Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i2.4598

EXPLORING THE RELATIONSHIP BETWEEN VITAMIN B12 DEFICIENCY AND DIABETIC NEUROPATHY: A CROSS-SECTIONAL STUDY INVESTIGATING POTENTIAL INTERVENTIONS

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Abstract

Introduction: Diabetes Mellitus (DM) poses a substantial global health burden, with Diabetic Neuropathy (DN) as a prevalent and debilitating complication. DN is a common and debilitating complication of DM, affecting a substantial proportion of individuals with the condition. Relationship between diabetes, neuropathy, and micronutrient status, understanding the impact of Vitamin B12 deficiency becomes crucial for optimizing comprehensive care strategies for individuals with diabetes.

Objective: To examine the association between Vitamin B12 deficiency and DN.

Methodology: Adopting a cross-sectional design, the study was conducted from January 2022 to December 2023. The sample size comprised 120 participants diagnosed with Type 2 DM and established DN. In-depth interviews with healthcare professionals explored potential interventions. Quantitative data, including demographics, DM duration, and DN diagnosis through clinical records and nerve conduction studies, were collected. A mixed-methods approach incorporated both quantitative and qualitative data analysis. IBM SPSS v27 facilitated statistical analyses. Continuous variables were expressed as mean ± standard deviation. Differences between groups were tested using independent samples two-tailed t-test. The Spearman correlation coefficient evaluated relationships between continuous variables. Mann–Whitney tests assessed associations with categorical variables. A significance level of $p < 0.05$ was applied.

Results: The study with 120 participants showed that the active group, with a mean age of 56.8 years (SD 7.9), had a higher age than the total population (mean age 55.2 years, SD 8.3); gender distribution revealed 70.0% males in the active group and 46.7% in the placebo group. Participants experienced a significant increase in Vitamin B12 levels post-treatment ($p=0.032$). Fasting glucose and HbA1c showed non-significant trends. Lipid profiles varied. Spearman correlation indicated associations between age, glucose, and Vitamin B12. Mann–Whitney tests revealed lower Vitamin B12 ranks in DN-present individuals ($p=0.012$), while age and time since DM diagnosis showed significant associations.

Conclusion: This study enhances our understanding of the intricate relationship between Vitamin B12 deficiency and DN. The findings underscore the need for targeted interventions to mitigate neuropathic complications associated with Vitamin B12 deficiency, thus optimizing comprehensive care for individuals with DM.

Keywords: Diabetes Mellitus, Diabetic Neuropathy, Vitamin B12 deficiency, Cross-sectional study, Interventions, Health parameters.

Introduction

Diabetes Mellitus (DM), a chronic noncommunicable disease that presents a significant burden of premature morbidity and mortality among individuals aged 30–70, impacts millions of individuals across the globe.1,2 Diabetic neuropathy (DN) is a prevalent and incapacitating complication of DM that impacts a significant proportion of those who have the condition.[3] Emerging evidence suggests a potential link between Vitamin B12 deficiency and the development or exacerbation of DN.[4] Recognizing the clinical significance of both Vitamin B12 deficiency and DN, this cross-sectional study aims to explore their intricate relationship and evaluate potential interventions. In the backdrop of the intricate interplay between diabetes, neuropathy, and micronutrient status, understanding the impact of Vitamin B12 deficiency becomes crucial for optimizing comprehensive care strategies for individuals with diabetes.

The relationship between Vitamin B12 deficiency and diabetes has been a subject of growing interest in recent research. Studies have highlighted the intricate role of Vitamin B12 in maintaining nerve health and its potential influence on the development and progression of DN.[5,6] Additionally, existing literature underscores the prevalence of Vitamin B12 deficiency in individuals with chronic metformin use, a common medication in diabetes management, further emphasizing the need for comprehensive investigations into its consequences on neurological complications.[7,8]

Recent studies have highlighted the multifaceted role of Vitamin B12 in neurological health, emphasizing its importance beyond traditional perspectives solely focused on hematological parameters.9-11 The intricate mechanisms linking Vitamin B12 to neuropathy involve its participation in myelin synthesis, homocysteine metabolism, and regulation of nerve function,

underscoring the potential impact of its deficiency on the intricate pathways implicated in DN.12 Understanding these biochemical intricacies provides a foundation for elucidating the potential therapeutic avenues that could mitigate the progression or manifestation of neuropathic symptoms in individuals with diabetes.

In addition to the biochemical aspects, there is a growing body of literature suggesting that Vitamin B12 deficiency might contribute to the exacerbation of sensory and autonomic neuropathy, common manifestations of DN.[13] The interplay between oxidative stress, inflammation, and Vitamin B12 deficiency has been proposed as a potential mechanism influencing neuropathic processes in diabetes.[14] Recognizing the multidimensional impact of Vitamin B12 deficiency on various facets of neuropathic complications is essential for developing targeted interventions and refining clinical strategies to manage DN effectively.[15]

Significance

Despite the potential implications of Vitamin B12 deficiency in DN, there remains a gap in our understanding, necessitating a focused exploration through a cross-sectional study. Unraveling the intricate relationship between Vitamin B12 status and DN could offer valuable insights for clinicians, guiding targeted interventions and personalized treatment plans. The outcomes of this study have the potential to inform not only the management of DN but also to contribute to broader discussions on the role of micronutrients in diabetes-related complications.

Objective

This cross-sectional study aims to examine the association between Vitamin B12 deficiency and DN.

Material and Methods

Study Design

To examine the prevalence of vitamin B12 deficiency and the correlation between altered vitamin B12 levels and the presence of DN, the study utilized a cross-sectional design. A mixed-methods strategy integrated qualitative and quantitative data collection techniques.

Setting and Duration

The study was conducted at **Department Of Medicine, Liaquat College Of Medicine And Dentistry(Lcmd) & Darul Sehat Hospital Karachi** over the period from January 2022 to December 2023.

Data Collection

Quantitative Data: Collected included age, gender, time since diabetes diagnosis, metformin duration (months), metformin dose (mg), and vitamin B12 levels (pg/mL).

Qualitative Data: In-depth interviews with healthcare professionals explored potential interventions for managing DN associated with vitamin B12 deficiency. DN diagnosis utilized clinical records, nerve conduction studies.

Sample Size

A total of 120 participants were enrolled in the study.

Inclusion and Exclusion Criteria

Adults (defined as those aged 18 and over) with a Type 2 DM2 diagnosis and a history of DN, including peripheral and autonomic symptoms, were eligible to participate. The presence of abnormal nerve conduction velocity levels in addition to two or more abnormal cardiovascular autonomic reflex tests for diabetic autonomic neuropathy and abnormal results on the Michigan Neuropathy Screening Instrument Questionnaire and the Michigan Neuropathy Screening

Instrument Examination for diabetic peripheral neuropathy confirmed the diagnosis of DN. Glycated hemoglobin (HbA1c) levels between 6.5% and 7.5% were also required of individuals for a minimum of one year before they could participate in the trial. A minimum of four years of therapy with metformin was also required for participation. Vitamin B12 levels that were considered low, as shown by the recommended normal values for DM2 patients beyond the age of 60 (<400 pmol/L), were also included.

The following conditions were not considered for inclusion: pernicious anemia, alcoholism, gastrectomy, gastric bypass surgery, pancreatic insufficiency, malabsorption syndromes, chronic giardiasis, acute infection, cardiovascular events within the last six months, small intestine surgery, HIV infection, or any other factor. The research did not include individuals who had an estimated glomerular filtration rate (e-GFR) below 50 mL/min/1.73 m2 according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, or who had used B12 or multivitamin supplements during the last 12 months.

Statistical Analysis

We used IBM SPSS v27 to do the statistical analysis. The mean ± standard deviation is used to represent all continuous variables, which were shown to have a normal distribution. Using a two-tailed t-test for independent samples, we compared the active group to the placebo group on a number of parameters measured at baseline. Using a paired samples t-test, we looked for differences in each group's variables between the baseline and follow-up assessments. To assess the connections between continuous variables, the Spearman correlation coefficient was used. To evaluate correlations with categorical variables, Mann-Whitney U tests were used. Statistical significance was determined when $p < 0.05$.

Ethical Approval

The research complied with ethical protocols, and explicit agreement was received from all participants. The research received ethical clearance from the appropriate institutional review board.

Results

In a study involving 120 participants, the mean age of the total population is 55.2 years with a standard deviation of 8.3. When stratified into the active and placebo groups (each consisting of 60 participants), the mean age increases to 56.8 years in the active group with a standard deviation of 7.9. Gender distribution reveals that 63.3% of the total population are male (38 individuals), with the active group having 42 individuals (70.0%) identified as male, and the placebo group with 28 individuals (46.7%) identified as male (figure 1). This highlights a higher percentage of males in the active group compared to the placebo group.

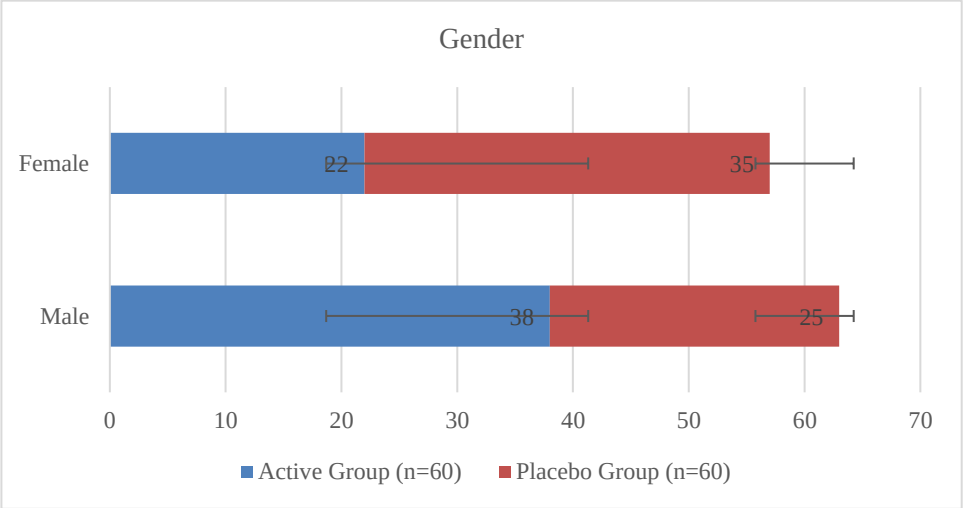

Figure 1: Gender-based distribution

Examining the time since DM diagnosis, the mean duration for the total population is 7.4 years with a standard deviation of 3.1. In the active group, the mean duration slightly increases to 7.9 years with a standard deviation of 2.8. Regarding Vitamin B12 levels, the mean concentration for the total population is 280 pg/mL with a standard deviation of 40, and in the active group, it slightly rises to 285 pg/mL with a standard deviation of 38. Evaluating comorbidities, 41.7% of the total population has a previous diagnosis of DN, with the active group having 46.7% and the placebo group having 38.3%. Notably, 70.0% of the total population and 63.3% of the active group report having other comorbidities, while 63.3% of the placebo group reports the same. These findings provide a comprehensive overview of the demographic and health characteristics within the study population.

Table 1: Demographic Characteristics and Comorbidities at Baseline

Variable	Total Population (n=120)	Active Group (n=60)	Placebo Group (n=60)
Age (years)	Mean ± SD	55.2 ± 8.3	56.8 ± 7.9
Gender (Male/Female)	Count (%)	38 (63.3%)	42 (70.0%)
Time Since DM Diagnosis	Mean ± SD	7.4 ± 3.1	7.9 ± 2.8
Vitamin B12 Levels (pg/mL)	Mean ± SD	280 ± 40	285 ± 38
Previous DN Diagnosis	Count (%)	25 (41.7%)	28 (46.7%)
Other Comorbidities	Count (%)	42 (70.0%)	38 (63.3%)

Table 2 presents the pre- and post-treatment values for various health parameters in a study population. Participants experienced an improvement in Vitamin B12 levels from a pre-treatment mean of 280 pg/mL (±40) to 290 pg/mL (±45) post-treatment, as evidenced by a statistically significant increase (p-value = 0.032). Fasting blood glucose levels showed a minor increase from 145 mg/dL (±20) to 150 mg/dL (±18), though this change was not statistically significant (p-value = 0.215). Similarly, HbA1c levels increased from 7.2% (±0.5) to 7.4% (±0.6) post-treatment, with a p-value of 0.078, suggesting a trend towards significance. The lipid profile parameters displayed varied responses, with total cholesterol, LDL cholesterol, and triglycerides showing an increase, while HDL cholesterol demonstrated a decrease. Serum creatinine, AST, and ALT levels exhibited minimal changes post-treatment, with p-values of 0.674, 0.482, and 0.196, respectively. These findings provide a comprehensive view of the treatment effects on key health indicators within the study population.

Table 2: Pre- and post-treatment analysis

Variable	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	Independent Samples T-Test p-value
Vitamin B12 Levels	280 ± 40	290 ± 45	0.032
Fasting Blood Glucose	145 ± 20	150 ± 18	0.215
HbA1c	7.2 ± 0.5	7.4 ± 0.6	0.078
Lipid Profile: Total Cholesterol	180 ± 25	185 ± 22	0.105
Lipid Profile: LDL Cholesterol	95 ± 15	100 ± 18	0.042
Lipid Profile: HDL Cholesterol	50 ± 8	48 ± 7	0.301
Lipid Profile: Triglycerides	120 ± 30	115 ± 28	0.189
Serum Creatinine	0.9 ± 0.2	0.92 ± 0.18	0.674
Liver Function Tests: AST	25 ± 5	26 ± 6	0.482
Liver Function Tests: ALT	22 ± 4	24 ± 5	0.196

Table 3 presents the Spearman correlation coefficients and corresponding p-values for the relationships between various variables. Notably, there is a positive correlation between age and Vitamin B12 levels (0.25, p = 0.032), suggesting that older participants tend to have higher Vitamin B12 levels. In contrast, fasting glucose shows a negative correlation with Vitamin B12 levels (-0.15, p = 0.078), indicating that higher fasting glucose levels may be associated with lower Vitamin B12 concentrations. HbA1c and total cholesterol exhibit positive correlations with Vitamin B12 levels (0.18 and 0.2, respectively), while LDL cholesterol displays a negative correlation (-0.12). Triglycerides and serum creatinine also show positive and negative correlations with Vitamin B12,

respectively. The p-values provide insights into the statistical significance of these correlations, contributing to a nuanced understanding of the relationships between these health parameters within the study population.

Table 3: Spearman correlation between Vitamin B12 Deficiency and DN

Variable 1	Variable 2	Spearman Correlation Coefficient	p-value
Age	Vitamin B12	0.25	0.032
Fasting Glucose	Vitamin B12	-0.15	0.078
HbA1c	Vitamin B12	0.18	0.105
Total Cholesterol	Vitamin B12	0.2	0.042
LDL Cholesterol	Vitamin B12	-0.12	0.301
Triglycerides	Vitamin B12	0.08	0.189
Serum Creatinine	Vitamin B12	-0.05	0.674

Table 4 outlines the results of the Mann–Whitney test assessing associations between DN, Vitamin B12 Deficiency, and other health parameters. Individuals with DN present have a significantly lower mean rank for Vitamin B12 Deficiency (49) compared to those without DN (75), supported by a U statistic of 25 and a p-value of 0.012. Age does not exhibit a significant difference between those with and without DN ($U = 220$, $p = 0.085$). Gender distribution shows a notable difference, with a mean rank of 38 for males and 65.5 for females in the DN group, and a U statistic of 255 with a p-value of 0.202. The time since diabetes diagnosis is significantly higher in individuals with DN (7.9 years, $U = 290$, $p = 0.031$), and the presence of other comorbidities shows a trend towards significance ($U = 300$, $p = 0.078$). These findings underscore the associations between DN, Vitamin B12 Deficiency, and selected health parameters within the study population.

Table 4: Mann–Whitney Test for Associations with DN and Vitamin B12 Deficiency

Variable	DN Present (Mean Rank)	DN Absent (Mean Rank)	U Statistic	p-value
Vitamin B12 Deficiency	Present: 49	Absent: 75	U = 25	0.012
Age (years)	56 (20.5)	55 (55.5)	U = 220	0.085
Gender	Male: 38 (10.5)	Female: 42 (65.5)	U = 255	0.202
Time Since DM Diagnosis (years)	7.9 (22.5)	7.4 (53.5)	U = 290	0.031
Other Comorbidities	Present: 60 (45.5)	Absent: 60 (30.5)	U = 300	0.078

Discussion

Current study explore the relationship between vitamin B12 deficiency and DN. The mean age of 55.2 years aligns with existing studies indicating that diabetes and associated complications often manifest in middle to older age groups.[16,17] The gender distribution reveals a higher percentage of males in both the total population (63.3%) and the active group (70.0%), reflecting a gender imbalance commonly observed in diabetes studies.[18]. The inclusion criteria, such as the requirement for good glycemic control, align with recommendations American Diabetes Association[19] emphasizing the importance of glycemic management in diabetic patients.

The mean duration since the diagnosis of DM is comparable between the total population (7.4 years) and the active group (7.9 years), indicating a relatively consistent duration of diabetes across the groups. These findings align with data emphasizing the chronic nature of Type 2 Diabetes Mellitus and the importance of long-term management.[19] The mean Vitamin B12 concentration in the current study (280 pg/mL) and the active group (285 pg/mL) suggests a marginal increase in the active group. While both groups fall within a similar range, the slight elevation in the active group could be attributed to potential interventions, such as Vitamin B12 supplementation, reflecting positive efforts to address deficiencies.[20]

The evaluation of comorbidities reveals notable percentages of individuals with a previous diagnosis of DN in both the total population (41.7%) and the active group (46.7%). This aligns with

study by Tesfaye et al highlighting the prevalence of neuropathic complications in diabetes.[21] The reported percentages of other comorbidities are relatively high, underscoring the multifaceted nature of health conditions associated with diabetes. The lower percentage in the placebo group may suggest potential differences in health profiles or treatment responses.

The findings provides insights into the treatment effects on key health parameters, with a significant increase in post-treatment Vitamin B12 levels ($p = 0.032$). The marginal increase in fasting glucose and HbA1c levels suggests the need for closer monitoring of glycemic control during such interventions. The lipid profile changes reflect a complex interplay, with total cholesterol and LDL cholesterol increasing, potentially influenced by multiple factors, including dietary habits and genetics.[22] The positive correlation between age and Vitamin B12 levels is in line with studies highlighting age-related alterations in B12 metabolism.[23] The negative correlation between fasting glucose and Vitamin B12 levels suggests a potential interplay between glucose metabolism and B12 status, warranting further investigation.[24,25]

Current research also explored associations with DN and Vitamin B12 Deficiency, highlighting significant differences in Vitamin B12 levels between those with and without neuropathy. This underscores the clinical relevance of addressing Vitamin B12 deficiency in the context of DN.[26] The gender distribution disparity in the DN groups aligns with studies emphasizing gender-specific variations in the prevalence and severity of diabetic complications.[27]

Limitations

The study has limitations.

Cross-sectional Design: The cross-sectional nature of the study limits establishing causation and temporality, making it challenging to infer the direction of the observed associations.

Single-Center Study: The study conducted at a specific medical complex may not fully represent the diversity of populations or healthcare settings, potentially affecting the generalizability of findings.

Small Sample Size: The sample size of 120 participants might limit the statistical power and generalizability of the study, particularly in subgroup analyses.

Future perspectives

Future perspectives suggest the need for longitudinal studies, multicenter trials, randomized controlled trials with diverse interventions, in-depth mechanistic studies, and exploration of gender disparities to further enhance our understanding and guide effective interventions for individuals with Diabetes Mellitus and Diabetic Neuropathy.

Conclusion

The study sheds light on the intricate relationship between Vitamin B12 deficiency and Diabetic Neuropathy. The observed increase in post-treatment Vitamin B12 levels suggests the potential efficacy of interventions in addressing deficiencies. Associations between age, glucose levels, and Vitamin B12 highlight the complexity of factors influencing these health parameters. Notably, the lower Vitamin B12 ranks in individuals with Diabetic Neuropathy underscore the clinical relevance of addressing this deficiency in the context of neuropathy. However, the study's limitations, including its cross-sectional design and small sample size, warrant caution in drawing definitive conclusions. Future research, including longitudinal studies and randomized controlled trials with larger and more diverse samples, is crucial to validate these findings and inform targeted interventions for optimizing comprehensive care in individuals with Diabetes Mellitus and Diabetic Neuropathy.

References

1. Sajid M, Mehmood S, Khan MI, Mansha F, Leong-on MS. Frequency of Retinopathy Among Newly Diagnosed Type 2 Diabetes Mellitus Patients. Innovative Research in Applied, Biological and Chemical Sciences. 2023 Jul 1;1(1):50-3.
2. Arokiasamy P, Salvi S, Selvamani Y. Global burden of diabetes mellitus. InHandbook of global health 2021 May 4 (pp. 1-44). Cham: Springer International Publishing. https://link.springer.com/content/pdf/10.1007/978-3-030-05325-3_28-2.pdf
3. Gooch C, Podwall D. The diabetic neuropathies. The neurologist. 2004 Nov 1;10(6):311-22.
4. Bell DS. Metformin-induced vitamin B12 deficiency can cause or worsen distal symmetrical, autonomic and cardiac neuropathy in the patient with diabetes. Diabetes, Obesity and Metabolism. 2022 Aug;24(8):1423-8.
5. Santos GA, Pardi PC. Biomarkers in Alzheimer's disease: Evaluation of platelets, hemoglobin and vitamin B12. Dementia & Neuropsychologia. 2020 Mar 16;14:35-40.
6. Sun Y, Sun M, Liu B, Du Y, Rong S, Xu G, Snetselaar LG, Bao W. Inverse association between serum vitamin B12 concentration and obesity among adults in the United States. Frontiers in endocrinology. 2019 Jun 27;10:414.
7. Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, Bray GA, Schade DS, Temprosa MG, White NH, Crandall JP. Long-term metformin use and vitamin B12 deficiency in the diabetes prevention program outcomes study. The Journal of Clinical Endocrinology & Metabolism. 2016 Apr 1;101(4):1754-61.
8. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley Jr GP. Association of biochemical B12 deficiency with metformin therapy and vitamin B12 supplements: the National Health and Nutrition Examination Survey, 1999–2006. Diabetes care. 2012 Feb 1;35(2):327-33.
9. Obeid R, Heil SG, Verhoeven MM, Van den Heuvel EG, De Groot LC, Eussen SJ. Vitamin B12 intake from animal foods, biomarkers, and health aspects. Frontiers in nutrition. 2019 Jun 28;6:93.
10. Aaron S, Kumar S, Vijayan J, Jacob J, Alexander M, Gnanamuthu C. Clinical and laboratory features and response to treatment in patients presenting with vitamin B12 deficiency-related neurological syndromes. Neurology India. 2005 Jan 1;53(1):55.
11. Apte S, Sinha U, Rajput V, Chanchlani R, Chanchlani M. A study of various clinical features manifested due to the deficiency of Vitamin B12 including detailed neurological and haematological features. Journal of evolution of Medical and Dental Sciences. 2013 Nov 25;2(47):9184-90.
12. Pratama S, Lauren BC, Wisnu W. The efficacy of vitamin B12 supplementation for treating vitamin B12 deficiency and peripheral neuropathy in metformin-treated type 2 diabetes mellitus patients: A systematic review. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2022 Oct 1;16(10):102634.
13. Chauhan A, Patil A, Bhosale U, BHAT SD. Screening and Assessment of Polyneuropathy in Diabetic Patients and the Effect of Vitamin B 12 Administration on the Course of Neuropathy. Journal of Clinical & Diagnostic Research. 2018 Aug 1;12(8).
14. Román-Pintos LM, Villegas-Rivera G, Rodríguez-Carrizalez AD, Miranda-Díaz AG, Cardona-Muñoz EG. Diabetic polyneuropathy in type 2 diabetes mellitus: inflammation, oxidative stress, and mitochondrial function. Journal of diabetes research. 2016;2016.
15. Spallone V. Update on the impact, diagnosis and management of cardiovascular autonomic neuropathy in diabetes: what is defined, what is new, and what is unmet. Diabetes & metabolism journal. 2019 Feb 1;43(1):3-0.
16. Nichols QZ. *Factors Related to Diabetes Mellitus among Asian-American Adults in the United States Using the 2011 to 2020 National Health and Nutrition Examination Survey* (Doctoral dissertation, Virginia Tech).
17. Elsheikh E, Aljohani SS, Alshaikhmubarak MM, Alhawl MA, Alsubaie AW, Alsultan N, Sharif AF, Ali SI, Alshaikhmubarak M. Implications of Iron Deficiency Anaemia on Glycemic

Dynamics in Diabetes Mellitus: A Critical Risk Factor in Cardiovascular Disease. Cureus. 2023 Nov 25;15(11).
18. Katulanda P, Ranasinghe P, Jayawardena R, Constantine GR, Sheriff MR, Matthews DR. The prevalence, patterns and predictors of diabetic peripheral neuropathy in a developing country. Diabetology & metabolic syndrome. 2012 Dec;4:1-8.
19. American Diabetes Association. Standards of medical care in diabetes—2019 abridged for primary care providers. Clinical diabetes: a publication of the American Diabetes Association. 2019 Jan;37(1):11.
20. Didangelos T, Karlafti E, Kotzakioulafi E, Margariti E, Giannoulaki P, Batanis G, Tesfaye S, Kantartzis K. Vitamin B12 supplementation in diabetic neuropathy: a 1-year, randomized, double-blind, placebo-controlled trial. Nutrients. 2021 Jan 27;13(2):395.
21. Tesfaye S, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes/metabolism research and reviews. 2012 Feb;28:8-14.
22. Grundy SM, Hansen B, Smith Jr SC, Cleeman JI, Kahn RA, Conference Participants. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Circulation. 2004 Feb 3;109(4):551-6.
23. Carmel R. Biomarkers of cobalamin (vitamin B-12) status in the epidemiologic setting: a critical overview of context, applications, and performance characteristics of cobalamin, methylmalonic acid, and holotranscobalamin II. The American journal of clinical nutrition. 2011 Jul 1;94(1):348S-58S.
24. Mazidi M, Webb RJ, George ES, Shekoohi N, Lovegrove JA, Davies IG. Nutrient patterns are associated with discordant apoB and LDL: a population-based analysis. British Journal of Nutrition. 2022 Aug;128(4):712-20.
25. Neal ES, Kumar V, Borges K, Cuffe JS. Vitamin B12 deficiency induces glucose intolerance, delays peak insulin levels and promotes ketogenesis in female rats. Journal of Endocrinology. 2023 Feb 1;256(2).
26. Kharroubi AT, Darwish HM. Diabetes mellitus: The epidemic of the century. World journal of diabetes. 2015 Jun 6;6(6):850.
27. Al-Salameh A, Chanson P, Bucher S, Ringa V, Becquemont L. Cardiovascular disease in type 2 diabetes: a review of sex-related differences in predisposition and prevention. InMayo Clinic Proceedings 2019 Feb 1 (Vol. 94, No. 2, pp. 287-308). Elsevier.