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Review Articles

Toxic Effects of Heavy Metals (Lead and Cadmium) on Sperm Quality and Male Fertility

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Male infertility with idiopathic etiology may be attributed to various environmental or occupational exposures to toxic substances, such as heavy metals. The accumulation of lead, cadmium, arsenic, bismuth, and other elements, even in low concentrations, induces strong toxic effects on the reproductive tract. It has been suggested that the risk is usually connected with both increased concentrations and exposition duration. The current review focuses on the toxic metals lead (Pb) and cadmium (Cd) as the main environmental pollutants, and their effects on the function of the male gonads (testes and spermatogenesis), as well as the related reproductive consequences as poor sperm quality and male infertility. Characteristic of all heavy metals is that they generate reactive oxygen species (ROS) and induce oxidative stress (OS) in a variety of systems, including the reproductive system. Massive degeneration of germ cells and alterations in the levels of LH, FSH and testosterone are also reported.

Key words: heavy metals, testis, male reproductive system, male fertility

Introduction

There are still debates concerning what exactly means the term „heavy metal" and which chemical/natural elements are classified as such. In general, this term is widely used about metals and/or metalloids with potential for toxicity (i. e., which form toxic soluble compounds in the organism) in humans, animals or the environment. Lead (Pb), cadmium (Cd), mercury (Hg) and arsenic (As) are prime examples of ‚heavy metals', not just because their chemical characteristics show a relatively high atomic number and atomic weight or density (>5g/cm^3), but also because they are major polluters of the environment [68]. Occupational exposure to metals can occur in different sectors of industry and can lead to significant morbidity and mortality in people working there. A large part of these elements can be eliminated from the body. Approximately 12% of the absorbed by the organism metal ions enter the bloodstream. From the blood, they

accumulate and are proven to cause severe damage to a variety of organs such as bones, kidney, liver, lungs, and brain [31]. The heavy metals' ions' toxic effects are expressed mainly by blocking and/or changing of the normal action of different enzymes [55, 57]. People exposed to heavy metals for a long time get chronic poisoning. However, other metals as zinc (Zn), cobalt (Co), and iron (Fe), besides toxic, are essential also about many biochemical processes in the human organism [19]. For instance, zinc is an important co-factor in many enzyme reactions in the human body, vitamin B_{12} contains cobalt ion (Co^{2+}), and the hemoglobin – iron ion (Fe^{2+}), respectively, in the active centers of its molecules. Analogically, copper, manganese, selenium, chromium, and molybdenum are trace elements that are essential for a living organism. Another subgroup of metals and metalloids, such as aluminum, bismuth, gold, gallium, lithium, silver, mercury, arsenic, etc., are included in the arsenal of pharmacological resources and have therapeutic application in medicine and cosmetics. Furthermore, radioactive metals have both chemical and radiation toxicity. Each one of these elements could be harmful to the organism, if it is applied in high dose or when the normal mechanisms of its elimination and/or metabolism are disrupted [68].

In their accumulation in the organism, the different metals could cause serious damage to various organs – more often in the lungs (as chronic bronchitis, pneumofibrosis, emphysema), liver (cirrhosis), kidneys (different types of nephropathies), the heart (cardiomyopathy and hypertonia), testes, brain (paraesthesia, polyneuritis disorders and different types of encephalopathies in the central nervous system – CNS), blood system (different types of anemia) and bones (osteoporosis, osteomalacia) [56]. They could also participate in the replacement of different substances in tissue structures. In this way, the tissues, constructing the arteries, joints, bones, and muscles show reduced function and/or morphological instability due to the replacement process. Potential risks are both acute and chronic intoxications with ions of heavy metals because of the impossibility about the regeneration of the normal functions of the injured tissues in the organism.

The known ways of metals to enter in the organism are: by inhaling metal vapor and smoke (in the industry), by ingestion (with food and water), as well as by absorption through the skin and mucous membranes during work, play, etc. The main moment in the study of the toxic effects of different substances on the body is the determination of the exposure time and dose-response relationship in the experimental model. In this regard, the reference values of the elements in the blood and urine are of important diagnostic matter. For example, the reference values of lead (Pb) in urine and blood in humans, are: 6.3-13.0 mkg/l, 8.0-269 mkg/l, respectively; for the cadmium (Cd) – 0.5-4.7 mkg/l in urine and 1.0 mkg/l in blood, and their increased levels indicate toxicity and necessity application of measures for prevention and/or treatment. Doses of 0,2-0,3 mg/kg body weight per day lead compounds (as Pb-acetate) are sufficient about the appearance of symptoms of intoxication. Usually, the risk is directly related to both the increase in lead concentration and the duration of exposure [4, 53]. Epidemiological studies in men (working in a Pb environment) with blood Pb levels ranging from 10 μg/dl to <40 μg/dl have shown an increased risk of infertility [53]. In another study, 4000 workers with blood Pb levels higher than 25 μg/dl, have significantly decreased insemination potential (childless men or with a small number of children) has been shown, compared with the control group of 5000 individuals [40].

From the most of the heavy metals, Cd has been the most widely studied and is considered a reproductive toxicant in experimental animals when administered

as a single high dose [61]. Cd concentration in blood is a marker of both recent and cumulative exposure, whereas urinary concentration mainly mirrors cumulative exposure [6, 19]. After smoking, the Cd content of smokers is 4-5 times higher than that of non-smokers [59]. On average, the daily Cd intake of humans is 1.06 μg/kg body weight [65]. The absorption of Cd and Cd compounds, such as Cd-chloride ($CdCl_2$), Cd-acetate and Cd-carbonate in the people, varies from 3,0% to 8,0% of the respectively applied dose [31]. Several other studies, however, have also reported adverse effects at lower environmental doses [68]. Despite the lower intake of Cd, the elimination half-life of Cd is longer (~ 20-40 years in humans) and can accumulate in the body [65]. Besides, the testis is the tissue in which Cd can accumulate in large amounts [61]. Cd exerts direct cytotoxicity within the testis, mainly targeting two specific cell populations, the Sertoli cells (SCs) and the Leydig cells (LCs), with consequent impairment of spermatogenesis and endocrine function [50].

The current review focuses on the toxic metals Pb, and Cd as the main pollutants of the environment, and their effects on the function of the male gonads (testes and spermatogenesis), as well as the related reproductive consequences as poor sperm quality and male infertility.

Testicular and hormonal effects of heavy metals

Chronic heavy metal intoxication (and/or their compounds) also affects the endocrine glands, including the testes and spermatogenesis. Studies with exposure of experimental animals to lead (Pb) have demonstrated macroscopic changes in the testes and accessory glands, such as testicular atrophy, decreased weight of the seminal vesicles, epididymis, ventral prostate, and alterations in semen quality [51, 58, 60]. Histological preparations have shown morphological damages in the testes with decreased population of germ cells [1], as well as disruption of the hypothalamic-pituitary-testicular (HPT) axis [58, 62] caused namely by the increased levels of Pb in rats. Other studies performed on mice (exposed to Pb) have shown the seminiferous tubules degeneration [25] and abnormal cytology of all types of germ cells [22]. According to one experiment of monkeys, exposed to Pb the electron-microscopic assay revealed that from even an early age, prolonged exposure caused testicular changes that persisted in their later life, even when blood Pb concentrations were significantly reduced [23]. Accumulation of lead preferentially in the epididymis and other accessory glands has also been noted [42]. Furthermore, the exposure of Pb leads to suppression of testosterone (TE) synthesis, which suggests that the probable target cells of Pb in the testis are Leydig cells [62], while Sertoli cell function does not appear to be affected.

According to literature data, cadmium (Cd) has been determined as a reprotoxic element, which affects directly the selected cellular populations in the testis, including impairment (cytotoxic and functional) of Sertoli and Leydig cells and induced oxidative stress in both somatic and germ cells. Data showed that Cd affects the male reproductive system from embryonic stages to adulthood, and has adverse effects on gonadal development [50, 61]. At doses that did not affect most organs, Cd caused damage to the testes within 24-48h. Men with varicocele usually show an increased accumulation of Cd in the testicular circulatory system, correlating with the increased percentage of apoptotic germ cells in the seminiferous tubules [9]. Indeed, it has been proven that Cd attacks and causes specific morphologic alterations and dysfunction in

blood vessels [5], to the internal spermatic artery, its testicular and epididymis branches, and the pampiniform plexus (in species with a scrotal testis including human), making them strongly permeable.

Exposure of rats to Cd of 1 mg/kg daily by gavage for 28 days can cause severe ultrastructure changes in adult SCs [27], and at a single dose of Cd (3μmol/kg) show vacuolation in the Sertoli cell cytoplasm and irregular chromatin condensation in late spermatids [21]. In adult mice exposed to Cd by inhalation for 28 days can cause severe mitochondrial changes in SCs [11]. Various studies have shown that Cd has a much stronger effect on the gonadal structure than Pb, by damaging vascular endothelium and blood-testis barrier (BTB) integrity [57], inducing in this way apoptosis and inflammation processes in testicular tissue [34]. BTB is a complex structure whose main component is SCs (by forming tight junctions – TJ between them) and which spatially divides mitotic from meiotic and post-meiotic germ cells in the seminiferous tubule structure. Cd attacks BTB by inducing defragmentation of actin filaments of SCs in rodents [69] and humans [70]. Molecular biology findings indicate that Cd perturbs the cytoskeleton of actin by disrupting F-actin organization in human SCs at 0.5-20μM after altering the expression of actin regulatory proteins Arp3 and Eps8 *in vitro* [70]. BTB damage is associated with germ cell loss and reduced total spermatozoa count, which determine subfertility or infertility conditions. *In vitro,* the addition of Cd to cell cultures of Sertoli [57] or SC and spermatocytes [17] disrupts the tight (occludin) connections between cells, thus facilitating the entry of toxic substances into cells. These studies also show that Cd has a dose-dependent effect on BTB integrity, by inhibiting the establishment or inducing the disruption of the TJ assembly between rat SCs, through downregulation of occludin (a TJ integral membrane protein) and urokinase plasminogen activator, without causing any apparent cytotoxicity and TE can protect it [17, 57]. Cd can down-regulate the focal adhesion kinase (FAK – non-receptor protein tyrosine kinase to regulate BTB) expression [65], by regulates TJ proteins (e.g., ZO-1 and occludin) in the rat testis [57]. In this connection, studies have indicated the negative influence of Cd on E-cadherin in the epithelial cells of seminiferous tubules [17, 36], which makes the testes particularly susceptible to the toxicity of this element. This is probably due to interaction of Cd with the putative Ca^{2+}-binding motif in the molecule of E-cadherin, suppressing in this way the cadherin-based cellular adhesion. Furthermore, E-cadherin is a separate part of a common structure with tight junction-proteins (e.g., occludin, claudins, JAM-A) at the BTB, which allows maximally fast access of Cd to E-cadherin in the epithelial cells. An important role in these processes probably plays the testosterone, which counteracts the disruptive effects of Cd by inducing the expression of TJ integral membrane proteins such as occludin, regulating in this way Sertoli cells TJ-permeability barrier [17]. These observations confirm the view that TE promotes BTB integrity and cell adhesion function in the testis [66], as well as the likelihood that this androgen (or a manipulation of the androgen receptor in SCs) will be a potential target factor to manage Cd-induced testicular pathology. Another investigation demonstrates that Cd disturbs BTB in the rat testis *in vivo* by up-regulating transforming growth factor β3 (TGF-β3), which in turn activates p38 MAPK signaling [41]. Interestingly, Cd also activates the JNK pathway at the same time to up-regulate α2-macroglobulin to counteract its adverse effects because JNK specific inhibitor can aggravate Cd-induced damage on BTB [69], indicating the JNK signaling is the protective mechanism in SCs after Cd treatment [74]. Cadmium also significantly decreased hCG-stimulated TE production by Leydig cells *in vitro* or

*in viv*o at doses that did not affect viability, which indicates that Leydig cells probably also suffer adverse effects. Independently of that, SCs are much more sensitive to Cd and Cd compounds than LCs (in contrast to the effects of Pb), showing major structural and functional changes after exposure, even at doses of Cd that do not lead to visible testicular damage [43]. The reproductive toxicity of Cd (compared to other heavy metals) has been studied in more detail in experimental animal models when administered as a single high dose [61]. An *in vivo* experimental rat model showed that Cd exposure induced testes inflammation. The Cd-induced inflammatory process in the testis develops with enhanced expression of the characteristic inflammation markers (including inducible nitric oxide synthase/iNOS, tumor necrosis factor-α/TNF-α, nuclear factor-kB/NF-kB, cyclooxygenase-2/COX-2, and heme oxygenase-1), leading to vacuolization of the seminiferous epithelium cells, together with hemorrhage and interstitial tissue edema and subsequent widely spread necrosis [24]. These pathological changes were associated with impairment of spermatogenesis [19]. Experimentally exposed to Cd rats (at different doses and duration), showed disorganization of the seminiferous epithelium, germ cell depletion, and release of immature gametes into the lumen [18, 49], but multinucleated giant cells increased [32] as well as rat's sperm count, motility, and viability declined, respectively [47].

The effects of Cd related to human fertility have been reviewed in several papers [19]. The data from epidemiological studies support the positive correlation between Cd and male subfertility/infertility. Sharma et al. analyzed the association between cases of hypospadias and serum Cd concentrations and established that the boys with hypospadias have significantly higher serum Cd levels compared to healthy control boys [54]. Similar studies give reason to suppose that most cases of unexplained subfertility in infertile couples or hypospadias, and/or other idiopathic diseases, a probable factor may be Cd reproductive toxicity [13].

Spermatogenesis-related hormonal disruptions.

Androgen hormones play a complex and important role in the regulation of spermatogenesis and maturation of male germ cells. The results of experimental studies in rats show many locations where the effects of heavy metals are involved in the dynamics of male sex hormones, mainly in the hypothalamic-pituitary-testicular axis [51]. For example, dependently of the levels and longevity of exposure of the rats under the influence of Pb, damage to the signaling systems in the hypothalamus and pituitary gland, including their hyperfunction, leading to over-production of gonadotropin hormone (gonadotropin-releasing hormone/GnRH) and luteinizing hormone (LH) [58] have been established. In support of animal experiments, studies of workers (industry workers with elevated Pb levels) have reported a positive relationship between serum LH levels and the duration of occupational exposure to Pb, finding confirmed, and in mean blood Pb levels of 35μg/dl [48]. In response to the stimulation with LH, the Leydig cells in the testes produce the main androgen hormone testosterone. In this aspect, studies on the serum TE in men professionally-exposed to Pb interpret in different ways the concentrations of this hormone. Semen Pb concentrations at a mean of 2 μg/dl have been reported to be inversely related to serum TE among occupationally-exposed men [4]. Smoking was correlated significantly positively with the levels of both TE and estradiol, suggesting it may have confounded those relationships. In

increased blood Pb levels have been observed significantly decreased levels of markers for prostate secretory function (seminal zinc, acid phosphatase activity, and citric acid). In experiments with mice exposed to Pb for 30 days [52], increased steroid-binding globulin levels and suppression of testicular TE levels were shown to be associated with increased duration of Pb exposure. Decreased testosterone levels and increased androgen binding protein levels have also been established in the cells of the epididymis [51]. According to other literature reports, increased serum testosterone concentrations have been assessed in men, exposed in both low (around 5 μg/dl) [60] to comparatively high (more than 40 μg/dl) Pb serum levels. In all cases, however, the continuous exposition in the presence of Pb influences the serum testosterone concentration. These findings suggest that except disrupting TE secretion (under the action of Pb) relative to the reproductive hormonal axis, it is possible to include other hormonal and/or feedback hormonal pathways, such as a lack of reflex in response to plasma testosterone, direct inhibitory androgen biosynthesis in LCs, or defects in LH regulation at the pituitary level [58]. This hypothesis could be confirmed by the molecular mechanisms (based on histopathological studies), revealing degenerative changes in LCs in experimental rats [68], which gives reason to consider these cells as a target of Pb intoxication. On the other hand, due to the imbalances in the hormonal axis caused by Pb exposure, pituitary cells release inappropriate LH levels and alter the steroid negative feedback loop [51], usually at the hypothalamic level [26]. Elevated concentrations of other sex hormones, such as follicle-stimulating hormone (FSH), secreted by the pituitary gland, have been observed after exposure to Pb in men [48] and rats treated with this metal. Furthermore, inappropriate inhibin B overproduction in excessively lead exposed subjects may be induced by Sertoli cells dysfunction, which suggests spermatogenesis impairment [44]. Investigations with male monkeys, however, have suggested as eventual reason about the changed functions of the Sertoli cells the decreased levels of inhibin/FSH [23], rather than the direct influence on the cells. Similar results have proposed the role of the Sertoli cells as indirect targets of Pb toxicity, and the disruption FSH levels by the lead's effects are the most probable reason about reproductive dysfunction, instead of direct influence. These studies have also demonstrated the protective role of BTB on the testicular cells against direct exposure to high levels of serum Pb. For these reasons and considering the wide spectrum of Pb toxicity on the hormones, it probably influences the male reproduction mainly by altering the gonadal hormonal axis, as well as on the hormonal control of the spermatogenesis, rather than by a direct effect on the cells of seminiferous tubules in the testes [63].

Cadmium (Cd) has also been shown to accumulate in the hypothalamus and pituitary glands, decreasing the blood prolactin level [38]. Once Cd enters cells through any damage, its influence has been attributed primarily to its interference with zinc-mediated metabolic processes, probably by molecular mimicry of Zn [12]. As a whole, data suggest both direct (via testicular and hypothalamus-pituitary toxicity) and indirect (via altered hormone secretion) effects may be involved in cadmium's reproductive influence and consistent with this is a hypothesized role of Cd as a metallohormone [14]. According to studies, performed by Jurasovic et al. [33], in men attending infertility clinic with median blood Cd levels of 0.85 mg/L, significant negative associations between serum Cd level and testis size have been observed, but not with the sperm parameters in models adjusted for potential confounders. Besides, serum Cd was positively associated with FSH, TE, and estradiol levels, as well as with seminal fluid acid phosphatase, an

indicator of prostate function [2, 33]. According to a study of 98 industrial workers (median serum Cd level 3.40 mg/L) and 51 subjects not occupationally exposed (median Cd level 1.83 mg/L) found significant positive correlations between pathologic sperm, LH, TE levels with blood Cd levels, but also a negative correlation with prolactin level in the total study population [60]. In another study conducted in Nigeria, in 60 male (with unusually high Cd levels) partners of couples attending an infertility clinic (excluding men who smoked, consumed alcohol, used steroids or fertility drugs, or had medical conditions that might impair spermatogenesis) showed that serum levels of LH and FSH, TE, and prolactin were significantly higher in the men with low or no sperm [2]. Other data, however, showed that Cd (compared to Pb) was positively associated with serum inhibin B levels in a model adjusted for age, BMI, and current smoking, and this association persisted even when the effects of the other metals were controlled, but no effects were seen on FSH or TE [45]. Inhibin B is considered the best available endocrine marker of spermatogenesis in subfertile men, but another study found it did not correlate with sperm parameters [37]. Various investigations conducted on a large scale prove that there is a negative association between serum Cd levels with total (or free) TE and sex hormone-binding globulin (SHBG) [15].

By taking in consideration the ethical limitations, many of the described studies on the reproductive organs have been performed on experimental animals (mainly rodents), where large doses of the heavy metal ions (administered by injection) have been applied to reveal their influence on cellular and tissue levels. However, the used experimental animal models substantially differ from human occupational and environmental exposure conditions (including that through smoking).

Influence of heavy metals on sperm quality and male fertility

The general effects of metal toxicity on the testicular tissue and endocrine function inevitably lead to impaired spermatogenesis and sperm quality. In most professionally men exposed on contact with Pb, a lot of changes in the parameters affecting the morphology and physiology of sperm are observed with increasing Pb concentration in seminal plasma or blood serum (usually at levels > 40 μg/dl, but often even at <10 μg/dl). These Pb levels are associated with reduced ejaculate volume (hypospermia) [26], decreased number/concentration (oligospermia) or sperm density [4, 46], and at higher levels (53 μg/dl) correlation has been shown with other pathological conditions, such as asthenospermia (immobile sperm) and teratozoospermia (gametes with various morphological defects) [39]. Other studies have found higher percentages of immature and abnormal sperm (with round or microcephalic heads, and/or short tails) in the ejaculate of workers exposed to both high and lower serum Pb levels [60]. Lead has been shown to incur detectable negative effects on blood, semen and/or spermatozoa quality in workers, such as inducing prolonged liquefaction time, decreasing sperm motility [46] and viability, even in serum levels ≤ 10μg/dl [28]. The harmful effect of this metal is also associated with reduced functional maturity of the germ cells (sperm chromatin condensation), especially in men with a mean serum Pb level of 45μg/dl [67]. On the other hand, concomitantly, significant improvements in the number of motile sperm has been reported after mean serum Pb decreased from 42 μg/dl to 20 μg/dl among the Pb factories workers [64]. According to studies in the field of the assisted reproductive techniques, a relationship between induced by Pb abnormal functions of the male gametes, premature capacitation and acrosome reaction has been observed [7], leading to decreased

ability of the sperm to penetrate through the *corona radiata* and *zona pellucida* and thus, fertilizing of the ovum [5]. The same authors have established an increased frequency of post-implantation embryonic loss in 0-2µg/ml Pb-acetate in the samples and at 40µg/dl serum Pb levels (or at 25-50mg/kg in food), respectively [5]. Benoff et al. (2003) have found a strong negative correlation between Pb levels in seminal plasma and rates of successful *in vitro* insemination in humans [8]. According to these results, Pb significantly increases the frequency of sperm function disorders in exposure cases both before and after ejaculation.

In several larger studies, associated with low levels of Pb exposure in different male groups/populations, adverse reproductive effects or sub-fertility were also observed. Results of regression models adjusted for confounders (age, smoking, alcohol, blood cadmium, and serum copper, zinc, and selenium), the serum Pb level (median serum Pb level: 49.2 mg/L or 57 mg/L and upper) correlate negatively with sperm count, the number of motile sperm (significantly lower percentage of progressively motile sperm), normal sperm and serum prolactin and positively associated with abnormal sperm morphology and, the percentage of slow sperm, serum TE and estradiol, respectively [60]. Also, a decrease in d-aminolevulinic acid dehydratase (ALAD), an indicator of long term lead exposure, was associated with decreased seminal plasma zinc levels indicating the adverse effects of lead on prostate function [60].

Studies focusing on the direct relationship between cadmium exposure to the environment and sperm quality in humans are often contradictory, despite the conclusion that Cd accumulation in germinal cells and Cd effects on sperm count and sperm motility are dose- and time-dependent [3]. Zhang et al. collect 11 research articles (1093 infertile subjects and 614 controls) and perform a meta-analysis and find that a high level of Cd in semen causes male infertility [73]. Some studies have suggested a significant negative correlation between Cd serum concentrations and sperm parameters, but other investigations have not shown any clear relationship between these two characteristics [19]. For instance, Asian [16, 71] and Nigerian men [2] with fertility problems and working in conditions with increased levels of Cd, who have had medium, even low levels of Cd in the serum, have shown decreased semen quality. At serum Cd levels between 0.78 mg/L and 1.31 mg/L, a decrease ejaculate volume and sperm density were observed [71], as well as an increase in the number of gametes with midpiece defects and immature forms (in mean Cd serum level – 1.35 mg/L) [16]. The mean level of serum Cd is higher only in men without sperm in the ejaculate (serum Cd levels – 460 mg/L) than in men with low or normal sperm count (serum Cd levels – 230 mg/L; vs. 210 mg/L) [2]. Besides sperm concentration, sperm motility is also severely affected by Cd. Men with low sperm motility had significantly higher serum Cd levels than did men with normal sperm motility [71]. In the investigation of fifty healthy men, de Franciscis et al. have found that serum Cd concentrations were positively associated with a reduction of sperm motility and the appearance of teratozoospermia [20]. Contradictory results have been reported by other smaller studies (Finnish and German) that did not detect significant effects of cadmium exposure on sperm parameters [30]. In comparative studies on the concentrations of Cd in the seminal fluid in industrial or refinery workers (n=27) and consecutive sperm donor candidates (n=45), the levels in the sperm of the industrial group have been significantly higher (mean Cd levels – 0.04 mg/kg) than in the sperm donors (0,005 mg/kg). However, the higher Cd levels in the first group did not show significant changes in sperm morphology and motility compared to the second group [30]. On the other hand, no correlation between the

semen Cd level and the sperm parameters has been observed. Several other studies also have not found significant correlations between serum and seminal plasma (or sperm) Cd levels [35], making it especially difficult to interpret the data. Analogous difficulties have also been reported when comparing low levels of Pb in the serum to semen parameters [4]. Contradictory opinions are probably based on the fact that different studies apply different methodologies in which specific variables, such as smoking and alcohol use by the men involved, are not sufficiently controlled, and thus may disguise differences related to male fertility. All the same, many experiments with animal models confirm the harmful influence of Cd on the sperm parameters, even in low concentrations. In a single low dose of Cd (0.05 or 1.0 mg/kg body weight), administered to adult rats, has resulted in failure of spermiation, the final phase of sperm differentiation [29], and also to reduced sperm concentration and motility [72]. Sperm motility is recognized to be more sensitive to this trace element, as the reduced sperm motility has been observed at a dose far below the dose affecting sperm production [10]. The data show that while animal experiments support an adverse effect of low Cd exposure on semen parameters, more research is needed to clarify this relationship in human males.

Conclusion

The presented data characterize the heavy metals as strongly toxic to the male reproductive system. Each of them shows a selective influence (directly or indirectly) on germ cells populations in the testes and functionally damages Sertoli cells and Leydig cells. These heavy metals also affect the endocrine system (hypothalamic-pituitary-gonadal axis), alter the normal expression of FSH, LH, TE, and other biologically-active proteins, which could disrupt spermatogenesis and lead to male infertility. Most of the literature points to the fact that probably the wide range of adverse effects is due to increased production of ROS and cause OS with pathological tissue damage as a result of prolonged exposure to high levels of heavy metals in humans and animals. Although the presented data are impressive, additional studies are necessary on the mechanisms of influence of the levels of the heavy metals on the male reproductive system and the quality of human sperm before making any conclusions in this direction.

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