Journal of Advances in Medical and Biomedical Research | ISSN:2676-6264

The Relationship of Cadmium, Nickel, and Manganese Trace Elements with Oxidative Stress in the Semen of Infertile Men

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Article Info

10.30699/jambs.31.147.372

Received: 2022/10/02;
Accepted: 2023/01/11;
Published Online: 27 Sep 2023;

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ABSTRACT

Background & Objective: Trace element levels are important for sperm function. On the other hand, oxidative stress is one of the most important causes of DNA damage. This study aimed to evaluate the relationship between cadmium (Cd), nickel (Ni), and manganese (Mn) trace elements and also oxidative stress in infertile men.

Materials & Methods: This case-control study was carried out on 50 oligozoospermic, 50 asthenozoospermic, and 50 normozoospermic men. All individuals were subjected to semen analysis. Cadmium, nickel, manganese, total antioxidant capacity (TAC), and total oxidant status (TOS) were detected using the manual assays. Superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities were analyzed using the ELISA.

Results: The findings revealed that there was a significant increase in TOS index in the patient groups compared to the normozoospermic group ($p = 0.045$, $p = 0.038$ respectively); however, these changes were downward for the TAC factor. The levels of SOD and GPx activities were significantly reduced in the patient groups compared to the normozoospermic group ($p = 0.015$, $p = 0.020$ respectively). Also, Cd and Ni levels were significantly elevated and had a negative association with TAC in the patient groups compared to the normozoospermic group. However, the results of Mn level showed a significantly lower value and a positive association with the TAC index.

Conclusion: Mn as a component of SOD enzyme is necessary for normal sperm functions. In contrast, high levels of Cd and Ni are toxic for human sperm and negatively correlated with TAC and sperm parameters.

Keywords: Trace Elements, Oxidative Stress, Oligozoospermia, Asthenozoospermia. Normozoospermia

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Introduction

Infertility refers to the inability of a couple to become pregnant after one year of unprotected intercourse without contraceptive methods (1). Infertility is a disorder that affects about 30–50% of men. So far, various factors such as structural problems (including varicocele), endocrine defects, genital tract infections, immunological defects, obesity, aging, drug use (such as smoking and alcohol consumption), environmental factors (such as pesticides, toxins and radiation), and genetic defects have been found effective in the etiology of male infertility (2).

One of the most important causes of DNA damage is elevated levels of oxidative stress. Studies have shown that oxidative stress reduces sperm viability and motility, and ultimately DNA damages the sperm (3). Oxidative stress not only causes the loss of sperm DNA health, but also reduces the fertilization potential of these cells through damage to proteins and fats in the sperm plasma membrane (3). Pro-oxidants are constantly produced in living cells and antioxidant defense systems are required to prevent oxidative stress. The more defense systems antioxidants enzymes are such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) (4). SOD enzyme modulates cellular oxidative stress by scavenging superoxide radicals and converting them to hydrogen peroxide. Then, GPX and CAT eliminate the hydrogen peroxide through oxidation of GSH and producing water respectively (5).

It has been proven that many trace elements have been associated with male reproductive health. For example, manganese (Mn) is an important trace element for human reproductive function. This element is part of a large number of enzymes, especially in Mn2 +-SOD (6). Although manganese is essential for the health and function of the human reproductive system, numerous studies have shown that high levels of manganese in seminal plasma can have a potentially toxic effect on sperm quality. However, there is currently no data on the normal range for physiological performance against the toxic effect of manganese on semen parameters (7). Meanwhile, cadmium (Cd) is ubiquitous, though the main source is tobacco smoke and the consequent bioaccumulation (8). Several studies have shown an association between low sperm motility and Cd level in seminal fluid (9). It is associated with changes in sperm parameters and reproductive toxicity. Cd accumulates in the testes and leads to induction of degeneration of the seminiferous tubules and steroid genesis impairment (10). Nickel (Ni) is a heavy metal that is present in all components of the environment. It has the lowest oxidation number: -1 in the lowest mode and +4 in the highest mode, and the most common nickel oxidation number is +2 (11). One of the important aspects of nickel poisoning is that it crosses the placental barrier and the testicular blood barrier, which can be detrimental to the proper fertility and growth of the embryo (12). Recent studies have concluded that elements can effectively clear reactive oxygen species (ROS) in human blood cells and reduce the damage caused by oxygen-free radicals. In addition, intake of some elements appears to be associated with the activity of GPx and SOD (13). Thus, in this study, our aim was to investigate the relationship between cadmium (Cd), nickel (Ni), plus manganese (Mn) elements and oxidative stress in the semen of oligozoospermic and asthenozoospermic groups.

Materials and Methods

Collection of samples

In this case-control study, semen samples of normozoospermic (n=50), oligozoospermic men (n=50) and asthenozoospermic (n=50) were recruited from the endometrium and endometriosis Research Center of Fatemieh Hospital Fertility Clinic (Hamadan, Iran). Informed written consent of each patient was obtained and all subjects were evaluated using a questionnaire that covered fertility parameters, medical history and chronic diseases. Approval was obtained from the ethics committee of Hamadan University of Medical Sciences (ethics committee code: IR.UMSHA.REC.1399.494). Patients with recognizable causes of male infertility such as obstructive oligozoospermic groups, varicocele, infections and diabetes were excluded. According to WHO 2010 criteria, Normozoospermic men were defined as samples with motility ≥40%, morphology ≥4% and sperm concentration ≥15 million/ml and were included as normozoospermia and samples low of these parameters were selected as oligozoospermia. Also, sperm motility <40% and progressive motility <32% is defined as asthenozoospermia. Semen analysis was conducted according to the 2010 World Health Organization criteria (14). All semen samples were collected in sterile containers after 3 to 5 days of sexual abstinence and were individuals divided into three groups: normozoospermic, oligozoospermic and asthenozoospermic groups. The samples were then incubated in a 37 ° C incubator with 5% CO2 for 30 to 40 minutes. Subsequently, semen liquid macroscopic tests were initially performed (15).

Sperm parameters

The semen sample was washed twice with 10 mL of Ham's medium with HEPES (Kiazist, Tehran, Iran) at 1500 rpm for 10 minutes to remove semen plasma. The Ham's culture medium was poured on the sediment to keep the sperm. The samples were then incubated at 37° C and 5% CO2 for 30 to 40 minutes and the sperm concentration and motility were assessed using computer-aided sperm analysis CASA (Hamilton Thorne, IVOS II, and Beverly, USA) and sperm morphology was evaluated by light microscopy (16).

Sperm count and motility

The concentration and motility of spermatozoa were evaluated using a computer-assisted sperm analysis (CASA) system by sperm test video software. At first, 3 µl sample was loaded into a 20 µm slide at 37 °C for analyses at 30 min intervals up to 180 min. Manual sampling was also performed to ensure the accuracy of the semen analyzer (17).

Sperm morphology

The sperm morphology was evaluated by quick-diff dye solutions. At first, a drop of the above samples were smeared then drying and staining were performed. The dried slides were incubated in fixation solution for 75 seconds, then in staining solution for 60 seconds, and finally in detaining solution for 35 seconds. After washing with distilled water and drying, their appearance was shown by microscope (18).

Total Antioxidant Capacity (TAC)

TAC measurement was performed by FRAP manual method. It assessed the ability of antioxidant compounds of the sample to reduce Fe3+-TPTZ complex to Fe2+-TPTZ. The reaction mixture comprised of 300µL FARP reagent (acetate buffer 300 mM, pH3.6, TPTZ 10mM and ferric chloride 20 mM) and 10µl of semen samples pipetted into a 96-well plate and incubated for 10min in the dark at 37°C. The concentrations of standards (1M FeSO4) and samples were measured by a Spectrophotometer (Bell-Italy) at a wavelength of 593 nm. The concentration of each sample was then determined according to the standard curve (19).

Total Oxidative Status (TOS)

TOS was evaluated with ferric-xylenol orange (FOX) assay based on the oxidation of ferrous ions to ferric ions which leads to producing a colored ferric-xylenol orange complex. The reaction mixture included 10µl of the

semen sample and 190µl of FOX reagent (250 µM ferrous ion, 150 µM xylenol orange, 100 mM sorbitol and 25 mM H2SO4, pH was 1.8) into 96-well plate. H2O2 and PBS were applied as standards and blank respectively. The absorbance at 560 nm was read after 10 min incubation in room temperature (20).

GPx enzyme activity

Glutathione peroxidase (GPx) activity was determined with a ready to use kiazist kit (Tehran, Iran) which was based on reduction of H2O2 by glutathione oxidation, which acts as an electron donor. GSH enzyme was converted to GSSG, and the remaining GSH in the reaction medium can regenerate DTNB and produce a yellow color that is absorbed in 412 nanometers. Color production was inversely related to enzyme activity. Finally, the GPx activity was reported as U / mg protein.

SOD enzyme activity

Superoxide dismutase (SOD) activity was assayed with a ready to use kiazist kit (Tehran, Iran). In this method, superoxide anion was used to convert resazurin to resorufin and is produced chromogen. Finally, the chromogen be measured in terms of calorific value at 420 nm and the results were reported as U/mg protein.

Nickel and manganese

First, standard nickel and manganese solutions are made and then placed at 200oC for one hour. Then, for every 10 ml of storage solution, one milliliter of lanthanum chloride solution (Sigma-Aldrich Co, Steinheim, Germany) is added to eliminate the interference of anions such as sulfate, nitrate and phosphate. Also, the pH of the solutions was reduced to 2 by HCL to ionize these metals. The regulatory specifications of the British atomic absorbing device (Thermo Fisher Scientific, Paisley, UK) were adjusted based on the cathode ray tube, acetylene flammable gas, air oxidizer and wavelength of the emission equal to 422.7 nm, which eventually led to the reduction of nickel and manganese. The semen samples are pH=2 before measurement and then filtered by a 0.22 micrometer filter and the absorption of the semen samples are measured and quantified by drawing a standard curve (9).

Data analysis

The results were entered into SPSS-16 software and related statistical tests were used to evaluate the relationship between the variables. To extract descriptive information; Frequency tables, statistical indicators and appropriate charts were used to analyze the data and compare the T-test groups. Also, correlation tests were used to investigate the relationship between the variables. The significance level of all statistical tests was considered to be 0.05.

Results

Demographic data

In the present study, the minimum age of men in three groups was 32 years and maximum 42 years and the mean age of the men was 37 years and the three study groups were matched by age ($p = 0.350$), pH($p = 0.280$) and volume ($p = 0.102$). The results of semen analysis are shown in Table 1. The two groups of oligozoospermic and asthenozoospermic had a significant difference in sperm morphology in comparison to the normozoospermic group ($p = 0.031$, $p = 0.023$ respectively). The sperm concentration had a significant difference between normozoospermic with asthenozoospermic groups, normozoospermic with oligozoospermic groups and asthenozoospermic with oligozoospermic groups ($p = 0.015$, $p = 0.021$, $p = 0.028$ respectively). Also, sperm motility had a significant different between normozoospermic with asthenozoospermic groups, normozoospermic with oligozoospermic groups and asthenozoospermic with oligozoospermic groups ($p = 0.018$, $p = 0.034$, $p = 0.025$ respectively).

Table 1. Spermogram parameters in three groups of Normozoospermia, Oligozoospermia and Asthenozoospermia men. Values are given as mean ± SD.

Variable	Normo (n=50)	Oligo (n=50)	Astheno (n=50)	*p*-value		
				Normo Vs Oligo	Normo Vs Astheno	Oligo Vs Astheno
Age (years)	37.04±4.99	37.14±4.89	36.84±4.89	NS	NS	NS
Semen pH	7.5±0.13	7.5±0.34	7.5±0.26	NS	NS	NS
Sperm morphology (%)	37.5±4.41	14.5±3.23	13.5±1.65	0.031	0.023	NS
Semen volume(ml)	3.97±0.87	4.09±1.23	3.82±0.63	NS	NS	NS
Sperm motility %	45.7±4.3	35.3±2.7	14.5±1.23	0.034	0.018	0.025
Sperm count (million/ml)	57.39±6.58	10.86±3.58	42.76±5.31	0.021	0.015	0.028

Note: Normo= Normozoospermics, Oligo = Oligozoospermics, Astheno = Asthenozoospermics

(TAC) and (TOS) levels

The finding showed there was a significant change in the oligozoospermic and asthenozoospermic groups for TOS index in comparison to the normozoospermic group (p = 0.045, p = 0.038 respectively). Also, TOS level was increased in asthenozoospermic groups in compared to the oligozoospermic group but it was not significant (Figure 1A). The comparison of TAC factor in semen between different groups showed that the amount of TAC in oligozoospermic and asthenozoospermic groups was changed significantly in comparison to the normozoospermic group (p = 0.047, p = 0.028 respectively). Also, TAC level was decreased in the asthenozoospermic groups in compared to the oligozoospermic group but it was not significant (Figure 1B).

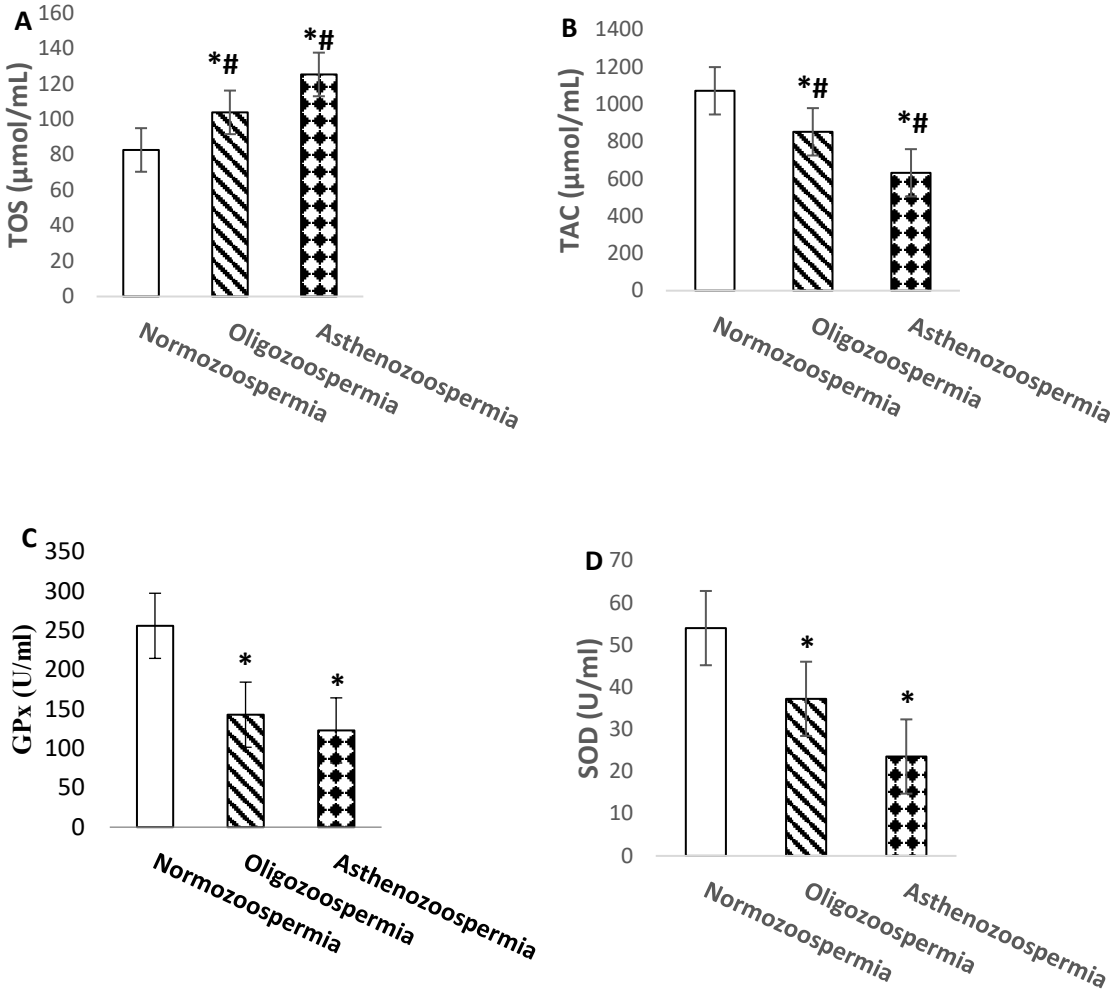

Figure 1. Results related to TOC (A), TAS (B), *GPx* (C) and *SOD* (D) levels in the patient groups and control group. Values are given as mean ± SD. The symbol (*) represents significant differences with control and the symbol (#) represents significant differences between patient groups (P<0.05).

(GPx) and (SOD) Activity

The results of the study of GPx enzyme activity showed that the activity of this enzyme was significantly reported despite the decrease in the oligozoospermic and asthenozoospermic groups compared to the normozoospermic group (p = 0.015, p = 0.020 respectively). Also, this enzyme activity was decreased in the asthenozoospermic groups in compared to the oligozoospermic group but it was not significant (Figure 1C). The results of SOD enzyme activity are given in Figure 1D. As can be seen, there is a significant reduction in the amount of this enzyme activity in the oligozoospermic and asthenozoospermic groups compared to the normozoospermic group (p = 0.034, p = 0.025 respectively). Also, this enzyme activity was decreased in the asthenozoospermic groups compared to the oligozoospermic group but it was not significant.

Nickel and manganese concentrations

The semen concentrations of cadmium, nickel and manganese ions in control and two patient groups are

shown in Table 2. The results of cadmium level showed that this element was significantly increased in the oligozoospermic and asthenozoospermic groups compared to the normozoospermic group (p = 0.031, p = 0.028 respectively). Also, it was found that the concentration of nickel ions in the oligozoospermic and asthenozoospermic groups significantly increase compared to the normozoospermic group (p = 0.035, p = 0.026 respectively). But, the results of manganese level showed that this element was significantly decreased in the oligozoospermic and asthenozoospermic groups compared to the normozoospermic group (p = 0.024, p = 0.019 respectively).

Table 2. Results related to Cadmium, Manganese and Nickel concentrations in Normozoospermic, Oligozoospermic and Asthenozoospermic groups. Values are given as mean ± SD.

Trace elements	Normo (n=50)	Oligo (n=50)	Astheno (n=50)	*p*-value		
				Normo Vs Oligo	Normo Vs Astheno	Oligo Vs Astheno
Cd (mg/L)	0.35 ± 0.09	1.82 ± 0.09	1.79 ± 0.05	0.031	0.028	NS
Mn (mg/L)	85.76 ± 3.23	42.82 ± 2.45	37.86 ± 3.05	0.024	0.019	NS
Ni (mg/L)	2.09 ± 0.27	4.62 ± 0.55	5.12 ± 0.28	0.035	0.026	NS

Note: Normo= Normozoospermics, Oligo = Oligozoospermics, Astheno = Asthenozoospermics

Finally, we found that according to data analysis, the cadmium had a negative association with TAC in oligozoospermic and asthenozoospermic groups (p -value = 0.031, β = -0.066), (p -value = 0.016, β = -0.166 respectively). But, Cd showed increased risk of TOS in oligozoospermic and asthenozoospermic groups by positive association (p -value = 0.045, β = 0.408), (p -value = 0.032, β = 0.379) respectively. Also, these associations remained Nickel variable that it had a significant negative association in oligozoospermic and asthenozoospermic groups with TAC (*p* -value = 0.018, β = -0.675), (p -value = 0.028, β = -0.427) respectively. But, Ni had a positive association with TOS in oligozoospermic and asthenozoospermic groups (*p* -value = 0.026, β = 0.452), (p -value = 0.0291, β = 0.510) respectively. The results analysis showed that unlike to before ions, manganese had a positive association with TAC in oligozoospermic and asthenozoospermic groups (*p* -value = 0.015, β = 0.509), (*p* -value = 0.044, β = 0.420 respectively). But, in return Mn had a negative association with TOS in oligozoospermic and asthenozoospermic groups (*p* -value = 0.035, β = -0.675), (p -value = 0.031, β = -0.549) respectively.

Discussion

In this study we found that the high concentrations of Ni and Cd in semen, may contribute to oxidative stress and eventually lead to a decline in human semen quality, whereas Mn may have beneficial effects.

Sperm DNA health is one of the essential factors for fertilization and fertility that any endogenous and exogenous factors can lead to its damage and endanger the health of the embryo. Recent clinical studies suggest that approximately 60% of men with idiopathic infertility refer to severe or moderate damage to sperm DNA (21, 22). One of the most important causes of DNA damage is increased levels of oxidative stress. In fact, oxidative stress not only causes to denature of the sperm DNA, but also reduces the fertilization potential of these cells through lateral damage to proteins and fats in the sperm plasma membrane (23). The pathophysiological significance of reactive oxygen species (ROS) in the etiology of male infertility has not yet been fully elucidated. However, ROS have been shown to be highly reactive and oxidizing substances that belong to the free radical group and do not contain one or more electron pairs that are continuously produced by metabolic and pathophysiological processes (24). It is assumed that oxidants interfere with the normal functioning of sperm through membrane lipid peroxidation and fragmentation of nucleic acids, which ultimately leads to sperm dysfunction (25). Our results showed that the amount of TAC in the semen of oligozoospermic and asthenozoospermic groups was decreased significantly in comparison to the normozoospermic group.

The study of Venkatesh et al. (2009) showed that total antioxidant capacity (TAC) of the seminal plasma was significantly lower in infertile cases compared with fertile cases. They evaluated TAC parameter and found that it significantly lower in infertile men compared with the fertile controls (26). On the other hand, this study found that there was a significant change in the oligozoospermic and asthenozoospermic groups for TOS level in comparison to the normozoospermic group. TOS is a more index of ROS effects on the cells especially sperms. Low levels of ROS have been shown to be essential for fertilization, acrosome reaction, hyperactivation, motility, and capacitation (27). When seminal leukocyte concentrations are abnormally high such as infection and inflammation, ROS level was increased and sperm damage occurs. The study revealed that this damage may initiate by the reactions of free radicals with fatty

acid chains and release lipid free radicals that lead to forming the lipid peroxyl radical. One of the productions of lipid peroxidation is malondialdehyde (MDA) as a biochemical factor for monitoring of TOS index (28). Studies have shown that antioxidants have a widespread effect in andrology. Seminal plasma contains main enzymatic antioxidants: SOD, CAT, and GPX (29). It was clear that Antioxidants have been shown to decrease the DNA fragmentation induced by oxidative stress. Hence, seminal plasma is considered to be the central source of antioxidants that protect sperm cells against oxidative damages (30). These results suggest that some elements may have a negative or positive influence on sperm parameters by changing oxidative stress factors. For example, Nickel deprivation significantly decreased sperm motility in the time of sperm and low sperm production rate. Of course, there are conflicting studies on the effects of nickel on fertility, for example in contrast, Bian et al. (2019) reported for the first time that Ni could improve sperm motility (31). It were found that the concentration of Nickel ions in the oligozoospermic and asthenozoospermic groups significantly increase compared to the normozoospermic group. Results analysis remained Nickel variable that had a significant negative association in oligozoospermic and asthenozoospermic groups with TAC but, Ni had a positive association with TOS in oligozoospermic and asthenozoospermic groups. Oxidative stress mechanisms play a significant role in nickel–induced toxic effects on sperms. It seems, nickel toxicity may be related to enhanced production of reactive oxygen species, probably mediated through oxidative damage of DNA (32). Also, it was found that Nickel deficiency decreased the weights of the seminal vesicles and prostate glands. So that, in animal's testes nickel induced morphological changes, inhibition of spermatogenesis and decrease of testosterone production. The molecular mechanism of the genotoxic effects of nickel compounds and the underlying mechanisms of male infertility are not fully understood. The theory of free radicals can explain part of this effect (33, 34). Free radicals, like the rest, are produced in the phenytoin reaction, which requires the presence of H2O2 and ions (Fe (II) and Cu (II)). The product of this reaction is a highly reactive hydroxyl radical (OH • -) that reacts with all the molecules around it. This substance damages nucleic acids and causes oxidation of nucleic bases, ribose and deoxyribose (35). This product is probably a promoter and causes carcinogenic changes in children whose fathers have been exposed to nickel compounds. One of the effects of free radical reactions is the replacement of other metals with nickel at the joints. Protamine 2 (P2) is the target of nickel attack. This substance is an essential protein for the production and maturation of sperm in mammalian cells (36).

The effects of Cd on sperm parameters are still unclear. Cd has a very long biological half-life (from 10 to 40 years) and leads to changes in sperm parameters and reproductive toxicity (7). The results of cadmium level showed that this element was significantly increased in the oligozoospermic and asthenozoospermic groups compared to the normozoospermic group. The cadmium had a negative association with TAC in oligozoospermic and asthenozoospermic groups but, Cd showed an increased risk of TOS in oligozoospermic and asthenozoospermic groups by positive association. The previous studies suggest that mechanisms of Cd toxicity, cause mitochondrial dysfunction, high level of ROS and reduce antioxidant defenses, which lead to oxidative DNA damage (37). In a study was seen that higher level Cd in seminal plasma in infertile patients was significantly inverse correlation between the levels of this metal and sperm concentration and motility (38).

Mn is an important trace element for reproductive function because it is a component of several enzymes, particularly Mn2+-SOD as an antioxidant enzyme against oxidative damages. Mn maintains the thiol level by reducing oxidative stress in human spermatozoa (39). Also, Mn is a potent stimulator for sperm motility by the stimulation of adenylate cyclase activity. Therefore, the absence of Mn can lead to the inhibition of enzyme systems required for sperm motility. Of course, a few studies have demonstrated that high levels of Mn may be toxic to the reproductive system and sperm quality (40). So, there are conflicting findings regarding the effect of Mn on semen quality in infertile men, and further studies are required to confirm its impacts and to explore the dose threshold values for infertility.

Conclusion

In the present study, it was observed that human semen Mn is necessary for normal sperm, motility and morphology since it is a component of SOD enzyme as an antioxidant enzyme against oxidative damages. Therefore, lowered level of Mn may negatively affect sperm quality. In contrast, other elements such as Cd and Ni are toxic for human sperm and negatively correlated with sperm parameters, as it was shown that these elements increased the risk of TOS in oligozoospermic and asthenozoospermic groups with a positive association. Thus, it seems that a significant reduction or elevation in these trace elements can be considered a major reason for idiopathic male infertility.

Acknowledgments

The authors wish to acknowledge the financial support Hamadan university of medical sciences (Project NO: 9906254315).

Conflict of Interest

Authors declare no conflict of interest.

Funding

None Declared.

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How to Cite This Article:

Gharabaghi A, Yavari Bazl M S, Baranizadeh K, Heshmati A, Shafiee G. The Relationship of Cadmium, Nickel, and Manganese Trace Elements with Oxidative Stress in the Semen of Infertile Men. J Adv Med Biomed Res. 2023; 31(147): 372-80.

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