

ORIGINAL ARTICLE

Evaluation of the Biological Effects of Exposures to Magnetic Resonance Imaging on Single-Strand DNA: An *In-vivo* Study

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ABSTRACT

Introduction: Magnetic resonance imaging (MRI) is a powerful diagnostic technique used to acquire detailed information on the structure and function of the body's organs. Data on the extent of genetic damage following exposure to electromagnetic fields in MRI is variable, necessitating further evidence. This study aims to examine the biological effect of exposure to MRI at various magnetic strengths on the DNA single-strand. **Methods:** The study was an in-vivo non-randomized controlled experiment involving New Zealand rabbits (n=39, males) scanned using three different MRI strengths (0.5, 1.5 and 3.0 T) and at different time intervals (10, 20, 30, and 40 minutes). The alkaline comet assay was used to study DNA damage by quantifying single-strand breaks. In addition, tail length (TL), tail moment (TM), and the fraction of total DNA in the tail were evaluated. **Results:** The DNA single-strand breaks were significant for all tested parameters in both MRI 1.5 T (p<0.01) and 3.0 T (p<0.001). In addition, 3.0 T for 40 minutes had the most comet tails and tail moment (13.87), resulting in greater %DNA damage (mean=22.37). Exposure to 0.5 T was found to be only significant at 30 and 40 minutes (p<0.001). **Conclusion:** Higher MRI strength for a longer duration resulted in a significant increase in DNA single-strand breaks. Understanding the interaction between the magnetic fields generated by MRI and DNA will optimize safe and effective MRI scanning in both patients and healthy individuals.

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INTRODUCTION

Magnetic resonance imaging (MRI) is a medical imaging technique that uses a magnetic field and computer-generated radio waves to create detailed images of the organs and tissues of the body. Three main magnetic fields are used during an MRI examination to create three-dimensional images [1]; i) High static magnetic fields (SMF), a measure of the proton density, ii) gradient magnetic fields (GMF) with up to 200 mT/m/ms of slew rate and amplitudes in the range of 100 mT/m [2][3], spatial fast switching gradient fields, they affect how gradient fields interact with biological tissues [4][5], and iii) radiofrequency (RF) electromagnetic wave (10 to 400MHz) that excites magnetization vectors allowing MRI scanners to detect them thereby converting tissue properties into MR images [1].

Studies have demonstrated that exposure to MRI components (SMF and RF) can cause biological effects [6][7][8]. For example, Pacini et al. (1999) showed how a static magnetic field produced by 0.2 T affected a normal human neural cell culture. They discovered that after 15 minutes of exposure, the cells had significant morphological changes, forming branched dendrites with synaptic buttons [9]. Advanced analysis of SMF's effects on oxidative stress showed exposure to SMF could increase the activity, concentration, and lifetime of paramagnetic free radicals, leading to oxidative stress, genetic mutation, and apoptosis in biological systems [10][11]. In addition, as the scanner's strength increases, the exposure levels also increase, suggesting substantial development of transient health symptoms that may lead to semipermanent health effects [12]. Furthermore, RF power can cause tissue overheating, cell death in the affected tissue, and DNA changes in the surrounding cells, resulting in abnormal cell multiplication [13] [14] This effect, however, can be avoided by limiting RF energy to the maximum specific power absorption rate (SAR) [15]. The International Agency for Research

on Cancer (IARC) Monograph Working Group has recently discussed and classified RF field exposure as a potential carcinogenic agent to humans [16]. Therefore, the main biological effects associated with exposure to RF energy are related to the thermogenic properties of the electromagnetic field [17-19], such as heating, chemical reaction modifications, or electric currents induction on tissues and cells [20]. In recent times, the contradictory evidence for DNA damage in human lymphocytes following cardiac MRI has resurfaced [21] [22]. While some studies found increased DNA damage or genotoxicity [23,24], others did not [25]. Similarly, Fiechter et al. found that MRI 1.5T significantly affect the DNA double-strand break of human lymphocytes [26]. However, another study reported no significant effect of MRI 3T exposure on DNA double-strand [27].

Therefore, to better understand the effect of MRI scanning on DNA damage, the present study aims to evaluate the biological effects of radiofrequency and magnetic fields on DNA (single-strand break) at various MRI RF densities and magnetic strengths. Furthermore, because the study was conducted in-vivo, it is anticipated that the findings will be more accurate and could better clarify the conflicting arguments regarding DNA damage during MRI scanning. The comet test used in the study provides a quick and precise microdosimetric approach that may be suitable for in-vivo human biomonitoring [28,29].

MATERIALS AND METHODS

Animal ethics

The study was approved by Universiti Sains Malaysia, Institutional Animal Care and Use Committee with approval reference [IACUC/ (128) (1140)]. Another approval from the Central Committee for Bioethics was obtained from the University of Kufa in Iraq with approval reference (6667/2021).

Study design and animals

The study was an in-vivo non-randomized controlled experiment using New Zealand rabbits (n=39, males, 4.5 to 5.5 months, and 2.5-3.0 kg) obtained from Baghdad's Serum and Vaccine Institute in Al-Ammriah, Iraq.

Experimental procedure

The rabbits were divided into control group (n=3) and the exposed group. The exposed group was divided into three subgroups (n=12) for each magnetic field strength. During the MRI scanning, all samples were exposed to different scan times (10, 20, 30, and 40 minutes) across the three different magnetic field strengths (0.5, 1.5, and 3.0 T). The three MRI magnetic strengths assessed the biological effects of MRI scanning; 1) closed type with 3.0T (RF:128 MHz, Achieva; Philips Healthcare) available at the Neuroscience Center, 2) closed type with 1.5T (RF:64MHz, Achieva & Intera; Philips Healthcare) available at Alkarkh Hospital, Iraq and 3) open type with 0.5 T (RF:21.4 MHz, Siemens-Concerto) available

at Alkarama Hospital, Iraq. During the scanning of the sample, the spine coils and multiple echo sequences were chosen from the standard protocol.

MRI exposure

The rabbits (n=12) were divided into two groups (GPs 10 and 20 minutes) and (GPs 30 and 40 minutes) at 1.5T magnetic strength. The rabbits were given anesthesia (ketamine: 10 mg/kg + xylazine: 3 mg/kg) in the muscles prior to the MRI exposure. During the MRI scanning, all rabbits were placed on the MRI couch and then exposed at different scan times (10, 20, 30, and 40 minutes) across the three different magnetic field strengths (0.5, 1.5, and 3.0 T). All exposures were carried out at room temperature (20-22°C).

Blood sampling

Before and after MRI exposure, 2 ml of blood (whole blood) was drawn from the rabbit's venipuncture from the ear. The blood was immediately placed into EDTA K3 tubes and refrigerated while being handled under dimmed or yellow light to prevent DNA damage from ultraviolet light.

Comet analysis

The comet analysis was performed using the lymphocytes isolated from the whole blood at an external laboratory (Alrawan Laboratory, Alkeradah City, Baghdad, Iraq) [30]. The alkaline comet assay was used with little modification (pH>13) (31). The Comet Assay Silver kit (TA4251-050 K.50 test, Trevigen) was used to coat the slides with 1% normal agarose. Each sample was analyzed (50 cells per slide), and 2 ml of blood was placed in the plain tube and mixed with a full 10 ml of 1X RBC lysis. The cells suspension was centrifuged for 10 minutes at 10000 rpm, the supernatant was discarded, (steps repeated three times). The pellets were thereafter washed once with cold 4°C of 1X phosphate-buffered saline (Ca⁺⁺ and Mg⁺⁺ free) pH 7.2. About 500 µl of the buffer was mixed with the pellets using a vortex device at 10 minutes. Then a 10 µl cell sample was placed in Eppendorf, mixed with 250 µl of agarose at 37°C. The mixture (50 µl/well) was quickly added on the Comet slide carefully and the slide was covered. The slides were then quickly frosted on an ice block.

As the agarose solidified, the coverslips were transferred into a small basin and submerged in 25 ml/slide of 1X lysis solution buffer at 4°C, pre-chilled lysis buffer remain submerged for 24 hours, the sample was kept in a cool place and away from sunlight. Next, excess buffer was tapped off from the slides and placed in freshly prepared alkaline solution pH>13 for 10 minutes at room temperature in the dark space. The slide was then properly washed with distilled water. The slide was then transferred to alkaline electrophoresis pH >13 in a horizontal chamber power supply set at 25 V/cm and 300 mA for 40 minutes. Excess alkaline was gently tapped off for 5 minutes at 37°C with air dry. The cells

were stained with SYBR Green (diluted / deionized) 50 µL applied on the slide for fluorescent DNA imaging. The slides were examined using a fluorescence microscope (Zeiss / Germany) with a green maximum excitation filter. Complex systems, including microscopes, computers (Windows 10) analysis software packages, and cameras, were used. Numerous comet parameters were determined using the Tri Tek Comet ScoreTM 2006 programme. This study used three parameters for comet analysis: tail DNA percentage, tail length (µm), and tail moment. Undamaged cells resemble intact nuclei without tails, whereas damaged cells resemble a comet. The length of DNA migrated to the comet tail is an estimate of DNA damage measured with an ocular micrometre [32].

The study used the Comet Assay (Alkaline) due to its well-established sensitivity in detecting DNA damage and its versatility in assessing various types of DNA lesions. The alkaline version of the Comet Assay is particularly useful for evaluating single-strand breaks, alkali labile sites, and other forms of DNA damage. Additionally, it allows for the quantification of DNA damage at the individual cell level, providing valuable insights into the heterogeneity of cellular responses.

Statistical analysis

Statistical analyses were conducted using IBM SPSS version 24. The continuous values were expressed as mean ± standard error (SE). Differences between means were compared using one-way analysis of variance (ANOVA) followed by the least significant difference (LSD) post-hoc tests. A p-value <0.05 was considered statistically significant [33].

RESULTS

DNA single-strand breaks (SSBs) following exposure to 3.0 T MRI (RF=128 MHz) over different duration

The cellular DNA molecules in the control group (n=3) ranged from (4.05 - 7.22), with a mean value of (5.58 ± 0.92). The percentage of cells destroyed in the group exposed to 3.0 T MRI was increased to 12.65 ± 1.0 after 10 minutes of exposure. In contrast, the mean percentage of damaged cells in the group exposed for 20 minutes was (15.27 ± 0.46). On the other hand, the group exposed for 30 minutes showed a significant increase in the mean percentage of damaged cells (19.72 ± 1.75). Finally, the group exposed for 40 minutes had the highest mean percentage of damaged cellular DNA, (22.37 ± 1.56). The mean percentage of DNA SSBs was higher significant in all groups exposed to 3.0 T MR at different exposure times (10, 20, 30, and 40 minutes) (p<0.01), compared to the control group. The greatest level of significance was observed after 40 minutes of MRI exposure (Figure 1).

Table I shows that the values of three comet score parameters are statistically significant for 3.0 T MRI.

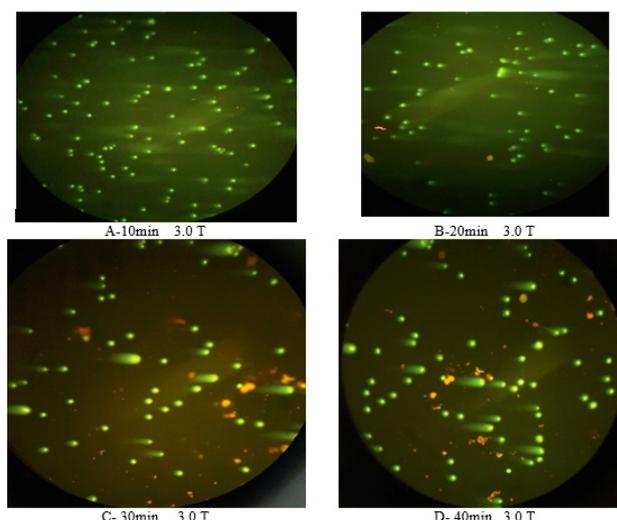


Figure 1: A, B, C, and D shows comet tail corresponds to DNA SSBs following exposure to 3.0 T (RF=128 MHz) observed over different exposure times under 10X magnification

These parameters vary with exposure duration and RF density. The mean percentage of DNA tail measurement is the most useful parameter in comet assays [34]. The highest significant mean percentage for DNA tail were observed at 30 and 40 minutes of exposure (51.76 ± 0.64) (57.07 ± 2.57) (p<0.001), followed by 20, and 10 minutes were significant (p<0.01). While tail length (TL) and tail moment (TM) high significant at all exposure times (p<0.001) compared to the control group.

DNA SSBs following exposure to 1.5 T MRI (RF=64 MHz) over different duration

After 10 minutes of exposure, the mean value (10.65 ± 1.12) of DNA damage was significant (p<0.01). The mean value of % DNA damage in a group exposed 20 minutes (13.79 ± 0.90) was high significant (p<0.001). In addition, the groups exposed for 30 and 40 minutes had a significant increase in destroyed cell DNA (Figure

Table I: Comet score parameters of DNA SSBs exposed to 3.0 T MRI (RF=128 MHz) over different duration

Comet parameters	Exposure duration	Mean ± SE
Tail Length (µm)	Control	3.50 ± 0.25
	10 min.	14.13 ± 0.44***
	20 min.	14.80 ± 0.35***
	30 min.	19.23 ± 0.66***
	40 min.	22.07 ± 1.00***
%DNA Tail	Control	21.85 ± 1.99
	10 min.	32.45 ± 1.92**
	20 min.	33.95 ± 2.62**
	30 min.	51.76 ± 0.64***
	40 min.	57.07 ± 2.57***
Tail Moment	Control	0.10 ± 0.12
	10 min.	10.43 ± 0.38***
	20 min.	11.40 ± 0.52***
	30 min.	13.35 ± 1.43***
	40 min.	13.87 ± 1.15***

Keys: n=3, Significant at *p<0.05, **p<0.01, ***p<0.001 compared to control, compared to control, using One-way ANOVA followed by LSD tests, SEM, standard error of mean, MRI, magnetic resonance imaging, RF, radio frequency

2), with a mean value of (17.93 ± 0.64) and (19.71 ± 0.83) for both groups ($p < 0.01$). The mean percentage of SSBs was significantly higher in all groups exposed to 1.5T MRI at different exposure times (Table II).

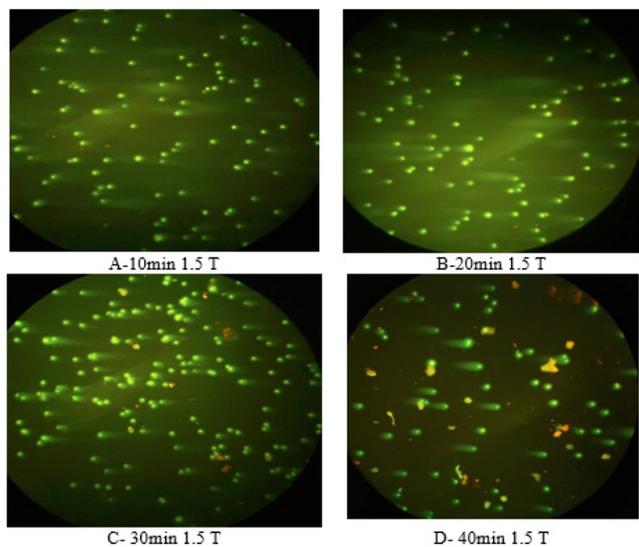


Figure 2: A, B, C, and D shows comet tail corresponds to DNA SSBs following exposure to 1.5 T (RF=64 MHz) observed over different duration under 10X magnification. The tail appeared more in (C) and (D)

Table II shows the three important comet score parameters that were chosen to measure the DNA effect when exposed to 1.5 T MRI. Whereas the parameter tail DNA % when exposure times at 10 and 20 minutes were significant ($p < 0.05$), ($p < 0.01$). As for, exposure at times 30, and 40 minutes were high significant ($p < 0.001$) compared to a control group.

The groups exposed at 30 and 40 minutes were more significant than the other exposure times. However, for the same exposure times, the % of DNA damage caused by MRI 3.0T was higher than 1.5T MRI, depending on power magnetic field.

In terms of tail length (TL) and tail moment (TM), the mean values observed after 1.5 T exposure at 20, 30 and 40 were highly significant ($p < 0.001$) and at time 10 minutes was significant ($p < 0.05$) compared to a control group. It was observed that groups exposed for 30 and 40 minutes exhibited greater significance than those exposed for other durations.

DNA SSBs following exposure to 0.5 T MRI (RF=21.4 MHz) over different duration

However, a high significant level of % DNA SSBs were observed exposed groups at 30 and 40 minutes ($p < 0.001$), ($p < 0.01$) respectively. In contrast, rabbits exposed to 0.5T MRI for 10 and 20 minutes showed of DNA single-strand non-significant ($p > 0.05$) (Figure 3(A) and (B)).

As shown in Table III, in comparison to a control group, the tail moment and tail length after 30 and 40

Table II: Comet score parameters of DNA SSBs following exposure to 1.5 T (RF=64 MHz) over different duration

Parameter	Exposure duration (MRI 1.5 T)	Mean \pm SEM
Tail Length (μ m)	Control	3.50 \pm 0.25
	10 min.	6.10 \pm 0.61*
	20 min.	9.07 \pm 0.58***
	30 min.	11.67 \pm 0.98***
	40 min.	13.93 \pm 0.70***
%DNA Tail	Control	21.85 \pm 1.99
	10 min.	30.98 \pm 3.85*
	20 min.	35.94 \pm 1.36**
	30 min.	44.70 \pm 1.61***
	40 min.	45.68 \pm 1.33***
Tail Moment	Control	0.10 \pm 0.12
	10 min.	2.56 \pm 0.37*
	20 min.	5.05 \pm 0.38***
	30 min.	10.97 \pm 0.48***
	40 min.	11.04 \pm 0.38***

Keys: n=3, Significant at *= $p < 0.05$, **= $p < 0.01$, ***= $p < 0.001$ compared to control, compared to control, using One-way ANOVA followed by LSD tests, SEM, standard error of mean, MRI, magnetic resonance imaging, RF, radio frequency

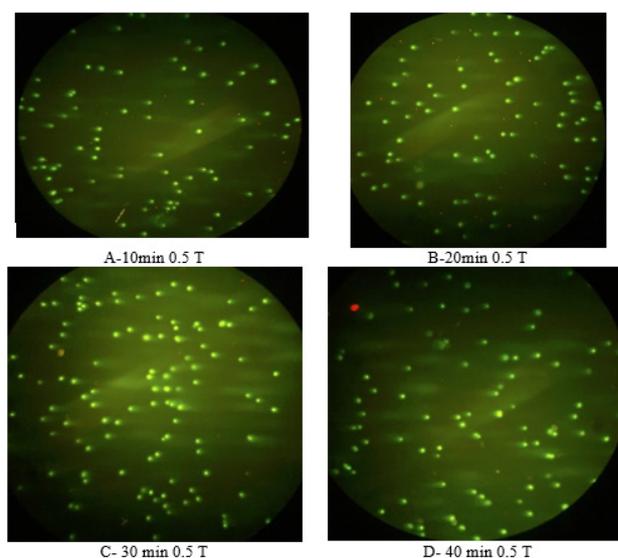


Figure 3: A, B, C, and D shows comet tail to DNA SSBs following exposure to 0.5 T (RF=21.4 MHz) observed over different duration under 10X magnification for 0.5 T MRI. The tail appeared more in (C) and (D). While there is no effect in sections (A) and (B)

minutes of exposure to 0.5T MRI were highly significant ($p < 0.001$). Also, after 30 and 40 minutes the %DNA in tail was significant ($p < 0.01$). The groups exposed to 10 and 20 minutes were non-significant ($p > 0.05$) all three parameters.

Comparison of DNA SSBs following exposures to 0.5, 1.5, and 3.0 T MRI over different duration

As shown in Tables IV, in comparison all MRI types used (0.5, 1.5, and 3.0 T) at different periods exposure. Both 3.0 and 1.5 T MRI at all exposures times (10, 20, 30 and 40minutes) resulted in statistically significant SSB to DNA compared to the control group. The MRI 3.0 T (RF=128MHz) showed the highest significant DNA SSB

Table III: Comet score parameters of DNA SSBs following exposure to 0.5 T (RF=21.4 MHz) over different duration

Parameter	Exposure duration MRI 0.5 T	Mean ± SEM
Tail Length (µm)	Control	3.50 ± 0.25
	10 min.	3.97 ± 0.09
	20 min.	4.59 ± 0.53
	30 min.	7.27 ± 0.47***
	40 min.	8.30 ± 0.63***
%DNA Tail	Control	21.85 ± 1.99
	10 min.	22.03 ± 1.02
	20 min.	18.51 ± 4.58
	30 min.	33.63 ± 1.16**
	40 min.	38.22 ± 1.28**
Tail Moment	Control	0.10 ± 0.12
	10 min.	1.11 ± 0.08
	20 min.	1.60 ± 0.18
	30 min.	4.07 ± 0.06***
	40 min.	6.36 ± 0.62***

Keys: n=3, Significant at *=p<0.05, **=p<0.01, ***=p<0.001 compared to control, compared to control, using One-way ANOVA followed by LSD tests, SEM, standard error of mean, MRI, magnetic resonance imaging, RF, radio frequency

Table IV: Comparisons of DNA SSBs exposed to 0.5, 1.5, and 3.0 T MRI over different duration

Exposure	Mean ± SEM			
	10 min	20 min	30 min	40 min
Control	5.58 ± 0.92	5.58 ± 0.92	5.58 ± 0.92	5.58 ± 0.92
MRI 0.5 T (RF=21.4 MHz)	5.82 ± 0.38	6.54 ± 0.35	10.41 ± 0.43*	13.93 ± 1.16**
MRI 1.5 T (RF=64 MHz)	10.65 ± 1.12**	13.46 ± 0.90**	17.93 ± 0.64**	19.71 ± 0.83***
MRI 3.0 T (RF=128 MHz)	12.66 ± 1.09**	15.27 ± 0.46**	19.72 ± 1.75**	22.38 ± 1.56***

Keys: n=3, Significant at *=p<0.05, **=p<0.01, ***=p<0.001 compared to control, compared to control, using One-way ANOVA followed by LSD tests, SEM, standard error of mean, MRI, magnetic resonance imaging, RF, radio frequency

when exposed for 30 minutes (19.72 ± 1.75) (p<0.01) and 40 minutes (22.38 ± 1.56) (p<0.001) compared to the control group. In addition, exposure to MRI 0.5 T (RF21.4MHz) showed significant increase in DNA SSB only for 30 and 40 minutes (10.41 ± 0.43) (p<0.05) and 40 minutes (13.93 ± 1.16) (p<0.01) compared to the control group.

DISCUSSION

This *in-vivo* study employs three different types of MRI systems with varying magnetic strengths and RF densities: 0.5 T (RF: 21.4MHz), 1.5 T (RF:64 MHz), and 3.0 T (RF:128 MHz). DNA single-strand break damage was observed in both 1.5 and 3.0 T across all the exposure times (10, 20, 30, and 40 minutes). Similarly, studies by Simi et al.[23], Fiechter et al. [26], and Fand Lancellotti et al. [35] found that exposing human cell lymphocytes to electromagnetic fields generated during 1.5 T MRI scanning increased DNA damage significantly. Lee JW et al. [36] conducted an *in-vitro* study in which they exposed human cell lymphocytes to 3.0 T for 22, 45,

67, and 89 minutes and found a significant increase in single-strand DNA break frequency, chromosome aberrations (CA), and micronuclei (MN). Our research agreed with these studies; however, all of them *in-vitro* study, except for Simi et al, who did *in-vivo* on patient donors. This study was conducted *in-vivo* with directly MRI exposure on healthy mammals with different times exposure set.

In contrast to our study, Szerencsi and colleagues [37] used the same *in vitro* conditions as Lee JW et al. [36], exposing three healthy donors to electromagnetic fields generated by 3.0 T MRI for 0, 22, 45, 67, and 89 minutes. The study discovered no evidence of DNA damage. Other studies, including those by Schwenzer et al. [38], and Fasshauer et al. [27], found no mutagenic or co-mutagenic effects of the 3.0T magnetic field. In addition, studies by Yildiz et al. [39], Reddig et al. [40], and Brand et al. [21] utilizing MRI 1.5T no find of DNA damage in donors' patients.

The DNA damage can be observed and measured using tail length (TL), tail moment (TM), and % DNA in the tail. According to our findings, the percentage of DNA damage increased with long duration exposure and when high exposed of magnetic field strength (3.0T MRI has higher RF density (RF:128MHz)). The tail length is a measurement of 22.07 µm, while the tail moment is 13.87, and % DNA in the tail is 57.07 %. In our study, as magnetic strength, and exposure time increased, so did the mean value of tail length. This effect indicates that more DNA was damaged.

Notably, no significant single-cell DNA damage was observed after 0.5 T exposure for 10 and 20 minutes. Other findings are consistent with those obtained, namely no genotoxicity in static fields less than 1.0 T MRI [41][42]. While other studies have produced conflicting results, DNA single-strand breaks significantly increase the micronucleus frequency detected in human fibroblasts exposed to 50 Hz power line signals after very low concentrations [43]. Another study found that exposure to 4 to 15 kHz increased DNA synthesis in human fibroblasts [44]. While the current results demonstrate a significant increase in DNA (SSB) at 30 and 40 minutes time points during MRI 0.5 T exposure.

Numerous studies have reported increases and decreases in DNA damage depending on the type, strength, and duration of DNA damage signals studied, implying that the fields may affect cell healing as studied by Tsybulin et al. [45]. To draw firm conclusions about the long-term effects, Vijayalaxmi et al. [46] stated that it is necessary to compare SMF exposure levels, long-term effects, and duration of exposure. The study found that prolonged exposure causes more DNA damage than the control group, which is supported by De Vocht et al., [47]. It also claimed that all reported health effects are dependent on the MRI scanner's power and exposure time. Kubinyi

et al. [48] demonstrated increased DNA migration in human lymphocytes exposed to inhomogeneous (0.3, 1.2, or 47.7 T/m) SMF only. Recently in-vitro study 2016, approve a significant increase in the rate of recurrence of single-strand DNA breaks after exposure of an SMF of 1.5T at 50 minutes [49]. In a reasonable and good analysis by Blank and Goodman, 2008 [50] regarding the mechanisms underlying the genetic impacts of EMF exposure, it was discovered that EMF can start electron transfer and displacement in DNA. The displacement has an immediate impact on the hydrogen bonds, which oversee maintaining DNA integrity and spatial DNA geometry. The consequence is the separation and transcription of the DNA chain. While, according to the World Health Organization Monograph, precautions should be taken to avoid risks of attraction to fields greater than 3.0 T.

However, it is important to acknowledge the limitations of the Alkaline Comet Assay. One notable limitation is that the assay primarily measures DNA strand breaks and alkali-labile sites but may not be as sensitive to certain types of DNA damage, such as oxidative damage or specific base modifications. Additionally, the interpretation of comet assay results can be subjective, relying on visual scoring, which may introduce variability. Despite these limitations, the Alkaline Comet Assay remains a valuable tool for assessing genotoxicity and DNA damage, provided its application is mindful of its constraints and complemented with other assays when necessary.

CONCLUSION

The study confirmed that different magnetic field strengths and radiofrequency densities can cause significant effects on DNA single-strand breaks in leukocytes at different exposure times. Following 40 minutes of MRI exposure, the maximum DNA damage was observed at 3.0 T. The low RF power (21.4 MHz) and short exposure period of 0.5 T for 10 and 20 minutes are insufficient to cause DNA SSB. While the magnetic field generated by an MRI does not directly cause biophysical effects, it does induce energy conversions that lead to a significant amount of energy within the body. Consequently, prolonged exposure to the high magnetic force of an MRI necessitates direct and close monitoring.

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