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REPRODUCTIVE HORMONES AMONG ELECTROPLATERS EXPOSED TO CHROMIUM AND NICKEL AT A FACTORY FOR METALLIC INDUSTRIES IN EGYPT

By

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Abstract

Introduction: Exposure to chromium (Cr) and nickel (Ni) is prevalent at workplace. Although they are toxic, human studies on their effect on the reproductive system are few and contradictory. **Aim of work:** To evaluate the association of male reproductive hormone levels with the concentrations of blood chromium and nickel among electroplaters in a factory for metallic industries in Egypt. **Materials and methods:** A cross sectional comparative study was conducted on 48 electroplating workers and 48 non-occupationally exposed subjects used as controls. Personal interview with specially designed questionnaire were fulfilled. Blood nickel and chromium concentrations were determined and the reproductive hormones levels [follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone and inhibin] were assayed for all participants. **Results:** The study showed a statistically significant high levels of the mean values of blood Cr and Ni among electroplating workers compared to the control group (1.2±0.93 and 1.3±1.02 μg/L vs 0.4±0.1 and 0.39±0.2 μg/L respectively; p<٠,٠٠١). Also, a statistically significant high levels of FSH and LH were detected among exposed workers (5.19±2.08 mIU/L and 6.85± 2.67 IU/L respectively) compared to controls (1.95±0.7 mIU/L and 3.97± 0.85 IU/L respectively) with low levels of testosterone and inhibin. Significant positive correlations (p<0.05) were found between FSH level and heavy metals (Cr and Ni) levels (r=0.28 and r=0.63; p=0.05 and p<0.002 respectively). Conversely, significantly negative correlations were detected as regards testosterone level (r=-.323 for chromium and r=-.571 for nickel; p<0.05 for each). Blood nickel was found to be a significant predictor for FSH and testosterone level, and smoking index was predictor for all measured reproductive hormones among exposed electroplaters. **Conclusion:** Exposure to high levels of Cr and Ni might affect reproductive hormones levels among male electroplating workers. Regular wearing of good quality's personal protective equipment, especially masks and gloves, to decrease exposure to electroplating fumes, is highly recommended.

Keywords: Chromium, Nickel, Reproductive hormones, Electroplating workers and Biological monitoring

Introduction

Chromium (Cr) and nickel (Ni) are among the heavy metals with extensive use in modern society in many industrial and commercial settings. They are widely distributed at workplace in electroplating, welding, flame cutting, and mold making, also used in the manufacture of jewelry, coinage, cutlery and cooking utensils. Such industrial activities are associated with elevated temperatures along with emissions of metal dust, fumes and oxides which can be easily inhaled making human exposure inevitable (Liu et al., 2012).

In the electroplating process, workers are exposed to chromic acid in its hexavalent form which is used as an electrolyte forming mist during the plating process. Exposure also occurs during weighing and mixing of acid powders, and during transfer of liquids and articles to and from plating baths. Most chromium plating processes are associated with nickel plating; thus chrome platers mostly are exposed to nickel compounds in the form of powders and mists of nickel sulphate and nickel chloride (Qayyum et al., 2012).

Most researches on chromium and nickel toxicity have been targeting the respiratory, dermal or carcinogenic effects (Liu et al., 2012). However, accumulating evidence suggests that these heavy metals, even at degrees that are considered subclinical, can cause alterations in reproductive hormone levels by interacting with the estrogen and androgen receptors and could be harmful to male reproductive health (Meeker et al., 2010 and Pizent et al., 2012).

Data on the reproductive effects of metals except lead are scanty, and relatively few studies have been conducted on workers occupationally exposed to nickel and chromium with conflicting results (Danadevi et al., 2003 and Sancini et al ., 2014).

The entire male reproductive system is dependent on many regulatory hormones for the activity of cells or organs; of which are the follicle-stimulating hormone (FSH) for sperm production and luteinizing hormone (LH) to stimulate the production of testosterone which is necessary to continue the process of spermatogenesis and also important in the development of male characteristics. Rising levels of testosterone act on the hypothalamus and anterior pituitary by a negative feedback system to inhibit the release of gonadotropin releasing hormone

(GnRH), FSH, and LH. The hormone inhibin is produced by cells in the testes that are responsible for monitoring the health and maturation of sperm. When the sperm count is too high, the Sertoli cells produce the hormone inhibin to inhibit the release of GnRH and FSH, and hence slow down spermatogenesis and they cease its release when the sperm count reaches 20 million/ml allowing it to increase (Matsumoto et al., 2008 and Kusev et al., 2017).

Measurements of Cr and Ni in blood and urine are considered most reliable method for detecting nearly accurate levels of occupational exposures (ATSDR, 2012).

Studies on the effects of occupational exposure to Cr and Ni on male reproductive hormones values are deficient and to our knowledge this is the first study to investigate the association between chromium and nickel exposure and reproductive hormone levels among Egyptian electroplaters.

Aim of work

To evaluate the association of male reproductive hormone levels with the concentrations of blood chromium and nickel among electroplaters in a factory for metallic industries in Egypt.

Materials and methods

Study design: It is a cross-sectional comparative study.

Place and duration of the study: The study was carried out at a factory for metallic industries at Helwan district, Cairo, Egypt during the period from May to August 2018.

Study sample: All workers at the electroplating department in the studied factory (56 workers) were invited to participate in the study. They were exposed to chromium and nickel fumes and they were continuously employed at the factory for (8hrs/day, 6 days/ week) for a minimum 6 years to a maximum 40 years. After exclusion of non-responders, and application of exclusion criteria, the recruited workers were 48. Exclusion criteria included the participants who were under medical treatment of cancer, liver, kidney or diabetes mellitus. The control group was composed of 48 participants from the administrative departments at the same factory not exposed to known harmful chemicals and was matched for age, sex, lifestyle and economic status with the exposed group.

Study methods:

1- Personal interview and a

detailed questionnaire intended to elicit information on the subject's age, smoking habits, work duration and use of personal protective equipment, medical complaints and medicine usage. Inquiries about the subject's reproductive history, fertility problems and investigations carried out for fertility impairment were obtained from all subjects.

2-Investigations:

-Blood collection: 7 ml of venous blood was taken from each subject through a vein puncture using a dry plastic disposable syringe under complete aseptic condition. Out of that, 3 ml of blood was kept in a tube, allowed to clot, and then centrifuged to separate the serum for determination of Cr and Ni levels. The remaining 4 ml of blood was kept in a tube, allowed to clot, and then centrifuged to separate the serum, and an aliquot of serum samples was stored in a freezer (-20°C) until analysis of reproductive hormones [FSH, LH, testosterone and inhibin]. All the samples were analyzed at the Biochemical Department, Cairo University.

-Sample analysis for blood chromium and nickel: Their levels were measured by Graphite Furnace Atomic Absorption Spectrophotometer with Zeeman background correction (Thermo elemental M6, Cambridge, England). External calibrators for chromium and nickel were used for plotting standards curves to allow interpretation of metal concentration (Christensen et al., 1999 and Olmendo et al., 2010).

-Analysis of reproductive hormones: The immunoassay method (EIA) was used to analyze the plasma FSH, LH, testosterone and inhibin.

Consent

All subjects were informed about the purpose of the study and agreed to participate using signed consent forms. All personal information about the study participants was kept confidential.

Ethical approval

This study was approved by the Faculty of Medicine Committee at Cairo University for Medical Research Ethics. Approval from the factory manager was obtained.

Data Management

Data were coded and entered using the statistical package SPSS version 22, IBM Company, Chicago, USA, and they were summarized using mean and standard deviation, frequency and range. Comparisons between the two groups were done using unpaired Student's t test and Chi-squared test for normally distributed variables and nonparametric Mann–Whitney test for quantitative variables, which were not normally distributed. Correlations between quantitative variables were done using Pearson correlation coefficient. Regression analysis was used for prediction of studied variables on reproductive hormones. p value of ≤0.05 was considered statistically significant in the presented results of the study (Chan, 2003).

Discussion

The majority of metal toxicity reports on the reproductive system are

Results

Table 1: Demographic characteristics and associated symptoms of the studied groups.

Parameters	Electroplaters (No= 48)	Control group (No = 48)	p value
#Age (yrs.) Mean ± SD Range (yrs.)	50.79 ± 4.27 (45–59)	50.47± 4.13 (45–58)	0.7
Work duration (yrs.) Mean ± SD Range (yrs.)	27.77 ± 7.8 (6-40)	-	-
Smoking status No (%) ## Smoker Non-smoker	27(56.3%) 21(43.8%)	27(56.3%) 21(43.8%)	1.0

Smoking index £, ### (Mean± SD)	250±328	234±329	0.8
Chest manifestations: No (%) ## Yes NO	33(68.8%) 15(31.3%)	3(6.3%) 45(93.7%)	**<0.001****
Skin dermatitis: No (%) ## Yes NO	3(6.3%) 45(93.7%)	0(0%) 100(100%)	0.078
Fertility problems: No (%) ## Yes NO	3(6.3%) 45(93.7%)	0(0%) 100(100%)	0.078
Allergic rhinitis: No (%) ## Yes NO	6(12.5%) 42(87.5%)	1(2.1%) 47(97.9%)	**0.05***
Sinusitis: No (%) ## Yes NO	9(18.8%) 39(81.2%)	3(6.3%) 45(93.7%)	0.064
PPE: No (%) @ Yes NO	6(12.5%) 42(87.5%)		

#: Unpaired t test (Mean ± SD) ## Chi-square (X2) ### Mann-Whitney test.

£: Smoking index: number of cig. /day × duration of smoking in years.

@: PPE: Using personal protective equipment among exposed workers.

*: Statistically significant **: Highly statistically significant

Table 1 showed that the exposed electroplaters and control group were matched as regards age and smoking status. There were a statistically significant difference as regards chest manifestations and allergic rhinitis. Minority of electroplaters (12.5%) were using personal protective equipment.

Table 2: Levels of serum chromium and nickel among electroplaters and control groups (Unpaired t- test).

	Normal range	Electroplaters (No= 48)	Control (No = 48)	p value
Serum Cr (µg/L) Mean ± SD Range	(0.6 - 1)	1.2±0.93 (0.21-3.1)	0.4±0.1 (0.2-0.65)	**<0.001****
Serum Ni (µg/L) Mean ± SD Range	(0.3 - 1.1)	1.3± 1.02 (0.2- 3.2)	0.39± 0.2 (0.04- 0.8)	**<0.001****

**: Highly statistically significant

There was highly statistically significant difference in the mean serum concentrations of both Cr and Ni among exposed electroplaters compared to the control group (Table 2).

Table 3: Reproductive hormone levels of the studied groups (Unpaired t test).

	Normal range provided with the kits	Electroplaters (No = 48) Mean ± SD	Control (No = 48) Mean ± SD	p value
FSH (mIU/L)	0.4-4	5.19±2.08	1.95±0.7	**<0.001****
LH (IU/L)	1.24-7.4	6.85± 2.67	3.97± 0.85	**<0.001****
Testosterone (ng/dl)	250-950	239± 48.9	413± 88.8	**<0.001****
Inhibin (pg/ml)	2-10	4.58± 1.98	8.63± 2.9	**<0.001****

FSH: Follicle stimulating hormone LH: Lutinizing hormone

**: Highly statistically significant

There were highly statistically significant difference in the mean plasma levels of both FSH and LH and lower testosterone and inhibin levels among exposed workers compared to the control group (Table 3).

Table 4: Correlation between blood heavy metals (chromium and nickel) and age, duration of employment, smoking index and hormones levels among exposed electroplaters using Pearson correlation.

Variables	Blood chromium		Blood nickel	
	r	p	r	p
Age (yrs.)	-.183	.21	.065	.66
Duration of exposure (yrs.)	.16	.27	.175	.234
Smoking index	.023	.87	.337	**.019***
FSH	.28	**.05***	.632	**.002****
LH	.08	.57	.259	.076
Testosterone	-.323	**.02***	-.571	**.001****
Inhibin	.162	.27	.013	.929

r: correlation coefficient.

*: Statistically significant, **: Highly statistically significant

Among exposed electroplaters, significant positive correlations were found between FSH and heavy metals (Cr and Ni) levels. Conversely, significant negative correlations were detected as regards testosterone level. Positive correlation between serum nickel and smoking index was found (Table 4).

Table 5: Multiple linear regression model for detecting predictors of reproductive hormones levels (FSH, LH, testosterone and inhibin) among exposed workers.

Parameters		ß	p value	95.0% Confidence Interval	
				Upper Bound	Lower Bound
Predictors of FSH	Smoking index	.919	**.001****	.005	.006
	Chromium	.017	.607	-.108	.183
	Nickel	.323	**.001****	.514	.791
Predictors of LH	Smoking index	.896	**.001****	.005	.010
	Chromium	-.067	.615	-.956	.572
	Nickel	.087	.536	-.503	.954
Predictors of testosterone	Smoking index	-.674	**.001****	-.135	-.066
	Chromium	-.176	.113	-20.656	2.258
	Nickel	-.239	**.042***	-22.276	-.437
Predictors of inhibin	Smoking index	-.816	**.001****	-.007	-.003
	Chromium	.092	.596	-.543	.933
	Nickel	.220	.230	-.279	1.127

*: Statistically significant **: Highly statistically significant

FSH: Follicle stimulating hormone LH: Lutinizing hormone

Table 5 showed that nickel was a significant predictor for FSH and testosterone levels among exposed electroplaters, and smoking index was the predictor of all measured reproductive hormones.

coming from experimental studies on animals that are usually performed with high doses of exposure and/or short-term exposures. Moreover the potential for fertility and the reproductive system dysfunction in human may differ from those of other mammals, as well as his susceptibility to different metals. Epidemiological studies are therefore needed to validate the effect identified in experimental models. The data on the toxicity of metals on the human reproductive system for the moment are few and usually limited to groups of subjects non-occupationally exposed and residents near areas with high levels of air pollution (Pasanen et al., 2012) and to groups of subjects exposed to metals through consumption of contaminated food or water (Perino, 2005). These data, reporting the toxicity of metals on the human reproductive system, are also limited to only a few metal ions, lead above all. The effects on the reproduction of other metals such as Cr and Ni are very few with conflicting results (Rotatori et al., 2003). So our study was designed to clarify the effect of occupational Ni and Cr exposure on reproductive system among electroplaters.

In the present study, more than half of examined electroplaters were smokers. The majority of electroplating workers complained of chest manifestations (cough and breathing difficulty) and about 12.5% of them had allergic rhinitis with significant higher frequency than controls. Minority of electroplaters was using personal protective equipment in the form of gloves and eye goggles (Table 1).

Several studies reported that exposure to chromium and nickel fumes causes runny nose, sneezing, coughing, itching, and a burning sensation from irritation of the nose, throat, and lung. Work-related asthma, wheezing and shortness of breath may develop. Direct contact also can cause dermal irritation, slow-healing ulcers and nasal septum lesions (Qayyum et al., 2012). This may be contributed to improper ventilation in the working area, lack of use of protective equipment, additional effects of chronic exposure to heavy metals and synergistic effect of smoking.

About 6% of our exposed workers were complaining of allergic dermatitis that was higher when compared to the control subjects although it didn't reach significant level (Table 1, $p>0.05$). This was in agreement with several studies as Royle, 1975, on his study of the toxicity of chromic acid in chromium plating industry and El Safty et al., 2018 in their study on the effects of exposure to chromium and nickel among electroplating workers.

Results of the present study showed

that the mean serum levels of Cr and Ni among exposed electroplaters were significantly higher than those in the matched control participants ($p < 0.001$, Table 2).

In electroplating process, workers are exposed to vapors or fumes of chromium in high concentration and to those of nickel in appreciable quantities only. Workers in these industries are, therefore, likely to concentrate and retain significant amounts of these two metals in their body. Heavy metals' levels (nickel, chromium) in the blood of our exposed group are quite alarming and are comparable to those reported in studies on industrial exposures among chromate workers (El Safty et al., 2018).

Significant high plasma FSH and LH, and lower testosterone and inhibin levels were detected among exposed electroplaters compared to control ($p<0.001$, Table 3). This was expected according to several previous reports (although few) that demonstrated the toxic effects of chromium and nickel on Leydig-cell function which is the site of synthesis and excretion of testosterone, causing positive feedback on the hypothalamic hormones (FSH and LH) increasing their secretion as they are the main stimulators of testosterone secretion (Matsumoto et al., 2008 and Kusev et al., 2017). These findings support the interpretation that the increase in FSH concentration indicates diminished negative feedback from the seminiferous tubules. The decrease in inhibin levels among electroplaters may be related to the direct toxic effect of heavy metals (chromium and nickel) on the Sertoli cells, or known response to disturbance of spermatogenesis due to toxic metals exposure by electroplating workers (Pizent et al., 2012 and Xu et al., 2012).

These results were in agreement with the findings of Sancini et al. (2014) who reported that occupational exposure to low doses of Ni present in the urban environment is able to influence some lines of the hypothalamic-pituitary-gonadal axis among exposed workers, and he demonstrated negative correlation between urinary nickel and testosterone plasma values.

Experimental studies reported adverse effects of Ni on reproduction through disruption of steroidogenesis and spermatogenesis (Kročkova et al., 2011 and Xu et al., 2012). It also has the ability to bind to estrogens and the androgens receptors, together with other heavy metals and then could interfere with reproductive hypothalamic hormones LH and FSH and with testosterone (Kortenkamp, 2011).

Few clinical studies on exposed human subjects associated the Cr and Ni exposure with an increased risk of abnormal spermatogenesis and testicular toxicity. Danadevi et al. (2003) demonstrated decreased sperm motility and increased abnormal forms among exposed workers to Cr and Ni fumes compared to controls with significant positive correlation between the percentage of tail defects and blood nickel concentration. The sperm concentration showed a negative correlation with blood chromium content among exposed workers. More recent study found significantly higher mean seminal chromium levels of oligospermic and asthenoligospermic infertile men than that of the fertile group (Bassey et al., 2013). This was explained by previous reports suggest that Cr can affect the male reproductive system directly by affecting the specific target organs, or indirectly by its action on the neuroendocrine system, as it can accumulate in the epididymis, in the prostate, the seminal vesicles or fluid and thereby alter the motility and the vitality of sperms (De Rosa et al., 2003) or it can cause hormonal imbalances that affecting the gonadal or neuroendocrine system. According to Jensen and colleagues in 2006, occupational exposure to Cr can disrupt the secretion of androgen by the Leydig cells or the inhibin B by the Sertoli cells. Occupational exposure to Cr and its possible effects on the reproductive system have not been well studied yet.

The current work clearly indicates that there is no correlations between blood metals excretion and each of age the duration of exposure ($p>0.05$) (Table 4) which may be explained by the higher turnover of these metals avoiding large accumulation and retention in the biological system (Weisse et al., 2013).

The concentration of FSH in the serum showed significant positive correlations with blood chromium and nickel, but the association was only borderline significant ($p=0.05$) with chromium and strongly significant as regards nickel ($p<0.002$). Negative correlations were found as regards testosterone ($p<0.02$ and $p<0.001$) for chromium and nickel respectively (Table 4). These results were confirmed by multiple linear regressions which indicated that Ni was a significant predictor which can contribute to the alterations of the FSH and testosterone levels among the exposed electroplaters (Table 5). This was in agreement with many studies which reported an inverse association between exposure to chromium and nickel fumes and testosterone levels, and a positive dose-related relationship with FSH (Bonde, 1990 and Sancini et al., 2014).

Conversely, another European study found no associations between Cr and Ni fumes and FSH, LH or testosterone levels (Hjollund et al., 1998). However, the latter study included workers in the welding industry with low exposure levels at workplace as chromium and nickel are present in trace quantities in the welding fumes which is different to electroplating fumes.

Findings of the present study demonstrated that smoking index was a significant predictor of all measured reproductive hormones (Table 5). Our results were compatible with several reports found that tobacco consumption acts as an endocrine disruptor on the male hormone profile by affecting hypothalamic gonadal axis (Blanko-Munoz et al., 2012 and Jandíková et al., 2017).

Conclusion and recommendations

Exposure to high levels of Cr and Ni might affect reproductive hormones levels among male electroplating workers. Regular wearing of good quality's personal protective equipment, especially masks and gloves, to decrease exposure to electroplating fumes, is highly recommended.

Limitation of the present study was the collection of only a single blood sample from each participant for measurement of metals and hormone levels. It may introduce exposure measurement error because the biologic half-lives for the metals measured in the present study vary considerably. However, a single measure may represent exposure over a longer period of time even for those with short half-lives (Egeghy et al., 2005). In addition, requiring multiple blood samples from participants would likely result in a reduced participation rate and lower statistical power.

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Conflict of interest

There is no conflict of interest.

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