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Opioid–induced hypogonadism: the role of androgens in the well–being and pain thresholds in men and women with advanced disease

Abstract

Hypogonadism is probably very common among patients with advanced disease. It may result from the disease itself but might also be caused or exacerbated by the drugs used to treat these patients and their symptoms. Opioids are notorious for their ability to depress the production of androgens by both adrenals and gonads. The corticosteroids used in more than 30% of patients with advanced disease may also contribute to hypogonadism. The symptoms of hypogonadism may involve not only fatigue, lack of energy and loss of libido, but also most probably increased sensitivity to pain. In many cases this may lead to increased doses of opioids and increased inhibition of androgen production. Opioid-induced hypogonadism may thus contribute to the development of opioid tolerance. Treatment with androgens for these indications is still controversial and not widely accepted. Androgens may have different adverse effects and their effect on pain has not yet been confirmed in clinical trials. Many patients (with breast and prostate cancers) may have hypogonadism induced pharmacologically in order to inhibit tumour growth. Treatment with androgens in these cases may be contraindicated. Conversely, patients with iatrogenic hypogonadism may suffer more pain and other symptoms which may negatively influence their quality of life.

Key words: androgens, pain threshold, hypogonadism, testosterone, dehydroepiandrosterone, opioid tolerance

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Introduction

A healthy male synthesizes about 5 mg of testosterone per 24 hours. Testosterone is converted in the androgen-sensitive peripheral tissues to the more active dihydrotestosterone (DHT). These tissues include the testes, prostate gland, hair follicles and muscles. Conversion of testosterone to DHT is critical to the development of external genitalia in boys.

Testosterone is also converted to estradiol and androstenedione in adipose tissue. When androstenedione is formed in adipose tissue, it may be converted to a form of estrogen called estrone.

In men, 95% of circulating testosterone is synthesized in the testes, 5% in the adrenals. Only 20% of DHT comes from the testes, while 80% comes from conversion in the peripheral tissues facilitated by 5-α-reductase. In women, approximately half the

androgens are produced in the adrenals and ovaries and the other half come from the peripheral conversion from androstendione and dehydroandrostendione. Androstendione is the precursor of dehydroepiandrosterone (DHEA), which is the main androgen in women and is produced mainly in the adrenals. DHEA is a weak androgen and most of it is found in plasma as sulphate. In women, 20% of the testosterone in circulation is produced in the adrenals.

An important factor that determines the transport, metabolism and activity of testosterone is a protein produced in the liver, the sex hormone-binding globulin (SHBG). This protein binds approximately half of the available testosterone, DHT and estradiol; the remaining hormones are bound to the albumins. A free fraction of testosterone (1–2% of the total) is biologically active. All processes that influence the level of SHBG also play a part in the activity of testosterone. Neither DHEA-S nor androstendione bind to SHBG.

Hypogonadism

Hypogonadism or hypoandrogenism in men can be primary, due to testicular insufficiency, or secondary, due to inhibition of the hypophyseal gonadotrophic hormones FSH and LH. In the case of primary hypogonadism, the gonadotrophins are usually increased (hypergonadotrophic hypogonadism); while in the secondary condition the levels of gonadotrophins are usually decreased (hypogonadotrophic hypogonadism). This latter condition is the subject of this mini review, as it is a significant factor contributing to the poor well-being of patients with advanced disease.

Hypogonadism in men (both primary and secondary) is defined as a low total testosterone level in combination with typical symptoms such as fatigue, loss of motivation and confidence, irritability, reduced libido and erectile strength and, most probably, increased sensitivity to pain. The cut-off value of testosterone characteristic for hypogonadism in men is defined as 8 nmol/L. Although total testosterone is a good predictor for hypogonadism, it is still unclear which fraction of testosterone is biologically active in the ageing population. Endocrinologists are used to determining both free and bound testosterone as well as the levels of SHBG.

Hypogonadism may result in osteoporosis with increased risk of fractures, decreased muscle strength and risk of falls. Testosterone is beneficial

for the functioning of the brain and the immune system. The "normal" variant of hypogonadism, related to age, is defined as late-onset hypogonadism. Studies in large populations show a marked decrease of testosterone levels with age in men [1]. The incidence of late-onset hypogonadism in men aged between 50–79 is at least 8.4% [2]. Low levels of testosterone are associated with increased morbidity and mortality due to many different conditions, including cardiovascular diseases, diabetes and cancer [3]. Because late-onset hypogonadism affects only part of the population, the term andropause is misleading and should not be used. There is wide discussion as to whether testosterone substitution in this population is beneficial for the quality and length of life or not.

Hypogonadism in patients with advanced disease

Against this "normal" background of hypogonadism present in 8% of the ageing male population, clinicians should recognize the secondary forms of this condition. These may be related to the diseases and the use of different drugs. Many centrally-acting drugs may cause hypogonadism, mainly through inhibition of the hyphyseal-gonadal axis. Among the drugs with these properties are some which are very relevant to palliative care: opioids [4–6], corticosteroids [7] and gabapentin [8]. Cancer chemotherapy is also frequently related to decreased gonadal function [9–12]. Furthermore, zinc deficiency may be another risk factor for the development of hypogonadism in advanced disease [13].

The prevalence of hypogonadism is higher in obese patients, those with Type 2 diabetes, coronary heart disease, chronic obstructive lung disease and various autoimmune diseases [14]. While opioids and hypogonadism induced by opioids and gabapentin are associated with weight gain and obesity, naltrexone, an opioid antagonist, usually causes decrease in appetite and weight loss [15, 16]. Low levels of testosterone may be related to another symptom common in advanced disease, namely nausea and vomiting. Women who vomit in early pregnancy have much lower levels of testosterone than their non-vomiting controls [17].

Hypoandrogenism in women is much more difficult to diagnose. In women, it seems that it is not the absolute values of androgens but the dynamics of their change that contribute to the symptoms. Levels of LH are certainly less important for the diagnosis than in men. Conversely, a diagnosis of hypo-

estrogenism in women is simple and is based on the levels of estradiol and FSH.

Androgens and pain

The influence of androgens on pain threshold has been suspected for many years [18–20]. Hypogonadism in laboratory animals was associated with decreased pain thresholds and increased pain sensitivity. In humans, however, these relationships are more controversial. In men, low levels of testosterone are certainly associated with increased pain sensitivity. However, women with lower levels of testosterone also have reduced pain thresholds [21] but the relationship is more complex and it is too simple to state that androgens are the only factor responsible for pain modulation.

Opioids may depress androgen levels

Hypogonadism was first noticed in patients who had been using methadone for a long time [22] but this condition was later confirmed for many other, if not all, opioids [4, 23, 24]. The effect is seen in patients receiving opioids via different routes, intrathecal [6] as well as systemic [4, 5, 25, 26]. It seems probable that buprenorphine causes less gonadal suppression than the other opioids [24, 27].

Opioids inhibit the release of hypophyseal gonadotrophins, thus opioid-induced hypogonadism can be best described as hypogonadotrophic hypogonadism. The hypogonadotrophic effect of opioids can be observed even after the administration of a single opioid dose, both in laboratory animals [28] and in humans. While the gonadotrophins are depressed by opioids, hypophysis may secrete more prolactin under the same circumstances [29]. Pyridoxine may counteract this effect [30]. Opioid-induced hyperprolactinaemia may occasionally cause painful swelling of the nipples and galactorrhoea [31].

Depression of the hypophysis is not limited to the gonadotrophins alone. Opioids may also inhibit ACTH release [32] and in such a way cause adrenal hypofunction. This effect may be even more pronounced when the patient receives steroids.

The relationship between hypogonadism and sensitivity to pain

Hypogonadism induces several generic symptoms (such as fatigue, weakness and irritability) which may also be caused by other multiple factors.

Potentially, administration of testosterone may be beneficial to fatigued cancer and HIV patients but large clinical trials have not yet been completed [33–35]. Of more interest is the relationship between hypogonadism and increased sensitivity to pain. This relationship is very well defined in laboratory animals [18–20, 36, 37] but can only be detected in humans indirectly. Men have higher thresholds for cold-induced pain than women [38]. There are no studies supporting the idea that testosterone therapy may assist pain treatment. However, we recently published a case series suggesting that in many cases of pain which is difficult to treat, the addition of testosterone may be beneficial (Roantree, Zylicz, Adv. Pall. Med. 2009; 8: 69–74 — this issue).

Does DHEA play an important role in the symptoms of hypogonadism?

Dehydroepiandrosterone (DHEA) and its sulphate esters (DHEA-S) are the most abundant androgens in the circulation, DHEA and DHEA-S playing an especially important role for women. However, the androgen effect of these steroids is weak. The levels of DHEA are depressed in hypogonadism alongside testosterone, but the evidence for the long-term benefit of DHEA replacement, alone or in combination with testosterone in hypogonadism, is lacking [39]. Opioids may depress both testosterone corticosteroids and DHEA [40].

Which preparation of testosterone to use?

As opioids are responsible for hypogonadism and testosterone replacement, either using or not using DHEA-S has the potential to improve pain control one should notice that there are several snags. Androgens may be tried and occasionally produce more effective pain control and improved quality of life. Testosterone should be applied as a transdermal patch, as it is not only simple to start but also easy to discontinue in the case of adverse effects. Transdermal testosterone may be effective within 24–48 hours, although it usually takes weeks of substitution to increase the plasma levels of this hormone. Blood levels of DHEA-S increase much more rapidly. It looks as if testosterone has the potential to increase not only the efficacy but also the toxicity of opioids (Roantree, Zylicz, Adv. Pall. Med. 2009; 8: 69–74 — this issue). This is the reason why the slow release preparations injected intramuscularly are initially contraindicated. Transdermal patches can be replaced

by a transdermal gel preparation when higher doses are needed. Oral tablets containing testosterone can be prescribed, although they are stigmatized by a higher probability of liver toxicity [41].

Contraindications for testosterone therapy

Despite (potential) benefits of therapy with androgens, there are also several contraindications. Obviously, patients suffering from prostate cancer, and deliberately deprived of androgens in order to halt tumour growth and invasion, should not be treated with androgens. Similarly, patients with breast cancer should avoid androgens as a proportion of them may be metabolized to estrogens and hence stimulate tumour growth. Other contraindications are relative. Hypogonadism in males is associated with an enhancement of fibrinolytic inhibition via increased synthesis of the plasminogen activator inhibitor PAI-1 [42]. Androgens may have profibrinolytic effects. Patients with high and toxic doses of opioids should avoid androgens as they may further increase toxicity. The dose of opioids should be decreased before starting a patient on androgens. Testosterone may increase sensitivity to insulin in diabetic patients [43] and in such a way induce dangerous hypoglycaemia.

In young males, testosterone can be used in supraphysiologic doses, while in older men the doses should be limited to substitution only. In females, androgens may cause unpleasant skin reactions (acne) and liver function changes, as well as hirsuitism and masculinization. It seems probable that in women testosterone should be used together with hormone replacement therapy (HRT). Combinations of oestrogens and methyltestosterone are available on the market.

Do patients with androgen deprivation experience more pain?

The treatment of hormone-responsive prostate cancer is based on androgen deprivation, either through treatment with hormones that inhibit the release of gonadotrophins from the hypophysis, blocking synthesis of androgens, or through providing blockers of the androgen receptors. Treatment with corticosteroids is also seen as beneficial for prostate cancer, as it further decreases the adrenal synthesis of androgens [7]. This deprivation, in the light of the facts discussed above, may contribute to decreased pain thresholds and more com-

plaints of pain. To my knowledge, there are no data to confirm the anecdotes that those with prostate cancer consume more opioids for their pain or experience greater discomfort than other patients. In my own pain practice, I am interested in the pain induced by the compression of small cutaneous nerves against bony prominences. This kind of pain is usually overlooked and can easily be treated with local depo-steroid injections (Zylicz et al, 2009, in press). Most of the patients seeking this kind of treatment in my practice are patients with prostate cancer.

Does testosterone therapy increase the risk of prostate cancer?

Therapy with androgens is continuously questioned, especially with regard to the risk of prostate cancer. Long-term studies have failed to provide a definitive answer to this question. An in-depth analysis of 18 studies found no association between testosterone blood levels and risk of prostate cancer [44]. As many older patients may harbour clinically silent prostate cancers, an increase in androgen substitution may still potentially be detrimental to them.

Hypogonadism in itch of cholestasis

Pruritus of cholestasis is no longer thought (only) to be associated with the accumulation of bile acids [45]. Instead, there is ample evidence that a cholestatic liver produces large amounts of endogenous opioids [46], which may depress levels of testosterone and DHEA-S and induce hypogonadism. Low levels of androgens may sensitize the spinal cord and facilitate itch. There are some old anecdotal data suggesting that testosterone may be beneficial in the treatment of cholestatic pruritus [47, 48]. This therapy did not become popular, as testosterone also has the potential to increase the cholestasis.

Conclusion

Testosterone and other androgens may play an important role in the well-being of patients with advanced disease. Substitution of these hormones may, potentially, improve a patient's quality of life and increase the pain threshold. Evidence for this effect is still lacking and clinical trials are needed to confirm case reports. Hypogonadism may be the key to understanding opioid insensitivity and tolerance.

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