Effects of different doses of computed tomography radiation on the oxidation markers, antioxidant enzymes, and lipid profiles of male albino rats

K.C. Ogbanya¹, E.K. Mgbe^{2*}, E.O. Modebe², I.G. Abah³, T.O. Nnaji¹

¹Department of Veterinary Surgery and Radiology, University of Nigeria, Nsukka, Nigeria ²Department of Radiation Medicine, University of Nigeria, Teaching Hospital, Enugu, Nigeria ³Department of Radiology, University of Uyo, Akwa Ibom, Nigeria

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*Corresponding author: Emeka Kevin Mgbe,

E-mail:

emeka.mgbe@unn.edu.ng

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ABSTRACT

Background: The study investigates the effects of four different doses of computed tomography (CT) x-ray radiation on the oxidation markers, endogenous antioxidant enzymes, and lipid profiles of male Wistar albino rats. Materials and methods: Thirty healthy male Wistar albino rats weighing 180-200g were assigned into five groups of 6 rats each. Rats in groups A, B, C, and D underwent non-contrast helical total body irradiation and received varying doses of CT radiation, while group E received sham irradiation and served as a control. Glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT) activities, serum levels of malondialdehyde (MDA), oxidized glutathione (GSSG), nitric oxide (NO), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were investigated using standard methods. Results: At 72 hours' post-irradiation, the mean serum activities of GPx, SOD, and CAT in the irradiated groups decreased significantly, while the serum levels of MDA, GSSG, TC, and LDL increased significantly compared to the control. Conclusion: The four different doses of CT radiation in the current study caused a significant decline in the endogenous antioxidant enzymes (GPx, SOD, and CAT) and, in contrast, induced a significant serum elevation of MDA and GSSG in the irradiated rats. The LDC and TC mean serum levels were also significantly elevated in the irradiated groups.

INTRODUCTION

The introduction of computed tomography (CT) in revolutionized 1970s has diagnostic decision-making in clinical practice (1,2). Better surgery, cancer detection and treatment, stroke recovery, and heart problem recovery have all been made possible by the use of CT (3,4). Compared to other imaging modalities, CT has significant advantages since it is widely available and can be completed in a matter of minutes. This helps medical professionals to more confidently and quickly confirm or rule out a diagnosis (5). Surgery has greatly benefited from CT, which has reduced the requirement for emergency surgery from 13% to 5% and all but eliminated numerous exploratory surgical procedures (5). It is not surprising, given these benefits, that its use has skyrocketed since its debut (6). However, the use of CT and its rapid increase in clinical utilization have brought with them significant public health concerns with regards to the harmful effects of its ionizing radiation in the body (7).

Ionizing radiation, such as x-rays, used in CT, creates electrically charged particles or ions when it interacts with matter (8). Living tissues are affected by ionizing radiation both directly and indirectly.

Ionizing radiation directly affects target molecules like enzymes and deoxyribonucleic acid (DNA) by transferring energy to them. Releasing free radicals into the environment by hydrolyzing the water in the cells, and causing these radical to react with other molecules within the cells are some of the indirect impacts of ionizing radiation. Thus, indirect effects account for 70% of the biological impacts of ionizing radiation (8). The body's beginning of free radical reaction is influenced by ionizing radiation from radiological exams. Ionizing radiation affects water molecules after it has passed through the cell membrane, which results in the creation oxygen free radicals (9). After radiolysis, the water molecule produces a hydrated electron (e-aq) and cation radical H₂O⁺⁺, which quickly breaks down into a hydroxyl radical OH. The destructive action of ionizing radiation is predominantly due to reactive oxygen species (ROS), including superoxide radicals (O₂-), hydroxyl radicals (OH2), and hydrogen peroxide (H₂O₂) which are generated by the decomposition of water (10). Correct ROS formation and presence inside cells are necessary for protein phosphorylation, transcription factor activation, apoptosis, immunity, and differentiation; these processes must be controlled at a low level (11).

Reactive oxygen species (ROS) starts to negatively impact vital cellular constituents like proteins, lipids, and nucleic acids when their synthesis increases. An increasing body of research indicates that oxidative stress may play a part in the onset and / or development of numerous illnesses such as cancer, diabetes, metabolic disorders, cataracts, macular degeneration, arteriosclerosis, atherosclerosis, and cardiovascular diseases (12). Oxidative stress occurs if the rates of reactive oxygen species production exceeds the rates of cellular clearance (13).

Cells rely on the development of the antioxidant defense system, which includes both enzymatic and non-enzymatic antioxidant defense mechanisms, due to the significant harmful potential of ROS (14). The important endogenous antioxidant enzymes involved in the cellular antioxidative defense systems are superoxide dismutase (SOD), catalase glutathione reductase, and glutathione peroxidase (GPx), and these are utilized in assessing the progression and the degree of oxidative stress injury (15). The SOD enzyme catalyzes the dismutation of O_2 into H₂O₂. H₂O₂, which can be transformed into H₂O and O2 by CAT and GPx enzymes. In addition, nitric oxide has the ability to regulate multiple physiological processes in a highly diffusible manner. This is implicated in the cellular response to ionizing radiation, as multiple experiments have demonstrated $(16)_{.}$ Malondialdehyde production, a byproduct of lipid peroxidation is one of the indicators of oxidative damage (17,18). The capacity for biological membranes to regulate cellular contacts and signals, in addition to subsequent to the metabolic processes, hinges upon on their chemical and biological integrity (19). Consequently, red cell membrane damage caused by radiation-induced protein and lipid membrane oxidation may be responsible for increasing in permeability to monovalent and divalent ions (20,21). Lipids are an integral part of biological membranes and are involved in many aspects of biological systems. For example, lipid bilayer structures allow cells to function relatively independently of their external environment, provide a hydrophobic medium in which membrane proteins can interact, and facilitate the enzymatic reactions that result in the production of second messengers (22). Reactive oxygen species are known to induce lipid peroxidation, one of the primary mechanisms of membrane degradation (23). Despite the harmful effects of ionizing radiation to the body, CT scans are routinely performed in most hospitals and diagnostic centers. Owing to the paucity of literature on the effect of CT x-ray ionizing radiation on the antioxidant system of the body, this became an important subject of our interest, and informed the decision to undertake research to determine the effects of different doses of CT radiation on the body lipids and antioxidant biomarkers in Wistar male albino rats that

underwent non-contrast helical total-body (TBI) CT irradiation.

This research work has a novel finding of establishing cell-level biochemical changes and injuries that go unnoticed during diagnostic and therapeutic radiation in animals and humans. This work will emphasize the need to adhere strictly to as low as reasonably achievable (ALARA) principle in the dispensing of radiation as well as serve as strong advocacy for the development of radiation protection.

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 ± 3°C under conventional laboratory circumstances, which included 12 hours of light and 12 hours of darkness. Water and a normal pellet meal were given to the rats on an as-needed basis. After one week of acclimatization, the rats were randomly assigned into five groups (groups A, B, C, D and E) of six rats each. The University of Nigeria, Nsukka, Faculty of Veterinary Medicine Institutional Animal Care and Use Committee (IACUC, FVM UNN) approved the study with approval number FVM-UNN-IACUC-2023-06/105, and all study protocols and animal care and handling followed its recommendations.

Irradiation

Irradiation was carried out at Champion Diagnostics Clinic, 74 Nike Road, Abakpa, 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 (ASiR) features that allow manual entry of diagnostic exposure parameters to achieve the desired radiation dose.

Radiation protocols

There were four irradiated groups (A, B, C and D) and one sham-irradiated control group (group E) of six rats each. Six (6) rats in each group of groups A, B, C, and D were immobilized with a customized fixator and a round plastic basket and were correctly positioned and centered within the gantry of the GE Revolution CT scanner. Two (2) scout images, anterior-posterior (AP) and lateral, for each group of the irradiated groups were first acquired with the same 20 kilovolts (20 kv) and 80 milliampereseconds (80 mAs) so as to prevent x-ray wastage and ensure the centering accuracy of the irradiated rats. mAs and kv were manually selected, and different values were manually entered for each group and radiation dose for each group was automatically

estimated by scanner software and displayed on the CT scanner screen as volume-weighted computed tomography dose index (CTDIvol) and dose-length product (DLP) values, which are standardized measures of radiation dose during CT examination (9). A non-contrast helical scan was carried out for each group once a week for two weeks. Rats in group A were irradiated with 80 kV and 100 mAs and received a total radiation dose of 2.76 mGy CTDIvol and 74.74 mGy/cm DLP. Rats in group B were irradiated with 100 kV and 140 mAs and received total radiation dose of 8.36 mGy CTDIvol and 352.38 mGy/cm DLP. Group C rats were irradiated with 120 kV and 150 mAs and received total radiation dose of 14.92 mGy CTDIvol and 628.6 mGy/cm DLP, while group D rats were irradiated with 140 kV and 160 mAs and received total radiation dose of 78.74 mGy CTDIvol and 1388.42mGy/cm DLP. Group E rats received sham-irradiation and served as control.

Blood/serum collection

After the last irradiation, blood was taken from the orbital plexus 72 hours later. The serum was then separated and kept at 80° C until it was analysed concurrently. Centrifugation was performed at 3000 revolutions per minute (rpm) for 5 minutes at 4° C.

Determination of oxidation markers and antioxidant enzymes activities

Oxidation markers and antioxidant enzyme activities in the serum were determined using reagent kits purchased from Randox Laboratories Ltd (UK) and Jenway Spectrophotometer (Germany). Superoxide dismutase (SOD) activity was determined using the manufacturer's (Randox instruction. The production of superoxide radicals by xanthine and xanthine oxidase, which react with 2-(4iodophenyl)-3-(4-nitrophenol) 5-phenyltetrazolium chloride to generate a red formazon dye, was used to measure SOD activity (24). The determination of the serum activities of glutathione peroxidase (GPx) was carried out based on the fact that GPX catalyzed the oxidation of glutathione by cumene hydroperoxide (24). While containing glutathione reductase and nicotinamide adenine dinucleotide phosphate (NADPH), the oxidized glutathione was immediately converted to the reduced form with the concomitant oxidation of NADPH to NADP+. GPX activities were determined according to the manufacturer's (Randox kit, UK) instruction and expressed as U/mL. Catalase the serum was determined activity in spectrophotometrically by the method of Koroliuk et al. (25). The catalase activities in the serum were determined as contained in the Randox Kit (UK) and were expressed as U/mL.

Serum levels of malondialdehyde were determined by utilizing the thiobarbituric acid reaction method as described by Placer *et al.* (26). The quantification of the thiobarbituric acid-reactive

substances was evaluated at 532nm by comparing the absorption to the standard curve of MDA equivalents generated by acid-catalyzed hydrolysis of 1,1,3,3-tetramethoxypropane. The MDA level in the serum was measured based on the manufacturer's instructions and expressed as μ mol/L. Oxidized glutathione (GSSG) was assayed by an enzymatic recycling procedure as described by Griffith, and Beutler and Kuhl (27,28). In order to determine the GSSG, the yellow colour created by the erythrocytes' interaction with DTNB (50,5 0 (2- Dithiobis nitrobenzoic acid) at 412 nm in the spectrum was measurewd. In μ mol/L, the values were computed.

Determination of nitric oxide (NO)

The Jenway Spectrophotometer (Germany) and Nitric Oxide Assay Kit (Creative Biolabs, US) were used to measure nitric oxide (NO) in accordance with the manufacturer's instructions. The absorbance was measured at 540 nm (29).

Determination of lipid profiles

The serum was tested for triglycerides, highdensity lipoprotein, low-density lipoprotein, and total cholesterol using the methods of Allan and Roxon, Demacer et al., Friedewald et al., and Fossati and Prencipe, respectively (30-33). The serum total cholesterol (TC) level was determined using the RayBiotech Total Cholesterol Colorimetric Assay Kit Jenway Spectrophotometer Determination of serum total triglycerides (TG) level was carried out using a commercial kit developed by Cromatest Cholesterol MR (Linear Chemicals S.L., Barcelona, Spain) and Jenway Spectrophotometer (Germany). Serum levels of LDL and HDL were determined using Cholestest LDL and Cholestest NHDL (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan).

Statistical analysis

The data is presented as the mean ± standard error of the mean. Statistical Package for Social Sciences (SPSS) was used in carrying out statistical analysis of the obtained data. Using one-way analysis of variance (one-way ANOVA), significant differences between groups were assessed. Least-significant difference (LSD) was employed for comparisons across groups. A significance level of P < 0.05 was applied.

RESULTS

A sample CT image of rats used in assessing the results of varying dosages of computed tomography radiation on the oxidation markers, antioxidant enzymes and lipid profiles of male albino rats is shown in figure 1. The mean serum levels of endogenous antioxidant activities of GPx, SOD, and CAT are presented in table 1. The mean serum levels

of oxidation markers MDA, GSSG, and NO are presented in table 2, while the mean serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides (TG) are presented in table 3. As expected, the mean serum levels of GPx, SOD, and CAT in the irradiated groups A, B, C, and D declined significantly at 72 hours post-irradiation compared to the sham-irradiated control, group E. The observed decrease in the antioxidant enzyme activities showed dependent effects, as the lowest activities of the antioxidant enzymes were recorded in group D rats that received the highest dose of radiation (table 1).

The average serum MDA and GSSG within the irradiated groups increased significantly (P < 0.05) in a dose-dependent manner at 72 hours' post-irradiation when compared with the sham-irradiated control group (table 2). The highest serum levels of MDA and GSSG were observed in group D rats that received the highest radiation dose. However, the mean serum levels of NO in the irradiated groups did not differ significantly (P > 0.05) from the sham-irradiated control group (table 2).

Serum TC levels in the irradiated groups A, B, C, and D increased significantly (P < 0.05) at post-irradiation day 7 compared to the sham-irradiated control group E. Similarly, the mean serum levels of LDL in the irradiated groups C and D increased significantly (P < 0.05) when compared with the sham-irradiated control. However, the mean serum levels of HDL and triglycerides in the irradiated groups showed no significant variation (P > 0.05) as seen from the sham-irradiated control (table 3).



Figure 1. A sample CT image of rats used in assessing the results of varying dosages of CT radiation on the oxidation markers, antioxidant enzymes and lipid profiles in male albino rats.

Table 1. Serum levels (mean ± SEM) of the endogenous antioxidants activities in rats with different doses of total-body

er radiation.						
GROUPS	GPx (U/ml)	SOD (U/ml)	CAT (U/ml)			
GROUP A						
(CTDIvol=2.76mGy &	5.30±0.28 ^a	2.79±0.31 ^a	0.49±0.03 ^a			
DLP=74.74mGy/cm)	5.30±0.28	2./9±0.31	0.49±0.03			
GROUP B						
(CTDIvol=8.36mGy &	4.01±0.16 ^b	2.16±0.31 ^{ab}	0.36±0.05 ^a			
DLP=352.38mGy/cm)						
GROUP C						
CTDIvol=14.92mGy &	2.15±0.25 ^b	1.97±0.22 ^b	0.23±0.01 ^b			
DLP=628.6mGy/cm)						
GROUP D						
(CTDIvol=78.74mGy &	1.43±0.39 ^{bc}	1.43±0.09 ^b	0.19±0.02 ^b			
DLP=1388.46 mGy/cm)						
GROUP E (sham	11.02±0.17 ^d	6.94±0.37 ^c	0.68±0.08 ^c			
irradiated control)	11.UZIU.17	0.54±0.57	0.00±0.08			

 $^{^{}a,\,b,\,c,\,d}$ Results with different superscript across the columns indicate significant difference (P < 0.05).

Table 2. Serum levels (Mean ± SEM) of the oxidation markers in rats with different doses of total-body computed tomography (CT) radiation.

GROUPS	MDA (μmol/L)	GSSG (μmol/L)	NO (mg/dl)
GROUP A			
(CTDIvol=2.76mGy & DLP=74.74mGy/cm)	5.30±0.28 ^a	0.87±0.02 ^a	6.04±0.17 ^a
GROUP B			
(CTDIvol=8.36mGy &	6.09±0.16 ^b	0.87±0.02 ^a	6.07±0.19 ^a
DLP=352.38mGy/cm)			
eGROUP C CTDIvol=14.92mGy & DLP=628.6mGy/cm)	6.85±0.25 ^b	0.93±0.03 ^a	6.21±0.08 ^a
GROUP D (CTDIvol=78.74mGy & DLP=1388.46 mGy/cm)	7.43±0.39 ^{bc}	1.27±0.15 ^b	6.32±0.03 ^a
GROUP E (sham irradiated control)	1.75±0.17 ^d	0.58±0.03 ^c	6.15±0.09 ^a

Table 3. Serum levels (Mean ± SEM) of the lipid profile of rats with different doses of total-body computed tomography (CT) radiation.

GROUPS	TC (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	TG (mg/dl)
GROUP A (CTDIvol=2.76mGy & DLP=74.74mGy/cm)	82.20 ± 2.58 ^a	64.80 ± 0.24 ^a	17. 60 ± 0.75°	104.60 ± 1.33°
GROUP B (CTDIvol=8.36mGy & DLP=352.38mGy/cm)	86.20 ± 2.58 ^a	63.60 ± 2.00°	17.80 ± 0.86ª	102.60 ± 1.94 ^a
GROUP C CTDIvol=14.92mGy & DLP=628.6mGy/cm)	86.00 ± 2.00 ^a	66.40 ± 3.49 ^a	18. 00 ± 0.71 ^a	105.80 ± 1.50°
GROUPD (CTDIvol=78.74mGy & DLP=1388.46 mGy/cm)	90.00 ± 1.36 ^a	68.00 ± 2.20 ^a	20.20 ± 1.36 ^a	101.00 ± 1.84°
GROUP E (sham irradiated control)	76.60 ± 0.13 ^b	65.00 ± 1.41°	13.20 ± 1.39 ^b	102.00 ± 1.30°

 $^{^{\}bar{a},b,c,d}$ Results with different superscript across the columns indicate significant difference (P < 0.05).

DISCUSSION

Reactive oxygen species (ROS), superoxide anion, hydrogen peroxide, hydroxyl radicals, peroxide radicals, and other free radicals, are produced intracellularly by ionizing radiation, which causes ionization events that in turn cause damage to DNA, proteins, or membrane lipids. Cells rely on the development of the antioxidant defense system, which includes both enzymatic and non-enzymatic oxidant defense mechanisms, due to the significant harmful potential of reactive oxygen species (ROS) (14). The important endogenous antioxidant enzymes involved in the cellular anti-oxidative defense systems and monitoring of the development and amount of oxidative stress damage is done by the major endogenous antioxidant enzymes, including glutathione reductase (Gr), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) (15).

The assessed endogenous antioxidant enzymes in this study revealed a radiation-induced dosedependent decline in their serum activities. The serum activities of GPx, SOD and CAT in the irradiated groups decreased significantly in a dosedependent manner compared to the sham-irradiated control group. GPx is a crucial antioxidant that, in mitochondria and occasionally in the cytoplasm, converts hydrogen peroxide (H2O2) into water. It is the most significant enzyme in intracellular compartments guards' that lipids peroxidation (34). In order to safeguard cells from damage and preserve the dynamic balance of oxidation and antioxidant reactions, SOD has super protective functions and can accelerate the dispersion of reactive oxygen and scavenge free radicals (35). The SOD enzyme catalyzes the dismutation of O_2 into H_2O_2 . The CAT enzyme is responsible for neutralization through decomposition of hydrogen peroxide into water and oxygen (H₂O and O₂), thereby maintaining an optimum level of the molecule in the cell, which is essential for cellular signaling processes (36). The observed significant decline in serum activities of GPx, SOD, and CAT is an indication radiation-induced oxidative stress (36-38,8). Our findings are related to those by Bryll et al., who detected a notable decline in the serum levels of CAT and glutathione in humans after high-resolution CT (HRCT) (9). Our results are also related to the work by Celik et al., who found that individuals working in radiation conditions had higher ROS and reduced antioxidant status values (39). Similarly, Shedid et al. found that male albino rats exposed to a 950 MHz electromagnetic field had significantly lower SOD, CAT, and GPx activity (40). Radiation-induced depletion of endogenous antioxidant enzymes, as observed in this study is a major cause of oxidative stress. Antioxidant enzymes are considered excellent indicators of cell health, as their depletion represents vulnerability to oxidant attack ⁽³⁸⁾. The observed notable decline in the endogenous enzymes activities of SOD, CAT, and GPx in the current study indicates that animal homeostasis was compromised by the varying doses of CT radiation, which also altered the level of innate antioxidant enzymes. This led to further stress and a decrease in the animal's capacity to operate ^(41,42). A pathogenic route implicated in all organ dysfunction or disease is oxidative stress via a decrease in antioxidant capacity ⁽⁴²⁾.

In the present study, a dose-dependent serum elevation of MDA in the irradiated groups compared to the sham-irradiated control group was observed. This finding is an indication that CT x-ray radiation at varying doses used in this study induced oxidative stress in the irradiated rats. The primary result of lipid peroxidation is malondialdehyde (MDA), which is typically utilized as a sign of oxidative stress (38). Oxidative stress induced by CT radiation was also reflected in the increased oxidation of glutathione. This is because the serum level of oxidized glutathione (GSSG) in the irradiated groups also increased significantly compared to that of the control group, with the highest concentration at the highest radiation dose. The post-irradiation elevation of serum MDA and GSSG observed in this study is consistent with the findings of Gunduz et al., who discovered that, in the comparison to the pre-image period, there was a notable rise in MDA levels in individuals in the early moments following CT (8). Similarly, Origuat and Ammari reported a postirradiation increase in the oxidized form of glutathione (GSSG) and MDA in mice irradiated with an x-ray radiation dose of 2 Gy (38). However, the mean serum level of nitric oxide (NO) in the irradiated groups did not differ significantly from the sham control group. Numerous studies have demonstrated the involvement of NO in the cellular response to ionizing radiation (16). Nitric oxide (NO) plays an essential role in mammalian life (43,44). Unregulated production of NO can cause nitrosative stress, leading to damage to proteins and DNA and to cell injury and death (45,46). The observed nonsignificant variation in the mean serum levels of NO in the irradiated groups and the sham-irradiated control group indicates that the CT radiation doses used in the study did not induce unregulated production of NO in the irradiated groups of rats.

The results of the present investigation demonstrated that exposure of rats to CT radiation revealed significant elevations in serum total cholesterol and low-density lipoprotein at post-irradiation day 7. The observed serum elevation of TC and LDL in the irradiated groups in the current study is similar to the results of El-Bahkery and Mohammed, who reported a significant elevation in the lipid profile indices excluding for HDL plasma levels in humans exposed to 4Gy and 8Gy CT radiation (47). Our

observations are related to the previous results of Ramadan, who documented a significant increase in total cholesterol (TC) and low-density lipoprotein (LDL) in female albino rats exposed to 5 Gy gamma irradiation (48). Our findings align with earlier research by Ragab and Ashry, and Abou Safi et al., who noted that ionizing radiation may accelerate other pathways of cholesterol formation, such as an increased rate of biosynthesis in the liver and other tissues or the destruction of cell membranes, which could account for the elevation in serum lipid fractions (49-50). Additionally, LDL cholesterol receptors are impacted by ionizing radiation, which results in hypercholesterolemia. This condition mostly affects polyunsaturated fatty acids and raises lipid peroxidation (51). Ionizing radiation generates oxidative stress, which might impact hepatic lipid metabolism and serum lipoproteins (52). Ionization radiation is linked to increased levels of lipid fractions and LDL in addition to the development of oxidative stress, according to Onody et al. (53). Radiation-induced cellular biomembrane damage may have led to enhanced fat mobilization from adipose tissues, which may have resulted in the elevated serum levels of TC and LDL seen in the irradiated rats in this study. Furthermore, a decline in the clearance aspect of lipoprotein lipase activity diminishes the amount of fat that adipose cells absorb. Similarly, as an early response needed for biomembrane repair, increased synthesis cholesterol may account for the elevated total cholesterol level (54).

CONCLUSION

Different doses of CT radiation in the current study caused significant decline in the endogenous antioxidant enzymes (GPx, SOD, and CAT) and, in contrast, induced a significant serum elevation of MDA and GSSG in the irradiated rats. The mean serum levels of TC and LDL were also significantly elevated in the irradiated groups. We concluded this condition as being in a state of radiation-induced oxidative stress, caused by free radicals, which overwhelmed the antioxidant defense systems due to exposure to CT ionizing radiation.

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Ethical consideration: The University of Nigeria, Nsukka, Faculty of Veterinary Medicine Institutional Animal Care and Use Committee (IACUC, FVM UNN) approved the study with approval number FVM-UNN-IACUC-2023-06/105, and all study protocols and animal care and handling followed its recommendations.

Authors' contribution: KCO and EKM designed and performed the experiments; EOM and IGA collected data; KCO analyzed and interpreted the results; TON, EOM and IGA supervised, directed and managed the study; KCO prepared the draft manuscript; KCO, EKM, EOM, IGA, and TON revised and approved the final version to be published.

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