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Cardiovascular responses among occupationally nickel exposed workers

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Most literature examined the effect of nickel on experimental animals. The present study investigated the cardiovascular responses in human due to occupational nickel exposure. Cross-sectional comparative study including fifty electroplating male workers exposed to nickel and 43 controls that underwent questionnaire, clinical examination and ECG. Air and urinary nickel concentrations, serum lipids, apolipoprotein E, high sensitive C-reactive protein and fibrinogen were measured. Urinary Nickel level was significantly higher among the exposed workers. Dyspnea with mild exertion and blood pressure were significantly higher in nickel -exposed workers. Urinary nickel levels were significantly higher among the hypertensive compared to the normotensive workers. Abnormal QRS complex, axis deviation and T-wave ECG findings were significantly higher among exposed workers. Total cholesterol and low density lipoprotein were significantly higher while apolipoprotein E, high density lipoprotein were significantly lower among exposed workers. These findings suggest cardiovascular influences due to nickel exposure.

Keywords: Nickel-exposed workers; ECG; blood pressure, lipids, inflammatory markers

INTRODUCTION

Nickel (Ni) is a widely used metal, particularly in various alloys, stainless steel, batteries and Ni-plating. Occupational exposure to Ni occurs due to Ni release into air, or skin contact with Ni-containing or Ni-plated tools. Occupational exposures may lead to the retention of 100 µg/day of Ni (Grandjean, 1984). Previous studies stated that exposure to Ni may link to the cardiovascular diseases as hypertension and atherosclerosis (Cuevas et al., 2010; Ying et al., 2013).

The few laboratory-based studies considering Ni cardiovascular toxicity included exposures at higher concentrations than those considered to be related to surrounding air exposures (Campen et al., 2001; Muggenburg et al., 2003). A previous study (Lippmann ET AL., 2006) represented a significant increase of human health risks due to exposures to Ni in air mainly to cardiovascular risks. They concluded that Ni was particularly influential in producing cardiovascular responses in humans.

In Ni refinery workers, significant increased risks of cardiovascular diseases were demonstrated (Chashschin et al., 1994). Particulate matter (PM) arising from most pollution sources contain metal ions such as Ni beside other several ions and trace elements (Jaiprakash et al., 2017). Metals accompanying the inhaled PM have the ability to transfer from lung into systemic circulation causing adverse effects on cardiovascular system (Wallenborn et al., 2007). Lung inflammation may lead to systemic inflammation (Yamawaki and Iwai, 2006), causing

many cardiovascular diseases (Sin and Man, 2003).

An animal study has reported cardiovascular toxicity of PM metal components including Ni (Chuang et al., 2013). Some studies suggested that inhaled Ni can provoke systemic cardiovascular effects (Campen et al., 2001; Lippmann et al., 2006). Moreover, another previous study (Brook, 2008) suggested that atherosclerosis which resulted from the chronic effects of air particles on the cardiovascular system may be due to production of a chronic proinflammatory state.

Elevated systemic inflammatory markers may increase the risk for cardiovascular diseases with prediction for undesirable cardiovascular outcomes, but without clear exact mechanism (Kim et al., 2005).

C-reactive protein (CRP), an acute phase serum protein secreted by liver, is the portent in chasing inflammatory markers and highly specific in predicting cardiovascular risks (Devaki et al., 2001). CRP was broadly considered a biomarker in combination with a lipid profile to provide extra information about cardiac disease risk in humans (Koenig et al., 2006).

Fibrinogen is an acute-phase reactant, meaning that high fibrinogen levels can be seen in the following conditions: "inflammation, tissue damage/trauma infection, acute coronary syndrome, strokes, myocardial infarction, cancer and peripheral arterial disease". Many health practitioners believe that fibrinogen activity measurements give them extra information that may lead them to be more forceful in treating those risk factors that they can treat such as unhealthful levels of cholesterol (Monroe et al., 2010).

Apo lipoprotein E (APO-E) is a class of apolipoprotein secreted by liver responsible for the metabolism of triglycerides and cholesterol (Song et al., 2004). It plays a key role in regulating the clearance of triglyceride-rich lipoproteins as VLDL and HDL from the plasma by serving as the ligand for binding to specific cell-surface receptors, including the LDL receptor family members (Holtzman et al., 2012; Huang and Mahley, 2014). Previous studies showed that APO E has proinflammatory properties and mediates the presentation of lipid antigens to the immune system and in thus lead to chronic inflammation (vandenElzen et al., 2005; Mooijaart et al., 2006).

Till now, few studies examined occupational Ni exposure effects on the cardiovascular system among workers. Most literature on Ni comes from toxicological studies that examine the effect of Ni on experimental animals. However, the inferences from such studies could not be adopted unless verified and reinforced by further evidences from human or epidemiologic studies. The present study investigated the cardiovascular responses due to occupational Ni exposure.

MATERIALS AND METHODS

Study design and population

The present study was done at a Ni-electroplating factory located in Greater Cairo Governorate, Egypt. Recruitment of the participants lasted three months from August to October 2016. The present study was a cross-sectional comparative study that included two groups: Ni-exposed workers (n=50) representing all available Ni-exposed workers and controls (n=43). Both groups were all males non- smokers with comparable ages (45.8±10.1 vs. 42.9±6.9 years respectively) and body mass index.

Ni-exposed workers had a mean duration of exposure 22.6±11.4 years. Controls were clerks from administration jobs with no past or current history of occupational exposure to heavy metals.

Exclusion criteria: past medical history of hypertension or cardiovascular diseases prior to present job, diabetes mellitus, evidence of chronic liver diseases, kidney diseases, thyroid diseases and regular drug intake (e.g. antihypertensive medication) or anti-inflammatory drugs and statins, or injuries which may raise the level of C-reactive protein (CRP) and gives a falsely elevated estimate.

Methods

1- Environmental air samples of the factory were collected using personal air sampler over an 8-hour morning shift from 9 am to 5 p.m. Three samples were collected from the factory from three different departments at the respirable zone of the Ni-exposed workers. The filter paper was sent to NRC labs to analyze the precipitated dust using atomic absorption spectrophotometry (SOLAAR-UNICAM 989) Perkin Elmer, Jena, Germany.

2- An interview questionnaire was filled by all participants. The questionnaire comprised personal data, smoking habit, occupational history, past and current medical history.

3- All participants were submitted to clinical examination including pulse rate and blood pressure. A standard mercury sphygmomanometer with a 14-cm cuff was used

to measure systolic BP (SBP) and diastolic BP (DBP) in the sitting position. According to Blood Pressure UK Association, if the SBP is 140 or more regardless the DBP or the DBP is 90 or more regardless the SBP refers to high blood pressure. Blood pressure (140/90 or higher**)** refers to hypertension (Blood Pressure UK Association, 2008).

4-Electrocardiogram (ECG) was done using CARDIMAX portable apparatus, FX-7102 electrocardiograph Ver.02. FUKUDA DENSHI CO., LTD. Japan. The ECG was interpreted by a clinician (one of the authors) according to (Goldberger et al., 2017):

P wave: A positive wave representing atrial depolarization, duration: 0.08 seconds

PR interval: 0.18 seconds

QRS complex: represents depolarization of the ventricles and interventricular septum, 0.08 seconds

ST segment: an isoelectric segment

T wave: A positive wave representing ventricular repolarization, 0.16 seconds

QT interval: Normally 0.44 seconds

Axis: The electric axis of the heart normally makes an angle of – 30 degree to + 110 degree

Axis less than – 30 means left axis deviation and more than + 110 degree means right axis deviation. (Goldberger et al., 2017)

- We interpret the results of ECG findings as (Normal and Abnormal)

5- A random morning urine sample was collected from each participant in a plastic container and centrifuged at 4500 rpm for 10 min; then the top 15 ml of the supernatant was stored frozen at −20°C in aliquots without preservatives until urinary Ni was measured. Prior to metal determination, all samples were digested using nitric acid, where it is an acceptable matrix for flame atomic absorption and it is also used to provide acceptable and consistent recovery compatible with the analytical method (Rice et al., 2015). All heavy metal analyses were performed on Agilent 5100 Inductively Coupled Plasma – Optical Emission Spectrometer (ICP-OES) with Synchronous Vertical Dual View (SVDV).

6- Blood sample was collected with 5 ml syringes and divided in 2 parts, one part collected as clotted blood and centrifuged to separate serum to estimate lipid profile including: serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), triglycerides (TG). APO E and high sensitive CRP (hs-CRP) were also measured. The other part of blood sample was collected on an anticoagulant citrate and centrifuged to separate plasma to estimate fibrinogen levels. The serum and plasma samples were immediately frozen at –20^{o}C until analyzed.

Laboratory investigations

- Serum TC was measured by enzymatic colorimetric test-GPO-PAP Method (Roeschlau et al., 1974).

- Serum TG was measured by enzymatic colorimetric test-GPO-PAP Method (Jacobs and Vandemark, 1960).

- Serum HDL-c was measured using the precipitaion with phosphotungstic acid (Lopes-Virella et al., 1977).

All the previous kits were purchased from Centronic GmbH AM Kleinfeld 11, 85456 Wartenberg/Germany

- Serum very low density lipoprotein cholesterol (VLDL-c) was calculated (Lopes-Virella,et al 1977) VLDL = TG/5

-Serum low density lipoprotein cholesterol (LDL-c) was calculated (Lopes-Virella,et al 1977). LDL-c = TC-(HDL-c+ VLDL-c)

-Determination of serum Human Apo E Quantikine ELISA Kit: R&D Systems Inc. Minneapolis, USA

-Determination of serum hs-CRP by a microplate immunoenzymometric assay Monobind Inc., AccuBind Elisa wells, USA (Kimberly et al., 2003).

-Fibrinogen processing: Electromagnetic mechanical clot detection; 2 mL from cuvette is run through an automated machine (COATRON ^{R} M1) that physically detects the coagulation factor using Dia-FIB fibrinogen reagent DIAGON Ltd. Budapest, Hungary. The method of Clauss relies on the excess amount of thrombin, which forms fibrin rapidly. In this case the logarithm of clotting time (thrombin time in sec) is directly proportional to the logarithmic concentration of fibrinogen (mg /dl) (Koepke et al., 1975).

7- The data was statistically analyzed using the “Statistical Package for Social Science (SPSS) version 18 Inc., Chicago, IL, U.S.A.”. Independent t-test and chi-square (X^2) were used to compare quantitative and qualitative data of the studied groups. Pearson’s bivariate correlation coefficient was also calculated. The alpha level of significance was set at $p< 0.05$.

RESULTS

The environmental measurements recorded that the mean value of Ni concentration was 9.7±0.75 µg/m^3. The percentage of dyspnea with mild exertion was statistically significantly higher

in Ni-exposed workers compared to controls (54.0% vs. 18.6% respectively) X^2 =10.9 and P value (0.001).

Table1: Mean levels of blood pressure and heart rate and Percentage distribution of abnormal ECG findings among Ni-exposed workers and controls

ECG findings	Ni-exposed N=50	Controls N=43	statistic	p-value
Abnormal QRS complex	19(38.0%)	4 (9.3%)	8.7[x]	0.003**
Left axis deviation	17 (34.0%)	4(9.3%)	6.7 [x]	0.010*
Abnormal T wave	17(34.0%)	6 (14.0%)	4.2 [x]	0.040*
Irregular rhythm	14 (28.0%)	21(48.8%)	3.4 [x]	0.298
Abnormal P wave	13(26.0%)	5 (11.6%)	2.2 [x]	0.137
Abnormal P-R interval	3(6.0%)	0(0.0%)	1.1 [x]	0.246
Abnormal S-T interval	10 (20.0%)	4(9.3%)	1.3 [x]	0.251
Abnormal Q-T interval	5(10.0%)	0(0.0%)	2.8 [x]	0.059
SBP (mmHg)	130.0±15.0	121.9±11.4	3.0 [t]	0.004**
DBP(mmHg)	89.2±11.8	82.3±7.2	3.5[t]	0.001**
Heart rate (beat/minute)	76.0±13.8	73.8±8.7	0.9 [t]	0.352

[x2], chi-square; [t], independent t-test, ECG (electrocardiography); *, significant (p<0.05); **, highly significant (P<0.01). Systolic blood pressure (SBP), Diastolic blood pressure (DBP).

As regards ECG, abnormal QRS complex, left axis deviation and T-wave were the only ECG findings that were significantly higher among Ni-exposed workers compared to controls [table1].

In Ni-exposed workers, the abnormal QRS complex was shown as ventricular extra systoles in 14 cases and wide M shaped QRS suggestive of bundle branch block was found in 5 cases and abnormal T-wave in the form of tall peaked in 15 cases and inverted in 4 cases. Cases are diagnosed as arrhythmia? BBB or associated with other abnormalities e.g. ST or P wave abnormalities.

PR interval abnormalities were short in two cases (diagnosed as arrhythmia), prolonged in three cases (associated with T wave abnormality) and variable in one case (arrhythmia). ST intervals were elevated in 5 cases and depressed in 5 cases, either alone or combined with T changes. These cases are diagnosed as ventricular arrhythmia, or ? bundle branch block (BBB). QT changes were prolonged in 5 cases of arrhythmia. Most cases of arrhythmia were ventricular extrasystole, but some cases supraventricular and atrial arrhythmia were among our workers.

Examples of these ECG findings in the Ni-exposed workers were shown in [Figure 1] including left axis deviation (a), ventricular arrhythmia (in the long strip lead II) (b), M shape QRS in V2 (suggestive of BBB) (c) and tall peaked T wave in V3,4 (d).

Mean levels of SBP and DBP were significantly higher in the Ni-exposed workers compared to controls [table1]. The percentage of hypertensive cases were significantly higher in the Ni-exposed workers compared to controls (62%(31/50) vs 16.3%(7/43) respectively, X^2 =19.1 and P=0.000).

Mean urinary Ni level was significantly higher among the exposed workers (9.87±3.95 µg/L) compared to the controls (6.9±1.69 µg/L) with t test = 4.4 and P value (0.000).

Mean urinary Ni level was significantly higher among the hypertensive compared to normotensive exposed workers group [table 2].

Apo E, HDL-c were significantly lower in the exposed than the controls. TC and LDL-c were significantly higher in the exposed than the controls [table3].

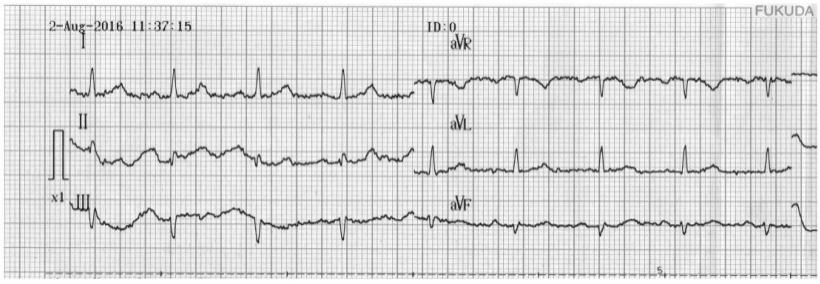
Cumulative Ni exposure has no effect as all measured parameters between the 2 subgroups of the exposed group with urinary Ni level ≤ 8 µg/L and > 8 µg/L revealed no significant difference (non-tabulated data). Also, there was no correlation between urinary Ni level and duration of exposure.

Figure (2):showed that in the present study, the cutoff point of high risk is hs-CRP =4 mg/L. We found that 55.9% (52/93) of the studied groups had hs- CRP ≤ 4 and 44.1% (41/93) had hs–CRP ≤ 4. HDL –c was significantly lower in

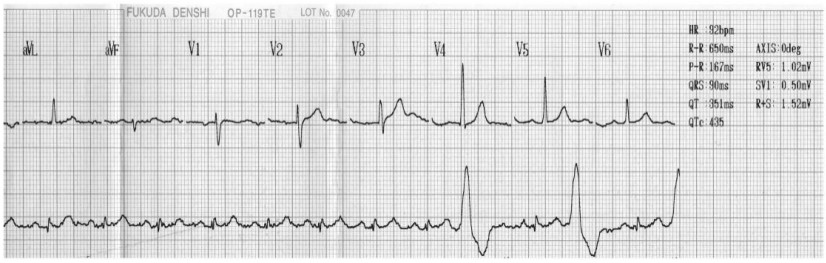
the studied groups with hs CRP>4 than those with hs- CRP ≤4 while fibrinogen was significantly higher in the studied groups with hs CRP>4 than those with hs- CRP ≤ 4 [table4]. Table 5 showed that Apo E correlated negatively with TG and VLDL-c. While Hs-CRP was positively correlated with fibrinogen.

Figure 1: Examples of commonly found ECG changes in the Ni-exposed workers (a) Left axis deviation; (b) ventricular arrhythmia (in the long strip lead II); (c) M shape QRS in V2 (suggestive of BBB) (d) Tall peaked T wave in V3,4

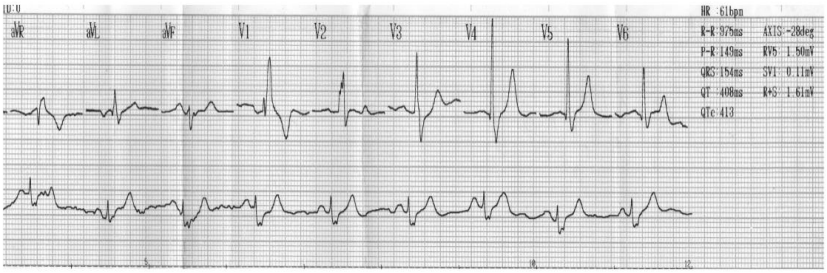
(a)



(b)



(c)



(d)

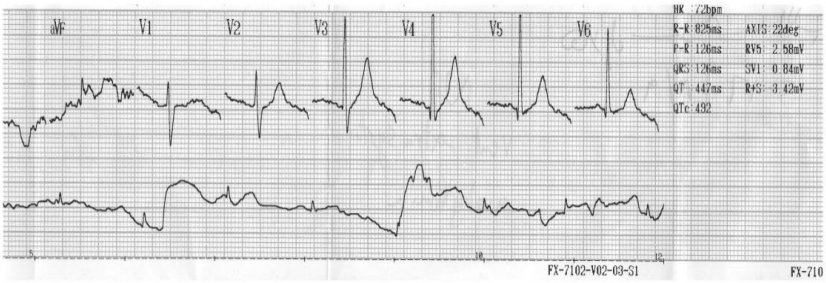


Table 2: Mean levels of urinary Ni among hypertensive and normotensive studied groups

Groups		Blood Pressure groups	Mean	Std. Deviation	T test	P value
Exposed	u_Ni (µg/L)	Hypertensive	10.67	4.12	2.04	0.04*
		Normotensive	8.30	3.31		
Control	u_Ni (µg/L)	Hypertensive	7.80	1.39	1.4	0.16
		Normotensive	6.82	1.71		

Urinary Nickel (u_Ni) , * Significant $p < 0.05$

Table 3: Mean levels of measured biochemical parameters among the studied groups

	Exposed N=50	Controls N=43		
	Mean±SD	**Mean±SD**	**t-test**	**P-value**
ApoE(µg/ml)	24.8±15.9	54.8±70.6	2.7	.004**
TC (mg/dl)	298.1±69.7	251.4±73.8	3.1	.002**
HDL-c(mg/dl)	32.9±6.5	40.3±10.5	4.0	.000**
LDL-c(mg/dl)	202.1±52.4	168.4±69.2	2.6	.010**
VLDL-c(mg/dl)	50.1±26.5	45.6±13.7	1.0	.302
TG(mg/dl)	250.3±132.7	220.9±66.8	1.4	.174
Hs-CRP(µg/ml)	5.3±5.7	4.9±4.3	.4	.687
Fibrinogen(mg/dl)	252.0±137.2	245.2±86.9	.3	.773

TC (total cholesterol), HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; VLDL-c, very low density lipoprotein cholesterol; TG (triglycerides); Apo E, apolipoprotein E; Hs-CRP (high sensitive C-reactive protein); ** Significant $p<0.01$

Figure (2):showed that in the present study, the cutoff point of high risk is hs-CRP =4 mg/L. We found that 55.9% (52/93) of the studied groups had hs- CRP ≤ 4 and 44.1% (41/93) had hs–CRP ≥ 4.

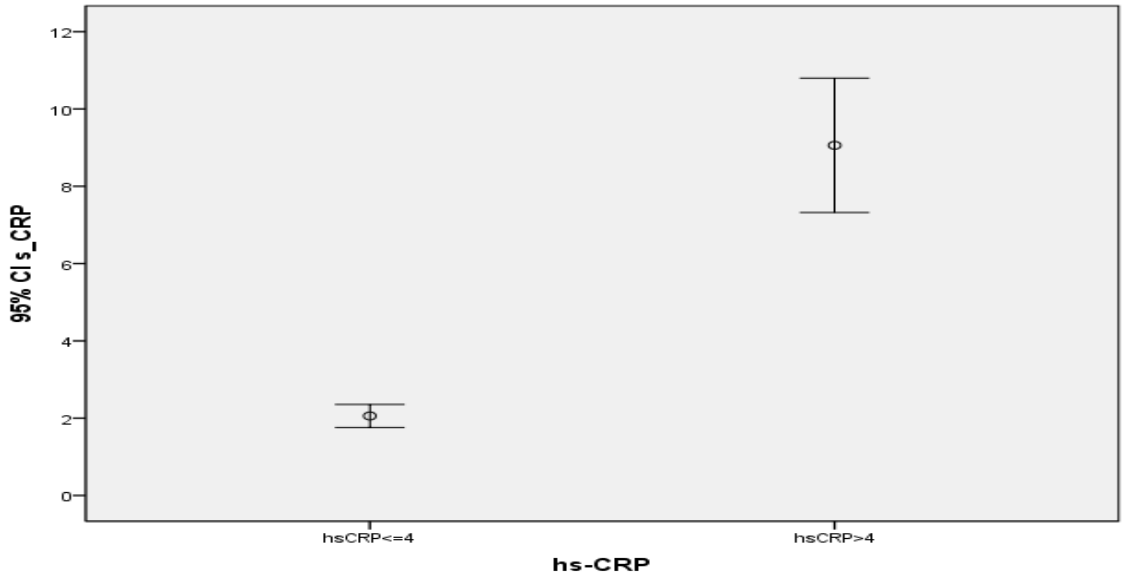


Table 4: Mean levels of measured biochemical parameters among the studied groups according to the level of Hs-CRP

	Hs-CRP ≤ 4 mg/L (N=52)	Hs-CRP >4mg/L (N=41)		
	Mean±SD	Mean±SD	t-test	P-value
ApoE(µg/ml)	42.5±47.5	33.7±56.1	0.8	.798
TC (mg/dl)	269.5±83.1	277.5±64.8	0.5	.086
HDL-c(mg/dl)	38.0±10.9	34.2±6.1	2.0	.005**
LDL-c(mg/dl)	180.8±67.2	188.2±60.2	0.6	.293
VLDL-c(mg/dl)	45.6±20.9	51.1±22.4	1.2	.253
TG(mg/dl)	227.7±104.3	248.0±112.6	0.9	.257
Fibrinogen(mg/dl)	237.7±92.8	263.0±140.1	1.0	.005**

TC (total cholesterol), HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; VLDL-c, very low density lipoprotein cholesterol; TG (triglycerides); Apo E, apolipoprotein E; Hs-CRP (high sensitive C-reactive protein); ** Significant p<0.01

Table5: Correlation between the different measured biochemical parameters in the exposed group

		Serum TC	Serum TG	Serum HDL-c	Serum LDL-c	Serum VLDL-c	Hs-CRP	Apo_E
Hs-CRP	r	-.008	.075	-.154	-.025	.129	---	
	p	.939	.473	.140	.812	.220		
Apo_E	r	-.179	-.213*	.179	-.142	-.224*	-.170	---
	p	.085	.040	.087	.174	.031	.103	
Fibrinogen	r	-.065	-.116	.147	-.063	-.109	.237*	-.037
	p	.533	.268	.159	.546	.298	.022	.724

TC (total cholesterol), TG, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; VLDL-c, very low density lipoprotein cholesterol; Hs-CRP (high sensitive c- reactive protein); Apo E, apolipoprotein E; *, significant ($p<0.05$).

DISCUSSION

The environmental measurements recorded that the mean value of "Ni' concentration was 9.7 ±0.75 µg/m^3, which was higher than recommended exposure limit set by the "Agency for Toxic Substances and Disease Registry" (ATSDR, 2005). But, this concentration was within the normal limit set by the "Egyptian Law 4/1994, Executive Regulations, Annex 6, Table 2, Maximum Limit (Ceiling) of Emission of Ni".

As there is a good correlation between the concentrations of Ni in the air versus urinary Ni of exposed subjects, urinary Ni represents the most suitable test for the assessment of occupational exposure to this metal (Campurra and Agenti, 2010). The level of urinary Ni in Ni-exposed workers of the present study was higher compared to controls reflecting higher occupational exposure to Ni fumes and fine particles in their work environment. Many studies reported high urinary Ni among Ni-exposed workers in an electroplating factory compared to their controls (El-Shafei, 2011; Beshir et al., 2016), agreeing with the present study and signifying higher exposure to Ni.

Ni, vanadium and iron contents of PM (2.5) were significantly associated with increased SBP among persons on antihypertensive treatment (Jacobs et al., 2012), agreeing with the present study. In the present study, the high SBP and DBP of Ni-exposed workers might lead to hypertrophy of left ventricle and subsequently dyspnea. Dyspnea is the most typical and common symptom of heart and lung diseases. Impairment of heart muscle can build up pressure within the lungs and the chambers of the heart, generating the sensation of breathlessness (Berliner et al., 2016).

Several mechanisms had been suggested in raising BP in Ni- exposed' workers. Ni deposited in the lung might transfer into the general circulation and directly interrelate with cardiovascular tissues to induce damage or inflammation through oxidative stress (Yamawaki and Iwai, 2006).

In the presence of oxidative stress, reactive oxygen species (ROS), cause tissue damage by directly attacking and denaturing functional/structural molecules. Oxidative stress plays a serious part in the pathogenesis of hypertension and cardiovascular disease (Vaziri and Rodriguez-Itrube, 2006).

Ni exposure may elevate blood pressure by allowing ROS production and ROS-mediated inhibition of endothelium derived relaxing factor (Ying et al., 2013). Ni may increase sympathetic activity, as it act through a neural mechanism to change cardiac autonomic function (Nurkiewicz et al., 2006).

Also, Ni may perturb vascular smooth muscle Ca2 signaling. It has been stated that Ni ions provoke vasoconstriction and early after depolarization in the heart and vasculature of experimental animals by increasing Ca2+ influx into vascular smooth muscle cells (Golovko et al., 2003; Koller et al., 1982; Rubanyi and Kovach, 1980). Ni is an inorganic calcium antagonist (Nossen et al., 1987). Release of intracellular calcium is required for contraction of the heart muscle. Consequently, changes in signaling due to antagonism that stops real increase of cytosolic calcium would possibly impair contractility (Pepine et al., 2003).

Also, higher BP in the Ni- exposed workers may be due to imitated hypoxia effect of Ni. Replacement of iron by nickel in the oxygen carrier, changes signal to permanent hypoxia (Salnikow et al., 2000). As chronic hypoxia is accompanied with increased sympathetic activity, it increases heart rate (HR) and blood pressure

(Oliveira et al., 2017).

Ni has also been shown to have effects on the functionality of the heart. "The Prospective Investigation of the Vasculature in Uppsala Seniors" (PIVUS) study noticed that amplified Ni was accompanied by left ventricular hypertrophy and wall thickness (Lind et al., 2012). However, a Chinese study established positive relation between Ni and SBP (Wu et al., 2013).

ECG changes in the present study showed very variable heart problems including axis deviation, conduction problems (M shape of QRS), depolarization problems of atria and ventricles (P wave vs. QRS complex), repolarization changes (T wave), suggesting a generalized mechanism that involves the cardiac muscle cells, the conducting system and the electrical activity of the heart.

The findings of ECG in our exposed workers may be due to the effect of Ni as a metal on cardiac cells, both the muscle cells and the conducting tissues i.e. SA node, AV node and the rest of the conducting system. Similarity of Ni as a metal and the ions responsible for the action potential (AP) of the cells; depolarization and repolarization changes can interfere with these physiologic events in a manner causing these pathological, heterogenous effects found in ECG. Additionally, in the periodic table of elements, "Ni" is cited near Na, K, and Ca (their ions which are responsible for the AP changes of the cardiac muscle cells) and all are classified as metals. Ni may interfere with these ions during the (AP) causing manifest pathological changes in ECG. In addition, gene alterations, or oxidation reactions, as suggested by the previously mentioned studies may be the mechanisms by which Ni exert its effects on cells (Yamawaki and Iwai, 2006; Vaziri and Rodriguez-Itrube, 2006).

Another explanation for heterogeneous ECG findings in the present work is that the effect of Ni exposure as a xenobiotic is unique. It is not expected to give the classic picture of the effect of cardiovascular pathology on ECG. Thus, we did find left axis deviation, but without voltage criteria of left ventricular hypertrophy.

Elevated lipid profile may be due to disorder in the metabolism of lipids or may be due to reduced clearance from plasma which favoritisms liver dysfunction. As a result hyperlipidemia, hypercholesterolemia, premature atherosclerosis and excessive deposition of fat occur (Mehra et al., 2005).

HDL-c (protective against artherogenesis) send back excess cholesterol deposited in blood vessel walls to the liver for catabolism (Toth DF and Wonger, 2003). In the present study, an increase of LDL-c, TC, and TG levels and a decrease in the HDL-c level in the exposed group is agreeing with a previous study (Das et al., 2006) findings. Liver illness arising from exposure to Ni has been proposed to decrease the HDL-c content, to cause dyslipidemia and disrupt the biotic functions of HDL-c (Das et al., 2006).

Moreover, those authors (Das et al., 2006) stated a mechanism which could explain the rise of serum LDL-c, TC and TG and fall of HDL-c observed in the present study. Changes in the gene expression of hepatic enzymes like hydroxy methylglutaryl-CoA reductase depresses LDL receptor gene expression, interfering with cholesterol uptake from the blood stream, resulting in elevated levels of TC and LDL-c. Lead-induced change in the gene expression of hydroxymethylglutaryl-CoA reductase in rats has been reported (Kojima et al., 2004).

In addition this study (Das et al., 2006) stated that rise in TG in Ni exposed workers is possibly due to a lack of activity of lipoprotein lipase in blood vessels, which breaks up the triglyceride inside the chylomicrons which could explain the rise of TG in the current study.

The atherosclerotic process is characterized by a low-grade inflammation changing the endothelium of the coronary arteries and is associated with an elevated level in inflammatory markers (Madjid and Willerson, 2011). Ni exposure may play a key role in leukocyte recruitment in the vasculature leading to vascular inflammation and dysfunction, resulting in worse progression of atherosclerosis seen in mice exposed to concentrated ambient-air fine PM (Sun et al., 2005).

CRP decrease the appearance of nitric oxide synthase and prostacyclin synthase, and binds LDL-C and increase its uptake by macrophages, also up-regulates the expression of adhesion molecules on endothelial cell. All these phenomena are associated with formation of atherosclerotic plaques (Mehta et al., 2007).

Hs-CRP has been endorsed by several public health organizations as a biomarker of cardiovascular disease risk "(European Association for Cardiovascular Prevention and Rehabilitation, 2011; ACC/AHA Guideline on the Assessment of Cardiovascular Risk. Circulation, 2014; National Lipid Association recommendations for patient-centered management of dyslipidemia, 2014)". A "MESA" analysis established a mean hs-CRP level of 3.76

mg/l, which did significantly differ between those with and without future coronary events (Detrano et al., 2008).

In the present study we found that hs-CRP was significantly correlated with fibrinogen which confirm the findings of previous studies (Pepys and Hirschfield, 2003; Shishehbor and Bhatt, 2004; Ridker, 2007) which demonstrated that they are markers for inflammation and predictors of CVD. Also HDL–c was lower in the studied group with hs CRP>4 which means that this group is at risk for artherogenesis than the other group with hs-CRP≤4.

A previous study (Ridker et al., 2002) found that the studied group with elevated hs-CRP and decreased LDL-C was at larger threat for CVD than the group with decreased hs-CRP and elevated LDL-C levels. He found that hs-CRP was a powerful predictor of CV actions than LDL-C, however, screening for both biological markers is more prognostic than either alone.

APO E is necessary for the normal catabolism of triglyceride-rich lipoprotein constituents. It was documented for its importance in lipoprotein metabolism and CVD (Huang and Mahley, 2014). It is produced by macrophages and its secretion has been shown to be limited to classical monocytes in peripheral blood, and the secretion of Apo E by monocytes is down regulated by inflammatory cytokines (Braesch et al., 2013).

Apo E in the present study was significantly lower in the exposed group than the controls as it is down regulated by inflammatory cytokines as there is inflammation in the exposed group as confirmed by the higher levels of hs-CRP which is correlated with fibrinogen as acute phase reactants. Also, Apo E was negatively correlated with TG and VLDL-c which were higher in the exposed workers than the controls.

Apo E has significant immunoregulatory properties that could also play a role in Apo E associated antiatherogenic function (Jofre-Monseny et al., 2008).

Fibrinogen level in the exposed workers in the present study was higher than the controls. Previous studies (Scharrer et al., 2007; Järvelä et al., 2013) found that workers exposed to steel welding and grinding fumes and dusts, showed no changes as regards the fibrinogen levels. However, another study found decreased fibrinogen levels among welders. This may be due to the circadian variation of fibrinogen (Bremner et al., 2000).

CONCLUSION

In conclusion, our findings among Ni-exposed workers suggest that Ni was particularly influential in producing cardiovascular responses in human. Cumulative Ni exposure is not associated with increased effect on the measured parameters. Even if inflammatory markers (Apo E, hs-CRP, fibrinogen) are not directly a part of causes of CVD, they may be considered an early valuable sign of clinical significance for possible diseases. It might be recommended to incorporate follow-up schedule of biometric measurements (such as blood pressure, ECG, serum lipids and inflammatory markers) into occupational health services for Ni-exposed workers. Health education and health promotion strategies and interventions can be adopted by authorities of different levels. Small sample size was a great limitation in the current study as it was restricted to subjects with complete Ni exposure and outcome data. Also, evaluation of liver functions and oxidative stress for the studied groups was another limitation in the current study. More studies have to be done to clarify the cellular and molecular mechanisms of Ni action on cardiovascular system.

Follow-up of the hypertensive exposed workers after giving them an antioxidant therapy course as it will significantly improve the oxidative stress and the hypertension is recommended.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest".

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AUTHOR CONTRIBUTIONS

SB creator of the idea of the research, performed the laboratory investigations and participated in writing the manuscript. SH did & interpreted the ECG. WS did the clinical examination, questionnaire and participated in writing the manuscript. SEL did the statistical analysis and reviewed the manuscript. EMS shared in performing the laboratory investigations and reviewed the manuscript. GES clinical

examination. All authors read and approved the final version.

REFERENCES

Grandjean P, 1984. Human exposure to nickel. The International Agency for Research on Cancer (IARC) Scientific Publications 53:469-485.

Cuevas A, Liberda E, Gillespie P, et al., 2010. Inhaled nickel nanoparticles alter vascular reactivity in C57BL/6 mice. Inhal Toxicol 22(2): 100–106.

Ying Zh, Xu Xi, Chen Mi et al., 2013. A Synergistic Vascular Effect of Airborne Particulate Matter and Nickelin a Mouse Model. Toxicol Sci 135(1): 72-80·

Campen MJ, Nolan JP, Schladweiler MC, et al., 2001. Cardiovascular and thermoregulatory effects of inhaled PM-associated transition metals: a potential interaction between nickel and vanadium sulfate. J Toxicol Sci 64(2):243–252.

Muggenburg BA, Benson JM, Barr EB, Kubatko J, Tilley LP, 2003. Short-term inhalation of particulate transition metals has little effect on the electrocardiograms of dogs having preexisting cardiac abnormalities. Inhal Toxicol 15:357–371.

Lippmann M, Ito K, Hwang JS, et al., 2006. Cardiovascular effects of nickel in ambient air. E H P *114*:1662–1669.

Chashschin VP, Artunina GP, Norseth T., 1994. Congenital defects, abortion and other health effects in nickel refinery workers. Sci. Total Environ 148(2-3):287-291.

Jaiprakash, Singhai A, Habib G, Raman RS, Gupta T, 2017. Chemical characterization of PM1.0 aerosol in Delhi and source apportionment using positive matrix factorization. 2Environ Sci Pollut Res Int 4(1):445-462.

Wallenborn JG, McGee JK, Schladweiler MC, Ledbetter AD, Kodavanti UP, 2007. Systemic translocation of particulate matter-associated metals following a single intratracheal instillation in rats.Toxicol Sci 98(1):231–239.

Yamawaki H, Iwai N, 2006. Mechanisms underlying nano-sized air-pollution-mediated progression of atherosclerosis: carbon black causes cytotoxic injury/inflammation and inhibits cell growth in vascular endothelial cells. Circ J 70(1):129–140.

Sin DD, Man SF, 2003. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 107(11):1514–1519.

Chuang HC, Hsueh TW, Chang CC, Hwang JS, Chuang KJ, Yan YH, 2013. Nickel-regulated heart rate variability: the roles of oxidative stress and inflammation. Toxicol Appl Pharmacol 266(2):298–306.

Campen MJ, Nolan JP, Schladweiler MC, Kodavanti UP, Evansky PA, Costa DL, 2001. Cardiovascular and thermoregulatory effects of inhaled PM-associated transition metals: a potential interaction between nickel and vanadium sulfate. Toxicol Sci 64(2):243–252.

Lippmann M, Ito K, Hwang JS, Maciejczyk P, Chen LC, 2006. Cardiovascular effects of nickel in ambient air. Environ Health Perspect 114:1662–1669.

Brook RD, 2008. Cardiovascular effects of air pollution. Clin Sci 115(6):175–187.

Kim JY, Chen JC, Boyce PD, Christiani DC, 2005. Exposure to welding fumes is associated with acute systemic inflammatory responses. Occup Environ Med 62:157–163.

Devaki RN, Basavana GH, Suma MN, Prashanth V, Akila P, Anjali Devi BD, 2011. A study of C-reactive protein and its relationship with CHD and lipid metabolism. Int J Pharm Sci Rev Res 6:125–7.

Koenig W, Khuseyinova N, Baumert J, et al., 2006. Increased concentrations of C-reactive protein and IL-6 but not IL-18 are independently associated with incident coronary events in middle-aged men and women: results from the MONICA/KORA Augsburg case-cohort study, 1984-2002. Arterioscler Thromb Vasc Biol 26(12):2745-2751.

Monroe DM, Hoffman M, Roberts HR, 2010. Molecular Biology and Biochemistry of the Coagulation Factors and Pathways of

Hemostasis. Prchal JT, Kaushansky K, Lichtman MA, Kipps TJ, Seligsohn U, eds. In: Williams - Hematology. 8th ed. New York chapter 115.

~~20)~~ Song Y, Stampfer MJ, Liu S, 2004. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. Ann Intern Med 141: 137-47.

Holtzman DM, Herz J, Bu G, 2012. Apolipoprotein E and apolipoprotein E receptors: normal biology and roles in Alzheimer disease. Cold Spring Harb Perspect Med 2:a006312.

Huang Y, Mahley RW, 2014. Apolipoprotein E: Structure and Function in Lipid Metabolism, Neurobiology, and Alzheimer's Diseases. Neurobiol Dis 72PA: 3-12.

vandenElzen P, Garg S, Leon L, Brigl M, et al., 2005. Apolipoprotein-mediated pathways of lipid antigen presentation. Nature 437:906–10.

Mooijaart SP, Berbée JF, van Heemst D, et al., 2006. ApoE plasma levels and risk of cardiovascular mortality in old age. PLoS Med 3:e176.

Blood Pressure UK Association 2008
www.bloodpressureuk.org/BloodPressureandyou/Thebasics/Bloodpressurechart

Goldberger A, Goldberger Z, Shvilkin A, 2017. Goldberger's Clinical Electrocardiography. 9th Edition. Elsevier.https://lifeinthefastlane.com/ecg-library/basics.

Rice EW, Baird RB, Eaton AD, et al., 2015. Standard methods for the examination of water and wastewater. American Public Health Association (APHA). 23rd ed. Washington, DC, USA.

Roeschlau P, Bernt E, Gruber W, 1974. Enzymatic determination of total cholesterol in serum. Z Klin Chem Klin Biochem 12(5):226.

Jacobs NJ, Vandemark PJ, 1960. The purification and properties of the alpha-glycerophosphate-oxidizing enzyme of Streptococcus faecalis 10C1. Arch Biochem Biophys 88:250–255.

Lopes-Virella MF, Stone P, Ellis S, Colwell JA, 1977. Cholesterol determination in high-density lipoproteins separated by three different methods. Clin. Chem 23(5):882-884.

Kimberly MM, Vesper HW, Caudill SP, et al., 2003. Standardization of immunoassays for measurement of high-sensitivity C-reactive protein. Phase I: evaluation of secondary reference materials. Clin Chem 49(4):611-616.

Koepke JA, Gilmer PR Jr, Filip DJ, Eckstein JD, Sibley CA, 1975. Studies of fibrinogen measurement in the CAP survey program. Am J Clin Pathol 63 (6 SUPPL):984-989.

ATSDR (Agency for Toxic Substances and Disease Registry), 2005. Tox Guide for nickel. *ATSDR/US Public Health Service, ATSDR/TP-7440-02-0*, Atlanta, GA, USA.

Campurra G, Agenti C, 2010. Manuale medicina dellavoro. Wolters Kluwer; 868-869.

El-Shafei HM, 2011. Assessment of liver function among nickel-plating workers in Egypt. East Mediterr Health J 17(6):490-494.

Beshir S, Ibrahim KS, Shaheen W, Shahy EM, 2016. Hormonal Perturbations in Occupationally Exposed Nickel Workers. OAMJMS 4(2):307–311.

Jacobs L, Buczynska A, Walgraeve C, et al., 2012. Acute changes in pulse pressure in relation to constituents of particulate air pollution in elderly persons. Environ Res 117: 60-67.

Berliner D, Schneider N, Welte T, et al., 2016. The differential diagnosis of dyspnea. Dtsch Arztebl Int 113(49):834–845.

Yamawaki H, Iwai N, 2006. Mechanisms underlying nano-sized air-pollution-mediated progression of atherosclerosis: carbon black causes cytotoxic injury/inflammation and inhibits cell growth in vascular endothelial cells. Circulation 70(1):129–140.

Vaziri ND, Rodriguez-Itrube B, 2006. Mechanisms of disease: oxidative stress and inflammation in the pathogenesis of HTN. Nat Clin Pract Nephrol 2: 582–593.

Ying Z, Xu X, Chen M, et al., 2013. A synergistic vascular effect of airborne particulate matter and nickel in a mouse model. Toxicological sciences : an official J of the Soc of Toxicol 135(1):72–80.

Nurkiewicz TR, Porter DW, Barger M, et al., 2006. Systemic microvascular dysfunction and inflammation after pulmonary particulate matter exposure. EHP 114:412–419.

Golovko VA, Bojtsov IV, Kotov LN, 2003. Single and multiple early afterdepolarization caused by nickel in rat atrial muscle. Gen Physiol Biophys 22 : 275–278.

Koller A, Rubanyi G, Ligeti L, Kovach AG, 1982. Effect of verapamil and phenoxybenzamine on nickel-induced coronary vasoconstriction in the anaesthetized dog. Acta Physiol Acad Sci Hung 59:287–290.

Rubanyi G, Kovach AG, 1980. Cardiovascular

actions of nickel ions. Acta Physiol Acad Sci Hung 55(4):345–353.

Nossen JO, Rustan AC, Drevon CA, 1987. Calcium-antagonists inhibit secretion of very-low-density lipoprotein from cultured rat hepatocytes. The Biochem J 247(2):433–9.

Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al., 2003. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA 290(21):2805–16.

Salnikow K, Su W, Blagosklonny MV, et al. 2000. Carcinogenic metals induce hypoxia-inducible factor-stimulated transcription by reactive oxygen species-independent mechanism. Cancer Res 60:3375-3378.

Oliveira AZ, Rohan PA, Gonçalves R, Soares PP, 2017. Effects of Hypoxia on Heart Rate Variability in Healthy Individuals: A Systematic Review. Int J Cardiovasc Sci 30(3):251-261.

Lind PM, Olsen L, Lind L, 2012. Elevated circulating levels of copper and nickel are found in elderly subjects with left ventricular hypertrophy. Ecotoxicol and environ safety 86:66–72.

Wu S, Deng F, Huang J, et al., 2013. Blood pressure changes and chemical constituents of particulate air pollution: results from the healthy volunteer natural relocation (HVNR) study. Environ H persp 121(1):66–72.

Mehra VC, Ramgolam VS, Bender JR, 2005. Cytokines and cardiovascular disease. J Leuk Biol 78(4): 805–818

Toth DF, Wonger H, 2003.Clinical Chemistry Textbook, ed 3. pp. 423, Oxford–University Press, Oxford.

Das KK, Gupta AD, Dhundasi SA, et al., 2006. Effect of L-ascorbic acid on nickel-induced alterations in serum lipid profiles and liver histopathology of rats. J.of Bas and Clin Phys and Pharma 17:29-44.

Kojima, M., Masui, T., Nemoto, K., Degawa, M, 2004. Lead nitrate induced development of hypercholesterolemia in rats; Sterol independent gene regulation of hepatic enzymes responsible for cholesterol homeostasis. Toxicol. Lettrature 154:35–44.

Madjid M, Willerson JT, 2011. Inflammatory markers in coronary heart disease. Br Med Bull 100:23–38.

Sun Q, Wang A, Jin X, Natanzon A, et al., 2005. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. JAMA 294:3003–3010

Mehta JL, Sukhija R, Romeo F, Sepulveda JL, 2007. Value of CRP in coronary risk determination. Ind Heart J 59:173–7.

Detrano R, Guerci AD, Carr JJ, et al., 2008. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med.; 358:1336–45.

Pepys MB, Hirschfield GM, 2003. C-reactive protein: a critical update. J Clin Invest 111:1805–12.

Shishehbor M.H., Bhatt D.L., 2004. Inflammation and atherosclerosis. Curr Atheroscler Rep 6:131–139.

Ridker P.M., 2007. Inflammatory biomarkers and risks of myocardial infarction, stroke, diabetes, and total mortality: Implications for longevity. Nutr Rev 65:S253–S259.

Ridker PM, Rifai N, Rose L, Buring JE, Cook NR., 2002. Comparison of Creactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 347: 1557–65.

Braesch AS, Paulie S, Smedman C, Mia S, Kumagai BM, 2013. ApoE production in human monocytes and its regulation by inflammatory cytokines. PloS One 8 (11): e79908.

Jofre-Monseny L, Minihane AM, Rimbach G., 2008. Impact of apoE genotype on oxidative stress, inflammation and disease risk. Mol Nutr Food Res 52:131-45

Scharrer E, Hessel H, Kronseder A, et al., 2007. Heart rate variability, hemostatic and acute inflammatory blood parameters in healthy adults after short-term exposure to welding fume. Int Arch Occup Environ Health 80(4):265-72.

Järvelä M, Kauppi P, Tuomi T, et al., 2013. Inflammatory response to acute exposure to welding fumes during the working day. Int J Occup Med Environ Health 26(2):220-9.

Bremner WF, Sothern RB, Kanabrocki EL, et al., 2000. Relation between circadian patterns in levels of circulating lipoprotein(a), fibrinogen, platelets, and related lipid variables in men. Am Heart J 139:164–73.