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Review

Lifestyle and testicular dysfunction: A brief update

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Abstract

The incidence of testicular cancer, cryptorchidism and defective spermatogenesis is increasing probably due to environmental and lifestyle-related factors. The aim of this review is to briefly describe and comment on the principal lifestyle factors. The recent findings that the electromagnetic waves following the use of the cell phone and the prolonged exposure to the noise stress cause relevant testicular dysfunction in man or animals reinforce the hypothesis of the importance of lifestyle-related factors.

Keywords: Lifestyle; Testicle; Spermatogenesis

1. Introduction

The incidence of testicular cancer, cryptorchidism and defective spermatogenesis is increasing [1]. Genetic factors are supposed to play a marginal role [1,2]. The principal hypotheses suggest that testicle is damaged by environment and lifestyle-related factors either at perinatal or at puberty time. Concerning the factors which may affect the adult tests, the environmental hormone disruption hypothesis lacks the epidemiological evidence [2] and the effects of tobacco, alcohol and sedentary work have not been well documented. Heat exposure, ionizing radiations, dibromochloropropane, estrogens and anabolic steroids are definite important damaging factors [1,2]. The occurrence of the above reported diseases, disorders or factors in the developmental age and the fact that Sertoli cells are key regulators of germ cells and Leydig cells' development provide a rational basis for their association [1].

However, recent data suggest the occurrence of new types of lifestyle-related damaging factors.

The aim of this brief report is to describe and comment on the recently reported effects of acoustic waves in animals and of the electromagnetic waves related to the use of cell phone in man.

2. Lifestyle-related factors

In Table 1 the principal lifestyle factors with the potential to affect human male sperm production and fertility have been summarized.

3. Scrotal temperature and effect of lifestyle

It is well known that testicular temperature within scrotum is 1–2 °C lower than core body temperature and increase in testicular temperature can affect spermatogenesis. However, recent changes in lifestyles make testes more susceptible to heat. Exposure to hot occupational environment (bakers, welders, foundry workers), sedentary work habits, traveling in car for long time during commute to and from work, tight clothing, all these can disrupt regulation of intrascrotal temperature and can lead to increase in testicular temperature [8,2].

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Table 1
Principal lifestyle-related factors

Mechanism/factor	Lifestyle-related factor	Ref.
Heat	Dresses, hot and thermal baths	[1,2]
Estrogens	Contraception (body image)	[1,2]
Androgens	Body image and performance	[1,2]
Alcohol[a]	Various	[3,4]
Smoking[b]	Various	[3,4]
Ionizing radiations	Excessive radiological screening and diagnostics	[5]
Tadalafil[c]	Sexual intercourses	[6]
Prolonged urban automobile driving	Reported in taxi drivers (extended to other drivers?)	[7]

[a] Increase in XY frequency in sperm affects already poor semen quality.
[b] Increase in sperm disomy.
[c] A single dose reduces sperm motility in young infertile patients.

4. Smoking

It is well established that smoking has a detrimental effect on male reproductive system. Saleh et al. demonstrated cigarette smoking leads to increase in reactive oxygen species (ROS) level and decrease in ROS-TAC score [9]. They reported high level of leukocytospermia in smokers and suggested that oxidative stress is due to ROS generation by activated leukocytes [9]. Various compounds of cigarette smoke (i.e., polycyclic aromatic hydrocarbons) and smoking metabolites may act as chemotactic stimuli and thereby induce an inflammatory response, recruitment of leukocyte and subsequent generation of ROS [9,10]. In a recent study, Gaur et al. showed that motility is one of the first sperm parameters affected and asthenozoospermia may be an early indicator of reduced semen quality in light smokers [11]. They reported significantly high teratozoospermia in heavy smokers compared to non-smokers [11]. Studies have shown that maternal smoking affects reproductive parameters of their offspring (male) during adolescence [10,12].

5. Effect of environmental toxicants and endocrine active compounds

5.1. Role of lead

Main sources of lead are deteriorated lead-based paints and resulting dust and soil contamination. Other minor sources are plumbing system with lead pipes and lead-gazed ceramic pottery [13]. Lead can cause oxidative stress by interfering with antioxidant enzymes and also by its effect on cell membrane polyunsaturated fatty acids (PUFA) [14]. Various animal and human studies reported lead can cause adverse effect on male reproductive organs [15–17].

5.2. Role of phthalates

Phthalates are constituents of many consumer plastic products. Oral exposure is the major route of exposure in general population. In 1998, Santhosh et al. reported increase in lipid peroxidation in cultures of rat hepatocytes due to exposure to DEHP [di-(2-ethylhexyl) phthalate] [18]. Later on, in 2002 Kasahara et al. demonstrated oral administration of DEHP causes increased generation of ROS in rat testes. They suggested that this may be due to induction of cytochrome *c* release from germ cell mitochondria [19].

Discussion of all environmental toxicants and endocrine active compounds is out of context of this article.

6. Effect of cell phone on male fertility

The frequency of cell phone radiation ranges between 850 and 1900 MHz. As energy carried by cell phone radiation [radiofrequency electromagnetic waves (RF-EMW)] is extremely low compared to ionizing radiation, i.e., X-rays (frequency, 10^{10}–10^{18} MHz), they do not cause ionization of molecule. However, exposure to RF-EMW causes a number of effects on biological systems [20–28]. Results of various studies demonstrating effects of cell phone radiation on male fertility are conflicting due to heterogeneity of data and research methods [20,29–41].

Recently, epidemiological studies, including one from our center, have proposed cell phone usage may cause decrease in sperm parameters [29,30,34,37,41]. Most remarkable finding of our study was significant association of cell phone usage with reduced sperm motility in men using cell phone >4 h/day vs. men not using at all ($67.80 \pm 6.16\%$ vs. $44.81 \pm 16.30\%$, $p < 0.0001$) [29]. In a recent cross-sectional study, Baste et al. studied infertility among military men employed in the Royal Norwegian Navy [30]. They reported odds ratio (OR) of 1.86 for infertility (95% confidence interval (CI): 1.46–2.37) among military personnel who self-reported exposure to RF-EMW relative to those who reported no work near RF-EM (electromagnetic) field [30].

Chronic exposure of RF-EMW can affect mitochondrial genome and nuclear β-globin locus of epididymal spermatozoa [30] causing increased expression of adhesion protein on spermatozoa [42]. Dasdag et al. demonstrated a decrease in mean seminiferous tubule diameter after exposure of rats ($n = 18$) to cell phone radiation [32]. However, these results could not be reproduced in a follow up study [33].

Various animal studies demonstrated production of oxidative stress after cell phone exposure [16,39,43,44]. Animal models are not a good candidate for the purpose to study effect of RF-EMW on human reproductive system, because their testicular dimensions are smaller and during experiment animals have a different level of exposure compared to human testes in real life (i.e., carrying cellular phone in trouser pocket or clipped on trouser belt) [45,46]. However, as a supporting evidence to animal studies, Friedman et al. have suggested production of free radical due to cell phone radiation may be due to stimulation of mammalian cell plasma membrane NADH oxidase [24].

Studies on in vitro effect of RF-EMW on human sperm are conflicting [35,36]. Erogul et al. studied ($n = 27$) the effect of cell phone radiation for 5 min on neat semen of human volunteer. They demonstrated significant decrease in rapid progressive motility (Grade A, $p = 0.0007$), an increase in

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slow progressive motility (Grade B, $p = 0.0007$) and an increase in percentage of immotile sperm (Grade D, $p = 0.0003$) [35]. However, Falzone et al. found no effect on purified mature spermatozoa (exposure duration 1 h) [36]. We have recently demonstrated for the first time that RF-EMW exposure can cause oxidative stress in ejaculated human semen (duration 1 h, specific absorbance rate (SAR) 1.46 W/kg, temperature of 20 °C). We found significant increase in reactive oxygen species (ROS) level and decrease in ROS-TAC score (reactive oxygen species-total antioxidant capacity) after cell phone exposure.

7. Effect of noise on testicular functions

It is well established that stress can cause increased level of glucocorticoids and leads to decrease in testosterone level [47]. Recently, Ruffoli et al. demonstrated chronic noise stress leads to accumulation of lipofuscin in mouse testis and subsequent decrease in testosterone production [48]. This was in support of previously established finding that administration of corticosterone causes production of free radical formation in the mitochondria of the Leydig cell and free radical generation is known to stimulate lipofuscin formation [49,50]. Therefore, lifestyle and work environment involving high level of noise exposure may be detrimental to testicular function [48].

8. Conclusion

Many acquired factors can damage human testicular function. Some of them are lifestyle related and are associated to a high probability of testicular damage. New lifestyle-related risks recently described seem to derive from cell phone electromagnetic radiations and chronic noise stress.

References

[1] Sharpe RM. Lifestyle and environmental contribution to male infertility. Br Med Bull 2000;56(3):630–42.
[2] Bonde JP, Storgaard L. How work-place conditions, environmental toxicants and lifestyle affect male reproductive function. Int J Androl 2002;25(5):262–8.
[3] Robbins WA, Elashoff DA, Xun L, Jia J, Li N, Wu G, et al. Effect of lifestyle exposures on sperm aneuploidy. Cytogenet Genome Res 2005; 111(3–4):371–7.
[4] Goverde HJ, Dekker HS, Janssen HJ, Bastiaans BA, Rolland R, Zielhuis GA. Semen quality and frequency of smoking and alcohol consumption – an explorative study. Int J Fertil Menopausal Stud 1995; 40(3):135–8.
[5] Oldereid NB, Rui H, Purvis K. Male infertility. Significance of life and occupation. Tidsskr Nor Laegeforen 1994;114(20):3308–11.
[6] Pomara G, Morelli G, Canale D, Turchi P, Caglairesi C, Moschini C, et al. Alterations in sperm motility after acute oral administration of sildenafil or tadalafil in young, infertile men. Fertil Steril 2007;88(4): 860–5.
[7] Figà-Talamanca I, Cini C, Varricchio GC, Dondero F, Gandini L, Lenzi A, et al. Effects of prolonged autovehicle driving on male reproduction function: a study among taxi drivers. Am J Ind Med 1996;30(6): 750–8.
[8] Ivell R. Lifestyle impact and the biology of the human scrotum. Reprod Biol Endocrinol 2007;5:15.
[9] Saleh RA, Agarwal A, Sharma RK, Nelson DR, Thomas Jr AJ. Effect of cigarette smoking on levels of seminal oxidative stress in infertile men: a prospective study. Fertil Steril 2002;78(3):491–9.
[10] Richthoff J, Elzanaty S, Rylander L, Hagmar L, Giwercman A. Association between tobacco exposure and reproductive parameters in adolescent males. Int J Androl 2008;31(1):31–9.
[11] Gaur DS, Talekar M, Pathak VP. Effect of cigarette smoking on semen quality of infertile men. Singapore Med J 2007;48(29):119–23.
[12] Jensen MS, Mabeck LM, Toft G, Thulstrup AM, Bonde JP. Lower sperm counts following prenatal tobacco exposure. Hum Reprod 2005;20(9): 2559–66.
[13] Centers for Disease Control and Prevention (CDC). Third national report on human exposure to environmental chemicals. NCEH Publication No. 05-0570; 2005.
[14] Hsu PC, Guo YL. Antioxidant nutrients and lead toxicity. Toxicology 2002;180:33–44.
[15] Batra N, Nehru B, Bansal MP. Influence of lead and zinc on rat male reproduction at 'biochemical and histopathological levels'. J Appl Toxicol 2001;21(6):507–12.
[16] Joffe M, Bisanti L, Apostoli P, Kiss P, Dale A, Roeleveld N, et al. Time to pregnancy and occupational lead exposure. Occup Environ Med 2003; 60(10):752–8.
[17] Shiau CY, Wang JD, Chen PC. Decreased fecundity among male lead workers. Occup Environ Med 2004;61(11):915–23.
[18] Santhosh A, Nair KG, Arun P, Deepadevi KV, Manojkumar V, Lakshmi LR, et al. Effect of DEHP [di-(2-ethyl hexyl) phthalate] on lipid peroxidation in liver in rats and in primary cultures of rat hepatocytes. Indian J Med Res 1998;108:17–23.
[19] Kasahara E, Sato EF, Miyoshi M, Konaka R, Hiramoto K, Sasaki J, et al. Role of oxidative stress in germ cell apoptosis induced by di(2-ethylhexyl)phthalate. Biochem J 2002;365(Pt. 3):849–56.
[20] Aitken RJ, Bennetts LE, Sawyer D, Wiklendt AM, King BV. Impact of radio frequency electromagnetic radiation on DNA integrity in the male germline. Int J Androl 2005;28(3):171–9.
[21] Balci M, Devrim E, Durak I. Effects of mobile phones on oxidant/antioxidant balance in cornea and lens of rats. Curr Eye Res 2007; 32(1):21–5.
[22] Capri M, Scarcella E, Fumelli C, Bianchi E, Salvioli S, Mesirca P, et al. In vitro exposure of human lymphocytes to 900 MHz CW and GSM modulated radiofrequency: studies of proliferation, apoptosis and mitochondrial membrane potential. Radiat Res 2004;162(2):211–8.
[23] Carlo GL, Jenrow RS. Scientific progress – wireless phones and brain cancer: current state of the science. MedGenMed 2000;2(3):E40.
[24] Friedman J, Kraus S, Hauptman Y, Schiff Y, Seger R. Mechanism of short-term ERK activation by electromagnetic fields at mobile phone frequencies. Biochem J 2007;405(3):559–68.
[25] Lai H, Singh NP. Single- and double-strand DNA breaks in rat brain cells after acute exposure to radiofrequency electromagnetic radiation. Int J Radiat Biol 1996;69(4):513–21.
[26] Leszczynski D, Joenväärä S, Reivinen J, Kuokka R. Non-thermal activation of the hsp27/p38MAPK stress pathway by mobile phone radiation in human endothelial cells: molecular mechanism for cancer- and blood–brain barrier-related effects. Differentiation 2002;70(2–3): 120–9.
[27] Moustafa YM, Moustafa RM, Belacy A, Abou-El-Ela SH, Ali FM. Effects of acute exposure to the radiofrequency fields of cellular phones on plasma lipid peroxide and antioxidase activities in human erythrocytes. J Pharm Biomed Anal 2001;26(4):605–8.
[28] Stopczyk D, Gnitecki W, Buczynski A, Markuszewski L, Buczynski J. Effect of electromagnetic field produced by mobile phones on the activity of superoxide dismutase (SOD-1) and the level of malonyldialdehyde (MDA) – in vitro study. Med Pr 2002;53(4):311–4.
[29] Agarwal A, Deepinder F, Sharma RK, Ranga G, Li J. Effect of cell phone usage on semen analysis in men attending infertility clinic: an observational study. Fertil Steril 2008;89(1):124–8.
[30] Baste V, Riise T, Moen BE. Radiofrequency electromagnetic fields; male infertility and sex ratio of offspring. Eur J Epidemiol 2008;23(5): 369–77.

Please cite this article in press as: Agarwal A et al., Lifestyle and testicular dysfunction: A brief update, Biomed Pharmacother (2008), doi:10.1016/j.biopha.2008.07.052

[31] Dasdag S, Akdag MZ, Ulukaya E, Uzunlar AK, Yegin D. Mobile phone exposure does not induce apoptosis on spermatogenesis in rats. Arch Med Res 2008;39(1):40–4.
[32] Dasdag S, Ketani MA, Akdag Z, Ersay AR, Sari I, Demirtas OC, et al. Whole-body microwave exposure emitted by cellular phones and testicular function of rats. Urol Res 1999;27(3):219–23.
[33] Dasdag S, Zulkuf Akdag M, Aksen F, Yilmaz F, Bashan M, Mutlu Dasdag M, et al. Whole body exposure of rats to microwaves emitted from a cell phone does not affect the testes. Bioelectromagnetics 2003; 24(3):182–8.
[34] Davoudi M, Brossner C, Kuber W. The influence of electromagnetic waves on sperm motility. J Urol Urogynäkol 2002;9(3):18–22.
[35] Erogul O, Oztas E, Yildirim I, Kir T, Aydur E, Komesli G, et al. Effects of electromagnetic radiation from a cellular phone on human sperm motility: an in vitro study. Arch Med Res 2006;37(7):840–3.
[36] Falzone N, Huyser C, Fourie F, Toivo T, Leszczynski D, Franken D. In vitro effect of pulsed 900 MHz GSM radiation on mitochondrial membrane potential and motility of human spermatozoa. Bioelectromagnetics 2008;29(4):268–76.
[37] Fejes I, Zavaczki Z, Szollosi J, Koloszar S, Daru J, Kovacs L, et al. Is there a relationship between cell phone use and semen quality? Arch Androl 2005;51(5):385–93.
[38] Forgacs Z, Somosy Z, Kubinyi G, Bakos J, Hudak A, Surjan A, et al. Effect of whole-body 1800 MHz GSM-like microwave exposure on testicular steroidogenesis and histology in mice. Reprod Toxicol 2006; 22(1):111–7.
[39] Ozguner M, Koyu A, Cesur G, Ural M, Ozguner F, Gokcimen A, et al. Biological and morphological effects on the reproductive organ of rats after exposure to electromagnetic field. Saudi Med J 2005;26(3):405–10.
[40] Ribeiro EP, Rhoden EL, Horn MM, Rhoden C, Lima LP, Toniolo L. Effects of subchronic exposure to radio frequency from a conventional cellular telephone on testicular function in adult rats. J Urol 2007;177(1): 395–9.
[41] Wdowiak A, Wdowiak L, Wiktor H. Evaluation of the effect of using mobile phones on male fertility. Ann Agric Environ Med 2007;14(1): 169–72.
[42] Yan JG, Agresti M, Bruce T, Yan YH, Granlund A, Matloub HS. Effects of cellular phone emissions on sperm motility in rats. Fertil Steril 2007; 88(49):957–64.
[43] Meral I, Mert H, Mert N, Deger Y, Yoruk I, Yetkin A, et al. Effects of 900-MHz electromagnetic field emitted from cellular phone on brain oxidative stress and some vitamin levels of guinea pigs. Brain Res 2007; 1169:120–4.
[44] Ozguner F, Bardak Y, Comlekci S. Protective effects of melatonin and caffeic acid phenethyl ester against retinal oxidative stress in long-term use of mobile phone: a comparative study. Mol Cell Biochem 2006; 282(1–2):83–8.
[45] Cairnie AB, Harding RK. Cytological studies in mouse testis irradiated with 2.45-GHz continuous-wave microwaves. Radiat Res 1981;87(1): 100–8.
[46] Oktem F, Ozguner F, Mollaoglu H, Koyu A, Uz E. Oxidative damage in the kidney induced by 900-MHz-emitted mobile phone: protection by melatonin. Arch Med Res 2005;36(4):350–5.
[47] Monder C, Miroff Y, Marandici A, Hardy MP. 11 beta-Hydroxysteroid dehydrogenase alleviates glucocorticoid-mediated inhibition of steroidogenesis in rat Leydig cells. Endocrinology 1994;134(3): 1199–204.
[48] Ruffoli R, Carpi A, Giambelluca MA, Grasso L, Scavuzzo MC, Giannessi F. Diazepam administration prevents testosterone decrease and lipofuscin accumulation in testis of mouse exposed to chronic noise stress. Andrologia 2006;38(5):159–65.
[49] Gao HB, Tong MH, Hu YQ, You HY, Guo QS, Ge RS, et al. Mechanisms of glucocorticoid-induced Leydig cell apoptosis. Mol Cell Endocrinol 2003;199(1–2):153–63.
[50] Terman A, Brunk UT. Lipofuscin. Int J Biochem Cell Biol 2004;36(8): 1400–4.

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