Association of Vitamin D with Haematological Inflammatory Indices in Patients with Back Pain

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ABSTRACT

Objective: To assess the relationship between vitamin D and haematological inflammatory indices (HII) in chronic low back pain (CLBP) patients.

Study Design: Descriptive study.

Place and Duration of the Study: Harran University Hospital, Sanliurfa, Turkiye, between September 2023 and February 2024.

Methodology: A total of 100 CLBP patients were divided into three groups according to their vitamin D levels as deficiency (<20 µg/L), insufficiency (20-30 µg/L), and sufficiency (30-80 µg/L). Demographic characteristics, serum parameters, and HII were compared among the three groups. Additionally, the association between vitamin D and other parameters were investigated.

Results: The three groups were similar in terms of age (p = 0.640), gender distribution (p = 0.057), body mass index (BMI, p = 0.855), C-reactive protein (CRP, p = 0.965), leucocyte count (p = 0.979), neutrophil count (p = 0.525), lymphocyte count (p = 0.246), monocyte count (p = 0.485), platelet count (p = 0.878), and HII including neutrophil-to-lymphocyte ratio (NLR, p = 0.335), monocyte-to-lymphocyte ratio (MLR, p = 0.227), platelet-to-lymphocyte ratio (PLR) (p = 0.898), neutrophil-to-lymphocyte*platelet ratio (NLPR, p = 0.543), systemic inflammatory index (SII, p = 0.300), systemic inflammatory response index (SIRI, p = 0.187), and aggregate index of systemic inflammation (AISI, p = 0.219). No significant correlation was found between vitamin D concentration and other parameters (p >0.05).

Conclusion: The coexistence of vitamin D deficiency and increased HII may accompany inflammatory conditions. However, no significant association was found between vitamin D level and HII in non-inflammatory CLBP.

Key Words: *Inflammation, Low back pain, Neutrophil, Complete blood count, Vitamin D*.

How to cite this article: Ozkan Y, Alpayci M, Delen V. Association of Vitamin D with Haematological Inflammatory Indices in Patients with Back Pain. *J Coll Physicians Surg Pak* 2024; **34(11)**:1815-1818.

INTRODUCTION

Vitamin D is a nutrient and hormone with immunomodulatory and anti-inflammatory effects.[1] Although the paramount importance of vitamin D has been revealed in calcium balance and skeletal diseases,[2,3] there has been a substantial change in the semantics of vitamin D over time. Today, the anti-inflammatory and immunomodulatory effects of vitamin D are better understood.[4] Vitamin D receptors are located in almost all parts of the body, and many diseases such as osteoporosis, osteomalacia, dermatoporosis, multiple sclerosis, diabetes mellitus, rheumatoid arthritis, inflammatory bowel diseases, and cancer are associated with diminished protective effects of vitamin D including anti-inflammatory and immunomodulatory functions.[2-5]

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Received: May 09, 2024; Revised: August 15, 2024; Accepted: October 04, 2024
DOI: https://doi.org/10.29271/jcpsp.2024.11.1815

Haematological inflammatory indices (HII) are popular indexes derived from blood cells, typically known as easy, simple, objective, reproducible, and inexpensive laboratory indicators. Commonly known HII include neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte*platelet ratio (NLPR), neutrophil*platelet-to-lymphocyte ratio, also known as SII (systemic inflammatory index), neutrophil*monocyte to lymphocyte ratio, also known as SIRI (systemic inflammatory response index), and neutrophil*platelet*monocyte to lymphocyte ratio, also known as AISI (aggregate index of systemic inflammation).[6-8] It has been reported that HII can be used as diagnostic,[9] prognostic,[7] and predictive[8] markers in numerous clinical conditions.

Literature on the relationship between vitamin D and HII is limited. In various clinical conditions such as diabetes mellitus[10] and ischaemic heart disease,[11] it has been reported that HII is significantly higher in patients with lower vitamin D concentrations. Additionally, the studies reported inverse correlations between HII and serum vitamin D levels. In some other studies, the coexistence of vitamin D deficiency and high HII has been shown in obesity[12] and osteoporosis.[3] Considering

that vitamin D deficiency[13] and osteoporosis[14] are associated with low back pain, it can be hypothesised that an expressive relationship and inverse correlation between vitamin D and HII may be seen in chronic low back pain (CLBP). Therefore, the present study aimed to test this hypothesis.

If this relationship can be demonstrated, HII, which are accessible blood tests in every healthcare centre, may be utilised to predict vitamin D status, particularly in situations where it is not possible to assess vitamin D levels.

METHODOLOGY

This descriptive study was conducted at Harran University, Medical School Hospital, between September 2023 and February 2024, in accordance with the principles of the Declaration of Helsinki. An ethical approval was obtained from the Clinical Research Ethics Committee of the Harran University (REC No.: HRU/24.01.38).

A total of 100 cases with CLBP were divided into three groups based on their vitamin D levels: (i) Deficiency (n = 49), (ii) Insufficiency (n = 27), and (iii) Sufficiency (n = 24). Patients' data were obtained from medical records of the hospital. Demographic and clinical data of the patients were retrieved from their medical records. Laboratory parameters including C-reactive protein (CRP), and leucocyte, neutrophil, lymphocyte, monocyte, and platelet counts were recorded for each patient. Subsequently, HII including NLR, MLR, PLR, NLPR, SII, SIRI, and AISI were calculated from these parameters. It is known that HII is valuable biomarkers towards diagnosis, prognosis, and mortality prediction in various different diseases.[7-9]

Inclusion criteria were diagnosis of CLBP, age between 18 and 65 years, and provision of written informed consent. Patients with mechanical, non-specific, and non-inflammatory CLBP were included in the study. Exclusion criteria were traumatic or inflammatory low back pain, spinal anatomical abnormalities such as fracture, scoliosis, fusion or deformity, inflammatory rheumatic disorders (e.g., rheumatoid arthritis and ankylosing spondylitis), infection, malignancy, lactation, pregnancy, mental diseases, severe anaemia (haemoglobin<8 g/dL), and severe obesity (BMI ≥35 Kg/m^2).

Serum vitamin D level was measured using the Elecsys Vitamin D total III assay, which allows for *in vitro* quantitative method for measuring total 25-hydroxyvitamin D, which is the major circulating form of vitamin D and also the most ideal marker of vitamin D obtained from both cutaneous and dietary sources.[15] The assay included three incubation reactions based on the competition principle, and the results were determined *via* curves. Based on the results, serum vitamin D levels were graded as deficiency (<20 µg/L), insufficiency (20-30 µg/L), and sufficiency (30-80 µg/L). The patients were grouped based on this classification. The groups were statistically compared with regard to their demographic characteristics, serum parameters, and HII. In addition, correlations between vitamin D levels and these parameters were analysed.

Statistical analyses were performed using SPSS for Windows version 27.0. Normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Since all the variables in all three groups had normal distribution, One-Way ANOVA test was used for comparing variables among the three groups. However, when the normality test was applied to all patients as one group (n = 100), CRP values and AISI scores exhibited non-normal distribution, for which Pearson's and Spearman's correlation tests were used. Continuous variables were presented as mean ± standard deviation (SD) (min.-max.). Categorical variables were compared using the Chi-Square test and were presented as frequencies (n) and percentages (%). A p-value of <0.05 was considered significant.

RESULTS

The study comprised 100 patients, including 49 (49%) patients who had deficiency, 27 (27%) patients who had insufficiency, and 24 (24%) patients who had sufficient vitamin D levels.

Table I presents a statistical comparison of demographic characteristics, CRP, vitamin D, and serum parameters among the three groups. These three groups were similar in terms of age (p = 0.640), gender distribution (p = 0.057), body mass index (BMI) (p = 0.855), CRP (p = 0.965), leucocyte count (p = 0.979), neutrophil count (p = 0.525), lymphocyte count (p = 0.246), monocyte count (p = 0.485), and platelet count (p = 0.878).

Table I: Statistical comparisons according to serum vitamin D levels.

	Deficiency (<20 µg/L) (n = 49)	Insufficiency (20-30 µg/L) (n = 27)	Sufficiency (>30 µg/L) (n = 24)	p-value
Age, years	43.88 ± 10.19 (23-64)	45.59 ± 12.05 (23-64)	42.75 ± 10.90 (18-57)	0.640
Gender, F/M, n(%)	38(77.5)/11(22.5)	15(55.6)/12(44.4)	13(54.2)/11(45.8)	0.057
BMI, kg/m^2	27.6 ± 2.7 (20.96-34.5)	27.8 ± 3.8 (21.6-34.9)	27.3 ± 3.1 (22.0-34.9)	0.855
CRP, mg/L	3.05 ± 2.35 (0.24-9.13)	3.19 ± 2.46 (0.17-10.2)	3.14 ± 2.16 (1.0-8.4)	0.965
Vitamin D, µg/L	12.08 ± 4.3 (2.3-19.6)	23.6 ± 3.09 (20.6-29.5)	39.7 ± 5.6 (31.2-53.8)	<0.001
Leucocyte (10^3/mL)	7.31 ± 1.65 (3.99-10.49)	7.27 ± 1.12 (5.47-9.5)	7.24 ± 1.37 (3.99-10.7)	0.979
Neutrophil (10^3/mL)	4.16 ± 1.32 (1.95-7.16)	4.14 ± 1.01 (2.51-6.46)	3.84 ± 0.98 (2.12-6.40)	0.525
Lymphocyte (10^3/mL)	2.51 ± 0.62 (1.48-4.09)	2.28 ± 0.34 (1.77-3.18)	2.47 ± 0.65 (1.40-3.75)	0.246
Monocyte (10^3/mL)	0.54 ± 0.20 (0.26-1.35)	0.55 ± 0.12 (0.36-0.70)	0.50 ± 0.11 (0.26-0.70)	0.485
Platelet (10^3/mL)	291.0 ± 63.9 (181-452)	283.3 ± 64.7 (179-442)	286.3 ± 68.3 (180-417)	0.878

Values were presented as mean ± SD (min.-max.) or n(%).

Table II: Statistical comparisons of HII among groups.

	Deficiency (<20 µg/L) (n = 49)	Insufficiency (20-30 µg/L) (n = 27)	Sufficiency (>30 µg/L) (n = 24)	p-value
NLR	1.74 ± 0.65 (0.58-4.06)	1.86 ± 0.54 (0.79-3.40)	1.61 ± 0.44 (0.88-2.66)	0.335
MLR	0.22 ± 0.07 (0.08-0.42)	0.25 ± 0.06 (0.14-0.35)	0.22 ± 0.08 (0.12-0.44)	0.227
PLR	121.7 ± 32.6 (51.4-206.4)	125.7 ± 28.3 (77.2-172.5)	123.3 ± 48.5 (76.9-297.9)	0.898
NLPR	0.006 ± 0.003 (0.0-0.02)	0.007 ± 0.002 (0.0-0.01)	0.006 ± 0.003 (0.0-0.01)	0.543
SII	505.9 ± 207.2 (129.2-996.3)	515.1 ± 164.3 (245.4-1084.6)	445.2 ± 107.0 (278.1-677.2)	0.300
SIRI	0.95 ± 0.52 (0.34-2.61)	1.04 ± 0.42 (0.46-1.97)	0.81 ± 0.32 (0.49-1.86)	0.187
AISI	286.9 ± 184.3 (66.9-995.5)	284.9 ± 112.6 (95.7-629.1)	225.3 ± 86.4 (133.9-474.0)	0.219

*NLR: Neutrophil / lymphocyte; MLR: Monocyte / lymphocyte; PLR: Platelet / lymphocyte; NLPR: Neutrophil / (lymphocyte*platelet); SII (neutrophil*platelet / lymphocyte): Systemic inflammatory index; SIRI (neutrophil*monocyte / lymphocyte): Systemic inflammatory response index; AISI (neutrophil*platelet*monocyte / lymphocyte): Aggregate index of systemic inflammation.*

Table III: Statistical correlations of vitamin D with blood cells, CRP, and HII.

(n = 100)	Leucocyte	Neutrophil	Lymphocyte	Monocyte	Platelet	CRP
r	-0.007	-0.078	-0.063	-0.030	-0.048	-0.051
p	0.947	0.438	0.535	0.764	0.635	0.615
(n = 100)	**NLR**	**MLR**	**PLR**	**NLPR**	**SII**	**SIRI**
r	-0.043	0.099	0.038	0.013	-0.092	-0.032
p	0.673	0.328	0.704	0.895	0.364	0.755

*NLR: Neutrophil / lymphocyte; MLR: Monocyte / lymphocyte; PLR: Platelet / lymphocyte; NLPR: Neutrophil / (lymphocyte*platelet); SII (neutrophil*platelet / lymphocyte): Systemic inflammatory index; SIRI (neutrophil*monocyte / lymphocyte): Systemic inflammatory response index; AISI (neutrophil*platelet*monocyte / lymphocyte): Aggregate index of systemic inflammation.*

Table II presents a comparison of HII among the three groups. The three groups were similar in terms of NLR (p = 0.335), MLR (p = 0.227), PLR (p = 0.898), NLPR (p = 0.543), SII (p = 0.300), SIRI (p = 0.187), and AISI (p = 0.219).

Table III presents statistical correlations of serum vitamin D levels with serum parameters, CRP, and HII. No significant correlation was found between vitamin D levels and these parameters (p >0.05 for all).

DISCUSSION

In this observational comparative study, HII was evaluated according to serum vitamin D levels in cases with CLBP. The results indicated that all three groups were similar in terms of HII and no significant correlation was found between serum vitamin D levels and these indices. Therefore, no significant relationship between HII and serum vitamin D concentration was found in CLBP patients. However, it is worth mentioning that, as this is the first study on this subject matter, its limitations should be considered, and its results need to be substantiated by the future studies.

Literature indicates that high HII levels are manifestations of systemic inflammation and can present inflammatory background of various diseases, such as restless leg syndrome[16] and depression,[17] which are also known to be associated with vitamin D deficiency.[18,19] Additionally, previous studies have reported an inverse correlation between HII and serum vitamin D concentrations in various clinical conditions.[11,20] Likewise, high HII and low vitamin D concentrations have been demonstrated in both obesity[12] and osteoporosis.[3] Considering the association between low back pain and low vitamin D levels[13] and osteoporosis,[14] a relationship and a negative correlation between vitamin D and HII might be evident in CLBP. Accordingly, the present study focused on this potential relationship.

To date, HII have been suggested as diagnostic,[9] prognostic,[7] and predictive[8] indicators in various conditions including inflammation. However, there is limited literature on the relationship between vitamin D and HII, and to the authors' knowledge, this relationship has not yet been addressed in CLBP patients.

The present study revealed that although the three groups varied in terms of vitamin D levels, they were similar in terms of the HII evaluated in the study. Moreover, there was no significant correlation between HII and vitamin D concentration. Accordingly, the hypothesis was not confirmed by the results, which may be due to the inclusion of non-inflammatory and exclusion of inflammatory causes of CLBP. On the contrary, coexistence of high HII and low vitamin D levels have been demonstrated in newborns,[20] Diabetes mellitus,[10] and ischaemic heart disease.[11] This contradiction may be associated with the anti-inflammatory and immuno- modulatory role of vitamin D[4] and the inflammatory nature of the clinical conditions evaluated in those studies.[10,11,20] In these clinical conditions, coexistence of high HII and low vitamin D levels may be a manifestation of reduced anti-inflammatory effect of vitamin D.[4] On the other hand, these conditions may have caused vitamin D deficiency.

This study has several limitations. First, it was a single-centred study and had a small sample size, both of which may have limited its generalisability and statistical power. Second, its retrospective design may have resulted in limited data. Finally, there was no control group and thus, the authors could not determine if the results were specific to CLBP.

CONCLUSION

The coexistence of high HII and low vitamin D levels may accompany inflammatory conditions. Nonetheless, a relationship between HII and vitamin D was not seen in non-inflammatory CLBP.

ETHICAL APPROVAL:
The Ethics Committee of Harran University, School of Medicine approved the study with the protocol number HRU/24.01.38, dated 12 February 2024.

PATIENTS' CONSENT:
The study was conducted on the medical record of patients who had provided informed consent.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
YO, MA, VD: Conceptualised the study and drafted the manuscript.
VD: Cared for patients and provided samples and revised the manuscript critically.
YO, MA: Performed the statistical analysis and revised the manuscript critically.
All authors approved the final version of the manuscript to be published.

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