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Assessing the Relationship between Opioid Therapy and Osteoporosis

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Opioid use is extensively linked to adverse bone health outcomes, including increased risks of fractures, impaired bone repair, and diminished bone mineral density (BMD). Opioids such as morphine and dilaudid inhibit bone formation, leading to bone loss, while chronic opioid use exacerbates bone turnover and suppresses bone formation. These effects, observed in both males and females, frequently result in osteoporosis. Opioid-induced endocrinopathies, including hypogonadism and testosterone deficiency, significantly contribute to decreased bone density and heightened fracture risk. Observational studies report a higher prevalence of hip fractures among chronic opioid users, emphasising the necessity of routine BMD screening, particularly in high-risk populations. The interaction between opioid use and bone health mandates comprehensive monitoring and risk assessment strategies for long-term opioid users.

Key Words: bone health, bone mineral density, fractures, opioids, osteoporosis.

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INTRODUCTION

Osteoporosis and opioid use represent critical public health issues with intersecting implications that affect a substantial global population. Osteoporosis manifests as diminished bone strength, reduced bone mineral density (BMD), and compromised bone tissue microarchitecture, culminating in heightened bone fragility and susceptibility to fractures [1-3]. This condition predominantly afflicts older adults, with significant prevalence rates observed among women (one in three) and men (one in twelve) over the age of 50 worldwide [1]. Fragility fractures, particularly in the hip, spine, forearm, humerus, and pelvis, contribute substantially to morbidity and mortality associated with osteoporosis [4,5].

Public health initiatives targeting osteoporosis prevention and promoting physical activity among older adults play a crucial role in enhancing preventive behaviours and improving bone health [6,7]. Early detection of skeletal abnormalities and optimisation of bone health are also vital for individuals undergoing cancer therapy, aiming to mitigate long-term skeletal complications and maintain quality of life [2]. The economic impact of osteoporosis is considerable, driven by substantial healthcare expenditures related to the treatment of osteoporotic fractures [4]. Low BMD emerges as a predominant risk factor for fractures, underscoring the public health significance of osteoporosis [3]. Innovative therapeutic approaches, including monoclonal antibodies and pharmacological interventions, are being developed to manage osteoporosis and its complications [8,9].

Multiple risk factors contribute to the onset of osteoporosis, encompassing familial predisposition, early menopause, ethnic background, sedentary lifestyle, tobacco use, inadequate calcium intake, slender physique, nulliparity, and excessive alcohol consumption [9]. Postmenopausal women, especially those with additional risk factors such as advanced age, personal or

family history of fractures, poor health, smoking, low body weight, alcohol dependence, and insufficient physical activity, face heightened susceptibility [10]. Age, sex, family history, sex hormones, and thyroid function also influence osteoporosis risk, with men affected by factors like familial history, prior fractures, height loss, smoking, excessive alcohol consumption, and rheumatoid arthritis [11]. Furthermore, low body mass index (BMI) increases susceptibility in individuals with type 2 diabetes and primary osteoporosis, whereas high BMI raises risks among menopausal women [12].

Concurrently, opioids are extensively prescribed for pain management, highlighting their efficacy and broad impact on public health [13-16]. While opioids effectively alleviate moderate pain [17,18] their prolonged use in chronic pain management has contributed to a global crisis, with substantial implications for public health and welfare [19]. Chronic opioid therapy often proves ineffective and carries potential harm, with gastrointestinal disturbances, particularly constipation, being prevalent adverse effects [20,21].

Global opioid use remains prevalent, with significant statistics from Australia, where approximately 3 million adults annually utilise opioids, and notable patterns in the United States and Finland revealing demographic-specific prescription trends [22-24]. Concerns persist regarding the increasing prevalence of long-term opioid use during pregnancy, despite heightened awareness of associated risks [25]. Shifts in opioid types, such as a decline in codeine use and a rise in potent opioids like morphine and oxycodone, further underscore evolving usage patterns [26]. Moreover, opioid utilisation in outpatient surgical settings continues to rise [27].

Given these considerations, exploring the interplay between opioid use and osteoporosis assumes critical importance due to opioids' potential impact on bone health. Evidence suggests that prolonged opioid therapy correlates with reduced BMD and heightened osteoporosis risk [28]. Opioid-induced androgen deficiency, a common consequence of prolonged opioid use, further compounds osteoporosis risk [29]. This poses significant implications for chronic opioid users, who face increased vulnerability to hormonal disturbances and compromised BMD [29]. While the precise mechanisms remain elusive, opioids are believed to influence bone metabolism and potentially contribute to osteoporosis development [30].

The suppression of hypothalamic gonadotrophin-releasing hormone by opioids can lead to hypogonadism, exacerbating BMD loss [31]. Additionally, opioid-induced hypogonadism and direct effects on bone formation are proposed mechanisms contributing to osteoporosis development [32]. Studies document adverse impacts of opioids on bone remodelling, density, and healing, correlating with increased rates of non-union fractures in opioid users [33]. Thus, opioids' potential to weaken bone structure and reduce BMD further underscores their implications for bone health [34].

In light of these findings, addressing the intersection of opioid use and osteoporosis presents formidable public health challenges. Understanding the mechanisms through which opioids influence bone health, identifying predisposing factors, and formulating strategies to mitigate these effects are imperative. This review aims to synthesise existing research on the relationship between opioid therapy and osteoporosis, examining biological mechanisms, clinical implications, and potential management strategies.

METHOD

A comprehensive literature search was conducted to identify relevant studies on the impact of opioid use on bone health. The databases searched included PubMed, MEDLINE, EMBASE, and Cochrane Library. The search strategy involved the use of keywords and medical subject headings (MeSH) terms such as “opioids,” “bone health,” “osteoporosis,” “fractures,” “bone mineral density,” and “endocrinopathies.” Boolean operators (AND, OR) were employed to refine the search results. The search was restricted to studies published in English from inception until May 2024.

OPIOIDS AND BONE HEALTH

Opioid use has been extensively researched in clinical studies to elucidate its impact on bone health. Numerous investigations have consistently demonstrated a significant association between opioid use and adverse bone health outcomes, with evidence indicating that individuals using opioids are at a height-

ened risk of fractures and impaired bone repair compared to non-users [35]. Opioids such as morphine and dilaudid have been found to inhibit bone formation, leading to bone loss; however, the precise mechanisms underlying this effect remain elusive [36]. Furthermore, research has shown that sustained delivery of morphine suppresses bone formation and alters metabolic and circulating miRNA profiles, highlighting the detrimental effects of opioids on bone turnover [37].

The detrimental impact of opioids on bone metabolism is further supported by studies indicating that both men and women undergoing chronic opioid treatment face an increased risk of reduced BMD [29]. Despite the recognised inhibitory effects of opioids on testosterone production and bone formation, there remains a gap in research regarding the necessity of routine BMD screening in male subjects using opioids for pain management [38]. Case reports have underscored the adverse impact of chronic opioid use on bone health, with instances of opioid-induced osteoporosis leading to fracture [39].

Observational studies have revealed a higher prevalence of hip fractures among individuals with a history of chronic opioid consumption, further corroborating the link between opioids and bone fragility [40]. Additionally, research on opioid use in patients with advanced cancer and bone metastases has shown an association between analgesic use, pain, and bone complications in this population [41]. Studies on men with opioid dependence have identified a correlation between opioid use and low BMD, indicating a potential risk factor for fractures in this group [42].

In females, the impact of opioid-induced androgen deficiency (OPIAD) on bone health is significant, with opioid use being a risk factor for the development of osteoporosis due to their smaller and thinner bones compared to men [40,43]. Additionally, an increased prevalence of osteoporosis has been observed in postmenopausal women, with rates reaching 9.2% in some populations [11]. Additionally, factors such as nutritional status, daily opioid use, and comorbidities like cancer and disabilities have been associated with increased opioid use among females, potentially exacerbating the risk of osteoporosis [44-46].

The endocrine effects of opioids on bone metabolism have garnered significant interest, with studies highlighting how opioids induce testosterone deficiency and impair osteoblastic activity, contributing to bone loss [44]. Opioid-induced endocrinopathies have been examined in the context of bone health, emphasising the need for further research to fully understand opioids' impact on bone density and integrity [45]. Furthermore, the use of opioids in chronic non-cancer pain management has been associated with accelerated BMD loss and hypogonadism due to the suppression of hypothalamic gonadotropin-releasing hormone [31].

In patients receiving opioid replacement therapy, studies have investigated factors contributing to low BMD, providing insights into variables that may influence bone density in this population [28]. Research on testosterone deficiency in non-cancer opioid-treated patients has further clarified the direct effects of opioids on bone formation and hormonal balance [32]. Additionally, investigations of patients undergoing long-term intrathecal opioid delivery therapy have revealed associations between hypogonadism and low BMD, underscoring the importance of comprehensive management in this patient group [47].

FRACTURE RISK

Opioid use consistently increases the risk of falls and fractures, underscoring its significant impact on bone health. The relationship between opioids, bone density, and fracture risk encompasses multiple physiological pathways. A primary mechanism through which opioids elevate fracture risk involves their effect on the central nervous system, resulting in adverse side effects such as sedation and dizziness [48]. These effects heighten the propensity for falls, particularly among vulnerable demographics like the elderly, consequently amplifying fracture susceptibility. Furthermore, opioids exert a direct influence on bone density by impacting osteoblast activity, crucial for bone formation [29]. This direct modulation of bone metabolism can lead to reduced BMD, further predisposing individuals to fractures.

Chronic opioid use is also associated with hypogonadism, characterised by diminished sex hormone levels, which detrimentally affects bone health [49]. Opioid-induced hypogonadism is particularly concerning as it contributes to decreased bone density, thereby augmenting fracture risk. The intricate interplay between opioids, hypogonadism, and bone health underscores

the complexity of their association with fracture risk. Research has additionally highlighted opioids' role in influencing fracture risk through their impact on psychomotor function, bone metabolism, and osteogenesis [50]. These findings emphasise the necessity for comprehensive assessments of opioid effects on bone health to mitigate associated risks.

Meta-analyses consistently support the association between opioid use and fracture risk, with pooled data consistently indicating opioids significantly contribute to overall fracture susceptibility [34]. The substantial magnitude of this risk underscores the critical consideration of potential skeletal consequences when prescribing these medications, particularly in clinical settings where opioids are prevalent. Additionally, studies have demonstrated that opioid exposure increases the likelihood of specific fracture types, such as hip fractures, necessitating cautious opioid prescription, especially among high-risk populations [51].

In addition to direct effects on bone health, studies have explored the relationship between opioid dosage and fracture risk, suggesting that higher doses of opioids correlate with increased fracture risk [52]. This dose-dependent relationship emphasises the importance of optimising opioid therapy to mitigate potential skeletal complications. Furthermore, research has examined the impact of opioids on specific patient populations, such as individuals with chronic pain or those undergoing intrathecal opioid therapy, revealing unique considerations regarding bone health in these cohorts [53,54].

MECHANISMS

The interaction between opioid use and osteoporosis is intricate, involving diverse biological pathways. A critical component is opioid-induced endocrinopathy, which manifests in conditions such as hypogonadism and hypoadrenalism [29]. These disruptions in endocrine function are particularly significant as OPIAD has been linked to an increased susceptibility to osteoporosis [29]. Therefore, vigilant monitoring of patients receiving chronic opioid therapy, particularly those on higher dosages, is essential to promptly identify and address hormonal imbalances and diminished BMD [29].

Opioids impact bone health through both direct and indirect mechanisms. Indirectly, opioids contribute to reduced BMD by inducing conditions like hypogonadism [55]. Hypogonadism, commonly resultant from opioid use, adversely affects bone turnover and density [55]. Additionally, opioids exert direct effects on bone metabolism, further decreasing BMD [55]. This reduction in bone formation may occur through the inhibition of osteocalcin synthesis, a pivotal marker of bone formation, via opioid receptors on osteoblast-like cells [56]. Studies have demonstrated that opioid agonists can suppress osteocalcin secretion by interacting with mu receptors on these cells [56].

Furthermore, opioid addiction can influence BMD and elevate fracture risk through both direct and indirect pathways [39]. Central nervous system effects of opioids, such as dizziness, heighten the risk of falls, thereby contributing to increased fracture susceptibility [47]. High-dose opioid usage has been associated with a twofold rise in fracture risk, highlighting the necessity of comprehending the impact of opioids on bone health [57].

Long-term opioid use has been correlated with substantial deterioration in bone health and the onset of osteoporosis [58]. Opioid-induced endocrinopathies, including hypogonadism, detrimentally affect muscle mass and bone health, thereby increasing the likelihood of fractures [59]. Additionally, opioids' inhibitory effects on the hypothalamo-pituitary-adrenal axis can exacerbate these issues, highlighting the multifaceted impact of opioids on bone metabolism [59].

RISK ASSESSMENT

To evaluate osteoporosis risk in opioid users, various strategies based on current literature can be implemented. Opioid use has been associated with heightened osteoporosis risk due to opioid-induced androgen deficiency, which leads to hormonal imbalances and reduced BMD [29]. Monitoring patients on chronic opioid therapy, particularly those on higher doses, for hormonal imbalances and changes in bone density is crucial for early detection of osteoporosis risk [29]. Studies have highlighted the challenges in osteopenia screening in women compared to men due to more subtle symptoms, necessitating gender-specific assessment approaches [60].

The mechanisms through which opioids contribute to osteoporosis risk involve multiple pathways. Opioids can increase

the risk of falls through psychomotor effects, impact bone metabolism via opioid-induced hormonal imbalances, and directly hinder bone formation, all of which elevate fracture and osteoporotic event likelihoods [50]. Hence, a comprehensive risk assessment strategy should encompass evaluations of bone density, fall risk, and hormonal profiles in long-term opioid therapy patients.

Furthermore, the association between opioid use and fractures, particularly in specific patient cohorts, underlines the importance of personalised risk assessment strategies. For instance, in patients with spinal cord injuries initiating opioid therapy, careful attention to fracture prevention is recommended, particularly with higher opioid doses [54]. Similarly, in individuals undergoing hip fracture surgery, careful consideration of the benefits and risks of opioid use is essential for optimising postoperative care and long-term outcomes [61].

In chronic pain management, where opioids are commonly prescribed, understanding the impact of opioid use on bone health is critical. Patients on long-term intrathecal opioid therapy should be assessed for hypogonadism and associated changes in BMD to identify those at risk of osteopenia or osteoporosis [47]. Additionally, evaluating the influence of concurrent medications, such as gabapentinoids, alongside opioids on fall-related injuries in older adults with chronic noncancer pain can provide insights into comprehensive risk mitigation strategies [62].

Screening tools for assessing osteoporosis risk, such as the Simple Calculated Osteoporosis Risk Estimation and Fracture Risk Assessment Tool, can aid in identifying individuals who may require closer monitoring and preventive interventions [63]. These tools, coupled with regular monitoring of hormonal profiles, bone density scans, and fall risk assessments, can enhance the accuracy of osteoporosis risk evaluation in opioid-using patients (Fig. 1).

MONITORING

Monitoring bone health in individuals using opioids is crucial due to the significant impact of these medications on bone metabolism. Chronic opioid therapy consistently leads to opioid-induced endocrinopathies, which decreases BMD and increase susceptibility to osteoporosis [55,64]. The correlation between opioid use and heightened fracture risk, particularly prevalent

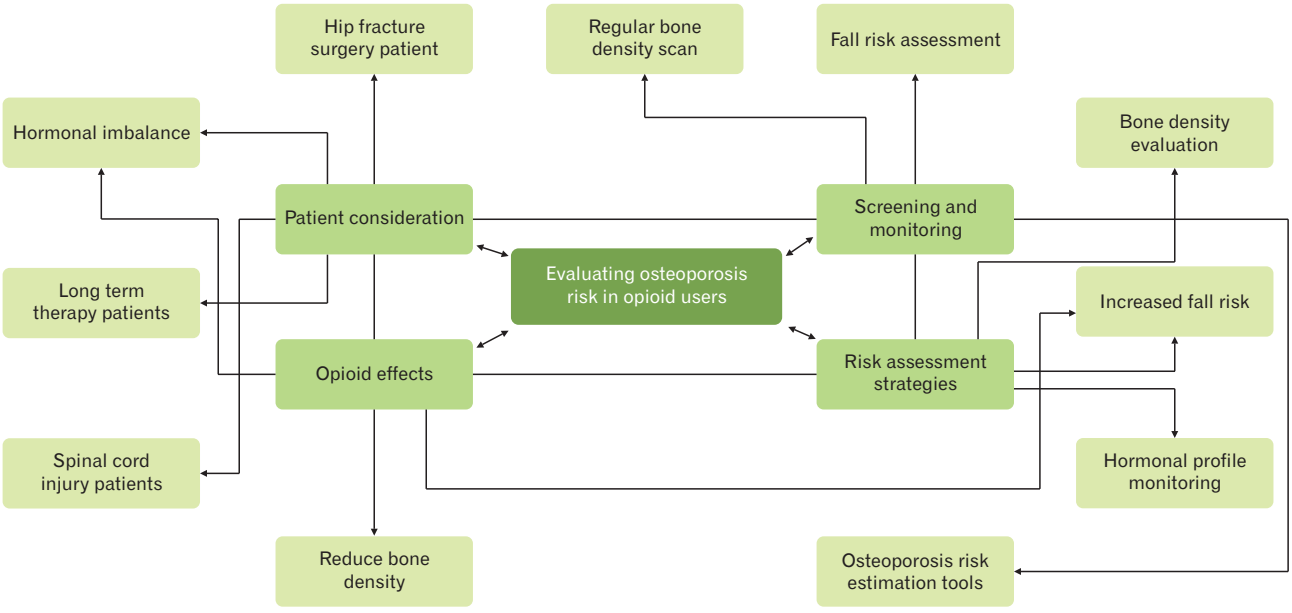

Fig. 1. Strategies and factors in evaluating osteoporosis risk in opioid users. This diagram focuses on the osteoporosis risk in opioid users, highlighting four main areas. Opioid effects include hormonal imbalances, increased fall risk, and reduced bone density. Risk assessment involves evaluating bone density, fall risk, and hormonal profiles. Patient considerations covers specific groups like spinal cord injury patients, hip fracture surgery patients, and those on long-term therapy. Screening and monitoring utilise risk estimation tools, regular bone density scans, and fall risk assessments.

among older chronic pain patients, emphasises the critical necessity for vigilant monitoring [52]. Although specific standards have not been established, all patients on chronic opioid therapy (especially at doses ≥ 100 mg morphine daily) should be monitored for early signs of hormonal impairment and low BMD [22].

OPIAD specifically contributes to an elevated risk of osteoporosis, highlighting the importance of regular assessments of hormonal levels and BMD in patients on long-term opioid therapy [29,65]. Recommendations advocating for routine bone density screening in chronic opioid users aim to facilitate early detection of osteoporosis, potentially mitigating its adverse outcomes [66].

Furthermore, certain opioids, such as methadone, have been identified as exacerbating factors in BMD decline, necessitating individual evaluation strategies, particularly for female populations [67]. The multifaceted impact of opioids on bone health is further evidenced by studies indicating exacerbated baseline knee osteoarthritis and accelerated degenerative changes among opioid users [68]. This observation highlights the complexity of managing bone health in this population and underscores the need for comprehensive monitoring protocols.

Chronic heroin users, who exhibit multiple risk factors for low BMD, experience significant reductions in bone mass, underlining the critical role of ongoing bone health assessments in opioid users [69]. Testosterone deficiency associated with opioid use not only predisposes individuals to sexual dysfunction but also heightens the risk of osteoporosis and fractures, necessitating regular evaluations of hormone levels [70].

While the precise mechanisms through which long-term opioid use affects bone metabolism and promotes osteoporosis are still being elucidated, emerging evidence consistently emphasises the detrimental impact of these medications on skeletal integrity [30]. Middle-aged men with long-term opioid dependency are particularly vulnerable to low bone mass, implicating partial androgen deficiency as a potential mediator of bone health deterioration among opioid users [42].

MANAGEMENT

Osteoporosis presents a significant concern among individuals using opioids due to the adverse effects of these medications on bone health. Extensive research consistently demonstrates a correlation between opioid use and an increased risk of osteoporosis, particularly in patients experiencing OPIAD [29]. This highlights the critical necessity for monitoring patients undergoing chronic opioid therapy, especially those on higher doses, to detect hormonal impairment and low BMD early for timely intervention [29]. Concerns have also been raised regarding the prevalence of osteopenia in opioid users, emphasising the importance of screening to identify subtle signs of bone impairment, which can pose unique challenges in female patients [60].

To mitigate the risk of osteoporosis in individuals using opioids, several strategies have been proposed. A key approach involves ensuring that patients receive appropriate osteoporosis therapy, particularly following events such as hip fractures, where opioid analgesic users may be less likely to receive adequate treatment [71]. Additionally, interventions aimed at enhancing medication adherence and promoting lifestyle modifications have been recommended to mitigate risk factors associated with osteoporosis [72]. Pharmacist-led initiatives encompassing osteoporosis risk screening and personalised counselling on adherence and risk reduction play a pivotal role in optimising osteoporosis care [72].

In orthopaedic trauma care, which often involves opioid prescriptions, specialised pain management strategies incorporating life care specialists have demonstrated efficacy in improving pain management outcomes and reducing opioid-related risks [73]. These interventions are designed to address the complex pain needs of orthopaedic trauma patients, thereby mitigating the likelihood of prolonged opioid use and its associated complications, including osteoporosis [73]. Furthermore, interdisciplinary approaches integrating long-term patient support, prudent opioid prescribing practices, and comprehensive risk mitigation strategies are essential for managing opioid misuse in musculoskeletal patients [74].

Efforts to mitigate opioid-related adverse events include the development of risk stratification tools such as the Veterans Health Administration's Stratification Tool for Opioid Risk Mitigation (STORM), which identifies high-risk patients and personalised interventions to enhance safety [75]. These personalised approaches to opioid prescribing emphasise individual risk factors and aim to optimise treatment outcomes while minimising healthcare costs [75]. Furthermore, strategies focused on mini-

mising drug interactions, particularly among [76].

In perioperative settings, interventions aimed at reducing opioid exposure, such as integrating complementary medicine into multimodal analgesia strategies, have proven effective in minimising postoperative opioid consumption [77]. By incorporating complementary approaches into pain management protocols, healthcare providers can effectively mitigate opioid-related risks, including those affecting bone health [77]. Similarly, innovative techniques such as wide-awake local anaesthesia no tourniquet (WALANT) hand surgery offer potential in eliminating the need for postoperative opioid pain management, thereby further reducing associated risks in the postoperative period [78].

TREATMENT

Patients diagnosed with osteoporosis who concurrently use opioids present a multifaceted clinical challenge necessitating careful consideration of treatment approaches. When managing osteoporosis in this patient population, healthcare providers must address the potential impact of opioids on bone metabolism. Research indicates that individuals receiving opioid therapy may be at higher risk of inadequate osteoporosis treatment, potentially predisposing them to complications such as fractures [71]. Thus, ensuring these patients receive appropriate osteoporosis management is crucial to mitigate adverse outcomes.

In cases where osteoporosis is suspected to stem from specific factors like heroin use, a comprehensive evaluation considering the unique aetiology is essential for accurate diagnosis and effective management [39]. Additionally, guidelines such as those outlined by the National Osteoporosis Foundation play a pivotal role in guiding healthcare professionals towards initiating pharmacological treatments for patients diagnosed with osteoporosis or osteopenia [79]. These guidelines serve as indispensable tools for optimising treatment decisions in patients with osteoporosis who also use opioids.

Furthermore, in patients with chronic obstructive pulmonary disease (COPD) who face heightened osteoporosis risks due to factors such as glucocorticoid use, initiating treatment based on specific criteria is critical for mitigating bone health deterioration [80]. Similarly, for individuals undergoing long-term intrathecal opioid delivery therapy, regular monitoring of hypogonadism and BMD levels is essential to prevent osteoporosis and associated fractures [47]. These findings highlight the necessity of personalised approaches to osteoporosis management in patients using opioids.

Additionally, the impact of opioids on testosterone levels and subsequent effects on bone health underline the interplay between endocrine function and bone metabolism [70]. For patients with conditions like rheumatoid arthritis, where osteoporosis risks are heightened due to factors including glucocorticoid use, integrating tools such as the Fracture Risk Assessment (FRAX) tool into treatment protocols can enhance the precision of osteoporosis management strategies [81]. By considering multiple risk factors and employing comprehensive assessment tools, healthcare providers can personalise treatment strategies to address the unique needs of patients with osteoporosis and concurrent opioid use.

In the context of orthopaedic surgery, where effective perioperative pain management is crucial, employing multimodal approaches encompassing regional blockade and diverse pharmaceutical options can optimise pain control in chronic opioid users [82]. Furthermore, in patients with low back pain, despite recommendations for conservative therapies such as physical therapy, persistent opioid use emphasises the imperative for alternative pain management strategies in this population [82]. Understanding the complexities associated with opioid use in varied clinical contexts is essential for devising effective treatment plans for patients with osteoporosis.

Furthermore, the association between long-term opioid use and limited improvements in health-related quality of life highlights the challenges of managing chronic pain with opioids [83]. In elderly patients with hip fractures, prior opioid use has been linked to sustained opioid dependence, necessitating comprehensive pain management strategies personalised to this vulnerable population [84]. These findings highlight the importance of addressing pain effectively in patients with osteoporosis to mitigate risks associated with opioid use.

Furthermore, in patients undergoing lung cancer resection, the prevalence of opioid dependence postoperatively necessitates a nuanced approach to pain management to prevent adverse outcomes [85]. Similarly, in individuals with knee osteoarthritis, factors influencing early opioid use underline the need

for personalised treatment approaches that consider both the underlying condition and potential risks associated with opioid therapy [86]. Personalising interventions to meet the specific needs of patients with osteoporosis and comorbidities such as knee osteoarthritis can enhance treatment outcomes and patient safety.

In postoperative pain management, particularly in non-opioid-naive patients undergoing hand and upper-extremity surgery, challenges in effectively managing pain highlight the importance of personalised pain management strategies that account for individual opioid tolerance [87]. Additionally, the relationship between chronic opioid use and central sleep apnoea highlights the multifaceted effects of opioids on various physiological processes, necessitating a comprehensive approach to managing both pain and associated complications [88]. By addressing the complexities associated with opioid use in patients with osteoporosis, healthcare providers can optimise treatment outcomes and enhance patient well-being.

CURRENT KNOWLEDGE GAPS

Opioids have been implicated in the pathogenesis of osteoporosis through multiple mechanisms, including OPIAD, inhibition of bone formation, altered bone metabolism, and diminished BMD [29,36,40,89]. Chronic use of opioids, particularly at higher doses, has been associated with hormonal disturbances and reduced bone mass density, underscoring the critical need for monitoring and early detection of these deleterious effects [29]. Evidence suggests that opioids like morphine and hydromorphone can impede bone formation, although the precise underlying mechanisms remain incompletely elucidated [36]. Additionally, chronic misuse of opioid substances has been linked to altered bone metabolism and decreased trabecular bone mass, partly attributable to gonadal dysfunction [89].

The relationship between opioids and osteoporosis is complex, with divergent studies proposing direct impacts on bone metabolism while others suggest mediation through opioid-induced gonadal dysfunction, as seen in treatments like methadone maintenance therapy (MMT) [90]. Research indicates that sustained administration of morphine may suppress bone formation and disrupt metabolic profiles, potentially influencing bone remodelling processes [37]. Furthermore, the use of opioids for chronic non-cancer pain has been linked to elevated incidences of hypogonadism in men, necessitating further investigation into the long-term effects of opioid use on gonadal status and BMD [90].

While OPIAD is prominently discussed as a contributor to bone fragility, other factors likely contribute to the association between opioid use and osteoporotic fractures [91]. Studies have reported increased fracture risks associated with oral opioid medications, albeit assessments of BMD in these contexts have been limited [47]. It is imperative to evaluate the potential ramifications of opioid use on bone health, especially within populations where opioid utilisation is prevalent, such as individuals receiving long-term intrathecal opioid therapy [47].

The endocrine repercussions of opioids, encompassing hypogonadism and alterations in testosterone levels, have emerged as probable influencers of bone loss and fragility [92]. Nevertheless, knowledge gaps persist regarding the necessity for routine BMD screening in males utilising opioids for pain management, highlighting the need for further research in this area [38]. Studies have demonstrated significant reductions in BMD among opioid users compared to non-users, even after adjusting for factors influencing bone health, though comprehensive data on sex hormone levels concerning bone health remain scarce [55].

The utilisation of opioids in cancer pain management, particularly among patients with bone metastases, raises concerns regarding its impact on bone health and the imperative for effective pain management strategies that minimise opioid consumption [93,94]. While opioids are frequently prescribed for managing pain in diverse conditions such as postherpetic neuralgia and herpes zoster, the burden of opioid use and its potential implications for bone health underline the necessity to explore alternative approaches to pain management [95].

LIMITATIONS OF STUDIES

Existing studies on opioids and osteoporosis have emphasised several critical limitations that necessitate attention from researchers and healthcare providers. A significant challenge lies in diagnosing and screening for opioid-induced endocrinopathy, particularly opioid-induced hypogonadism, which has been

linked to an increased osteoporosis risk [29]. This difficulty is compounded by the subtlety of symptoms, making screening more arduous in women compared to men [60]. Additionally, the scarcity of literature specifically addressing heroin-induced osteoporosis highlights gaps in understanding the differential impacts of various opioids on bone health [39].

Studies have indicated a higher prevalence of hypogonadism among men with chronic non-cancer pain on long-term oral opioids compared to women, emphasising the necessity for gender-specific considerations in both research and clinical settings [91]. While the association between oral opioid use and reduced BMD has been established, comprehensive evaluations assessing hypogonadism alongside bone health markers remain inadequate [47]. This gap highlights the urgent need for more thorough investigations into the mechanisms underlying opioid-induced osteoporosis in patients undergoing long-term opioid therapy.

Furthermore, the presence of opioid receptors in osteoblast-like cells and the effects of opioid agonists on bone-related markers suggest a direct influence of opioids on bone metabolism [56]. However, translating these findings into clinical practice and developing targeted interventions for opioid-induced osteoporosis necessitates further exploration. Concerns have also been raised about the under-recognition of osteoporosis risk factors, including opioid use, particularly among males, indicating deficiencies in screening and initiating appropriate treatments within this demographic [96].

The heightened risk of fractures associated with high doses of opioids in older individuals with chronic non-cancer pain accentuates the imperative for a nuanced approach to pain management in this vulnerable population [97]. Factors such as osteoporosis, recent cancer diagnoses, and greater disabilities have been correlated with daily opioid use, highlighting the interplay between pain management, opioid therapy, and bone health [46]. Furthermore, the underutilisation of osteoporosis therapy among patients using opioid analgesics points to gaps in managing bone health among those with chronic pain conditions [71].

Despite the well-documented risks of chronic opioid therapy on bone health, adherence to osteoporosis pharmacotherapy remains suboptimal, reflecting a disparity in translating evidence-based guidelines into clinical practice [98]. This treatment gap in osteoporosis management, exacerbated by concerns over side effects and long-term drug efficacy, underlines the necessity for a more holistic and patient-centred approach to osteoporosis care [99]. Addressing these gaps demands concerted efforts to enhance screening protocols, improve diagnostic accuracy, and initiate timely treatments among at-risk populations, including individuals on chronic opioid therapy [100].

FUTURE RESEARCH

To comprehensively address the complex relationship between opioids and osteoporosis, future research should prioritise investigation in several critical areas. Firstly, there is a pressing need to investigate the endocrine impacts of opioids on bone metabolism, particularly focusing on OPIAD, which has been associated with heightened osteoporosis risk [29]. Monitoring and managing hormonal disruptions induced by opioids, especially in patients on high opioid dosages, could significantly enhance early detection and intervention for low BMD.

Secondly, it is imperative to explore the direct mechanisms by which opioids influence bone formation, potentially through modulation of osteoblastic activity via specific receptors [101]. Gaining insights into these pathways could illuminate novel therapeutic targets aimed at mitigating osteoporosis risk in chronic opioid users.

Additionally, research efforts should aim to disentangle the multifaceted factors contributing to opioid use and misuse among patients with orthopaedic injuries, as highlighted in studies [102]. Understanding these factors is crucial for developing targeted interventions aimed at preventing opioid misuse and its detrimental effects on bone health.

Additionally, investigating the interplay between opioids, sex hormones, and bone density, as explored in recent studies [90], can provide valuable insights into whether opioids directly mediate adverse skeletal effects or if these are secondary to factors such as gonadal dysfunction induced by opioid treatment.

Furthermore, exploring the necessity and efficacy of routine BMD screening in male subjects undergoing opioid therapy for pain management, as suggested by previous research [38], can facilitate the early identification of individuals at risk of osteoporosis due to opioid use, thereby enabling timely implementation of preventive measures.

By prioritising these research avenues, we can advance our understanding of the mechanisms linking opioids and osteoporosis, ultimately paving the way for more effective strategies to mitigate bone health complications in patients undergoing opioid therapy.

CONCLUSION

The intersection of opioid use and osteoporosis presents a complex clinical challenge with significant implications for patient management and public health. Clinical studies have consistently demonstrated that chronic opioid use is associated with reduced BMD and an increased risk of fractures. The multifaceted mechanisms underlying this relationship include opioid-induced hormonal imbalances, such as hypogonadism, and direct effects on bone metabolism. The central nervous system side effects of opioids, such as sedation and dizziness, also contribute to a higher incidence of falls, further exacerbating fracture risk.

In clinical practice, these findings necessitate a proactive approach to the management of patients on long-term opioid therapy. Regular monitoring of bone health, including routine BMD screenings and assessment of hormonal profiles, is essential. Strategies to mitigate osteoporosis risk should include optimising opioid dosing to the minimum effective amount, addressing endocrine abnormalities, and considering alternative pain management options where possible. Additionally, incorporating comprehensive risk assessment tools can help identify patients at higher risk and personalise preventive measures accordingly.

Public health initiatives should focus on raising awareness about the bone health risks associated with opioid use and promoting guidelines for the monitoring and management of these risks in clinical settings. Interdisciplinary collaboration among healthcare providers, including primary care physicians, endocrinologists, pain specialists, and pharmacists, is critical to developing and implementing effective strategies for the prevention and treatment of opioid-induced osteoporosis.

Overall, the growing body of evidence highlights the urgent need for integrated care approaches to manage the dual burden of chronic pain and osteoporosis in opioid users. Addressing this intersection effectively can lead to improved patient outcomes, reduced fracture incidence, and enhanced quality of life for individuals affected by both conditions. Further research is warranted to explore the underlying mechanisms in more detail and to develop targeted interventions that can mitigate the adverse skeletal effects of opioid therapy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported. We have no affiliations, financial involvement, or personal relationships with any organizations or individuals that could be perceived as influencing the content or conclusions of this manuscript.

All authors have reviewed and approved the final manuscript and agree to its submission for publication.

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