Fertility in the Aging Male: Molecular Pathways in the Anthropology of Aging

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A B S T R A C T

The aging process is a normal stage in development characterized by the gradual deterioration of all life functions. As far as reproduction is concerned, aging is characterized by a significant limitation of fertility in both sexes. This process is, at least partially, attributed to the action (or loss of action) of sex steroids, coinciding with low activity of the pituitary-gonad axis. From an anthropological point of view, the study of reproductive aging is a unique opportunity to investigate various environmental and endogenous factors influencing sexual behavior and, thus, playing a significant role in human biology. Various techniques are now widely available to allow the detailed examination of reproductive hazards using only minor samples of genetic material. These methods are highly sensitive and specific and allow the characterization of distortions at subcellular and even molecular level. This short review briefly summarizes the current understanding of reproductive aging, as well as its potential clinical and anthropological impact.

Key words*: androgens, aging, reproduction, infertility, male, sex*

Introduction

In older men, as opposed to aged women in which menopause marks the end of their reproductive period, maintenance of spermatogenesis and continuation of androgen production, although in diminished quantities, sustain sexuality and fertility[1]. This situation may persist until an advanced age unless pathological conditions, particularly those implicating an increase of reactive oxygen species (ROS), impair semen quality. In the absence of pathology, spermatogenesis continues until a very old age (95 years), although a gradual decline of endocrine function in conjunction with deterioration in some of the sperm parameters is normally observed, reflecting the age-related structural changes that occur in the testis[2]. Within the aging male population the gradual decrease in androgen plasma levels has been considered the prelude of entering the third age (andropause). Within the spectrum of changes observed in aged men, several symptoms can be distinguished, namely decreased libido, psychological and emotional disturbances, erectile dysfunction, decrease in muscle strength and bone density, all contributing greatly in the distinct social and biological role of the elderly in any society. Concerning general semen parameters, a reduction of approximately 25% is observed in all major qualities and this implies an analogous reduction in the fertilizing ability of older in comparison with younger men.

Gonadal Status of the Old Man

Within the testis of old men, a smaller number of Leydig cells can be detected in the interstitial tissue and those that remain accumulate the »ageing« pigment lipofuscin, crystalline inclusions, and residual bodies[3]. A mechanism involving an age-related increase in cyclooxygenase-2 activity and its tonic inhibition of steroidogenesis in rat Leydig cells has been suggested[4]. Smaller numbers of germinal and Sertoli cells are also counted. The ultrastructure of this progressive testicular involution reveals multinucleated and degenerating germ cells that are phagocytosed by Sertoli cells which appear vacuolated with lipid droplets accumulated in their cytoplasm[5]. Concomitant increase in the thickness of the tunica propria outlining the seminiferous tubules, as well as the tunica albuginea, is also observed. Age-related alterations of spermatogenesis are described by Holstein, who noticed reduction in dark type and intratubular clustering of pale type spermatogonia in the spermatic

epithelium of aged men[6]. Additionally, he reported the presence of spermatocytes (type I) with large nuclei and an arrest of spermatogenesis at this stage concomitant with numerous malformations of spermatids. Nevertheless, this histological pattern is usually found in small areas of the aging testis with a varying frequency among individuals. Inversely, seminiferous tubules with complete spermatogenesis could be found in the testis until advanced age (95 years), according to the data reported from a study of 36 men, 61–102 years of age, among which 17 were found having an efficient spermatogenesis (the oldest was 95 years old). The others presented spermatogenesis arrest and in 15 of them this situation was observed in a precocious stage[1]. These histological alterations at the testicular level are related with the reduction in blood testosterone concentration and this phenomenon influences many physiological functions, such as bone mineral density (BMD), muscle strength and libido[8].

Decline in Testosterone Production with Age

The age-associated decline in physical and reproductive competence following the decline in testicular function, Leydig cell numbers and androgens, is observed in the elderly and is commonly described as andropause or late onset hypogonadism (LOH)[8,9]. This is a clinical and biochemical entity which combines diminution of testosterone levels below the young adult healthy male reference range with low libido and sexual activity, erectile dysfunction, decreased muscle mass and strength, osteoporosis accompanied by increased risk of fractures, obesity and increase in visceral fat, weakness, diminution of body hair, depression or irritability and sleep disturbances[9,10]. The anabolic effects of androgens are necessary for the maintenance of bone density and the slow decline observed with age is linearly associated with low bone mass[11]. In addition to bone loss, a number of other extra-osseous factors make a greater contribution to male osteoporosis: thus, 50–70% of cases are related to hypercorticism, alcohol abuse, smoking, liver or gastrointestinal disorders.

These symptoms are analogous to those observed in young males suffering from hypogonadism, which can be easily evaluated using ADAM (Androgen Deficiency in Aging Males) questionnaire or AMSS (Ageing Male Symptom Score)[9]. Nevertheless, these are not considered specific to the low levels of testosterone but rather indicative of androgen insufficiency[10,12-13].

Consequent to the gradual decrease of testicular androgen production after 40 years of age, the function of multiple organs is affected leading to the progressive development of various symptoms having a detrimental impact on life quality. After the age of 50 years, the decline in serum and free testosterone levels is between 0.4 and 1.2% per year, respectively[14]. At the age of 75 years, mean plasma testosterone levels are only 65% of those found in young adults but there are inter-individual variations

and, importantly, a quarter of men aged over 75, have testosterone levels comparable to those of young men[15].

Multiple causes are hiding under the etiology of these symptoms. For example, a correlation between decreased libido and low plasma testosterone levels might exist, but other causes such as depression, illness or the death of a spouse, should also be considered. This situation can be improved following testosterone therapy in 70–80% of affected persons[1]. Defective erections are also associated with low testosterone levels. This implies decrease in nitric oxide synthase (NOS) enzyme, an endothelium-derived relaxation factor (former ERDF) implicated in penile erection along with other neurotransmitters. In this case testosterone treatment improves the quality of erections produced by phosphodiesterase-5-inhibitors[16].

Relatively recently, the association of hypogonadism-related symptoms and signs to age has been evaluated in a series of 1647 (mean age 52.4±13.1 years) male patients with sexual dysfunction. From the hormonal and biochemical data and psychological parameters it was shown that low testosterone (T) was associated with higher waist circumference and triglyceride levels and promptitude to develop metabolic syndrome. In the oldest age group, subjects with higher T levels showed better lipid profile and penile flow. Thus, older men present with increasing frequency an association of low T with sexual and metabolic dysfunction[17].

Laboratory assessment of hypogonadism is necessary in all these cases and implies measurements of total serum testosterone levels (TT <200 ng/dL). Borderline results (TT >200 ng/dL to TT <350 ng/dL), impose repeated assay with determination of bioavailable serum testosterone (bT) and free T (FT), but threshold values for bioavailable testosterone are not generally offered. It is well known that after the age of 55 years the gradual reduction of androgens affects both TT and FT. TT reduction is 0.8% per year and this results in a mean value of 60% in men 75 years old compared to that obtained in young men (30 years). More important is the reduction of FT, given that it starts earlier and it is calculated at about 1.4% per year so that at 75 years of age its mean value corresponds to the 40% of the value seen in young men. Furthermore, with advanced age a gradual increase of SHBG occurs, while the circadian rhythm of T secretion is lost. It should also be noted that estrogens present a gradual decrease in aging men as well, although less evident compared to that of androgens[18,19]. This can alternatively be interpreted as a relative increase of the estrogen/androgen ratio due to increased peripheral aromatization, with further implications for their respective effects. In any case, for the establishment of a diagnosis of hypogonadism it is important to gather total testosterone measurements rather than free testosterone values only[10]. Harmonization of immunological assays can distinguish normal to low testosterone men but performance of mass spectrometry offers an accurate and reliable method for evaluating plasma testosterone levels.

Other causes affecting androgen levels in the aging man include critical illness which is characterized by

hypogonadotropic hypogonadism due to impairment of the hypothalamo-pituitary-testicular axis. Also, chronic diseases such as diabetes mellitus, metabolic syndrome, chronic renal disease, chronic respiratory disease, chronic infections and acute infectious diseases. The situation is aggravated by smoking, consumption of alcohol or drugs, such as anabolic steroids and glucocorticoids, obesity and secondary hypogonadism. The laboratory confirmation of hypogonadism is given from the reduced levels of Testosterone (Total serum Testosterone <200 ng/dL). It should be noted that the normal range of serum testosterone is very wide and fluctuates between 300 and 1100 ng/dl. Diurnal variations are observed with the higher rate (peak) being at 08.00 in the morning and the lower (nadir) at 22.00 in the night. This circadian rhythm of testosterone secretion follows the pulsatile secretion of the LH.

Hypogonadism is the main indication for testosterone substitution in ageing males[20]. Therapy aims to prevent or reverse hypotestosteronemia, increased negative feedback of testosterone in the pituitary gland, irregular production of GNRH from the hypothalamus and loss of circadian rhythm in testosterone secretion. It should be noted, however, that not only the reduced level of gonadal steroids, but also the secretion of other endocrine glands shows alterations in the elderly. Detailed description of these adaptive changes is still missing, and there is no concomitant estimation of other hormones e.g. growth hormone, insulin-like growth factor-1, oestradiol, thyroid hormones, cortisol, ACTH, dehydroepiandrosterone sulfate and melatonin quantifications are not performed unless there is suspicion of pertinent disorders[10,21,22]. Small-scale clinical studies have shown that it is beneficial to boost growth hormone and IGF-1 levels for periods of up to 12 months, and testosterone for up to 36 months, to reverse at least some age-related changes in body composition[23].

Old men receiving testosterone claimed satisfactory results on reproductive competence and well-being. Until recently, it was advisable to avoid side effects by keeping plasma testosterone levels within the physiological range for the entire period between two consecutive doses. But this is no longer acceptable because a large variation of the so called physiological thresholds is observed among individuals and the amount of androgen required for every biological function is different[24]. Hence, the results of larger, long term, well-controlled studies are needed to establish a stronger recommendation regarding routine testosterone substitution in elderly men. For the time being, the therapeutic goal targets to mid – lower young adult levels of serum testosterone[25]. In men suffering from osteoporosis and hypogonadism testosterone administration proved beneficial and their BMD was restored to the level of aged-matched men who had no shortage of testosterone, provided that treatment was given over a period of 3 years[26].

Concerning the choice of testosterone preparations, it seems that transdermal gels and intramuscular testosterone undecanoate administration are the best suited

when taking into account the above mentioned criteria. In any case testosterone therapy in the ageing male has to be monitored closely, especially regarding erythropoiesis and prostate epithelial proliferation. Concerning the latter, an absolute contra-indication for testosterone supplementation is clinical prostatic carcinoma. Men treated with androgen depletion therapy for prostate cancer develop severe osteoporosis and are in strong risk of bone fracture[27].

Sex Steroids and their Effect on the Metabolic Syndrome

In the aging male population, low SHBG and free testosterone coincides with an increased prevalence of the MS components, i.e. obesity, dyslipidemia, hypertension and insulin resistance/diabetes mellitus. In certain comparative studies, it has been demonstrated that sex hormone-binding globulin (SHBG) and testosterone levels are in fact a significant determinant of fat accumulation, both subcutaneously and in the abdomen, bearing a clearly protective role. However, this benefit has not extended to other major parameters of the MS, such as insulin resistance itself, implying a more complex mechanism for their sustained presence in the aging male population[28–30].

Findings such as those described above have led to a series of studies on the necessity of hormonal intervention and androgen substitution in the elderly (late-onset hypogonadism model). In particular, testosterone decrease has been found to be proportional to the metabolic and functional features of male aging, such as impaired adipose tissue-lean body mass ratio, muscle weakness, increased bone decomposition and proneness to develop the MS and its various life-threatening complications. However, tissue sensitivity to androgens varies considerably and, thus, the limit from desired function to adverse effects is not easily determined. Indeed, results indicate some beneficial role of androgen substitution (e.g. lower total cholesterol) but simultaneously unwanted phenomena (e.g. lower HDL-cholesterol). The fact that other studies have failed to verify this finding or even propose an opposite effect (improved HDL-cholesterol) only shows that several unidentified confounders may still be present and no generalized recommendation for androgen substitution can be reasonably adopted at this point[31–33].

Aging and the Quality of the Ejaculate (Sperm Parameters)

From earlier studies it has been reported that age has only minimal effects on the quality of the ejaculate[34]. However, recent data comparing semen parameters from young and old men groups state that in older men semen volume production is reduced almost by 50% and further associated with low sperm count[35,36]. Others claimed that age seems to affect some semen parameters, such as motility and morphology of spermatozoa, while there is no significant difference on sperm concentration between

the two groups[35,37]. In fact, a higher percentage of spermatozoa with abnormal morphology, abnormal tail, presence of cytoplasmic droplet, reduced vitality and increased index of teratozoospermy (TZI) has been observed. Nevertheless, the rate of head and neck abnormalities has been reported not to differ importantly between groups of young and old men[37].

In another study among infertile patients and normal men, sperm motility was also reduced and this was the only parameter affected in the older age group[38]. An association of reduced motility with significant increase of spermatozoa DNA fragmentation has been observed in the same study. Several other studies demonstrated that older men seem to produce more spermatozoa with double strand DNA breaks and showed a strong association of DNA Fragmentation Index (DFI) with age[38–44]. One possible way to interpret this could lead back to the effects of oxidative stress, implying that the increase in DNA fragmentation in older men may result from a higher exposure to oxidative stress in their reproductive tracts[45,46]. Another may implicate the increased production of spermatozoa with fragmented DNA due to a reduced effectiveness of Fas-mediated apoptosis and deficiencies in the ligation of DNA strand breaks during chromatin packaging[47,48]. In any case, recent data confirm the effect of age on sperm DNA damage in infertile male population using the TUNEL technique for the evaluation of sperm DNA fragmentation and found a significant increase in sperm DFI with age[49]. This was in contrast with an earlier study showing no association between DNA damage and age in spermatozoa collected after swim-up wash, which can possibly be considered the culprit by eliminating the fraction of spermatozoa bearing fragmented DNA[50].

Molecular Cytogenetics

Advancing paternal age has been implicated in failure of fertilization, spontaneous abortions and unsuccessful pregnancies. The use of spermatozoa with DNA damage, whose rate is directly correlated with age, has been associated with an accompanying increased risk for transmission of genomic errors to the offspring[51, 52]. Furthermore, histomorphometric studies of testes in old men showed an increased aneuploidy rate in postmeiotic cells in the seminiferous epithelium[2]. Age induces relatively minor changes in sperm chromosomes, but when the male partner is more than 50 years old, fertilizing ability seems to decrease. Assays in clinical use include: 1) Karyotype and Fluorescent in situ hybridization-FISH[53], 2) PCR detection of microdeletions of the Yq[54] and 3) TUNEL and Chromomycin A3 for the detection of DNA damage and chromatin packaging abnormalities[55–57].

Finally, in semen from aged men chromosome abnormalities, namely linear increase of diploidy and disomy of chromosome 9, have been observed[37]. Increased sperm DNA damage has been associated with chromosomal abnormalities, developmental loss and birth defects in mouse model systems[58] as well as an increase in the percentage of human embryos that failed to develop after ICSI[59]. The evaluation of the spermatozoon nucleus as a novel target in previously unexplained male infertility is an important breakthrough in reproductive biology and remains a challenge for large-scale epidemiological research within the context of trans-regional population anthropology. The application of the relevant molecular diagnostic techniques requires the development of accredited biomedical laboratories supervised by adequate, specialized academic and technical staff[60,61].

Conclusions

The increase in the number of researchers and units involved with fertility studies in males will enable the exploration of various classic anthropological questions. These include, for instance, evolutionary dynamics among various human populations (using the male to male transfer of the Y chromosome as a heredity index), demographic trends and inequalities (using the male fertility potential to predict future birth rates), inter-species comparative genetics studies (estimating the common characteristics of reproductive biology and the aging process in mammals, with particular reference to primates) and paternity identification, in cases of forensic and/or archeological-historical interest. Therefore, the potential gain from such scientific applications justifies the increased academic interest in male reproductive biology in recent years and calls for interdisciplinary cooperation in the field.

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PLODNOST U STARIJIH MUŠKARACA: MOLEKULARNI PUTEVI U ANTROPOLOGIJI STARENJA

S A Ž E T A K

Starenje je normalna postaja u procesu karakteriziranom kao postupna propadanje svih životnih funkcija. Što se reprodukcije tiče, starenje je karakterizirano značajnim ograničenjem plodnosti obaju spolova. Ovaj process može se barem djelomično pripisati djelovanju (odnosno smanjenom djelovanju) spolnih steroida. Iz antropološke perspective, istraživanje reproduktivnog starenja je jedinstvena prilika za istražiti različite okolišne i endogene čimbenike koje utječu na seksualno ponašanje i tako igraju značajnu ulogu u biologiji čovjeka. Danas su široko dostupne razne tehnike za detaljnu analizu uz minorne količine genetičkog materijala. Ove metode su izrazito osjetljive i specifične te omogućuju karakterizaciju distorzija na subcelularnom te čak i molekularnom nivou. Ovaj kratak pregled sažima sadašnja razumijevanja reproduktivnog starenja kao i njihove potencijalne kliničke i antropološke učinke.