Cadmium and male infertility

Alaee S¹, Talaiekhozani A²³, Rezaei S⁴, Alaee K⁵, Yousefian E⁶

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-
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.

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

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 germline 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.

<table>
<thead>
<tr>
<th>Model of research</th>
<th>Cadmium administration method</th>
<th>Doses of cadmium</th>
<th>Duration of treatment</th>
<th>Sperm count</th>
<th>Sperm motility</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Wistar male rats</td>
<td>Subchronic exposure to CdCl₂</td>
<td>40 mg/l, per os</td>
<td>30 days</td>
<td>S Decrease</td>
<td>S Decrease</td>
<td>(14)</td>
</tr>
<tr>
<td>Adult BALB/c male mice</td>
<td>Orally administration of CdCl₂</td>
<td>23 mg/kg BW, once per day</td>
<td>45 days</td>
<td>NS Decrease</td>
<td>NS Decrease</td>
<td>(15)</td>
</tr>
<tr>
<td>Adult Wistar male rats</td>
<td>Oral administration of CdCl₂</td>
<td>(0.2 mg/kg)</td>
<td>15 days</td>
<td>S Decrease</td>
<td>NE</td>
<td>(21)</td>
</tr>
<tr>
<td>Adult Wistar male rats</td>
<td>Cd-contaminated radish bulb</td>
<td>1.1 µg Cd/g of diet</td>
<td>4 weeks</td>
<td>NS Decrease</td>
<td>NE</td>
<td>(29)</td>
</tr>
<tr>
<td>Adult Sprague Dawley male rats</td>
<td>Subcutaneous injection</td>
<td>0.6 mg Cd/kg once per day</td>
<td>6 weeks</td>
<td>S Decrease in testicular SG and SC</td>
<td>NE</td>
<td>(31)</td>
</tr>
<tr>
<td>Adult Sprague Dawley male rats</td>
<td>Oral administration of CdCl₂</td>
<td>5 mg/kg BW</td>
<td>15 days</td>
<td>S Decrease</td>
<td>S Decrease</td>
<td>(33)</td>
</tr>
<tr>
<td>Adult male rats</td>
<td>CdCl₂, 1 mg kg</td>
<td>3 days</td>
<td>S Decrease</td>
<td>S Decrease</td>
<td>(45)</td>
<td></td>
</tr>
</tbody>
</table>

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
15. Monsefi M, Alaee S, Moradshahi A, Rohani L. Cadmium induced infertility in male mice. Environ


42. Fende PL, Niewenhuis RJ. An electron microsco-
pic 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.
44. Kotsonis FN, Klaassen CD. Toxicity and
distribution of cadmium administered to rats at
sublethal doses. Toxicol Appl Pharmacol. 1977;
Ameliorative effects of curcumin against acute
cadmium toxicity on male reproductive system in
Impact of lead given in drinking water on the
endocrine and exocrine sexual activity in
pubescent rats. Determination of an apoptotic
47. Lafuente A, Gonzalez-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.
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
51. Zylber-Haran, EA, Gershman H, Rosemann E,
Spitz IM. Gonadotrophin, testosterone and
prolactin interrelationships in cadmium-treated
Reproductive effects of low acute doses of
cadmium chloride in adult male rats. Toxicol Appl
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
the androgen environment within the human testis:
minimally invasive method to obtain intratesticular
Intratesticular testosterone concentrations
comparable with serum levels are not sufficient to
maintain normal sperm production in men
receiving a hormonal contraceptive regimen. J
quality and reproductive endocrine function in
relation to biomarkers of lead, cadmium, zinc, and
copper in men. Environ Health Persp. 2000;
58. Benoff S, Jacob A, Hurley IR. Male infertility and
environmental exposure to lead and cadmium.
59. Xu L, Wang S, Yang X, Wang X. Effects of
cadmium on rat sperm motility evaluated with
computer assisted sperm analysis. Biomed Environ
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
Jl. Cadmium toxicity: a possible cause of male
infertility in Nigeria. Reprod Biol. 2006; 6(1): 17-
30.
Cadmium level in seminal plasma may affect the
pregnancy rate for patients undergoing infertility
evaluation and treatment. Reprod Toxicol. 2008;
25(4): 481-484.
Contrasting associations of blood and semen
lead concentrations with semen quality among lead
469.
64. Dawson EB, Ritter S, Harris WA, et al. Comparison of sperm viability with seminal
plasma metal levels. Biol Trace Elem Res. 1998;
correlation between cadmium in seminal plasma
and fertility status of nonexposed individuals and
two cadmium-exposed patients. Reprod Toxicol.


