https://jksus.org

ScientificScholar® Knowledge is power
Publisher of Scientific Journals

Journal of King Saud University – Science

2025 37 (2) 3542025

Research Article

Correlation between vitamin B12 deficiency and hemoglobin A1c in patients with diabetes mellitus

Yahya Madkhali[a,*], Sami G. Almalki[a]

[a]Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Majmaah University, Al Majmaah, 11952, Riyadh, Saudi Arabia

ARTICLE INFO

Keywords:
Age group analysis
Diabetes mellitus
Glycemic control
Hemoglobin A1c
Vitamin B12

ABSTRACT

Diabetes mellitus is characterized by poor glycemic control, as indicated by circulating levels of glycosylated hemoglobin A1c (HbA1c). Recent reports have implicated vitamin B12 deficiency in worsening glycemic control, leading to complications like neuropathy and anemia. We aimed to assess the association between vitamin B12 deficiency and elevated HbA1c levels in patients with diabetes. Data collected from a cohort of 364 patients with diabetes encompassed circulating levels of HbA1c, vitamin B12, age, and sex. Participants included 202 women (55.5%) and 162 men (44.5%) and were classified by age (≤60 years and >60 years) and sex. The statistical methods employed included Pearson's correlation, Welch's t-test, and the Chi-square test via RStudio software. Our findings revealed that the mean HbA1c percentage is significantly lower in patients with vitamin B12 deficiency compared with their non-deficient counterparts (2.5 ± 0.58 versus 2.8 ± 0.64, respectively; p = 0.000). Further, the correlation between vitamin B12 and HbA1c levels demonstrates a weakly positive relationship (r = 0.22), which is statistically significant (p < 0.001). The prevalence of vitamin B12 deficiency is consistent across both age groups (12.68% of patients aged ≤60 years and 11.25% of those >60 years). Our data suggests a significant but negative correlation between vitamin B12 deficiency and HbA1c levels in patients with diabetes. The observed correlation between vitamin B12 deficiency and improved glycemic control warrants further investigation and may enhance the management of patients with diabetes.

1. Introduction

Diabetes mellitus is characterized by persistent hyperglycemia (Aroda *et al.*, 2016). Current research indicates a strong correlation between the development of diabetes and glycemic management based on measurement of the circulating levels of glycosylated hemoglobin A1c (HbA1c) (de Boer *et al.*, 2011). Since elevated HbA1c levels are associated with micro- and macrovascular illness, it is critical to identify modifiable aspects of glucose metabolism. Recent studies have focused on vitamin B12 insufficiency because of its possible link to glycemic dysregulation (De Groot *et al.*, 2013). Recent studies indicate that vitamin B12 deficiency may disrupt glucose homeostasis and, especially in patients with type 2 diabetes undergoing metformin treatment (De Groot *et al.*, 2013). This may indicate a correlation between vitamin B12 deficiency and HbA1c levels. To build on this, it is essential to understand the physiological importance of vitamin B12.

The production of RBCs, DNA synthesis, and nervous system function all depend on vitamin B12, a water-soluble vitamin (He *et al.*, 2022). Vitamin B12 deficiency is very common and affects a significant percentage of people with type 2 diabetes mellitus (T2DM) and older adults (Liu *et al.*, 2022). Vitamin deficiency is known to cause numerous conditions, including megaloblastic anemia and neuropathy (established side effects of diabetes) (Malla *et al.*, 2022; Obeid *et al.*, 2013). Fatigue, weakness, migraines, and nerve damage are all signs of a B12 deficiency. Even though the human liver can store B12 for many years, poor diet or illnesses like diabetes can lead to its deficiency (Swidan and Ahmed, 2016). B12 plays a crucial role in two key biochemical processes: homocysteine to methionine conversion (important for healthy cell function) and promoting cellular energy metabolism (Jatoi *et al.*, 2020). Vitamin B12 deficiency can lead to toxin accumulation, nerve myelin sheath damage, and nerve-related conditions ranging from sensory changes and memory loss to more severe conditions, such as spinal cord disease and Alzheimer's disease (AD) (Swidan and Ahmed, 2016; Jatoi *et al.*, 2020; Infante *et al.*, 2021). Given its systemic role, identifying contributing factors to B12 deficiency becomes critical in diabetic patients.

Metformin (used for T2D treatment) can cause vitamin B12 malabsorption and may lead to its deficiency in patients with diabetes (He *et al.*, 2022; Niafar *et al.*, 2014). A recent meta-analysis has shown that patients with T2D receiving metformin had significantly reduced vitamin B12 levels, likely because metformin may impair long-term gastrointestinal B12 absorption; this may result from various factors, including a decrease in calcium-dependent absorption, slowed digestion, bacterial overgrowth, or changes in bile acid metabolism. However, studies have shown that this effect can be mitigated by taking calcium supplements, which help restore normal B12 absorption. Vitamin B12 deficiency is typically diagnosed through blood tests, although the specific diagnostic thresholds may vary slightly between different medical organizations (Swidan and Ahmed, 2016; Jatoi *et al.*, 2020; Infante *et al.*, 2021; Niafar *et al.*, 2014). Such findings support the need to evaluate how vitamin B12 status may intersect with diabetic treatment regimens and patient outcomes.

***Corresponding author**
E-mail address: y.madkhali@mu.edu.sa (Y. Madkhali)

Received: 13 February, 2025 **Accepted:** 06 May, 2025 **Published:** 31 May, 2025

DOI: 10.25259/JKSUS_354_2025

Mathai *et al.* studied the correlation between vitamin B12 levels and metformin use in patients with T2DM, comparing changes in vitamin B12 levels with glycemic control, metformin dose, and treatment duration (Ko *et al.*, 2014). The blood glucose profiles of participants were assessed using fasting glucose concentration (FGC) and postprandial blood glucose levels (PPBG). The results showed that individuals in Category 3 (those with poor blood sugar control) had significantly higher FGC, PPBG, and HbA1c levels compared to those in Category 2 (good control) and Category 1 (healthy individuals). Additionally, an inverse relationship was found between vitamin B12 status and both the dose of metformin and the duration of its use in participants from Categories 2 and 3. The study concluded that patients who took higher doses of metformin or had been using the drug for a longer period were more likely to have lower vitamin B12 levels (Ko *et al.*, 2014). This raises the question of whether vitamin B12 status might directly influence glycemic biomarkers such as HbA1c.

Current literature presents conflicting data on the correlation between vitamin B12 and HbA1c. Several studies implicate vitamin B12 deficiency with glycemic dysregulation, while others argue that this correlation may reflect inaccurate measurements, particularly in patients with reduced erythrocyte turnover (Kibirige and Mwebaze, 2014). Sex and age may also impact vitamin B12 levels and their relationship with HbA1c (see Table 1), although these relationships are not well understood (Umay *et al.*, 2011). Considering these discrepancies, a focused investigation is needed to clarify this relationship across different demographic groups.

We aimed to assess the relationship between vitamin B12 levels and HbA1c in patients with diabetes and identify differences across age and sex (Owen *et al.*, 2021). We employed statistical methods to identify factors associated with vitamin B12 deficiency and diabetes control, and evaluated whether targeted interventions may improve diabetes management.

2. Materials and Methods

2.1 Study design and ethical approval

We conducted a cross-sectional study at King Khaled Hospital, Majmaah City, Saudi Arabia, between 1 January 2021 and 31 December 2022. Ethical approval for this research was granted by the Ministry of Health, Saudi Arabia (Institutional Review Board Approval Number: 22-485E) for the ethical treatment of participants. This study complied with the principles of the Helsinki Declaration, and all patient-specific data were effectively secured and protected.

2.2 Participant selection and data collection

The inclusion criteria required participants to have a confirmed diagnosis of diabetes and recent measurements of HbA1c and vitamin B12 levels (Jatoi *et al.*, 2020). The dataset included 364 participants, comprising 162 men (44.5%) and 202 women (55.5%), with ages ranging from 5 to 91 years (mean: 49.3 years, standard deviation [SD]: 13.9). HbA1c and vitamin B12 levels were compared with regard to sex and age.

2.3 Laboratory measurements and definitions

The dataset included demographic parameters such as age and sex, along with HbA1c and vitamin B12 levels (pg/mL). Serum vitamin B12 was measured using ROCH COBAS e-411 analyzer, where the principle of the test is a competitive protein binding immunoassay with electrochemiluminescence (ECLIA) detection. Additional parameters included hemoglobin (Hb), RBC count, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) (Table 2). For analysis, age was categorized into two groups: <60 and ≥60 years to correspond with clinical cut-offs for defining Vitamin B12 deficiency, with levels consistently <200 pg/mL considered indicative of deficiency.

2.4 Statistical analysis

RStudio software (RStudio, PBC, Boston, MA, USA) was utilized for data cleaning, preparation, and analysis. Data normality was assessed for continuous variables like HbA1c and vitamin B12 levels by the Shapiro-Wilk test. Outliers and missing values were identified to ensure dataset integrity. Vitamin B12 levels were categorized into deficient (<200 pg/mL) and non-deficient (≥200 pg/mL) groups. Further stratifications included sex and age.

Descriptive statistics were computed for all continuous variables, including means and SD for both HbA1c and vitamin B12 levels. The counts and proportions of categorical variables, such as vitamin B12 deficiency, age group, and sex, were also summarized. To assess the relationship between vitamin B12 and HbA1c levels, Pearson's correlation

Table 1.
Summary of various studies on Vitamin B12 deficiency and HbA1c levels in patients with diabetes.

Reference	Study focus	Key findings	Conclusion
(Akabwai *et al.*, 2015)	Vitamin B12 deficiency in diabetic patients	10.7% prevalence of vitamin B12 deficiency; associated with lower hemoglobin and poor glycemic control (HbA1c ≥ 7%)	Routine screening for vitamin B12 deficiency is recommended for diabetic patients with anemia or poor glycemic control.
(Al-Fawaeir *et al.*, 2022)	Vitamin B12 deficiency in metformin users vs non-users	Higher prevalence of B12 deficiency in metformin users (32%) compared to non-users (9%)	Long-term metformin use is associated with vitamin B12 deficiency; monitoring is essential in these patients.
(Mukhtar *et al.*, 2024)	Vitamin B12 levels in T2DM patients using metformin	High homocysteine levels (8.4%) indicate impaired B12 metabolism in T2DM patients	Metformin use may impact B12 metabolism, but further studies are needed to explore this.
(Huynh *et al.*, 2024)	Vitamin B12 deficiency in metformin users in Vietnam	18.6% prevalence of vitamin B12 deficiency; risk increases with long-term use (>48 months) and higher doses (>1000 mg/day)	Regular screening for B12 deficiency is recommended in long-term metformin users.
(Yazidi *et al.*, 2024)	Metformin use and vitamin B12 deficiency in T2DM patients	6%-50% of metformin users had B12 deficiency; anemia was common in these patients	There is a significant link between metformin use and vitamin B12 deficiency, warranting screening in T2DM patients.
(Wagner *et al.*, 2024)	Long-term effects of metformin on vitamin B12 deficiency	Age and duration of metformin use associated with B12 deficiency; younger patients at higher risk	The duration of metformin use correlates with B12 deficiency, especially in younger patients.
(Srinath *et al.*, 2024)	Association of IDA and HbA1c in diabetic vs non-diabetic patients	Diabetic IDA patients had significantly higher HbA1c (8.69%) than non-diabetic IDA patients (5.87%)	IDA may lead to falsely elevated HbA1c levels, independent of glycemic status.
(Rathore *et al.*, 2018)	Anemia and vitamin B12 deficiency in T2DM patients	32.5% prevalence of anemia in T2DM patients, with 40% macrocytic anemia due to B12 deficiency	Prolonged metformin use leads to vitamin B12 deficiency, which may affect HbA1c levels.
(Al Shawabkeh *et al.*, 2017)	Effect of rosemary on blood sugar and Vitamin B12 in diabetic patients	Rosemary increased B12 levels and reduced HbA1c in both healthy and diabetic participants	Rosemary supplementation may help improve both vitamin B12 levels and blood sugar control in diabetic patients.
(Bokade *et al.* 2023)	Long-term metformin therapy and its effects on B12 levels	42.1% of diabetic patients on metformin had B12 deficiency compared to 10.7% in controls	Prolonged metformin use leads to a significant increase in vitamin B12 deficiency, which can affect hematological parameters.

Table 2.
Descriptive statistics of key health metrics in patients with diabetes (n=364).

Categories	Mean	Median	Min	Max
Age (Years)	49.26	50	5	91
Hemoglobin A1c (HbA1c) (%)	8.55	8.1	6.7	16.8
Hemoglobin (Hb)	13.26	13.45	7.02	18.1
Red blood cells (RBC)	7.6	4.96	3.05	33.7
Hematocrit (Hct)	39.46	41.5	9.64	55.9
Mean corpuscular volume (MCV)	81.98	86.2	36	110.8
Mean corpuscular hemoglobin (MCH)	27.94	28.3	16.5	39
Mean corpuscular hemoglobin concentration (MCHC)	29.53	32.2	3.7	36.9
Vitamin B12	460.34	413.15	36.9	1476

coefficient was calculated, accompanied by a 95% confidence interval (CI). Statistical significance was determined through hypothesis testing using a p-value. To identify potential differences between the groups, the study employed Welch's t-test to compare the mean HbA1c levels between individuals with and without vitamin B12 deficiency. Mean vitamin B12 and HbA1c levels were examined across different age and sex categories. Vitamin B12 deficiency distribution across age groups was evaluated via a chi-square test.

3. Results

Data from 364 patients with diabetes, including 202 women and 162 men, were used to assess the relationship between vitamin B12 deficiency and HbA1c levels, with additional comparisons to age and sex.

3.1 Descriptive statistics

Table 3 presents descriptive statistics for two cohorts based on sex and age, focusing on two key measures: HbA1c and vitamin B12 levels. These Tables show the minimum, maximum, mean, and SD values of HbA1c and vitamin B12 levels for each subgroup. Overall, the mean vitamin B12 value was 460.34 pg/mL (SD = 256.36, range, 36.90-1476.0 pg/mL). The mean HbA1c value for the overall population was 8.55% (SD = 1.77; range, 6.7% –16.8%). When comparing age groups, individuals ≥ 60 years exhibited a higher mean vitamin B12 value (556.31 pg/mL, SD = 303.43) than those <60 years (430.65 pg/mL, SD = 232.66). The mean HbA1c values were slightly higher in the ≥ 60 (8.76%, SD = 1.67) compared with the <60 years group (8.48%, SD = 1.80). Examining gender differences, men had a higher mean vitamin B12 value (489.10 pg/mL, SD = 254.72) than women (437.27 pg/mL, SD = 255.97). The mean HbA1c level for men was higher (8.67%, SD = 1.85) compared with women (8.46%, SD = 1.70). Within specific subgroups, men <60 years of age displayed a mean vitamin B12 value of 451.37 pg/mL, while women <60 years had a mean value of 416.24 pg/mL. For those ≥ 60, men displayed a mean B12 value of 578.71 pg/mL, and women exhibited a mean B12 value of 528.01 pg/mL. Interestingly, HbA1c levels were higher for women ≥ 60 (9.07%, SD = 1.90) compared with men ≥ 60 years (8.52%, SD = 1.44).

The analysis showed that HbA1c levels tended to increase with age, with older individuals (60+) having higher mean HbA1c values compared to younger ones. For women, the mean HbA1c increased from 8.31% to 9.07%, and for men, it shifted from 8.73% to 8.52%. In contrast, vitamin B12 levels were higher in older adults, with mean values rising from 416.24 pg/mL in women <60 to 528.01 pg/mL in those ≥ 60, and from 451.37 pg/mL in men <60 to 578.71 pg/mL in those ≥ 60. The data also showed increased variability in both HbA1c and vitamin B12 levels with age, suggesting that both HbA1c and vitamin B12 levels rise in older adults, with greater variability observed across the groups (Fig. 1).

3.2 Correlation analysis

We conducted a Pearson's correlation to examine the relationship between vitamin B12 and HbA1c levels across different groups, including overall, sex, and age categories (Table 4). In the overall category, the correlation was 0.217 (95% CI: 0.12, 0.31; $p < 0.001$), indicating a weakly positive association between vitamin B12 and HbA1c. In the <60 age group, the correlation of 0.185 was weak but significant (95% CI: 0.02, 0.33; p = 0.024). For the ≥ 60 age group, the correlation increased to 0.304 (95% CI: 0.06, 0.48; p = 0.016), indicating a stronger association between vitamin B12 and HbA1c. In women, the correlation was 0.173 (95% CI: 0.02, 0.33; p = 0.032), which is weak but significant. For men, the correlation was 0.22 (95% CI: 0.05, 0.39; p = 0.011), suggesting a slightly stronger positive relationship between vitamin B12 and HbA1c compared to women. These results indicate that while there is a significant association between vitamin B12 and HbA1c, the strength of the correlation varies by age and sex, with the strongest correlation observed in individuals ≥ 60 years old.

3.3 Statistical comparison of HbA1c levels between vitamin B12 deficient and non-deficient groups

We conducted Welch's two-sample t-test to evaluate the impact of vitamin B12 deficiency on HbA1c levels by comparing the mean HbA1c values between patients with and without vitamin B12 deficiency. Table 5 shows that individuals with vitamin B12 deficiency had a lower mean HbA1c value (07%, n = 45) compared with those who were non-deficient (8.62%, n = 319; 95% CI: -1.04, -0.05). Statistical testing using Welch's t-test resulted in a t-statistic of -2.156 and a p-value of 0.035, indicating a statistically significant difference between the two groups. This discrepancy is consistent with the slightly lower mean HbA1c levels that have been observed in women.

To better illustrate the distribution of mean values in our population sample, we created a scatter plot (Fig. 2).

Table 3.
Descriptive statistics for patient cohort.

Group	Vitamin B12 (pg/mL) mean	Vitamin B12 (pg/mL) min	Vitamin B12 (pg/mL) max	Vitamin B12 (pg/mL) SD	HbA1c (%) mean	HbA1c (%) min	HbA1c (%) max	HbA1c (%) SD
Overall	460.34	36.9	1476	256.36	8.55	6.7	16.8	1.77
< 60	430.65	36.9	1476	232.66	8.48	6.7	16.8	1.8
> 60	556.31	79.14	1476	303.43	8.76	6.7	14.4	1.67
Men	489.1	93.14	1476	254.72	8.67	6.7	16.8	1.85
Women	437.27	36.9	1476	255.97	8.46	6.7	14.5	1.7
< 60, Men	451.37	93.14	1476	220.55	8.73	6.7	16.8	2
< 60, Women	416.24	36.9	1476	240.32	8.31	6.7	14.5	1.62
> 60, Men	578.71	118.1	1476	306.02	8.52	6.7	12.9	1.44
> 60, Women	528.01	79.14	1476	301.81	9.07	6.7	14.4	1.9

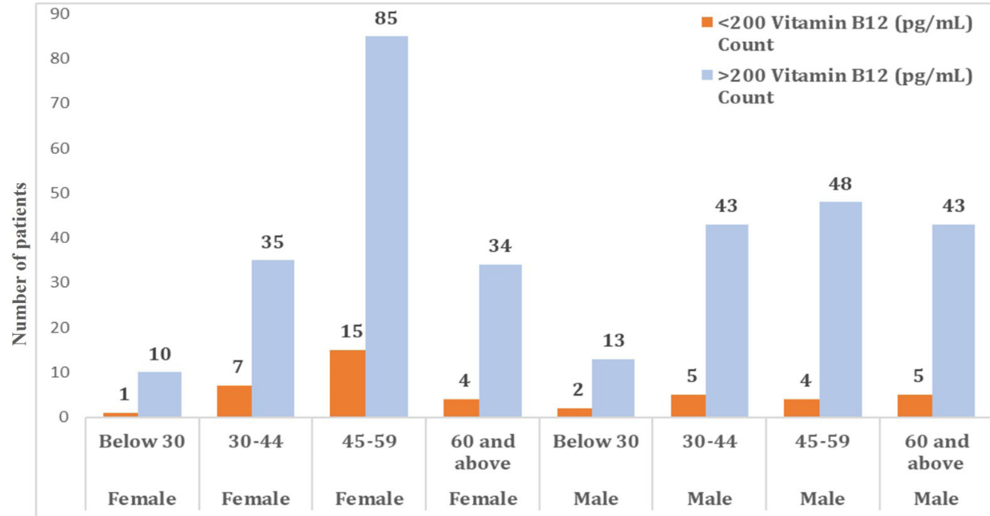

Fig. 1. Vitamin B12 levels in study participants. This data illustrates the distribution of Vitamin B12 levels across different age categories for both women and men, categorizing individuals with levels either below or above 200 pg/mL.

Table 4.
Correlation test results.

Group/ Category	Variable 1	Variable 2	Correlation coefficient (r)	p-value	95% Confidence interval for r
Overall	Vitamin B12	HbA1c	0.217	< 0.001	0.12 to 0.31
Age group: ≤ 60	Vitamin B12	HbA1c	0.185	0.024	0.02 to 0.33
Age group: > 60	Vitamin B12	HbA1c	0.304	0.016	0.06 to 0.48
Women	Vitamin B12	HbA1c	0.173	0.032	0.02 to 0.33
Men	Vitamin B12	HbA1c	0.22	0.011	0.05 to 0.39

Table 5.
T-test results comparing mean values of circulating levels of HbA1c and Vitamin B12.

Vitamin B12 group	Mean HbA1c levels	Count	t-Statistic	p-value:	95% Confidence interval for difference
Deficient	8.07	45	-2.156	0.035	(-1.04, -0.05)
Non-Deficient	8.62	319			

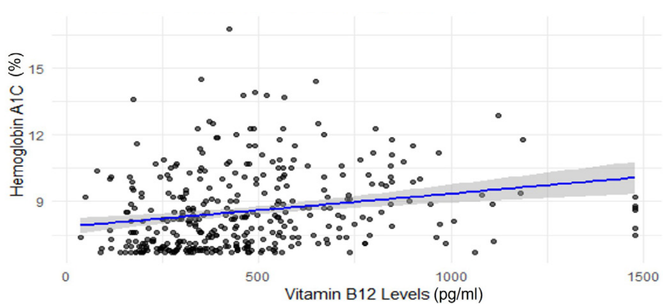

Fig. 2. Scatterplot of HbA1c versus vitamin B12 levels.

3.4 Vitamin B12 deficiency proportional analysis

Table 6 provides an analysis of the vitamin B12 deficiency status in the <60 years and ≥60 years age groups. The threshold for vitamin B12 deficiency is commonly considered to be <200 pg/mL, although some guidelines may recommend slightly different values. Table 6 also presents the count and proportion of individuals in our patient cohort who were deficient and non-deficient in vitamin B12. Among those aged 60 and below, 36 individuals (12.67%) were B12 deficient, while 248 individuals (87.32%) were B12 non-deficient. In the ≥60 age group, nine individuals (11.25%) were B12 deficient, and 71 individuals (88.75%) were B12 non-deficient. Our data indicates that the B12 deficiency proportion was slightly higher in the <60 compared with the ≥60 age group. However, in both age categories, the vast majority of individuals were B12 non-deficient. A chi-square test examining the distribution of vitamin B12 deficiency between the two age groups yielded a p-value of 0.682, indicating that there was no significant difference in B12 deficiency rates between the groups.

Our data revealed a higher prevalence of B12 deficiency in the <60 years age group (36 cases) compared with the ≥60 years age group (nine cases). However, vitamin B12 non-deficiency was also more common in the <60 years age group (248 cases) compared with the ≥60 years age group (71 cases) (Fig. 3).

Table 6.
Age proportional analysis.

Age group	Deficient count	Non-deficient count	Deficient proportion	Non-deficient proportion
60 and below	36	248	0.1267	0.8732
Above 60	9	71	0.1125	0.8875
In the given data, individuals aged 60 and below had a higher prevalence of deficiency (36 cases) compared to those above 60 years (nine cases). However, no deficiency was more common in the younger group (248 cases) than in the older group (71 cases) (Fig. 3).				

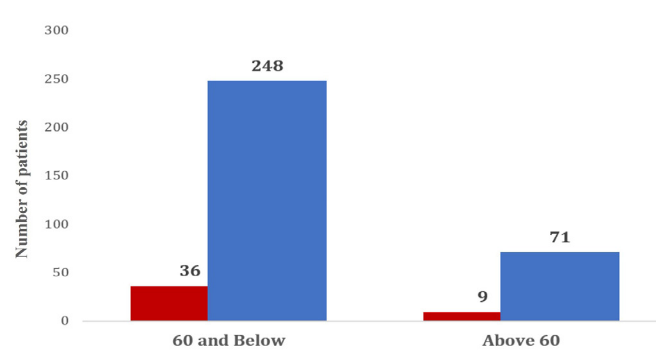

Fig. 3. Comparison of deficiency rates between younger and older age groups.

4. Discussion

This study elucidates the association between vitamin B12 insufficiency and glycemic regulation, with a specific focus on age- and sex-based stratification. By utilizing real-world clinical data, the analysis enhances current understanding of the demographic determinants that may modulate this metabolic relationship. Statistical analyses showed nuanced results. Pearson's correlation analysis showed a correlation between vitamin B12 and HbA1c levels across different subgroups based on the overall population, age, and sex. The overall population showed a weakly positive association ($r = 0.217$) where elevated vitamin B12 levels correlated with increased HbA1c levels (CI, 0.12 to 0.31; p-value <0.001). For patients aged $\leq$ 60, vitamin B12 and HbA1c showed a weakly positive correlation ($r = 0.185$). Our present data align with previous reports showing that hyperglycemia leads to vitamin B12 becoming trapped in the bloodstream, leading to elevated vitamin B12 and HbA1c levels (Akabwai *et al.*, 2015; Looker *et al.*, 2007; Obeid *et al.*, 2011; Li *et al.*, 2022).

The results of Welch's two-sample t-test (Table 5) indicate that vitamin B12 deficiency may be associated with lower HbA1c levels (vitamin B12 deficient versus non-deficient group: HbA1c = 8.07 versus 8.62; t-test = -2.156, 95% CI, -1.04 to -0.05, respectively; p = 0.035). Likewise, data from Table 3 show that vitamin B12 levels increase with age ($\geq$60 versus <60 age group: vitamin B12 levels = 556.31 pg/mL versus 430.65 pg/mL), possibly due to dietary factors, supplementation, or physiological changes with age. HbA1c levels show a modest increase with age ($\geq$60 versus <60 age group: HbA1c levels = 8.76% versus 8.48%, respectively). Our data aligns with previous reports showing that HbA1c levels increase with age. The age-related elevation in HbA1c may be ascribed to diminished insulin sensitivity, compromised beta-cell functionality, and modified erythrocyte turnover, even in the absence of worsening glycemia (Dubowitz *et al.*, 2014; Forbes *et al.*, 2018; Oikonomidis *et al.*, 2021; Langan *et al.*, 2011).

Sex, age, and vitamin B12 deficiency comparisons revealed no significant difference in mean HbA1c values between women and men (8.46% vs. 8.67%, respectively), reflecting a predisposition among women to seek medical advice more readily and adhere to prescribed treatment regimens for diabetes. This feminine predisposition may also explain the slightly higher vitamin B12 levels in women, indicating a greater propensity for vitamin B12 supplementation.

Vitamin B12 deficiency prevalence differed with age (<60 age group: 36/284, 12.7% versus $\geq$60 age group: 9/80, 11.25%) but was not statistically significant, indicating possible age-related variations in vitamin B12 absorption, although dietary habits, comorbidities, and medication use (especially metformin) may also contribute (Oikonomidis *et al.*, 2021). These data align with previous studies showing an association between vitamin B12 status and diabetes management, which suggests that low vitamin B12 levels may contribute to glycemic dysregulation and increased insulin resistance, although mechanisms remain unclear (Dubowitz *et al.*, 2014). Our findings reinforce the hypothesis that vitamin B12 deficiency is prevalent among diabetics, especially those undergoing prolonged medication regimens that adversely impact nutrient absorption.

Although our findings provide valuable insights, they must be interpreted with caution due to several limitations. The cross-sectional study design restricts our ability to establish causal inferences regarding vitamin B12 deficiency and HbA1c levels. Future longitudinal studies involving larger, more diverse populations are warranted to determine directionality for this relationship. Further, other factors may influence vitamin B12 and HbA1c levels, including dietary habits, medication history, and genetic predisposition.

5. Conclusion

This study reveals a statistically significant positive correlation between vitamin B12 and HbA1c levels in diabetics, with B12-deficient individuals demonstrating lower HbA1c levels than those with sufficient B12 levels. Higher vitamin B12 levels in older adults may be attributed to physiological changes, dietary habits, or supplementation. No significant differences in vitamin B12 deficiency were found across age or sex groups. The results align with existing literature, indicating a potential impact of B12 deficiency on glycemic control, possibly due to impaired glucose metabolism. Although the cross-sectional nature of the study limits causal inferences, these findings highlight the importance of vitamin B12 monitoring in diabetics, especially those undergoing prolonged metformin treatment. Further, longitudinal studies are warranted to explore the directional relationship between B12 status and glycemic control in diabetes management.

CRediT authorship contribution statement

All the authors contributed equally to this research article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

All data associated with this study have been presented in the manuscript.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

Acknowledgments

The authors extend the appreciation to the Deanship of Postgraduate Studies and Scientific Research at Majmaah University for funding this research work through the project number (R-2025-1764).

Funding

This work was supported by the Deanship of Scientific Research at Majmaah University (project number no. R-2025-1764).

References

Akabwai, G.P., Kibirige, D., Mugenyi, L., Kaddu, M., Opio, C., Lalitha, R., Mutebi, E., Sajatovic, M., 2016. Vitamin B12 deficiency among adult diabetic patients in Uganda: Relation to glycaemic control and haemoglobin concentration. J Diabetes Metab Disord 15, 26. https://doi.org/10.1186/s40200-016-0250-x

Al Shawabkeh, M.J., Al Jamal, A., 2017. Effect of rosemary on fasting blood glucose, hemoglobin A1c and Vitamin B12 in healthy persons and type 2 diabetic patients taking Glucomid and/or Metformin. National Journal of Physiology, Pharmacy and Pharmacology 8, 87–90. http://dx.doi.org/10.5455/njppp.2018.8.0723812102017

Al-Fawaeir, S., Al-Odat, I., 2022. Influence of metformin intake on serum vitamin B12 levels in patients with type 2 diabetes mellitus. PLoS One 17, e0279740. https://doi.org/10.1371/journal.pone.0279740

Aroda, V.R., Edelstein, S.L., Goldberg, R.B., Knowler, W.C., Marcovina, S.M., Orchard, T.J., Bray, G.A., Schade, D.S., Temprosa, M.G., White, N.H., Crandall, J.P., 2016. Long-term metformin use and Vitamin B12 deficiency in the diabetes prevention program outcomes study. J. Clin. Endocrinol. Metab. 101, 1754-1761. https://doi.org/10.1210/jc.2015-3754

Bokade, V., Gosavi, R.V., Panchalwar, V., 2023. A Study of hematological parameters and Vitamin B12 Levels in type 2 diabetics on long term metformin therapy. Journal of Cardiovascular Disease Research 14, 224–231.

de Boer, H.C., Hovens, M.M., van Oeveren-Rietdijk, A.M., Snoep, J.D., de Koning, E.J., Tamsma, J.T., Huisman, M.V., Rabelink, A.J., van Zonneveld, A.J., 2011. Human CD34+/KDR+ cells are generated from circulating CD34+ cells after immobilization on activated platelets. Arterioscler. Thromb. Vasc. Biol. 31, 408-415. https://doi.org/10.1161/ATVBAHA.110.216879

de Groot-Kamphuis, D.M., van Dijk, P.R., Groenier, K.H., Houweling, S.T., Bilo, H.J., Kleefstra, N., 2013. Vitamin B12 deficiency and the lack of its consequences in type 2 diabetes patients using metformin. Neth. J. Med. 71, 386-390.

Dubowitz, N., Xue, W., Long, Q., Ownby, J.G., Olson, D.E., Barb, D., Rhee, M.K., Mohan, A.V., Watson-Williams, P.I., Jackson, S.L., Tomolo, A.M., Johnson, T.M., Phillips, L.S., 2014. Aging is associated with increased HbA1c levels, independently of glucose levels and insulin resistance, and also with decreased HbA1c diagnostic specificity. Diabet. Med. 31, 927-935. https://doi.org/10.1111/dme.12459

Forbes, A., Murrells, T., Mulnier, H., Sinclair, A.J., 2018. Mean HbA1c, HbA1c variability, and mortality in people with diabetes aged 70 years and older: A retrospective cohort study. Lancet Diabetes Endocrinol 6, 476-486. https://doi.org/10.1016/S2213-8587(18)30048-2

He, J., Jiang, D., Cui, X., Ji, C., 2022. Vitamin B12 status and folic acid/vitamin B12 related to the risk of gestational diabetes mellitus in pregnancy: A systematic review and meta-analysis of observational studies. BMC Pregnancy Childbirth 22, 587. https://doi.org/10.1186/s12884-022-04911-9

Huynh, D.T., Nguyen, N.T., Do, M.D., 2024. Vitamin B12 deficiency in diabetic patients treated with metformin: A cross-sectional study. PLoS One 19, e0302500. https://doi.org/10.1371/journal.pone.0302500

Infante, M., Leoni, M., Caprio, M., Fabbri, A., 2021. Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind. World J Diabetes 12, 916-931. https://doi.org/10.4239/wjd.v12.i7.916

Jatoi, S., Hafeez, A., Riaz, S.U., Ali, A., Ghauri, M.I., Zehra, M., 2020. Low vitamin B12 levels: An underestimated cause of minimal cognitive impairment and dementia. Cureus 12, e6976. https://doi.org/10.7759/cureus.6976

Kibirige, D., Mwebaze, R., 2013. Vitamin B12 deficiency among patients with diabetes mellitus: Is routine screening and supplementation justified?. J Diabetes Metab Disord 12, 17. https://doi.org/10.1186/2251-6581-12-17

Ko, S.H., Ko, S.H., Ahn, Y.B., Song, K.H., Han, K.D., Park, Y.M., Ko, S.H., Kim, H.S., 2014. Association of vitamin B12 deficiency and metformin use in patients with type 2 diabetes. J. Korean Med. Sci. 29, 965-972. https://doi.org/10.3346/jkms.2014.29.7.965

Langan, R.C., Zawistoski, K.J., 2011. Update on vitamin B12 deficiency. Am. Fam. Physician 83, 1425-1430.

Li, W., Zhao, J., Zhu, L.L., Peng, Y.F., 2022. Serum vitamin B12 levels and glycemic fluctuation in patients with type 2 diabetes mellitus. Ther Adv Endocrinol Metab 13, 20420188221102800. https://doi.org/10.1177/20420188221102800

Liu, Y., Geng, T., Wan, Z., Lu, Q., Zhang, X., Qiu, Z., Li, L., Zhu, K., Liu, L., Pan, A., Liu, G., 2022. Associations of serum folate and vitamin B12 Levels with cardiovascular disease mortality among patients with type 2 diabetes. JAMA Netw Open 5, e2146124. https://doi.org/10.1001/jamanetworkopen.2021.46124

Looker, H.C., Fagot-Campagna, A., Gunter, E.W., Pfeiffer, C.M., Sievers, M.L., Bennett, P.H., Nelson, R.G., Hanson, R.L., Knowler, W.C., 2007. Homocysteine and vitamin B12 concentrations and mortality rates in type 2 diabetes. Diabetes/Metabolism Research and Reviews 23, 193–201. https://doi.org/10.1002/dmrr.660

Malla, D., Bajracharya, M.R., Karki, B.B., Rajouria, A.D., Shrestha, P.S., 2021. Prevalence of vitamin B12 deficiency in patients with type II diabetes mellitus on metformin. Jour of Diab and Endo Assoc of Nepal 5, 39-43. https://doi.org/10.3126/jdean.v5i1.38916

Mukhtar, M., Mohamed, Y.S., Elbagir, M., Tesfa, Y., Kenz, S., Kumar, V., Skaria, S., Baraka, M.A., Darwiche, G., Elmalti, A., 2024. Vitamin B12 status among patients with type 2 diabetes mellitus. J Endocrinol Metab 14, 33-39. https://doi.org/10.14740/jem928

Niafar, M., Hai, F., Porhomayon, J., Nader, N.D., 2015. The role of metformin on vitamin B12 deficiency: A meta-analysis review. Intern. Emerg. Med. 10, 93-102. https://doi.org/10.1007/s11739-014-1157-5

Obeid, R., Jung, J., Falk, J., Herrmann, W., Geisel, J., Friesenhahn-Ochs, B., Lammert, F., Fassbender, K., Kostopoulos, P., 2013. Serum vitamin B12 not reflecting vitamin B12 status in patients with type 2 diabetes. Biochimie 95, 1056-1061. https://doi.org/10.1016/j.biochi.2012.10.028

Obeid, R., Shannan, B., Herrmann, W., 2011. Advanced glycation end products overload might explain intracellular cobalamin deficiency in renal dysfunction, diabetes and aging. Med. Hypotheses 77, 884-888. https://doi.org/10.1016/j.mehy.2011.08.002

Oikonomidis, I.L., Tsouloufi, T.K., Kritsepi-Konstantinou, M., Soubasis, N., 2022. The effect of age and sex on glycated hemoglobin in dogs. J. Vet. Diagn. Invest. 34, 331-333. https://doi.org/10.1177/10406387211065046

Owen, M.D., Baker, B.C., Scott, E.M., Forbes, K., 2021. Interaction between metformin, folate and vitamin B12 and the potential impact on fetal growth and long-term metabolic health in diabetic pregnancies. Int. J. Mol. Sci. 22, 5759. https://doi.org/10.3390/ijms22115759

Petkov, C.I., Flecknell, P., Murphy, K., Basso, M.A., Mitchell, A.S., Hartig, R., Thompson-Iritani, S., 2022. Unified ethical principles and an animal research 'Helsinki' declaration as foundations for international collaboration. Current Research in Neurobiology 3, 100060. https://doi.org/10.1016/j.crneur.2022.100060

Rathore, S., Singh, P.K., Kumar, A., 2018. Anemia in Type 2 Diabetes Mellitus (T2DM) and its association with vitamin B12 deficiency. Indian Journal of Pathology and Oncology 5, 51–54. https://doi.org/10.18231/2394-6792.2018.0010

Srinath, K.M., Akash, N., Siddappa, A.L., Madhu, B.G., Shashidhara, K.C., Ramaswamy, P.K.H., 2024. Effect of iron deficiency anemia on HbA1c levels among diabetic and nondiabetic patients. D Y Patil J Health Sci 12, 51-57. https://doi.org/10.4103/dypj.dypj_53_23

Swidan, A.K., Ahmed, M.A.S., 2023. Should we follow the guidelines on vitamin B12 deficiency and diabetes? A retrospective analysis of data from middle eastern population. Alexandria Journal of Medicine 59, 36-41. https://doi.org/10.1080/20905068.2023.2209410

Umay, E., Cevıkol, A., Avluk, O., Unlu, E., Cakcı, A., 2011. Relationship between limited joint mobility syndrome and duration, metabolic control, complications of diabetes as well as effects of the syndrome on quality of life. Int J Diabetes Dev Ctries 31, 207-215. https://doi.org/10.1007/s13410-011-0048-9

Wagner, R., Mahashabde, R., Painter, J., Boehmer, K., 2024. Factors associated with an increased risk of vitamin B12 deficiency in patients with type 2 diabetes mellitus on metformin. Journal of Pharmacy Practice and Research 54, 236-241. https://doi.org/10.1002/jppr.1913

Yazidi, M., Kammoun, E., Oueslati, I., Chihaoui, M., 2024. Metformin-induced vitamin B12 deficiency in patients with type 2 diabetes: a narrative review with a practical approach for screening, diagnosing, and managing vitamin B12 deficiency. Korean J Fam Med 45, 189-198. https://doi.org/10.4082/kjfm.24.0090