MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.59218/makrjms.2024.5.237.242

The Role of Inflammatory Markers as a Mediator Between Vitamin D and Non-specific Low Back Pain: A Prospective Study

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OPEN ACCESS

Key Words
Deficiency, hypovitaminosis D, inflammatory markers, mediation, nonspecific low back pain, vitamin D

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Received: 29 December 2023
Accepted: 27 January 2024
Published: 29 January 2024

Citation: K.M. Sandeep, K.B. Monesh and Adithya Reddy, 2024. The Role of Inflammatory Markers as a Mediator between Vitamin D and Non-specific Low Back Pain: A Prospective Study. Res. J. Med. Sci., 18: 237-242, doi: 10.59218/makrjms.2024.5.237.242

ABSTRACT

The association between Decreased Vitamin D levels and non-specific low back pain (Ns-LBP) has been established. Nonetheless, there is limited understanding regarding the potential role of inflammation as a mediator in the relationship between Vitamin D levels and Ns-LBP. To investigate the intervening effects of inflammatory markers (ESR and CRP) on the relationship between vitamin D levels and pain outcomes. Prospective study. Place of Study: Department of Orthopaedics of Raja Rajeshwari Medical College and Hospital, Bangalore. For this cross-sectional investigation, participants were chosen, including individuals with non-specific acute low back pain (Ns-ALBP, n = 30) and non-specific chronic low back pain (Ns-CLBP, n = 30). Additionally, 60 individuals without non-specific low back pain (Ns-LBP) were selected as controls within the period from April 2023 to September 2023. The study involved the examination of serum 25(OH)D levels and ESR and CRP. To assess the potential mediating effects of inflammatory markers on the connection between vitamin D and pain, regression and causal mediation analyses were employed. The average serum concentrations of vitamin D among the control, Ns-ALBP and Ns-CLBP cohorts were determined to be 22.70±10.04, 18.44±8.46 and 15.25±8.05ng/mL, respectively ($p<0.001$). Following adjustments for clinical variables, a correlation was established between vitamin D deficiency and Ns-LBP ($p<0.05$). According to mediation analysis, the overall mediated effect in Ns-CLBP patients was estimated to be -0.461 ($p<0.001$). A Prospective analysis inherently carries potential biases. This study did not explore more sensitive bio-markers. The assessment of pain intensity through the visual analogue scale unavoidably introduces a subjective element. Individuals experiencing Ns-LBP exhibited reduced vitamin D levels and elevated ESR and CRP levels. Consequently, it is imperative to conduct extensive clinical trials to explore the practical effectiveness of vitamin D supplementation in mitigating inflammation and alleviating Ns-LBP.

INTRODUCTION

Low back pain (LBP) is portrayed as a disorder essentially introducing as pain restricted in the lower back, lumbosacral and hip regions, regardless of radiation pain in the lower limits. It is very well may be sorted into three types: acute, subacute and chronic[1]. Research shows that around 80% of people will encounter shifting levels of LBP during their lifetime[2]. The reasons for pain might come from disorders in muscles, tendons, joints, intervertebral discs, vertebral bodies, nerve capability, contaminations, or aggravation. However, the most common type of LBP is non-specific low back pain (Ns-LBP)[3], which misses the mark on relationship with any basic pathology. People with non-specific acute low back pain (Ns-ALBP) may advance to non-specific chronic low back pain (Ns-CLBP), prompting huge clinical expenses, joblessness, misery and antagonistic impacts on private and social turn of events[4]. The boundless commonness of hypovitaminosis D has arisen as a worldwide general well being concern[5]. A meta-analysis[6] has laid out a connection between hypovitaminosis D and LBP, with especially articulated affiliations saw in ladies and those under 60 years of age. However, the relationship between vitamin D levels and pain stays questionable. Vitamin D assumes a pivotal part in calcium and bone metabolism, as well as in the inflammatory/immune reaction components of inflammatory disorders[7] like atherosclerosis, asthma, inflammatory bowl disease and CKD[8]. Thus, hypovitaminosis D might intensify constant pain through enhanced inflammatory cell infiltration and inflammatory cytokine release.

Different pain related pathologies, including LBP, migraine and fibromyalgia, are related with raised serum levels of inflammatory biomarkers suchas, Erythrocyte Sedimentation Rate (ESR) and C-responsive protein (CRP)[9]. The relationship between the levels of these inflammatory markers and Ns-LBP has been affirmed. For example, CRP, an acute-phase protein showing foundational irritation, was accounted for by Briggs *et al*.[12] to be raised in 15,322 patients with increased CRP (> 3.0 mg/dL), demonstrating a higher chances of encountering LBP. This peculiarity might be due to the essential job of inflammatory markers in neuronal remodeling and the improvement of damaging sensory transduction[13]. In spite of these discoveries, the causal idea of the connection between vitamin D, supportive of inflammatory biomarkers and Ns-LBP has not been totally researched. Taking into account the possible intercession of inflammatory biomarkers in LBP coming about because of lack of vitamin D, we have planned a review to evaluate vitamin D status and levels in Ns-ALBP and Ns-CLBP patients. The assembled information will illuminate vitamin D appraisal practices and assist with deciding the suitability of supplementation for reducing LBP.

MATERIALS AND METHODS

Patient population: This observational cross-sectional investigation aimed to explore the potential mediation of inflammatory biomarkers in the relationship between vitamin D levels and non-specific low back pain (Ns-LBP). Following stringent inclusion and exclusion criteria, a total of 60 patients, comprising 30 with non-specific acute low back pain (Ns-ALBP) and 30 with non-specific chronic low back pain (Ns-CLBP), were recruited through the Out Patient Department in our hospital. A control group of 60 healthy individuals, matched for age, gender, socioeconomic status and other basic demographic characteristics, was enrolled during routine health checkups at our hospital. The sampling process commenced in April 2023 and concluded in September 2023. Approval for the study was obtained from our hospital's ethics committee and written informed consent was secured from each participant. The definition of acute and subacute low back pain (LBP) did not provide a specific cutoff to distinguish between the two. Therefore, we adopted guidelines[14] that categorized acute LBP as lasting <12 weeks and chronic LBP as lasting >12 weeks.

Inclusion criteria for this study encompassed patients with Ns-ALBP and Ns-CLBP meeting diagnostic criteria for LBP[15], defined as pain between the costal angles and gluteal folds that may radiate down one or both legs. Participants were required to be over 18 years of age, participate voluntarily and provide written informed consent for the use of their complete information. Additionally, patients had to reside at a latitude between 30° and 40° north to ensure roughly equivalent exposure to light intensity.

Exclusion criteria included:

- A specific etiology of LBP diagnosed based on signs, symptoms and radiographic/magnetic resonance imaging (MRI) examination, encompassing various neoplastic diseases, trauma/fracture, inflammatory systemic diseases or infections (e.g., systemic lupus erythematosus, rheumatoid arthritis and symptomatic osteoarthritis of the hip, knee and ankle) and spine-related diseases (e.g., spondylodiscitis, lumbar disc herniation, spinal stenosis). Serious underlying cardio-cerebrovascular, blood and digestive system diseases and severe hepatorenal function damage
- Severe osteoporosis
- Pregnancy or current breast-feeding
- Undergoing treatment with estrogen, vitamin D supplementation, nonsteroidal anti-inflammatory drugs, or corticosteroids
- C-reactive protein (CRP) levels exceeding 10 mg/L, as this is indicative of acute infection and tissue damage

Data Collection and Evaluation Tools: Blood tests were gotten during patients' visits to the orthopedic clinic and an autoanalyzer gadget was used to decide serum centralizations of 25 (OH)D, ESR, CRP. Vitamin D levels were ordered as deficiency (≤20ng/mL), insufficiency (21-29ng/mL) and sufficiency (≥ 30ng/mL). Double energy X-beam absorptiometry was utilized to survey all out lumbar and hip region bone mineral density and a T score of <-2.5 demonstrated osteoporosis[16]. Lumbar spine X-ray imaging was directed utilizing an Achieva 1.5-T double X-ray imaging framework.

The seriousness of low back pain (LBP) was assessed utilizing a visual analougue scale (VAS) score[17] and practical inability and personal satisfaction were surveyed with the Modified Oswestry Disability Questionnaire (MODQ)[18], both estimated on a 100-point scale. Meetings and interviews were utilized to accumulate data on patient's age, drinking status (alcohol drinking = one standard beverage no less than one time per month: yes/no)[19], smoking history (smoked ≥400 cigarettes in a lifetime: yes/no)[20], Body mass Index (BMI), hypertension status, diabetes status, vitamin D supplementation, level of schooling, active work (practice bringing about perspiring somewhat recently: < 2 days or ≥2 days) and pain severity.

Statistical Analysis: The comparison of general demographics and inflammatory marker plasma levels among the three groups using the chi-squared test and analysis of variance, followed by a least significant difference test. The relationship between 25(OH)D and inflammatory cytokine levels and pain intensity was assessed using Spearman's correlation. To explore whether the connection between vitamin D and pain intensity might be mediated by inflammatory cytokines, we followed Baron and Kenny's guidelines[21] . Multiple regression analysis, adjusting for relevant maternal factors (age, BMI, gender ratio, hypertension, diabetes, drinking, smoking, season, level of education and physical activity), was conducted. Subsequent models examined the potential mediating role of inflammatory markers by adjusting for them to determine whether a significant vitamin D-pain intensity coefficient became non-significant. IBM SPSS Statistics version 25 was used for all data analyses and a $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSIONS

Patient Characteristics: Table 1 presents the characteristics of the study population under consideration. The 60 participants included in the study exhibited a mean age of 63.42±11.26 years, ranging from 33-80 years. No significant differences were observed among the groups concerning age, BMI, gender ratio, hypertension, diabetes, drinking, smoking, season, level of education, physical activity ($p>0.05$). However, notable differences were found in CRP, ESR and 25(OH)D levels ($p<0.05$). The mean serum 25(OH)D concentrations for the control, Ns-ALBP and Ns-CLBP groups were 22.70±10.04, 18.44±8.46 and 15.25±8.05ng mL^{-1}, respectively, with statistically significant differences noted (control vs. Ns-ALBP, $p<0.05$, control vs. Ns-CLBP, $p<0.05$). Furthermore, CRP, ESR levels were higher in the Ns-LBP group compared to the control group ($p<0.05$, see Table 1).

Association Between Vitamin D Concentration, Inflammatory Marker Levels and Pain Outcomes: In the overall study cohort, 48 individuals (48.99%) were categorized as having deficient vitamin D levels, 39 (31.31%) as insufficient and 33 (19.70%) as sufficient. However, levels of other inflammatory markers (CRP, ESR, neutrophils, WBC,) did not show significant differences across the three groups ($p>0.05$). Spearman's correlation analysis revealed a negative correlation between vitamin D and IL-6 levels in both the Ns-ALBP ($r = -0.158$, $P = 0.027$) and Ns-CLBP groups ($r = -0.426$, $p<0.001$). Conversely, CRP, ESR, neutrophil, WBC levels were not correlated with vitamin D levels ($P > 0.05$). In patients with Ns-CLBP, VAS and MODQ scores exhibited a negative correlation with vitamin D levels ($r = -0.317$ and -0.310, $p<0.001$), while in Ns-ALBP, no significant correlations were observed ($r = -0.123$ and -0.106, $p>0.05$).

Exploratory analysis of potential role of inflammatory markers: When incorporating age, BMI, gender ratio, hypertension, diabetes, drinking, smoking, season, level of education and physical activity as covariates in the multiple logistic regression, vitamin D emerged as a significant predictor of both non-specific acute low back pain (Ns-ALBP) (OR = 0.93, P = 0.002) and non-specific chronic low back pain (Ns-CLBP) (OR = 0.95, P = 0.017). However, upon adjusting for inflammatory markers such as CRP, ESR, neutrophils, WBC, the association between 25(OH)D levels and baseline pain became insignificant.

Our study's key discoveries demonstrate a vital negative relationship between 25(OH)D levels and pain intensity in patients with non-specific low back pain (Ns-CLBP). As far as anyone is concerned, this examination is the debut study looking at the association between lack of vitamin D and low back pain, explaining the job of inflammatory cytokines as intermediaries. The raising prevalence of hypovitaminosis D has turned into a worldwide concern, connecting it to an increased risk of developing infection, breast cancer, atherosclerosis, ongoing renal illness and other muscluloskeletal pain. Various investigations have focused on the relationship between hypovitaminosis D and Non-specific low back

Table 1: Demographic charecteristics of the 3 groups based on pain status

Characteristic	No pain (n = 60)	Ns-ALBP (n = 30)	Ns-CLBP (n = 30)	P-Value
Age (year)	62.31±11.06	64.46±10.45	63.17±12.49	0.531
Body mass index (kg/m^2)	24.80±2.90	23.94±2.93	23.64±3.22	0.090
Gender (Men/Women)	18/42	8/22	10/20	0.104
Diabetes (Yes)	20 (33.3%)	17 (28.3%)	19 (24.4%)	0.510
Hypertension (Yes)	19 (31.7%)	20 (33.3%)	24 (30.8%)	0.949
Smoking (Yes)	8 (13.3%)	10 (16.7%)	16 (20.5%)	0.537
Drinking (Yes)	11 (18.3%)	15 (25%)	17 (21.8%)	0.675
Level of education				
< High school	31 (51.7%)	34 (56.7%)	49 (62.8%)	
> High school	29 (48.3%)	26 (43.3%)	29 (37.2%)	
Level of physical activity				0.898
< 2 times/week	49 (81.7%)	47 (78.3%)	62 (79.5%)	
≥ 2 times/week	11 (18.3%)	13 (21.7%)	16 (20.5%)	
VAS	-	38.64±9.26	35.28±11.56	
MODQ	-	33.81±9.47	31.38±8.37	
CRP,ng/mL	4.43±0.52	5.99±2.56a	5.14±2.36a, b	< 0.001
Neutrophils,ng/mL	3.61±2.05	4.38±6.94	4.00±2.07	0.628
WBC,ng/mL	5.82±2.44	5.86±1.84	6.15±2.42	0.659
25(OH)D levels	25.70±10.04	21.44±8.46a	18.25±8.05a, b	< 0.001
Deficiency (≤ 20 nmol/L)	19 (31.7%)	15 (50.0%)	14 (46.6%)	
Insufficient (20-30 nmol/L)	17 (28.3%)	10 (35.0%)	12 (40%)	
Normal (= 30 nmol/L)	24 (40%)	5 (15%)	4 (13.4%)	

pain (Ns-LBP). Panwar *et al*.[24] revealed a higher frequency of lack of vitamin D among patients with chronic and subacute low back pain, joined by raised VAS and MODQ scores. Ghai *et al*.[25] noticed relief from discomfort and further developed usefulness in ongoing low back pain patients following vitamin D supplementation. However, clashing perspectives exist in regards to the relationship between serum 25(OH)D levels and persistent low back pain, as confirmed by Thörneby *et al*.[26].

Ghai, *et al*.[27] tracked down that among 328 patients, 217 (66%) of patients with CLBP had lack of vitamin D, in any case, the review coming up short on demographically matched control bunch, accordingly, it is hard to reach firm determinations in regards to predominance. A new meta-analysis has tracked down existing lower quality proof to help the connection between lack of vitamin D and Ns-CLBP[28]. Therefore, it is of great importance to perform large sample, prospective, randomized controlled studies to explore the effect of serum vitamin D level on Ns-ALBP and Ns-CLBP, avoiding confounding factors, such as latitude and race. Our study may help provide evidence further supporting this relationship. Vitamin D assumes a critical part in the etiology and supportive of progression of different persistent pain conditions through its physical, hormonal, neurological and immunological impacts on the body [29,30]. In the first place, von Känel *et al*.[31] observed that lower vitamin D fixations were associated with expanded fringe and focal torment sensitivity during mechanical excitement in patients with CLBP.

This might be on the grounds that vitamin D usefully affects neurite and astrocyte outgrowth and relieves neuropathic pain by balancing opiod signaling [32,33]. The more by and large acknowledged view is that the advantageous impacts of vitamin D on pain are intervened by inflammatory cytokines. A new methodical survey detailed that the concentration CRP and ESR decidedly correlates with the seriousness of Ns-LBP, emphatically connects with the presence of Ns-LBP[34]. Ngo *et al*.[36] found that in 253 healthy people aged 51-77 years had vitamin D levels which negatively correlated with high-sensitivity C-reactive protein (hsCRP) levels. Our study additionally had a few constraints. In the first place, the cross-sectional nature of as far as possible its capacity to identify direct relationship between vitamin D, inflammatory cytokines, pain intensity and functional disability. In any case, we can't ignore that low vitamin D levels might be recommended to be a biomarker of poor healthy resulting from inflammatory process. Second, some more sensitive biomarkers that were not accessible for our review included dissolvable IL-6 receptors (sIL6r and sgp130), solvent TNF receptors, (sTNFR1 and sTNFR2) and hsCRP levels. These cytokines might be smarter to clarify the connection between vitamin D with numerous provocative biomarkers and the aggravation framework. Last, assessment of pain intensity utilizing the VAS score framework is unavoidably subjective. Contrasts in scope, race and dietary circumstances might imply that the outcomes can't be summed up to broadly various populaces. Further examinations are as yet required. In spite of these impediments, our review was quick to show that fiery markers might intercede the connection between vitamin D and Ns-LBP. We accept that our information are clinically valuable for spinal specialists and pain physicians assessing vitamin D status and feature new restorative methodologies in patients with Ns-LBP patients later on.

CONCLUSION

Our study showed that patients with Ns-LBP have a high prevalence of hypovitaminosis D and elevated levels of inflammatory cytokines. Hypovitaminosis D is likewise connected with more elevated levels of inflammatory cytokines and higher

VAS scores. This relationship between hypovitaminosis D and Ns-CLBP might be intervened by ESR and CRP. Therefore, huge scope for clinical preliminaries are justified to research the clinical viability of vitamin D and ease Ns-LBP. In any case, its advantage for Ns-LBP can't be underestimated in view of the intervention of the provocative pathways examined in this review. The systems hidden in this relationship ought to keep on being investigated.

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