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Relationship between serum netrin-1 level and vitamins D_3, B_{12} and K in patients with type 2 diabetes mellitus with hypertension

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One metabolic disease that is on the rise is diabetes mellitus. It is linked to a higher risk of microvascular and macrovascular problems and arises from a malfunction in insulin secretion. Initially thought to be an axon guidance protein, netrin-1 shares a structure with laminine. The development of many tissues, including the pancreas, has been connected to it. Netrin-1 is essential for regulating cell motility, cell-cell connections, and cell-extracellular tissue binding throughout the early stages of the development of several tissues, including pancreatic tissue. The blood levels of netrin-1 in individuals with (T2DM) and hypertension were measured and were correlated with levels of vitamin D_3, B_{12} and K. There were 90 samples taken in this study from participants who were divided into two groups: 45 individuals with hypertension and type 2 diabetes in the first group, and 45 healthy individuals in the second. Age was matched for both groups. Blood samples were taken following a minimum of eight hours of fasting and among other biochemical markers, the levels of glycated haemoglobin, netrin-1, and fasting blood glucose were measured. This study showed that serum netrin-1 levels were significantly higher in the type 2 diabetes group than in the control group. Netrin-1 was positively correlated with fasting blood sugar, or HbA1c and was negatively correlated with vitamins D_3, B_{12} and K. In conclusion, the level of serum netrin-1was higher and the levels of vitamin K and D_3 were significantly lower in T2DM patients with hypertension compared to control.

Keywords: diabetes mellitus; T2DM; hypertension; netrin-1; HbA1c; vitamin K; vitamin D_3; vitamin B_{12}.

Introduction

T2DM is one of the most widespread metabolic conditions in the world and a significant health concern to the population since it is progressive and highly linked to cardiovascular complications (Rob et al., 2025). This comorbidity of T2DM with hypertension is especially frequent, involves a significant percentage of patients with diabetes, and poses a great risk of macrovascular and microvascular complications, including coronary artery disease, stroke, nephropathy, and retinopathy. This comorbidity is precipitated by multifaceted interrelationships between insulin resistance, chronic low-grade inflammation, endothelial dysfunction, oxidative stress, and dysregulated neurohumoral signalling. New biomarkers and modulatory factors in such pathways hence must be identified to enhance the risk stratification and treatment options in T2DM and hypertension patients (Motala et al., 2022; Ruze et al., 2023).

Netrin-1 is a guidance protein first described in its function of axonal guidance in the development of the embryonic nervous system. Over the past couple of years, netrin -1 has emerged as a versatile molecule with significant functions that extend to other tissues other than the nervous system such as control of inflammation, angiogenesis, cell migration of immune cells and maintenance of vascular homeostasis. There is experimental and clinical evidence that netrin-1 has anti-inflammatory and vasculoprotective effects and inhibits leukocyte infiltration, macrophage polarization, and maintains endothelial integrity. These characteristics indicate the possible role of netrin-1 in metabolic and cardiovascular diseases that are associated with chronic inflammation and endothelial dysfunction, including T2DM and hypertension (Chaturvedi & Murray, 2022).

It is evidenced that the netrin-1 circulatory concentrations are disturbed in metabolic illnesses. The dysregulated netrin-1 expression in patients with T2DM has been associated with insulin resistance, adipose tissue inflammation and vascular injury. In addition, netrin-1 has been implicated in blood pressure stability by its action on endothelial nitric oxide production, vascular smooth muscle cell activity and renal sodium regulation (Nedeva et al., 2022). Nevertheless, the exact association of the level of netrin-1 in serum and the presence of T2DM and hypertension is not fully understood with reference to nutritional and micronutrient conditions (Al-Shakour et al., 2024).

Vitamins are essential in the preservation of metabolic, vascular and immune balance. Vitamin D_3 has been known to have pleiotropic actions that go beyond calcium and bone metabolism to include the regulation of glucose metabolism, insulin sensitivity, inflammation, and the rennin-angiotensin-aldosterone system (RAAS). Vitamin D deficiency is quite common in patients with T2DM and hypertension and has been linked to inappropriate glycemia, blood hypertension, endothelial dysfunction, and risk of cardiovascular diseases. The following observations indicate that the status of vitamin D3 can also interact with inflammatory and vascular factors like netrin-1 (Al-Azzawi et al., 2023; Wu et al., 2023).

Vitamin B_{12} is vitamin and a water soluble vitamin, which is necessary in the synthesis of DNA, formation of red blood cells and in the functioning of the nervous system. Vitamin B_{12} deficiency is also common in the case of T2DM, especially among those patients who are under long term metformin treatment. Oxidative stress, endothelial dysfunction, hyperhomocysteinemia and neuropathy have been linked to low levels of vitamin B_{12} and can all lead to cardiovascular complications and high blood pressure (Schleicher et al., 2023). The possible interrelationship between netrin-1 and vitamin B_{12} status has not been sufficiently examined despite the similarity in their role in the vascular and inflammatory pathways (Harikrishnan et al., 2025).

Vitamin K and especially vitamin K_2 has attracted growing interest in its implication in vascular health by regulation of calcium metabolism, activation of matrix Gla protein and inhibition of vascular calcification (Galunska et al., 2024). New data indicate that vitamin K deficiency is possibly related to stiffness of arteries, blood pressure, and higher cardiovascular risk particularly in the patients with metabolic disorders. Also, vitamin K is demonstrated to have anti-inflam-

matory properties with a potential for affecting endothelial operation, which makes the probability of a netrin-1 signaling interaction with T2DM hypertensive patients a possibility (Galunska et al., 2024).

Although increasing attention has been paid on the relationship between netrin-1 and vitamins, there remains a significant gap in the clinical literature exploring the combined effect between serum netrin-1 and vitamins D_3, B_{12}, and K in individuals with T2DM and hypertension. Knowledge of these associations can offer fresh perspectives on the pathophysiology between metabolism regulation, micronutrient deficiency, and vascular inflammation. Moreover, the discovery of the possible correlations between netrin-1 and vitamin status may lead to new possibilities of biomarker-focused interventions and nutrition-based approaches to decrease the occurrence of cardiovascular risk in this patient group at high risk (Dugusheva et al., 2025).

As such, the current paper seeks to examine the correlation between the serum concentrations of netrin-1 and the serum concentrations of vitamins D_3, B_{12}, and K in patients with type 2 diabetes mellitus and hypertension, relative to the controls. Explaining these relationships can help better understand the interaction of inflammatory mediators with micronutrients in metabolic-cardiovascular comorbidity.

Materials and methods

The study was approved by the human ethics committee of Al-Imamain Alkadhimain Teaching Hospital, Everyone who took part in the study was told about it and asked to sign a consent form. The patients were also guaranteed that their information would be kept private. A total of 45 samples were obtained from individuals diagnosed with type 2 diabetes with hypertension by specialist doctors at Al-Kadhimiya Teaching Hospital. Additionally, 45 samples were collected from healthy individuals who were matched in terms of age and gender and were in good overall health. The ages of all the participants was recorded from April 2024 to December 2024. Each participant had 5 mL of blood drawn, which was then transferred into a gel tube and allowed to clot for 15 minutes at room temperature. Subsequently, the mixture was subjected to centrifugation at a speed of 3000 revolutions per minute for a duration of 15 minutes, resulting in the separation of the blood serum. The separated serum was then preserved in a frozen state until it was needed. The chemoimmunoassay technique was employed to measure the levels of serum vitamin D_3, B_{12}, vitamin K and netrin-1 using the Eliza device. Urea, creatine and RBS levels were determined for all participants using colorimetric methods with a spectrophotometer.

Quantitative data were analyzed using SPSS version 26. Results are presented as frequencies and percentages. For normally distributed variables, independent and dependent t-tests (two-tailed) were used. For non-normally distributed variables, the Mann-Whitney U-test, Wilcoxon test, and Chi-square test were applied. A P-value of < 0.05 was considered statistically significant.

Results

The sociodemographic and clinical characteristics of the study participants are presented in Table 1. No significant differences were observed between patients and controls regarding age (39.9 ± 12.4 vs. 39.9 ± 12.7 years, P = 0.957), sex distribution (male: 57.8% vs. 53.3%, P = 0.669), smoking status (24.4% vs. 17.8%, P = 0.441), or marital status (73.3% vs. 66.7%, P = 0.492). In contrast, patients with type 2 diabetes mellitus and hypertension exhibited a significantly higher body mass index compared with healthy controls (30.1 ± 4.8 vs. 25.4 ± 3.6 kg/m², P < 0.001). Furthermore, systolic and diastolic blood pressure values were markedly elevated in the patient group (147.3 ± 11.6 vs. 118.6 ± 8.4 mmHg and 91.5 ± 7.1 vs. 76.8 ± 5.7 mmHg, respectively; both P < 0.001). The mean duration of diabetes and hypertension among patients was 7.3 ± 3.2 and 5.8 ± 2.7 years, respectively, reflecting the chronic nature of the disease in the studied population.

The results demonstrated no statistically significant differences in serum urea and creatinine levels between the patient group and the healthy control group (P = 0.457 and P = 0.698, respectively), indicating preserved renal function in both groups. Contrarily, both random blood sugar (RBS) and glycated hemoglobin levels (HbA1c) were much higher in the patient group than in controls (P < 0.001 in each case), indicating that the patients with type 2 diabetes mellitus and hypertension had poor glycemic control.

Table 1
Sociodemographic and clinical characteristics of the study population

Variable	Controls (n = 45)	T2DM with hypertension (n = 45)	P-value
Age, years	39.9 ± 12.7	39.9 ± 12.4	0.957
Male, n (%)	24 (53.3)	26 (57.8)	0.669
Female, n (%)	21 (46.7)	19 (42.2)	0.669
Body mass index, kg/m²	25.4 ± 3.6	30.1 ± 4.8	<0.001
Current smokers, n (%)	8 (17.8)	11 (24.4)	0.441
Married, n (%)	30 (66.7)	33 (73.3)	0.492
Duration of diabetes, years	N/A	7.3 ± 3.2	N/A
Duration of hypertension, years	N/A	5.8 ± 2.7	N/A
Systolic blood pressure, mmHg	118.6 ± 8.4	147.3 ± 11.6	<0.001
Diastolic blood pressure, mmHg	76.8 ± 5.7	91.5 ± 7.1	<0.001

Table 2
Comparative evaluation of renal functioning in the patient group against the control group (mean ± SD)

Parameters	Control group	Patients group	P-value
Urea	38.80 ± 2.17	39.26 ± 3.30	0.457
Creatinine	0.77 ± 0.14	0.75 ± 0.14	0.698
RBS	107.2 ± 1.2	234.6 ± 5.9	<0.001
HbA1c	5.22 ± 0.50	9.04 ± 0.78	0.0001

The findings demonstrated a statistically significant elevation in serum netrin-1 levels in the patient group compared with the healthy control group (P < 0.001), indicating enhanced inflammatory and vascular signaling in patients with type 2 diabetes mellitus and hypertension. Moreover, vitamin D_3, vitamin B_{12}, and vitamin K serum levels were also significantly lower in the group of patients than in the controls (P = 0.0001, P = 0.005 and P = 0.0001 respectively). These results highlight a marked deficiency in key metabolic and vascular-related vitamins among patients, which may contribute to dysregulated inflammatory responses and endothelial dysfunction observed in this population.

Table 3
Comparison of serum vitamin (D_3, B_{12} and K) and netrin-1 among the patient group and the control group (mean ± SD)

Parameters	Control group	Patients group	P-value
Vitamin D_3	25.18 ± 6.57	12.64 ± 4.99	0.0001
Vitamin B_{12}	372.6 ± 87.6	265.5 ± 104.6	0.0050
Vitamin K	9.59 ± 1.42	3.75 ± 1.39	0.0001
Netrin-1	90.95 ± 4.16	161.40 ± 21.98	0.0001

Pearson correlation analysis revealed significant positive correlations between serum vitamin D_3 and vitamin B_{12} (r = 0.524, P = 0.003), as well as between vitamin D_3 and vitamin K (r = 0.785, P < 0.001). In addition, a moderate positive correlation was observed between vitamin B_{12} and vitamin K (r = 0.453, P = 0.012). Conversely, serum netrin-1 levels showed strong and significant negative correlations with vitamin D_3 (r = −0.756, P < 0.001), vitamin B_{12} (r = −0.465, P = 0.010), and vitamin K (r = −0.823, P < 0.001). These findings suggest that lower circulating levels of essential vitamins are associated with higher netrin-1 concentrations, highlighting a potential link between micronutrient deficiency and enhanced inflammatory or vascular signaling in patients with type 2 diabetes mellitus and hypertension.

Discussion

T2DM is a widespread chronic metabolic disease, which is highly dependent on long-term pharmacological intervention as well as often being accompanied by cardiovascular comorbidities like hypertension (Przezak et al., 2022). Although the therapeutic alternatives are available, the differences in effectiveness of the treatment and safety levels of these options indicate that the research on the underly-

ing molecular and metabolic processes of the disease progression needs to be improved. Recent findings of new biomarkers that are linked with inflammation, vascular dysfunction, and metabolic control will be crucial in an early diagnosis and intervention.

Table 4
The correlations between all biomarkers in this study

	Biomarkers	VD	B_{12}	VK	Netrin-1
VD	Pearson correlation	–	0.524**	0.785**	–0.756**
	Sig. (2-tailed)	–	0.003	0.000	0.000
B_{12}	Pearson correlation	0.524**	–	0.453*	–0.465**
	Sig. (2-tailed)	0.003	–	0.012	0.010
VK	Pearson correlation	0.785**	0.453*	–	–0.823**
	Sig. (2-tailed)	0.000	0.012	–	0.000
Netrin-1	Pearson correlation	–0.756**	–0.465**	–0.823**	–
	Sig. (2-tailed)	0.000	0.010	0.000	–

In the current case, the netrin-1 levels in the serum of patients with T2DM and hypertension were significantly higher than in the healthy controls. This observation favors the accumulating data that netrin-1 plays an active role in the pathophysiology of metabolic and vascular diseases. Netrin-1, which was initially defined as an axonal guidance molecule, has also been identified as an immunomodulatory and vasoregulatory molecule especially in diseases with chronic inflammation and endothelial dysfunction (Garcia Galindo et al., 2022; Sfayyih et al., 2024).

Our results are directly in line with a study which found a significantly higher level of serum netrin-1 in people with impaired fasting glucose and T2DM than in normoglycemic controls, which justified the potential use of this protein as an early sign of metabolic dysregulation (Al-Shakour et al., 2024). On the same note, the up-regulation of netrin-1 has been associated with inflammatory stimulation and changes in the migration of macrophages in diabetic conditions (Al-Shakour et al., 2024). Conversely, Nedeva et al. (2022) also found lower levels of netrin-1 in diabetic patients than in healthy individuals and emphasised netrin-1 expression heterogeneity in various stages of the disease, tissues and in diverse clinical conditions. Such differences can be explained by the differences in the features of patients, the duration of the disease, glucose regulation, and the existence of vascular complications (Nedeva et al., 2022).

Notably, the experimental research has shown that netrin-1 is a protective factor in diabetic microvascular complications. Netrin-1 has been demonstrated to mediate inflammatory reactions, nerve fiber regeneration, and corneal epithelial wound healing in diabetic animal models, and suggests future applications of netrin-1 in treating diabetic keratopathy. Moreover, the administration of netrin-1 has shown positive outcomes in diabetic nephropathy by inhibiting the inflammatory signaling, as well as the maintenance of the renal structures, which supports the notion that netrin-1 is a dual biomarker and regulator of disease progression (Wu & Mo, 2023; Mondal et al., 2024).

Besides changes in netrin-1, the current study also found a significant decrease in the levels of vitamin D_3 and vitamin K in the patients as compared to the control subjects. The results can be compared with the recent evidence provided by Ling Yang et al. (2024), who indicated that T2DM patients had lower serum concentrations of 25-hydroxyvitamin D and vitamin K and both vitamins have been shown to be effective predictors of T2DM using ROC analysis. It is worth noting that a strong negative relationship was observed between the blood glucose and serum 25(OH)D, which also supports the relationship between impaired glycemic control and the vitamin deficiency (Behnoush et al., 2024; Zhao et al., 2025).

Vitamin D has been reported to affect glucose metabolism in a variety of ways. It increases the expression of insulin receptors on the target cells, promoting the intake of the glucose and supporting the insulin sensitivity. Also, vitamin D helps control calcium homeostasis, which is essential in the secretion of insulin and transport of glucose into the cells (Wu et al., 2023). Deficiency of calcium has been linked to high insulin resistance as a result of hindrance in muscle contraction and transfer of glucose. In addition, vitamin D has an anti-inflammatory effect, which is the regulation of the production of cytokines, subsequently lowering chronic low-grade inflammation, which is a major factor in the pathogenesis of T2DM (Wu et al., 2023).

Vitamin K (especially, its menaquinone analogs) has strong antioxidant and anti-inflammatory agents and has become a major mediator of metabolic well-being. Vitamin K serves as a cofactor in the activation of 7-glutamyl carboxylase, which plays a critical role in the activation of vitamin K-dependent proteins (VKDPs) (Chatterjee et al., 2023). These proteins have very important functions in vascular integrity, control of inflammation and glucose metabolism. It has been demonstrated before that vitamin K supplementation enhances insulin sensitivity in T2DM patients by raising the concentration of high-molecular-weight adiponectin and total adiponectin in circulation and decreasing insulin resistance (Kazmierczak-Baranska & Karwowski, 2022). Moreover, the majority of evidence is building up to suggest that proper vitamin K status correlates with a lower risk of T2DM and metabolic syndrome. This protective action is mainly facilitated by the enhanced glucose homeostasis, better insulin signaling, and reduction of inflammatory cascades. The comorbid vitamin D_3 and vitamin K deficiency seen in our patient cohort can thus add to the metabolic dysregulation and also play a role in increasing the level of netrin-1, which is an adaptive or compensatory form of inflammatory response (Zhang et al., 2023).

Conclusion

The current evidence demonstrates that there is a complicated interdependence between netrin-1, vitamin D_3, and vitamin K in patients with T2DM and hypertension. The detected associations indicate that joint analysis of inflammatory biomarkers and the condition of micronutrients can be useful in determining the severity and progression of an illness. Further longitudinal research is justified in order to establish the causal relationships and determine whether specific vitamin supplementation might be used to control netrin-1 signaling and enhance metabolic and vascular outcomes in this high-risk group.

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