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ORIGINAL ARTICLE

Long-term opioid treatment and endocrine measures in chronic non-cancer pain patients

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Abstract

Background: The prevalence of chronic non-cancer pain (CNCP) has increased dramatically the past decades, which combined with indiscriminate use of prescribed opioids has become a public health problem. Endocrine dysfunction may be a complication of long-term opioid treatment (L-TOT), but the evidence is limited. This study aimed at investigating the associations between L-TOT and endocrine measures in CNCP patients.

Methods: Cortisol (spot and after stimulation), thyrotropin (TSH), thyroxin (T4), insulin-like growth factor 1 (IGF-1), prolactin (PRL), 17-hydroxyprogesterone, androstenedione, dehydroepiandrosterone (DHEAS), sex hormone-binding globulin (SHBG), total testosterone (TT) and free testosterone (fT) were measured. Group comparisons were done between CNCP patients in L-TOT and controls as well as between patients on high- or low-dose morphine equivalents.

Results: Eighty-two CNCP patients (38 in L-TOT and 44 controls not receiving opioids) were included. Low TT ($p = 0.004$) and fT concentrations ($p < 0.001$), high SHBG ($p = 0.042$), low DEAS ($p = 0.017$) and low IGF-1 ($p = 0.003$) in men were found when comparing those in L-TOT to controls and high PRL ($p = 0.018$), low IGF-1 standard deviation score (SDS) ($p = 0.006$) along with a lesser, but normal cortisol response to stimulation ($p = 0.016$; $p = 0.012$) were found when comparing L-TOT to controls. Finally, a correlation between low IGF-1 levels and high opioid dose was observed ($p < 0.001$).

Conclusions: Our study not only supports previous findings but even more interestingly disclosed new associations. We recommend future studies to investigate endocrine effects of opioids in larger, longitudinal studies. In the meanwhile, we recommend monitoring endocrine function in CNCP patients when prescribing L-TOT.

Significance: This clinical study found associations between L-TOT, androgens, growth hormone and prolactin in patients with CNCP compared to controls. The results support previous studies as well as add new knowledge to the field, including an association between high opioid dose and low growth hormone levels.

Compared to existing research this study has strict inclusion/exclusion criteria, a fixed time period for blood sample collection, and adjustments for potential confounders, which has not been done before.

1 | INTRODUCTION

Over the past decades, the prevalence of chronic non-cancer pain (CNCP) has increased dramatically in the Western world (Birke et al., 2016; Colvin et al., 2019; Ekholm et al., 2022). For instance, from 2000 to 2017, the prevalence of CNCP in Denmark increased from 19.5% to 27.8% (Ekholm et al., 2022). This is a serious public health issue particularly when associated with indiscriminate use of prescribed opioids (Birke et al., 2016; Hamina et al., 2022; Ju et al., 2022).

According to an estimate based on recent growth in opioid consumption in Norway, approximately 14% of all new opioid users progress to long-term use (Hamina et al., 2022), which is concerning given the limited evidence of efficacy of long-term opioid treatment (L-TOT) for chronic non-cancer pain (Busse et al., 2018; Currow et al., 2016; Krebs et al., 2018; Sehgal et al., 2013) and the numerous opioid-related adverse events that have been reported in this population (Els et al., 2017).

Many potential side effects and long-term consequences of L-TOT are still not fully understood, particularly in CNCP patients (Birke et al., 2017; Diasso et al., 2019, 2021; Elsesser & Cegla, 2017; Højsted & Sjøgren, 2007; Katz & Mazer, 2009), and CNCP patients may not receive adequate information, examination, monitoring and treatment due to this knowledge gap. Ultimately, it could lead to poorer health and health-related quality of life. Endocrine dysfunction has been cited as one possible consequence of L-TOT; however, there exist few clinical studies in CNCP patients.

Animal studies have shown both acute and more chronic alterations of endocrine measures due to opioid consumption (Katz & Mazer, 2009; Vuong et al., 2010). These alterations can be centrally mediated through the hypothalamic–pituitary pathways and/or peripherally through a direct effect on endocrine glands (Katz & Mazer, 2009; Vuong et al., 2010). The suggested mechanism behind is that opioids bind to specific opioid receptors mainly in the hypothalamus interfering with the normal pulsatility of hormones, but also in the pituitary gland, testis and the ovaries and thereby modulate gonadal function (Genazzani et al., 1993; Jordan et al., 1996; Ortman & Siegel, 2020; Veldhuis et al., 1984).

Furthermore, opioid intake can alter the adrenal production of dehydroepiandrosterone (DHEA), the precursor of testosterone and oestrogen, and thereby indirectly induce hypogonadism (Daniell, 2006). A few studies investigated patients with acute and cancer-related pain using opioids and in heroin abuse; hypogonadism was found in more than half of the male opioid users (de Vries et al., 2020). Furthermore, such studies also demonstrated insufficient GH secretion (Abs et al., 2000) and adrenocortical deficiency (Drolet et al., 2001; Oltmanns et al., 2005; Ortman & Siegel, 2020). Finally, it has been suggested that L-TOT may lower insulin levels and alteration of glucocorticoids (Aurilio et al., 2011; Lamprecht et al., 2018; Mueller et al., 2018; Nenke et al., 2015; Ozyuvaci et al., 2004). However, in general the evidence of endocrine effects of L-TOT in CNCP patients is limited due to few studies with high risk of bias (Diasso et al., 2021). The methodology in previous studies has been marked by limited exclusion criteria, and therefore possibly confounders like body mass index (BMI) and medication intake. The use of essential exclusion criteria and statistical adjustments for possible confounders distinguishes this study from prior research in the field (Diasso et al., 2021). The endocrine measures examined in this study were chosen partly based on findings from previous studies and partly on clinical expertise.

Based on the sparse knowledge regarding possible consequences of opioid treatment, this exploratory study aimed to investigate the possible effects of L-TOT on endocrine measures in patients with CNCP.

2 | METHODS

2.1 | Design, settings and ethics

A cross-sectional comparative study was carried out at the Multidisciplinary Pain Center (MPC), Rigshospitalet, Copenhagen University Hospital, Denmark, from October 2014 until June 2021. The study was approved by the Danish Data Protection Agency (30-1317) and the Regional Ethics Committee of Copenhagen, Denmark (H-1-2014-063).

2.2 | Participants

All patients were screened from the daily clinics lists at the MPC to identify eligible participants. All eligible patients were provided with information about the study and had 24 h to reflect about participation. Inclusion criteria were patients aged 18–65 years with CNCP for

≥6 months, who were fluent in both spoken and written Danish, had at least six years of schooling, and were treated at the MCP. Those CNCP patients who accepted to participate were included into two groups (1) opioid group—with the specific inclusion criterion of continuous, minimum morphine equivalents daily dose (MEDD) (Dowell et al., 2016; The Danish Health Authority, 2017) of ≥30 mg for at least 4 weeks, and (2) control group—with the specific inclusion criterion of no opioid use for at least 4 weeks. The exclusion criteria for both groups were: hormonal or anti-hormonal treatment or on-going therapy with medication known to interfere with endocrine function including menopausal hormone replacement therapy and contraceptives in the last 6 months, adjuvant analgesics in the last 4 weeks (anticonvulsants, antidepressants and others), benzodiazepines and hypnotics in the last 4 weeks, known endocrine or immune diseases, active malignancy, previously diagnosed liver disease, renal insufficiency, pregnancy or lactation. Patients who used adjuvant analgesics, benzodiazepines and hypnotics were not included in this study due to their potential interference on endocrine system (Grandison, 1983). It was impossible to find patients at the MPC without paracetamol and/or nonsteroidal anti-inflammatory drugs (NSAID). As there is a lack of conclusive evidence about the effects of these medications on the endocrine system of humans in adulthood, both groups were allowed to continue these treatments (Boizet-Bonhoure et al., 2022; Høyer et al., 2017; Kristensen et al., 2018). No financial compensation was offered for participation in this study. Furthermore, we divided the opioid group into high doses (>90 mg MEDD) and low doses of opioids (<90 mg MEDD) based on the definition from the Food and Drug Administration and Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 2021; Food and Drug Administration, 2021).

2.3 | Assessment and procedures

All included patients were assessed once at the MPC between 09:00 AM and 12:00 PM to ensure homogeneity in time-dependent measures. Information regarding socio-demographics, pain characteristics, opioid treatment, other medications, smoking habits, alcohol consumption, height and weight were obtained. Type of pain had previously been assessed by a pain specialist and was collected from the patient journals by the research team. Blood samples were collected between 09:45 and 12:45 in a non-fasting state to measure cortisol, thyrotropin (TSH), thyroxin (T4), insulin-like growth factor 1 (IGF-1), prolactin (PRL), 17-hydroxyprogesterone, androstenedione, dehydroepiandrosterone (DHEAS), sex hormone-binding globulin (SHBG) and total testosterone (TT). All assays were caried out at the Department of Clinical Biochemistry, Rigshospitalet, University Hospital Copenhagen, except IGF-1 which was analysed at the Department of Growth and Reproduction at the same hospital. Plasma concentrations of cortisol, TSH and T4 were analysed by Roche's electrochemiluminescence assay on Cobas instrument (Roche, Mannheim, Germany). Plasma concentrations of 17-hydroxyprogesterone, androstenedione, DHEAS, and TT were analysed by LC–MS/MS (Roche) and SHBG by Immulite 2000 (Roche). Free testosterone (fT) was calculated from the concentrations of TT and SHBG as $\frac{-b+\sqrt{b^2+4a[T]}}{2a}$. PRL was analysed on B•R•A•H•M•S′ Kryptor instrument using the Time Resolved Amplified Cryptate Emission (TRACE)® technology (Brahms, GmbH). IGF-1 was analysed by chemiluminescence assay (IDS-iSYS) Multidiscipline Automated Analyser (IDS-iSYS, Poeilly-en Anxoic).

Adrenocortical function was tested as an exploratory sub-study in the first 20 patients in each group with a 30 min adrenocorticotropic hormone (ACTH) test. After collecting the patient's blood sample for all the measurements including spot cortisol, synthetic ACTH was administered directly into the patient's blood circulation. After 30 min a new blood sample for cortisol was collected. A normal adrenocortical function was categorized as a plasma cortisol concentration of ≥420 nmol/L after stimulation (Danish Endocrinological Society, 2021). General blood samples were obtained for the evaluation of haematology, infectious parameters, liver and kidney function.

2.4 | Statistical analysis

It was not possible to perform a power calculation on the selected outcomes for this study due to the limited data available. Analysis was planned considering (a) the absolute hormone levels separated by sex and menopausal status, because the values of androgens, PRL and IGF-1 differs between sexes and menopausal status, and (b) the standard deviation scores (SDS) of IGF-1 from the known mean for the same age and sex.

Numerical data were analysed by the Wilcoxon two-sample test and categorical data by the chi-square test. Unpaired multiple regression analysis was applied to control for the following confounders: age, BMI, alcohol and smoking, as these variables differed between groups or have a known influence on the outcome parameters. Group comparisons were done between patients and controls as well as between patients on high- or low-dose morphine equivalents.

MEDD was measured by summarizing the mean morphine equivalent daily intake.

Data are reported as mean ± SD, median (minimum-maximum) and standard error of the mean (SEM). Regarding the significance level we chose to classify into intervals to prevent overinterpreting the results due to multiple outcomes: $0.01 < p < 0.05$ indicated a weak association between L-TOT and the outcome, $0.001 < p < 0.01$ indicated a moderate association, and $p < 0.001$ strongly indicated an association (Johnsen et al., 2014; Wasserstein et al., 2019). All analyses were conducted using SAS v. 9.4 (SAS Institute Inc.).

3 | RESULTS

3.1 | Sociodemographic, L-TOT and clinical variables

A total of 1279 patients were screened; 259 were found eligible for inclusion. Fifty-three declined to participate and 124 were excluded (Figure 1). Finally, 38 patients were included in the opioid group and 44 patients in the control (Figure 1). Significant differences in smoking habits, alcohol consumption, and BMI were detected between the opioid and the control group (Table 1). The opioid group was characterized by overweight with a mean BMI of 26.6 ± 4.3, whereas the control group was characterized by normal weight, with a mean BMI of 24.6 ± 4.2 ($p = 0.02$). There was no significant difference in age and sex distribution between the two groups.

The type of opioid consumption variated widely in the opioid group; however, most were treated with morphine ($n = 14$, 36.8%), the remaining opioids were tramadol ($n = 10$, 26.3%), methadone ($n = 9$, 23.7%), oxycodone ($n = 8$, 21.1%), fentanyl ($n = 2$, 5.3%), tapentadol ($n = 1$, 2.6%) and buprenorphine ($n = 1$, 2.6%). The mean MEDD was 136.9 mg (±122.1) with a median of 95 mg (SEM = 19.81). The opioid intake was a mixture of immediate- and sustained release formulations. Twenty-two patients were on high-dose opioids (57.9%) and 16 patients were on low-dose opioids (42.1%). There were no significant sociodemographic differences between the patients receiving high or low doses of opioids (data not shown).

There were no significant differences regarding haemoglobin, estimated Glomerular Filtration Rate (e-GFR), creatinine, calcium, potassium, sodium, alanine transaminase (ALAT), alkaline phosphatase or albumin between the groups (data not shown).

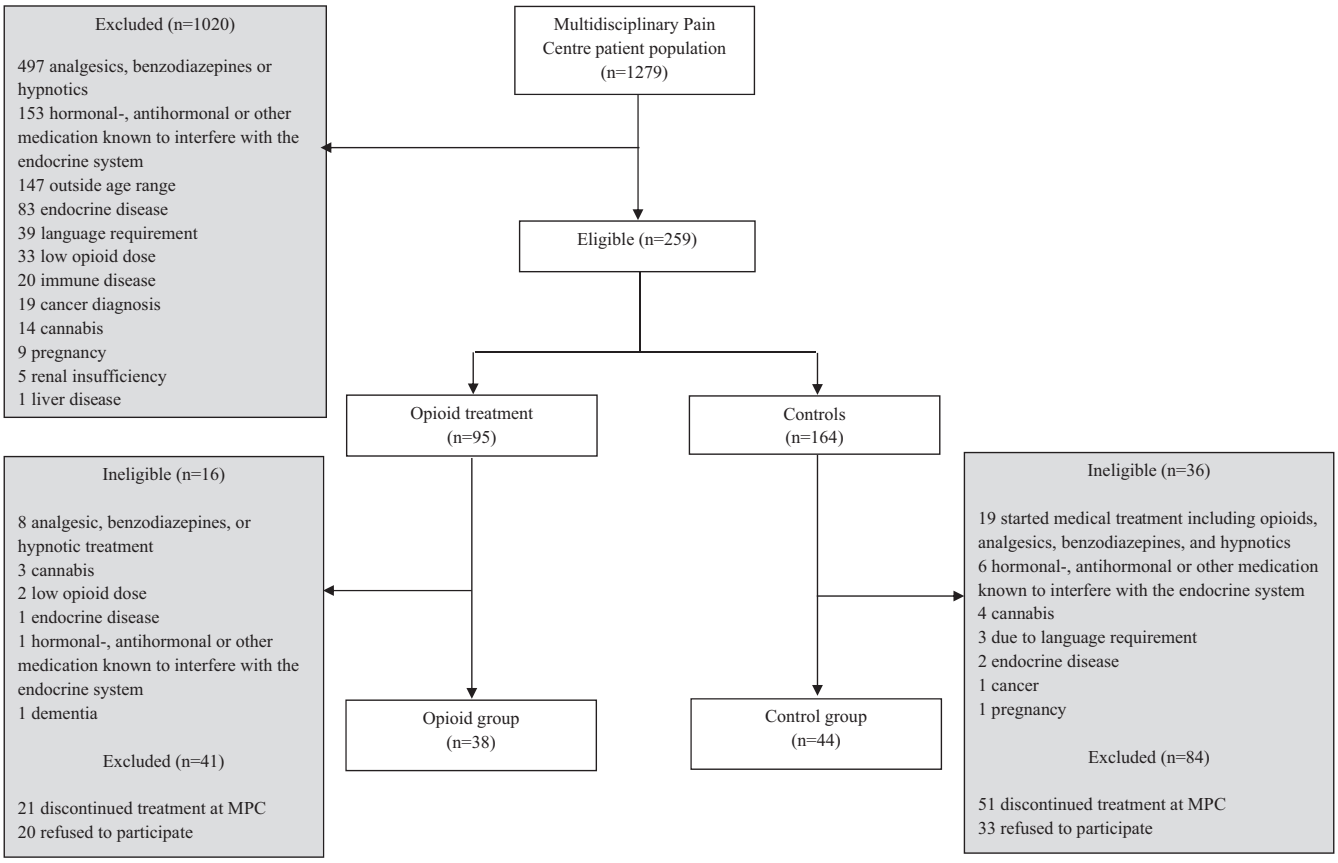

FIGURE 1 Flowchart of patient inclusion.

TABLE 1 Characteristics of the study population.

Variables	Opioid group ($n = 38$)	Control group ($n = 44$)	p-value[a]
Sex			0.125
Male, *n* (%)	22 (57.9)	18 (40.9)	
Female, *n* (%)	16 (42.1)	26 (59.1)	
Age, years			0.059
Mean (SD)	48.5 (±10.7)	43.3 (±12.3)	
Median (min–max)	50 (26–64)	46 (22–63)	
Civil status			0.182
Cohabitation, *n* (%)	27 (71.1)	25 (56.8)	
Alone, *n* (%)	11 (29.0)	19 (43.2)	
Schooling, years			0.217
Mean (SD)	14.9 (±4.3)	14.0 (±3.6)	
Median (min–max)	16 (7–23)	15 (6–20)	
Work			0.818
Yes, *n* (%)	13 (34.2)	14 (31.8)	
No, *n* (%)	25 (65.8)	30 (68.2)	
Income, DKK			0.875
<200.000, *n* (%)	18 (47.4)	21 (47.7)	
200–500.000, *n* (%)	19 (50)	20 (45.5)	
>500.000, *n* (%)	1 (2.63)	3 (6.8)	
Smoking			0.018
Yes, *n* (%)	22 (57.9)	14 (31.8)	
No, *n* (%)	16 (42.1)	30 (68.2)	
Smoking, cigarettes per day			0.081
Mean (SD)	8.4 (±9.6)	5.8 (±10.2)	
Median (min–max)	3.5 (0–30)	0 (0–40)	
Alcohol			0.044
Yes, *n* (%)	14 (36.8)	26 (59.1)	
No, *n* (%)	24 (63.16)	18 (40.91)	
Alcohol, units per week			0.092
Mean (SD)	2.3 (±5.4)	2.8 (±4.1)	
Median (min–max)	0 (0–30)	1 (0–15)	
BMI			0.02
Mean (SD)	26.6 (±4.3)	24.6 (±4.2)	
Median (min-–max)	27.4 (18.21–33.8)	24.4 (16.9–35.1)	
BMI			0.117
Underweight (<18.5), *n* (%)	2 (5.3)	4 (9.1)	
Normal (18.5–24.9), *n* (%)	10 (26.3)	20 (45.5)	
Overweight (25–29.9), *n* (%)	18 (47.4)	17 (38.6)	
Obesity (<30), *n* (%)	8 (21.1)	3 (6.8)	
Pain duration, years			0.41
Mean (SD)	12.113 (9.4)	11.033 (8.9)	
Median (min-max)	9.5 (2–46)	7.75 (2–40)	

TABLE 1 (Continued)

Variables	Opioid group ($n=38$)	Control group ($n=44$)	p-value[a]
Pain characteristics			0.681
Neuropathic, n (%)	9 (23.7)	13 (29.6)	
Nociceptive somatic, n (%)	10 (26.3)	12 (27.3)	
Nociceptive visceral, n (%)	0 (0)	0 (0)	
Nociceptive visceral and neuropathic, n (%)	1 (2.63)	0 (0)	
Nociceptive somatic and neuropathic, n (%)	18 (47.4)	19 (43.2)	

[a]Categorical data: chi-square test. Numerical data: Wilcoxon two-sample test.

3.2 | Endocrine measures

3.2.1 | Adrenal function

Spot cortisol

There were no significant differences in spot cortisol between the controls and the opioid group ($\beta=1.3$; $p=0.962$). Both groups had spot cortisol levels in the high end of the normal range for clock time (normal range morning from 06 to 10 AM: 133–537 nmol/L) (Table 2).

ATCH stimulation test

All participants had a normal response to ACTH stimulation with no peak cortisol levels under the cut-off value of 420 nmol/L after 30 min. Thus, none had adrenal insufficiency. However, a significant difference in the peak cortisol concentration after stimulation was found between the two groups. Patients in the control group had a higher peak cortisol to stimulation than the patients in L-TOT ($\beta=-74$; $p=0.016$) (Table 2). The absolute cortisol increases after the ATCH stimulation test showed that both the opioid group and the control group had an acceptable response >200 nmol. However, a significant difference was found, showing that the control group had a greater response ($p=0.012$).

High/low-dose opioid

There were no significant difference between high and low opioid dose regarding spot cortisol ($\beta=41$; $p=0.249$). The relationship between opioid dosage and the results from the ATCH stimulation test were not analysed due to small sample size.

3.2.2 | Androgens and related outcomes

Men

Lower TT levels ($\beta=-5.4$; $p=0.004$), fT levels ($\beta=-0.2$; $p<0.001$), DHEAS levels ($\beta=-1.7$ $p=0.017$), and higher SHBG levels ($\beta=8.6$; $p=0.042$) were found in male patients in L-TOT compared to male controls (Table 2). No differences were found regarding 17-hydroxyprogesterone or androstenedione.

Women

No difference was found regarding TT, fT, SHBG, DHEAS, 17-hydroxyprogesterone or androstenedione in pre- or postmenopausal women in L-TOT compared to controls.

Total sample

Patients in L-TOT had significantly higher levels of PRL compared to controls ($\beta=45$; $p=0.018$).

High/low-dose opioid

No significant difference was detected in either TT or fT between male CNCP patients on high- and low-dose opioids ($\beta=2.7$ $p=0.342$; $\beta=0.1$ $p=0.162$ respectively). In premenopausal women receiving high doses of opioids significant lower fT was found compared with women on low-dose opioids ($\beta=0.01$; $p=0.015$).

3.2.3 | Other endocrine outcomes

Men

Lower IGF-1 levels were found in male patients in L-TOT compared to male controls ($\beta=-47$; $p=0.003$).

Women

No difference was found regarding IGF-1 in pre- or postmenopausal women in L-TOT compared to controls.

Total sample

The opioid group had significantly lower levels of IGF-1 SDS compared to the control group ($\beta=-0.8$; $p=0.006$) (Table 2). No significant difference between groups was detected regarding TSH ($\beta=-0.2$; $p=0.598$) and T4 ($\beta=4.6$; $p=0.23$) (Table 2).

High/low-dose opioid

A correlation between low levels of IGF-1 and high opioid dose ($\beta=-59$; $p<0.001$) was found.

TABLE 2 Endocrine measures.

	Opioid group ($n=37$)		
		Female ($n=16$)	
Variables mean ± SD median (min–max)	**Male ($n=21$)**	**Premenopausal ($n=11$)**	**Postmenopausal ($n=5$)**
Hypothalamic–pituitary–adrenal axis			
Cortisol (nmol/L)	254.6 ± 118.2 256 (65–559)		
Cortisol increase during ACTH stimulation test (nmol/L)	431.1 ± 143.7 463 (141–602) ($n=19$)		
Cortisol peak after 30 min ACTH stimulation test (nmol/L)	697.5 ± 60.3 693 (572–844) ($n=19$)		
Hypothalamic–pituitary–gonadal axis			
Testosterone (nmol/L)	12.4 ± 6.4 12.3 (3.6–26.5)	0.7 ± 0.4 0.8 (0.1–1.4)	0.6 ± 0.2 0.6 (0.4–0.8)
Free testosterone (nmol/L)	0.2 ± 0.1 0.3 (0.1–0.4)	0.01 ± 0.01 0.02 (0.01–0.03)	0.007 ± 0.003 0.006 (0.005–0.01)
17-hydroxyprogesterone (nmol/L)	4.3 ± 4.0 3.1 (0.3–18.9)	2.9 ± 2.7 2.3 (0.3–8.5)	2.0 ± 2.3 1.2 (0.3–5.9)
Androstenedione (nmol/L)	3.2 ± 2.0 2.7 (0.5–9.9)	4.3 ± 2.8 3.9 (0.8–10.7)	3.1 ± 1.6 2.3 (1.8–4.9)
SHBG (nmol/L)	49.7 ± 18.9 47 (18.7–98)	50.1 ± 11.6 50.7 (33–67)	103.4 ± 73.8 69 (39.9–206)
DHEAS (μmol/L)	2.4 ± 1.3 2.2 (0.7–5.1)	2.6 ± 1.3 2.9 (0.4–4.0)	1.7 ± 1.1 1.36 (0.7–3.6)
Prolactin (nmol/L)	152.4 ± 89.8 130 (48–452)	196.4 ± 133.8 162 (62–554)	140.4 ± 65.2 107 (85–232)
Prolactin (nmol/L)	163.8 ± 102 134 (48–554)		
Hypothalamic–pituitary growth axis			
IGF-1 (μg/L)	117.6 ± 45.9 122 (18–230)	134 ± 58.7 118 (76–264)	
IGF-1 SDS	−0.6 ± 1.3 −0.5 (−4.8–2.1)		
Hypothalamic–pituitary–thyroid axis			
TSH (nmol/L)	1.7 ± 0.8 1.4 (0.5–4.2)		
T4 (nmol/L)	97.6 ± 18.5 95 (52–136)		

Abbreviations: F pre, premenopausal female participants; F post, postmenopausal female participants.

[a]Multiple regression analysis controlled for age, smoking, alcohol and BMI.

[b]Multiple regression analysis controlled for smoking, alcohol and BMI (age and sex is controlled in the value from the laboratory).

[c]Multiple regression analysis controlled for smoking, alcohol, BMI, age and sex.

Control group ($n = 42$)				
	Female ($n = 24$)			
Male ($n = 18$)	Premenopausal ($n = 16$)	Postmenopausal ($n = 8$)	Reference values	p-value
278.6 ± 117.6 262.5 (107–771)			Morning 06–10: 133–537 Afternoon 16–20: 68–327	0.962[a]
448.1 ± 123 448 (212–767) ($n = 19$)			>200 nmol/L	0.012
756.6 ± 101.3 740 (615–983) ($n = 19$)			>420 nmol/L	0.016[a]
16.4 ± 5.0 16.7 (8.7–25.1)	0.8 ± 0.3 0.8 (0.3–1.5)	0.7 ± 0.3 0.6 (0.3–1.3)	M 20–50 years: 8.6–29 M > 50 years: 6.7–26 F 20–50 years: 0.4–1.7 F > 50 years: 0.4–1.4	M: 0.004[a] F pre: 0.454[a] F post: 0.841[a]
0.4 ± 0.1 0.4 (0.2–0.6)	0.01 ± 0.01 0.01 (0.004–0.02)	0.01 ± 0.007 0.009 (0.006–0.027)	M 20–49 years 0.2–0.7 M 50–69 years 0.2–0.6 F pre 0.006–0.03 F post 0.005–0.02	M: <0.001[a] F pre: 0.971[a] F post: 0.84[a]
4.3 ± 2.2 3.9 (1.7–9.9)	2.2 ± 1.5 2.1 (0.3–5.5)	1.5 ± 1.7 0.7 (0.3–4.1)	M < 8 F pre in follicular phase <3 F in luteal phase <10 F post <2	M: 0.846[a] F pre: 0.34[a] F post: 0.132[a]
3.9 ± 1.8 3.4 (1.7–8.1)	3.6 ± 1.8 3.6 (1.5–6.7)	2.5 ± 1.5 1.8 (1.0–5.5)	M 20–49 years 1.7–6.9 M 50–69 years 1.6–6.5 F pre 2.4–8.9 F post 0.8–4.8	M: 0.133[a] F pre: 0.459[a] F post: 0.169[a]
37.5 ± 10.5 34.7 (18.9–60.5)	63.3 ± 28.3 52 (40.2–145)	59 ± 30.1 47.8 (29.4–121)	M 20–50 years 15.8–55.5 M > 50 years 19.3–83.4 F 20–50 27.1–46 F > 50 years 21.8–142	M: 0.042[a] F pre: 0.193[a] F post: 0.483[a]
4.8 ± 3.5 3.3 (0.6–11.1)	3.6 ± 1.4 3.4 (1.3–7.1)	2.3 ± 1.5 1.86 (0.6–52)	M 20–39 years 3–12 M 40–59 years 1–10 M 60–69 years 0.7–7 F pre 1.2–9.5 F post 0.5–4.5	M: 0.017[a] F pre: 0.127[a] F post: 0.937[a]
111.4 ± 43.2 96 (58–202)	159 ± 81.4 133 (72–360)	104.8 ± 31.5 104.5 (63–148)	M 69–266 × 10–3 IU/L F 59–304 × 10–3 IU/L	M: 0.163[a] F pre: 0.704[a] F post: 0.177[a]
128.6 ± 61.9 114 (58–360)				0.018[c]
170.9 ± 54.9 164.5 (81–274)	153.4 ± 53.6 152 (58–257)			M: 0.003[a] F: 0.803[a]
0.3 ± 0.9 0.3 (−1.6–2.9)				0.006[b]
1.7 ± 1.135 1.3 (0.7–5.4)			0.40–4.80 × 10–3 IU/L	0.598[a]
89.2 ± 14.2 87.5 (61–123)			70–140 nmol/L	0.23[a]

4 | DISCUSSION AND CONCLUSIONS

This explorative study showed that L-TOT was strongly associated with lower fT in men and lower IGF-1 SDS, moderately with lower TT and lower IGF-1 in men, and weakly with lower DHEAS and higher SHBG in men, as well as higher PRL and less cortisol response to the ACTH stimulation test. A strong association between opioid dose and IGF-1 levels was also detected. These results support earlier findings regarding TT, fT, cortisol and DHEAS and provide interesting new information regarding IGF-1, PRL and SHBG. The endocrine effects of opioid treatment in this study were subtle, that is most patients were within the normal reference ranges for the respective hormone and only few percent of the patients were above or below +2/−2 SD. However, on a group level we found some significant differences. Hormonal reference ranges are physiologically very broad, and in clinical practice the 'natural set point' for an individual is unknown. Changes in this set-point, however, even within the reference ranges may cause symptoms and require intervention.

In former studies, opioid intake has been linked to hypogonadism (Aloisi et al., 2009; Diasso et al., 2021; Gadelha et al., 2022; Gudin et al., 2015; Katz & Mazer, 2009). Opioid intake has been shown to suppress and alter the pulsatile secretion of GnRH in the hypothalamus, decrease gonadotropin secretion by the pituitary gland and also decrease steroidogenesis in the gonads (Fountas et al., 2018; Vuong et al., 2010). Although there are very few studies investigating L-TOT in CNCP patients, the overall results point towards low LH, FSH, TT, fT estradiol and DHEAS as a consequence to L-TOT (Aloisi et al., 2005; Daniell, 2008; Duarte et al., 2013; Lamprecht et al., 2018; Roberts et al., 2002; Valverde-Filho et al., 2015; Wong et al., 2011). Reduced libido, erectile dysfunction, irregular menstruations and infertility are all potential consequences of hypogonadism (Gadelha et al., 2022). Furthermore, TT reflects both bound and unbound testosterone and is dependent on the concentration of SHBG. SHBG is synthesized in the liver and affected by multiple factors, for example thyroid hormones, physical exercise, insulin, diet and androgens (Kotsopoulos et al., 2009; Vuong et al., 2010). In this study, L-TOT was associated with high SHBG levels in men, but not in women. However, all women had high SHBG levels compared to normal range, especially women in the control group. As SHBG is also regulated by cortisol it is possible that CNCP could interfere with SHBG levels as a result of chronic distress (Lennartsson et al., 2012). In addition, hypogonadism may contribute to increased pain perception and hyperalgesia development, based on data from a single randomized controlled trial investigating the effects of testosterone replacement therapy. Men receiving replacement therapy experienced less pain and hyperalgesia (Basaria et al., 2015). It has also previously been suggested that opioids induce PRL secretion and, as a response, reduce GnRH release, which lowers the concentration of sex hormones (de Vries et al., 2020). To our knowledge, higher PRL levels in CNCP patients as a result of L-TOT have only been shown in one previous study, which showed no effect on sexual function (Wong et al., 2011).

Elevated cortisol levels as a reaction to acute stress is vital, whereas sustained stress may lead to adrenal dysfunction (Hannibal & Bishop, 2014). In a systematic review, L-TOT for CNCP has been linked to suppressed adrenal function (Diasso et al., 2021). CNCP patients in the control group had a higher cortisol response to the ATCH stimulation test (peak cortisol and absolute cortisol increase) compared with the opioid group. However, both groups were within the normal range not exhibiting adrenal insufficiency. Our results do not contradict the hypothesis by others that opioids may decrease the ability of the pituitary gland to react on corticotropin-releasing hormone (CRH) (Vuong et al., 2010). As the ATCH test uses supraphysiological doses, the group difference may reflect a low set-point of the spontaneous CRH-ACTH secretion axis in patients receiving opioids. IGF-I promotes muscle and bone growth, particularly in childhood and puberty, and is involved in glucose homeostasis including insulin secretion and lipolysis (Clemmons, 2004). Low IGF-1 levels could result in lower insulin secretion leading to hyperglycaemia (Vuong et al., 2010). Our results are in line with one previous study (Lamprecht et al., 2018) which described reduced IGF-1 levels in CNCP patients as a result of L-TOT. In our study higher BMI and PRL were seen in the opioid group. PRL stimulates adipogenesis and inhibits the lipolysis, thus leading to more fat tissue (Ruiz-Herrera et al., 2017). Finally, changes in BMI may also have an impact on several other hormone axes, either directly or through change in binding proteins. However, due to the study design it is impossible to determine whether the low IGF-1 levels are a result of the physical and mental stress patients receiving L-TOT, or causally related to the opioid administration. An overall spot cortisol in the higher end of the reference range was detected in both groups. Previous studies in CNCP patients have shown diverse findings with both higher and lower levels of cortisol as a result of L-TOT with a predominance of low levels (Aurilio et al., 2011; Lamprecht et al., 2018; Nenke et al., 2015; Ozyuvaci et al., 2004).

Previous studies have indicated that opioid dosage and the degree of hormonal alteration were related (Lamprecht et al., 2018; Wong et al., 2011). In a systematic review an association between opioid dose and low TT and fT was found (Diasso et al., 2021). However, this

study did not identify such association which may be due to the small sample size or a lack of a true threshold for endocrine effects of opioids. However, the study found an association between low IGF-1 levels and high opioid dosages, which has to our knowledge not been described in previous studies.

There are certain limitations in this work that should be considered. First, as the study is cross-sectional, no firm causal conclusions can be drawn. Second, due to the relatively small population sample, we did not attempt to match the groups for age and sex, which could be important for the androgen results as well as IGF-1 and PRL. Similarly, the sample size did not allow us to study effect differences for various opioid types. This could be relevant because various opioids bind to different receptors with various efficiency (Pasternak, 2014; Pasternak & Pan, 2013). Additionally, the ACTH stimulation test was only performed in a small subgroup due to logistic constraints and as we could not perform a power calculation at study start, there may be a risk of overlooking other group differences. Furthermore, the number of outcomes explored in this study increases the risk of random findings. No statistical correction, for example Bonferroni test, was used due to its conservative and inadequate handling of exploratory data (Perneger, 1998). Instead, the significance levels divided into intervals going from strongly significant to weakly significant, which also was the recommendation by a consulting statistician (Wasserstein et al., 2019). This study has strict inclusion and exclusion criteria and a standardized time window for blood samples as an attempt to minimize the effect of possible confounders, which gives it a robust design in a patient population with high complexity. Furthermore, the significance level has been divided into intervals to prevent the results to be overstated. The findings support previous discoveries regarding possible associations of L-TOT on TT, fT and DHEAS. Interestingly new associations were found between L-TOT, IGF-1, SHBG and PRL. We recommend future studies to investigate endocrine effects of opioids in larger, longitudinal studies. In the meanwhile, clinicians should be cautious when prescribing opioids for CNCP and follow recently developed guidelines (Busse et al., 2017; Dowell et al., 2016). Finally, as symptoms of endocrine dysfunction may be subtle and non-specific, we recommend measurement of hormonal levels at baseline and at regular intervals during opioid treatment until more knowledge is provided.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

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REFERENCES

Abs, R., Verhelst, J., Maeyaert, J., Van Buyten, J. P., Opsomer, F., Adriaensen, H., Verlooy, J., Van Havenbergh, T., Smet, M., & Van Acker, K. (2000). Endocrine consequences of long-term intrathecal administration of opioids. *The Journal of Clinical Endocrinology and Metabolism*, *85*, 2215–2222.

Aloisi, A. M., Aurilio, C., Bachiocco, V., Biasi, G., Fiorenzani, P., Pace, M. C., Paci, V., Pari, G., Passavanti, G., Ravaioli, L., Sindaco, G., Vellucci, R., & Ceccarelli, I. (2009). Endocrine consequences of opioid therapy. *Psychoneuroendocrinology*, *34*(Suppl 1), 162–168.

Aloisi, A. M., Pari, G., Ceccarelli, I., Vecchi, I., Ietta, F., Lodi, L., & Luana, P. (2005). Gender-related effects of chronic non-malignant pain and opioid therapy on plasma levels of macrophage migration inhibitory factor (MIF). *Pain*, *115*, 142–151.

Aurilio, C., Ceccareli, I., Pota, V., Sansone, P., Massafra, C., Barbarisi, M., Pace, M. C., Passavanti, M. B., Bravi, F., & Aoisi, A. M. (2011). Endocrine and behavioural effects of transdermal buprenorphine in pain-suffering women of different reproductive ages. *Endocrine Journal*, *58*, 1071–1078.

Basaria, S., Travison, T. G., Alford, D., Knapp, P. E., Teeter, K., Cahalan, C., Eder, R., Lakshman, K., Bachman, E., Mensing, G., Martel, M. O., Le, D., Stroh, H., Bhasin, S., Wassan, A. D., & Ewards, R. R. (2015). Effects of testosterone replacement in men with opioid-induced androgen deficiency: A randomized controlled trial. *Pain*, *156*, 280–288.

Birke, H., Ekholm, O., Sjøgren, P., Kurita, G., & Højsted, J. (2017). Long-term opioid therapy in Denmark: A disappointing journey. *European Journal of Pain*, *21*, 1516–1527.

Birke, H., Kurita, G. P., Sjøgren, P., Højsted, J., Simonsen, M. K., Juel, K., & Ekholm, O. (2016). Chronic non-cancer pain and the epidemic prescription of opioids in the Danish population: Trends from 2000 to 2013. *Acta Anaesthesiologica Scandinavica*, *60*, 623–633.

Boizet-Bonhoure, B., Déjardin, S., Rossitto, M., Poulat, F., & Philibert, P. (2022). Using experimental models to decipher the effects of acetaminophen and NSAIDs on reproductive development and health. *Front Toxicol*, *4*, 1–17.

Busse, J. W., Craigie, S., Juurlink, D. N., Buckley, D. N., Li, W., Couban, R. J., Agoritsas, T., Akl, E. A., Carrasco-Labra, A., Cooper, L., Cull, C., Da Costa, B. R., Frank, J. W., Grant, G.,

Iorio, A., Persaud, N., Stern, S., Tugwell, P., Vandvik, P. O., & Guyatt, G. H. (2017). Guideline for opioid therapy and chronic noncancer pain. *CMAJ*, *189*, 659–666.

Busse, J. W., Wang, L., Kamaleldin, M., Craigie, S., Riva, J. J., Montoya, L., Mulla, S. M., Lopes, L. C., Vogel, N., Chen, E., Kirmayr, K., De Oliveira, K., Olivieri, L., Kaushal, A., Chaparro, L. E., Oyberman, I., Agarwal, A., Couban, R., Tsoi, L., … Guyatt, G. H. (2018). Opioids for chronic noncancer pain: A systematic review and meta-analysis. *Jama*, *320*, 2448–2460.

Centers for Disease Control and Prevention, U.S. (2021). *Opioid Prescribing Guideline Resources*.

Clemmons, D. R. (2004). The relative roles of growth hormone and IGF-1 in controlling insulin sensitivity. *The Journal of Clinical Investigation*, *113*, 25–27.

Colvin, L. A., Bull, F., & Hales, T. G. (2019). Perioperative opioid analgesia — When is enough too much? A review of opioid-induced tolerance and hyperalgesia. *Lancet*, *393*, 1558–1568.

Currow, D. C., Phillips, J., & Clark, K. (2016). Using opioids in general practice for chronic non-cancer pain: An overview of current evidence. *The Medical Journal of Australia*, *204*, 305–309.

Daniell, H. W. (2006). DHEAS deficiency during consumption of sustained-action prescribed opioids: Evidence for opioid-incluced inhibition of adrenal androgen production. *The Journal of Pain*, *7*, 901–907.

Daniell, H. W. (2008). Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *The Journal of Pain*, *9*, 28–36.

Danish Endocrinological Society. (2021). *Adrenocrotical insufficiency - National Guideline Denmark*.

de Vries, F., Bruin, M., Lobatto, D. J., Dekkers, O. M., Schoones, J. W., van Furth, W. R., Pereira, A. M., Karavitaki, N., Biermasz, N. R., & Zamanipoor Najafabadi, A. H. (2020). Opioids and their endocrine effects: A systematic review and meta-analysis. *The Journal of Clinical Endocrinology and Metabolism*, *105*, 1020–1029.

Diasso, P. D. K., Birke, H., Nielsen, S. D., Højsted, J., Sjøgren, P., Kurita, G. P., & Main, K. M. (2019). The effects of long-term opioid treatment on the immune system in chronic non-cancer pain patients: A systematic review. *European Journal of Pain*, *24*, 481–496.

Diasso, P. D. K., Frederiksen, B. S., Nielsen, S. D., Main, K. M., Sjøgren, P., & Kurita, G. P. (2021). Long-term opioid treatment and endocrine measures in chronic non-cancer pain patients: A systematic review and meta-analysis. *European Journal of Pain*, *25*, 1859–1875.

Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC guideline for prescribing opioids for chronic pain. *JAMA*, *315*, 1624–1645.

Drolet, G., Dumont, E. C., Gosselin, I., Kinkead, R., Laforest, S., & Trottier, J. F. (2001). Role of endogenous opioid system in the regulation of the stress response. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *25*, 729–741.

Duarte, R. V., Raphael, J. H., Southall, J. L., Labib, M. H., Whallett, A. J., & Ashford, R. L. (2013). Hypogonadism and low bone mineral density in patients on long-term intrathecal opioid delivery therapy. *BMJ Open*, *3*, 1–6.

Ekholm, O., Diasso, P. D. K., Davidsen, M., Kurita, G. P., & Sjøgren, P. (2022). Increasing prevalence of chronic non-cancer pain in Denmark from 2000 to 2017: A population-based survey. *European Journal of Pain*, *26*, 624–633.

Els, C., Jackson, T. D., Kunyk, D., Lappi, V. G., Sonnenberg, B., Hagtvedt, R., Sharma, S., Kolahdooz, F., & Straube, S. (2017). Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: An overview of Cochrane reviews. *Cochrane Database of Systematic Reviews*, *10*(10), 1–43.

Elsesser, K., & Cegla, T. (2017). Long-term treatment in chronic noncancer pain: Results of an observational study comparing opioid and nonopioid therapy. *Scandinavian Journal of Pain*, *17*, 87–98.

Food and Drug Administration, U.S. (2021). *Overlooked definition choices inhibit interpretation of morphine equivalence: definition of high- and low dose opioid use*.

Fountas, A., Chai, S. T., Kourkouti, C., & Karavitaki, N. (2018). Mechanisms of endocrinology: Endocrinology of opioids. *European Journal of Endocrinology*, *179*, 183–196.

Gadelha, M. R., Karavitaki, N., Fudin, J., Bettinger, J. J., Raff, H., & Ben-Shlomo, A. (2022). Opioids and pituitary function: Expert opinion. *Pituitary*, *25*, 52–63.

Genazzani, A., Genazzani, A., Volpogne, C., Pianazzi, F., Li, G., Surico, N., & Petraglia, F. (1993). Opioid control of gonadotrophin secretion in humans. *Human Reproduction*, *8*, 151–153.

Grandison, L. (1983). Actions of benzodiazepines on the neuroendocrine system. *Neuropharmacology*, *22*, 1505–1510.

Gudin, J. A., Laitman, A., & Nalamachu, S. (2015). Opioid related endocrinopathy. *Pain Medicine*, *16*(Suppl 1), 9–15.

Hamina, A., Hjellvik, V., Handal, M., Odsbu, I., Clausen, T., & Skurtveit, S. (2022). Describing long-term opioid use utilizing Nordic prescription registers — A Norwegian example. *Basic & Clinical Pharmacology & Toxicology*, *130*, 481–491.

Hannibal, K., & Bishop, M. (2014). Chronic stress, cortisol dysfunction, and pain: A psychoneuroendocrine rationale for stress management in pain rehabilitation. *Physical Therapy*, *94*, 1816–1825.

Højsted, J., & Sjøgren, P. (2007). An update on the role of opioids in the management of chronic pain of nonmalignant origin. *Current Opinion in Anaesthesiology*, *20*, 451–455.

Høyer, B. B., Ramlau-Hansen, C. H., Bonde, J. P., Larsen, S. B., & Toft, G. (2017). Use of non-prescription analgesics and male reproductive function. *Reproductive Toxicology*, *74*, 70–76.

Johnsen, A., Petersen, M., Gluud, C., Linschou, J., Fayers, P., Sjøgren, P., Pedersen, L., Neergaard, M., Vejlgaard, T., Damkier, A., Nielsen, J., Strömgren, A., Higginson, I., & Groenvold, M. (2014). Detailed statistical analysis plan for the pulmonary protection trial. *Trials*, *15*, 1–10.

Jordan, D., Tafani, J., Ries, C., Zajac, J., Simonnet, G., Martin, D., Kopp, N., & Allard, M. (1996). Evidence for multiple opioid receptors in the human posterior pituitary. *Journal of Neuroendocrinology*, *8*, 883–887.

Ju, C., Wei, L., Man, K. K. C., Wang, Z., Ma, T. T., Chan, A. Y. L., Brauer, R., Chui, C. S. L., Chan, E. W., Jani, Y. H., Hsia, Y., Wong, I. C. K., & Lau, W. C. Y. (2022). Global, regional, and national trends in opioid analgesic consumption from 2015 to 2019: A longitudinal study. *The Lancet. Public Health*, *7*, 335–346.

Katz, N., & Mazer, N. A. (2009). The impact of opioids on the endocrine system. *The Clinical Journal of Pain*, *25*, 170–175.

Kotsopoulos, J., Eliassen, A. H., Missmer, S. A., Hankinson, S. E., & Tworoger, S. S. (2009). Relationship between caffeine intake and plasma sex hormone concentrations in premenopausal and postmenopausal women. *Cancer*, *115*, 2765–2774.

Krebs, E. E., Gravely, A., Nugent, S., Jensen, A. C., DeRonne, B., Goldsmith, E. S., Kroenke, K., Bair, M. J., & Noorbaloochi, S. (2018). Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. *JAMA*, *319*, 872–882.

Kristensen, D. M., Desdoits-Lethimonier, C., Mackey, A. L., Dalgaard, M. D., De Masi, F., Munkbøl, C. H., Styrishave, B., Antignac, J. P., Le Bizec, B., Platel, C., Hay-Schmidt, A., Jensen, T. K., Lesné, L., Mazaud-Guittot, S., Kristiansen, K., Brunak, S., Kjaer, M., Juul, A., & Jégou, B. (2018). Ibuprofen alters human testicular physiology to produce a state of compensated hypogonadism. *Proceedings of the National Academy of Sciences of the United States of America*, *115*, E715–E724.

Lamprecht, A., Sorbello, J., Jang, C., Torpy, D. J., & Inder, W. J. (2018). Secondary adrenal insufficiency and pituitary dysfunction in oral/transdermal opioid users with non-cancer pain. *European Journal of Endocrinology*, *179*, 353–362.

Lennartsson, A. K., Kushnir, M. M., Bergquist, J., Billig, H., & Jonsdottir, I. H. (2012). Sex steroid levels temporarily increase in response to acute psychosocial stress in healthy men and women. *International Journal of Psychophysiology*, *84*, 246–253.

Mueller, C., Chu, L. F., Lin, J. C., Ovalle, F., & Younger, J. W. (2018). Daily opioid analgesic use reduces blood insulin levels. *Journal of Opioid Management*, *14*, 165–170.

Nenke, M. A., Haylock, C. L., Rankin, W., Inder, W. J., Gagliardi, L., Eldridge, C., Rolan, P., & Torpy, D. J. (2015). Low-dose hydrocortisone replacement improves wellbeing and pain tolerance in chronic pain patients with opioid-induced hypocortisolemic responses. A pilot randomized, placebo-controlled trial. *Psychoneuroendocrinology*, *56*, 157–167.

Oltmanns, K. M., Fehm, H. L., & Peters, A. (2005). Chronic fentanyl application induces adrenocortical insufficiency. *Journal of Internal Medicine*, *257*, 478–480.

Ortman, H. A., & Siegel, J. A. (2020). The effect of methadone on the hypothalamic pituitary gonadal axis and sexual function: A systematic review. *Drug and Alcohol Dependence*, *207*, 1–17.

Ozyuvaci, E., Alnigenis, N. Y., & Altan, A. (2004). The effect of transdermal fentanyl treatment on serum cortisol concentrations in patients with non-cancer pain. *Journal of Pain and Symptom Management*, *28*, 277–281.

Pasternak, G. W. (2014). Opioids and their receptors: Are we there yet? *Neuropharmacology*, *76*, 198–203.

Pasternak, G. W., & Pan, Y. (2013). Mu opioids and their receptors: Evolution of a concept. *Pharmacological Reviews*, *65*, 1257–1317.

Perneger, T. V. (1998). What's wrong with Bonferroni adjustments. *British Medical Journal*, *316*, 1236–1238.

Roberts, L. J., Finch, P. M., Pullan, P. T., Bhagat, C. I., & Price, L. M. (2002). Sex hormone suppression by intrathecal opioids : A prospective study. *The Clinical Journal of Pain*, *18*, 144–148.

Ruiz-Herrera, X., De Los Ríos, E. A., Díaz, J. M., Lerma-Alvarado, R. M., De La Escalera, L. M., López-Barrera, F., Lemini, M., Arnold, E., De La Escalera, G. M., Clapp, C., & Macotela, Y. (2017). Prolactin promotes adipose tissue fitness and insulin sensitivity in obese males. *Endocrinology*, *158*, 56–68.

Sehgal, N., Colson, J., & Smith, H. S. (2013). Chronic pain treatment with opioid analgesics: Benefits versus harms of long-term therapy. *Expert Review of Neurotherapeutics*, *13*, 1201–1220.

The Danish Health Authority, D. (2017). *The National Recommendation List: Pharmacological treatment of chronic nociceptives (Danish title: Den Nationale Rekommandationsliste Farmakologisk behandling af kroniske nociceptive)*. 1–62.

Valverde-Filho, J., Carneiro, B., da Cunha Neto, M., Fonoff, E. T., Meirelles, E. d. S., & Teixeira, M. J. (2015). Chronic spinal and oral morphine-induced neuroendocrine and metabolic changes in noncancer pain patients. *Pain Medicine*, *16*, 715–725.

Veldhuis, J. D., Rogol, A. D., Samojlik, E., & Ertel, N. H. (1984). Role of endogenous opiates in the expression of negative feedback actions of androgen and estrogen on pulsatile properties of luteinizing hormone secretion in man. *The Journal of Clinical Investigation*, *74*, 47–55.

Vuong, C., Van Uum, S. H. M., O'Dell, L. E., Lutfy, K., & Friedman, T. C. (2010). The effects of opioids and opioid analogs on animal and human endocrine systems. *Endocrine Reviews*, *31*, 98–132.

Wasserstein, R. L., Schirm, A. L., & Lazar, N. A. (2019). Moving to a world beyond "$p < 0.05$". *The American Statistician*, *73*, 1–19.

Wong, D., Gray, D., Simmonds, M., Rashiq, S., Sobolev, I., & Morrish, D. (2011). Opioid analgesics suppress male gonadal function, but opioid use in men and women does not correlate with symptoms of sexual dysfunction. *Pain Research & Management*, *16*, 311–316.

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