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PROTECTIVE EFFECTS OF B-CAROTENE ON GAMMA RADIATION-INDUCED RENALHISTOLOGICAL AND ULTRASTRUCTURAL CHANGES IN ALBINO RATS

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ABSTRACT

The present work was conducted to investigate the histological, and ultra-structural changes that occurred in the kidney tissues of albino rats due exposure to gamma-radiation. Also we investigated how to protect the tissues from the damaging effects of gamma radiation using a natural product such as Beta-carotene. Thirty four male albino rats were divided into four main groups; the first group served as control (5 rats). Rats of the second group (5 rats)) received 5mg/kg body wt. of β-carotene at a daily oral dose for 2 consecutive weeks .The rats of the third main group (12 rats) were exposed to a sub-lethal dose (6Gy) of whole body γ-irradiation and then divided into four equal subgroups. Rats of the fourth main group (12 rats) received β-carotene before being exposed to gamma radiation and then divided into four equal subgroups. Treated rats were autopsied at four intervals; one day, one week, two weeks and four weeks post irradiation. The histological studies of the groups that exposed to gamma radiation revealed progressive pathological lesions as represented by severe damage in glomerular tuft with wide Bowman's space and severe hemorrhagic areas scattered in between degenerated renal tissues, increase in mesangial cells and renal tubules which suffered various degrees of degeneration. The ultra-structural studies revealed that epithelial cells lining the proximal and distal convoluted tubules showed an increase in the swollen mitochondria , dilation in the rough endoplasmic reticulum and electron dense in the nuclear chromatin. Thickness in basement membrane and dilation of infolded were observed. Damage of brush boarder and collagen fibers was also observed. The treatment with β-carotene (5mg/kg b. wt. for two consecutive weeks) pre-exposure to gamma radiation attenuated most of these changes. Therefore, the present study has implication for the potential use of β-carotene as a radioprotector.

KEY WORDS:

γ-irradiation, albino rat, Kidney, β-carotene, histology, electron microscopy.

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INTRODUCTION

Gamma-radiation has major histological and physiological effects on kidney. Dewit et al. (1990) stated that the mammalian kidney is among the most radiosensitive organs in the abdomen. Some scientists focused research on the renal diseases-induced by kidney irradiation as a clinicopathologic study on the human. Keane et al. (1976) found that radiation injury to the renal parenchyma is an unusual cause of renal insufficiency.

Soranson and Denekamp (1986) declared that the tubular cells are among the most important target cells for radiation injury in the kidney.

Robbins et al. (1995 and 2002) found that the Renal irradiation resulted in a progressive decline in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF). Also they confirmed that the renal irradiation resulted in significant alterations in glomerular and tubular cell proliferation and morphology within 2-4 weeks of irradiation.

The capacity of glomerular cells to generate reactive oxygen species in response to several stimuli independently of infiltrating polymorphonuclear leukocytes and monocytes suggests that reactive oxygen species may also play an important role in renal injury (Gonzalez et al., 1996).

Ionizing irradiation has been shown to induce an increased release of von Willebrand factor (vWF) in human endothelial cells in-vitro. Van Kleef et al. (1998) denoted that the increased expression of vWF may initiate prothrombotic changes, and the resultant vascular damage could cause renal failure.

After higher irradiation doses the drugs became less effective in protecting the kidney's tissues and fibrosis induced due to gamma-irradiation (Martin et al., 2001).

Abu Nour (2002) recorded that whole body Gamma-irradiation of mice induced definite microscopic changes in kidney represented by degeneration of convoluted tubules. El-sayed (2004) stated that kidney sections of post-irradiated rats revealed obvious degenerative features, distal convoluted tubules appeared atrophied which resulted in widening in its lumens, its nuclei were partially damaged and pushed inside the lumen, and cell nuclei showed marked signs of pyknosis. Beta-carotene (Pro-vitamin A) enables the body to produce vitamin A as this nutrient is needed (Solomons, 2001). Also beta-carotene is highly effective quencher of singlet oxygen and a direct scavenger of free radicals. Beta-carotene survives the process of absorbing singlet oxygen intact. Therefore, a single molecule of beta-carotene can arrest up to 1,000 molecules of singlet oxygen (Gaby and Singh, 1991). Researchers found that beta-carotene can protect the skin from the damaging effects of erythropoietic protoporphyria, an inherited disease in which the skin becomes red and swollen when exposed to sunlight (Tesoriere et al., 1995).

Many synthetic antioxidant components have shown toxic and/or mutagenic effects, which have directed most attention on naturally occurring antioxidants. The antioxidant capacity of carotenes against free radicals and oxidative damage was widely studied by many authors. Carotene intake prevents skin lipid peroxidation caused by UV irradiation (Someya et al., 1994), and contributes to the defense of membrane against oxidative stress. Antioxidants reduce the mutagenicity of many chemicals and offer a significant protection against the generation of single strand breaks of DNA (Sarkar et al., 1997).

MATERIALS AND METHODS

In the present investigation a total number of 34 male albino rats weighting about (80-120 g) were divided into four groups.

- Group 1 (5 rats): The rats of the experimental group 1 remained as a control group.
- Group 2 (5 rats): The rats of the experimental group 2 were received 5mg/kg b.wt. of β-carotene at a daily oral dose for 2 consecutive weeks.
- Group 3 (12 rats): The rats of the experimental group 3 were subjected to whole body gamma irradiation at a sub-lethal single dose level of 6Gy and then divided into four equal subgroups where the first subgroup was sacrificed after one day, the second after one weeks , the third after two weeks and the fourth after four weeks post-irradiation.
- Group 4 (12 rats): The rats of the experimental group 4 received 5mg/kg b.wt. of β-carotene at a daily oral dose for 2 consecutive weeks, then subjected to whole body gamma irradiation at a sub-lethal single dose level of 6Gy. This group was divided into four equal subgroups; the first subgroup was sacrificed after one day, the second after one week, the third after two weeks and the fourth after four weeks post- irradiation.

The kidneys of control and treated rats were dissected out and washed in normal saline to remove the blood, then cut into pieces and put in suitable fixative. For routine histopathological evaluation under light microscopy; the fixative used was 10% buffered formalin, stained with haematoxylin and eosin (Lillie, 1954). Some tissue samples were examined by transmission electron microscope (TEM) JEOL (JEM 100CX) at The National Center for Radiation Research and Technology, Cairo, Egypt. Glutaraldehyde (4%) buffered with 0.2 M sodium cacodylate; then Osmium tetroxide (2%) buffered with 0.3 M sodium cacodylate were used for fixation. A series of ethyl alcohol were used for dehydration and the specimens were embedded in a resin, Araldite-Epon Kit (EMBed 812) methods recommended by Hayat (1981).

RESULTS

Histological Studies

The kidney of control rat showed a normal structure of the renal cortex which consists of renal corpuscles, proximal and distal convoluted tubules (Fig.1). No pathological changes were observed in the kidneys of rats which received 5mg/kg b.wt/day of beta-carotene for 2 consecutive weeks in comparison with the control group (Fig.2). Whole body gamma-irradiation of rats with a single dose of 6 Gy, induced at the 1st day post exposure, bleeding and some lesions in the renal tubules (Fig.3). Whereas, 1 week consequent to irradiation showed progressive pathological lesions represented by severe damage in glomerular tuft with wide Bowman's space and severe bleeding scattered in between degenerated renal tissues (Fig.4). Two weeks post-irradiation of rats pointed out atrophy in gromerular tuft with widening in the glomerular space, rupture in Bowman's capsule, an increase in mesangial cells, hemorrhagic lesions, destruction of cells lining the proximal and the distal tubules

(Fig.5). While in the 4th week post-irradiation of rats, some destruction occurred in glomerular corpuscles and rupture in Bowman's capsule. In addition, some renal tubules were degenerated and hemorrhagic areas were present in between them (Fig.6). Rats treated with Beta-carotene for 2 consecutive weeks before being exposed to γ-radiation induced at 1st day post-irradiation, an improvement which occurred in renal corpuscles and regeneration in epithelial convoluted tubules (Fig.7). One week post-irradiation revealed that an improvement occurred in the glomerular tuft with normal Bowman's space with intact Bowman's capsule as well as an increase in mesangial cells with rupture in some renal tubules (Fig.8).After 2 weeks of irradiation, some changes were still noticed in the renal tissues, in comparison with the control group, while some glomerular tufts were lobulated and there was an increase in the cellularity. Also, there was a slight degeneration in the renal tubular epithelial cells (Fig.9). Four weeks post-irradiation, examination showed repair in convoluted tubular epithelial cells but shrinkage in gromerular tuft with rupture in Bowman's capsule (Fig.10).

Ultra Structural Studies

Electron microscopic study of the cortex of the control group showed that the proximal convoluted tubules were lined by large cells with basal membrane infolding and elongated mitochondria. The nuclei appeared rounded, vesicular with smooth nuclear membrane (Fig.11).The cells of distal convoluted tubules showed spherical euchromatic nuclei and few apical microvilli. The cells showed also an extensive basal infolding in between elongated basal mitochondria (Fig.12). Rats exposed to whole body gamma irradiation exhibited, after 4 weeks, severe degeneration in the proximal and distal tubules. Ultra-structural changes were detected in the epithelial cells lining the proximal convoluted tubules showing an increase in the swollen mitochondria with rupture of its cristae. Also, there was dilation in the rough endoplasmic reticulum and electron dense in the nuclear chromatin. Thickness in basement membrane and dilation of infolded were observed. Damage of brush boarder was also noticed (Figs.13). The epithelial cells lining the distal convoluted tubules showed pyknotic nuclei and ill-defined cytoplasmic organelles, also damages in basement membrane and, in addition collagen were seen (Fig.14). Rats which were treated by oral administration with Beta-carotene pre-irradiation revealed an improvement of proximal convoluted tubules. Normal round shape nucleus was observed. Also, the sections revealed an improvement of apical region and regeneration of brush boarder (Fig. 15). In the distal convoluted tubules there were also an improvements in the basement membrane including normal infolded. Normal rounded nucleus, normal apical region and normal microvilli which were recorded (Fig. 16).

RESULTS

Histological Studies

Fig. (1): Photomicrograph of normal kidney section of control rat showing normal glomerular tuft (G) (renal corpuscles) with normal renal tubules (T). (H & E; X 400)

Fig. (2): Photomicrograph of kidney section of treated rat with Beta-carotene, showing normal structure of glomerular corpuscles (G) with thin membrane of Bowman's space (BS) and normal renal tubules (T). (H & E; X 400).

Fig. (3): Photomicrograph of kidney section of irradiated rat 1st day post exposure showing hemorrhagic areas (H) between the damaged renal tubules (T). (H & E; X 400).

Fig. (4): Photomicrograph of kidney section of irradiated rat with 1 week post exposure showing damages in glomerular tuft (G) with wide Bowman's capsule (BC) and damage in renal tubules (T), plus hemorrhagic areas (H) in renal tissues. (H & E; X 400).

Fig. (5): Photomicrograph of kidney section of irradiated rat with 2 weeks post exposure showing collapse in glomerular tuft (G) and an increase in mesangial cells (M). Large hemorrhagic lesions (H) and degeneration of convoluted tubules (T). (H & E; X 400).

Fig. (6): Photomicrograph of kidney section of irradiated rat 4 weeks post exposure showing damages in glomerular corpuscles (G) and rupture in Bowman's capsule (B.C) with damages in renal tubules (T) and hemorrhagic areas (H). (H & E; X 400).

Fig. (7): Photomicrograph of kidney section of treated rat with Beta-carotene pre-irradiation 1st day post exposure showing an improvement in renal glomerular corpuscles (G) and regeneration in epithelial convoluted tubules (T). (H & E; X 400).

Fig. (8): Photomicrograph of kidney section of treated rat with Beta-carotene pre-irradiation 1week post exposure showing an improvement in the glomerular tuft (G) with normal Bowman's space (BS) with intact Bowman's capsule (BC) and an increase in mesangial cells (M) with rupture in some renal tubules (T). (H & E; X 400).

Fig. (9): Photomicrograph of kidney section of treated rat with Beta-carotene pre-irradiation 2 weeks post exposure showing lobulated glomerular tuft (G) with an increase in mesangial cells (M) and some degeneration in renal tubular epithelial cells (T). (H & E; X 400).

Fig. (10): Photomicrograph of kidney section of treated rat with Beta- carotene pre-irradiation 4 weeks post exposure showing repair in convoluted tubular epithelial cells (T) and shrinkage in glomerular tuft (G) with rupture in Bowman's capsule (BC) and an increase in mesangial cells (M). (H & E; X 400).

Ultrastructural Studies

Fig. (11): Electron micrograph of a part of a normal proximal convoluted tubule of an albino rat's kidney whic showed basal spherical nucleus (N) with euchromatin, brush border (BB), numerous apical vacuoles (V) and many elongated mitochondria (M). Notice the thin basement membrane (BM) and the normal basal infolding (↑). (X4600).

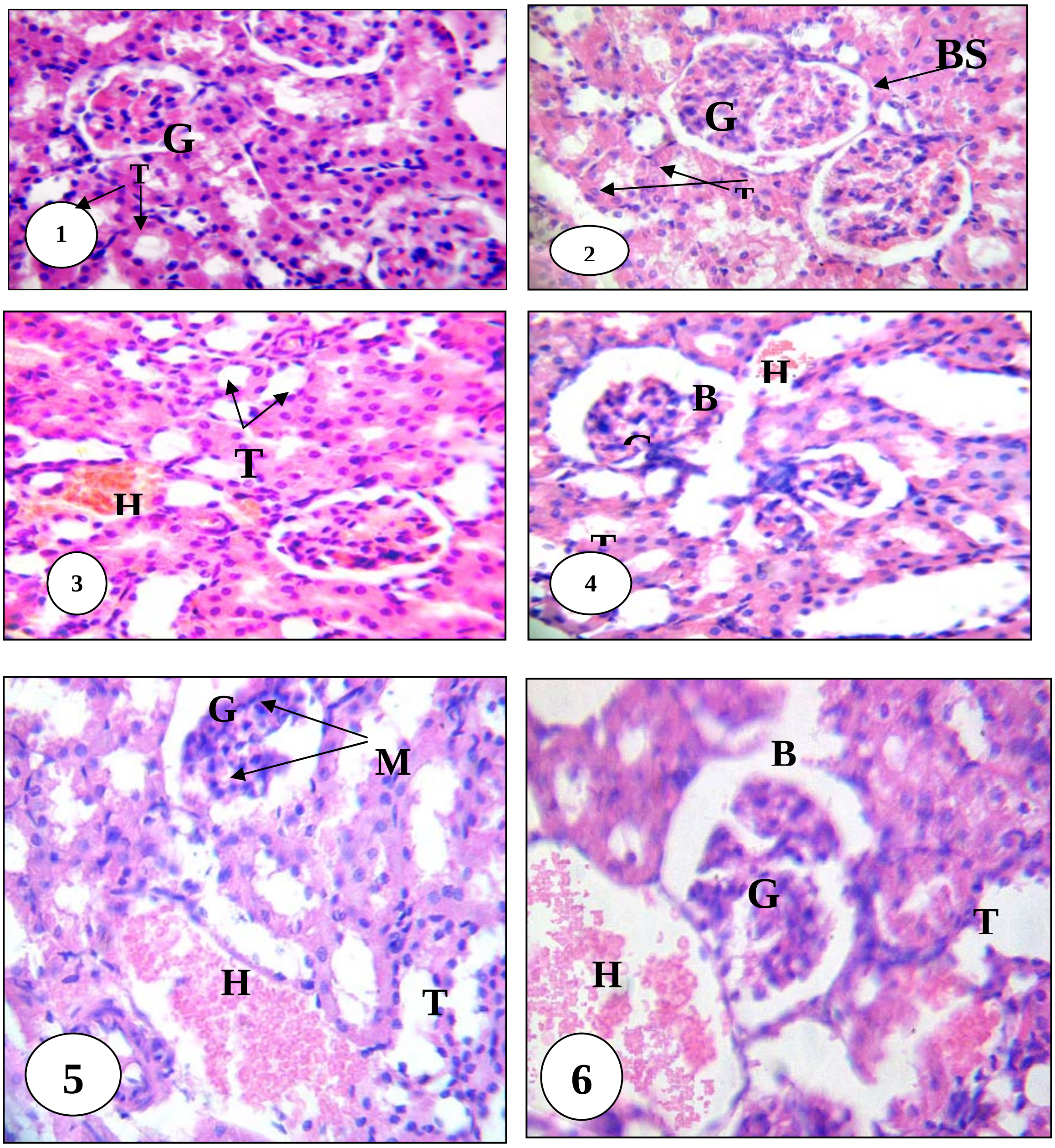
Fig. (12): Electron micrograph of a part of a normal distal convoluted tubule of an albino rat's kidney which showed the apical part with few microvilli (↑), normal and oval nucleus (N) and many elongated mitochondria (M) arranged in between the numerous basal infolding (X4600).

Fig. (13): Electron micrograph of an irradiated rat 4 weeks post exposure showing severe degeneration in the proximal tubules, an increase in the swollen mitochondria (M) with rupture of its cristae , dilations of rough endoplasmic reticulum and electron dense in the nuclear chromatin (N). Thickness in basement membrane and dilation of infolded (↑). The damage of brush border also was noticed (✶). Also large areas of hemorrhage (H) in between renal tubules. (X 2800).

Fig. (14): Electron micrograph of an irradiated rat 4 weeks post exposure showing severe degeneration in the distal tubules, degeneration of mitochondria (M), pyknotic nuclei (N) and dilation of rough endoplasmic reticulum, thickness in basement membrane (BM) and dilated infolded (↑) . Narrowing in the lumen (LU) with hyaline cast and cell depressions. Notice that the collagen fibers (CF) can be seen near or around the distal tubules (X 3600).

Fig. (15): Electron micrograph of the rat treated with Beta-carotene pre-irradiation showing regeneration of proximal convoluted tubules, normal rounded nucleus (N). Improvement of the apical region (↑) and regeneration of the brush border (BB). (X 3600).

Fig. (16): Electron micrograph of treatment with Beta-carotene pre-irradiation showing an improvement of distal convoluted tubules including intact basement membrane (BM) with normal infolded (↑). Normal rounded nucleus (N). Normal apical region and normal microvilli ▲) (X 6000).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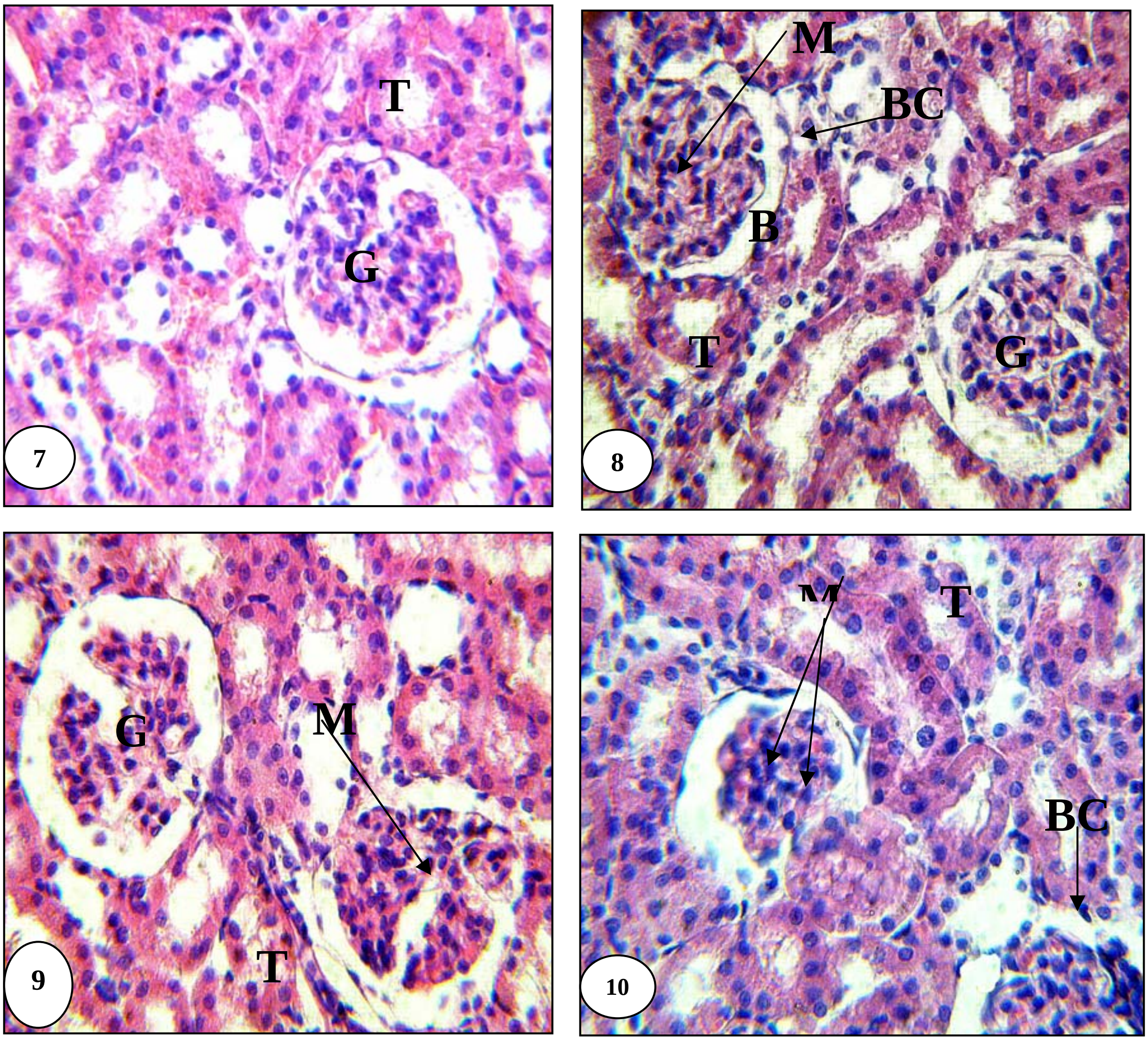
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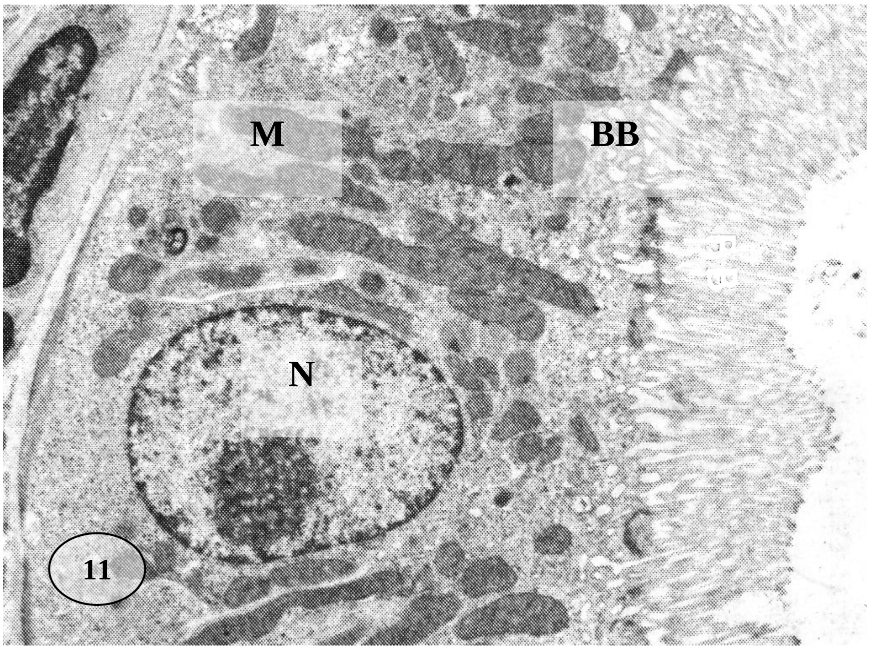
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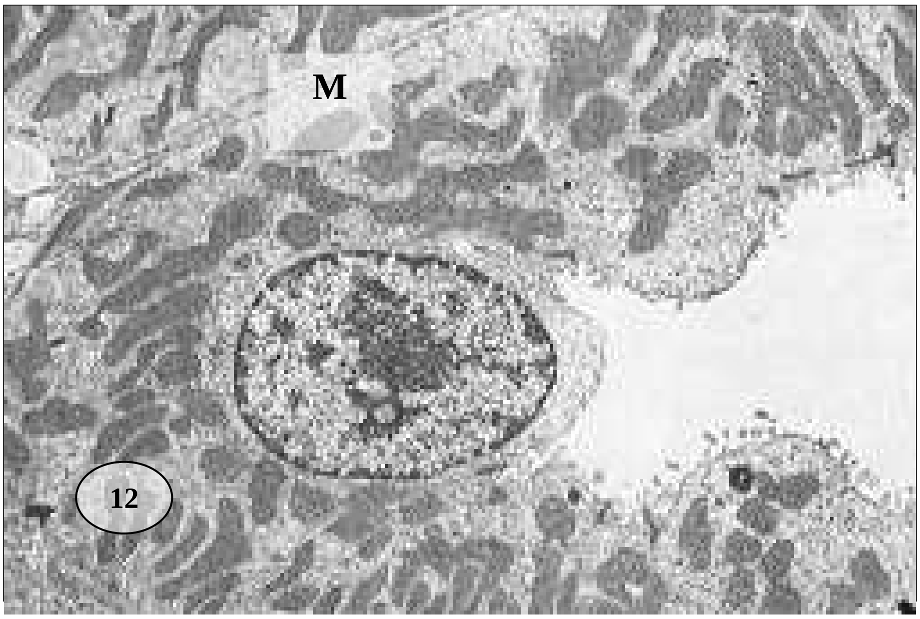
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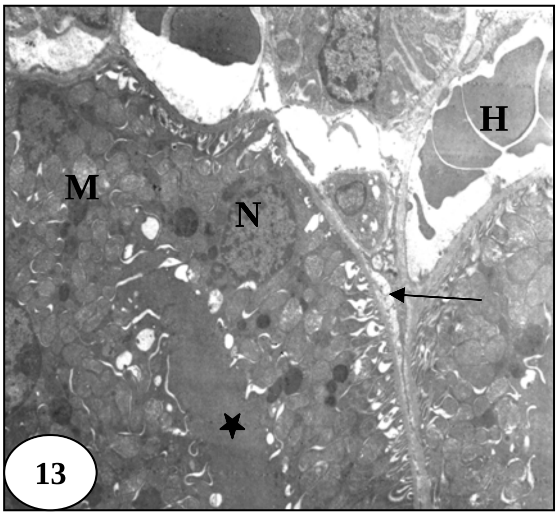
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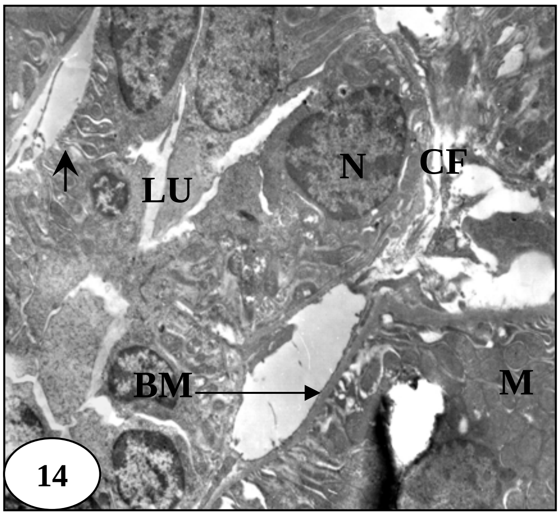
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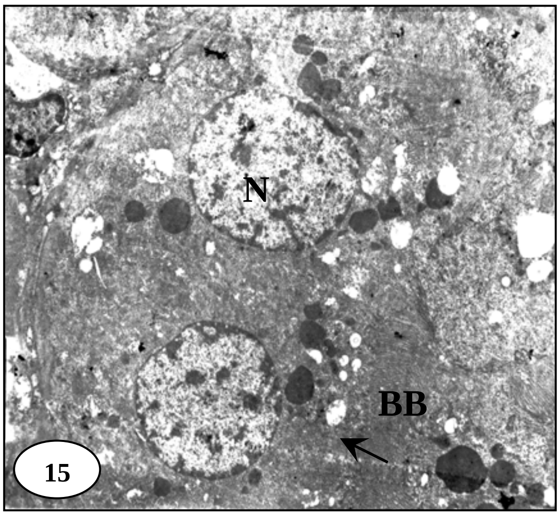
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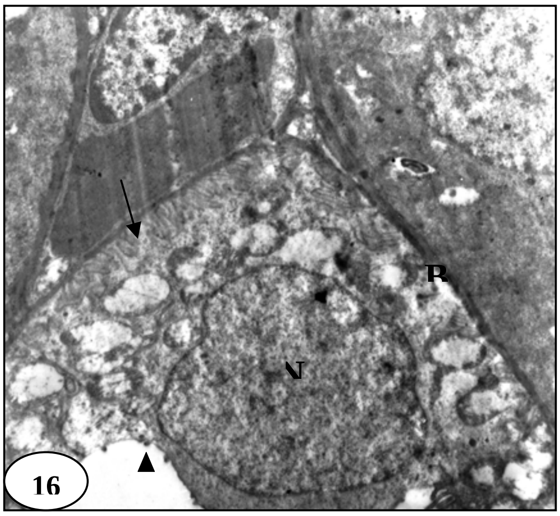
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DISCUSSION

The kidney is one of the organs that show high sensitivity toward gamma-radiation (Dewit et al., 1990). In the present study damage in glomerular tuft was noticed with widening in Bowman's space then rupture in later stages. This was in agreement with the finding of Stephens et al. (1995) who indicated that, the structural changes have led to the concept that glomeruli appeared to be very radiosensitive because after the clinically relevant dose of 24 Gy in 12 fractions essentially all glomeruli were altered in the irradiated kidneys as compared to controls.

The present study also found lobulation and shrinkage in some glomerular tufts with rupture in Bowman's capsule and an increase in mesangial cells due to the gamma-irradiation of rats. Also, there was a moderate increase in the cellularity. Slight degeneration in the renal tubular epithelial cells was noticed.

Robbins et al. (1995) mentioned that, the renal irradiation resulted in a progressive decline in glomerular filtration rate (GFR), alterations in glomerular and tubular cell proliferation and morphology within 2-4 weeks of irradiation. Irradiation can also induce complete glomerular capillary obstruction due to thrombus formation (Van Kleef et al., 1998).

The experimental data for mice, pigs and primates as well as data from clinical studies suggested that, glomerular damage develops before tubular damage (Glastein et al., 1977; Robbins et al., 1991 and Jaenke et al., 1993) and that, glomerular damage is mainly responsible for renal failure (Robbins et al., 1995). These data were in agreement with the present results. The earliest histological damage due to radiation exposure which was observed in the present work was noticed in glomerular capillary endothelial cells. These observations found considerable supports with the findings of Robbins et al., (1991); Jaenke et al., (1993) and Robbins et al., (1995).

The present results revealed that glomerular changes were characterized by thickening of glomerular capillary walls, tuft shrinkage and focal sclerosis. Tubular changes were marked by flattening of tubular epithelium, focal cell loss, and focal interstitial fibrosis that were in agreement with those of Van Kleef et al. (1998) who reported that, histological examination of irradiated rats was performed and evaluated separately for glomerular and tubular changes.

Also the emerged results revealed severe hemorrhagic areas scattered in-between degenerated renal tissues, due to gamma-irradiation of rats. Moreover, some lesions in the renal tubules were also noticed. The increase in the mesangial cells observed in the present study might be resulted as a defense mechanism. Destruction of cells lining the proximal and distal tubules was similar to that observed by Soranson and Denekamp (1986) and Abu Nour (2002). They concluded that, the tubular cells are among the most important target cells for radiation injury in the kidney.

Some other researchers came to the conclusion that the endothelial cell injury represents the primary site of radiation damage in the rat's kidney (Jaenke et al., 1993).

The present results proved that, β-carotene can act effectively as radio-protector and showed that, the treatment with β-carotene for two weeks prior to gamma-irradiation decreases the harmful effects of radiation exposure. Its working mechanism depends on scavenging the free radicals and quenching the singlet oxygen (the unstable oxygen metabolites with altered energy states) (Gaby and Singh, 1991; Someya et al., 1994 and Tesoriere et al., 1995). Also, examination of kidney sections demonstrated an improvement in renal corpuscles, thin membrane of Bowman's capsule with intact Bowman's capsule and regeneration in epithelial convoluted tubules as it were observed. However, some histo-pathological changes still noticed in the renal tissues, in comparison with the control group.

The results of the ultra-structural examinations showed that, whole body gamma irradiation of rats induced degeneration in the proximal and distal tubules in the kidneys. These results are in agreement with those of Dewit et al. (1990) who reported that, the kidney is one of the most radiosensitive organs and is dose-limiting in cancer patients treated with total-body or abdominal irradiation . The present results revealed that, the epithelial cells lining the proximal convoluted tubules showed an increase in the swollen mitochondria with rupture of its cristae. These findings concord with those recorded by Al Karaz et al. (1990) and Thannoo et al. (1996) who assured that, the affected mitochondria are of swollen aspect and have their cristae partially or completely destroyed.

Moreover, Ghadially (1988) referred that, the mitochondrial swelling and destruction of their cristae are due to the influx of water into the inner and outer mitochondrial chambers, which is accompanied by separation of the inner and outer mitochondrial membranes. Since mitochondria are the site of the main energy production in the cells, their damage may result in lowered energy output. Therefore, the failure of the mitochondrial activity in the damaged cells may be regarded as a factor causing cell degeneration.

Also the present results revealed dilations in the rough endoplasmic reticulum induced from exposure to 6 Gy of gamma-radiation. Similar changes were also reported by Huijbers et al. (1979) who observed that, the rough endoplasmic reticulum represent the main site of protein synthesis in the cells, and thus the damage of the rough endoplasmic reticulum (RER) reflect the impairment of protein synthesis in such cells.

In the present study whole body gamma-irradiation of rats induced damage in the proximal and distal convoluted tubules and showed destruction of brush border and microvilli. These changes could be attributed to the degenerative changes involving the whole tubules as well as to thickening of tubular basement membrane. These observations agree with those Huijbers et al. (1979) and Cohen (2000) who indicated that, the previous changes of which occurred were probably caused by a detergent-like effect of the per-oxidation on membrane lipids.

Also, ultra-structural studies carried on gamma-irradiated albino rats showed that, focal tubular alterations were detected (Mulder et al. 2002). On the 6th day, and 10th week, electron dense material within lysosomes of tubular cells was also detected.

In the present study the results revealed that, there was a relation between exposure to whole body gamma-irradiation and the alterations which induced in both functions and structures of renal tissues. Kilberg and Neuhaus (1978) and Kapyaho et al. (1983) found that, the whole body irradiation of rats led to a degeneration of tissue proteins that inhibit the protein synthesis due to degradation of cellular tissues.

On the other hand, beta-carotene has shown to have a good antioxidant effect which reduced the effect of gamma-radiation on the kidney of rats. In the present study it was found that, rats treated by oral administration with Beta-carotene for 2 consecutive weeks, and then exposed to γ-radiation, showed an improvement in proximal convoluted tubules, normal rounded nucleus. Also, an improvement occurred in the apical region and in addition to regeneration of brush border. Moreover, the distal convoluted tubules exhibited an improvement in the basement membrane including normal infolded. Also, normal rounded nucleus, normal apical region and normal microvilli were recorded.

Manda and Bhatia (2003) indicated that, the antioxidant property of beta-carotene against gamma-radiation could be due to free radical scavenging capacity and singlet oxygen quenching.
The antioxidant and protective properties of organic compounds led to the conclusion that, these compounds prevent the development of subsequent oxidizing chain reactions, (Zhuravlev, 1957). Satyamitra et al. (2001) and Cherdyntseva et al. (2005) found that some vitamins induce excellent protection against radiation exposure hazards. Tukalenko et al. (2006) found that, Beta-carotene demonstrated the largest protective effect alone and as a component in complex compounds.

In conclusion, Beta-carotene administration to rats prior to exposure to ionizing radiation could minimize the harmful and deleterious effects on kidney. It is therefore suggested that, beta-carotene could be considered as an effective antioxidant that, could scavenge free radicals and active oxygen species formulated in the animal body as a result of gamma radiation exposure.

RECOMMENDATIONS

- Avoiding gamma-radiation as much as possible.
- Using all the precaution means when dealing with gamma-radiation.
- Using beta-carotene in diet specially for people who works in the radiation field or under radiotherapy.
- Regular check up on people who expose to gamma-radiations in their work.

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