Journal of Elementology ISSN 1644-2296

Skolarczyk J., Budzyński M., Pekar J., Małecka-Massalska T., Skórzyńska-Dziduszko K. 2018. *The impact of cadmium on male infertility*. J. Elem., 23(1): 35-44. DOI: 10.5601/jelem.2017.22.2.1320

REVIEW PAPER

THE IMPACT OF CADMIUM ON MALE INFERTILITY

Justyna Skolarczyk, Michał Budzyński, Joanna Pekar, Teresa Małecka-Massalska, Katarzyna Skórzyńska-Dziduszko

Chair and Department of Human Physiology
Medical University of Lublin, Poland

Abstract

Cadmium is a metal which was discovered in 1817. Because it is easily absorbed and accumulated in living organisms, a high concentration of this chemical element in water, air and soil poses a risk to people and the environment. Cadmium is also used in industry. It is not degraded and has a long half-life. The objective of our study was to search several databases (PubMed, Web of Science, Cochrane Library and Medline) to find papers relating to the impact of cadmium on male infertility (in both animals and humans). The main sources of cadmium for humans are occupational exposure and food. The major sources of cadmium in the human diet are grains, fish, vegetables and fruit contaminated with this metal. Another important source of cadmium is cigarette smoke, which in some cases may be the main source of exposure. Daily cadmium intake from food by adults in different countries ranges from 11 to 200 micrograms. In Poland, daily intake of this element is 11-30 µg. The tolerable weekly intake of cadmium, which takes into account safety conditions and the degree of environmental pollution by cadmium, is set at 2.5 µg kg^{-1} body weight/week. Cadmium in the human organism can cause various health consequences, including morphological changes in the reproductive organs. Morphological changes induced by cadmium include necrosis of the seminal tubules and interstitial edema, which leads to decreased testosterone synthesis and impaired spermatogenesis. Cadmium is also a recognized carcinogen, which is mutagenic and genotoxic. Cadmium in animal cells can also cause dysfunction of some metabolic pathways, which can lead to carcinogenesis. The increasingly recognized impairment of fertility in men can be attributed to growing environmental exposure to this chemical element.

Keywords: cadmium, spermatogenesis, infertility.

Katarzyna Skórzyńska-Dziduszko, M.D., Ph.D., Chair and Department of Human Physiology, Medical University of Lublin, Radziwiłłowska 11, 20-080 Lublin, Poland, phone: (81) 448 60 80, fax: (81) 448 60 96, e-mail: katarzyna.skorzynska-dziduszko@umlub.pl

INTRODUCTION

Cadmium is a chemical element included among the metals. In the periodic table of chemical elements, cadmium is in group 12 and period 5. It was discovered in 1817 by Fredrich Stromeyer. Cadmium represents 0.00005% of the Earth's crust. Because cadmium has a high concentration in air, water and soil, is easily absorbed and accumulated in living organisms, and moves quickly in the soil-plant-man pathway, it poses a risk to the environment and people (Czeczot et al. 2010).

Cadmium is produced during the incineration of waste and combustion of oil and coal. It is used in the production of batteries and corrosion resistant coatings, and the non-ferrous metals industry is one of the major sources of this element (Martynowicz et al. 2005)

Once introduced into the environment, cadmium is continually in circulation and is not degraded. Its long half-life translates directly to its accumulation in humans, plants and animals. Environmental exposure to cadmium can lead to absorption of large quantities of this chemical element and to toxic effects on the body (Ostrowska 2008).

The main sources of cadmium for humans are occupational exposure and food. Major sources of cadmium in the human diet are grains, fish, vegetables and fruit contaminated with this metal. Significantly, the amount of cadmium taken in with food depends on eating habits as well as on the type and degree of contamination. Seventy-five percent of the cadmium in the human diet is derived from vegetable products, primarily potatoes – for example, 25% in the USA and 55% in Australia (Marzec et al. 1992). In the diet of infants and children, cadmium comes mainly from carrots (Wojciechowska-Mazurek et al. 2003). In animal products, cadmium is present in various amounts. Fish and shellfish contain cadmium in concentrations ranging from 0.01 to 0.02 mg kg^{-1}, while offal (e.g. liver or kidneys) contains much more cadmium – from 0.2 to 1.6 mg kg^{-1} (Marzec et al. 1992).

Daily cadmium intake from food by adults in different countries ranges from 25 to 200 μg. In Poland, daily intake of this element is 11-30 μg. The tolerable weekly intake of cadmium, which takes into account safety conditions and the degree of environmental cadmium pollution, is set at 2.5 μg kg^{-1} body weight/week (Codex Alimentarius Commission 1998). According to the recommendations of the FAO/WHO, the tolerable cadmium intake by an adult is 0.4-0.5 mg/week and 60-70 μg/day (Wojciechowska-Mazurek et al. 2003).

Another important source of cadmium is cigarette smoke, which in some cases may be the main source of exposure (Huff et al. 2007). Cadmium in the human organism can cause a variety of health consequences, such as itai-itai disease (chronic high-dose effects), diabetes, diabetic nephropathy, hypertension, problems with reabsorption of minerals and vitamins, cancer,

and increased risk of peripheral artery disease (PAD) and lung disease (Satarug et al. 2010).

Cadmium in animal cells can cause dysfunction of some metabolic pathways. Metabolic pathways which undergo induction or dysfunction by cadmium are presented in Table 1 (Waisberg et al. 2003).

Table 1

Genes and gene products whose action is inhibited or stimulated by cadmium (Waisberg et al. 2003)

Induction or dysfunction	Genes or gene products	Function
1	2	3
Immediate early response genes (IEGs)	C-fos; c-myc; c-jun	Cd causes overexpression of IEGs genes which encode transcription factors. These factors are mitogenic signals stimulating cell proliferation and growth.
Stress response genes	metallothionein genes	Metallothioneins sequester cadmium with high affinity, resulting in decreased availability of Cd^{2+} capable of interacting with cellular targets.
	heat-shock genes (HSP)	Cadmium induces protein denaturation or generation of incorrect proteins. Induction of HSP enables functions which are necessary to the survival of the cell.
	genes controlling glutathione	Cadmium ions generate reactive oxygen species, which are removed from the cell by glutathione peroxidase and glutathione reductase.
	translation factors	Overexpression of genes encoding translation initiation factor IF-3 and translation elongation factor EF-1 has been found in cells transformed by cadmium ions.
Disruption of E-cadherin--mediated cell-cell adhesion	E-cadherin	Research shows that cadmium binds to a polypeptide which corresponds to one of the Ca^{2+}-binding regions of mouse E-cadherin and changes its conformation. This damages associations between cells, causing them to separate in the culture.
Induction of apoptosis	caspase-9, p53	Cadmium induces apoptosis by disrupting the structure and function of the tumor suppressor p53 and by activating caspase-9 in a mitochondria-dependent pathway.

cont. Table 1

1	2	3
Inhibition of repair DNA	protein XPA, formamido-pyrimidine-glycosylase	Research shows that cadmium inhibits the repair of oxidative damage in mammalian cells. Cadmium inhibits removal of dimers of thymine generated by UV rays. In addition, cadmium inhibits the bacterial enzyme formamido-pyrimidine-glycosylase and the mammalian protein XPA, which are essential to recognition of DNA damage.

Changes in metabolic pathways induced by cadmium can cause carcinogenesis, but its mechanism of carcinogenesis is not simple, because it acts on multiple molecular targets (Waisberg et al. 2003).

MATERIAL AND METHODS

We searched several electronic databases (PubMed, Web of Science, Cochrane Library and Medline) to find papers relating to the impact of cadmium on male infertility (in both animals and humans). A keyword approach was used. The search terms were "cadmium," "cadmium male infertility," "cadmium male reproductive system," "cadmium spermatogenesis," and "cadmium testis." The search was conducted in August 2016. Initial screening of reports was based on a review of titles. Abstracts and/or full texts were also checked when necessary. The search took into account publications written in English or Polish.

RESULTS AND DISCUSSION

The first study we will present concerning the effect of cadmium on spermatogenesis was conducted on animals. Oxidative stress induced by cadmium was found to cause degenerative changes in several tissues. One of the more sensitive organs is the testis, which is highly susceptible to acute cadmium toxicity. Studies on animals show that cadmium causes a decrease in testicle weight, in the amount of testosterone produced, and in sperm count and activity. A reduced sperm count is caused by disturbances in the cell cycle, DNA repair and cell proliferation (Yari et al. 2010). In the early stages of spermatogenesis, cadmium has a negative effect on the release of sperm from the epithelium lining the nucleus, thus reducing the efficiency and quality of sperm produced. Deterioration of sperm production is also caused

by an increased serum testosterone level. In addition, subcutaneous administration of cadmium has caused histological changes in the testicles, such as necrosis, degradation and desquamation in the germinal epithelium of the seminal tubules. All of these changes affect sperm quality. Negative changes in testicle tissue have been observed even after administration of single doses of cadmium. Histological changes have been reported in the prostate gland as well. Three-month administration of cadmium caused dysfunction of the prostate gland and decreased secretion capacity (Farag et al. 2016). The effects of cadmium on spermatogenesis in animals are shown in Table 2. Studies show that treatment with antioxidants such as L-carnitine can increase sperm count (Yari et al. 2010). Some studies also indicate that vitamin C and E can mitigate the effects of cadmium poisoning (Acharya et al. 2008). These characteristics have also been observed in spiruline (Farag et al. 2016) and selenium (Ren et al. 2012). Tests carried out on adult rats for 16 days

Table 2

Collective representation of the effects of cadmium on the germ cells of animals in the studies analyzed

Author	Animals	Material and methods	Effect of cadmium
1	2	3	4
Yari et al. (2016)	adult rats	cadmium chloride, administered intraperitoneally for 16 days at intervals of 48 h between treatments	decrease in the number and viability of cauda epididymis sperm, in cell proliferation, in the amount of free serum testosterone and in Johnsen Scores in the seminiferous tubules
Yari et al. (2010)	adult rats	cadmium chloride (1 mg kg^{-1} body weight) injected intraperitoneally for 16 days at intervals of 48 h between treatments	decrease in viability and number of cauda epididymis sperm, cell proliferation, and Johnsen Scores in the seminiferous tubules
Yang et al. (2006)	six-week-old male Sprague-Dawley rats	cadmium at doses of 0 (control), 1.000, 2.000, 4.000 or 8.000 mg kg^{-1} by the intraperitoneal route	cadmium at 1.000 mg kg^{-1} caused no changes in testicular histology relative to controls; cadmium at 2.000 mg kg^{-1} contributed to the appearance of undifferentiated spermatids; increased dead Sertoli cells in the seminiferous tubules; decreased interstitial cells; increased inflammatory cells in the interstitial tissues; decreased numbers of elongated spermatids (M1) and round spermatids (M2); increased the number of 2c stage cells (M3, diploid)
Yuan et al. (2016)	*Bombyx mori* larvae	$CdCl_2$ incorporated in an artificial diet (0, 6.250, 12.50, 25.00, and 50 mg kg^{-1})	Cd deformed and affected the maturation of spermatozoa

cont. Table 2

1	2	3	4
Farag et al. (2016)	rats	$CdCl_2$ (2 mg kg^{-1} body weight) by subcutaneous injection daily for 10 days	$CdCl_2$ administered to animals caused lower testicular weight gain than in controls; epididymal sperm counts and motility decreased; the incidence of abnormal spermatozoa significantly increased; the serum level of testosterone significantly decreased; steroidogenic gene mRNA expression was significantly downregulated compared to the control; in the seminal vesicle – severe vacuolation, hyperplasia in the epithelial lining, edema, congestion, hemorrhage, and a few round cell infiltrations. In the prostate glands – severe dilation of some acini with presence of corpora amylacea, inflammatory edema with a few round cell infiltrations, and hyperplasia and nuclear stratification in the epithelial lining with no evidence of prostatic fluid. These epithelia were enlarged with vacuolated cytoplasm and large vesicular nuclei.
Ren et al. (2012)	mice	$CdCl_2$ (5.000 mg kg^{-1} body weight)	A significant decrease in body weight, sperm concentration and motility as well as a decrease in the plasma testosterone level.
Ji et al. (2010)	Male CD-1 mice	intraperitoneally injected with $CdCl_2$ (1.000 mg kg^{-1}) daily from postnatal day 35 to postnatal day 70	A significant decrease in the number of spermatozoa in the epididymides; reduced weight of testes, epididymides and prostate and seminal vesicle; a significant decrease in serum and testicular testosterone when Cd was administered during puberty; reduced mRNA and protein levels of testicular StAR, P450scc, P450(17alpha) and 17beta-HSD.
Oliveira et al. (2006)	ICR-CD1 mice	1.000, 2.000 and 3.000 mg $CdCl_2$ kg^{-1} body weight by single subcutaneous injection	The highest doses of $CdCl_2$ decreased the number of haploid cells and increased the number of diploid, S phase and tetraploid cells.

during which cadmium was administered intraperitoneally showed that cadmium contributes to a decrease in the number and viability of cauda epididymis sperm, the amount of free serum testosterone, cell proliferation, and Johnsen Scores in the seminal tubules (Yari et al. 2010, 2016). A study conducted on six-week-old male Sprague-Dawley rats revealed that cadmium at 1 mg kg^{-1} caused no changes in testicular histology relative to controls, but at 2 mg kg^{-1} increased undifferentiated spermatids and the number of dead Sertoli cells in the seminal tubules, decreased the number of interstitial cells, and increased the number of inflammatory cells in the interstitial tissues. The numbers of elongated spermatids (M1) and round spermatids (M2) decreased, but that of 2c stage cells (M3 or diploid) increased (Yang et al. 2006). In a study using Bombyxmori larvae, cadmium caused deformation of spermatozoa and affected their maturation (Yuan et al. 2016). Research on mice showed that administration of cadmium leads to a significant decrease in body weight, sperm concentration and motility, as well as the plasma testosterone level (Ren et al. 2012). A study conducted on male CD1 mice which were treated with $CdCl_2$ from postnatal day 35 to postnatal day 70 showed that cadmium significantly decreased the number of spermatozoa in the epididymides; reduced the weight of the testes, epididymides, prostate and seminal vesicle; significantly decreased the serum and testicular testosterone level when cadmium was administered during puberty; and reduced mRNA and protein levels of testicular StAR, P450scc, P450(17alpha), and 17beta-HSD (Ji et al. 2010). Research on germ cells of ICR-CD1 mice confirmed that administration of cadmium caused a decrease in the number of haploid germ cells and an increase in the number of diploid, S-phase and tetraploid germ cells (Oliveira et al. 2006). Prenatal exposure to the toxic effects of cadmium seems especially interesting. The metal causes a number of changes to the fetus in experimental animals, including disorders of organogenesis and testicular descent and modification of sexual behavior (Salvatori et al. 2004).

The mechanism of toxicity of cadmium is still unclear. Histopathological examination has shown vascular nuclei injury, and damage to the vascular endothelium, which is especially sensitive to this metal, appears to be crucial (Nolan, Shaikh 1986). The mechanisms of toxicity of cadmium on the endothelium are complex, and include impairment of endocrine function, endothelial mediator activity, endothelial cell proliferation, angiogenesis, coagulation, and the fibrinolysis system, as well as damage to the gene expression system (Martynowicz, Skoczynska 2003). Cadmium is a source of free radicals in the organs of humans and animals, which may cause damage to the brain and testicles (El-Missiry, Shalaby 2000). In low doses (0.13 mg 100 g^{-1} b.w), cadmium mainly causes apoptosis, while in the case of high doses mainly necrosis is observed (Sen Gupta et al. 2004). A reduction in the population of germ cells, e.g. via apoptosis, leads to changes which irreversibly impair testicle function and fertility. Cadmium reduces the weight of the testicles, which is clear evidence of damage (Biswas et al. 2001). Particularly suscepti-

ble to the effects of cadmium are the mitochondria of Sertoli cells. The percentage of mitochondrial defects observed by electron microscopy depends on the dose and time of exposure. Cadmium causes more damage than lead, while the most severe mitochondrial damage is observed during exposure to both of these metals (Bizarro et al. 2003). This is an important consideration due to frequent occupational and environmental exposure to both of these elements.

CONCLUSIONS

Epidemiological studies conducted in recent decades indicate impaired male fertility. Over the past five decades, sperm count, volume and other parameters have declined by about 50% (Swan et al. 1997). These changes may be linked to increasing exposure to environmental toxins damaging the reproductive system. Cadmium has the most significant role among toxic metals affecting the reproductive system. Cadmium is one of the factors impairing the function of the testicles. The mechanisms of action of cadmium in the nucleus are highly complex, and involve damage to the vascular endothelium germ cells, Sertoli and Leydig cells, and intercellular junctions. This metal intensifies the effects of free radicals, causes changes in the activity of enzyme systems and induces an inflammatory response. The morphological changes induced by cadmium include interstitial edema and necrosis of the seminal tubules. This results in a reduction (at different levels) in testosterone levels and impaired spermatogenesis (Czeczot, Skrzycki 2010).

REFERENCES

Acharya UR., Mishra M., Patro J., Panda MK. 2008. *Effect of vitamins C and E on spermatogenesis in mice exposed to cadmium*. Reprod. Toxicol., 25(1): 84-8. DOI: 10.1016/j.reprotox.2007.10.004

Biswas N.M., Sen Gupta R., Chattopadhyay A., Choudhury G.R., Sarkar M. 2001. *Effect of atenolol on cadmium-induced testicular toxicity in male rats*. Reprod. Toxicol., 15(6): 699-704. http://dx.doi.org/10.1016/S0890-6238(01)00184-8

Bizarro P., Acevedo S., Nino-Cabrera G., Mussali-Galante P., Pasos F., Avila-Costa M.R. et al. 2003. *Ultrastructural modifications in the mitochondrion of mouse Sertoli cells after inhalation of lead, cadmium or lead-cadmium mixture*. Reprod. Toxicol., 17(5): 561-566. http://dx.doi.org/10.1016/S0890-6238(03)00096-0

Czeczot H., Skrzycki M. 2010. *Cadmium – an element completely unnecessary for the organism*. Postępy Hig. Med. Dośw., 64: 38-49. (in Polish) http://www.phmd.pl/fulltxt.php?ICID=904693

Czeczot H., Majewska M. 2010. *Cadmium – exposure and its effects on health*. Farm Pol., 66(4): 243-250. (in Polish) http://ptfarm.pl/pub/File/Farmacja%20Polska/2010/04-2010/02%20%20Kadm.pdf

El-Missiry M.A., Shalaby F. 2000. *Role of beta-carotene in ameliorating the cadmium-induced oxidative stress in rat brain and testis*. Biochem. Mol. Toxicol., 14: 238-243. DOI: 10.1002/1099-0461(2000)14:5<238::AID-JBT2>3.0.CO;2-X

Farag M.R., El-Aziz R.M.A., Ali H.A., Ahmed S.A. 2016. *Evaluating the ameliorative efficacy of Spirulina platensis on spermatogenesis and steroidogenesis in cadmium-intoxicated rats*. Environ. Sci. Pollut. Res., 23(3): 2454-2466. DOI: 10.1007/s11356-015-5314-9

Huff J., Lunn R.M., Waalkes M.P., Tomatis L., Infate P.F. 2007. *Cadmium-induced cancers in animals and in humans*. Int. J. Occup. Environ. Health, 13(2): 202-212. DOI: 10.1179/oeh.2007.13.2.202

Ji Y.L., Wang H., Liu P., Wang Q., Zhao X.F., Meng X.H. et al. 2010. *Pubertal cadmium exposure impairs testicular development and spermatogenesis via disrupting testicular testosterone synthesis in adult mice*. Reprod. Toxicol., 29(2): 176-83. DOI: 10.1016/j.reprotox.2009.10.014

Martynowicz H., Skoczyńska A. 2003. *Effects of cadmium on the vascular endothelium function*. Med. Pr., 54(4): 383-388. (in Polish) http://test.imp.lodz.pl/upload/oficyna/artykuly/pdf/full/Mart11-04-03.pdf

Martynowicz H., Skoczyńska A., Kaczmarek-Wdowiak B., Andrzejak R. 2005. *Effects of cadmium on testis function*. Med. Pr., 56: 167-174. (in Polish) http://test.imp.lodz.pl/upload/oficyna/artykuly/pdf/full/Mar8-02m-05.pdf

Marzec Z., Kunachowicz H., Iwanow K., Rutkowska U. 1992. *Tables of trace elements in food products*. Inst. Żyw. Żywn., 60: 1-122. (in Polish)

Nolan C.V., Shaikh Z.A. 1986. *The vascular endothelium as a target tissue in acute cadmium toxicity*. Life Sci., 39(16): 1403-1409. DOI: 10.1016/0024-3205(86)90543-6

Oliveira H., Loureiro J., Filipe L., Santos C., Ramalho-Santos J., Sousa M. et al. 2006. *Flow cytometry evaluation of lead and cadmium effects on mouse spermatogenesis*. ReprodToxicol., 22(3): 529-35. DOI: 10.1016/j.reprotox.2006.03.009

Ren X.M., Wang G.G., Xu D.Q., Luo K., Liu Y.X., Zhong Y.H. et al. 2012. *The protection of selenium on cadmium-induced inhibition of spermatogenesis via activating testosterone synthesis in mice*. Food ChemToxicol., 50(10): 3521-3529. DOI: 10.1016/j.fct.2012.07.021

Salvatori F., Talassi C.B., Salzgber S.A., Spinosa H.S., Bernardi M.M. 2004. *Embryotoxic and long-term effects of cadmium exposure during embryogenesis in rats*. Neurotoxicol. Teratol., 26(5): 673-680. DOI: 10.1016/j.ntt.2004.05.001

Satarug S., Garret H.S., Sens A.M., Sens A.D. 2010. *Cadmium, environmental exposure, and health outcomes*. Environ. Health Persp., 118(2): 182-190. DOI: 10.1289/ehp.0901234

Sen Gupta R., Kim J., Gomes C., Oh S., Park J., Im W.B. et al. 2004. *Effect of ascorbic acid supplementation on testicular steroidogenesis and germ cell death in cadmium-treated male rats*. Mol. Cell Endocrinol., 221(1-2): 57-66. DOI: 10.1016/j.mce.2004.03.012

Swan SH., Elkin EP., Fenster L. 1997. *Have sperm densities declined? A reanalysis of global trend data*. Environ. Health Perspect., 105(11): 1228-1232. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1470335/

Waisberg M., Joseph P., Hale B., Beyersmann D. 2003. *Molecular and cellular mechanisms of cadmium carcinogenesis*. Toxicology, 192(2-3): 95-117. http://dx.doi.org/10.1016/S0300-483X(03)00305-6

Wojciechowska-Mazurek M., Starska K., Brulinska-Ostrowska E., Karłowski K., Grudzińska B. 2003. *Rating of perceptron of heavy metals with day-long nutritional rations of children and adolescents in selected provinces*. Bromat. Chem. Toksykol., 36 (Supl.): 267-274. (in Polish) http://agro.icm.edu.pl/agro/element/bwmeta1.element.agro-article-6f88af89-8863-438f--a6c1-e84da7e7453a

Wojciechowska-Mazurek M., Starska K., Brulińska-Ostrowska E., Ostrowska P. 2008. *Cadmium – occurence, use and methods of recycling*. Gospodarka Surowcami mineralnymi, 24(3): 255-260. (in Polish) http://meeri.eu/Wydawnictwa/GSM2433/ostrowska.pdf

Yang H.S., Han D.K., Kim J.R., Sim J.C. 2006. *Effects of alpha-tocopherol on cadmium-induced toxicity in rat testis and spermatogenesis*. J Korean Med. Sci., 21(3): 445-451. ISSN: 1011-8934, PMID: 16778387

Yari A., Asadi M. H., Bahadoran H., Dashtnavard H., Imani H., Naghii M.R. 2010. *Cadmium toxicity in spermatogenesis and protective effects of L-carnitine in adult male rats*. Biol. Trace Elem. Res., 137: 216-225. DOI: 10.1007/s12011-009-8577-5

Yari A., Sarveazad A., Asadi E., Raouf Sarshoori J., Babahajian A., Amini N. et al. 2016. *Efficacy of Crocus sativus* L. *on reduction of cadmium-induced toxicity on spermatogenesis in adult rats*. Andrologia. DOI: 10.1111/and.12568 (Epub ahead of print)

Yuan H., Qin F., Guo W., Gu H., Shao A. 2016. *Oxidative stress and spermatogenesis suppression in the testis of cadmium-treated. Bombyx mori* larvae. Environ. Sci. Pollut Res. Int., 23(6): 5763-70. DOI: 10.1007/s11356-015-5818-3