Aging and the Male Gonads

Khaleeq ur Rehman, MBBS, MS(Urol),
Department of Urology, McGill University, Montreal, QC.

Serge Carrier, MD, FRCS(C),
Department of Urology, McGill University, Montreal, QC.

The increase in male life expectancy has raised concerns about the impact of aging on the male reproductive system. Male testicular function declines gradually with advancing age. In general, testicular perfusion is reduced, aging pigment is accumulated, and the tunica albuginea of the testes and basal membrane of the seminiferous tubules are thickened. The function of Sertoli cells and Leydig cells declines. Among the semen parameters, semen volume, sperm motility and sperm morphology are decreased. The hypothalamic-pituitary-gonadal axis is affected at all levels. In some aging men, the reduction of testosterone levels leads to sexual dysfunction and "andropause". Children born to older fathers carry a higher risk of genetic diseases. This review focuses on the effect of aging on the male gonads.

Key words: aging, gonads, fertility, testosterone.

Advancing age leads to a gradual decline of male testicular function. Unlike females who lose fertility abruptly at menopause, males can father children at a fairly advanced age. In spite of this fact, noticeable effects of aging on the testes have been observed in the older male. In general, testicular perfusion is reduced with aging. The basal membrane of seminiferous tubules and the tunica albuginea of the testes are thickened, and the aging pigment lipofuscin is accumulated in some testicular cells.[1,2] Numerous age-related effects on Sertoli cells and Leydig cells are seen, with subsequent effects on the production of sperm and testosterone. Following is an outline of the effects of aging on testes.

Sertoli Cell Aging

Sertoli cells play a very important role in spermatogenesis. During sperm maturation, as the immature diploid spermatogonia progress to the haploid stage, they become immunologically less competent and are distinguished as non-self by the body. Sertoli cells isolate them from the systemic circulation and keep them restricted to the tubular compartment by creating a blood-testes immunological barrier.[3] This process involves a complex interaction between Sertoli cells and sperm, and there is evidence that at least some part of this interaction is affected by aging.

Furthermore, the appearance of Sertoli cells in some aging tubules is found to be altered, and the number of sperm cells in these tubules is reduced. Mitochondrial damage of Sertoli cells also is seen in aging testes. Oxidative stress has been proposed as a mechanism for these changes, but further direct evidence is required to confirm this.[4-6]

Leydig Cell Aging

Leydig cells produce testosterone under the influence of luteinizing hormone (LH). This hormone binds to receptors on the Leydig cell plasma membrane, initiating a cascade of events including intracellular cAMP production and cholesterol transport to the mitochondria (Figure 1). The whole process culminates in the conversion of pregnenolone to testosterone through a series of reactions in the smooth endoplasmic reticulum. In aging rat testes, it has been found that the number of LH receptors is reduced, cAMP production is reduced and the activities of steroidogenic enzymes of the smooth endoplasmic reticulum are diminished. Mitochondrial damage also has been reported in aging Leydig cells.[5,6]

Aging and Testosterone

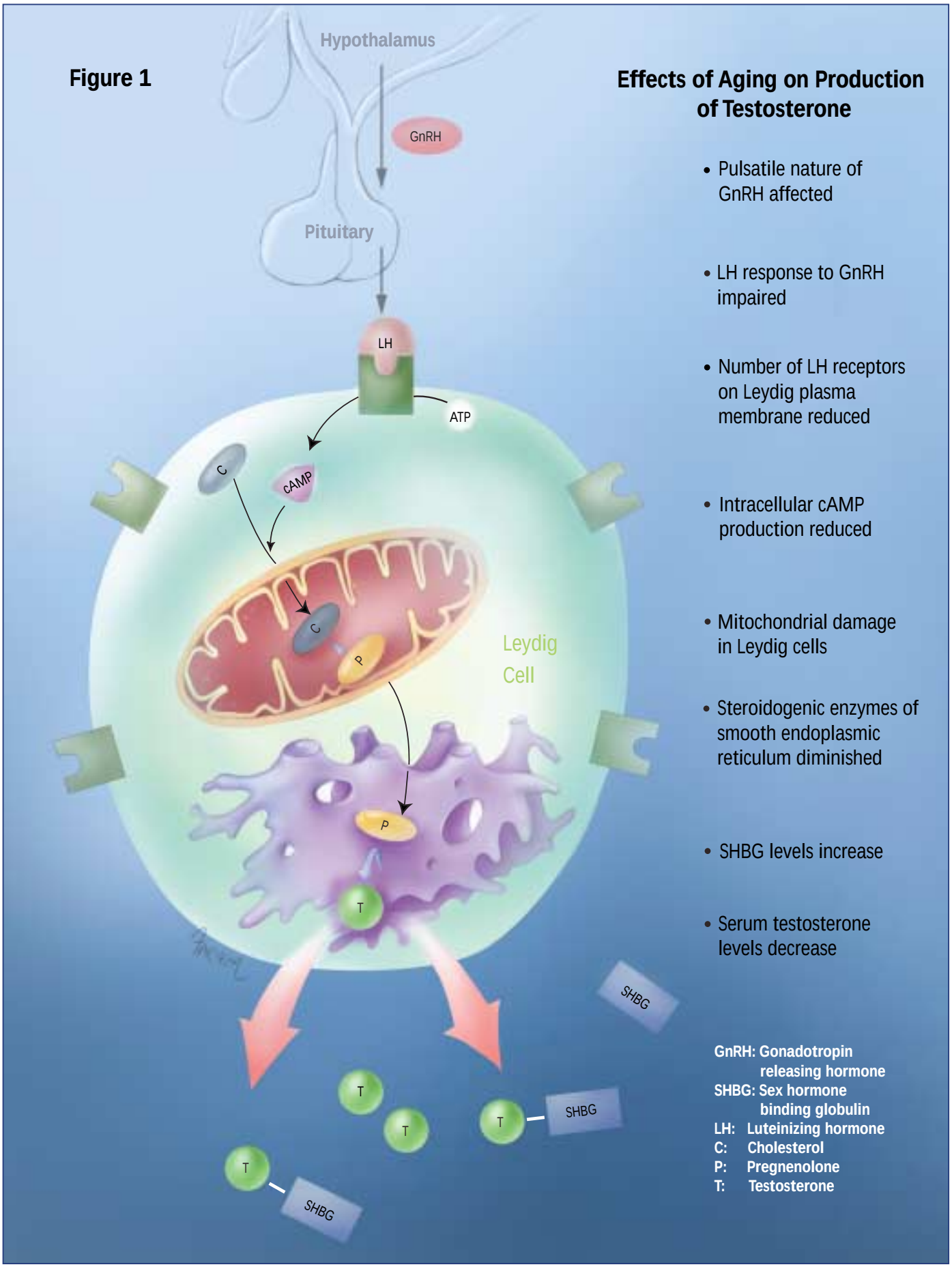
In human beings, Leydig cells are the major source of testosterone production. Only a small amount of testosterone is generated by the adrenal. There is agreement that serum total, free and bioavailable testosterone levels decrease with aging. Initially supported by cross-sectional studies, this has now been confirmed by longitudinal studies as well.[7-12] Decline in free testosterone is greater than the reduction in total testosterone because of the higher levels of sex hormone binding globulin (SHBG) in older males that bind to testosterone. With aging, the hypothalamic-pituitary-gonadal axis is affected at all levels. The response of testosterone to LH is attenuated and the feedback relationship between the two is disturbed. The LH response to gonadotropin releasing hormone (GnRH) is impaired and the pulsatile nature of GnRH release is affected.[13]

Testosterone and Sexual Function in Aging

Testosterone primarily affects sexual interest and motivation in males. In addition, it has been found that testosterone regulates nitric oxide synthase activity in cavernosal smooth muscle of the penis.[14] Thus, it is possible that a certain critical level of testosterone is essential for erection. There remains a lot of confusion regarding the relationship of androgen deficiency to erectile dysfunction, and further studies are required to fully understand this issue. It is known that testosterone does not improve sexual function in older impotent men with normal testosterone levels. It also has been reported that in some older men with low testosterone, androgen replacement will not improve erectile function.[15]

In the body, a part of testosterone is converted to estrogen by tissue aromati-

Figure 1



Effects of Aging on Production of Testosterone

- Pulsatile nature of GnRH affected
- LH response to GnRH impaired
- Number of LH receptors on Leydig plasma membrane reduced
- Intracellular cAMP production reduced
- Mitochondrial damage in Leydig cells
- Steroidogenic enzymes of smooth endoplasmic reticulum diminished
- SHBG levels increase
- Serum testosterone levels decrease

GnRH: Gonadotropin releasing hormone
SHBG: Sex hormone binding globulin
LH: Luteinizing hormone
C: Cholesterol
P: Pregnenolone
T: Testosterone

zation, a conversion that is accelerated in aging men. The ratio of free testosterone to free estradiol is reduced with aging. It should be noted that estradiol values in elderly men (2–3ng / mL) are higher than in postmenopausal women, and estradiol plays a variety of roles in men, including gonadotropin feedback regulation and sexual interest.[16]

It is clear that in some men around the age of 50, a true decrease in testosterone develops. This decrease is associated with a range of symptoms defined under the name "andropause", or partial androgen deficiency of the aging male (PADAM).[17] Studies examining the management of these individuals with testosterone therapy will hopefully resolve many issues, including the relationship of sexual function and testosterone levels in older males.

Aging and Semen Parameters

Most studies show a decline of semen parameters with aging. Although some have shown preservation of spermatogenesis with increasing age,[18] Kidd *et al.* reviewed 20 years of literature on the association between male age and semen quality and found that a number of studies needed adjustment for confounding factors, such as period of abstinence and age. Well-designed studies showed 3–22% reduction in semen volume, 3–37% reduction in sperm motility and 4–18% decrease in sperm morphology in 50-year-old men compared to men 30 years old. No definite evidence for effect of aging on sperm concentration was found.[19]

Aging and Fertility

Fertility potential is the outcome of male and female health. Usually, older males have older female partners. Increasing maternal age clearly is related to decreased fertility and therefore acts as a confounding factor in most of the studies concerning aging males and fertility. Studies that control for female age show that there is a 23–38% decrease in pregnancy rates for 50-year-old men when compared to men 30 years old. The risk of sub-fecundity in various age groups ranges from 11–250%.[19] In conclusion, the weight of evidence suggests that there is an association between increasing male age and decreasing pregnancy rate. Furthermore, aging in males is associated with increased time to pregnancy and frequency of sub-fecundity.[19]

Genetic Risks of Aging

The genetic risks of maternal age to offspring have been studied thoroughly, but the genetic risks of paternal age need further evaluation. Compared to younger fathers, the risk of autosomal dominant diseases in children born to older fathers is increased. It has been found that increasing paternal age is associated with autosomal dominant diseases, such as achondroplasia, familial adenomatous polyposis coli, Marfan syndrome, Apert syndrome and basal cell nevi.[20] There is no clear evidence for associations between aging and structural or numeric chromosomal abnormalities.[20] The American Society for Reproductive Medicine (formerly the American Fertility Society) recommends an age limit of 50 years or younger for sperm donors.[21]

Summary

Although older males often retain the ability to father children, aging influences various aspects of their gonads. The structure and function of Sertoli cells and Leydig cells are affected, and sperm motility and morphology are partially disturbed. Semen volume is reduced, genetic risk of autosomal diseases to children is increased and serum testosterone levels are reduced. ◆

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