IMPACTS OF AGING ON THE MALE REPRODUCTIVE SYSTEM: HORMONAL, METABOLIC AND REPRODUCTIVE CHANGES

IMPACTOS DO ENVELHECIMENTO NO SISTEMA REPRODUTOR MASCULINO: ALTERAÇÕES HORMONAIS, METABÓLICAS E REPRODUTIVAS

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ABSTRACT

Aging gradually affects the male genital system due to profound hormonal and metabolic changes. The reduction in the proportion of testicular blood vessels reduces the supply of oxygen and other nutrients to the organ's parenchyma, increasing inflammatory conditions and oxidative stress, which can significantly affect sperm viability and morphology. Aging has an impact on lipid and protein metabolism, which can compromise sperm structure and functionality. In addition, sperm can accumulate significant changes in their DNA, increasing the chance of mutations with consequent harmful consequences for their offspring, such as autism spectrum disorders, schizophrenia, and attention deficit disorders. Therefore, understanding the male aging process and its consequences for men's reproductive health is of utmost importance for the prevention and treatment of diseases related to the male genital tract.

KEYWORDS: reproduction, testicles, epididymis, elderly, aging.

RESUMO

O envelhecimento afeta gradualmente o sistema genital masculino, devido a profundas mudanças hormonais e metabólicas. A redução da proporção de vasos sanguíneos testiculares reduz o aporte de oxigênio e outros nutrientes para o parênquima do órgão, aumentando quadros inflamatórios e de estresse oxidativo, o que pode afetar sobremaneira a viabilidade e morfologia espermática. O envelhecimento causa impacto no metabolismo de lipídeos e proteínas, que podem comprometer a estrutura e funcionalidade do espermatozoide. Além disso, o espermatozoide pode acumular alterações significativas em seu DNA, aumentando a chance de mutações com consequentes consequências danosas para seus filhos, como desordens do espectro autista, esquizofrenia e desordens de déficit de atenção. Portanto, entender o processo de envelhecimento masculino e suas consequências para a saúde reprodutiva do homem é de suma importância para a prevenção e tratamento de doenças relacionadas ao trato genital masculino.

PALAVRAS-CHAVE: reprodução, testículo, epidídimo, idoso, envelhecimento.

INTRODUCTION

Aging is a natural process that affects all cells and systems of the human body, bringing gradual changes in the functioning of organs and the body's ability to adapt to the environment[1]. As we age, the entire body shows signs of wear, including the male reproductive system[1,2]. Aging causes several transformations in the testicles, one of the most significant is the decrease in blood circulation, which reduces the supply of essential nutrients and oxygen[3]. This affects the health of testicular tissues and increases susceptibility to inflammations, such as epididymitis and orchitis, which result from an exaggerated immune response[4].

Aged testicles lose part of their ability to adapt to different conditions, such as temperature variations or stress situations[5, 6]. Sensitivity to reproductive hormones, such as testosterone, FSH, and LH, also decreases with age[2,7], as hormone receptors in the testicles become less efficient. This decline in hormonal response directly affects cell energy production, as the function of mitochondria – the "powerhouses" of cells – deteriorates over the years[8]. Another important aspect is that aging impacts the metabolism of lipids and proteins in sperm, which compromises their structure and functionality. This leads to changes in the shape, concentration, and quality of sperm and the composition of seminal fluid, directly influencing male fertility[2,9,10].

With advancing age, these factors add up, not only decreasing the chances of conception[2,10] but also increasing the risk of health problems for the offspring, should pregnancy occur. Research indicates that advanced paternal age is associated with a higher risk of genetic disorders and health conditions in descendants, such as autism and schizophrenia[11-13]. Therefore, understanding how aging affects the male reproductive system is essential for assessing fertility and reflecting on the possible impacts on the health of future generations[6].

THE EFFECTS OF AGING IN THE TESTICULAR VASCULARIZATION (IMMUNE SYSTEM AND INFLAMMATION - EPIDIDYMITIS AND ORCHITIS)

As men age, changes occur in the blood vessels of their testes, which lead to decreased formation of blood vessels and dysfunction in the lining of the blood vessels, causing issues with delivering oxygen and nutrients effectively, worsening oxidative stress levels within the testis' environment[2,4,14]. This increase in oxidative stress makes Leydig and Sertoli cells more susceptible to damage from reactive oxygen species, impacting the production of hormones and sperm development[14]. At the same time, immune cells within the testes of older individuals tend to produce more reactive oxygen species, leading to an increase, in inflammation that contributes to further damage and dysfunction at the cellular level[4,7,14].

Testes lose some of the protection they once had against attacks because the blood-testis barrier weakens over time[2,8]. This weakening allows immune cells, such as macrophages and T cells, to enter the epithelial easily, secreting high levels of interleukins, and tumor necrosis factor-alpha. This ongoing inflammation can trigger the death of germ cells and the deterioration of the testicles over time[2,7,10].

Epididymis and testis inflammation is a common disease in older men[2,4,14,15]. Epididymitis is most commonly due to bacterial infections or urinary reflux from prostate enlargement and presents with fever, swelling, and pain[8,9]. On the other hand, orchitis can be caused by viral infections like mumps or autoimmune diseases[8,11]. Both conditions can lead to chronic problems, including testicular scarring, reduced sperm formation, and infertility[2,4,11,14,15]. In brief, autoimmune orchitis exemplifies how the loss of immune tolerance with age can mediate the elaboration and enhancement of inflammatory pathways targeting germ cell antigens to cause testicular damage[14,15,16].

Prostaglandins, especially COX2–dependent prostate agonists, are important in the inflammatory processes occurring in aging testes[11,16]. Upregulated COX2 expression in testicular macrophages enhances prostaglandin synthesis,

sustaining local inflammation while also limiting androgen production from Leydig cells, thereby further affecting testicular activity[2,4,11,16].

Therapeutic approaches targeting oxidative stress, inflammation, and hormonal homeostasis are crucial for combating these age-related maladies[6,12,14]. Emerging options for antioxidants, COX2 inhibition, and androgen replacement represent a potential way to minimize the impact of aging on the male reproductive tract[2,10,14]. Ongoing studies are needed to better elucidate the complex mechanisms involved in age-associated inflammation that ultimately causes deterioration of reproductive health and loss of quality of life with advancing male age and towards the development of effective therapeutics[12]. However, the morphological alterations of the basement membrane during testicular aging are contradictory in the literature[2,7].

THE ALTERATION OF LIPID AND PROTEIN METABOLISM IN SPERM

Sperm are highly specialized cells that rely on strict lipid regulation and protein metabolism for function, motility, and fertilization potential. Disruptions in these metabolic pathways can drastically deteriorate sperm quality and are frequently linked with male infertility[5,17,18].

Lipids are key components of sperm cell membranes, which play critical roles in their fluidity, structure, and functioning. The sperm plasma membrane is especially enriched with polyunsaturated fatty acids (PUFA), which are important to maintain the fluidity necessary for sperm movement and fertilization events, such as the acrosome reaction. Still, the excessive levels of PUFAs leave sperm membranes vulnerable to oxidative injury[5,18]. Enhanced production of reactive oxygen species (ROS), frequently occurring due to environmental challenges or metabolic disorders, causes lipid peroxidation, resulting in loss of membrane integrity, motility, and fertilization ability[3,5,18].

Cholesterol plays a vital role in maintaining the structural integrity of sperm membranes. Cholesterol efflux during sperm maturation and capacitation is crucial for preparing the sperm membrane for fertilization. An imbalance in cholesterol,

which may result from changes in metabolism or environmental factors, can disrupt this mechanism, altering membrane fluidity and impairing sperm function [18]. Additionally, abnormalities in lipid metabolism can change the lipid composition of the sperm membrane, leading to defects in sperm viability and motility[5].

This is important because proteins from fertilizing sperm can alter expression and affect sperm function. Phosphorylation, ubiquitination, and glycosylation are common regulators of sperm cell activity, controlling pathways such as motility and those involved in acrosomal exocytosis and egg[18]. Spermatogenesis, the process of sperm production and maturation in the epididymis, has highly regulated protein metabolism[17].

Capacitation is one of the major processes that change sperm protein composition, during which sperm gain the capacity to undergo the acrosome reaction when they contact the oocyte. This is associated with sperm protein remodeling, for example, phosphorylation of end-thoughts, such as tyrosine phospho-residues on sperm proteins from the tail and head [5]. Because of oxidative stress, these phosphorylation events undergo alterations that can impair sperm motility while decreasing the ability to bind to zona pellucida, therefore lowering its fertilization potential[5,18].

The overproduction of ROS contributes to protein oxidation that can cause modifications in essential sperm proteins, causing loss of function and structural damage. Such oxidative stress contributes to a range of sperm defects such as impaired motility, DNA fragmentation, and decreased sperm-egg binding ability[5,18].

Coordination of lipid and protein metabolism is required for reproductive function in sperm lipid rafts, unique microdomains that are rich in cholesterol and sphingolipids, present scaffolds for protein-protein interactions that are essential events during sperm capacitation and the acrosome reaction[17]. Changes in lipid composition, such as cholesterol depletion or overload, disrupt these microdomains, affecting the function of some membrane-bound proteins required for sperm-egg recognition and fertilization. Defects in maintaining adequate interactions of lipids

and protein within these domains can directly affect sperm motility, acrosomal integrity, and ultimately fertilization success[5].

RELATIONSHIP BETWEEN AGING AND CHANGES IN THE MORPHOLOGY, CONCENTRATION, AND QUALITY OF SPERM – COMPOSITION OF SEMINAL FLUID

The decline in semen quality as men age not only lowers the quantity of sperm but also affects motility, as less fluid volume can hinder sperm's ability to travel effectively through the female reproductive tract[2,12]. Although sperm concentration appears to increase with age, this is likely due to the faster reduction in semen volume than in total sperm count [12]. However, this increased concentration does not mitigate the adverse effects of aging, such as DNA damage and impaired motility[12,13].

Motility decline is especially critical, as sperm must move efficiently to reach and fertilize the egg. One of the most concerning age-related changes is the decline in DNA integrity, measured by the DNA fragmentation index (DFI), and DFI rates increase substantially in men over 40, with elevated levels associated with lower fertility potential, decreased embryo quality, and a greater risk of miscarriage or genetic abnormalities in offspring[19-21]. Elevated DFI levels correlate inversely with key fertility parameters, such as sperm concentration, motility, and morphology, meaning that as DNA damage intensifies, these parameters continue to decline[18-21].

Additionally, high DNA stainability (HDS) indicates chromatin immaturity in sperm and also decreases with age. Chromatin condensation is crucial for DNA stability, and lower HDS suggests compromised chromatin structure, further impairing the sperm's ability to contribute to successful fertilization[2,22]. Aging also leads to significant changes in seminal fluid composition, critical for sperm protection and function[14]. Oxidative stress, driven by an imbalance between ROS and antioxidants in the seminal plasma, emerges as a key factor contributing to DNA damage in older men[9]. While ROS are necessary for specific physiological

functions, including sperm maturation, excess ROS can lead to extensive DNA fragmentation, chromatin degradation, and reduced motility[2,18,20,21]. Older men exhibit higher ROS levels in their seminal fluid, which correlate with increased DFI, decreased HDS, and overall declines in sperm health[22].

THE ASSOCIATION BETWEEN AGING AND THE INCREASING RISK OF HEALTH ISSUES FOR THE HEIRS

The aging of parents, especially of fathers, has deep consequences for the health of their offspring, with the issue of too-advanced paternal age being a significant concern[13,21]. Paternal age at birth is associated with a wave of molecular changes within the cell as the aging process of all cell types in the body is synchronized. Due to aging, sperm is much more vulnerable to DNA mutation and fragmentation because of oxidative stress, which is increasingly happening with age[13,21]. This increase in oxidative stress is a stage in the series of events that will cause DNA repair mechanisms to malfunction, and then the end product will be a sperm cell with a higher mutational load. Some studies purport that specific genetic mutations, for instance, those in fibroblast growth factor receptor (FGFR) genes, occur more often as the cells' biological ages. These mutations relate to disorders such as achondroplasia and Apert syndrome. Additionally, telomere dynamics are the main thing. Although the testicles are the same length for telomeres with age for fathers, thereby giving some degree of protection from cellular aging, the growth of telomeres is the cause of cancer and other proliferative disorders in offspring[13,21].

Aging fathers provide a greater possibility of developmental disorders in offspring, such as autism spectrum disorders (ASDs), schizophrenia, and attention deficit hyperactivity disorder (ADHD). Children of fathers who were older at birth have often been shown to display a higher rate of educational challenges[21]. In addition, older parents may face higher chances of their children getting physical health conditions such as congenital heart defects and skeletal dysplasia[13,21].

These relationships are based on two main mechanisms: oxidative stress and selfish spermatogonial selection. Oxidative stress is a significant issue as it attacks

cellular components including DNA, proteins, and lipids with the loss of quality and function of sperm as the final result. “Selfish spermatogonial selection” is used when the stem cells showing mutations that give them a selective edge over others expand. It occurs in the aging testicular cell environment, leading to a situation where such cells with altered, mutated genes are largely represented in the sperm population[13].

A deeper understanding of the issues of aged fathers should have a central role in informing the appropriate guidance of parenthood in families. Raising awareness of the above dangers in families can be very useful for developing strategies, for instance, a communication campaign encouraging the use of antioxidant therapy could be highly beneficial in reducing oxidative stress-related mutations in sperm DNA when they occur[13,21].

CONCLUSION

Aging has a significant impact on men's reproductive systems, which leads to a plan to reduce fertility and reproductive health, hormones, and metabolic changes. Reduced blood flow, oxidative loads, and testicular inflammation contribute to the reduction of sperm quality, including changes in lipid and protein metabolism. This change reduces the mobility of semen, DNA honesty, and chromosome buildings and increases the risk of genetic diseases of offspring. In addition, age-related changes make the efficacy of sperm further by worsening the oxidation damage of serum fluid. Status such as autism, schizophrenia, congenital heart defects, and genetic syndrome are associated with aging mutations and telomeres dynamics. Understanding this process is important for developing prevention and treatment methods. This knowledge emphasizes the importance of antioxidant therapy, preserves sperm health, and guarantees better reproductive performance for the aging of men and their families.

CONFLICT OF INTEREST

There is no conflict of interest to declare.

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