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Review

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Hypogonadism: cardiometabolism and gonadal function in men

Matthew Noble[1], David Cahill[2]

[1]Women's Health, Liverpool Women's Hospital, Liverpool L8 7SS, UK.
[2]Academic Unit of O&G, University of Bristol, St Michael's Hospital, Bristol BS2 8EG, UK.

Correspondence to: Prof. David Cahill, Academic Unit of O&G, University of Bristol, St Michael's Hospital, Southwell St, Bristol BS2 8EG, UK. E-mail: d.j.cahill@bristol.ac.uk

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Abstract

Hypogonadism is a relatively rare condition in men, which increases in frequency as men age, but also as they become less active and gain weight. In the past 20 years, developing knowledge on the relationship between hypogonadism and cardiovascular and cerebrovascular health and on aspects of metabolic health has become clearer. The relationship between hypogonadism and specific endocrine abnormalities of spermatogenesis is much longer established. Long- and short-term testosterone replacement therapies have well-recognised effects on cardiovascular and cerebrovascular health and on aspects of metabolic health. This leads to a sense of safety when it comes to considering these options as ways of managing the recognised symptoms of hypogonadism and the hidden adverse findings. That confidence has yet to be proven by long-term randomised controlled studies. The use of exogenous gonadotrophins to raise endogenous testosterone levels is a cost-efficient method of achieving spermatogenesis but is not suitable for long-term testosterone maintenance therapy.

Keywords: Gonadotrophins, testosterone, cardiovascular health, hypogonadism, hypogonadotropic hypogonadism

INTRODUCTION

Hypogonadism is characterized by a reduction in gonadal function, exhibited either as spermatogenic failure, deficiency of testosterone, or both. Testosterone deficiency is noted by decreased libido, impaired

erectile function, muscle weakness, increased adiposity, depressed mood, and decreased vitality, but these are subtle symptoms in the adult male. If the cause is related to a failure of endocrine stimulation from the pituitary or higher, hormone stimulation to the testis will be low, resulting in hypogonadotrophic hypogonadism (with low testosterone and low FSH levels). Spermatogenic failure presents as oligo- or azoospermia, and consequent infertility. In recent years, evidence has been building that hypogonadism is associated with adverse events in the cardiovascular and metabolic systems, but more encouragingly, that testosterone replacement therapy appears to be beneficial in reducing the incidence of myocardial infarctions and cerebrovascular accidents[1]. If the cause is due to a testicular fault, there will be adequate or increased stimulation to the testis (with low testosterone levels and high FSH levels).

This paper addresses the relationship between hypogonadism and cardiometabolic disorders, recognizing the current evidence supporting the value of testosterone supplementation to improve outcomes in cardiovascular and metabolic diseases but also the need to be cautious in the absence of any long-term data to support testosterone replacement therapy in this way.

HYPOGONADISM AND CARDIOVASCULAR AND METABOLIC DISORDERS

An accumulation of evidence linking hypogonadism with erectile dysfunction and adverse cardiovascular events leads us to consider the underlying basis for this link. In men, hypogonadism is experienced symptomatically by the subtle symptoms noted above (decreased libido, impaired erectile function, muscle weakness, increased adiposity, depressed mood, and decreased vitality) and these are expressed to different levels in different men, in our experience. Biochemically, hypogonadism is considered when total testosterone < 12.1 nmol/L in the presence of hypogonadal symptoms. Erectile dysfunction can be subjective, but a validated assessment system allows for its categorization[2]. Causative factors for erectile dysfunction include androgen deficiency (though clinical trials show major discrepancies) and may include vascular disorder, hence its relevance to our discussion. Men with hypertension and men who smoke have an increased risk of erectile dysfunction (odds ratio: 1.34 for those not on medication and 1.4, respectively)[3].

Much of the data on the link between hypogonadism with erectile dysfunction and adverse cardiovascular events come from large observational registry studies, and these are generally in agreement with each other. Saad showed that when men with hypogonadism are not offered or do not accept testosterone supplements in the presence of hypogonadism, the incidence of adverse cardiovascular events (morbidity and mortality from myocardial infarction and strokes) rises significantly. Encouragingly, however, they also show that the addition of regular testosterone over time brings about a major reduction in this reported morbidity[4]. Other prospective studies show some conflict in their outcomes. The Western Australian health in men study showed lower testosterone linked to an increased risk of a stroke[5], while the United Kingdom Biobank study found no link between testosterone and myocardial infarction, or stroke (of haemorrhagic or ischaemic nature)[5]. In their literature review (not a meta-analysis), Elagizi *et al.* highlight the confusion that exists in the literature on the link between testosterone and cardiovascular health, but they also conclude that normal testosterone levels are linked with good cardiovascular health and that testosterone deficiency is associated with an unfavourable metabolic profile and increased cardiovascular risk[6]. Mann *et al.*, again using an observational registry study, demonstrated that in adults with testosterone deficiency (Testosterone £10.1 nmol/L), using testosterone undecanoate reduced mortality risk compared to men on no treatment (HR 0.41, 95%CI: 0.2-0.86)[7].

Beyond cardiovascular disease, evidence for the increase in metabolic disorders in men with hypogonadism is accumulating, demonstrating rises in type 2 diabetes mellitus and thyroid disorders, as well as links to

obesity. Insulin resistance, a feature of type 2 diabetes mellitus, has an uncertain and unclear relationship with testosterone levels, reported as being found in both low and excess levels of androgens[8]. The generally beneficial effects of testosterone therapy can be observed in one randomised double-blind controlled study, testing testosterone gel, a dihydrotestosterone gel, compared with a placebo gel[8]. In this study, the authors showed distinct changes in favour of testosterone only, in a range of measured parameters: waist and hip circumference, fasting blood sugars, insulin, cholesterol and triglycerides, and diastolic blood pressure, with no change in urinary flow or prostate volume (as measured by ultrasound). A number of small studies have confirmed this, but have not yet offered sufficiently high levels of evidence[9]. Further data are awaited to confirm or refute this.

EXTENT OF THE CONDITION

The frequency of hypogonadism is low in the general population, with prevalence rates of between 1-2/1,000 of the male population (though population studies are sparse)[10]. However, in the Hypogonadism in Males study, 38% of men over the age of 45 years had hypogonadism as defined by a testosterone level of < 300 ng/dl or 10.4 nmol/L[11]. That proportion of men may be falsely elevated by the cutoff levels for Total Testosterone (TT) in the Mulligan study; other workers used much higher levels of TT to define hypogonadism[12]. Additionally, the Mulligan data were drawn from men attending primary care clinics[11], not the general population[11].

The evidence supporting a causal relationship between hypogonadism and metabolic syndrome (and Type 2 diabetes mellitus) is growing. It appears that initial epidemiological studies linking hypogonadism and testosterone deficiency focussed more on hormone levels than on symptomatic presentations - hormone measurements are always going to be a firmer marker than symptoms, of course[10]. Now the links between testosterone levels and the co-morbidities associated with obesity as an inverse relationship are more recognised, and the seeming benefits of altering testosterone levels become more attractive[13].

What is the nature of the relationship between testosterone levels and benign prostatic hypertrophy? Most investigators have found that there is no link between these, though Lin *et al.* recently showed that benign prostatic hypertrophy is directly linked to testosterone levels. Is it likely that this was related to the study design they used (Mendelian randomization design), but they did find that "bioavailable testosterone level was able to induce BPH based on nearly all combination methods"[14]. They recognise the innovative nature of these data and call for further work to substantiate or refute them. These are new approaches to explore.

DIAGNOSTIC LIMITATIONS

Hypogonadism refers to a failure of gonadal function. In men, this can relate to spermatogenesis or failure of production of testosterone. Spermatogenetic failure is rarely complete, leading to azoospermia in 6% of infertile men[13]. A more useful description of sperm disorder is either sperm dysfunction[13] or dysspermatogenesis[10]. These terms recognise that sperm numbers may appear normal, but sperm morphology or motility is significantly disordered, which affects their function profoundly. Male infertility itself accounts for up to 20% of infertile couples[15], but in global, regional, or national populations, it is not possible to determine an unbiased prevalence of male infertility[10]. The figure of 20% is from a well-defined and local population[15]. A similar study in a geographically confined area of the Netherlands found that 25% of the infertile population had sperm disorders and 5% had azoospermia[16].

The range of diagnostic possibilities are outlined in Table 1. These are broad, and some of them are amenable to treatment, while some are not (though, of course, most are manageable by testosterone replacement - but this is at the cost of fertility). Some are clearly related to a past medical or surgical

Table 1. Classification of causes of male infertility[30]

Primary sperm production defect (testicular level)
Idiopathic
Chemotherapy
Klinefelter syndrome
Genetic mutations
Pelvic irradiation or surgery
Orchidectomy
Testicular cancer
Trauma
Large varicoceles*
Cryptorchidism
Infection (such as mumps orchitis)
Anejaculation
Drugs
Endocrine disorders that affect sperm production
Hypothalamic-pituitary disease
Hyperprolactinemia
Thyroid dysfunction
Obesity
Cushing syndrome
Defects in sperm transportation
Obstruction
Congenital absence of the vasa deferens
Acquired ejaculatory duct obstruction
Ejaculatory dysfunction
Anejaculation
Retrograde ejaculation
Sexual disorders
Erectile dysfunction
Failure to have intercourse
Lack of libido
Relationship dysfunction
Anorgasmia

*: 2021 European urology association guidelines recommend surgery if large.

intervention, and some have no recognisable aetiology. One factor not even listed is that of age, which is hardly a cause, but as men age beyond 40 years, reduced testosterone, increasing levels of DNA fragmentation, and falling sperm quality are recognised as contributors to male hypogonadism and fertility[17].

IATROGENIC HYPOGONADISM

Table 1 lists a broad range of underlying causes behind male infertility and hypogonadism. Some of these iatrogenic causes are understandable and often necessary to prolong life, for example - chemotherapy, radiotherapy, or orchidectomy. In such cases, steps should be taken to ensure men who wish to do so are at least offered an opportunity to store sperm before proceeding with fertility-altering treatment. In this table, drugs and pharmacological causes are listed - morphine derivatives (prescription and not so) are recognised to suppress GnRH activity, and this will ultimately suppress testosterone secretion[18]. Anti-inflammatory

drugs such as sulfasalazine and infliximab are recognised to affect sperm quality, but the factor most recognised in our clinical practice is the ingestion of anabolic steroids or testosterone supplements (sometimes unknowingly) used by bodybuilders, but also young men looking to have more sculpted physiques.

IDIOPATHIC HYPOGONADISM

There is a further range of conditions that are likely to give rise to hypogonadism and for which no attributable and remediable cause can be found. We consider these under the label of idiopathic (as opposed to iatrogenic), which is a misnomer, as a cause can sometimes be found, though it is generally not remediable. These causes are generally related to a genetic disorder. These include Kallmann's syndrome, disorders of the Y chromosome, and Klinefelter syndrome.

Kallmann's syndrome is a genetic disorder (associated with defects of the KAL gene, located in the Xp22.3 region, that explains the X-linked form of the disease) associated with failure of the GnRH-releasing neurons to migrate to the olfactory lobe during development, often associated with failure of the sense of smell, anosmia[19]. While there is no direct treatment for Kallmann's syndrome, it can be bypassed by providing exogenous gonadotrophins (see next paragraph). Disorders of the Y chromosome are a genetic cause of non-obstructive azoospermia. The Y chromosome consists of two main regions: the pseudoautosomal region, and the male-specific region, which cannot be recombined and represents ≥ 90% of the Y chromosome. In this male-specific region are several important determinants of the male phenotype, including sections known as the azoospermia factor (AZF) regions (there are three known regions, AZFa, AZFb, and AZFc). Deletions of this section can lead to azoospermia. Klinefelter syndrome, with a XXY genotype, is generally associated with a severe to complete absence of sperm, and hypogonadism. However, its occurrence in clinical practice is relatively rare.

Unrelated to hypogonadism, but not infrequent in clinical practice, congenital bilateral absence of the vas deferens (CBAVD) is generally, though not always, associated with cystic fibrosis (up to 20% of men with CBAVD will not have a genetic cause such as cystic fibrosis)[20]. Some men may be compound heterozygotes for abnormalities of the CTFR gene and, as such, may have CABVD but exhibit very mild or no other symptoms of cystic fibrosis.

HYPOGONADISM IN MEN LEADING TO INFERTILITY

While hypogonadism directly contributes to male fertility impairment, it is infrequently the primary cause. Most (90%) causes of infertility in men are related to a disorder of sperm function (poor sperm numbers, impaired function, or a combination of both)[15,21], and the remainder of the causes are ejaculatory problems (including anejaculation, premature ejaculation or retrograde ejaculation), hypogonadism (see Figure 1 for the relationship of endocrine function and spermatogenesis), and conditions such as testicular atrophy, cryptorchidism, or blockage of the vas deferens. In adolescent obese males, biochemical evidence of hypogonadism is noted with total testosterone < 7 nmol/L, which increased to > 13 nmol/L 5 years after weight loss[20]. Testicular atrophy may be unexplained and idiopathic, or possibly secondary to past trauma, infection, or inadvertent surgical damage. Vas deferens blockage may be amenable to surgery if the blockage gap is short, but it is crucial to note the recognised link between congenital absence of the vas deferens and cystic fibrosis[21]. As men age, their sperm quality diminishes, as seen in increasing levels of DNA fragmentation and a major reduction in the number of men reaching World Health Organisation criteria for normality in men over 50 years of age[19]. Increasing obesity levels are recognized as a cause of hypogonadism, with up to 30% of young obese men having testosterone levels under the lower limit of normal[22].

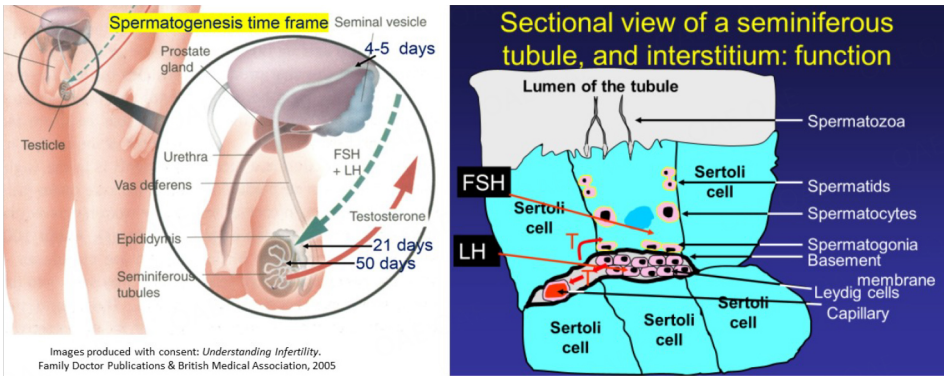

Figure 1. Endocrine control of spermatogenesis. An illustration of the Leydig and Sertoli cells, with the immunologiccal basement membrane barrier separating them. The Leydig cells producing testosterone under LH stimulation, that testosterone crossing the basement membrane into Sertoli cells and priming them to respond to FSH. This response is expresssed as sperm cell production and extrusion, into the Seminiferous tubular lumen. FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone.

The efficacy of treatment options is quite limited and related directly to finding a cause amenable to treatment. Most causes are not amenable to treatment. Finding a drug-related cause is encouraging because there is the potential to stop the medication, though sometimes the medication might be critical to maintaining a condition such as Crohn's disease at bay. Where opiate addiction is a factor, the management of drug withdrawal is much more complex. Generally, associated forms of sperm disorders and dysfunction are not amenable to medical intervention. The European Urological Society's Guideline[23] recommends surgery in the case of a large varicocele. Nonsignificant increases in assisted conception pregnancy rates were noted in men having a varicocelectomy compared to an embolisation (clinical pregnancy rate OR: 2.07; 95%CI: 0.92-4.65; $P = 0.08$)[24]. Meta-analyses, however, support varicocele repair in advance of assisted conception[25].

We recognise that both idiopathic and iatrogenic hypogonadotrophic hypogonadism can be amenable to medical intervention to promote fertility. We have presented data on the success of these treatments elsewhere[26]. In brief, 70% of men started on gonadotrophin treatment produced sperm and 50% succeeded in fathering a biological child, mostly after assisted conception of some nature. The treatment protocols used to achieve these results have also been reported[27]. Briefly, allowing for washout of any exogenous supplementary testosterone, initial treatment consists of hCG administration until endogenous testosterone levels exceed 10 nmol/L. This may take 1-3 months. Once that level is achieved, it is likely that FSH receptors will have been induced on the Sertoli cells in the testis and spermatogenesis can be initiated using exogenous FSH injections. Sperm production takes 9-12 weeks to be seen in the ejaculate, and once identified, steps should be taken to cryopreserve adequate sperm for future treatments - 2-3 ejaculates are usually sufficient. Few side effects are seen with this therapy, though local reactions in injection sites can be noted[28]. When treatment is stopped, the man needs referral back to his endocrinologist to recommence testosterone replacement therapy, probably within two months of the cessation of gonadotrophin therapy - sex steroid levels will have fallen by then. Only one man in our series experienced spontaneous conception during the second phase of treatment, and couples should not be encouraged to expect this rare event[26]. That couple also froze sperm for further treatment.

Treatments are lengthy and require considerable commitment from the man involved[26]. Treatment duration frequently exceeded a year and the mean duration was 453 days (95%CI: +/- 170 days). Given this long treatment duration, the female partner's ovarian reserve, as can be ascertained through measurement of anti-mullerian hormone (AMH) level, should be considered, as in cases of low ovarian reserve, waiting

for spermatogenesis may lead to further decline in ovarian reserve. In these cases, it might be appropriate to offer oocyte freezing while the male undergoes treatment. In our case series, the mean cost exceeded GBP 4,000. These costs are undeniably high, but what is the cost of a biological child? Despite the clinical effectiveness of this treatment, it is not widely considered a treatment option for men with hypogonadotrophic hypogonadism, certainly in the UK, perhaps due to time and cost commitment[29]. These prolonged treatments with injectable gonadotrophins will, of course, raise testosterone levels to more normal physiological levels. However, they do not provide a cost-effective or simple means of doing so - monthly or longer injections of testosterone undecanoate and similar formulations are as effective, simpler, and much less costly as a means of testosterone replacement therapy.

CONCLUSION

What then should be the recommendation for managing hypogonadism in men with specific reference to long-term cardiovascular and metabolic diseases? Long-term (more than 8 years) data suggest that monthly testosterone supplementation injection appears to be beneficial in reducing the risk of both cardiovascular and cerebrovascular morbidity, and cardiovascular mortality[1,4]. Metabolic abnormalities are certainly affected for the better by short-term transdermal testosterone[8] and to a lesser extent in longer-term studies[1]. Short-term therapies to raise endogenous testosterone levels when the cause of the hypogonadism is in the pituitary or higher are effective in treating associated fertility problems, but their daily administration and cost make them unrealistic as long-term treatment options for testosterone replacement[26].

On the face of it, there may be some justification for giving all men over the age of 40 or older regular testosterone supplementation. However, as alluded to earlier in this paper, we caution against the over-adoption of these therapeutic inventions in the absence of long-term, controlled studies to examine all the ramifications of these treatments. Interventions involving weight loss regimens such as those proposed by Wittert *et al.* are worth replicating, though Wittert *et al.* had a treatment arm with testosterone as well as a lifestyle intervention arm[30]. Separation of these two interventions would help to clarify which is more useful.

As a note of caution, it is imperative to remember how gynaecologists and reproductive endocrinologists prescribed estrogen replacement therapy (HRT) for women until a series of papers in the early 1990s blew the use of HRT in women out of the water - the more regrettable as many of those studies were incorrectly reported on and later had doubts cast on them. Our view would be that in the absence of prospective RCTs, treatments should be provided to those with low testosterone and symptoms and/or signs only.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Noble M, Cahill D

Performed data acquisition, as well as provided administrative, technical, and material support: Noble M, Cahill D

Guarantor: Cahill D

Availability of data and materials

Not applicable.

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Both authors declared that there are no conflicts of interest.

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Not applicable.

Consent for publication
Not applicable.

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