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Comprehensive Review

Opioid-Induced Hypogonadism: Why and How to Treat It

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Background: Gonadal hormones are critical factors in modulating the experience of pain, as suggested by the several sex differences observed: women have a greater risk of many clinical pain conditions, and postoperative and procedural pain may be more severe in them than in men. A growing body of literature demonstrates the role of estrogen in the female pain experience, whereas less attention has been given to testosterone and its functions.

Nevertheless, testosterone has an appreciable role in both women and men: adequate serum levels are required in males and females for libido and sexuality; cellular growth; maintenance of muscle mass and bone; healing; blood-brain barrier; and for central nervous system maintenance. Pain therapy, and particularly opioid therapy, has been shown to affect testosterone plasma levels. Thus, the chronic administration of pain killers, such as opioids, requires the physician to be aware of both the consequences that can develop due to long-term testosterone impairment and the available means to restore and maintain physiological testosterone levels.

Objective: The objective is to highlight to pain physicians that the endocrine changes occurring during chronic pain therapy can participate in the body dysfunctions often present in chronic pain patients and that there are possible hormone replacement methods that can be carried out in men and women to improve their quality of life.

Study Design: A comprehensive review of the literature.

Methods: A comprehensive review of the literature relating to opioid-induced hypogonadism, as well as other very common forms of hypogonadism, its endocrine effects, and possible therapeutic actions. The literature was collected from electronic and other sources. The reviewed literature included observational studies, case reports, systematic reviews, and guidelines.

Outcome Measures: Evaluation of the endocrine changes described in chronic pain therapy was the primary outcome measure. The secondary outcome measures were functional improvement and adverse effects of hormone replacement.

Results: The results of the survey clearly show that sex hormone determination is very rare in pain centers. Given the complexity and widespread nature of pain therapy, there is a paucity of qualitative and quantitative literature regarding its endocrine consequences. The available evidence is weak for pain relief, but is consistent for many collateral effects, possibly deriving from pain therapy, such as fatigue, depression, and neurodegenerative diseases.

Limitation: This is a narrative review without application of methodological quality assessment criteria. Even so, there is a paucity of literature concerning both controlled and observational literature for the endocrine effects of most analgesic drugs.

Conclusion: Testosterone replacement suffers from old prejudices about its utility and safety. With this review we illustrate the available therapeutic choices able to maintain T concentration into physiological ranges and reduce nociception with a final goal of improving patients' quality of life.

Key words: Pain, pain therapy, hypogonadism, adverse effects, morphine, HRT, testosterone.

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Background

Awareness of the need to adequately treat pain, particularly chronic pain, is important to both patients and pain physicians. Opioids are generally recognized as useful analgesic drugs in the treatment of chronic pain, notwithstanding the several side effects already widely known by physicians and patients. However, one side effect almost always not considered is hypogonadism (1-4). As recently described, intrathecal and oral opioids are able to suppress testosterone (T) secretion throughout their period of administration (5-7). Interestingly, although this opioid-induced condition was noted decades ago, and research groups have sporadically described cases with endocrine disruptions (8-11), its clinical management is still far from being considered, particularly in pain centers.

Objectives

In our review, we included data on opioid-induced hypogonadism and data on testosterone physiopathology to underline the several recognized syndromes occurring when testosterone levels remain chronically low, as during opioid therapy. Moreover, other recognized conditions of hypogonadism are reported, together with literature referring to possible hormone replacement therapies.

Methods

The methodology utilized here follows a narrative review process. However, some aspects of the systematic review process derived from observational studies, and a systematic review of observational studies and other guidance were used, along with previous systematic reviews. The search involved multiple sources including PubMed. The search terminology included chronic pain, testosterone, and opioids.

Discussion

Hypotestosteronemia

Ideas about the role of gonadal hormones, and testosterone in particular, are slowly changing. Now generally considered more than a "sex hormone," testosterone's sexual effects appear to be the least of its physiological properties. In fact, testosterone is generally described as playing multiple roles, from intrauterine life to advanced age, and it is recognized as an important contributor to the robust metabolic functioning of multiple body systems. As can easily be seen from the literature, a broad spectrum of demonstrated physiological and pathophysiological functions and associations have been shown (12-13). The main anabolic effects include stimulation of muscle mass increase and strength (14). Other important effects include linear growth and maturation of bone and its essential influence on health and well-being via its action on mood and cognition centers in the brain (15). Recent studies have demonstrated that some steroids, including testosterone, are also secreted and/or used by neuronal and glial cells and that they act as neuroactive steroids with a neuroprotective role. Neurosteroids are synthesized in the central and peripheral nervous systems (especially in myelinating glial cells) from cholesterol or steroidal precursors (such as testosterone intermediate) imported from peripheral sources (16-17).

Opioids, both endogenous and exogenous, modulate gonadal function primarily by acting on opioid receptors in the hypothalamus (18), inducing the decreased release or disruption of the normal pulsatility of gonadotropin releasing hormone (GnRH) secretion. This results in a reduction of the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland and of testosterone or estradiol (E2) from the gonads. Opioids may also have direct effects on the pituitary gland and the testes (19,20).

Testosterone concentration is decreased by multiple factors, including aging, intercurrent disease states, lifestyle (for example, smoking, lack of regular physical exercise), high body mass index (BMI) and an excess of fat tissue with android distribution (21-23). In turn, in congenital or acquired hypotestosteronism or hypotestosteronemia, abnormally low testosterone levels are inversely associated with fat mass, BMI, insulin and glucose levels, total cholesterol, low density lipoprotein cholesterol, triglycerides, inflammatory cytokines and leptin sensitivity, while they are positively associated with high density lipoprotein cholesterol (HDL-C) levels, muscle mass and strength, and all factors linked to obesity (24-26).

Moreover, severe androgen deficiency in both sexes has repeatedly been associated with weight gain (with increased visceral adiposity), loss of muscle mass and strength, osteoporosis, symptoms of fatigue, impaired glucose tolerance, dyslipidemia, mood alterations, depression, increased anxiety, reduced quality of life, and emotional disturbances (27,28). Interestingly, testosterone administration to hypogonadal men decreases adipose tissue (29-30), improves bone density (31), increases muscle mass (32), and enhances quality of life in chronic pain patients (5).

Long-term opioid abuse or use is also a major cause of hypogonadism in women (3,6). In fact, opioids lead to a decline in LH, FSH, E2, testosterone and progesterone, thus affecting menstruation (4,9,18). Exogenous opioids were reported to have a drastic effect on the female menstrual cycle: after long-term intrathecal opioid administration, almost 70% of premenopausal women developed amenorrhea and 30% developed irregularities in menstruation (3). The profound inhibition of ovarian sex hormone and adrenal androgen production described among women chronically consuming sustained-action opioids was shown to have important consequences on menstrual flow and reduced fertility, but also was shown to significantly increase opioid-associated depression, osteoporosis, and hyperalgesia (18). Interestingly, the route of opioid therapy was found to influence the development of hypogonadism in the sexes. Intrathecal opioid administration to patients with chronic noncancer pain resulted in decreased sex steroids in both male and female patients (3), causing a high prevalence of hypogonadism in both men and women. However, in patients taking long-term oral opioids, the prevalence of hypogonadism was significantly lower in women than in men (10).

Data on opioid use by chronic pain patients mostly refer to morphine. Nevertheless, several studies on methadone-maintained men and heroin addicts have demonstrated decreased testosterone levels consistent with central hypogonadism (8).

In addition to opioid-induced hypogonadism, there is a fairly common iatrogenic hypogonadism related to the treatment of prostate cancer. The use of LH-releasing hormone (LHRH) analogs has emerged as an effective form of androgen deprivation therapy for this androgen-sensitive tumor (33). As expected, androgen deprivation therapy for males with prostate cancer results in a hypogonadal state that may have important, but as yet undetermined, effects. For instance, men with prostate cancer rendered hypogonadal by LHRH analog therapy experience increased central arterial pressure (33). Interestingly, although prostate cancer is one of the leading causes of death in men, many prostate cancer patients die of other, unrelated causes, with a particularly strong association with cardiovascular disease as a possible cause of death (34). The observation of improved arterial compliance after the cessation of treatment suggests a reversible phenomenon. This raises the possibility that prostate cancer itself, or the treatment with hormone manipulation therapy, somehow adversely affects vascular function and aggravates the natural course of vascular disease.

Moreover, some recent population studies have shown that low serum testosterone levels are associated with coronary heart disease (CHD) mortality and that baseline testosterone levels are inversely related to deaths due to CHD (35). Cardiovascular disease is the leading cause of mortality in the United States but also in many areas of Europe. A higher CHD prevalence among men has been attributed to gender-related dyslipidemia, such as lower serum HDL-C levels than what is seen in premenopausal women (25). Indeed, the evidence linking hypogonadism and metabolic syndrome (MetS)/CHD (22) is strong enough that the definition of MetS in men may be expanded in the future to include hypogonadism as a diagnostic parameter.

Hypogonadism and the elderly

As we age, the body undergoes multiple degenerative changes at multiple sites and in multiple systems (36). Among the changes occurring with aging are those that affect several aspects of the endocrine system, decreasing its secretions to varying degrees in different individuals: a decrease identified by a poor but widely recognized appellation, the "pauses" (37). Included in these conditions is the acquired form of hypotestosteronism in aging men (37). Since demographic data clearly demonstrate that the percentage of the population in the older age group is increasing, androgen deficiency in the aging male has become a topic of increasing interest and debate (38,39).

In men, there is a slow but continuous decline in average serum testosterone after the age of 20–30 years; both testosterone and the free testosterone index decrease progressively by up to 1% per year, with the lowest levels seen in men 70 years of age and older (39). Approximately 20-30% of men 60 years and older are estimated to have low testosterone (40), which is often accompanied by undesirable signs and symptoms. Whether these associations translate into a higher pain incidence and/or reduced survival is less clear.

The decrease in androgen levels with aging is the result of both gonadal and hypothalamic-pituitary failure. Multiple functional alterations in the hypothalamic-pituitary-thyroid axis, specifically linked to distinct risk factors, are simultaneously superimposed on a background of progressive testicular impairment associated with increasing age. In turn, serum sex hormone-binding globulin (SHBG) concentration increases with aging, resulting in a "free" or bio-T level that decreases to a greater extent than total testosterone (41).

Therefore, of even greater significance is the steeper fall of the most biologically active fraction of total testosterone below the normal values determining a condition of hypogonadism.

Several other physiological changes related to increasing age have been documented in men: muscle mass, muscle strength, and bone density decrease while the proportion of adipose tissue increases with advancing age (42-44).

Testosterone replacement therapy in hypogonadal men and women

Despite the evidence on the effects of T, general population screening for androgen deficiency is still not recommended and morning total testosterone is measured only in men with one or more of the following signs: incomplete sexual development, reduced libido, decreased spontaneous erections, gynecomastia, loss of body hair, low sperm count, decreased energy, and reduced strength. Moreover, prescribing testosterone treatment to all older men with low testosterone is not recommended; replacement therapy is reserved for symptomatic men (45). The rationale for administering testosterone to those men comes from studies showing that testosterone improves decreased energy, reduced strength, and sometimes sexual function.

Biochemical assessments for suspected hypogonadism include measures of total T, free T, SHBG (46,47), FSH and LH. Regardless of age or disease etiology, men with a total testosterone level less than approximately 300 ng/dL often develop signs and symptoms associated with classic hypogonadism (48). Indeed, the diagnosis of hypogonadism in men is based on a combination of clinical signs and symptoms in addition to laboratory tests (45). However, as stated in the latest US guidelines (49), there is no agreement on the threshold testosterone level below which symptoms and adverse effects related to low circulating androgens occur. Hence, there is no absolute rule regarding when to start testosterone replacement therapy. Although most men feel the effects of androgen deficiency when total testosterone is below 300 ng/dL (10.4 nmol/L), the circulating levels of testosterone are extremely variable and thus evaluation of symptoms and signs is detrimental for prescribing replacement therapy.

Apart from the circadian rhythm of secretion, known to become less acute with age (50), testosterone levels are influenced by several factors (51): SHBG and albumin levels, conditions such as diabetes mellitus, obesity, hypothyroidism and altered hepatic function. Moreover, glucocorticoids, progestins, estrogens, androgenic steroids, and anticonvulsants are known to have an effect on testosterone concentration and must be considered in the medical history of a man with suspected androgen deficiency.

When testosterone replacement treatment is considered, scrupulous attention should be paid in order to exclude men with breast or prostate cancer, with elevated levels of prostate-specific antigen or a palpable prostate nodule with no additional urological evaluation, and with hematocrit > 50%.

Deciding when to start testosterone replacement therapy and which candidates can benefit from the treatment is still a critical issue. International guidelines (45) are an essential support, but practical clinical recommendations to identify men who can really take advantage from testosterone supplementation are still scanty. A valid first-line instrument is a 12-item structured interview (Androtest) given to symptomatic patients. This questionnaire provides a score useful for a first screening of male hypogonadism (52). Men obtaining a score > 8 (considered pathological) can then undergo laboratory testing to measure Total T, SHBG, and calculated Free T. The association of both symptoms and low testosterone levels will then justify the need for testosterone treatment.

When the decision to treat a man with hypogonadism is made, then the goal is to provide a testosterone replacement treatment able to maintain testosterone levels within normal ranges for healthy young male adults.

There are many testosterone formulations for replacement therapy on the market but only a few are for prescription, namely intramuscular and transdermal preparations. The aim of an ideal testosterone replacement therapy is to maintain the testosterone concentration within the normal range throughout the interval between administrations. Many testosterone formulations used in the past have now been abandoned because of the sharp fluctuations in testosterone circulating levels.

When first released on the market, oral testosterone preparations seemed to be a good option for testosterone treatment in terms of acceptability and compliance. However it soon became evident that, apart from showing moderate hepatotoxicity (17α methyltestosterone, fluoxymesterone), they induced supraphysiological testosterone concentrations right after their consumption, followed by a sudden drop to subphysiological concentrations before the subsequent intake (testosterone undecanoate, TU).

Prescription of sublingual, nasal, and rectal formulations has been abandoned for the same reasons, and the older intramuscular testosterone preparations had similar problems: the esters of T, such as testosterone enanthate and testosterone propionate, are associated with supraphysiological testosterone peaks. This means that increasing the dose of administration only results in accentuating the peaks and does not increase the time interval of testosterone's presence in the blood.

Although it has been about 30 years since testosterone undecanoate (TU) became available as an oral formulation, the recognition of the favorable pharmacokinetics of its intramuscular formulation is much more recent. After the injection of 1,000 mg of TU in castor oil, the serum levels of testosterone remain above the lower limit of the normal range for more than 100 days and the maximal testosterone concentration remains within the normal range and is significantly lower than the testosterone peaks reached with other formulations (53-55). Therefore, intramuscular TU is particularly well accepted as a long-term form of replacement therapy because one injection of 4 mL (250 mg TU/mL x 4mL = 1000 mg TU) allows a between-administration interval of up to 14 weeks, maintaining sufficient testosterone levels and not leading to accumulation. The most frequently reported undesirable effects are acne and injection site pain. It is of great importance that the injection, being an oily solution, is administered very slowly.

Transdermal testosterone is a safe and effective alternative: patches and creams for both scrotal and nongenital skin have been used; today the most acceptable way of transdermal testosterone administration seems to be a 1% hydroalcoholic gel. testosterone gel, applied on nongenital skin, dries very fast and has good bioavailability (9-14%); daily application is required and the testosterone concentration reaches a steady state in 48 to 72 hours (after the first application. A standard dose of 5 g of gel (equivalent to 50 mg of testosterone) is recommended, but the dosage can be adjusted on an individual basis, being careful not to exceed the dosage of 10 mg/d. testosterone gel is the first option in older men needing testosterone supplementation; its pharmacokinetics allow it to be rapidly discontinued whenever an adverse effect happens. Men using transdermal testosterone have to be aware that testosterone gel can be transferred to other persons by close skin-to-skin contact, resulting in increased testosterone serum levels and possibly adverse effects (e.g., growth of facial and/or body hair, deepening of the voice, irregularities of the menstrual cycle) in cases of repeated contact (inadvertent androgenization). We have recently administered transdermal testosterone in opioid-treated patients (5) and observed that the amount of time required to obtain an effective increase in blood Total Testosterone was significantly longer in men treated with opioids compared to those not on opioid treatment.

Men on long-term testosterone treatment should be checked periodically. Hemoglobin, hematocrit, and liver function must be monitored in addition to the testosterone concentrations.

In conclusion, intramuscular TU (1,000 mg every 10-14 weeks) and transdermal testosterone (50 mg/ d) are 2 convenient options for testosterone replacement therapy in hypogonadal men.

Women also might need testosterone replacement therapy. testosterone is secreted by the ovaries and adrenal glands and slowly declines with age. After gonadal removal, testosterone declines by approximately 50% within days after surgery. testosterone prescribed to a woman who has been oophorectomized is indicated when she develops a hypoactive sexual desire disorder (HSDD) attributed to a lack of androgens. In the 2 most important studies (56,57), total satisfying sexual activity (the primary endpoint), sexual desire, and distress associated with low sexual desire (the secondary endpoints) were evaluated; a significantly higher percentage of women receiving testosterone patches reported a benefit in the endpoints (which they considered clinically important) compared to women who received a placebo.

The diagnosis of androgen deficiency in women is particularly difficult because the common tests for measuring circulating testosterone are not precise and accurate for physiologically low female testosterone concentrations. Therefore, the diagnosis of HSDD has to be made on a clinical basis. At the moment, the indication for testosterone treatment is only for women who have undergone bilateral oophorectomy and are already taking estrogens.

In women, testosterone can be prescribed as a testosterone patch (in fact, the only formulation authorized for prescription in women) designed to systemically deliver 300µg/d, which achieves testosterone concentrations compatible with premenopausal levels. Following application of the patch on abdominal skin, maximum serum concentrations of testosterone are reached within 24-36 hours, with a wide inter-individual variability. Serum testosterone concentrations reach a steady state after application

of the second patch when applied in a twice-a-week regimen. The testosterone patch is generally well tolerated and the most common adverse effects are application site reaction, hirsutism, and acne. More studies are needed to extend the prescription indications for testosterone replacement therapy to other groups of women and to confirm the safety of the treatment.

Conclusion

Opioid-induced hypogonadism is under-recognized and undertreated. While there are no current standards for monitoring these patients, the available evidence suggests that we should routinely screen patients on opioid treatment for manifestations of hypogonadism and arrange for laboratory investigations to assess gonadal function.

Opioid-induced hypogonadism in males is often ignored by pain physicians and is rarely considered for treatment despite its high frequency (almost 100%). Persistence is important not only because of the endocrine aspect of the illness but also because it cannot be excluded that opioid-induced hypogonadism in chronic pain patients could determine an increasing pain sensitivity.

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