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Hypogonadism in Male Sexual Dysfunction

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Abstract

Normal testosterone level is influencing all the steps of the male psychosexual development: intrauterine neonatal and final psychosexual development.. At pubertal stage, the quality of testosterone secretion is conditioning the development of the mature male phenotype. In adult life, eugonadism sustains desire, arousal, determines spontaneous erections, facilitates stimulated erection, influencing the response rate to medication. Moreover, eugonadism sustain daydreaming and phantasies, both needed for a normal sexual life. The pathogenic mechanism of all these actions is presented. Talking about hypogonadism means not only the classical types of hypogonadism: due to classical testicular disease of central, hypothalamic and hypophysis disease, but also the partial testosterone deficiency induces by aging (late onset hypogonadism), weight increase (up to 30% of males with metabolic syndrome and 50% of males with diabetes) or secondary hypogonadism described in chronic use of steroids or after long exposure to stress, especially in young males. All these types of hypogonadism, that affect young, middle aged or old males will be presented separately. A therapeutic approach that is individualized for each type of hypogonadism, should consider positive and possible negative effects and all alternatives will be presented: life style changes, sustained weight loss, increase exercise, supplemental therapy, pro fertility treatment.

Keywords: male sexual function, hypogonadism, late-onset hypogonadism, testosterone, supplemental treatment

1. Introduction

Testosterone is an essential hormone that influences part of sexual function in males.

Androgens directly influence the formation of male genital structures as an active process, start in the intrauterine life, sustain the phenotypic complete adult male pattern during development in puberty, and maintain the male phenotype during the entire life. Also androgens, together with other sexual steroids, do regulate sexual behavior, testosterone being the principal determinant of the sex drive not only in males but also in females. Male sexual response involves the presence of erection, a phenomenon influenced/sustained and modulated by testosterone levels. In these cases, the response rate to treatment is also dependent on the intratesticular testosterone. Psychosexual development is also conditioned by testosterone presence during childhood and puberty. Testosterone deficiency, regardless of inherited diseases, iatrogenic causes, metabolic disease or acquired causes, will impair normal sexual life and will condition the response to hormonal and non-hormonal treatment. Testosterone deficiency should be considered not only in the classical hypogonadism cases, with central or peripheral forms of disease, but also in the more frequent cause of subclinical, late onset of disease that affects half of the diabetic population, 30% of the metabolic syndrome male population and some of the elderly male population.

2. Role of testosterone in sexual function in males

Normal sexuality in both male and women presumes a normal phenotypic structure, sexual identity development and sexual orientation. Especially in males, testosterone influences all aspects of normal sexual function. In order to develop a normal sexual response, we need complete, congruent or not, sexual structures, sexual development and psychosexual components.

2.1. Testosterone effects in male sexualization: organic aspects

After the fertilization of the egg, the chromosomal sex is formed. According to the karyotype [1], there are two ways of evolution:

The active way: In the presence of the sexual active chromosome Y, mainly the SRY gene, located on the short arm, favors the preprogrammed male gonadic development. The expression of SRY induces the organization of indifferent gonads to Sertoli cell differentiation [2], Antimüllerian hormone production (AMH) [3], and secondary to testosterone synthesis from the Leydig cells [4]. The androgen presence will generate the evolution of Wolff tract structure (paracrine effect on the homonymous site) masculinization of the external genitals (weeks 12–16) and involution of Müller tract structures. Notably, testosterone in order to be active at the external genital ridge has to be converted to 5 α -dihydrotestosterone. Also, the testicular descent from the abdominal cavity is a dihydrotestosterone-dependent phenomenon. Normal testosterone levels, normal enzymatic apparatus and also normal testosterone receptor activity are needed to obtain the physiological effects.

The passive way: Feminization appears only in the absence of active Y chromosome expressing SRY gene, when regardless of the karyotype (46XX, 46 XY, 45X, 45 XX/45 XY), their evolution

follows the free, automatic female gonad development, that only starts after the 3rd month of intra-gestational development [5]. In the absence of testosterone, there is an involution of the Wolff tract structures with a spontaneous, preprogrammed differentiation of Muller tract structures: fallopian tubes, uterus and superior one-third of the vagina. **Figure 1** summarizes the intrauterine changes in the genital area in both the sexes.

We can consider that the steroids have a major function in somatosexual development: organizational function—in the development phases, causing permanent changes in the body but also in the brain, and an activational function, active later in life, which will guide behavior.

The dimorphic brain changes are described by numerous studies. Testosterone is considered to be anxiolytic, anti-depressant and facilitates spatial abilities [6].

The postnatal somatosexual differentiation comprises small changes during early childhood. There are minimal somatic differences between sexes, steroid-independent: more female sex babies, boys are lesser matured compared to girls, growth increase sooner in girls than boys, with increased size of extremities, increased mandibula, flattening of the trunk with important changes in cognition [7].

The puberty period represents the major second transformation period, both in genital and in nongenital spheres [8]. Secondary to the hypothalamus-hypophysis axis disinhibition,

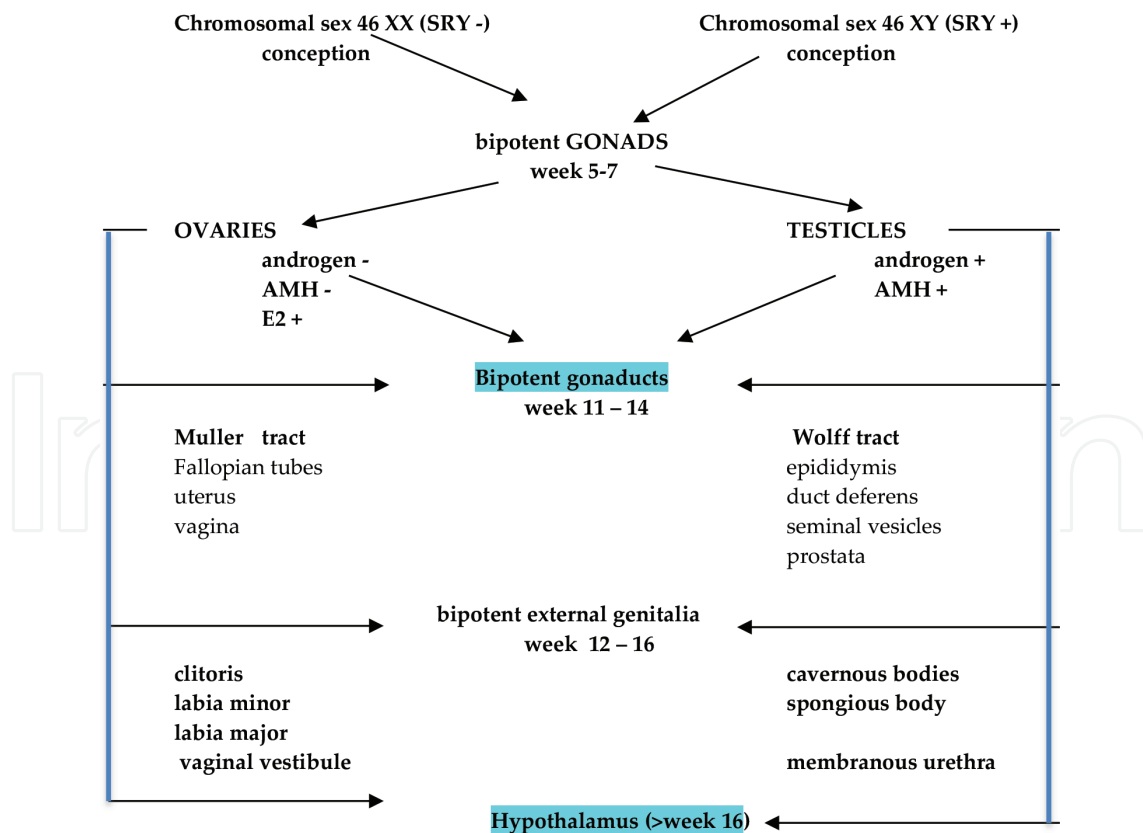


Figure 1. Scheme of the somatosexual differentiation in the intrauterine period.

between 8 and 13 years of age in females and 9–13.5 years of age in boys, the production of sexual steroids increases dramatically and significant bodily changes appear secondary to exposure to sexual steroids. The somatic changes are measurable by the Tanner stage evaluation of secondary sexual characters (breast and pubic hair development in girls, external genitals and pubic hair in boys). In males, the following changes are described, all androgen dependent [9]: testosterone-dependent effects are increase in muscular mass, bone growth, growth of larynx and deepening of voice, inhibition of breast development, stimulation of spermatogenesis, whereas the dihydrotestosterone-dependent effects are phallic growth, development of pubic hair, and activity of sebaceous glands.

Table 1 summarizes the somatic changes observed in puberty, with the onset timing.

At the end of puberty, we have clear somatic differences between males and females, all sexual steroid-dependent [8, 9]. Notably, the full male pattern is present at the end of puberty, but the complete emotional evolution is not yet present. This is a high-risk period for sexual experiences.

During adulthood, eugonadism is important to maintain and sustain the previous organic changes. It has only a permissive role for maintaining normal sexual responses.

Regardless of diseases, aging is associated with physiological hormonal changes. There are several studies [10–12] suggesting that aging is one of the major factors involved in sexual

| Male gender | Mean age (years) |
|---------------------------------------|------------------|
| Increase penis length | 11–12 |
| Increase testes volume | |
| Acne | 12 |
| Prostate growth | 12.5 |
| Pubarche (P2) | 12–13 |
| Growth spurt | 12–13 |
| Sesamoid bone | 13 |
| Accelerate increase in penis diameter | 13–14 |
| Axillary hair (AH1) | 14–15 |
| Pubarche (P4) | 14.5 |
| Voice change | 14–15 |
| Facial hair | 14–15 |
| Pubarche (P5) | 15–16 |
| Complete spermatogenesis | 16 |
| Epiphyseal plate closure | >17 |

Table 1. Somatic changes in male puberty.

functional changes in males. There is physiological involution of all endocrine glands, with decreases in thyroid, adrenal and gonadal hormone production [12].

Many epidemiological studies describe a physiological decrease in total and free testosterone levels [13–15]. Many changes are described with important sexual symptoms, similar to the presence of overt hypogonadism, with important diseases linked to this testosterone deficiency: bone demineralization [16], increased cardiovascular risk [17], frailty [18], weight gain [19], dyslipidemia [20] and increased general mortality [21–23].

2.2. Testosterone role in male sexuality: psychosexual aspects

The psychosexual development is conditioned from the beginning in neonatal life.

Psychosexual differentiation refers to gender identity, respectively, self-identification as male or female, gender role, comprising different behavior in males and females, gender orientation, representing the choice of sexual partner, respectively cognitive differences [24]. Classically, gender identity was considered imprinted postnatally only by social attitudes, words, family dynamics, comparison of own body to peers, cultural differences, degree of exposure to nakedness [24], learning theory (gender identity is shaped by personal models and cultural influences, according to the interaction with parents), cognitive development theory (observation and imitation of behaviors appropriate for each gender), and biosocial interaction (society norms influencing subsequent behavior patterns in the childhood) [24].

Testosterone influences cell survival, anatomical connections and neurochemical activity, being responsible for brain differences in structure and function [25]. It is known that prenatal androgen exposure influences children's sex-typed play behavior [26]. Genetic diseases with abnormal sexual steroid hormones can be used in the evaluation of sexual steroid impact on sexual identity: exposure to androgenic progestins increases male-typical behavior [27], and exposure to antiandrogenic products will decrease female-typical behaviors [28, 29]. There is a correlation between testosterone levels in maternal blood and amniotic fluid and sex-type behavior in childhood [30, 31]. Also, the new explanation for the "toy theory" is that androgen exposure favors interest for space movements, by influencing the development of visual fields [32, 33].

There is clear evidence that testosterone and dihydrotestosterone exposure can influence gender identity [33, 34]. Androgens have a facilitating and not a determinant role in gender identity development [35].

During childhood, psychosexual development is mainly socially dependent and not steroid-dependent: starting at approximately 1 year of age, boys and girls are aware of gender differences at an age of 2–3 years of their own gender, at 3 years of the behavior that belongs to the gender role, and from age 5 they play with the same gender peers. Before the age of 6 "sexual—genital" behaviors are reported but have no conscious significance, being just a pleasure action. After the age of 6 years, these behaviors are stable due to the juvenile pause. The development is free of androgen influence, due to the gonadostat inhibition, that stays till the spontaneous disinhibition of gonadotropic-gonadal axis. Still indirect effects are seen.

Puberty is a period with important changes in psychosexual behavior. In early adolescence, exposure to increased testosterone levels in boys will induce increased aggression and social dominance [36], whereas premature estrogen exposure in girls will favor mood changes [37]. During puberty, steroid hormones-related changes in the frontal lobe are different in boys and girls, favoring phonological skills in women and special skills in boys [38].

The hormonal and physical changes that occur during puberty also contribute in indirect ways to differences between adolescent boys and adolescent girls. In girls, secondary sexual changes will induce social reactions from peers, parents, teachers, and friends. Adolescence is associated with changing social roles, and there is good reason to believe that gender socialization intensifies at that time of life [39, 40].

During adolescence typical sexual behaviors will appear: in early adolescence physical changes dominate, with insecurity, sexual curiosity and exploration. Auto stimulation is reactivated, typical sexual in this case, different from the unconscious stimulation in the early childhood period. Androgens are the most important hormones that induce sexual drive [41]. Monogamously focused relationships, growing maturity, and responsibility characterize middle adolescence, and late adolescence is the period of beginning of mature sexuality and accumulation of sexual skills.

The relationship between testosterone and sexual behavior is more complex in humans than in animals, where sexual receptivity of the female and sexual interest in males is steroid-dependent [42]. In humans, there is a complex interference between genetic, hormonal, cultural, social, moral, and environmental influences.

In adults, testosterone sustains secondary sexual characters that were previously formed during puberty and directly influences all levels of sexual behavior:

Sexual fantasies are linked to testosterone levels, with a bimodal relationship, testosterone favors phantasies, and phantasies affect the testosterone levels [43]. Low testosterone levels in adult males change sexual interest even at the level of sexual fantasies [44, 45]. Even day-dreaming is modulated by normal testosterone levels [45, 46].

Autostimulation and sexual actions are active behaviors, dependent on testosterone levels. The best evaluation of testosterone's involvement in these behaviors is represented by different hypogonadism males, due to different causes [47, 48]. Autostimulation is considered a testosterone-dependent behavior; some hypogonadism questionnaires (ANDROTEST) consider impaired masturbation as a positive criterium for hypogonadism [49].

2.3. Testosterone implication in male sexual responses

The classic male sexual response as described by Masters' and Johnson' comprises the following event succession: excitement, plateau, orgasm, and resolution [42] corresponding to different levels of arousal.

The most important sign of excitement is the appearance of erection. There are three types of erections.

2.3.1. *Erection*

Stimulated erection is the most complicated and sensitive type of erection, appearing triggered by voluntary actions (kissing, touching, reading, seeing, and smelling), verbal or non-verbal message, anyhow after an interaction with a partner, appearing within few seconds after correct sexual stimulation, regardless of the type of stimulation. After stimulation, the brain releases stimulatory neurotransmitters (dopamine, nitric oxide, oxytocin, serotonin), from oxytoninergic, serotonergic, and dopaminergic neurons located in “erection centers” in the limbic system (paraventricular and supraoptic nuclei) that will generate proerectile impulses via the parasympathetic system [50–53]. Parasympathetic impulses stimulate the spinal parasympathetic reflexogenic erection centers located at level S2–S4 [50] that will directly induce the vascular changes in the cavernous bodies, dilatation of arterioles, increased blood flow, decreased venous outflow due to compression of the subtunical venular plexuses, increase in oxygen pressure raising the penis, with subsidiary contraction of the ischiocavernosus muscles.

Testosterone influences erection both at central and at peripheral levels.

At CNS level, testosterone stimulates the synthesis, storage and release of proerectile neurotransmitters: dopamine, nitric oxide, and oxytocin [54–56].

At spinal level, the somatic innervation (motoneurons) of bulbo- and ischiocavernosus muscles is testosterone-dependent, meaning that testosterone influences both the rigidity of the erection and the orgasmic capacity [57, 58].

At the corpus cavernosum level, testosterone influences parasympathetic nerves that generate nitric oxide, facilitating NO secretion [59]. Testosterone also influences the quality of cavernosum muscle relaxation, influencing the expression of alpha adrenoreceptors [60, 61]. Also, androgen deprivation favors cavernosum muscle smooth cells apoptosis [62].

Testosterone and its metabolites at both central and peripheral neural pathways are crucial for maintaining and restoring erectile capacity. The mechanism of enhanced erection with testosterone depends not only on the peripheral neural pathway but also on the central neural pathway.

- Spontaneous erections are automatic, not controlled by a specific emotional content or response, being purely androgen-dependent. The mechanism of this erection is incompletely understood, but androgens play an important role [63, 64]. The role of this autonomous erection is nutritive for maintaining regular blood flow and oxygenation of the penis. Testosterone deficiency, depression, sleep apnea and altered REM phase sleep will impair this type of erection [65]. This type of erection is a very important diagnostic tool in the evaluation of erectile dysfunction and differentiation of organic from psychogenic erections.
- Mechanical erection is the most “independent” type of erection to testosterone level. The somatic pathway is active in cases of stimulated central erections, but also independent, in local mechanical stimulation. Testosterone is indirectly influencing this type of erection only by changing the properties of the cavernosum smooth muscle units.

Desire is not present in the classical male sexual response but still is a very important step in male sexuality. Desire is considered to consist of a drive—biological component, cultural component (wish) and motivational component (individual and relational psychology) [66]. Testosterone and other androgens sustain the drive component [67].

3. Testosterone deficiency

In all cases of hypogonadism, major sexual symptoms are described [68–70]:

- Alteration of sexual desire and arousal with a significant decrease in frequency of sexual activity
- Decrease/altered quality of spontaneous erections
- Partial alteration of psychic erections: decrease in frequency, amplitude, and rigidity
- Alteration of orgasm and ejaculation proprieties
- Altered response to phosphodiesterase-5 inhibitors

The implication of testosterone deficiency is clear, but the level of deficiency where symptoms appear is still debatable. Effects of testosterone on sexual function are dose-dependent up to a level close to the lower limit of normal range. From this threshold level, the effects are maximal. In cases with testosterone levels very close to this limit, the benefits of testosterone replacement are minimal. Below the threshold, the sexual function is impaired [67]. Different thresholds are described according to the wanted effect of testosterone [71]. Also the threshold value is variable and may increase with aging concerning sexual function, higher testosterone levels are needed with aging for the same result [72], with possible individual values, according to personal sensitivity [73]. The prevalence of sexual symptoms increases as testosterone levels decrease: low libido and vigor for values lower than 15 nmol/L (4.3 ng/mL), disturbed sleep at values less than 10 nmol/L, neurovegetative symptoms and erectile dysfunction at values less than 8 nmol/L (2.3 ng/mL) [71] and 1.5–2 ng/mL for nocturnal erection [74]. Other studies describe other testosterone values: below 8.5 nmol/L for erectile dysfunction, below 11 nmol/L for decreased frequency of morning erections and below 13 nmol/L for diminished vigor [75].

Because of all this individual variability and also because of different testosterone thresholds for different symptoms, there is still no consensus from the major professional societies about the definition of hypogonadism [76–78].

3.1. Hypogonadism types

There are several types of hypogonadism that all lead to alteration of testosterone effects on target cells:

- Primary hypogonadism is due to different testicular causes: chromosomal diseases (Klinefelter syndrome being the most frequent disease [79]) or testicular tumors with testosterone deficiency after treatment [80]. Orchitis, acquired anorchia, idiopathic testicular atrophy, congenital anorchia, 46 XY sexual development disorders, gonadal dysgenetic syndrome,

Noonan Syndrome or LH receptor mutations are other causes of possible primary hypogonadism [76].

- Secondary hypogonadism is due to central, hypothalamic or hypophyseal causes: functional or tumoral hyperprolactinemia, Kallmann syndrome, isolated LH deficiency, pituitary adenomas, autoimmune hypophysitis, iatrogenic pituitary insufficient (surgery, radiotherapy), CNS tumors Prader-Willi syndrome, congenital adrenal hyperplasia [76].

Both gonad and hypothalamus insufficiency: late onset hypogonadism due to aging or overweight or both is a typical mechanism that is seen in late onset hypogonadism. The hypothalamic pulsatile secretion of gonadotropin-releasing hormone is blunted, due to increased hypothalamic sensitivity to negative feedback from the peripheral androgens, with preservation of the responsiveness of the pituitary gonadotrophs. From a peripheral point of view, testicular volume as well as Leydig cell mass and reserve function are diminished. There is a reduced testosterone secretion with associated loss of nycthemeral variability [81]. The combined defects are responsible for a progressive decrease of testosterone level with 1–2% per year [14]. Chronic ill men, obesity and metabolic syndrome also determine testosterone deficiency in high percentages with a variable prevalence of 25% [82] up to 50% [83]. Taken all into consideration up to 20% of all men over 60 years of age have inappropriate testosterone levels [84].

- Androgen receptor insensitivity/resistance is a very rare form of hypogonadism, due to total or partial androgen receptor insensitivity or 5-alpha reductase deficiency.

Regardless of type of hypogonadism, the clinical picture is dependent on the moment of onset of hypogonadism.

Prenatal testosterone deficiency will alter genital development, inducing all possible alteration of external genital aspects and formation: hypospadias, with different severity degrees, cryptorchidia, and ambiguous external genitals to female external genitals. These anatomical changes will impair future sexual function. The changes are irreversible and need surgical treatment for correction. The general surgical rule is to make the surgical treatment as soon as possible and to choose the gender, which is easier to be achieved with reconstructive treatment [85] but also in accordance to the intrauterine hormonal exposure. The goal is to complete the surgical correction till the age of 2 [86]. It is also important to evaluate, in the presence of nonfunctional/dysgenetic gonads, to evaluate the malignancy potential and to make the right treatment choices [87]. The major problems in many cases are unrecognized and undiagnosed at birth and are difficult to treat after 2 years of age because of organic causes and also due to the already established gender identity, gender role and sexual orientation. Testosterone replacement treatment is imperative, following the moment of physiological onset.

In cases of prepubertal testosterone deficiency, we will always observe a delayed puberty, defined in boys as no secondary sexual characters (increase in testes) before the age of 14 [88]. In severe causes of hypogonadism, the clinical picture is typical: small testes, cryptorchidia, gynecomastia, high-pitched voice, constant linear growth, eunuchoid habitus, sparse body and facial hair, decreased bone and muscle mass. From a sexuality point of view, these boys do not show sexual interest, have a decreased tendency of autostimulation, and have decreased phantasies and dreams. Untreated hypogonadism will affect all the levels of sexuality, with no

normal development of sexuality. In the absence of normal androgen impregnation, there will be no erectile performance, altered sexual behavior, altered sense of well-being and globally affected sexual function [89]. If untreated, there will be no normal development of an adult male phenotype with serious impairment of sexual life.

Adult onset testosterone deficiency will induce different symptoms compared to previously mentioned forms of hypogonadism. The patients have normal developed genitals, normal developed secondary sexual characters, normal sexual function and behavior till the onset of hypogonadism. The clinical picture is dominated by metabolic and sexual symptoms. Sexual symptoms include loss of libido, erectile dysfunction, decrease in sexual phantasies, loss of body hair and hot flushes. Metabolic complications are loss of bone mass, sarcopenia, weight gain, increased body fat and increased vascular risk [90–92].

4. Treatment principles in testosterone deficiency in males

4.1. Life style changes

Life style changes are important only in late-onset hypogonadism, significant weight reduction, decrease of body fat and regular exercise can increase endogenous testosterone level [93, 94]. Life style changes can improve testosterone balance, in absence of active hormonal replacement treatment [95, 96] but unfortunately significant weight loss of more than 10% is difficult to maintain [96]. This is the motif for which, in majority of cases, supplemental treatment is needed [97]. Even if possible results are interesting, in the testosterone normalization in diabetic and overweight patients with metabolic syndrome (what is this?), the compliance to sustained weight reduction is low in the long run, so decreased testosterone will reappear whenever a new weight increase occurs. Testosterone deficiency prevention is still a goal, with management and treatment of modifiable factors, such as weight control, regular sport activities, and decreased alcohol consumption, but in the majority of cases, it is difficult to sustain.

4.2. Testosterone supplemental therapy

Currently, testosterone supplemental therapy is the golden standard for management of testosterone deficiency symptoms, regardless of physical, psychological or sexual domains [98].

There is no clear consensus for an accepted lower limit of normal testosterone. Various guidelines for the diagnosis of hypogonadism are available: late-onset hypogonadism [78] (total testosterone < 8 nmol/L) should be treated with testosterone therapy, those with total testosterone level of 8–12 nmol/L and hypogonadal symptoms should be given a trial of testosterone replacement therapy, and those with total testosterone level > 12 nmol/L are not hypogonadal and should not be treated [99]. Other guidelines recommend treatment for values below 8 nmol/L only in cases of physical symptoms [76, 100].

Testosterone measurements should be measured in the morning, between 07 and 11 AM, on two different days, and both values should be low in order to confirm the testosterone deficiency. Total testosterone measurements are used in order to make a positive diagnosis.

Interventional studies have shown a beneficial effect of testosterone replacement therapy on insulin resistance [101]. The increase in insulin sensitivity is present in obese men [102, 103], patients with heart failure [104], with better glycemic controls in diabetic males under testosterone replacement therapy [105, 106].

There are some recommendations of active testosterone screening in special risk categories of males [76, 100, 107]:

1. Type-2 diabetes mellitus
2. Metabolic syndrome
3. Moderate to severe chronic lung disease
4. Osteoporosis
5. History of infertility
6. Treatment with steroids, opiates and anticonvulsants
7. Alcohol abuse
8. ED or loss of spontaneous erections
9. Loss of sexual desire

The debate is around the type of symptoms that should be addressed for treatment. If correctly screened, with validated questionnaires, less than 5% of men with type-2 diabetes is asymptomatic, free of altered erectile performance, no present ED or altered arousal capacity [108].

The main concern in recommended testosterone replacement therapy is the vascular safety [109–111] because of the suggestion of increased stroke risk, despite the reduction in major adverse cardiovascular events, as death, nonfatal myocardial infarction and stroke. Some studies suggest beneficial effects of testosterone on cardiovascular risk factors [112], low testosterone being associated with increased cardiac mortality [113, 114].

The benefits for the cardio metabolic risk profile are clear, not only in the direction of insulin sensitivity, as seen before, but untreated testosterone deficiency is also associated with a four-fold risk of developing type-2 diabetes in men [97]. Some studies suggest that testosterone replacement therapy induces favorable changes in total and low-density lipoprotein profile, lipoprotein, body fat composition and glycated hemoglobin levels [108, 115, 116].

Recent studies showed different results suggesting an increase in vascular events in the presence of testosterone supplemental therapy [117–119]. Because of this opposing data, the FDA (Food and Drug Administration) still recommends that larger interventional studies are needed to have a definitive conclusion regarding testosterone treatment on cardiac safety [120]. Observational studies did not confirm the increase in cardiovascular events in long-term follow-up studies [121]. The EMA (European Medicines Agency) had agreed by consensus that there is no consistent evidence of an increased risk for heart problems with testosterone replacement in men lacking the hormone [122].

However, caution should be taken in cases with preexisting cardiovascular disease, especially in cases with increased hematocrit levels, due to increased primary thrombotic risk [123, 124].

Similar unresolved issues are seen when evaluating the associated presence of the following:

- Obstructive sleep apnea, classically considered a contraindication for testosterone treatment, because of neutral studies, with no worsening of the disease [125–127]
- Lower urinary tract symptoms, which do not worsen under testosterone treatment, as classically considered [128–130]
- Congestive heart failure is still a relative contraindications for replacement treatment, but controversial, since excellent results are seen in testosterone treatment in cases with well controlled congestive heart failure [131]. Maybe untreated/uncontrolled heart failure should be considered as a contraindication.
- Prostate safety: Prostate cancer is still a contraindication, but positive results start to emerge [76] with respect to lack of increased risk of prostate cancer under supplemental therapy. Also symptomatic hypogonadal men with localized prostate cancer, treated surgically, without active disease can be cautiously considered for testosterone therapy [132–134]

Taking all these recommendations into consideration, testosterone has clear benefits regarding sexual health [97]. There is a significant effect on sexual desire, intercourse satisfaction and overall sexual satisfaction, when evaluated with FSFI questionnaire [135]. There are clear benefits on erectile function, with satisfactory sexual intercourses after at least 3 months of testosterone supplementation [135, 136]. Also, testosterone treatment, in hypogonadal men, improves the therapeutical response to phosphodiesterase-5 inhibitors [137], converting non-responders to responders [138]. In general, testosterone supplementation has a positive effect on orgasmic and ejaculatory function [139]. Sexual interest appears after the first 3 weeks of use and reaches plateau in 6 weeks [136].

Except the late-onset hypogonadism, classical indications for testosterone supplementation are delayed puberty, Klinefelter syndrome, low bone mass in adult hypogonadism, hypopituitarism, and testicular dysgenesis. The therapy should be started at the appropriate age of puberty onset (in prepubertal forms of diseases) or after the clear diagnosis of hypogonadism (in postpubertal forms of diseases) [76]. Active follow-up should be performed in patients treated with testosterone supplementation therapy [76, 140]:

- Symptoms response at every visit, minimum after 3 months of treatment, and then annually.
- Formulation of specific adverse effects should be evaluated at each visit.
- Testosterone level should be measured periodically, for a correct supplemental therapy at 3, 6 and 12 months after onset of the treatment.
- All and each adverse event should be reported immediately.
- Bone mineral density should be measured every 1–2 years
- PSA measurement should be performed every 3 months, in the 1st year of treatment and then annually

- Hematocrit measurement should be monitored at 3, 6 and 12 months and, thereafter, annually. Whenever the levels increase above 0.54, testosterone treatment should be discontinued.

5. Conclusion

When we think about hypogonadism, we should keep in mind not only the classical types of hypogonadism due to classical testicular disease of central, hypothalamic and hypophyseal disease, but we should also emphasize the partial testosterone deficiency that is described due to age increase (late-onset hypogonadism) or secondary to weight increase (up to 30% of males with metabolic syndrome and 50% of males with diabetes) or the secondary hypogonadism described after chronic use of steroids or after long exposure to stress, especially in young males. All these types of hypogonadism that affect young, middle-aged or old males are presented separately. The therapeutic approach should be individualized for each type of hypogonadism and should consider positive and possible negative effects. All alternatives are presented: life style changes, sustained weight loss, increased exercise, supplemental therapy and pro-fertility treatment.

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