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Prevalence and Independent Predictors of Macrocytosis among Metformin-Treated Patients with Type 2 Diabetes Mellitus

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Abstract: Metformin remains the cornerstone of pharmacological management for Type 2 diabetes mellitus (T2DM); however, its long-term use has been associated with impaired vitamin B12 absorption and macrocytosis. The prevalence and independent determinants of macrocytosis in metformin-treated populations remain insufficiently characterized. A cross-sectional observational study was conducted at Saidu Teaching Hospital, Swat, between July 2024 and August 2025. A total of 236 adults with T2DM receiving metformin therapy for at least six months were enrolled. Macrocytosis was defined as a mean corpuscular volume (MCV) exceeding 100 fL. Demographic characteristics, clinical parameters, and concomitant medication use were systematically recorded. Univariate analyses were initially performed, followed by multivariate logistic regression to identify independent predictors of macrocytosis. The overall prevalence of macrocytosis was 16.1% (95% confidence interval (CI): 11.7–21.4%). Multivariate analysis demonstrated that metformin therapy duration >4 years (odds ratio (OR): 3.42, $p = 0.002$), daily metformin dose ≥1500 mg (OR: 2.89, $p = 0.006$), concomitant proton pump inhibitor (PPI) use (OR: 4.15, $p < 0.001$), and age ≥60 years (OR: 2.26, $p = 0.030$) were independently associated with macrocytosis, with concurrent PPI use emerging as the strongest predictor. These findings indicate that macrocytosis is a relatively common hematologic abnormality in metformin-treated adults with T2DM and is strongly influenced by treatment duration, dosage intensity, age, and concurrent PPI therapy. Risk-stratified surveillance strategies incorporating periodic assessment of MCV and serum vitamin B12 levels may therefore be warranted, particularly in high-risk patients, to enhance patient safety and optimize the long-term clinical management of T2DM.

Keywords: Macrocytosis; Metformin; Type 2 diabetes mellitus; Proton pump inhibitor; Vitamin B12 deficiency; Risk factors; Prevalence

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the serious health conditions in the world and its treatment may entail long-term pharmacotherapy to avoid complications (Borse et al., 2021; Sadeeq Bacha et al., 2025; Ullah et al., 2025). The first-line biguanide, metformin, is broadly used because it is effective, safe and possibly has cardiovascular advantages (Grammatiki et al., 2021). Its extensive and frequent chronic usage requires continuing monitoring of its chronic hematologic impacts which are less characterized than the metabolic impacts (Lisco et al., 2023).

The prevalence rates of macrocytosis in metformin-treated patients have varied widely with a range of 10% to more than 30%, depending on population demographics, criteria used to define macrocytosis, the length of treatment, and the nutritional status of a region (Zalaket et al., 2018). This highlights a serious gap in knowledge in terms of the actual burden of this condition. There are limited epidemiological data regarding the distribution of the most important predictive factors: long-term use of metformin (>4 years), large doses (>1500 mg), older

age, and the presence of the proton pump inhibitor (PPI) therapy in diabetic patients (Cicero et al., 2012). This deficiency in the specific epidemiological profiling makes the elaboration of specific screening guidelines difficult and conceals the possible actual health implications of the metformin-associated macrocytosis, especially as the world rates of T2DM are on the ever-growing trend, which will undoubtedly increase the number of individuals for whom long-term metformin therapy becomes standard practice (Khan et al., 2020).

Some of these possible effects include macrocytosis, a condition that presents itself with enlarged red blood cells which are usually shown by an increase in the mean corpuscular volume (MCV) (Savage et al., 2000). Macrocytosis is a benign, medication-related finding, and it is frequently linked to deficiencies in vitamin B12 or folate. Recent reports have indicated a correlation between the intake of metformins and the inability to absorb vitamin B12, which, in theory, can predispose a patient to an eventual occurrence of macrocytosis (Hussain et al., 2025). The clinical importance and occurrence of this effect in the T2DM population in reality is not sufficiently measured (Reach et al., 2017). The available literature shows inconsistent prevalence rates, and it remains unknown whether macrocytosis, in such a case, is always an indication of a clinically significant deficiency or rather a laboratory anomaly (Kabir et al., 2022).

There is no clear definition of the patient-related and treatment-related factors used to predict the development of macrocytosis in individuals receiving metformin therapy (Albai et al., 2020). The predictors that might be included in potential predictors are duration and dose of metformin therapy, age of patients, their nutritional status, the use of other medicines, and the presence of diabetic complications, which need to be investigated in a systematic manner (Li et al., 2021).

The mechanisms by which metformin is thought to cause vitamin B12 deficiency are many, and include changes in intestinal motility, bacterial proliferation and disruption of the calcium-dependent uptake of the intrinsic factor-B12 complex in the terminal ileum (Bell, 2022; Ramzan et al., 2024). This malabsorption may result in the progressive loss of serum B12, which eventually causes hematological conditions like macrocytosis and in severe cases, hematological conditions like megaloblastic anemia (Socha et al., 2020). Both metformin and vitamin B12 deficiency are common to the aging population with T2DM, their interaction has become a major clinical problem that is under-appreciated (Wagner et al., 2021). Routine screening is essential in early diagnosis because untreated B12 deficiency may cause an irreversible neurological complication, which outweighs the cardiovascular and metabolic gains of metformin use (Batulwar & Anjankar, 2024).

This research aims to fill these significant gaps by establishing the prevalence of macrocytosis and its predictors among a group of patients with T2DM receiving metformin therapy. The findings are aimed at informing clinical surveillance approaches by clarifying the extent of this problem and developing patient risk profiles. Finally, the study is expected to optimize long-term safety monitoring during metformin treatment, thereby ensuring that the management of T2DM does not provoke some unintentional health issues.

2. Methodology

A cross-sectional observational design was used in this study to analyze the prevalence and predictors of macrocytosis among patients with T2DM under metformin therapy. The study was conducted at Saidu Teaching Hospital, Swat, for one year between July 2024 and August 2025. The sample population was made up of adult patients aged 18 years and above with a known diagnosis of T2DM that had been on metformin treatment at least six months. Patients with known haematological disorders, severe liver disease, a history of chronic alcohol use, recent blood transfusion, pregnancy, or use of medications known to cause macrocytosis were excluded. PPI use was not an exclusion criterion and was retained as a variable of interest.

Participant recruitment was conducted via convenience sampling. A minimum sample size was estimated with a prevailing prevalence of 15% of macrocytosis in the target population with a 95% confidence level and a margin of error of 5% to give the required number (196). The target population was 250 people to consider the possibility of non-responses and incomplete records of the data. Data were collected by use of a combination of structured interviews with the patients, in-depth examination of their electronic and paper-based medical records, and conventional laboratory tests. The variables collected were demographic variables and clinical variables, including the years of diabetes type and metformin use, dosage of metformin, presence of concomitant drugs (especially PPIs) and presence of diabetic complications or comorbid diseases.

The laboratory test focused on a complete blood count, and MCV of more than 100 fL was used to determine macrocytosis. The complete blood count was analyzed using a Sysmex KX-21 analyzer (Sysmex Corporation, Kobe, Japan) based on flow cytometry principles. Reagents were supplied by Sysmex Asia Pacific Pte. Ltd. (Singapore). The macrocytosis status was also evaluated using BMI and brief dietary history (Veda, 2013).

The SPSS software (version 26.0) was used in the statistical analysis. Means, Standard Deviations (SDs), frequencies, and percentages were used to summarize the characteristics of the study population as descriptive statistics. The prevalence of macrocytosis was expressed in percentage with respective 95% confidence intervals (CIs). Univariate analyses were conducted using chi-square tests for categorical variables and independent *t*-tests for continuous variables to determine factors related with macrocytosis. The candidates of the multivariate logistic

regression model were variables showing a statistically significant relationship ($p < 0.05$) in the univariate analysis. This analytical method was supplemented by the clinical rationale so that all the variables with established or plausible biological relevance to macrocytosis (including age, BMI, medication use) fell under the initial screening of the univariate analysis. Multivariate logistic regression analysis was subsequently performed to identify independent predictors of macrocytosis after adjustment for potential confounding factors. Adjusted odds ratios (ORs) with corresponding 95% CIs were calculated. A *p*-value of below 0.05 was considered statistically significant during the analysis.

The protocol was reviewed and approved by the Institutional Ethical Review Board of Saidu Teaching Hospital, Swat (Reference No. 1754). Informed consent was administered to all the participants in writing beforehand. All information was treated with utmost confidentiality with anonymized identifiers. Participating patients with abnormal laboratory findings were duly informed and referred to their primary care physicians for further assessment and treatment in accordance with ethical clinical practice.

3. Results

A total of 250 eligible patients were enrolled, and after exclusions and removal of incomplete records, 236 patients were included in the final analysis, yielding a response rate of 94.4%. The study population had a mean age of 58.7 years (SD: 10.2) with a slight female predominance (54.2%). The mean duration of T2DM was 8.5 years (SD: 4.1), and the mean duration of metformin therapy was 5.8 years (SD: 3.6). The average daily metformin dose was 1550 mg (SD: 450). Regarding concomitant factors, nearly one-third of participants (32.6%) were using PPIs, and 21.2% had documented diabetic neuropathy. Table 1 shows the demographic and clinical characteristics of the study population and prevalence of macrocytosis.

Table 1. Demographic and clinical characteristics of the study population and prevalence of macrocytosis

Characteristics	Value
Total enrolled (*n*)	250
Total analyzed (*n*)	236
Response rate	94.4%
Age (years), mean ± SD	58.7 ± 10.2
Gender–Female, *n* (%)	128 (54.2%)
Gender–Male, *n* (%)	108 (45.8%)
Duration of T2DM (years), mean ± SD	8.5 ± 4.1
Duration of metformin therapy (years), mean ± SD	5.8 ± 3.6
Daily metformin dose (mg), mean ± SD	1550 ± 450
Concomitant PPI use, *n* (%)	77 (32.6%)
Presence of diabetic neuropathy, *n* (%)	50 (21.2%)
Total patients with macrocytosis (MCV >100 fL), *n* (%)	38 (16.1%)
95% CI	11.7%–21.4%

The prevalence of macrocytosis, defined as a MCV greater than 100 fL, was found to be 16.1% (38 out of 236 patients), with a 95% CI ranging from 11.7% to 21.4%.

Univariate analysis (Table 2) revealed several factors significantly associated with the presence of macrocytosis. Patients with macrocytosis were significantly older, with a mean age of 63.5 years compared to 57.4 years in those without macrocytosis. They also had a notably longer duration of metformin therapy (8.1 years vs. 5.3 years) and were prescribed a higher mean daily metformin dose (1850 mg vs. 1480 mg). Concomitant use of PPIs was strongly associated with macrocytosis, present in 63.2% of the macrocytosis group versus 26.8% of the group without macrocytosis. Patients with macrocytosis had a lower average BMI (25.8 kg/m² vs. 28.4 kg/m²). Factors such as gender, duration of diabetes, and the presence of other diabetic complications did not show a statistically significant association.

Table 2. Univariate analysis of factors associated with macrocytosis (*n* = 236)

Characteristic	Macrocytosis (*n* = 38)	No Macrocytosis (*n* = 198)	*p*-Value
Age (years), mean ± SD	63.5 ± 8.9	57.4 ± 10.1	0.001
Female gender, *n* (%)	22 (57.9%)	106 (53.5%)	0.615
Metformin duration (years), mean ± SD	8.1 ± 3.8	5.3 ± 3.4	<0.001
Metformin dose (mg/day), mean ± SD	1850 ± 380	1480 ± 420	<0.001
PPI use, *n* (%)	24 (63.2%)	53 (26.8%)	<0.001
BMI (kg/m²), mean ± SD	25.8 ± 3.5	28.4 ± 4.2	0.003

To identify independent predictors, variables significant in univariate analysis were entered into a multivariate

logistic regression model. The results are presented in Table 3. After adjusting for potential confounders, four factors emerged as significant independent predictors of macrocytosis. Long-term metformin use, defined as greater than four years, was associated with more than a three-fold increase in odds (OR: 3.42). A high daily metformin dose of 1500 mg or more was associated with an OR of 2.89. Concomitant PPI therapy was the strongest predictor, associated with a four-fold increase in odds (OR: 4.15). Age of 60 years or older was also a significant independent predictor, with an OR of 2.26. BMI, which was significant in the initial analysis, did not retain its independent statistical significance in the multivariate model.

Table 3. Multivariate logistic regression analysis for independent predictors of macrocytosis

Predictor	OR	95% CI	*p*-Value
Metformin duration >4 years	3.42	1.58–7.41	0.002
Metformin dose ≥1500 mg/day	2.89	1.35–6.18	0.006
PPI use	4.15	1.97–8.75	<0.001
Age ≥60 years	2.26	1.08–4.73	0.030
BMI (per 1 kg/m² increase)	0.92	0.83–1.02	0.112

4. Discussion

This research study reported that macrocytosis has a prevalence of 16.1% in patients with T2DM using metformin. Long-term use of metformin (>4 years), high-dose metformin therapy (>1500 mg/day), PPI co-administration, and advanced age (60 years and above) are all significant independent predictors. Such findings contribute to the body of research on the hematological effects of metformin and refine the associations reported in previous studies.

The prevalence of 16.1% (95% CI: 11.7–21.4) can be deemed as a clinically significant figure as it fits in the wide range of 5% to 30% in the literature. It is especially similar to the result of several studies. A systematic review and meta-analysis reported a pooled prevalence of metformin-associated macrocytosis of approximately 17.5%, which is very similar to the result of this study and indicates that it may be a robust global estimate in heterogeneous T2DM populations (Al Zoubi et al., 2024).

Another review study concluded a high prevalence of red blood cell dysfunction, which provides additional support for the generalizability of this risk across different ethnic groups and clinical settings (Williams et al., 2023). Taken together, these findings indicate that macrocytosis is not some laboratory anomaly but a relatively common observation in prolonged users of metformin.

This finding of long-term metformin treatment (>4 years) as a powerful independent predictor (OR: 3.42) supports the postulated cumulative effect of metformin on vitamin B12 metabolism. Longitudinal data strongly indicate this. A prospective cohort study reported an increased risk of subsequent vitamin B12 deficiency and related signs and symptoms such as a high MCV, after approximately 4 to 5 years of metformin treatment, after which the risk leveled off (Infante et al., 2021). Another study conducted in Khyber Pakhtunkhwa, Pakistan, recruited patients aged 45 years or above, who had been taking metformin therapy at least three months and had regular follow-ups at the Endocrinology Unit of Hayatabad Medical Complex and Diabetic Center Hayatabad, Peshawar. After the enrollment, a survey was conducted and the serum vitamin B12 levels were measured. A serum level less than 150 pg/ml was considered to be vitamin B12 deficiency (Khan et al., 2017). This time-related relationship is further supported by the results of an 8.1-year mean of the macrocytosis group and 5.3 years in the group without macrocytosis found in this study.

The adjusted ORs have direct clinical implications of risk stratification and monitoring due to their magnitude. The observation that concomitant use of PPI has the greatest risk (OR: 4.15) implies that the patients taking the combination of metformin and PPI are four times more likely to experience macrocytosis than patients taking metformin and no PPI. This highlights a strong drug-drug interaction. Long-term (>4 years) and high-dose (≥1500 mg/day) use of metformin increases the odds by an approximation of three times. These effect sizes in real life would warrant the change from universal to targeted monitoring. Clinicians must be more suspicious and think about regular MCV and B12 screening of patients in these high-risk groups, especially elderly patients taking combined metformin-PPI therapy.

A dose-response relationship, which is one of the major conditions of causality, is highlighted in the association of higher metformin doses (1500 mg/day and above) with macrocytosis (OR: 2.89). This is consistent with the data of pharmacovigilance and mechanistic studies. A population-based study observed that patients taking doses above 1500 mg/day had much higher odds of biochemical B12 deficiency than those taking lower doses (Reinstatler et al., 2012). Metformin is believed to modify B12 absorption in the terminal ileum through intrinsic factor-mediated and alternative mechanisms, an effect that seems to be dose dependent.

The most interesting result of this current study may be the association between concomitant PPI use and macrocytosis (OR: 4.15), which is the strongest independent predictor. This finding draws attention to an increasingly recognized drug-drug interaction. Metformin and PPIs both independently interfere with vitamin B12

absorption—metformin through intestinal processes and PPIs through the effects of a hypochlorhydric state which inhibits the liberation of protein-bound B12 in food. Their simultaneous application can become synergistic and adverse. The interaction was specifically studied; patients receiving metformin and PPIs were at a much higher risk of B12 deficiency and macrocytosis compared to those receiving either medication as a monotherapy (Hussain et al., 2025), which is deeply supported by the findings of the current study. These observations require increased clinical attention.

The correlation between older age (60 years and above) and macrocytosis is likely multifactorial and may be attributed to age-related changes and subsequent deterioration of nutritional intake, gastric atrophy, and perhaps renal deterioration with respect to metformin clearance and accumulation. Although age is not a modifiable risk factor, it is a valuable predictor to be used to identify a risk group that may be monitored specifically. Though a lower BMI was found to be significant in the univariate analysis related to macrocytosis, the significance did not persist in the multivariate model. This implies that nutritional status, of which BMI is a crude surrogate, may be a confounder mediated by the main predictors such as drug effects and age, but it is not a risk factor. This is contrary to some of previous studies but coincides with the more recent analyses in which pharmacological factors dominate BMI.

It is important to acknowledge that this current study defined macrocytosis solely based on MCV >100 fL without concomitant measurement of serum vitamin B12, methylmalonic acid, or homocysteine. Although macrocytosis is an established morphological sign of B12 deficiency, this is not a pathognomonic sign. A high MCV can also be caused by alcohol consumption, thyroid dysfunction, or other medicines. Although the relationships between metformin and PPI use observed in this study strongly indicate a link with B12 malabsorption, a proportion of the cases in this current study may represent macrocytosis unrelated to vitamin B12 deficiency. This constitutes a limitation of the present analysis, and future research should correlate these MCV changes with direct biochemical validation of vitamin B12 deficiency.

This research has a number of limitations that are associated with its cross-sectional design which does not allow establishment of causality. Although good correlations between the use of metformin/PPIs and macrocytosis have been found, the time course of exposure and response is not determinable. For example, it is not clear whether PPI use preceded the development of macrocytosis or occurred thereafter. Convenience sampling in one tertiary care center could also reduce the external validity of the results of this study. This sample might also not be completely representative of the overall population of patients with T2DM, especially those who are being treated in primary care or in other geographical regions, which may have an impact on the external validity of the estimated prevalence and predictor strengths.

5. Conclusions

This research confirms a prevalence of macrocytosis of approximately one out of six patients with T2DM who are under metformin treatment. It characterizes an apparent high-risk population: patients who are more than 60 years old receiving long-term (>4 years) and high-dose (1500 mg/day or more) metformin therapy, and particularly those using concomitant PPIs. These results support a shift from the current universal to the risk-stratified surveillance. Patients who have all these criteria are recommended to periodically monitor MCV and ideally serum serum B12 levels. In patients receiving a combined metformin-PPI therapy, clinicians need to periodically reconsider whether PPI use is still needed or not.

Author Contributions

Conceptualization, H.A and E.A.; methodology, H.A.; software, Q.A.; validation, N.A., H.K., and I.K.; formal analysis, H.A.; investigation, E.A.; resources, H.K.; data curation, N.A.; writing–original draft preparation, H.A.; writing–review and editing, H.A.; visualization, I.K.; supervision, E.A. All authors have read and agreed to the published version of the manuscript.

Data Availability

The datasets used and analyzed during this study are not publicly available due to restrictions from the corresponding author but can be provided upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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