

Impact of Meditation and Yoga on Oxidative DNA Damage in Sperm: Clinical Implications

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Introduction

The generation of excessive reactive oxygen species (ROS) leads to the disruption of cellular homeostasis, a condition known as Oxidative Stress (OS). There is damage caused to almost all biomolecules like carbohydrates, lipids, proteins and even nucleic acids by several ways like programmed cell death with apoptosis, autophagy and the promotion of aging dependent processes. Free radicals subserve numerous functions at physiological levels; however supraphysiological levels are detrimental to all biomolecules and several redox dependent reactions. Almost every cell (both somatic and germ cells) is targeted by free radicals. However, the sperm is most vulnerable to OS. The uniqueness of sperm, a highly polarized cell, lies in its morphology, chromatin structure and function, characterized by a myriad of changes which occur during spermatogenesis and spermiogenesis. Human sperm chromatin is relatively less compact as it retains 5–15% of histones in comparison to other mammalian species like bulls, stallions, hamsters, and mice, which retain <5% of histones. To aid in its functions, it assumes hydrodynamic shape post spermiogenesis and loses majority of its cytoplasm. This results in loss of majority of its antioxidants and compaction of sperm nucleus to a size $1/6^{\text{th}}$ to $1/20^{\text{th}}$ to that of somatic cell. Due to this highly compact chromatin sperm assumes a relatively transcriptionally and translationally inert state. But, Ioannou et al. reported the epigenetic role for the retained histones as the peripheral histone bound nucleosome complex remains transcriptionally active and susceptible to the environmental insult [1]. The contribution of sperm to embryonic development is frequently overlooked and is considered to be quiescent, whose only function is thought to be mere a delivery vehicle of the paternal genome to the oocyte. But oxidative damage to sperm DNA disrupts the integrity of its DNA and RNA so limits not only its fertilizing potential but also adversely affects development potential of embryo through dysregulation of sperm transcripts.

Various causes of sperm DNA damage like abortive apoptosis, sperm chromatin re-modelling and defective DNA packaging processes due to altered levels of protamines and PRT1/PRT2 ratio have been proposed but oxidative stress being the major causative factor [2]. Any insult to the paternal genome, persistence of DNA damage and mutagenic oxidative adducts like 8-OHdG (8-hydroxy-2'-deoxyguanosine) in the DNA may adversely affect embryonic development and increase childhood morbidity and even cancer [3]. Male germ cells are targeted by a wide variety of endogenous and exogenous exposures to physical agents (temperature variations, electromagnetic radiations), chemicals (therapeutic drugs, cancer chemotherapeutics) and environmental toxicants (pesticides, insecticides, metals or components of tobacco smoke or air pollutants). Such exposures may adversely affect the spermatogenesis and sperm function. Psychological stress associated with elevated levels of cortisol is associated with raised systemic and testicular free radical levels. All these factors result in OS [4]. The sperm is highly vulnerable to oxidative damage by virtue of its high content of polyunsaturated fatty acids, limited cytosolic anti-oxidants and a highly truncated DNA damage detection and repair mechanism [5,6]. OS not only results in generation of highly mutagenic DNA adducts, it accelerates

telomere shortening and causes genome wide hypomethylation and dysregulation in sperm transcription. Junk fast nutritionally depleted processed food eating habits, environmental pollution, sedentary and highly stressful lifestyle and chronic psychosocial stress may precipitate oxidative stress. Thus it is important to be aware of the causes of OS and be able to diagnose it promptly to prevent mitochondrial and nuclear genome damage. OS may result in premature testicular ageing and results in hypospermatogenesis and may result in oligospermia to azoospermia. Consumption of tobacco exerts adverse effects on different aspects of health [7]. Nicotine consumed in any form (smoke/oral) was shown to be a potential oxidant agent, which affects plasma membrane fluidity and causes loss of DNA integrity. This damage to DNA is critical in germ cells where integrity is vital for birth of healthy offspring [8,9]. Accumulation of oxidative DNA adducts and loss of sperm DNA integrity has been documented to be the underlying cause of idiopathic cases of infertility, recurrent spontaneous abortions, congenital malformations and complex neuro-psychiatric disorders like autism and even childhood cancer by induction of genetic and epigenetic changes in the sperm DNA [10].

In our study, we observed that the fathers of children with Non-familial Retinoblastoma who were nicotine and alcohol consumers had higher levels of systemic and seminal ROS in comparison with nicotine and alcohol non-consumers. We also found the levels of DNA Fragmentation Index (DFI), were elevated in fathers who consumed nicotine in any form as compared to nicotine non-consumers, thus, nicotine in any form adversely affect DNA integrity. Tremellen also documented that smoking induces tissue inflammation and increase in inflammatory cytokines and thus induces oxidative stress. OS may not only directly damage the nuclear and mitochondrial genome by inducing mutations, accumulation of oxidized mutagenic adducts, single and double strand breaks and telomere shortening. But OS also modulates the epigenome and this adversely affects the developmental trajectory of the embryo and fetus and affects lifelong health of child and may also have transgenerational effects. This emphasizes role of healthy lifestyle even before planning a child and that biological parenting commences well before birth & even prior to conception [11]. It is evident from the present study that sperm DNA damage induced by oxidative stress may lead to accumulation of mutations in sperm genome due to presence of mutagenic oxidative adducts in DNA. This may predispose the rapidly dividing germ cells or embryo to develop mutations and thus, majority

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(90%) of denovo germline mutations are paternal in origin. This study highlights the impact of lifestyle habits of father preconceptionally and its lifelong impact on offspring's health. Sperm being transcriptionally and translationally inert with a very basic repair mechanism is unable to repair DNA damage and may overwhelm oocyte repair mechanism if damage is extensive and thus damage may persist post fertilization and lead to accumulation of damaged DNA in each cell of zygote. Sperm thus works in concert with the oocyte to retain the damaged DNA as it lacks APE and XRCC1. This DNA damage with mutagenic oxidative adducts may lead to accumulation of mutations in both sperm DNA (germline) or in zygote (somatic), which predisposes the germline or zygote to develop mutation (first hit may be a *de novo* germ line mutation or in somatic cell zygote/second hit in retinal tissue). Majority of mutations arise during cell replication and as sperm has a limited capacity for DNA damage detection and repair, it is highly susceptible to accumulate mutations. Paternal unhealthy lifestyle habits like smoking, alcohol or tobacco consumption are associated with loss of sperm DNA integrity and the risk of childhood cancers like non-familial heritable Retinoblastoma [8,10]. We have already documented that the risk of occurrence of Retinoblastoma in the children of alcohol users was 6.7 times greater, whose ROS>27 RLU/s/million sperm and DFI ≤ 28%, i.e., OR 6.7, 95% CI: (0.5-91.3), and was statistically not significant (p=0.155). But the odds of occurrence of Retinoblastoma in children were 13.3 times in combination of ROS>27 RLU/s/million sperm and DFI>28%, i.e., OR 13.3, 95% CI: (1.1-166.4), and was statistically significant (p=0.044*) [8]. Thus, social habits affect sperm DNA health and thus it is recommended that simple lifestyle modifications (diet rich in antioxidants, fruits and vegetables/meditation/yoga) may improve sperm DNA integrity and thus reduce childhood diseases [12].

Many pathological changes are associated with psychological stress which significantly alter human performance. Psychological stress induces OS by increase in cortisol levels and is associated with accelerated aging. There are several antioxidants available, some increase sperm

concentration and some motility, but few have impact at therapeutic doses on sperm DNA integrity and thus results in transmission of damaged DNA to the offspring and a heightened disease burden on next generation. However our study has shown that yoga & meditation results in rapid significant decline in free radical levels (systemic and seminal) but it takes about 6 months for significant improvement in DNA integrity as is evident by lowered DFI (Figures 1A and 1B) and decreased levels of 8-hydroxy-2'-deoxyguanosine (8OHdG) [12]. Thus simple lifestyle intervention can significantly impact DNA integrity and thus can be used as a therapeutic intervention resulting not only decrease in OS but also increase in quality of life. The potential of yogic breathing practices have proved their significant impact on common mental health conditions like depression, generalized anxiety disorder, etc. Breathing techniques such as alternate nostril, Sudarshan Kriya and Bhastrika utilize rhythmic breathing to guide practitioners into a deep meditative state of relaxation and promote self-awareness. Yogic breathing techniques physiologically optimize the human performance by enhancing the cognitive function, i.e., mind, vigilance, etc. and physical performance, i.e., cardiorespiratory, metabolism, exercise, whole body [13]. Mindfulness meditation is a type of mind training that teaches participants to be more aware, to relate differently to thoughts, feelings and sensations and to express greater moment-to-moment awareness. Such attributes cultivate a more adaptive, healthier response pattern and a strong coping mechanism to stress [14]. The levels of glucocorticoids and oxidative stress showed a significant decline in the people who practiced meditation regularly and was also associated with upregulation in levels of β -endorphin, IL-2, IL-4 (anti-inflammatory cytokines) and downregulation in the levels of MAPK10 and MAPK15, which was first assessed by Microarray analysis using Agilent 8x60K Platform and further validated by real-time PCR. Stress induced hormonal levels like plasma cortisol levels are lower in people who meditate than in people who do not, suggesting that it is possible to modulate the neuroendocrine system through neurological pathways.

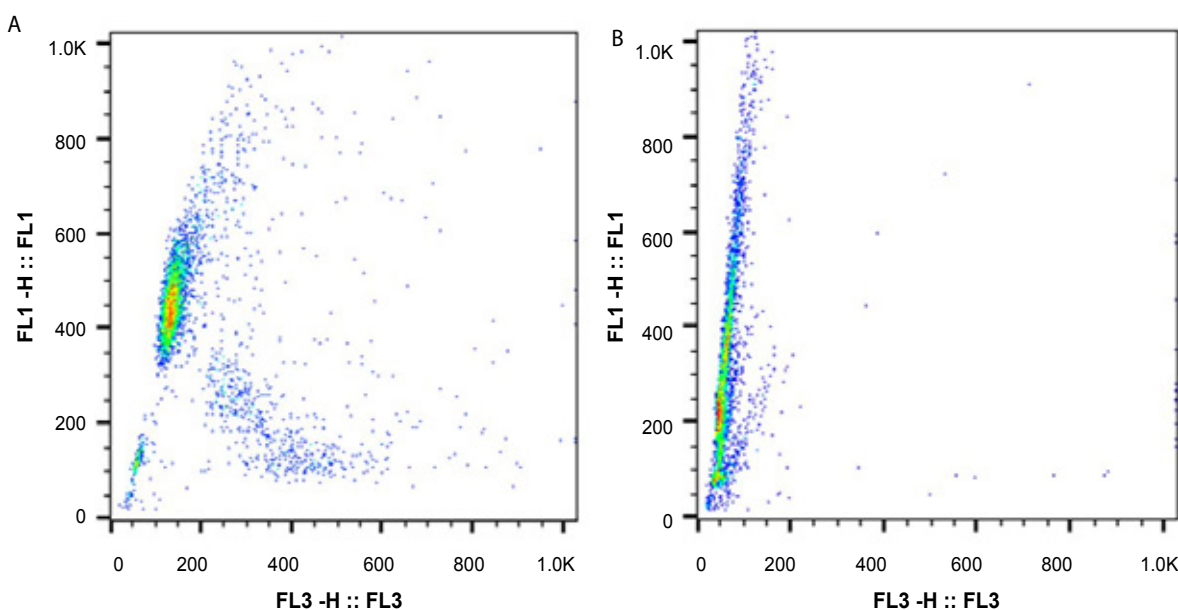


Figure 1: Dot plot cytograms of semen samples of an infertile normozoospermic patient with raised DFI at day 0 (Figure 1A) and 6 months (Figure 1B) of yoga respectively by SCSA. X-axis (FL3) represents fragmented DNA and Y-axis (FL1) represents native DNA showing (DFI %) the percentage of spermatozoa with high levels of DNA fragmentation. Each cytogram dot represents a single spermatozoon with dual-parameter green and red fluorescence values. The debris (bottom-left corner) was excluded from the analysis.

Analysis of oxidative stress levels in people who meditate indicated that meditation and yoga resulted in lowering oxidative stress levels within 10 days of practice [12]. Meditation and deep breathing has shown to increase the melatonin levels which have antioxidant properties and also helps in the modulation of hormones like β endorphins and the immune system [15]. Hence, such manifestations lead to the reversal of oxidative stress and in physiological levels of free radicals benefit for the physiology and homeostasis.

In our laboratory, we have documented that short term yoga and meditation based lifestyle intervention causes a significant decrease in inflammatory markers, seminal free radical levels and gradual improvement in sperm DNA health in terms of decreased DFI levels following 6 months practice of meditation and yoga [12]. Such findings are highly relevant because though genetic causes of Infertility, Recurrent Spontaneous Abortions (RSA) and congenital malformations are irreversible but oxidative DNA damage can be minimized or reversed by adopting a healthy lifestyle and making meditation and yoga an integral part of our daily routine. Thus early diagnosis of oxidative sperm DNA damage and adopting such a healthy lifestyle could actually reverse the condition. This may reduce the incidence of infertility, RSA, congenital malformations, childhood cancers and other neuropsychiatric disorders.

In a previous study, it has been reported that patients with a chronic disorder like Glaucoma are 6.9 times likely to have depression and even assessed the magnitude of care-givers burden and found that primary care-givers have significant emotional and psychological burden and moderate depression in 1/3rd of individuals giving primary care [16,17]. We also found in couples with primary idiopathic infertility, frequent pregnancy loss, children with congenital malformation and cancers with mild to moderate depression and following this practice of meditation and yoga, there was significant decline in cortisol levels and up regulation in levels of endorphins and improvement in quality of life and reduced psychological stress and severity of depression and improved all 4 domains of quality of life as per WHOQOL BREF questionnaire. In all the complex diseases, meditation resulted in significant decline in free radical levels and reduced the severity of disease. In a pilot study in our laboratory on 100 apparently healthy individuals who adopted yoga based lifestyle intervention for 6 months, we observed decrease in levels of cortisol and IL-6; decline in free radical levels and up regulation in levels of telomerase. In long-term yoga practitioners who has been practicing yoga for several months to years, these practices may positively affect gene expression profiles in immune cells in the circulation [18]. Hence, it may be inferred that these simple lifestyle interventions (meditation/yoga practices) improve spiritual, physical, mental and reproductive health and may aid in reducing incidence of genetic and epigenetic disorders in children.

Thus, we recommend that yoga and meditation should be integral part of our lifestyle to improve health and reverse testicular aging.

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