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Effects of mobile phone radiofrequency radiation on sperm quality

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Review Article

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Summary

In the last decades, the universal use of mobile phones has contributed to radiofrequency electromagnetic radiation environmental pollution. The steady growth in mobile phone usage has raised concerns about the effects of phone radiation on male reproductive health. Epidemiological studies report a sharp decline in sperm counts in developing countries, and worldwide with *c.* 14% of couples having difficulties to conceive, many of which are attributed to a male infertility factor. Environment and lifestyle factors are known to contribute to male infertility. Exposure to heat, radiation, or radioactivity might induce damage to biological tissue organs, including the testis. Given the ubiquitous use of mobile phones, the potential adverse effects of the resulting environmental radiation needs to be elucidated further. It seems to be an apparent relationship between the increased exposure to mobile phone radiofrequency and sperm quality decline, but the evidence is not conclusive. Our review summarizes the evidence concerning the possible adverse effects of cell phone radiation on the male reproductive system, with a focus on sperm quality. Also, we critically analyze the effects of elevated testicular temperature and oxidative stress on male fertility and how these factors could interfere with the physiological activities of the testis.

Introduction

In the last decades, there has been an increase in the number of couples facing infertility problems, with reports indicating that *c.* 14% of couples in industrialized countries experience difficulties conceiving (Wilkes *et al.*, 2009), several of whom will ultimately need medically assisted reproduction (MAR) treatments, which are complex and expensive procedures (Thoma *et al.*, 2013). *In vitro* fertilization (IVF) has markedly evolved over the past 40 years, resulting in the birth of more than 8 million babies globally (De Geyter *et al.*, 2018). In addition, in recent times, the world has noticed a marked evolution in communication technology. At this time, cell phones have become an integral part of everyday life. Their use is likely to continue to grow as the services offered by providers expand and go far beyond communication. As a result, radiofrequency electromagnetic radiation (RF-EMR) has increased in public areas and at home, raising concerns about possible adverse effects on human health.

The human body can absorb localized RF-EMR, which might cause harm (Grell *et al.*, 2016). Indeed, associations between exposure to RF-EMR and adverse health outcomes have been reported. The IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (IARC, 2013) has classified RF-EMR as a possible human carcinogen based on evidence for an association with brain tumours (Baan *et al.*, 2011). Also, other health impairments might be related to RF-EMR, such as lymphoma (Hardell *et al.*, 2005) and childhood leukaemia (Ha *et al.*, 2007; Teepen and van Dijck, 2012; Kesari *et al.*, 2013; Eghlidospour *et al.*, 2017). The potential adverse effects of RF-EMR on male reproductive health have also been investigated (Agarwal *et al.*, 2011; La Vignera *et al.*, 2012; Adams *et al.*, 2014). It has been suggested that the adverse effects of RF-EMR on biological tissues and organs are attributable to heat (Coulton *et al.*, 2004; Foster and Colombi, 2017). The fluctuating current and transfer of energy generated by the RF-EMR can increase testicular temperature, with consequential effects on sperm quality (Challis, 2005). However, it has also been suggested that the damage could be non-thermal, involving excessive oxidative stress due to increased production of reactive oxygen species (ROS), leading to changes in protein conformation and binding properties as well as sperm DNA damage (La Vignera *et al.*, 2012; Adams *et al.*, 2014; Sciorio and Smith, 2019).

Although RF-EMR is classified as non-ionizing radiation and in theory unable to induce ionization of atoms or molecules (Erogul *et al.*, 2006), some evidence has indicated a potential adverse effect of non-ionizing radiation on human health, including headaches (Oftedal *et al.*, 2000), hypertension (Braune *et al.*, 1998), abnormal electroencephalogram patterns during sleep

(Huber *et al.*, 2000), and infertility (La Vignera *et al.*, 2012). Infertility due to male factors is commonplace, with estimates indicating that c. 40% of the treatments provided by Fertility Centre worldwide are male infertility related (Bechoua *et al.*, 2016; Gatimel *et al.*, 2017), many of which are of unknown aetiology. At this time, most men of reproductive age in high-income or middle-income countries have at least one mobile phone, which emits RF-EMR (Agarwal *et al.*, 2011).

Human testicles seem to be particularly sensitive to RF-EMR (Dasdag *et al.*, 2003; Othman *et al.*, 2017). However, the published literature remains equivocal concerning the effect of mobile phone use and sperm parameters, with studies reporting decreased sperm motility, sperm concentration, and poor morphology (Agarwal *et al.*, 2009, 2011; Adams *et al.*, 2014), whereas others have shown no apparent effect on sperm quality and quantity (Liu *et al.*, 2014). Therefore, we sought to summarize the effects of RF-EMR on human male reproductive health, particularly on sperm quality. An extensive search was performed by retrieving relevant literature from PubMed up to June 2020. The searching strategies and keywords used were 'cell phone and sperm damage' or 'radiofrequency radiation and sperm quality' or 'cell phone radiofrequency radiation and human spermatozoa' and 'spermatogenesis' and returned 136 papers. In total, 32 original articles were used for data extraction, and their major findings are summarized in this manuscript.

Current status of RF-EMR on human health: sources of radiofrequency radiation

Mobile phones emit low-level RF-EMR (Agarwal *et al.*, 2011). This radiation includes electromagnetic microwaves that do not generate enough energy to completely remove an electron from atoms or molecules, therefore it is defined as a 'non-ionizing radiation'. Instead, radiation such as X-rays, γ-rays, and α-particles is termed 'ionizing radiation', which brings sufficient energy to remove electrons from atoms or molecules, thereby ionizing an atom or a molecule (Erogul *et al.*, 2006).

Significant sources of ionizing γ-rays include natural sources such as the decay of uranium in the earth, whereas artificial sources include radioactive waste, X-rays from medical procedures, and other devices. Such radiation might induce cancer by triggering chromosomal damage and instability (Baverstock, 2000). Martin and collaborators (1986) showed that an increase in chromosomal abnormalities could result from radiation exposure. The widespread use of RF-EMR radiation on biological systems started during the Second World War, with radar development. Since the 1960s, several devices generating RF-EMR radiation have been manufactured and widely used, including AM and FM radio and television transmissions, and mobile phones. Moreover, major sources of these waves are airport security scanners and anti-theft devices operating at banks and shops.

Specific absorption rate

The rate of energy absorption in the presence of an electromagnetic field over a volume of tissue is called 'specific absorption rate' (SAR value). The SAR is used to measure radiofrequency energy absorption in the body, expressed in watts per kilogram (W/kg). The safe exposure in humans depends upon the frequency of the electromagnetic field (IEEE, 1992; International Commission on Non-Ionizing Radiation Protection, 2010; Teixeira and Hasan, 2016). The body SAR reaches maximal values when the human body's long axis is parallel to the radiofrequency field vector.

The rate of energy absorbed depends on several factors, including the size of the exposed body. For instance, the exposure standards for the head and torso differ from those for the limbs. For heavy and tall individuals, the resonant absorption frequency is somewhat lower. For short adults, children or babies, and seated individuals, it may be increased. Furthermore, the energy absorbed by human tissue depends on the intensity, the duration of exposure, and the device's position when used.

The exact path and magnitude of the resulting current induced in any part of the body will also depend on the tissue's electrical conductivity as not all the body is electrically homogeneous (International Commission on Non-Ionizing Radiation Protection, 2010). It has been reported that a higher radiation absorption rate occurs when an individual is talking on the phone, keeping the phone near the head, in the pants' pocket, or nearby the testicles (Agarwal *et al.*, 2011).

The testicles are indeed one of the most sensitive organs to this type of radiation; spermatogonia (the precursors of spermatozoa), can be damaged by radiation exposure (Xu *et al.*, 2008). Several decades ago, Prausnitz and Susskind (1962) illustrated for the first time the effects of microwave radiation on the testes. Agarwal *et al.* (2008) examined the effect of cell phone usage on semen parameters. The authors found a correlation between cell phone usage and decreased sperm quality in terms of number, motility, morphology, and consequently infertility. The drop was associated with the duration of daily exposure to cell phones and was found to be independent of the initial semen quality. This conclusion has been reinforced by several authors (Agarwal *et al.*, 2009, 2011; Avendaño *et al.*, 2012; Shokri *et al.*, 2015; Kesari *et al.*, 2018).

Thermal and non-thermal effects

Although the specific biological mechanism between cell phone use and its effect on human health is not fully understood, there is evidence suggesting that the toxic effect of radiation relates to thermal action given the capacity of RF-EMR to increase heat in tissues (Deepinder *et al.*, 2007; Kesari *et al.*, 2018). Exposure to electromagnetic fields at frequencies above 100 kHz can induce a significant absorption of energy and, consequently, temperature may rise.

Several studies have analyzed the tissue heating mechanism and reported that oscillating current and transfer of energy generated by the RF-EMR could induce rapid heating, with possible damage to body tissues and organs (Challis, 2005; Avendaño *et al.*, 2012; Kesari *et al.*, 2018). The so-called 'thermal effect' occurs when RF-EMR exposure is at high levels, and the absorption of energy by a biological system overcomes its ability to regulate the body temperature.

Thermal effects may disrupt cell function and development (Deepinder *et al.*, 2007). Radiation exposure may prompt biological tissue heating, and damage may occur if the body cannot dissipate the excessive heat. The human testicle is particularly vulnerable to heat; a thermoregulatory system exists involving countercurrent heat exchange in the pampiniform plexus to dissipate heat stress (National Radiological Protection Board, 2004). A boost in tissue or body temperature in response to radiation exposure has been shown to cause reversible spermatogenesis damage (Kandeel and Swerdloff, 1988; Jung and Schill, 2000). Moreover, RF-EMR exposure can induce minimal temperature changes in localized areas of body tissues, leading to conformational

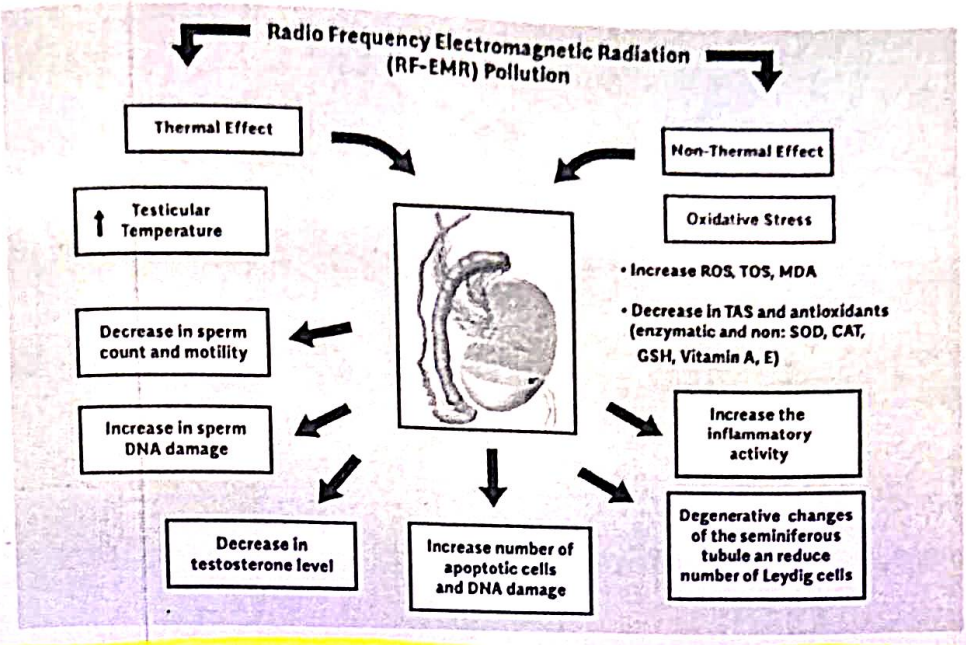

Figure 1. Schematic representation of the mechanisms by which RF-EMR exposure might damage the testis. CAT, catalase; GSH, glutathione; MDA, malondialdehyde; ROS, reactive oxygen species; SOD, superoxide dismutase; TAC, total antioxidant capacity; TOS, total oxidant status.

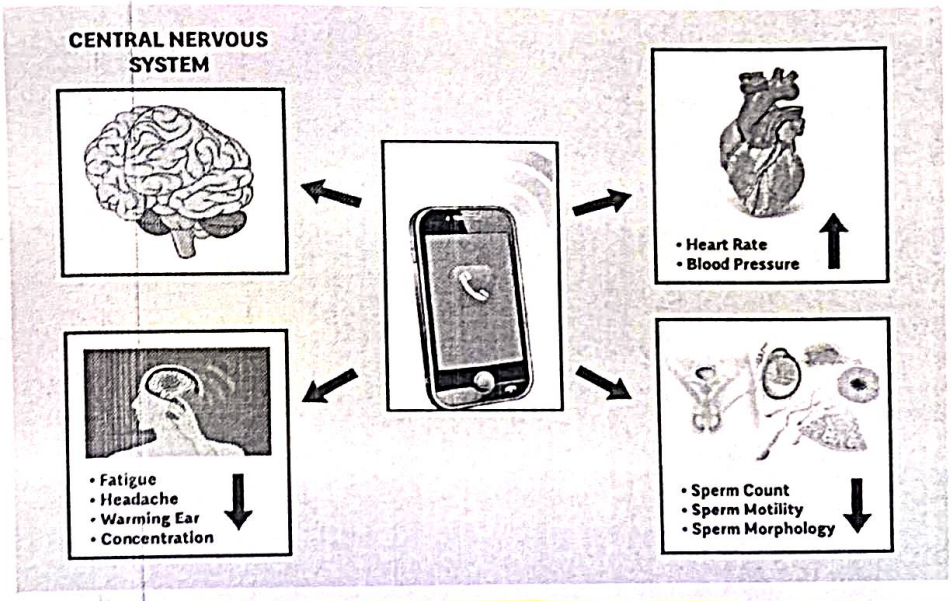

Figure 2. Effects of cell phone exposure to human body. Changes might include the central nervous system, and cardiovascular and reproductive systems.

changes in temperature-sensitive proteins and inducing the expression of heat-shock or stress response proteins (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans] 2013).

Increasing scrotal temperature is one of the primary mechanisms by which the damage is caused (Deepinder *et al.*, 2007). As the human testis is an external organ, it represents an easy target as it can absorb more RF-EMR compared with internal organs. It is well established that the testicular temperature is 2°C or 3°C lower than body temperature, which is the optimal temperature for spermatogenesis (Kandeel and Swerdloff, 1988; Durairajanayagam *et al.*, 2015).

A concern is that the radiation might have an adverse effect on the reproductive system by altering testicular function through thermal and oxidative stress damage (Deepinder *et al.*, 2007). On this basis, the habit of keeping a mobile phone in the trouser pocket and the prolonged use might influence the effect of hyperthermia on adjacent biological tissues and organs (Deepinder *et al.*, 2007; Kesari *et al.*, 2018).

A study published in 2005 found that carrying cell phones close to the waist decrease sperm concentration compared with men not using phones or keeping in another place (Kilgallon and Simmons, 2005). However, to consider a 'thermal noise", the temperature

should increase at least by 1°C (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2013), which is quite unusual, particularly if the device is used according to the manufacturers' recommendations. However, it has been reported that elevated scrotal temperature might promote testicular germinative tissue loss and spermatogenic arrest in humans (Munkelwitz and Gilbert, 1998; Durairajanayagam *et al.*, 2015). Furthermore, a Danish study found that decreased inhibin B levels (a biochemical marker of spermatogenesis), might lead to lower sperm counts (Jensen *et al.*, 1997; Hjollund *et al.*, 2002).

The effects of increased temperature and heating stress have also been investigated on germ cells, which are very sensitive as they have high mitotic activity (Shiraishi *et al.*, 2012). Among them, human spermatocytes and early round spermatids are the most vulnerable to heating stress (Carlsen *et al.*, 2003). In animal models, the evidence is more supportive, as several studies have demonstrated that exposure to RF-EMR directly affects the seminiferous tubular epithelium by increasing testicular temperature. These studies show histological alteration of the seminiferous epithelium and semen abnormalities, including decreased sperm count and morphology (Varma and Traboulay, 1975; Kowalczuk *et al.*, 1983; Aitken *et al.*, 2009).

Adverse effects have also been described on the germ cells; the main mechanisms of damage include germ cell apoptosis (Yin *et al.*, 1997; Lue *et al.*, 1999), autophagy (Zhang *et al.*, 2012), and formation of ROS (Ikeda *et al.*, 1999), which will be discussed later.

Additionally, there is an ongoing debate concerning non-thermal biological effects as a result of exposure to RF-EMR. Recent studies seem to indicate that testicular damage related to non-thermal effects involves the oxidative stress (OS) pathway (Adams *et al.*, 2014; Tök *et al.*, 2014).

Non-thermal effects of mobile phones comprise raised generation of seminal ROS and reduction in antioxidant enzymes, chromosomal abnormalities, micronuclei formation, and change the spermatozoa membrane potential, as well as increased apoptosis (Agarwal *et al.*, 2011; Merhi, 2012). Leydig cells, seminiferous tubules, and spermatozoa are the main targets of the damage caused by the OS-mediated mobile phones' adverse effect on the male reproductive tract. In particular, the injury might supress testicular steroidogenesis and reduce testosterone levels, with a consequent adverse effect on spermatogenesis (La Vignera *et al.*, 2012; McGill and Agarwal, 2014). Furthermore, Desai and co-workers (2009) reported that RF-EMR exposure might induce DNA sperm damage due to increased OS and accelerate spermatozoal cell death. Figure 1 shows the thermal and non-thermal effects following the exposure to RF-EMR on male reproductive organs.

Oxidative stress and ROS formation

The non-thermal effect represents a critical factor in creating damage to the male reproductive organ, through excessive ROS production that results in increased OS. Oxidative stress is a condition in which the natural balance between oxidants and antioxidants is lost. Free radicals are oxygen-containing molecules with an uneven number of electrons, which react with other molecules to cause a series of chemical reactions that might be toxic to cells, tissues, and organs (Elsayed, 2001), as well as gametes and embryos (Sciorio and Smith, 2019). It has been suggested that OS is a central element causing sperm chromatin and DNA damage (De Iuliis *et al.*, 2009; Roque and Esteves, 2018; Esteves *et al.*, 2020).

Exposure to cell phone radiation may induce OS leading to enhanced lipid peroxidation and changes in the body's antioxidant activities. The increase in lipid peroxidation (Oksay *et al.*, 2014; Shahin *et al.*, 2014) and 8-hydroxy-2′-deoxyguanosine activity, a marker of nucleic acid damage, may harm the sperm fertilizing potential (Atasoy *et al.*, 2013). Although seminal plasma has a high endogenous antioxidant ability to protect spermatozoa from oxidative damage (Fraga *et al.*, 1991), cell phone exposure leads to the induction of OS through the generation of ROS in the sperm plasma membrane by activation of NADH oxidase (Aitken and Curry, 2011; Shi *et al.*, 2012; Jamaludin *et al.*, 2017; Ding *et al.*, 2018).

It has been found that OS, nitric oxide levels, and total oxidant status were increased following exposure to RF-EMR (Wiesner *et al.*, 2008). These observations are consistent with a decrease in the spermatogonia and Leydig cell enzymatic antioxidant capacity (Shahin *et al.*, 2014; Almášiová *et al.*, 2018). Spermatozoa seem to be particularly vulnerable to RF-EMR induced OS. Under physiological conditions, ROS play a crucial role in sperm capacitation, acrosome reaction, and sperm–oocyte binding (Garrido *et al.*, 2004). However, a contrary effect occurs in the presence of excessive ROS (Aitken and Curry, 2011), which is also seen in animal models when semen specimens are exposed to mobile phone radiation (Kumar *et al.*, 2010; Kesari *et al.*, 2011a).

Along these lines, it is well known that mitochondrial dysfunctions negatively effect sperm motility (Pellicciône *et al.*, 2011). Mitochondria regularly supply the energy for sperm motility; any metabolic disruption in the electron transport chain can significantly increase the mitochondrial ROS production, affecting sperm motility (Aitken *et al.*, 2012; Agarwal *et al.*, 2014). Mobile phone exposure can increase mitochondrial ROS production, induce sperm DNA fragmentation, and decrease sperm motility and viability (De Iuliis *et al.*, 2009; Awanti *et al.*, 2010).

The association between OS and male infertility has been well documented (Desai *et al.*, 2009; Aitken *et al.*, 2012; Guz *et al.*, 2013). Excessive ROS can alter the function of several seminal enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which play a crucial sperm protective role from ROS attack. It has been reported that a reduction in glutathione and superoxide production after exposure to mobile phone radiation relates to the disruption in sperm membranes as a consequence of induced OS and ROS formation (Moein *et al.*, 2007; Kesari and Behari, 2012). Accordingly, a few studies have investigated the protective role of antioxidants. A well studied antioxidant is melatonin (Reiter *et al.*, 2000; Meena *et al.*, 2014; Reiter *et al.*, 2016), which can decrease OS and protect membrane lipids, proteins, nuclear and mitochondrial DNA from oxidative damage (Reiter *et al.*, 1997).

In addition, melatonin stimulates antioxidative enzymes (Ozguner *et al.*, 2006) and prevents the decline in the mitochondrial membrane potential; the latter effect helps prevent the apoptotic cascade trigger (Martín *et al.*, 2000; Rodriguez *et al.*, 2000; Zhang *et al.*, 2020). Figure 2 summarizes the effect of cell phone exposure on the human body (Figure 2).

Summary evidence

Sperm DNA damage

Cell phones have been recognized as a lifestyle factor DNA damage as a result of an overproduction of RO study, Kumar and colleagues (2014) have shown that te sure to 3G mobile phone radiation for 2 h per day for induced DNA strand break damage in rat sperm.

ble 1. Summary evidence of human studies evaluating sperm parameters after exposure to cell phone radiation

Studies	Patients	Exposure parameters (SAR W/kg)	Outcome
Zalata *et al.*, 2015	Human semen ($n = 26$)	850 MHz SAR 1.46 Exposure for 1 h	DNA fragmentation were increased significantly in the exposed sperm Significant decrease in sperm motility and sperm linear velocity
Agarwal *et al.*, 2009	Human semen Healthy donors ($n = 26$) Infertile patients ($n = 9$)	850 MHz SAR 1.46 Exposure for 1 h	Motility and viability significantly Decreased, increased in ROS level
De Iuliis *et al.*, 2009	Human semen	1.8 GHz SAR 0.4–27.5 Exposure time 16 h	Increases mitochondrial ROS Decrease sperm motility and viability
Gorpinchenko *et al.*, 2014	Human semen ($n = 32$)	900–1800 MHz Exposure: intermittent every 10 min for 5 h	Significantly increase in DNA fragmentation Decrease sperm motility
Erogul *et al.*, 2006	Human semen ($n = 27$)	900 MHz Exposure to commercially available mobile phones	Decreased sperm motility
Falzone *et al.*, 2008	Human semen ($n = 12$)	900 MHZ SAR 2–5.7 Exposure for 1 h	Decreased sperm motility
Agarwal *et al.*, 2008	Human semen ($n = 361$)	850 MHz	Decreased sperm motility, morphology and sperm count
Fejes *et al.*, 2005	Human semen ($n = 371$)	Exposure to commercially available mobile phones	Decreased sperm motility

ROS, reactive oxygen species.

Comet assay, the authors noticed a significant increase in sperm DNA damage in the exposed group compared with the control group. Interestingly, they also observed that the duration of exposure and power density was directly correlated with the magnitude of the effect size.

Other investigators have also found that exposure to RF-EMR could increase sperm DNA fragmentation (Sheikh *et al.*, 2008; Avendaño *et al.*, 2012), and induce DNA breakage in epididymal spermatozoa (Baverstock, 2000). However, it has also been shown that short-term exposure might not be strong enough to cause sperm genomic modification (Agarwal *et al.*, 2011).

In another study, Nikolova and co-workers (2005) reported that RF-EMR could induce DNA damage and double-stranded DNA breaks in neural progenitor cells. The authors also reported a significant increase in transcript levels of apoptosis-related genes. Apoptosis regulates the number of proliferating germ cells during spermatogenesis (Blanco-Rodríguez, 1998; Berensztein *et al.*, 2002).

In another study, apoptosis was tested using terminal deoxynucleotide transferase dUTP nick end labelling assay, and it was found that the frequency of sperm showing apoptosis increased as a function of mobile phone radiation exposure (14.30% ± 1.92%, $P < 0.005$) compared with the control group (7.43% ± 1.30%, $P < 0.005$), respectively. In addition, a significant decrease in the levels of glutathione peroxidase (GPx) and SOD activities, as well as an increase in catalase (CAT) activity, was observed in the exposed group, indicating that radiation exposure may cause apoptotic in the testis and exert a negative effect on male reproductive function (Kesari and Behari, 2010).

Semen parameters

Spermatogenesis is a complex and delicate process that might be disrupted by radiation exposure (Kumar *et al.*, 2014; Meena *et al.*, 2014). Although male infertility causes are multifactorial (Wilkes *et al.*, 2009; Bechoua *et al.*, 2016; Gatimel *et al.*, 2017), the increasing usage of cell phones with RF-EMR could contribute to infertility by decreasing semen parameters. The relationship between cell phone radiation and semen quality has been reported in many animal models and human trials (Oni *et al.*, 2011).

Overall, these studies indicate a link between cell phone usage and changes in sperm count, motility, normal morphology, and viability (Tables 1 and 2). Nevertheless, the role of confounders is difficult to ascertain, as numerous other factors might alter semen quality, including co-morbidities, advanced paternal age, lifestyle factors (e.g. obesity, alcohol consumption, recreational drugs consumption or cigarette smoking).

Sperm count

Cell phone usage has been associated with a reduction in the epididymis and seminal vesicle weight in rats, as well as in sperm count (Meo *et al.*, 2011) and sperm maturation (Sullivan and Mieusset, 2016). Using flow cytometry, Kesari and collaborators (2011b) investigated the sperm count in the rat model after cell phone exposure for 2 h per day for 1 month. The authors showed a significant reduction in sperm count in the exposed group compared with the sham group (31.14 ± 13.6% vs. 61.33 ± 3.68%, $P < 0.0001$).

Several other authors have confirmed the association between decreased epididymal weight and reduced sperm count in an animal model (Kesari and Behari, 2010; Saygin *et al.*, 2011; Shahin *et al.*, 2014). In humans, the few studies available have yielded mixed results. A 1997 study investigated whether increased scrotal temperature was associated with decreased sperm production in 21 healthy male volunteers. The authors were unable to demonstrate a relationship between the increased scrotal temperature and reduction in sperm number.

Additionally, in a 2014 systematic review and meta-analysis, including 1376 participants, a clear reduction in sperm concentration during cell phone radiation exposure was not obtained (Adams

Table 2. Summary evidence of animal trials evaluating sperm parameters after exposure to cell phone radiation

Studies	Animal model applied	Exposure parameters (SAR W/kg)	Outcome
Pandey *et al.*, 2017	Male Swiss albino mice, $n = 8$	902.4 MHz SAR 0.0516 Exposure: 4 h/day, 8 h/day for 35 days	Significant increase in abnormal cells (spermatogonia and spermatids) Significant histological changes in seminiferous tubules DNA damage increased
Odacı and Özyılmaz, 2015	Sprague Dawley male rats, $n = 8$	900 MHz SAR 0.025 Exposure: 1 h/day for 30 days	Significant increase in apoptosis and oxidative stress (high levels of SOD, CAT, LPO)
Yan *et al.*, 2007	Sprague Dawley rats	1.9 Hz Exposure: distance of 1 cm for 6 h/day for 18 weeks	Significant decrease in sperm motility
Meo *et al.*, 2010	Male albino Wistar rat	900 MHz Exposure: 1 h/day for 3 months	Decreased testosterone level
Mailankot *et al.*, 2009	Male albino Wistar rat	0.9–1.8 GHz Exposure: 1 h/day for 28 days	Decreased sperm motility Increase oxidative stress (ROS)
Kesari and Behari, 2010	Male Wistar rats ($n = 6$)	2.45 GHz SAR 0.11 Exposure: 2 h/day for 35 days	Significant decrease in sperm count Changes in antioxidant enzyme (SOD, CAT) and DNA fragmentation Increase apoptosis process
Kesari *et al.*, 2011a	Male Wistar rats ($n = 6$)	900 MHz SAR 0.9 Exposure: 2 h/day for 45 days	Decrease sperm concentration Increased apoptosis and oxidative stress (ROS) Affect the level of antioxidant enzymes and testosterone level
Meena *et al.*, 2014	Male Wistar rats, ($n = 6$)	2.45 GHz SAR 0.14 Exposure: 2 h/day for 45 days	Increase in DNA damage, apoptosis process and oxidative stress (ROS) Decrease in testosterone level
Kumar *et al.*, 2011	Male Wistar Rats, ($n = 6$)	10 GHz SAR 0.014 Exposure: 2 h/day for 45 days	Significant increase in ROS level and apoptotic cells

CAT, catalase; LPO, lipid peroxidation; ROS, reactive oxygen species; SOD, superoxide dismutase.

et al., 2014). Similar results were also noted by another meta-analysis published in the same year (Liu *et al.*, 2014). Evidence from current studies suggests potential harmful effects of mobile phone use on semen parameters. However, overall, the literature remains equivocal, and additional standardized studies are needed to assess the risk of mobile phone use on the reproductive system.

Motility, morphology, and viability

Fejes and colleagues (2005) found that the prolonged use of cell phones might have adverse effects on sperm motility. The authors analyzed three main aspects in 371 White men of reproductive age (mean age 30.8 ± 4.4 years, range 17–41): including duration of phone possession (in months), duration of standby position closer than 50 cm to the patient (in hours) and duration of daily transmission (in minutes), which was divided into low transmitters (less than 15 min per day) and high transmitters (over 60 min per day). The authors showed that the duration of cell phone possession correlated negatively with the proportion of rapid progressive motile sperm and positively with the proportion of slow sperm motility. The low and high transmitter groups diverged significantly in the proportion of rapid sperm motility (48.7% vs. 40.6% $P = 0.01$).

Similar results were found by Erogul and co-workers (2006), who exposed unprocessed raw spermatozoa to the cell phone radiation. In total, 27 males were included in the study. The semen sample obtained from each man was divided into two parts. One part was exposed to the radiation emitted by an activated 900 MHz cellular phone (10 cm for 5 min), whereas the other was not. The authors found a significant differences in percentage of sperm with rapid progressive motility (13.6% ±10.2% vs 9.1% ± 7.9%, $P = 0.0007$), and slow progressive motility (43.7% ± 19.4% vs 33.9% ± 20.6%, $P = 0.0007$) in the exposed group compared with the control group.

In another retrospective study involving 304 men of reproductive age, Wdowiak and colleagues (2007) reported a significant decrease in the percentage of sperm with normal forward progressive motility under the exposure of cell phone radiation. In this trial, 65.7% of patients who did not use cell phones had over 50% of sperm with forward progressive motility compared with only 17% of patients who frequently used cell phones and had been using them for more than 2 years.

Another observational study investigated the effect of cell phone use on semen quality (Agarwal *et al.*, 2009). The study included more than 300 men undergoing infertility treatments, divided into four groups according to their cell phone usage (from 0 to >4 h per day). The authors showed a significant reduction in sperm motility (42.0% ± 17.2% vs. 58.9% ± 12.3%, $P < 0.05$), viability (44.6% ± 17.5% vs. 62.4% ± 12.8%, $P < 0.05$), and normal morphology (14.9% ± 9.1% vs. 27.7% ± 13.1%, $P < 0.05$) in men using cellular phones for variable lengths of time compared with men who did not use them.

Gorpinchenko and collaborators (2014) selected 32 healthy men (age 27.5 ± 3.5 years) with normal semen parameters to study the influence of mobile phone radiation on sperm quality. Semen samples were split into two parts: one was placed in a thermostat,

d the second was placed into another thermostat for the same riod of time, and at the same temperature of 27°C and exposure mobile phone radiation (range 900/1800 MHz). After 5 h of ubation, an operator – blinded to which specimen had been posed to cell phone radiation – analyzed both samples. sults showed that the number of spermatozoa with progressive ovement was statistically lower in subjects exposed to mobile one radiation than the control group (66.5% ± 6.3% vs. 81.3% 7.2%, $P < 0.05$). The same trend was also seen in the number sperm with non-progressive motility (25.3% ± 4.7% vs. 12.8% 5.8%, $P < 0.05$).

Adams and colleagues (2014) outlined the effects of mobile hones on sperm motility in their meta-analysis, which combined 448 samples from 1353 men. The mean total motility ranged from 6.6% to 86.8%. Six studies found a significant negative effect of nobile phone exposure on human sperm motility. The authors lso investigated sperm viability in five studies, including 816 sam- les. The mean viability ranged from 52.3% to 89.0%, and results evealed a significant negative association between mobile phone xposure and sperm viability.

Lastly, Falzone and colleagues (2011) have analyzed the sperm competence to fertilize the oocyte after exposure to RF-EMR. They used motile human spermatozoa collected from healthy donors, exposed for 1 h to mobile phone radiation to evaluate the sperm's ability to undergo acrosome reaction and bind to the zona pellucida. They found that although RF-EMR exposure did not negatively affect the acrosome reaction rate, it reduced the sperm ability to bind the zona pellucida compared with unexposed sperm. The authors of the above study also performed a computerized morphometric sperm assessment, and a significant reduction in sperm head area (9.2 ± 0.7 μm^2 vs. 18.8 ± 1.4 μm^2) and acrosome percentage of the head area (21.5 ± 4% vs. 35.5 ± 11.4%) was reported among exposed sperm compared with controls.

These findings suggest an adverse effect of cell phone radiation on sperm fertilization potential. Overall, the existing evidence from human studies seems to indicate that exposure to mobile phone radiation decreases sperm motility, particularly rapid progressive motility, normal morphology, and viability. These abnormalities seem to be directly related to the duration of mobile phone use, with longer duration to lower sperm quality.

Limitations of existing studies

Despite several studies investigating the association between mobile phone radiation exposure and semen quality, the literature remains inconclusive. The reasons relate to the challenges in designing such studies and controlling for the many possible confounders. Factors such as inclusion of an adequate control group, cell phone type, testing procedure, device use duration, presence of other lifestyle confounders and co-morbidities, to cite only a few, account for these difficulties.

Naturally, it is difficult to find a control group of reproductive age individuals who have not been exposed to any form of mobile phone radiation. If such individuals exist, they most probably comprise older men. Furthermore, there is no standardized method to analyze the effects of cell phone exposure; no consensus has been reached on the accepted SAR value for different cell types, including sperm. Added to this, the distance between the cell phone device and the exposed tissue/organ, length of exposure concerning transmission model, type of mobile, usage mode (e.g. stationary at one point or in movement as when travelling in a car, bus, or train, and use in standby or not) are confounders that might impact the study results.

The SAR effect in a biological system depends on many factors, such as frequency, intensity, polarization, the distance from the source. Also, the SAR is related to the size, shape, and electrical properties of the investigated biological system. Unlike other animal species, humans have particular reproductive tract anatomical and physiological characteristics, therefore precluding the translation of animal trial findings to humans.

In addition, mobile phone technology continues to develop and increase in its complexity. At this time, multi-use smartphones with constant internet connection became the norm, and is associated with higher SAR compared with older mobile phones. On both an individual and societal level, little effort has been made to regulate the RF-EMR environmental pollution properly.

Future perspectives and conclusions

The rapid technological advances in personal computers and communication devices might pose a risk for human health. Cell phone devices emit radiofrequency electromagnetic waves that seem to affect male reproductive health and other body functions (McClelland 3rd and Jaboin, 2018; Sage and Burgio, 2018; Wall *et al.*, 2019). Although the current data are not unequivocal, it seems sound to speculate that mobile phone exposure might be contributing to subfertility. However, the existing evidence primarily relates to adverse effects on sperm motility and morphology, which are limited endpoints for evaluating the male fertility potential.

The exact mechanisms of how RF-EMR might affect the testis, epididymis, and sperm have not yet been fully understood. Additional studies are warranted, particularly prospective studies assessing sperm functional markers, such as sperm DNA integrity and OS, in fertile and subfertile men. Equally important will be to analyze whether the decreased sperm quality associated with mobile phone exposure translates into impaired pregnancy chances. The effects of short-term and long-term exposure and energy intensity should be also investigated in more detail, taking into account relevant confounders. Only then will scientific societies and regulatory bodies be able to provide users with transparent information concerning the risks and guidance for proper use.

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