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DISTURBED HOMEOSTASIS OF CERTAIN HEAVY METALS ON EXPOSED MALE ALBINO RATS

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Abstract: **The heavy metal pollutants well known to be highly toxic to both human and animals, are widely distributed due to its use in various industries. One of them and caused highly effects is Lead which naturally occurring elements. The salts of them are soluble and forming aqueous solutions, cannot be separated by usually physical means of separation. Lead intervenes with a diversity of most of body processes and is toxic to many tissues, exposure for long time to a sub lethal dose associated with oxidative stress, damage of DNA and revealed to be a risk factor for kidney, liver. Cadmium affects cell proliferation, differentiation, apoptosis and other cellular activities. The exposure lead to renal dysfunction, hepatic damage, anemia, and hypertension. Cadmium may made oxidative damage in different tissues. In this study were carried out on investigate the most toxic effects of lead, cadmium, and zinc with trial to estimate this toxicity, on the biochemical blood parameters and function of liver and kidney on heavy metals-unprotected animals. Oral administration of their salts, we found Lead and Cadmium had significantly decreased RBC count, WBC, hemoglobin level, hematocrit value, MCHC, Total protein, albumin, and A/G ratio. In contrast, MCV, MCH, urea, creatinine, MDA, SOD, AST, and ALT were significantly increased. At kidneys and liver, the observed alterations could be a compensatory reaction to unlike heavy metals accretion in the organs. Moreover, the probable individual mechanisms in ROS eradication. In conclusion lead induces oxidative stress in various tissues.**

Key word: **Heavy metals, Lead, Cadmium, Zinc, Rats, Biochemical, Kidney, liver.**

1. INTRODUCTION

Heavy metals Environmental pollution is accumulative as a result of more urbanization and utilization. The discarding of industrial emissions is becoming the most important problem [1].

Lead (Pb) harming has been documented as a main public health danger, predominantly in developing countries. Though several occupational and public health measures have been assumed in order to control lead introduction, circumstances of lead poisoning are still described. Acquaintance to lead products several deleterious effects on the hematopoietic, renal, reproductive and central nervous system, chiefly through increased oxidative stress. These modifications show a noticeable part in disease appearances. Modulation of cellular thiols for defense against reactive oxygen species (ROS) has been used as a therapeutic policy against lead toxicity. Lead toxicity is a principally insidious risk with the potential of causing permanent health effects. It is known to restrict with a number of body functions and it is mainly affecting the central nervous, hematopoietic, hepatic and renal system producing serious conditions [2].

Severe toxicity is related to occupational introduction and is quite rare. Prolonged toxicity on the other hand is much more common and occurs. It can be much more severe if not cured in time and is considered by persistent vomiting,

encephalopathy, lethargy, delirium, convulsions and coma [3]. Lead straight affects the hematopoietic system through preventive the synthesis of hemoglobin by inhibiting different key enzymes intricate in the heme synthesis trail. It also shrinks the life span of circulating erythrocytes by increasing the flimsiness of cell membranes. The shared aftermath of these two processes chiefs to anemia [4]. Lead meaningfully affects the heme synthesis pathway in a dose dependent method by downregulating three key enzymes elaborate in the synthesis of heme [5]. The mechanism liable for shortening the life cycle of erythrocytes is not well unstated. One of the earliest detected hematological effects of lead discovered basophilic dotting of red blood cells, which is also a probable biomarker for the discovery of lead poisoning. These aggregates are filth products of ribonucleic acid [6]. Renal dysfunction happens mostly at high levels of lead exposure but damage at lower levels has also been informed [7]. Renal functional defect can be of two types: acute nephropathy and chronic nephropathy. Acute one is described functionally by an impaired tubular transport mechanism and morphologically by the presence of degenerative changes in the tubular epithelium along with the occurrence of nuclear inclusion bodies containing lead protein complexes. It does not reason of protein to appear in the urine but can give rise to abnormal excretion of glucose, phosphates and amino acids, a combination referred to as Fanconi's syndrome. Otherwise the chronic, is much more severe and can result in irreversible functional and morphological changes. It is characterized by glomerular and tubule-interstitial changes, lead to renal breakdown, hypertension and hyperuricemia [8].

When the body is chronically exposed to cadmium that metal accumulates in the liver and the kidney; by acute exposure, it primarily accumulates in the liver [9]. Characteristic through hepatotoxicity which was indicated via such changes as swelling of hepatocytes, fatty changes, and focal necrosis or necrosis in a wide area [10]. Cadmium is predominantly a concern in environmental pollution because it is said to accumulate in the human body causing renal dysfunction, pulmonary emphysema, kidney damage and osteoporosis [11].

Breakdown of zinc and zinc-containing compounds can result in a variety of chronic effects in the gastrointestinal, hematological and respiratory systems along with amendments in the cardiovascular and neurological systems of humans.

In this report, we provide evidence physiological alterations and their correlations with structural modifications of the kidney and liver cells of heavy metals-showing rats.

2. METHODS

Animals and intoxication manner

Albino male rats (100-200 g) were got from breeding center of laboratory animals' research center Faculty of Veterinary Medicine, Zagazig University, Benha branch and kept for a week for adaptation under ordinary circumstances and constant temperature (25±1C°) with water and food until beginning the experiment and haphazardly divided into four groups of 7 rats for each one. The first group was non-exposed (control group); this group drank water without heavy metals for all time of experiment. The second group was daily intoxicated with lead acetate (RIEDEL-DEHOEN AG SEELZE - HANNOVER, WEST GERMANY), to obtain 1 mg of lead per kg body weight in drinking water, while the third one was daily intoxicated with Cadmium chloride (RIEDEL-DEHOEN AG SEELZE - HANNOVER, WEST GERMANY), to obtain 2.5 mg of cadmium per kg body weight in drinking water, and the fourth group was daily intoxicated with Zinc sulphate (RIEDEL-DEHOEN AG SEELZE - HANNOVER, WEST GERMANY), to obtain 1 mg of zinc per kg body weight in drinking water.

Determination of blood and renal related parameters

Rats were placed in individual metabolic cages without food and water for 12 hrs in the light prior to collection of blood samples. The first tube contained calcium EDTA for complete blood count (CBC) analysis, otherwise second tube was left for a short time to allow clotting. Clear serum samples were obtained by centrifugation at 3000 rpm for 10 min and then kept in the refrigerator for determination of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities, then kept in a deep freeze at -20°C until used for consequent biochemical parameters: Total protein, Albumin, globulin, albumin/globulin ratio, total Urea, creatinine, lipid peroxidation (L-Malondialdhyde).

Histopathological analysis for organs

Animals were sacrificed, and tissue samples from (liver and kidney) were acquired from all animals in all groups for purpose of cyto-level changes in cytology of tested organs. Sample preparation under light microscopy after fixation of tissues by formaldehyde 10% solution, they were directly dehydrated in a graded serious of ethanol and embedded in

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paraffin. Thin sections, 5-6 micrometers, were cut by using a microtome and stained with Hematoxylin and Eosin and examined by using a light microscope. All changes from the normal structure were recorded.

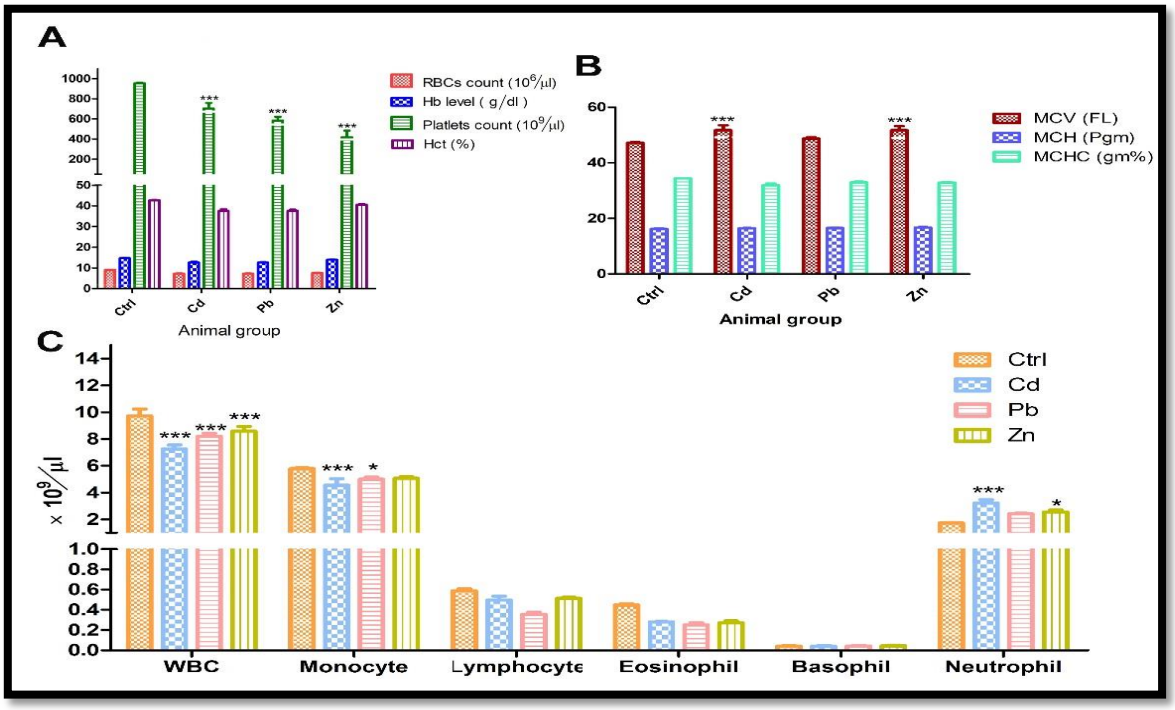
Statically data analysis

All statistical analyses were performed using (GraphPad Prism, San Diego, CA, USA).

3. RESULTS

Hematological Parameters

Red blood cell (RBC) count in control and investigational groups of animal. There is no significant alteration was detected in RBC count among control group ($P \leq 0.05$). In the animal groups given lead acetate, cadmium chloride, and zinc sulphate the regular values of RBC count were decreased, paralleled to control one. Hemoglobin (Hb) Hemoglobin content of control and experimental groups of animals is obtainable in Fig. **1** (A). The change in Hb content of control group was not significant. While the effect of heavy metals toxicity on Hb content was equivalent to its action on RBC count. In general, the previous changes were highly significant ($P \leq 0.05$), Hematocrit (Hct) Fig. 1 (A), shows Hct values of control and experimental animals. There were no significant changes at control group. In animals heavy metals treated, Hct was decreased, associated to control values ($P \leq 0.05$). For platelet count there was a significant ($P \leq 0.001$) decrease in the platelet count of rats in the heavy metals- exposed groups compared to control group.



*Data are presented as (means ± S.E)

*Mean with different superscript letters in the same column are significantly different at ($P \leq 0.05$, $P \leq 0.001$).

Fig. 1: Effect of Lead, Cadmium, and Zinc treatment on Hematological Parameters of white male albino rat

In Fig. **1** (B) the MCV in all heavy metals-treated groups was comparatively higher compared to control group. However The MCH in all heavy metals-exposed groups was comparatively slightly higher compared to control group. The results lower with the MCHC. At Fig. **1** (C) The effect of treatment on total WBC count, the WBC count in the treated animal groups with heavy metals was moderately lower compared to control group. The monocyte was decreased significantly ($P \leq 0.05$) with lead exposed groped animal while decreased significantly ($P \leq 0.001$) with cadmium one. The eosinophil counts in between the groups were not significantly different. The lymphocyte count in the control group decreased significantly ($P \leq 0.05$) relative to the heavy metals-exposed animals. However, the eosinophil and basophil count in the treated groups was comparatively lower compared to control one. The absolute differential leukocyte count revealed significant ($P \leq 0.05$) change in the neutrophil count in between the groups by increasing with zinc while increased significantly ($P \leq 0.001$) with cadmium one.

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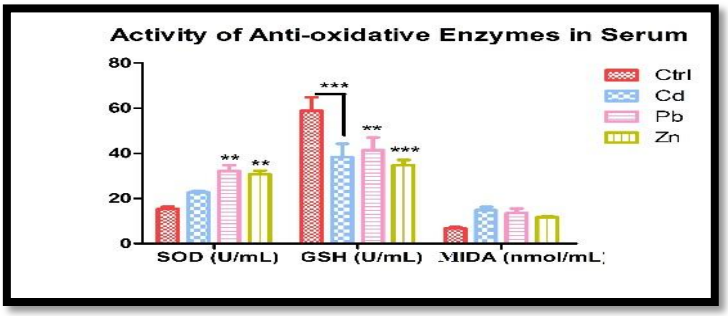
Activity of Anti-oxidative Enzymes in Serum

As shown in Fig. ***2***, we found the increasing of SOD anti-oxidative enzymes in serum of rats. Compared with the control group, the activities of GSH in treated groups were lower than those in the control group.



*Data are presented as (means ± S.E)
*Mean with different superscript letters in the same column are significantly different at ($P \leq 0.01$, $P \leq 0.001$).

Fig. 2: Serum activity of SOD and GSH and the Serum levels of MDA

Products of Lipid Peroxidation in Serum

As shown in Fig. ***2***, there was a significant increase in serum MDA in treated groups (nmol/mL) compared with normal one nmol/mL.

Renal related parameters (Non-protein nitrogen constituents)

Serum urea concentration of control and experimental animal groups. No significant change in serum urea was found in control group, on the other hand cadmium chloride was highly significant increase ($P \leq 0.001$) in urea, compared to control followed by zinc sulphate then Lead acetate. Serum Creatinine concentration of control and experimental animal groups. No significant change in control group. Lead acetate intake at dose produced regular significant increase in creatinine, compared to controls ($P \leq 0.05$), and the same marked increase with cadmium chloride and zinc sulphate. All that result was clear in Fig. **3: Renal indicted parameters**

Fig. *3* (C).

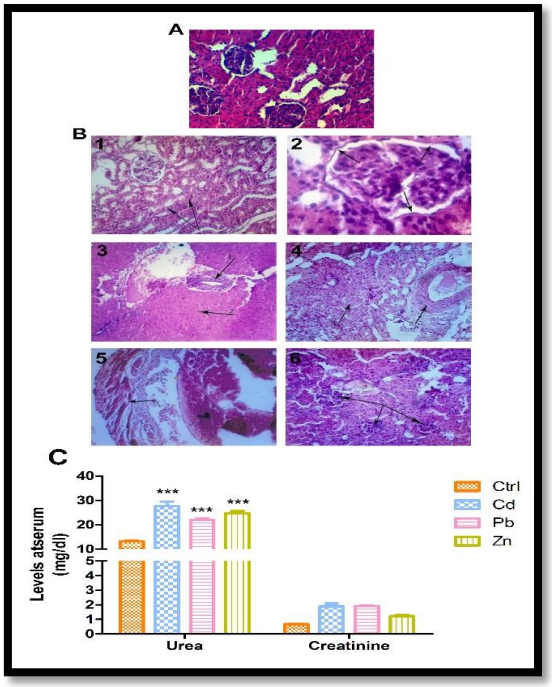


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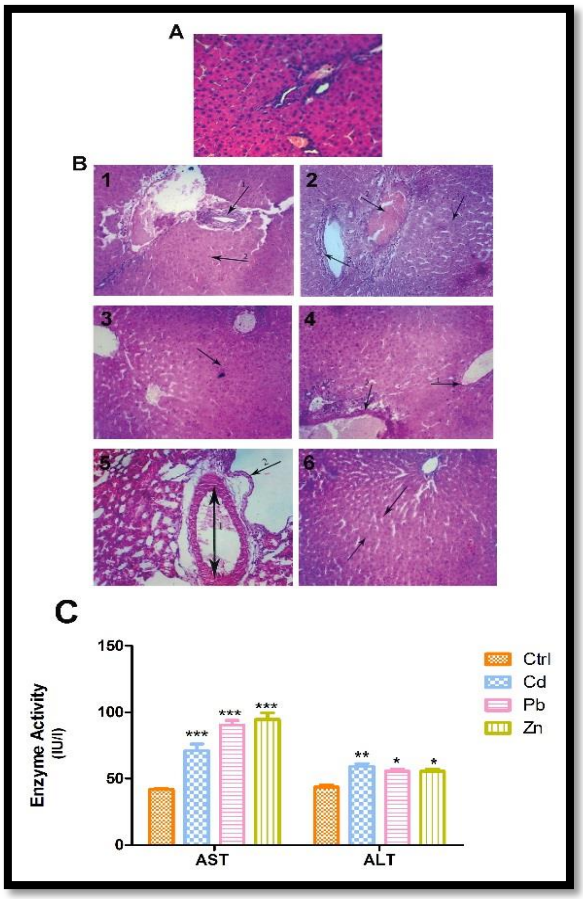
Fig. 3: Renal indicted parameters

Fig. 3: Renal indicted parameters: A: kidney of control group. B: B (1 and 2): kidney of rat treated with cadmium (B1): showing hyalinization in the renal tubules (H&E 300). (B2): showing desquamation of the epithelial cells lining the glomeruli (H&E 1000).

B (3 and 4): kidney of rat treated with lead (B3): showing hyalinization of renal tubular cells proliferation of the endothelial cells lining the medullary renal blood vessels (H&E 300). (B4): showing thickening of the renal blood vesicle and desquamation of the epithelial cells lining the renal pelvis (H&E 300). B (5 and 6): kidney of rat treated with zinc (D5): showing shrinking of renal glomeruli (H&E 300). (B6): showing hyalinization of the renal tubules (H&E 250) C: Chart of indicated renal parameters in blood.

Hepatic function indicated parameters

In the case of hepatic function, the parameters including plasma AST and ALT activities were used to check liver function in the intoxicated animals relative to the health normal rats (Fig. *5* (C)). These results showed that Zn highly and significantly stimulated the activity of AST, that followed by Pb^{2+} then Cd, while with ALT, Cd highly and significantly stimulated the activity, that followed by Pb^{2+} then Zn.



*Data are presented as (means ± S.E)

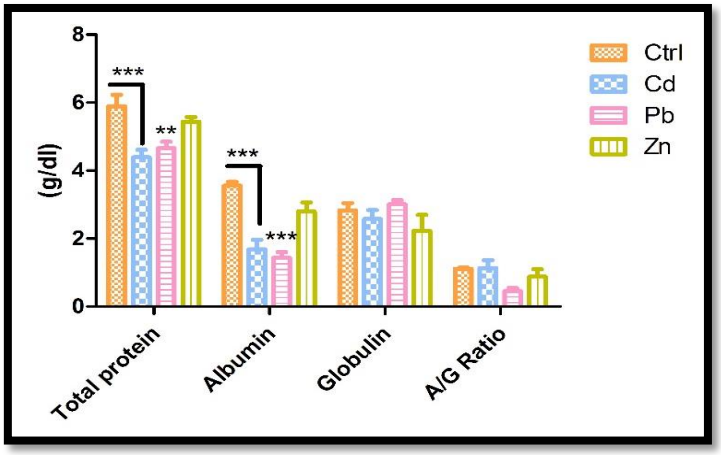
*Mean with different superscript letters in the same column are significantly different at ($P \leq 0.05$, $P \leq 0.01$, $P \leq 0.001$).

Fig. 4: Effect of heavy metals on liver

Fig. 5: Effect of heavy metals on liver A: liver of control group. B (1 and 2): liver of rat treated with cadmium (B1): showing diffused area of coagulative necrosis and normal hepatic cords (H&E 250). (B2): showing thrombosis of the portal blood vessels and hyperplasia of the bile ducts (H&E 600). B (3 and 4): liver of rat treated with lead (B3): diffused area of coagulative necrosis. (B4): showing hyperplasia of the epithelial cells lining the bile ducts and diffused area of coagulative necrosis (H&E 300). B (5 and 6): liver of rat treated with zinc (B5): showing defused area of coagulative necrosis (H&E 300). (B6): showing hyperplasia of the epithelial cells lining the bile ducts and lymphocytic aggregation

(H&E 600). C: Effect of Cadmium, lead and Zinc treatment on Serum, AST, ALT, activities, (U/L) of white male albino rat.

Another parameters, Protein profile of plasma was changed under the ingestion of heavy metals. The results reported significant reduction in total soluble protein and albumin, and globulin, while plasma globulin value was insignificantly changed (Fig. ***6***).



*Data are presented as (means ± S.E)
*Mean with different superscript letters in the same column are significantly different at ($P \leq 0.01$, $P \leq 0.001$).

Fig. 6: Total protein, albumin, globulin levels and A/G ratio

Morphological alterations on liver and kidney

***In liver at animal group exposed to heavy metals*:** showed hyperplasia of the epithelial cells lining of the bile ducts and diffused area of coagulative necrosis.

While in kidney: showed hyalinization of renal tubular cells and proliferation of the endothelial cells lining the medullary renal blood vessels plus to thickening of the renal blood vesicle and desquamation of the epithelial cells lining the glomeruli and the epithelial cells lining the renal pelvis, and shrinking of renal glomeruli that all was clear in Fig. **3: Renal indicted parameters**

Fig. *3*.

4. DISCUSSION

Widespread special effects of heavy metal pollution on all body organs, a blood, and on the anti-oxidant enzymes have been well documented. In varieties of disease development processes, the toxic metabolites have emerged an as major final common entity that encourages the damage, where heavy metals extant in drinking water lead to in severe oxidative stress after month with the doses tested, that due to many constituents of the cell are the potential substrates of free radical attacks. The outcomes of the current study revealed that administration of heavy metals for 4 weeks lead to a significant decrease of RBCs count Hb, HCt, MCV, MCH and MCHC as compared with control group, this finding is in agreement with Al-Attar who described that hematopoietic and leucocyte are two dynamic systems which react quickly to chemical intoxication, and condition maintain of hemostasis by an organism [12]. Zinc salt can precipitate an acute fall in hemoglobin and hematocrit levels and intravascular hemolysis may follow. These results run equivalent to those described by Mylroie who noted down a decrease in RBCs count, Hb and Ht in rats treated with (1mg Pb/mL) lead acetate in drinking water for 5 weeks [13]. The drop of Hb inveterate the decreases in RBCs which may be attributed to the toxicity of heavy metals.

WBCs count was found to be significantly decrease in rat treated with lead a acetate and cadmium chloride, while the decrease of WBCs in zinc sulfate treated group animals which is non-significant as compared with control which in agreement with Ajayi who reported that zinc deficiency is associated with increased WBCS because zinc is essential for integrity of the immune system, deficiency results in reduced immune-competence and decreased resistance to infection

and this increase due to zinc deficiency may indicate an activation of the animal's defense mechanism and immune system [14] ,while other studies reported that zinc supplementation increase number of WBCs [15].

Lymphopenia, neutropenia, eosinopenia and Monocytopenia were recorded after chronic intoxication with heavy metals in rat. From another hand, Abu-El-Zahab make a note a decrease in lymphocytes percentage and an increase in neutrophils, and monocytes percentage in mice and rats treated with 1/10 and 1/5 LD50 of water hyacinth extract as a result of severe acute stimuli to the haemopoietic system if exposed to toxic materials [16]. But monocytosis followed for phagocytic the damaged cells occasioned from the toxic effect of water- hyacinth extract on the rats organs.

Our study indicates that decreased GSH concentrations following exposure to all heavy metals. These results are consistent with the findings of Sandhir who described that lead exerts its toxic effect by enhancing peroxidative damage to the membranes of liver cells [17]. Since GSH functions both as a scavenger for ROS and as a cofactor in the metabolic detoxification of ROS [18] this decrease in indicates enhanced ROS generation in heavy metals-exposed.

MDA is an end product of the lipid peroxidation process which can be well-defined as oxidative deterioration of polyunsaturated lipids [19]. Here, MDA concentrations increased significantly in rats that received heavy metals in their drinking water. These results are in agreement with those of Lawton who detected the same resulted with lead exposed animal [20]. Numerous studies have pointed to ROS generation, namely hydrogen peroxide and superoxide anion, in lead toxicity [21]. Therefore it is plausible for lead to boost lipid peroxidation, a process that is known to be triggered by ROS.

Besides, the cell membrane is the focal target of the oxidative damage formed by xenobiotics, together with heavy metals [22]. Cellular systems are sheltered from cell damages produced by reactive oxygen species (ROS) by various defenses involving of antioxidants with diverse functionalities [23]. When the ROS present in the cellular system subdue these defense systems, oxidative stress is prompted, and this could product cellular injuries and ultimately development of diseases. Heavy metals toxicity has shown to form free radical damage by two distinct pathways: 1) the production of ROS, inclusive of singlet oxygen, and hydrogen peroxide and 2) the direct reduction of antioxidant reserves.

Excrete the waste products of metabolism and to adjust the body concentration of water and salt that is the main function of the kidneys [24]. In the present research, heavy metals treated rat had significant increasing of renal indices such as serum urea and creatinine. These results are also in settlement with those of Khalil-Manesh [25] and Mohammed [26]. Oral administration of lead acetate in the diet of mice at concentration 0.5% (W/W) for 1 month induced a significant increase in serum urea and creatinine in comparison with the control group [14]. Administration Orally of 1000 or 2000 ppm lead acetate in albino rats caused significantly increasing in serum urea, uric acid and creatinine[27]. And [28] in broiler chicks with cadmium. The attendance of the increased level of urea concentration in the blood proposes the inability of the kidney to excrete these products [29]. This dysfunction is established by the increase in blood creatinine which appearances a decrease in excretory power of nephrons and even a tendency to renal failure [30].

The present results of the parameters of liver function (ALT and AST) showed the injury in liver cell of lead, cadmium, and zinc intoxicated animals. These interpretations are in agreement with erstwhile study which recounted that lead has hepatotoxic effect [31]. The high plasma ALT and AST activities are complemented by high liver microsomal membrane fluidity, free radical generation and change in the liver tissue histogram. For instance, the values of serum ALT and AST increased significantly ($p<0.001$), while total protein, albumin, globulin and A/G ratio decreased significantly with the animal exposed to lead and cadmium ($p<0.001$) that agreement with Ibrahim [32] and Ibiam [33]and significantly with the animal exposed to zinc.

Acute exposure to heavy metals cause histological lesions in the kidney and liver. With lead these lesions are characterized by the occurrence of intranuclear inclusion bodies, which were prompted at significantly lower concentrations than those associated with clinical toxic manifestations [34]. Additional to that histological indication of lead toxicity in the kidney of rat is the karyomegaly of tubular cells [35]. Tubular, interstitial and glomerular injury are also characteristic renal lesions due to lead toxicity. Tubular changes happen earlier than glomerular and interstitial changes, including development of pathognomonic intranuclear inclusions in the renal tubular epithelium [36], Our data showed clear renal lesions related to acute lead toxicity and characterized by varying degrees of damaged glomeruli, and degenerated proximal tubules in all exposed rats to lead acetate,70% of exposed rats showed necrotic cortical tubules. Ceruti presented a correlation between histological alterations and lead concentration [37]. That all may revealed to the improvement of histological findings in the kidneys, especially the number of cells exhibiting karyomegaly and

intranuclear inclusions. A previous work confirmed that chronic lead exposure caused changes in the extracellular protein expression and ultrastructural modifications such as a decrease in the thickness of the glomerular basal membrane in exposed rat kidney [38]. The prominent histopathological changes in lead acetate exposed kidney include thickening of glomerular basement membrane, degeneration of tubular epithelial cells, atherosclerotic changes and disintegration of brush border membrane, which may be accountable for the detected renal dysfunction.

Introduction of rats to heavy metals such as lead has adverse effects on hepatic cells because after lead introduction, liver is one of the main organs involved in the storage, biotransformation and detoxification [39]. Lead prompts a wide range of biochemical and structural alterations to hepatic cells, this is symptomatic of liver toxicity [40]. The current study revealed that serum level of ALT and AST significantly increased in lead treated group when compared with the control rats. This is an indication of diminished liver function. Increased liver enzyme activity may redirect hepatocyte or biliary epithelial necrosis, compromise of hepatocyte membrane integrity, and cholestasis [41]. Injured of the membrane of hepatocytes possibly as a result of lead induced hepatotoxicity releases the enzymes into circulation causing a upsurge of these enzymes in the blood circulation.

In rats exposed to cadmium for 4 weeks, various morphological changes in the renal cortex were marked. Histologically, some of the proximal tubules exhibited loss of brush borders. Fibroid changes are caused by increased fibronectin production in glomeruli and in the tubular interstitium. There may be two possible mechanisms for the increase of fibronectin: Either there is an overproduction of fibronectin in the renal cortex or its breakdown may be inhibited [42].

The nephrotoxicity especially glomerulus and tubular changes; degeneration of the glomeruli; and vacuolated cytoplasm of tubules were observed after treatment with Cadmium in the recent work. This results was in accord with Jemai who bring into being that Cadmium affected the glomeruli especially glomerular capillaries in favour of Bowman's space, atrophy of some glomerulus [43]. Several histopathological revisions revealed the toxic effect of Cadmium in the kidney; Oedema was usually found [44] as well as proximal tubular necrosis, apoptosis, and tubular degeneration [45]. Cadmium-prompted nephrotoxicity is thought to be mediated through the cadmium metallothionein (Cd-Mt) complex, which is produced in the liver, released into circulation and taken up by renal proximal tubule cells [46]. Indeed, when the synthesis of Mt becomes insufficient for binding all Cd ions in the liver, Cd not bound to Mt produce hepatocyte injury and a Cd-Mt complex is released into the blood stream. The complex in the plasma is then filtered through the glomeruli in the kidney and taken up by the proximal tubular cells [47]. On its way through the kidney, this complex origins injury, mainly in the cortical region, reaching the proximal tubule and causing a gradual loss of the organ's function [48]. Furthermore, these alterations may be due to the accretion of free radicals as the consequence of increased lipid peroxidation by free Cadmium ions in the renal tissues of Cd- exposed rats [49].

The liver is the major target organ following acute systemic cadmium exposure. The uptake of cadmium into the liver is serious for the development of overall toxicity induced by the heavy metal. Approximately half of cadmium absorbed systemically is rapidly accumulated in the liver, which resulted in the reduced availability of cadmium to such organs as the kidneys and testes, which are more sensitive to its toxic actions [50]. In the current work, the administration of cadmium lead to severe hepatocyte necrosis, fatty changes, degeneration signs and inflammatory cell infiltrations. These effects were comparable to the acute and chronic effects of Cd documented by previous studies [51], [52]. Hepatic necrosis has been described in rats and mice after acute exposure to cadmium [53], [54]. Subchronic exposure with cadmium chloride lead to liver damage, confirmed by histopathological adaptations; moderate degeneration (ballooning) and discrete necrosis [55]. The necrosis was mostly centrilobular and extending through the whole liver lobule [56]. The histopathological alterations of the liver treated with cadmium might be due to the formation of highly reactive radicals and subsequent lipid peroxidation induced by cadmium. The accumulated hydroperoxidase can cause cytotoxicity, which is associated with the peroxidation of membrane phospholipids by lipid hydroperoxidase, the basis of hepatocellular damage [52].

5. CONCLUSION

From the aforementioned discussion, we can be concluded that, the heavy metals (lead and cadmium) had adverse effects on haemato-biochemical parameters in albino rat and a potential to induce hepatotoxicity and nephrotoxicity . So that, the populations of high risk to lead and cadmium should be advised to avoide or decrease contact. Further studies are necessary to elucidate exact mechanism of protection of haemato-biochemical toxicity and potential usefulness of heavy metal and try to find a sutiable protective agent against heavy metals toxicity in clinical trials.

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