PERSPECTIVES ON MALE AGING AND THERAPEUTIC IMPLICATIONS

Received: August 2, 2023
Accepted: September 10, 2023

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Abstract
This article provides an in-depth analysis of the molecular and cellular alterations linked to the aging process in males. It elucidates the physiological disruptions that give rise to different diseases and a decrease in functional ability. The inquiry explores the complex correlation between aging, sexual dysfunction, and infertility in males, with a focus on the physiological alterations in spermatogonial stem cells and the impact of oxidative stress on male reproductive capacity. The function of testosterone replacement therapy and its potential advantages in enhancing sexual activity, bone density, and overall health in older males are highlighted. Nevertheless, it is prudent to exercise caution as there is a correlation between testosterone replacement therapy and heightened cardiovascular risk. The article summarizes rehabilitation options for elderly men, specifically focusing on exercise regimens and cardiac rehabilitation, as means to tackle erectile dysfunction and mitigate mortality risks. The advantages of yoga in enhancing mental and physical well-being in males, particularly those grappling with prostate cancer or infertility are mentioned. The significance of adopting a comprehensive and interdisciplinary strategy towards men's health is emphasized, with particular attention given to the contributions of primary care physicians, urologists, and nurses. The significance of customized communication tactics for males and the necessity of periodic examinations for promoting healthier aging are emphasized.

Keywords: Men's health, Aging, Fertility, Rehabilitation


INTRODUCTION
The molecular and cellular changes that occur as individuals age lead to physiological dysregulation, contributing to the onset of various diseases and a decline in functional capacity in males [1].

In older men, there is an increased prevalence of various conditions. The occurrence of benign prostatic hyperplasia (BPH) and prostate cancer (PCa) ranges from 5% to 10% in men at the age of 40, increasing to 80% in those aged 70–80 [2]. In the United States, cardiovascular disease (CVD) is the primary cause of mortality, accounting for 24% of male deaths in 2017 [1]. Among Dutch men aged 65, 70, 75, 80, and 85, coronary heart disease (CHD) causes the most
extended period of living with morbidity, ranging from 7.6 years at age 65 to 3.7 years at age 85 [3].

Compared to males with normal weight, the hazard ratio (HR) for CVD incidence is 1.2 (95% CI, 1.1-1.3) for overweight men, and the HR for CVD in obese males is 1.9 (95% CI, 1.7-2.0). A higher body mass index (BMI) shows the most significant association with the onset of cardiac insufficiency [4].

Males with obesity-related functional hypogonadism and serum testosterone levels less than 16 nmol/L are at an increased risk of incident type 2 diabetes (T2D) [5]. The results of a meta-analysis involving 68 studies and approximately 20,000 obese males showed that 43% had a serum total testosterone below 10.4 nmol/L (<300ng/dl). Importantly, an increase in BMI from 25 to 30kg/m² is associated with a decrease in serum testosterone concentration of 13-15% [5].

Given this consideration, our aim was to examine the pathogenic processes associated with aging in males, with particular emphasis on sexual dysfunction, infertility, psychological characteristics, and rehabilitation strategies.

Search strategy
We searched through Medline/PubMed, Scopus, and Directory of Open Access Journals (DOAJ) databases for relevant original articles, case studies, and reviews published by December 21, 2023. The following keywords were employed: men’s health, aging, male, fertility, and rehabilitation. MeSH terms were taken into consideration when determining the keywords. Our search strategy was in line with previously published recommendations [6].

Sexuality and fertility in aging men - main issues
It is recognized that sexual function tends to decrease, and the prevalence of erectile dysfunction rises in men after the age of 40. The quality and functionality of sperm change with age, posing significant implications and consequences for the health of the offspring [7]. Male sexual dysfunction is a prevalent condition, with around one-third of the male population likely to experience at least one form of male sexual dysfunction in their lifetime. The psychosexual state significantly impacts relationships with others [8]. Challenges in family planning and fertility issues are commonly described as the most stressful periods for many couples. Erectile dysfunction, known to hinder fertility by reducing successful vaginal intercourse, can lead to a loss of erotic value in sexual interactions. The absence of sexual intimacy may contribute to sexual dysfunction [8]. Erectile dysfunction in men with infertility is recognized to be higher compared to the general population. This elevated prevalence is attributed to the significant depression and anxiety experienced by infertile men, often stemming from societal pressures [8].

It is established that spermatogonial stem cells (SSCs) are capable of self-renewal and spermatogonia production. These cells undergo continuous DNA replication and cell division, accumulating various genetic changes throughout a man’s reproductive lifespan. Notably, germline mutations are higher in men compared to women. Some mutations can result in selective growth, leading to clonal expansion of mutants in older men, a phenomenon referred to as “selfish spermatogonia selection” [9].

The microdeletion in the Y chromosome, an extension of telomere length, continuous DNA damage, and diminished repair capabilities, is associated with reduced male fertility due to aging [10].

Numerous male fertility disorders are connected to external adverse factors. Furthermore, testicular aging closely correlates with older individuals' BMI. Older men with elevated BMI experience more pronounced testicular changes associated with aging [10].

Recent research has observed a reduction in the size of testicles as men age. A typical feature of testicular aging includes a mosaic of lesions within the seminiferous tubules. This is characterized by diminished tubule diameters, thickening of the basal membrane, and a decrease in the count of Sertoli cells and spermatogenic cells, eventually resulting in the halt of spermatogenesis [11].

With age, the incidence of infertility rises, impacting about 15% of couples of reproductive age and constituting half of male infertility cases. Additionally, the prevalence of male infertility is observed to increase by approximately 0.3% each year [12].

Individuals aged 70 and above exhibit increased proliferation of undifferentiated spermatogonia in the testes, reduced spermatogenic efficiency, and elevated proliferating A-dark spermatogonia. The aging process appears to stimulate compensatory proliferation in A spermatogonia, raising concerns about the potential compromise to the integrity of germ cells [13].

A cross-sectional study examined the semen quality pattern in elderly men and identified thresholds for
semen parameters. The participants were divided into three age groups: I) 18-29 years old, II) 30-39 years old, and III) 40-49 years old. The study analyzed the correlations between age and sperm parameters. Group I exhibited significantly higher characteristics in total sperm number, progressive motility rate, and normal morphology rate than the other groups (p < 0.001). The mean semen volume and total motility rate were also significantly higher in group I than in the other groups (p = 0.001) [14].

As men age, the decline in antioxidant protection contributes to accumulating a substantial amount of reactive oxygen species in spermatozoa. This buildup leads to functional disorders in spermatozoa, thereby significantly impacting male fertility [15].

In the case of oxidative stress, there is a notable increase in reactive oxygen species, which not only contribute to regulating sperm maturation but also have the potential to initiate DNA damage and apoptosis. Additionally, oxidative stress can exert a significant influence on sperm function. Sperm are especially vulnerable to oxidative stress due to the high concentration of polyunsaturated fatty acids in their plasma membranes, insufficient antioxidant protection, and limited capacity for cellular repair [12].

Physical activity, body images issues, and stress-coping in aging men
Inevitable physical, mental, and social changes characterize the aging process. It is recognized that diminished testosterone levels may be linked to a heightened risk of depression in men [16]. A systematic review has revealed a correlation between vitamin D deficiency and the onset of depression in aging men. Additionally, there is a positive association between vitamin D and testosterone, with previous research indicating a substantial impact of testosterone on mood. Consequently, vitamin D exerts a protective influence on depression by influencing testosterone levels. As a result, recommendations suggest that middle-aged or older men consider taking vitamin D supplements or exposing themselves to sunlight to prevent depression [17].

In a study exploring how men aged 65 to 83 perceived age-related changes in appearance, body function, and health, participants displayed mixed attitudes toward their aging bodies. The findings indicated that older men held diverse views about their bodies as they aged, expressing concerns about specific changes and highlighting the importance of approaching these changes with a pragmatic awareness of the complex emotions associated with aging. Despite these concerns, participants demonstrated a commitment to physical activity and a healthy diet. Thus, it is very significant to enhance awareness and provide information to men about psychological adaptation during the aging process [18].

It is crucial for men to address and navigate age-related changes through diverse physical and social activities. Consequently, there is a pressing need to develop a comprehensive understanding of how men manage the transformations in their bodies as they age within the framework of interpersonal relationships [19].

A correlation exists between the aging process in men and the development of eating disorders. In this regard, the assessment of endocrinological parameters, especially testosterone levels, is of paramount importance. Employing diverse assessment approaches is recommended to comprehensively understand the situation [20]. The body mass index (BMI) is the most robust indicator of body appearance satisfaction for both men and women. However, men tend to link their satisfaction with appearance more strongly to their bodies' functionality than women [21].

Psychological issues and the perception of the aging process can harm the quality of life. Therefore, efforts to enhance the quality of life through psychological support should be directed toward men facing psychological challenges during aging [22].

Similarly, alterations in the locomotor system can adversely affect daily functioning. Impaired motor function in older adults is often associated with a decline in muscle mass, a phenomenon observed as early as the third decade of life. It accelerates notably after the age of 50 [23].

One of the researchers explored the relationship between physical activity and aging symptoms in males. Subjects with higher physical activity were significantly less likely to develop aging symptoms compared to those with lower physical activity, both with (odds ratio [OR] = 0.8, 95% confidence interval [CI]: 0.6 to 1.0) and without (OR = 0.7, 95% CI: 0.6 to 0.9) adjustments for age, BMI, smoking, alcohol consumption, and chronic disease. Furthermore, there was a negative correlation between physical activity and the Aging Males' Symptoms Scale (AMS) total score (p < 0.01) as well as scores for somatic (p < 0.01) and sexual (p = 0.04) health. Even after adjusting for covariates, the negative correlation between physical
activity and all AMS scores remained significant (p < 0.01) [24].

The high-impact physical activities may have a positive influence on bone health. Elderly men with high-impact physical activities maintained greater bone mineral density, and an increased level of energy expenditure was linked to a decreased risk of falls [25]. Additionally, continuous aerobic exercise improves endothelial function in elderly males by inhibiting oxidative stress and preserving nitric oxide (NO) bioavailability [26].

**Testosterone replacement therapy**

Testosterone, the primary male hormone, is crucial for developing men’s secondary sexual characteristics and fertility. The total and free testosterone levels in men’s blood serum gradually diminish with age. However, this aging-related decline is influenced by the natural aging process and various coexisting conditions such as obesity and certain genetic factors. Testosterone treatment has been shown to better sexual activity in aging men with low testosterone levels [27].

However, it is essential to note that testosterone replacement therapy has been associated with a substantial increase in the risk of CVDs [28]. Additionally, testosterone replacement therapy is effective primarily in mild cases of erectile dysfunction, and its efficacy in severe cases of vascular damage can be enhanced when combined with other medications [29].

Thus, the Endocrine Society does not advocate universal testosterone therapy for all elderly men with low testosterone levels. Instead, it emphasizes the significance of an individualized approach tailored to those men with consistently low testosterone levels [27].

Additionally, several clinical trials have indicated that testosterone replacement therapy in older men enhances bone density, strengthens bones, increases lean body mass, decreases body fat mass, improves physical activity, and raises hemoglobin concentration while lowering the risk of anemia [30].

For men aged 40 and older with a serum testosterone level below 12 nmol/L, temporary testosterone treatment can enhance erectile function, irrespective of the patient’s age, level of obesity, or the extent of low testosterone levels [31].

In a randomized clinical trial involving men with hypogonadism and either pre-existing CVD or a high risk of cardiovascular events, testosterone therapy demonstrated non-inferiority to placebo regarding the incidence of adverse cardiac events [32].

For young men experiencing hypogonadism linked to conditions affecting the hypothalamus, pituitary gland, and testicles, testosterone therapy proves beneficial with a low incidence of side effects. A randomized trial has indicated that testosterone replacement in elderly men with low testosterone levels enhances sexual desire, overall sexual quality, muscle strength, and bone strength. Testosterone treatment does not exacerbate lower urinary tract symptoms [33].

Various forms of testosterone are accessible, ranging from topical gels to intramuscular injections [34]. Subcutaneous (SC) administration of testosterone is more convenient for self-administration by patients [35]. Following SC testosterone administration, it reaches adipose tissue beneath the dermis, less vascularized than skeletal muscles. Subcutaneous injections demonstrate more consistent vascular absorption patterns than intramuscular (IM) injections [35].

Aromatizable androgens, such as testosterone, might be preferable for androgen replacement in hypogonadal men compared to non-aromatizable modified androgens [36]. Furthermore, tablets containing 17 alpha-alkylated modified testosterone are recognized for potential liver toxicity and effects on decreasing HDL cholesterol while increasing LDL cholesterol concentrations. However, a novel oral formulation of testosterone undecanoate in a self-emulsifying drug delivery system successfully maintained average testosterone concentrations within the adult male range in 87% of hypogonadal men, comparable to the effects of transdermal testosterone lotion/gel [36].

The nasal administration of testosterone was found to positively impact hypogonadism, maintaining luteinizing hormone and follicle-stimulating hormone within the reference range in 70 to 80% of cases. Moreover, the spermatozoa concentration exceeded 5 million/ml in 90% of men [36].

**Rehabilitation**

The rehabilitation of individuals during the aging process presents numerous challenges as the changes associated with aging are compounded by various factors, including psychological and social elements [37].

For men experiencing erectile dysfunction, various exercise intensities and regimens can be employed.
However, conducting a comprehensive examination of the medical and physical aspects is crucial before recommending physical rehabilitation. This thorough assessment helps determine the type, intensity, and duration of the rehabilitation program tailored to each patient's needs [38].

Cardiac rehabilitation is of utmost significance in reducing the risk of mortality associated with aging in men [39].

Engaging in physical exercises can enhance cerebrovascular functioning and cognitive abilities in individuals over 50, irrespective of their health status [40].

The appropriateness of physical activities is vital for effective rehabilitation, allowing for the utilization of different intensities. Group training serves multiple purposes, and the active participation of families can contribute positively to rehabilitation outcomes. Furthermore, involving a multidisciplinary team enhances the overall quality of the rehabilitation process [41].

Resistance exercises play a crucial role in maintaining normal blood glucose, lipids, and cholesterol levels, thereby contributing to improved management of chronic diseases such as diabetes and cardiovascular conditions. Additionally, these exercises help prevent muscle damage and enhance overall well-being [42]. Engaging in a daily regimen of resistance training among older individuals diminishes the likelihood of falls, enhances the strength of the flexor and extensor muscles around the elbow and knee joints, and improves overall strength in both the upper and lower limbs [43].

Participating in moderate to high-intensity resistance circuit training also demonstrates a rise in lean body mass, enhances functional capacity, and increases the strength of both the upper and lower limbs in older men. Therefore, encouraging progressive strength circuit training is essential for ensuring healthy and proper aging [44].

Additionally, gait and balance disorders are frequently seen in various neurological conditions in older individuals, significantly impacting their quality of life. Therefore, invasive brain stimulation technologies are commonly employed as a means to enhance walking balance in diseases like stroke and Parkinson's disease [45].

Yoga exercises conducted during the perioperative period enhanced the quality of life, stimulated an immune response, and mitigated inflammation in men diagnosed with prostate cancer [47].

Yoga plays a pivotal role as a stress management tool for individuals dealing with infertility, providing favorable effects on fertility that contribute to successful childbirth for couples [49].

Holistic collaboration for men's health care
A multidisciplinary team and individualized treatment are crucial for achieving better outcomes in men's health concerns [50]. General Practitioners (GPs) play a crucial role in providing holistic care for men's health, recognizing that men often seek medical attention less frequently than women. GPs are responsible for encouraging men to undergo regular and thorough examinations, contributing to the potential for a healthier aging male population [51]. Therefore, it is essential to educate physicians on effective communication strategies tailored to men and raise awareness about men's health concerns [51].

Men frequently visit urology departments due to concerns related to sexual function, offering urologists the opportunity to identify and prevent chronic diseases in men at an early stage [52]. However, it is emphasized that urologists should not limit their expertise solely to urological issues; instead, they should embrace a role as primary healthcare providers [52].

The role of nurses in men's health appears uncertain based on recent studies, revealing a lack of clarity among nurses and men regarding the nurse's role in...
men's health. Developing positive inter-professional relations, effective communication, and ensuring the preparedness of nurse education may facilitate the creation of alternative approaches to address men's healthcare needs [53].

CONCLUSIONS
Elderly males, particularly during the process of progressive aging, encounter increasing challenges related to fertility, sexual functioning, body image, and psychological well-being, often associated with declining testosterone levels. It is essential to comprehensively assess the intricacies of male aging, considering the potential influence of genetic and social factors in advanced age. Additionally, exploring effective therapeutic approaches becomes crucial to optimize the health and well-being of older men.

FUNDING
None

References


34. Snow L. Hormone therapy: testosterone replacement therapy. FP Essent 2023;531:7-14.


Терапевтические возможности йоги. Упоминаются преимущества йоги в улучшении психического и физического здоровья мужчин, при этом особое внимание уделяется вкладу врачей первичной медико-санитарной помощи, урологов и медсестер.