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Hypogonadism and low bone mineral density in patients on long-term intrathecal opioid delivery therapy

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ABSTRACT

Objectives: This study aimed to investigate the hypothalamic-pituitary-gonadal axis in a sample of male patients undertaking intrathecal opioid delivery for the management of chronic non-malignant pain and the presence of osteopaenia and/or osteoporosis in those diagnosed with hypogonadism.

Design: Observational study using health data routinely collected for non-research purposes.

Setting: Department of Pain Management, Russells Hall Hospital, Dudley, UK.

Patients: Twenty consecutive male patients attending follow-up clinics for intrathecal opioid therapy had the gonadal axis evaluated by measuring their serum luteinising hormone, follicle stimulating hormone, total testosterone, sex hormone binding globulin and calculating the free testosterone level. Bone mineral density was measured by DEXA scanning in those patients diagnosed with hypogonadism.

Results: Based on the calculated free testosterone concentrations, 17 (85%) patients had biochemical hypogonadism with 15 patients (75%) having free testosterone <180 pmol/L and 2 patients (10%) between 180 and 250 pmol/L. Bone mineral density was assessed in 14 of the 17 patients after the exclusion of 3 patients. Osteoporosis (defined as a T score ≤−2.5 SD) was detected in three patients (21.4%) and osteopaenia (defined as a T score between −1.0 and −2.5 SD) was observed in seven patients (50%). Five of the 14 patients (35.7%) were at or above the intervention threshold for hip fracture.

Conclusions: This study suggests an association between hypogonadism and low bone mass density in patients undertaking intrathecal opioid delivery for the management of chronic non-malignant pain. Surveillance of hypogonadism and the bone mineral density levels followed by appropriate treatment may be of paramount importance to reduce the risk of osteoporosis development and prevention of fractures in this group of patients.

ARTICLE SUMMARY

Article focus

- Hypogonadism is common in intrathecal opioid therapy patients, but there is a dearth of literature investigating bone mineral density in this population.
- We aimed to prospectively investigate if undiagnosed hypogonadism in intrathecal opioid therapy patients may result in low bone mineral density levels.

Key messages

- Undiagnosed hypogonadism in intrathecal opioid therapy patients may lead to low bone mineral density levels.
- Hypogonadism and bone mineral density levels surveillance may be of paramount importance to reduce the risk of osteoporosis and fractures in patients undertaking intrathecal opioid therapy.

Strengths and limitations of this study

- To our knowledge, this is the first study to specifically address the potential decrease in bone mineral density as a consequence of long-term intrathecal opioid therapy.
- Further studies are warranted to assess the effectiveness of early detection and adequate treatment to prevent bone mineral density decrease and to investigate the value of hormonal replacement therapy to normalise bone mineral density levels.

INTRODUCTION

Treatment strategies for the management of chronic pain start with the lowest risk and least invasive intervention and progress if a treatment is not effective. Intrathecal drug delivery (IDD) is considered a last resort treatment for the management of severe chronic pain owing to its invasive nature, concerns about long-term opioid use and the possible complications related to this modality of treatment. Intrathecal spinal analgesia has become a recognised treatment for chronic non-malignant pain since the first reservoir was implanted in 1981.[1] The use of opioids via intrathecal drug delivery allows for a selective concentration to reach an

important site of pain transmission, the spinal cord dorsal horn.[2] Opioid administration into the intrathecal space achieves its effects at lower doses than by using the epidural route.[3] The drug is highly localised, so its analgesic efficacy is maximised at lower doses.[4] Moreover, opioid dose escalation over the years may be modest.[5][6] These factors lead to a decrease in the possible opioid side effects.

The potential effect of intrathecal opioid delivery on the endocrine system is one that is least recognised and investigated.[7] Currently, opioid-induced hypogonadism is under-recognised and undertreated.[8][9] Some patients may attribute the signs and symptoms of hypogonadism, such as decreased libido, tiredness, loss of muscle mass and strength, among others, to the chronic pain and its related conditions rather than to the intrathecal medication.[7][10] Moreover, symptoms of hypogonadism are often neither disclosed by the patient nor documented by the physician.[11] Currently, limited clinical awareness of the opioid effects on the endocrine system, together with the lack of information on their long-term consequences, is likely to result in a lack of information provision to the patient when long-term opioid therapy is being considered.[12]

Animal studies suggest that opioids affect gonadotropin release via the inhibition of the gonadotropin releasing hormone (GnRH) by β-endorphin,[13] most likely at the μ-receptors.[14] This inhibition reduces the release of the luteinising hormone (LH) and the follicle stimulating hormone (FSH) by the pituitary gland and consequently the production of testosterone by the gonads, resulting in hypogonadism and loss of libido. This is characterised by the low or low-normal LH and FSH levels and low testosterone levels.[11] Most of the circulating testosterone is bound to the sex hormone-binding globulin (SHBG). A lesser fraction is non-specifically bound to albumin and only a small percentage of the testosterone is unbound.[15] Historically, free testosterone was thought to be the only biologically-active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, as well as being readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable.

Hypogonadism is an important risk factor for development of osteoporosis in both sexes, but opioids have not been considered as a risk factor.[16] To our knowledge, the assessment of bone mineral density (BMD) in patients undertaking intrathecal drug delivery is limited to one study, which suggested a tendency towards decreased BMD in these patients, but the prevalence of osteopaenia or osteoporosis in these patients was not reported in this study.[17]

The aim of this study was to investigate the hypothalamic-pituitary-gonadal axis in a sample of male patients undertaking intrathecal opioid delivery for the management of chronic non-malignant pain and to assess the prevalence of osteopaenia and/or osteoporosis in those diagnosed with hypogonadism.

METHODS

Patients

Twenty consecutive male patients attending follow-up clinics for IDD therapy at Russells Hall Hospital, Dudley, UK, for the management of chronic non-cancer pain were included in this observational study using health data routinely collected for non-research purposes. All assessments were performed as part of routine clinical care. No additional procedures were carried out for research purposes. None of these patients received testosterone supplementation within the previous 3 months. The pain syndrome experienced by the patients was classified as nociceptive (58.8%), neuropathic (5.8%) and mixed nociceptive-neuropathic (35.3%). All the patients were receiving intrathecal opioids for the management of their pain. Intrathecal morphine was the only medication administered to 50% of the sample. In individual cases, other substances were added to the intrathecal medication, with combinations of morphine with bupivacaine (12.5%), morphine with bupivacaine and clonidine (25%), and morphine with bupivacaine and baclofen (12.5%).

Laboratory methods

Blood samples were collected between 08:00 and 11:00 during a 7-month period (April–October 2010), as part of routine clinical care, for the measurement of serum LH, FSH, prolactin (PRL), total testosterone (TT) and SHBG. All assays were carried out by the Department of Clinical Biochemistry at Russells Hall Hospital, Dudley, UK. LH, FSH, PRL and TT were measured according to the manufacturer's instructions by immunoenzymometric fluorimetric assay on the Tosoh AIA 2000 LA analyser (Tosoh Bioscience N.V., Tessenderlo, Belgium). The inter-assay imprecision (%CV) quoted by the manufacturer was 2.6% for LH, 2.3% for FSH and 5.3% for testosterone. SHBG was measured according to the manufacturer's instructions by chemiluminescent immunometric assay on the Immulite 2000 XPi analyser (Siemens Healthcare Diagnostics Ltd, Camberley, Surrey, UK). The inter-assay variability (%CV) for SHBG was 5%. Calculations of free testosterone (FT) were carried out using the Vermeulen equation.[15] Serum TT <8 nmol/L and/or FT <180 pmol/L was considered as biochemical hypogonadism. Serum TT 8–12 nmol/L and/or FT 180–250 pmol/L were considered as borderline/low.[18]

Assessment of bone mineral density

Bone mineral density was measured by DEXA scanning of the femur (neck and hip) and lumbar spine or left forearm using the Lunar Prodigy DEXA (GE Lunar Corp., Madison, Wisconsin, USA). Bone densitometry DEXA scans were carried out by the Department of Radiology at Corbett Hospital, Dudley, UK. A lumbar spine scan was not carried out on patients who had previous spinal surgery. In those cases, assessment was performed at the left forearm site. Results are presented as BMD (g/cm^2), T and Z scores. Reference values for

T scores were based on the UK (ages 20–40) femur, spine or forearm reference population (v107). Osteopaenia was defined as a T score between −1.0 and −2.5 SD, and osteoporosis as a T score at or below −2.5 SD. Measurements of height, weight and body mass index (BMI) were also performed. The BMI scores were categorised according to the WHO key cut-off points as <18.5 (underweight), ≥18.5 and ≤24.9 (normal weight), ≥25 and ≤29.9 (overweight) and ≥30 kg/m^2 (obese). The 10-year probability of fracture was calculated based on the Fracture Risk Assessment Tool (FRAX).[19] In addition to the BMD value or T score (femoral neck), this tool takes into account clinical risk factors for the development of osteoporotic or hip fractures such as previous fractures, a history of hip fracture in the patient's parents and hypogonadism, among other factors.

Data analysis

A Kolmogorov-Smirnov test was performed to test the distribution of numerical data, followed by the appropriate statistical tests. Comparisons between groups were carried out with the Mann-Whitney test. Data are reported as median (minimum–maximum). The 95% CIs for the TT and FT median values were calculated for comparison with normal reference values. Statistical significance was judged at the 5% level. Statistical tests were performed using the Predictive Analytics SoftWare (PASW) (V.18.0, SPSS Inc, Chicago, Illinois, USA).

RESULTS

Assessment of sex hormones

The median age at the time of blood collection was 58 years (47–69). The median duration from implantation of the IDD system to hormone assay was 100 months (15–203) with an intrathecal opioid dose of 2.68 mg/day (range 1–9.7) (table 1). The duration of pain prior to the start of IDD was 9 years (range 3–35).

The median TT level with 95% CIs was 4.95 nmol/L (3.0 to 10.1), which was significantly lower than the cut-off level of 12 nmol/L for borderline/low testosterone. The median FT levels with 95% CIs (69.45 (47.3 to 127.0))

were also significantly lower than the cut-off level of 180 pmol/L for low FT (t=−3.403, p<0.005, r=0.61). The mean LH, FSH and SHBG concentrations were within the respective reference ranges. Prolactin levels were above the reference range in two patients. One of these patients had low TT and FT values and the other patient presented a borderline/low TT value. Based on TT calculations, 17 (85%) patients presented biochemical hypogonadism values with 12 (60%) at less than 8 nmol/L and 5 (25%) presented with TT values between 8 and 12 nmol/L (borderline/low). Based on FT calculations, 17 (85%) patients were biochemically hypogonadal with 15 (75%) patients at less than 180 pmol/L and two (10%) patients between 180 and 250 pmol/L. Only one of the patients had TT and FT values within the quoted reference ranges, two patients presented borderline/low TT and normal FT values, one patient had low FT values and normal TT values, and one patient had borderline/low FT values and normal TT values.

Assessment of bone mineral density

Considering that free testosterone reflects more accurately the clinical situation than total testosterone in plasma,[15] the 17 male patients diagnosed as hypogonadal through calculated FT values were considered for assessment of bone mineral density. Three patients were excluded (one patient was excluded on the basis that the primary indication for IDD use was spinal osteoporosis, one patient had the intrathecal opioid therapy discontinued and one patient passed away.

The median age of the 14 patients at the time of BMD assessment was 62.5 years (48–70). All the patients investigated for BMD were Caucasian. The BMI score was 29.4 kg/m^2 (20.1–45.4). According to the BMI score, the majority of patients (64.3%) were either overweight or obese and none of the patients were underweight.

Table 2 shows the results of the BMD assessment. Individual T scores below −1.0 SD in at least one site were identified in 10 (71.4%) patients. Osteopaenia, defined as a T score between −1.0 and −2.5 SD, was observed in seven (50%) patients. Osteoporosis, defined as a T score at or below −2.5 SD, was detected in three (21.4%) patients. When considering the Z scores, one (7.1%) of the participants presented a value at or below −2.5 SD, indicating osteoporosis, and four (28.6%) other patients had Z scores between −1.0 and −2.5 SD representative of osteopaenia.

Seven patients had T scores below −1.0 SD in more than one assessed site (table 3). Three patients had osteoporosis and/or osteopaenia in two sites compared with four patients in three sites. Three of the patients presented Z scores lower than −1.0 SD in three sites compared with one patient in two sites. No statistical differences were observed between the patients within normal reference range values and those with osteopaenia or osteoporosis for age (p=0.72) or BMI (p=0.48).

Several known clinical risk factors for low bone mineral density were present in this sample, including

Table 1 Reference ranges and levels in 20 men undertaking intrathecal opioid administration

	Reference range	Intrathecal opioid patients
LH (IU/L)	2.2–13.3	1.9 (0.2–19.9)
FSH (IU/L)	1–7	5.3 (0.3–23.9)
SHBG (nmol/L)	13–71	51 (17–123)
PRL (mU/L)	0–445	225 (53–614)
TT (nmol/L)	9.47–28.3	4.95 (1.2–18.8)
FT (pmol/L)	185–437	69.45 (14–328)

Statistics are presented as median (minimum–maximum). FSH, follicle stimulating hormone; FT, free testosterone; LH, luteinising hormone; PRL, prolactin; SHBG, sex hormone binding globulin; TT, total testosterone.

Table 2 Bone mineral density measurements

Site of measurement	BMD (g/cm^2)	T score	Z score
Femoral neck (n=14)	0.925 (0.734–1.176)	−1.10 (−2.6–0.8)	−0.10 (−1.9–2.0)
Total hip (n=14)	0.947 (0.686–1.222)	−1.10 (−3.1–1.0)	−0.40 (−2.6–1.9)
Forearm (n=10)	0.736 (0.665–0.845)	−0.40 (−3.2–1.2)	0.30 (−2.4–1.7)
Lumbar (n=4)	1.185 (0.876–1.487)	−0.40 (−2.4–2.0)	0.00 (−1.9–2.3)

Statistics are presented as median (minimum-maximum).
BMD, bone mineral density.

hypogonadism in all the patients. Investigation of osteoporosis-related fractures through x-rays was not performed. Although the patients in the studied group did not report any incident fractures, assessment of the 10-year probability of major osteoporotic or hip fracture based on the FRAX tool indicated a median probability of 5.7% (2.3–17) for major osteoporotic fracture and 1.1% (0.1–11) for hip fracture. Five (35.7%) patients were at or above the intervention threshold for hip fracture.

DISCUSSION

Our study showed that 85% of male patients on intrathecal opioid therapy were biochemically hypogonadal. The serum gonadotropin (LH and FSH) levels in these patients were inappropriately low or low-normal despite low serum testosterone concentrations, suggesting that testosterone suppression was caused through an inhibition of pituitary FSH and LH secretion (secondary hypogonadism). Raised serum prolactin may have contributed to the low testosterone in two patients. Although acute administration of morphine leads to an increase in PRL levels,[12] tolerance usually develops during chronic administration.[20] Previous studies investigating the chronic administration of intrathecal morphine have also reported a small proportion of patients with elevated PRL levels.[17 21] In a group of cancer survivors on opioids, 90% exhibited hypogonadism and low testosterone levels; LH levels, but not FSH levels, were found to be significantly lower when compared with cancer survivors not on opioid therapy.[22] The important role of endogenous opioids in the control of LH secretion has been demonstrated[23] and suppression of the hypothalamic-pituitary-gonadal axis by intrathecal

opioids may be caused by a mechanism similar to endogenous opioids.[24] Nevertheless, the suppression of LH levels may be less accentuated when the opioids are administered orally or transdermally rather than intrathecally.[12]

Hypogonadism is an important risk factor for the development of osteoporosis in both sexes.[16] To our knowledge, the incidence of osteopaenia or osteoporosis in patients undertaking intrathecal opioid therapy has not been reported previously. In our study, 50% of patients had osteopaenia and 21.4% had osteoporosis. Interestingly, an association between oral opioid administration and reduced BMD was demonstrated in one study but the presence or absence of hypogonadism was not assessed.[25] In a cross-sectional study, osteopaenia was present in 50% of the male patients undertaking oral opioids,[26] but again it was not clear if those patients were hypogonadal.

An association between oral opioid medication and an increase in fracture risk has also been reported[27] but assessment of bone mineral density was not performed. The authors suggested that this increase in fracture risk was possibly related to the risk of falls owing to the central nervous system side effect of dizziness caused by oral opioids. Opioid-induced dizziness is less likely to occur in IDD patients since only a fraction of the opioid delivered via the intrathecal route reaches the brain. Low bone mass is an important component of the risk of fracture as well as non-skeletal factors such as the propensity to fall.[16 28] Many fragility fractures occur in the absence of osteoporosis, although in the presence of this disease, the risk of fracture is higher.[29] Osteoporotic fractures are a significant cause of morbidity and mortality, especially in the developed countries,[30] and are associated with increased mortality, particularly in men.[31]

Table 3 Bone mineral density outcomes

Site of measurement	Normal	Osteopaenia*	Osteoporosis†
Femoral neck (n=14)	7/14 (50%)	5/14 (35.7%)	2/14 (14.3%)
Total hip (n=14)	7/14 (50%)	4/14 (28.6%)	3/14 (21.4%)
Forearm (n=10)	7/10 (70%)	2/10 (20%)	1/10 (10%)
Lumbar (n=4)	2/4 (50%)	2/4 (50%)	

Values represent the number of patients/total patients (%).
*Osteopaenia was defined as −2.5 SD<T score < −1.0 SD.
†Osteoporosis was defined as T score ≤−2.5 SD.

The assumption that hypogonadism is a risk factor for decreased BMD has not always been confirmed in the literature. No association between age-related hypogonadism (based on total testosterone) and decreased BMD was found in elderly men.[32] In contrast, free testosterone (calculated according to the Vermeulen equation) was demonstrated to be an independent predictor of BMD and fractures in elderly men[33] and a positive predictor of cortical bone size in young men at the age of peak bone mass.[34] These contradictory findings may have occurred because free testosterone is more important physiologically than total testosterone. SHBG levels, which generally are genetically determined, seem to play an important role in bone mass, hence the reason for free testosterone to be a stronger predictor than total testosterone alone. Recently, it has been suggested that the SHBG levels in healthy adult men at the age of peak bone mass were positively associated with cortical bone size independent of the sex-steroid levels.[35] However, in middle-aged and elderly men, SHBG elevation was significantly associated with the occurrence of osteoporotic fractures.[36] Although not yet confirmed, it has been suggested that the effect of SHBG on BMD may change with age and/or testosterone sufficiency or deficiency.[37]

It is important to note the limitations of this study. A small number of patients were included without a control group. The gonadal status and bone mineral density were not evaluated prior to the start of IDD therapy. Information on systemic opioids was not collected. A proportion of these patients are provided with oral opioid medication on an individual basis for occasional flare-ups. The strongest systemic opioid provided is tramadol at a dose ≤400 mg/day. Several possible factors may affect the sexual function in this group of patients. Chronic pain did not seem to be the cause of gonadal function reduction in patients undertaking intrathecal morphine therapy when compared with a control group of chronic pain patients who were not taking any form of opioid drugs.[24] Of the possible chronic illnesses identified in a longitudinal study with 890 male participants, only cancer (9%) was associated with a greater decrease in testosterone levels than the decrease that occurred with ageing alone.[38] Women were not included in this study. Low libido and amenorrhoea have been reported in female IDDS patients,[17 24] although the prevalence has been reported to be lower in women.[26] A large meta-analysis, which included approximately 39 000 men and women, has concluded that the age-specific risk of hip fracture is similar in both men and women with the same BMD and age.[39] Despite these limitations, the results of BMD assessment suggest that the IDD population may have an increased risk for osteoporotic fractures.

It is important to provide appropriate treatment to patients with low BMD. FRAX analysis is a simple tool that can be used to identify patients in whom osteoporosis prophylaxis is appropriate by taking into account multiple risk factors including BMD levels and hypogonadism.

BMD can be normalised and maintained within the normal range in men with either primary or secondary hypogonadism by continuous, long-term hormonal replacement therapy,[40] though the full effect on BMD may take up to 24 months.[41] Opioid-induced hypogonadism may be reversible. Clinically significant improvements in hypogonadal symptoms were observed in men with opioid-induced androgen deficiency following treatment with transdermal testosterone patches.[42] In patients undertaking intrathecal opioid delivery, recovery of serum testosterone levels following cessation of therapy or significant improvements in libido following hormonal replacement therapy have also been reported.[17 24]

Further studies in this patient group are warranted. Future studies should prospectively evaluate the gonadal axis, as well as the reported sexual health of the participants and BMD. It would also be important to compare these results with matched cohorts of chronic pain patients. Potential comparisons include patients on systemic opioids only, on a different course of intrathecal therapy (eg, ziconotide) or patients using spinal cord stimulation for the management of their chronic pain.

This study suggests an important association between hypogonadism and low bone mass density in patients undertaking intrathecal opioid delivery for the management of chronic non-malignant pain. However, since the gonadal status and BMD were not determined prior to initiation of intrathecal opioid delivery, we cannot conclude that the decreased BMD was caused by hypogonadism or opioid administration. Early detection of hypogonadism followed by appropriate treatment may be of paramount importance to reduce the risk of osteoporosis development and prevention of fractures in this population. Furthermore, surveillance of BMD levels in hypogonadal intrathecal opioid delivery patients should be considered.

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