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Review

Antioxidants modulation of sperm genome and epigenome damage: Fact or fad? Converging evidence from animal and human studies

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ABSTRACT

Increasing evidence suggests that oxidative stress plays a major role in the pathogenesis of sperm DNA damage. Oxidative stress was also recently found to modulate the epigenetic make up of sperm. Along these lines, a growing body of evidence in both experimental and clinical studies has implicated several regimens of antioxidants, by oral administration or in vitro supplementation to sperm-preparation media, in improving various sperm parameters namely DNA damage. While these studies exhibited heterogeneity in treatment regimens, and variability in methodology, there remains a lack of quality evidence on the association between micronutrients and sperm DNA integrity. Another ancillary effect of antioxidants administration on sperm is the shaping of the epigenome. It is beginning to surface that micronutrients function as potent modulators of the sperm epigenome-regulated gene expression through regulation of mainly DNA methylation in humans and experimental models. However, the few promising experimental studies on mice supported the notion that epigenetic marks in spermatogenesis are dynamic and can be modulated by nutritional exposure. More so, the sperm epigenome was proposed to transfer a so-called epigenomic map to the offspring which can influence their development. Here, we review and summarize the current evidence in human and animal models research regarding the link between genome and epigenome × micronutrients environment interactions on the sperm nuclear damage. Unfortunately, our conclusion is not very conclusive, rather, it opens an avenue to investigate the fortifying effect of antioxidants on sperm cells. Hopefully, further genome and epigenome-wide studies focusing on the prenatal environment, will serve as a promising route for embodying the possibility of "normalization" and restoration of some offspring health cues.

Contents

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1. Introduction

Once it is produced by the testicles, sperm starts a long journey of maturational processes and transits before it reaches the oocyte. Since, mammalian spermatozoa is rich in polyunsaturated fatty acids [1], it is very prone to reactive oxygen species (ROS) attacks.

As we know, the central tenet of oxidative stress is that an imbalance between oxidants and antioxidants in favor of the oxidants potentially leads to cellular damage.

Along these lines, oxidative-based damage in spermatozoa is characterized by several hallmarks of "incompetent" sperm primarily including DNA damage [2,3], reduced sperm numbers, diminished motility, abnormal morphology [4], and altered zona penetration [5].

However, in order for ROS to exhibit strong genotoxic damaging effects, several factors are implicated in sperm oxidative damage susceptibility. First off, a disruption in the sperm maturation process will make spermatozoa more susceptible to genotoxic ROS attacks. In this perspective, Aitken et al. 2009 [6], proposed a new hypothesis "the two-step hypothesis" that assigns the sperm DNA damage to a defective remodelling of sperm chromatin during spermiogenesis. This renders the nucleus more vulnerable to ROS attacks which will create DNA strand breaks. Furthermore, oxidative stress may further activate sperm endonucleases which will create DNA strand nicks [7,8]. Thus, the common management for sperm oxidative stress is micronutrients administration; namely antioxidants intake or supplementation. A very early attempt to study the impact of ROS on sperm was presented in a landmark paper by MacLeod et al. 1943 [9]. Interestingly, this study showed that hydrogen peroxide causes a rapid sperm motility loss, an effect which was reversed by catalase supplementation of culture media. Another study performed by Fraga et al. in 1991 [10] showed that an ascorbic acid-based diet for 28 days decreased the levels of sperm oxodGDNA – a biomarker for oxidation. Fast-forwarding to this era, it has been postulated that oxidative stress can modulate the epigenetic make up of sperm [11]. By definition, epigenetics refers to the study of heritable changes in gene expression that occur without a change in DNA sequence [12]. Hence, sperm epigenome was shown to regulate spermatogenesis, fertilization and embryogenesis [13]. Given the plausible role of antioxidants on oxidative-based sperm damage, we elected to examine the evidence in experimental and human studies involving the effect of antioxidants supplementation on the sperm genome and epigenome. Studies included in this overview encompass investigations of sperm nuclear status, not discriminating between the types of antioxidants (single antioxidants, multiple antioxidants, . . .).

2. Influence of antioxidants administration on sperm genome

DNA damage is the most common effect of oxidative stress on human spermatozoa. Since an imbalance between scavenging antioxidants and pro-oxidants have been implicated in the pathophysiology of oxidative-based DNA damage, the administration of antioxidants has been practiced for years in an attempt to improve sperm quality necessary for reproductive success. Recently, a growing body of evidence has implicated antioxidants, by oral administration or in vitro supplementation in animals and humans, in improving various sperm parameters namely DNA damage. Here, our primary analysis was limited to studies reporting DNA quality as a treatment endpoint. Thus, due to the relative plethora of data obtained from human studies, this section includes only discussions of human data.

2.1. In-vivo supplementation

The use of human models to evaluate the effects of antioxidants on sperm DNA damage has been emphasized over the years.

Many studies have used rats [14,15], dogs [16], and rabbits [17,18] as models. But human trial results that paralleled even exceeded those obtained from animal studies have further attested the impact of antioxidants on sperm.

A small placebo-randomized study by Greco et al. 2005 [19] examined the effects of antioxidants, on sperm with high DNA fragmentation (≥15% TUNEL – positive spermatozoa). The 64 patients enrolled were randomized between an antioxidant treatment (1 g vitamin C and 1 g vitamin E daily for 2 months) group and a placebo group. At the end of the treatment, the percentage of DNA-fragmented spermatozoa detected by TUNEL assay was found to be significantly lower in the treatment group. Another study specifically looked at sperm DNA integrity, protamination and apoptosis [20]. This prospective study included 45 men with oxidative stress confirmed by nitroblue tetrazolium (NBT) assay, who received one capsule of Menevit (Lycopene 6 mg, Vitamin E 400 IU, Vitamin C 100 mg, Zinc 25 mg, Selenium 26 μg, Folate 500 μg, Garlic oil 333 μg) for 3 months. At first, the levels of ROS significantly decreased post-treatment. In the light of this reduction several improvements in sperm quality were marked. Sperm DNA integrity, assessed by TUNEL, improved significantly. Furthermore, the observed improvements in sperm DNA quality were reflected by reductions in early apoptosis (annexin V positive, propidium iodide negative). Moreover, the levels of sperm DNA protamination, determined by Chromomycin A3 (CMA3), also statistically improved by the end of the treatment.

Surprisingly, Menezo et al. 2007 [21] noticed an "unexpected adverse effect". A total of 58 patients with high DNA fragmentation or high degree of decondensation (>15%) – detected by Sperm Chromatin Structure Assay (SCSA) – were enrolled, then treated with oral antioxidants consisting of Vitamin C (400 mg), Vitamin E (400 mg), β-carotene (18 mg), zinc (500 μmol) and selenium (1 μmol) for 3 months. While a highly significant decrease in DFI was observed post-treatment, at the same extent sperm decondensation significantly increased. This iatrogenic effect may be related to antioxidants namely vitamin C that reduces cystine to two cysteine moieties, and thus opening the interchain disulphide bridges. The most recent paper of Amar et al. 2015, treated 151 patients using a sequential regimen of treatment. A significant decrease in DFI and reduction in nuclear decondensation were noted, when those patients were treated with potent antioxidants for 5 weeks followed by a long duration of another combination of antioxidants components of the one carbon cycle [22]. In the one carbon cycle 1 carbon cycle, for example zinc and vitamins B2, 6 and 12 will nourish the homocysteine pathway this fortifies the endogenous antioxidant capacity as well as cysteine activity leading to an effect on methylation. In a study evaluating the effect of multivitamins on sperm DNA status specifically in the context of varicocele, Gual-Frau et al. 2015 [23] administrated multivitamins (1500 mg L-Carnitine, 60 mg vitamin C, 20 mg coenzyme Q10, 10 mg vitamin

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