Special Article

From Prenatal Life into Senescence, Testosterone is Essential Requirement for Manhood

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Prenatally, organisms have the bipotentiality to differentiate along either male or female lines, a process with different stages, each with a narrow window of time, during which testosterone plays a pivotal role in the case of male sexual differentiation. During puberty, the body directs the masculinization process with growth of the genitalia and prostate. Body contours become male, with an average height of 10-15 centimeters greater than that of females, a greater bone and muscle mass, a male hair pattern and a male-type fat distribution. These pubertal developments, largely reversible in case of severe androgen deficiency, require adult levels of testosterone throughout life. A new area of interest is in exploring how far age-related body changes (loss of bone and muscle mass, a shift into a higher ratio of body fat/lean body mass) are part of an age-related decline of testicular testosterone production. Therefore, throughout life, testosterone is essential for a normal male life.

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If, as Freud stated 'anatomy is destiny'[1], then the hormone testosterone, is a key player in our destinies. Indeed, testosterone determines whether we are born as a boy or a girl, and whether the former further successfully transitions from boyhood to manhood. Even then, its role is not completed. The male anatomy, as recent insight shows, needs life-long maintenance by testosterone. The age-related decline in circulating levels of testosterone may be an element in the manifestations of senescence. This review highlights both the role of testosterone in developing the male anatomy from conception to adulthood and the need for subsequent maintenance.

Testosterone

Testosterone is the major androgenic hormone and is for the most part (95%) synthesized in and secreted by the testis. A small, quantitatively insignificant amount for normal male physiology, is produced by the adrenal gland and in women by the ovary. In some target organs, testosterone is a pro-hormone and its action is not mediated by testosterone itself but by its local conversion products, 5α-dihydro-testosterone (DHT) and/or estradiol (E_2). DHT is the most potent natural androgen (with a biopotency of 3-7 times of testosterone itself), and it is formed exclusively in the target tissues through 5α-reduction of testosterone by the enzyme 5α-reductase. This enzyme has two forms produced by distinct, homologous genes with type1 5α-reductase expressed in liver, skin, and brain whereas type2 5α-reductase is characteristically expressed strongly in the prostate and at lower levels in skin and liver[2]. A so-called backdoor route to synthesis of DHT has also been described[3]. Circulating DHT levels are ~10% of the blood testosterone levels (1.7-2.1 nmol/L) mostly arising from the target tissues of DHT that express 5α-reductase. The daily DHT production is approximately 5-10% of the daily testosterone production[4].

Though the testis expresses type1 5α-reductase[5], it also makes a minor contribution to circulating levels of DHT. The prostate is regarded as the classical

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androgen target organ. To meet the androgen requirements for its development and secretory functions, the prostate has not only high levels of androgen receptors[6] but also a high activity of type2 5α-reductase, thus maximizing the effects of testosterone in the prostate. It appears that more than 95% of testosterone entering the prostate is converted to DHT[7]. Remarkably, the receptors for testosterone and DHT have an identical structure but the binding of DHT for the androgen receptor is about four times stronger, and the dissolution rate about five times slower. This explains the considerably higher bioactivity of DHT compared to testosterone itself. The conversion of testosterone to DHT is a biological amplification mechanism of testosterone action in those target organs where biological action of androgens needs to be maximized[8]. This mechanism is already operational prenatally and is a requirement for the formation of the prostate and male external genitalia, as evidenced by the syndrome of 5α-reductase deficiency characterized by genital malformations[9]. Beyond this stage of development, this conversion is still necessary, though less pivotal, for fully normal adult male development. In subjects with 5α-reductase deficiency, development and function of the prostate are subnormal, but, at puberty, fairly normal growth of the phallus, rugation and pigmentation of the scrotum and deepening of the voice are observed. Postpubertally, actions of testosterone may be more efficacious when testosterone is converted to DHT. However, reports on long-term use of the 5α-reductase type 2 inhibitor, finasteride, (in men generally over the age of 50 years for prostate problems) do not provide strong indications that this conversion to DHT is still vital. Finasteride treatment reduces circulating DHT by 60%[10], with less than 5% of patients complaining of decreased libido, impotence, and decreased volume of the ejaculate[11,12]. Another study showed that finasteride does not block the effects of testosterone on muscle and bone in adulthood[13]. Similar effects have been observed with another 5α-reductase type1 and 2 inhibitor, dutasteride[14]. No effects on lipids and erythropoiesis were observed but effects on sperm concentrations and motility have been reported[15]. Therefore, it seems that limitation of the reduction of testosterone to DHT produces no major adverse effects in adulthood, with the possible exception of properties of spermatogenesis.

Estrogens

Similar to DHT, estrogens in men are largely a product of peripheral aromatization of androgens. In men, testosterone (both endogenous and exogenous) and adrenal androgens (androstenedione, dehydroepiandrosterone), serve as precursors for chemical conversion to estrone (E_1) and estradiol (E_2) via the enzyme aromatase. The testis itself produces approximately 20% of the total E_2 and approximately 20% of the total amount of E_1 is produced by the adrenal from androstenedione[16].

The blood production rate of E_2 is about 30-40 μg/24 h, amounting to a secretion rate by the Leydig cells of $\pm$ 5-10 μg/day. Peripheral conversion of plasma testosterone accounts for about 20 μg with 10-15 μg coming from peripheral conversion of androstenedione[17]. E_2 is formed in peripheral tissues in quantities that may be much higher because part of the peripherally formed E_2 is further metabolized *in situ* (to E_1, estriol (E_3) or 2-hydroxy-estradiol) and, therefore, does not enter the peripheral circulation.

Although adipose tissue is the main source of estrogens in men, the brain, muscles, skin, liver, bone, and mammary tissue can also synthesize estrogens from precursors. In young men, the circulating E_2 levels are about 50 $\pm$ 15 pmol/L, much the same as those in the early follicular phase in women. Studies suggest that while plasma estrogen levels remain relatively constant with aging in men thereby resulting in an increased estrogen/androgen ratio, plasma testosterone levels show an age related decline[17-19].

The relatively stable levels of plasma E_2 in old age is explained by the very common relative increase in fat mass with aging and an increase in aromatase activity with aging. The clinical observation of the occurrence of gynecomastia in aging men is related to the increased estrogen/androgen ratio.

Often described as 'female hormones', estrogens show unexpected but significant effects on the male body[20]. It is becoming increasingly clear that estrogens have an important effect on the final phases of skeletal maturation and bone mineralization in puberty. In addition, some studies in aging men show that estrogen levels have a higher correlation with bone mineral density (BMD) than androgen levels[21]. Age related decreases of E_2, particularly when levels fall below 40 pmol/L, may be a major cause of bone loss in elderly men[22,23]. Although estradiol is required for the attainment of maximal peak bone mass in both sexes, the additional action of testosterone on stimulating periosteal apposition accounts for the larger size and thicker cortices of the adult male skeleton.

Severely impaired estrogen action in men leads to dyslipidemia and to impaired flow-dependent vasodilatation in peripheral arteries in response to an ischemic stimulus probably resulting from endothelial dysfunction[24]. Evidence suggests that the effects of estrogen on the vascular system are not exclusively mediated through the classical estrogen receptor and some actions are non-genomic[25]. Estrogen effects on the brain are also increasingly recognized[26]. Estrogens exert effects on cognitive function, co-ordination of movement, pain and affective state. In view of the effects of estrogen on many important organ systems in the (aging) male, further research into the role of estrogens is necessary. This may also be significant for the potentially negative effect of estrogens on prostate disease in old age (which will be addressed later). In summary, estrogens fulfill essential biological functions in men.

Prenatal Sexual Differentiation

The gender indifferent fetus undergoes sexually differentiation in stages, becoming identifiably male or female with regard to not only the external genitalia, but also the gonads and the genital tract. Each step in this process takes place within a well-defined window of time. The genetic information for the differentiation of the primitive undifferentiated gonad into a testis or an ovary is derived from the genetic sex evident in the chromosomal configuration.

The next step in the sexual differentiation process is the development of the internal and external genitalia, which will follow either a male developmental pattern in the presence of specific testicular hormones or that of a female in their absence. It is usually in the 6th week of embryonic life that the sexual difference in the gonads can be first observed. It is now more than 50 years since medical science first recognized the importance of the Y chromosome for the development of the testes, regardless of the number of X chromosomes present[27]. The main determinant appears to be the testis-determining factor (TDF), located on the Y chromosome. The molecular mechanisms steering the undifferentiated gonad towards a testis are not very well documented.

Testicular differentiation starts in human fetuses between 43-50 days of prenatal development. Leydig cells start to appear in the interstitial tissue after approximately 56 days. By then testicular cords have formed, and the Leydig cells soon start to produce testosterone. The presence of testosterone is pivotal for the further development of Wolffian ducts and the masculinization of external genitalia. Differentiation of fetal Leydig and early testosterone secretion depends on placental human chorionic gonadotropin in the first and second trimesters of fetal life and on the fetus's own pituitary luteinizing hormone of thereafter. Leydig cell numbers peak at mid-gestation and then slightly decrease. Testosterone production by the human fetal testis, while starting at approximately 60-65 days of prenatal development, reaches a maximum between 96-122 days and subsequently declines sharply. Postnatally, Leydig cells regress until puberty[28]. Sertoli cells originate from the primary sex cords after 42-43 days of prenatal life[29]. Sertoli cells express anti-Müllerian hormone (AMH) and account for the regression of the Müllerian ducts in the male fetus. The sexual differentiation of the fetus is a fine-tuned process requiring the presence of androgens in the right quantities within a narrow time window. There is no backtracking in sexual differentiation.

The internal reproductive tract is similar in male and female fetuses up to 56 days of prenatal development, and consists of a pair of two unipotential ducts, the Wolffian and Müllerian ducts. In the case of male differentiation of the internal genital tract, the Müllerian ducts regress upon exposure to the testicular product AMH. The differentiation of the Wolffian duct into male accessory organs requires the presence of androgens[30].

The upper part of the Wolffian duct differentiates into the epididymis. The more caudal part of the Wolffian duct develops a layer of smooth muscle to become the vas deferens.

Up to approximately 72-74 days, the urogenital sinus and external genitalia are not differentiated. Male development of the external genitalia starts by 72 days of prenatal development. Its first sign is the lengthening of the ano-genital distance[31]. The next step is the fusion of the labioscrotal folds to form the epithelial seam[32], inducing the closure of the primary urethral groove. This is followed by the extension of the urethral plate in the roof of the primary urethral groove to the tip of the penis. The development of the urethra is completed after approximately 98 days. A puzzling finding is that, up to that stage, in spite of large differences in circulating testosterone, there is no appreciable difference in size between the male penis and the female clitoris. Penile growth takes place in the third trimester of prenatal life, remarkably enough, when male testosterone levels are declining.

In the third trimester, fetal testosterone production depends on the fetus's own pituitary secretion of gonadotropins. Microphallus is a classical sign of congenital gonadotropin deficiency.

The paradigm of sexual differentiation of the internal/external genitalia is still in agreement with the classical experiments of Jost[33]. An embryo, regardless of its genetic sex, develops along female lines provided it is not exposed to testicular secretions. The development of Wolffian ducts depends on the presence of testosterone, normally produced by Leydig cells or by the adrenal gland in the case of overproduction of androgens on the basis of enzyme deficiencies shifting cortisol production to androgen production. Müllerian ducts regress under the influence of AMH produced by fetal Sertoli cells, acting through the AMH receptor. The urogenital sinus and external genitalia are virilized by androgens. In this case, it seems that a strong androgenic stimulus is required since this process depends on dihydrotestosterone, resulting from the reduction of testosterone by the enzyme 5α-reductase. Though testosterone and dihydrotestosterone act through the same androgen receptor, the biopotency of dihydrotestosterone is 4-7 times higher than of testosterone.

Disorders of Sexual Differentiation

Several clinical syndromes testify to the role of androgens in prenatal sexual differentiation. These syndromes represent a lack of androgens or androgen action prenatally in male fetuses or an excess of androgens in female fetuses.

Complete androgen insensitivity

Children afflicted with the androgen insensitivity syndrome (AIS) have a 46, XY karyotype and testes as gonads. An abbreviated blind vaginal pouch is present, but no uterus or fallopian tubes[34]. Because the external genitalia have a normal female appearance, the disorder of these patients is often unnoticed at birth. It is not rare that the testis is found in an inguinal hernia and its surgical repair may reveal the presence of a testis and may lead to the diagnosis of the condition. When the testis starts to produce hormones in puberty, part of the produced testosterone will be converted to estradiol and will have feminizing effects. By nature of the defect of this condition, there is no biological effect of testosterone itself. Where complete AIS occur, sex assignment and rearing are nearly always female. The differentiation of gender identity/role is feminine[35-44].

Another theoretically important aspect of this condition is the high circulating levels of estradiol, derived from their elevated levels of testosterone production (to which these subjects are insensitive). These levels of estradiol are sufficient to induce breast formation and a female fat distribution at puberty.

5α-reductase deficiency and 17β-hydroxysteroid dehydrogenase 3 deficiency

5α-dihydrotestosterone (DHT), the most potent natural androgen, is formed exclusively through 5α-reduction of T by the enzyme 5α-reductase[2,45]. Affected people are born with labioscrotal folds and a clitoridean penis. At puberty, they become moderately virilized or remain eunuchoid with enlargement of the clitoridean penis. No breast development is seen.

17β-hydroxysteroid dehydrogenase 3 is involved in the terminal step in the synthesis of testosterone in the Leydig cell and of estradiol in the ovarian granulosa cell[46]. Subjects with an XY chromosomal pattern and testes affected with 17β-hydroxysteroid dehydrogenase 3 deficiency have more or less female external genitalia due to lack of an effective androgenic stimulus at the time of the differentiation of the external genitalia[46-48]. Such children are usually assigned to the female sex at birth and raised as girls[48]. A particular feature of this disorder is that the testosterone production increases with time (due to a higher LH drive and alternative pathways of testosterone production), and subjects may have near-normal testosterone levels at the time of puberty inducing substantial virilization. Children with 5α-reductase and 17β-hydroxysteroid dehydrogenase 3 deficiencies have genital ambiguity on the basis of deficient prenatal androgen exposure. It is the nature of these endocrine defects that biological activity of androgens at the time of puberty becomes stronger compared to prenatal life.

Congenital adrenal (virilizing) hyperplasia

Congenital adrenal hyperplasia (CAH) is a disorder occurring in both sexes resulting in an undue/untimely exposure to androgens[49-51]. Congenital adrenal hyperplasia (CAH) is a family of inborn errors of steroidogenesis, each disorder characterized by a specific enzyme deficiency that impairs cortisol production by the adrenal cortex. The deficient production of cortisol leads to a diminished negative feedback signal to the hypothalamo-pituitary unit to produce ACTH. This, in turn leads to a higher output of ACTH and subsequently to an overproduction of

other adrenal hormones under control of ACTH, such as the adrenal androgens. In the severe or classical form of CAH, adrenal androgen overproduction causes prenatal virilization in females and continued masculinization, postnatally, in both sexes.

In utero, virilization occurs in genetic females (46, XX). Excessive adrenal androgens masculinize the external genitalia (female pseudohermaphroditism), so that an affected newborn female may present with varying degrees of virilization including a urogenital sinus, scrotalization of the labia majora, labial fusion, or clitoromegaly. In rare cases, the masculinization is so profound that the urethra is penile. As females with CAH have a 46, XX karyotype and do not have testes, anti-Müllerian hormone is not secreted, and Müllerian ducts develop normally into a uterus and fallopian tubes. Thus, females with 21-hydroxylase deficiency have the potential for fertility. The salient features of classical CAH are prenatal virilization and progressive postnatal masculinization with accelerated growth and advanced bone ages. As differentiation of the external genitalia is not affected in newborn males, only hyperpigmentation may suggest increased ACTH secretion and cortisol deficiency. Signs of hyperandrogenism in children affected with CAH include early onset of facial, axillary, and pubic hair, adult body odor, and rapid somatic growth. This early growth spurt is accompanied by premature epiphyseal maturation and closure, resulting in a final height that is below that expected from parental heights.

Sexual Differentiation of the Brain

From the beginning of the last century, it has become apparent from studies on rats, mice and other lower mammals, that their sexual differentiation is not completed with the differentiation of the external genitalia into either male or female, the traditional criterion to label them as male or female. In addition, the brain undergoes a sexual differentiation, which can be demonstrated neuroanatomically. It expresses itself in sex-dimorphic sexual behavior (such as copulatory positions) but also in sex-dimorphic non-sexual behavior such as aggression, defense of territory, and caring for the young. The paradigm of this step in the sexual differentiation process of lower mammals is similar to the previous ones: in the presence of androgens (normally produced by the testis of the male fetus) a male brain differentiation occurs, while in the absence of androgens (as is the normal situation in females) a female brain differentiation follows. In brief: the hormonal mechanisms governing the sexual differentiation of the genitalia also determine the sexual programming of the brain. This process has been termed the organization, the "wiring" of the brain to prepare it for future sexual/reproductive behavior and non-sexual behavior in agreement with the gonadal/genital status. This programming, laid down during the fetal period or shortly thereafter in lower mammals, becomes activated by the hormones at puberty.

Experimentally, it has been possible to transform this step in sexual differentiation due to the fact that it is androgen-dependent in lower mammals. It appeared possible to induce a male copulatory pattern in laboratory animals with a female chromosomal/gonadal/genital differentiation and, vice versa to induce a female copulatory pattern in a male rat by depriving it from its androgenic stimulus precisely at the window of time of the sexual differentiation of the brain.

Sexual Dimorphism of the Human Brain

The human brain shows a degree of sexual dimorphism but it is not clear how far this dimorphism has been induced by prenatal/perinatal/postnatal differences in concentrations of testosterone. Obviously, experimental manipulation of testosterone levels is ethically inadmissible. The brain structures of subjects whose prenatal/perinatal/postnatal endocrine milieu has been atypical for the male or female sex have not been studied. In experimental animals, morphological differences in brain structures are most pronounced in hypothalamic structures. Several studies have addressed sex differences in hypothalamic structures in the human usually with the aim of relating these sex differences to gender identity and/or sexual orientation. The volumes of four cell groups in this region (interstitial nuclei of the anterior hypothalamus (INAH) 1, 2, 3 and 4) have been studied. No sex differences were found between the groups in the volumes of INAH 1, 2, or 4. As Le Vay has shown[52], INAH 3 is more than double the size in heterosexual men as in women. Similarly, it is more than twice as large in heterosexual as in homosexual men, which suggests that in the case of homosexuals the sexual differentiation of the hypothalamus is partly in a female direction[52]. Later studies however have been unable to confirm this finding[53].

Swaab et al identified a cluster of cells they called sexually dimorphic nucleus (SDN). These are in the preoptic area of the human hypothalamus and contain approximately double the number of cells in young adult men as in women[54]. The magnitude of the SDN difference depends on age. At birth, the SDN

contains only some 20% of the cells found 2 to 4 years later. The cell numbers rapidly increase in boys and girls at the same rate until 2 to 4 years of age. After that, a decrease in cell numbers takes place in girls, but not in boys. This causes the sexual differentiation of the SDN occurring in postnatal life, when there are no significant differences in secretions of sex steroids between girls and boys. Swaab et al did not find that the SDN has different properties in homosexual men compared to heterosexual men[55]. Another morphological difference in homosexual men compared to heterosexuals was the midsagittal plane of the anterior commissure. In homosexual men this was 18% larger than in heterosexual women and 34% larger than in heterosexual men, pre-supposing underlying differences in cognitive function and cerebral lateralization among homosexual men, heterosexual men, and heterosexual women[56] although not confirmed in a later replication study[57].

The suprachiasmatic nucleus (SCN) is the hypothalamic biological clock. Environmental light serves as the main "Zeitgeber" to entrain the clock, which receives its input via the retinohypothalamic tract. In turn, the SCN and its projections communicate through synaptic pathways with various effector systems. These areas are known to be involved in the autonomic regulation of body temperature, blood pressure, sleep, arousal, energy metabolism, stress (HPA-axis), thyroid hormone (HPT-axis) and growth hormone regulation and in the regulation of the reproductive gonadal (HPG-) axis, via the cyclic release of gonadotropin-releasing- or luteinizing-hormone-releasing hormone[58]. Analysis in the human hypothalamus showing that SCN in homosexual men is 1.7 times larger than that of a reference group of male subjects. It contains 2.1 times as many cells[59]. During development, the SCN volume and cell count reaches peak values around 13-16 months after birth. At this age the SCN contains about the same number of cells as the SCN of adult male homosexuals, whereas in the reference group of male subjects the cell numbers subsequently decline to the adult value, which is about 35% of the peak value.

Puberty

Clinical features

Clinically, the first signs of puberty are the secondary sex characteristics, such as pubic/axillary hair. For clinical assessment of the progression of puberty, a rating has been developed into five stages, the so-called Tanner's stages[60]. Pubertal development usually begins with enlargement of the testis, which is an expression of the development of seminiferous tubules. This process largely depends on the action of follicle stimulating hormone. The next step in development is growth of pubic hair and of the penis, which usually coincide since they are both expressions of increases in circulating androgens. The penis grows not only in length but also in girth. For clinical assessment, testicular volume can be estimated by comparison with ellipsoids of known volume (Prader's orchidometer), typically > 4 ml. Scrotum, testis, and penis grow further with development of the glans and further darkening of the scrotal skin. Pubic hair in boys usually appears initially on the scrotum and at the base of the penis and develops to the adult stage progressively, with a final distribution as an upright triangle. Facial hair appears initially on the corners of the upper lip and the upper cheeks and spreads to the rest of the face and chin. Furthermore, during puberty, the vocal cords lengthen and account for the deeper voices of men compared to women. In both sexes, the appearance of acne and seborrhea of the scalp are due to the increase in adrenal and gonadal steroids.

In boys, normal timing of puberty is after 9 and before 13.5 years of age[61]. In most boys, the pubertal growth spurt occurs during Tanner stages 3 to 4, and is completed by stage 5 in more than 95% of them. In males, growth velocity can be as low as 3.5 cm/year before puberty and increases from an average 5 cm/year to 7 cm/year during the first year of puberty, and is approximately 9 cm/year in the years thereafter.

Pubertal growth is dependent not only on testosterone[62]. Growth hormone (GH), insulin, insulin-like growth factor (IGF)-I, increase at puberty as well. The combination is responsible for most of the metabolic changes observed during puberty and for the growth spurt.

The prenatal process of sexual differentiation occurs within a well-defined window of time. Testosterone action in puberty, however, takes a different course, not limited to such a specific time period. In case of hypogonadism, pubertal development can be induced much later in life than the normal pubertal age. The specific bodily changes of puberty will be detailed in the following sections.

Skin

When hairs have reached the stage that they project outside of the skin, they are keratinized tubes of dead epithelial cells. The characteristics of hair vary

between different body parts, scalp hair, pubic hair, and fine hairs on the dorsal parts of hands. Each hair is produced by a hair follicle, via a process of epithelial cell division in the bulb, with an upward move of keratinocytes. By the time the hair reaches the surface of the skin, the cells are fully keratinized and dead[63].

Hair of eyelashes, eyebrows, and on the scalp is already present in childhood and obviously androgen-independent. Androgens are responsible for hair growth in the pubic area, axilla, face and the other parts of the body. Paradoxically, androgens may also inhibit hair growth on the scalp and induce baldness[63].

One of the first signs of puberty in both sexes is the gradual appearance of a few larger and more pigmented hairs, firstly in the pubic area and later in the axilla. Over time, longer and darker hairs appear and the area spreads. In boys, hair appears gradually on the face starting above the mouth and on the central chin, eventually spreading over the lower part of the face and parts of the neck gradually developing to adult beard growth[64]. The adult man's pubic hair distribution differs from that of women, extending in a diamond shape up to the navel. Subsequently, hairs on the chest, sometimes the back, arms, and legs, and buttocks develop. In all areas, the development is gradual, often taking many years. Beard growth may continue until the mid-thirties.

Men with 5α-reductase deficiency exhibit female hair patterns with very limited beard growth demonstrating the role of DHT in sexual hair development. Also the development of hair on other parts of the body may be slow, progressing over more than a decade.

The amount of hair is very variable and differs both between families within one race and between races, with Caucasians generally exhibiting more hair than Blacks and Asians. The differences have been related to hormonal differences in androgen physiology. In two racial subgroups in Namibia/Africa hair growth could be related to levels of DHT and the ratio of DHT and testosterone and of testosterone and estradiol[65,66]. Lookingbill et al found higher levels of 5 alpha reduced androgens and their metabolites in Caucasian versus Chinese men, which was related to racial differences in body hair growth[66].

The action of testosterone on the skin is induction of male-type hair growth and stimulation of sebum production in the pilosebaceous unit, which is comprised of the hair follicle and sebaceous gland. Pubertal increase in testosterone and administration of testosterone may lead to acne. Further male pattern baldness may occur over time[67]. DHT mediates the actions of testosterone on the skin. Initially it was believed that the predominant form of 5α-reductase was type 1, but recent studies show that 5α-reductase type 2 is present in the inner layer of the outer root sheath of hair and in the more proximal regions of the hair follicle[68].

In genetically predisposed men, androgenetic alopecia is induced by 5 alpha reduced androgens. This explains why finasteride, a selective inhibitor of 5α-reductase type 2, can reduce hair loss in men with male pattern baldness[69]. In sebaceous glands, the dominant 5α-reductase is type 1 but finasteride was also able to reduce sebum production[70]. Type 1 5α-reductase inhibitor is a potential therapeutic agent in the prevention/treatment of acne; a type 1 and 2 5α-reductase inhibitor may prevent or reduce male pattern baldness. Alternatively, androgens with selective properties, which cannot be 5α-reduced, are likely not to lead to acne and androgenetic alopecia.

Androgens and Hematopoiesis

Young hypogonadal men have lower red blood cell counts and hematocrits than age-matched controls. These values increase when androgens are administered to hypogonadal men. Older men in good health whose plasma testosterone levels fall with age tend to have similar or slightly lower hematocrit values than young adult men[71]. Androgens stimulate erythropoiesis[72] and in most studies of testosterone administration a 2-5% increase of the hematocrit over baseline has been observed, with 6-25% of subjects developing erythrocytosis with hematocrits over 50%[73]. Hematocrit values over 52% (or according to others over 54%) are regarded as a risk for thrombosis[74].

Penis

The penis increases in puberty in length and girth. The penis, measured in the stretched flaccid state, increases from an average length of 6.2 cm in prepuberty to 12.4 ± 2.7 cm in white adults and to 14.6 cm in black and 10.6 cm in Asian men[75]. Postnatally, there is a surge of plasma testosterone levels associated with an increase in the length of the penis[76]. Premature prepubertal exposure to androgens leads to growth of the penis. If diagnosed and treated, this growth will stop and resume during normal puberty. Eventual length of the penis is not larger than in normal controls suggesting that regardless of the time of exposure to

androgens there is a predetermined growth potential of the penis[77].

The powerful effects that testosterone exerts on a man's sexual functioning are impressively demonstrated by the physical and mental changes associated with puberty. In recent decades, the effects of testosterone on a man's sexual functioning have become better understood. It appeared from earlier studies that particularly sexual interest is stimulated by androgens. The direct effects of androgens on erectile function, as they emerged from these studies, were regarded as rather limited and secondary to effects on libido[78,79]. It appeared also that effects on libido could be maintained with plasma levels in the low range of normal[80].

The profound effects that testosterone has on the penile tissues involved with erection has become more evident in recent studies. It has also become apparent that testosterone deficiency affects the erectile mechanisms at the penile cellular level and impairs the anatomical, ultrastructural, biological, and physiological/functional substrate. This includes neurotransmission[81] of erectile capacity and is reversible upon androgen replacement[82].

Although animal experimentation is the source of much of these data, there are studies showing its relevance to human beings. The human corpus cavernosum contains androgen receptors[83]. Aversa et al showed how the administration of androgen improves the arterial inflow into the penis[84]. Studies by Foresta et al show that nocturnal penile tumescence, arterial carvernosus inflow and visually stimulated erection are normalized when testosterone is administered, restoring plasma testosterone to normal[85].

It is an established fact that nitric oxide (NO), which is a compound that is involved in penile erectile mechanism, is regulated by androgens[86,87]. Several studies show that androgen plays a critical role in restoring and maintaining the penile trabecular smooth muscle structure and function[88-90] as well as regulating the cell apoptosis[91]. Extracellular matrix and the fibroelastic properties, in biology and microanatomy, is also regulated by androgen. Even the "healthy" structure of the tunica albuginea is androgen dependent[92].

Singh et al had found that mesenchymal pluripotent cells follow a myogenic lineage with normal testosterone levels or, alternatively, an adipogenic lineage with low levels of testosterone[93]. Traish et al could demonstrate a similar mechanism in the rabbit if testosterone levels are low, with an accumulation of fat containing cells in the subtunical region of the corpus cavernosum thus impairing the veno-occlusive function of the corpus carvernosum[94]. The present study confirmed also that androgen deprivation leads to loss of trabecular smooth muscle and increase of connective tissue fibers. So, similar to bone and muscle, adult levels of testosterone are required to maintain anatomical and functional integrity of the penis.

Sex Differences in Fat Distribution

Adult men and women differ in their fat distribution; the regional distribution of body fat is a characteristic of masculinity and femininity. In pre-menopausal women, a larger proportion of fat is stored in peripheral fat depots such as breasts, hips, and thighs. Men tend to deposit excess fat in the abdominal regions (both subcutaneous and intra-abdominal or visceral fat depots) and generally have a larger visceral fat depot than (premenopausal) women. As regional localization of body fat is considered a secondary sex characteristic, it is likely that sex steroids are involved in the male and female patterns of fat deposition[95]. This view is strengthened by the observation that variations in sex steroid levels in different phases of (reproductive) life parallel regional differences in fat storage and fat mobilization. Until puberty, boys and girls do not differ very much in the amount of body fat and its regional distribution, although girls may have somewhat more body fat than boys. From puberty onward, differences become manifest. The ovarian production of estrogens and progesterone induce an increase in total body fat as well as selective fat deposition in the breast and gluteo-femoral region. Pubertal boys show a strong increase in fat free mass while the amount of total body fat does not change very much. Adolescent boys lose subcutaneous fat but accumulate fat in the abdominal region, which, in most boys, is not very visible in that stage of development but clearly demonstrable with imaging techniques[96]. The sex steroid induced regional distribution is not an all-or-none mechanism; it is a preferential accumulation of excess fat. Obese men and women still show their sex specific fat accumulation but store their fat also in the 'fat depots of the other sex'. Not only the fat distributions differ between the sexes from puberty onward, but also the dynamics of fat cell size and fat metabolism are different. The amount of fat in a particular depot is dependent on the number and size of the fat cells. Fat cells in the

gluteal and femoral regions are larger than in the abdominal region. The activity of lipoprotein lipase, the enzyme response for accumulation of triglycerides in the fat cell, is higher in the gluteo-femoral region than in the abdominal area. Conversely, lipolysis is regulated by hormone sensitive lipase, which in turn is regulated by several hormones and by the sympathetic nervous system. It is not an unreasonable speculation that the sex steroid dependent fat distribution serves (or maybe has better served!) the different roles of men and women in reproduction. The visceral fat depot has a high metabolic activity with a high turnover of triglycerides that releases rather acutely large amounts of free fatty acids (FFA). The visceral fat depot drains on the portal vein, which, in turn, drains its blood in the liver providing FFA as fuel for quick and high degrees of physical activity. Therefore, the reserve energy supplies of men can be mobilized fast and are readily available to fuel metabolism. Women's fat stores lend themselves less to quick mobilization. Pregnancy and lactation are situations that release energy from female stores at the buttocks and thighs but do so at a slow pace. Again, these sex differences are not absolute but a matter of predominance.

Elevated androgen levels in females increase the amount of visceral fat in women, those with the polycystic ovarian syndrome being the classical example[97]. In the medical literature, this is often presented as a paradox in the sense that high levels of androgens in women and low levels of androgens in men are associated with visceral obesity. The paradox is partially semantic: high testosterone levels in women (for instance 3-5 nmol/l translate to (very) low androgens in men. So the use of the term high and low testosterone must be related to the sex. A further element is the relation to age. Women with the polycystic ovarian syndrome are relatively young (of reproductive age) when they come to the attention of the medical profession while the relationship between visceral obesity and low androgen levels in men is typically an epidemiological finding in elderly men. Apparently, similar to the situation in androgen naïve teenage boys, androgens in women with polycystic ovarian syndrome are capable of visceral fat accumulation when these women are exposed to androgens post-pubertally, when their polycystic ovaries start to produce androgens.

In postmenopausal women there is a larger degree of (male type) upper body fat accumulation in comparison to the former gluteofemoral fat storage. Following menopause, androgen levels drop considerably in women. So, obviously premenopausal estrogen/progesterone levels are required to maintain a premenopausal female type of fat distribution also evidenced by the fact that postmenopausal hormone replacement (partially) restores the premenopausal fat distribution[98].

Aging

Several studies document that androgen levels decline with aging[99]. Longitudinal studies have documented a statistical decline of plasma testosterone by approximately 30% in healthy men between the ages of 25-75 years. Since plasma levels of sex hormone-binding globulin (SHBG) increase with aging, plasma testosterone not bound to SHBG decreases even more, by about 50%, over that period. Studies in twins have shown that genetic factors account for 63% of the variability of plasma testosterone levels, and for 30% of the variability of SHBG levels[100]. In addition, systemic diseases, increasing with age, are a cause of declining plasma levels of testosterone[101].

Effects on Body Composition

Body composition is seriously affected by the aging process[99,102-104]. Aging is almost universally accompanied by an increase in abdominal fat mass and a decrease of muscle mass. Androgens have a substantial impact on muscle mass and on fat distribution, and, therefore, the relationship between these signs of aging and T levels has been assessed.

Increase in fat mass

Several studies have convincingly documented an inverse correlation between abdominal fat mass and free T levels and it appears that this is independent of age. This finding has clinical relevance: the amount of visceral fat is highly significantly associated with an increased risk of cardiovascular disease, impaired glucose tolerance, and non-insulin dependent diabetes mellitus (the dysmetabolic syndrome,or just metabolic syndrome)[99,103,105-109]. Whether the abdominal, and more specifically visceral obesity is the consequence of the low T levels or vice versa, is not yet clear. It is clear, however, that visceral obesity leads to a decrease of T levels, mainly via a decrease in SHBG levels.

Decline in muscle mass and strength

There is an impressive age associated decline in muscle mass (12 kg between age 20 and 70 yrs)[110-113]. This loss of muscle mass is a major

contributor to the age-associated decline in muscle strength and fatigue. Maximal muscle strength shows a correlation with muscle mass, independently of age. This is again related to the occurrence of falls, fractures, and the consequent limitations of independent living. The correlation between testosterone levels and muscle mass appears stronger than the correlation with muscle strength.

Effects on Bone Mineral Density (BMD)

With aging, there is an exponential increase in bone fracture rate[99,102,114], which carries a clear association with the age-related decrease of BMD. In view of the significance of sex steroids in the maintenance of BMD at all ages, the question of whether the partial androgen deficiency in aging males plays an important role in the decrease of BMD is pertinent. A pivotal role of androgens in the decrease of BMD has, however, been difficult to establish. Not all scientific findings agree. Indeed, some studies find a significant, though weak, correlation between androgen levels and bone mineral density at some but not all bone sites. Others are unable to establish a correlation. There are some recent large-scale studies of several hundred elderly men that demonstrate that bone density in the radius, spine, and hip are correlated with levels of bioavailable testosterone. Interestingly, the correlation with levels of bioavailable estradiol was much more prominent, probably pointing to the significance of estrogens in men, also in old age.

Conclusion

In addition to the well-known effects of testosterone during prenatal life and pubertal development, it has become apparent that male body morphology is not definitive past these stages of development. A normal plasma testosterone is required for its maintenance. This applies not only to male hair distribution, bone, and muscle mass but also to the integrity of penile erectile mechanisms.

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เทสโทสเตอโรนในเพศชายมีความจำเป็นอย่างยิ่งยวดในช่วงก่อนคลอดจนกระทั่งถึงวัยชรา

วิสุทธิ์ ประดิษฐ์อาชีพ, อุดมศรี โชว์พิทธพรชัย

ทารกช่วงก่อนคลอดมีศักยภาพที่จะเจริญผ่านหลายขั้นตอนไปเป็นเพศชายหรือเพศหญิง ซึ่งแต่ละขั้นตอนนั้นมีช่วงเวลาเพียงสั้น ๆ ในช่วงก่อนคลอดฮอร์โมนเทสโทสเตอโรนมีบทบาทสำคัญอย่างมาก ที่กำหนดให้ทารกมีการพัฒนาเจริญไปเป็นเพศชาย ส่วนในช่วงวัยรุ่นจนถึงวัยชรานั้น ฮอร์โมนเทสโทสเตอโรนในระดับที่เหมาะสมมีความจำเป็นต่อการเสริมสร้างกล้ามเนื้อและกระดูก การเจริญของอวัยวะสืบพันธุ์และต่อมลูกหมาก การเจริญของรูปแบบของผมและขน และยังจำเป็นต่อการกระจายตัวของไขมันในเพศชาย โดยทั่วไปเพศชายจะมีความสูงเฉลี่ยมากกว่าเพศหญิง 10-15 เซนติเมตร การเจริญพัฒนาในช่วงนี้จะเกิดความผิดปกติได้ถ้าระดับของฮอร์โมนเพศชายมีไม่เพียงพอ ในปัจจุบันมีความสนใจศึกษาวิจัยถึงความสัมพันธ์ระหว่างการลดลงของระดับฮอร์โมนเทสโทสเตอโรนเมื่ออายุมากขึ้น กับการเปลี่ยนแปลงของรูปร่างเมื่อวัยสูงขึ้น (เช่น การลดลงของมวลกระดูกและกล้ามเนื้อ อัตราส่วนที่เพิ่มขึ้นระหว่างไขมันกับมวลกล้ามเนื้อของร่างกาย) ดังนั้นจะเห็นได้ว่า ฮอร์โมนเทสโทสเตอโรนมีความจำเป็นอย่างยิ่งยวดตลอดชีวิตของเพศชาย