Environmental Science and Pollution Research (2019) 26:18017–18031
https://doi.org/10.1007/s11356-019-05096-z

REVIEW ARTICLE

The possible global hazard of cell phone radiation on thyroid cells and hormones: a systematic review of evidences

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Received: 28 October 2018 / Accepted: 4 April 2019 / Published online: 6 May 2019
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Abstract

The aim of this review was to investigate the effects of possible harmful waves from either cell phone use or being within the range of the cell phone from 450 to 3800 MHz on the thyroid cells and hormones. Eight electronic datasets were systematically searched using MeSH terms, including "cell phone," "mobile phone," "GSM," "radio frequency," "smartphone," "triiodothyronine," "thyroxin," "thyroid-stimulating hormone," "T3," "T4," "TSH," and "morphological" and all possible combinations, to identify relevant studies published up to Dec 2018. We also manually searched the reference lists of potentially selected studies to identify further relevant publications. About 161 relevant studies were initially found. After screening titles and abstracts, 139 studies were excluded, and finally 22 studies (comprising 7182 cases) were included in the qualitative synthesis. Of the 22 included studies, 11 studies reported changes in T3 and T4 levels (six reported a decrease in T3 levels and one reported increase in it); moreover, five found decreased T4 levels and two studies an increased level. In other 10 studies, TSH alteration was reported. Of these, two studies reported a decrease in TSH level and one reported an increase in the hormone levels, while in the remaining studies non-significant changes were reported. Finally, seven studies examined histological changes in the thyroid gland follicles and showed that the volume of these cells was reduced. Based on the evidence discussed above, the reduction in diameter of thyroid follicles is potentially linked with cell phone radiation. Exposure may negatively influence the iodine uptake in the thyroid gland or increases temperature effect on the thyroid gland. However, further research are needed in order to show that the level of TSH and thyroid hormone suppression by microwave.

Keywords Cell phone · Thyroid hormones · Triiodothyronine · Thyroxin · Thyroid-stimulating hormone (TSH)

Responsible editor: Philippe Garrigues

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11356-019-05096-z) contains supplementary material, which is available to authorized users.

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Introduction

Background

The spectrum of electromagnetic field (EMF) waves varies through a wide range of frequencies and wavelengths, including very low frequencies, radio frequencies, radio and radar waves, microwaves, infrared and ultraviolet radiation, visible light, X-rays, and gamma rays (Allison 2013). Microwaves are a form of EMF waves with a frequency of 300 MHz to 300 GHz (Baharara et al. 2004; Banik et al. 2003). Today, mobile phones have become an integral part of human's life and with the advancement of technology, its usage has increased. Mobile phones use a microwave with a frequency of 450 to 3800 MHz. To explain the interaction between electromagnetic fields and living organisms, researchers have proposed two types of mechanisms, including thermal and non-thermal mechanisms (Ferreri et al. 2006).

When microwave radiation collides with body molecules, its energy absorbs molecules and triggers molecular vibration or temperature changes. The biological effects of the microwave are complicated and controversial, and there is evidence that these waves produce deleterious biological effects in terms of radiation intensity and frequency. This electromagnetic radiation is non-ionizing and absorbed at the molecular level, which consequently causes change in the kinetic energy of the molecules and the generation of heat (Allison 2013).

The thyroid gland secretes thyroid hormones, which primarily responsible for normal growth and development, as well as regulation of metabolism. Thyroid hormones triiodothyronine (T3) and thyroxin (T4) are synthesized from iodine and tyrosine. The thyroid also produces calcitonin hormone, which plays a role in calcium homeostasis (Hall 2015).

Metabolomics imitates phenotypic and pathophysiological changes in the biological systems; therefore, it denotes the supreme "downstream" level of molecular life of a cell. Metabolomics' alterations reveal changes in enzyme concentration, cellular regulation, and control of signaling pathways, genetic variations, and catabolic and anabolic reactions (Sinha 2008). The main drawback of metabolomics studies, reflecting chemical variability of this cellular component, is the fact that there is no single analytical method allowing simultaneous measurement of such broad spectrum of bioactive compounds (Bauer et al. 2008).

Several studies proved that metabolomics approaches allowed for classification of different types of malignancies and identification of potential biomarkers in the case of the brain (Ossenkopp et al. 1972), breast (Kirsten 2000), kidney (Thibodeau and Patton 1997), and prostate (Cheng et al. 2010) cancers. Although studies regarding metabolome of thyroid cancer are not very common, there are several recent works showing that metabolomics approach could help to discriminate different types of thyroid lesions and provide significant information about their progression. Here, we aim to review recent progress in the field of thyroid metabolomics and discuss its contribution to understanding thyroid tumorigenesis and potential refinement of molecular classification of thyroid cancers. Therefore, the thyroid gland is one of the most exposed organs and may be a target for any kind of electromagnetic radiation (Sinha 2008).

Rationale for this review

Understanding the effects of waves from either cell phone use or being within the range of cell phone on the function of the thyroid hormone and its tissue, due to the sensitivity, as well as changes in the levels of the hormones of the thyroid gland (Bauer et al. 2008; Bernal 2007), can have a negative impact on brain functions (Ossenkopp et al. 1972) (Fig. 1).

Objectives

The purpose of this systematic review was to investigate the scientific evidences on the effects of cell phone waves or being within the range of the mobile phone waves from 450 to 3800 MHz on the thyroid hormones and tissues. Here, we attempt to find out whether such waves could cause a change in thyroid hormones, as well as atrophy of thyroid follicles due to tissue destruction by the production of free radicals in the various body organs. Thus, we first have gone through the explanation of thyroid hormone structure, thyroid tissue, and the effect of the pituitary glands and hypothalamus on thyroid gland, hypothyroidism, hyperthyroidism, and thyroid cancer. Finally, the scientific pieces of evidence on the thyroid hormone and a possible tissue alteration due to exposure to cell phone waves are discussed.

Hormones, pathological background

The thyroid gland is one of the largest endocrine glands in the human body, normally weighing approximately 15 to 20 g in the adult. It secretes two major hormones, which are required for the normal function of a variety of physiologic processes affecting almost every organ of the human body. The thyroid gland comprises several follicular cells that store the thyroid hormones until they are required by the body (Kirsten 2000). The thyroid gland secretes many hormones, including thyroxin (T4), triiodothyronine (T3), and calcitonin. Of these hormones, T4 is the principal secretory product comprising approximately 90% of thyroid secretion, but T3 is the more potent and the considerably more active l thyroid hormone (Kirsten 2000; Thibodeau and Patton 1997). The thyroid hormone is necessary for normal development and growth, as well as neural differentiation, and regulating metabolism in

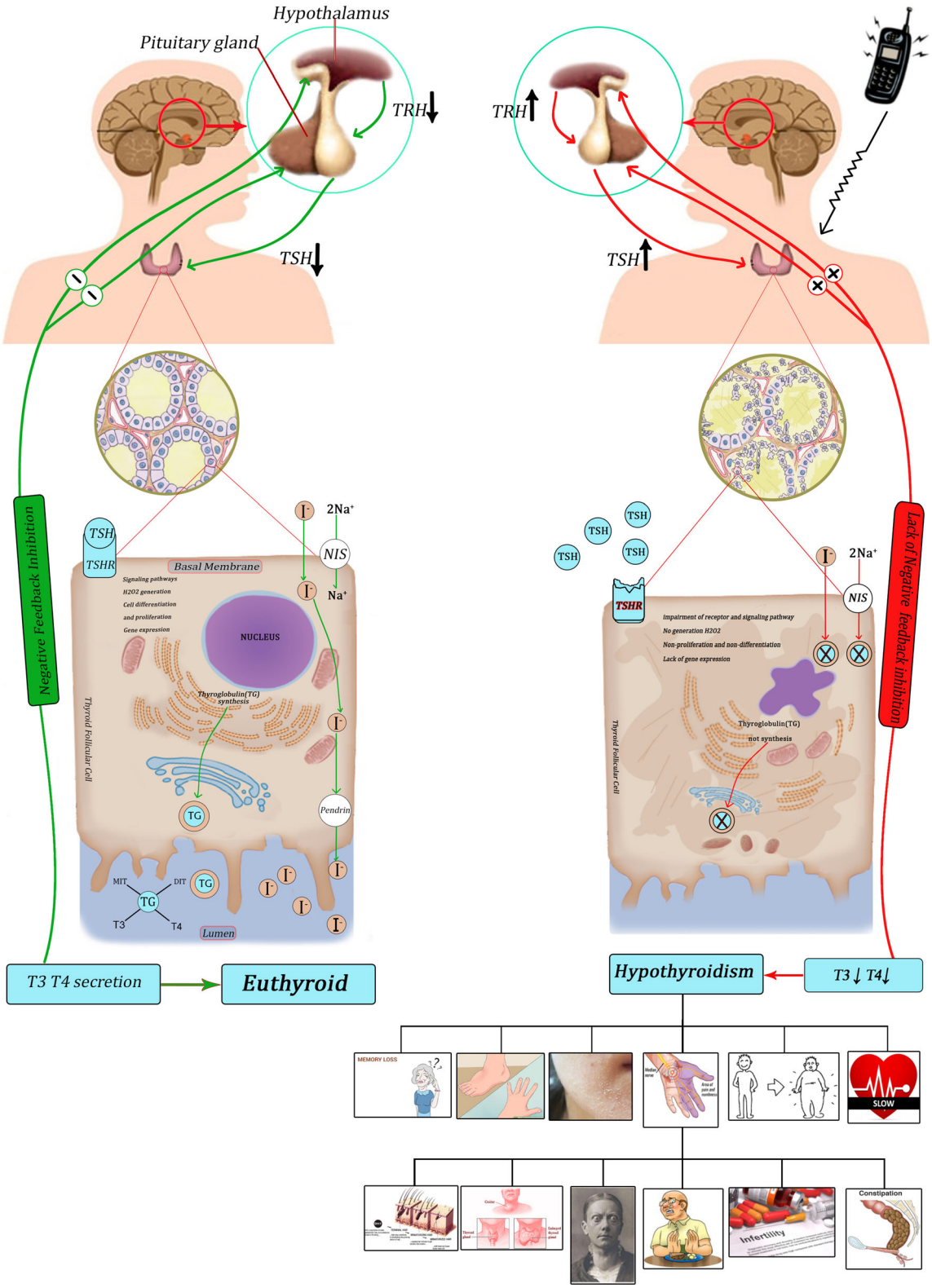


Fig. 1 Schematic view of comparison between normal and pathologic thyroid

mammals (Cheng et al. 2010; Tata 2013; Williams 2008). The thyroid-stimulating hormone (TSH) is secreted by the anterior pituitary gland in response to feedback from the circulation of the thyroid hormone, acting directly on TSH receptor expression (TSH-R) of the basolateral membrane follicular cell in the thyroid (Chiamolera and Wondisford 2009). TSH was

regulated by the sodium/iodide symporter (NIS), followed by a series of steps in thyroid hormone synthesis (Brent 2012). Thyrotropin-releasing hormone (TRH), produced in the periventricular nucleus (PVN) of the hypothalamus, is the principal positive regulator of TSH synthesis and a crucial component of normal thyroid gland function(Hollenberg et al. 1995). TRH binds to the TRH receptors, stimulating the TSH subunit gene expression via the phosphatidylinositol pathway (Gershengorn 1989). Furthermore, TRH regulates TSH glycosylation, which leads to the modulation of the biological activity of TSH (Weintraub et al. 1989). In the absence of TRH, animals have low circulating TSH levels (Yamada et al. 1997). Hyperthyroidism is a pathological disorder in which an extra thyroid hormone is synthesized and secreted by the thyroid gland. It is characterized by normal or high thyroid radioactive iodine uptake (thyrotoxicosis with hyperthyroidism or true hyperthyroidism). Thyrotoxicosis without hyperthyroidism is caused by extra sources of thyroid hormone or by a release of preformed thyroid hormones into the circulation with a low radioactive iodine uptake (Hedberg et al. 1987). Hyperthyroidism can be overt or subclinical. Overt hyperthyroidism is characterized by low serum thyroid-stimulating hormone (TSH) concentrations and raised serum concentrations of thyroid hormones: thyroxin (T4), triiodothyronine (T3), or both. Subclinical hyperthyroidism is characterized by low serum TSH, but normal serum T4 and T3 concentrations (Cooper and Biondi 2012). Hypothyroidism is one of the most common chronic disorders in Western populations. In the UK, the annual incidence of primary hypothyroidism in women is 3.5 per 1000 and in men 0.6 per 1000 (Vanderpump et al. 1995). The most common cause of hypothyroidism in developed countries is autoimmune thyroiditis, which may be associated with a goiter (Hashimoto's thyroiditis) or, with equal frequency, thyroid atrophy. Radioiodine ablation or surgical thyroidectomy that is considered as treatment for hyperthyroidism or thyroid cancer is also responsible for considerable numbers of patients with hypothyroidism. Less often, hypothyroidism may be drug induced (suggesting the possibility of reversibility) or be secondary to disorders of the pituitary or hypothalamus (central or secondary hypothyroidism). Congenital hypothyroidism, due to thyroid aplasia, or hypoplasia or defective thyroid hormone biosynthesis, occurs in one in every 4000 live births (Harris and Pass 2007). Over the past several decades, tremendous increases in the incidence of thyroid cancer have been found to be different (Davies and Welch 2014). Thyroid cancer is the most common malignant tumor of the endocrine, but only contains about 1% of all tumors. Over 90% of thyroid cancers are of the follicular or papillary variants often termed differentiated thyroid cancer (Mazzaferri 1999). There are forms of thyroid cancer comprising medullary thyroid cancer arising from parafollicular C-cells, thyroid lymphoma, anaplastic carcinoma, Hurthle cell carcinoma, squamous cell carcinoma, and the very rare intrathyroid sarcoma (Segev et al. 2003).

Methods of the systematic review

Inclusion and exclusion criteria

Types of study design

Inclusion criteria All published, original articles reporting on the association of RF (450 to 3800 MHz) with the thyroid gland experimental factors.

Exclusion criteria (1) Original articles on population other than the intended study population. (2) Any reviews (narrative, systematic review, meta-analysis review and umbrella review). (3) Letters to the editor without original data, commentaries, and editorials. (4) Case series, case reports, and other single-arm studies.

Participants and type of exposure

No limit to the community used in studies was considered for this systematic review, and all human samples (female, male) and animal were analyzed.

Outcome measures

Finally, the effects of waves on the thyroid gland, T3 and T4 secreted from this gland, as well as TSH secreted from the hypothalamus and pituitary gland, exposure type, duration of exposure, and specific absorption rate (SAR) were examined.

Search strategy for identification of studies

We systematically searched electronic datasets, including PubMed, Scopus, Cochrane library, CINAHL, ISI Web of Science, Science Direct from inception, PROSPERO, and Embase using medical subject headings (Mesh) terms, such as "cell phone," "mobile phone," "global system for mobile (GSM) ," "radio frequency," "smartphone," and were combined with key terms "triiodothyronine," "thyroxin," "thyroid-stimulating hormone," "T3," "T4," "TSH," and "morphological," to identify relevant studies. The search included the period from 1980 to 2018. We also manually searched through the reference lists of potentially selected studies to identify further relevant publications.

Data extraction method and quality assessment

Screening was done by two reviewers (F.R. and K.SH.) independently, considering selection criteria; then, the data were extracted and cross-checked. Any inconsistencies were resolved by consultation with a third reviewer (J.F.). The information including author name, publication year and location, target group, exposure, exposure duration (h),

and outcomes was extracted. Study quality was evaluated based on a modified 12-point checklist with a median quality score of 6 (Hirst et al. 2013).

Results

Overall, 161 relevant studies were initially found. After screening titles and abstracts, 139 studies were excluded, and 22 studies were used for the systematic review (Adam and Taha 2008; Bergamaschi et al. 2004; Bhargav et al. 2017; de Seze et al. 1998; Dimida et al. 2011; Djeridane et al. 2008; Elsayed and Jastaniah 2016; Eskander et al. 2012; Esmekaya et al. 2010; Fattahi-asl et al. 2013; Geronikolou et al. 2015; Hajioun and Elahizadeh 2015; Jin et al. 2013; Karadede et al. 2009; Kim et al. 2013; Koyu et al. 2005a; Koyu et al. 2005b; Mohammad et al. 2009; Pawlak et al. 2014; Shahryar et al. 2009; Shaukat et al. 2013; Silva et al. 2016). Figure 2 outlines the search method and the number of studies identified and selected during each phase of the search.

Table 1 provides a detailed overview of the 22 reviewed studies. Then, all 22 selected studies were stratified according to the experimental model (animal, human, or cell line). A total of 22 studies comprising 7182 cases were examined: 10 studies on human comprising 3106 cases (1570 (50.54%) males and 1529 (49.46%) females) and 12 studies on various animal models comprising 4076 cases (Tables 2, 3, 4, and 5).

Exposure equipment

The range of frequency used in studies was 800–2100 MHz and the range of SAR was 0.082–4.6 W/kg. Most of the studies ($n = 10$) used GSM simulator for exposure equipment, nine of these studies used an EMF generator and another used code division multiple access (CDMA), wideband code division multiple access (WCDMA), and radiofrequency identification (RFID) antenna.

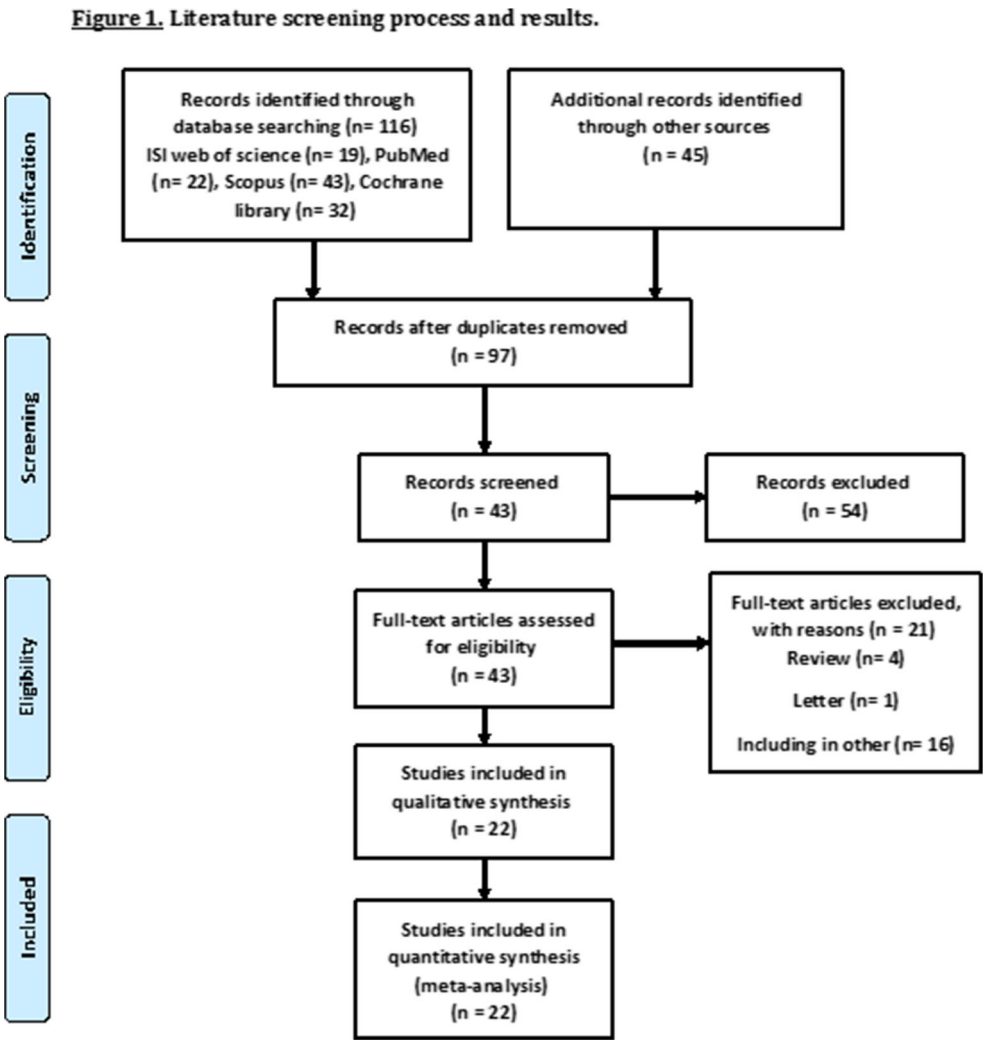


Fig. 2 Literature screening process and results

Table 1 General characteristics of the included studies

Study ID	Study type	Target group	Mean Age	Exposure
de Seze et al. 1998	Human	20 healthy male volunteers	28.1 ± 6.3 years	Global System for Mobile (GSM): 900 MHz, SAR was 2 W/kg
Bergamaschi et al. 2004	Human	2598 employees (1355 men and 1243 women)	Males 29.94 ± 6.19 Females 27.84 ± 6.11	Electromagnetic fields (EMF's) 900 MHz
Koyu et al. 2005a	Sprague-Dawley rats	30	12 weeks	Electromagnetic field (EMF): 900 MHz, SAR was 2 W/kg
Koyu et al. 2005b	adult male rats	20	20 weeks	Electromagnetic field (EMF): 1800 MHz, SAR was 2 W/kg
Adam and Taha 2008	Adult male Sprague-Dawley rats	50	12 weeks	Electromagnetic field (EMF): 900 MHz
Djeridane et al. 2008	Human	20 healthy male volunteers	(20–32) years	Global System for Mobile (GSM): 900 MHz
Karadede et al. 2009	Male, adult, New Zealand albino rabbits	14	3–4 months	GSM simulator 900 PM10 type
Mohammad et al. 2009	Human	77 healthy volunteers (23 males, 54 females)	22.82 ± 2.52 years	Global System for Mobile (GSM): 900 MHz
Shahryar et al. 2009	Male Syrian golden hamsters	72	–	Electromagnetic field (EMF): 900 MHz
Esmekaya et al. 2010	Male Wistar rats	30	8 weeks	Radiofrequency (RF) generator: 900 MHz, 1.35 W/kg
Dimida et al. 2011	Cell line	Fisher rat thyroid cells	–	EMF (800–900 MHz, power-frequency of mobile communication systems)
Eskander et al. 2012	Human	82 mobile phone volunteers (31 men and 51 women)	14–60 years	Global System for Mobile (GSM): 900 MHz
Shaukat et al. 2013	Adult Balb/C male mice	20	–	Global System for Mobile (GSM): 900 MHz
Kim et al. 2013	Male Sprague-Dawley rats	162	6 weeks	Radiofrequency identification (RFID) antenna: 915 MHz, SAR 3.2 to 4.6 W/kg
Fattahi-asl et al. 2013	Cell line	29 human serum samples (21 women and 8 men)	41.2 ± 14.3 years	Global System for Mobile (GSM): 900 MHz
Jin et al. 2013	Sprague-Dawley (SD) rats	240 specific pathogen-free male (120) and female (120)	6 weeks	Code division multiple access (CDMA): 848.5 MHz and wideband code division multiple access (WCDMA): 1950 MHz, total SAR 4 W/kg
Pawlak et al. 2014	Chicken embryos, newly hatched chicks	300	1–18 days	Electromagnetic field (EMF): 1800 MHz, SAR 0.1 W/m^2
Geronikolou et al. 2015	Human	28 healthy primary school	11–14 (12.5 ± 1.5 years)	Global System for Mobile (GSM): 900 MHz
Hajioun and Elahizadeh 2015	Rats	40	(80–90) days	Global System for Mobile (GSM): 900 MHz
Silva et al. 2016	Human	11 mostly females patients who underwent surgery	(20–60) years	Global System for Mobile (GSM): 895–900 MHz, SAR 0.082–0.170 (W/kg)
Elsayed and Jastaniah 2016	Human	180 (110 females and 70 males)	40 (15–65) years	Radiofrequency energy (RFE)
Bhargav et al. 2017	Human	61 healthy right-handed healthy teenagers (22 males and 39 females)	17.40 ± 0.24 years	RF-EMF was a 2100 MHz 3G mobile phone, SAR of 0.4 W/kg and body SAR of 0.54 W/kg

Study ID	Exposure duration (h)	Outcomes	Country
de Seze et al. 1998	40	There was a significant change only in thyrotropin concentration, showing a 21% decrease on the seventh sampling	France
Bergamaschi et al. 2004	–	No statistically significant difference regarding TSH and T3 values was observed	Italy
Koyu et al. 2005a	10	TSH values and T3–T4 at the 900 MHz EMF group were significantly lower than the sham-exposed group ($p < 0.01$)	Turkey

Table 1 (continued)

Koyu et al. 2005b	10	T3 and T4 levels were significantly higher than in control group; the TSH levels, there were no significant changes in sera of the rats	Turkey
Adam and Taha 2008	10	TSH values and T3–T4 at the 900 MHz EMF group were significantly lower than the sham-exposed group ($p < 0.01$)	Egypt
Djeridane et al. 2008	40	900 MHz EMF exposure, at least under our experimental conditions, does not appear to affect endocrine functions in men	France
Karadede et al. 2009	180	There was not any significant difference in neither hormonal nor biochemical parameters between experimental and control groups before exposure ($p > 0.05$)	Turkey
Mohammad et al. 2009	–	A higher than normal TSH level, low mean T4 and normal T3	Iran
Shahryar et al. 2009	50	The levels of T3 in the control group were higher than that of the long-term exposure group ($p < 0.01$), and levels of T4 in the 900 MHz EMF group for the long-term and short-term exposure groups were higher than that of the control group ($p < 0.01$)	Iran
Esmekaya et al. 2010	42	Observed formation of apoptotic bodies and increased caspase-3 and caspase-9 activities in thyroid cells of the rats	Turkey
Dimida et al. 2011	24, 48, and 96	EMF does not seem to be able to interfere with the biochemical properties of FRTL-5 cells in vitro	Italy
Eskander et al. 2012	6 years	Stations suffered high significant ($p < 0.01$) decrease in their serum T3 and T4 levels	Egypt
Shaukat et al. 2013	60	Size of thyroid follicles, decrease in size of follicles of thyroid gland of mice	Pakistan
Kim et al. 2013	80–640	No changes in T3, T4, or TSH were observed over time between the sham- and RFID-exposed groups	Korea
Fattahi-asl et al. 2013	18 min	There was no significant difference in serum T3 in the exposed group compared to the control group ($p = 0.541$)	Iran
Jin et al. 2013	30	Exposure for 8 weeks to simultaneous CDMA and WCDMA RF did not affect serum levels in rats of melatonin	Korea
Pawlak et al. 2014	40 min	T4 and T3 concentrations increased in the embryos and in the newly hatched chicks	Poland
Geronikolou et al. 2015	5 min	The hormonal and biochemical concentrations in the two groups did not differ $t(11) = 1.65, p > 0.05$	Greece
Hajioun and Elahizadeh 2015	60	Reduction in the number of cubic cells and disorder among them, as well as a reduction in the amount of follicular fluid and follicular diameter	Iran
Silva et al. 2016	3–65	RFE exposure conditions have no potential carcinogenic effect on thyroid cells	Israel
Elsayed and Jastaniah 2016	–	A total of 46.7% of our participants had abnormal findings of the thyroid gland more in non-smart phone users and more in females	Saudi Arabia
Bhargav et al. 2017	15 min	Thyroid gland, significantly lesser after RF-EMF exposure compared to sham	India

Table 2 Literature review of thyroid-stimulating hormone (TSH) for cell phone radiation

Study ID	Finding			Outcome
	TSH mean (μIU/ml)			
	Pre-exposure/control	Exposure	Post-exposure	
de Seze et al. 1998	Week 1: 1.69 Week 2: 1.61 Week 3: 1.51	Week 4: 1.40 Week 5: 1.44 Week 6: 1.36 Week 7: 1.27	Week 8: 1.53 Week 9: 1.64	–
Bergamaschi et al. 2004	< 0.4	–	Males: 1.56 ± 0.98 Females: 1.58 ± 1.18	–
Koyu et al. 2005a	Control: 0.23 ± 0.05	–	0.13 ± 0.04 sham-exposed: 0.21 ± 0.05	↓
Koyu et al. 2005b	Control: 0.31 ± 0.06	–	0.36 ± 0.08	–
Adam and Taha 2008	Control: 0.26 ± 0.05	–	0.15 ± 0.04 sham-exposed: 0.21 ± 0.05	↓
Djeridane et al. 2008	40 ± 13 (μIU/ml × h)	Week 2: 38 ± 13 Week 3: 38 ± 15 (μIU/ml × h)	34 ± 12 (μIU/ml × h)	–
Mohammad et al. 2009	2.70 ± 1.75	_	Group 1: 4.25 ± 2.13 Group2: 3.75 ± 2.05	↑
Karadede et al. 2009	Control: 0.0073 ± 0.001 Experimental: 0.007 ± 0.001	_	1 month Control: 0.0076 ± 0.001 Experimental: 0.067 ± 0.001 3 months Control: 0.0087 ± 0.001 Experimental: 0.083 ± 0.001	–
Jin et al. 2013	Male 4 weeks: 3.68 ± 0.99/8 weeks: 4.91 ± 2.31 Female 4 weeks: 2.85 ± 1.13/8 weeks: 4.06 ± 1.93 ng/dl	–	Experimental Male 4 weeks: 3.67 ± 1.47/8 weeks: 4.99 ± 2.26 Female 4 weeks: 2.76 ± 0.50/8 weeks: 4.11 ± 1.90	–
Kim et al. 2013	Control 2 weeks: 1.04 ± 0.41/4 weeks: 1.37 ± 0.25/8 weeks: 0.78 ± 0.13/16 weeks: 0.88 ± 0.04	–	2 weeks: 0.72 ± 0.18/4 weeks: 1.14 ± 0.14/8 weeks: 1.75 ± 0.24/16 weeks: 0.89 ± 0.16 Sham 2 week: 1.12 ± 0.27/4 weeks: 1.04 ± 0.18/8 weeks: 1.11 ± 0.25/16 weeks: 0.89 ± 0.16	–
Geronikolou et al. 2015	Group A (control) 1.9 ± 0.69	–	Group B (cell phone use) 2.68 ± 1.77	–

↑, increasing; ↓, decreasing; –, no change reported

Animal model

Among the 21 screened records, 11 studies were conducted to evaluate the effect of cell phone radiation on the thyroid gland in animal model studies (Adam and Taha 2008; Esmekaya et al. 2010; Hajioun and Elahizadeh 2015; Jin et al. 2013; Karadede et al. 2009; Kim et al. 2013; Koyu et al. 2005a; Koyu et al. 2005c; Pawlak et al. 2014; Shahryar et al. 2009; Shaukat et al. 2013). Overall, 11 studies were selected, including 7 records examined rat, 1 record examined rabbit, 1 record examined hamster, 1 record examined mice, and 1 record examined embryos of chicken. These studies were located in Turkey ($n = 4$), Egypt ($n = 1$), Iran ($n = 2$), Pakistan ($n = 1$), South Korea ($n = 2$), and Poland ($n = 1$).

Cell line

Out of the 21 records, 2 studies were based on cell line studies (Dimida et al. 2011; Fattahi-asl et al. 2013). These studies were located in Iran ($n = 1$) and Italy ($n = 1$).

Table 3 Literature review of triiodothyronine hormone for cell phone radiation

Study ID	Finding			Outcome
	T_3 (ng/dl)			
	Pre-exposure/control	Exposure	Post-exposure	
Koyu et al. 2005a	Control: 120.45 ± 11.04	–	86.67 ± 9.79 sham-exposed: 112.66 ± 10.71	↓
Koyu et al. 2005b	110.33 ± 14.63	–	170.22 ± 17.85	↑
Adam and Taha 2008	Control: 127.45 ± 11.04	–	92.67 ± 9.79 sham-exposed: 117.66 ± 10.71	↓
Karadede et al. 2009	Control: 1.044 ± 0.191 Experimental: 0.939 ± 0.172 ng/ml	–	1 month control: 1.008 ± 0.116 Experimental: 0.981 ± 0.223 3 month Control: 1.155 ± 0.055 Experimental: 1.143 ± 0.129	–
Mohammad et al. 2009	1.15 ± 0.27 ng/ml	–	Group 1: 1.25 ± 0.27 Group 2: 1.18 ± 0.30	↓
Shahryar et al. 2009	Control: 73.03	–	Short-term: 73.00 Long-term: 50.35	↓
Eskander et al. 2012	1 year Age 1: 105.2 ± 1.3/age 2: 102.0 ± 1.1 3 years Age1: 101.7 ± 1.2/age 2: 98.6 ± 2.1 6 years Age 1: 103.6 ± 1.1/age 2: 99.0 ± 1.4	–	1 year Age 1 S: 96.3 ± 1.2 M: 100.0 ± 0.6 W: 102.1 ± 1.3 Age 2 S: 93.9 ± 1.1 M: 98.1 ± 0.3 W: 99.0 ± 0.7	↓
Fattahi-asl et al. 2013	Control: 4.93 ± 0.34 μg/l	–	4.55 ± 0.53	–
Kim et al. 2013	Control 2 weeks: 31 ± 3.47/4 weeks: 36.33 ± 1.44/8 weeks: 16.54 ± 1.06/16 weeks: 32.69 ± 0.17	–	2 weeks: 44.83 ± 1.66/4 weeks: 42.27 ± 1.88/8 weeks: 19.90 ± 1.79/16 weeks: 29.40 ± 0.43 Sham 2 weeks: 46.50 ± 1.63/4 weeks: 39.18 ± 1.68/8 weeks: 20.64 ± 1.97/16 weeks: 29.09 ± 0.61	–
Jin et al. 2013	Male 4 weeks: 19.33 ± 1.96/8 weeks: 19.38 ± 1.41 Female 4 weeks: 18.57 ± 1.93/8 weeks: 16.68 ± 3.12 ng/ml	–	Experimental Male 4 weeks: 19.42 ± 0.84/8 weeks: 19.14 ± 1.17 Female 4 week: 18.85 ± 0.39/8 weeks: 16.20 ± 1.69	–
Pawlak et al. 2014	Control E12 embryos: 0.212 ± 0.055 D1 group: 3.396 ± 0.673	–	E12 embryos: 0.105 ± 0.057	↓
Geronikolou et al. 2015	Group A (control) (pg/mL) 1.4 ± 0.19	–	Group B (cell phone use) (pg/mL) 1.44 ± 0.39	–

↑, increasing; ↓, decreasing; –, no change reported

Human

Nine studies were conducted to evaluate the effect of cell phone radiation on the thyroid gland in human (Bergamaschi et al. 2004; Bhargav et al. 2017; de Seze et al. 1998; Djeridane et al. 2008; Elsayed and Jastaniah 2016; Eskander et al. 2012; Geronikolou et al. 2015; Mohammad et al. 2009; Silva et al. 2016). These studies were located in France ($n = 2$), Italy ($n = 1$), Iran ($n = 1$), Egypt ($n = 1$), India ($n = 1$), Saudi Arabia ($n = 1$), Israel ($n = 1$), and Greece ($n = 1$).

Table 4 Literature review of thyroxin hormone for cell phone radiation

Study ID	Finding			Outcome
	T_4 (μg/dl)			
	Pre-exposure/control	Exposure	Post-exposure	
Bergamaschi et al. 2004	–	–	Males: 2.99 ± 3.74 Females: 2.90 ± 3.70	–
Koyu et al. 2005a	Control: 6.23 ± 0.54	–	5.18 ± 0.53 sham-exposed: 5.98 ± 0.66	↓
Koyu et al. 2005b	5.82 ± 0.63	–	10.59 ± 1.24	↑
Adam and Taha 2008	Control: 6.23 ± 0.54	–	5.9 ± 0.53 sham-exposed: 5.98 ± 0.66	↓
Karadede et al. 2009	Control: 3.731 ± 0.395 Experimental: 3.597 ± 0.544	–	1 month Control: 2.810 ± 0.394 Experimental: 3.284 ± 0.814 3 months Control: 3.874 ± 0.546 Experimental: 4.091 ± 0.673	–
Mohammad et al. 2009	8.42 ± 2.72	–	Group 1: 7.76 ± 1.73 Group 2: 7.75 ± 1.14	↓
Shahryar et al. 2009	Control: 2.52	–	Short-term: 2.94 Long-term: 2.87	↑
Eskander et al. 2012	1 year Age 1: 7.8 ± 0.6/age 2: 6.9 ± 1.4 3 years Age 1: 7.7 ± 1.1/age 2: 6.5 ± 0.7 6 years Age1: 7.1 ± 0.3/age 2: 6.6 ± 2.1	–	1 year Age 1 S: 6.9 ± 0.1 M: 7.0 ± 0.1 W: 6.9 ± 0.1 Age 2 S: 6.3 0.8 M: 6.2 ± 1.2 W: 6.0 ± 1.0	↓
Kim et al. 2013	Control 2 weeks: 2.7 ± 0.26/4 weeks: 3.42 ± 0.16/8 weeks: 2.65 ± 0.11/16 weeks: 6.58 ± 0.3	–	2 weeks: 3.60 ± 0.24/4 weeks: 2.85 ± 0.27/8 weeks: 2.42 ± 0.10/16 weeks: 6.07 ± 0.33 Sham 2 weeks: 4.08 ± 0.27/4 weeks: 3.78 ± 0.25/8 weeks: 2.61 ± 0.15/16 weeks: 6.01 ± 0.16	–
Jin et al. 2013	Male 4 weeks: 31.81 ± 1.69/8 weeks: 31.55 ± 1.42 Female 4 weeks: 33.46 ± 4.31/8 weeks: 33.26 ± 4.04 ng/dl	–	Experimental Male 4 weeks: 30.16 ± 0.51/8 weeks: 31.47 ± 0.34 Female 4 weeks: 34.09 ± 2.09/8 weeks: 33.47 ± 2.24	–
Pawlak et al. 2014	Control E12 embryos: 0.27 ± 0.084 D42 group: 21.75 ± 3.265	–	E12 embryos: 0.13 ± 0.026 D42 group: 22.49 ± 3.427 sham-exposed E12 embryos: 0.29 ± 0.059 D42 group: 20.12 ± 2.569	↓
Geronikolou et al. 2015	Group A (control) 8.43 ± 148	–	Group B (cell phone use) 7.3 ± 1.3	–

↑, increasing; ↓, decreasing; –, no change reported

Morphology, pathological

Among the 22 screened records, 7 studies were based on morphology studies (Bhargav et al. 2017; Dimida et al. 2011; Elsayed and Jastaniah 2016; Esmekaya et al. 2010; Hajioun and Elahizadeh 2015; Shaukat et al. 2013; Silva et al. 2016). Overall, 7 studies were selected, including 3 records examined human, 3 record examined animal, and 1 record examined cell

Table 5 Literature review of Morphology, pathological for cell phone radiation

Study ID	Finding mean ± SE (μm)	Outcome
Esmekaya et al. 2010	Control: 36.8 Sham: 34 Exposure: 64	↓
Dimida et al. 2011	–	↓
Shaukat et al. 2013	Control: 117.56 ± 5.03 Experimental: 92.50 ± 2.25	↓
Hajioun and Elahizadeh 2015	–	↓
Silva et al. 2016	–	↓
Elsayed and Jastaniah 2016	–	↓
Bhargav et al. 2017	–	↓

↑, increasing; ↓, decreasing; –, no change reported

line. These studies were located in South Korea ($n = 1$), Pakistan ($n = 1$), Italy ($n = 1$), Iran ($n = 1$), India ($n = 1$), Saudi Arabia ($n = 1$), and Israel ($n = 1$).

Thyroid-stimulating hormone

Animal model Investigating the effect of 900 MHz waves on male rats showed that these waves reduced the level of TSH in the intervention group. Also, there was no significant difference between control and sham-exposed groups (Koyu et al. 2005a). Also, investigating the effect of 1800 MHz on male rats showed that these waves did not affect the TSH level of the radiation mice group (Koyu et al. 2005b).

With 900 MHz waves for 10 h at 4 weeks of radiation, these waves on 20 male rats showed that TSH levels in both control and sham-exposed groups were not significantly different but between the two intervention and sham-exposed groups, there is a significant difference in the intervention having group decreased hormone levels (Adam and Taha 2008). In the study, by using systems (CDMA 849 MHz and WCDMA 1.95 GHz) on male and female rats, these waves did not affect the TSH hormone in rats (Jin et al. 2013). Using 915 MHz RFID waves, male rats did not see a change in the level of TSH in both interventional and sham-exposed groups (Kim et al. 2013). A 900-MHz RF exposure did not change some important biochemical and hormonal parameter levels after 90 days exposure (Karadede et al. 2009).

Human By reviewing 18 healthy volunteers, mobile phones (GSM) roamed at 900 MHz for 2 h a day, 5 days a week for 4 weeks. After this time and analysis of the samples, they found that the level of the hormone in 7 of the population decreased by 21% (de Seze et al. 1998). But with the statistical level, 2598 mobile workers said that RF waves do not have an effect on the level of TSH (Bergamaschi et al. 2004). It was also concluded that RF waves have a very mild effect on the level of TSH, and in fact, its effect can be ignored (Djeridane et al. 2008; Geronikolou et al. 2015).

By studying 77 female and male students in three levels: high, medium and low, the mobile phone used, unlike other experimental studies showed increased levels of the hormone Mohammad et al. 2009. In this study, the level of TSH in both men and women was calculated to be better for women due to the hormone cycle in women, as well as a specific rule for determining the groups of users using cellular phone and its amount in this form. Perhaps this increase is due to a test error (Mohammad et al. 2009).

Triiodothyronine hormone

Animal model According to this study, waves of 1800 MHz EMF increase the T3 level in male rats (Koyu et al. 2005b). But another study with EMF 900 MHz observed that the level of the hormone decreases (Koyu et al. 2005a). By examining the effect of the 900 MHz EMF wave in male rats, the serum level decreased (Adam and Taha 2008) and with no effect in serum T3 (Jin et al. 2013; Karadede et al. 2009; Kim et al. 2013). Shahryar et al. showed that with the use of 900 MHz EMF waves for a long time, we are seeing a decrease in serum T3 (Shahryar et al. 2009). Pawlak et al. also showed that levels of this hormone in their community declined (Pawlak et al. 2014).

Human We found two studies, of which after testing the samples, normal T3 levels were reported (Geronikolou et al. 2015; Mohammad et al. 2009), whereas the study showed a significant decrease in volunteers' thyroid hormone levels, for young females (Eskander et al. 2012).

Cell line According to Fattahi-asl et al. (2013), by examining 29 healthy subjects (21 women and 8 men) with mean age 41.2 + 14.3 years, followed by radiation 900 MHz (GSM) for 18 min, mobile phone radiation has no effect on the levels of T3.

Thyroxin hormone

Animal model EMF waves of 900 MHz reduce the level of T4 hormone (Adam and Taha 2008; Eskander et al. 2012; Koyu et al. 2005a). However, another study showed that from 1800 MHz waves, hormone levels increase (Koyu et al. 2005b). But waves (EMF) 900 MHz increase rat T4 levels (Kim et al. 2013; Shahryar et al. 2009). However, Jin et al. (2013) and Karadede et al. (2009) have shown that waves do not affect the serum T4 level. Pawlak et al. (2014) checked hormone levels after radiation of 1800 MHz in chicken embryo and found that these waves decreased serum T4 level (Pawlak et al. 2014).

Human Though the effect of EMFs at 900 MHZ on T4 levels alongside occupational stress in a community was observed significantly, they claimed that establishing whether this consequence is due to exposure or the instruments using stress was not possible (Bergamaschi et al. 2004; Geronikolou et al. 2015), while Eskander et al. and Mohammad et al. surprisingly showed that the irradiation group had a decrease in T4 levels than the control group (Eskander et al. 2012; Mohammad et al. 2009).

Morphology, pathological

Some studies could not establish a link between thyroid cancer and EMF waves (Silva et al. 2016). Typically a whole-body exposure to a RF radiation pulse released by the global mobile phone system (GSM) can lead to pathological alterations in the thyroid through the structural changes and increasing the apoptosis-dependent pathways (Esmekaya et al. 2010). A study indicates that exposure to mobile phone-generated EMF radiation decreases the size of the thyroid gland follicles and its activity of mice (Shaukat et al. 2013). Exposing the thyroid to radiation such as cell phone can lead to fatal damage, and applying preventive and protective methods does not always mitigate the *impact* of this exposure on human body (Hajioun and Elahizadeh 2015). The electrophotonic imaging (EPI), as a promising technique, shows these effects and the possible energy level reduction of the intestinal tubers, including the thyroid gland (Bhargav et al. 2017). Moreover, it was reported that thyroid dysfunction and a hormone-lowering profile alongside increased TSH levels are present in approximately 30% of smartphone users (Elsayed and Jastaniah 2016). Besides, in vitro evidences revealed that EMF does not able to modify the biochemical properties of cultured thyroid cells such as FRTL-5 cells (Dimida et al. 2011).

Study quality scores

Study quality was evaluated based on a modified 12-point checklist with a median quality score of 6, which showed 7 (33%) stated whether a potential conflict of interest existed, and 6 (27%) described compliance with animal welfare policy. Three (14%) studies compared more than one model. Surprisingly, none of the studies described the blinded outcome assessment or reported a sample size calculation. Stratification by the number of study quality checklist item score accounted for significant heterogeneity between studies ($\chi^2 = 1373$, $df = 6$, $p < 0.00385$), with higher quality studies reporting lower efficacy (Supplementary table).

Discussion

The aim of this review was to assess all available epidemiologic evidences on the possible pathological changes in thyroid gland structure and hormones level due to mobile phone exposure and find out there is a potential association between long-term mobile phone use and apoptotic follicular cells damages.

Frequency refers to the rate at which electromagnetic field (EMF) direction changes and is expressed in hertz (Hz) unit (Humans 2013). Analogue phones have been allocated the frequencies between 450 and 900 MHz; hence, digital phones allocate to the frequencies between 1800 and 1990 MHz. Moreover, microwave devices use the frequency of 3800 MHz. Mobile phones are expected to produce non-considerable local heating, which unlikely make any harmful consequences (Koyu et al. 2005a).

Specific absorption rate (SAR) is a factor which is directly related to the mass density, conductivity, and the internal E-field strength of the tissue, and its unit is "W/kg" (Yang et al. 2013). According to the Federal Communications Commission (FCC) standard, cell phones are allowed to produce with SAR values below 1.6 W/kg for 1 g of body in the USA and 2 W/kg for 10 g of body in Europe (Federal Communications 2013). The range of SAR reported in this study was 0.082–4.6 W/kg. Silva et al. stated that RFE exposure conditions have no potential carcinogenic effect on thyroid cells with 0.082–0.170 (W/kg) SAR (Silva et al. 2016). It is expected that reducing this factor will reduce the risk of cell phone waves, but Bhargav et al. show that thyroid gland hormones are significantly lesser after RF-EMF with 0.54 W/kg SAR exposure compared to sham (Bergamaschi et al. 2004), and other studies show contradictory results about the role of SAR and hormonal effects. Despite the fact that SAR is a very important criterion for judging the highest energy of a radio signal released from a source of a particular model of a mobile phone, it alone cannot provide enough information to compare the amount of radio signal released by different phones to users.

Radiofrequency electromagnetic fields (RF-EMF) were classified as possibly human oncogenic factor by the International Agency for Research on Cancer (IARC) (Humans 2013; Sivani and Sudarsanam 2012). One of the concerns of the community is the effect of increasing the likelihood of getting cancer by using radio waves (Gong et al. 2014; Repacholi et al. 2012). Experimental researches highlight that pesticide exposure could generally lead to hypothyroidism. In a large population, the existence of subclinical hypothyroidism, especially in the case of iodine deficiency, as well as its long-term health-related consequences, has been much debated recently (Boas et al. 2012). The prevalence of subclinical type of hypothyroidism varies by gender, age,

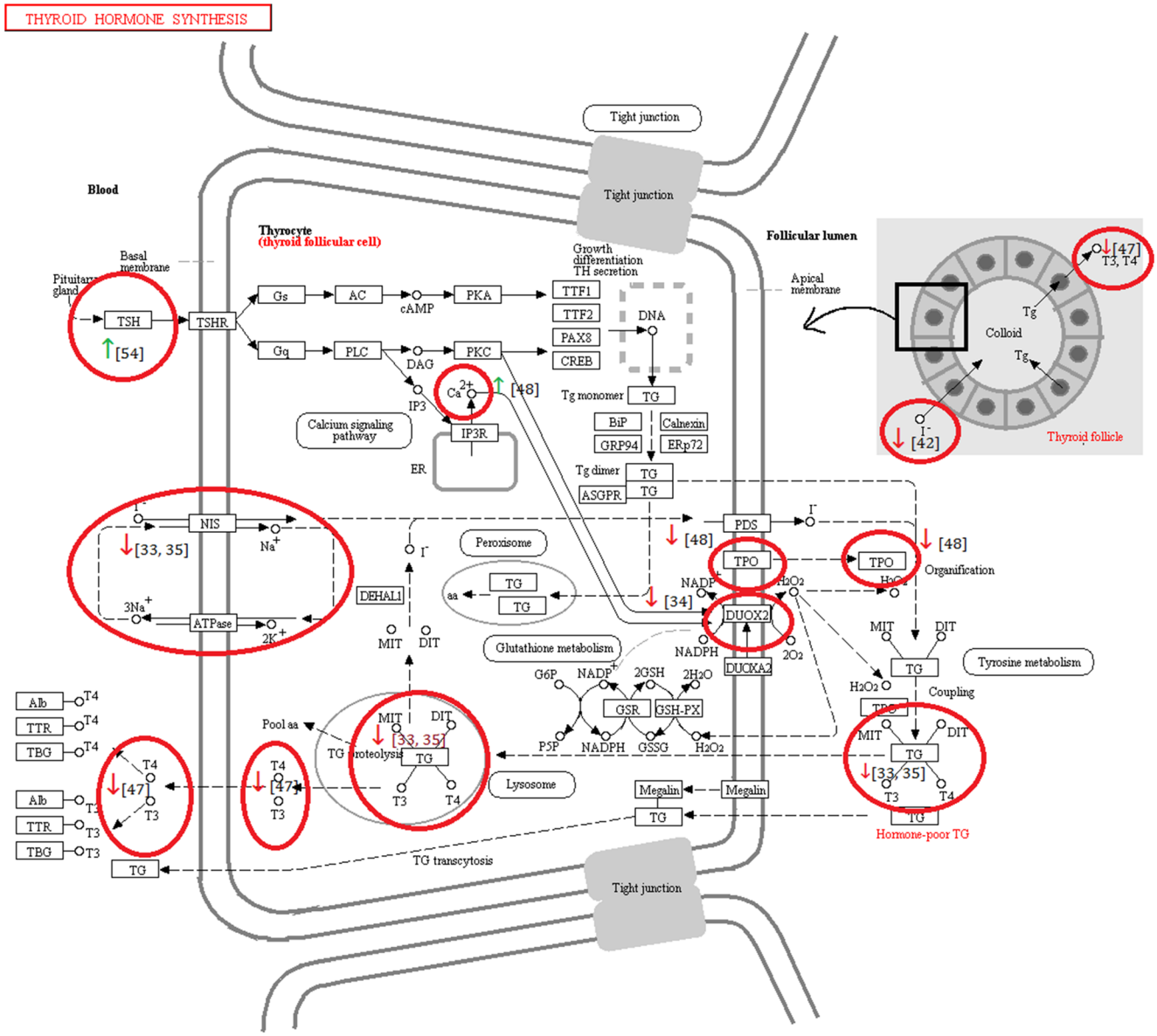


Fig. 3 Hypothetical metabolic pathway change due to cell phone radiation

ethnicity, and geographic location, ranging from 0.4 to 16.9% (Hennessey and Espaillat 2015) and even reaching 20% in some populations (Cooper 2001). Thyroid hormones (TH) are necessary and critical for development during fetal life, as fetal brain neurodevelopment is dependent on TH levels. Lack of TH diminishes neuronal growth and affects the cerebral cortex, hippocampus, and cerebellum differentiation. Consequently, epidemiological evidences have revealed that even a relatively slight decrease in T4 levels during pregnancy may lead to decrease of cognitive functions in offspring (Haddow et al. 1999; Pop et al. 2003). In this regard, Eşmekaya et al. stated that cell phone has the potential to cause pathological consequences in the thyroid gland via changing organ structure, as well as increasing the activity of caspase-dependent pathways related to apoptosis (Esmekaya et al. 2010). Silva et al. show the exposure to RFE seems to have no possible oncogenic consequence on human thyroid cells (Silva et al. 2016). Nonetheless, it is quite difficult to perform a study exploring the impacts of EMFs on a fetus or child due to ethical concerns (Sangun et al. 2015).

Exposure to EMF may negatively affect the iodine uptake in the thyroid gland and may lead to increasing the effect of temperature on pituitary gland hormone. According to this study, frequency of 900 MHz EMF produced by digital mobile radio-telephones decreases TSH and thyroid hormones under the conditions used (Koyu et al. 2005a). As non-ionizing radiation does not impose sufficient energy to dislodge electrons, it being unable to cause thyroid glands disorders. This review has synthesized the current evidence for cell phone radiation effect on function of thyroid glands. This

result can be possibly due to frequency between 450 to 3800 MHz EMF made by cell phones. Based on the evidence, the diameter of thyroid follicles reduces in contact with cell phone radiation, as well as many metabolic pathway elements related to thyroid changes consequently (Fig. 3).

Conclusions and future perspective

Tissue heating may be usually linked to nonspecific stress reaction induced by microwave exposure. Exposure negatively influences the iodine uptake in the thyroid gland, or may influence with increased temperature effect on the thyroid gland. However, with the advent of new generations of communications like the 5 G, further research are needed in order to show the level of TSH and thyroid hormone suppression by microwave.

Acknowledgements This research was the result of a project affiliated by Deputy of Research Affairs, Metabolomics and Genomics Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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