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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 osteopenia 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, United Kingdom.

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 calculation of free testosterone. Bone mineral density was measured by DEXA scanning in those patients diagnosed with hypogonadism.

Results

Based on 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 osteopenia (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.

Conclusion

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 bone mineral density levels followed by appropriate treatment may be paramount to reduce the risk of osteoporosis development and prevention of fractures in this group of patients.

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 due 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 recognized 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 using the epidural route.[3] The drug is highly localized, so its analgesic efficacy is maximized at lower doses.[4] Moreover, opioid dose escalation throughout 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 of the 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] The current 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 μ-receptors.[14] This inhibition reduces the release of luteinizing hormone (LH) and 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 characterized by low or low-

normal LH and FSH levels, and low testosterone levels.[11] Most circulating testosterone is bound to sex hormone-binding globulin (SHBG). A lesser fraction is non-specifically bound to albumin and only a small percentage of 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, and is 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 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 osteopenia 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 osteopenia 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. Patients who had received testosterone supplementation within the previous three months were excluded. 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 during a seven-month period (April to October 2010), as part of routine clinical care, for the measurement of serum LH, FSH, total testosterone (TT) and SHBG. All assays were carried out by the Department of Clinical Biochemistry at Russells Hall Hospital, Dudley, UK. LH, FSH and testosterone (TT) were measured according to the manufacturer's instructions by immuno-enzymometric 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] The quoted reference ranges were: LH (2.2-13.3 IU/L), FSH (1-7 IU/L), SHBG (13-71 nmol/L) and TT (≥ 12 nmol/L). A FT < 180 picomoles per liter (pmol/L) was considered as biochemical hypogonadism and FT 180-250 pmol/L 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, WI, USA). Bone densitometry DEXA scans were carried out by the Department of Radiology, at Corbett Hospital, Dudley, UK. Lumbar spine scan was not carried out in 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-scores and Z-scores. Reference values for T-score were based on UK (ages 20-40) femur, spine or forearm reference population (v107). Osteopenia 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 World Health Organisation 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, history of hip fracture in the patient's parents and hypogonadism, among other factors.

Data analysis

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

commencement of IDD was 9 years (range 3-35).

Table 1. Sample characteristics

Patients (N)	20
Age (years)	58 (47-69)
IDDS duration (months)	100 (15-203)
Opioid dose (mg/day)	2.68 (1-9.7)
LH (IU/L)	1.9 (0.2-19.9)
FSH (IU/L)	5.3 (0.3-23.9)
SHBG (nmol/L)	51 (17-123)
TT (nmol/L)	4.95 (1.2-18.8)
FT (pmol/L)	69.45 (14-328)

Key: LH - luteinizing hormone; FSH - follicle stimulating hormone; SHBG - sex hormone binding globulin; TT – total testosterone; FT - free testosterone

Statistics are presented as median (minimum-maximum)

The median TT levels with 95% confidence intervals was 4.95 nmol/L (3.0-10.1), which were significantly lower than the cut-off level of 12 nmol/L for borderline/low testosterone. The median FT levels with 95% confidence intervals [69.45 (47.3-127.0)] 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. Based on FT calculations, 17 (85%) patients were biochemically hypogonadal with 15 (75%) at less than 180 pmol/L and two (10%) patients between 180 and 250 pmol/L.

Assessment of Bone Mineral Density

The 17 male patients diagnosed as hypogonadal through calculated free testosterone (FT) were considered for assessment of bone mineral density. Three patients were exclude (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). The BMI score was 29.4 kg/m^2 (20.1-45.4). According to the BMI score, the majority of the 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%) of the participants. Osteopenia defined as a T-score between -1.0 and -2.5 SD was observed in seven (50%) of the patients. Osteoporosis defined as a T-score at or below -2.5 SD was detected in three (21.4%) of the subjects. 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 Z-scores between -1.0 and -2.5 SD representative of osteopenia.

Table 2. Bone Mineral Density measurements

Site of measurement	BMD (g/cm2)	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)

Key: BMD - Bone Mineral Density

Statistics are presented as median (minimum-maximum)

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

Table 3. Bone Mineral Density outcomes

Site of measurement	Normal	Osteopenia[a]	Osteoporosis[b]
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%)	

[a] Osteopenia was defined as -2.5 SD < T-score < -1.0 SD

[b] Osteoporosis was defined as T-score ≤ -2.5 SD

Values represent the number of patients/total patients (%)

Several known clinical risk factors for low bone mineral density were present in this sample including hypogonadism in all of the patients. Although no incident fractures occurred in the studied group, assessment of the ten 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%) of the participants 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). 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.[20] The important role of endogenous opioids in the control of LH secretion has been demonstrated [21] and suppression of the hypothalamic-pituitary-gonadal axis by intrathecal opioids may be caused by a similar mechanism to that of endogenous opioids.[22] Nevertheless, the suppression of LH levels may be less accentuated when the opioids are administered orally or transdermally rather than intrathecally.[12]

Several possible factors may affect the sexual function in this group of patients. Psychological aspects such as depression, passive coping strategies and catastrophising are some of the factors hypothesized to influence the sexual function in chronic pain patients.[23] However, 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.[22] 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.[24]

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 previously reported. In our study, 50% of patients had osteopenia 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, osteopenia 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 due 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 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 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]

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 SHBG levels in healthy adult men at the age of peak bone mass were positively associated with cortical bone size independently of 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 commencement of IDD therapy. Women were not included in this study. Low libido and amenorrhea have been reported in female IDDS patients,[17,22] 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.[38] 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 of patients in whom osteoporosis prophylaxis is appropriate by taking into account multiple risk factors including BMD levels and hypogonadism. BMD can be normalized and maintained within the normal range in men with either primary or secondary hypogonadism by continuous, long-term hormonal replacement therapy [39] though the full effect on BMD may take up to 24 months.[40]

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. Early detection of hypogonadism followed by appropriate treatment may be paramount 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.

ARTICLE SUMMARY

Article focus

- Hypogonadism is common in intrathecal opioid therapy patients but there is limited 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 paramount 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.

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Competing interests statement

The authors report no conflicts of interest.

Contributorship statement

RVD, JHR, JLS, MHL, AJW and RLA have made substantial contributions to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

Ethics approval

All assessments were performed as part of routine clinical care. No additional procedures were carried out for research purposes.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 2-4**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 4**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4,5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 4-6** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4,5**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 4,5**
Bias	9	Describe any efforts to address potential sources of bias **Page 4**
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 6**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 6**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 6**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 6,7**
		(b) Give reasons for non-participation at each stage **Page 7**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 6-8**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 7-9**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 7**
		(*b*) Report category boundaries when continuous variables were categorized **Page 5-6**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 11,12**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 9-12**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 12**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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

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Keywords: bone density; chronic pain; hypogonadism; drug delivery systems, implantable

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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 osteopenia 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, United Kingdom.

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 calculation of free testosterone. Bone mineral density was measured by DEXA scanning in those patients diagnosed with hypogonadism.

Results

Based on 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 osteopenia (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.

Conclusion

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 bone mineral density levels followed by appropriate treatment may be paramount to reduce the risk of osteoporosis development and prevention of fractures in this group of patients.

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 due 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 recognized 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 using the epidural route.[3] The drug is highly localized, so its analgesic efficacy is maximized at lower doses.[4] Moreover, opioid dose escalation throughout 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 of the 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] The current 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 μ-receptors.[14] This inhibition reduces the release of luteinizing hormone (LH) and 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 characterized by low or low-

normal LH and FSH levels, and low testosterone levels.[11] Most circulating testosterone is bound to sex hormone-binding globulin (SHBG). A lesser fraction is non-specifically bound to albumin and only a small percentage of 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, and is 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 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 osteopenia 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 osteopenia 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 three 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 8am and 11am during a seven-month period (April to 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 immuno-enzymometric 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] The quoted reference ranges were: LH (2.2-13.3 IU/L), FSH (1-7 IU/L), SHBG (13-71 nmol/L) and PRL (0-445 mU/L). 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 was 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, WI,

USA). Bone densitometry DEXA scans were carried out by the Department of Radiology, at Corbett Hospital, Dudley, UK. Lumbar spine scan was not carried out in 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-scores and Z-scores. Reference values for T-score were based on UK (ages 20-40) femur, spine or forearm reference population (v107). Osteopenia 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 World Health Organisation 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, history of hip fracture in the patient's parents and hypogonadism, among other factors.

Data analysis

Kolmogorov-Smirnov test was performed to test distribution of numerical data, followed by the appropriate statistical tests. Comparisons between groups were carried out with the Mann-Whitney test. Data is reported as median (minimum-maximum). The 95% confidence intervals for the TT and FT median values were calculated for comparison with normal reference values. Statistical significance was judged at 5% level. Statistical tests were performed using Predictive Analytics SoftWare (PASW) (version 18.0, SPSS Inc., Chicago, IL, 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 commencement of IDD was 9 years (range 3-35).

Table 1. Sample characteristics

Patients (N)	20
Age (years)	58 (47-69)
IDDS duration (months)	100 (15-203)
Opioid dose (mg/day)	2.68 (1-9.7)
LH (IU/L)	1.9 (0.2-19.9)
FSH (IU/L)	5.3 (0.3-23.9)
SHBG (nmol/L)	51 (17-123)
PRL (mU/L)	225 (53-614)
TT (nmol/L)	4.95 (1.2-18.8)
FT (pmol/L)	69.45 (14-328)

Key: LH - luteinizing hormone; FSH - follicle stimulating hormone; SHBG - sex hormone binding globulin; PRL - prolactin; TT – total testosterone; FT - free testosterone
Statistics are presented as median (minimum-maximum)

The median TT levels with 95% confidence intervals was 4.95 nmol/L (3.0-10.1), which were significantly lower than the cut-off level of 12 nmol/L for borderline/low testosterone. The median FT levels with 95% confidence intervals [69.45 (47.3-127.0)] 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 and the other patient presented borderline/low TT. Based on TT, 17 (85%) of the patients presented biochemical hypogonadism values with 12 (60%) at less than 8 nmol/L and 5 (25%) with TT values between 8 and 12 nmol/L (borderline/low). Based on FT calculations, 17 (85%) patients were biochemically hypogonadal with 15 (75%) 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 quoted reference ranges, two patients presented borderline/low

TT and normal FT, one patient had low FT values and normal TT, and one borderline/low FT and normal TT.

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 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 the 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%) of the patients. Osteopenia defined as a T-score between -1.0 and -2.5 SD was observed in seven (50%) of the patients. Osteoporosis defined as a T-score at or below -2.5 SD was detected in three (21.4%) of the subjects. 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 Z-scores between -1.0 and -2.5 SD representative of osteopenia.

Table 2. Bone Mineral Density measurements

Site of measurement	BMD (g/cm2)	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)

Key: BMD - Bone Mineral Density

Statistics are presented as median (minimum-maximum)

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

Table 3. Bone Mineral Density outcomes

Site of measurement	Normal	Osteopenia[a]	Osteoporosis[b]
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%)	

[a] Osteopenia was defined as -2.5 SD < T-score < -1.0 SD

[b] Osteoporosis was defined as T-score ≤ -2.5 SD

Values represent the number of patients/total patients (%)

Several known clinical risk factors for low bone mineral density were present in this sample including hypogonadism in all of the patients. Investigation of osteoporosis related fractures through x-rays were not performed. Although the patients in the studied group did not report any incident fractures, assessment of the ten-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%) of the 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 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 similar mechanism to that of 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]

Several possible factors may affect the sexual function in this group of patients. Psychological aspects such as depression, passive coping strategies and catastrophising are some of the factors hypothesized to influence the sexual function in chronic pain patients.[25] However, 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.[26]

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 previously reported. In our study, 50% of patients had osteopenia 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.[27] In a cross-sectional study, osteopenia was present in 50% of the male patients undertaking oral opioids [28] 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 [29] 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 due 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 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 propensity to fall.[16,30] Many fragility fractures occur in the absence of osteoporosis, although in the presence of this disease, the risk of fracture is higher.[31] Osteoporotic fractures are a significant cause of morbidity and mortality especially in the developed countries,[32] and are associated with increased mortality, particularly in men.[33]

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.[34] In contrast, free

testosterone (calculated according to the Vermeulen equation) was demonstrated to be an independent predictor of BMD and fractures in elderly men [35] and a positive predictor of cortical bone size in young men at the age of peak bone mass.[36] 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 SHBG levels in healthy adult men at the age of peak bone mass were positively associated with cortical bone size independently of sex-steroid levels.[37] However, in middle aged and elderly men, SHBG elevation was significantly associated with the occurrence of osteoporotic fractures.[38] 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.[39]

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 commencement 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. Women were not included in this study. Low libido and amenorrhea have been reported in female IDDS patients,[17,24] although the prevalence has been reported to be lower in women.[28] 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.[40] 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 of patients in whom osteoporosis prophylaxis is appropriate by taking into account multiple risk factors including BMD levels and hypogonadism. BMD can be normalized and maintained within the normal range in men with either primary or secondary hypogonadism by continuous, long-term hormonal replacement therapy [41] though the full effect on BMD may take up to 24 months.[42] 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. [43] 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, 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 (e.g. 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 paramount 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.

ARTICLE SUMMARY

Article focus

- Hypogonadism is common in intrathecal opioid therapy patients but there is limited 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 paramount 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.

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Competing interests statement

The authors report no conflicts of interest.

Contributorship statement

RVD, JHR, JLS, MHL, AJW and RLA have made substantial contributions to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

Ethics approval

All assessments were performed as part of routine clinical care. No additional procedures were carried out for research purposes.

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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 osteopenia 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, United Kingdom.

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 calculation of free testosterone. Bone mineral density was measured by DEXA scanning in those patients diagnosed with hypogonadism.

Results

Based on 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 osteopenia (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.

Conclusion

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 bone mineral density levels followed by appropriate treatment may be paramount to reduce the risk of osteoporosis development and prevention of fractures in this group of patients.

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 due 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 recognized 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 using the epidural route.[3] The drug is highly localized, so its analgesic efficacy is maximized at lower doses.[4] Moreover, opioid dose escalation throughout 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 of the 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] The current 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 μ-receptors.[14] This inhibition reduces the release of luteinizing hormone (LH) and 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 characterized by low or low-

normal LH and FSH levels, and low testosterone levels.[11] Most circulating testosterone is bound to sex hormone-binding globulin (SHBG). A lesser fraction is non-specifically bound to albumin and only a small percentage of 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, and is 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 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 osteopenia 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 osteopenia 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 three 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 8am and 11am during a seven-month period (April to 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 immuno-enzymometric 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] The quoted reference ranges were: LH (2.2-13.3 IU/L), FSH (1-7 IU/L), SHBG (13-71 nmol/L) and PRL (0-445 mU/L). 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 was 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, WI,

USA). Bone densitometry DEXA scans were carried out by the Department of Radiology, at Corbett Hospital, Dudley, UK. Lumbar spine scan was not carried out in 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-scores and Z-scores. Reference values for T-score were based on UK (ages 20-40) femur, spine or forearm reference population (v107). Osteopenia 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 World Health Organisation 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, history of hip fracture in the patient's parents and hypogonadism, among other factors.

Data analysis

Kolmogorov-Smirnov test was performed to test distribution of numerical data, followed by the appropriate statistical tests. Comparisons between groups were carried out with the Mann-Whitney test. Data is reported as median (minimum-maximum). The 95% confidence intervals for the TT and FT median values were calculated for comparison with normal reference values. Statistical significance was judged at 5% level. Statistical tests were performed using Predictive Analytics SoftWare (PASW) (version 18.0, SPSS Inc., Chicago, IL, 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 commencement of IDD was 9 years (range 3-35).

Table 1. Sample characteristics

Patients (N)	20
Age (years)	58 (47-69)
IDDS duration (months)	100 (15-203)
Opioid dose (mg/day)	2.68 (1-9.7)
LH (IU/L)	1.9 (0.2-19.9)
FSH (IU/L)	5.3 (0.3-23.9)
SHBG (nmol/L)	51 (17-123)
PRL (mU/L)	225 (53-614)
TT (nmol/L)	4.95 (1.2-18.8)
FT (pmol/L)	69.45 (14-328)

Key: LH - luteinizing hormone; FSH - follicle stimulating hormone; SHBG - sex hormone binding globulin; PRL - prolactin; TT – total testosterone; FT - free testosterone
Statistics are presented as median (minimum-maximum)

The median TT levels with 95% confidence intervals was 4.95 nmol/L (3.0-10.1), which were significantly lower than the cut-off level of 12 nmol/L for borderline/low testosterone. The median FT levels with 95% confidence intervals [69.45 (47.3-127.0)] 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 and the other patient presented borderline/low TT. Based on TT, 17 (85%) of the patients presented biochemical hypogonadism values with 12 (60%) at less than 8 nmol/L and 5 (25%) with TT values between 8 and 12 nmol/L (borderline/low). Based on FT calculations, 17 (85%) patients were biochemically hypogonadal with 15 (75%) 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 quoted reference ranges, two patients presented borderline/low

TT and normal FT, one patient had low FT values and normal TT, and one borderline/low FT and normal TT.

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 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 the 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%) of the patients. Osteopenia defined as a T-score between -1.0 and -2.5 SD was observed in seven (50%) of the patients. Osteoporosis defined as a T-score at or below -2.5 SD was detected in three (21.4%) of the subjects. 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 Z-scores between -1.0 and -2.5 SD representative of osteopenia.

Table 2. Bone Mineral Density measurements

Site of measurement	BMD (g/cm2)	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)

Key: BMD - Bone Mineral Density

Statistics are presented as median (minimum-maximum)

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

Table 3. Bone Mineral Density outcomes

Site of measurement	Normal	Osteopenia[a]	Osteoporosis[b]
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%)	

[a] Osteopenia was defined as -2.5 SD < T-score < -1.0 SD

[b] Osteoporosis was defined as T-score ≤ -2.5 SD

Values represent the number of patients/total patients (%)

Several known clinical risk factors for low bone mineral density were present in this sample including hypogonadism in all of the patients. Investigation of osteoporosis related fractures through x-rays were not performed. Although the patients in the studied group did not report any incident fractures, assessment of the ten-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%) of the 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 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 similar mechanism to that of 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]

Several possible factors may affect the sexual function in this group of patients. Psychological aspects such as depression, passive coping strategies and catastrophising are some of the factors hypothesized to influence the sexual function in chronic pain patients.[25] However, 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.[26]

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 previously reported. In our study, 50% of patients had osteopenia 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.[27] In a cross-sectional study, osteopenia was present in 50% of the male patients undertaking oral opioids [28] 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 [29] 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 due 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 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 propensity to fall.[16,30] Many fragility fractures occur in the absence of osteoporosis, although in the presence of this disease, the risk of fracture is higher.[31] Osteoporotic fractures are a significant cause of morbidity and mortality especially in the developed countries,[32] and are associated with increased mortality, particularly in men.[33]

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.[34] In contrast, free

testosterone (calculated according to the Vermeulen equation) was demonstrated to be an independent predictor of BMD and fractures in elderly men [35] and a positive predictor of cortical bone size in young men at the age of peak bone mass.[36] 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 SHBG levels in healthy adult men at the age of peak bone mass were positively associated with cortical bone size independently of sex-steroid levels.[37] However, in middle aged and elderly men, SHBG elevation was significantly associated with the occurrence of osteoporotic fractures.[38] 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.[39]

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 commencement 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. Women were not included in this study. Low libido and amenorrhea have been reported in female IDDS patients,[17,24] although the prevalence has been reported to be lower in women.[28] 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.[40] 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 of patients in whom osteoporosis prophylaxis is appropriate by taking into account multiple risk factors including BMD levels and hypogonadism. BMD can be normalized and maintained within the normal range in men with either primary or secondary hypogonadism by continuous, long-term hormonal replacement therapy [41] though the full effect on BMD may take up to 24 months.[42] 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. [43] 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, 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 (e.g. 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 paramount 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.

ARTICLE SUMMARY

Article focus

- Hypogonadism is common in intrathecal opioid therapy patients but there is limited 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 paramount 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.

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Competing interests statement

The authors report no conflicts of interest.

Contributorship statement

RVD, JHR, JLS, MHL, AJW and RLA have made substantial contributions to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

Ethics approval

All assessments were performed as part of routine clinical care. No additional procedures were carried out for research purposes.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 2-4**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 4**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4,5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 4-6** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4,5**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 4,5**
Bias	9	Describe any efforts to address potential sources of bias **Page 4**
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 6**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 6**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 6**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 6,7**
		(b) Give reasons for non-participation at each stage **Page 7**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 6-8**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 7-9**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 7**
		(*b*) Report category boundaries when continuous variables were categorized **Page 5-6**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 11,12**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 9-12**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 12**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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

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ARTICLE SUMMARY

Article focus

- Hypogonadism is common in intrathecal opioid therapy patients but there is limited 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 paramount 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.

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 osteopenia 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, United Kingdom.

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 calculation of free testosterone. Bone mineral density was measured by DEXA scanning in those patients diagnosed with hypogonadism.

Results

Based on 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 osteopenia (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.

Conclusion

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 bone mineral density levels followed by appropriate treatment may be paramount to reduce the risk of osteoporosis development and prevention of fractures in this group of patients.

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 due 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 recognized 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 using the epidural route.[3] The drug is highly localized, so its analgesic efficacy is maximized at lower doses.[4]

Moreover, opioid dose escalation throughout 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 of the 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] The current 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 μ-receptors.[14] This inhibition reduces the release of luteinizing hormone (LH) and 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 characterized by low or low-normal LH and FSH levels, and low testosterone levels.[11] Most circulating testosterone is bound to sex hormone-binding globulin (SHBG). A lesser fraction is non-specifically bound to albumin and only a small percentage of 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, and is 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 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 osteopenia 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 osteopenia 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 three 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 8am and 11am during a seven-month period (April to 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 immuno-enzymometric 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 was 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, WI, USA). Bone densitometry DEXA scans were carried out by the Department of Radiology, at Corbett Hospital, Dudley, UK. Lumbar spine scan was not carried out in 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-scores and Z-scores. Reference values for T-score were based on UK (ages 20-40) femur, spine or forearm reference population (v107). Osteopenia 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 World Health Organisation 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, history of hip fracture in the patient's parents and hypogonadism, among other factors.

Data analysis

Kolmogorov-Smirnov test was performed to test distribution of numerical data, followed by the appropriate statistical tests. Comparisons between groups were carried out with the Mann-Whitney test. Data is reported as median (minimum-maximum). The 95% confidence intervals for the TT and FT median values were calculated for comparison with normal reference values. Statistical significance was judged at 5% level. Statistical tests were performed using Predictive Analytics SoftWare (PASW) (version 18.0, SPSS Inc., Chicago, IL, 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 commencement of IDD was 9 years (range 3-35).

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)

Key: LH - luteinizing hormone; FSH - follicle stimulating hormone; SHBG - sex hormone binding globulin; PRL - prolactin; TT - total testosterone; FT - free testosterone

Statistics are presented as median (minimum-maximum)

The median TT levels with 95% confidence intervals was 4.95 nmol/L (3.0-10.1), which were significantly lower than the cut-off level of 12 nmol/L for borderline/low testosterone. The median FT levels with 95% confidence intervals [69.45 (47.3-127.0)] 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 and the other patient presented borderline/low TT. Based on TT, 17 (85%) of the patients presented biochemical hypogonadism values with 12 (60%) at less than 8 nmol/L and 5 (25%) with TT values between 8 and 12 nmol/L (borderline/low). Based on FT calculations, 17 (85%) patients were biochemically hypogonadal with 15 (75%) 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 quoted reference ranges, two patients presented borderline/low TT and normal FT, one patient had low FT values and normal TT, and one borderline/low FT and normal TT.

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 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 the 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%) of the patients. Osteopenia defined as a T-score between -1.0 and -2.5 SD was observed in seven (50%) of the patients. Osteoporosis defined as a T-score at or below -2.5 SD was detected in three (21.4%) of the subjects. 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 Z-scores between -1.0 and -2.5 SD representative of osteopenia.

Table 2. Bone Mineral Density measurements

Site of measurement	BMD (g/cm2)	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)

Key: BMD - Bone Mineral Density

Statistics are presented as median (minimum-maximum)

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

Table 3. Bone Mineral Density outcomes

Site of measurement	Normal	Osteopenia[a]	Osteoporosis[b]
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%)	

[a] Osteopenia was defined as -2.5 SD < T-score < -1.0 SD
[b] Osteoporosis was defined as T-score ≤ -2.5 SD
Values represent the number of patients/total patients (%)

Several known clinical risk factors for low bone mineral density were present in this sample including hypogonadism in all of the patients. Investigation of osteoporosis related fractures through x-rays were not performed. Although the patients in the studied group did not report any incident fractures, assessment of the ten-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%) of the 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 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 similar mechanism to that of 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 previously reported. In our study, 50% of patients had osteopenia 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, osteopenia 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 due 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 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 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]

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 SHBG levels in healthy adult men at the age of peak bone mass were positively associated with cortical bone size independently of 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 commencement 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 amenorrhea 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 of patients in whom osteoporosis prophylaxis is appropriate by taking into account multiple risk factors including BMD levels and hypogonadism. BMD can be normalized 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, 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 (e.g. 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 paramount 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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The authors report no conflicts of interest.

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RVD, JHR, JLS, MHL, AJW and RLA have made substantial contributions to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

Ethics approval

All assessments were performed as part of routine clinical care. No additional procedures were carried out for research purposes.

Data sharing

No additional data available

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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 osteopenia 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, United Kingdom.

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 calculation of free testosterone. Bone mineral density was measured by DEXA scanning in those patients diagnosed with hypogonadism.

Results

Based on 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 osteopenia (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.

Conclusion

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 bone mineral density levels followed by appropriate treatment may be paramount to reduce the risk of osteoporosis development and prevention of fractures in this group of patients.

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 due 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 recognized 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 using the epidural route.[3] The drug is highly localized, so its analgesic efficacy is maximized at lower doses.[4] Moreover, opioid dose escalation throughout 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 of the 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] The current 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 μ-receptors.[14] This inhibition reduces the release of luteinizing hormone (LH) and 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 characterized by low or low-

normal LH and FSH levels, and low testosterone levels.[11] Most circulating testosterone is bound to sex hormone-binding globulin (SHBG). A lesser fraction is non-specifically bound to albumin and only a small percentage of 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, and is 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 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 osteopenia 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 osteopenia 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 three 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 8am and 11am during a seven-month period (April to 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 immuno-enzymometric 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 was 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, WI, USA). Bone densitometry DEXA scans were carried out by the Department of Radiology, at

Corbett Hospital, Dudley, UK. Lumbar spine scan was not carried out in 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-scores and Z-scores. Reference values for T-score were based on UK (ages 20-40) femur, spine or forearm reference population (v107). Osteopenia 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 World Health Organisation 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, history of hip fracture in the patient's parents and hypogonadism, among other factors.

Data analysis

Kolmogorov-Smirnov test was performed to test distribution of numerical data, followed by the appropriate statistical tests. Comparisons between groups were carried out with the Mann-Whitney test. Data is reported as median (minimum-maximum). The 95% confidence intervals for the TT and FT median values were calculated for comparison with normal reference values. Statistical significance was judged at 5% level. Statistical tests were performed using Predictive Analytics SoftWare (PASW) (version 18.0, SPSS Inc., Chicago, IL, 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 commencement of IDD was 9 years (range 3-35).

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)

Key: LH - luteinizing hormone; FSH - follicle stimulating hormone; SHBG - sex hormone binding globulin; PRL - prolactin; TT - total testosterone; FT - free testosterone

Statistics are presented as median (minimum-maximum)

The median TT levels with 95% confidence intervals was 4.95 nmol/L (3.0-10.1), which were significantly lower than the cut-off level of 12 nmol/L for borderline/low testosterone. The median FT levels with 95% confidence intervals [69.45 (47.3-127.0)] 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 and the other patient presented borderline/low TT. Based on TT, 17 (85%) of the patients presented biochemical hypogonadism values with 12 (60%) at less than 8 nmol/L and 5 (25%) with TT values between 8 and 12 nmol/L (borderline/low). Based on FT calculations, 17 (85%) patients were biochemically hypogonadal with 15 (75%) 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 quoted reference ranges, two patients presented borderline/low TT and normal FT, one patient had low FT values and normal TT, and one borderline/low FT and normal TT.

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 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 the 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%) of the patients. Osteopenia defined as a T-score between -1.0 and -2.5 SD was observed in seven (50%) of the patients. Osteoporosis defined as a T-score at or below -2.5 SD was detected in three (21.4%) of the subjects. 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 Z-scores between -1.0 and -2.5 SD representative of osteopenia.

Table 2. Bone Mineral Density measurements

Site of measurement	BMD (g/cm2)	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)

Key: BMD - Bone Mineral Density

Statistics are presented as median (minimum-maximum)

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

Table 3. Bone Mineral Density outcomes

Site of measurement	Normal	Osteopenia[a]	Osteoporosis[b]
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%)	

[a] Osteopenia was defined as -2.5 SD < T-score < -1.0 SD
[b] Osteoporosis was defined as T-score ≤ -2.5 SD
Values represent the number of patients/total patients (%)

Several known clinical risk factors for low bone mineral density were present in this sample including hypogonadism in all of the patients. Investigation of osteoporosis related fractures through x-rays were not performed. Although the patients in the studied group did not report any incident fractures, assessment of the ten-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%) of the 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 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 similar mechanism to that of 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 previously reported. In our study, 50% of patients had osteopenia 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, osteopenia 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 due 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 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 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]

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 SHBG levels in healthy adult men at the age of peak bone mass were positively associated with cortical bone size independently of 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 commencement 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 amenorrhea 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 of patients in whom osteoporosis prophylaxis is appropriate by taking into account multiple risk factors including BMD levels and hypogonadism. BMD can be normalized 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, 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 (e.g. 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 paramount 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.

ARTICLE SUMMARY

Article focus

- Hypogonadism is common in intrathecal opioid therapy patients but there is limited 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 paramount 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.

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Competing interests statement

The authors report no conflicts of interest.

Contributorship statement

RVD, JHR, JLS, MHL, AJW and RLA have made substantial contributions to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

Ethics approval

All assessments were performed as part of routine clinical care. No additional procedures were carried out for research purposes.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 2-4**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 4**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4,5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 4-6** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4,5**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 4,5**
Bias	9	Describe any efforts to address potential sources of bias **Page 4**
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 6**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 6**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 6**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 6,7**
		(b) Give reasons for non-participation at each stage **Page 7**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 6-8**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 7-9**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 7**
		(*b*) Report category boundaries when continuous variables were categorized **Page 5-6**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 11,12**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 9-12**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 12**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.