Review Article

Interaction of Millimetre Waves Used in 5G Network with Cells and Tissues of Head-and-Neck Region: A Literature Review

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Abstract

Fifth-generation mobile technology is supposed to revolutionise the world. It has many features which can benefit humankind, but at the same time, it will expose us to much radiation. Therefore, we need to understand the importance and ill effects of 5 G technology. An online literature search was conducted through PubMed and Scopus databases from April 2021 to May 2021, using the Boolean operators OR, AND and NOT and the keywords '5G Network', 'Human tissues', and 'Animal tissues'. The literature is very scarce in studies on the effects of millimetre waves on various tissues. A total of 1269 studies were identified, and 24 were selected for qualitative evidence synthesis. Randomised control trials, laboratory studies, in-vitro studies, in-vivo studies and ex-vivo studies were included. Data from the studies were collected using the data extraction form, and all the relevant information was summarized. Five of 24 studies were done on animals, four on humans, five on models, and ten on various cells. Ten of 24 studies demonstrated the harmful effects of millimetre waves. Results are ambivalent, and no association is found between particular frequency and impact on tissue, animals or humans. Pathophysiological effects observed in most studies were mild, reversible, and limited to the cellular level. Available evidence reported temperature rise after millimetre wave exposure, which was within safety limits. Any biological impact on a cellular level noticed due to radiation's thermal effects were insignificant and did not affect the organ level. However, only a few studies have mentioned non-thermal impact, but those effects should not be overlooked. Clinical trials on a large population and for a longer duration are required to establish the safety of millimetre waves before deploying a 5G network worldwide.

Keywords: 5G network, millimeter waves, orofacial tissues

Introduction

5G is the fifth generation of wireless cellular network technology anticipated to revolutionise the world with faster mobile speed, faster data transfer and low latency. However, simultaneously, it will expose humans and the environment to millimetre waves for the first time. Millimetre waves are non-ionising high-frequency waves. Microwaves used in the 4G Network have been studied extensively, but significantly less data are available related to millimetre waves.

5G network technology uses three bandwidths: low, mid, and high frequency.[1] The high-frequency spectrum includes millimetre waves, a type of radiofrequency (RF) wave with higher frequency, i.e., 30–300 GHz, which is used for radars and microwaves. It provides the highest speed of all three bands but minimal coverage. The mid-frequency spectrum (2–3 GHz) includes microwaves already used in 4G networks. It will allow higher speed compared to the low band but has limitations in terms of coverage area and penetration of signals. Low-frequency spectrum (1–2 GHz): Provide excellent coverage, but very low internet and data exchange speed (i.e. the maximum speed is limited to 100 Mbps). The high-frequency band used in the USA is 28[2,3] and the European Commission approved 26[4] GHz. Since 5G uses all these frequencies, their combined effect must be evaluated.

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5G network has already been rolled out in many countries. Therefore, it is essential to understand the effect of the 5G network on human tissues, particularly orofacial tissues, as they are in close proximity to the device while calling. In this review, we have focused mainly on the effect of high-frequency waves (high-frequency microwaves and millimetre wave [MMW]) on orofacial tissues.

Effect of Radiations from Previous Generation Networks on Animal and Human Tissues

Studies with laboratory animals exposed to RF radiation have shown to affect various physiological parameters in mammals, such as leakage of the blood − brain barrier, downregulation or overexpression of proteins, testicular dysfunction and DNA damage in sperms. When exposed to 3.5 GHz, Zebra-Fish Embryos showed moderate depression of sensorimotor function. Chronic exposure to RFR emitted from the previous generation (i.e., 2G and 3G) cell phones on chick embryo liver causes various structural changes and DNA damage.[5] RF exposure by 3G mobile systems at 1950 MHz under the described exposure conditions did not induce inflammation in the skin tissue *in vitro*. However, 24-h RF exposure significantly reduced the MMP-1 enzyme concentration when studied after UV exposure.[6] Few studies done on 4G have shown that it causes damage to oral tissues in animals. Rats exposed to 900 MHz microwave exposure for 10 months (2 h/day) showed a statistically significant difference in the control group's vasodilation in PDL and alveolar bone.[7] ELFMF has the potential to alter oral tissues and teeth histologically and may affect the mineralization of enamel negatively.[8] A study demonstrated that ELF-MF could have significant effects on teeth mineral content.[9] However, one study on rat teeth failed to show any impact on enamel microhardness after exposure to 900 MHz RF radiation for 2 h per day for 10 months.

A review mentioned that electromagnetic radiation emitted from cell phones causes dysfunction of facial nerves, increases salivary flow rate and adversely affects oral mucosa. EMR exposure has been shown to cause metal ions leakage from metallic dental appliances and amalgam restorations.[10]

Besides directly affecting human tissues, electromagnetic radiations may have an indirect effect too by affecting the normal microflora of humans. Exposure of *Escherichia coli* and *Listeria monocytogenes* to electromagnetic radiation has been associated with changes in cell growth and morphology and decreased sensitivity to certain antibiotics.[11] Electromagnetic radiation may perturb the human microbiome, particularly the oral microbiome, due to the proximity of mobile to oral structures during its use.

Materials and Methods

A narrative review was conducted because the literature was relatively scarce. Scientific evidence was searched in the Scopus and PubMed Central databases, using the Boolean operators OR, AND and NOT and keywords '5G Network', 'oral tissues' (All Fields), and 'human tissues' (All Fields). Articles published in English during the last 5 years were included. Five-year filter was selected while searching online databases. The *in vitro* study, laboratory studies and randomised controlled trials were included.

Inclusion criteria

Studies were done on MMWs and high-frequency microwaves (>24GHz).

In-vitro studies, *in-vivo* studies, *ex-vivo*, laboratory studies, device trials, clinical trials.

Exclusion criteria

Studies published before 2016.

Studies in languages other than English.

Abstracts from conferences, letters to the editor, reviews and systematic reviews, etc.

Results

Literature-search results

A total of 1269 studies were identified, 1205 in PubMed and 53 in Scopus. Few other studies were selected from the reference list of selected articles. Four duplicate articles were removed. Titles and abstracts of identified studies were screened to find the relevant articles. Thirty-seven articles were selected for full-text screening. Twenty-four were selected for qualitative evidence synthesis [Flow Chart 1].

Selected studies are very heterogeneous regarding the frequency of MMW used and subjects and samples included in the study. 5 of 24 studies were done on animals including mice, rats, rabbits and leech. Four studies on human subjects were related to hypoalgesic effect of MMW, skin reflectance, the relationship between thermal effect and age, and cornea, five on models and ten on various cells including melanocytes, keratinocytes, fibroblasts, neutrophils, glioblastoma, malignant melanoma and PC-12 cells.

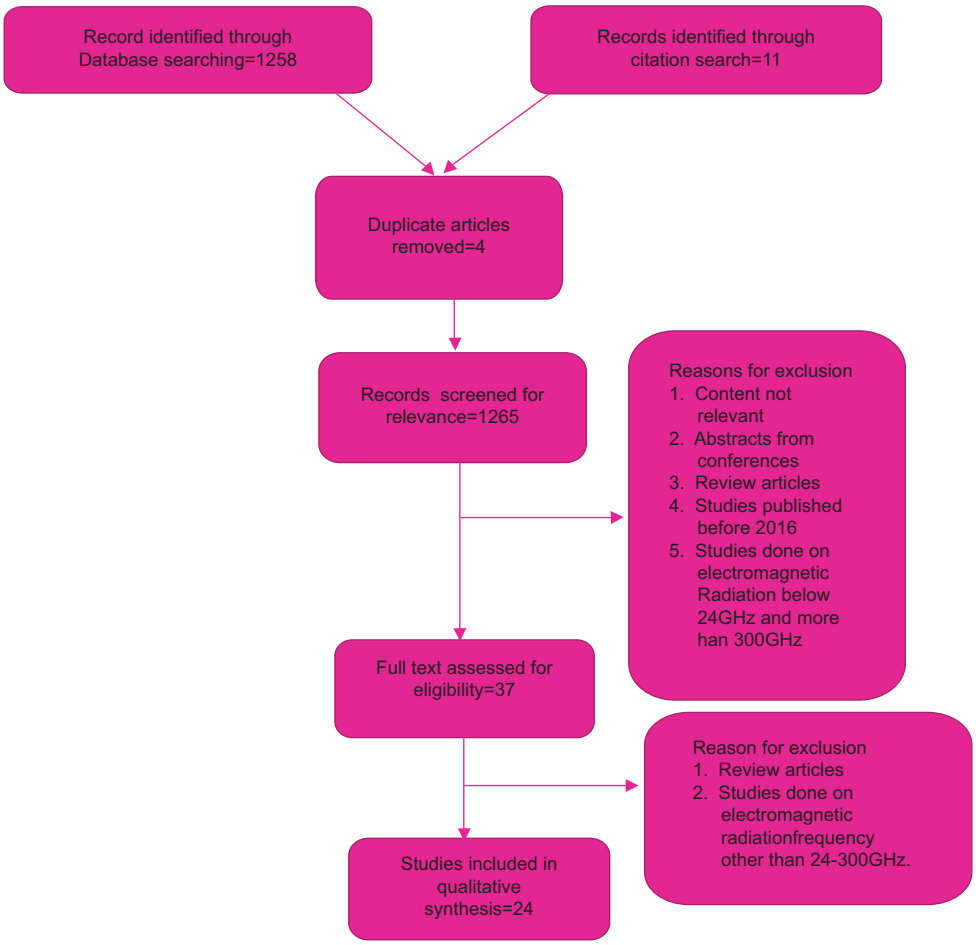
Eleven of 24 studies demonstrated the harmful effects of MMWs, whereas seven did not find any ill-effect. The other six studies were related to the factors affecting the absorption of MMW and its therapeutic effects. All animal studies demonstrated harmful effects. Harmful effects observed in most of the studies were mild. Results are summarised in Table 1.

Effect of millimetre-wave exposure on models, cells and organs

Interaction between millimetre waves and skin cells

The MMW energy is rapidly absorbed within the epidermis and dermis[12] and merely penetrate the superficial layers of the human skin (i.e., 2 mm thickness), i.e., about 0.4 mm (1/64 inch), while microwaves radiation penetrates tissues about 17 mm, which is 0.67 inches;[13] therefore, MMW is less likely to affect deeper organs.[14] Since MMW is absorbed mainly in the skin, it might be the most crucial

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Flow Chart 1: Identification and selection of studies.

target organ of the RF exposure to 5G.[6] The local SAR peak value in specific and highly localised superficial points of human models was found to be significant, especially in the eyes, where tissues are more susceptible to heat due to less blood perfusion.[12]

MMWs are just below infrared in the spectrum and are non-ionising, which means that the photons have insufficient energy to eject orbital electrons and therefore do not produce harmful free radicals such as ionising radiations, which may cause long-term thermal and non-thermal effects mainly in skin cells. Hyperthermia (>42°C) has been shown to induce cell cycle growth arrest, which eventually reduces cell viability.[15] Thermotolerance [Li GC] occurs when cells are subjected to sublethal temperatures (39°C–42°C). In a few studies, MMW irradiation has been shown to cause non-thermal injury by interacting with water molecules and affecting the proteome that inhibits cell growth;[16] whereas few studies failed to find any non-thermal effect.[17,18]

A study showed that LTE (1.78 GHz) and 5G (28 GHz) did not strongly affect melanin synthesis or cell viability in human or murine melanoma cells or a 3D pigmented skin model. Still, mRNA levels of a slight increase in melanogenic enzyme levels were observed, suggesting that exposure for a prolonged time may affect skin pigmentation. In addition, it should be studied in the presence of melanogenic stimuli that can occur together with RF exposure, such as ultraviolet radiation or heat.[19] In a study done on human foetal and adult fibroblasts, telomere length remains unchanged; direct DNA damage and apoptosis were not observed after 25 GHz MMW exposure. Both types of cells were equally sensitive to radiation. An increase in the total micronuclei in exposed samples was reported, suggesting aneuploidy induction.[20]

In another study, continuous MMW exposure, with a widely tunable source sweeping at increments of 1 GHz for 94 h, does not affect cell growth of normal human skin fibroblast and human glioblastoma cells with no additional non-thermal effect.[17]

MMW treatment alone neither affects human primary keratinocyte transcriptome (60.4 GHz-MMW at an IPD of 20 mW/cm^2 for 3 h) in athermic conditions nor alters the ATP contents of exposed human neonatal cells. MMW interferes with the cellular response only with 2dG stressed keratinocytes. 2dG is a competitive inhibitor of glucose that interferes with the increase of potential cytokine-cytokine receptor interaction, interfering with cellular communication and disrupting the glucose pathway. 2dG is used to mimic the

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Table 1: Summary of studies selected for the review

Author	Title	Type of study	Frequency of MMW	Results
Sacco *et al*. (2021)[39]	Age-dependence of electromagnetic power and heat deposition in near-surface tissues in emerging 5G bands	Human study	30.90 W m^{-2} at 26 GHz and 26.65 W m^{-2} at 60 GHz	The maximal steady-state heating increases with age, and reaches its maximum at 70 years. For older ages the temperature increase is enhanced as a consequence of the higher absorbed power and reduced blood flow that limits the heat dissipation in skin
Foster *et al*. (2021)[32]	Nonuniform exposure to the cornea from MMWs	Human study	94-100 GHz	The peak temperature increases in the cornea from short exposures (up to 10 s) to high-intensity mm-wave pulses are 1.7-2.8 times the median increase depending on the polarization of the incident energy
Morelli *et al*. (2021[12]	Numerical analysis of electromagnetic field exposure from 5G mobile communications at 28 GHZ in adults and children users for real-world exposure scenarios	3D realistic human models	28 GHz	All studied exposure scenarios comply with the safety limits relative to RF exposure in all models. MMW energy is rapidly absorbed within the epidermis and dermis and does not reach the deeper tissues in the body
Owda *et al*. (2020)[38]	The reflectance of human skin in the MMW band	Human study	80-100 GHz	In females, due to thin skin, higher reflecting blood vessels are closer to the surface that increase the reflectance of the skin
Kyuri Kim *et al*. (2020) [19]	Effects of electromagnetic waves with LTE and 5G bandwidth on the skin pigmentation *in vitro*	*In vitro* (human melanoma cells)	28 GHz	*In vitro* LTE or 5G may not affect skin pigmentation or cell viability of melanocytes. Macroscopic skin pigmentation was not observed, mRNA levels of melanogenic enzymes (i.e., TYR and TRP-1) were slightly increased by LTE and 5G
Vilagosh *et al*. (2020) [25]	Computer simulation study of the penetration of pulsed 30, 60 and 90 GHz radiation into the human ear	Use of a computational phantom modelling	30, 60 and 90 GHz	Very low penetration of signal into the ear canal at 30 GHz at all angles, which is unlikely to have a significant thermal impact on the tympanic membrane. However, effect may become severe beyond 60 GHz, particularly in the case of tympanic membrane perforations
Orlacchio *et al*. (2019)[35]	MMW pulsed heating *in vitro*: cell mortality and heat shock response	Malignant melanoma cells (*in vitro* study)	58.4 GHz	Both pulsed and continuous waves induced apoptosis but the effect was significantly stronger in case of pulse waves with same average temperature rise
Le Pogam *et al*. (2019) [22]	Untargeted metabolomics unveil alterations of biomembranes permeability in human HaCaT keratinocytes upon 60 GHz MMW exposure	*In vitro* (HaCaTs)	60 GHz	Dysregulations do not result from change in gene expression but rather from alterations in membrane permeability. Slight change in all lipid-omic sequences and intracellular metabolomic profile occured whereas drastic changes in extracellular metabolomic sequences were reported
Romanenko *et al*. (2019) [27]	MMW radiation activates leech nociceptors via TRPV1-like receptor sensitization	Animal study	80-170 mW/cm^2 at 60 GHz	Significant changes in the functional properties of thermosensitive primary sensory neurons subjected to MMW radiation that differs from the impact of direct thermal heating
Vilagosh *et al*. (2019)[26]	Computational simulations of the penetration of 0.30 THz radiation into the human ear	Computer-based phantoms	0.30 THz	With excitation parallel to the ear canal, the average power flux density within the central tympanic membrane region is 97% of the incident excitation. The structures of the outer ear are highly protective; less than 0.4% of the power flux density is directed at 45° from the parallel reached the same region
Davide Colombi *et al*. (2018) [40]	RF energy absorption by biological tissues in close proximity to MMW	Done on model	>24 GHz frequency	Reactive near field body interaction are negligible in case of MMW compared with lower frequency-band
Yaekashiwa *et al*. (2018) [18]	Investigation of the nonthermal effects of exposing cells to 70-300 GHz irradiation using a widely tunable source	Normal human skin fibroblast and human glioblastoma cells	70-300 GHz	Continuous exposure of MMW for 94 h does not affect cell growth and has no additional nonthermal effect. This could not confirm the phenomena affecting cell proliferation and cell activity when increasing frequency of exposure from 70 GHz to 300 GHz in increments of 1.0 GHz
Hamed *et al*. (2018)[23]	SAR calculation and temperature response of human body exposure to EMRs at 28, 40 and 60 GHz MMW frequencies	Humal tissue model	28, 40 and 60 GHz	SAR at 60 GHz are higher than those at 28 and 40 GHz. The maximum temperature rise of 0.59°C is found at 60 GHz in 3 layer model which is below the acceptable temperature limit (1°C) according to guidelines by IEEE

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Table 1: Contd...

Author	Title	Type of study	Frequency of MMW	Results
Bantysh *et al*. (2018)[34]	Peculiar effects of electromagnetic MMWs on tumor development in BALB/c mice	Animal study	130 GHz	Cancer development slowed down in experimental group but initiated pathological reactions in liver tissues in control group
Masami Kojima *et al*. (2018)[33]	Ocular effects of exposure to 40, 75, and 95 GHz MMWs	Animal study (rabbit)	40, 75 and 95 GHz	Occular damage differs with frequency and duration of MMW exposure. Slight damage was reported after 10 min of exposure (i.e., corneal thickness decreased), corneal edema after 1 day which normalized after 3 days
Franchini *et al*. (2018)[20]	Genotoxic effects in human fibroblasts exposed to microwave radiation	*In vitro*, human fetal and adult fibroblasts	25 GHz	No direct DNA damage and apoptosis to human fetal and adult fibroblasts exposed to microwaves. An increase in the total number of micronuclei and centromere positive micronuclei observed in exposed samples in both cell lines
Partyla *et al*. (2017)[31]	Remote effects of electromagnetic MMWs on experimentally induced cold pain: A double-blinded crossover investigation in healthy volunteers	Human study	42.25 GHz, with a power of 185 mW	42.25 GHz frequency of MMW induce hypoalgesic effect. Slight delay in onset of cold sensation and pain threshold was noticed
Haas *et al*. (2017)[17]	Effect of acute MMW exposure on DA metabolism of NGF-treated PC12 cells	NGF-treated PC12 cells	Exposure at 60.4 GHz, with an IPD of 5 mW/cm^2	DA turnover and DAT protein expression level were unaffected by MMW exposure. Insignificant extracellular accumulation of DOPAC was found due to the thermal effects, and overall, no evidence of nonthermal effects of MMW exposure were observed on DA metabolism
Irina I. Vlasova *et al*. (2017)[36]	EHF EMR enhances neutrophil response to particulate agonists	*Ex vivo* study done on isolated neutrophils and neutrophils in blood sample	EHF EMR (32.9-39.6 GHz, 100 W/m^2)	Response of neutrophils were enhanced for zymosan and *Escherichia coli* when blood was exposed to MMW radiation for 15 min. Suspensions of isolated neutrophils in plasma showed similar response
Haas *et al*. (2016)[30]	Impact of 60-GHz MMWs on stress and pain-related protein expression in differentiating neuron-like cells	Neuroscreen-1 cell line (a PC12 subclone)	60 GHz	No impact of MMW exposure on expression of studied proteins. No change observed in level of studied markers expressed by specific cell sub-populations. An insignificant increase in HSP70 expression and an increase in protein expression variability within cell population was noted in exposed cells which was related to thermal effect
Haas *et al*. (2016)[29]	Effects of 60-GHz MMWs on neurite outgrowth in PC12 cells using high-content screening	PC12 cells	60 GHz	No direct effect was noticed with neurite outgrowth and differentiation of NGF-treated PC12 cells after acute MMW exposure
Jauchem *et al*. (2016)[37]	Pathophysiological alterations induced by sustained 35-GHz RFE heating	Animal study (rats)	35-GHz RFE with a power density of 75 mW/cm^2	After 38 min exposure serum glucose, creatinine, uric acid levels were significantly raised. Rats died due to profound hypotention caused by rapid cutaneous heating
Mahamoud *et al*. (2016)[21]	Additive effects of MMWs and 2 dG co-exposure on the HaCaT transcriptome	HaCaT cells	60.4 GHz-MMW at an IPD of 20 mW/cm^2 for 3 h in athermic conditions	MMW treatment alone neither affect human primary keratinocyte transcriptome in athermic conditions nor alter the ATP contents of exposed cells. MMW interfere with the cellular response only when cells were co-treated with 2 dG. Acute MMW exposure alone had no impact on gene expression
I.B. Sivachenko *et al*. (2016)[28]	Effects of MMW EMR on the neurophysiologic mechanism of anti-cephalagic effect	Animal study (rats)	40 GHz, power output of 0.01 mW	Exposure cause suppression of neuronal excitability in the spinal trigeminal ganglion

MMW: Millimetre wave, IPD: Incident power density, 2 dG: 2-deoxyglucose, DA: Dopamine, DOPAC: 3, 4-dihydroxyphenylacetic acid, DAT: DA transporters, LTE: Long term evolution, TYR: Tyrosinase, TRP-1: TYR-related protein 1, IEEE: Institute of electrical and electronics engineers, NGF: Nerve growth factor, RF: Radio frequency, EMR: Electromagnetic radiation, EHF: Extremely high frequency, RFE: RF energy, ATP: Adenosine triphosphate, HSP: Heat shock protein, HaCaT: Human keratinocyte, SAR: Specific absorption rate, TRPV1: Transient receptor potential vanilloid subtype 1, BALB: BAGG ALBINO mouse

Warburg effect. In 2dG treated cells, six genes were identified to be MMW-sensitive. Although, acute MMW exposure alone had no impact on gene expression.[21] A study assessing the biological effects of 60 GHz MMW exposure on human keratinocytes demonstrated slight changes in intracellular metabolomic profiles but drastic changes in exo-metabolomic sequences. These changes suggest altered cell-membrane permeability secondary to exposure to MMW, as transcriptome

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analysis showed that these are not related to any alteration in gene expression.[22]

3D skin model was exposed to 28, 40 and 60 GHz in both one-layer and three-layer models, SAR was calculated, and temperature response of the human body was noted. The maximum temperature rise, which was 0.59°C at 60 GHz in the case of a three-layer model, is below the acceptable temperature limit (1°C) according to safety limit guidelines by Institute of Electrical and Electronics Engineers (IEEE) on MMW radiations.[23,24]

Effect of millimetre wave on tympanic membrane

The absorption, reflection and diffraction properties of the tissues of the outer ear and the ear canal radius affect the progress of the radiation. The power density of radiation with a frequency of 30 GHz is 0.2% in the tympanic membrane. At 90 GHz, it is 13.8%, and a temperature rise of 0.032°C was noted within the tympanic membrane, which is within the safety limit.[25] Simulations at 300 GHz have shown that 54% of the power density presented to the front of the ear penetrates the tissues of the tympanic membrane.[26] Although, the study was well conducted, the generalisability is limited because the absorption of MMW is largely affected by variations in the anatomy of the ear canals and tympanic membrane.

Effect of MMW on neural tissues

As the penetration of MMW is limited to the upper layers of the skin, it is possible that it activates nerve endings. A study done on leech nociceptors suggested the presence of some mechanism of radiation injury other than thermal. Exposure to 60 GHz MMW caused changes in the functional properties of thermosensitive primary sensory neurons, which were different from the effect of direct thermal heating. The results showed that MMW exposure reduced the threshold for activation of the AP more than thermal heating. The difference may be due to a change in perimembranous osmolarity, a possible non-thermal effect caused by MMW exposure.[27] Millimetre-wave electromagnetic radiation of 40 GHz frequency suppresses neuronal response to an electric stimulus of duramater in 5 min after first exposure in rats. This suggests that exposure reduces neuronal excitability which results in suppression of pain impulse conduction from meninges.[28] A study on PC12 cells (obtained from rat pheochromocytoma) demonstrated a slight and insignificant increase in neurite outgrowth after 60 GHz MMW exposure. Results from the control group suggested that this effect was similar to heating.[29,30] In a human study to evaluate the effects of various frequencies of MMW on hypoalgesia, MMW exposure of 42.25 GHz induced a hypoalgesic effect. A slight delay was observed in the onset of cold sensation, pain threshold, and the beginning of increasing pain. It suggests that MMW interacts with peripheral neural receptors and might influence central pain modulation. Changes in diastolic BP upon exposure to 42.25 GHz were noticed, which was suggestive of activation of BP regulating regions of the brain stem. However, the hypoalgesic effect was not significantly different from the placebo effect.[31]

Ocular effects of millimetre wave

A study by Foster *et al*. reported peak temperature increases in the cornea from short exposures up to 10 s.[32] Another study on rabbit eyes concluded that ocular damage differs by the frequency and duration of MMW exposure but is unrelated to eye surface temperature. Forty GHz was found to be more damaging than 75 and 95 GHz. The corneal disorders were primarily due to the cellular death of corneal epithelium induced by MMW exposure and caused corneal oedema and opacity, although cured within 1–2 days after injury. Damage to the corneal epithelium is less likely to occur in human eyes as humans blink eyes more frequently than rabbits.[33]

Millimetre wave and tumour

After exposure to 130 GHz MMW, pathological reactions reflected by the hepatic biochemical indices accompanied by the development of dystrophic and microcirculatory alterations in the liver tissue were observed. However, the experimental mice did not develop macroscopic malignant tumours or microscopic morphological changes in the tissues of the brain, GIT, and lymph nodes.[34] In an *in-vitro* study, exposure to 58.4 GHz frequency waves induced apoptosis in malignant melanoma cells.[35]

Effect on cells of the immune system

Response of neutrophils was enhanced for zymosan and *E. coli* when blood was exposed to MMW radiation of 32.9–39.6 GHz, 100 W/m^2 for 15 min, whereas red blood cell and platelets remained unaffected. Suspensions of isolated neutrophils in plasma showed a similar response as neutrophils in the blood.[36] Data from the control group suggest that response resulted from blood heating. Before adding *E. coli* and Zymosan, most of the neutrophils were inactivated in both control and irradiated samples. The percentage of highly activated neutrophils was six times higher in the irradiated samples compared to the control sample after adding *E. coli* and Zymosan.

Other pathophysiological effects

After 38 min exposure to 35-GHz RFE with a power density of 75 mW/cm^2, serum glucose, creatinine and uric acid levels were significantly raised. Histopathological changes involved hyperaemia and vacuolar structure. Although no full skin burns were observed, vacuolar structures were similar to vacuolisation in the skin vessels of humans after heat stroke. Rats died due to profound hypotension secondary to rapid cutaneous heating. The hypotension mechanism was unknown but was not histamine-mediated as no heat-mediated degranulation was observed.[37] Lethality was strongly associated with mean arterial blood pressure was <80 mmHg.

Factors affecting absorption of millimetre waves

Absorption of MMW increases with the thickness of the skin. It also varies with water content and blood circulation. These factors are affected by weather, age, gender and health of

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person and affect reflectance too. Reflectance value increases when the skin is wet.[38]

A study on 26 and 60GHz MMW demonstrated that maximum heating increases with age and is highest at the age of 70 years. Results suggested that at 60 GHz, skin thickness has a negligible effect on power transmission coefficient but at 26 GHz, the effect was more pronounced, particularly in individuals below 25 years of age, which was attributed to tissue permittivity at both frequencies. The peak SAR is almost double at 60 GHz compared to 26 GHz. The power absorbed in tissues (i.e. SAR) depends on transmission coefficient and thermal conductivity. This occurs as a result of reduced blood flow which in turn reduces heat dissipation, but the value is far below the natural environmental fluctuation.[39]

According to Colombi *et al*., the contribution of reactive near-field body interaction is very less in the case of MMW as compared to low-frequency EM waves (i.e. below 10 GHz) when the distance between the device and the human body is more than 4 mm. Therefore, absorbed power is directly related to the incident power and not the sum of multiple antenna-body interactions as in the case of low-frequency waves.[40]

Discussion

Very less studies were found related to the biological effect of MMW on tissues, animals and humans. Published evidence suggests that MMW mainly absorbs in the superficial layers of the skin and does not penetrate deeper organs directly. The harmful effects are primarily related to the thermal effects. However, the temperature rise is reported to be <1°C, which is within safety limits according to the guidelines by IEEE. Few studies suggested a mechanism other than thermal responsible for damaging deeper organs like the liver. One study even reported the death of study animals due to profound hypotension secondary to rapid cutaneous heating. However, these studies were done on animals and due to differences in body size; results cannot be directly extrapolated to humans. Few other studies failed to identify any non-thermal effect due to MMW.[17,18]

Included studies are heterogeneous in terms of the frequency of MMW applied and the subject or sample used in the study; therefore, it is difficult to reach any conclusion. Results from the published studies are very contradictory. In most of the studies, 60 GHz frequency was studied but in 4 studies, it showed a positive effect, whereas 3 studies failed to find any significant effect. No relationship was found between the frequency applied and the effect. Similar results were obtained by a meta-analysis that there was no dose-response relationship between the SAR and the ES.[41]

A review highlighted that frequencies above 20 GHz would cause similar effects as heating of the body tissues. This will result in the inducement of electromagnetic fields that will cause various types of polarization in the human body, which is dipolar in nature.[42] Few studies reported mild changes in cells due to heating, such as an increase in neurite outgrowth in PC12 cells (60.4 GHz),[29] enhanced response of neutrophils to *E. coli* and Zymosan (32.9–39.6 GHz),[36] apoptosis in human melanoma cells.[35] Other changes in cells, which may not be directly related to thermal effects, reported after exposure to MMW were altered membrane permeability in human keratinocytes (60 GHz),[22] altered peri-membrane osmolarity in primary sensory neurons in the leech (60 GHz),[27] altered gene expression in 2dG stressed human neonatal keratinocytes (60 GHz),[21] altered hepato-biochemical indices in mice (130 GHz),[34] increase in mRNA levels of melanogenic enzymes in murine melanoma cells (28 GHz),[19] damage in the corneal epithelium of rabbit (40, 75, 95 GHz),[33] chromosome loss in human adult and foetal fibroblasts (25 GHz)[20] and decrease in neuronal excitability in rats (40 GHz).[28] One study on humans reported changes to diastolic BP, which indicate activation of BP-regulating regions of the brain stem at the exposure of 42.25 GHz.[31] Another study reported the death of mice due to severe hypotension secondary to radiation exposure.[37] Most of the alterations in cellular biology may be very mild but may become significant after chronic exposure to MMW. Therefore, an in-depth study of the consequences of these cellular effects on various frequencies on humans and the environment is required to ensure safety.

All animal studies demonstrated harmful effects. This may be due to the small body size of the animals studied; they are more affected by radiation exposure. Many studies failed to show any harmful effect may be due to less duration of the study. After deployment of the 5G network, humans will be exposed throughout their life; therefore, chronic effects are required to be studied to establish safety guidelines. Some studies have mentioned the possibility of non-thermal effects too and all standard international guidelines are generally based on thermal effects only. Therefore, any possibility of any damaging mechanism other than thermal effects needs to be ruled out.

However, most of the studies have shown that public exposure by 5G network complies with the safety guidelines provided by IEEE but studies have shown minor effects on cells that may be significant after chronic exposure. The effect of RF in real-life scenarios can be understood when it is studied in combination with other factors such as UV rays.[6]

We have included frequencies from 24 to 300 GHz and for convenience, we used the term millimetre waves for 24–29 GHz as they are used in some countries for 5G networks, and frequencies are similar to millimetre waves. Due to the scarcity of literature, all *in vitro*, *in-vivo*, laboratory studies, human studies and studies done on models were included to collect as much evidence as possible. The limitation of this review is that it includes only articles published in English, in PubMed and Scopus databases. MMW are used for therapeutic purposes, too but in this review, we focused only on their biological effects on different kinds of orofacial tissues.

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Mobiles are in close proximity to tissues of the head and neck region, and hence, they may negatively affect them. Clinical trials are required to discover the effect of various frequencies on human tissues and particularly tissues of the head-and-neck region, with a more standardised approach. Many questions are still unanswered, such as the effect of chronic exposure on the skin, particularly in a real-life situation where many other harmful stimuli affect the skin too.

Conclusion

Very few studies published related to the effects of millimetre waves on various tissues. Therefore, it is very difficult to reach to a clear conclusion. Available evidence suggests that heating effects in tissues due to MMW exposure cause temperature rise. However, the temperature rise was found to be within safety limits for the short duration of exposure, but biological effects on the cellular level were observed in a few studies. It is unclear how these changes will affect organs or individuals when the population is exposed to radiation continuously for a lifetime. Very few studies have shown harmful non-thermal effects too. These effects should not be overlooked. Special attention should be paid to the tissues of the head and neck region as they are in close proximity to electromagnetic devices. More research is required to confirm those findings and the chronic thermal and non-thermal effects of MMW and to establish safety before the deployment of 5G networks all over the world. Technological advancement is necessary for human race development but not at the cost of our health. We need to limit the use of certain frequencies at workplaces where a high amount of data is required to be transferred at high speed and find the safest frequency for widespread use so that our environment and the next generations can be protected from hazardous effects.

Future study recommendation

Very few studies have been done on the effects of millimetre waves on humans. Clinical trials on a large population and for longer duration are required to establish the safety of millimetre waves before the 5G network roll out all over the world. The effect of other environmental toxic stimuli should be considered while studying the effect of MMW. Other factors that affect the absorption of MMW, such as the shadowing effect, reflection from surroundings tissues, angle of a screen of a device, thickness of skin and the water content of the skin should be considered.

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Conflicts of interest

There are no conflicts of interest.

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