### Metabolism and Target Organ Damage

**Hypogonadism: cardiometabolism and gonadal function in men**

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Hypogonadism: cardiometabolism and gonadal function in men

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 have become clearer. The relationship between hypogonadism and specific endocrine abnormalities of spermatogenesis are much longer established. Long- and short-term testosterone replacement therapies and some aromatase inhibitor therapies have well recognised beneficial effects of 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 testosterone maintenance therapy.

Keywords

Gonadotrophins, Testosterone, Cardiovascular health, Hypogonadism, Hypogonadotropic hypogonadism

Introduction

Hypogonadism is characterised by a failure of gonadal function, exhibited either as spermatogenic failure, absence of testosterone or both. Testosterone absence 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 to hypogonadotrophic hypogonadism (with low testosterone and low FSH levels). Spermatogenic failure presents as oligo- or a-zoospermia, and consequent infertility. In recent years, evidence is 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 (Saad, Caliber et al. 2020). 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).

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 categorisation (Cappelleri, Rosen et al. 1999). Erectile dysfunction is considered to be a manifestation of a vascular disorder, hence its relevance to our discussion.
Much of the data on the link between hypogonadism with erectile dysfunction and adverse cardiovascular events comes from large observational registry studies, and these are generally in agreement with each other. Data from two registry studies are summarised in Table 1. These show that when men with hypogonadism are not offered or do not accept testosterone supplements in the light 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 mortality and morbidity.

Beyond cardiovascular disease, evidence for the increase in metabolic disorders in men with hypogonadism is increasing, demonstrating rises in Type II Diabetes Mellitus and thyroid disorders, as well as links to obesity. Insulin resistance, a feature of in Type II Diabetes Mellitus, has an uncertain and unclear relationship with testosterone levels, reported as being found in both low and excess levels on androgens (Márin, Holmång et al. 1993). The generally beneficial effects of testosterone therapy can be observed in one randomised double blind controlled study, testing testosterone gel, against dihydrotestosterone gel against a placebo gel (Márin, Holmång et al. 1993). In this study, the authors showed distinct changed 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). This is slightly counterintuitive as antiandrogen therapies such as 5 alpha reductase inhibitors are frequently used in benign prostatic hypertrophy (Andriole, Bruchovsky et al. 2004).

Extent of the condition

The frequency of hypogonadism is low in the general population, with prevalence rates of between 1-2/1000 of the male population (though population studies are sparse) (Thirumalai and Anawalt 2022). However, in the Hypogonadism in Males study, men over the age of 45 years had a rate of 38% of hypogonadism as defined by a testosterone level of <300 ng/dl or 10nmol/L (Mulligan, Frick et al. 2006).

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 (Hull, Glazener et al. 1985). A more useful description of sperm disorder is either sperm dysfunction (Hull, Glazener et al. 1985) or dysspermatogenesis (Thirumalai and Anawalt 2022). These terms recognise that sperm numbers may appear normal, but sperm morphology or motility are significantly disordered as to affect their function profoundly. Male infertility itself accounts for up to 20% of couples (Hull, Glazener et al. 1985) but in global, regional or national populations, it is not possible to determine an unbiased prevalence of male infertility (Thirumalai and Anawalt 2022). The figure of 20%, is from a well-defined and local population (Hull, Glazener et al. 1985). 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 (Snick, Snick et al. 1997).

The range of diagnostic possibilities are outlined in Table 2. These are broad and some of them are amenable to treatment, some are not (though of course, most are manageable by testosterone replacement). Some are clearly related to a past medical or surgical 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 (Morris, Mavrelos et al. 2020).
Iatrogenic hypogonadism

Table 2 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 suppress testosterone secretion ultimately (Buchanan and Davis 1984). 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 which 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 congenital bilateral absence of the vas deferens (CBAVD). 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) (Bieth, Hamdi et al. 2021). 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.

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 (Cocuzza, Alvarenga et al. 2013). It cannot be treated of itself, but 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 itself is divided in two, a pseudoautosomal region, and the male-specific region, which cannot recombine 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. The underlying aetiology is not clear, nor is it amenable to any invention (Peña, Kohn et al. 2020).

Hypogonadism in men leading to infertility

As a direct cause of male fertility impairment, hypogonadism is rarely the cause. Most (90%) causes of infertility in men are related to a disorder of sperm function (poor sperm numbers, function or a combination of both)(Hull, Glazener et al. 1985, Leaver 2016), 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 or blockage of the vas deferens. 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 be aware of the recognised link between congenital absence of the vas deferens and cystic fibrosis (Wong, Gu et al. 2020). 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 (Morris, Mavrellos et al. 2020). 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 (Halappanavar and Pakhetra 2020).
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 addition is a factor, the management of the 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 (Minhas, Bettocchi et al. 2021) recommend surgery in the case of a large varicocele but in our clinical experience over almost 40 years (DJC), this has never been observed to be successful and therefore a degree of scepticism follows that recommendation. 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) (Esteves, Miyaoka et al. 2016).

We recognise that both idiopathic and iatrogenic hypogonadotrophic hypogonadism can be amenable to medical intervention to promote fertility. We have elsewhere presented data of the success of these treatments (Morris, Lloyd-Evans et al. 2021). In brief, 70% of men started on 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 (Morris and Cahill 2021).

Briefly, allowing for washout of any exogenous supplementary gonadotrophins, 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 is usually sufficient. Few side effects are seen with this therapy though local reaction in injection sites can be noted (Sohan, Cahill et al. 1999). 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. In only one man in our series did a spontaneous conception occur in the second phase of treatment, and couples should not be encouraged to expect this rare event (Morris, Lloyd-Evans et al. 2021). That couple also froze sperm for further treatment.

Treatments are lengthy and require considerable commitment of the part of the man in question (Morris, Lloyd-Evans et al. 2021). Treatment duration frequently exceeded a year and 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 4000. 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 as a treatment option for men with hypogonadotrophic hypogonadism, certainly in the UK, perhaps due to time and cost commitment (Holt-Kentwell and Cahill 2019). These prolonged treatments with injectable gonadotrophins will of course raise testosterone levels to more normal physiological levels. However, they do not provide a cost effect or simple means of doing so – monthly injections of testosterone undecanoate and similar formulations are as effective, simpler, and much less costly. Alternatives have been explored in the form of aromatase inhibitors, and in particular, clomifene citrate (Huijben, Lock et al. 2022). This meta-analysis showed biochemical improvement with clomifene citrate, though symptomatic improvement was less impressive, and not convincing (Huijben, Lock et al. 2022). As the longest follow up was no more than 52 months, there are no data presented to represent the recognised beneficial effects on cardiovascular events form testosterone supplementation.

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 testosterone supplementation by monthly injection appears to be beneficial in reducing the risk of both cardiovascular and cerebrovascular morbidity, and cardiovascular mortality (Traish, Haider et al. 2017, Saad, Caliber et al. 2020). Metabolic abnormalities are certainly affected by for the better by short term transdermal testosterone (Mårin, Holmäng et al. 1993) and to a lesser extent in longer term studies (Saad, Caliber et al. 2020). Short term therapies to raise endogenous testosterone levels when the cause of the hypogonadism is in the pituitary or higher are effective, but their daily administration and cost make them unrealistic as long-term treatment options. On the face of it, there is some justification for giving all men over the age of 40 regular testosterone supplementation. Perhaps, but don’t forget the way gynaecologists and reproductive endocrinologists were prescribing 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 symptoms and/or signs only.

References


