Journal of Infertility and Reproductive Biology

Journal of Infertility and Reproductive Biology, 2014, Volume 2, Issue 2, Pages: 62-69

Cadmium and male infertility

Alaee S[1*], Talaiekhozani A[2,3], Rezaei S[4], Alaee K[5], Yousefian E[6]

1. Department of Reproductive Biology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran
2. Institute of Environmental and Water Resources Management, Water Research Alliance, Universiti Teknologi Malaysia, UTM Skudai, 81310 Johor Bahru, Malaysia
3. Jami Institute of Technology, Department of Civil Engineering, Isfahan, Iran
4. Department of Obstetrics and Gynecology, Shiraz University of Medical Sciences, Shiraz, Iran
5. Department of Radiology, Shiraz University of Medical Sciences, Shiraz, Iran
6. Department of Midwifery, Falavarjan Branch, Islamic Azad University, Isfahan, Iran

Abstract

Cadmium (Cd) is a heavy metal to which humans are exposed both occupationally and environmentally. For many years cadmium has been understood as a toxic element to human health, and an elevated level of cadmium exposure has been shown to be related to adverse reproductive effects, especially in men. In this review we studied published data about the toxic effects of this trace element on the total male reproductive system, including gonadal development, testes, testosterone, spermatogenesis and accessory sex glands, to clarify how cadmium causes male fertility problems. For this purpose, in the next sections after introducing this trace element thoroughly, we will separately mention cadmium's effects on each part of male reproductive system.

Keywords: Cadmium, Male, Testis, Sperm, Reproduction

1. Introduction

Heavy metals are natural components of the earth's crust and cannot be degraded or destroyed. Cadmium is a heavy metal, used in industrial activities such as the manufacture of nickel-cadmium batteries, electroplating, pigments, ceramics, plastic stabilizers, and fertilizers, as well as in other industrial, mining, agricultural activities and in the widespread use of phosphate-based fertilizers (1-3). Consequently, there is a high level of cadmium contamination at many locations worldwide, which leads to pollution of the water and air. After cadmium enters the environment, it pollutes air and water and at last is discharged into the food chain, detrimentally affecting living organisms (4, 5). The toxicity of cadmium was first described by Friedrich Stromeyer in 1817. In the 1940s, environmental exposure to cadmium's toxicity was reported in Japan's Jinzū river basin, where a disease called itai-itai tormented many people. These patients showed a wide range of symptoms, such as low-grade bone mineralization, a high rate of fracture, an increased rate of osteoporosis and intense bone-associated pain. This affliction occurred because the river basin's inhabitants had consumed local rice, which had been grown in fields irrigated with cadmium-contaminated water (3).

Cadmium has molecular homology with zinc and calcium and compensates with them for resorption to the body (6, 7). Studies have shown that in humans, cadmium can be absorbed into the body through the gastrointestinal, respiratory and dermal systems (8). The major source of inhalative cadmium intoxication is smoking, and the human lung resorbes 40-60% of the cadmium content in cigarette smoke (9). As a result, smokers receive a dose of cadmium daily and generally have cadmium blood levels 4-5 times more than those of nonsmokers (2, 8, 10). In nonsmokers, most uptake of cadmium is through cadmium-

[*]**Corresponding Address:** Dr. Sanaz Alaee, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran. Email: sanazalaee@yahoo.com

contaminated drinking water and food, particularly cereals, such as rice and wheat, and also potato and green leafy vegetables (2, 8, 10, 11).

It has been documented that the total amount of cadmium uptake to the human body depends on the consumed dose. Several factors can increase this uptake, such as low intake of vitamin D, calcium and iron (8). It has been demonstrated that cadmium uptake in people with anemia and habitual iron deficit, such as children or menstruating women, is higher than in other people (12). In addition, it is estimated that dietary intake of cadmium is higher in men than women (13).

A higher level of cadmium intake, more than the standard level, has an significant adverse effect on growth rate (14, 15), but its toxic effects on tissues are not the same in all tissues, i.e., vary from tissue to tissue and are seen primarily in sensitive tissues such as liver, kidney, ovary and especially testes (16).

Studies of cadmium toxicity have introduced it as an ubiquitous environmental human carcinogen (17) and one of the best-known reproductive toxicants in a wide variety of animals (18-22). In humans, chronic exposure to environmentally-relevant cadmium results in high cadmium level, especially in infertile men (23, 24). Therefore, in the current study we reviewed available literature to determine which part of the male reproductive system is most affected by cadmium and how cadmium causes male fertility problems.

2. Effects of cadmium on gonadal development

Collected data showed that cadmium affects the male reproductive system from embryonic stages to adulthood, and has adverse effects on gonadal development (25). In mouse embryos, administration of cadmium caused reduced genital ridge size and retarded migration of germ cells into the genital ridges, resulting in attenuated populations of germ cells, aberrant maturation of gametes and subfertility (26). In young rabbits treated with 1.0-2.25 mg/kg body weight cadmium, significant damage to the germinal epithelial and basement membrane after 48 hours and a significant reduction in the volume of epididymis epithelium after 5 months' treatments were observed (27).

3. Effects of cadmium on reproductive system

3.1. Testes

Testis is one of the tissues that is very sensitive to the toxic effects of cadmium. Elevated accumulation of cadmium in testis has been measured using atomic absorption spectroscopy technique and confirmed by the presence of hyperchromatic cadmium precipitants in histological sections of seminiferous tubules of adult male mice treated with cadmium (15). Similarly, gonadal damage has been shown to develop following administration of cadmium to adult male rats either orally or subcutaneously (25).

In humans, testicular cadmium levels are age dependent and elevate after the fourth decade of life (28). Some studies show that cadmium accumulation in the testes has no effect on testicular weight (29-31), but there is some evidence showing that the weight of testis can be affected by cadmium accumulation in testicular tissue, rather than by total body weight; however, this depends on the level of applied cadmium, duration of treatment and the level of cadmium concentration in the testis (Table 1) (14, 15, 32, 33). Additionally, cigarette smoking has been reported to be associated with decreased testis size in men, related to the cadmium content of cigarettes (34).

Cadmium enters the seminiferous tubules through a breach of the blood-testis barrier and causes focal testicular necrosis and dystrophy with consequent reduction in germ cell numbers, leading to infertility (15, 25, 35, 36). Disruption of the blood-testis barrier by cadmium is a consequence of endothelial cell damage in testicular blood vessels and separation of endothelial cells, which has been confirmed by light and electron microscopy and is mediated by reduced occludin protein expression, indicating the involvement of cell junction breakdown in blood-testis barrier disruption (35-37).

Researchers report that high concentration of reactive oxygen species (ROS), generated by accumulation of cadmium in testicular tissue, exceeds the antioxidant capability of the testis cells, leading to lipid peroxidation, degeneration of seminiferous tubules, testicular hemorrhage, testicular necrosis, abnormal Leydig cells, fibrosis and reduced testicular size. Therefore, severe cellular injury in seminiferous tubules could be due to a high level of peroxidation in lipid membrane of testicular cells, observed in many studies (14, 15, 25, 33, 38-45). In one study by Monsefi et al., (2010) administration of cadmium chloride caused severe damage to seminiferous tubules, resulting in difficulty in identification of seminiferous tubules by light microscope and also consequent reduction in spermatogenesis, as there was no spermatozoid in the lumen of some seminiferous tubules (15).

3.2. Testosterone

Testosterone is the principle male sex hormone produced by Leydig cells, located in interstitial tissue of testis. Presence and function of this hormone is

crucial for accurate spermatogenesis process of seminiferous tubules, and evaluation of the plasma testosterone level is considered a useful indicator of testicular function (46, 47).

While many studies have been suggested that cadmium increases testosterone level (29, 48, 49), others showed that cadmium administration attenuates it (14, 15, 21, 50-54). However, according to Table 1, it can be concluded that the effect of cadmium on testosterone level is dependent on dose, duration and method of cadmium administration. In addition, modified Leydig cells in the interstitial tissue of testes of mice exposed to cadmium chloride have been reported (15). Nevertheless, we should mention that except for serum, the evaluation of testicular testosterone is important, and testicular testosterone levels are approximately one hundred fold higher than serum testosterone levels, and this high level is required to support spermatogenesis (55, 56).

Consequently, it is possible that testicular testosterone level can be more sensitive to the effects of cadmium than serum level, as was observed in rats treated with cadmium (14). Telisman et al. (2000) showed that cadmium has the ability to impair male fertility without effects on the male reproductive endocrine function (57). So it is concluded that cadmium affects testosterone synthesis through various mechanisms that depend upon experimental conditions.

Table 1. Studies about effects of cadmium on weight of testes, accumulation of cadmium in testes and plasma testosterone level.

Model of research	Cadmium administration method	Doses of cadmium	Duration of treatment	Weight of testes	Accumulation of cadmium in testes	Plasma testosterone level	Reference
Adult Wistar male rats	Subchronic exposure to Cd	(CdCl2, 40 mg/l, per os)	30 days	S Decrease	NE	S Decrease in plasma and testis	(14)
Adult BALB/c male mice	Orally administration by gavage	$CdCl_2$, 23 mg/kg BW	45 days	NS Decrease	NS Increase	S Decrease	(15)
		$CdCl_2$, 50 mg/kg BW once per day		S Decrease	S Increase	S Decrease	
Adult Wistar male rats	Orally	$CdCl_2$ (0.2 mg/kg)	15 days	NE	S Increase	S Decrease	(21)
Adult Wistar male rats	Cadmium-contaminated radish bulb	1.1 µg Cd/g of diet	4 weeks	No change	S Increase	NS Increase	(29)
			8 weeks	No change	S Increase	S Increase	
			12 weeks	No change	S Increase	NS Decrease	
Adult Sprague Dawley male rats	Subcutaneously	0.6 mg Cd/kg once per day	6 weeks	No Change	S Increase	NE	(31)
Adult Sprague Dawley male rats	Orally, administration by gavage	$CdCl_2$, 5 mg/kg BW	15 days	S Decrease	NE	NE	(33)
Adult Swiss Webster male mice	Intraperitoneal injection once a day	$CdCl_2$ 0.1 mg/kg BW once per week	4, 10, 26, and 52 weeks	NE	S Increase	NS Increase	(48)

S= Significant; NS= Non significant; NE= Not examined.

3.3. Spermatogenesis and semen parameters

Besides being detected in blood, cadmium can be identified in seminal plasma of cigarette smokers (58), but no relationship was reported between the levels of cadmium in blood and seminal plasma (59, 60).

In the literature, conflicting evidence exists regarding the correlation between the cadmium content of seminal plasma and semen parameters (20, 60-63). Where some studies demonstrated positive correlation between the cadmium content of semen and seminal quality (60, 64), others reported that seminal plasma cadmium level is unrelated to semen parameters and also fertility status (64-66).

Studies suggest that different cell populations within the testis can be as targets of cadmium toxicity (67, 68), and cadmium is able to be accumulated in germinal cells such as spermatogonia, spermatocytes,

spermatid and spermatozoa after the entrance of cadmium to testicular tissue (31, 44, 48). In one study, Sprague Dawley rats subcutaneously injected with daily 0.6 mg/kg doses of cadmium over a 6-week period developed an accumulation of cadmium in the testes, mainly in spermatogonia and spermatocytes, with consequent reduction in both of these cell types (31). However, in one study which used atomic absorption spectroscopy and particle-induced x-ray emission analyses, the presence of cadmium in germinal cells was not observed (48).

As shown in Table 2, treatment with different doses and durations of cadmium leads to sperm concentration reduction (14, 15, 21, 29, 31, 33). Haouem et al. (2008) observed that by increasing the duration of cadmium administration, sperm concentration decreases in male rats mainly because of high apoptosis of sperm cells (29), which was seen in male cigarette smokers, too, especially in heavy smokers. Therefore, cadmium could be a possible causative agent for the low sperm density among smokers (69).

Besides sperm concentration, sperm motility is also severely affected by cadmium. Sperm motility is recognized to be more sensitive to this trace element, as reduced sperm motility has been observed at a dose far below the dose affecting sperm production. However, it is concluded that cadmium accumulation in germinal cells and cadmium effects on sperm count and sperm motility are dose- and time-dependent (Table 2) (14, 24, 25, 27, 31, 70). Taha et al. (2012) observed that men with idiopathic male infertility had higher seminal cadmium levels (71), which was correlated with impairment of sperm motility, especially progressive sperm motility, lower percentages of viable sperms and more important, with higher sperm DNA fragmentation and semen ROS level (71).

Regarding the adverse effects of this heavy metal on sperm motility, some studies have suggested that motility of sperm can be used as an early and sensitive endpoint for the assessment of cadmium toxicity in the male reproductive system (59).

Table 2. Effects of cadmium on semen parameters.

Model of research	Cadmium administration method	Doses of cadmium	Duration of treatment	Sperm count	Sperm motility	Reference
Adult Wistar male rats	Subchronic exposure to $CdCl_2$	40 mg/l, per os	30 days	S Decrease	S Decrease	(14)
Adult BALB/c male mice	Orally administration of $CdCl_2$	23 mg/kg BW, once per day	45 days	NS Decrease	NS Decrease	(15)
		50 mg/kg WB, once per day	45 days	S Decrease	S Decrease	
Adult Wistar male rats	Oral administration of $CdCl_2$	(0.2 mg/kg)	15 days	S Decrease	NE	(21)
Adult Wistar male rats	Cd-contaminated radish bulb	1.1 µg Cd/g of diet	4 weeks	NS Decrease	NE	(29)
			8 weeks	NS Decrease	NE	
			12 weeks	S Decrease	NE	
Adult Sprague Dawley male rats	Subcutaneous injection	0.6 mg Cd/kg once per day	6 weeks	S Decrease in testicular SG and SC	NE	(31)
Adult Sprague Dawley male rats	Oral administration of $CdCl_2$	5 mg/kg BW	15 days	S Decrease	S Decrease	(33)
Adult male rats		$CdCl_2$,1 mg kg	3 days	S Decrease	S Decrease	(45)

S= Significant; NS= Non significant; NE= Not examined; SG= Spermatogonia; SC= Spermatocyte.

3.4 Sperm chromatin integrity and DNA stability

Chromatin condensation and DNA stability are indices of sperm quality, which can be identified through aniline blue and acridine orange, respectively, to reflect the possible disorders in sperm DNA and sperm maturation. Damage to sperm DNA seems to affect embryo and increases the risk of infertility, miscarriage, or serious diseases in the offspring (72, 73). Through the use of acidic aniline blue staining, it has been revealed that cadmium can inhibit the chromatin condensation process, which is important for sperm maturation. This is a significant

limiting factor in fertility potential; but incorporation of cadmium into sperm chromatin was not confirmed using Acridine orange staining (15).

3.5. Prostate and Seminal Vesicle

Although some studies have suggested the carcinogenic potential of cadmium on prostate tissue (17, 74), a critical study by Sahmoun et al. (2005) has shown that in contrast to laboratory animals, epidemiological analyses do not convincingly implicate cadmium as a cause of prostate cancer (75).

Exposure of rats to Cd resulted in a significant reduction in seminal vesicle (14, 15). Monsefi et al. (2010) showed that administration of cadmium to male mice causes reduced weight of seminal vesicles and high serum prostatic acid phosphatase activity. These effects may be due to hypertrophy or hyperplasia of the prostate gland, leading to increased synthesis or expression of this enzyme (15).

4. Conclusion

According to the literature, cadmium has adverse effects on the male reproductive system and the testes are the main target of cadmium.

Cadmium enters the body through contaminated air, water and food. It then circulates in the blood and reaches tissues such as testis, where it accumulates. Cadmium in the testis disrupts the blood-testis barrier, comes into close contact with different cells of testis and, by increasing the production of ROS and decreasing various antioxidants' levels, enhances the lipid peroxidation of cell membranes, causes apoptosis and necrosis of all testicular tissue leading to disturbance of spermatogenesis, reduces sperm's motility and finally leads to infertility.

Also oxidative damage of sperm's DNA causes paternal genomic disorder contributed to a variety of developmental disorders including early or late embryonic lethality. However, with regard to the literature, studies have failed to demonstrate the incorporation of cadmium into sperm chromatin.

In conclusion, subfertility following cadmium administration might result from penetration of cadmium to testicular tissue and damage to testicular tissue, leading to disturbance of the testes' function, manifested by disruption of spermatogenesis and sperm motility, with or without effects on the male reproductive endocrine function.

References

1. Aziz R, Rafiq MT, Yang J, et al. Impact Assessment of Cadmium Toxicity and Its Bioavailability in Human Cell Lines (Caco-2 and HL-7702). BioMed Res Int. 2014; 839538.
2. El-Dars FMSE, Bakr MHM, Gabre AM. Reduction of COD in Resin Production Wastewater Using Three Types of Activated Carbon. J Environ Treat Tech. 2013; 1(3): 126-136.
3. Fowler BA. Monitoring of human populations for early markers of cadmium toxicity: a review. Toxicol Appl Pharm. 2009; 238(3): 294-300.
4. Jamshidi B, Ehrampoush MH, Dehvari M. Utilization of Olive Kernel Ash in Removal of RB19 from Synthetic Textile Wastewater. J Environ Treat Tech. 2013; 1(3): 150-156.
5. Fazeli M, Hassanzadeh P, Alaei S. Cadmium chloride exhibits a profound toxic effect on bacterial microflora of the mice gastrointestinal tract. Hum Exp Toxicol. 2011; 30(2): 152-159.
6. Frías-Espericueta MG, Zamora-Sarabia FK, Osuna-López JI, et al. Cadmium, Copper, Lead, and Zinc Contents of Fish Marketed in NW Mexico. The Scientific World Journal, 2014; 546897.
7. Foulkes E. Interactions between metals in rat jejunum: implications on the nature of cadmium uptake. Toxicology. 1985; 37(1): 117-125.
8. Godt J, Scheidig F, Grosse-Siestrup C, et al. The toxicity of cadmium and resulting hazards for human health. J Occup Med Toxicol, 2006; 1(22): 1-6.
9. Elinder C-G, Kjellström T, Friberg L, Linnman BLL. Cadmium in kidney cortex, liver, and pancreas from Swedish autopsies. Arch Environ Health.1976; **31**(6): 292-302.
10. Järup L, Berglund M, Elinder CG, et al. Health effects of cadmium exposure–a review of the literature and a risk estimate. Scand J Work Env Hea. 1998: 2; 1-51.
11. Jin T, Frech W, Dumont X, et al. Cadmium bio-monitoring and renal dysfunction among a population environmentally exposed to cadmium from smelting in China (ChinaCad). Biometals. 2002; 15(4): 397-410.
12. Flanagan P, McLellan J, Haist J, et al. Increased dietary cadmium absorption in mice and human subjects with iron deficiency. Gastroenterology. 1978; 74(5): 841-846.
13. Watanabe T, Shimbo S, Nakatsuka H, et al. Gender-related difference, geographical variation and time trend in dietary cadmium intake in Japan. Sci Total Environ. 2004; 329(1): 17-27.
14. Amara S, Abdelmelek H, Garrel C, et al. Preventive effect of zinc against cadmium-induced oxidative stress in the rat testis. Reprod Dev. 2008; 54(2): 129-134.
15. Monsefi M, Alaee S, Moradshahi A, Rohani L. Cadmium induced infertility in male mice. Environ

Toxicol. 2010; 25(1): 94-102.
16. Orisakwe O. Lead and cadmium in public health in Nigeria: physicians neglect and pitfall in patient management. N Am J Med Sci, 2014; 6(2): 61.
17. Nakamura K, Yasunaga Y, Ko D, et al. Cadmium-induced neoplastic transformation of human prostate epithelial cells. Int J Oncol. 2002; 20(3): 543.
18. El-Ebiary EH, Wahbi OM, El-Greisy ZA. Influence of dietary Cadmium on sexual maturity and reproduction of Red Tilapia. Egypt J Aquat Res. 2013; 39(4): 313-317.
19. Wirth JJ, Mijal RS. Adverse effects of low level heavy metal exposure on male reproductive function. Syst Biol Reprod Med. 2010; 56(2): 147-167.
20. Xu D-X, Shen H-M, Zhu Q-X, et al. The associations among semen quality, oxidative DNA damage in human spermatozoa and concentrations of cadmium, lead and selenium in seminal plasma. Mut Res Gen Tox En. 2003; 534(1): 155-163.
21. Jahan S, Khan M, Ahmed S, Ullah H. Comparative analysis of antioxidants against cadmium induced reproductive toxicity in adult male rats. Syst Biol Reprod Med. 2014; 60(1): 28-34.
22. Rahman MS, Sasanami T, Mori M. Effects of cadmium administration on reproductive performance of Japanese quail (Coturnix japonica). J Poult Sci. 2007. 44.
23. Stassen MJ, Preeker NL, Ragas AM, et al. Metal exposure and reproductive disorders in indigenous communities living along the Pilcomayo River, Bolivia. Sci Total Environ. 2012; 427: 26-34.
24. Benoff S, Hauser R, Marmar JL, et al. Cadmium concentrations in blood and seminal plasma: correlations with sperm number and motility in three male populations (infertility patients, artificial insemination donors, and unselected volunteers). Mol Med. 2009; 15(7-8): 248.
25. Thompson J, Bannigan J. Cadmium: toxic effects on the reproductive system and the embryo. Reprod Toxicol. 2008; 25(3): 304-315.
26. Tam P, Liu W. Gonadal development and fertility of mice treated prenatally with cadmium during the early organogenesis stages. Teratology, 1985. 32(3): 453-462.
27. Toman R, Massanyi P, Uhrin V. Changes in the testis and epididymis of rabbits after an intraperitoneal and peroral administration of cadmium. Trace Elements Electrolytes. 2002; 19(3): 114-117.
28. Oldereid N, Thomassen Y, Attramadal A, et al. Concentrations of lead, cadmium and zinc in the tissues of reproductive organs of men. J Reprod Fertil. 1993; 99(2): 421-425.
29. Haouem S, Najjar MF, El Hani A, Sakly R. Accumulation of cadmium and its effects on testis function in rats given diet containing cadmium-polluted radish bulb. Exp Toxicol Pathol, 2008; 59(5): 307-311.
30. Foote RH. Cadmium affects testes and semen of rabbits exposed before and after puberty. Reprod Toxicol. 1999; 13(4): 269-277.
31. Aoyagi T, Ishikawa H, Miyaji K, et al. Cadmium-induced testicular damage in a rat model of subchronic intoxication. Reprod Med Biol. 2002; 1(2): 59-63.
32. Blanco A, Moyano R, Vivo J, et al. Quantitative changes in the testicular structure in mice exposed to low doses of cadmium. Environ Toxicol Pharmacol. 2007; 23(1): 96-101.
33. El-Demerdash FM, Yousef MI, Kedwany FS, et al. Cadmium-induced changes in lipid peroxidation, blood hematology, biochemical parameters and semen quality of male rats: protective role of vitamin E and β-carotene. Food Chem Toxicol. 2004; 42(10): 1563-1571.
34. Jurasović J, Cvitković P, Pizent A, et al. Semen quality and reproductive endocrine function with regard to blood cadmium in Croatian male subjects. Biometals. 2004 ;17(6): 735-743.
35. Chung NP, Cheng CY. Is Cadmium Chloride-Induced Inter-Sertoli Tight Junction Permeability Barrier Disruption a Suitable in Vitro Model to Study the Events of Junction Disassembly during Spermatogenesis in the Rat Testis? Endocrinology. 2001; 142(5): 1878-1888.
36. Wong C, Mruk DD, Lui W, Cheng CY. Regulation of blood-testis barrier dynamics: an in vivo study. J Cell Sci. 2004. 117(5): 783-798.
37. Yan HH, Cheng CY. Blood–testis barrier dynamics are regulated by an engagement/disengagement mechanism between tight and adherens junctions via peripheral adaptors. Proc Natl Acad Sci U S A. 2005; 102(33): 11722-11727.
38. Tremellen K. Oxidative stress and male infertility: A clinical perspective. Hum Reprod Update. 2008; 14(3): 243-258.
39. Alaee S. Monsefi M. Effect of cadmium on oxidative stress of testes in adult male mice. Iran J Reprod Med. 2013; 11(4): 39.
40. Berliner AF, Jones-Witters P. Early effects of a lethal cadmium dose on gerbil testis. Biol Reprod. 1975; 13(2): 240-247.
41. Niewenhuis RJ. Effects of cadmium upon regene-rated testicular vessels in the rat. Biol Reprod.

1980; 23(1): 171-179.
42. Fende PL, Niewenhuis RJ. An electron microscopic study of the effects of cadmium chloride on cryptorchid testes of the rat. Biol Reprod. 1977; 16(3): 298-305.
43. El-Ashmawy IM, Youssef SA. The antagonistic effect of chlorpromazine on cadmium toxicity. Toxicol Appl Pharmacol. 1999. 161(1): 34-39.
44. Kotsonis FN, Klaassen CD. Toxicity and distribution of cadmium administered to rats at sublethal doses. Toxicol Appl Pharmacol. 1977; 41(3): 667-680.
45. Oguzturk H, Ciftci O, Aydin M, et al. Ameliorative effects of curcumin against acute cadmium toxicity on male reproductive system in rats. Andrologia. 2012; 44(4): 243-249.
46. Gorbel F, Boujelbene M, Makni-Ayadi F, et al. Impact of lead given in drinking water on the endocrine and exocrine sexual activity in pubescent rats. Determination of an apoptotic process. C R Biol. 2002; 325(9): 927-940.
47. Lafuente A, González-Carracedo A, Romero A, et al. Cadmium exposure differentially modifies the circadian patterns of norepinephrine at the median eminence and plasma LH, FSH and testosterone levels. Toxicol Lett. 2004; 146(2): 175-182.
48. Bench G, Corzett M, Martinelli R, Balhorn R. Cadmium concentrations in the testes, sperm, and spermatids of mice subjected to long-term cadmium chloride exposure. Cytometry. 1999; 35(1): 30-36.
49. Zeng X, Jin T, Zhou Y, Nordberg GF. Changes of serum sex hormone levels and MT mRNA expression in rats orally exposed to cadmium. Toxicology. 2003; 186(1): 109-118.
50. Nordberg G. Effects of long-term cadmium exposure on the seminal vesicles of mice. J Reprod Fertile. 1975. 45(1): 165-167.
51. Zylber-Haran, EA, Gershman H, Rosemann E, Spitz IM. Gonadotrophin, testosterone and prolactin interrelationships in cadmium-treated rats. J Endocrinol. 1982; 92(1): 123.
52. Clark JT, Jimenez B, Evans SL, et al. Reproductive effects of low acute doses of cadmium chloride in adult male rats. Toxicol Appl Pharmacol. 1984; 73(2): 250-255.
53. Clark JT, Jimenez B, Evans SL, et al. Cadmium-induced sexual dysfunction does not involve increased hepatic metabolism of testosterone nor increased circulating levels of corticosterone. Physiol Behave. 1994; 56(5): 975-981.
54. Waalkes MP, Rehm S, Devor DE. The effects of continuous testosterone exposure on spontaneous and cadmium-induced tumors in the male Fischer (F344/NCr) rat: loss of testicular response. Toxicol Appl Pharmacol. 1997; 142(1): 40-46.
55. Jarow JP, Chen H, Rosner W, et al. Assessment of the androgen environment within the human testis: minimally invasive method to obtain intratesticular fluid. J Androl. 2001; 22(4): 640-645.
56. Coviello AD, Bremner WJ, Matsumoto AM, et al. Intratesticular testosterone concentrations comparable with serum levels are not sufficient to maintain normal sperm production in men receiving a hormonal contraceptive regimen. J Androl. 2004; 25(6): 931-938.
57. Telisman S, Cvitković P, Jurasović J, et al. Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. Environ Health Persp. 2000; 108(1): 45.
58. Benoff S, Jacob A, Hurley IR. Male infertility and environmental exposure to lead and cadmium. Hum Reprod Update. 2000; 6(2): 107-121.
59. Xu L, Wang S, Yang X, Wang X. Effects of cadmium on rat sperm motility evaluated with computer assisted sperm analysis. Biomed Environ Sci. 2001; 14(4): 312.
60. Pant N, Upadhyay G, Pandey S, et al. Lead and cadmium concentration in the seminal plasma of men in the general population: correlation with sperm quality. Reprod Toxicol. 2003; 17(4): 447-450.
61. Akinloye O, Arowojolu AO, Shittu OB, Anetor JI. Cadmium toxicity: a possible cause of male infertility in Nigeria. Reprod Biol. 2006; 6(1): 17-30.
62. Wu H-M, Lin-Tan D-T, Wang M-L, et al. Cadmium level in seminal plasma may affect the pregnancy rate for patients undergoing infertility evaluation and treatment. Reprod Toxicol. 2008; 25(4): 481-484.
63. Alexander BH, Checkoway H, Faustman EM, et al. Contrasting associations of blood and semen lead concentrations with semen quality among lead smelter workers. Am J ind Med. 1998; 34(4): 464-469.
64. Dawson EB, Ritter S, Harris WA, et al. Comparison of sperm viability with seminal plasma metal levels. Biol Trace Elem Res. 1998; 64(1-3): 215-219.
65. Keck C, Bramkamp G, Behre HM, et al. Lack of correlation between cadmium in seminal plasma and fertility status of nonexposed individuals and two cadmium-exposed patients. Reprod Toxicol. 1995; 9(1): 35-40.
66. Kasperczyk A, Kasperczyk S, Dziwisz M, et al.

Lead and cadmium concentration in human semen. Ginekologia polska. 2002; 73(5): 449-453.

67. Jin L, Lou Z, Dong J, Chen X. Effects of cadmium and mercury on DNA damage of mice bone marrow cell and testicle germ cell in vitro. Carcinog Teratog Mutag. 2003; 16(2): 94-97.
68. Yang HS, Han DK, Kim JR, Sim JC. Effects of α-tocopherol on cadmium-induced toxicity in rat testis and spermatogenesis. J Korean Med sci. 2006; 21(3): 445-451.
69. Chia S, et al. Effect of cadmium and cigarette smoking on human semen quality. Int J Fertil Menopausal Stud. 1994; 39(5): 292.
70. Dixon R, Lee I, Sherins R. Methods to assess reproductive effects of environmental chemicals: studies of cadmium and boron administered orally. Environ Health Persp. 1976; 13: 59.
71. Taha EA, Sayed SK, Ghandour NM, et al. Correlation between seminal lead and cadmium and seminal parameters in idiopathic oligoasthenozoospermic males. Cent Eur J Urol. 2013; 66(1): 84-92.
72. Wellejus A, Poulsen HE, Loft S. Iron-induced oxidative DNA damage in rat sperm cells in vivo and in vitro. Free radical Res. 2000; 32(1): 75-83.
73. Aitken RJ, Koppers AJ. Apoptosis and DNA damage in human spermatozoa. Asian J Androl. 2011; 13(1): 36-42.
74. Julin B, Wolk A, J-E Johansson JE, et al. Dietary cadmium exposure and prostate cancer incidence: a population-based prospective cohort study. Brit J Cancer. 2012; 107: 895-900.
75. Sahmoun AE, Case LD, Jackson SA, Schwartz GG. Cadmium and prostate cancer: a critical epidemiologic analysis. Cancer Invest. 2005; 23(3): 256-263.