Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 1307 - 1319
Received 05 March 2021; Accepted 01 April 2021.

Hematologic Evaluation and Histopathological Alteration of Nickel Nitrate Exposure in Male Rabbits

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Abstract

The current work was done to determine the impacts of sub- acute exposure with two doses of nickel nitrate on the body and organs weights, hematologic and some biochemical criteria as well as histological changes of heart, liver and kidney in adult male rabbits. Eighteen rabbits were used and distributed randomly into 3 groups, group one considered as control which was administered 1ml of distilled water orally, group two was administered 10mg/kg of nickel nitrate orally, group three was administered 20mg/kg of nickel nitrate orally. Our findings exhibited that nickel nitrate administration cause to moderate alteration of complete blood count values in rabbits treated with 10mg/kg dose while marked changes were seen in rabbits treated with 20mg/kg dose. The histopathological changes in two dosages of nickel nitrate were notable. In conclusion, it can be concluded from current outcomes that exposure to nickel nitrite causing pronounced adverse effects in the blood and organs (heart, liver and kidney) that indicating that nickel nitrate is hazard pollutant.

Key words: Hazard pollutant, Body and organs weights, Hematology criteria, Rabbits

Introduction

The exposure to one of natural or synthetic substances and environmental pollutants will probably cause a health hazard; toxic elements are also included of these substances which constitute a core group of aquatic pollutants. However, many elements are playing vital role in the physiological processes of plants, animals and humans (Annangi *etal*.,2016; Zhu *etal*.,2017). The exposure to heavy metals through industrial, domestic and agricultural discharge systems that transport through the blood where the ions are usually bound to proteins and consequently accumulated in different organs and tissues organisms (Gong *etal*.,2016). A gradual buildup of these toxins (substances) will occur through continuous exposure; excess concentration of metals is harmful thereby introducing stress to living creatures. Stress is a general and non-specific response to any factors disturbing homeostasis (Cao *etal*.,2016). Nickel is a natural element in the earth's makeup, it found primarily combined with salts which are considered an industrial health hazard. The nickel exposed through inhalation, drinking, ingestion and dermal contact leading to cause an adverse effect in the body include lung damage, allergic skin reactions, renal dysfunction and histopathological changes in the nasal mucosa (Kong *etal* .,2014; Sun *etal*.,2016). The nickel forms a complex with adenosine triphosphate, amino acids, peptides, proteins and deoxyribo-nucleic acid, also nickel may cause oxidative damage to isolated DNA and chromatin possibly due to the formation of

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reactive oxygen species (Tikare *etal*., 2013; Chang *etal*., 2017).The major sources of nickel exposure for most people occur through smoking tobacco, ingestion of polluted food and water, and dermal contact. In addition, exhaust fertilizers, superphosphate, hydrogenated fats- oils, food processing and testing of nuclear devices (Mahmoud *eta*l., 2017; De Carli *etal*., 2018). Nevertheless, little studies were done to demonstrate the adverse effect of nickel exposure on human and animals in Iraq, the current study was aimed to determine the impacts of nickel nitrate ($Ni(NO_3)_2$) on body and organs weights, estimation the alteration in blood and biochemical criteria combined with histological changes of heart, liver and kidney in adult male rabbits.

Materials and methods

Healthy male rabbits were selected as experimental animals, and purchased from market in Basra city with weighing (1200-1400 g), eighteen rabbits were used and put in standard cage/two each in animal house and remained under monitoring for seven days before initiation study, the diet and water *ad-libtum* were supplied daily. Animals were distributed randomly into 3 groups /six each. Group 1: was administered 1ml of distilled water orally and considered as control group, group 2: was administered 10mg/kg of nickel nitrate orally and group 3, was administered 20mg/kg of nickel nitrate orally, the exposure of animals to nickel nitrate continued for 14 days consecutive rabbits from control and experimental groups were anaesthetized by ether at the end of the working, blood was drawn from cardiac puncture of each animal and kept in EDAT as anticoagulant for hematologic studies and without anticoagulant, serum was separated and stored at-20 °C for biochemical examination.

Estimation of body and organ weights: Rabbits were weighed by digitalis balance before the start of the experiment and before sacrifice in order for determine the change in body weight and then all animals were killed after 14 days, the organs (heart, liver and kidney) were also removed and weighed in all rabbits by electronic balance to detect any change in weights of the tissue and then the organs heart, liver and kidney used for histopathological assay.

Hematology investigation: RBC count, PCV, Hb, MCV, MCH, MCHC, TWBC count thrombocytes count were estimated by using standard procedures with the count 60 hemotology analyzer Genix & USA.

Biochemical investigation: The fasting blood glucose (FBG) was estimated according to method (Trinder, 1969), the serum protein was determined by method of (Gornall *etal*.,1949), total cholesterol was measured according to method (Siedel *etal*.,1983), the triglyceride was also assayed by method (Fossati and Prencipe, 1982).

Histological techniques: The heart, liver and kidney from treated animals and their controls were excised immediately after killed animals and tissues were fixed in 10% buffered formation and then preparation for histological study (Luna, 1993).

The statistical analysis: Outcomes are expressed as means ± standard error (SE), statistical for experiment animals were evaluated using a one-way analysis of variance (ANOVA), a value at $P<0.05$ was considered statistically significant.

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Results

According to the outcomes obtained in table (1) indicating the exposure to nickel nitrate resulted a significant declined in final body weight at dosage 10mg/kg, whereas, caused marked reduced in final body weight at dosage 20 mg/kg in rabbits were observed, these findings when comparison to the respective initial body weight and values of control group. While, in the same table shown notable an increase in weights of heart, liver and kidney following of nickel nitrate exposure with both doses low and high. nickel nitrate also caused in significantly declined in blood indices (RBC, PCV, Hb, TWBC and PLT) values, the results in coupled with lowered in (MCV, MCH and MCHC) values at dose 10mg/kg, this decreased was more prominent with high dose of nickel nitrate in table (2 and 3). As well as results revealed that a significant an increase in blood glucose, total cholesterol, triglyceride and decreased in total protein after treated rabbits with nickel nitrate at dose 10mg/kg, while, the changes in these indices were more pronounced with high dose 20mg/kg of nickel nitrate in comparison with untreated animals were showed in table(4).

Table(1): Body weight and weight of organs in control group and treated groups with nickel nitrate

Groups	Initial body weight gm	Final body weight gm	Heart Weight	Liver weight	Kidney Weight
Control D.W	1340.22±0.42 a	1338.41±0.23 a	7.25±0.16 c	60.67±0.22 c	15.72±0.26 c
Nickel nitrate exposed at dose 10mg/kg	1300.33±0.39 a	1000.12±0.13 b	7.60±0.19 b	63.43±0.23 b	17.48±0.21 b
Nickel nitrate exposed at dose 20mg/kg	1330.24±0.45 a	900.71±40.5 b	8.00±0.12 a	67.32±0.29 a	19.56±0.23 a

Outcomes are expressed as Mean ± SE. the symbol represent statistical difference at($p < 0.05$) values compared to control animals

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Table(2):Erythrocyte count, Hemoglobin concentration, Packed cell volume percentage and Leukocyte count in control group and treated groups with nickel nitrate

Groups	RBC count $X10^6$ /µL	Hb g/dl	PCV%	TWBCcount $X10^3$ /µL
Control D.W	5.93±0.15a	11.07±0.10a	37.33±0.14a	5.2±0.19a
Nickel nitrate exposed at dose 10mg/kg	4.07±0.12b	8.54±0.23b	32.14±0.22b	4.98±0.21b
Nickel nitrate exposed at dose 20mg/kg	3.00±0.20c	6.50±0.12c	29.15±0.13c	3.52±0.16c

Outcomes are expressed as Mean ± SE. the symbol represent statistical difference at($p < 0.05$) values

compared to control animals

Table(3):Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration and thrombocytes count in control group and treated groups with nickel nitrate

Groups	MCV (fL)	MCH pg/dl	MCHC %	PLT $x10^3$ /µl
Control D .W	46.17±0.04a	25.21±0.11a	32.29±0.03a	287.57±.12a
Nickel nitrate exposed at dose 10mg/kg	43.61±0.02b	22.18±0.21b	29.16±0.01b	268.13±0.18b
Nickel nitrate exposed at dose 20mg/kg	39.92±0.2c	19.29±0.13c	26.59±0.3c	250.37±0.14c

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Outcomes are expressed as Mean ± SE. the symbol represent statistical difference at($p < 0.05$) values compared to control animals

Table (4): Fasting blood glucose Total cholesterol, Triglyceride and Total protein in control group and treated groups with nickel nitrate

Groups	FBG m g/dl	TC mg/dl	TG mg/dl	TP m g/dl
Control D .W	98.63±0.21c	116.42±0.15c	100.7±0.11c	6.19±0.02a
Nickel nitrate exposed at dose 10mg/kg	186.42±0.23b	167.4±0.31b	155.54±0,18b	5.35±0.05b
Nickel nitrate exposed at dose 20mg/kg	205.10±0.16a	183.67±0.21a	174.66±0.12a	4.88±0.01c

Outcomes are expressed as Mean ± SE. the symbol represent statistical difference at($p < 0.05$) values compared to control animals

Histopathological study explained some lesions were observed in the organs (heart, liver and kidney) following nickel nitrite exposure for 14 days, in heart shown presence vacuolation of the myocardial cell and myocardial fibrosis fig (2), whereas, observed congestion and minimal periportal fibrosis in the liver fig(5), in addition the kidney appeared minimal dilatation of cortical tubules of the cortical areas fig(8), these changes caused by (10 mg/kg) of nickel nitrate . Whereas, these lesions were more prominent in these organs following nickel nitrate exposure at dosage(20 mg/ kg), these alterations are including peripheral endocardial fibrosis in heart fig(3), fibrosis and mononuclear cells also congestion presence in the liver was showed fig(6), cortical areas of dilated tubules (moderate dilatation) and fibrosis fig(9), these lesions in comparison with normal organs in figs(1,4,7).

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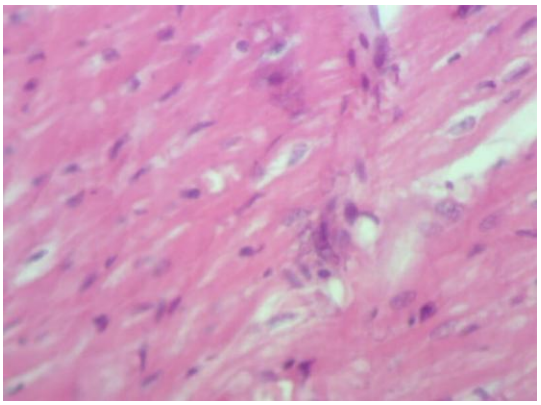
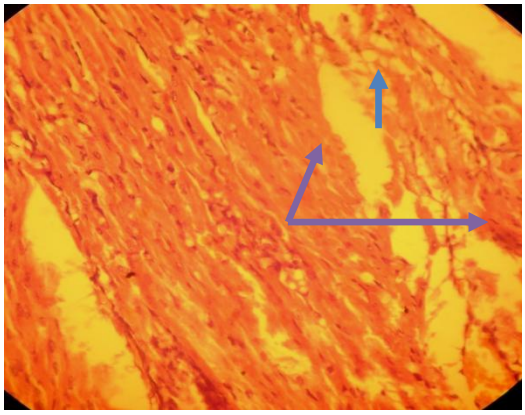
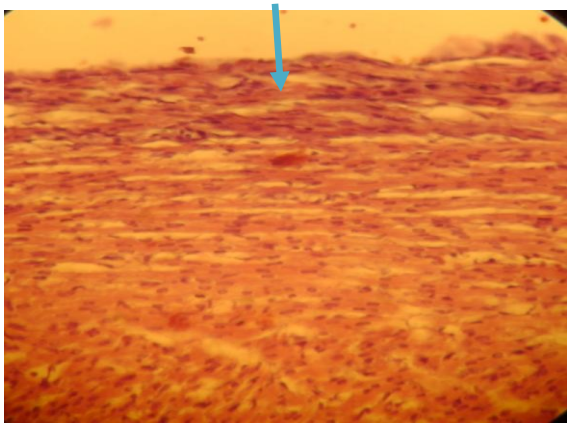


Figure(1):Heart from rabbits non-exposed to nickel nitrate H&E 400X



Figure(2): Heart from rabbits exposed to nickel nitrate 10mg/kg appear vacuolation of myocardial cell(→)and myocardial fibrosis (→) H&E100X



Figure(3):Heart from rabbits exposed to nickel nitrate 20 mg/kg appear peripheral endocardial fibrosis (→) H&EX400

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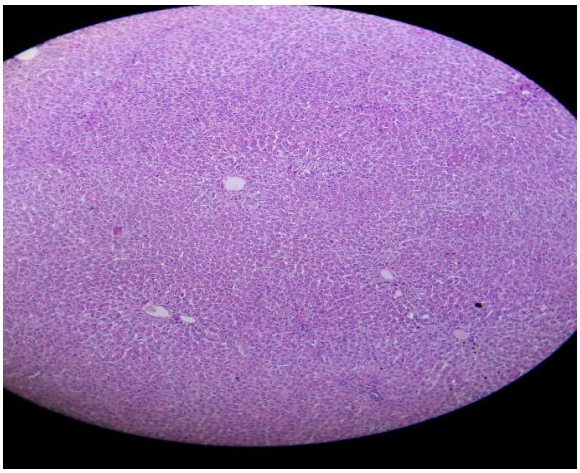
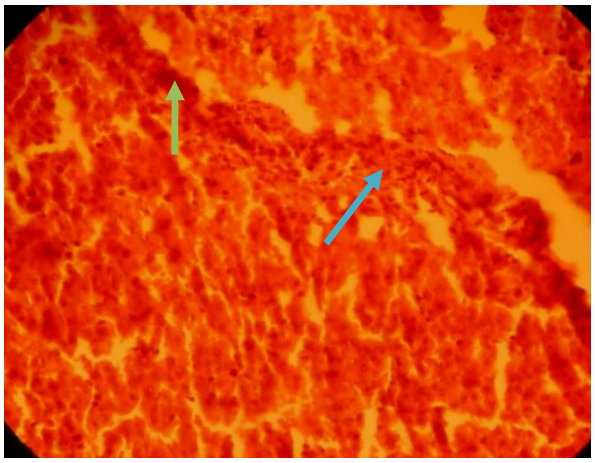
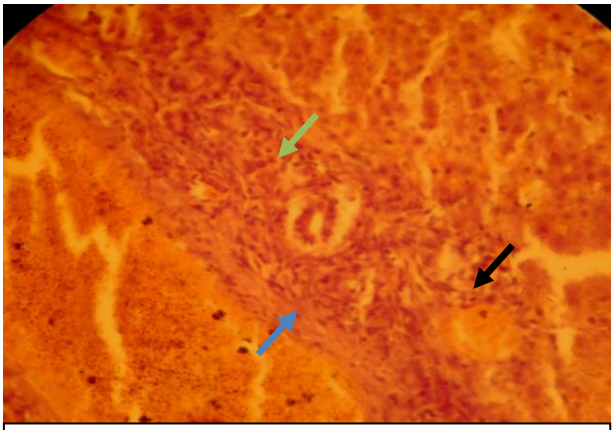


Figure(4):Liver from rabbits non-exposed to nickel nitrate H&E 100X



Figure(5): Liver from rabbits exposed to nickel nitrate 10mg/kg appear minimal periportal fibrosis(→) and congestion (→) H&E X100



Figure(6): Liver from rabbits exposed to nickel nitrate 20 mg/kg appear an area of periportal fibrosis (→) , mononuclear (→) and congestion (→) H&E X100

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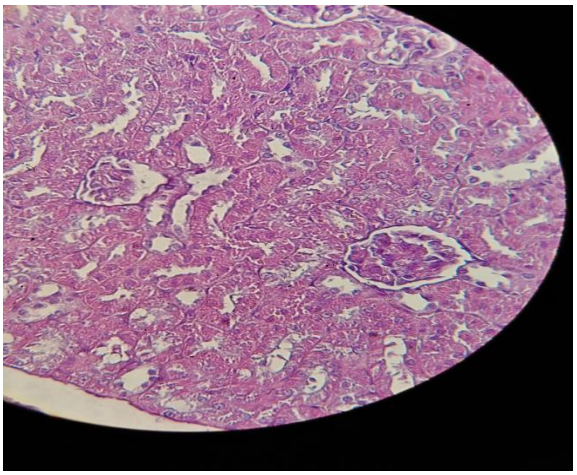
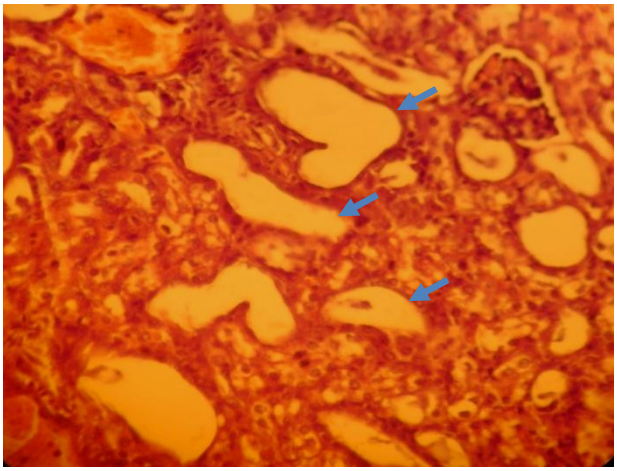
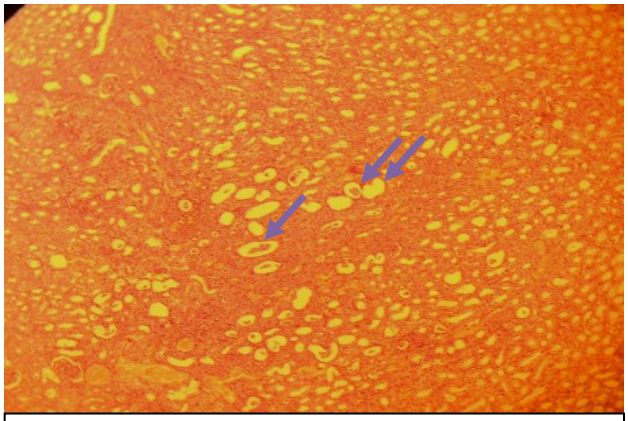


Figure(7):Kidney from rabbits non-exposed to nickel nitrate H&E 400X



Figure(8):Kidney from rabbits exposed to nickel nitrate100mg/kg appear cortical areas of minimal dilated tubules (⟶)H&E X400



Figure(9):Kidney from rabbits exposed to nickel nitrate200mg/kg appear cortical areas of dilated tubules (moderate dilatation) and vacuolation (⟶)H&E X100

Discussion

A major and global problem in our day is an increase of the pollution, this caused by utilization of xenobiotic substances, toxic chemicals and heavy metals (Genchi *etal*., 2020). The outcomes of this experiment indicating that exposure to oral nickel nitrate cause to several adverse effects, showed a significant decreased in final body weight in rabbits exposed to nickel nitrate concomitant with decline of the consumption food, this may be due to suppression of appetite and dysfunction of digestive system, also may be due to increased analysis of protein and lipid resulted in decrease growth rate, this decreased was pronounced with high dose of nickel nitrate in

experimental groups. Our results agree with reported was by (Yadav *etal*., 2018) observed remarkable decreased in body weight in rats exposed to nickel this may be attributed to interact of metal within metabolic pathway of diet contents and causing to lower body weight and delayed growth. Another research by (Alsoltane and Altaee, 2020) demonstrated that exposure to nickel and its compounds cause to GIT disorders, disappearance of appetite and decreased adipocytes in tissues leading to declined body weight in rats.

In our research, the results revealed a significant an increase in weights of organs (heart, liver and kidney) in animals exposed to nickel nitrate in both dosages low and high this may be due to accumulation of metal in the organs (Das *etal*., 2019).These findings are similar with outcomes in other studies have evidenced that metal or its compounds were accumulated in various organs and cause to enlargement of organs by aggregation of abnormal cells (Wang *etal.,* 2012; Sutunkova *etal*., 2019). Results are also obtained by Previous study by (Kubrak *etal*.,2012) who found that a significant increased in the relative organs weights of heart, spleen, liver and kidneys after rats exposed to heavy metals.

Other reports revealed that the heavy metals exposure resulting oxidative damage in tissues and significant changes in blood indices this attributed to increased in oxidative stress and depletion of antioxidant following the exposure to heavy metals in animals and human (Bouhalit *etal*.,2017). In current outcomes , showed a significant decreased in blood criteria involved (RBC, PCV, Hb, WBC, PLT, MCV,MCH and MCHC counts) as evidenced by anemia in the rabbits exposed to nickel nitrate compared with control, this may be due to the inflammatory effect of nickel on bone marrow and caused suppression of hematopoietic cells and leucocytopenia or maybe attributed to fragility of RBC membrane induced by accumulation of nickel in the RBC and eventually RBC lysis, exposure to nickel also cause to a decrease hemoglobin concentration as a result of suppression glycine and succinly pools and ALAD enzyme which are responsible for biosynthesis of hem. On the other , it can cause suppression ferrochelatase enzyme that required to connect between globin and iron or may be due to interacting with the iron resulted in iron accumulation leading to free radical formation. Results are consistent with the those observed by other authors (Al-Ghanim, 2011; Adjroud, 2013).

In current results indicating that the exposure to nickel nitrate also cause to hyperglycemia this elevation in blood glucose as a result of reduction glycogen value in liver and muscle due to metabolism of carbohydrate disturbance (Djemli and Kechrid, 2013; Dumala *etal*., 2017). These findings are agree with other researchers (Moosavi and Shamushaki,2015; Al-fatlawi and Al-Murshedi, 2015) show an increase blood glucose level as a result of glycogneolysis produced by stress of heavy metals. results in this research also appeared a significant increased in total cholesterol

and triglycerides levels may be due to dysfunction of liver and hypothyroidism induced by heavy metals pollution (Das *etal*., 2008; El-Shafei, 2011).These findings in accordance with previously studies are also recorded highest levels of triglycerides and total lipid in fish exposed to heavy metals (Bislimi *etal*., 2018). While, outcomes revealed a decrease in total protein level in animals exposed to nickel nitrate this may be attributed to an increase protein analysis, the results are also obtained by (Tikare *etal*.,2008).

Also nickel nitrate exposure caused oxidative damage in different organs as a result increasing formation of reactive oxygen species . ROS have many deleterious effects on different organs and tissues especially affecting the cell membrane (Das and Buchner, 2007). Histological alteration such as vacuolation of myocardial cell and myocardial fibrosis in heart, results in the experiment in accordance with results obtained by (Novelli *etal*.,2015) demonstrated that the cardiac and hepatic damage due to elevation activity of LDH and ALT enzymes following administration of nickel via intratracheal. Whereas , minimal periportal fibrosis and congestion in liver and cortical areas of minimal dilated tubules in kidney were showed . The same results are also obtained by (Tikare *etal*.,2013).

Moreover, the administration of nickel nitrate for the same period at dosage of 20mg/kg resulted in deleterious effects more remarkable in the above organs, such as peripheral endocardial fibrosis, the result also seen by (Zhang *etal*.,2019). concluded that the exposure to nickel is accompanied with increase the occurrence of congenital heart defect (CHDS)in maternal and fetal. In addition, vacuolation and damage of hepatic cells and cortical areas of dilated tubules and vacuolation were noticed, the outcomes agree with other researchers (Parekh *etal*.,2006; Fatmi *etal*.,2018).

Conclusion: It can be concluded from current outcomes that exposure to nickel nitrite causing pronounced adverse effects in the blood and organs (heart, liver and kidney) that indicating the nickel nitrate is hazard pollutant.

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