Systematic Review

Dalia Abou-Kassem*, Geana P. Kurita, Per Sjøgren and Pernille D. K. Diasso

Long-term opioid treatment and endocrine measures in patients with cancer-related pain: a systematic review

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Abstract

Objectives: Opioid analgesics are the main stay for cancer pain management; however, long-term opioid treatment (L-TOT) may suppress the endocrine system. This systemic review aimed at investigating effects of L-TOT on the endocrine system in patients with cancer-related pain.
Methods: A search on MEDLINE, EMBASE and Web of Science databases was performed. Inclusion criteria were clinical studies investigating endocrine measures in adult patients with cancer-related pain in L-TOT (≥4 weeks). Outcomes and quality of evidence were assessed.
Results: A total of 252 abstracts were identified; out of which 247 were excluded and five cross-sectional studies were included and analyzed. L-TOT was associated with lower serum concentration levels of total- and free testosterone in males, follicular stimulating hormone in females, and luteinizing hormone in both sexes. Moreover, higher morphine equivalent daily doses (MEDDs) were correlated with higher levels of cortisol and lower levels of LH in both sexes, and lower levels of total- and free testosterone in males. Sexual dysfunction was associated with low sex hormone levels. Level of evidence was low/very low.
Conclusions: The studies identified demonstrated that patients with cancer-related pain in L-TOT may have gonadal hypofunction causing sexual dysfunction, which may be correlated with opioid dose level. In addition, high serum concentrations of cortisol were positively correlated with high opioid dose levels. However, the evidence was weak and further research is necessary. PROSPERO, ID-number: CRD42020213059.

Keywords: cancer-related pain; endocrine; hormones; opioids.

Previous presentation: Presentation of study data at Danish Cancer Research Days in Odense, Denmark on 26. August 2021.

***Corresponding author: Dalia Abou-Kassem**, Department of Oncology, Rigshospitalet – Copenhagen University Hospital, Blegdamsvej 9, Copenhagen 2100, Denmark; and Multidisciplinary Pain Centre, Rigshospitalet – Copenhagen University Hospital, Ole Maaløes Vej 26, Copenhagen 2100, Denmark,
E-mail: daliia-ak@hotmail.com, Phone: +45 5193 8394
Geana P. Kurita, Department of Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark; Multidisciplinary Pain Centre, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark; and Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark,
E-mail: geana.kurita@regionh.dk
Per Sjøgren, Department of Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark; and Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark,
E-mail: per.sjoegren@regionh.dk
Pernille D. K. Diasso, Department of Oncology, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark,
E-mail: pernille.doessing.kwateng.diasso@regionh.dk

Introduction

The over-all prevalence of pain is 66% in patients with advanced cancer [1], which underpins a high demand for a sustained focus on improving pain management. The basis for cancer pain management is mainly pharmacological treatment, which includes opioids for moderate to severe pain [2]. Opioids are widely recommended due to their superior analgesic effect, multiple routes of administration, ease of titration and no dose-ceiling effect. Thus, opioid therapy is still the mainstay for achieving pain relief and to improve the quality of life for patients with cancer-related pain [3, 4]. However, opioids have well-known side effects such as constipation, nausea, vomiting, urinary retention and respiratory depression, and may have other long-term consequences such as development of tolerance, addiction, hyperalgesia, and alterations of the immune- and endocrine systems [5–11].

The effects of L-TOT on the endocrine system have been primarily investigated in chronic non-cancer pain patients. Studies have reported increased levels of prolactin (PRL) and suppression of the following endocrine measures: total testosterone (TT), luteinizing hormone (LH), follicular stimulating hormone (FSH), growth hormone (GH), cortisol, insulin like growth factor-1 (IGF-1), estradiol, progesterone, dehydroepiandrosterone (DHEA), adrenocorticotropic hormone (ACTH) and bone mineral density synthesis [11–15]. Most alterations described may be due to L-TOT inhibitory effects on the hypothalamic pituitary gonadal (HPG) axis involving opioid-induced androgen deficiency (OPIAD), which may result in sexual dysfunction, galactorrhea, amenorrhea, irregular menstrual cycle, infertility, and low libido, ultimately reducing the patients' quality of life [6, 8, 11, 13, 15, 16].

There are few reviews, which indicated effect of opioids on the endocrine system. However, they have peculiar characteristics as mixed populations with cancer and non-cancer diseases [17] and some limitations as no description of systematic search, among of factors. A former systematic review has investigated L-TOT effects on the HPG-axis and the increased risk of hypogonadism in patients with cancer-related pain [18]; however, the review was conducted in 2013 and included rather few studies with methodological limitations, no evidence assessment-based grading and focus on only hormones from the HPG-axis. Thus, to our knowledge no systematic reviews assessing evidence of L-TOT effects on hormones produced by other hypothalamic pituitary axes, peripheral glands, and other biomarkers in patients with cancer-related pain are existing. Therefore, to answer the research question "In adult patients with cancer-related pain who are in L-TOT, what are the effects of opioids on the endocrine system?", this systematic review was carried out with the aim to gather and investigate the evidence of effects of L-TOT on the endocrine system in patients with cancer-related pain.

Methods

This systematic review was elaborated based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) [19] and was registered at PROSPERO, ID-number: CRD42020213059 (https://www.crd.york.ac.uk/PROSPERO/).

Search strategy

The research question was constructed according to the elements of PICO method (problem/population, intervention, comparison, and outcome) [20]. The search strategy was developed using medical subject headings (MeSH) and terms related to endocrine outcomes, opioids, and cancer-related pain presented in the titles of abstracts or abstracts' content of the articles (Table 1).

Table 1: Search strategy.

PICO	Terms
Problem/ population:	Cancer* OR Neoplasm* OR Malignant* OR Tumor* OR Metastasis* Pain* OR Chronic pain*
Intervention:	Opioid* OR Opiate OR Opioid analgesics OR Morphine (CAS 57-27-2) OR Oxycodone (CAS 76-42-6) OR Buprenorphine (CAS 52485-79-7) OR Methadone (CAS 76-99-3) OR Fentanyl (CAS 437-38-7) OR Hydromorphone (CAS 466-99-9) OR Tapentadol (CAS 175591-09-0) OR Tramadol (CAS 27203-92-5) OR Codeine (CAS 76-57-3)
Comparison:	–
Outcome:	Endocrine system OR Hormone* OR Human Growth hormone OR Somatotropin OR Thyroid-stimulating hormone OR Adrenocorticotropic hormone OR Follicle-stimulating hormone OR Luteinizing hormone OR Prolactin OR Oxytocin OR Anti-diuretic hormone OR Vasopressin OR Triiodothyronine OR Thyroxine OR Tetraiodothyronine OR Insulin OR Glucagon OR Aldosterone OR Cortisol OR Corticosterone OR Dehydroepiandrosterone* OR Androstenedione OR Renin OR Calcitriol OR Erythropoietin OR Testosterone OR Estradiol OR Progesterone OR Estrone OR Insulin-like growth factor OR Parathyroid hormone

*A tool for searching databases that puts any possible suffix on the word after the star.

The database searches were performed in MEDLINE, Embase and Web of Science from inception dates to 12th November 2020. In addition, the reference lists of included studies and relevant existing reviews were scanned for related studies on 1st February 2021 (Table 2).

Inclusion and exclusion criteria

The inclusion criteria were as follows: observational and interventional studies (i.e., controlled trials) written in English, Norwegian, Swedish, or Danish investigating biomarkers of endocrine function in adult patients diagnosed with cancer-related pain in L-TOT (defined as a minimum of four weeks of opioid intake).

The exclusion criteria were as follows: studies comprising non-cancer diseases, experimental studies, case series with samples smaller than 10 patients, systematic reviews, retrospective studies (except for studies that analyzed blood samples stored or laboratorial information in patients journal records), study synopsis as well as patients in current hormone therapy. In addition, we also excluded studies with patients in chemotherapy known to affect the endocrine function and/or studies including patients diagnosed with endocrine diseases or conditions using anti-hormone therapies, supplementary therapies for infertility, diabetes, metabolic disorders (thyroid and parathyroid supplement therapy), hormonal anticonceptions, glucocorticoid therapy, and erythropoietin (EPO) for hemopoiesis. Finally,

Table 2: Study characteristics.

Observational study								
Cross-sectional								
Author, year	**n**	**Cancer type (%)**	**Age**	**Opioid dose (mg/day)**	**Route of administration**	**Duration**	**Outcomes**	**Findings associated with opioid exposure (group comparisons)**
[16]	20 pt. (13 male, 7 female) Comparison: normal reference values	75% metastases 10 visceral: (50%) 3 bone: (15%) 2 Bone and visceral: (10%)	Median: 50 years (24–72 years)	Median: 180 MEDD (10–420)	_	≥ 1 month	TSH µIU/mL fT_4 pg/mL ACTH pg/mL Cortisol µg/dL FSH mIU/mL LH mIU/mL TT ng/mL fT pg/mL GH ng/mL Estradiol pg/mL PRL ng/mL MEDD	TSH (n=20): ↓ in 5% and ↑ in 20% fT_4 (n=19): ↓ in 5.2% ACTH (n=18): ↓ in 5.5% Cortisol (n=20): ↓ in 15% and ↑ in 40% FSH (n=20) in female: ↓ in 30% and ↑ in 45% LH in female (n=20): ↓ in 30% and ↑ in 40% TT in male (n=16): ↓ in 68.7% fT in male (n=13): ↓ in 57.1% GH (n=19): ↑ in 5.2% Estradiol in female (n=8): ↓ in 25% and ↑ in 12.5% PRL (n=14): ↑ in 42.9% ↑ MEDD associated with ↓ TT (p=*0.040*) ↑ MEDD associated with ↓ fT (p=*0.041*)
[24]	77 pt. (48 male, 29 female) Comparison: normal reference value	33 Gastrointestinal: (43%) 21 Lung: (27%) 23 Other: (30%)	Median: 63 years (24–79 years)	MEDD <30 mg/day (n=35) Mean: 2.7 mg (SD: 3.8) MEDD ≥ 30 mg/day (n=42) Mean 122 mg (SD: 102)	_	_	Random cortisol µg/dL AM cortisol µg/dL TT ng/dL MEDD	Random cortisol ≤ 4 in 1% MEDD associated with random cortisol (r=0.25, p=*0.032*) TT ≤ 100 in 20.5% MEDD associated with TT in men (r=–0.52, p=*0.001*)
[25]	pt. Male: 90 Female: 77 Comparison (healthy controls): Male: 10 Female: 9	Pancreatic cancer	Male: 67 (43–94) Female: 69 (50–91)	Male: 80 mg (10–700) Female: 40 mg (10–360)	P.O TD morphine equivalents	8 weeks	TT nmol/L Calculated fT nmol/L Estradiol pmol/L LH U/L FSH U/L	median (range) TT Male pt.: 5.8 (0.9–18.4) and C: 13.8 (0.3–33.5) p<*0.001* Female pt.: 1.0 (0.5–59) and C: 0.9 (0.4–3.1) Calculated fT:

Table 2: (continued)

Observational study								
Cross-sectional								
Author, year	**n**	**Cancer type (%)**	**Age**	**Opioid dose (mg/day)**	**Route of administration**	**Duration**	**Outcomes**	**Findings associated with opioid exposure (group comparisons)**
	Cancer pain + L-TOT: Male: 25 Female: 18 Cancer pain – L-TOT: Male: 65 Female: 59							Male pt.: 0.058 (0.005–0.258) and C: 0.187 (0.012–0.568) p<*0.001* Female pt.: 0.009 (0.004–0.864) and C: 0.008 (0.003–0.036) Estradiol: Female pt.: 76 (32–1,434) and C: 75 (28–2070) LH Male pt.: 3.8 (0.3–10.6) and C: 4.7 (1.4–39.7) p=*0.019* Female pt.: 0.9 (0.9–4.2) and C: 23.9 (0.9–44.9) p=*0.033* FSH Male pt.: 4.6 (0.7–20.1) and C: 7.3 (1.4–55.1) p=*0.054* Female pt.: 2.1 (1–43.8) and C: 65.6 (1.5–130.2) p=*0.030* ↑ MEDD associated with ↓ TT (r^2=–0.494, p<*0.001*) ↑ MEDD associated with ↓ fT (r^2=–0.510, p<*0.001*) ↑ MEDD associated with ↓ LH (r^2=–0.259, p<*0.014*)
[27]	40 male pt. + L-TOT (n=20) –L-TOT (n=20)	Lung: pt.: 4 and C: 4 Sarcoma: pt.: 3 and C: 3 Head and neck: pt.: 3 and C: 3 Lymphoma: pt.: 2 and C: 2 Leukemia: pt.: 3 and C: 3 Gastrointestinal: pt.: 4 and C: 4	Median: 51 (11.3 SD) Median: 58 (13.7 SD)	MEDD ≥ 200 mg morphine equivalents	_	≥1 year	TT (nmol/L) FSH (IU/L) LH (mIU/mL) Secondary outcomes (median): SDI dyadic and solitary	Median (range) TT pt.: 5.0 (0.7–13.2) and C: 13.8 (5.9–33.9) p<*0.0001* FSH pt.: 2.85 (0.7–28.6) and C: 5.3 (1.8–23.6) LH pt.: 1.8 (0.5–6.9) and C: 4.2 (1.9–9.9) p=*0.0014*

Table 2: (continued)

Observational study								
Cross-sectional								
Author, year	**n**	**Cancer type (%)**	**Age**	**Opioid dose (mg/day)**	**Route of administration**	**Duration**	**Outcomes**	**Findings associated with opioid exposure (group comparisons)**
		Melanoma: pt.: 1 and C: 1						Association with opioid-intake (L-TOT vs. control): Dyadic score was 18.5 vs. 40 (p=*0.0114*) Solitary score was 0 vs. 5 (p=*0.0072*)
[26]	20 male pt. Comparison: normal reference values	Cancer survivors + chronic pain	50.1 (34–77)	MEDD ≥ 200 mg morphine equivalents	P.O	≥ 1 year	TT (ng/dL) FH (mIU/mL) LH (mIU/mL) Secondary outcomes (median): SDI dyadic and solitary	Median (range) TT: pt.: 140 (21–381) and ref.: (241–827) ND FSH: pt.: 3.44 (0.7–37.9) and ref.: (1.4–18.1) ND LH: pt.: 2.05 (0.5–11.8) and ref.: 1.5–9.3 ND Associations with opioid-intake (L-TOT vs. ref. values): SDI dyadic was 19.5 and ref.: 42.8 ± 8.9 SDI solitary was 0 and ref.: 10.6 ± 1.9

pt., patients; C, controls; L-TOT, long-term opioid treatment; ref., normal reference values; ND, not described; NS, not significant; SD, standard derivation; n, number of chronic cancer patients in L-TOT; MEDD, morphine equivalent daily dose. PO per oral; TD, transdermal. LH, luteinizing hormone; FSH, follicle-stimulating hormone; TT, total testosterone; fT, free testosterone; SHBG, sex hormone binding globulin; PRL, prolactin; TSH, thyroid-stimulating hormone; fT4, free thyroxine; ACTH, adrenocorticotropic hormone; GH, growth hormone, after midnight cortisol, AM cortisol.
[a]Risk of bias for cross-sectional studies according to the modified Newcastle-Ottawa Quality Assessment Scale. ↑ = high level. ↓ = low level.

studies with mixed populations which were composed by less than 10 patients with cancer or without separate results for patients with cancer were also excluded.

Screening and extraction

All abstracts from the literature search were imported into Covidence, an Internet based software program that facilitated collaboration between two of the authors (DAK and PD) during the selection process and data extraction (https://www.covidence.org/).

Duplications were excluded via the program. All the titles and abstracts were screened, and the full text was read individually and independently by the same two authors. Disagreements were resolved through discussion between the two authors or by involving a senior researcher (GK). DAK and PD performed hand-search by examining reference lists of the included studies and relevant review studies. The two authors extracted data independently and compared them together.

Analysis

Study outcomes: The primary outcomes of this review were biomarkers as follows: growth hormone (GH), somatotropin (SS), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicular stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), oxytocin (Oxt), anti-diuretic hormone (ADH), vasopressin, triiodothyronine (T_3), thyroxine (T_4), free thyroxine (fT_4), insulin, glucagon, aldosterone, cortisol, corticosterone, dehydroepiandrosterone sulfate (DHEAS), androstenedione (A4), renin, calcitriol, erythropoietin (EPO), total testosterone (TT), free testosterone (fT), estradiol, sex hormone binding globulin (SHBG), progesterone, estrone, insulin like growth factor (IGF-1) and parathyroid hormones (PTH).

The secondary outcomes of this review were diseases or conditions associated with alterations in the endocrine function during opioid use as follows: diabetes, metabolic disorders, hypertension, infertility, sexual dysfunction, osteoporosis, sleep disorders, and cancer recurrence.

Our analysis was based on the statistical significance of the results regarding endocrine outcomes and their associations with L-TOT.

Quality assessment: To investigate the possible risk of bias for each included study we used the modified Newcastle-Ottawa Quality Assessment Scale (NOS) [9, 21]. NOS was originally developed to evaluate cohort and case studies. The modified version is an adaptation to evaluated studies with cross-sectional design [9]. The modified NOS covers selection of the groups (population, sample size, ascertainment), the comparability of the groups (study control/confounding factors), and the outcomes of interest (assessment, statistical tests, funding). Each item was scored with a specific maximum number of points: four for selection procedure, two for comparability, and three for outcomes. An item was considered satisfactory if scores reached one or two points. The total score was calculated by the sum of each part and varies from 0 (high risk of bias) to 9 (low risk of bias) [21]. The assessment of risk of bias for each individual study was performed by two of the authors (DAK and PD). Disagreements were resolved by discussion between the two authors and a senior researcher (GK).

Quality of evidence: The quality of evidence for all the outcomes of interest was assessed using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) [22]. The GRADE method assesses the study limitations, imprecision, inconsistency of results, indirectness of evidence, and publication bias. These provide a total GRADE score from 0 to 4. Initial score based on type of evidence is four for large RCTs and two for observational studies. The quality of evidence was categorized into four levels: high (4 points), the true effect is close to the estimated effect; moderate (3 points), the true effect lies close to this and it is possible that there is a significant difference; low (2 points), there is limited confidence in the estimated effect and very low (1 point or less), there is very little confidence in the estimated effect [22, 23].

Results

The systematic database search comprised 236 studies; 45 of them were duplicates.

Thus, 191 studies were screened, out of them 179 were excluded and 12 articles were selected for full reading. Eight articles from the database search were excluded due to other outcomes (n=5) and non-opioid interventions (n=3). 16 articles were found by hand-search, five of them were duplicates. Ten articles from the hand-search were excluded due to other interventions (n=4), other outcomes (n=3), other patient populations (n=2) and other design (n=1). Finally, five cross-sectional studies were included in this review (Figure 1). Two studies have retrieved information about laboratorial blood analyses and collected data retrospectively [16, 24]. One study had four patients in treatment with thyroxine, who were in the control group without opioid treatment (n=167) [25]. Thyroxine did not significantly seem to affect the group's hormonal levels and accordingly the study was included in this review. Estradiol, TSH and fT_4 were analyzed [16, 25], but due to the very low number of patients with alterations (n=1), they were not mentioned in this section.

Study characteristics

In the five cross-sectional studies, samples were between 20 and 167 patients with cancer-related pain, including both patients in L-TOT and untreated patients in the control groups [16, 24–27]. The age of the participants ranged from 24 to 94 years, with a median age of 59 years. L-TOT doses ranged from 10 to 700 mg morphine equivalent daily doses (MEDDs). The duration of the L-TOT varied from one to 12 months. Comparisons were made between patients in L-TOT and control groups composed by patients with cancer-related pain without L-TOT [25, 27] or normal refence values [16, 24, 26]. None of the studies using control

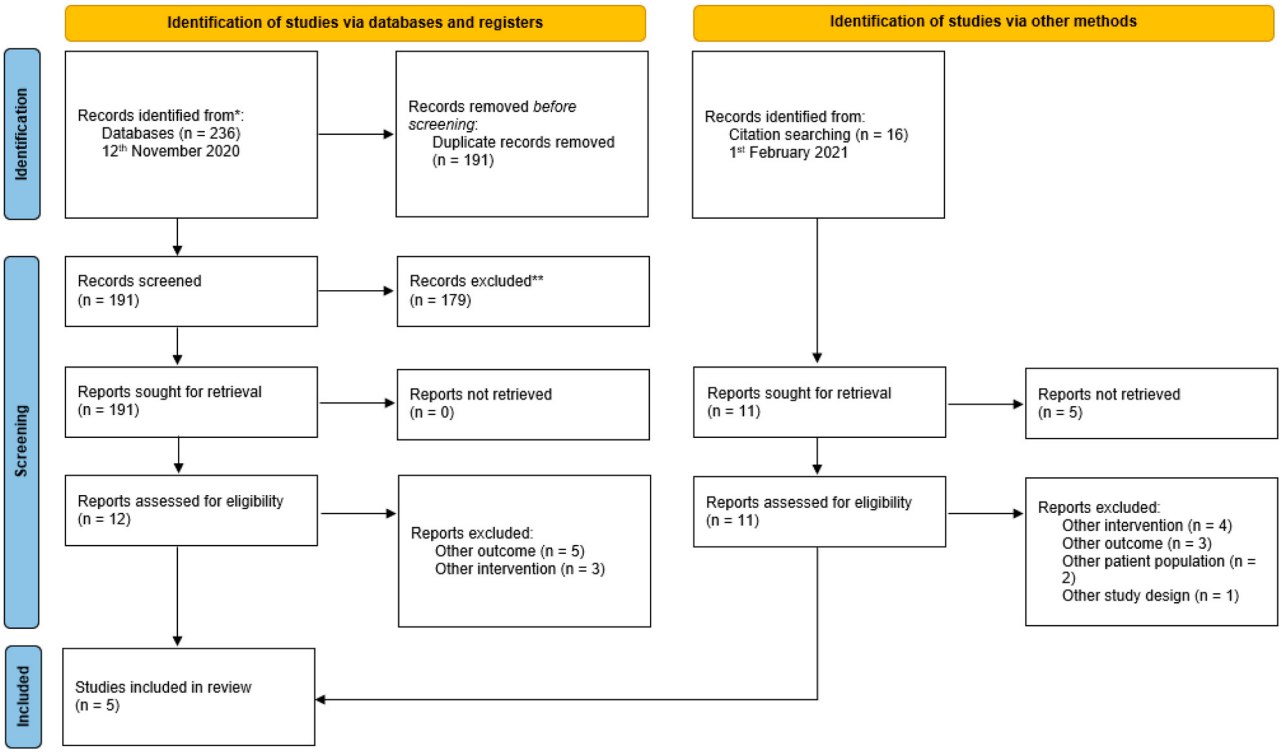

Figure 1: Flow chart of the studies selected for inclusion.

groups used sex-matched controls. In all studies of this review the included patients were not hormonal- or anti-hormonal therapy [16, 23–26]. The included studies were published between 2003 and 2016. See Table 2 for further descriptions of the studies.

Primary outcomes – biomarkers

All studies examined biomarkers of the hypothalamic-pituitary (HP) axis, which included the following sub-axes: hypothalamic pituitary gonadal (HPG), hypothalamic pituitary adrenal (HPA), hypothalamic pituitary thyroid (HPT), hypothalamic pituitary somatotropic (HPS) and hypothalamic pituitary prolactin (HPP) [16, 24–27].

L-TOT duration of one year or more [27] compared to L-TOT duration of 1–2 months [16, 25], showed significantly lower sex- and gonadotropic hormone levels, which is described in more details below. Only one of the included studies had information regarding included women's menstruation status [24]; however, none had information about when the blood samples had been collected during menstruation cycles.

Hypothalamic pituitary gonadal (HPG) axis

LH

Studies comparing patients in L-TOT with a control group of patients not on opioids demonstrated significantly lower levels of LH in both sexes ($p \leq 0.033$) [25, 27]. The studies that compared patients in L-TOT with normal reference values demonstrated high levels of LH in 40% of females (n=20), low levels of LH in 30% of females (n=20) [16] and no changes in males [26]. One study reported a correlation (r^2=−0.259, p=0.014) between higher MEDDs and lower LH levels in both sexes [25].

FSH

Studies comparing patients in L-TOT with a control group of patients not on opioids demonstrated that L-TOT was associated with significantly lower levels of FSH in postmenopausal female patients ($p = 0.030$) [25], whereas no change was observed in males [25, 27]. The studies comparing patients in L-TOT with normal reference values showed that FSH was high in 45 % (N = 20) and low in 30 % (N = 20) of females [16], whereas no change was observed in males [26].

TT

Studies comparing patients in L-TOT with a control group of patients not on opioids found significantly lower TT levels in the opioid treated male patients ($p < 0.001$) [25, 27]; however, no significant changes in postmenopausal females were observed [25]. The studies comparing patients in L-TOT with normal reference values showed lower levels of TT in 68.7 % (N = 20) and in 90 % (N = 20) males, retrospectively (16,26). Three studies reported a correlation ($p = 0.040$, $p = 0.001$, ($r^2 = -0.494$, $p < 0.001$)) between higher MEDDs and lower TT levels in male patients [16, 24].

fT

One study comparing patients in L-TOT with patients not on opioids found significantly lower levels of fT in opioid treated males ($p < 0.001$), whereas no change in postmenopausal females was observed [25]. Other study showed that 57.1 % (N = 14) of the patients in L-TOT had lower levels compared to normal reference values and found an association between higher MEDDs and lower fT levels in male patients ($p = 0.041$) [16]. One study reported a correlation ($r^2 = -0.510$, $p < 0.001$) between higher MEDDs and lower fT levels in male patients compared with patients not on opioids [25].

Hypothalamic-pituitary-adrenal (HPA) axis

ACTH

One study investigated the association between L-TOT and ACTH levels in 18 patients in L-TOT compared with reference values. Findings showed normal levels in 94.5% [16].

Cortisol

A comparison of cortisol levels in patients in L-TOT (n=20) with normal reference values showed higher levels in 40% (n=8) and lower levels in 15% (n=3) [16]. Another study reported a weak correlation between higher MEDDs and higher random cortisol levels (r=0.25, p=0.032) [24].

Hypothalamic-pituitary-prolactin (HPP) axis

PRL

One study analyzed PRL levels in patients in L-TOT (n=14) and compared with normal reference values [16]. Higher PRL levels were observed in 42.9% (n=6).

Secondary outcomes

Two studies have analyzed associations between opioid intake, hypogonadism, and symptoms of sexual dysfunction [26, 27]. The instrument applied was Sexual Desire Inventory (SDI), which assesses dyadic and solitary sexual desire in the absence of consummatory behavior. The study that compared patients in L-TOT with patients without opioid treatment showed that 90% (n=18) of the patients in L-TOT exhibited hypogonadism (low levels of TT, FSH, and LH) and sexual dysfunction according to median SDI dyadic (p=0.0114) and solitary scores (p=0.0072) [27]. The other study found that 90% (n=18) of the patients had low levels of TT compared to reference values and that mean scores for SDI dyadic, and solitary were low compared to the normative data [26].

Quality assessment

The risk of bias in each of the five cross-sectional studies [16, 24–27] was scored from three to six points out of nine possible points. The low scores were derived from flaws regarding sample sizes, comparisons according to control groups/confounding factors, statistical tests, and funding (Table 3).

The overall quality of evidence [22, 23] was very low, due to limitations in study design, the high risk of inconsistency, indirectness, publication bias and imprecision. The summary of the results is presented in Table 4.

Table 3: Analysis of the risk of bias.

Cross-sectional studies according to the modified Newcastle-Ottawa quality assessment scale								
Study	**Selection (****)**			**Comparability (**)**	**Outcome (***)**			
	Population	**Sample size**	**Exposure**		**Outcome**	**Statistical tests**	**Funding**	**Total score[a]**
[16]	*	–	*	–	*	–	–	3
[24]	*	–	*	–	*	*	*	5
[25]	*	–	*	*	*	*	*	6
[27]	*	–	*	–	*	*	–	4
[26]	*	–	*	–	*	–	–	3

[a]Modified version of the Newcastle-Ottawa Scale (NOS) [9, 21].

Table 4: GRADE evidence profile.

Quality assessment							Summary of findings				
							No. of patients				
Outcome	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**CCP+L-TOT**	**CCP−L-TOT**	**Pain-free controls**	**Finding associated with L-TOT**	**Quality**
HPG[a] axis											
LH	4 CS	Sample size not justified. Comparability Statistical test not described.	Difference in treatment[a]	Small samples	95% CI male cancer-patients [59.7–96.3] 95% CI males non-opioid use [112.8–151.2] 90%; 95% CI male cancer patients [65–68%] 40%; 95% CI male non-opioid use [19–64%]	3 CS no funding information	103	144	1 CS: 19 3 CS: Reference value	Comparing with pt. without L-TOT: ↓ in 2 CS Comparing with normal reference values: No change in 1 CS ↓ in 30% and ↑ in 40% pt. in 1 CS	Very low
FSH	4 CS	Sample size not justified. Comparability Statistical test not described.	Difference in treatment[a]	Small samples	95% CI male cancer-patients [59.7–96.3] 95% CI males non-opioid use [112.8–151.2] 90%; 95% CI male cancer patients [65–68%] 40%; 95% CI male non-opioid use [19–64%]	3 CS no funding information	103	144	1 CS: 19 3 CS: Reference value	Comparing with pt. without L-TOT: ↓ in 2 CS Comparing with normal reference values: No change in 1 CS ↓ in 30% and ↑ in 45% pt. in 1 CS	Very low
TT	5 CS	Sample size not justified. Comparability Statistical test not described.	Shown similar results. difference in treatment[a]	Small samples	95% CI male cancer-patients [59.7–96.3] 95% CI males non-opioid use [112.8–151.2] 90%; 95% CI male cancer patients [65–68%] 40%; 95% CI male non-opioid use [19–64%]	3 CS no funding information	180	144	1 CS: 19 3 CS: Reference value	Comparing with pt. without L-TOT: ↓ in 2 CS Comparing with normal reference values: ↓ in 3 CS	Low

Table 4: (continued)

Quality assessment							Summary of findings				
							No. of patients				
Outcome	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**CCP+L-TOT**	**CCP−L-TOT**	**Pain-free controls**	**Finding associated with L-TOT**	**Quality**
fT	2 CS	Sample size not justified. Comparability Statistical test not described.	Shown similar results. Difference in treatment[a]	Small samples	95% CI male cancer-patients [59.7–96.3] 95% CI males non-opioid use [112.8–151.2]	1 CS no funding information	63	124	1 CS: 19 1 CS: Reference value	Comparing with pt. without L-TOT: ↓ in 1 CS Comparing with normal reference values: ↓ in 1 CS	Low
Estradiol	2 CS	Sample size not justified. Comparability Statistical test not described.	Difference in treatment[a]	Small samples	95% CI male cancer-patients [59.7–96.3] 95% CI males non-opioid use [112.8–151.2]	1 CS no funding information	63	124	1 CS: 19 1 CS: Reference value	Comparing with pt. without L-TOT: No (1 CS) Comparing with normal reference values: ↓ in 25% and ↑ in 12.5% pt. in 1 CS	Very low
HPA[b] axis											
ACTH	1 CS	Sample size not justified. Comparability Statistical test not described.	–	Small sample	–	No funding information	20	–	Reference value	Comparing with normal reference values: ↓ in 5.5% pt. in 1 CS	Very low
Cortisol	2 CS	Sample size not justified. Comparability Statistical test not described.	Shown similar results. Difference in treatment[f]	Small samples	–	1 CS no funding information	97	–	Reference value	Comparing with normal reference values: ↑ in 1 CS ↑ in 40% pt. in 1 CS	Very low
HPT[c] axis											
TSH	1 CS	Sample size not justified. Comparability Statistical test not described.	–	Small sample size compared to reference values.	–	No funding information	20	–	Reference value	Comparing with normal reference values: ↑ in 20% and ↓ in 5% pt. in 1 CS	Very low

Table 4: (continued)

Quality assessment							Summary of findings				
							No. of patients				
Outcome	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**CCP+L-TOT**	**CCP−L-TOT**	**Pain-free controls**	**Finding associated with L-TOT**	**Quality**
fT_4	1 CS	Sample size not justified. Comparability Statistical test not described.	–	Small sample size compared to reference values	–	No funding information	20	–	Reference value	Comparing with normal reference values: ↓ in 5.2% pt. in 1 CS	Very low
HPS[d] axis											
GH	1 CS	Sample size not justified. Comparability Statistical test not described.	–	Small samples compared to reference values	–	No funding information	20	–	Reference value	Comparing with normal reference values: ↑ in 5.2% pt. in 1 CS	Very low
HPP[e] axis											
PRL	1 CS	Sample size not justified. Comparability Statistical test not described.	–	Small samples compared to reference values.	–	No funding information	20	–	Reference value	Comparing with normal reference values: ↑ in 42.9% pt.	Very low

[a]Hypothalamic-pituitary-gonadal axis; [b]Hypothalamic-pituitary-adrenal axis; [c]Hypothalamic-pituitary-thyroid axis; [d]Hypothalamic-pituitary- somatotropic axis; [e]Hypothalamic-pituitary-prolactin axis; [f]Difference in opioid type, route, and duration; CCP, chronic cancer-patients; CS, cross-sectional; pt, patients; ↑ = high level; ↓ = low level.

Discussion

In this systematic review regarding effects of L-TOT on the endocrine system in patients with cancer-related pain we found suppression of hormones originating from the HPG-axis including lower levels of TT, fT, LH and FSH. Moreover, alterations in the HPA-axis were observed, which involved higher levels of cortisol, respectively.

In addition, this systematic review found that patients with cancer-related pain who showed signs and symptoms of central hypogonadism and sexual dysfunction related to L-TOT, which is in accordance with findings from other studies [28, 29]. However, the overall assessment of quality of evidence was very low.

It is well-known that the gonadotropic hormones are particularly affected by opioids via a feedback mechanism [30], which affects the gonadal status by an indirectly inhibition of gonadotropin-releasing hormone (GnRH) from hypothalamus [8, 11]. These mechanisms may probably have been in play causing the low concentrations of TT, fT, LH and FSH, which were found in the studies included in the present systematic review [16, 24–27]. Further, opioids are also known to have a direct effect on the testes resulting in decreased TT and testicular interstitial fluid (TIF) [31]. This has also been observed in studies in other patient populations (chronic non-cancer pain and heroin addicted patients) in L-TOT [32, 33]. Hypogonadism can decrease bone density and mineral metabolism, and increase the risk of fractures [34, 35]. The increased risk of osteoporosis and fractures may be caused by inhibition of osteoblasts and osteocalcin synthesis via opioid receptors [6, 13, 36, 37]. Low TT levels may stimulate secretion of FSH and LH by a negative feedback loop; however, in this systematic review the opposite was observed (low levels of LH and FSH). An explanation for this finding may be that opioids bind to opioid receptors in the pituitary gland and reduce the secretion of LH and FSH. This reduction could also be due to opioid inhibition of the secretion of GnRH, which can decrease the secretion of LH and FSH and result in low TT and estradiol levels. Another explanation for our findings may be that PRL also plays a significant role in the regulation of the gonadal hormones. One of the included studies found increased levels of PRL in 42.9% of the patients (n=14) [16]. Opioid-induced hyperprolactinemia can decrease the pulsatile release of GnRH and decrease gonadal hormone levels (LH and FSH), which result in low levels of TT, which in turn may increase the risk of developing hypogonadism [38, 39].

In a study of the present review, an association between higher MEDDs and higher cortisol levels during L-TOT was reported [24]. The correlation between higher opioid doses and higher cortisol levels in patients with cancer-related pain, may be due to pain and/or stress caused by the cancer disease, which may result in hyperactivity of HPA causing increasing cortisol levels. The unchanged ACTH levels could possibly be due to the high cortisol levels in 40% of the patients (n=20), which may inhibit ACTH release by a negative feedback mechanism [16]. In contrast, the reverse effects have been seen in previous studies of opioid treated chronic non-cancer pain patients, in which low levels of ACTH and cortisol were found [40]. In chronic non-cancer pain patients in L-TOT a down-regulation of ACTH and cortisol and low levels of DHEAS [13, 40], may indicate opioid-induced adrenal insufficiency [6, 41]. Hormones derived from the HPA-axis play a significant role in the immune system. Previous studies found that L-TOT in patients with cancer was associated with higher levels of biomarkers of inflammation and infection [42]. L-TOT is known to suppress the immune system in patients with cancer and in chronic non-cancer patients – especially in those with adrenal insufficiency [9, 43–45]. Thus, the inflammatory response to the cancer disease and the resulting proinflammatory cytokines may affect the testes and result in suppression of TT, which may increase the risk of developing hypogonadism, anorexia, and even cancer-cachexia [13, 29]. Further, proinflammatory cytokines may stimulate aromatase activity in women and increase estradiol production [25]; however, no significant change in estradiol concentration was found during L-TOT in two of the studies of the present review [16, 25], which could possibly be due to the fact that the included female patients were postmenopausal women.

The exposure of endocrine system by L-TOT may be influenced by type of opioid, dose level and length of treatment. This systematic review could not assess effects of the different opioid types, doses, and length of treatment on the endocrine system, because this information was not available in all the included studies. Preclinical studies have shown that different types of opioids have differentiated effects on the endocrine system [8]. Thus, e.g., methadone intake might result in more suppression of TT compared to buprenorphine [46]. However, on the other hand methadone might result in less menstrual irregularity compared to other opioids [47]. In addition, previous studies have suggested that buprenorphine has less negative effect on the HPG-axis, which may make buprenorphine a better choice in terms of preserving TT level and sexual function [48–50].

According to the findings in the present review there may be some indications that opioid dose level may affect

the endocrine system. Four studies found significant associations between opioid doses and hormone serum concentrations [16, 24, 25, 27]. Thus, high opioid doses were associated with low levels of hormones including TT, fT and LH, however, cortisol levels were high during high opioid dose therapy. Finally, length of L-TOT seemed to play a role as L-TOT duration of one year or more [27] compared to L-TOT duration of 1–2 months showed significantly lower sex- and gonadotropic hormone levels [16, 25]. To evaluate the risk/benefit ratio concerning the use of specific types of opioids in patients with cancer we need more knowledge about the endocrinological effects from clinical studies combined with assessment of disease stage, anticancer treatment, performance status, survival prognostics, etc.

Only two studies assessed patient reported clinical outcomes. They found low sexual desire in the patients with cancer in L-TOT [26, 27], which may be in accordance with findings in other populations demonstrating strong associations between low sexual desire and low TT [51, 52] and fT levels [53, 54]. A pilot study in patients with advanced cancer has also indicated that hypogonadism may be associated with symptoms including sexual dysfunction [28]. Both the symptoms and sexual dysfunction may substantially reduce patients' quality of life.

Although the available literature is still sparse a strength of this systematic review is that it has included endocrine biomarkers from all hypothalamic pituitary axes. However, this systematic review also has some limitations. First, the different characteristics of the included studies make comparisons difficult (control groups/comparison methods, duration of L-TOT, variety of opioids, selection of outcomes, gender, and age of participants). Second, only few studies are available from existing literature. Third, all five included studies had a cross-sectional design resulting in lower quality of evidence and no reasoning of cause-effect relationship. Finally, some of the five studies had a high risk of bias due to small sample sizes, comparability and clinical reported outcomes including missing information about funding.

Conclusions

The findings of this systematic review suggest that L-TOT may affect the endocrine system including suppression of the HPG-axis and accordingly result in low levels of LH, FSH, TT and fT in patients with cancer-related pain on L-TOT. Sexual dysfunction and alterations on the HPA-axis including high levels of cortisol were also found. The studies have suggested an association between L-TOT and gonadal hypofunction, which was possibly correlated with high opioid dose level. However, the existing evidence is weak, and the overall quality is low. A future recommendation is to screen patients with cancer for sex hormone deficiency before and during L-TOT. Finally, further research to clarify the associations and investigate cause-effect relationship of L-TOT and endocrine system in patients with cancer-related pain is urgently needed.

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