Original Article

Exploring the Role of Vitamin D2, Parathyroid Hormone, and C-Peptides as Biomarkers in Diabetic Neuropathy Development

Ban Mahmood Shaker Al-Joda, Hayder Abdul-Amir Makki Al-Hindy[1], Mazin J. Mousa[2]

Department of Chemistry and Biochemistry, College of Medicine, University of Babylon, [1]Department of Pharmacology & Toxicology, College of Pharmacy, University of Babylon, [2]Department of Clinical Laboratories, College of Pharmacy, University of Babylon, Babylon, Iraq

Abstract

Background: Diabetic neuropathy affects significant individuals worldwide and is considered a chronic complication of diabetes. However, the exact mechanisms underlying the development of diabetic neuropathy are still not fully understood. **Objectives:** This study investigated the involvement of vitamin D2, PTH, and C-peptide in the onset of diabetic neuropathy. **Materials and Methods:** This study included 120 diabetic patients and 30 healthy controls. Diabetic patients were divided into group 1 with neuropathy (N = 80) and group 2 without neuropathy (N = 40). The following data were incorporated: sex, age, diabetes duration, and BMI. Biochemical evaluations involved HbA1C, C-peptide, PTH, and vitamin D2. **Results:** The study's population had a 52.2 ± 13.9 years mean age. Patients had 9.8 years average diabetes duration, were mostly overweight, and were poorly controlled (mean HbA1C = 8.8). Vitamin D2 was insufficient, particularly in diabetics, and C-peptide measures were markedly low. There were differences in the three parameters between diabetes and controls. Potential relationships among the parameters were detected namely, higher HbA1C, elder, lower vitamin D2, besides higher C-peptide and vitamin D2 levels. ROC-curve metrics for vitamin D2, PTH, and C-peptide, revealed varied diagnostic potential. All parameters were unable to distinguish between patients with or without neuropathy from healthy subjects. **Conclusion:** The study highlights the importance of glycemic control, insulin production, PTH, and vitamin D2 levels in the context of diabetic neuropathy. While these biomarkers show associations with neuropathy risk, their diagnostic potential is still limited. The associations between age, HbA1C levels, PTH, C-peptide levels, and vitamin D2 levels provide valuable insights into potential contributors to neuropathy risk.

Keywords: C-peptide, diabetes, HbA_1C, neuropathy, PTH

Introduction

Diabetic neuropathy, chronic sequelae of DM, affects a considerable proportion of the population worldwide.[1,2] It is characterized by neuronal damage that leads to numerous sensory-motor, and autonomic impairments. Despite widespread research, the detailed pathogenesis underlying the development of diabetic neuropathy remains moderately understood.[3] Evolving evidence suggests that numerous factors, including oxidative stress, metabolic derangements, and inflammation, contribute to the evolution of this debilitating pathology.[4] In recent years, a growing body of research has focused on the potential contributions of vitamin D2, PTH, and C-peptides as markers in the development and progression of diabetic polyneuropathy.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_1568_23

The interaction between PTH, vitamin D2, and C-peptide holds promise as an intricate but potentially valuable avenue for understanding the pathogenesis of diabetic polyneuropathy. Vitamin D2, a fat-soluble secosteroid, plays a crucial role in preserving bone health, immune function, and calcium homeostasis.[5-7] However, revisions have shown its additional contribution in modulating inflammation, oxidative stress, and neuronal physiology, hence showing a broad spectrum of pleiotropic effects.[8,9]

Address for correspondence: Dr. Ban Mahmood Shaker Al-Joda, Department of Chemistry and Biochemistry, College of Medicine, University of Babylon, Babylon 51001, Iraq.
E-mail: aljodaban@gmail.com

Submission: 15-Oct-2023 **Accepted:** 16-Dec-2023 **Published:** 17-Jul-2024

How to cite this article: Al-Joda BMS, Al-Hindy HAM, Mousa MJ. Exploring the role of vitamin D2, parathyroid hormone, and C-peptides as biomarkers in diabetic neuropathy development. Med J Babylon 2024;21:438-43.

Vitamin D deficiency has been associated with into the undean increased risk of several complications, including diabetic neuropathy. Studies have sightseen the associations between vitamin D2 measures and neuropathic manifestations, shedding light on its latent neuroprotective properties.[10]

Parathyroid hormone, a regulator of phosphate and calcium homeostasis,[5] has garnered attention for its potential participation in neuropathic processes. Emergent research suggests that altered PTH concentrations may contribute to neural dysfunction, oxidative stress, and inflammation, all of which are implicated in diabetes neuropathy.[11] The intricate association between PTH and vitamin D adds intricacy to their mutual effects on neuropathogenesis. Investigating the interplays between PTH, vitamin D2, and neuropathic pathways may deliver valuable understanding of the underlying mechanisms.

C-peptide, a byproduct of insulin biosynthesis, has gained appreciation beyond its role in diabetes management. While traditionally seen as a biomarker of insulin release, current reviews have highlighted its potential neuroprotective effects.[12] In parallel, as assays have become more sensitive, C-peptide has been shown to mitigate inflammation, oxidative stress, and apoptosis, processes implicated in diabetic neuropathy pathogenesis.[13,14] The exploration of C-peptide's multilayered role, predominantly its influence on neurovascular physiology and neuronal growth, provides a novel perspective on its significance as a biomarker for neuropathy risk evaluation.

This study aims to assess the roles of vitamin D2, PTH, and C-peptides as potential biomarkers in the development and progression of diabetic neuropathy to provide a deeper understanding of their contributions to neuropathic processes. This insight could offer a foundation for future research endeavors aimed at developing targeted interventions for preventing, diagnosing, and treating diabetic neuropathy.

Materials and Methods

Subjects sampling

This case-control study was carried out between February and August of 2022. While the biochemical analyses were carried out in the College of Pharmacy, University of Babylon, the blood samples were taken from patients (ages ranging from 30 to 70 years) in the Department of Diabetic Center at Merjan Medical City in Babylon Governorate, Iraq.

The sample size was 150 people, comprising patients with type II diabetes (N = 120) and healthy controls (N = 30). Two categories of diabetic patients have been defined. DM with diabetic neuropathy made up group 1 (N = 80), while DM without neuropathy made up group 2 (N = 40). In the Diabetic Centre, patients with diabetic neuropathy were admitted and carefully assessed based on their medical histories, clinical manifestations, and findings from nerve conduction tests. The healthy controls and the diabetic patients had the same sex. The study excluded participants who had type 1 DM, gestational diabetes, hepatic disorders, chronic heart disease, endocrine abnormalities, or chronic renal disease.

The subjects' age, sex, DM duration (months), weight (kg), height (m^2), and BMI were all recorded. In addition, once hematogenous samples from each participant were drawn, the biochemical evaluation of HbA_1C, C-peptide, PTH, and vitamin D levels was performed.

Biochemical evaluations

High-performance liquid chromatography (HPLC) was used to quantify the serum levels of glycated hemoglobin (HbA_1C). A C-Peptide ELISA Kit from the California-based Calbiotech Incorporation was used to measure the C-peptide. By using particular ELISA-Kits from Elabscience Biotechnology Ltd. TX, USA, PTH, and vitamin D3 were both tested.

Ethics approval

The Marjan Hospital's local ethical committee and the Babylon Health Directorate's ethical committee both gave their approval for the study and sampling procedure. Before the collection of samples, verbal consent was acquired from each patient.

Statistical analysis

All statistical calculations were performed using Microsoft Excel (2017, Microsoft Corp., Redmond, WA, USA) and IBM SPSS Statistics for Windows, Version 21. The data were all available as mean ± SD. It was statistically significant at P = 0.05. The presence of significant differences was estimated using the analysis of variance test. Regression analysis to determine whether correlations exist. Chi-square test to assess the variables that are categorically related.

Results

The study's population had a mean age of 52.2 ± 13.9 years, with the diabetic group being older than the control groups. The majority of the patients had DM for an average of 9.8 years and most of them were considered overweight. With a mean HbA_1C of 8.8, the diabetic group does not appear to be well controlled. The mean serum vitamin D levels were insufficient in the majority of cases, especially in diabetic individuals. C-peptide levels were also extremely low in the group of diabetics.

Table 1 provides valuable insights into the differences in various parameters among individuals with diabetes with and without neuropathy, and a control group. The statistical significance of these differences suggests potential factors

Table 1: Variations of main characteristics among the study groups

Variables	Diabetes with neuropathy ($N = 80$) Mean ± SE	Diabetes without neuropathy ($N = 40$) Mean ± SE	Control ($N = 30$) Mean ± SE	*P* value
Age (years)	59.4 ± 9.1	53.9 ± 9.9	30.9 ± 7.2	0.003
Male/female	37/43	18/22	15/15	0.92
BMI (kg/m^2)	27.9 ± 0.7	28.90 ± 0.8	27.2 ± 0.9	0.444
Duration of DM (years)	16.1 ± 6.6	4.2 ± 2.1	–	0.006
HbA_1C (%)	9.4 ± 2.3	10.5 ± 2.4	5.2 ± 0.1	0.000
C-peptide (ng/mL)	1.2 ± 0.1	1.7 ± 0.2	1.96 ± 0.3	0.002*
PTH (pg/mL)	10.7 ± 0.9	9.9 ± 0.9	8.32 ± 0.9	0.28
Vit D2 (ng/mL)	8.7 ± 0.5	10.5 ± 1.4	45 ± 2.0	0.001

*P value ≤ 0.01 by *post hoc* multiple comparisons among the three study groups

Table 2: Correlations of the study variables among each other's

Variables	Correlation	PTH	Vitamin D2	C-peptide	HbA_1C	BMI	Duration of DM	Age
PTH (pg/mL)	*r*	1						
	P							
Vitamin D2 (ng/mL)	*r*	−0.130	1					
	P	0.112						
C-peptide (ng/mL)	*r*	−0.010	0.267**	1				
	P	0.903	0.001					
HbA_1C (%)	*r*	0.158	−0.615**	−0.063	1			
	P	0.053	0.000	0.447				
BMI (kg/m^2)	*r*	0.075	−0.069	0.000	0.104	1		
	P	0.359	0.402	0.997	0.206			
Duration of DM (years)	*r*	0.092	−0.054	−0.159	−0.068	−0.06	1	
	P	0.318	0.553	0.082	0.460	0.512	0.001	
Age (years)	*r*	0.016	−0.676**	−0.177*	0.513**	0.01	0.291**	1
	P	0.848	0.000	0.030	0.000	0.904	0.001	

contributing to the development of neuropathy in diabetes patients, including age, diabetes duration, HbA_1C levels, C-peptide levels, and vitamin D2 levels.

Table 2 provides insights into the correlations between various variables in the study. It suggests potential relationships, such as the association of higher HbA_1C levels with older age and lower vitamin D2 levels, as well as the connection between higher C-peptide levels and higher vitamin D2 levels.

Tables 3–5 present performance metrics for various variables: PTH, vitamin D2, and C-peptide using ROC-curve metrics. The AUC values suggest varying levels of effectiveness in distinguishing between diabetic patients without neuropathy from healthy control for the different variables. While PTH and C-peptide show limited discrimination, vitamin D2's AUC is very low. None of the three biomarkers demonstrate strong diagnostic potential for distinguishing between diabetic patients with neuropathy and those without neuropathy.

Discussion

Diabetic neuropathy, a common complication of DM, poses noteworthy challenges due to its impact on patient's quality of life and healthcare systems.[1] In the current study, the researchers investigated potential factors contributing to the development of neuropathy in diabetes patients, focusing on age, diabetes duration, serum levels of HbA_1C, C-peptide, PTH, and vitamin D2 levels. The findings highlight the association between these factors and their potential diagnostic significance in identifying diabetic patients at risk of neuropathy.

The main outcomes of the current study were highly significant differences in the concentrations of vitamin D2 and C-peptide between the two diabetic groups. There was an association between higher HbA_1C levels with older age and lower vitamin D2 levels, as well as an association between higher C-peptide levels and vitamin D2 levels. None of the three biomarkers demonstrate a strong diagnostic potential for distinguishing between diabetic patients with neuropathy and those without neuropathy.

The study's population, characterized by a mean age of 52.2 ± 13.9 years, demonstrated a higher age in the diabetic group compared to the control group. This difference could suggest that age may contribute to neuropathy development, aligning with previous research indicating

Table 3: Ability of PTH, vitamin D2, and C-peptide to differentiate diabetic patients without neuropathy (*N* = 80) from healthy control (*N* = 30)

Variables	AUC	Sensitivity	Specificity	Significance	95% CI	
PTH	0.579	0540	0.60	0.262	0.443	0.714
Vitamin D2*	0.015	0.95	0.92	0.001	0.001	0.037
C-peptide	0.460	0.470	0.60	0.569	0.318	0.602

*Negative association

Table 4: Ability of PTH, vitamin D2, and C-peptide to differentiate diabetic patients with neuropathy (*N* = 80) from patients without neuropathy (*N* = 40)

Variables	AUC	Sensitivity	Specificity	Significance	95% CI	
PTH	0.503	0.460	0.520	0.951	0.394	0.613
Vitamin D2	0.478	0.520	0.580	0.695	0.358	0.598
C-peptide	0.349	0.460	0.520	0.007	0.247	0.452

Table 5: Ability of PTH, vitamin D2, and C-peptide to differentiate diabetic patients with neuropathy (*N* = 40) from healthy control (*N* = 30)

Variables	AUC	Sensitivity	Specificity	Significance	95% CI	
PTH	0.594	0.580	0.620	0.128	0.475	0.714
Vitamin D2*	0.000	0.030	0.050	0.001	0.000	0.000
C-peptide*	0.337	0.370	0.40	0.009	0.224	0.451

*Negative association

an age-related risk factor for diabetic complications.[1,15,16] In addition, the diabetic group had an average duration of diabetes of 9.8 years, which was significantly longer (P = 0.001) among diabetics with neuropathy compared to those without neuropathy, suggesting a potential cumulative influence of protracted hyperglycemia on the development of neuropathy. These findings corroborated those of earlier studies that had presented comparable findings.[17,18]

The suboptimal glycemic control observed in the diabetic group (mean HbA_1C of 8.8) is noteworthy, as it is indicative of poor diabetes management. HbA_1C levels were highest significantly in individuals with diabetes and neuropathy, followed by diabetes without neuropathy, and lowest in the control group. Elevated HbA_1C levels have been consistently associated with increased neuropathy risk. This aligns with the finding of an association between higher HbA_1C levels and older age, reinforcing the importance of glycemic control, especially in older individuals.[19,20]

Another key observation is the significance to those without neuropathy and the control group. This suggests a compromised insulin production, which might contribute to neuropathy development, which was in line with previous studies,[21,22] although it is still controversial.[23] Furthermore, the association between higher C-peptide levels and higher vitamin D2 levels raises interesting questions about the potential interplay between these two factors in diabetes and neuropathy.

In this investigation, there was no discernible variation in PTH levels across the study groups. There have been many who disagree, and it is challenging to be intrigued by our findings in the debate over the previously published data. In a study by Sun *et al*. 2021, neuropathy in diabetes patients with low serum PTH levels was substantially linked, although causality needs more research.[24] Concerning calcium homeostasis, PTH is crucial. The majority of neuromuscular symptoms, including tingling, numbness, paraesthesia, and seizures, are brought on by hypocalcemia because calcium, in turn, is essential for normal neuronal physiology.[5] New opportunities for better control with fewer dietary supplement requirements may arise with the advent of PTH replacement therapy. As a rebuttal to this point, a randomized, double-blind, placebo-controlled study found no additional effect of daily treatment with recombinant human PTH on the resolution of active Charcot neuropathy in diabetes.[25]

The investigation into serum vitamin D2 levels reveals a widespread insufficiency, particularly prominent in diabetic individuals. The role of vitamin D in neuropathy is complex, as it is involved in various physiological processes. The low vitamin D levels observed in the diabetic group are verified by several academics,[6,26,27] and could signify a potential risk factor for neuropathy, potentially exacerbating nerve damage.

PTH and BMI do not show strong correlations with any of the other variables. The correlation coefficient values are relatively low and do not appear to be statistically

significant. Vitamin D2 has a weak negative correlation with age, suggesting that as age increases, vitamin D2 levels tend to decrease, although this relationship is not statistically significant.

C-peptide has a significant positive correlation with vitamin D2, indicating that higher C-peptide levels are associated with higher vitamin D2 levels. C-peptide has a weak positive correlation with HbA_1C, suggesting a slight tendency for higher C-peptide levels to coincide with higher HbA_1C levels. HbA_1C has a weak positive correlation with age and BMI, implying that higher HbA_1C levels are associated with older age and a slight tendency to align with higher BMI values. HbA_1C has a significant negative correlation with vitamin D2, indicating that higher HbA_1C levels are associated with lower vitamin D2 levels. Duration of DM has a weak (although significant) negative correlation with age, suggesting that as the duration of diabetes increases, the age at which diabetic neuropathy tends to decrease. Meanwhile, age has a weak positive correlation with the duration of DM, suggesting that older individuals might have had diabetes for a longer duration. Further, age has a strong negative correlation with vitamin D2, indicating that older individuals tend to have lower vitamin D2 levels.

Still, many of these relationships are weak or only mildly significant, and further research is needed to better understand the underlying mechanisms and implications of these correlations.

The ROC-curve analyses aimed to evaluate the diagnostic potential of various biomarkers in distinguishing between diabetic patients with and without neuropathy. The relatively limited discrimination seen with PTH and C-peptide suggests that these biomarkers may have a more nuanced relationship with neuropathy. However, the notably low accuracy of vitamin D2 as a diagnostic tool is surprising, considering its widespread biological influence.[28,29]

Overall, the findings from this study shed light on several potential factors contributing to the development of neuropathy in diabetes patients. Age, diabetes duration, HbA_1C levels, C-peptide levels, and vitamin D2 levels collectively play roles in neuropathy risk. However, while these factors exhibit associations, their diagnostic potential for distinguishing between patients with and without neuropathy remains limited. This suggests that neuropathy development is likely influenced by a complex interplay of multiple factors beyond these biomarkers.

Conclusion

This study underscores the significance of glycemic control, insulin production, and vitamin D levels in the context of diabetic neuropathy. The associations observed between age, HbA_1C levels, PTH, C-peptide levels, and vitamin D2 levels provide valuable insights into potential contributors to neuropathy risk. However, the diagnostic potential of these biomarkers in identifying neuropathy remains limited, emphasizing the multifactorial nature of neuropathy development in diabetes. Further research is warranted to comprehensively elucidate the intricate mechanisms underlying neuropathy and to identify more robust diagnostic markers for early intervention and management.

Limitations

The current study had a few limitations. Because this was a cross-sectional study, prospective research is required to confirm if the presence of neuropathy in diabetes individuals may be predicted by levels of C-peptide, PTH, and vitamin D. Further research is required to determine whether C-peptide, PTH, and vitamin D supplementation can stop neuropathy in DM patients through large-scale randomized double-blind clinical trials. Factors like age, gender, and treatment might influence the biomarker levels and should be controlled for or analyzed for their impact. However, the presented tables were a starting point, and further analyses, including additional statistical tests and potentially incorporating clinical and demographic data, are required for a comprehensive assessment of the biomarkers' potential. Additionally, exploring a combination of biomarkers might enhance diagnostic accuracy. The low AUC values and mixed sensitivity and specificity values emphasize the need for further investigation and potentially exploring other biomarkers or combinations of biomarkers to improve diagnostic accuracy in this context.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Abdul-Aa'ama TK, Al- Saegh RMA, Al-hindy HAM. Does hypovitaminosis D have a correlation with peripheral polyneuropathy among uremic patients? HIV Nurs 2022;22:181-6.
2. Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, *et al*. Diabetic neuropathy. Nat Rev Dis Primers 2019;5:42.
3. Zaino B, Goel R, Devaragudi S, Prakash A, Vaghamashi Y, Sethi Y, *et al*. Diabetic neuropathy: Pathogenesis and evolving principles of management. Dis Mon 2023;69:101582.
4. Galiero R, Caturano A, Vetrano E, Beccia D, Brin C, Alfano M, *et al*. Peripheral neuropathy in diabetes mellitus: Pathogenetic mechanisms and diagnostic options. 2023;24:3554.
5. Masser JA-H, Mousa MJ, Makki HA-A, Al-Khafaji NSK, Al-Dahmoshi HOM, Mahdi ZA-A, *et al*. Calcium and phosphate

homeostasis in patients with recurrent nephrolithiasis. J Contemp Med Sci 2021;7.
6. Al-Shimmery AHS, Mahdi ZA, Al-Hindy HAM, Al-Mammori RTO, Mokif TA, Al-Dahmoshi HOM, *et al*. Immunological study of IFN-γ, ICAM-4, and vitamin D3 markers among gastrointestinal tumor patients in Babylon Province, Iraq. Asian Pac J Cancer Prev 2023;24:301-5.
7. Ramadan GM, Abdulabbas HA, Al-Hindy HAM. Assessment of serum vitamin D in transfusion-dependent B-thalassemia patients: Single-center observational study. History Med 2023;9:55-61.
8. Płudowski P, Kos-Kudła B, Walczak M, Fal A, Zozulińska-Ziółkiewicz D, Sieroszewski P, *et al*. Guidelines for preventing and treating vitamin D deficiency: A 2023 update in Poland. Nutrients 2023;15.
9. Al-Athari A, Aldhalmi A, Al-Hindy H. Association of high-sensitivity C-reactive protein and vitamin D with bronchial asthma. Open Access Maced J Med Sci 2022;10:931-6.
10. Khulood S, Salim BG, Al-Temimi AA. Prevalence of vitamin D deficiency among population in Iraq: Review article. Int J Med Sci Clin Res Stud 2023;3:731-4.
11. Dobolyi A, Dimitrov E, Palkovits M, Usdin T. The neuroendocrine functions of the parathyroid hormone 2 receptor. Front Endocrinol 2012;3:121.
12. Jolivalt CG, Rodriguez M, Wahren J, Calcutt NA. Efficacy of a long-acting C-peptide analogue against peripheral neuropathy in streptozotocin-diabetic mice. Diabetes Obes Metab 2015;17:781-8.
13. Luppi P, Drain P. C-peptide antioxidant adaptive pathways in β cells and diabetes. J Intern Med 2017;281:7-24.
14. Washburn RL, Mueller K, Kaur G, Moreno T, Moustaid-Moussa N, Ramalingam L, *et al*. C-Peptide as a therapy for type 1 diabetes mellitus. Biomedicines 2021;9:270.
15. Pfannkuche A, Alhajjar A, Ming A, Walter I, Piehler C, Mertens PR. Prevalence and risk factors of diabetic peripheral neuropathy in a diabetics cohort: Register initiative "diabetes and nerves". Endocr Metab Sci 2020;1:100053.
16. Mazin J, Mousa HSAS, Al-Hindy HAM. Low level laser (Biophotomodulation) therapy for the treatment of diabetic foot ulcers with 532nm KTP laser induces wound healing, fibroblast proliferation and over- expression of TGF. Syst Rev Pharm 2020;11:396-403.
17. Kebede SA, Tusa BS, Weldesenbet AB, Tessema ZT, Ayele TA. Time to diabetic neuropathy and its predictors among newly diagnosed type 2 diabetes mellitus patients in Northwest Ethiopia. Egypt J Neurol Psychiatry Neurosurg 2021;57:147. doi:10.1186/s41983-021-00402-4.
18. Al-Attaby AKT, Al-Lami MQD. MQDA-L. Effects of duration and complications of type 2 diabetes mellitus on diabetic related parameters, adipocytokines and calcium regulating hormones. Iraqi J Sci 2019;60:2335-61.
19. Jaid HK, Salman IN, Abd BA. Estimation of apelin levels in Iraqi patients with type II diabetic peripheral neuropathy. Baghdad Sci J 2023;2023:1-8.
20. Marzoq MAA. A study on diabetic foot disorders in Basrah, Southern Iraq. Iraqi Natl J Med 2021;3:11-24.
21. Al-Rikabi EH, Mazin JM. Assessment of the effect of C-peptide level on Na-K ATPase activity in individuals with type II diabetic peripheral neuropathy. J Comm Dis 2021;53:213-9.
22. Ryk A, Łosiewicz A, Michalak A, Fendler W. Biological activity of c-Peptide in microvascular complications of type 1 diabetes-time for translational studies or back to the basics? Int J Mol Sci 2020;21:9723.
23. Williams KV, Becker DJ, Orchard TJ, Costacou T. Persistent C-peptide levels and microvascular complications in childhood onset type 1 diabetes of long duration. J Diabetes Complicat 2019;33:657-61.
24. Sun S, Wang Y, Ma W, Cheng B, Dong B, Zhao Y, *et al*. Normal parathyroid hormone and non-proliferative diabetic retinopathy in patients with type 2 diabetes. J Diabetes Investig 2021;12:1220-7.
25. Petrova NL, Donaldson NK, Bates M, Tang W, Jemmott T, Morris V, *et al*. Effect of recombinant human parathyroid hormone (1-84) on resolution of active charcot neuro-osteoarthropathy in diabetes: A randomized, double-blind, placebo-controlled study. Diabetes Care 2021;44:1613-21.
26. Alzughaibi MA, Shumran AM, Al-Hindy HAAM, Al-Dahmoshi HOM, Al-Khafaji NSK, Al Jebory SA. The association of serum 1, 25-dihydroxy vitamin D2 status with asthma in a comparative study of Iraqi adults. Biochem Cell Arch 2022;22:1267-72.
27. Al-Shimmery A, Al-Alwany M, Chabuck Z, Al-Mammori R, Mokif T, Mahdi Z, *et al*. Assessment of tumor necrosis factor-α, interleukin-17, and vitamin D3 levels on a group of gastrointestinal tumor patients in Babylon Provence, Iraq. Med J Babylon 2023;20:362-7.
28. Yammine K, Wehbe R, Assi C. A systematic review on the efficacy of vitamin D supplementation on diabetic peripheral neuropathy. Clin Nutr 2020;39:2970-4.
29. Zhao WJ, Xia XY, Yin J. Relationship of serum vitamin D levels with diabetic microvascular complications in patients with type 2 diabetes mellitus. Chin Med J (Engl) 2021;134:814-20.