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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

OPEN ACCESS Pakistan Journal of Biological Sciences

ISSN 1028-8880
DOI: 10.3923/pjbs.2020.92.102

Research Article
Effect of Transplanted Bone Marrow on Kidney Tissue of γ-Irradiated Pregnant Rats and Their Fetuses

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Abstract

Background and Objectives: The damaging effects of ionizing radiation lead to cell death. The present study was performed to assess the possible ameliorating effects of bone marrow transplantation (BMT) on the histopathological and histochemical changes in the kidney tissue of γ-irradiated pregnant rats and their fetuses. **Materials and Methods:** Pregnant rats were divided into 5 sets (6 females in each set): Group C (untreated pregnant rats), group R7 (pregnant rats exposed to 2Gy of γ-rays on the 7th day of pregnancy), group R7+BM (pregnant rats exposed to 2Gy of γ-rays on the 7th day of pregnancy then injected by freshly BMT ($75\times10^{6}\pm5$ cells) intra peritoneally after 1 h of irradiation, group R14 (pregnant rats exposed to 2Gy of γ-rays on the 14th day of pregnancy), group R14+BM (pregnant rats exposed to 2Gy γ-rays on the 14th day of pregnancy and after 1 h received 1 dose of BMT). All pregnant rats were sacrificed on the 20th day of pregnancy and kidney samples of pregnant rats and their fetuses were removed for histopathological and histochemical studies. **Results:** Gamma rays caused many histological and histochemical deviations in the kidney tissue of mothers and their fetuses on day 7 or 14 of gestation, but bone marrow transplantation highly improved the damage were occurred due to γ-rays. **Conclusion:** Bone marrow transplantation has the ability to decrease the injury of gamma rays.

Key words: Ionizing radiation, bone marrow transplantation, gamma irradiated rats, gestation

Citation: Mervat Ahmed Abd Rabou, Nehal Ali Abu El Naga and Fatma Ahmed Eid, 2020. Effect of transplanted bone marrow on kidney tissue of γ-irradiated pregnant rats and their fetuses. Pak. J. Biol. Sci., 23: 92-102.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Prenatal exposure to ionizing radiation can overlap with embryonic and fetal development, depending on dose and gestational age. Radiation is usually explained as the emission and diffusion of energy in the form of waves or particles through space or substance[1]. It interrelates with matter by straight and indirect methods. Both methods cause molecular injury and that translated to biological destruction[2]. Exposure to ionizing radiation whether working or during radiotherapy cause severe systemic damage to numerous cellular and sub cellular structures[3]. Ionizing radiation forms radicals in the DNA and in the adjacent water particles of the hydration shell of the DNA which destroy DNA[4]. High doses of ionizing radiation may be deadly to the cell by damaging both DNA strands[5]. The occurrence of injured nuclear DNA in cells can cause genomic instability and numerous cell divisions[6].

Ionizing radiation embodied a possible teratogen for the fetus, but this risk has been found to be reliant on the dose and the belongings creatable to the gestation time at exposure[7]. Emergent mammalian embryo is more sensitive to ionizing radiation than adult. Radiation persuaded deviations in mammals are closely connected to the period of growth of embryos at which radiation is assumed[8]. Gama rays (2Gy) caused embryonic loss and deformities in mice[9].

Mutagenic belongings and organ-specific changes were induced by radiation exposure[10]. Kidney is the greater influential route for the absorption of adventurous materials conflict in the environment. The histopathological deviations reported due to radiation exposure were linked to a decline in kidney functions[11]. Cloudy cellular swelling, congestion and thick cellular penetration were occurred by gamma radiation on mice kidney tissue[12]. The kidney of gravid rats exposed at the dose level of 3Gy on days 7, 13 or 18 of pregnancy showed degeneration and provocative penetration within many convoluted tubules[13].

Bone marrow is a complex tissue consists of 2 sections, haematopoietic and stromal one. The stromal section is the structural basis of the haematopoietic microenvironment which is a complex tissue that contains a subset of cells called mesenchymal stem cells (MSCs)[14]. The MSCs maintain stem cell features, are used to recover the healing of hurt tissues. It are also used to indulgence dysfunction of other tissues, such as tissues of the nervous system, the cardiac system and lunate bone[15]. Bone marrow transplantation boosts the antioxidant level and defends from oxidative stress in irradiated rats[16]. Bone marrow derived mesenchymal stem cells (BMSCs) have shown great capacity for ischemic tissue reparation[17,18]. Human bone marrow-derived mesenchymal stem cell transplantation may have clinical requests for the treatment and repair of tissue injury made by radiation[10]. The present study was done to assess the possible ameliorating effects of BMT on the histopathological and histochemical changes in the kidney tissue of γ-irradiated pregnant rats and their fetuses.

MATERIAL AND METHODS

Experimental animals: Mature albino rats (*Rattus albinus*), their body weight from 120-150 g were kept in cages. The males were separated from females up to reproducing. One male were caged with two females of proestrus or estrous periods. In the next morning the gestation was assured by the occurrence of vaginal plug or presence of sperms in smears of vaginal content and that day was considered the 1st day of gestation.

Study area: The present study was performed in National Center for Radiation Research and Technology, Atomic Energy Authority, Cairo, Egypt from January to March, 2013.

Irradiation: Irradiation was done in the National Center for Radiation Research and Technology, Atomic Energy Authority, Cairo, Egypt by Gamma-cell 40 (137 Cesium).

Bone marrow transplantation: Donors and recipients of bone marrow transplantation were selected of the similar strain. The donors were sacrificed and femur bones were cleaned and both ends were fragmented by bone nibbling forceps. The marrow was driven of the femur into saline solution under sterilized conditions bounded by ice cubes and mixed by drawing and expelling it several times from the syringe without needle in order to avoid mechanical damage to the cells. Total viable of cells about $75\times10^6\pm5$ were injected one hour post irradiation[19].

Experimental groups: The pregnant rats were separated into 5 groups (6 females in each group), Group C (untreated pregnant rats), group R7 (Pregnant rats exposed to 2Gy of gamma rays on the 7th day of pregnancy), group R7+BM (pregnant rats exposed to 2Gy of gamma rays on the 7th day of pregnancy and received freshly BMT ($75\times10^6\pm5$ cells) by intra peritoneal admission 1 h post-irradiation, group of R14 (pregnant rats insecure to 2Gy of gamma rays on the 14th day of pregnancy), group of R14+BM (pregnant rats exposed to 2Gy gamma rays on the 14th day of pregnancy and after 1 h received one dose of BMT. All pregnant rats were sacrificed on the 20th day of pregnancy.

Histological and histochemical studies: After sacrifation the pregnant animals on the 20th day of pregnancy, small pieces of kidney tissues of mothers and their fetuses were quickly removed and fixed in 10% neutral buffer formol and Carnoy's fluid for histological and histochemical studies. Sections were stained by haematoxylin and eosin stain agreeing to the technique of Carleton *et al.*[20], collagen fibers were demonstrated by Mallory's trichrome stain[21], polysaccharides were demonstrated by periodic acid Schiff's technique[21], total protein were detected by mercuric bromophenol blue[22].

Statical analysis: The data analyzed using one way analysis of variance followed by Duncan's test. Differences between groups were considered significant at $p \leq 0.05$.

RESULTS

Histopathological and histochemical studies in the kidney tissue of pregnant rats

Histopathological results: Control kidney tissue consists of Malpighian s corpuscles with Bowman's capsules, Bowman's spaces, glomeruli, distal and proximal convoluted tubules (Fig. 1a). Kidney of pregnant rats of group R7 showed faintly stained cells and nuclei of the convoluted tubules, some nuclei appeared deeply stained (pyknotic), wide lumens in the distal convoluted tubules, ruptured brush borders of the proximal convoluted tubules, haemolysed RBCs in the glomeruli, hemorrhagic areas (Fig. 1b). Bone marrow treatment improved the kidney architecture in the pregnant rats of groups R7+BM (Fig. 1c). Highly distorted malpighian capsules, most nuclei of the proximal convoluted tubules cells were hypertrophied and pyknotic, others were karyolytic, large and small degenerated areas, atrophied glomeruli with debris of degenerated tubules were noted in R14 group (Fig. 1d, e). Improved the kidney architecture were noted in R14+BM (Fig. 1f).

Normal distribution of collagen fibers in the kidney tissue of control group (Fig. 2a). Thin collagen fibers are supporting walls of the blood vessels, distal convoluted tubules, proximal convoluted tubules, blood vessels and Bowman's capsules in kidney tissue of group R7 (Fig. 2b). A slight increase in the collagen fibers in walls of the distal and proximal convoluted tubules and in between and around Bowman's capsules in group R7+BM (Fig. 2c). Increased collagen fibers in the distal and proximal convoluted tubules and some glomeruli, but the remnant glomeruli are poorly stained were noted in R14 group (Fig. 2d). Increased collagen fibers in between and around Bowman's capsules were found in R14+BM group (Fig. 2e).

Histochemical results: Table 1 showed reduced mean optical transparency (MOT) of polysaccharides in the atrophied glomeruli and tubules of the kidney of groups R7 and R14 compared to the control group. The percentage of change in MOT was clearly approach to the normal values in the kidney tissue of the pregnant rats of groups R7+BM and R14+BM. Significant decrease in MOT value of total protein content in kidney tissue of pregnant rats in groups R7 and R14 were noted compared to the control group. Somewhat normal MOT of total protein was noticed in the glomeruli, distal and proximal convoluted tubules in groups R7+BM and R14+BM.

Histological and histochemical results of fetuses

Histological results: Normal fetal kidney tissue were noted in the control group (Fig. 3a). Radiation exposure on day 7 of gestation caused many dystrophic changes in the fetal kidney tissue maternally exposed to 2Gy γ-rays. These changes include: Degenerated convoluted tubules, some glomeruli are atrophied with dilated Bowman's spaces, numerous hemorrhagic areas, deeply stained pyknotic nuclei with debris of degenerated cells of the convoluted tubules (Fig. 3b). Bone marrow transplantation post-irradiation (2Gy) on day 7 of gestation showed normal appearance of the fetal kidney tissue (Fig. 3c). Highly distorted and degenerated cells of distal and proximal convoluted tubules which are surrounded by numerous fibrotic and hemorrhagic areas, glomeruli are atrophied, lobulated or hypertrophied with numerous pyknotic nuclei were noted in R14 group (Fig. 3d, e). Normal appearance of kidney tissue were found in R14+BM group (Fig. 3f).

Table 1: MOT and the percentage of change values of PAS+ve materials and total protein in the glomeruli and tubules of the pregnant rats

	MOT values of PAS+ve materials				MOT values of total protein			
	Glomeruli		Tubules		Glomeruli		Tubules	
Groups	Mean±SE	Change (%)	Mean±SE	Change (%)	Mean±SE	Change (%)	Mean±SE	Change (%)
Control	114.00±1.48		91.48±3.12		155.00±3.83		145.38±3.86	
R7	80.48±5.37*	29.40	74.03±3.25*	36.00	105.48±5.23*	31.95	102.33±3.12*	29.60
R7+BM	92.69±4.48*	18.70	54.33±2.95*	19.07	152.34±6.78	2.02	143.45±2.32	1.32
R14	89.00±3.53*	21.92	70.82±6.00*	22.58	110.89±3.36*	28.46	104.84±2.37*	27.88
R14+BM	91.89±6.02*	19.39	83.56±3.14*	8.65	147.89±3.57	4.58	138.78±3.74	4.53

*Values are considered significantly different ($p<0.05$), SE: Standard error 3.2

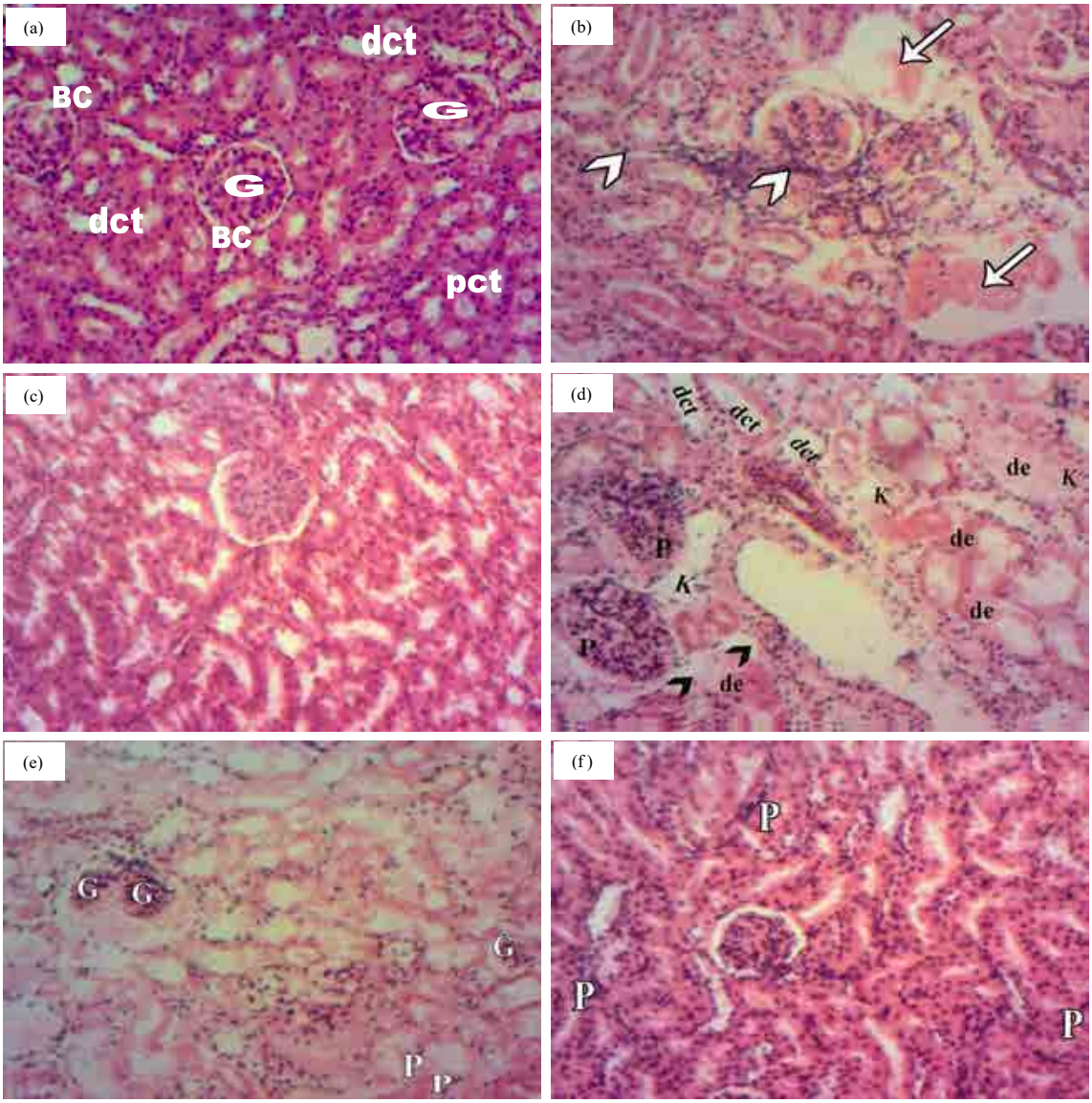

Fig. 1(a-f): Sections of kidney tissue of control and treated pregnant rats stained with Hx and E ×100, (a) Control group, malpighian corpuscles contain glomeruli (G), Bowman's capsules (Bc), Bowman's spaces (Bs), distal convoluted tubules (ds) and proximal convoluted tubules (pc), (b) R7 group: Faintly stained cells and nuclei of the proximal and distal convoluted tubules, some nuclei appear deeply stained (>), wide lumens in the distal convoluted tubules, ruptured brush borders of the proximal convoluted tubules, haemolysed RBCs can be detected in the glomeruli and hemorrhagic areas (↑), (c) R7+BM group: Well developed kidney architecture, (d, e) R14 group: Highly distorted malpighian corpuscles, distal and proximal convoluted tubules and most of their nuclei were hypertrophied and pyknotic (p), others are karyolytic (k), large and small degenerated areas (de), wide lumens of distal convoluted tubules (dct), ruptured brush borders of proximal convoluted tubules (pct) with debris of degenerated tubules (de) and atrophied glomeruli (G) and (f) R14+BM group: Kidney tissue restore its normal architecture, but some pyknotic nuclei (p) are still detected

Normal distribution of collagen fibers in walls of the convoluted tubules, glomeruli and stroma of the fetal control kidney cortex was observed in Fig. 4a. Highly increased collagen fibers were detected in the inner cortical part, but fibrosis and hemorrhagic areas in the outer part of the cortex acquired red coloration which indicating fibrosis with absence

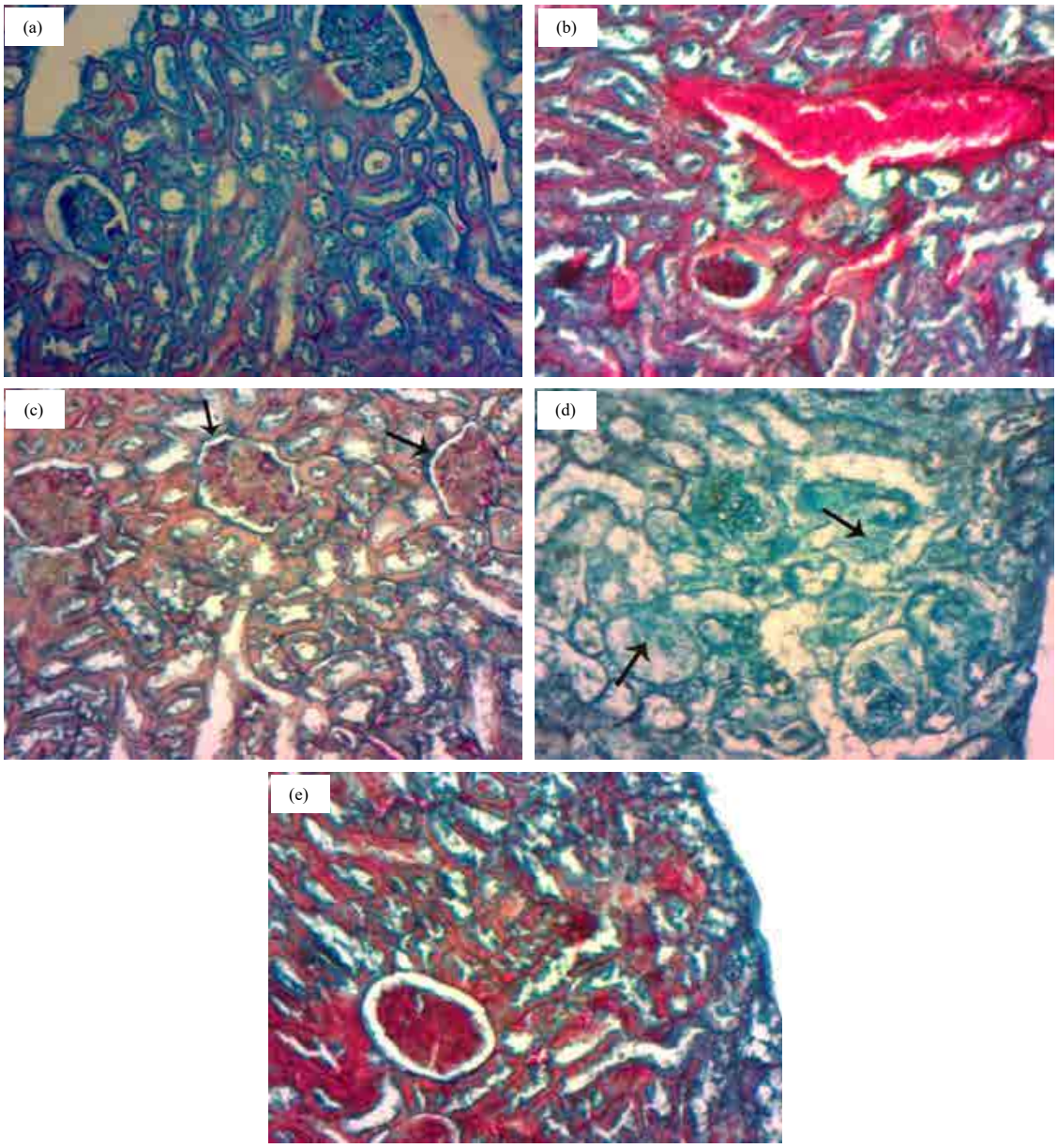

Fig. 2(a-e): Distribution of collagen fibers in the kidney tissue of control and treated pregnant rats stained with Mallory s trichrome stain (×100), (a) Control group: Thin collagen fibers supporting walls of the blood vessels, distal and proximal convoluted tubules, blood vessels and Bowman's capsules, (b) R7 group: Highly increased collagen fibers in walls of distal and proximal convoluted tubules and the brush borders of proximal convoluted tubules, (c) R7+BM group: A slight increase in the collagen fibers in walls of distal and proximal convoluted tubules and Bowman's capsules, (d) R14 group: Increased collagen fibers in the distal and proximal convoluted tubules and some glomeruli, but the remnant glomeruli are poorly stained (↑) and (e) R14+BM group: Increased collagen fibers in between and around Bowman's capsules

of kidney medulla in the fetal kidney tissue of group R7 (Fig. 4b). Deeply stained collagen fibers and signs of fibrosis were still detected in the fetal kidney tissue of group R7+BM (Fig. 4c). The fetal kidney tissue of group R14 showed decreased collagen fibers in the convoluted tubules and most glomeruli (Fig. 4d). Somewhat normal appearance of collagen fibers was detected in the fetal kidney tissue of group R14+BM (Fig. 4e).

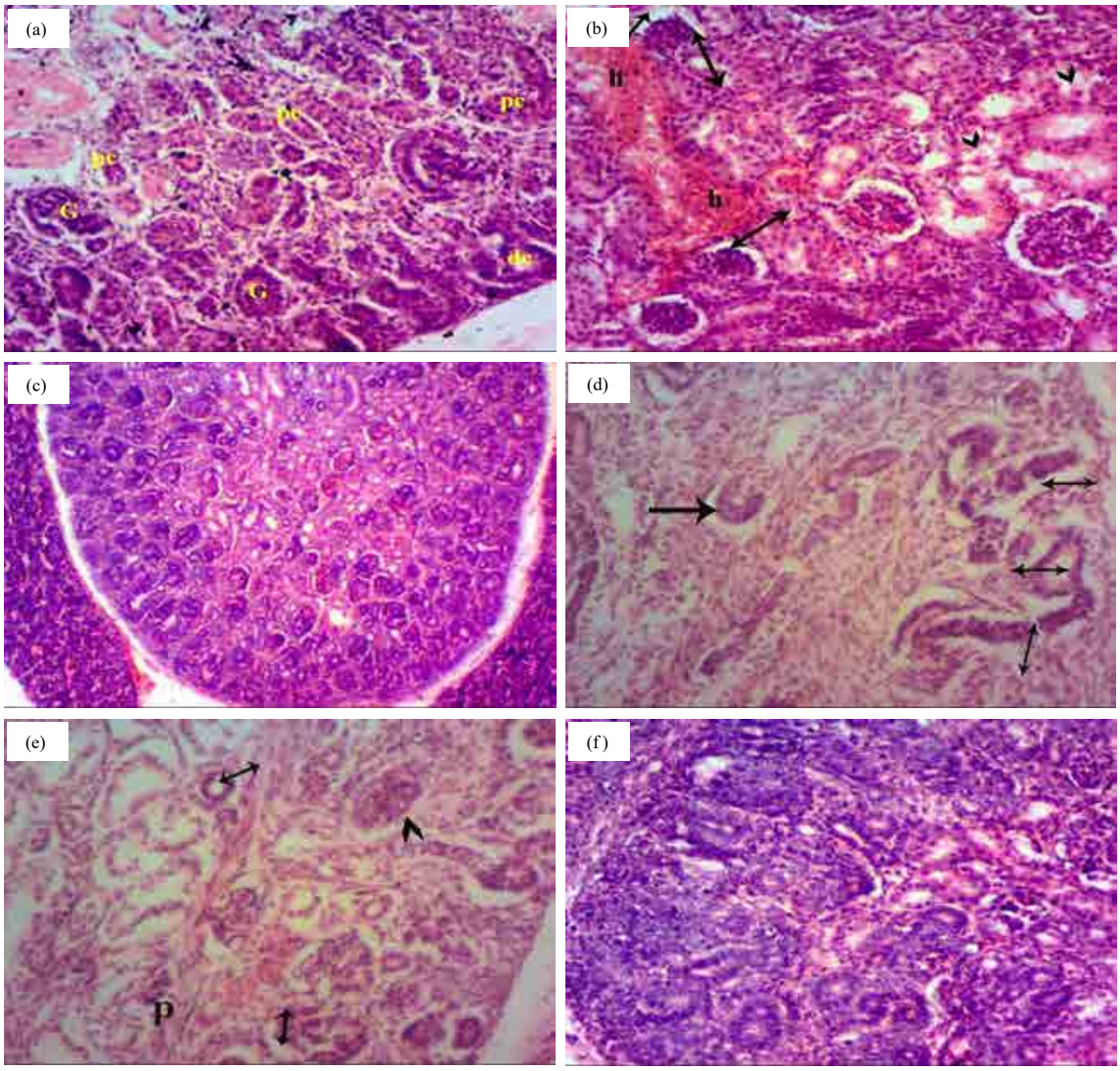

Fig. 3(a-f): Sections of kidney tissue of fetuses of the control and treated pregnant rats stained with Hx and E, (a) Control group: Kidney tissue which contains glomeruli (G), proximal convoluted tubules with their brush borders (pc) and distal convoluted tubules with their wide lumens (dc) (×100), (b) R7 group: Degenerated convoluted tubules, some glomeruli are atrophied with dilated Bowman's spaces (↑), numerous hemorrhagic areas (h), deeply stained pyknotic nuclei (↕) with debris of degenerated cells of the convoluted tubules (>) (×100), (c) R7+BM group: Normal kidney tissue (×50), (d, e) R14 group: Highly distorted and degenerated cells of distal and proximal convoluted tubules which are surrounded by numerous fibrotic and hemorrhagic areas, glomeruli are atrophied (↑), lobulated (↕) or hypertrophied (>) with numerous pyknotic nuclei (p) and (f) R14+BM group: Normal appearance of kidney tissue

Histochemical results: Table 2 showed MOT values of PAS+ve materials in the fetal kidney tissue. The glomeruli and tubules of fetal kidney tissue were poorly stained in groups R7 and R14 compared to the control group. Somewhat normal MOT values of PAS+ve materials were detected in group R7+BM. Also in group R14+BM, some of distal and proximal convoluted tubules and glomeruli restored their normal content of polysaccharides. Also, reduced MOT value of total protein were noted in the glomeruli and distal and proximal convoluted tubules in the fetal kidney of groups R7 and R14 compared to the control group. Bone marrow transplantation improved MOT value of total protein in the glomeruli and proximal convoluted tubules with less stain affinity in distal convoluted tubules was detected in the fetal kidney tissue of group R7+BM and R14+BM.

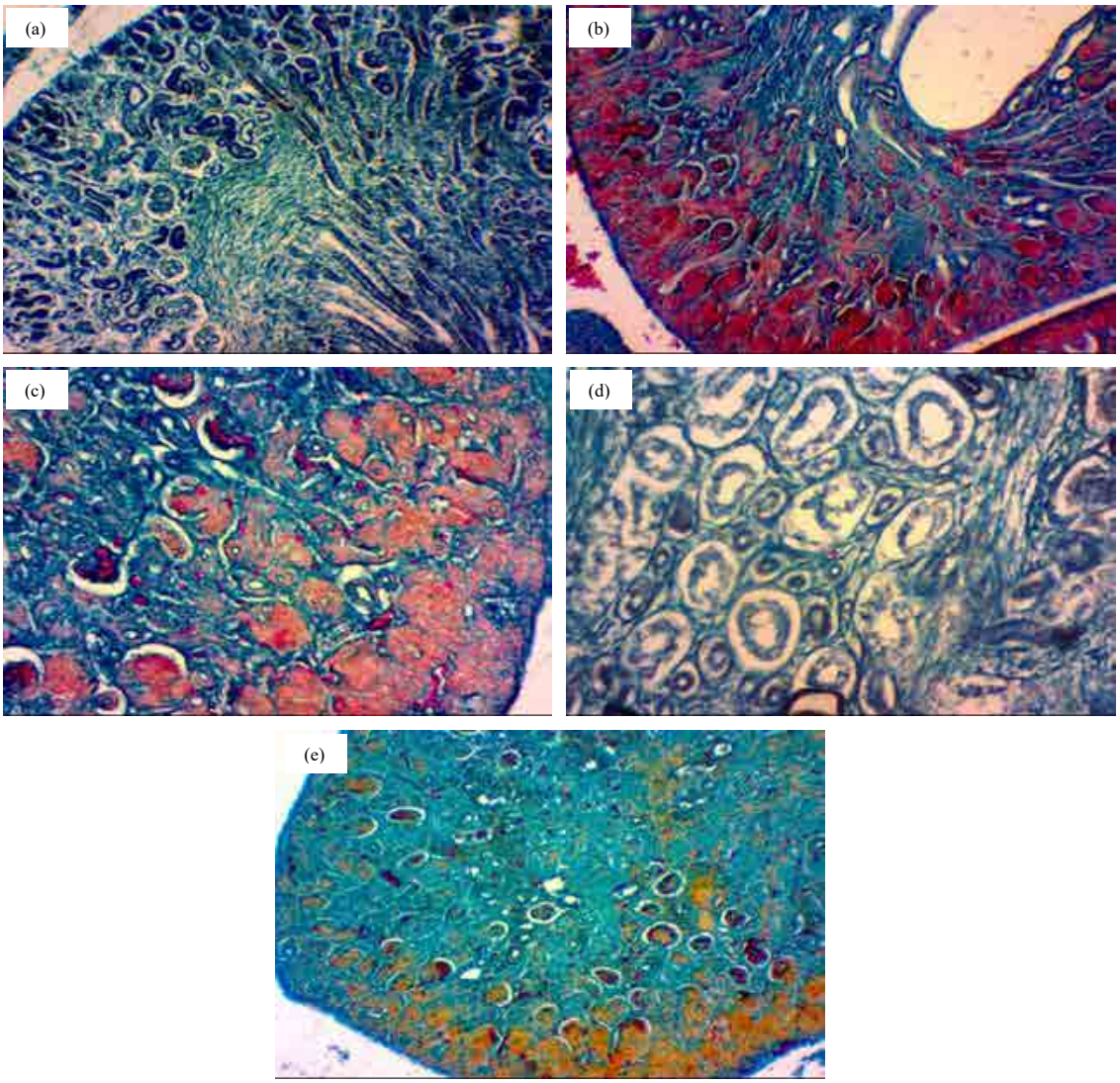

Fig. 4(a-e): Distribution of collagen fibers in the kidney tissue of fetuses of the control and treated pregnant rats stained with mallory s trichrome stain, (a) Control group: Normal distribution of collagen fibers in walls of the convoluted tubules, glomeruli and stroma of the kidney cortex (×50), (b) R7 group: Dense stain affinity of collagen fibers in the inner cortical part, but fibrotic and hemorrhagic areas in the outer part of the cortex acquire red coloration with absence of kidney medulla (×100), (c) R7+BM group: Deeply stained collagen fibers in the kidney cortex and signs of fibrosis are still detected (×100), (d) R14 group: Decreased collagen fibers in the convoluted tubules and most glomeruli (×100) and (e) R14+BM group: Somewhat normal appearance of collagen fibers, but signs of fibrosis were still detected (×50)

Table 2: MOT and the percentage of change values of PAS+ve materials and total protein in the fetal glomeruli and tubules

	MOT values of PAS+ve materials				MOT and percentage of change average values of total protein			
Groups	Glomeruli Mean±SE	Tubules change (%)	Glomeruli Mean±SE	Tubules change (%)	Glomeruli Mean±SE	Tubules change (%)	Glomeruli Mean±SE	Tubules change (%)
Control	126.26±4.41		60.51±5.86		143.03±4.57		125.82±6.88	
R7	99.28±3.00*	21.36	45.32±6.78*	25.10	121.21±6.14*	15.25	75.31±6.37*	40.14
R7+BM	124.64±6.24	1.28	58.87±5.03	2.71	138.34±4.15	3.27	119.65±5.68	4.90
R14	93.18±3.03*	23.82	43.56±6.03*	28.01	113.28±4.15*	20.76	80.92±7.60*	35.69
R14+BM	122.26±7.40	4.00	56.34±6.03	6.88	135.87±6.52	5.00	115.53±s	8.17

*Values are considered significantly different ($p<0.05$), SE: Standard error

DISCUSSION

Ionizing radiation caused many drastic alternations in the kidney tissue of pregnant rats and their fetuses. Gamma rays act either direct or indirect effect to produce biochemical injuries[23]. Low-dose of ionizing radiation may induce specific transcriptional responses in human keratinocytes[24].

Ionizing radiation induced late disruption of the genome in the progenies of living cells and that is called radiation induced genomic instability, is established by delayed induction of radiation effects, such as chromosomal deviations and mutation and cell loss[25]. It induces oxidative stress and generation of reactive oxygen species which lead to membrane destruction and that allow the entry of extra calcium into cells with sequential biochemical and micro functional cellular degranulation and necrosis[26].

Free radicals formed due to irradiation can cause a diversity of membrane changes such as lipid peroxidation, hydrolysis of phospholipids head groups, lipid-lipid crosslinks, disulfide bridge formation and amino acid rest hurt in membrane proteins and lipid protein crosslinks[27,28]. Radiation may be cancer-causing for a wide variety of tumors such as thyroid, breast and bone marrow cancers[29,30].

Gravidity should is a very important period which female go through several physical, hormonal and psychic alternations and that effect on embryos, this effect varies according to the ontogenetic stage and pregnancy stage and animal species[31-33]. In the present work kidney of the pregnant of groups R7 and R14 displayed many severe changes. These changes contain: Faintly stained and hypertrophied cells and nuclei of the convoluted tubules, some nuclei were deeply stained, ruptured brush borders of the proximal convoluted tubules, numerous haemolysed RBCs in the glomeruli, hemorrhagic areas, highly distorted malpighian capsules, large and small degenerated areas, atrophied glomeruli with debris of degenerated tubules. These results agree with those of Hussein[13], Augustine *et al.*[34]. Morphologic studies of radiation nephropathy have found signs of damage to blood vessels, glomeruli, tubular epithelium and interstitium[35]. These deviations may be due to degradation of tissue lipids as a result of lipid peroxidation[28]. Vacuoles formed in animal cells due to the breakdown of lipoprotein centers in the affected cells or may be destroy mitochondria, golgi apparatus and lysosomes[36].

In this study bone marrow treatment improved the kidney architecture. Signs of improvement in several tissues of gravid rats exposed to diverse doses of gamma rays then treated with bone marrow were noticed by many authors[37-39]. Bone marrow mesenchymal stem cells decrease radiation-made artery hurt by suppressing oxidative stress and inflammation[40].

Highly increased collagen fibers were noticed in the kidney tissue of the pregnant rats of groups R7 and R14. There is an indication that gamma rays injuries bone tissue via free radical attack on the collagen[41]. Increased collagen fibers post-irradiation in the various tissues were noticed by many authors[42-44].

A slight increase in collagen fibers was noticed in the kidney tissue of the pregnant rats after bone marrow transplantation. These outcomes agree with those of Abdel Naby[45] and Emam *et al.*[46]. Bone marrow-derived mesenchymal stem cells (BMSCs) have shown great promise for ischemic tissue repair[47].

Reduced polysaccharides in the atrophied glomeruli, distal and proximal convoluted tubules of kidney of mothers of groups R7 and R14. Glomeruli and brush borders of proximal convoluted tubules of the kidney cortex of irradiated pregnant rats showed increased stain affinity of PAS+ve materials reaction[48]. Also, decreased total protein in the glomeruli, Malpighian's corpuscles, walls of the convoluted tubules with negatively stained degenerated areas were noticed in the kidney cortex of mothers of R7 and R14, but treatment with bone marrow post-irradiation showed normal appearance of total protein content. Increase in stain affinity of total protein may be due to increased RBCs, increased collagen fibers or presence of fibrous tissue, but reduced stain affinity of total protein may be due to injured protein molecules by irradiation or reduced ability of tissue to produce proteins[49]. Histological examination showed a significant lessening of tissue damage with less inflammatory and apoptotic cells in bone marrow mesenchymal stromal cells treated animals compared to the control group[50].

Radiation exposure of mothers on day 7 or 14 of gestation caused many dystrophic changes in the fetal kidney. The fetal kidney tissue is more sensitive to γ-rays than the mothers. This sensitivity was conversed by many authors[51,52]. Highly affected glomeruli, distal and proximal convoluted tubules were more marked in embryos than their mothers[53].

Normal appearance of the fetal kidney tissue were noted in groups R7+BM and R14+BM. Bone marrow transplantation in irradiated pregnant rats has improved the developing fetus and it s placenta after radiation[38,46].

Results of the present study showed highly increased collagen fibers in fetal kidney. Decreased production of collagenolytic enzymes might contribute to additional accretion of collagen[54]. The progress observed in the fetal ileum tissue their mothers exposed to γ-rays and treated with bone marrow that may be due to the ability of bone marrow cells to differentiate to mature non-haematopoietic cells of multiple tissues[55,56].

In the present study, fetal kidney tissue of groups R7 and R14 indicated poorly stained polysaccharides. Highly reduced polysaccharides in fetal kidney cortex post-irradiation may be due to the degeneration and vacuolation detected in most cells of proximal and distal convoluted and renal Malpighian corpuscles or may be due to failure of Golgi apparatus to produce polysaccharides[48]. Normal distribution of polysaccharides were noted in groups of R7+BM and R14+BM. Bone marrow derived stem cells have cellular plasticity which provoked many detectives to use of these cells in the renewal of nonhematopoietic tissues[57].

The present study reduced stain affinity of total protein in the distal and proximal convoluted tubules and glomeruli was detected in the fetal kidney cortex of groups R7 and R14. Decreased protein in the fetal and maternal distal and proximal convoluted tubules and Malpighian corpuscles were also detected by Hanley and Knutson[58].

Normal distribution of total protein was observed in the glomeruli and proximal convoluted tubules with less stain affinity in the distal convoluted tubules of fetal kidney tissue of group R7+BM with normal distribution of total protein in the fetal kidney tissue of group R14+BM. Bone marrow transplantation is an effective strategy to decrease the harmful effects of total body irradiation in the colitis treatments[59]. Stem cells can be transplanted to replace non-functional stem cells in tissues to accelerate tissue therapeutic and return the original function[60]. The regenerative possibility of stem cells was studied by many authors[61-63]. This study included the rats during pregnancy, effect of irradiation on their fetuses and possible protective role of bone marrow transplantation to modify radiation injury during pregnancy. The study recommended that the pregnant mothers should avoid exposure to any type of radiation and numerous experiments should be hold to use of stem cells in radiation prevention and treatment of certain disease.

CONCLUSION

According to the present results gamma irradiation (2Gy) during day 7 and 14 of pregnancy caused many histopathological and histochemical changes in the kidney tissue of pregnant rats and their fetuses. Bone marrow transplantation post irradiation could decrease radiation injury in the kidney tissue of pregnant rats and their fetuses.

SIGNIFICANCE STATEMENT

Results from this present study indicated that bone marrow transplantation has the ability to decrease the injury of gamma rays. This study will help the researcher to uncover the critical role of bone marrow transplantation toward reducing the risk of radiation hazards during pregnancy.

ACKNOWLEDGMENT

Thank for Dr. Omaima Ashry in National Center for Radiation Research and Technology-Atomic Energy Authority, Egypt for the facilities to perform this experiment.

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