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Male hypogonadism with its systemic complications

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Abstract

Introduction and purpose: Total lack of testosterone or its level lower than 9-12 mmol/L (250-350 ng/dL) of serum in men is called hypogonadism. Due to the importance of testosterone in male body, hypogonadism usually causes a variety of symptoms, mostly of sexual nature – lack of libido, erectile dysfunction, infertility and associated psychological problems, it can though be the cause of more dangerous changes in the male body. The purpose of this study is to review possible systemic complications of male hypogonadism (with the emphasis on hypogonadotropic hypogonadism) apart from those sex-related.

State of knowledge: The lack of testosterone and gonadotropins was proven to cause a number of negative changes in different systems and various clinical situations. It can negatively impact the condition of skeletal system. Although testosterone is widely thought to increase cardiovascular risk some studies show that the hypogonadism has a negative impact on it as well. Some studies hypothesised the role of hypogonadism in anaemia development, but generally it isn't taken into account in investigation of this condition. Some studies show the impact of hypogonadism on higher risk of some metabolic and endocrine diseases. The most interesting conclusions were found in literature on oncological implications of testosterone and lack of it. It turns out that there is a number of studies showing the positive impact of relatively higher testosterone concentrations while androgen deprivation therapy is the main therapeutic option in advanced prostate cancer.

Conclusions: Due to very unpleasant and possibly dangerous complications of hypogonadism endocrinologists should stay alert to signs of hypogonadism to be able to start testosterone replacement in the right moment.

Keywords: hypogonadism; systemic complications; prostate cancer; cardiovascular risk; metabolic syndrome

Introduction and purpose

The fact of global decline in male fertility is undeniable and was inferred from studies on sperm count in men across the world. The decline in this index was estimated from 10% [1] up to tremendous 60% in some regions [2]. The list of potential causes of lower or lack of fertility is long and variable and among others it consists of various infections, genetic diseases, or environmental factors, the infertility can be the symptom of hypogonadism as well. Hypogonadism is a clinical condition of abnormally low serum testosterone levels (total testosterone under 9 – 12 nmol/L (250-350 ng/dl) and same as infertility can be caused by an abundance of factors both inborn or acquired. Two types of this state can be distinguished. Hypogonadotropic hypogonadism is diagnosed when the cause of testes disfunction lays in any of the upper floors of hypothalamus-pituitary-testes axis – the levels of gonadotropins only, or gonadotropin-releasing hormone (GnRH) and gonadotropins are low. Hypergonadotropic hypogonadism occurs when the low testosterone level is caused by abnormalities in testes specifically. Hypogonadism is usually the reason for significant quality of life reduction due to many complications, not only in the sexual aspects, but many others which often do not receive necessary attention.

This review presents most of the dangerous and quality-of-life-lowering complications of both hypergonadotropic and hypogonadotropic hypogonadism with the emphasis on the second type beyond sex-related and psychological problems. The reviewed articles include studies on humans and animals.

Current state of knowledge

Bones

Sex hormones are crucial for developing regular bone structure and increasing bone size, by stimulating longitudinal and transerve dimension growth. Androgens induce anabolic effects on bones via their androgen receptors (AR) or through 17-beta-estradiol, to which it is transformed by specific aromatase that then binds to estrogen receptor (ER). ERα acts as a protective factor on trabeculae by keeping their number and thickness optimal, also affecting positively cortical bone, directly or indirectly through increasing insulin-like growth factor-1 (IGF-1) serum level. On the other hand AR is only thought to act on a quantity of trabeculae, with stimulation of osteoblasts and osteocytes [3][4]. Although the difference between male and female skeletal strength and size is common, density is rather equal[5].

Study on one hundred ninety-eight men receiving goserelin, to suppress production of testosterone, and testosterone gel as supplementation, two hundred and two received the same treatment but also anastrozole to suppress conversion of androgens to estrogens, thirty-seven men served as control group. Far bigger decrease in bone mineral density (BMD) was observed in the group which was treated with both goserelin and anastrozole, which proves that estrogen is significant for maintaining bone structure and turn-over [6].

With that vast impact on skeletal system, any disturbance of sex hormones during early stages of life can lead to low BMD and bone strength [7], which increases risk of fractures compared to healthy individuals[8] and could lead to earlier development of osteoporosis[8].

Özbek et al. conducted a study where they showed that patients with hypogonadism, both hypogonadotropic and hypergonadotropic have lower BMD than healthy populations. Group consist of 33 adolescent girls, 14 of them being hypogonadotropic, that have been tested using dual energy X-ray absorptiometry (DXA) to estimate their BMD z-score, and later height adjusted (HA) BMD z-score to eliminate data scattered due to difference in height of girls. Patients with hypogonadotropic hypogonadism presented lower HA BMD z-score in the spinal column compared to healthy individuals in their age, with no correlation found in femur neck. When using age-correlated BMD z-score more patients showed lowered scores, than height-correlated, probably due to lack of estrogens necessary to maintain bone growth [9]. Same results were found in males with glycogen storage disease type 1 that also occured with hypogonadotropic hypogonadism. Low level of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone have an impact on the occurrence of several symptoms, which also includes low BMD in the lumbar region of spine, compared to hip [10].

Studies on mice showed that via estrogen substitution OPG/RANKL (osteoprotegerin/receptor activator of NF-kappa B ligand) ratio decreases which lower bone turn-over time by slowing maturation of osteoclasts and their activation [11].

Apart from estrogen, FSH may also have an impact on bone health. FSH receptor (FSHR) found on osteoclasts and osteoclast precursors [12] by increasing receptor activator for NF-kB (RANK) expression and production of tumor necrosis factor (TNFα), tartrate-resistant acid phosphatase (TRAP), matrix metallopeptidase 9 (MMP-9) and cathepsin K speeds up maturation of precursors and increases activity of osteoblast, while FSHR increases survivability of active osteoblasts [13]. That function of FSH seems to be important in rate of bone loss in peri- and postmenopausal women [14][15]. Lack of both FSH and estrogen as in hypogonadotropic hypogonadism may have presented completely different abnormalities, but further studies in this topic are necessary, due to lack of adequate research.

Some studies showed that patients with hypogonadotropic hypogonadism have lower BMD than hypergonadotropic ones [16], probably due to preserved function of pituitary gland in FSH and LH production, which contradicts the supposed pro-osteoclastic function of the gonadotropins mentioned earlier [12]. Further studies are required to identify relations between gonadotropins and BMD.

Clinical guidelines recommend supplementation of testosterone in men whose risk of bone fracture is high, and to raise BMD in patients with lowered testosterone level [17][18]. Although bisphosphate usage was considered in older patients with osteoporosis or during androgen deprivation therapy due to prostate cancer [19], studies on hypogonadotropic patients are yet to present.

Cardiovascular

As far as cardiovascular disease is concerned patients with low testosterone levels showed increased cardiovascular risk. Large meta-analysis performed by Corona et al. of papers published between 1988 and 2017 including 43 041 patients predicts not only cardiovascular morbidity but also mortality [20]. Some studies showed that obese, elder men were in greater risk of having several cardiovascular diseases, with such other factor like smoking, poor diet or lack of exercises further increasing this risk[21]-[23]. Such factors could be alleviated by dietary restrictions and weight loss, which also increase testosterone levels [24]. Congenital diseases, like Klinefelter syndrome in which hypogonadism leads to increased risk of cardiovascular disease [25].

Current studies in the subject of testosterone replacement therapy (TRT) are discrepant.

Vigen et al. conducted research where they analyzed trials of 8709 men with testosterone level below 300 ng/dL, 1223 of them received TRT. In the group of non-treated 681 died, 420 had MIs, and 486 had strokes, while in treated 67 died, 23 had MIs, and 33 had strokes. Those numbers translate into a difference of 5.8% higher chance of cardiovascular events in males who received TRT [26] and the same result was confirmed in other studies [27][28], while also pointing up that risk is higher at the beginning of treatment [29].

Haddad et al. in meta-analysis, consisting of 30 trials which included 1642 men, whom 808 were on TRT, showed that there has been no significant correlation between testosterone blood levels in patients with TRT or without it and cardiovascular event risk or parameters like total cholesterol, cholesterol fractions, triglycerides, blood pressure and blood glucose level [30], and same result was obtained in another studies [31][32].

In Calof et al. meta-analysis risk of cardiovascular event did not differ between males treated with testosterone and not treated but showed another adverse effect of TRT which is hematocrit level elevation above 50%, that men treated with testosterone have 3,67 times greater chance of developing. It is worth underlining that the increase in hematocrit in young, hypogonadal men was moderate, while older men had it far greater due to age-related decrease of natural testosterone production [33].

Most of the authors highlight that there is a lack of profound prospective trials of patients with cardiovascular risk and hypogonadism. Patients with thalassemia major could develop hypogonadotropic hypogonadism, due to iron accumulation in hormone-releasing cells [34][35]. Such decrease in gonadotropins could occur in other types of anemia like Fanconi anemia [36] which is intertwined with genetic disorder. Also, sickle cell anemia could lead to hypogonadism by occluding pituitary or/and testicular vessels and leading to their infarction [37][38]. Introducing testosterone supplementation in treatment of patients with lowered androgens levels as a result of aging or hypogonadism, treated for anemia have positive impact on hemoglobin concentration and production of erythropoietin, ferroportin, and transferrin receptors [39]. Deficiency of androgens is usually not taken into consideration in investigation of anemia [40].

Hormonal and metabolic

Defect of testosterone in hypogonadotropic hypogonadism may contribute to secondary hormonal disorders. In the diagnostic process of hypogonadotropic hypogonadism it is important to include measurements of prolactin, free T4, TSH, morning cortisol, IGF1 and analysis of growth curve [41].

Low level of testosterone results with the gain in fat mass, which would be a mediator of its effect on increased insulin resistance.

Another important correlation exists between testosterone and IGF-1 (insulin growth factor) level. Hypogonadism decreases IGF-I messenger RNA (mRNA) levels in skeletal muscle [42]. Low IGF-I also causes lowered expression and activity of enzymes necessary for steroidogenesis in Leydig cells [43][44]. Hypogonadal men are at risk for the development of osteopenia or osteoporosis caused by low testosterone, which is essential in bone development. By conversion to estradiol, testosterone inhibits osteoclastic activity and hence bone resorption. Also, through conversion to DHT, it can affect the axis of calcitonin and parathyroid hormone as well. Low bones density in hypogonadotropic hypogonadism and is caused by testosterone effect on bones. It also stimulates activity of the osteoblasts through conversion to DHT which contributes to bone degeneration. [45]

Testosterone is one of the erythropoietic hormone stimulators. Low testosterone contributes to less stimulation of the erythropoiesis in bone marrow and reins what have effect in the pathogenesis of the mild anemia in hypogonadal patients. [46]

Many studies show correlation between hypogonadotropic hypogonadism and metabolism. Low testosterone level is associated with increased risk of developing metabolic disorders and also is present in obesity, type-2 diabetes mellitus (T2-DM), and metabolic syndrome. Increasing visceral adiposity and insulin resistance in patients with gonadotropin releasing hormone deficiency contribute to the worsening of metabolic conditions. The same concerns patients subjected to androgen deprivation therapy in prostate cancer.

These metabolism disorders contribute in turn to a further reduction of testosterone levels and predicts an increased risk of developing incident hypogonadism. The majority of studies with testosterone replacement therapy on metabolism describe its beneficial effect on body weight, body mass index, cholesterol levels, and glycemic control and others. The effect was shown to appear the other way around as well - improved testosterone levels by correction of metabolic disorders [47]. These reports clearly show the bidirectional relationship between both disorders. According to the Study of Rancho Bernardo et. al in 2002 T2-DM developing risk increased in healthy men with lower levels of testosterone compared to those with higher levels [48]. Different study carried out on 15-years follow-up on 950 healthy aging men show the statistically significant association between sex hormones and metabolic syndrome. Decreasing levels of T and sex-hormone-binding globulin (SHBG) increased odds of metabolic syndrome. This association was stronger with abdominal obesity and dyslipidemia than with diabetes. [49]

The exact mechanism by which low testosterone levels contribute to metabolic disorders is still unknown. However, deficiency of the testosterone has an influence in increasing lipoprotein lipase activity, resulting in adipocyte proliferation and accumulation of visceral adipose tissue (VAT) [52], [53]. VAT accumulation results in promoting aromatization of testosterone to estradiol, which increases the level of inflammatory mediators: tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), and interleukin-1b (IL-1b). These mediators are responsible for suppressed secretion of GnRH and pituitary luteinizing hormone (LH) as a result.

Implications of leptin increase have also emerged in the hypothesized pathophysiology of hypogonadism. It directly inhibits hCG-stimulated testosterone production by Leydig cells and testicular tissue [54] as well as leptin resistance resulting in reduction of hypothalamic-pituitary hormones levels.

Important role of the testosterone level and metabolic disorders is associated with SHBG levels, which are decreasing in obesity and T2-DM. It is pointed out that visceral fat in patients with metabolic syndrome and T2-DM increases levels of proinflammatory cytokines, such as TNF-a and IL-1b, which might be responsible for reduction of SHBG levels. It results in negative feedback on the HPT axis and is the reason for the testosterone deficiency [55]-[58].

Testosterone deficiency-induced metabolic disorders might be caused by GnRH deficiency and also pharmacologically-induced hypogonadism for androgen deprivation therapy (ADT). Yialamas MA et. al proved that insulin sensitivity in young healthy IHH men is reduced by deprivation of the androgens and after 2 weeks of testosterone replacement therapy (TRT) withdrawal fasting insulin level and IR were significantly increased [59].

In men with hypogonadotropic hypogonadism and prostate cancer subjected to androgen deprivation therapy the treatment have been found to correlate with increased fat mass [60]–[62], reduced insulin sensitivity [60], [63], and high risk of metabolic syndrome and T2-DM [18]. Compared to the latest case, in which patients had high VAT levels, these patients present a rather increase in subcutaneous adipose tissue [62]. Studies show that the risk of T2-DM development is significantly higher in patients with ADT-induced hypogonadotropic hypogonadism [65].

Hypogonadotropic hypogonadism and related metabolic disorders can be treated by testosterone replacement therapy and alternative options with human chorionic gonadotropin, aromatase inhibitors and selective estrogen receptor modulators [50]. Furthermore, there are reports about insulin sensitizing metformin treatment [51].

Oncological

One of the most important actions of testosterone in male body are those related with anabolic functions. Due to its interactions with various growth factors and other anabolic hormones (e.g. growth hormone) it causes extensive protein synthesis and cell proliferation, and as a result tissue maturation and growth, which includes muscle, bone, testes, prostate tissues, blood (hematopoiesis) and others.

Prostate cancer (CaP) is the neoplasm most commonly linked to androgenic hormones. According to a worldwide GLOBOCAN 2018 study it accounts for 7.1% of all malignancies and is the second most frequent cancer among males (13.5%) [66]. The most prostate cancers are diagnosed when the disease is still organ-confined and has a good prognosis. Due to SEER Cancer Statistics Review [67] the 5-year survival rates among American men was about 98%. The data collected in EUROCARE-5 project [68] shows the 5-year survival rate of Europeans as about 83% (variations of 76% in eastern countries to 88% in Central Europe). The screening usually consists of prostate specific antigen (PSA) among other tests.

The first scientific paper regarding the link between androgens and CaP was published in 1941 and introduced the androgen-dependant model of CaP pathogenesis and progression [69], which was solidified with many in vitro and animal studies [70], [71] and prevailed over other models which is visible in clinical practice guidelines [72]. On the other hand the literature consists of many publications describing hypogonadism as a factor that increases CaP genesis risk and disease aggressiveness, which was first noted by Morgentaler et al. in analysis of CaP prevalence among hypogonadal patients (low total of free testosterone) which turned out to be significantly higher than anticipated [73].

Zhou et al. tested the influence of low testosterone levels on mice prostate cellular composition and physiology – the animals were castrated and supplemented with the hormone to achieve castrate, subphysiological or normal serum testosterone concentrations. After 6 weeks it turned out that mice from different testosterone treatment groups had similar prostate testosterone and dihydrotestosterone concentrations. Organs of specimens from the lowest testosterone groups underwent significant changes – many alterations in the expression of androgen-synthesis-related genes, higher percentages of stem and transit amplifying cells and major transcriptional changes in those cells – which caused higher rate of inflammatory responses and possibly higher CaP development risk [74]. The authors of 2010 study divided 568 patients after prostate biopsy into groups of high testosterone level (above median which was 3.85ng/ml, n=285), and low testosterone level (below median, n=283) and found out that the low testosterone group had much higher CaP incidence of 38.9% compared with 29.5% in the high testosterone group, although it wasn't associated with more aggressive disease [75]. Mearini et al. in 2013 measured testosterone and gonadotropins levels in 206 patients with benign prostatic hyperplasia or CaP and only testosterone levels were significantly lower in cancer patients – testosterone level below 2.4 ng/ml turned out to be an independent predictor of CaP [76].

The results of 2016 retrospective study on 681 men after prostate biopsy divided into groups of low and normal testosterone levels (threshold of 300ng/dL) showed strong association of CaP detection risk (OR= 2.545) and higher grade disease (OR 3.324) with low testosterone level in comparison to high testosterone group [77]. Xu et al. in 2018 published a study on dynamic patterns of testosterone levels impact on CaP risk and their findings suggested that the later testosterone levels in individuals decreased below 3,5 ng/dL, the lower was their risk of CaP development (HR 0.68) [78].

The existing data much wider and more consistently describes the relationship between hypogonadal testosterone levels and higher CaP grades in Gleason scale (table 1), which helps to estimate the aggressiveness of the disease – the less differentiated tumor cells the higher Gleason score (the predominant and lesser cell population patterns are scored 1-5, and their sum is Gleason score), which is associated with more aggressive cancer and poorer survival.

Table 1. Summary of the latest studies on hypogonadism relationship with prostate cancer grade.

Authors, year	Results	Reference
Léon et al., 2015	Prospective study on 345 patients post RP, TT below 3ng/mL in 54 patients, BT below 1.5ng/mL in 70 patients, FT below 65pg/mL in 62 patients Significantly more often GS ≥7 in low TT (46% vs 32.9%), low BT (44.3% vs 33.1%;), and low FT (46.8% vs 32.9%) groups Only BT and FT levels were independent predictors of GS≥ (OR 1.76; OR 1.39 respectively) and GS increase (OR 2.82; OR 1.71 respectively)	[79]
Neuzillet et al., 2015	Prospective study on 937 patients pre RP, 139 of them were hypogonadal (TT below 3ng/mL or low BT) Mean GS was 6.8±0.5, 291 patients (31.1%) had a PrdGP 4 PrdGP 4 more frequent in hypogonadal group (41.7% vs 29.2%) Higher weight and BMI in hypogonadal patients	[80]
Shiota et al., 2015	Prospective study on 128 patients pre treatment GS <7 for 58 patients (45.3%), 7 for 52 patients (40.6%) and >7 for 18 patients (14.1%) 50% of patients from lowest quartile (below 3,62 ng/mL) had GS ≥7 Low pretreatment serum testosterone level was predictive of aggressive prostate cancer	[81]

Fuentes-Pastor et al., 2016	Retrospective study on 686 patients, TT below 3.5ng/mL in 133 patients, TB below 150ng/dL in 99 patients, TF below 6.5ng/dL in 107 patients LOH, low FT and low BT was associated with higher rate of GS ≥7 (61.54% vs 37.5%; 54.17% vs 34.12%; 54.35% vs 34.48%, respectively) Association of LOH, low FT and low BT with **higher prevalence of CaP** (51% vs. 35%; 44.86% vs. 33.33%; and 46.46% vs. 33.08%, respectively)	[82]
Ferro et al., 2017	Retrospective study on 338 patients post RP, TT below 3ng/mL in 53 patients (15.7%) Low testosterone was significantly associated with upgrading (27.4% of all), upstaging (50%), unfavourable disease (63.6%), PrdGP 4 (45.2%) and positive surgical margins (27.8%)	[83]
Llukani et al., 2017	Retrospective study on 502 patients post RP, TT below 1.93ng/mL in 33 patients, FT below 47pg/mL in 102 patients Low TT and FT among middle-aged men (45-64 years old) was associated with higher GS (8-10) (19.2% vs. 5.1%; 13.3% vs. 4.8%, respectively) and greater tumor volumes in comparison to normal testosterone group No significant differences among hypogonadal and eugonadal men ≥ 65 years old	[84]
Tu et al., 2017	Prospective study on 762 untreated men, TT below 2.3ng/mL in 316 patients Low testosterone was significantly associated with higher risk of development intermediate risk CaP (OR 2.92), high risk CaP (OR 5.63), metastatic CaP (**OR 72.3** [sic]) compared with the normal testosterone patients	[85]
Albuquerque et al., 2017	Retrospective study on 423 patients post RP divided by 2 different TT thresholds – 3.0ng/mL and 2.5ng/mL – below 3.0ng/mL (threshold 1) in 160 patients and below 2.5ng/mL (threshold 2) in 101 patients Both hypogonadal groups had higher chance of GS ≥7 (OR 1.79 for threshold 1; OR 2.08 for threshold 2)	[86]

Atkins et al., 2018	Retrospective study on 58 men, TT below 2.8ng/mL at PSA failure in 11 patients 10 patients died of CaP, 8 of which had low testosterone at PSA failure (72.7% vs 4.3% with normal TT)	[87]
Neuzillet et al., 2019	Retrospective study on 1343 patients post RP, TT below 3ng/mL in 150 patients, BT below 0.8 ng/mL in 173 patients Low testosterone was significantly associated with more often PrdGP 4 occurrence (17.4% vs 10.7% in low BT group; 14.2% vs 9.7% in TT group)	[88]
Izzo et al., 2019	Prospective study on 121 untreated patients Testosterone below 3ng/mL was most common among patients with higher GS grades (GS ≥7 80% vs 12.6% GS <7)	[89]

RP – radical prostatectomy; TT – total testosterone; BT – bioavailable testosterone; FT- free testosterone; GS – Gleason score; OR- odds ratio; PrdGP- predominant Gleason pattern; LOH- late onset hypogonadism

Hypogonadism can be treated by testosterone replacement therapy, gonadotropin-releasing hormone (GnRH) or other drugs that can cause rise in serum testosterone levels. Despite initial fear of testosterone increasing the risk of CaP development now the safety of therapy is well proven by high quality studies – such as the 2020 study on U.S. commercial insurance claims database, 2019 meta-analysis, and many more. First study included approximately 59 million researchable covered lives from which a cohort with over 1 million men was distinguished – almost 200 000 on testosterone replacement therapy and over 800 000 controls - the rate of CaP was the same among testosterone users and control group [90]. Authors of the meta-analysis included results of 21 studies found out that the rate of cancer recurrence among patients treated with testosterone wasn't higher in none of included papers [91]. Finally, the American Urological Association [92], British Society for Sexual Medicine [93], International Society for Sexual Medicine [94] and International Society for the Study of the Aging Male [95] stated, that there is no increased risk of CaP in men on testosterone replacement therapy which is current consensus.

Conclusions

The positive impact of normal testosterone level on men's health cannot be overstated, it's a crucial element of male homeostasis. All of the negative effects of hypogonadism listed and described above are the reasons why endocrinologists should try and keep their patients' hormonal homeostasis as normal as possible – even in oncological conditions.

Thanks to extensive research there are new therapeutic options being created that allow the testosterone to oscillate around normal level (for example therapeutic tactic called bipolar androgen therapy) thus allowing the patients' quality of life to stay at relatively high level. The existing results of research though are often inconclusive and mutually exclusive, so further studies with larger sample sizes are needed to draw a firm conclusion

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