**International Journal of Diabetes and Endocrinology**
2022; 7(1): 13-17
http://www.sciencepublishinggroup.com/j/ijde
doi: 10.11648/j.ijde.20220701.12
ISSN: 2640-1363 (Print); ISSN: 2640-1371 (Online)

# A Case of Secondary Hypogonadism with Increased Risk of Fractures in a 57-year-old Male Patient on Methadone Maintenance Therapy

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## To cite this article:

Mario Sebastian Campana, Maria Riofrio, Raja Jadav, Guido Macchiavello. A Case of Secondary Hypogonadism with Increased Risk of Fractures in a 57-year-old Male Patient on Methadone Maintenance Therapy. *International Journal of Diabetes and Endocrinology.* Vol. 7, No. 1, 2022, pp. 13-17. doi: 10.11648/j.ijde.20220701.12

**Received**: December 4, 2021; **Accepted**: January 14, 2022; **Published**: January 20, 2022

**Abstract:** Oral maintenance opioid agonists have an important role in the management of heroin addiction and chronic pain. Methadone is one of the most popular and effective treatments for opioid dependence, however many patients following methadone's clinics can develop a few metabolic and sexual side effects. Methadone can induce a few hormonal disbalance over time, including hypogonadotropic hypogonadism with sexual dysfunction, muscle weakness, and decreased bone mass density. Most of the side effects are dose-related especially when methadone is above 100 mg daily. Low levels of testosterone increase the risk of erectile dysfunction, loss of libido, sexual unsatisfaction, osteopenia, and osteoporosis, giving a poor quality of life in patients on methadone maintenance therapy. We present a case of a 57 -year-old male patient complaining about erectile dysfunction and loss of libido secondary to central hypogonadism induced by methadone with decreased bone density. The purpose of this case report is to bring these patients to the primary care world and improve their management with a multidisciplinary team including primary care, endocrinologists, and psychologists. Physicians should be aware of opioid-induced endocrinopathies and address properly with early sex hormones work up, bone density screening, and encourage methadone tapering every visit.

**Keywords:** Males, Methadone, Hypogonadism, Osteoporosis, Testosterone

## 1. Introduction

The prescriptions of methadone for opioid withdrawal maintenance therapy have been increasing over the years. Despite the efficacy of methadone in the control of opioid withdrawals, some patients can develop sexual dysfunction secondary to hypogonadism with low levels of testosterone [1]. Male patients can present with fatigue, weight gain, decreased libido, erectile dysfunction, infertility, osteopenia, and osteoporosis known as opioid-induced hypogonadism (OHG) or opioid-induced endocrinopathy (OIE) [2].

OIE can be secondary to a derangement of the pulsatile release of GnRH with low levels of FSH, LH, estrogen, progesterone, and androgens (testosterone) [3, 4]. Chronic opioid use can suppress peripheral androgens, decreasing the expression of 5-α-reductase and increasing the catabolism of testosterone. Because androgens and estradiol play an important role in bone remodeling status, patients with OIE have an increased risk of osteopenia, osteoporosis, hyperprolactinemia, and mechanical fractures [3].

In the United States is estimated that around 5 million men suffer from OIE without full diagnostic workup and this brings more episodes of depression and anxiety [5].

Patients on chronic opioid therapy like methadone maintenance program for addiction control need to be assessed for testosterone levels especially if symptoms or signs of hypogonadism are present on any control visit. One way to decrease the risk of these side effects is to have an active tapering program every visit and avoid keeping the patient on high doses of methadone [1, 6].

Androgen replacement therapy can be considered in men with low levels of testosterone and showed to be beneficial in improving symptoms and tolerance, requiring lower doses of opioids [3, 6].

## 2. Case Presentation

We report a case of a 57-year-old-male with PMH of morbid obesity (BMI: 44), OSA on CPAP, asthma, osteoarthritis (OA), and history of heroin abuse on methadone maintenance therapy (170 mg daily) followed with medicine and addiction clinic complaining about the loss of libido, erectile dysfunction, and fatigue; the first time in 2015. The patient also started to notice weight gain, lower back pain three years ago.

The patient saw a primary doctor for the first time in 2012 for asthma and OA. He had a history of heroin abuse since 2010 and was started on methadone maintenance therapy in 2012 (170mg daily).

Patient's medications since 2015 were albuterol, budesonide-formoterol, ibuprofen, sildenafil, and methadone.

In 2016 patient came to the office complaining of lower back pain, weight gain, low sexual desire, and weak erections despite the treatment with sildenafil. On physical exam, blood pressure, heart rate, and respiratory rate were within normal limits. Cardiopulmonary and abdomen exams didn't show any abnormality. Prolactin levels were 18.2 ng/ml (2.0-18.0 ng/ml), TSH 1.31 IU/mL (0.34-5.60 IU/mL) and total testosterone 32 ng/dL (264-916 ng/dL). The patient was referred to the endocrinology clinic for further workup regarding hypogonadism induced by opioids (methadone).

The patient was seen by the endocrinology clinic in 2017. During the physical exam, he had decreased testicular size without gynecomastia or visual field defects. Vital signs and the rest of the physical exam were within normal limits. A sexual hormone panel with free AM testosterone, FSH, LH, and scrotum ultrasound was requested and shown in table 1. The ultrasound didn't show any focal pathology.

Laboratory analysis in table 1 confirmed that the patient has hypogonadotropic hypogonadism.

***Table 1.*** *Hemoglobin, Hematocrit and Hormone panel.*

| Labs | Value | Reference |
|---|---|---|
| Hemoglobin, gm/dL | 13.4 | 11.2-15.7 |
| Hematocrit, % | 44% | 34.1-44.9 |
| Testosterone Total, ng/dL | 22 | 264-916 |
| Free Testosterone, pg/mL | 3.3 | 7.2-24.0 |
| %, Free Testosterone | 1.5% | 1.5-3.2% |
| FSH, mIU/mL | 0.5 | 1.5-12.4 |
| LH, mIU/mL | < 0.3 | 1.7-8.6 |
| TSH, IU/mL | 1.31 | 0.34-5.60 |
| T4, ug/dL | 7.8 | 6.0-12 |
| Prolactin, ng/ml | 18.2 | 2.0-18.0 |
| Cortisol, ug/dL | 20 | AM reference (5-23) |

gm=grams; %=percentage; ng=nano grams; pg=pico grams; mIU/mL=milli international units/milliliter; IU/mL=international units/milliliter; ug/dL=micro grams/decilliter.

The patient was started on daily transdermal testosterone and an MRI brain was ordered to rule out suprasellar mass with new prolactin levels.

On the next follow-up in 2019 patient's MRI didn't show any pituitary mass or evidence of acute intracranial process but refers to improvement in his libido and erectile dysfunction after testosterone replacement. In this new visit, he complains about constant fatigue and lower back pain. Following PSA, hemoglobin, hematocrit, and prolactin levels are shown in table 2. The patient's condition increased the risk of osteopenia and osteoporosis, so bone densitometry was ordered for the next appointment.

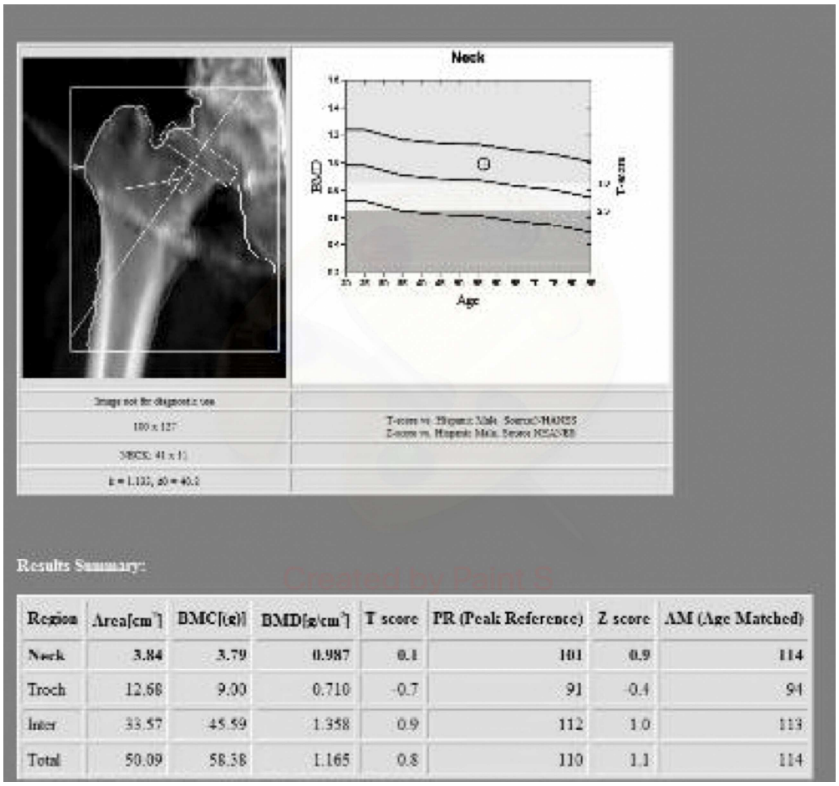
***Table 2.*** *Follow up labs after testosterone replacement.*

| Labs | Value | Reference |
|---|---|---|
| Hemoglobin, gm/dL | 14.4 | 11.2-15.7 |
| Hematocrit, % | 45% | 34.1-44.9 |
| PSA, ng/L | 0.1 | 0.0-0.4 |
| Prolactin, ng/ml | 10 | 2.0-18.0 |
| Testosterone Total, ng/dL | 22 | 264-916 |
| Free Testosterone, pg/mL | 3.3 | 7.2-24.0 |
| %, Free Testosterone | 1.5% | 1.5-3.2% |
| FSH, mIU/mL | 0.5 | 1.5-12.4 |
| LH, mIU/mL | < 0.3 | 1.7-8.6 |

gm=grams; %=percentage; ng=nano grams; pg=pico grams; mIU/mL=milli international units/milliliter.

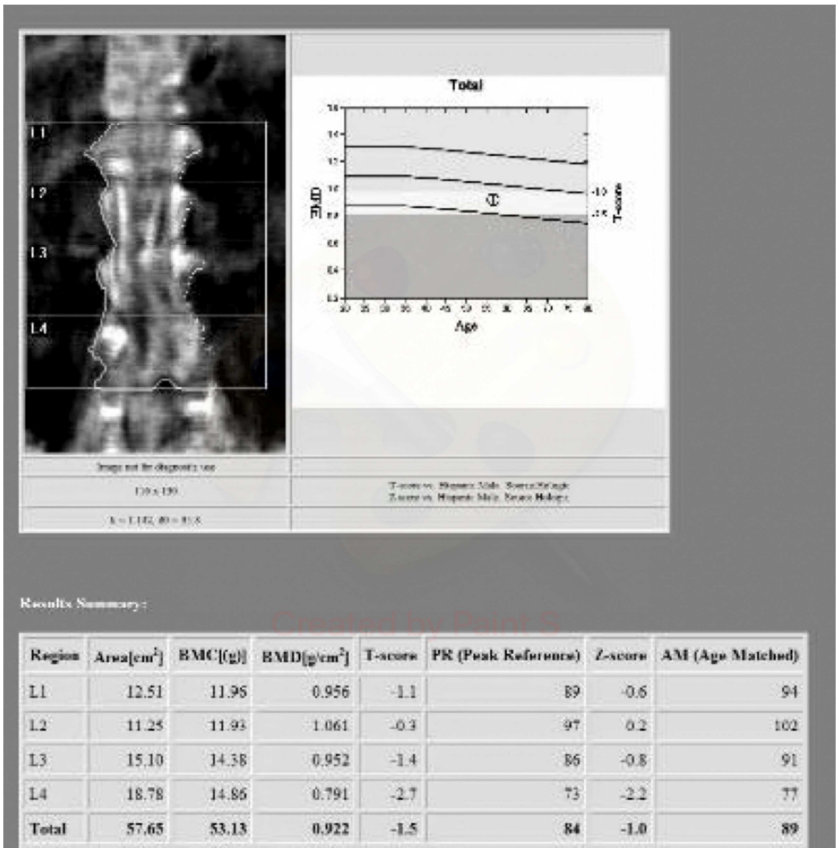
Last, follow up in 2020 patient's Dual-energy X-ray absorptiometry (DEXA) scan results showed a lumbar spine T score of -1.5 and Z score of -1.0 (Figures 1 and 2). CBC and CMP results were within the normal limits. Despite the DEXA scan didn't show osteopenia or osteoporosis is important to keep a continuous follow-up and monitor his Z

score because of the risk factors of hypogonadism (OSA and obesity), including opioid use.




| Region | Area[cm²] | BMC[g] | BMD[g/cm²] | T score | PR (Peak Reference) | Z score | AM (Age Matched) |
|---|---|---|---|---|---|---|---|
| **Neck** | **3.84** | **3.79** | **0.987** | **0.1** | **101** | **0.9** | **114** |
| Troch | 12.68 | 9.00 | 0.710 | -0.7 | 91 | -0.4 | 94 |
| Inter | 33.57 | 45.59 | 1.358 | 0.9 | 112 | 1.0 | 113 |
| Total | 50.09 | 58.38 | 1.165 | 0.8 | 110 | 1.1 | 114 |

***Figure 1.*** *Bone Density Scan Hip and Pelvis.*




| Region | Area[cm²] | BMC[g] | BMD[g/cm²] | T-score | PR (Peak Reference) | Z-score | AM (Age Matched) |
|---|---|---|---|---|---|---|---|
| L1 | 12.51 | 11.95 | 0.956 | -1.1 | 89 | -0.6 | 94 |
| L2 | 11.25 | 11.93 | 1.061 | -0.3 | 97 | 0.2 | 102 |
| L3 | 15.10 | 14.38 | 0.952 | -1.4 | 86 | -0.8 | 91 |
| L4 | 18.78 | 14.86 | 0.791 | -2.7 | 73 | -2.2 | 77 |
| **Total** | **57.65** | **53.13** | **0.922** | **-1.5** | **84** | **-1.0** | **89** |

***Figure 2.*** *Bone Density Scan Lumbar Spine.*

# 3. Discussion

Patients with a history of heroin use disorder and chronic pain have been treated with daily doses of methadone for many months and even years. Many studies have demonstrated that any chronic opioid therapy can increase the risk of androgen deficiency secondary to hypogonadotropic hypogonadism. Opioid-induced hypogonadism or endocrinopathy has a prevalence of 20 to 35% in men [1, 7, 8]. Despite it is unclear the risk factors for patients to develop OIE, there is an association with a higher dose, time of treatment, and patient's age. Hypogonadal effects are more common in older patients with methadone doses higher than 100mg and long-term treatment at least more than 4-6 weeks [1, 3, 9].

There are several mechanisms to explain OIE, one of them is that endogenous and exogenous opioids can bind to their receptors in the hypothalamus and can impair the release of gonadotropin-releasing hormone (GnRH), resulting in reduced secretion of FSH and LH from the pituitary glands as well as estrogen and testosterone in the gonads [3, 10].

Patients with OIE will present with decreased libido, erectile dysfunction, fatigue, weight gain, muscle weakness, infertility, depression, and high risk of fractures (osteopenia and osteoporosis) with low serum testosterone and estrogen but with low or normal LH and FSH [1, 10]. Some studies showed that besides the suppression of GnRH release from the hypothalamus, chronic opioids therapy also decreases peripherally the levels of androgens by inhibiting the activity of 5-α- reductase and increasing the catabolism of testosterone [3].

Metabolic conditions like OSA and obesity are associated with increased severity of OIE. Obesity has an important link with low levels of testosterone because of an inflammatory process in the adipose tissue and an insulin-resistant state. This increases the expression of aromatase, which converts testosterone to 17β-estradiol. On the other hand, OSA has less REM sleep, reduced deep sleep time, increased nighttime awakenings, sleep fragmentation, and reduced sleep efficiency, which also decreases the production of testosterone [14].

Opioids like morphine and methadone with full mu-opioid agonist activity are associated with a high risk of OIE because both can produce a transit elevation of prolactin levels by inhibiting dopamine release in the hypothalamus [3]. High levels of prolactin also inhibit the secretion of GnRH [3, 11].

Some studies demonstrated that chronic opioid use could affect the adrenal system with adrenal crisis; as well as 15% of patients can develop GH (Growth hormone) deficiency and hypothyroidism. Despite the patient had never presented with clinical signs or symptoms of hypothyroidism, adrenal crisis, or GH deficiency; it is important to be aware of these endocrinopathies during clinical evaluation and assessment [10].

Opioids especially full agonists like methadone can increase the risk of osteopenia and osteoporosis among men with established suboptimal estrogen and testosterone levels [3, 5] Studies have shown that estradiol and dihydrotestosterone (DHT) has an inhibitory effect on RANKL, suppressing the differentiation of osteoclasts [3]. Therefore, low levels of sexual hormones secondary to OIE would increase the osteoclast's resorption activity in the bone.

Vertebral and hip fractures in men are less common unless patients have risk factors like steroids, alcohol, or smoking history. Although this patient is not in the WHO classification for osteopenia or osteoporosis, he has an increased risk to develop in the future [12].

This case report and similar cases bring the opportunity to improve and establish an osteoporosis screening assessment in male patients in addiction clinics that are on methadone maintenance therapy with symptoms of hypogonadism and low testosterone levels. The fracture risk assessment tool (FRAX) score is another scale to predict the ten-year probability of fracture in these patients with previous abnormal bone density tests.

Patients with known anorgasmia, erectile dysfunction, loss of libido with low levels of pituitary and sex hormones can be initiated on testosterone replacement therapy (TRT) [13]. In many clinical trials, testosterone replacement improves symptoms of hypogonadism, fatigue, anxiety, depression, weakness, and tolerance, requiring lower doses of opioids [3]. All patients on TRT need to be aware of the side effects of the treatment: polycythemia, hyperlipidemia, and sleep apnea [1].

# 4. Conclusion

Male patients with suboptimal levels of sexual hormones that are on chronic opioid management, especially on methadone maintenance therapy are at high risk for developing OIE. Therefore, physicians should be aware of these adverse effects and should develop a screening protocol for hypogonadism and osteoporosis by doing appropriate assessments and tests (sexual hormone levels, bone mineral density test, and FRAX score). In men, these conditions are overlooked, and further studies are needed to bring these patients to the primary care world. Patients with OIE should be treated in a multidisciplinary team approach, between primary care physicians and endocrinologists.

# Abbreviations

Opioid induced hypogonadism (OHG),
Opioid induced endocrinopathy (OIE),
Osteoarthritis (OA),
Gonadotropin-releasing hormone (GnRH),
GH (Growth hormone),
Dihydrotestosterone (DHT),
Testosterone replacement therapy (TRT),
Dual-energy X-ray absorptiometry (DEXA)

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