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LETTER TO EDITOR

How much does mitochondrial dysfunction affect male infertility?

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To the Editor

Nowadays male infertility is considered one of the most important “diseases” worldwide (1). More than 15% of couples are infertile, in half of these cases it is related to male factors, and in approximately 60% of idiopathic male infertility it is closely related to decreased sperm motility (2).
Mitochondria are particularly structurally and functionally organelles in male gametes, involved into *adenosine triphosphate* (ATP) production through *oxidative phosphorylation* (OXPHOS) to support sperm mobility, production of steroid hormones in the testis, regulation of cell proliferation, regulation of *reactive oxidation species* (ROS) signaling, calcium homeostasis, capacitation, acrosome reaction, and metabolism (3, 4). Approximately 80 mitochondria are present in the midpiece of spermatozoa (5). To the best of our knowledge mitochondrial dysfunction is often associated with the aging process and it is related to several diseases, includes male infertility (6). Oxidative stress (OS) due to the overproduction of ROS in mitochondria is one of the major causes of these disorders accounting approximately 30-80% of male infertility (7). Exposure to ROS induces structural and functional damage in proteins, membrane, calcium homeostasis, DNA in spermatozoa, and this affects sperm motility, ability to penetrate oocytes, and embryonic development (7-10). Even though the exact mechanisms of mitochondrial dysfunction in male fertility impairment remains still unclear, it is known that age-dependent alterations of the epididymis can cause alterations in sperm mitochondrial functioning (11, 12). Mitochondrial are involved into all spermatogenesis and fertilization mechanisms: sperm motility, gamete production, steroid hormone production, cell signaling, proliferation, epigenetic regulation, cell differentiation and cell death (6). Steroidogenesis involves the mobilization of cholesterol from lipid droplets and/or the plasma membrane, its transportation into mitochondria under the pulsatile secretion of LH and consequent cAMP production, the formation of pregnenolone within the mitochondria, and the subsequent conversion of pregnenolone into the ultimate steroid products by enzymes located in the smooth endoplasmic reticulum (13). Spermatozoa’s ability to move relies entirely on the functionality of the OXPHOS pathways (14). Given that sperm *mitochondrial DNA* (mtDNA) contains genes that encode OXPHOS-related proteins, any deviation in mtDNA could potentially affect sperm motility. In the last twenty years, research has emphasized the connection between the quality of mtDNA and sperm motility by examining mutations, duplications, and deletions in human sperm mtDNA (15). These investigations have shown that point mutations, *single nucleotide polymorphisms* (SNPs), and haplogroups within mtDNA can significantly impair semen quality (16). Sperm mitochondrial deletion is a marker of mtDNA integrity and damage. Men with suboptimal semen parameters tend to exhibit a higher prevalence of sperm mitochondrial DNA deletions compared to men with normal sperm parameters (17). The sperm mitochondrial DNA copy number, representing the number of mtDNA copies per nuclear DNA copy, serves as a sensitive biomarker of male fertility. Variations in human mtDNA copy numbers are linked to decreased sperm motility and fertility decline (18).
Finally, oxidative stress initiates the spermatozoa's progression along the intrinsic apoptotic pathway, starting from the loss of *mitochondrial membrane potential* (MMP), which leads to the formation of oxidative DNA adducts, DNA fragmentation, and ultimately culminates in cell death (19).
Several oral supplements have been proposed in male infertility treatments as well as L-carnitine, arginine, alpha-lipoic acid, coenzyme Q10, vitamins, zinc, selenium, and they regulate mitochondrial homeostasis. *Coenzyme Q10* (CoQ10) is abundant in mitochondria and plays a crucial role in the electron transport chain, facilitating ATP production. Additionally, CoQ10 possesses potent antioxidant properties that can potentially surpass those of cellular antioxidants

such as tocopherol and resveratrol, making it effective in countering attacks from ROS (20, 21). Carnitine plays an important role in fatty acid metabolism by transporting fatty acids across the mitochondrial membrane (22). Vitamin D prevents protein oxidation, lipid peroxidation, autophagy, mitochondrial dysfunction, inflammation, oxidative stress, epigenetic modifications, DNA abnormalities, and calcium and ROS signaling (23).
Due to the pivotal role of mitochondria in sperm motility and overall fertility, assessing mitochondrial functionality becomes an essential topic in male infertility treatment, aiding in the development of targeted interventions to improve reproductive outcomes. Furthermore, several randomized controlled trial, in vitro and in vivo studies research are necessary to better highlighted their involvement in the physiopathology of infertility.

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