

The Link between Oxidative Stress and Cancer: Prevention through Yoga

Surabhi Gautam, Shilpa Bisht, and Rima Dada

Laboratory for Molecular Reproduction and Genetics, Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India

Correspondence: rima_dada@rediffmail.com (R.D.)

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ABSTRACT | Sperm DNA damage induced by oxidative stress may lead to accumulation of mutations in sperm genome due to the presence of mutagenic oxidative adducts in DNA. This may contribute to the development of male infertility, recurrent pregnancy loss, congenital malformations, neurodevelopmental disorders, and childhood cancers. This article highlights the impact of lifestyle habits of father preconceptionally, its lifelong impact on offspring's health and impact of yoga-based lifestyle intervention on sperm genome and epigenome. Sperm is transcriptionally and translationally inert with a very basic repair mechanism and is thus unable to repair DNA damage and this may persist postfertilization and lead to accumulation of damaged DNA in each cell of zygote. This DNA damage with high levels of mutagenic oxidative base adducts may lead to accumulation of mutations in both sperm DNA (germline) and zygote (somatic). 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 accumulation of mutations. Paternal unhealthy lifestyle habits like smoking, alcohol, or tobacco consumption are positively associated with the risk of childhood cancers like nonfamilial sporadic heritable retinoblastoma. Lifestyle interventions like yoga improve sperm DNA integrity by reducing levels of oxidative DNA damage, optimizing oxidative stress, and by increasing the expression of genes responsible for DNA repair, cell-cycle control, and anti-inflammatory effects. Thus, social habits affect sperm DNA health and as such, it is recommended that simple lifestyle modifications (diet rich in fruits and vegetables, yoga, meditation) improve DNA health and may thereby decrease the incidence of childhood morbidity and cancer. Hence, biological parenting commences well before birth and even prior to conception, which highlights the need for fathers to adopt a healthy lifestyle.

KEYWORDS | Childhood cancer; DNA; Epigenome; Lifestyle intervention; Oxidative stress; Reactive oxygen species; Retinoblastoma; Yoga

ABBREVIATIONS | BDNF, brain-derived neurotrophic factor; DHEAS, dehydroepiandrosterone; DNMT, DNA methyltransferases; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; IL-6, interleukin-6; MDA, malondialdehyde; Mit, mitochondrial; NFSHRb, nonfamilial sporadic heritable retinoblastoma; NOS1, nitric oxide synthase 1; NOS3, nitric oxide synthase 3; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; OS, oxidative stress; ROS, reactive oxygen species; TAC, total antioxidant capacity; TNF- α , tumor necrosis factor- α ; YBLI, yoga-based lifestyle intervention

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1. INTRODUCTION

Oxidative stress (OS) plays a major role in the development of cancer [1]. High levels of reactive oxygen species (ROS) are closely related to the pathogenesis of cancer creating an imbalance to the normal cellular homeostasis [2]. The dual faced ROS may play both beneficial and pathological roles depending upon their relative concentrations. Both endogenous and exogenous sources of ROS result in modifications of cellular macromolecules like proteins, lipids, and nucleic acids as a consequence of increased OS [3]. The reduced efficiency of intracellular ROS-scavenging machinery further precipitates the peroxidative damage to plasma membrane and fragmentation of nuclear/mitochondrial DNA, and further producing mutations and dysregulation in the levels of downstream transcripts [4]. Cellular aging, chronic inflammation, and cancer result from the accumulation of OS-induced DNA damage over time [5]. The major consequences of OS-induced injury to DNA include genetic mutations, accumulation of oxidized mutagenic adducts, single and double strand breaks, telomere shortening, and epigenetic modifications such as chromatin reorganization, histone modifications, defects in DNA methylation, and miRNA regulation [6]. OS is largely associated with modifiable lifestyle-related factors such as smoking, alcohol consumption, pesticide exposure, occupational hazards, excessive mobile phone usage, psychological stress, a sedentary lifestyle, lack of exercise, dysfunctional eating habits, and regular intake of nutritionally depleted junk food [7]. Apart from adoption of healthy lifestyle modifications, antioxidant supplementation aids in lowering OS levels. However, indiscriminate chronic consumption of antioxidant supplements can give rise to a condition called 'reductive stress' which leads to alteration of cellular redox equilibrium [8]. Reductive stress results in reduced cellular metabolism, diminished cell

growth signaling responses, altered mitochondrial function, and modified transcriptional activity, thus contributing to the development of certain inflammatory conditions, such as aggregation protein cardiomyopathy, muscular dystrophy, pulmonary hypertension, rheumatoid arthritis, cancer, and Alzheimer's disease, among others [9].

Prevention of cancer has emerged as a promising treatment goal and a challenge to healthcare sector. Childhood cancers are a rare entity, which contributes to 5-7% of the total cancer burden in India but showed significant increase in last decade [10]. Increased levels of environment pollutants, dysfunctional eating habits, psychological stress, depression, and sedentary lifestyle may not be mutagenic but impact epigenome. Childhood cancers are assumed to be multifactorial and an increase in childhood morbidity has been reported in children born to fathers with oxidative sperm DNA damage [11, 12]. The contribution of the paternal genome to offspring viability and health may depend on levels of sperm DNA integrity and highlights the impact of paternal habits preconceptionally. Unhealthy habits like excessive alcohol consumption, smoking, and psychological stress not only damage the nuclear and mitochondrial genomes but profoundly impact the highly dynamic epigenome and thus the effects may be transgenerational and impact developmental trajectory and lifelong health of the child [12–14]. Simple lifestyle modifications including adoption of yoga and meditation improves the sperm DNA integrity by regulating oxidative stress levels (reducing ROS levels, elevating total antioxidant capacity), reducing the levels of a mutagenic base, 8-hydroxy-2'-deoxyguanosine (8-OHdG), and increasing the expression of genes responsible for DNA repair, cell-cycle control, maintaining homeostasis, and anti-inflammatory effects [6, 15, 16]. Hence, the levels of OS can be normalized by the use of simple lifestyle interventions and can thereby reduce the incidence of

various complex lifestyle disorders, male infertility, recurrent spontaneous abortions, congenital malformations, complex neuropsychiatric disorders like autism, and even childhood cancer.

2. ROLE OF ROS IN CANCER PATHOGENESIS

The highly reactive oxidizing agents like superoxide anion, peroxy radical, hydroxyl radical, and singlet oxygen are required to drive various physiological pathways and can also disrupt homeostasis at supraphysiological levels. Various transcription factors can be activated by virtue of oxidative stress including NF- κ B, AP-1, p53, HIF-1 α , PPAR- γ , β -catenin/Wnt, and Nrf2 resulting in expression of genes related to growth factors, cell cycle check points, inflammatory cytokines, and apoptosis, which mediate cancer progression [17]. ROS trigger the development of tumor including transformation, survival, proliferation, invasion, metastasis, and angiogenesis, and hence considered as pro-neoplastic molecules. ROS inhibit the genes related to apoptosis during the promotion stage of a developing neoplasm and also increase the intracellular Ca²⁺ levels which activate the proto-oncogenes like c-fos, c-jun, and c-myc, or activate protein kinase C (PKC) [18]. ROS are known to regulate signaling molecules required for cell cycle progression [19]. OS-induced DNA methylation triggers the activation of proto-oncogenes and suppression of tumor suppressor genes, and hence plays a key role in tumorigenesis. OS induces genome-wide hypomethylation and locus-specific hypermethylation in tumor suppressor genes. The vicious cycle of OS and cancer results in genomic instability due to various modifications like single or double strand DNA breaks, replication errors, base modification, base oxidation, and DNA cross-linking, leading to cell dysfunction, cell death, and DNA mutation [20, 21]. Excessive ROS production leads to the formation of reactive toxic intermediates and the most common oxidative DNA base adduct, 8-OHdG, which is known to cause mutations and prevent methylation, serves as the most potential indicator of OS-mediated DNA damage, and is a risk factor for many diseases like cancer [22]. 8-OHdG is the most extensively studied and is known to cause the majority of oxidative DNA lesions and is elevated in various human cancers [23]. 8-OHdG also pro-

duces dose-related increases in cellular transformation and capable of inducing mutations that are commonly observed in neoplasia [18, 23, 24]. That is why, in our studies, we estimated the levels of 8-OHdG as a marker of oxidative DNA damage in paternal sperm and its plasma levels in their offspring affected with cancer. We found seminal 8-OHdG levels to be significantly higher in fathers of nonfamilial sporadic heritable retinoblastoma (NFHRb) children as compared to fathers of healthy children ($66,020 \pm 2,910$ vs. $32,100 \pm 2,710$ pg/ml; $p = 0.029$) and also the plasma 8-OHdG levels were significantly higher in NFHRb patients as compared to healthy children (7579 ± 58 vs. 6179 ± 78 pg/ml; $p = 0.016$) [25]. Hence, a redox balance is critical to the maintenance of cellular homeostasis and disease prevention [26].

Apart from oxidative damage to DNA, elevated ROS levels also damage protein-coding or non-coding RNA which may lead to defective protein synthesis and dysregulation of gene expression. Reactive aldehydes like malondialdehyde (MDA), acrolein, and 4-hydroxy-2-nonenal (4-HNE) are generated as a result of lipid peroxidation [18]. MDA and MDA-MDA dimers are said to be mutagenic and carcinogenic for a cell. Oxidative DNA damage results in accumulation of mutagenic bases, leads to G:C→T:A transversions and single and double strand breaks which may lead to mutations in sperm DNA. In addition to ROS, reactive nitrogen species (RNS) are also generated and cause nitrative DNA damage to form 8-nitroguanine, also a mutagenic DNA lesion causing G:C→T:A transversions, which are a feature of mutated tumor suppressor genes and oncogenes [18, 24].

3. OXIDATIVE STRESS, MALE GERMLINE, AND CHILDHOOD CANCER

Paternal sperm DNA integrity is essential for the birth of a healthy offspring. Increasing incidence of idiopathic infertility, recurrent implantation failures, recurrent spontaneous abortions, preterm births, congenital malformations, complex neuropsychiatric disorders, and even childhood cancers may be attributed to paternal sperm DNA damage [27]. Advanced paternal age, psychological stress, and unhealthy lifestyle factors contribute to OS, sperm DNA damage, accumulation of de novo germline

mutations, and epi-mutations leading to cancer [6, 13, 28]. OS triggers global heterochromatin loss, oxidative alteration of histones, changes in DNA replication and transcription, and apoptosis [29, 30]. As a consequence of oxidative DNA damage and accumulation of mutagenic oxidative products and a defective DNA repair mechanism, sperm accumulates mutations at a much higher rate than the oocyte. A high mutagenic load may overburden the oocyte repair mechanism post fertilization and results in higher mutations in the zygote genome [31]. This may increase the incidence of congenital anomalies, childhood morbidity, and childhood cancers like NF5HRb [7, 8]. The exact etiology of NF5HRb is not known and can be attributed to impact on sperm epigenome during preconception period due to external and internal insults, which may directly or indirectly affect the outcome of fertilization and increase the risk of genetic and epigenetic disorders in the offspring. OS leads to sperm DNA damage and accelerated testicular aging, and causes aberrant sperm DNA methylation, leading to male infertility and poor reproductive outcomes including childhood cancers in the progeny. DNA damage in human spermatozoa has been correlated with adverse clinical outcomes including impaired fertilization, disrupted preimplantation, low rates of implantation, increased incidences of miscarriages, high rate of morbidity in the offspring, and diminished fertility [32, 33].

One of the major causes of defective sperm function is OS, which not only disrupts the integrity of sperm DNA but also limits its fertilizing potential as a result of collateral damage to proteins and lipids in the plasma membrane of sperm [32–34]. OS involves the sperm mitochondria, which have a tendency to generate high levels of superoxide anion as a prelude to entering the intrinsic apoptotic pathway [35]. The factors responsible for inducing this DNA damage are unknown, although physical factors, such as heat and electromagnetic radiation, as well as a range of various xenobiotic compounds, abnormalities of lipid metabolism, and age have been implicated in sperm DNA damage [36]. OS is also induced by psychological stress and depression, which raises cortisol levels and causes persistent activation of the hypothalamic-pituitary-adrenal (HPA) axis and dysregulation of immune system. This leads to chronic inflammation and results in autism spectrum disorder and cancer [37]. It is documented that dam-

age to human sperm DNA may adversely affect reproductive outcomes and that spermatozoa of infertile men possess substantially more DNA damage than do spermatozoa of fertile men which further increased the burden of childhood diseases including childhood cancers in the next progeny [7, 8].

4. ANTIOXIDANTS VERSUS LIFESTYLE MODIFICATIONS IN CANCER TREATMENT

Antioxidants serve as free radical-scavenging agents in the aerobic system which can be either produced endogenously like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR), or supplemented exogenously through food or commercial dietary supplements like vitamin E, vitamin C, carotenoids, trace metals (selenium, manganese, zinc), flavonoids, and omega-3 and omega-6 fatty acids [38]. The restoration of antioxidants becomes essential as the antioxidant itself becomes oxidized when it scavenges a free radical. The mode of action of antioxidant scavenging is via two ways, i.e., chain breaking and prevention. During the chain breaking process, the cascade of free radical reaction is stabilized by a chain-breaking antioxidant and results in the formation of a nonreactive product, whereas in preventive process, the antioxidant halts the radical chain initiation [36, 38, 39]. Dietary supplementation with antioxidants is supposed to nullify OS by reducing ROS levels and oxidative DNA damage, thereby preventing cancer. However, the state of reductive stress in a cell may result from overload of antioxidants and inadequate control of ROS levels [2]. The effect of antioxidants on sperm has been controversial; there is little effect on the sperm DNA integrity, hence highlighting a need for alternative medicine. Antioxidant like resveratrol is known for its excellent scavenging properties, inhibition of tumorigenesis, suppression of vascular endothelial growth factor (VEGF) and HIF-1 α expression, suppression of PI3K/Akt and MAPK signaling pathways, and protection against lipid peroxidation and oxidative DNA damage [40].

In addition to antioxidants, fight against increased ROS and oxidative damage is effected via defense mechanisms, which may be impaired, and includes three levels of protection: prevention, interception, and repair. The first line of defense against OS-

induced damage is prevention of ROS formation which may be via chelation of transition metals. Interception is a chain breaking process leading to the formation of a non-radical end product. Repair mechanism (lower OGG1 levels) and DNA damage detection (lower PARP levels) in spermatozoa are inefficient and hence become susceptible to oxidative insult [41]. Human spermatozoa are most vulnerable to OS-induced damage as they contain high concentrations of unsaturated fatty acids, possess low levels of cytosolic antioxidant enzymes, cannot undergo apoptosis, can generate ROS via their mitochondria, and possess nuclear DNA that is incompletely protaminated and poorly compacted [31]. Lifestyle factors like smoking, alcohol consumption, excessive mobile phone usage, sedentary lifestyle, psychological stress, dysfunctional eating habits, lack of exercise, and pesticide exposure result in high oxidative stress [6]. Hence, improvement of lifestyle/social habits becomes necessary for the men seeking to improve their fertility and for their future generations by cessation of smoking, avoidance of excessive alcohol consumption, adoption of simple lifestyle intervention like yoga and meditation, minimizing the exposure to harmful xenobiotics, and increased dietary uptake of antioxidant-rich fruits and vegetables.

5. YOGA-BASED LIFESTYLE INTERVENTION: IMPACT ON OXIDATIVE STRESS AND CANCER PREVENTION

Yoga is mind-body medicine which helps improve overall quality of life by reduction of psychological stress and has promotive, preventive, curative, and rehabilitative potential [42]. The increased risk of childhood cancers may be attributed to loss of sperm DNA integrity, aberrant methylation patterns (hypomethylation of oncogenes and hypermethylation of tumor suppressor genes), rapid telomeric attrition, mitochondrial dysfunction, preoxidative damage to sperm plasma membrane, microsatellite instability, and dysregulation in levels of mRNAs/transcripts. These factors may result in OS and chemically induced carcinogenesis as well as associated epigenetic disorders in the offspring [7, 8, 13, 33]. Highly stressful lifestyle, adulterated food, and exposure to pesticides/insecticides and occupational hazards may lead to the persistence of an inflammatory state by

activation of pro-inflammatory cytokines, increased OS, decreased expression of genes associated with cell cycle check point and DNA repair, and disturbances in neuro-biochemical environment affecting primary gonads via the hypothalamic-pituitary-gonadal (HPG) axis [6–8, 15, 16]. Proper functioning of HPG axis is of prime importance for the maintenance of redox balance.

Yoga has been shown to reduce psychological stress, anxiety, and depression [37, 43, 44]. Also, it improves overall quality of life, reduces systemic inflammation, and improves cognitive abilities [45–47]. These changes can be brought about by regulating ROS levels rather than simply lowering them. A delicate balance between oxidants and antioxidants is formed in cells in order to maintain a redox homeostasis. Although antioxidant therapy can decrease ROS levels, it does not regulate ROS levels; therefore, indiscriminate usage of such approaches might be detrimental and not able to restore a healthy oxidative pool. An important underlying mechanism for the effect of yoga specifically is that it reverses stress-related processes and alters the expression of genes that regulate oxidative stress [33]. Yoga-based lifestyle intervention (YBLI) is a popular alternative and complementary medicine to treat reproductive health problems to produce successful pregnancy outcomes [42]. Yogic techniques especially kundalini yoga and moola bandha act via endocrine axes to enhance male reproductive functions thereby promoting reproductive health by improving reproductive behavior and mood [42]. Studies from our laboratory have reported that YBLI can reduce OS, improve sperm DNA integrity, and reduce the incidences of childhood cancer by reducing OS-induced damage to paternal genome [33].

YBLI is a mind-body practice which is used to foster wellness, stress management, and maintenance of energy balance to improve physical fitness and autonomic function improvement [6, 15, 16, 42]. YBLI regulates oxidative stress levels to prevent reductive stress and decrease inflammation; it is ideal to adopt yoga to combat OS-induced sperm DNA damage and its sequelae. A study from our laboratory reported the improvement in sperm DNA integrity by estimation of DNA fragmentation index, ROS levels, total antioxidant capacity (TAC), and seminal 8-OHdG levels at baseline and after 4 weeks of YBLI [16]. A decline in seminal ROS levels within 10 days of yoga and meditation practice has been noted along with

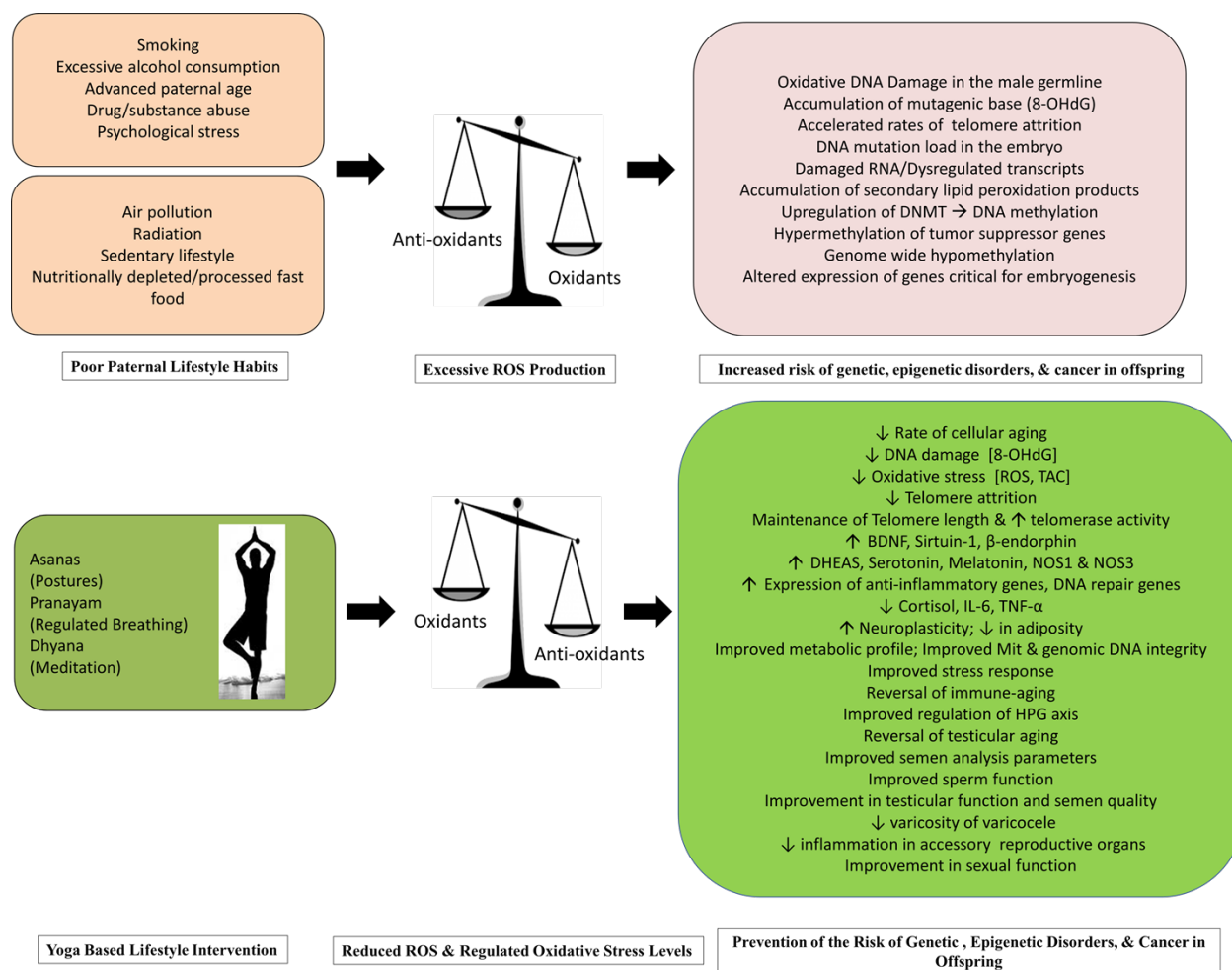


FIGURE 1. Schematic diagram showing the effect of paternal lifestyle factors and the potential role and mode of action of Yoga-based lifestyle intervention in preventing the risk of childhood cancers. Abbreviations: BDNF, brain-derived neurotrophic factor; DHEAS, dehydroepiandrosterone; DNMT, DNA methyltransferases; HPG, hypothalamic-pituitary-gonadal; IL-6, interleukin-6; Mit, mitochondrial; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; NOS1, nitric oxide synthase 1; NOS3, nitric oxide synthase 3; ROS, reactive oxygen species; TAC, total antioxidant capacity; TNF- α , tumor necrosis factor- α .

gradual reduction of DNA damage and improvement in sperm DNA integrity over a period of 6 months [11, 28]. In our study, we have found significantly higher levels of ROS, DNA fragmentation index (DFI), and 8-OHdG (p value < 0.0001 for all the parameters) in fathers of NFSHRb children as compared with fathers of healthy children [48]. 8-OHdG, one of the most commonly used indicators of oxidative damage of cells, is a potent mutagenic oxidative DNA base lesion. The children with cancer also had

significant higher level of this mutagenic base. This base persists post fertilization if sperm DNA damage is extensive and thus overwhelms oocyte repair mechanism. Our studies showed a reduction in the levels of 8-OHdG after 4 weeks of YBLI, followed by improvement in sperm DNA integrity, and that lowering of OS levels may provide genomic stability and reduce genetic and epigenetic alterations and thus reduce the risk of developing cancer in the offspring [11, 16, 28]. In a yet unpublished study on

impact of yoga on sperm epigenome from our laboratory done in collaboration with Dr. Rakesh Kumar from Centre for Cellular and Molecular Biology (CCMB), Hyderabad, India, we found post-yoga changes in sperm epigenome, i.e., hypomethylation in tumor suppressor genes and hypermethylation in oncogenes and various anti-inflammatory genes.

YBLI normalizes the levels of sperm transcripts, maintains telomere length, and upregulates telomerase activity, and hence maintains genomic stability and chromosomal integrity and reduces rate of cellular aging and positively impacts sperm epigenome [33, 34] (**Figure 1**). YBLI is a technique and a science of inner wellbeing as it maintains the intricate balance between oxidants and antioxidants, triggers neuro-hormonal mechanisms, improves sperm motility and count, improves abnormal mood functioning, reduces stress and anxiety, and promotes parasympathetic nervous system dominance [42]. The holistic science of yoga has proved to be a boon for modern medicine which not only targets a particular system, but also impacts the body and mind as a whole, thereby promoting physical, mental, and reproductive health and improving quality of life.

6. CONCLUSION

Unhealthy lifestyle habits and environmental exposures are associated with OS-induced DNA damage and adversely impact sperm epigenome; therefore, adoption of a healthy lifestyle like yoga intervention, helps reduce the risk of oxidative DNA damage to mitochondrial and nuclear genomes and its sequelae, improve sperm function, reduce the rate of testicular and biological aging, and thereby improve the health of the offspring and reduce the incidence of childhood cancers.

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