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ORIGINAL ARTICLE

# Effect of 50-Hz Magnetic Fields on Serum IL-1β and IL-23 and Expression of *BLIMP-1*, *XBP-1*, and *IRF-4*

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*Abstract*— Investigations demonstrated that magnetic fields (MFs) change cytokine production and expression of some immune system genes. This alteration can affect the immune system function and may lead to some diseases. Therefore, this study investigated two important inflammatory cytokines, *i.e.*, IL-1β and IL-23 at two phases of pre- and post-immunization of the immune system. In addition, the expressions of three important genes in the humoral immunity, *i.e.*, B lymphocyte-induced maturation protein-1 (BLIMP-1), X-box-binding protein-1 (XBP-1), and interferon regulatory factor-4 (IRF-4) were evaluated at post-immunization phase. Eighty adult male rats were divided into four experimental groups and a control. The experimental groups were exposed to 50 -Hz MFs with magnetic flux densities of 1, 100, 500, and 2000 μT, 2 h/day for 2 months. The animals were injected by human serum albumin (100 μg/rat) on days 31, 44, and 58 of exposure. The cytokine levels in serum were measured with enzyme-linked immunosorbent assay (ELISA), and the expression of genes was evaluated with reverse transcription quantitative polymerase chain reaction (RT-qPCR). Serum IL-1β was decreased at pre-immunization phase after exposure to 1 and 100 μT of 50-Hz MFs. In contrast, serum IL-23 was increased at post-immunization phase in 100 μT group. No change was observed in serum IL-1β and IL-23 in each group at pre-immunization phase compared with post-immunization. Furthermore, exposure to 100 μT downregulated expression of *BLIMP-1*, *XBP-1*, and *IRF-4*. In conclusion, exposure to 50-Hz MFs may decrease inflammation at short time and increase it at longer time exposures. In addition, 50-Hz MF exposure may decrease the humoral immune responses. It seems that 50-Hz MFs cause more alteration in immune system function at lower densities (100 μT).

**KEY WORDS:** interleukin-1β; interleukin-23; BLIMP-1; XBP-1; IRF-4; magnetic fields.

## INTRODUCTION

Due to inevitable use of electrical appliances, concerns about the destructive effects of magnetic fields (MFs) on human health are increasing. These fields are able to penetrate into biological tissues and affect their functions

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like alteration in cell signaling, cell adhesion, cell membranes, and gene expression. Whether these effects can induce human health hazards have been widely debated [25, 35, 39, 40].

Some researchers have shown that exposure to 50-Hz MFs is associated with prevalence of some diseases like cancers and autoimmunity [13, 27]. The immune system has essential role in these disorders by preventing development or by influencing on progress of them. Several investigations have also done regarding to the effects of exposure to 50-Hz MFs on different components of the immune system [15, 16, 25, 28, 32].

Interleukin (IL)-1β and IL-23 have critical roles in the immune system function. IL-1β with pleiotropic functions is not only a main mediator of inflammation but also has important role in the host defenses. Various types of cells including B cells, T cells, dendritic cells, and macrophages produce IL-1β. Investigations have shown that during an immune response, IL-1β can activate various types of cells including monocytes, macrophages, NK cells, B cells, T cells, and antigen-presenting cells (APCs). In addition, there is a report that IL-1β has pivotal role in the humoral immune response by priming T cells that is important in both T cell-APCs and T cell-B cell interactions [8, 17, 18].

IL-23 belongs to the IL-12 superfamily and is one of the immunomodulatory cytokines produced by APCs such as dendritic cells and macrophages. IL-23 also plays crucial role in the regulation of T helper 17 (Th17) differentiation [3, 36]. IL-23 affects plasma cell functions and production of antibody by them and induces IgM secretion by plasma cells. Therefore, it is speculated that IL-23 mainly involved in primary immune responses [2].

Humoral immunity is one of the important parts of the immune system characterized by B lymphocyte activation and antibody production. During an immune response against an antigen, B lymphocytes localize in the spleen and identify antigen in combination with signals from T helper and dendritic cells. Then, they will be activated and differentiated into non-dividing effector cells called plasma cells. Formation of plasma cells is associated with acquired distinct alternations in morphology, lifespan, and gene expression [19, 31]. Expression of the transcription factors B lymphocyte-induced maturation protein-1 (BLIMP-1), X-box-binding protein-1 (XBP-1), and interferon-regulatory factor-4 (IRF-4) are critical for function of plasma cells. During B cell differentiation to plasma cell, BLIMP-1 and XBP-1 induce many phenotypic changes including the increase of cell size, organelle mass, functions, and protein synthesis. These alternations terminate the proliferation of cell and increase antibody synthesis. Furthermore, BLIMP-1 and XBP-1 have role in class switching, B cell activation, and homing [9, 29]. The transcription factor IRF-4 is also a pivotal B cell modulator that regulates immunoglobulin class switching recombination and plasma cell differentiation. It is also required for formation and generation of the germinal centers [20, 22].

According to roles of IL-1β, IL-23, BLIMP-1, XBP-1, and IRF-4 in the inflammation and immune system functions, we investigated the effect of exposure to different magnetic flux densities of 1, 100, 500, and 2000 μT of 50-Hz MFs on serum IL-1β and IL-23 before and after stimulation of immune system with human serum albumin (HSA). The effects of 50-Hz MFs on expression of BLIMP-1, XBP-1, and IRF-4 were also evaluated in Wistar albino male rats.

## MATERIALS AND METHODS

### Animals

Eighty Wistar albino male rats weighing 202.5 ± 8 g, 8 weeks old, were purchased from the animal facilities of Hamadan University of Medical Sciences. The rats were housed in plastic cages in a temperature-controlled room (21–22 °C, humidity 55–65%) with free access to drinking water and standard food pellets. After 1 week of adaptation, the animals were randomly divided into five groups (a control and four exposures). The experimental groups were exposed to magnetic flux densities of 1, 100, 500, and 2000 μT, frequency of 50 Hz, from 8 to 10 am, 2 h/day for 2 months. The controls were maintained like experimental group with no magnetic field. All the protocols of the study were approved by Committee of Ethics for Hamadan University of Medical Sciences, Hamadan, Iran (Code: IR.UMSHA.REC.1396.96) [16, 25].

### Magnetic Fields Exposure Systems

The exposure systems and magnetic fields of this study were described in our previous studies [16, 25]. Briefly, the exposure units were consisted of solenoids (lengths 2 m, internal diameters 40 cm). The solenoids were coiled with different turns of copper wires (diameter 2 mm) around polyvinyl chloride cylinders (PVCs). The solenoids were connected to power supplies and adaptors producing different electric voltage. Combination of different turns of wires with different electrical potential in each solenoid, they could produce 50-Hz MFs with magnetic flux density of 1, 100, 500, and 2000 μT. The density of the magnetic fields was measured by Survey Meter (HI-

3604, Holaday Ind., USA) at the middles of solenoids. The background magnetic field density in the animal laboratory was about 0.07 ± 0.03 μT of 50-Hz MFs [16, 25].

### Immunization Procedure

After 1-month exposure, 5 ml blood was drawn from the retro-orbital plexus of each rat and sera were separated and stored at − 70 °C for cytokine analysis (pre-immunization phase). It was proposed that during the immune system response, genes of BLIMP-1, XBP-1, and IRF-4 would be activated and expressed. Therefore, in order to stimulate the immune system and expression of the these genes and generation plasma cells, all the rats were injected with HSA (100 μg/rat). HSA was in combination with incomplete Freunds adjuvant and intraperitoneally injected on days 31, 44, and 58 of the exposure. At the end of the exposure, all rats were weighed and sacrificed. Then, total bloods of rats were drained from vena cava vein, and sera were separated and assigned as post-immunization samples. The spleens were removed and frozen at − 70 °C for assessment of genes expression by RT-qPCR [16, 32].

### Cytokines Measurement

The serum concentrations of IL-1β and IL-23 were determined by enzyme-linked immunosorbent assay (ELISA) according to the suggested procedures in the manuals of the kits (EastBiopharm, China). All assays were carried out in duplicate. The kit's sensitivity for IL-1β was 10.23 pg/ml and for IL-23 was 1.52 pg/ml [30, 38].

### Total RNA Extraction

Five milligrams of each spleen was homogenized by mortar and pestle in 1 ml kit-provided cold reaction solution (RNX-plus) and transferred to a microtube. Total RNA was isolated according to manufacturer's instruction (CinnaGen, Tehran, Iran). Quantity of total RNA was calculated by absorbance at 260 nm, and its quality was determined *via* absorbance at 260/280 nm with a NANO-200 microspectrophotometer (A&E Laboratories, Guangzhou, China). The acceptable range for absorbance at 260/280 nm was considered 1.8–2.1 [16, 32].

### cDNA Synthesis

Each complementary DNA (cDNA) was synthesized using 5 μg splenic total RNA, oligonucleotides (dT), deoxynucleotides (dNTPs), and reverse transcriptase enzyme of Moloney Murine Leukemia Virus (M-MuLV) according to the manufacturer's instruction. Briefly, 5 μg total RNA (1 μl) was mixed with 1 μl oligo dT (40 μM), 1 μl dNTPs (10 mM), and 7 μl nuclease-free water. The reaction was incubated at 65 °C for 5 min and chilled on ice for 2 min in first step of the process. Then, 2 μl buffer (10×), 0.5 μl M-MuLV (100 U/ml) enzyme, and 7.5 μl nuclease-free water were added to the reaction. The mixture was incubated at 42 °C for 60 min, and the process was terminated at 85 °C for 5 min. The cDNAs were stored at − 20 °C and used for RT-qPCR amplifications [16, 37].

### RT-qPCR

Reverse transcription quantitative polymerase chain reaction (RT-qPCR) was used to detect the expression of *BLIMP-1*, *XBP-1*, and *IRF-4* genes. RT-qPCR amplification was performed by a Light Cycler® 96 System instrument (Roche Diagnostics GmbH, Germany) and SYBR Premix EX TaqII PCR Kit (Takara, Japan). Each RT-qPCR reaction was performed in volume of 20 μl containing: 10 μl Takara master mix (2×), 0.5 μl forward primer (10 mM), 0.5 μl reverse primer (10 mM), 2 μl cDNA, and 7 μl diethylpyrocarbonate (DEPC) water. The thermal parameters were as follows: initial activation at 95 °C for 30 s, followed by 38 cycles: denaturation at 95 °C for 5 s, annealing for β-actin at 58 °C, 30 s; for *BLIMP-1* at 54 °C, 30 s; for *XBP-1* at 58 °C, 30 s and for *IRF-4* at 64 °C, 30 s, and extension at 72 °C for 30 s. The final extension was 95 °C for 5 min. The threshold cycle (Cq) of the β-actin was used to calculate the normalized expression ($2^{-\Delta Cq}$) of the target genes by $2^{-[Cq\ (BLIMP\text{-}1,\ XBP\text{-}1,\ or\ IRF\text{-}4)\text{-}Cq\ \beta\text{-}actin]}$ formula. The relative expression of each gene was measured by $2^{-\Delta Cq\ in\ each\ group}/2^{-\Delta Cq\ control}$ [16, 26]. The primer sequences used in this study are shown in Table 1.

### Statistical Analysis

One-way analysis of variance (ANOVA) test and complementary *post hoc* (Tukey's test) were performed to compare the groups. Paired samples *t*-test was also used to compare the values in pre-immunization with post-immunization phases. The *P* values less than 0.05 were considered to be significant. Statistical analysis was performed by SPSS 16.0 package (SPSS Inc., IL, USA). Data were expressed as means ± standard deviation (SD).

**Table 1.** Specific Primers Used for Amplifications in RT-qPCR

| Gene | Primers sequences | GenBank accession no. | Amplicon size |
|---|---|---|---|
| *β-actin* | F: 5′-CGCGAGTACAACCTTCTTGC-3′<br>R: 5′-ATACCCACCATCACACCCTGG-3′ | NM_031144.3 | 200 |
| *IRF-4* | F: 5′-TCAGGGAACGGAAGTCTAAACCAG-3′<br>R: 5′-AAGAGGAGGGAGCAAACAGGATAC-3′ | NM_001106108.1 | 199 |
| *XBP-1* | F: 5′-TTCCTGGCTATGGTGGTG-3′<br>R: 5′-GTCTGTGCTGCTACTCTG-3′ | NM_001271731.1 | 153 |
| *BLIMP-1* | F: 5′-GCCTGCCAGAACGGAATGAAC-3′<br>R: 5′-ACTGCTGTATTGCTTTGGGTTG-3′ | NM_008772991.2 | 177 |

## RESULTS

### Effect of 50-Hz MFs on Serum IL-1β and IL-23

Serum levels of IL-1β were significantly decreased to 415.33 ± 96.3 pg/ml ($P = 0.009$) in 1 μT and to 414.63 ± 84.2 pg/ml ($P = 0.008$) in 100 μT exposure groups from 587.07 ± 56.2 pg/ml in the control at pre-immunization phase, but the amount of IL-1β after immunization with HSA has no difference among the groups ($P = 0.216$) (Table 2). Instead, the serum level of IL-23 did not revealed any alteration at pre-immunization phase among the studied groups ($P = 0.232$). However, its serum concentration increased ($P = 0.023$) to 57.19 ± 9.1 pg/ml in 100 μT exposure group from 35.27 ± 8.1 pg/ml in the control at post-immunization phase (Table 2).

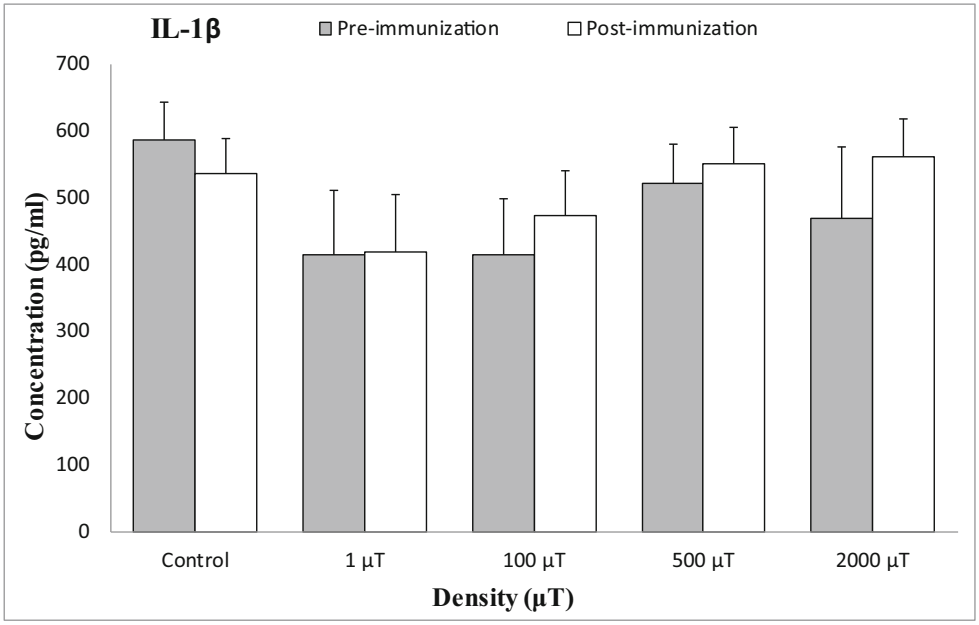
There were also no statistically significant ($P > 0.05$) alteration in concentrations of IL-1 β and IL-23 in a group at pre-immunization phase compared with post-immunization phase (Fig. 1). It means that in overall, stimulation of the immune system by HSA did not statistically change the serum levels of these two cytokines. Therefore, any alteration in their levels among the experimental groups could be due to 50-Hz MFs and time course.

**Table 2.** Serum IL-1β and IL-23 in 50-Hz MF-Exposed and Control Groups at Pre- and Post-immunization Phases

| Group | IL-1β (pg/ml) | | IL-23 (pg/ml) | |
|---|---|---|---|---|
| | Pre-immunization | Post-immunization | Pre-immunization | Post-immunization |
| 1 μT | 415.33 ± 96.3[a,†] | 417.72 ± 86.6 | 48.68 ± 7.1 | 41.96 ± 9.5 |
| 100 μT | 414.63 ± 84.2[††] | 473.83 ± 65.9 | 42.69 ± 5.6 | 57.19 ± 9.1[†††] |
| 500 μT | 521.04 ± 59.3 | 549.59 ± 54.5 | 49.51 ± 12.6 | 44.09 ± 7.0 |
| 2000 μT | 469.53 ± 106.5 | 561.17 ± 56.1 | 50.03 ± 7.5 | 40.09 ± 7.0 |
| Control | 587.07 ± 56.2 | 535.53 ± 52.3 | 37.58 ± 5.8 | 35.27 ± 8.1 |
| *P*[b] | 0.004 | 0.216 | 0.232 | 0.038 |

[a] Results are presented as mean ± SD

[b] ANOVA test was used to compare the serum levels of IL-1β and IL-23 among the different magnetic flux densities and control groups at pre- and post-immunization phases. Serum level of IL-1β was significantly decreased at pre-immunization phase, whereas serum IL-23 level was increased at post-immunization phase. At post-immunization phase, the immune systems of rats were stimulated by HSA at 31, 44, and 58 days of exposure. No distinct differences were observed among IL-1 β and IL-23 at post- and pre-immunization phases, respectively. †$P = 0.009$, ††$P = 0.008$, and †††$P = 0.023$ compared with controls (Tukey's complementary test)



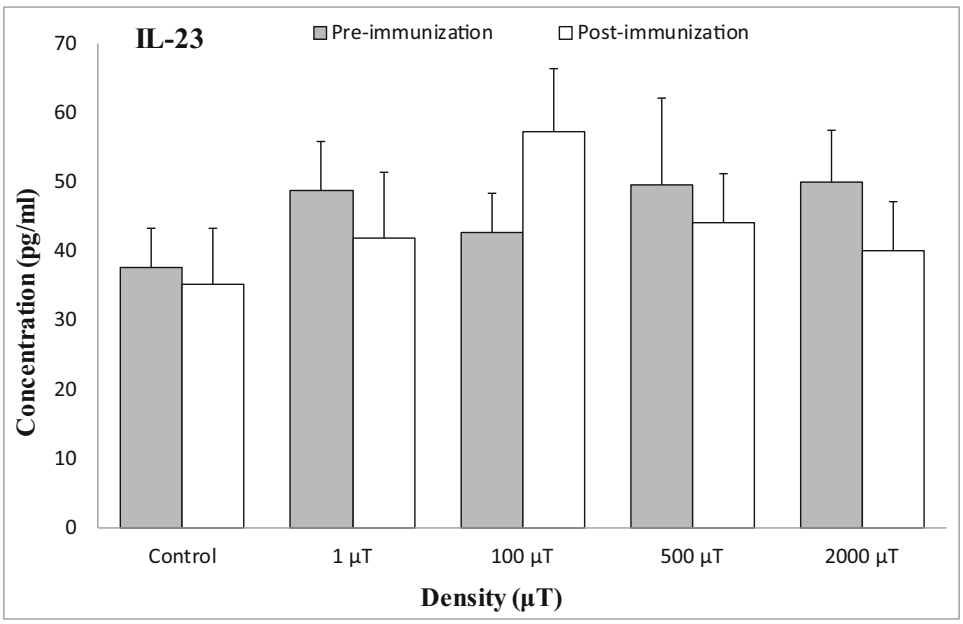




**Fig. 1.** Serum IL-1β and IL-23 at pre- and post-immunization phases. Paired-samples *t* test was used to compare the levels of IL-1β and IL-23 in a group at two phases of the pre- and post-immunization. The results of the test demonstrated that the mean levels of the two cytokines were not different in all groups due to immunization with human serum albumin at post-immunization phase compared with pre-immunization phase.

### Effects of 50-Hz MFs on BLIMP-1, XBP-1, and IRF-4 Expression

The normalized expression of *BLIMP-1*, *XBP-1*, and *IRF-4* genes were analyzed by ANOVA and followed with complementary Tukey's test. The results showed that the relative expressions of *BLIMP-1*, *XBP-1*, and *IRF-4* genes significantly decreased at magnetic flux density of 100 µT of 50-Hz MFs ($P = 0.014$, $P = 0.012$, $P = 0.020$, respectively) compared with the controls (Fig. 2).

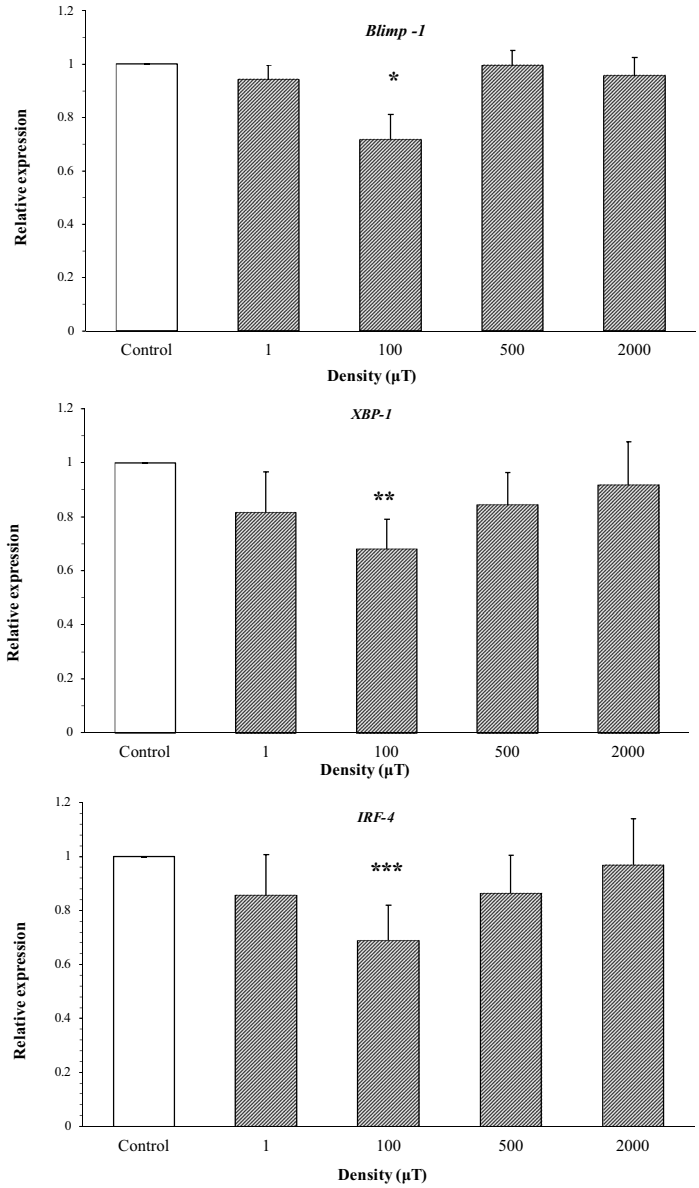



**Fig. 2.** Relative expression of *BLIMP-1*, *XBP-1*, and *IRF-4* genes. The spleens of rats were removed after 60-day exposure to different magnetic flux densities of 1, 100, 500, and 2000 μT of 50-Hz MFs. All groups were immunized with HSA at 31, 44, and 58 days of exposure. Data analyzed by one-way analysis of variance (ANOVA) tests among the groups to compare expression of BLIMP-1, XBP-1, and IRF-4 and followed by Tukey's test. Results showed that expression levels of *BLIMP-1*, *XBP-1*, and *IRF-4* significantly decreased in 100 μT group compared with the controls. $*P = 0.014$, $**P = 0.012$, $***P = 0.020$. Data are presented as mean values ± SD.

## DISCUSSION

One of the important points of this study was investigation the effect of different magnetic flux densities of 50-Hz MFs on the immune system. In addition, the effects of 50-Hz MFs on serum levels of IL-1β and IL-23 at two phases (pre- and post-immunization), the expression of BLIMP-1, XBP-1, and IRF-4 in immunized rats were also analyzed for the first time.

According to the results, exposure of rats to 1 and 100 μT magnetic flux densities of 50-Hz MFs suppressed production of IL-1β at pre-immunization phase compared with control, while at post-immunization phase, production of IL-1β was not altered among the groups. These results are consistent with studies by Hefeneider et al. They exposed ewe lambs (age of 8–10 weeks) to MF with magnetic flux density of 3.5–3.8 μT for 10 months and found a decline in IL-1β activity although; long-term (27 months) exposure of sheep did not affect IL-1β activity [6]. An investigation by Rohde et al. also supports our finding. In a double-blind, placebo-controlled, randomized study, they showed that exposure to pulsed electromagnetic fields caused strongly significant decrease in wound exudates IL-1β level, in post-operative pain and inflammation in breast reconstruction surgery [23]. In contrast, an acute exposure (24 h) of humans to 50-Hz MFs with magnetic flux density of 10 μT did not have any effect on serum IL-1 [28]. The reasons underlying discrepancy in these studies may be due to differences in age and strain of the cases, *in vitro* or *in vivo* exposure conditions, pulsed or sinusoid MFs, duration, strength, and frequency of exposure [5, 6]. We have also some unpublished data that during the 50-Hz MF exposure, serum IL-10 (as an anti-inflammatory cytokine) increased at pre-immunization phase and serum TNF-α (as pro-inflammatory cytokine) declined. The studies showed that inflammatory cytokines can take part in acute or chronic inflammation. IL-1β plays an important role in both acute and chronic phase of inflammation [21]. It seems that 50-Hz MFs can also be used in tissue repair [24].

This study also showed that serum level of IL-23 increased at post-immunization phase (after induction of rats' immune system) in 100 μT group compared with control, while at pre-immunization phase, its level was not changed among the experimental groups; IL-23 is a necessary cytokine for maturation of Th17 effector cells in the terminal stage, and this cytokine caused expression of some factors that are necessary for functions of Th17 [4].

It seems that 50-Hz MF exposure reduces the secretion of IL-1β at short time (1-month exposure, pre-immunization phase) and may be effective in healing inflammatory diseases. While in a longer time (2-month exposure, post-immunization phase), secretion of some other cytokines like IL-23 is induced and affects inflammatory immune responses and suppresses the body's protective response and occur inflammatory diseases [12, 14].

The present study also demonstrated that 50-Hz MF exposures with different magnetic flux densities reduced expression of *BLIMP-1*, *XBP-1*, and *IRF-4* genes in the spleen of immunized rats. Some investigations have shown that induction of immune system of rats with HSA cause a considerable proliferation of the plasma cells in the spleen. According to the role of BLIMP-1, XBP-1, and IRF-4 in B cell differentiation and formation to plasma cells, it seems that exposure to 50-Hz MFs led to suppression of plasma cells and antibody production through suppression of BLMP-1, XBP-1, and IRF-4 expression. These results are also in the favor with a study that showed pulsed electromagnetic wave decreased serum level of IgG, IgA, and IgM antibodies in rats [1].

In addition to the role of BLIMP-1, XBP-1, and IRF-4 in the humoral immunity and antibody production, they may also associate with the innate immunity and inflammation. In various studies, it has been identified that BLIMP-1 modulated functions of dendritic cells (DCs) and macrophages [10, 11]. Deletion of BLIMP-1 in animal model also showed that it is required to protect against the autoimmunity and inflammation [11]. Furthermore, IRF-4 is essential for DC development, differentiation, and function. IRF-4 expression also caused to suppress the production of proinflammatory cytokines of TNF-α and IL-6 by macrophages in response to toll-like receptor (TLR) stimulation [7].

The expression levels of IRF-4, BLIMP-1, and XBP-1 were downregulated in the lower density (100 μT) groups of 50-Hz MFs, while the expression of *BLIMP-1*, *XBP-1*, and *IRF-4* genes under the influence of 50-Hz MFs at 500 and 2000 μT densities were not significantly altered compared to the control group. The reason for this can be supposed that exposure to a relatively lower density of magnetic fields cause a mild stress condition and affect immune response functions. While at 500 and 2000 μT magnetic flux density exposure, the body activates its protective responses against adverse effects of waves that can inhibit them and normalize the production of agents involved in normal defense system. There are some reports that heat shock proteins (HSPs) can have this role. HSPs act as a chaperon and protect the cells from adverse effect. HSPs can only express due to stronger stressor compared with the weaker stressors [33, 34, 40].

In conclusion, it can be concluded that exposure to 50 Hz-MFs can decrease IL-1β (an inflammatory cytokine) at short time exposure and caused increase IL-23 (another inflammatory cytokine) at longer duration. In addition, 50-Hz MF exposure downregulates some critical gene expressions (*BLIMP-1*, *XBP-1*, and *IRF-4*) that are important in humoral immune response. An interesting point in all this is that these effects of the 50-Hz MF fields have been effective in low densities (100 μT).

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## COMPLIANCE WITH ETHICAL STANDARDS

All the protocols of the study were approved by Committee of Ethics for Hamadan University of Medical Sciences, Hamadan, Iran (Code: IR.UMSHA.REC.1396.96)

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