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Association between Baseline Vitamin D Levels and Quality of Life and Pain in Chronic Pain Patients on Long-Term Opioid Therapy

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Abstract

This work aimed to determine whether baseline serum 25-hydroxyvitamin D (25-OHD) concentrations show any link with quality of life (QoL) and pain perception in patients experiencing chronic pain who had been on long-term prescription opioids ahead of planned opioid detoxification. A prospective evaluation was performed on 45 patients with chronic pain maintained on extended prescription opioid therapy and scheduled for elective detoxification. Serum 25-OHD levels were quantified at baseline, before the start of detoxification, and patients were classified as vitamin D deficient (< 75 nmol/L) or sufficient (≥ 75 nmol/L). Quality of life was measured using the SF-36v2TM questionnaire, and pain intensity was recorded using a Visual Analog Scale (VAS) before any intervention. Before detoxification, the mean pain scores for patients with adequate baseline 25-OHD levels versus those with deficient levels were 6.06 ± 2.32 and 6.86 ± 2.10, respectively (corresponding normalized scores: 1.22 ± 0.571 versus 0.950 ± 0.632; p = 0.164). Review of the SF-36v2™ questionnaire data indicated only minor differences between the groups (35.00 ± 14.198 versus 34.97 ± 13.52), suggesting no meaningful association between vitamin D status and QoL (p = 0.913). Analysis of pretreatment 25-OHD concentrations with quality-of-life scores and pain ratings failed to reveal a statistically significant correlation. This suggests that variations in baseline vitamin D levels are unlikely to exert a substantial effect on either QoL or perceived pain intensity in this patient group. Future research is needed to establish clearer guidance on the assessment and management of vitamin D status among individuals with chronic pain who require prolonged prescription opioid treatment.

Keywords: Chronic pain, Vitamin D, Prescription opioids, Quality of life

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Introduction

Opioids have long been regarded as effective agents for relieving severe acute pain and pain stemming from advanced chronic diseases [1]. Nevertheless, their long-term administration is now subject to considerable debate due to significant safety concerns and unwanted side effects [2]. Although an opioid crisis has developed in the United States during the past decade, accompanied by growing international alarm over addiction and misuse, opioid analgesics continue to be routinely prescribed for the control of chronic pain [3]. At the same time, doubts have increased about their lasting value, since accumulating evidence indicates that non-opioid

medications and various interventional strategies frequently deliver better overall results [4]. Extended opioid exposure is also connected with multiple serious complications, such as constipation, sleep-related respiratory disturbances, increased fracture risk, disruption of the hypothalamic–pituitary–adrenal axis, danger of overdose, and elevated chances of developing addictive behavior [2, 5]. In addition, the appearance of tolerance and opioid-induced hyperalgesia creates further difficulties for the safe, prolonged clinical use of these medications [2, 5].

Over the past few years, scientific interest in the possible role of vitamin D in pain relief has grown. Vitamin D is known to influence a wide range of physiological activities, including regulation of immune responses, dampening of inflammation, inhibition of tumor development, antioxidant effects, and protection of neural tissue [6-10].

Lower-than-normal baseline vitamin D concentrations have repeatedly been linked to reduced physical capability, heightened pain sensitivity, and more pronounced fatigue. These factors together tend to lower patients' overall sense of quality of life, especially when chronic pain is present [11]. Various published reports have described associations between vitamin D status and the likelihood or intensity of both acute and chronic pain syndromes [12-15].

People living with chronic pain commonly show insufficient or frankly deficient vitamin D levels. Several lines of research have connected these lower concentrations with reports of more severe pain [15-17]. Vitamin D deficiency also appears to be associated with poorer health-related quality of life, potentially through mechanisms that increase central sensitization and amplify responses to mechanical stimuli. However, its influence on the spontaneous, ongoing pain that patients describe seems comparatively weaker [11].

Moreover, some findings indicate that reduced 25-OHD levels may coincide with higher opioid dosage requirements, raising the question of whether vitamin D deficiency could play a role in accelerating opioid tolerance [8, 18, 19].

Despite these associations, the exact biological pathways through which vitamin D deficiency might contribute to pain development or persistence remain unclear [16]. Although several studies have examined whether vitamin D supplementation reduces pain and improves QoL, the results remain inconsistent.

The current study set out to investigate possible relationships between baseline serum 25-OHD concentrations and both quality of life and pain perception in patients with chronic pain who were about to begin opioid detoxification after extended periods of prescription opioid use. Because the present findings are based on a limited number of participants, they should be viewed as preliminary. Larger-scale investigations will be required before firm conclusions can be drawn about the relationships among serum 25-OHD levels, QoL, and pain perception.

Materials and Methods

The procedures followed in this investigation represent an extension of the methodology applied in our prior work [20], which explored how prescription opioid detoxification affects quality of life and pain severity.

This prospective observational study ran from 2019 to 2023 and enrolled 45 patients who were admitted for detoxification from prescription opioids at the Toxicology Center of Republican Vilnius University Hospital, Lithuania. Ethical clearance was granted by the Vilnius Regional Committee on Biomedical Research Ethics (approval no. 2019/10-1153-644), and written informed consent was obtained from every participant before enrolment. Referrals to the Toxicology Center came from both primary care doctors and specialists working in secondary care settings, including the National Center for Cancer and Pain Clinics, where suitability for opioid detoxification was first evaluated.

Inclusion in the study required that participants be adults with a verified history of prolonged prescription opioid use to treat chronic pain, evidence of developed opioid tolerance, confirmed dependence on prescribed opioids, and elective admission to the Toxicology Center specifically for detoxification. Opioid tolerance was understood as the progressive need for higher doses to sustain the same level of pain relief because of reduced drug responsiveness. Patients were not eligible if they had acute opioid intoxication, addiction to illicit opioids, or dependence on multiple psychoactive substances.

Measurement of serum 25-hydroxyvitamin D (25-OHD) concentrations was performed in an outpatient setting before detoxification commenced. Individuals whose baseline serum 25-OHD fell below 75 nmol/L were placed in the deficient vitamin D category, while those with values of 75 nmol/L or higher were placed in the sufficient category.

It is worth noting that the medical literature offers varying definitions of vitamin D deficiency, insufficiency, and ideal serum concentrations. In 2021, the Lithuanian College of Family Physicians released "Guidelines for the Diagnosis, Prevention, and Treatment of Vitamin D Deficiency", suggesting that optimal serum 25-OHD levels lie between 100–150 nmol/L and that values from 75–100 nmol/L should be viewed as suboptimal [21]. The European Food Safety Authority considers 50 nmol/L an acceptable target for serum 25-OHD [22]. In contrast, the International Society of Endocrinology, through its "Guidelines for the Evaluation, Treatment, and Prevention of Vitamin D", set 75 nmol/L as the standard normal value

for serum 25-OHD [23]. This last threshold was selected as the dividing line for our study. Determining the most suitable definition of adequate serum 25-OHD remains a topic of ongoing discussion and should be decided on a case-by-case basis, depending on the clinical setting [24].

At hospital admission, key clinical and demographic details were recorded. These included the patient's age, how long the pain had persisted, the main site or cause of the pain, the amount of opioid being taken, and the total duration of opioid therapy. The opioid dose on admission was determined by combining the patient's own report with a careful examination of medical documentation. To simplify comparison, all opioid amounts were later converted into oral morphine equivalents (MEDs).

Patients in the cohort had been prescribed opioids chiefly to manage several types of persistent pain, such as headaches, pain linked to cancer, back pain, rheumatoid arthritis, gastrointestinal conditions, chronic muscle pain, and arthrosis affecting the humerus. Of note, every cancer patient participating in the study was in remission and was not receiving any active cancer therapy while data were being gathered.

The detoxification program used here was constructed according to the framework established in our earlier research [25].

Quality of life was evaluated with the Lithuanian-language version of the SF-36v2™ questionnaire. Pain levels were assessed using the Visual Analog Score (VAS). The VAS scale used in this study ranged from 0 to 10, where 0 indicated no pain at all and 10 the most intense pain one could imagine **(Table 1)**.

Table 1. VAS scoring criterion.

VAS Score Range	Interpretation of Pain Intensity
0	Absence of pain
1–3	Mild level of pain
4–6	Moderate intensity pain
7–9	Severe pain
10	Maximum imaginable pain

It should be noted that the wider research project [20], of which this is part, involved repeated collection of quality-of-life and VAS pain measurements before and after the detoxification process. For the specific aims of the present analysis, however, we focused solely on the data obtained before detoxification. These pre-detoxification SF-36v2™ questionnaire results and VAS pain scores were then compared with baseline serum 25-OHD concentrations, with patients split into two groups based on their initial vitamin D status (deficient versus sufficient). This strategy was adopted to investigate possible connections among quality of life, pain perception, and vitamin D levels before any detoxification.

On the first day of the detoxification process, patients with deficient baseline serum 25-OHD levels received D single 50,000 IU dose of cholecalciferol. The choice of oral solution and the exact dosing schedule were guided by the recommendations contained in the Lithuanian College of Family Physicians Guidelines for the management of vitamin D deficiency [20]. When patients left the hospital, continuation of supplementation together with follow-up by a family physician was advised for everyone. Serum 25-OHD concentrations were not reassessed after the inpatient detoxification phase ended, because the main focus of this study was how baseline 25-OHD levels related to quality of life and pain perception measured before detoxification.

This study tested the null hypothesis that baseline vitamin D levels are not associated with pre-detoxification quality of life or VAS pain scores.

The data were processed and analyzed using Microsoft Excel spreadsheets and IBM SPSS version 23.0. All continuous measures were summarized using means along with their standard deviations, whereas categorical information was shown in the form of percentages.

To explore potential links between 25-OHD concentrations, VAS pain ratings, and QoL scores recorded before opioid detoxification, a linear regression model relying on ordinary least squares (OLS) estimation was applied. In this model, 25-OHD values (log-transformed to reduce skewness and improve linearity) and pre-detoxification VAS pain ratings (reversed and log-transformed) were independent variables, and the overall QoL score was the dependent variable. The threshold for statistical significance was fixed at 0.05, and each predictor's importance was judged according to its t-statistic and associated P-value.

Furthermore, an independent-samples t-test that did not assume equal variances was performed to compare the two subgroups: patients with sufficient 25-OHD levels ($\geq$ 75 nmol/L) versus those with deficient levels (< 75 nmol/L). This comparison focused on mean differences for the main outcome measures — the reversed and log-transformed pre-intervention VAS pain rating, together with responses from the QoL SF-36v2™ questionnaire. Outcomes were reported as observed mean differences, their standard errors, and p-values evaluated at the 0.05 level.

These procedures ensured that suitable transformations were applied to normalize data distributions and facilitate more straightforward interpretation of the relationships examined in both the regression model and the group comparisons.

Results and Discussion

The findings presented here are based on 45 patients, including 28 women (62.22% of the group). Participants had a mean age of 53.62 ± 12.70 years. On average, they

had been receiving prescribed opioids for 60.51 ± 67.81 months, and the typical daily opioid dose stood at 139.8 ± 153.9 mg when expressed in oral morphine equivalent doses (MEDs) **(Table 2)**.

Table 2. Patient characteristics.

Parameter	Value
Mean duration of opioid therapy	60.51 ± 67.81 months
Daily opioid dose (mg/day, MED equivalents)	139.8 ± 153.9
Indication for opioid therapy, n (%)	
Oncological (remission phase)	14 (31.1%)
Neurological disorders	14 (31.1%)
Musculoskeletal conditions	10 (22.2%)
Rheumatoid diseases	2 (4.44%)
Gastrointestinal conditions	2 (4.44%)
Other indications	3 (6.67%)
Pain intensity by condition (VAS, mean ± SD)	
Oncological (remission phase)	5.9 ± 2.6
Neurological disorders	6.1 ± 1.6
Musculoskeletal conditions	7.7 ± 2.1
Rheumatoid diseases	6.8 ± 1.1
Gastrointestinal conditions	8.5 ± 0.7
Other indications	8.5 ± 0.4
Serum 25-hydroxyvitamin D levels (mean nmol/L ± SD)	
≥75 nmol/L (n = 16)	98.4 ± 28.0
<75 nmol/L (n = 29)	38.3 ± 17.2
Quality of life scores by vitamin D status (% ± SD)	
≥75 nmol/L (n = 16)	35.00 ± 14.198
<75 nmol/L (n = 29)	34.96 ± 13.52
Pain scores by vitamin D status (VAS points ± SD)	
≥75 nmol/L (n = 16)	6.06 ± 2.32
<75 nmol/L (n = 29)	6.86 ± 2.10
Opioid medications used, n (%)	
Tramadol	13 (28.9%)
Codeine	9 (20%)
Morphine	9 (20%)
Fentanyl	4 (8.9%)
Pethidine	2 (4.4%)
Methadone	1 (2.2%)
Oxycodone	1 (2.2%)
Combination opioid therapy, n (%)	
Morphine + Fentanyl	2 (4.5%)
Fentanyl + Tramadol	2 (4.5%)
Morphine + Tramadol	1 (2.3%)
Codeine + Morphine + Tramadol	1 (2.3%)

Within this patient group, opioids were prescribed most often to address headaches and cancer-related pain, each responsible for 14 out of the 45 cases. Back pain ranked next, appearing in 10 out of 45 cases. Rheumatoid arthritis and gastrointestinal conditions each accounted for 2 out of 45 cases. Even fewer patients had been prescribed opioids for post-burn after-effects, ongoing muscle pain, or arthrosis of the humerus, with each of these affecting just 1 out of 45 cases **(Table 2)**.

A range of different opioid medications had been used. Tramadol was the most frequent choice, administered to 13 patients. Codeine and morphine followed, each given to 9 patients. Transdermal fentanyl was used by four patients, pethidine by two patients, and both methadone and oxycodone by one patient apiece. Several individuals received more than one type of opioid at the same time: two patients combined morphine with fentanyl, another two combined fentanyl with tramadol, one patient took morphine together with tramadol, and one patient was prescribed codeine, morphine, and tramadol all at once.

Across the whole cohort, the average serum 25-OHD level measured 58.3 ± 35.2 nmol/L. In the subgroup with levels ≥75 nmol/L (n = 16), the mean concentration reached 98.39 ± 28.04 nmol/L. By comparison, patients with levels <75 nmol/L (n = 29) showed a mean of 38.26 ± 17.22 nmol/L **(Table 2)**. In total, 64.4% of participants were placed in the deficient category because their serum 25-OHD levels remained below the 75 nmol/L cut-off. **Figure 1** presents the mean 25-hydroxyvitamin D (25-OHD) concentrations (nmol/L) by underlying pain condition.

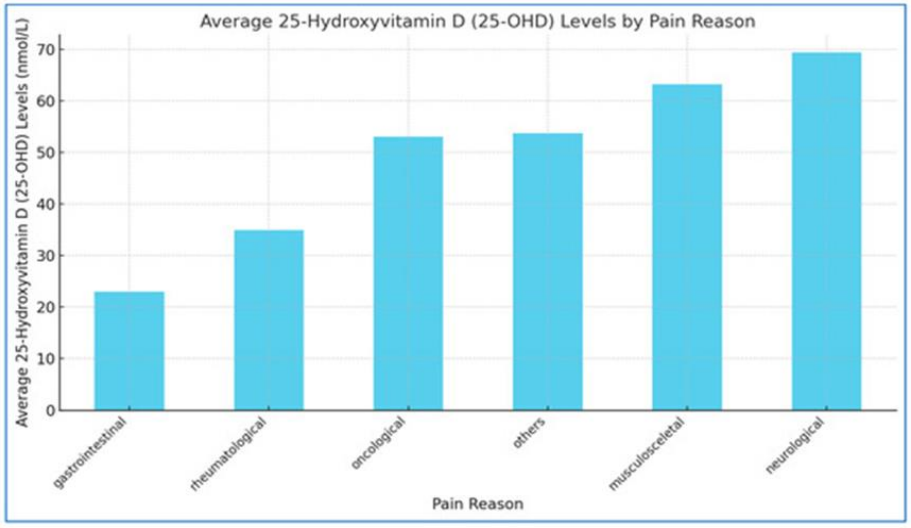

Figure 1. Average 25-hydroxyvitamin D (25-OHD) levels by pain reason.

Association of 25-OHD levels, pain scores, and quality of life: regression findings

A linear regression analysis was carried out to assess the relationships among log-transformed 25-OHD concentrations, reversed and log-transformed pre-detoxification VAS pain ratings, and QoL scores. Overall model performance was modest, with a correlation coefficient of R = 0.123 and an R-squared value of 0.0150. This indicates that the predictors together accounted for only 1.5% of the total variation in QoL SF-36v2™ questionnaire scores.

The intercept term proved statistically significant (β = 35.32, SE = 13.37, t = 2.642, P = 0.012), showing that the expected QoL score at reference levels of the predictors differed from zero. However, neither the coefficient for 25-OHD levels (β = −1.79, SE = 7.88, t = −0.227, P = 0.821) nor the coefficient for VAS pain scores (β = 2.73, SE = 3.42, t = 0.796, P = 0.430) reached statistical significance, which implies that no clear relationships existed between these predictors and QoL scores.

Association between serum 25-OHD levels and QoL SF-36v2™ questionnaires

Results from the independent-samples t-test showed no statistically significant differences in QoL measures between patients with sufficient 25-OHD levels and those with deficient levels. In particular, the overall SF-36v2™ questionnaire responses regarding quality of life did not differ significantly (t(43) = 0.110, P = 0.913). The observed mean difference between the groups amounted to 0.472 (SE = 4.286). Patients in the sufficient vitamin D group had a mean score of 35.44 (SD = 14.198), while those in the deficient group had a mean score of 34.97 (SD = 13.524). Taken together, these outcomes suggest that achieving sufficient vitamin D status did not lead to significant changes in QoL scores in this sample **(Figure 2)**.

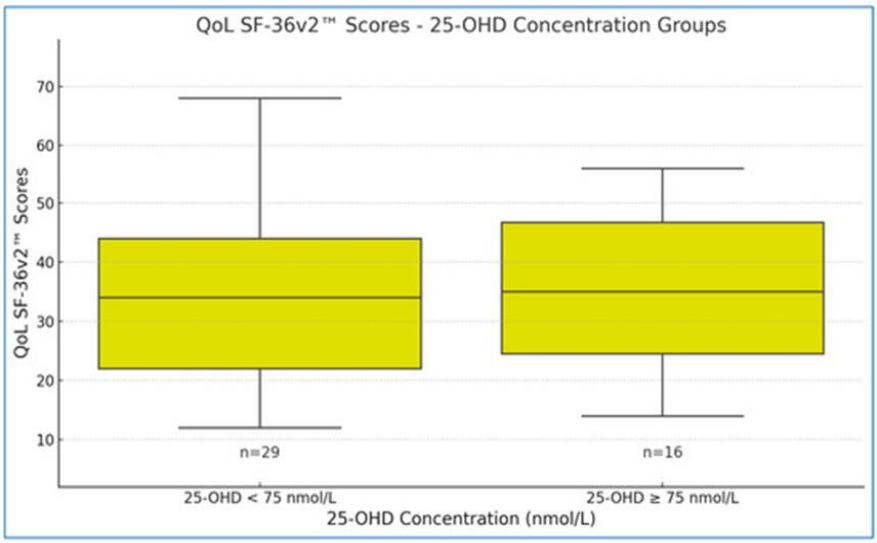

Figure 2. The association between 25-hydroxyvitamin D (25-OHD) levels and quality of life (QoL) as measured by the SF-36v2™ Questionnaire score.

Association between serum 25OHD levels and VAS pain scores

An independent-samples t-test was performed to compare VAS pain scores between two groups categorized by serum 25-OHD concentration (≥ 75 nmol/L versus < 75 nmol/L). Individuals with serum 25-OHD levels ≥ 75 nmol/L (n = 16) recorded a mean VAS pain score of 6.06 ± 2.32, whereas participants with levels below 75 nmol/L (n = 29) recorded a mean of 6.86 ± 2.10 **(Table 2)**. Normalized scores were 1.22 ± 0.571 for the first group and 0.950 ± 0.632 for the second group.

Results of the t-test showed no statistically significant difference in VAS pain scores between the groups (t(43) = 1.415, P = 0.164), with a mean difference of 0.269 (SE = 0.190). Although the sufficient vitamin D group displayed a slightly higher mean normalized VAS score (M = 1.22, SD = 0.571) than the deficient group (M = 0.950, SD = 0.632), the difference did not reach statistical significance. This finding implies that vitamin D status had no meaningful impact on pain intensity scores within this study population **(Figure 3)**.

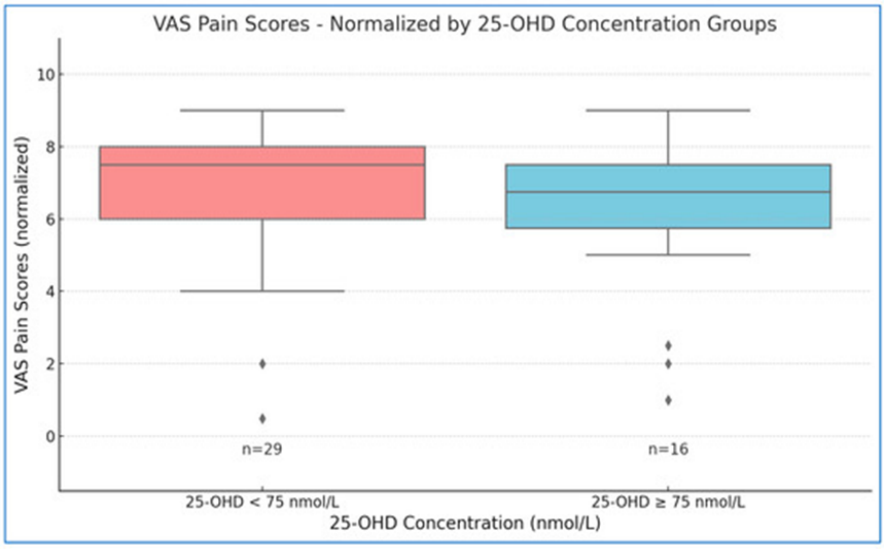

Figure 3. The association between 25-hydroxyvitamin D (25-OHD) levels and pain intensity.

Vitamin D insufficiency and deficiency remain major public health problems worldwide. Population-based studies report that roughly 40% of adults in the USA have insufficient serum vitamin D concentrations, while deficiency prevalence across Europe ranges from 13% to 60% [26-28]. In Lithuania, inadequate vitamin D status is also widespread, with estimates indicating that up to 70% of adults are affected [29, 30]. The present study reflects these broader patterns, revealing that 64.4% of the sample had 25-OHD levels below the normal threshold.

While earlier investigations have proposed an association between reduced 25-OHD concentrations and increased risk of both acute and chronic pain [12-15], this study failed to demonstrate a statistically significant association between serum 25-OHD levels and VAS pain scores. These results differ from previous reports showing that vitamin D supplementation can lower pain intensity, improve VAS scores, and decrease opioid requirements in palliative cancer patients [18, 31-34]. The lack of significant findings here underscores the multifaceted, complex interplay between vitamin D status and pain experience [12, 13, 16].

According to WHO recommendations, mild to moderate pain may be treated without strong opioids or using weak opioids such as codeine [35]. Although vitamin D supplementation might theoretically improve VAS scores for both chronic pain sufferers and clinicians [31-34], the current analysis did not identify a meaningful relationship between baseline vitamin D levels and reported pain scores. It could be speculated that providing vitamin D during detoxification would alter pain perception; however, the absence of notable differences in pain outcomes—coupled with the lack of vitamin D measurements after detoxification—prevents firm conclusions. This limitation arises because vitamin D metabolism occurs slowly [36] and the detoxification period was relatively brief, making it improbable that substantial, sustained changes in 25-OHD levels would occur.

Studies examining the influence of vitamin D on quality of life (QoL) among chronic pain patients have produced inconsistent findings. Some research indicates that supplementation may enhance physical functioning and psychological well-being [37, 38]. In contrast, other studies find little or no effect and stress that baseline vitamin D levels alone are unlikely to affect QoL without accounting for co-existing variables such as general health and pain severity [39]. In addition, routine vitamin D

supplementation appears to exert only a modest influence on QoL, with positive outcomes mainly observed in short-term clinical trials [40].

Furthermore, existing literature suggests that detectable improvements in QoL from vitamin D supplementation typically demand longer-term, consistent treatment, which is difficult to achieve or evaluate during a short detoxification program [41]. Consequently, this study may not have captured the possible extended effects of vitamin D on QoL that could emerge in research designs featuring longer follow-up periods and repeated vitamin D assessments.

The present study likewise found no statistically significant relationship between baseline 25-OHD levels and QoL scores. This outcome is in line with evidence that QoL in individuals with chronic pain is shaped by numerous interacting factors beyond vitamin D status alone [40]. The absence of a clear association in this cohort may be explained by the dominant influence of elements related to opioid dependence and the detoxification process itself—including withdrawal symptoms, psychological distress, and levels of social support—on patients' perceived quality of life during this phase.

The results of this study reveal only a weak connection between serum 25-OHD levels, pain scores, and quality of life (QoL) measures in people going through opioid detoxification. Linear regression showed that 25-OHD levels, together with baseline VAS pain scores, accounted for only a small fraction (1.5%) of the variation in QoL scores, and neither predictor reached statistical significance. This indicates that neither vitamin D status nor the severity of pain at the start of treatment has a major effect on QoL in this group, suggesting that other factors are more influential during the detoxification process.

In addition, independent-samples t-tests found no significant differences in QoL between individuals with sufficient and deficient 25-OHD levels. Scores on the SF-36v2™ questionnaire were similar in both groups, confirming that vitamin D sufficiency (defined as 75 nmol/L or above) did not have a substantial impact on perceived quality of life in this population.

Although the study explored vitamin D as a possible factor affecting pain perception, the data did not confirm a clear relationship between baseline 25-OHD levels and pain perception in patients before opioid detoxification. Interestingly, those with sufficient 25-OHD levels actually showed a slightly higher average pain score. This finding is in line with recent studies that challenge the idea of vitamin D playing a direct role in pain regulation, especially among people with chronic pain or opioid dependence.

Despite the constraints of the study, the present analysis provides useful early insights, given that it is one of the first to look at the link between baseline vitamin D levels and pain perception in chronic pain patients before they begin opioid detoxification. Although the results did not achieve statistical significance, they pointed to an interesting pattern that justifies examination in a larger sample.

Together with earlier work of which it forms a part [20], this study suggests that stopping opioid use itself, rather than baseline vitamin D status, is the main driver of changes in QoL and pain perception during detoxification. While the current focus was limited to baseline serum 25-OHD levels and their relation to pre-detoxification QoL and pain, future research should measure 25-OHD levels both before and after detoxification, preferably with bigger samples or different study designs, to investigate possible links more thoroughly.

Overall, these findings underscore the multifaceted nature of the factors shaping QoL and pain experiences during detoxification, suggesting that factors beyond baseline vitamin D levels likely exert greater influence. Future investigations should examine other biological, psychological, and social variables, using larger samples where possible, to clarify vitamin D's potential role in QoL and pain management. More studies are also needed to pinpoint what drives pain perception and determine whether add-on treatments, such as vitamin D supplementation, might help particular patient subgroups. Still, the initial results support the value of opioid detoxification for achieving meaningful pain reduction in opioid-dependent people, regardless of their starting vitamin D status.

Future work should consider these multiple influences and use adequately powered samples to more clearly define vitamin D's contribution to QoL and pain management.

Limitations

This study has several notable limitations. With only 45 patients, the small sample size may limit the extent to which the results can be generalized. In addition, because the research was conducted at a single center, questions remain about whether the findings would hold in other clinical settings, especially given regional differences in vitamin D levels.

The absence of serum 25-OHD measurements after detoxification makes it impossible to track changes in vitamin D status or to evaluate how such changes might affect pain outcomes over the course of treatment. Although the Visual Analog Scale (VAS) carries some subjective elements, it is a well-established and validated tool for assessing pain intensity, so its use here remains reasonable for documenting patients' pain experiences.

Inconsistent definitions of vitamin D deficiency and sufficiency across clinical guidelines make it harder to interpret 25-OHD results, underscoring the importance of reaching consensus in future studies. Potential

confounders such as co-existing medical conditions and the specific types of opioids used were not taken into account; however, the decision not to divide participants by pain or opioid type was made deliberately to preserve sufficient statistical power and sample size, thereby strengthening the reliability of the results.

In summary, although this study adds useful preliminary information about the links between baseline vitamin D levels, QoL, and pain in patients preparing for opioid detoxification, the listed limitations emphasize the necessity for more robust research to understand these relationships better and to improve pain management approaches in this group.

Conclusion

Baseline vitamin D levels were expected to influence pain perception and QoL in individuals suffering from chronic pain who had been using prescription opioids long-term. However, the early findings failed to show a clear connection between baseline 25-OHD levels, QoL, and pain perception.

The data instead point toward opioid withdrawal itself as the dominant factor affecting pain perception and QoL, rather than pre-existing vitamin D levels. Nevertheless, a numerical pattern emerged suggesting that higher 25-OHD levels were associated with somewhat lower pain scores, hinting at a possible link that deserves closer study. Even without statistical significance, the results highlight the potential value of checking and correcting vitamin D status in patients with chronic pain who are on long-term prescription opioids, bearing in mind that responses can differ between individuals and that the advantages of adequate vitamin D levels should not be ignored.

To clarify the potential role of vitamin D in pain management, larger, more diverse studies are needed. These should include measurements of vitamin D both before and after detoxification and should explore a range of methodological approaches. Such efforts will help generate stronger evidence and a deeper understanding of how baseline vitamin D status relates to QoL and pain perception in people who have developed tolerance to opioids. In this sense, the present study represents an initial contribution to this field and stresses the importance of continued research on these intricate relationships.

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Conflict of interest: None

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Ethics statement: This study protocol was approved by the Vilnius Regional Committee on Biomedical Research Ethics (license no. 2019/10-1153-644) on 8 October 2019. Written informed consent was obtained from all patients involved in the study before inclusion.

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