

Evaluation of the effects of radiation doses from computed tomography on the biochemical parameters of the hepatorenal organs of albino rats

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Abstract

Background/Aims: Computed tomography (CT) uses X-rays which are ionizing radiation. Interaction of ionizing radiation with the body may result in harmful effects on the organism depending on the radiation dose. This study aimed to evaluate the impact of different doses of CT radiation on the hepatorenal organs of male albino rats using biochemical parameters as the pathological response of the organs to radiation.

Materials and Methods: Thirty healthy male Wistar albino rats weighing 180–200 g were assigned into five groups of six rats each. Rats in groups B, C, D, and E underwent noncontrast helical total body CT irradiation and received varying doses of CT radiation while group A received sham irradiation and served as control. At 72 h postirradiation, blood was collected using conventional methods, and serum was harvested for the determination of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TB), total protein (TP), albumin (Alb), urea, uric acid, and creatinine.

Results: The mean serum levels of TP in the control (group A) and in the irradiated groups B, C, D, and E were 8.21 ± 0.34 , 6.08 ± 0.30 , 5.86 ± 0.42 , 5.22 ± 0.30 , and 4.72 ± 0.16 , respectively. The mean values of TP in the irradiated groups decreased significantly in a dose-dependent manner compared to the control. The mean serum levels of ALP in the group A and in the irradiated groups B, C, D, and E were 75.20 ± 3.14 , 111.60 ± 1.60 , 117.60 ± 1.12 , 124.40 ± 2.48 , and 133.60 ± 2.46 , respectively. The mean serum levels of AST in the group A and in the irradiated groups B, C, D, and E were 33.80 ± 0.58 , 54.40 ± 2.29 , 52.60 ± 1.78 , 58.60 ± 2.64 , and 63.60 ± 0.81 , respectively. The mean serum levels of ALT in the group A and in the irradiated groups B, C, D, and E were 21.20 ± 0.86 , 36.00 ± 0.84 , 40.40 ± 1.17 , 37.40 ± 0.93 , and 41.60 ± 1.03 , respectively. The mean serum levels of TB in the group A and in the irradiated groups B, C, D, and E were 2.78 ± 0.28 , 3.70 ± 0.18 , 4.77 ± 0.40 , 5.88 ± 0.11 , and 6.34 ± 0.04 , respectively. The mean serum levels of Alb in the group A and in the irradiated groups B, C, D, and E were 3.68 ± 0.16 , 5.96 ± 0.21 , 6.65 ± 0.26 , 8.15 ± 0.23 , and 8.91 ± 0.17 , respectively. The mean serum levels of urea in the group A and in the irradiated groups B, C, D, and E were 42.40 ± 0.17 , 54.40 ± 1.33 , 56.00 ± 1.76 , 54.60 ± 1.72 , and 57.80 ± 1.39 , respectively. The mean serum levels of uric acid in the group A and in the irradiated groups B, C, D, and E

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were 5.65 ± 0.36 , 8.32 ± 0.46 , 8.87 ± 1.11 , 9.13 ± 0.29 , and 9.91 ± 0.29 , respectively. The mean serum levels of creatinine in the group A and in the irradiated groups B, C, D, and E were 2.05 ± 0.13 , 4.44 ± 0.32 , 5.81 ± 1.17 , 6.31 ± 0.03 , and 6.63 ± 0.40 , respectively. The mean values of ALP, AST, ALT, TB, Alb, urea, uric acid, and creatinine increased significantly in the irradiated groups compared to the control group.

Conclusion: From the lowest to the highest doses of CT irradiation in the study, alterations in the biochemical parameters were evident and significant. Moreover, this suggests a possible deleterious biological effect of CT radiation on the hepatorenal organs probably due to the effects of radiation-induced free radicals which adversely affected the hepatorenal organs.

Keywords: Computed tomography, ionizing radiation, kidney, liver, radiation dose, X-rays

INTRODUCTION

Progressive development in all fields of science and technology in the world has predisposed both humans and animals to a huge number of various sources of radiation. These include space exploration, mobile communications, computed tomography (CT), digital X-ray, fluoroscopy, gamma radiation, and nuclear weapons.^[1,2] CT uses X-rays which are ionizing radiation. Interaction of ionizing radiation with the body results in harmful effects on the organism due to its direct and indirect effects. X-rays and gamma rays are classified as ionizing radiations. Exposure of organisms to high doses of these radiations can cause considerable cell damage, which may eventually even lead to cell death.^[3] Ionizing radiation is used in getting rid of unwanted cells within a living system and has emerged as one of the successful strategies in cancer treatment by way of radiotherapy (RT).^[4] Radiation-induced liver diseases have been reported in humans with normal liver function, causing hepatomegaly and a mild increase in alkaline phosphatase (ALP) concentration and this may develop fibrosis, cirrhosis, and finally liver failure.^[5]

Biochemical mechanisms that are triggered on exposure of a liver cell to ionizing radiations include the generation of oxygen-derived free radicals, namely hydroxyl radical, superoxide radical, hydronium ion, alkoxy-radical, peroxy-radical, and oxides of nitrogen.^[6] Injury caused by these free radicals is well advocated by their fatal interactions with lipids, proteins, DNA, and RNA of cell membranes and organelles.^[7,8] The kidneys are essential organs that regulate the organism's fluids, electrolytes, and acid-base metabolism. Kidneys excrete waste metabolites, modulate blood pressure, and produce erythropoietin to stimulate erythropoiesis and activate Vitamin D.^[9]

Radiation nephropathy is a kidney injury induced by ionizing radiation. In a clinical setting, ionizing radiation is used in RT. Ionizing radiation causes double-strand breaks in the DNA, followed by cell death including apoptosis

and necrosis of renal endothelial, tubular, and glomerular cells.^[10] Following radiation injury, kidney dysfunction leads to anemia, hypertension, and osteodystrophy. Toxic waste metabolites accumulate and cause uremia, electrolyte disorders such as hyperkalemia, hyperphosphatemia, hypocalcemia, and ultimately chronic renal failure.^[11] Irradiation of both kidneys to a modest dose of about 30 Gy gamma radiation in 2 Gy fractions (3000 rad in 200-rad fractions) has resulted in nephropathy with arterial hypertension and anemia and the radiation damage develops slowly and may not become evident for months.^[12] Dilatation of Bowman's capsule, degeneration of tubular epithelium, and congestion of renal blood vessels were the significant findings that described the acute gamma radiation effects in rats exposed to a single dose of 20 Gy whole-body irradiation.^[13] Alterations in the levels of mRNA after chronic low-dose-rate gamma exposure have been observed in the liver, kidney, and testis of male C57Bl/6 mice.^[14] So also, many of the genes in the kidneys and testes of mice were differentially expressed after long-term irradiation with low-dose-rate gamma rays as determined through microarray analysis.^[15] Exposure of rats to a single dose of gamma radiation (6 Gy) has been shown to cause a significant rise in the activities of plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALP, and the levels of bilirubin.^[16] Hanafy and Kandil reported significant elevation of plasma creatinine, uric acid, and urea levels in response to whole-body gamma irradiation of albino rats.^[17] Most of the earlier studies have reported the effects of different doses of gamma radiation in the body but there is a scarcity of information on the effects of different doses of CT radiation in the body. Lowe *et al.*,^[18] stated that despite decades of research to understand the biological effects of ionizing radiation, there is still much uncertainty over the role of dose rate. To the best of knowledge, no previous studies have investigated the effects of different doses of CT radiation-induced biochemical changes either in humans or animals. This study, therefore, emphasizes the biochemical alteration of

the hepatorenal organs of Wistar albino rats exposed to various doses of CT radiation.

MATERIALS AND METHODS

Animals

Thirty healthy male Wistar albino rats weighing 180–200 g obtained from the Department of Veterinary Medicine, University of Nigeria, Nsukka, were used. The rats were housed under standard laboratory conditions (12 h light and 12 h dark) in a room with a controlled temperature ($24^{\circ}\text{C} \pm 3^{\circ}\text{C}$) during the experimental period. The rats were provided a free standard pellet diet and water *ad libitum*. After 1 week of acclimatization, the rats were randomly assigned into five groups (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.

Equipment

Irradiation was carried out using GE 16 Slice (General Electric) Revolution ACTs CT scanner (GE Hangwei Medical Systems Co. Ltd, China) with adaptive statistical iterative reconstruction features that allow manual entry of diagnostic exposure parameters to achieve desired radiation dose.

Methods

Radiation protocols

There were four irradiated groups (B, C, D, and E) and one sham irradiated control group (group A) of five rats each. The six rat per group were immobilized with a customized fixator in supine position with head first. Centering laser beam was at the mid sagittal plane and mid neck before axial beam total body irradiation was acquired from the tip of the nose to the tail. Two scout images, anterior-posterior and lateral for each group of the irradiated groups were first acquired with the same kV (80) and mAs (20) so as to prevent X-ray beam wastage and to ensure centering accuracy. Tube current (mAs) and tube potential (kV) were manually selected. The radiation dose for each group was automatically estimated by scanner software and displayed in the CT scanner screen as volume-weighted CT dose index (CTDIvol) and dose-length product (DLP). These values are standardized measures of radiation dose during CT examination.^[19] A noncontrast helical scan was carried out for each group once a week for 2 weeks.

Group A rats received sham irradiation and served as control. Sham irradiation is the control group that received

zero irradiation (0 mGy). Rats in group B were irradiated with 80 kV and 100 mAs. Rats in group C were irradiated with 100 kV. Group D rats were irradiated with 120 kV and 150 mAs while group E rats were irradiated with 140 kV and 160 mAs.

Blood/serum collection

Blood was collected from the orbital plexus at 72 h after the last irradiation. Then serum was separated by centrifugation at 3000 rpm/min for 5 min at 4°C and stored at 80°C until simultaneously studied.

Determination of biochemical parameters

Serum ALT, AST, ALP, total bilirubin (TB), total protein (TP), albumin (Alb), globulin (Glob) urea, uric acid, and creatinine were assessed colorimetrically using commercial kits (Randox, UK).

The activities of AST and ALT activities were evaluated according the method of Reitman and Frankel^[20] while ALP was determined by the method of Tietz *et al.*^[21] as outlined in Randox kit. The TP and Alb contents were determined using methods outlined by Buzanovskii.^[22] Serum uric acid level was determined by an enzymatic method (uricase) as outlined in the Randox/UK kit.^[23] The level of urea in the serum was determined by an enzymatic method (urease-modified Berthelot reaction) as outlined in the Randox/UK kit.^[24] Serum level of creatinine was determined based upon the colorimetric method with deproteinization using Syrbio/France kit.^[25]

Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Science (SPSS) software version 22 (IBM company, Armonk, New York, USA). The data obtained were expressed as means \pm standard error of the mean. One-way analysis of variance was performed among the mean values the groups followed by Duncan's multiple range test. The statistical difference was considered significant at $P < 0.05$.

RESULTS

Group A rats (sham irradiation control group) received 0.0 mGy radiation dose. Rats in group B received a total radiation dose of 2.76 mGy CTDIvol and 74.74 mGy/cm DLP. Rats in group C received a total radiation dose of 8.36 mGy CTDIvol and 352.38 mGy/cm DLP. Group D rats received a total radiation dose of 14.92 mGy CTDIvol and 628.6 mGy/cm DLP while group E rats received a total radiation dose of 78.74 mGy CTDIvol and 1388.42 mGy/cm DLP.

The mean serum levels of liver indices, TP, ALP, AST, ALT, TB, Alb, and globulin were presented in Table 1. The

study showed that serum levels of TP in the irradiated groups decreased significantly ($P < 0.05$) compared to the sham irradiated control group. In reverse, the mean serum levels of ALP, AST, ALT, TB, and Alb in the irradiated groups of rats increased significantly ($P < 0.05$) against the sham irradiated control group. CT radiation showed dose-dependent decrease in the serum levels of TP while the serum levels of ALP, AST, ALT, TB, Alb, and globulin increased in a dose-dependent manner.

The mean serum level of renal indices, urea, uric acid, and creatinine were presented in Table 2. The present study results showed significant elevation ($P < 0.05$) in serum levels of urea, uric acid, and creatinine in the irradiated groups compared to the sham irradiated control group. A dose-dependent increase in the urea, uric acid, and creatinine was observed in the present CT radiation dose study.

DISCUSSION

The current study focuses on the toxic effects of different doses of CT radiation on the hepatorenal organs after 2 weeks of weekly whole-body CT irradiation in Wistar male albino rats. From our study, all the radiation doses induced significant decline in serum levels of TP in a dose-dependent manner while dose-dependent serum elevation of ALP, AST, ALT, TB, and Alb was observed. Transaminases are involved in protein and amino acid metabolism. They are present in most of the cells of the tissues in the body, however, ALT and AST levels are the most specific markers for hepatic cell destruction and loss of hepatocyte integrity. Since they are present in cytoplasm, they are released into the circulation following diseases

or injuries.^[4,26] Our findings are related to the results by Sohrabi *et al.*^[4] who observed high serum concentrations of liver enzymes in rats exposed to 2.00 and 8.00 Gy gamma radiation. Our results are also similar to the findings of Makhlof and Makhlof^[27] who showed that levels of liver enzymes (ALT and AST) increased significantly in serum of rats after gamma irradiation. Kafafy^[28] reported similar results in rats exposed to gamma radiation. The results of the current study are also consistent with those found previously which reported significant increase in liver enzyme levels in rats exposed to 8.00 Gy gamma radiation.^[29,30] Our results are in agreement with reports by Abdelhafez and Kandeal^[2] who showed that the mean serum levels of ALT, AST, and ALP increased significantly in rats exposed to single 4 Gy whole-body gamma radiation. The biochemical alterations observed in the current CT radiation are consistent with the previous studies which reported that whole-body gamma irradiation induced hepatotoxicity and increased serum ALT and AST activities.^[29,31,32] Similarly, Eshak and Osman^[33] and El-Desouky *et al.*^[34] noticed elevations in ALT, AST, and ALP in sera of gamma irradiated (4 and 6 Gy) albino rats. Our observations are closely related to the previous results of Ramadan^[35] who documented significant increase in ALT and AST in female albino rats exposed to 5 Gy gamma irradiation. The increase in the serum levels of liver enzymes in this study could be attributed to the CT radiation-induced damage of cellular membranes of hepatocytes, which leads to an increase in the permeability of cell membranes and facilitates the passage of these enzymes outside the cells. This is because increase in serum levels of liver enzymes are related to the extensive breakdown of liver parenchyma.^[4] The observed elevations

Table 1: Mean \pm SEM of serum levels of liver indices in rats with different doses of total-body computed tomography (CT) radiation

Group	TP (mg/dL)	ALP (mg/dL)	AST (mg/dL)	ALT (mg/dL)	TB (mg/dL)	Albumin (mg/dL)
Group A control (sham irradiation)	8.21 \pm 0.34 ^a	75.20 \pm 3.14 ^a	33.80 \pm 0.58 ^a	21.20 \pm 0.86 ^a	2.78 \pm 0.28 ^a	3.68 \pm 0.165 ^a
Group B (CTDIvol=2.76 mGy and DLP=74.74 mGy/cm)	6.08 \pm 0.30 ^b	111.60 \pm 1.60 ^b	45.40 \pm 2.29 ^b	36.00 \pm 0.84 ^b	3.70 \pm 0.18 ^b	5.96 \pm 0.21 ^b
Group C (CTDIvol=8.36 mGy and DLP=352.38 mGy/cm)	5.86 \pm 0.42 ^b	117.60 \pm 1.12 ^c	52.60 \pm 1.78 ^c	40.40 \pm 1.17 ^c	4.77 \pm 0.40 ^c	6.65 \pm 0.26 ^c
Group D (CTDIvol=14.92 mGy and DLP=628.6 mGy/cm)	5.22 \pm 0.30 ^{b,c}	124.40 \pm 2.48 ^d	58.60 \pm 2.64 ^d	37.40 \pm 0.93 ^b	5.88 \pm 0.11 ^d	8.15 \pm 0.23 ^d
Group E (CTDIvol=78.74 mGy and DLP=1388.46 mGy/cm)	4.72 \pm 0.16 ^c	133.60 \pm 2.46 ^d	63.60 \pm 0.81 ^d	41.60 \pm 1.03 ^c	6.34 \pm 0.04 ^d	8.91 \pm 0.17 ^e

^{a,b,c,d}Different superscripts across the column indicate significant ($P < 0.05$) variation in the mean values. Abbreviation of hepatic parameters and standard CT radiation dose indices: TP - Total protein, ALP - Alkaline phosphatase, AST - Aspartate aminotransferase, ALT - Alanine aminotransferase, TB - Total bilirubin, CTDIvol - Volume weighted computed tomography, DLP - Dose-length product

Table 2: Mean \pm SEM of serum levels of renal indices in rats with different doses of total-body CT radiation

Group	Urea (mg/dL)	Uric acid (mg/dL)	Creatinine (mg/dL)
Group A control (sham irradiation)	42.40 \pm 1.17 ^a	5.65 \pm 0.36 ^a	2.05 \pm 0.13 ^a
Group B (CTDIvol=2.76 mGy and DLP=74.74 mGy/cm)	54.40 \pm 1.33 ^b	8.32 \pm 0.46 ^b	4.44 \pm 0.32 ^b
Group C (CTDIvol=8.36 mGy and DLP=352.38 mGy/cm)	56.00 \pm 1.76 ^b	8.87 \pm 0.11 ^b	5.81 \pm 0.17 ^b
Group D (CTDIvol=14.92 mGy and DLP=628.6 mGy/cm)	54.60 \pm 1.72 ^b	9.13 \pm 0.29 ^{b,c}	6.31 \pm 0.03 ^b
Group E (CTDIvol=78.74 mGy and DLP=1388.46 mGy/cm)	57.80 \pm 1.39 ^b	9.91 \pm 0.29 ^c	6.63 \pm 0.40 ^b

^{a,b,c}Different superscript across the column indicate significant ($P < 0.05$) variation in the mean values. Abbreviation of CT radiation dose indices: CTDIvol - Volume weighted computed tomography, DLP - Dose-length product

could be also due to a hypoxia state in the liver cells or mitochondrial membrane induced by ionizing radiation.^[28,36]

Radiation-induced serum elevation of urea, uric acid, and creatinine was observed in the irradiated groups compared with the sham irradiated control group. This significant rise in serum urea, uric acid, and creatinine in the irradiated groups are indication of radiation-induced renal impairment. These data were consistent with the findings of Hanafy and Kandil^[17] who showed that the plasma creatinine, uric acid, and urea levels were significantly increased in response to whole-body gamma irradiation of albino rats. Similarly, Elmonem *et al.*^[16] noticed significant increase in creatinine, urea and uric acid in rats exposed to whole-body 6 Gy, single dose gamma irradiation.

Based on the biochemical changes observed in the present results, it could be concluded that from the lowest to the highest doses of CT radiation, alteration in the biochemical parameters was evident and significant. This suggests possible deleterious biological effects of the different doses of CT radiation on the hepatorenal organs probably due to the effects of radiation-induced free radicals which adversely affected the hepatorenal organs.

Statement of ethics

This study was performed in line with the principles of the Declaration of Helsinki. 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.

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Conflicts of interest

There are no conflicts of interest.

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