Study the Protective Role of Zinc, Vitamin E and Selenium as Antioxidants in Pregnant Rats Exposed to Cadmium with Special Reference to Biochemical and Pathological Aspects

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Abstract: The aim of this study was to investigate the possible protective role of the zinc, vitamin E (Vit.E) and selenium as antioxidants against cadmium (Cd) -induced renal and hepatic damage in pregnant rats using biochemical and histopathological approaches. Ninety pregnant rats were used, randomly allocated into nine equal groups. The first four groups were treated with low dose of cadmium (0.3mg $cdcl_2$/kg.b.wt). The second four groups were treated with high cadmium dose (1.5mg $cdcl_2$/kg.b.wt). Three of the low and 3 of the high cadmium exposed groups were treated, in addition, with one of the following antioxidants zinc sulphate ($ZnSO_4$), vitamin E or sodium selenite ($NaSeO_3$) respectively. The remaining group was kept as control. Blood samples were collected and the plasma was separated for estimation the activity of alanine amino transferase (ALT), aspartate amino transferase (AST) and γ-glutamyl transferase (γ GT), and determination of creatinine concentration. Tissue specimens from liver and kidney were taken for histopathological examination. Results indicated the level of ALT was decreased significantly in plasma of zinc treated group. There were significant decreases of γ GT in low and high dose Cd treated group with vit. E and low dose Cd treated with selenium. Meanwhile, non significant changes in creatinine concentration in high dose Cd exposed rats treated with different antioxidants were recorded. Histopathological findings of liver showed edema with dilatation in the portal vein and mononuclear leucocytes infiltration in the portal areas and in between the hepatocytes in low dose cadmium exposed pregnant rats with vit. E. and selenium. On the other hand, the histopathological picture of kidney was focal interstitial hemorrrhage at the corticomedullary junction and hyperemia of the tuft of the glomeruli in low dose cadmium exposed pregnant rats with zinc and selenium. It could be concluded cadmium administration induced elevation of ALT, AST, γ-GT activities and creatinine concentration and histopathological changes in liver and kidney. Moreover, administration of antioxidants zinc, vit. E and selenium showed partial protective effect on liver and kidney through reducing the Cd- induced pathological changes especially at the low dose Cd and improving the biochemical parameters when compared with Cd alone treated group.

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1. Introduction

Cadmium is a potent toxic heavy metal and widespread environmental and industrial pollutant in food, water, air and cigarette smoke that causes damage to various human and animal organs with an exact cellular mechanism of toxicity [1, 2].

Previous several experimental studies have been shown that kidney and liver are the major target organs for cadmium –induced nephro and hepatic toxicity [3] since the metal is known to accumulates principally in the hepatic and renal tissues producing histopathological changes and functional disturbance [2, 4-9].

Efforts have been made to minimize the severity of Cd toxicity via enhanced its sequestration and elimination using different agents. It is believed that antioxidant should be one of the important components of an effective treatment of cadmium poisoning. There is an increasing interest towards the use of naturally occurring antioxidants with renal and hepatoprotective activity in cadmium intoxication therapy. Zinc, vitamin E, and selenium are among the important non enzymatic antioxidant defense systems, which may modulate the toxicity of cadmium by an antioxidative mechanism [10]. Zinc is an important antioxidant, decreasing reactive oxygen species (ROS) production [11]. Some studies have reported the ability of Zn to interact with essential elements such as Cu and Fe, decreasing their content in tissues and retarding the oxidative processes [12]. It is involved in cell membrane stabilization, metallothionein (Mt) synthesis [13] and superoxide dismutase (Cu/Zn SOD) structure. Numerous studies have shown that Zn supply may reduce Cd absorption

and accumulation, and also prevent or reduce the adverse actions of Cd [14, 15] whereas Zn deficiency can intensify Cd accumulation and toxicity [16, 17].

Vitamin E has been shown to act as an antioxidant in cells, interrupting the propagation of lipid peroxidation (LPO) in the plasma membrane to preserve membrane integrity [18, 19].

It is known, that selenium has a certain protective role from the toxic actions of Cd and other heavy metals [20]. This protection includes the capability of selenium to alter the distribution of Cd in tissues and induces binding of the Cd-Se complexes to proteins, which are similar to metallothioneins [9].

Selenium is an essential part of the enzyme glutathione (GSH) peroxidase, which functions as a part of an a part of an antioxidant defense system (AOS) to protect membranes and essential proteins from the potentially damaging effects of reactive oxygen and lipid peroxides [19].

The aim of the present study was to assess the possible protective role of antioxidants against cadmium –induced structure lesions in liver and kidney of pregnant rats with special reference to clinical and pathological changes.

2. Materials and Methods

Animals

Mature female rats (Sprague Dowly) rats were obtained from National Research Center Animal House. Animals were hand mated using mature males. Animals showed vaginal plugs and/ or sperm in vaginal smear were considered pregnant. A total number of 90 pregnant rats was used in this experiment. The experiment was conducted under normal environmental conditions of nutrition and water supply.

Heavy Metals

Cadmium chloride (CdCl2.) was used in two concentrations (0.3 and 1.5 mg/kg b.wt.), which represent 1/200 and 1/40 of LD50 according to El Gindy [21].

Antioxidants

A- Zinc sulphate $ZnSO_4$ 2mg/ Kg BW was given according to Claverie *et al.* [22].

B- Vitamin E (α- tocopherol acetate). It was available in soft gelatinous capsules of 100 mg. Each capsule was dissolved in 10 ml. corn oil and each animal was administered one ml orally [18].

C- Sodium Selinite Na_2SeO_3 1.5mg/ Kg BW was given according to Yiin *et al.* [23].

Experimental Design: Table (1)

Rats were randomly allocated into nine groups (1 –9). Animals were exposed to either low or high doses of $CdCl_2$ either alone or in combination with antioxidants $ZnSO_4$, vitamin E or Sod. Selenite as shown in table (1) which illustrates treatments of the different groups.

Table 1: Different experimental groups of pregnant rats.

Group	No.	Treatment*
1	10	Control Negative
2	10	Low dose (L.D.) $CdCl_2$ 0.3 mg / kg b.wt.
3	10	Low dose $CdCl_2$ + 2mg $ZnSO_4$ / kg b wt
4	10	Low dose $CdCl_2$ + 10 mg vitamin E / animal
5	10	Low dose $CdCl_2$ + 1.5 mg Sod. selenite / kg b wt.
6	10	High dose (H.D.) $CdCl_2$ 1.5 mg/ kg b. wt.
7	10	High dose $CdCl_2$ +2mg $ZnSO_4$ / kg b wt.
8	10	High dose $CdCl_2$ + 10 mg vitamin E / animal
9	10	High dose $CdCl_2$ + 1.5 mg Sod. selenite / kg b wt.

*Treatments were dissolved in distilled water except vitamin E was dissolved in corn oil. Treatments were given in drinking water. Vitamin E was given per os. $CdCl_2$ was given 3 times/ week from day of removing males till parturition. Antioxidants were given 5 days before putting males and continued daily till parturition.

Sampling:

a- Blood samples

Three blood samples were collected from the retro orbital venous plexus of all animals of the different groups. The first sample was taken during pregnancy (7-10 days), the second and third samples were taken after 15and 30 days of parturition. The collected blood samples were received into heparinized tubes and were centrifuged at 3000 r.p.m. for 10 minutes and the clear supernatant plasma was kept at – 20 ^{o}C till assayed for activities of ALT, AST and γ GT, and determination of creatinine.

b- Tissue sampling:

Tissue specimens from liver and kidneys of pregnant rats were fixed in 10% formaline for histopathological examination.

b-Biochemical analysis

1-Transaminases activities

Alanine amino transferase (ALT) and aspartate amino transferase (AST) activities were determined spectrophotometrically according to the method of Reitman and Frankel [24].

2- Gamma glutamyl transferase (γ GT) activity:

Gamma glutamyl transferase activity was determined spectrophotometrically according to the method of **Szasz [25].**

3 -Creatinine

Creatinine was determined spectrophotometrically according to **Bartel [26].**

Histopathological Studies

Specimens from liver and kidneys were taken from the pregnant rats and fixed in 10 % neutral formalin. Paraffin sections of 4 – 5 microns were

prepared and stained with hematoxylin and eosin after Bancroft *et al.* [27].

Statistical analysis

Data were statistically analyzed using one way analysis of variance (ANOVA) according to the method of Snedecor and Cochrane [28] and Statistical Package for Social Science (SPSS) version 11.0 (2001).

3.Results

Biochemical parameters

1. Plasma enzymes

The mean values of plasma enzymes of pregnant rats received doses of cadmium chloride with or without antioxidants are illustrated in table (2).

a- Aspartate amino transferase activity (AST)

The present results revealed non significant changes of AST activity in rats exposed to low and high dose cadmium.

Assessment of the effect of different antioxidants on AST of low dose cadmium exposed rat's revealed significant elevation allover the experimental intervals in selenium treated group. The high dose cadmium exposed rat's revealed significant elevation all over the experimental intervals in vit. E and selenium treated groups.

b- Alanine amino transferase activity (ALT)

Effect of cadmium exposure on ALT activity of pregnant rats during different periods compared to control showed significant elevations in low dose and high dose all over the experimental intervals.

The effect of different antioxidants on ALT of low dose cadmium exposed rats revealed significant decrease in zinc treated group 15 days after birth.

c- Gamma glutamyl transferase activity (γGT):

Results showed non significant changes in γGT activity of pregnant rats in low and high dose cadmium groups compared to control.

Regarding the effect of different antioxidants on γGT of low dose cadmium exposed rats; significant elevation was shown at 30 days after birth in zinc treated group. There were significant decreases during pregnancy and 30 days after birth in low dose cadmium treated group with vit. E and 30 days after birth in treated group with selenium. In high dose group, significant decrease was noticed all over the experimental intervals in group treated with vit. E.

2. Creatinine concentration

The mean values of plasma creatinine concentration of pregnant rats received doses of cadmium chloride with or without antioxidants are illustrated in table (3).Results showed significant elevation during pregnancy in high dose cadmium exposed group. Assessment of antioxidants effect on cadmium exposure revealed significant elevations of creatinine during pregnancy in low dose cadmium treated group with vit. E. The high dose cadmium exposed rats showed non significant changes after treatment with different antioxidants.

Histopathological findings

Liver: The histopathological examination of liver of pregnant rats exposed to low dose of cadmium showed focal necrosis in the hepatic parenchyma associated with dilatation in the portal vein with mononuclear leucocytes inflammatory cells infiltration in the portal area. There was dilatation in the hepatic sinusoids with diffuse proliferation of kupffer cells in between the degenerated hepatocytes (Fig. 1). Such previous changes were still present in the liver of low dose cadmium exposed pregnant rats with zinc. Meanwhile, in low dose cadmium exposed pregnant rats with vit. E. and selenium, edema was noticed in the portal area with dilatation in the portal vein (Fig. 2). Mononuclear leucocytes were infiltrating the portal areas.

While, the histopathological picture of high dose cadmium exposed pregnant rats was characterized by focal severe degenerative changes of hepatocytes. Multiple foci of hepatic cell necrosis also were noticed (Fig.3). There were dilatation in the central and portal veins with diffuse proliferation of kupffer cells in between the hepatocytes associated with mononuclear leucocytes inflammatory cells infiltration in the portal area and in between the hepatocytes. In high dose cadmium exposed pregnant rats with vitamin E, the pathological changes were dilatation in the portal vein with edema associated with diffuse proliferation of kupffer cells and mononuclear leucocytes inflammatory cells infiltration. In high dose cadmium exposed pregnant rats with zinc, mononuclear leucocytes were detected in an infiltrating or aggregated manner between the degenerated hepatocytes associated with focal extravasations of red blood cells (Fig. 4) .The portal area showed mononuclear leucocytes inflammatory cells infiltration. In high dose cadmium exposed pregnant rats with selenium, there was dilatation in the central and portal vein with diffuse kupffer cells proliferation in between the hepatocytes. Mononuclear leukocytes were observed infiltrating in between the degenerated hepatocytes.

Table 2: Effect of different doses of cadmium given with and without antioxidants on plasma enzymes (u/l) of female rats at different intervals of the experiment.

Parameters		AST			ALT			γ-GT		
Periods / Groups		During* pregnancy	After birth (15 days)	After birth (30 days)	During pregnancy	After birth (15 days)	After birth (30 days)	During pregnancy	After birth (15 days)	After birth (30 days)
Control		45.80^{a} ±1.94	51.67^{ab} ±5.00	55.33^{ac} ±3.74	27.88^{a} ±0.63	29.40^{ab} ± 1.12	30.20^{ac} ±1.09	3.91^{a} ± 0.75	4.29^{ab} ± 0.67	5.34^{ac} ± 0.86
L.D.	Cd	51.33^{a} ±3.74	49.33^{ab} ±2.45	53.33^{ac} ±4.47	34.75^{a} ±1.61	39.80^{ab} ±2.42	39.20^{ac} ±2.62	5.04^{a} ± 0.89	4.08^{ab} ± 0.78	5.63^{ac} ± 1.13
	Cd + Zn	47.33^{a} ±4.00	49.33^{ab} ±2.45	49.23^{ac} ±2.44	34.10^{a} ±1.93	34.10^{ab} ±2.62	33.22^{ac} ±2.54	3.70^{a} ± 0.56	2.44^{ab} ± 0.59	7.93^{c} ± 0.47
	Cd + Vit. E	45.33^{a} ±2.00	47.33^{ab} ±5.09	54.00^{ac} ±6.86	40.30^{a} ±0.25	41.40^{ab} ±2.03	35.60^{ac} ±2.86	2.69^{ac} ± 1.16	4.25^{ab} ± 0.76	3.33^{ac} ± 0.35
	Cd + Se	76.67^{a} ±0.05	76.77^{ab} ±0.03	76.66^{ac} ±0.03	39.80^{a} ±0.25	39.70^{ab} ±0.64	40.25^{ac} ±0.32	5.14^{a} ± 0.42	3.78^{ab} ± 0.87	3.26^{ac} ± 0.52
H.D.	Cd	47.33^{a} ±4.00	53.33^{ab} ±3.16	47.33^{ac} ±2.45	36.88^{a} ±1.85	40.40^{ab} ±1.76	39.10^{ac} ±0.60	4.22^{a} ± 1.78	4.72^{ab} ± 1.67	3.56^{ac} ±0.36
	Cd + Zn	45.33^{a} ±2.00	45.83^{ab} ±4.79	45.33^{ac} ±3.74	34.60^{a} ±2.52	38.80^{ab} ±2.96	39.10^{ac} ±1.96	2.74^{a} ± 0.58	4.54^{ab} ± 0.98	3.48^{ac} ± 0.64
	Cd + Vit. E	67.50^{a} ±5.67	76.66^{ab} ±0.00	83.33^{c} ±3.85	36.60^{a} ±0.48	42.00^{b} ±1.01	39.30^{ac} ±1.56	1.78^{a} ± 0.30	2.22^{b} ± 0.30	1.36^{ac} ± 0.12
	Cd + Se	82.00^{a} ±3.26	84.66^{ab} ±3.27	79.33^{ac} ±2.67	39.80^{a} ±0.25	40.70ab ±0.51	40.63^{ac} ±0.38	3.44^{a} ± 0.52	6.77^{b} ± 0.19	4.39^{ac} ± 0.73
LSD		9.09	9.38	10.98	6.02	5.38	5.34	1.73	2.12	1.84

*Samples were taken 7 to 14 days during pregnancy

Values represent means ± standard error. Cd =cadmium, L.D. =low dose, H.D. =high dose, Zn =zinc, Se =selenium.

Means with different superscripts (a, b, c) within row are significantly different at $p<0.05$

Difference between means in the same column higher than LSD indicates significance.

Table 3: Effect of different doses of cadmium given with and without antioxidants on biochemical parameters of female rats at different intervals of the experiment.

Parameters		Creatinine (mg/dl)		
Periods / Groups		During* pregnancy	After birth (15 days)	After birth (30 days)
Control		0.37^{a}± 0.07	1.23^{b}± 0.20	1.47^{c}± 0.29
L.D.	Cd	0.68^{a} ± 0.11	1.05^{ab}± 0.23	1.19^{ac}± 0.27
	Cd + Zn	0.53^{a}± 0.03	0.96^{b}± 0.23	1.44^{c}± 0.06
	Cd + Vit. E	1.77^{a}± 0.11	1.05^{b}± 0.15	1.01^{c}± 0.25
	Cd + Se	1.10^{a} ± 0.21	0.97^{ab} ± 0.14	0.91^{ac}± 0.13
H.D.	Cd	1.17^{a}± 0.22	0.77^{ab}± 0.09	1.12^{ac}± 0.18
	Cd + Zn	0.87^{a}±0.76	0.81^{ab}± 0.15	0.90^{ac}± 0.10
	Cd + Vit. E	0.99^{a}± 0.24	1.06^{ab}± 0.11	1.17^{ac}± 0.19
	Cd + Se	0.99^{a}± 0.23	0.85^{ab}± 0.07	1.19^{ac}± 0.08
LSD		0.45	0.44	0.55

*Samples were taken 7 to 14 days during pregnancy.

Values represent means ± standard error. Cd =cadmium, L.D. =low dose, H.D. =high dose, Zn =zinc, Se =selenium.

Means with different superscripts (a, b, c) within row are significantly different at $p<0.05$

Difference between means in the same column higher than LSD indicates significance.

Kidney

The histopathological examination of kidney of pregnant rats exposed to low dose of cadmium revealed hyperemia in the glomerular tuft associated with mononuclear leucocytes inflammatory cells infiltration surrounding the glomeruli and in between the renal tubules (Fig. 5). In low dose cadmium exposed pregnant rats with zinc and selenium, there were focal extravasation of red blood cells in between the renal tubules at the corticomedullary junction (Fig.6) and hyperemia of the tuft of the glomeruli meanwhile, degenerative changes were observed in the epithelial cells lining of the renal tubules with hyperemia in the tufts of the glomeruli in low dose cadmium exposed pregnant rats with vit. E.

In high dose cadmium exposed pregnant rats, the renal tubules showed severe degenerative changes in the lining epithelial cells (Fig.7), with hyperemia in the glomerular tuft. There was focal extravasation of red blood cells in between the tubules as well as in the tubular lumen at the medullary region. In high dose cadmium exposed pregnant rats with zinc, there were severe dilatation of the intertubular blood vessels and capillary tufts of the glomeruli (Fig.8), with appearance of homogenous eosinophilic casts in the lumen of some renal tubules. In high dose cadmium exposed pregnant rats with vitamin E, focal extravasation of blood cells was detected in between the renal tubules. Meanwhile, in high dose cadmium exposed pregnant rats with selenium mild degenerative changes were observed in the epithelial cells lining of some renal tubules associated with hyperemia in the tufts of the glomeruli.

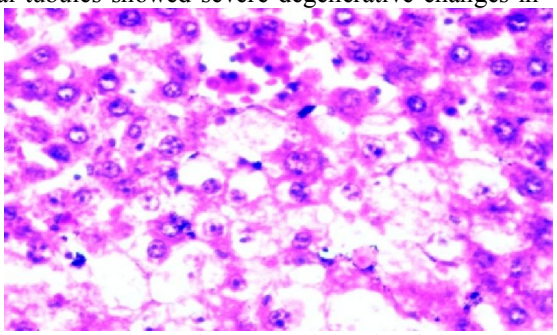

Fig. 1: Liver of a rat given L.D.Cd showing degenerative changes in the hepatocytes in a focal manner (H&E, X 160)

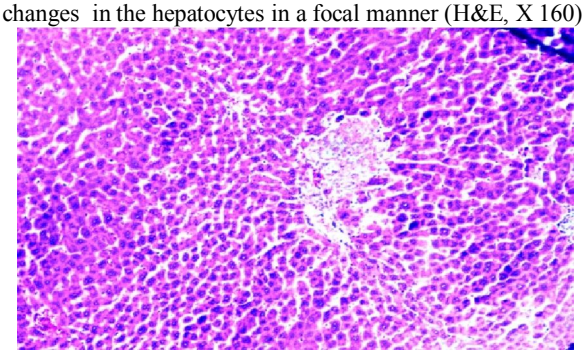

Fig.3: Liver of a rat given H.D.Cd showing focal necrosis in the hepatic parenchyma (H&E, X 40)

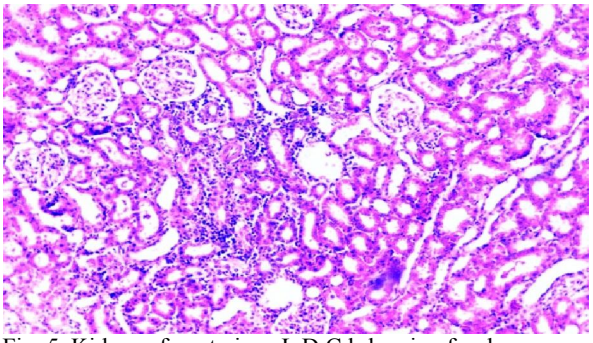

Fig. 5: Kidney of a rat given L.D.Cd showing focal interstitial mononuclear leucocytes infiltration (H&E, X 40)

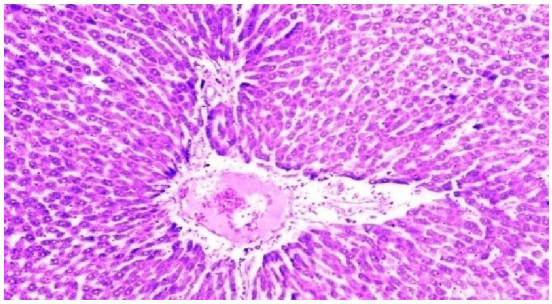

Fig 2: Liver of a rat given L.D.Cd with vit. E. and/ or selenium showing edema in the portal area with dilatation in the portal vein (H&E, X 40).

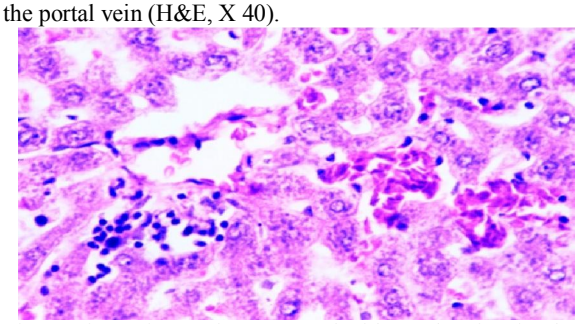

Fig. 4: Liver of a rat given H.D.Cd with Zn showing focal extravasated red blood cells as well as focal mononuclear leucocytes inflammatory cells aggregation in the hepatic parenchyma (H&E, X 160).

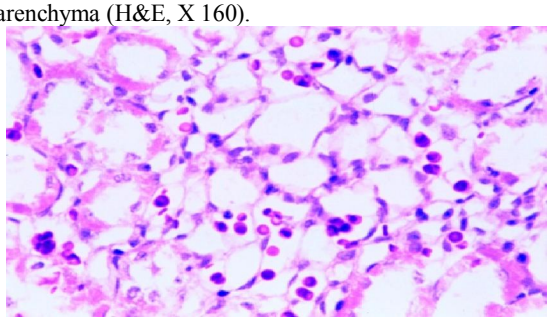

Fig. 6: Kidney of a rat given L.D.Cd with zinc and or selenium showing extravasations of red blood cells in between and in the lumen of the renal tubules at the medullary portion (H&E, X 160).

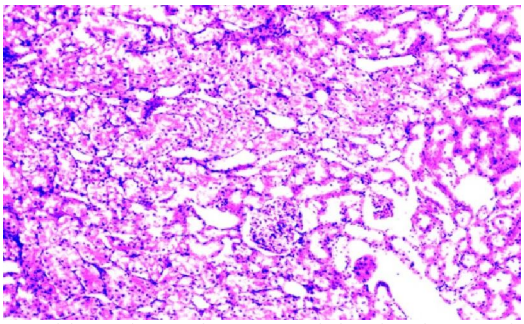

Fig. 7: Kidney of a rat given H.D.Cd showing degeneration in the epithelial cells lining the renal tubules (H&E, X40).

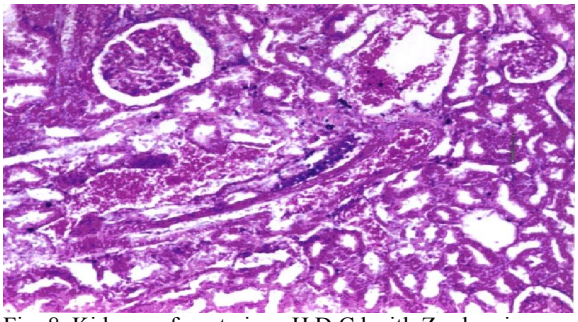

Fig. 8: Kidneys of a rat given H.D.Cd with Zn showing severe dilatation of the intertubular blood vessels and capillary tufts of the glomeruli (arrows) (H&E, X 40).

4. Discussion

Cadmium is a toxic metal that is widely used in different industries. It promotes an early oxidative stress and afterward contributes to the development of serious pathological conditions because of its long retention in some tissues [29]. Previous studies had demonstrated that cadmium stimulates free radical production resulting in oxidative deterioration of lipids, proteins and DNA, and initiating various pathological conditions in humans and animals [30-32].

Results of AST and ALT activity in low and high doses exposed pregnant rats during different periods showed significant elevations allover the experimental intervals compared to control group. Similar results were reported by Rana and Verma [10], Tandon *et al.* [33] and Drozdz *et al.* [34] who found that AST and ALT show correlation with the extent of morphological changes in the liver. Significant increase of AST and ALT levels reflects damage to the liver and could be attributed to degenerative changes of hepatocytes [7, 22, 35]. Effect of different antioxidants on ALT of low dose cadmium exposed rats showed significant decrease in zinc treated group. Meanwhile, level of γ-G T was significantly decreased in low and high dose cadmium treated group with vitamin E and low dose cadmium treated with selenium. The present changes in hepatic enzymes were accompanied by histopathological alterations in the liver. In this respect, [32, 36] recorded that vitamin E protects the animals against hepatic toxicity whereas its protective role might be due to the quenching of hydroxyl radicals .Moreover, vitamin E has the ability to protect the cell membrane through transferring a hydrogen atom of its phenolic group (-OH) to peroxyl free radicals of polyunsaturated fatty acid during peroxidation of lipids present in cell membrane leading to break the chain reactions of free radicals [7, 37]. It has been found that zinc is a helping factor in the prevention of cadmium-induced hepatotoxicity [22].

Results of kidney function parameters showed marked elevation of creatinine concentration during pregnancy in female rats exposed to high dose compared to control group. These results agree with observations recorded in guinea pigs [4] and in rats [10]. Such elevation of creatinine concentration reflected damage to the kidney and could be attributed to the degenerative changes in the lining epithelial cells of renal tubules [7, 35]. On the other hand, non significant changes in creatinine level in high dose Cd exposed rats treated with different antioxidants were recorded.

The histopathological picture of liver of pregnant rats subjected to low and high dose cadmium was characterized by focal necrosis, inflammatory cells infiltration and diffuse proliferation of kupffer cells in between the degenerated hepatocytes. Similar findings were recorded by Rana and Verma [10], Yamano *et al.* [38] and Jihen *et al.* [2] who stated that cadmium exposure induced severe hepatic pathological changes including fatty change, Kupffer cell dysfunction and infiltration of inflammatory cells in rats. On the other hand, kidney of rats subjected to low and high doses of cadmium revealed pathological alterations including degenerative changes of renal tubules, hyperemia in the tuft of the glomerulus and hemorrhage. These findings agree with Masahiro *et al.* [36], Rana and Verma [10], Dominicza and Mikulski [5] and Jihen *et al.* [2]. The above-mentioned histopathological changes in both liver and kidney were confirmed by the biochemical tests of kidney and liver function of the present work. Kidney is the principal target organ of cadmium toxicity. The nephrotoxic action of cadmium may be resulting from the release of cadmium metalothionine (Cd MT) complex from the damaged liver cells and its accumulation and degradation in the renal tubular epithelial cells [39, 40]. The injury affects the main resorptive part (Proximal convoluted tubules and straight tubules) and the filtering part (Glomeruli) of the nephron [6]. The necrotic changes and inflammatory cell infiltration in cadmium treated rats might be due to the accumulation of cadmium and its

content in tissue, which could also increase the lipid peroxidation as a basis for cellular damage of soft tissues [35]. It has been shown that cadmium disturbs the membranes integrity, generates reactive oxygen species and involves cytotoxic and inflammatory mediators in liver and kidney [2].

Concerning supplementation with vit. E and or selenium with low dose cadmium, the histopathological picture of the liver was less in degree of severity in comparison with cadmium group meanwhile, there was leucocytic inflammatory infiltration associated with degenerative changes in high dose cadmium with zinc and or selenium groups. In this respect, Shaikh *et al.* [32] reported that 100-150 mg /kg vitamin E injected s/c with cadmium –induced lipid peroxidation , protected the animals against hepatic and renal toxicity. The reduction of acute and chronic cadmium toxicity by zinc administration is related to metalothionine (MT) synthesis [22, 36]. Selenium and zinc have a cooperative effect in the protection against cadmium induced structural damage in liver but not in the kidney [2]. Selenium efficiently protects liver and kidneys from cadmium-induced oxidative damage. This protection includes the capability of selenium to alter the distribution of cadmium in tissues and to induce binding of the cadmium-selenium complexes to proteins, which are similar to metallothioneins [9].

Regarding the effect of antioxidants against cadmium toxicity on kidneys, the main pathological alterations in low dose of cadmium with zinc and selenium groups were hemorrhage at the corticomedullary junction and hyperemia of tuft of glomeruli. Meanwhile, degenerative changes of renal tubules were observed in high dose cadmium exposed pregnant rats with vit E. zinc and selenium. Previous studies indicated that zinc protection is attributed to redistribution of cadmium since zinc is able to induce synthesis of MT in liver and kidney [2, 22]. In this respect, Xiao *et al.* [41] stated that zinc or selenium could partially alleviate the oxidative stress induced by cadmium in kidney, but administration of cadmium in combination with zinc and selenium efficiently protects kidney from cadmium-induced oxidative damage. Treatment with zinc in rats protects against the renal toxic effects of cadmium by either inhibition of apoptosis [42] or reducing the number of necrotic and apoptotic cells as well as maintained oxygen consumption at control levels [43].

It could be concluded cadmium toxicity induced elevation of ALT, AST, γ-GT and creatinine levels and histopathological changes in liver and kidney. Moreover, administrations of antioxidants zinc, vit. E and selenium showed partial protective effect on the liver and kidney through reducing the cadmium –induced pathological changes and preserving their normal histological architecture especially at the low dose Cd , in addition to improving the biochemical parameters when compared with cd alone treated group.

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