Original Article

Histopathological investigation of the cytotoxic impact of low and high doses of computed tomography ionizing radiation on the hepatorenal organs, testis, and brain tissues of albino rats

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Abstract

Background/Aim: Computed tomography (CT) radiation compared with the plain film radiography involves much higher doses of radiation, resulting in a marked increase in radiation exposure to the patient and radiological team. This study is aimed to investigate the possible cytotoxic impact of low and high doses of CT ionizing radiation on the hepatic, renal, testis, and brain tissues of albino rats following whole-body irradiation.

Materials and Methods: Thirty healthy male Wistar albino rats aged 9–10 weeks, weighing 180–200 g, were randomly assigned into five groups (A, B, C, D, and E) of six rats each. Rats in Groups A, B, C, and D underwent noncontrast helical total-body CT irradiation once a week for 2 weeks and received varying doses of CT radiation, while Group E rats were not irradiated and served as control. At 72 h after the last irradiation, five animals of each group were sacrificed, and liver, kidney, testis, and brain tissues were immediately and carefully dissected and fixed in 10% buffered formalin solution for 24 h followed by dehydration in ascending series of ethyl alcohol, clearing in xylene, and embedding in paraffin wax and then sectioned at 4 µthickness by sledge microtome. The sections were mounted on glass slides and stained with hematoxylin and eosin.

Results: The rats in Groups A and B received low dose-length product (DLP) of 74.74 mGy/cm and 352.38 mGy/cm, respectively. Groups C and D rats received high DLP of 628.6 mGy/cm and 1388.42 mGy/cm, respectively. Group E rats were not irradiated and received 0 mGy/cm (control). Histological findings showed that the rats in Groups C and D had evidence of radiation-induced microscopic lesions on the studied organs with the exception of kidney, whereas the rats in Groups A and B that received low DLP did not induce any structural changes in the photomicrographs of the studied organs.

Conclusion: Cell-level microscopic lesions in the body organs of the irradiated rats were observed only in the groups that received the highest DLP of the CT radiation (Groups C and D). From the cellular structural

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changes observed in the liver, testis, and brain of the irradiated rats, it is concluded that CT radiation at a DLP of 628.6 mGy/cm per exposure and 1388.46 mGy/cm per exposure becomes inimical to the vital organs. These findings emphasize the need to adhere strictly to as low as reasonably achievable principle in the dispensing of CT radiation in both human and animal radiological procedures.

Keywords: Brain, computed tomography, histology, kidney, liver, radiation dose, testis

INTRODUCTION

Computed tomography (CT) is a valuable imaging tool that can be performed on every region of the body for a variety of reasons ranging from diagnostic, treatment planning, interventional, or screening.[1] CT scan is a special X-ray that scans an area one layer (slice) at a time. X-rays are an integral component for image formation with CT, and there is an obligatory radiation exposure during CT examination.[2] X-rays and gamma rays are defined as ionizing radiation because they have sufficient energy to displace electrons from molecules. Free electrons, in turn, can damage the cellular component of the body. X-rays carry enough energy that they can knock out electrons from molecules, such as water, protein, and DNA, with which they interact.[3] If CT is compared with plain film radiography, CT involves much higher doses of radiation, resulting in a marked increase in radiation exposure to the patient and radiological team.[4] Humans and animals are constantly exposed to varying radiation and almost all of this exposure is due to medical radiation, largely from diagnostic and therapeutic procedures such as plain radiography, CT, radiotherapy, and fluoroscopy scan.[2] Ionizing radiation has been demonstrated to increase the risk of cancer in individuals exposed to high doses.[1] Ionizing radiation has been increasingly applied in medicine and it is now firmly established as an essential tool for diagnosis and therapy. Despite the medical benefits, high-dose ionizing radiation has been proven to have adverse biological effects to different body organs.[2] This adverse effect results from the direct ionization of cellular structures, especially DNA, or from the indirect effect through free radicals produced by radiolysis of water.[5]

High-dose ionizing radiation has been shown to affect several organs within the body.[6,7] Rodent studies have revealed that whole-body irradiation at a dose level of 7 Gy induced brain injury through the impairment of brain mitochondrial function and cranial irradiation with a single dose of 20 Gy induced oxidative stress in both brain tissue and blood.[8,9] Recently, it was observed that head irradiation at a dose level of 10 Gy induced DNA damage associated with a significant increase of the apoptotic and inflammatory markers (caspase-3, tumor necrosis factor-α, interleukin 1 β, and NF-κB) and a significant decrease in neurotransmitter concentrations of brain tissue.[5] Radiation-induced reactive oxygen and nitrogen species have been implicated as the key mediators of renal injury and nephrotoxicity in high-dose ionizing radiation.[10] Ionizing radiation is one of the environmental pollutants that may contribute to liver dysfunction due to its oxidative stress. High doses of gamma irradiation of animals have been shown to induce severe histopathological alterations in liver cells.[11] Although there is no doubt about the harmful effects of high doses of ionizing radiation, the biological effects of low doses of radiation are often controversial. It has been assumed that the response to low doses of ionizing radiation may be loci specific and has both beneficial and detrimental consequences.[12,13] The present study, therefore, was aimed to investigate the cytotoxic impact of low and high doses of CT ionizing radiation on the hepatorenal organs, testis, and brain tissues of albino rats.

MATERIALS AND METHODS

Experimental animal

Thirty healthy male Wistar albino rats aged 9–10 weeks, weighing 180–200 g, and obtained from the Department of Veterinary Medicine, University of Nigeria, Nsukka, were used. Throughout the study, the rats were kept in a room with a constant temperature of 24°C ± 3°C under conventional laboratory circumstances, which included 12 h of light and 12 h of darkness. Water and a normal pellet meal were given to the rats on an as-needed basis. After 1 week of acclimatization, the rats were randomly assigned into five groups (A, B, C, D, and E) of six rats each. All the study's protocols and the animal care and handling were in accordance with the guidelines set by the University of Nigeria, Nsukka Faculty of Veterinary Medicine Institutional Animal Care and Use Committee (IACUC, FVM UNN) with approval number FVM-UNN-IACUC-2023-06/105.

Radiation facility

Irradiation was carried out at Champion Diagnostics Clinic, Enugu, Nigeria, using a GE 16-Slice (General Electric) Revolution ACTs CT scanner (GE Hangwei Medical Systems Co. Ltd., China) with adaptive

statistical iterative reconstruction features that allowed manual entry of diagnostic exposure parameters to achieve the desired radiation dose.

Methods

Radiation protocols

There were four irradiated groups (A, B, C, and D) and one unirradiated control group (Group E) of six rats each. The six rats per group were immobilized with a customized fixator in supine position with head first. Centering of the laser beam was done at the midsagittal plane and midneck before axial beam total-body irradiation was acquired from the tip of the nose to the tail. Two (2) scout images, anterior-posterior (AP), and lateral for each of the irradiated groups were first acquired with the same kV (80) and mAs (20) s to prevent X-ray beam wastage and to ensure centering accuracy. Tube current (mAs) and tube potential (kv) were manually selected. Radiation dose for each group was automatically estimated by scanner software and displayed in the CT scanner screen as volume weighted CT dose index and dose-length product (DLP)values, which are standardized measures of radiation dose during CT examination.[14] A noncontrast helical scan was carried out for each of the irradiated groups once a week for 2 weeks. The rats in Group A were irradiated with exposure factors of 80 kV and 100 mAs. The rats in Group B were irradiated with exposure factors of 100 kV and 140 mAs. Group C rats were irradiated with exposure factors of 120 kV and 150 mAs, while Group D rats were irradiated with exposure factors of 140 kV and 160 mAs. Group E rats were not irradiated and served as control.

Histopathological studies

Five rats of each group were sacrificed a day after the last irradiation. The liver, kidney, testis, and brain tissues were immediately and carefully dissected and fixed in 10% buffered formalin solution for 24 h followed by dehydration in ascending series of ethyl alcohol, clearing in xylene, and embedding in paraffin wax and then sectioned at 4 μ thickness by sledge microtome. The sections were mounted on glass slides and stained with hematoxylin and eosin according to the method described by Bancroft and Stevens.[15] The stained sections were examined by oil immersion light microscopy, and several digital images were taken using a Kodak digital camera.

RESULTS

Radiation dose

Group A rats received 74.74 mGy/cm per CT exposure, with total accumulated DLP of 149.48 mGy/cm. The rats in Group B received 352.38 mGy/cm per CT exposure, with total accumulated DLP of 704.76 mGy/cm. Group C rats received 628.6 mGy/cm per CT exposure, with total accumulated DLP of 1257.2 mGy/cm. The rats in Group D received 1388.42 mGy/cm per CT exposure, with total accumulated DLP of 2776.84 mGy/cm. Group E rats received 0.0 mGy/cm and served as control.

Microscopic findings

The liver sections of rats in the control Group E and irradiated Groups A and B that received the lowest CT DLP of 74.74 mGy/cm and 352.38 mGy/cm per exposure, respectively, showed apparently normal hepatocyte radiating away from the central vein (CV) [Figure 1a, b, and e]. However, the liver section of the rats in the irradiated Groups C and D that received highest DLP of 628.6 mGy/cm and 1388.46 mGy/cm per exposure, respectively, showed hepatocyte swelling and vacuolar degenerations [Figure 1c and d].

Microscopic examination of the kidney sections of rats in the irradiated Groups A, B, C, and D showed apparently

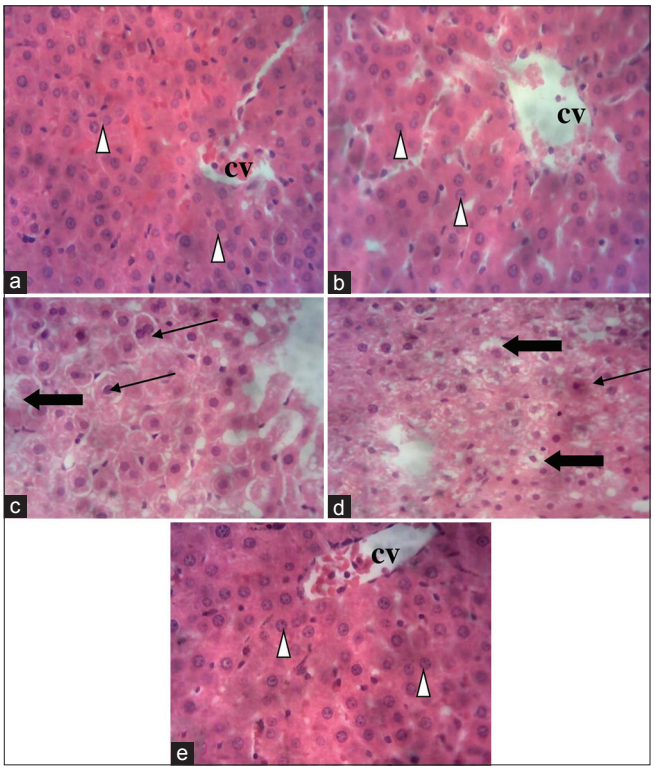

Figure 1: Photomicrograph of the liver sections from the experimental groups: (a) liver of rats exposed to computed tomography (CT) dose-length product (DLP) of 74.74 mGy/cm per exposure, (b) liver of rats exposed to CT DLP of 352.38 mGy/cm per exposure, and (e) liver of un-irradiated control rats showing apparently normal hepatocytes (arrowheads) radiating away from the central vein, while the liver of rats exposed to CT DLP of 628.6 mGy/cm per exposure (c) and CT DLP of 1388.46 mGy/cm per exposure (d) shows hepatocyte swelling (thin arrow) and vacuolar degenerations (thick arrows) (H and E, ×400)

normal renal tubular epithelium and glomerulus with no histological variation compared to the unirradiated control Group E [Figure 2a-e].

The testicular sections of the rats in Groups A and B irradiated with the lowest CT DLP and the unirradiated control Group E rats showed apparently normal germinal epithelium of the seminiferous tubules [Figure 3a, b, and e]. However, the testicular sections of the rats in Groups C and D with the highest CT DLP of 628.6 mGy/cm and 1388.46 mGy/cm per exposure, respectively, demonstrated evidence of eosinophilic granular degeneration of spermatocytes [Figure 3c and d].

The brain sections of the rats in Groups A and B with the lowest CT radiation DLP and the unirradiated control Group E rats showed apparently normal histological features [Figure 4a, b, and e]. Notably, the brain sections of rats in Groups C and D with the highest CT DLP of 628.6 mGy/cm and 1388.46 mGy/cm per CT exposure, respectively, had evidence of neuronal vacuolation with perivascular edema [Figure 4c and d].

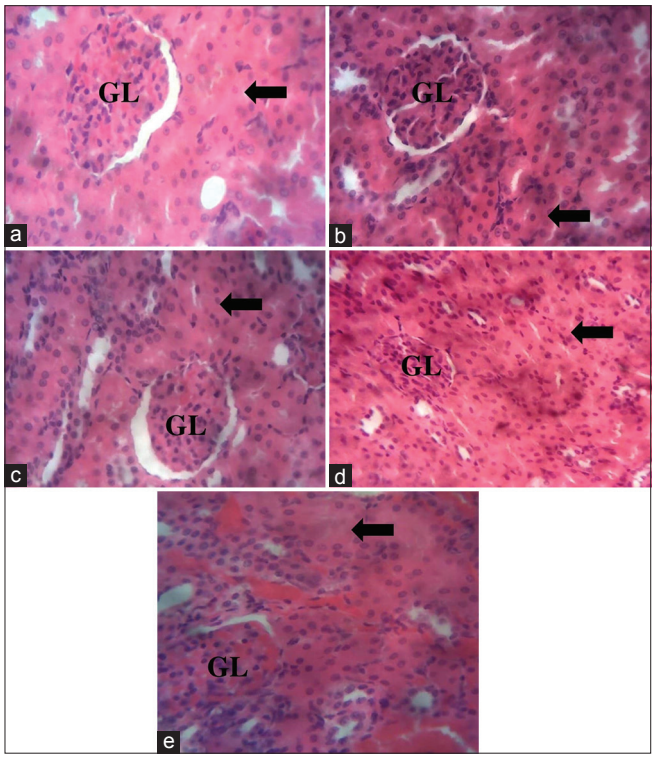

Figure 2: Photomicrograph of the kidney sections from the experimental groups. (a) kidney of rats exposed to computed tomography (CT) dose-length product (DLP) of 74.74 mGy/cm per exposure, (b) kidney of rats exposed to CT DLP of 352.38 mGy/cm per exposure, (c) kidney of rats exposed to CT DLP of 628.6 mGy/cm per exposure, (d) kidney of rats exposed to CT DLP of 1388.46 mGy/cm per exposure, and (e) kidney of nonirradiated control rats showing apparently normal renal tubular epithelium (arrows) and glomerulus (H and E, ×400)

DISCUSSION

In radiation damage, radiation dose, fractionation, and volume play an important role. Radiation dose is one of the most important factors determining the severity of damage and the latent period between irradiation and the occurrence of lesions.[16] The basic mechanism of ionizing radiation-induced organ damage occurs in two ways, either by causing cell death or by the mechanism of indirect action.[17] The actual injury is caused by the indirect mechanism. Ionized radiation generates reactive oxygen species (ROSs) that are created by the ionization of water in the environment.[18] The resulting ROS leads to the oxidation of macromolecules such as proteins,DNA, and lipids and mediates the damaging effect of ionizing radiation in biological systems. As a result, lipid peroxidation and protein oxidation products increase.[19-21]Despite the medical benefits of radiation, high-dose ionizing radiation has been proven to have adverse biological effects to different body organs.[2,6,7] The current research is aimed at evaluating the cytotoxic impact of

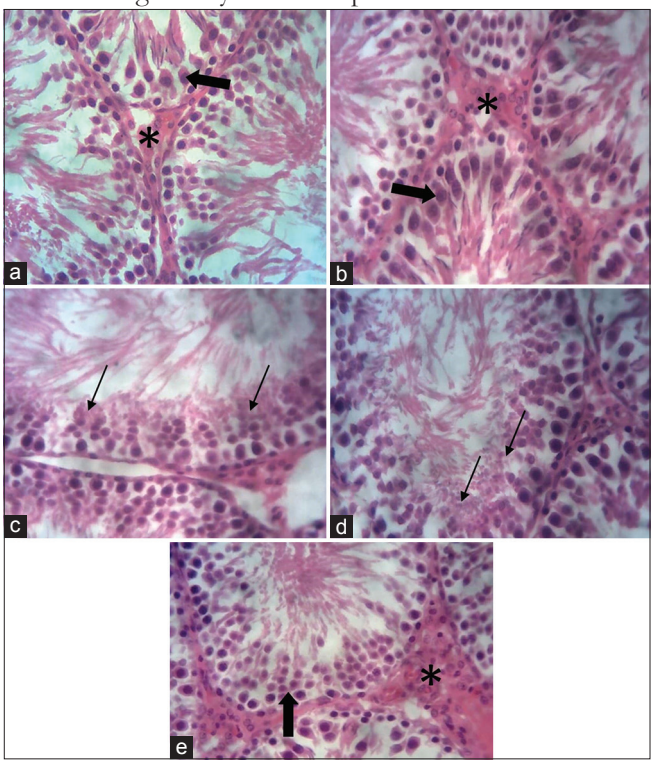

Figure 3: Photomicrograph of the testis from the experimental rat groups. (a) testis of rats exposed to computed tomography (CT) dose-length product (DLP) of 74.74 mGy/cm per exposure, (b) testis of rats exposed to CT DLP of 352.38 mGy/cm per exposure, and (e) testis of un-irradiated control rats showing apparently normal germinal epithelium of the seminiferous tubules (arrows) and interstitium (asteriks), while the testes of rats exposed to CT DLP of 628.6 mGy/cm per exposure (c) and CT DLP of 1388.46 mGy/cm per exposure (d) show eosinophilic granular degeneration of spermatocytes (thin arrow) (H and E, ×400)

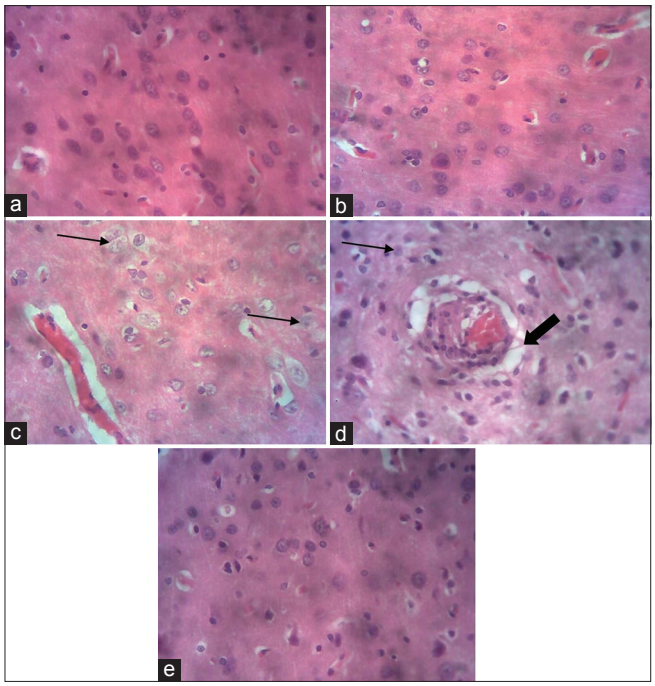

Figure 4: Photomicrograph of the brain section from the experimental rat groups. (a) brain section of rats exposed to computed tomography (CT) dose-length product (DLP) of 74.74 mGy/cm per exposure, (b) brain section of rats exposed to CT DLP of 352.38 mGy/cm per exposure and (e) brain section of un-irradiated control rats showing apparently normal histological features, while the brain sections of rats exposed to CT DLP of 628.6 mGy/cm per exposure (c) and CT DLP of 1388.46 mGy/cm per exposure (d) show neuronal vacuolation (thin arrows) with perivascular edema in D (thick arrow) (H and E, ×400)

varying doses of CT ionizing radiation on the hepatorenal organs, testis, and brain tissues of albino rats exposed to total-body irradiation weekly for 2 weeks.

Several studies have indicated that the kidneys are radiation-sensitive organs.[22] Microscopic study of rat kidneys exposed to chronic electromagnetic radiation have shown evidence of tubular damage with hyaline deposition, glomerular damage, dilatation of Bowman's capsule, formation of large spaces between tubules, perivascular edema, and inflammatory cellular infiltrate.[23] In contrast, the present whole-body CT radiation exposure in healthy adult male albino rats did not show any histological variation in the kidney photomicrograph compared to the unirradiated control group irrespective of the dose.

In the present study, rats irradiated with the highest CT DLP of 628.6 mGy/cm and 1388.46 mGy/cm showed histopathological changes characterized by hepatocyte swelling and vacuolar degenerations 24 h after the last irradiation. Similarly, Soliman[24] observed hepatic cells necrosis, dilatation, and congestion of the CV and sinusoids with blood petechiae in rats exposed to ionizing radiation. The observed cytotoxic impact of CT ionizing radiation on the liver in the current research is related to the findings of Abdelhafez and Kandeal,[25] who reported corrugated and ruptured endothelial lining of the CV which contained hemolyzed blood cells, numerous vacuolated hepatocytes with increased signs of pyknosis and karyolysis in nuclei of hepatocytes; highly dilated and congested hepatic portal vein, numerous hemorrhagic areas and destroyed bile ducts in the liver tissues of rats exposed to whole-body gamma irradiation. The postirradiation microscopic changes observed in the current study are supported by the study of Abdel-Mottaal and Nakajima *et al*.[26,27] who documented postirradiation severe liver injuries with lymphocytic infiltration between the degenerated hepatocytes. Similarly,Gokcimen *et al*.[28] observed changes in liver tissue such as sinusoidal dilatation, mixed cell infiltrations in the periportal area, necrosis, vacuolar degeneration, congested CVs, and stagnant hypoxia in rats exposed to magnetic field. The findings of the current study are also related with the results of Waer and Shalaby,[29] who observed hepatocellular damage in male rats exposed to an accumulated dose of 0.5 Gy of γ-radiation every 2 days for 1 month. The study by Abdel-Rahman[30] reported similar distortion in the architecture of hepatic lobules, degeneration of liver cells, and lymphocytic infiltration of rats exposed to whole-body gamma-radiation at the dose level of 7 Gy. In rats' pups that were exposed to daily 900 MHz for 1 h during days 13–21 of pregnancy, marked hydropic degeneration in the liver parenchyma, particularly in pericentral regions, vacuolization in the mitochondria, expansion in the endoplasmic reticulum, and necrotic hepatocytes were observed.[31] The observed radiation-induced liver injury in the current study is also closely related to the findings by Sohrabi *et al*.,[32] who reported radiation-induced hepatic injury characterized with vacuolated cytoplasm, liver necrosis, fibrosis, and vascular lesions in rats exposed to different intensities of 2 Gy and 8 Gy gamma irradiation.

Furthermore, the testicular sections of rats in groups with the highest CT radiation DLP of 628.6 mGy/cm and 1388.46 mGy/cm demonstrated evidence of eosinophilic granular degeneration of spermatocytes. Similarly, Amer *et al*.[33] reported mild degenerative changes in the seminiferous tubule with a spermatogenic cell reduction after 3 days postirradiation, whereas at postirradiation day 14, severe seminiferous tubule necrosis with shrinkage, disorganized, less compact tubule wall, vacuolation of the seminiferous epithelium, absence of spermatogenic cells, and poorly developed Leydig cells were observed in the testicular tissues of rats exposed to 4 Gy gamma irradiation. In a similar microscopic study by Kamal El-Dein and Anees,[34] widening of the interstitial spaces between seminiferous tubules with ruptured connective

tissue and epithelia layer of the basement membrane of the seminiferous tubules were observed in rats exposed to fractionated whole-body γ-radiation. The primary aspect in male sterility is oxidative stress, as spermatogenic lineage cells are predominantly susceptible to radiation-induced reactive oxygen species (ROS) since they are constantly beneath meiosis or mitosis.[35] Recent study reported that ionizing radiation disrupted circadian rhythms of reproductive markers, including decreased sperm motility and disrupted clock gene expression in the testis.[36] Radiation exposure might cause infertility by lowering sperm count and testosterone levels by destroying Leydig and spermatogonial stem cells.[37] A previous study showed that ionizing radiation disrupts redox balance, induces oxidative DNA injury, activates P53, and stimulates inflammation and apoptosis.[38] Radiation with single doses of >1 Gy might initiate inflammatory reactions associated with oxidative stress and reduced antioxidant capacity of the testes.[39] Inflammatory signaling associated with ionizing radiation might induce testicular damage.[40]

Notably, microscopic brain lesions were observed in the brain sections of rats irradiated with the highest CT radiation DLP of 628.6 mGy/cm and 1388.46 mGy/cm. Evidence of neuronal vacuolation with perivascular edema in the irradiated rats were observed in the current study. Similarly, Kale *et al*.[17] observed hypertrophy, numerical increase, and mild clustering of nuclear chromatin in the astrocytes, vascular dilatation, congestion, and edema in rats exposed to a single 20 Gy gamma cranium irradiation. Yang *et al*.[16] reported that radiation-induced brain injuries include glial atrophy, demyelination, necrosis, varying degrees of vascular changes, and other histopathological alterations. The observed microscopic lesions in the brain in the current study could be linked to the fact that brain is a radiosensitive organ and highly susceptible to oxidative stress due to its high oxygen consumption and lipid-rich content and the relative inadequate of antioxidants.[41] Ionizing radiation leads to formation of free radicals. Excessive production of reactive oxygen and nitrogen species (free radicals) due to radiation often overwhelms the endogenous antioxidant defense mechanisms and might be insufficient to fully scavenge postirradiated free radicals. The imbalance between the endogenous antioxidant defense system and free radical production leads to state of oxidative stress in the irradiated rats. It is well established that ionizing radiation at high dose induces structural and functional damage in the brain.[42]

CONCLUSION

Radiation dose is of utmost importance when considering the risk of radiation-induced injury to the body systems. The current study is aimed at investigating the cytotoxic impact of varying doses of CT radiation on the histological features of selected organs of albino rats. Cell-level microscopic lesions in the body organs of the irradiated rats were observed only in the groups that received the highest DLP of the CT radiation. From the cellular structural changes observed in the liver, testis, and brain of the irradiated rats, it is concluded that CT radiation at a DLP of 628.6 mGy/cm and 1388.46 mGy/cm becomes inimical to the vital organs. These findings could suggest that there could be serious microscopic structural changes that go unnoticed during diagnostic and therapeutic CT irradiation in both animals and humans and emphasize the need to adhere strictly to as low as reasonably achievable principle in the dispensing of CT radiation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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