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Electromagnetic Fields and Its Harmful Effects on the Male Reproductive System

Azab Elsayed Azab[1, *], Abdurazag Mohamed Khalat[2], Shaban Ali Ebrahim[3], Mohamed Omer Albasha[4]

[1]Department of Physiology, Faculty of Medicine, Sabratha University, Sabratha, Libya
[2]Faculty of Engineering, Sabratha University, Sabratha, Libya
[3]Department of Physics, Faculty of Science, Alejelat, Zawia University, Alejelat, Libya
[4]Department of Zoology, Faculty of Science, Alejelat, Zawia University, Alejelat, Libya

Abstract

The progress of science will provide the world with new electromagnetic fields (EMFs) emitting technologies and subsequently with new problems. Cell phones have become a vital part of everyday life. It creates an EMF around them when in use, thus increasing the electromagnetic contamination. Male individuals generally carry their cell phones in their pockets close to their testes in standby mode increases the importance of study the effects of EMF on the male reproductive system. This review aimed to highlight the effects of exposure to EMFs on the male reproductive system in humans and experimental animals. Telecommunications technology has advanced rapidly and explosively in recent years. Exposure to EMFs has shown that serious patho-physiological changes on the male reproductive system. It induced decreases in serum levels of testosterone, sperm count, motility, morphometric abnormalities, and significant increases in serum luteinizing hormone level, lipid peroxidation, and DNA damage in sperm cells. Histologically, EMFs caused degeneration in the seminiferous tubules, spermatogonia apoptosis, decreases in the height of the germinal epithelium, and the number of Leydig cells. Also, exposure to EMFs induced a significant increase in catalase, and a significant decreases in glutathione peroxidase, histone kinase, and superoxide dismutase. It can be concluded that exposure of human and experimental animals to EMFs have been a negative effect on the male reproductive system by causing histopathological changes and disturbances in the functions of the male reproductive system. The main cause of infertility in man is oxidative stress. The potential male reproductive health effects of EMF should be continually reassessed as new research results become available. Additional studies might increase our understanding of the sensitivity of male reproductive to EMF.

Keywords

EMF, Male Reproductive System, Pathophysiological Changes, Testis Histopathology, Oxidative Stress

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1. Introduction

The progress of science will provide the world with new EMF emitting technologies and subsequently with new problems [1]. Today, cell phones have become a vital part of everyday life [2]. Cell phone technology is an integral part of everyday life and its use is not only restricted to voice conversations but also conveying news, high- resolution pictures, and internet. However, these advances in technology are accompanied by a progressive boost in the intensity and frequency of the emitted electromagnetic waves without consideration of their health consequences [3]. Environmental exposure to electromagnetic radiation has

* Corresponding author
E-mail address: azabelsaied@yahoo.com (A. E. Azab)

been increasing with the increasing demand for communication devices [4].

Exposure to intermediate frequency (IF) fields is increasing due to new applications such as induction heating cookers, wireless power transfer, and electronic article surveillance systems [5]. Wireless local area networks (WLANs) are an increasing alternative to wired data networks in workplaces, homes and public places. Nevertheless, as previously reported for other electromagnetic radiation sources, the rapid increase in WLANs in our daily environment, especially in private, academic and clinical surroundings, has caused great public concern about the possible effects on human health. This concerning situation requires further investigation of the possible biological effects of exposure to WLAN signals, requiring new experiments both in vivo and in vitro [4, 6]. The artificial sources of electromagnetic radiation have risen tremendously because of the ongoing needs of electricity, telecommunications, and electronic devices. New technologies which use the spectrum of high-frequency emissions are incorporated in many aspects of telecommunications. As a consequence, there is a lot of interest about the possible effects of the radiation emitted from the machines which are engaged in the telephony such as hand phones, base stations and transmitters [1]. The mobile phone technology is based on radiofrequency radiation with a transmission of microwaves carrying frequencies between 880 and 1800MHz [1, 7]. Mobile phones create an EMF around them when in use, thus increasing the electromagnetic contamination, also known as "electrosmog", in the vicinity [8].

Electromagnetic radiation (EMR) emitting from the natural environment, the use of industrial appliances, constantly influences the human body. It may be expected that the interactions between electromagnetic radiation and the living organism would depend on the amount of the transmitted energy and type of tissue exposed. Electromagnetic waves exert an influence on human reproduction by affecting the male and female reproductive systems [9]. The biological effects of EMFs generally can be divided into thermal effects by the electromagnetic field energy absorption, stimulation function by the induced electric current, and athermic action by the long-term exposure [10-12]. Thermal effects are defined as the heat generated by EMFs in a specific area. The non-thermal effects depend on the absorption of energy and changes in the behavior of tissues without producing heat. EMFs have high penetration power, and they are capable of moving charged particles, such as the electrons and ions of large macromolecules and polymers [10, 11].

Increasing use of cell-phone is one of the most important risk factors for population health [13]. The fact that male individuals generally carry their cell phones in their pockets close to their testes in standby mode increases the importance of study the effects of EMF on the male reproductive system [12]. The animal studies could provide useful information on the comprehension of the interaction of EMF with the living organism and on the possible commonality with the humans [1]. The duration of cell phone use was negatively correlated with the proportion of rapid progressive motile spermatozoa and motility [14]. Recently, evidence from several studies supports a growing claim that cell phone usage may have a detrimental effect on sperm parameters leading to decreased male fertility. Nonetheless, other studies showed no conclusive link between male infertility and cell phone usage [2].

Our bodies act as parasitic antennas that receive EMW and convert them into electric and magnetic fields. The male reproductive system is highly compartmentalized and sensitive biological system that requires the integration of intrinsic and extrinsic factors to properly function. The generated electrical currents may alter the testicular microenvironment, and hormonal milieu necessary for sperm production. Additionally, sperms are electrically active cells and their exposure to cell phone electromagnetic waves and currents may affect their motility, morphology and even their count [3].

The reproductive system is controlled by the nervous and endocrine systems, EMFs can affect the two systems mentioned above, so the genital system also is involved [11, 15]. EMF exposure can weaken reproduction ability [16]. The cell phone uses negatively affects sperm quality in men [17]. It might adversely affect the quality of semen by decreasing mostly motility but also the sperm counts, viability, and morphology [18]. Exposure to a low-level of electromagnetic radiation from cell phones induced 8% reduction in sperm motility, and 9% reduction in sperm viability [19, 20]. Exposure to Wi-Fi-equipped laptop computers for four hours cause a significant decreased in sperm motility and an increase in sperm DNA fragmentation [21]. EMF exposure can weaken reproduction ability [16].

Testes are very important organs situated externally to the body and enclosed by the scrotum. The testicular parenchyma is the site of an intense proliferation and differentiation of the germinal cells that will become the sperm cells. Testes are very sensitive to temperature variations and for this reason, the scrotum, which contains the testicular parenchyma, has a specialized contractile structure [1]. Electromagnetic fields can have destructive effects on sex hormones, and gonadal function. So people must be aware of the negative effects of EMFs. Although the impact of the waves varied at different frequencies, it is

better to stay as far away as possible from their origin because of the risks associated with exposures to these waves [11].

2. Types of Electromagnetic Fields

EMFs can be considered to consist of four different types. The first type of EMFs refers to extremely low frequency (ELF) EMFs, which are EMFs that are below 300 HZ, and they are produced by military equipment and railroads. The second type, known as the intermediate frequency (IF) EMFs, have frequencies in the range of 300 Hz to 10 MHZ, and they are produced by industrial cables and electrical equipment in homes, such as televisions and computer monitors. The third type is hyper frequency (HF) EMFs that have frequencies in the range of 10 MHz to 3000 GHz and are produced by mobile phones and radio broadcasting. Radio frequencies (RFs) also are a part of this category, which has frequencies up to 100 MHz [11, 15]. There are also static EMFs that are produced by MRI and geomagnetism and have specified with zero frequency [11, 22].

3. Generation of Cellular Phones

Telecommunications technology has advanced rapidly and explosively in recent years. The first-generation of cellular phones was the Nordic mobile telephone. The second-generation of cell phones that replaced the older analog type is the digital models have increased voice capacity, provided faster data transfer speeds, longer battery life, less power use and better signal quality than the first generation cell phones. The cell phone technologies that are commonly used nowadays are the global system for mobile communication (GSM) and code division multiple access (CDMA). Both of these technologies are used by cell phone companies in the USA. The GSM technology uses narrow-band time division multiple access (TDMA), whereas CDMA incorporates the wider band that allows more users without interference and better security by providing every user with a unique code. The third-generation cell phones, consist of universal mobile telecommunications system (UMTS)/ wideband code division multiple access (W-CDMA) and the high-speed downlink packet access (HSDPA) phones. The UMTS utilizes a GSM infrastructure with a W-CDMA air interface (the specification of the radio transmission between a mobile phone and the base station), which adds advantages to UMTS over GSM technology. The HSDPA is based on the W-CDMA technology with improved downlink speed that allows even higher data transfer speeds and capacity. In most other parts of the world, the frequency bands used are 900 MHz and 1800 MHz. The newer phones offer a quad-band feature, which means that they can operate on the four common frequencies (850/900/1800 and 1900 MHz), and they have the capacity to switch automatically among these four frequencies [23].

Specific absorption rate (SAR) is the energy flow per unit of mass (watts/kg; W/kg). It is a measurement of the power or heat absorbed by the tissue either in a local area of a human tissue or averaged over the whole body. The Federal Communications Commission has set a SAR safety limit of 1.6 W/kg, averaged over a volume of 1 g of tissue, for most parts of the body. Exposure guidelines for RF protection had adopted the value of 4 W/kg averaged over the whole body (SAR WB) as the threshold for the induction of adverse thermal effects associated with an increase of the body core temperature of about 1°C in animal experiments [23, 24].

4. Effects of EMF on Serum Testosterone Level

Testes perform two important functions: spermatogenesis and steroidogenesis. Leydig cells secrete testosterone, which has the regulatory role in stimulating and maintaining sperm production [2]. Leydig cells are among the most susceptible cells to EMW and that injury to these cells may affect spermatogenesis [2, 25]. Many researchers have reported that exposure to EMFs induced changes in serum levels of testosterone [11, 26-29]. Qi *et al.,* [16], and Al-Akhras *et al.,* [30] reported that serum testosterone level of exposed rats to 50 Hz, 25 lT ELF-EMF for 18 weeks was associated with a significant decrease after 6 and 12 weeks of exposure. Adult rats that were exposed to 900-MHz EMFs for 30 min five days a week had decreased serum levels of testosterone [26]. At high frequencies, especially 2.45 GHz, EMFs reduced the number of Leydig cells and increased apoptosis at seminiferous tubule in rats [31]. Also, exposure of male rats to EMF induced a reduction in the number of Leydig cells and testosterone production as well as increases in luteinizing hormone levels and apoptotic cells [4]. Oxidative stress and EMW induced alteration in PKC enzyme complex which is present in seminiferous tubules and Leydig cells can explain the deranged function of Leydig cells in response to cell phone [2, 32]. EMW not only alters serum testosterone but also affects the expression of mRNA for P450 cholesterol side chain lyase (the first enzyme in steroidogenesis) in Leydig cells [2, 33].

5. Effect of EMF on Semen Quality

Exposure to EMF caused a decrease in sperm motility In vivo and in vitro [18, 34-37]. Agarwal *et al.,* [38] reported that use of cell phones for longer durations caused a decreasing in the sperm counts, motility, and viability. Wdowiak *et al.,* [39] reported that males who had used GSM equipment for more than 2 years showed an increase in the percentage of sperm cells of abnormal morphology with the duration of exposure to GSM phone. Leaky plasma membranes, calcium depletion, and oxidative stress are the postulated cellular mechanisms mediating the harmful effects of cell phones radiation on sperm and male fertility potentials [3].

La Vignera *et al.,* [40] reported that the results of studies conducted in rats, mice, and rabbits using a similar design based upon mobile phone RF exposure for variable lengths of time have shown that RF-EMR decreases sperm count and motility and increases oxidative stress. In humans, 2 different experimental approaches have been followed: one has explored the effects of RF-EMR directly on spermatozoa and the other has evaluated the sperm parameters in men using or not using mobile phones. The results showed that human spermatozoa exposed to RF-EMR have decreased motility, morphometric abnormalities, and increased oxidative stress, whereas men using mobile phones have decreased sperm concentration, decreased particularly rapid progressive motility, normal morphology, and decreased viability. These abnormalities seem to be directly related to the duration of mobile phone use.

6. EMFs and Fertility

Fertility is the ability to have a child and success in reproduction. On the other hand, infertility is the malfunction in reproduction and the problems relating this matter is known as one of the most important issues in couples' life [13, 41]. Infertility represents one of the most common diseases and affects between 17 and 25% of couples [2]. Of these, male factor infertility is responsible for approximately 50% of the infertility cases [2, 42]. The prevalence of male infertility at the reproductive age has been estimated to be up to 7-8%, and there has been a tendency to increase in recent decades. With the exception of obstructive causes, idiopathic male infertility originates from decreased sperm quality with no organic, genetic, or endocrine alterations in the genital tract [12, 14]. The most common cause of males' infertility is their inability to produce enough healthy and active sperm [13, 43, 44]. In the last few decades, the quality of sperm and its fertility power has had a significant decrease throughout human society [13, 41, 43].

Fatehi *et al.,* [13] found a reduction in the number of sperms and two-cell embryos in the exposed mice to cell-phone RF waves. The RF waves probably impair the acrosome, resulted in DNA damage; consequently, induce death of the sperm. Furthermore, cell-phone waves affect the structure and morphology of the mice sperm resulted in a reduction of the capacity of the sperm in the fertilization process. These induced the reduction in the number of fertilized oocyte and two-cell embryos. When the RF waves are absorbed by the body, they contain energy that can produce free radicals. Free radicals can break a chemical bond and become a chain of biological events including damage in the cell membrane of sexual cells [13, 45]. Electromagnetic waves increase the amount of oxygen free radicals in the body of animals. These free radicals disturb the spermatogenesis process and changes in the cell membrane of the sperm, which causes changes in the capacity and acrosome response of the sperm cell. This process causes disorder in the process of binding the sperm to the oocyte. An incomplete finding leads to failure of normal fertility or laboratory one [13].

Bernabo *et al.,* [46] reported that the irradiation of wild pigs with 50 Hz electromagnetic fields 12 h daily for 6 days caused acrosome degradation, decreased acrosome reaction capacity and fertilization process, as well as a reduction in sperm fertility. SLF-EMFs had reduced intracellular calcium levels as compared to the control group, and there were reduced motility and fertilization [11, 15, 47]. This process takes place by interfering with the intracellular calcium homeostasis, resulting in disability in sperm function [11]. Kumar *et al.,* [48] found that a significant reduction in testicular weight, sperm count, and seminiferous tubules in male albino rats exposed to EMF when compared with sham-exposed control group. Authors concluded that exposure to mobile phone radiation can affect sperm functions via mechanisms that involve oxidative stress. The main cause of infertility in man is oxidative stress.

7. Testicular Histopathological Change Induced by Exposure to EMF

Dasdag *et al.*, [49] investigated whether there are adverse effects due to microwave exposure emitted by cellular phones in male Wistar albino rats. The animals (n = 18) were divided into three groups (control, standby exposed group, speech exposed group). Specific energy absorption rate (SAR) was 0.141 W/kg. Rats in the experimental groups were exposed for 2 h/day for 1 1 month in the standby position; whereas phones were turned to the speech position three times for 1 min. Histological changes were especially observed in the testes of rats in the speech group. The

seminiferous tubular diameter of rat testes in the standby and speech groups was found to be lower than the sham group. Rectal temperatures of rats in the speech group were found to be higher than the sham and standby groups. The rectal temperatures of rats before and after exposure were also found to be significantly higher in the speech group. A study of male rats indicated that a 50-Hz frequency for 8 h/day for eight months caused histological variations of the testis that included weight loss and a reduction in the average diameter of the seminiferous tubule [15]. Rajaei *et al.*, [50] reported that exposure to EMF for long periods could decrease the diameter of reproductive ducts and the length of the epithelial cells. Khaki *et al.* [27] reported that exposure to EMF caused profound changes in the shape of seminiferous tubules and their boundary tissue. EMFs induced cell death in testicular germ cell in mice [51], and a decrease in germ cell population in the testis of rats [52]. Also, Lee *et al.,* [53] recorded that exposure of BALB/c mice to electromagnetic field 60 Hz, 0.5 mT 24 h/day for 8 weeks showed a decrease in normal seminiferous tubules, increased in the germ cell death, spermatogonia apoptosis and DNA damage in the testis compared to controls. Ozguner *et al.* [54] reported that during the experiment, 20 male Sprague–Dawley rats (5 months of age) were either exposed to 900MHz CW (average power density 1±0.4 mW/cm^2) or not (control group). Rats exposed 30 min/day, for 5 days/week for 4 weeks. The authors were observed the mean height of the germinal epithelium was found decreased in the group of rats that had been irradiated.

Qi *et al.,* [16] investigate that the effects of the extremely low-frequency electromagnetic field on the fertility. Ten pregnant C57BL/6NCrj mice were exposed to 50 Hz field 500 mG for 1 week (12 h per day), and 24 male and 42 female B6C3F1 mice born of them were further exposed up to 15.5 months. Control group, 10 pregnant mice were bred without exposure, and produced mice were observed without exposure for the same period. The testicular weights of the EMF exposed group mice (0.11 ± 0.021 g) were significantly decreased than the control group mice (0.12 ± 0.030 g), ($P<0.01$). The sizes of seminiferous tubules were significantly smaller than the control groups (197.4 ± 18.8 μm vs. 205.7 ± 23.9 μm) ($P<0.01$) (Figure 1).

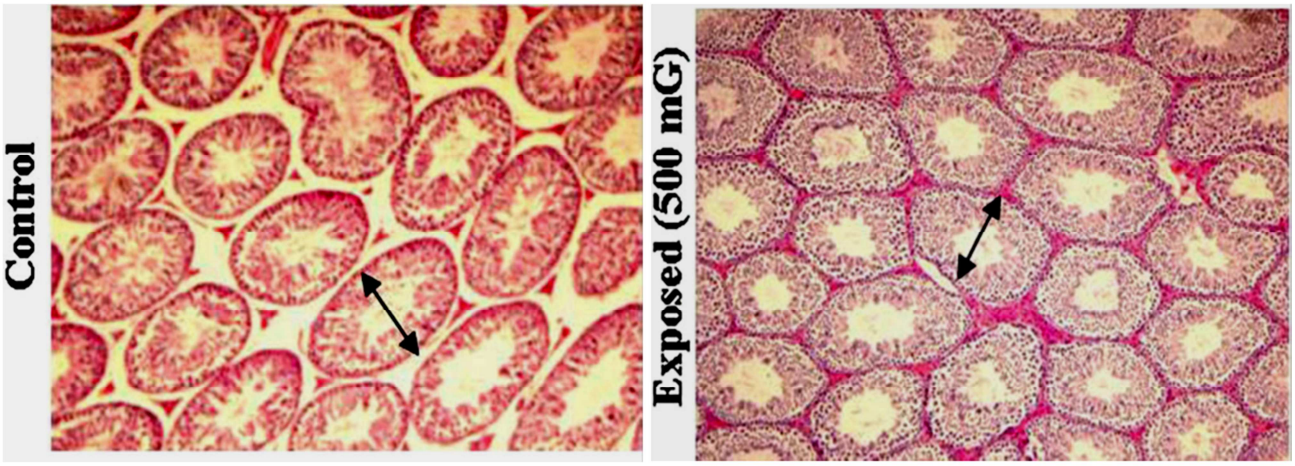

Figure 1. Seminiferous tubules of the controls groups and the EMF exposed groups B6C3F1 male mice. The diameters (double-headed arrow) of the seminiferous tubules were measured using light microscopy [16].

Oh *et al.,* [12] investigate the effect of long duration exposure to the electromagnetic field from mobile phones on spermatogenesis in rats using 4G-LTE. Twenty Sprague-Dawley male rats were placed into 4 groups according to the intensity and exposure duration: Group 1 (sham procedure), Group 2 (3 cm distance + 6 h exposure daily), Group 3 (10 cm distance + 18 h exposure daily), and Group 4 (3 cm distance + 18 h exposure daily). After 1 month, the degree of interstitial edema was variable area by area; however, no significant difference was noted among the groups. No histologic abnormality was noted in the epididymis of each group. Semi quantitative histopathologic analysis revealed decreased elongated spermatids in Group 4 (Figure 2 (d)) compared with the other groups, whereas no morphologic abnormality was noted in germ cells (Figure 2). Authors concluded that a long duration of 4G-LTE based EMF had a harmful effect on spermatogenesis. In particular, the sperm and Leydig cell count significantly decreased in the long duration exposure group, showing that continuous cell phone use could be hazardous for fertile men, especially adolescent men.

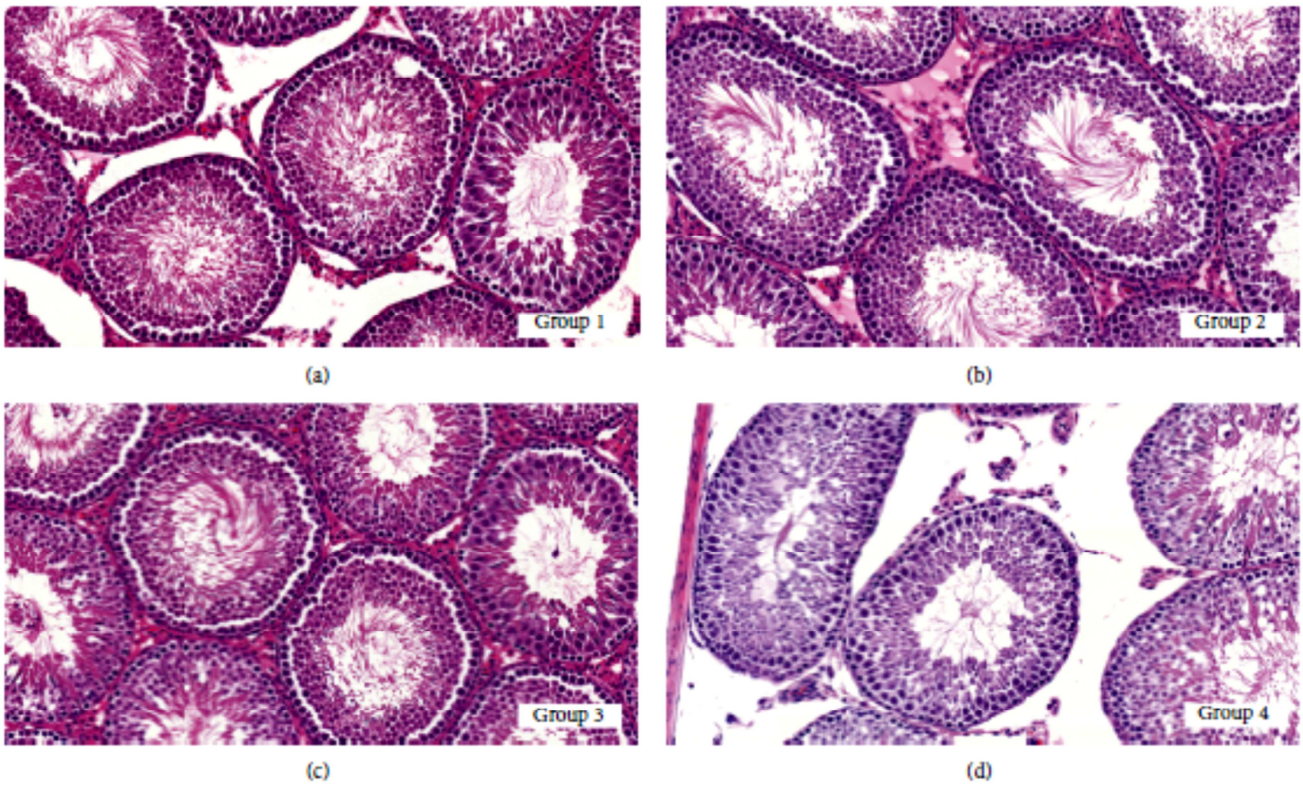

Figure 2. Photomicrographs of testes in each group. Note the decreased elongated spermatids (late spermatids) in Group 4 (d) compared with other groups [(a) Group 1, (b) Group 2, (c) Group 3]. (a–d) H&E, ×400 [12].

Khayyat, [55] investigated that the possible histopathological effects of isothermal non-ionizing EMFs on the testis of mice. Forty five adult male BALB/c mice were divided into two experimental groups and a control group. One group was exposed to frequency electromagnetic radiation between 3.9 x 10/4 Hz and 7.5 x 1014 Hz for 8 h per day for 3 days and the other group was exposed to frequency electromagnetic radiation between 3.9 x 1014 Hz and 7.5 x 1014 Hz for 8 h per day for 12 days. At the end of the exposed period, light microscopical studies. The testis showed atrophied seminiferous tubules and interstitial tissue expended the space between the seminiferous tubules, necrosis in the germinal epithelial cells of the seminiferous tubules, a decrease in Sertoli cells, deceleration of spermatogenesis, and degeneration of germ cells (Figure 3). In the testis of animals exposed for 12 days to EMF, marked and severe alterations were noticed. The Leydig cells and intertubular connective tissue showed signs of hypoplasia and the intertubular space became wider. Most of the seminiferous tubules had an irregular shape and the boundary tissue was thinner and breaks in its continuity were seen at multiple locations. Damage in the epithelium germinal layer, maturation arrest in the spermatogenesis, and disorder in the germinal cell distribution were recorded. Moreover, atrophied seminiferous tubules decrease in the germ cell population, and fusion between some seminiferous tubules were observed (Figure 4).

Aydin *et al.* [56] found that exposure of rats to EMF caused deceleration of spermatogenesis and degeneration of germ cells. Ai and Soleymanirad [57] reported that exposure of rats to an electromagnetic field lead to a significant reduction in the number of spermatogenic cells, spermatids, and sperm, and to a significant increase in the number of primary spermatocytes.

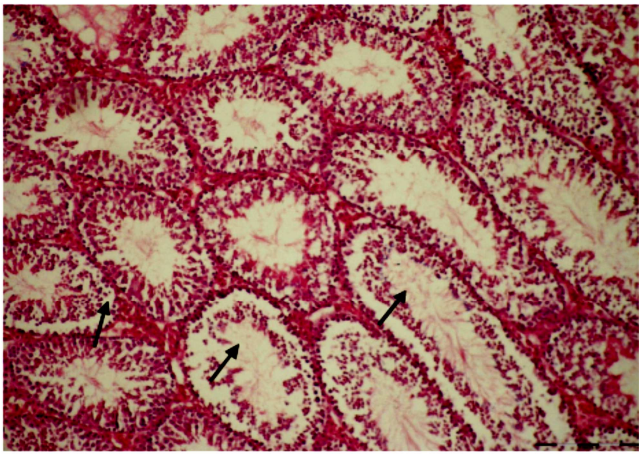

Figure 3. A section of the testis of the mouse exposed to EMF for 3 days showing massive intertubular tissue, the disorganized arrangement of spermatogenic cysts (arrows) and proliferation of the Leydig cells necrotic spermatogonia, low height epithelium, a lower number of spermatozoa, and proliferation of the Leydig cells. (X100) [55].

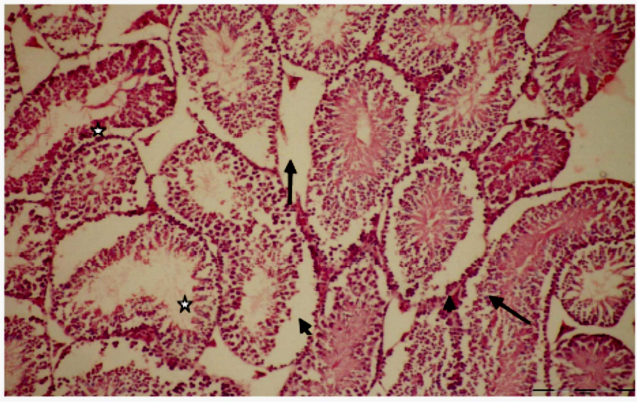

Figure 4. A section of the testis of the mouse exposed to EMF for 12 days showing detachment of spermatogonia from the basal membrane (arrows) hypoplasia in the intertubular connective tissue, Leydig cells, and germinal epithelia. Notice the wide tubular lumen with no sperm (asterisk), detachment of the spermatogonia from the basal membrane (arrow heads), necrotic germ cells, and degenerated and disorganization of spermatocytes (X 100) [55].

Al-Damegh, [8] investigated that the effect of exposure of rats to the EMR emitted by a GSM cellular phone (900/1800/1900 MHz, 2-W) for 15, 30, and 60 min daily for two weeks. After two weeks of exposure, the sections of the testis showed degeneration in the seminiferous tubules with the complete absence of spermatozoa, and some spermatogenic nuclei, and showed karyomegaly and a high incidence of mitotic divisions (Figure 5). The seminiferous tubules diameters were significantly increased and the mean height of the germinal epithelium was significantly decreased in the testes of exposed rats as compared with the unexposed EMR rats. A reduction in the spermatid numbers within the lumen of the seminiferous tubules marked mitotic divisions and pyknosis of some spermatogenic nuclei were observed in the testis sections after a two-week exposure to EMR (Figure 5). EMFs penetrate living organisms and alter the cell membrane potential [8, 58]. This alteration may affect free-radical processes within the cell and alter the activities of antioxidant enzymes, particularly CAT and c-GPx, in different organs. At the level of the testes, oxidative stress is capable of disrupting the steroidogenic capacity of Leydig cells [8, 59] and the capacity of the germinal epithelium to differentiate normal spermatozoa [8, 60]. Wang *et al.,* [61] suggested that RF-EMR may change the permeability of the blood-testis barrier. RF-EMR-mediated ROS formation can lead to heat shock protein (hsp) production and phosphorylation, which can alter the secretion of growth factors and mediate an increase in the blood-testis barrier permeability, as suggested by Desai *et al*. [62].

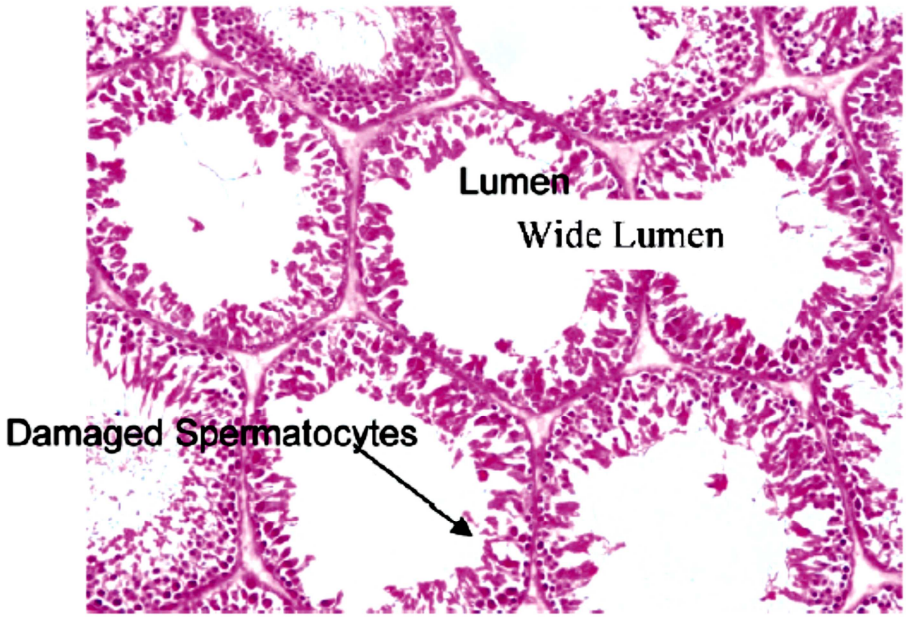

Figure 5. Photograph of a section of rat testis exposed to EMR for 60 minutes showing the damaged spermatocytes and spermatids, marked mitotic divisions and pyknotic nuclei of some spermatogonia, widening of the seminiferous tubular lumen and absence of spermatozoa within the lumen. (H&E6100) [8].

Radio-frequency (RF) waves of cell-phones and other electronic equipment, affect the biological system via thermal and non-thermal effects [13, 63]. Nazıroglu *et al.,* [4] reported that exposure of male rats to EMF caused degeneration in the seminiferous tubules, and apoptotic cells. Gharamaleki *et al.,* [64] reported that the testicular morphological structure of male pups kept until maturity of pregnant rats exposed to 3mT EMF, 50Hz for 21 days showed the seminiferous epithelium contained many small irregular empty spaces as the sign of cellular sloughing, spermatogenic cells appeared to be disrupted. The nuclei of spermatogonia cells were heterochromatic, also dense of germinal epithelium and the number of spermatozoa was decreased (Figure 6).

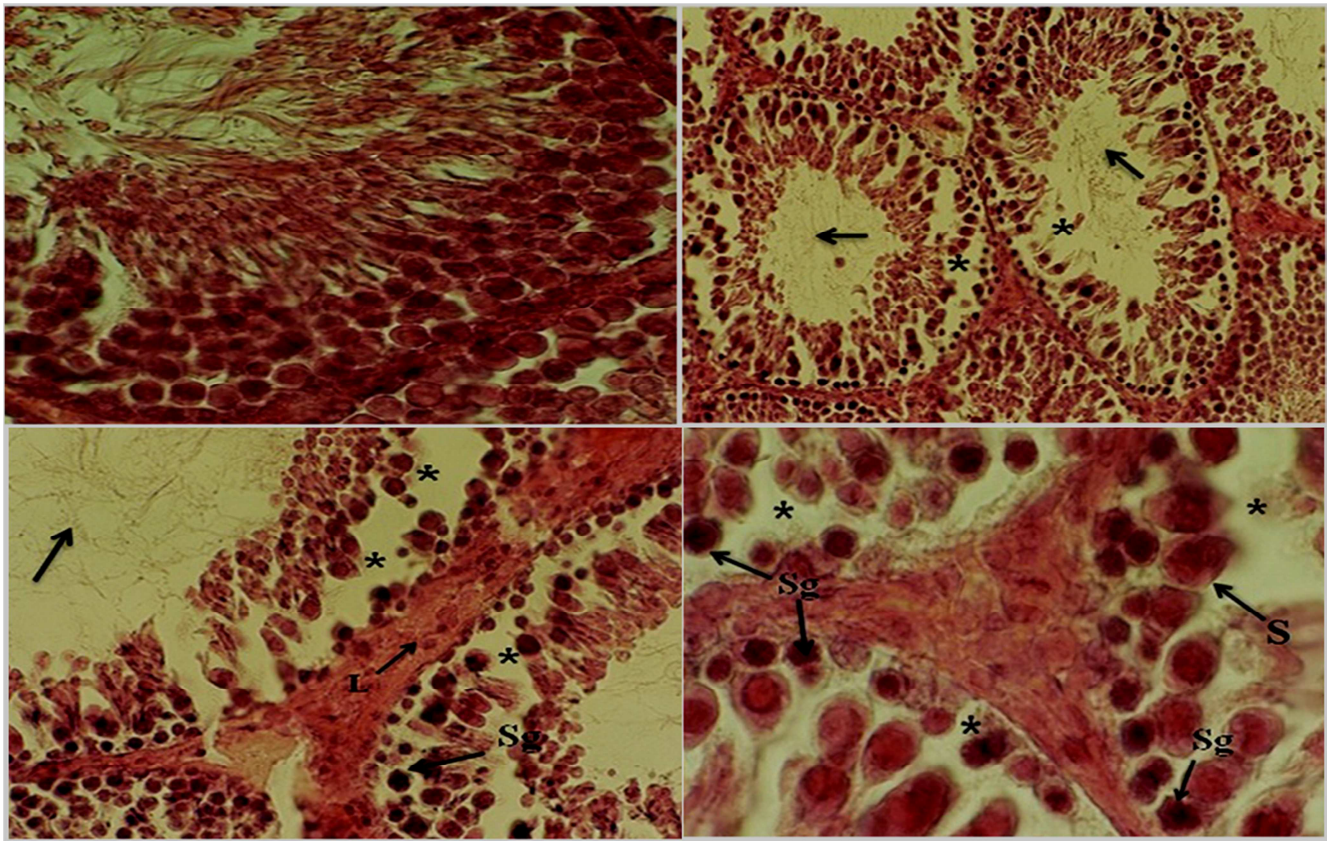

Figure 6. A: Light microscopic micrograph of the testis in control group. The normal seminiferous tubules, interstitium, spermatids and spermatogenic cells at different stages of development. H&E staining. 512 X. B: Light microscopic micrograph of seminiferous tubules from the adult rat in the treatment group (EMF-expose). Note spermatogenesis arrest disorders in germinal cell distribution (*) and a significant decrease in spermatid and spermatozoa (arrow). H & E Staining, 256X. C: Light Microscopic micrograph of seminiferous tubules from the adult rat in the treatment group. Note irregular intercellular spaces (*). Increasing of lumen space and a decrease of spermatozoa (arrow) Spermatogonia with a dense nucleus (Sg) and Leydig cells (L). H&E staining. 512 X. D: Light Microscopic micrograph of seminiferous tubules from the adult rat in the treatment group. Spermatogonia with a dense nucleus (Sg), Sertoli cells (S) and intercellular spaces (*) H&E staining. 1280 X [64].

8. Effects of EMF on the Ultrastructure of Testis

Hamada *et al.*, [3] reported that exposure to EMF caused pathological effects on various cellular components of testes (Figure 7). Celik *et al.,* [65] investigate whether the low-intensity electromagnetic waves transmitted by cell phones cause ultrastructural changes in the testes of Wistar-Kyoto rats. The ultrastructure of the testes of the exposed group showed that growth of electron-dense structures, the existence of large lipid droplets, and vacuolization in the cytoplasm of the Sertoli cells, the membrana propria thickness, the collagen fiber contents, and the capillary veins extended were increased (Figure 8).

Hamada *et al.,* [3] reported that at the cellular and sub-cellular level, EMW may exert direct or indirect effects on cell membranes, cytoplasm, and nucleus. Exposure to RF-EMW can induce alterations in many sub-cellular mechanisms. Changed plasma membrane potential and calcium efflux with resultant calcium depletion leads to decrease in the activity of protein kinase C (PKC). This decrease leads to the alteration in many enzymes, ion pumps, channels and proteins as well as inducing apoptosis. RF-EMW also induce ROS production through disturbance of the mitochondrial membrane bound NADH oxidase. ROS has the impact on PKC, histone kinase, heat shock protein, DNA, and apoptosis. Heat shock protein (hsp) increases in response to electromagnetic radiation and ROS. Hsp slows the metabolism of the sperm and impairs the blood-testis barrier, and interferes with apoptosis of damaged and transformed sperm. Genotoxic effect of RF-EMW on sperm is either through ROS production or through direct clastogenic chromatin breaking effect (Figure 9).

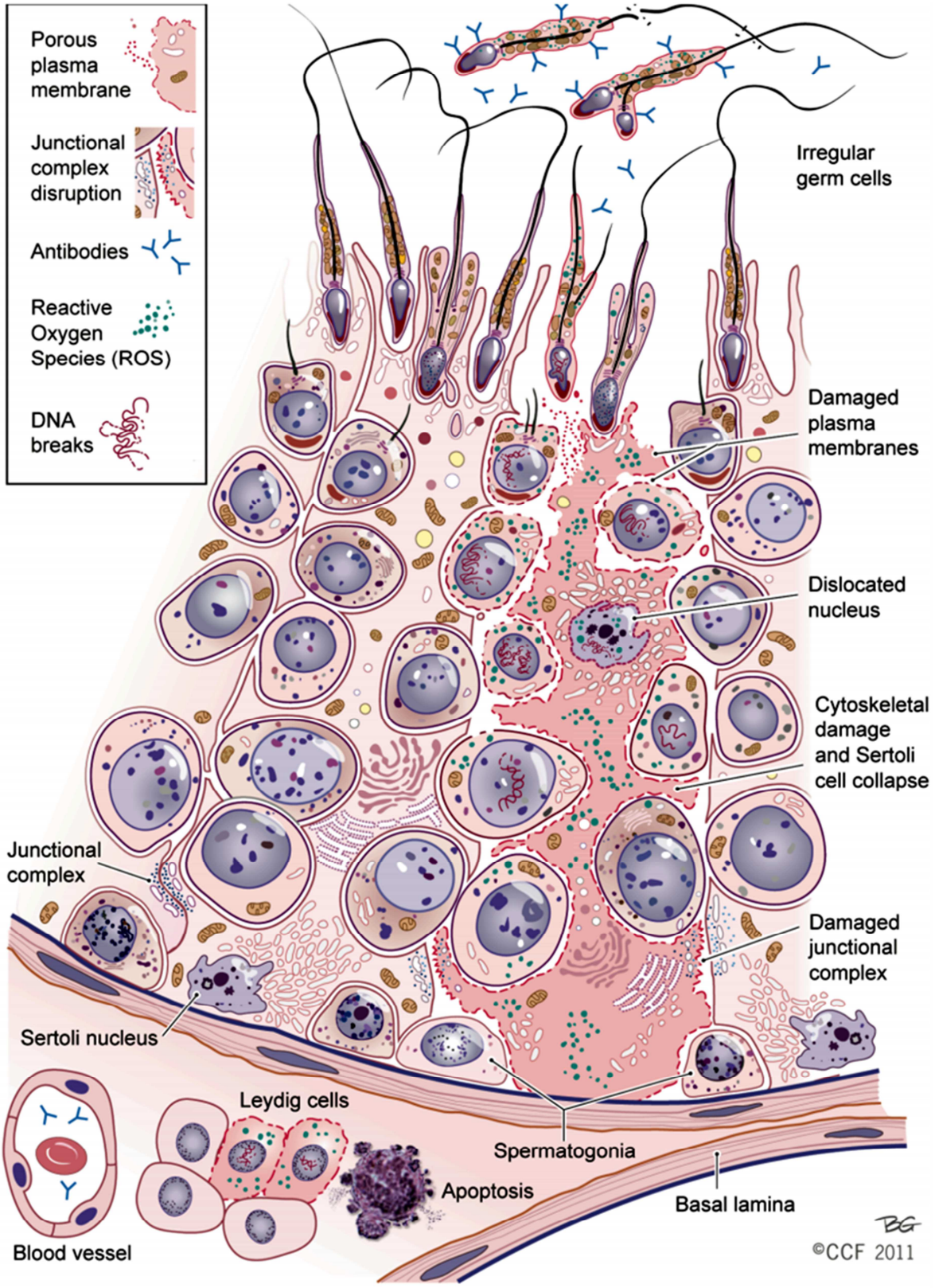

Figure 7. In sperm: a) plasma membrane becomes leaky and porous due to EMW induced electroporation, b) cytoplasmic mitochondria generate excess ROS resulting in oxidative stress, c) nuclear DNA and chromatin undergo breaks and damage. In Sertoli cells: a) damage to plasma membrane tight junctional complexes compromises the integrity of BTB and increases its permeability resulting in exposure of sperm antigens to immune system and formation of ASA, b) damage to cytoskeleton results in cell collapse with c) production of excess ROS, and d) dislocation of nucleus to a more central position. In Leydig cells: a) plasma membrane sustains damage with b) excessive cytoplasmic ROS generation, and c) nuclear DNA damage resulting in apoptosis [3].

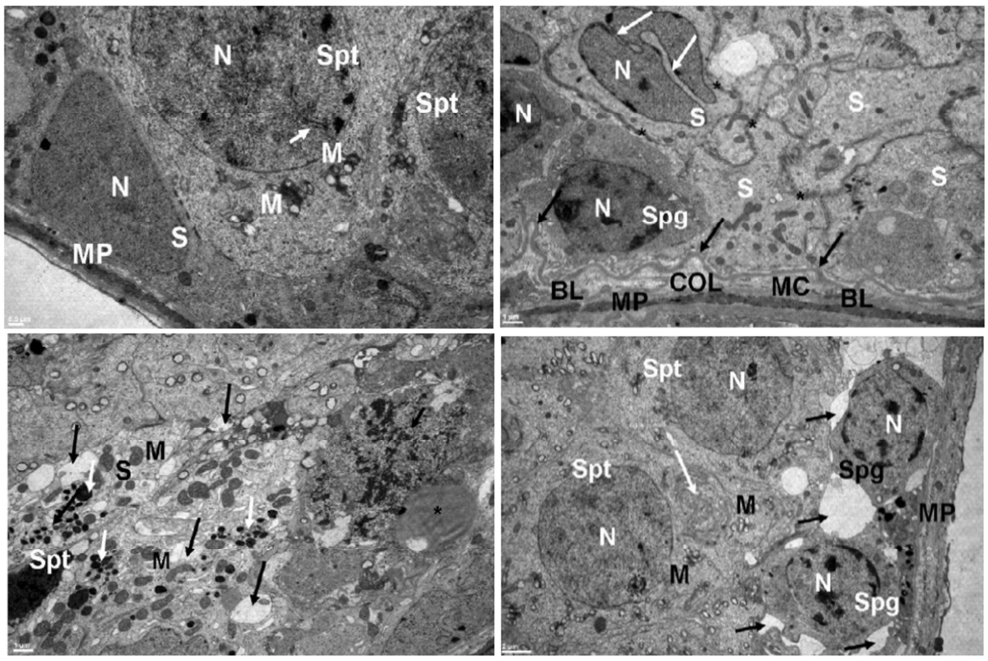

Figure 8. A: Control group. Normal membrane propria (MP), Sertoli cells (S), spermatocytes (Spt), and synaptonemal complexes (white arrow) are seen in the thin incision of the seminiferous tubule. Nucleus (N), mitochondrion (M). Bar =0.5 µm. B: Experimental group. Electron microscopic view of the seminiferous tubule. The thickness of the membrana propria (MP) is observed to increase. The irregularity of the basal lamina (BL) and its protrusion towards the tubule (arrow) are seen. Myoid cells (MH) are seen in addition to electron dense coloring. The collagen fiber (COL) amount increases. The Sertoli cell nucleus has an irregular contour, with deepened invaginations (white arrow). Tight junctions (*) between Sertoli cells (S) are normally observed. mitochondrion (M); nucleus (N); spermatogonium (Spg). Bar = 1 µm. C: Experimental group. Electron microscopic view of the seminiferous tubule. Widespread vacuolization due to the widening of the SER cysterna (black arrow), an increased incidence in electron-dense structures (white arrow), and huge lipid droplets (*) and cup-shaped mitochondria (M) are observed in the cytoplasm of Sertoli cells (S). A spermatocyte (Spt) in lysis and a cell in a mitotic state (arrowhead) are seen. Bar = 1 µm. D: Experimental group. Electron microscopic view of the seminiferous tubule and membrana propria (MP). The empty spaces around the cell periphery are observed in spermatogonia (Spg) because of contraction (black arrow). Well-developed Golgi complexes (white arrow) and grouped mitochondria (M). N _ nucleus. Bar = 2 µm [65].

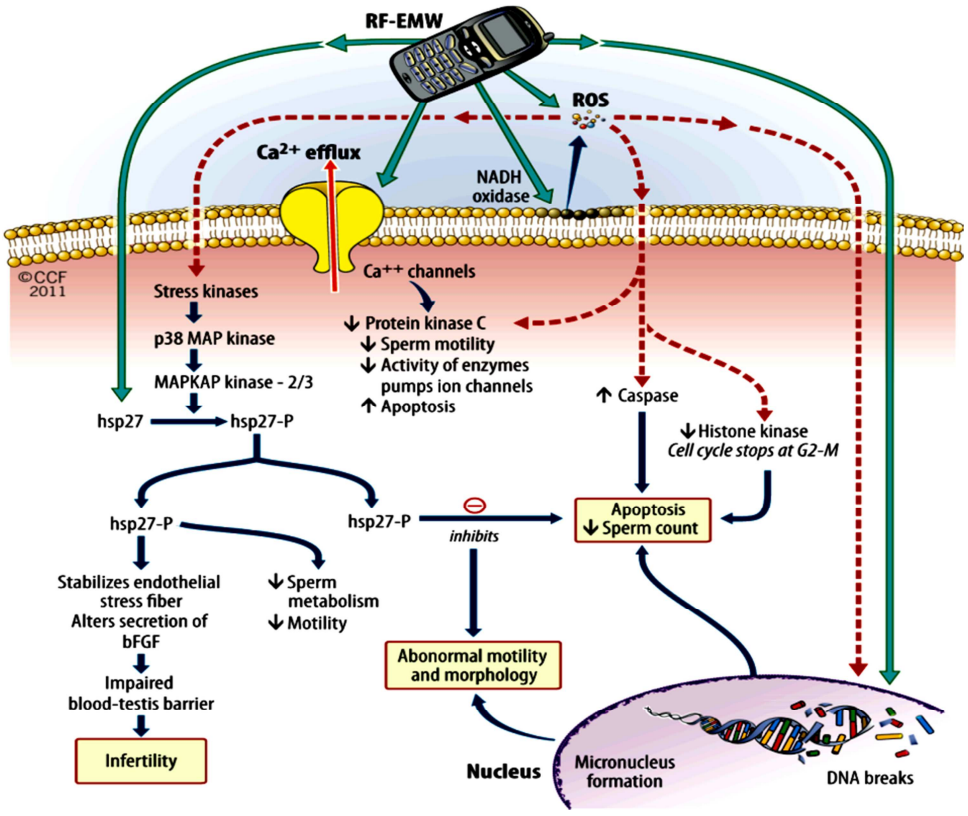

Figure 9. Effects of RF-EMW on cellular and sub-cellular structures [3].

9. Testicular Oxidative Stress Induced by Exposure to EMF

The study of Nazıroglu *et al.,* [4] indicated that oxidative stress from exposure to Wi-Fi and mobile phone-induced EMR is a significant mechanism affecting male reproductive systems. Although ROSs produced by radiation are toxic, intracellular ROS produced in physiological conditions is regulated as essential signal molecules that regulate multiple cellular processes, the ROS spectrum produced in the short run after radiation is similar to metabolic processes [13, 66, 67].

Kesari and Behari, [68] reported that exposure of male Wistar rat to microwave waves at the frequency of 50 Hz (2 h/ daily for 45 days) caused a significant decrease in the antioxidant enzymes of superoxide dismutase, glutathione peroxidase, and activity of histone kinase; while they found to increase in catalase, which enzymatic changes result in catastrophe cascade in male reproductive system as well as apoptosis and finally failure fertility and reproduction. They believed that these events are an important indicator of infertility in male rats.

Nazıroglu *et al.,* [4] reported that in some cases of male infertility, increased levels of oxidative stress and lipid peroxidation and decreased values of antioxidants such as melatonin, vitamin E and glutathione peroxidase were reported in animals exposed to EMR. Kumar *et al.,* [48] reported that exposure of male albino rats to EMF caused a significant increase in the lipid peroxidation damage in sperm cells, and DNA damage when compared with sham exposed control. EMF inhibited MnSOD expression in the rat testis and induced oxidative stress on testis and testicular apoptosis [16, 31, 69, 70].

10. Conclusion

It can be concluded that exposure of human and experimental animals to EMFs have been a negative effect on the male reproductive system by causing histopathological changes and disturbances in the functions of the male reproductive system. The potential male reproductive health effects of EMF should be continually reassessed as new research results become available. EMF exposure guidelines also need to be updated or reconsidered as new scientific information on EMF and male reproductive health risks are produced. However, additional studies might increase our understanding of the sensitivity of male reproductive to EMF.

References

[1] Pourlis AF. (2009). Reproductive and developmental effects of EMF in vertebrate animal models. Pathophysiol, 16: 179-189.

[2] Agarwal A, Singh A, Hamada A, and Kesari K. (2011). Cell Phones and Male Infertility: A Review of Recent Innovations in Technology and Consequences. Inter Braz J Urol, 37 (4): 432-454.

[3] Hamada AJ, Singh A, and Agarwal A. (2011). Cell phones and their impact on male fertility: Fact or fiction. Open Reprod Sci J, 3 (216): 125-137.

[4] Nazıroglu M, Yuksel M, Kose SA, and Ozkaya MO. (2013). Recent reports of Wi-Fi and mobile phone-induced radiation on oxidative stress and reproductive signaling pathways in females and males. J Membrane Biol, 246: 869-875.

[5] Kumaria K, Capstickb M, Cassarab AM, Herralaa M, Koivistoc H, Naaralaa J, Tanilac H, Vilukselaa M, and Juutilainena J. (2017). Effects of intermediate frequency magnetic fields on male fertility indicators in mice. Environ Res, 157: 64-70.

[6] Mailankot M, Kunnath AP, Jayalekshmi H, Koduru B, and Valsalan R. (2009). Radio frequency electromagnetic radiation (RF-EMR from GSM 0.9/1.8 GHz) mobile phones induces oxidative stress and reduces sperm motility in rats. Clinics (Sao Paulo), 64: 561-565.

[7] Valberg PA, van Deventer TE, and Repacholi MH. (2007). Workgroup report: base stations and wireless networks-radiofrequency exposures and health consequences. Environ Health Perspect, 115: 416-424.

[8] Al-Damegh MA. (2012). Rat testicular impairment induced by electromagnetic radiation from a conventional cellular telephone and the protective effects of the antioxidants vitamins C and E. Clinics, 67 (7): 785-792.

[9] Wdowiak A, Mazurek PA, Wdowiak A, and Bojar I. (2017). Effect of electromagnetic waves on human reproduction. Annals Agric Environ Med, 24 (1): 13-18.

[10] Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). (2015). Potential health effects of exposure to electromagnetic fields. Scientific committee on emerging and Newly Identified Health Risks.

[11] Asghari A, Khaki AA, Rajabzadeh A, and Khaki A. (2016). A review on Electromagnetic fields (EMFs) and the reproductive system. Electronic Physician, 8 (7): 2655-2662.

[12] Oh JJ, Byun SS, Lee SE, Choe G, and Hong SK. (2018). Effect of Electromagnetic Waves from Mobile Phones on Spermatogenesis in the Era of 4G-LTE. Bio Med Res Inter, Article ID 1801798, 8 pages. https://doi.org/10.1155/2018/1801798

[13] Fatehi D, Anjomshoa M, Mohammadi M, Seify M, and Rostamzadeh A. (2017). Biological effects of cell-phone radiofrequency waves exposure on fertilization in mice; an in vivo and in vitro study. Middle East Fertil Soc J, (in press). https://doi.org/10.1016/j.mefs.2017.10.002

[14] Fejes, I., Závaczki, Z., Szöllősi, J., Koloszár, S., Daru, J., Kovacs, L., and Pal, A. (2005). Is there a relationship between cell phone use and semen quality?. Arch androl, 51 (5): 385-393.

[15] Gye MC, and Park CJ. (2012). Effect of electromagnetic field, exposure on the reproductive system. Clin Exp Reprod Med, 39 (1): 1-9. doi: 10.5653/cerm.2012.39.1.1. PMID: 22563544, PMCID: PMC3341445.

[16] Qi G, Zuo X, Zhou L, Aoki E, Okamula A, Watanebe M, Wang H, Wu Q, Lu H, Tuncel H, Watanabe H, Zeng S, and Shimamoto F. (2015). Effects of extremely low-frequency electromagnetic fields (ELF-EMF) exposure on B6C3F1 mice. Environ Health Prev Med, 20: 287-293.

[17] Gutschi T, Mohamad AI-Ali B, Shamloul R, Pummer K, and Trummer H. (2011). Impact of cell phone use on men's semen parameters. Andrologia. 43: 312-316.

[18] Jurewicz J, Hanke W, Radwan M, and Bonde JP. (2009). Environmental factors and semen quality. Int J Occup Med Environ Health, 22 (4): 305-329.

[19] Adams JA, Galloway TS, Mondal D, Esteves SC, and Mathews F. (2014). Effect of mobile telephones on sperm quality: a systematic review and meta-analysis. Environ Int, 70 (C): 106-112.

[20] Gorpinchenko I, Nikitin O, Banyra O, and Shulyak A. (2014). The influence of direct mobile phone radiation on sperm quality. Central European J Urol, 67 (1): 65-71.

[21] Avendano C, Mata A, Sanchez Sarmiento CA, and Doncel GF. (2012). Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. Fertil Steril, 97 (1): 39-45.e2.

[22] Juutilainen J. (2005). Developmental affects of electromagnetic fields. Bioelectromagn, 107-15.

[23] Agarwal A. (2009). Cell phones: modern man's nemesis?. Reprod Bio Med, 18 (1): 148-157.

[24] Barnes FS, and Greenebaum B. (2007). Bioengineering and biophysical aspects of electromagnetic fields. In: Barnes FS, Greenebaum B (eds) Handbook of Biological Effects of Electromagnetic Fields 3rd ed. CRC Press, Boca Raton, USA.

[25] Wang SM, Wang DW, Peng RY, Gao YB, Yang Y, Hu WH, *et al.* (2003). Effect of electromagnetic pulse irradiation on structure and function of Leydig cells in mice. Zhonghua Nan Ke Xue, 9: 327-330.

[26] Aitken RJ, Bennetts LE, Sawyer D, Wiklendt AM, and King BV. (2005). Impact of radio frequency electromagnetic radiation on DNA integrity in the male germline. Int J Androl, 28 (30): 171-179.

[27] Khaki AA, Soleimanirad J, Arjani H, Mohadjel Shoja MA, Zarrintan S, Khalili A, et al. (2006). Study of effects of electromagnetic fields on men infertility and the ways for decrease of its harmful effects. Med J Tabriz Univ Med Sci, 28 (4): 41-47.

[28] Khaki AA, Zarrintan S, Khaki A, and Zahedi A. (2008). The effects of EMF on the microstructure of seminal vesicles in rat: a light and transmission electron microscope study. Pak J Biol Sci, 11 (5): 692-701.

[29] Hamdi BA, Soleimanirad J, Khiki AA, and Roshangar L. (2011). Developmentel exposure to emf and its effect on spermatogenesis in adulthood in mice. Inter J Reprod Biomed, 9 (1): 67.

[30] Al-Akhras MA, Darmani H, and Elbetieha A. (2006). Influence of 50 Hz magnetic field on sex hormones and other fertility parameters of adult male rats. Bioelectromagn, 27: 127-131.

[31] Saygin M, Caliskan S, Karahan N, Koyu A, Gumral N, and Uguz A. (2011). Testicular apoptosis and histopathological changes induced by a 2.45 GHz electromagnetic field. Toxicol Ind Health, 27 (5): 455-463.

[32] Nikula H, Naor Z, Parvinen M, and Huhtaniemi I. (1987). Distribution and activation of protein kinase C in the rat testis tissue. Mol Cell Endocrinol. 49: 39-49.

[33] Zhou W, Wang XB, Yang JQ, Liu Y, and Zhang GB. (2005). Influence of electromagnetic irradiation on P450scc mRNA expression in rat testis tissues and protective effect of the shield. Zhonghua Nan Ke Xue, 11: 269-271.

[34] Davoudi M, Brossner C, and Kuber W. (2002). The influence of electromagnetic waves on sperm motility. Urol Urogynaecol, 19: 18-22.

[35] Kilgallon JS, and Simmons LW. (2005). Image content influences men's semen quality. Biol Lett, 1 (3): 253-255.

[36] Erogul O, Oztas E, Yildirim I, Kir T, Aydur E, Komesli G, *et al.* (2006). Effects of electromagnetic radiation from a cellular phone on human sperm motility: an in vitro study. Arch Med Res, 37 (7): 840-843.

[37] Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E, *et al*. (2009). Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study. Fertil Steril, 92 (4): 1318-1325.

[38] Agarwal A, Deepinder F, Sharma RK, Ranga G, Li J. (2008). Effect of cell phone usage on semen analysis in men attending infertility clinics: an observational study. Fertil Steril, 89 (1): 124-128.

[39] Wdowiak A, Wdowiak L, and Wiktor H. (2007). Evaluation of the effect of using mobile phones on male fertility. Ann Agric Environ Med, 14: 169-172.

[40] La Vignera S, Condorelli RA, Vicari E, D'Agata R, and Calogero AE. (2012). Effects of the exposure to mobile phones on male reproduction: a review of the literature. J Androl, 33 (3): 350-356.

[41] Petrelli G, and Mantovani A. (2002). Environmental risk factors and male fertility and reproduction. Contraception, 65: 297-300.

[42] Dunson DB, Baird DD, and Colombo B. (2004). Increased infertility with age in men and women. Obstet Gynecol, 103: 51-56.

[43] Olea N, and Fernandez MF. (2007). Chemicals in the environment and human male fertility. Occup Environ Med, 64: 430-431.

[44] Khaki A, Fathiazad F, Nouri M, Khaki AA, Ozanci CC, Ghafari-Novin M, and Hamadeh M. (2009). The effects of Ginger on spermatogenesis and sperm parameters of rat, Int. J. Reprod. BioMed, 7: 7-12.

[45] Boerma M, Schutte-Bart C, Wedekind L, Beekhuizen H, and Wondergem J. (2003). Effects of multiple doses of ionizing radiation on cytokine expression in rat and human cells. Int J Radiat Biol, 79: 889-896.

[46] Bernabo N, Tettamanti E, Russo V, Martelli A, Turriani M, Mattoli M, and Barboni B. (2010). Extremely low frequency electromagnetic field exposure affects fertilization outcome in swine animal model, Theriogenol, 73: 1293-1305.

[47] Roychoudhury S, Jedlicka J, Parkanyi V, Rafay J, Ondruska L, Massanyi P, and Bulla J. (2009). Influence of a 50 Hz extra low frequency electromagnetic field on spermatozoa motility and fertilization rates in rabbits. J Environ Sci Health A Tox Hazard Subst Environ Eng, 44 (10): 1041-1047.

[48] Kumar S, Nirala JP, Behari J, and Paulraj R. (2014). Effect of electromagnetic irradiation produced by 3G mobile phone on male rat reproductive system in a simulated scenario. Indian J Exper Biol, 52: 890-897.

[49] Dasdag S, Ketani MA, Akdag Z, Ersay AR, Sari I, Demirtas OC, and Celik MS. (1999). Whole body microwave exposure emitted by cellular phones and testicular function of rats, Urol Res, 27: 219-223.

[50] Rajaei F, Mahdi F, Nazem G, Sarreshtehdari M, Gheybi NA, and Sahneh SM. (2009). Effect of electromagnetic field on mice epididymis and vas deferen- A morphometric study. J Gorgan Univ Med Sci, 11 (1): 1-7.

[51] Kim YW, Kim HS, Lee JS, Kim YJ, Lee SK, Seo JN, Jung, KC, Kim N, and Gimm YM. (2009). Effects of 60 Hz 14 micro T magnetic field on the apoptosis of testicular germ cell in mice. Bioelectromagn, 30 (1): 66-72.

[52] Ozguner FI, Dindar H, Yagmurlu A, Savas C, Gokcora HI, and Yucesan S. (2002). The effect of electromagnetic on undescended testis after orchiopexy. Inter Urol Nephrol, 33: 87-93.

[53] Lee JS, Ahn SS, Jung KC, Kim YW, and Lee SK. (2004). Effects of 60 Hz electromagnetic field exposure on testicular germ cell apoptosis in mice, Asian J Androl, 6: 29-34.

[54] Ozguner M, Koyu A, Cesur G, Ural M, Ozguner F, Gokcimen A, and Delibas N. (2005). Biological and morphological effects on the reproductive organ of rats after exposure to electromagnetic field. Saudi Med J, 26: 405-410.

[55] Khayyat LI. (2011).The histopathological effects of an electromagnetic field on the kidney and testis of mice. Eurasia J Biosci, 5: 103-109. DOI: 10.5053/ejobios.2011.5.0.12.

[56] Aydin, M, Turk Gaffari, Yuksel Murat, Cevik A, Apaydin AM, and Yilmaz S. (2007). Effect of electromagnetic field on the sperm characteristics and histopathological status of testis in rats. Medycyna Weterynaryjna, 63 (2), 178-183.

[57] AI J, and Soleymanirad J. (2008). Evaluation of the histopathological changes induced by a 120 gauses electromagnetic field and the protective effect of epinephrine on spermatogenesis in adult rats. Jundishapur Sci Med J, 7 (57): 196-204.

[58] Naziroglu M, Karaoglu A, Aksoy AO. (2004). Selenium and high dose vitamin E administration protects cisplatin-induced oxidative damage to renal, liver and lens tissues in rats. Toxicol, 195 (2-3): 221-230.

[59] Hales DB, Allen JA, Shankara T, Janus P, Buck S, Diemer T, et al. (2005). Mitochondrial function in Leydig cell steroidogenesis. Ann NY Acad. Sci. 1061: 120-34, http://dx.doi.org/10.1196/annals.1336.014.

[60] Naughton CK, Nangia AK, Agarwal A. (2001). Pathophysiology of varicoceles in male infertility. Hum. Reprod. Update, 7 (5): 473-81.

[61] Wang XW, Ding GR, Shi CH, Zhao T, Zhang J, Zeng LH, et al. (2008). Effect of electromagnetic pulse exposure on permeability of blood-testicle barrier in mice. Biomed Environ Sci, 21 (3): 218-221.

[62] Desai NR, Kesari KK, and Agarwal A. (2009). Pathophysiology of cell phone radiation: oxidative stress and carcinogenesis with focus on male reproductive system. Review Reprod Biol Endocrinol, 7: 114.

[63] Mevissen M, Buntenkotter S, and Loscher W. (1994). Effects of static and time-varying (50-Hz) magnetic fields on reproduction and fetal development in rats, Birth Def Res, 50 (A): 229-237.

[64] Gharamaleki H, Parivar K, Rad JS, Roshangar L, and Shariati M. (2014). Effects of electromagnetic field exposure during the prenatal period on biomarkers of oxidative stress and pathology of testis and testosterone level of adult rats in F_1 generation. Acta Endocrinol (Buc), 10 (4): 577-587.

[65] Celik S, Aridogan IA, Izol V, Erdoğan S, Polat S, and Doran S. (2012). An evaluation of the effects of long-term cell phone use on the testes via light and electron microscope analysis. Urology, 79 (2): 346-350.

[66] Attaran M, Pasqualotto E, Falcone T, Goldberg JM, Miller KF, Agarwal A, and Sharma RK. (2000). The effect of follicular fluid reactive oxygen species on the outcome of in vitro fertilization. Int J Fert Women's Med, 45: 314-320.

[67] Bedaiwy MA, Falcone T, Mohamed MS, Aleem AA, Sharma RK, Worley SE, Thornton J, and Agarwal A. (2004). Differential growth of human embryos in vitro: role of reactive oxygen species, Fert Steril, 82: 593-600.

[68] Kesari KK, and Behari J. (2010). Microwave exposure affecting reproductive system in male rats. Appl Biochem Biotechnol, 162: 416-428.

[69] Zeng LH, Ji XT, Zhang YJ, Miao X, Zou C, Lang H, Zhang J, Li Y, Wang X, Qi H, and Ren D. (2011). MnSOD expression inhibited by electromagnetic pulse radiation in the rat testis. Electromagn Biol Med, 30: 205-218.

[70] Esmekaya MA, Ozer C, and Seyhan N. (2011). 900 MHz pulse-modulated radiation induces oxidative stress on heart, lung, testis and liver tissues. Gen Physiol Biophys, 30: 84-89.