ROS

REVIEW ARTICLE

Mind-Body Interventions Significantly Decrease Oxidative DNA Damage in Sperm Genome: Clinical Implications

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ABSTRACT | Mind-body interventions (MBIs) have been broadly categorized into a group of interventions which facilitate mind's capacity to affect the functions of the body. There is a growing body of evidence suggesting the adoption of MBIs like yoga, meditation, Tai Chi, and Qigong as an adjunct in the management of various complex lifestyle-related disorders. This review summarizes the importance of simple yoga- and meditation-based lifestyle intervention as a critical component of male infertility therapy. Defective chromatin integrity is one of the hallmarks of male factor infertility. Regular practice of yoga and meditation affects and targets the whole body, decreases free radical levels, and causes collateral increase in levels of antioxidants, not only resulting in improvement in standard sperm parameters, but also becoming ideal in treating oxidative stress and oxidative DNA damage and modulating levels of sperm transcripts through affecting the sperm methylome. This may aid in reversing testicular aging and improving the overall health and quality of life of male infertility patients and of the next generation.

KEYWORDS | Embryogenesis; Gene expression; Infertility; Meditation; Mind-body interactions; Oxidative DNA damage; Oxidative stress; Yoga

ABBREVIATIONS | IVF, in vitro fertilization; MBI, mind-body intervention; MDA, malondialdehyde; 8-OH-dG, 8-hydroxy-2′-deoxyguanosine; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SOD, superoxide dismutase

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1. INTRODUCTION

Mind-body interventions (MBIs) have gained significant interest in the current age of urbanization and comprise of a set of practices employing the use of brain in conjunction with the body for facilitating the healing process. MBIs have been defined by the United States National Institutes of Health as "interventions that use a variety of techniques designed to facilitate the mind's capacity to affect bodily functions and symptoms" [1]. Emerging evidence from past decades has suggested the surge of various complex "lifestyle-related" disorders like diabetes, heart disease, infertility, and pregnancy [2, 3]. The psychological burden associated with certain emotional states (e.g., depression), behavioral dispositions (e.g., withdrawal, hostility), and psychological stress not only affects physiological functions but also is associated with adverse health outcomes [3, 4]. Despite widespread ongoing research and awareness to address the current epidemic of such lifestyle disorders, the various associated psychosocial factors still continue to be overlooked and unaddressed in many clinical scenarios. Reproductive disorders, such as infertility and early pregnancy loss, are such complex disorders characterized by a myriad of various genetic and epigenetic causal factors [2]. Apart from the advent of newer technologies and advancements in modern medicine, the incidence of couples experiencing the above conditions continues to rise. The purpose of the present review is to address the efficacy of various MBIs as an adjunct in the management of alarming burden of infertility and pregnancy loss.

2. MIND-BODY INTERVENTIONS

There is a growing interest in the modification of lifestyle factors as well as the adoption of diverse holistic, complementary and alternative approaches as an important component of "male infertility therapy" [3]. Various MBIs including yoga, meditation, Tai Chi, and Qigong have gained immense popularity in the recent years [5]. While a majority of these are based on ancient practices and traditions, they have undoubtedly proven to exert beneficial effects on mental and physical health alongside managing the distressing symptoms and improving the wellbeing [6]. These BMIs have proven to be effective in reducing the symptoms and improving quality of life, and research has begun to examine the impact of these therapies on biological processes, including inflammation, oxidative stress, gene expression, and epigenetic modifications. More consistent findings were seen for genomic markers, with trials showing decreased expression of inflammation-related genes and reduced signaling through the proinflammatory transcription factor NF-κB. Potential mechanisms for these effects are discussed, including alterations in neuroendocrine, neural, and psychological and behavioral processes [5].

Different types of MBIs which have received considerable research attention and are widely available to clinical and community populations are mainly Tai Chi, Qigong, yoga, and meditation. Tai Chi and Qigong are traditional Chinese medicine practices which combine specific movements or postures, coordinated breathing, and mental focus. Yoga with roots in ancient Indian philosophy is widely adopted and practiced in the West, includes physical postures (asanas), breathing, and meditation or relaxation, though there is considerable variability across different schools of yoga and specific interventions. Meditation has been aptly defined as "intentional self-regulation of attention", a systemic mental focus on particular aspects of inner or outer experience [1, 7]. It refers to a broad range of practices that involve training the mind, typically to focus attention. In particular, mindfulness meditation teaches individuals to bring attention to present moment experiences with openness, curiosity, and non-judgment [3, 5]. Various other MBIs are relaxation techniques, guided imagery, hypnosis, biofeedback, and cognitive behavioral therapy. These MBIs have been considered for inclusion as an adjunct complementary and alternative therapies for various medical conditions [1].

Numerous researches have suggested the beneficial effects of yoga- and meditation-based lifestyle interventions on myriad aspects of psychological health, and the current literature suggests that they can improve symptoms of depression, anxiety, stress, post-traumatic stress disorder, and other psychological problems (for reviews, see [8–11]) as well as exert a positive impact on quality of life, promoting well-being, including life satisfaction and happiness [12, 13]. Various pathways and explanations have been proposed for these salutary effects, but there is still a lack of an overarching framework in which these mechanisms should be put to understand them.

3. BURDEN OF INFERTILITY

Infertility, defined as the inability of a couple to achieve spontaneous pregnancy after 1 year of regular, unprotected sexual intercourse, is a complex lifestyle disorder with a phenomenal increase in its incidence. It affects almost 180 million (~9% of the population) in the reproductive age group in India. Male infertility is responsible for nearly half of the infertility cases. Although 8–10% men of reproductive age group are affected, only 2.5–12% of these adult men seek consultation for infertility. It had often been a neglected issue but has now been considered as a critical component of reproductive health. Derangements in sperm function have been one of the biggest causes of male infertility. The primary causes of these defects in sperm function are undoubtedly multifactorial including genetic, environmental, and lifestyle factors either acting alone or in combination. Advanced paternal age (>40 years of age) due to various lifestyle and professional commitments exerts a compounding effect on the burden of infertility [14]. Modern sedentary lifestyle with low levels of physical activity, obesity, smoking, consumption of alcohol, use of recreational drugs, and exposure to pesticides, xenobiotics, and radiations lead to oxidative stress [15–17]. Excessive consumption of high-energy diet including intake of processed nutritionally depleted food deficient in vital nutrients and antioxidants has resulted in a spike in the incidence of metabolic disorders leading to a decline in male reproductive health. Furthermore, the integration of the deleterious effects of all the cited factors in the current lifestyle of western society eventually culminates in oxidative stress, which tends to impair the structural and functional integrity of the male germ cells and exerts detrimental effects on the health of the progeny. Thus, the adoption of a healthy lifestyle with increased intake of fruits, vegetables, and incorporation of MBIs as an integral component of our daily regimen might reduce oxidative stress in the sperm cells, reducing the incidence of male infertility and pregnancy losses, and decreasing the burden of childhood disorders.

4. OXIDATIVE STRESS IN MALE GERM LINE

Oxidative stress describes the condition generated because of an increase in the level of oxygen and oxygen-derived free radicals, which overpowers the natural antioxidant defense mechanisms of the cell. This culminates in a state of oxygen paradox whereby the free radicals are required for the normal physiological cellular processes of the cell, but, at increased concentrations, impede metabolic processes. Impending oxidative stress in the germline is associated with the generation of reactive oxygen species (ROS) including superoxide anions, hydrogen peroxide, peroxyl radical, and hydroxyl radical, among others [16–20]. Oxidative stress is one of the potential causes of dysfunction in the spermatozoa and one of the main causes of infertility in 30–80% infertile men due to impairment of both structural and functional integrity of the spermatozoa [16]. While low levels of ROS are required for redox-sensitive physiological processes in the spermatozoa like capacitation and hyperactivation, the supra-physiological levels negatively affect sperm membrane fluidity and permeability. The dose-dependent analysis of impact of low and high levels of ROS on sperm functions is thus shown to be a biphasic response [21]. ROS can originate from a host of endogenous and exogenous sources. The major source of ROS in the sperm continues to be activated leucocytes in the seminal plasma and sperm mitochondria, which are also the target of free radical oxidation. Endogenous sources of ROS include oxidative phosphorylation, cytochrome P450-catalysed drug metabolism, peroxisomes, and inflammatory cell activation [16].

Susceptibility of the highly differentiated sperm cells to oxidative stress is mainly because the sperm plasma membrane is highly rich in polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid containing six carbon-carbon double bonds per molecule [16, 17, 21]. This structure thus provides a susceptible target for oxidation by free radicals. Also, the carbon-hydrogen dissociation energies of PUFAs are lowest in bisallylic methylation position, thus rendering them vulnerable to oxidation. These reactions further tend to produce lipid radicals, thus perpetuating the lipid peroxidation chain reaction resulting in the generation and accumulation of electrophilic lipid aldehydes such as malondialdehyde (MDA), 4-hydroxynonemal (4-HNE), and acrolein [16, 22–24]. Lipid peroxidation induced by the increasing ROS levels compromises the membrane permeability and membrane potential, thus negatively impacting the cellular integrity. These end prod-

ucts are not only mutagenic but also produce DNA adducts, which have the potential to cause mutations in oncogenes and tumor suppressor genes. MDA is considered to have the highest mutagenic potential owing to its unstable nature. These lipid aldehydes, owing to their electrophilicity, have the potential to bind to mitochondrial proteins causing a conformational change and further triggering the production of ROS.

Sperm motility is one of the early functions, which is affected by oxidative stress and lipid peroxidation. Sperm plasma membrane modifications by the impending oxidative attack disrupt the membrane fluidity eventually leading to loss of motility and also impaired membrane fusion events such as acrosome reaction and sperm-oocyte fusion [21]. Reduction in sperm motility was seen to be directly proportional to the levels of lipid peroxidation induced by ROS [25]. The dramatic effects of ROS on the capacity of sperm to fuse with the vitelline membrane of the oocytes compromise the fertilizing capacity of the spermatozoa under conditions when the sperm motility is normal [25, 26]. The definitive mechanisms under which the sperm motility decreases are not certain, but oxidative damage to the sperm axoneme and depletion of intracellular adenosine triphosphate (ATP) stores are the putative mechanisms [17, 21, 27, 28]. High levels of ROS are associated with significant decline in the integrity of both the mitochondrial and nuclear genomes of human spermatozoa [29]. These reactive metabolites further attack the nucleotide bases and phosphodiester backbone, thus destabilizing the DNA structure and creating the cellular condition which eventually results in fragmentation of the DNA. Previous studies from our laboratory have documented that the incorporation of a healthy yoga-based lifestyle intervention program has resulted in significant improvement in seminal oxidative stress and oxidative DNA damage [30]. A significant decline in ROS, improvement in sperm progressive motility, and an increase in sperm count (assessed on 2 samples) with the yoga-based lifestyle intervention as early as 21 days have been seen in our previous study in male partners of primary infertility patients who failed attempts in in vitro fertilization (IVF) [2].

A brief, 12-week yoga-based lifestyle intervention for infertile men with major depressive disorder showed significant improvements in basic semen parameters based on the World Health Organization (WHO) 2010 criteria by the reduction in both oxidative and psychological stress. Our results showed a significant increase in sperm count and progressive sperm motility (Type A+B) in 80% of patients after intervention as a primary outcome. Secondary outcomes included improvement in the quality of life (WHOQOL-BREF scale) and reduction in the severity of depression [Beck Depression Inventory–II (BDI-II)] [31].

5. OXIDATIVE DNA DAMAGE AND GENOMIC INSTABILITY

DNA fragmentation in the spermatozoa is one of the hallmarks of male factor infertility. The loss of genomic integrity in the spermatozoa in such cases has been clinically associated with many adverse reproductive outcomes such as poor fertilization rate, impaired embryonic development, decreased cleavage and blastocyst quality, increased incidence of miscarriage, and birth defects including childhood carcinomas [32, 33]. Spermatozoa are particularly vulnerable to oxidative DNA damage following spermiogenesis, especially when they are stored in the epididymis for 12–14 days and thus lack the protection provided by the antioxidant-rich seminal plasma. Although the detailed etiology of this damage is still unresolved, it has been shown to have a high correlation with the efficiency of DNA compaction during the terminal stages of spermiogenesis in epididymis and evidence of oxidative stress [34].

The causes of oxidative DNA damage that occurs in the spermatozoa are diverse and the type of damage produced is also equally diverse. The various recognized types of oxidative DNA damage in the sperm are: (i) single-strand and double-strand breaks; (ii) introduction of abasic sites due to the loss of a base; (iii) fragmentation of the DNA; (iv) chemical modification of bases (e.g., oxidation or alkylation); (v) DNA-DNA cross-linking; and (vi) DNA-protein cross-linking [20, 35, 36]. The above damages result in arrest or induction of gene transcription, induction of signal transduction pathways, accelerated telomeric DNA attrition, replication errors, and genomic instability. Notably, the damage occurs primarily at the guanine base out of all the 4 bases. Guanine is the most susceptible to oxidation, due to its low oxidation potential [37]. Out of all the oxidative DNA lesions, the creation of the oxidative base-adduct, 8-hydroxy-2′-deoxyguanosine (8-OH-dG), is particu-

larly mutagenic. The accumulation of 8-OH-dG has the propensity to form a stable base pair with adenine, resulting in the GC to TA transversion mutations [16, 17, 38].

As already highlighted before, oxidative stress in the spermatozoa is associated with damage to both nuclear and mitochondrial genome as well as epigenome. The mitochondrial genome is more vulnerable to oxidative attack owing to its very limited capacity of repair due to the complete lack of nucleotide-excision repair pathway enzymes [16]. The repair of oxidative DNA damage in the human spermatozoa is incomplete as it only possesses the initial enzyme 8-oxoguanine glycosylase 1 (OGG1) which cleaves this adduct to the exterior and lacks the downstream enzymes APE1 and XRCC1. The repair of the above DNA damage is thus dependent on the oocyte repair mechanisms, which possess the above downstream enzymes [21, 39]. Previous studies from our laboratory in men with idiopathic infertility who underwent yoga intervention have shown a significant decline in oxidative stress within 10 days. The study also documented lower levels of poly(ADP-ribose) polymerase 1 (PARP1), which is responsible for the detection of oxidative DNA damage in sperm [40]. The DNA fragmentation index (DFI) showed a minimal non-significant improvement with 21 days of incorporation of yoga in lifestyle in recurrent implantation failure patients [2]. Significant improvement in the genomic integrity took nearly 6 months as evidenced by a decline in DNA fragmentation index and also in the levels of oxidative DNA base-adduct 8-OH-dG [16, 30, 41].

Various studies have indicated poor chromatin remodeling in the origin of sperm DNA damage. Spermatozoa, which exhibit poor nuclear protamination, are highly susceptible to oxidative DNA attack due to greater accessibility of their DNA bases and backbone to ROS. This remodeling of the sperm chromatin during spermiogenesis involves the replacement of histones with positively charged protamines and the spermatozoon's genetic material packaging from solenoid into toroid-like structures spanning 50 kb linked by matrix attachment regions [17, 39]. This chromatin packaging arrangement approaches the physical limits of molecular compaction and is theoretically designed to protect the paternal genome from damage [29]. However, such high levels of compaction also limit the capacity of sperm chromatin to execute DNA repair [20].

6. PREVENTIVE REMEDY

By virtue of the fact that sperm has very basic and incomplete DNA repair mechanisms, it becomes pertinent to follow the golden policy that prevention is better than cure. Thus, it is important to minimize the exposure to factors, which predispose to a situation with overwhelming oxidative stress, thereby culminating in a state of compromised genomic integrity. If diagnosed with high levels of oxidative stress, the usual norm is the prescription of antioxidants. Most of the studies carried to date have measured the impact on seminal oxidative stress and sperm motility especially in asthenozoospermic patients and have been shown to be significant. But only a few antioxidant supplementations have been shown to impact the nuclear DNA damage at therapeutic doses. A quest to develop novel antioxidant formulations and their combinations with optimized safety and efficacy still seems to continue. In this regard, well designed clinical studies are among the top priorities.

The adoption of simple lifestyle interventions may normalize high levels of oxidative stress. In this context, yoga and meditation may significantly impact free radical levels and cause a collateral increase in antioxidant defenses to an extend that benefits physiology. Indeed, indiscriminate use of antioxidants may cause very low levels of free radicals resulting in impaired sperm function and several redox-sensitive metabolic reactions. In line with this notion, Mishra et al. [41] have reported that mild oxidative stress is beneficial in the maintenance of sperm telomere length while low and very high levels of seminal ROS are associated with shorter telomeres and loss of genomic integrity. In our previous studies, we have also reported an increase in telomerase activity and a decline in seminal free radical levels and increase in total antioxidant capacity following a short-term (21 days) of the practice of yoga and meditation [31, 42]. These findings are highly relevant because though genetic causes of infertility, recurrent spontaneous abortion, and congenital malformations are irreversible, oxidative DNA damage can be minimized by adopting a healthy lifestyle. This may reduce the number of couples needing assisted reproductive technology and reduce the incidence of recurrent pregnancy loss, congenital malformations, childhood cancer, and complex neuropsychiatric disorders in children, and thus impact the lifelong health of offspring.

7. YOGA AND MEDITATION FOR REDUCING OXIDATIVE STRESS

Yoga- and meditation-based lifestyle interventions lower oxidative stress, reduce DNA fragmentation, and lower mutagenic load in sperm DNA, and thus are therapeutic for oxidative stress and oxidative DNA damage [2, 30, 42, 43]. Since psychosocial stress also induces oxidative stress, yoga and meditation result in the reduction of both psychological and oxidative stress and improvement in the quality of life. Yoga and meditation were associated with increased levels of superoxide dismutase (SOD), catalase, and glutathione, and a decrease in the blood lactate levels in practitioners, compared to non-practitioners [44]. Five months of practice were recently shown to be associated with significantly increased total glutathione, catalase, and SOD [45]. Regular practice of meditation has been seen to influence human biophoton emission [46] immediately within 10 minutes; an elevation of total glutathione and SOD levels has been seen in 65 minutes [44, 47]. It causes decline in many reactive oxygen metabolites within 8–24 hours and precipitates an increase in total antioxidant capacity within 24 hours. Yoga and meditation do not only have short-term effects; histone modification is the mechanism of long-term yoga- and meditation-based regulation of gene expression [48]. Dhawan et al. [2] reported normalization of the levels of spermatozoal transcripts critical for embryonic development in male partners of couples who experienced implantation failure in IVF cycles with a brief yoga-based lifestyle intervention for 21 days. In previous studies, we also found positive changes in gene expression pattern in patients suffering from primary open angle glaucoma using whole genome microarrays [41, 49, 50]. In a cohort, we showed upregulation in genes involved in cellular repair and nerve growth maintenance while observing a downregulation of pro-apoptotic and pro-inflammatory genes [41, 49, 50] in the central as well as peripheral tissues. Thus, yoga and meditation have multisystem effects and are ideal for the management of infertility and reversing testicular aging.

8. CONCLUSION

Infertility is a complex lifestyle disease with multiple genetic and environmental factors each paying an additive role, but the etiology of male infertility is largely unknown. Previous studies from our laboratory documented that about 60% infertile men especially those with normozoospermia, high seminal free radical levels, and low antioxidant levels. This culminates in oxidative DNA damage to both mitochondrial and nuclear genomes. This is now believed to be the major cause of defective sperm function. However, these parameters are least investigated and go untreated, and in many cases, indiscriminate uses of antioxidants adversely affect sperm function and genomic integrity. Thus, practices like yoga and meditation which affect and target the body as a whole, not only decrease free radical levels and cause collateral increase in levels of antioxidants, but also upregulate expression levels of cell cycle repair genes and anti-inflammatory cytokines and down-regulate levels of several proinflammatory genes. These collectively not only result in improvement in standard sperm parameters but also are ideal in treating oxidative stress and oxidative DNA damage. This strategy may not only reverse testicular aging but also result in overall improvement in health and quality of life of such men and of the next generation.

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