

Yoga: Impact on sperm genome and epigenome – clinical consequences

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Integrity of sperm DNA and RNA is a decisive component in determining the fate of reproductive outcome and health of offspring. Sperm nuclear DNA/RNA damage not only affects the reproductive sequel but also impacts embryonic growth and development and hence, acts as a crucial factor in determining the health trajectory of the offspring. Oxidative stress (OS) in the male germ line is the prime contributor of oxidatively induced sperm DNA fragmentation dysregulation of sperm epigenome and its associated pathologies[1,2]. There is a strong mechanistic link between DNA damage in the male germ line and increased *de novo* germ line mutation rate and hypomethylation of sperm epigenome thus, predisposing to an increased risk of genetic and epigenetic disorders in the offspring[3].

The “Yin and Yang” nature of the OS in the male germ line has been studied extensively and in a coherent manner. The “Yin” nature of sperm OS is associated with poor outcomes in assisted reproductive techniques (IVF, ICSI)[4], male infertility[5], recurrent pregnancy loss (RPL)[6], offspring mortality, high rates dominant genetic disorders (achondroplasia and Apert’s syndrome)[7], complex polygenic disorders[8], neuropsychiatric ailments (autism, bipolar disorder, schizophrenia, epilepsy)[9,10] and a high incidence of childhood cancers[11,12]. The “Yin” nature of OS in the sperm lies in the fact that mild (physiological levels) OS is essential for sperm function as it induces sperm hyperactivation, moderate the tyrosine phosphorylation required for sperm capacitation, mediates cellular homeostasis and redox-sensitive signal-transduction pathways and also helps in the maintenance of telomere length which is required to ensure proper fertilisation[13,14]. The adequacy of sperm function lies beneath the fact that the “Yin” and “Yang” aspects of sperm OS should be in a balanced state to ensure appropriate sperm function of transmitting the proper (intact) genetic material to the next generation.

Due to its highly truncated DNA damage detection and repair mechanism (inefficient base-excision repair pathway), high polyunsaturated fatty acid and limited cytosolic content, and deficient antioxidant capacity, sperm are most vulnerable to OS induced injury and hence, dependent upon the oocyte for the repair prior to initiation of S-phase of the first mitotic

division[15]. However, the ageing oocyte and the extent of the damage in the sperm determine the oocyte’s capacity to repair the damage post-fertilisation. This possible mechanism may explain the high prevalence of childhood morbidities (cancers, epigenetic diseases, congenital abnormalities) in children whose father have experienced higher levels of seminal OS and oxidative DNA damage as a result of advanced age, poor lifestyle habits (smoking, alcohol intake) dysfunctional eating habits and environmental factors (air pollutants, bisphenol A, heavy metals, etc.)[1,11,16]. Also, infertility is a disease with strong psychosomatic component and associated with high cortisol levels and lower serotonin levels[17]. Cortisol further causes persistent activation of the Hypothalamic-pituitary-adrenal (HPA) axis which enhances immune susceptibility to autoimmune disorders and cancers[18]. Cortisol is also neurotoxic and is associated with lower hippocampal volumes and higher levels of inflammatory markers[19]. Cortisol also has inverse correlation with total antioxidant capacity and thus, induced OS mediated damage to both mitochondrial and nuclear genomes. It is also associated with lower levels of brain derived neurotrophic factor (BDNF) and sirtuins[20].

8-hydroxy-2'-deoxyguanosine (8-OHdG) is an oxidative base adduct and a predictive biomarker for oxidative induced DNA damage in the sperm. 8-OHdG levels correlate directly with the sperm nuclear DNA damage and genome wide hypomethylation caused due to OS [21]. Kelly *et al.*, described that sperm cells with higher accumulation of 8-OHdG adducts impair the function of *de novo* DNA methyltransferases and hence, lead to global decline in methylation (hypomethylation) which affects the genomic stability and hence, predispose to epimutations, thus the levels of transcripts critical for early embryonic development are dysregulated and impair embryogenesis and development of various tissues and organ systems[22]. We have reported higher levels of seminal 8-OHdG in the fathers of children affected with non-familial sporadic heritable retinoblastoma as compared to the fathers of healthy children. We have also found elevated plasma 8-OHdG levels in sporadic retinoblastoma patients which may predispose these children to develop somatic mutations in

the *RB1* gene which could be a probable factor for retinoblastoma and other childhood cancers[11,23].

Yoga is a profound science of inner well being and aims to promote health and prevent onset of diseases. It also has curative and rehabilitative potential. Yoga based lifestyle intervention (YBLI) has gained tremendous popularity in the last decade as it improves cellular health and mind-body communications which optimizes brain health by improving neurotransmitter homeostasis, circadian rhythm, neuroplasticity, and neural networks[24]. In a recent study published from our lab, we have reported a significant decline in Beck depression inventory-II (BDI-II) scale, and significant improvement in biomarkers of neuroplasticity such as significant increase in BDNF, dehydroepiandrosterone sulphate (DHEAS), sirtuin1, and telomerase activity levels and decreased cortisol and IL-6 in the patients of major depressive disorder followed by 12-weeks of YBLI when compared to the control group (not undergoing YBLI) [20]. In an another study from our lab, we have reported decline in the severity of rheumatoid arthritis (RA) due to reduction in the levels of various systemic markers of inflammation such as acute phase reactants (ESR and CRP), pro-inflammatory and anti-inflammatory cytokines (IL-6, IL-17A, TNF- α and TGF- β) and immunomodulatory marker-soluble HLA-G; and there was a significant improvement in biomarkers of neuroplasticity-BDNF, serotonin, β -endorphins; biomarkers for cellular aging-telomerase activity and telomere length in the RA patients followed by 8-weeks of YBLI when compared to the control group (not undergoing YBLI and allocated to routine medical therapy only)[25]. No study in the literature so far has reported the impact of YBLI on improving the sperm genomic as well as epigenomic integrity and thus, reduction in the disease burden in the next progeny. There is only one study by Harkess KN et al. which has explored the role of epigenomic alteration (DNA methylation) in chronically stressed women who were subjected to a brief YBLI of 8-weeks. This was the first study which has explored the effect of short term yoga on genome-wide DNA methylation patterns in LINE-1 repetitive element (global methylation indicator) and immune candidate genes such as IL-6, tumor necrosis factor and C-reactive protein [26]. For the first time, we have investigated the decline in OS and oxidative DNA damage and overall improvement in sperm DNA integrity following adoption of 6-months YBLI practice by the fathers of retinoblastoma patients. Thus, it may be postulated that YBLI improves the sperm DNA integrity and may reduce disease burden of genetic and epigenetic diseases in the next generation [27]. In a preliminary study on impact of yoga on sperm epigenome in infertile male patients (study was conducted in collaboration with Dr. R K Mishra, CCMB, Hyderabad), we found differentially methylated regions on the sperm genome with 229 hypermethylated genes and 147 hypomethylated genes post-YBLI {the technique employed was reduced representation bisulfite sequencing (RRBS)}. Out of these genes the hypermethylated genes were the following: *TNFRSF18* (TNF receptor superfamily member 18), *TP73*

(tumor protein p73), *CAMTA1* (calmodulin binding transcription activator 1), *STK32C* (serine/threonine kinase 32C), *MRPL23* (mitochondrial ribosomal protein L23), *KMT5A* (lysine methyltransferase 5A) and the hypomethylated genes were the following: *TNFRSF8* (TNF receptor superfamily member 8), *GCSAML* (germinal center associated signaling and motility like), *KMT5B* (lysine methyltransferase 5B), *RELB* (RELB proto-oncogene NF-kB subunit), *HDAC4* (histone deacetylase 4) and *LRRC24* (leucine rich repeat containing 24). The lists of genes obtained from RRBS was further clustered according to gene ontology terms to determine the biological processes associated with the hypomethylated genes and we found that genes that showed hypomethylation post-YBLI are mainly associated with the following pathways: DNA damage response and detection of DNA damage, intrinsic apoptotic signalling pathway in response to OS, negative regulation of reactive oxygen species metabolism, folate membrane transport and folic acid transport. Thus, we may conclude that YBLI has positive impact on sperm genome and epigenome and further positively impacts the health of the next generation. Infertile men have higher stress levels and also higher levels of various inflammatory markers and lower levels of BDNF, DHEAS, serotonin and melatonin. A higher expression of proinflammatory genes and lower expression levels of tumour suppressor genes in infertile patients may predispose them to develop cancer and a higher risk of childhood cancers and complex neuropsychiatric disorders in the offspring. Thus Yoga may be used as an adjunct therapy to improve sperm DNA integrity and thereby reduce disease burden in the next generation

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