations and necrosis was found in testis. Completely arrest spermatogenesis	[49]
Cadmium chloride monohydrate ($CdCl_2.H_2O$)	Sprague-Dawley rat	Drinking water	15 ppm	30 days	Damage in seminiferous tubules, degeneration and disintegration in spermatogenic cells and loss of Leydig cells were observed	[50]
Chromium potassium dichromate ($K_2Cr_2O_7$)	Human workers	Occupational	-	-	Damage in seminiferous tubuler epithelium, reduction of spermatozoa formation and increase in teratospermia	[51]
	Non-human primate (*M. radiata* Geoffroy)	Drinking water	100, 200, 400 ppm	6 months	Disrupts spermatogenesis	[30]
	Rat seminiferous tubule culture	-	(10 μg/L)	12 days	Strongly delocalize the gap junction protein connexin 43 from the membrane to the cytoplasm of sertoli cells and alter blood testis barrier	[52]
	Mouse	-	150 ppm	12 weeks	Severe disintegration of spermatocytes, resulting in spermatogenic arrest, with moderately severe tubular necrosis and severe Leydig cells hyperplasia, and moderate calcification of inspissated spermatozoa was observed	[53]
	Wistar rats	I.p.	1 or 2 mg/kg b.wt.	15 days	Morphological alterations with enlarged intracellular spaces, tissue loosening and loss of gametes in the lumen of the seminiferous tubules	[54]
Cobalt chloride ($CoCl_2$)	Hamster	I.p.	20, 10, 5 mg/kg b.wt.	Single	Volume of seminiferous epithelium was significantly decreased whereas lumen diameter of seminiferous tubule and volume of interstitium was increased	[55]
	Mouse	Drinking water	200, 400, 800 ppm	12 week	Hypertrophy of interstitial Leydig cells, congested blood vessel and degeneration of spermatogonial cells and necrosis of both the seminiferous tubules and the interstitial tissue was observed	[56]

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Table 1: Contd...

Transition metal	Animal model	Route of exposure	Dose	Duration	Effect	Reference
Copper (Cu)	Mouse	Drinking water	30 ppm	7 weeks	Seminiferous tubules showed complete absence of spermatogonia, spermatozoa and loss of spermatogenesis	[32]
Copper sulfate ($CuSO_4$)	Rat	Gavage	100, 200 mg/kg b.wt./day	8 weeks	Significant depletion in the germinal layers with the presence of vacuoles in the seminiferous epithelium. Decrease in percentage of spermatogenesis, meiotic index and also in the mean diameter of seminiferous tubules	[57]
Mercuric chloride ($HgCl_2$)	Rat	I.p.	5, 10 and 20 mg/kg b.wt./day	Single	Histological study of testis revealed undulation of basal membrane, dilatation of blood vessels in interstitium and occurrence of empty spaces in germinal epithelium. Decreased relative volume of germinal epithelium, increased relative volume of interstitium and increased apoptosis	[31]
	Rabbit	Diet	1 g/kg food	3 weeks	Cellular necrosis, accompanied by the absence of spermatozoa in the seminiferous tubules and an increase in interstitial space in testis	[58]
	Tropical fish (*G. carapo*)	I.p.	5/10/20 and 30 μM	24 h/48 h/72 h/96 h	Complete disorganization in cysts arrangement with congestion of blood vessels, reduction of germ cells and proliferation of interstitial tissue in testis	[59]
Methyl mercury (CH_3Hg^+)	Tropical fish (*G. carapo*)	I.p.	140 μg/kg b.wt./day	14 days	Reduction in body weight gain, testes weights, reduced sperm production, and increased histopathological abnormalities in testis	[60]
Nickel chloride ($NiCl_2$)	Tropical fish (*G. carapo*)	I.p.	20 mg/kg b.wt.	Single	Decrease in germinal epithelium and increase in the relative volume of the interstitium of seminiferous tubule. Diameter of the seminiferous tubule was markedly decreased	[61]
	Mouse	Diet pellets	10 mg/kg b.wt./day	3, 6, 9 and 12 weeks	Relative volume of empty spaces in the seminiferous epithelium and luminization of the tubules significantly increased and seminiferous tubule diameter was significantly decreased	[62]
Nickel subsulfide (Ni_3S_2)	Rat	Intra-testicular	0.6-10 mg	Acute	Necrosis of seminiferous tubules and interstitial cells resulting atrophic changes in testes	[63]
Nickel sulfate ($NiSO_4$)	Rat	Dermal exposure	0, 40, 60 and 100 mg/kg b.wt/day	15 and 30 days	Degenerated sperms and edematous fluid were observed in the testes	[64]
	Rat	I.p.	2.0 mg/100 g b.wt.	10 doses for alternate days	Testicular glycogen and cholesterol were increased but total protein concentration decreased in nickel treated rats	[65]
Platinum complex	Rat	Oral	10 mg/kg b.wt./day	4 weeks	Testicular enlargement and degeneration/atrophy of the seminiferous epithelium, formation of multinucleated giant cells and vacuolar degeneration of sertoli cells were also seen	[66]
Platinum-N-heterocyclic carbine complex	Sprague-Dawley rat	I.p.	5, 10 mg/kg b.wt.	10 days	Increased histological damage and decrease serum testosterone level	[67]
Ruthenium (II)-NHC (Ru^{II})	Sprague-Dawley rat	I.p.	5, 10 mg/kg b.wt.	1 time	Significantly caused histopathological and spermatologicall damage	[68]
Silver nano particles (Ag NPs) 70 nm	Sprague-Dawley rat	Oral feed	5, 10 mg/kg b.wt.	48 days	Significant reduction in the number of primary spermatocytes and spermatids as well as spermatozoa. No significant differences between different groups for Sertoli cell number and seminiferous tubule diameter	[69]
Silver nano particles (Ag NPs) 60 nm	Wistar rat	Gavage	25, 50, 100, and 200 mg/kg/day	45 days	Significant reduction in number of Leydig cells. Decrease in sperm motility and morphology was also found	[70]

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Table 1: Contd...

Transition metal	Animal model	Route of exposure	Dose	Duration	Effect	Reference
Vanadium pentoxide (V_2O_5)	Guinea pig	I.p.	4.5-12.5 mg/kg b.wt.	48 h	Reduction in number of spermatogonia, destruction of seminiferous tubules, necrosis of the testicular tissues, and vacoulation	[71]
Vanadium sulphate ($V_2(SO_4)^3$)	Sprague-Dawley rat	I.p.	40 mg/kg. b.wt.	Once	Degeneration of seminiferous epithelium and spermatogonia and increase in apoptosis of germ cells. Decrease in protein content of testes	[72]
Semen quality						
Cadmium	Cigarette smokers	Inhalation	-	-	Serum and seminal fluid cadmium concentration was significantly elevated in smokers than control. No differences were found in semen quality or fertility between smokers and nonsmokers	[73]
	Human	Occupational	-	-	Decrease in sperm motility and an increase in abnormal sperm morphology and serum testosterone. Seminal fluid concentration of Cd was increased	[74]
	Human	Environmental exposure	-	-	Decline in semen quality and induce DNA damage	[75]
Cadmium chloride ($CdCl_2$)	Human	Drinking water	0, 23, and 50 mg/kg b.wt.	45 days	In the high dose group, sperm count, motility, maturity and the level of testosterone decreased	[76]
Chromium sulfate	Human	Occupational	-	-	Significant increase in the number of morphologically abnormal sperm in exposed workers	[77]
Potassium dichromate ($K_2Cr_2O_7$)	Monkey (*M. radiata*)	Drinking water	50, 100, 200 and 400 ppm/day	6 months	Decreased sperm count and sperm motility	[34]
	Rabbit	Gavage	3.6 mg/kg/day	10 weeks	Sperm count and motility was reduced and the number of dead sperms increased in semen	[35]
	Mouse	Sub-cutaneously	5, 10 mg/kg b.wt.	4 days	Increase in percentage of multiple morphological abnormalities. Sperm motility and acrosome integrity decrease	[78]
Chromic acid (CrO_3)	Mouse	I.p.	1 mg/kg b.wt.	Single	Altered sperm morphology	[79]
Gold nanoparticle	Donor semen sample	-	Mixture of 500 mL of gold nanoparticle solution and semen	15 min	Sperm motility was reduced. Penetration of gold nanoparticles into the sperm head and tails and fragmentation of sperm were also observed	[80]
Manganese (Mn)	Mouse	Oral	7.5, 15.0, and 30.0 mg/kg b.wt./day	43 days	Decrease in sperm motility and sperm counts, no alterations in the fertility or histology of the testes when compared with the controls	[33]
	Human	Occupational	-	-	Harmful effects on sperm morphology and motility	[5]
Mercuric chloride ($HgCl_2$)	Mouse	Oral	1.25 mg/kg b.wt./day	45 days	Reduction in epididymal sperm count, sperm motility and sperm viability	[81]
	Wistar rats	Sub-cutaneously	5 mg/kg b.wt.	Single dose	Decrease in epididymal sperm count, motility and plasma testosterone level	[82]
	Wistar rats	I.m.	First dose 4.6 μg/kg, subse-quent doses 0.07 μg/kg/day	30 days	Reduction in sperm quantity (testis and epididymis) daily sperm production and sperm motility. Head and tail morphologic abnormalities were increased	[83]
Methyl mercury (CH_3Hg^+)	Monkeys (*M. fascicularis*)	Gavage	0.025 or 0.035 mg/kg b.wt./day	20 weeks	The mean percentage of motile spermatozoa and the mean sperm speed were significantly decreased for both treatment groups. Morphological abnormality i.e., tail defects (primarily bent and kinked tails) was also observed	[84]
	Human	Occupational	-	-	Sperm viability, motility and count decreased	[85]
	Wistar rats	Oral	0, 0.5, 1.0 or 3.0 mg/kg b.wt./day	14 days	Sperm motility, the relative sperm count in the epididymis was reduced. Increased number of sperm head abnormalities, decrease in serum testosterone levels. Increased Hg content in reproductive organs	[27]

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Table 1: Contd...

Transition metal	Animal model	Route of exposure	Dose	Duration	Effect	Reference
Molybdenum (Mo)	Mice	Drinking water	≥ 100 mg/L	Sub acute	Adversely affects the sperm quality through inducing the testicular oxidative stress	[36]
Nickel (Ni)	Mouse	Oral	5 and 10 mg/kg b.wt/day	35 days	Decrease in sperm motility and sperm count was observed	[86]
	Mouse	Oral	5, 10 or 20 mg/kg b.wt./day	35 days	Epididymal sperm count and motility decreased and numbers of abnormal sperm were increased dose dependently	[87]
	Human (Indian welders)	Occupational	-	-	A significant positive correlation between the percentage of tail defects in spermatozoa and blood nickel concentration was observed in workers	[88]
	Human	Occupational	-	-	Sperm abnormalities (broken flagellum, flagellum torso and separated flagellum) occur	[89]
Vanadium vanadyl sulphate ($VOSO_4$)	Rat	Oral	100 mg/kg b.wt./day	60 days	Degeneration of testicular morphology and function. Reduced sperm counts and absolute concentration of motile sperms	[90]
Zinc sulfate	Mouse	Drinking water	1.5 and 2.5 g/100 mL	3 weeks	The sperm count and motility were reduced. Degenerative changes, including spermatic arrest, degeneration of seminiferous tubules and fibrosis in interstitial tissue were observed	[91]
Zinc chloride ($ZnCl_2$)	Rat	Oral	7.50, 15 and 30 mg/kg b.wt./day	100 days	Sperm viability and count decreased	[92]
Hormone profile						
Cadmium (Cd)	Human	Feed (rice)	-	-	No significant correlations was observed between blood cadmium level and serum testosterone, FSH, or LH levels, however, serum testosterone levels ($>95^{th}$ percentile for controls) abnormally increased with exposure to cadmium	[93]
	Human	Occupational	-	-	Reduction in serum testosterone level and sperm count	[94]
	Sprague-Dawley rat	I.p.	5 mg/kg b.wt.	Single dose	Reduced testicular levels of TNF-α, serum levels of MDA and testicular level of Bax gene, and increased levels of IL-4, Zn-Cu SOD, Bcl-2 gene and serum testosterone. Extensive germ cells apoptosis	[95]
	Human	I.p.	-	-	FSH and LH mean values were significantly reduced	[96]
Cadmium acetate	Pregnant rats	Sub-cutaneously	0.05 mg/kg b.wt/day	Throughout the gestational-lactational period	Significant reduction in the activities of testicular key steroidogenic enzymes and serum testosterone concentration in F1 generation males	[39]
Cadmium chloride ($CdCl_2$)	Wistar rat	Sub-cutaneously	1·2 mg/kg b.wt./day	56 days	Decrease in plasma testosterone and relative weight of the testis, epididymis, ventral prostate and seminal vesicle	[37]
Manganese (II) chloride tetrahydrate ($MnCl_2 \cdot 3H_2O$)	Hyline cocks	Basal diet	600/900/1800 mg/kg of diet	30^{th}, 60^{th}, and 90^{th} day	Dose-dependent decrease of testosterone and LH and daily increase of Mn and decrease of Cu, Fe, Zn and Ca contents in testis	[28]
Mercury (Hg)	Human	Occupational	-	-	Inhibin B serum levels increased with increasing mercury exposure among the Greenland Inuit	[97]
Molybdenum (Mo)	Human	Occupational	-	-	Decreased in serum testosterone level.	[21]
Cis-platinum	Rat	I.p.	0.5 mg/kg b.wt./day	9 weeks	Circulating and intratesticular levels of testosterone and LH declined with no effect on FSH	[98]
Zinc (Zn)	Human	Occupational	-	-	Elevated Mn and Zn are inversely associated with testosterone production	[38]
Oxidative stress						

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Table 1: Contd...

Transition metal	Animal model	Route of exposure	Dose	Duration	Effect	Reference
Cadmium chloride ($CdCl_2$)	Mouse	I.p.	2.5 mg/kg or 5 mg/kg b.wt.	Single	Inhibition of CAT and SOD activities, reduction in ascorbic acid and increase in LPO levels, indicating oxidative stress and testes damage	[99]
	Cocks	Diet	150 mg/kg of diet	60 days	Significantly lowered SOD and GPx activity. Increased amount of LPO, apoptotic cells and cadmium concentration in the testis	[43]
	Cocks	Diet	2.5 mg/kg b.wt.	Single dose	Reduction in testicular weight and volume. Significant increase in ROS and LPO level with concomitant reduction in SOD activity	[100]
	Mouse	I.p.	2.5 mg/kg b.wt.	Single dose	Reduction in the ascorbic acid and NPSH levels as well as an inhibition on SOD, δ-ALA-D and GST enzyme activities	[101]
	Mouse	I.p.	6.5 mg/kg b.wt./ day	5 days	Increased weights of the testes, MDA and NO levels in the testicular tissues. Reduction in GSH level, SOD, CAT, GPx, and GR activities, serum testosterone level and body weight. Induced extensive germ cell apoptosis	[44]
Chromic acid (CrO_3)	Mouse	I.p.	1 mg/kg b.wt.	Single	Induced an increase in ROS in testes and altered sperm morphology. Suppressed antioxidant enzymes and ascorbic acid simultaneously, with an increase in the level of LPO	[79]
Hexavalent chromium Cr (VI)	Mouse	I.p.	1 mg/kg b.wt./day	5-8 week	Significantly decline in PD and CAT activities, decreased sperm count & markedly increased the rate of sperm abnormality and the level of LPO	[79]
	Rats	Orally	10 mg/kg/day b.wt.	13 days	Increased MDA concentration and decreased GSH, CAT, SOD and GST activities were observed in both testicular and epididymal tissues	[102]
Mercuric chloride ($HgCl_2$)	Wistar rats	Gavage	1 mg/kg b.wt./day	4 weeks	Increase in the TBARS level and a decrease in the SOD, CAT, GPx activities	[103]
Nickel chloride ($NiCl_2$)	Mouse	I.p.	1.25, 2.5, and 5.0 m mol/100 g b.wt./day	3 days	In testis, increased LPO and apoptosis was observed	[104]
Platinum cisplatin (CIS)	Wistar rats	I.p.	10 mg/kg b.wt.	Single	Testicular MDA levels and MPO activity was elevated while SOD and CAT activity reduced in testis. Germ-cell apoptosis was also increased	[105]
Platinum-N-heterocyclic carbine complex	Sprague-Dawley rat	I.p.	5, 10 mg/kg b.wt.	10 days	Increased oxidative stress, significant decrease in SOD, CAT, GPx and GSH level in testis	[68]
Fertility						
Cadmium dust	Male workers	Occupational	-	-	Decline in fertility	[106]
Manganese (II) chloride tetrahydrate ($MnCl_2 \cdot 3H_2O$)	Mice	Drinking water	1000, 2000, 4000 and 8000 mg/L	12 weeks	Fertility was reduced at high level	[107]
Manganese oxide (Mn_3O_4)	Rat	Diet	350, 1050, 3500 ppm	224 days	Fertility and serum testosterone level were reduced	[108]
Manganese salts (dioxide, carbonate, sulfate)	Male workers	Occupational	-	-	Statistically significant deficit in the number of children during their period of exposure to the manganese salts	[109]
Mercury (Hg)	Human	Diet (sea-food)	-	-	Infertile male with abnormal semen	[110]
Mercuric chloride ($HgCl_2$)	Human	Oral	0.00, 0.25, 0.50, and 1.00 mg/kg b.wt./day	-	Fertility and survival indices were significantly reduced	[111]
Mercuric chloride ($HgCl_2$)	Sprague-Dawley rats	Gavage	0.0, 1.0, or 2.0 mg/kg b.wt./day	60 days	Significant adverse effects on male rat reproduction endpoints including fertility	[112]

δ-ALA-D: δ-aminolevulic acid dehydratase, b.wt.: Body weight, CAT: Catalase, FSH: Follicle stimulating hormone, GPx: Glutathione peroxidase, GSH: Glutathione, GST: Glutathione S-transferase, i.m.: Intramuscular, i.p.: Intraperitoneal, LH: Luteinzing hormone, LPO: Lipid peroxidation, MDA: Malondialdehyde, NO: Nitric oxide, NPSH: Non-protein thiols, PD: Peroxidase, ROS: Reactive oxygen species, SOD: Superoxide dismutase, TBARS: Thiobarbituric acid-reactive substances, TNF-α: Tumor necrosis factor, *M. radiate: Macaca radiate, Gymnotus carapo*: *G. carapo*, GR: Glutathione reductase, MPO: Myeloperoxidase, i.p.: Intraperitoneal

Although, transition metals are essential components of biological functions, but at the same time they can be toxic at higher concentrations beyond those necessary for their physiological requirement [1]. The toxicities produced by the transition metals involve the neurotoxicity, hepatotoxicity, nephrotoxicity and reproductive toxicity [11,12].

Several studies indicate that the human male reproductive capacity has deteriorated considerably during the past few decades [13-15]. This decreasing trend in male fertility has led to speculation that recent environmental, dietary and/or lifestyle changes are interfering with a man's ability to produce spermatozoa [16]. Transition metals constitute an important group of environmental factor that can disturb normal functioning of male reproductive system. Studies have shown a considerable increase in transition metal contamination in relation to the worldwide distribution, anthropogenic activity and extensive use of transition metals [17,18]. Men are, usually, exposed to transition metals through diet, air, drinking polluted water and ingestion of dust [19]. Unlike organic pollutants, metals cannot be degraded easily and accumulate throughout the food chain, producing potential human health risks and ecological disturbances [20,21]. Increased levels of transition metal ions in blood plasma or semen appear to be significantly and positively correlated with male infertility [19,22].

Transition metals can interact additively, synergistically, or antagonistically and affect each other's absorption, distribution, and excretion [21,23]. Toxic transition metals mimic essential metals and thereby gain access to and potentially disrupt key cellular function. There is increasing concern about transition metals and chemical pollutants that can act as hormonal mimics. In either case, these metals serve to disrupt the normal action of endogenous hormones and thus known as "endocrine disruptors" [24]. Hypothetically, the strength of the toxic effect of transition metals depends principally on the absorption, concentration, and its site of action. As the final toxicant metal species reacts with the endogenous target molecule such as receptors, enzymes, DNA, protein, or lipid and critically alters the biological environment, producing structural and functional changes that result in toxic damage [25].

Toxicological studies have demonstrated that many transition metals can accumulate in testes and/or epididymis impairing their endocrine and reproductive functions [26-28]. Transition metals adversely affect spermatogenesis and can cause testicular necrosis through a direct effect on the testicular vasculature [29-32]. Some transition metals also seem to have a direct effect on sperm cells by reducing their motility, viability and/or affecting their morphology [5,33-36]. Several studies reported a significant decline in serum testosterone level in exposed experimental animals [21,37,38]. This may be due to inhibition of the action of the steroidogenic enzymes in Leydig cells [39].

There is growing evidences that oxidative stress is implicated in the pathogenesis of male infertility [40,41]. Several transition metals including cadmium, chromium, mercury, nickel and platinum may increase reactive oxygen species production, decrease glutathione and other antioxidant levels, enhance the lipid peroxidation of the cell membrane, cause apoptosis, and contribute to the oxidative damage of DNA [11,42-44].

A summary of the findings of some important research papers published on the adverse effects of different transition metals on male reproductive system and fertility with the possible mechanism of such effects is presented in the Table 1.

CONCLUSION

The overall result of this review provide an evidence that certain transition metals such as Cd, Cr, Hg, Mn, Mo, Ni, V and Zn may adversely affect male reproductive functions including spermatogenesis, sperm quality, secretory functions of accessory glands, libido, fertility, serum testosterone level and antioxidant defense system. Most of the reports on the reproductive toxicity of transition metals are from experimental animal studies. However, data in men are limited and insufficient to provide a quantitative dose response relationship or no- observed- adverse- effect exposure threshold. Therefore, more epidemiological studies are needed to validate the effects identified in experimental models. Findings from different studies indicated that the degree of toxic manifestation of different transition metal in animals depends on the dose, duration and route of administration. Therefore, we concur that better designed long-term studies are needed to explore the influence and effect of transition metals on reproduction and fertility in males and possible mechanism(s) of such adverse effects.

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