Volume 15, No 2 | International Journal of Radiation Research, April 2017

Induction of DNA damage, apoptosis and micronuclei in peripheral blood lymphocytes following injection of contrast media in patients with abdominal CT scan

S. Azimi[1], H. Mozdarani[2*], A. Mahmoudzadeh[3]

[1]*Department of Radiology, School of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[2]*Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran*
[3]*Novin Medical Radiation Institute, Tehran, Iran*

► ***Original article***

Corresponding author:
Prof. Hossein Mozdarani,
Fax: *+98 21 88006544*
E-mail:
mozdarah@modares.ac.ir

Revised: May 2016
Accepted: July 2016

Int. J. Radiat. Res., April 2017; 15(2): 149-155

DOI: 10.18869/acadpub.ijrr.15.2.149

ABSTRACT

Background: Medical diagnostic procedures such as X-ray and computed Tomography (CT) scan account for considerable percent of patient's exposure to ionizing radiation. The exposure of cells to Ionization radiation results in induction of DNA damage and chromosomal aberrations. Contrast media (CM) are widely used in diagnostic radiology and CT scan. The aim of this study was to study adverse genetic effects of combined administration of non ionic contrast media and low dose X-rays in peripheral blood Lymphocytes of patients following abdominal CT scan. ***Materials and Methods:*** A total of 55 patients underwent abdominal CT scan with injection of non ionic contrast media (30 patients with omnipaque 300 mg/ml and 25 patients with visipaque 270 mg/ml) as well as 13 patients undergoing abdominal CT scan (without contrast), selected as control group, were enrolled in this study. Peripheral blood leukocytes were obtained in heparin containing tubes and cultured for the micronucleus test, or were directly used for apoptosis and DNA damage with the neutral comet assay. ***Results:*** The frequency of micronuclei, apoptosis and percentage of DNA damage was increased in most patients after the injection of contrast media, significantly different from the control group as compared with the samples obtained before and after injection of contrast media ($P<0.05$). ***Conclusion:*** The present study suggest that non ionic contrast media (omnipaque 300 mg/ml and visipaque 270 mg/ml) may cause a significant increase of cytogenetic damage in peripheral blood lymphocytes. This effect might be caused by the enhancement of radiation dose by CM that eventually may lead to the manifestation of ill health such as cancer.

Keywords: *Contrast media, micronuclei, apoptosis, DNA damage, computed tomography, lymphocytes.*

INTRODUCTION

Contrast media (CM) are widely used to enhance the contrast of body structures in medical imaging procedures such as angiography, computed tomography, among others, especially the visibility of blood vessels and of gastrointestinal system structures [(1)]. Chemical and physical properties of CM, like density, number of atoms of iodine per milliliter of solution, viscosity and osmolarity, are related to their efficacy and safety. CM with high osmolarity CM (HOCM) are more likely to cause various adverse reactions. In turn low osmolarity agents (LOCM) are associated with less discomfort and fewer cardio-vascular and anaphylactic type reactions. However, the cost of LOCM is significantly higher than HOCM, a limitation for exclusive use [(2)]. CM osmolarity is yet another detrimental factor that may lead to

[Downloaded from ijrr.com on 2026-11-01]

[DOI: 10.18869/acadpub.ijrr.15.2.149]

toxicity in kidney. Therefore it is possible to say that different kinds of CM may exert different adverse renal toxicity [3]. The hydrophilicity of a contrast medium is its preference for aqueous solvents, whereas its lipophilicity refers to its preference for fat-like (lipid) organic solvents such as the chemical solvent n-butanol. Lipophilicity has been correlated with the toxicity of ionic CM. It seems that non-ionic contrast media are too hydrophilic. Protein-binding refers to the percentage of contrast medium which becomes bound to the plasma proteins in the blood stream. Radiological contrast media do not only increase the absorbed dose, but may also enhance the sensitivity of blood cells to the radiation induced cell damage [4]. The previous studies suggested that the increase of chromosomal aberrations observed after radiographic examination is mainly due to the presence of contrast media which, by them or in combination with radiation, are capable of breaking chromosome and formation of micronuclei [5, 6]. The nephrotoxic and cytotoxic effects of using iodinated contrast agents are well-documented, while little is known about their effects on DNA damage and apoptosis during CT or diagnostic radiology. The purpose of this study was to evaluate cytogenetic effects of nonionic contrast agents (omnipaque 300 mg/ml and visipaque 270 mg/ml) on the induction and formation of micronuclei and apoptosis as well as DNA damage in patients undergoing abdominal CT scan. Manifestation of adverse biological effects such as chromosomal aberrations (CA) and micronuclei (MN) in a non target tissue like peripheral blood lymphocytes reflects similar events in carcinogenic process [7]. Therefore cytogenetic biomarkers may serve as early indicator of hazards of contrast media used in this study, thus preventing adverse effects.

MATERIALS AND METHODS

Subjects and treatments

Two groups of patients undergoing abdominal computed tomography were selected randomly in order to evaluate genotoxic effects of non-ionic contrast agents (Omnipaque 300 mg/ml and Visipaque 270 mg/ml, both from GE health care USA). Thirty patients (17 male and 13 females) mean age, 46.1 ± 14 years; age range, 20-70 years) were enrolled for micronucleus assay and 25 patients (12 males, 13 females, mean age, 40.3 ± 13.2 years; age range, 20 -70 years) were enrolled for the comet assay to evaluate DNA damage and apoptosis. Fifteen patients with mean age, 51.2 ± 15.5 years; age range, 20-70 years) undergoing abdominal CT scan (without contrast) were selected as control group. Sampling was done in accordance with and approval of the Ethical Committee of the Shahid Beheshti University of Medical Sciences (Tehran, Iran). Patients were informed and gave their written consent for contribution in the study. Patients were excluded from the study if they had leukemia or lymphoma, undergone radiation therapy, and diagnostic X-ray or nuclear medicine studies in the past. Blood sampling was done shortly before CM injection and 30 minutes towards the end of examination. The following imaging parameters were used for all patients: tube voltage, 120 kVp; rotation time, 0.8 second, MA 200 and matrix, 512 × 512; CTDIv (mGy), 22.7. All patients were exposed to X-rays under similar condition.

Cytochalasin block micronucleus assay

Lymphocytes cultures were established according to standard protocols [8, 9]. Briefly 0.5 ml of blood were added to 4.5 ml of RPMI 1640 complete culture medium supplemented with 10% fetal calf serum, penicillin (100 IU/ml)/ streptomycin (100 µg/ml) and 0.1 ml phytohemaglutinin (all reagents from Gibco-BRL). The culture vessels were incubated in a humidified incubator with 37 °C and an atmosphere containing 5% CO2 for 44h. Cytochalasin –B (Sigma-Aldrich) was added to the cultures at a final concentration of 6µg/ml and incubated further up to 72h. Cells were then collected by centrifugation at 1200 rpm and re suspended in potassium chloride (KCl) (0.075 M) for 2 min. KCl was removed by centrifugation and cells were fixed in Carnoys' fixative (methanol: acetic acid, 6:1) at room temperature

[Downloaded from ijrr.com on 2026-11-01]

[DOI: 10.18869/acadpub.ijrr.15.2.149]

for 20 min. Cells were washed twice with the same fixative. The cell suspension was dropped on to clean glass slides and allowed to dry. Air dried slides were stained in 10% Giemsa solution for 10 minutes. A total of 1000 binucleate cells were scored for the presence of micronuclei and the frequency of micronuclei recorded. Figure 1 shows sample photomicrograph of binucleate cells with or without micronuclei.

Lymphocyte preparation for comet assay

Lymphocytes were separated from blood of 27 patients (14 patients with injection of omnipaque 300 and 13 patients with injection of visipaque 270) with the use of Histopack- Ficoll (Bahar Afshan, Iran) according to the procedure instructed by the producer. The lymphocytes were then transferred to microtubes (Eppendrof) under a laminar flow hood, containing complete RPMI-1640 medium (Gibco BRL). For DNA damage study, cell suspensions were directly used for the comet assay, but for scoring apoptotic cells, samples were incubated for 48-hour in culture medium and at 37 °C.

Neutral comet assay:

Neutral comet assay was used to study both double strand DNA damages and apoptosis induced in lymphocytes of patients. The assay was performed based on the procedure of neutral comet previously reported by Mozdarani and Ghoraeian (2008) [10]. In brief, lymphocytes in suspension were centrifuged at 1000 rpm for 7 min, and then the supernatant was discarded. Cell suspension was mixed with 200µl of 0.75% low melting point (LMP) agarose (Fermentas) then 50µl of this suspension was transferred to each window of the two chamber comet slides pre-coated with a supporting layer of 1% normal melting point (NMP) agarose (Fermentas). The windows were covered with cover slips and kept in 4°C for about 5 min in a dark to allow solidification of agarose gel. The cover slips were removed, then the slides were placed horizontal in a dish containing fresh lyses solution made up with 2.5M NaCl, 10mM Tris Base, 0.1M Na2EDTA, 10% dimethyl sulphoxide (DMSO) (all from Merck), 1% N-lauryl sarcosine (Sigma) and 1% triton X-100 (Sigma) at a final pH of 10. It was crucial to leave slides in lyses solution at 4°C in a dark for about 30 min in order to lyses all cell contents except nucleus. The slides were then washed 3 times in electrophoresis buffer, composed of 90mM Tris base, 90mM Boric acid and 2.5mM Na2EDTA at a final pH of 8.2-8.4. The slides were subjected to electrophoresis in a horizontal chamber filled with fresh electrophoresis buffer at 30 volts (0.8 V/cm), 8 mA for about 10 minutes. The slides were washed with distilled water for about 5 minute and dried at room temperature, then fixed in absolute ethanol for 5 min.

Staining and microscope analysis:

The air-dried slides were stained with ethidium bromide solution (Merck, 20µg/ml) and covered with cover slips. The slides were analyzed in a two-sided blind manner under a fluorescent microscope (ZEISS) equipped with video camera (Sony). A total of 1000 cells were evaluated for the presence of apoptosis for each sample. The frequency of DNA damaged cells were evaluated by counting a total number of 1000 cells per slide and determining DNA damage (DD%). To calculate DD%, various extent of migration of DNA; which formed the tail of comet, were scored qualitatively as distinct categories of n0, n1, n2, n3 and n4; from absolute normal cell (scored as 0) to the most severe damaged one (scored as 4). DD% was then assessed using the equation 1.

$$DD\ \% = (0n0 + 1n1 + 2n2 + 3n3 + 4n4)/(\Sigma/100) \quad (1)$$

Where; DD% is defined as percent DNA damage, n1- n4, as total counted comets of n1-n4 and Σ as total counted comets including normal cells. Figure 2A and B show sample photomicrograph of comets showing DNA damages (a) and apoptosis (b).

Statistical analysis:

Statistical analysis was performed with SPSS statistical software (version 18). The statistical difference between the number of micronuclei, apoptosis and percent of DNA damage in patients (with and without administration of contrast agents) was tested by using a paired sample *t*-test. P-value less than 0.05 ($p<0.05$) was considered as significant difference.

[Downloaded from ijrr.com on 2026-11-01]

[DOI: 10.18869/acadpub.ijrr.15.2.149]

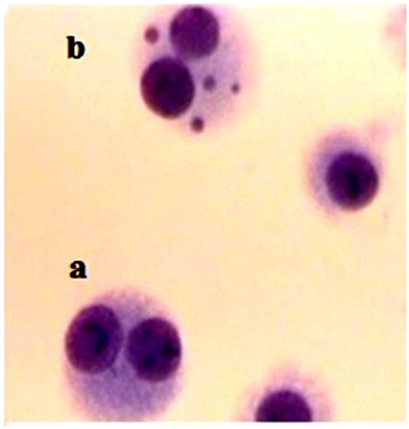


Figure 1. photomicrograph showing binucleate lymphocyte without MN (a) and with MN (b). Magnification ×400.

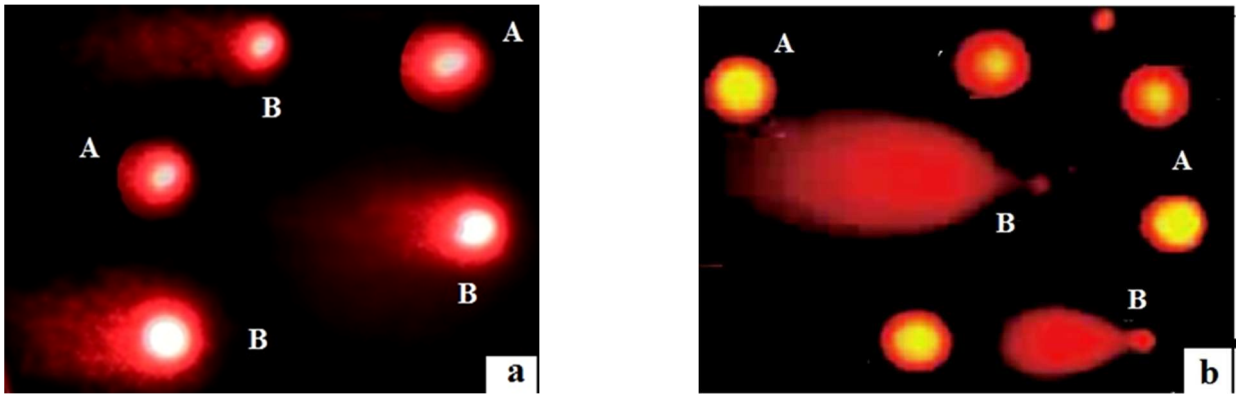


Figure 2. Photomicrograph in panel (a) is showing lymphocytes without DNA damage (A) and with DNA damage seen as comets (B). Photomicrograph in panel (b) shows intact cells (A) and apoptotic cells (B). Magnification ×1000.

RESULTS

Results are summarized in tables 1 and 2 and shown in figures 3-5. As seen for control patients who underwent abdominal CT scan alone without injection of CM, the frequency of micronuclei in lymphocytes of patients was not significantly different before and after CT scan. Injection of omnipaque (300mg/ml) induced similar frequency of MN to control before or after CT. However when combined with CT, a significantly high frequency of MN was observed ($p<0.01$) (table 1, figure 3). Unlike omnipaque, visipaque induced a significantly high frequency of MN compared to control before and after CT ($p<0.05$). In combination with CT, visipaque (270 mg/ml) led to a significant increase in MN ($p<0.01$). The increase was significantly higher than the effect of omnipaque with CT (12.9 versus 8.9) (figure 3).

As seen in table 2 and figure 4, percent of DNA damage in leukocytes of patients after CT was slightly higher than samples obtained before CT scan, but the increase was not statistically significant different ($p>0.05$). After injection of omnipaque and visipaque alone, the percent of DNA damage was not different from the control before or after CT, but omnipaque in combination with CT led to a dramatic increase in DNA damage significantly different from control or even with visipaque in combination with CT ($p<0.05$). DNA damage induced by visipaque and CT was slightly higher than other groups not significantly different ($p>0.05$), except omipaque with CT. Similar observation for DNA damage was observed for apoptosis, however, the frequency of apoptosis induced by omnipaque with CT was not significantly different with visipaque and CT ($p>0.05$) (figure 5).

[Downloaded from ijrr.com on 2026-11-01]

[DOI: 10.18869/acadpub.ijrr.15.2.149]

Table 1. The mean frequency of micronuclei in binucleate lymphocytes of patients with abdominal CT scan before and after injection of non ionic contrast media

Study Groups	Number of subjects	Gender	Mean age ± SD	Time of sampling	MN Mean ± SD
Control	15	7 (Male)	51.2 ± 15.0	Before CT	6.9 ± 3.5
		8 (Female)		After CT	6.8 ± 2.1
Omnipaque 300 mg/ml	30	17 (Male)	46.0 ± 13.6	CT alone	6.6 ± 4.7
		13 (Female)		CT + Omni	9.3 ± 5.1
Visipaque 270 mg/ml	25	12 (Male)	40.3 ± 13.2	CT alone	8.9 ± 4.8
		13 (Female)		CT + Visi	12.9 ± 7.1

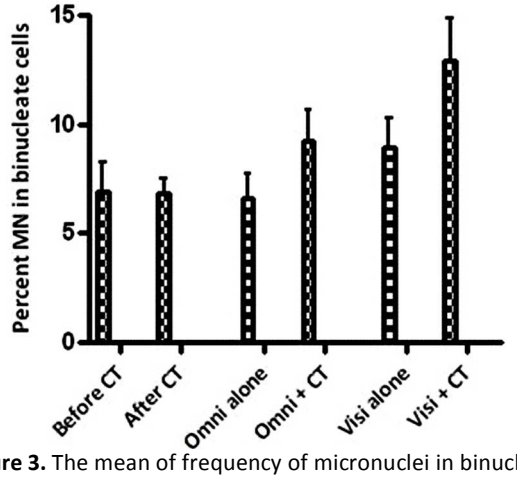


Figure 3. The mean of frequency of micronuclei in binuclear cells in patients undergoing Abdominal CT scan with injection of contrast media, visipaque and omnipaque and control group (without contrast).

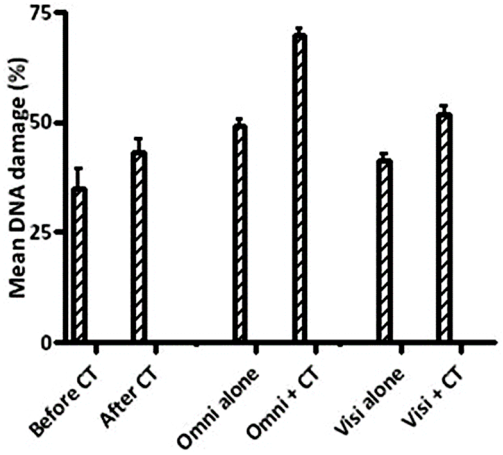


Figure 4. The mean frequency of DNA damage in leukocytes of patients with injection of omnipaque.

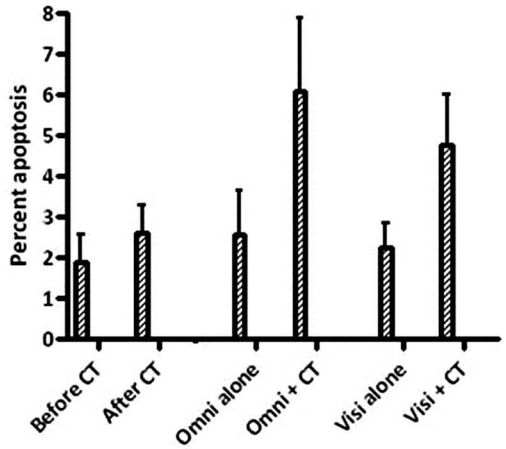


Figure 5. The mean frequency of apoptosis in the leukocytes of patient with injection of visipaque.

Table 2. The mean frequency of apoptosis and percentage of DNA damage in the lymphocytes of patients with abdominal CT scan before and after injection of non ionic contrast media.

Study Groups	Number of subjects	Gender	Mean age ± SD	Time of sampling	Apoptosis Mean ± SD	DNA damage Mean ± SD
Control	15	7 (Male)	51.2 ± 15.0	Before CT	1.9 ± 1.8	35.5 ± 12.0
		8 (Female)		After CT	2.6 ± 1.8	43.0 ± 8.0
Omnipaque 300 mg/ml	14	7 (Male)	49.0 ± 13.4	CT alone	2.6 ± 2.8	49.2 ± 37.4
		7 (Female)		CT + Omni	6.1 ± 4.8	69.7 ± 40.3
Visipaque 270 mg/ml	13	6 (Male)	51.0 ±15.5	CT alone	2.2 ± 1.5	41.1 ± 44.5
		7 (Female)		CT + Visi	4.8 ± 3.2	51.8 ± 47.6

DISCUSSION

Contrast media (CM) are frequently used in diagnostic radiology and in computed tomography. These compounds have been shown to induce adverse reaction as well as mutagenicity [11, 12]. Because of their density, iodinated contrast agents absorb more X- rays

[Downloaded from ijrr.com on 2026-11-01]

[DOI: 10.18869/acadpub.ijrr.15.2.149]

than soft tissues in addition the generation of secondary electrons, strongly dependent on the density of the absorbing material. These secondary electrons could potentially be the major cause of X-ray induced DNA damage [13]. Formation of oxygen- free radicals or decreased antioxidant enzyme activity might be triggered by contrast media administration. Free radicals react with various cellular components including DNA, protein, lipids/fatty acids and glycation and products. These reactions between cellular components and free radicals lead to DNA damage, mitochondrial mal-function, cell membrane damage and eventually cell death (apoptosis) [14]. As shown in table 2 and figures 4 and 5, effect of radiation dose deliveded during abdominal CT to lymphocytes was not significantly different with control unirradiated lymphocytes. However, omnipaque induced a high percentatge of DNA damage when combined with CT. However, all DNA damages observed with the comet assay might not translate into chromosomal aberrations. It was previously shown that CM induces chromosomal aberrations and micronuclei only when combined with diagnostic radiation [15]. Micronuclei arise due to clastogenic or aneugenic activity of chemical and physical agents. The observations indicate contrast agents are capable of inducing chromosomal aberrations or micronuclei irrespective of ionic or osmolarity differences. Patients administered diatrizoate CM exhibited an increase in micronuclei formation [16]. Mozdarani and Fadaei (1998) [5] evaluated the cytogenetic effects (chromosomal aberration) *in vivo* of two ionic CM, urografin 76% (a sodium-meglamine diatrizoate), and Telebrix38 on lymphocytes of patients undergoing brain CT, before and after examination. It was shown that both CM used in the study led to an increase in chromosomal aberrations when combined with CT. Results shown in table 2 and figure 3 clearly indicate that both omnipaque and visipaque when combined with CT lead to a dramatic increase of the frequency of micronuclei ($p<0.01$). The results showed no difference in micronuclei frequency for patients who underwent abdominal CT without CM, when compared to controls. Therefore, both CM exhibited clastogenetic effects on peripheral lymphocytes *in vivo*. Studies with other contrast agents such as metrizoate [17] and iothalamate [15] showed that they can exert clastogenic effects. In other study on mouse bone marrow polychromatic erythrocytes (PCE), higher frequency of MN was observed in PCE following *in vivo* administration of ionic and non-ionic contrast media [18-20].

In the present study, we demonstrated that non ionic contrast omnipaque 300 mg/ml and visipaque 270 mg/ml significantly increased the frequency of micronuclei and apoptosis as well as DNA damage in the peripheral blood lymphocytes of patients undergoing abdominal CT scan ($P< 0.05$).

Visipique showed to be more effective than omnipaque in induction of micronuclei (figure 3) but omnipaque was more potent in induction of DNA damage and apoptosis (figures 4 and 5). These results clearly indicate the CM induces genome instability in somatic cells when combined with low level X-rays used for imaging. The mechanisms by which CM cause genome instability are not well understood and established. It is most likely that CM cause generation of additional secondary electrons when X-rays are absorbed. Moreover, by entering into cells, CM might inhibit mitochondrial resperation that eventually lead to formation of superoxide and hydroxyl radicals [21, 22]. Therefore induction of DNA damage, apoptosis and micronuclei by the CM used in this study might be due to free radicals induced by these agents in lymphocytes in combination with low level ionizing radiation. Zhang *et al*. (2000) [23] investigated the effects of various CM on human vascular endothelial cells and showed reduced proliferation and increased apoptosis of these cells. Previous studies have also suggested that factors other than osmolarity may cause DNA damage and micronuclei by CM. An increased frequency of DNA damage and micronuclei in somatic cells of a population may be considered as a risk factor for cancer. DNA damage and genome instability induced by chemical and physical agents might lead to activation of proto-oncogenes and

[Downloaded from ijrr.com on 2026-11-01]

[DOI: 10.18869/acadpub.ijrr.15.2.149]

elimination of tumour suppressor genes involved in carcinogenesis [24]. Despite new achievements and considerable safety of iodinated contrast media, their utilities are not without risk. Therefore it would be valuable if in routine clinical trials contrast media with minimum genotoxicity is used.

ACKNOWLEDGEMENTS

The authors would like to express their thanks to the staff of the Novin Medical Radiation Institute and Dr. M.R Aghamiri for their valuable cooperation.

***Conflicts of interest*: Declared none.**

REFERENCES

1 . Araujo A (2007) Tomografi a Computadorizada: Princípios Físicos e Aplicações, n. 1. São Paulo: Corpus, 160 p.
2. Thomas G and Maddox M (2002) Adverse reactions to contrast material: recognition, prevention, and treatment. *Am Fam Physician* ***66:*** *1229-1234*.
3. Hsueh-Wei Y, Hsiang-Chun L, Wen-Te L, Sheng-Husiung S (2007) Effects of acetylcysteine and probucol on contrast Medium-induced Depression of Intrinsic Renal Glutathione peroxidase activity in diabetic rats. *Arch Med Res* ***38:*** *291-296*.
4 . Cohran ST and Norman A (1994) Induction of micronuclei in lymphocytes of patients undergoing excretory urography with ioversol. *Invest Radiol,* ***29:*** *210-2.*
5 . Mozdarani H and Fadaei S (1998) Similar cytogenetic effects of sodium-meglumine diatrizoate and sodium-meglumine ioxithalamate in lymphocytes of patients undergoing brain CT scan. *Toxicol Lett* ***98:*** *25-30*.
6. Parvez Z, Kormano M, Satokari K, Moncada R and Eklund R (1987) Induction of mitotic micronuclei by X-ray contrast media in human peripheral lymphocytes. *Mutat Res,* ***88:*** *233-239.*
7. Sorsa M, Wilbourn J, Vainio H (1992) Human cytogenetic damage as a predictor of cancer risk. In: Vainio H, Magee PN, McGregor DB, Mc Michael AB (eds.), Mechanisms of carcinogenesis in risk identification. *International Agency for Research on Cancer, DARC*, Lyon, pp. 543-554.
8. Gourabi H and Mozdarani H (1998) A cytokinesis bloked micronucleus study of the radioadaptive response of lymphocytes of individuals occupationally exposed to chronic doses of radiation. Mutagenesis, **13**: 475-480.
9. Thomas P and Fenech M (2011) Cytokinesis-block micronucleus cytome assay in lymphocytes. *Methods Mol Biol,* ***682:*** *217-34.*
10. Mozdarani H and Ghoraeian P (2008) Modulation of gamma-ray-induced apoptosis in human peripheral blood leukocytes by famotidine and vitamin C. *Mutat Res,* ***649(1-2):*** *71-8*.
11. Norman A, Adams FH, Riley RF (1978) Cytogenetic effects of contrast media and triiodobenzoic acid derivatives in human lymphocytes. *Radiology,* ***129:*** *199-202*.
12. Weeler L, Norman A , Riley R (1980) Mutagenicity of diatrizoate and other triiodobenzoic acid derivatives in Ames Salmonella microsome test. *Proc West Pharmacol Soc,* ***23:*** *249-253.*
13. Eric Barnes *et al.* (2015) Adding contrast to CT doubles DNA damage from radiation. *Radiology,* ***275 (3):*** *692-697*.
14. Peng PA, Wang L, Ma Q, Xin Y, Zhang O, Han HY, Liu XL, Ji QW, Zhou YJ, Zhao YX (2015) Valsartan protects HK-2 cells from contrast media-induced apoptosis by inhibiting endoplasmic reticulum stress. *Cell Biol Int,* ***39(12):*** *1408-17*.
15. Matsubara S, Suzuki S, Suzuki H, Kuwabara Y and Okano T (1982) Effects of contrast medium on radiation induced chromosome aberrations. *Radiology,* ***144:*** *295-201*.
16. Sinues B, Nuñez E, Bernal ML, Alcala A, Saenz MA and Conde B (1991) Micronucleus assay in biomonitoring of patients undergoing excretory urography with diatrizoate and ioxaglate. *Mutat Res,* ***260****: 337-342*.
17. Stenstrand K and Edgren J (1981) Cytogenetic *in vivo* and *in vitro* effects of low dose radiation and contrast agents. *Eur J Radiol,* ***1(1):*** *76-8*.
18. Li D, Machado FL, Welker AG, Peres LM, Santos-Mello R (2008) Micronucleus induction in mouse polychromatic erythrocytes by an X-ray contrast agent containing iodine. *Mutat Res,* ***672:*** *65-68*.
19. Toulany M, Kehlbach R, Rodemann HP, Mozdarani H (2010) Radiocontrast media affect radiation-induced DNA damage repair *in vitro* and *in vivo* by affecting Akt signaling. *Radiother Oncol,* ***94:*** *110-116*.
20. Belle MBB, Leffa DD, Mazzorana D, De Andrade VM (2013) Evaluation of the mutagenic effect of the iodinated contrast medium Urografina® 292 using the micronucleus test in mouse bone marrow cells. *Annals of the Brazilian Academy of Sciences,* ***85*** *(2): 737-744.*
21. Hodnick WF, Roettger WJ, Kung FS, Bohmont CW, Pandpardinin RS (1986) Inhibition of mitochondrial respiration and production of superoxide and hydrogen peroxide by flavonoids: a structure activity study. Plant flavonoids. In: Cody *et al*. (eds.) Biology and Medicine. Alan R. Liss, New York.
22. Nordby A, Tredt KE, Halgunset J, Kopstad G, Haugen OA (1989) Incorporation of contrast media in cultured cells. *Invest Radiol,* ***23:*** *703-710.*
23. Zhang H, Holt CM, Malik N, Morcos SK (2000) Effects of radiographic contrast media on proliferation and apoptosis of human vascular endothelial cells. *British Journal of Radiology,* ***73(874):*** *1034-41*
24. Heim S and Mitelman F (2015) Cancer cytogenetics: Chromosomal and molecular genetics aberrations of tumor cells. 4th Edition, Wiley-Blackwell, USA.

[Downloaded from ijrr.com on 2026-11-01]

[DOI: 10.18869/acadpub.ijrr.15.2.149]

[DOI: 10.18869/acadpub.ijrr.15.2.149] [Downloaded from ijrr.com on 2026-11-01]