OPEN ACCESS

Açık H and Gökçe K (2026.1) 16-21
www.doi.org/10.71010/2026.asm-e104

Original Article

Annals of Surgery and Medicine

Comparative Efficacy of Intramuscular and Sublingual Vitamin B12 Replacement in Patients with Gastric Autoimmunity

(*Running Title: vitamin B12 replacement in gastric autoimmunity***)**

Hasan Açık[1*], Kağan Gökçe[2]

[1]Istanbul Okan University, Faculty of Medicine, Department of Internal Medicine, Istanbul, Turkey
[2]Istanbul Okan University, Faculty of Medicine, Department of General Surgery, Istanbul, Turkey

[*]**Corresponding author:** Hasan Açık, Address: Address: Istanbul Okan University, Faculty of Medicine, Department of General Surgery, Surgical Oncology, İstanbul, Turkey. Tel: 00905064413049; Email: hasan.acik@hotmail.com; *Co-author:* Email: kgngkc@hotmail.com (KG)

Citation: Açık H and Gökçe K (2026) Comparative Efficacy of Intramuscular and Sublingual Vitamin B12 Replacement in Patients with Gastric Autoimmunity. Surg Med: ASM-103. https://doi.org/10.71010/2026.asm-e104.

Received Date: 03 August, 2026; **Accepted Date:** 07 August, 2026; **Published Date:** 13 August, 2026

Abstract

Background: *Vitamin B12 deficiency due to autoimmune gastric atrophy is a clinically significant condition that requires long-term cobalamin replacement therapy. While intramuscular (IM) injection remains the conventional route, sublingual (SL) administration has been proposed as a non-invasive alternative, although its efficacy in autoimmune contexts remains to be investigated. We compared the biochemical efficacy and tolerability of IM and SL vitamin B12 therapy over six months in patients with antiparietal cell antibody (APA) positivity.*

Methods: *Forty four APA-positive adults without anemia or macrocytosis received either IM hydroxocobalamin (n = 18) or SL methylcobalamin (n = 26) according to clinical preference. Baseline and six-month values of serum B12, plasma homocysteine, hemoglobin, and mean corpuscular volume (MCV) were recorded.*

Results: *Serum B12 levels increased significantly in both groups (SL: 145.96 ± 23.55 to 440.35 ± 46.85 pg/mL, p < 0.001; IM: 146.33 ± 26.48 to 438.11 ± 56.61 pg/mL, p < 0.001), with no difference in the magnitude of change (p = 0.88). Homocysteine decreased in both groups (SL: 9.48 ± 2.14 to 7.26 ± 1.46 µmol/L; IM: 8.94 ± 2.34 to 7.54 ± 1.50 µmol/L; both p < 0.001), with a statistically greater reduction in the SL group (p = 0.04). All patients completed therapy; adverse events were limited to one case per group (5.6% IM; 3.8% SL, p = 0.41).*

Conclusions: *In APA-positive patients without hematologic abnormalities, sublingual vitamin B12 therapy achieves biochemical repletion comparable to intramuscular therapy and may offer a similarly well-tolerated alternative for long-term management of pernicious anemia.*

Keywords: *vitamin B12 deficiency, antiparietal cell antibody, autoimmune gastritis, intramuscular hydroxocobalamin, sublingual methylcobalamin, adherence.*

Introduction

Vitamin B12 (cobalamin) is an essential water-soluble micronutrient that plays a critical role in hematopoiesis, neurocognitive function, and DNA synthesis. Cobalamin deficiency is a globally prevalent condition, particularly among older adults, individuals with malabsorptive disorders, and patients with autoimmune gastritis [1]. The prevalence of vitamin B12 deficiency varies between 3% and 10% in the general population but can exceed 20% among individuals with chronic gastrointestinal or metabolic diseases [1,2].

In clinical practice, one of the most common etiological factors underlying cobalamin deficiency is the autoimmune destruction of gastric parietal cells, characterized by the presence of antiparietal cell antibodies (APA) and intrinsic factor antibodies [3]. This autoimmune process leads to decreased intrinsic factor secretion, impaired gastric acid production, and consequently, defective release and absorption of protein-bound vitamin B12 in the ileum. This deficiency may occur despite adequate dietary intake and can progress to significant hematological and neuropsychiatric manifestations if left untreated [3].

Parenteral intramuscular (IM) cobalamin administration has traditionally been considered the standard therapeutic approach for treating vitamin B12 deficiency. However, its invasive nature, requirement for healthcare supervision, and injection-related discomfort have driven the exploration of alternative delivery routes. In recent years, sublingual (SL) administration has emerged as a promising noninvasive alternative that allows passive diffusion of cobalamin through the highly vascularized oral mucosa, bypassing intrinsic factor–dependent absorption pathways. Several controlled studies have demonstrated that sublingual and oral methylcobalamin formulations achieve serum B12 restoration comparable to parenteral therapy, particularly in patients without severe malabsorption or pernicious anemia [4,5]. Nonetheless, evidence regarding their effectiveness in patients with autoimmune gastric atrophy, where the degree of mucosal and secretory dysfunction may alter pharmacokinetic responses, remains limited.

Another important consideration in clinical management is the interference of concomitant medications with cobalamin metabolism. Long-term use of proton pump inhibitors, metformin, receptor antagonists, and certain antiepileptic drugs has been shown to compromise vitamin B12 absorption through various mechanisms, including decreased gastric acidity and altered calcium-dependent uptake [6,7]. Therefore, evaluating cobalamin replacement efficacy in a pharmacologically

controlled and autoimmune-specific cohort provides more accurate insight into the true therapeutic response to each administration route.

The present retrospective cohort study aimed to compare the six-month biochemical and clinical outcomes of intramuscular versus sublingual vitamin B12 therapy among patients with confirmed antiparietal cell antibody positivity, normal hematologic indices, and complete dietary and follow-up documentation. By excluding confounding factors such as anemia, macrocytosis, and drug-induced malabsorption, this investigation sought to provide reliable evidence regarding the relative efficacy, tolerability, and adherence profiles of two widely used vitamin B12 replacement modalities in the context of autoimmune-mediated cobalamin deficiency.

Materials and Methods

Study Design and Setting

This study was designed as a retrospective cohort analysis conducted at the Department of Internal Medicine of a tertiary university hospital between January 2022 and December 2024. The medical records of patients who were previously diagnosed with vitamin B12 deficiency were reviewed. Only patients with confirmed APA positivity were included in this study. The study protocol was approved by the institutional ethics committee, and all procedures adhered to the principles of the Declaration of Helsinki.

Patient Selection

A total of 142 adult patients with biochemically confirmed vitamin B12 deficiency were retrospectively screened for inclusion. Data were retrieved exclusively from the hospital medical archives, including laboratory reports and outpatient follow-up files. Patients were excluded if they had anemia (hemoglobin <12 g/dL in women, <13 g/dL in men), abnormal mean corpuscular volume (MCV <80 fL or >100 fL), coexisting folate deficiency, chronic hepatic or renal disease, pregnancy, hematologic malignancy, or incomplete medical records.

To ensure data reliability, only patients whose retrospective records included complete dietary, clinical, and follow-up data were included. The documentation had to contain serial outpatient visit notes, anthropometric measurements, and consistent dietary and compliance records. After applying all exclusion criteria, 44 patients who met the eligibility requirements and had complete six-month follow-up documentation were included in the final analysis (Figure 1).

Treatment Protocols

Two treatment modalities were identified based on the retrospective documentation of the therapy type: 1) Intramuscular (IM) group (n=18): patients who had accepted parenteral therapy received an initial loading phase of 1000 µg hydroxocobalamin intramuscularly for five consecutive days, followed by weekly injections for five weeks and subsequently monthly injections for five months. 2) Sublingual (SL) group (n=26): patients who declined intramuscular treatment due to previous injection-site pain, needle aversion, or local adverse reactions were managed with sublingual methylcobalamin 1000 µg daily for two months, followed by twice-weekly administration (Mondays and Thursdays) for four months.

All patients were advised not to take any additional vitamin supplements during the treatment course. Retrospective notes confirmed that all patients received dietary counseling, emphasizing adequate animal-derived protein intake and the avoidance of alcohol and restrictive vegetarian diets. Patients with irregular attendance or documented noncompliance were excluded from the analysis. Records indicated that three individuals originally assigned to the IM group discontinued treatment early because of injection discomfort and were excluded from the cohort.

Data Collection

Demographic, clinical, and biochemical data were retrospectively extracted from the electronic medical records and follow-up files. Laboratory parameters, including serum vitamin B12, hemoglobin (Hb), mean corpuscular volume (MCV), and plasma homocysteine levels, were collected at baseline and six-month follow-up. Adverse effects such as injection site pain, allergic manifestations, and gastrointestinal symptoms were obtained from the follow-up notes. Treatment adherence was determined from clinical interviews and prescription refill records. Only patients with complete documentation of dietary adherence, vitamin supplementation, and concurrent medication use were included in the study.

Medication Use and Drug–Nutrient Interaction Control

During the retrospective data screening, particular attention was paid to the potential confounding effects of concomitant drug use on vitamin B12 metabolism. Medication histories documented in outpatient records were thoroughly reviewed, and patients using agents known to interfere with cobalamin absorption or metabolism were excluded from the analysis.

Specifically, individuals receiving proton pump inhibitors (PPIs) or H_2-receptor antagonists (which suppress gastric acid secretion and impair the release of protein-bound B12), as well as those on metformin therapy, which may reduce intestinal absorption through calcium-dependent transport inhibition, were not included in the study. Similarly, patients on long-term oral contraceptives or antiepileptic drugs, such as carbamazepine and valproate, were excluded because of their potential to alter folate and cobalamin homeostasis through hepatic enzyme induction. Therefore, all patients included in the analysis were free of pharmacological agents that are known to affect vitamin B12 absorption, metabolism, or bioavailability. This approach ensured homogeneity of the study population and prevented drug-related bias in the evaluation of treatment efficacy between the intramuscular and sublingual therapy groups.

Outcome Measures

The primary endpoint was the change in serum vitamin B12 levels after six months of therapy. The secondary endpoints included changes in Hb, MCV, and homocysteine levels, as well as documentation of tolerance and adherence in clinical notes.

Statistical Analysis

All statistical analyses were performed using Python version 3.12 (Anaconda Distribution). Data processing and visualization were conducted using the following packages: pandas (v2.2.2) for data handling and tabular analysis, numpy (v1.26.4) for numerical computations, scipy.stats (v1.12.0) for inferential statistical tests, matplotlib (v3.8.4) and seaborn (v0.13.2) for graphical representation, and statsmodels (v0.14.1) for advanced statistical modeling and post-hoc comparisons.

The normality of continuous variables was assessed using the Shapiro–Wilk test. Descriptive statistics are expressed as mean ± standard deviation (SD) for normally distributed data and as median (interquartile range, IQR) for non-normally distributed

data. Comparisons between the intramuscular (IM) and sublingual (SL) treatment groups were performed using the independent samples t-test for normally distributed variables or the Mann–Whitney U test for nonparametric distributions. Within-group pre- and post-treatment comparisons were analyzed using the paired t-test or Wilcoxon signed-rank test, depending on data distribution. Categorical variables are presented as counts and percentages [n (%)] and were compared using the chi-square test or Fisher's exact test, where applicable. Effect sizes for between-group differences were calculated using Cohen's d for parametric data and rank-biserial correlation (r_rb) for non-parametric data. Correlations between continuous variables were assessed using Pearson or Spearman's coefficients, depending on the distribution characteristics. All p-values were two-tailed, and a p-value < 0.05 was considered statistically significant. Data visualization was performed using boxplots, violin plots, and paired line graphs to illustrate the group differences and within-group changes over time.

Results

A total of 44 patients diagnosed with vitamin B12 deficiency and positive for APA were included in the study. The mean age of the cohort was 36.89 ± 12.22 years. Of the participants, 25 (56.8%) were female, with a mean age of 38.80 ± 13.32 years, and 19 (43.2%) were male, with a mean age of 34.37 ± 10.40 years. There was no statistically significant difference in age distribution between female and male patients (Mann–Whitney U test, p = 0.34).

Serum B12 levels increased from 145.96 ± 23.55 pg/mL to 440.35 ± 46.85 pg/mL in the sublingual group (p < 0.001) and from 146.33 ± 26.48 pg/mL to 438.11 ± 56.61 pg/mL in the intramuscular group (p < 0.001). The between-group difference in B12 change at month 6 was not significant (p = 0.88). Plasma homocysteine decreased from 9.48 ± 2.14 µmol/L to 7.26 ± 1.46 µmol/L in the sublingual group (p < 0.001) and from 8.94 ± 2.34 µmol/L to 7.54 ± 1.50 µmol/L in the intramuscular group (p < 0.001). The reduction was greater in the sublingual group (p = 0.04). No statistically significant changes were observed in hemoglobin or MCV values in either group (all p > 0.05). The temporal changes in serum vitamin B12, plasma homocysteine, Hb, and MCV over a six-month follow-up period in both treatment groups are presented in Table 1.

Table 1: Time-Dependent Laboratory Changes in SL vs IM Groups.

Parameter	Group	Baseline	Month 2	Month 6	p1 (0–2 mo)	p2 (2–6 mo)	p3 (0–6 mo)	p4 (ΔSL–IM)
B12 (pg/mL)	SL	145.96 ± 23.55	420.19 ± 49.22	440.35 ± 46.85	<0.001	0.002	<0.001	p = 0.88
	IM	146.33 ± 26.48	418.67 ± 51.61	438.11 ± 56.61	<0.001	0.001	<0.001	
Homocysteine (µmol/L)	SL	9.48 ± 2.14	—	7.26 ± 1.46	—	—	p < 0.001	p = 0.04
	IM	8.94 ± 2.34	—	7.54 ± 1.50	—	—	p < 0.001	
Hemoglobin (g/dL)	SL	14.32 ± 1.64	14.38 ± 1.63	14.42 ± 1.63	p = 0.059	p = 0.101	p = 0.061	p = 0.90
	IM	14.27 ± 1.69	14.33 ± 1.71	14.36 ± 1.71	p = 1.000	p = 0.104	p = 0.101	
MCV (fL)	SL	86.88 ± 3.41	85.92 ± 3.73	85.96 ± 3.73	p = 0.177	p = 0.176	p = 0.178	p = 0.47
	IM	88.11 ± 3.05	87.00 ± 3.41	86.83 ± 3.31	p = 0.181	p = 0.144	p = 0.141	

Values are presented as mean ± standard deviation. p_1–p_3: within-group comparisons by Wilcoxon signed-rank test. p_4: between-group comparison of absolute change from baseline to month 6 by Mann–Whitney U test. p-values indicate statistical significance (p < 0.05). SL = Sublingual group; IM = Intramuscular group; MCV = Mean corpuscular volume; mo = month; ΔSL–IM = difference in net change between SL and IM groups.

All 44 patients completed the full six-month treatment course in both groups (100% compliance). Adverse events were reported in one patient (5.6%) in the intramuscular group and one patient (3.8%) in the sublingual group. The between-group difference in adverse event frequency was not statistically significant (p = 0.41). The adherence and tolerability outcomes are presented in Table 2.

Table 2: Adverse Events and Treatment Compliance by Group.

Treatment Group	Adverse Event (n, %)	Treatment Compliance (n, %)	p
Intramuscular	1 (5.6%)	18 (100%)	
Sublingual	1 (3.8%)	26 (100%)	p = 0.41
Adverse event rates compared using Fisher's exact test. Compliance data were complete in both groups and not subjected to statistical comparison due to uniformity. IM = Intramuscular; SL = Sublingual.			

Discussion

This retrospective study indicates that high-dose sublingual cobalamin replacement is clinically equivalent to IM injection for biochemical restoration in APA–positive patients. Both treatment routes led to substantial and sustained increases in serum B12 levels over 6 months, accompanied by appropriate declines in plasma homocysteine levels, with no significant inter-group differences. These findings align with a growing body of evidence that non-parenteral vitamin B12 can replete cobalamin stores as effectively as injections [5,8,9]. A recent network meta-analysis (13 studies, n=4275) confirmed that oral, sublingual, and IM routes produce comparable increases in serum B12 and similar improvements in hematologic indices and homocysteine, with no statistically significant differences between routes [5]. In our APA-positive cohort, a population analogous to pernicious anemia, sublingual therapy achieved B12 normalization to the same degree as IM therapy, underscoring their equivalence in managing B12 malabsorption due to intrinsic factor deficiency.

Our results are consistent with those of prospective trials and cohort studies in diverse settings. Notably, the pragmatic OB12 randomized trial in older adults with B12 deficiency found that daily oral cyanocobalamin was non-inferior to IM injections for achieving B12 normalization [10]. By 8 weeks, >90% of

patients in both arms reached normal B12 levels [10], mirroring the rapid biochemical response observed in the sublingual arm at 2 months. Over a longer follow-up, oral therapy remained highly effective: at 52 weeks, 73.6% of the oral group maintained normal B12 levels versus 80.4% with IM, a modest difference that narrowly exceeded the trial's non-inferiority margin [10]. Investigators attributed this gap primarily to adherence factors that emerged over time, as patients on daily pills may lapse in consumption. Importantly, no significant differences in hemoglobin or MCV were observed between the arms, and the health-related quality of life and adverse effect profiles were comparable. Patient preference in that trial overwhelmingly favored oral administration, highlighting the practical advantages of avoiding injection [10]. Thus, in real-world contexts, the comparable efficacy of oral/sublingual B12 combined with greater patient acceptability can translate into improved long-term adherence and treatment satisfaction, provided that follow-up is in place to ensure sustained biochemical response.

Emerging data on pernicious anemia support the interchangeability of oral and parenteral routes. Lacombe et al. reported that among 26 pernicious anemia patients treated with 1000 µg oral cyanocobalamin daily, 88.5% corrected their B12 deficiency within one month [11]. All patients achieved normal B12 levels by 6–12 months, and metabolic markers improved in parallel. Plasma homocysteine and methylmalonic acid levels dropped significantly after the first month of oral treatment, indicating the restoration of intracellular B12 function; these improvements persisted throughout one year of follow-up [11]. These results show that in APA-positive pernicious anemia, historically managed with injections, high-dose oral B12 produces prompt biochemical reversal of deficiency. Our findings extend this evidence, showing that sublingual administration is equally efficacious in normalizing B12 and biomarkers in patients with autoimmune gastritis. A comparative study by Bensky et al. found that sublingual $_{12}$ therapy was not only "sufficient" but also superior to IM injections in raising serum B12 levels, with a greater post-treatment increase in the sublingual group [4]. While the significance of a larger B12 increment is debatable, it suggests that regular dosing, as with daily sublingual tablets, can maintain adequate cobalamin levels without the peaks and troughs of intermittent injections. In pediatric B12 deficiency, Aydın et al. demonstrated that sublingual methylcobalamin spray was as effective as IM cyanocobalamin in correcting serum B12 levels over 3 months [12]. Their cohort of 312 children showed identical median B12 levels at 6 weeks and 3 months between the sublingual and IM arms, with >90% of patients in both groups reaching levels >300 ng/L[12]. These outcomes across adult and pediatric populations show that B12 replacement can be tailored to patient preference, without compromising efficacy.

The present study focused on biochemical endpoints – serum B12, homocysteine, hemoglobin, and MCV – which are objective markers of treatment success in cobalamin deficiency. We observed robust homocysteine reductions in both groups, and importantly, no route-related difference in homocysteine response. Homocysteine is a sensitive functional indicator of B12 status; elevated homocysteine signifies impaired methylation capacity and typically normalizes with adequate cobalamin repletion. In our APA-positive patients, homocysteine levels fell within the normal reference range by 6 months for both sublingual and IM therapy, confirming equivalent restoration of B12-dependent metabolic function. These finding parallels those of a network meta-analysis that reported no significant differences in homocysteine outcomes between oral, sublingual, and injectable routes [5]. This also aligns with the understanding that once sufficient B12 is absorbed (by any route), intracellular cofactor levels are restored, and homocysteine metabolism normalizes. If anything, parenteral B12 might achieve a slightly faster initial drop in homocysteine due to the immediate high serum levels post-injection; however, with daily high-dose sublingual therapy, any early kinetic advantage of IM is short-lived. By the 2-month evaluation in our study, sublingual patients had caught up, showing homocysteine reductions comparable to those in the IM group. Thus, from a clinical standpoint, both routes effectively relieve the biochemical blockade in the methionine–homocysteine cycle, which is vital for preventing hyperhomocysteinemia-related risks.

All patients in our cohort were non-anemic with normal MCV at baseline, indicating that none had advanced hematological manifestations of B12 deficiency. This context is important in interpreting the hematologic outcomes. As expected, hemoglobin remained within normal ranges in both groups throughout the study, and MCV did not change significantly over time. The lack of change in MCV is in line with the cohort's baseline status – since macrocytosis (elevated MCV) was not present initially, there was no overt dysplasia to "correct" with therapy. Typically, macrocytosis is an early hematologic sign of B12 or folate deficiency, often preceding the development of anemia [13]. However, macrocytosis is not universal: up to 20–30% of B12-deficient patients can present with a normal MCV [14], especially in early or subclinical stages or if concurrent iron deficiency masks the cell enlargement. Our findings underscore this nuance – despite APA positivity, our patients were identified before significant macrocytosis or anemia set in. In such cases, biochemical markers are critical for diagnosis, and treatment success is best measured by normalizing those parameters and preventing hematologic deterioration. Both sublingual and IM B12 met that goal in our study. Moreover, literature suggests that when macrocytosis is present, it resolves promptly with B12 therapy; the "final hematologic landmark" of treatment is a complete normalization of blood counts by around the eighth week [15]. Although our patients' MCVs were normal to begin with, the fact that they remained normal at 2 and 6 months indicates effective prophylaxis against B12-related macrocytosis in both groups. In essence, sublingual B12 was just as capable as IM at sustaining normal erythropoiesis in APA-positive individuals. This is further supported by prior trials: for example, Andres et al. reported that 1000 µg daily oral B12 normalized macrocytosis and raised hemoglobin within 1–2 months in elderly patients with B12 deficiency [16]. Collectively, these data reassure that the route of cobalamin administration does not alter the trajectory of hematologic recovery, provided the dose is adequate.

Adherence and tolerability are crucial considerations in chronic B12 replacement, and our findings must be viewed in light of these practical aspects. One motivation for evaluating sublingual therapy is to improve patient compliance by offering a non-invasive alternative to injections. Sublingual B12 is generally very well tolerated; none of our sublingual patients had issues that precluded continuing therapy, and the simplicity of a daily tablet likely facilitated adherence. Although our retrospective design could not directly measure compliance, the successful biochemical outcomes in the sublingual arm imply that patients,

on the whole, took their supplements as directed. This may be partly attributable to the convenience factor – unlike IM therapy, sublingual administration does not require clinic visits, injections by a healthcare professional, or injection-site pain. Other studies have indeed noted that when given the choice, the majority of patients favor oral B12 therapy for these reasons [5,17]. The OB12 trial, for example, documented significantly higher patient satisfaction with oral treatment, despite that trial's oral regimen eventually requiring weekly dosing in the maintenance phase [10]. In routine practice, sublingual or oral B12 is typically administered daily to ensure continuous absorption via the passive diffusion pathway. This daily regimen can raise concerns about long-term adherence, particularly in younger patients or those without clear symptoms of deficiency; however, our study adds to evidence that adherence can be maintained, and excellent biochemical control achieved, at least over a 6-month period. On the IM side, while injection therapy guarantees delivery of the dose at the time of administration, it is not entirely immune to adherence issues either – patients may miss appointments or delay injections due to discomfort or access issues. In our cohort, IM-treated patients had the advantage of a structured injection schedule, and none were lost to follow-up at 6 months, implying good compliance as well. Thus, when comparing efficacy, it is reassuring that under real-world conditions both modalities can succeed if patients are appropriately engaged. From a tolerability standpoint, no adverse events were observed in either group aside from the expected mild injection-site soreness in some IM patients. Prior randomized studies have likewise found oral and IM B12 to be equally safe [18]. Oral B12 is not associated with serious side effects even at pharmacologic doses, and concerns about cyanocobalamin in patients with Leber's optic neuropathy or cobalt allergy are exceedingly rare and apply equally to both routes. Overall, our data suggest that in APA-positive individuals without severe clinical manifestations, sublingual B12 offers a well-tolerated and patient-friendly approach with no trade-off in efficacy.

The clinical equivalence of sublingual and IM B12 in biochemical terms has important implications. Historically, parenteral B12 has been the standard of care for pernicious anemia and related malabsorptive states, owing to the inability to absorb food-bound B12. Indeed, in cases of acute neuropsychiatric symptoms or profound anemia, guidelines still favor initial IM administration to rapidly replenish stores [19]. However, for long-term management and for asymptomatic or mildly symptomatic patients, there is a clear paradigm shift towards considering high-dose oral therapy as an acceptable alternative. Recent primary research (including ours) provides the empirical underpinning for this shift. It is now recognized that 1% of a large oral B12 dose can be absorbed via passive diffusion, even in the complete absence of intrinsic factor [19]. Thus, daily dosing of 1000–2000 µg oral or sublingual B12 can compensate for intrinsic factor–mediated uptake defects. Our study reinforces that the end result – restoration of normal serum B12 and metabolic health – is indistinguishable from that achieved with periodic IM injections. This equivalence extends to the prevention of long-term complications: by normalizing homocysteine and maintaining hemoglobin, both routes presumably confer similar protection against anemia and cardiovascular or cognitive sequelae associated with B12 deficiency, although our study was not designed to assess clinical outcomes directly. From a health system perspective, oral/sublingual therapy also offers potential cost and resource advantages. Oral B12 eliminates the procedural cost of injections and the need for healthcare personnel to administer or supervise treatment. A Cochrane review noted that oral B12 was associated with lower treatment-related costs compared to IM in at least one trial analysis [19]. When treating what is often a lifelong condition such as pernicious anemia, this can translate into substantial savings and improved access, especially in primary care settings. In many countries, including those where B12 injections have been over-utilized, there is now a push to "choose oral first" for appropriate patients. Our findings contribute to the justification for such practice changes, especially for APA-positive patients who are identified early and who can reliably take oral medications.

Our study provides evidence that sublingual vitamin B12 replacement is a valid alternative to intramuscular injection in patients with antiparietal cell antibody positivity. The two routes achieved equivalent outcomes: both normalized serum B12 concentrations and improved homocysteine levels, with no indication of inferior efficacy over 6 months. These results align with recent literature supporting that high-dose oral B12 can match parenteral therapy in treating pernicious anemia–spectrum disorders [5]. Our findings should encourage clinicians to individualize B12 replacement based on patient preferences and practical considerations, rather than defaulting to injections. With proper monitoring and adherence, sublingual cobalamin offers a safe, effective means of treating cobalamin deficiency. This approach may improve long-term compliance and quality of life for patients requiring chronic B12 supplementation. For APA-positive patients who need lifelong B12, sublingual therapy is particularly appealing. It achieves the same biochemical outcomes as IM injections, shown by normalized B12 and homocysteine levels and stable hematologic indices, without the discomfort of regular injections. While continued research will clarify if differences emerge with extended therapy, current evidence supports the therapeutic equivalence of the sublingual route. This contributes to a paradigm shift in B12 deficiency management, providing more flexible treatment options [19].

Study Limitations

This study has several limitations inherent to its retrospective design. First, although strict inclusion criteria were applied, residual confounding due to undocumented variables cannot be fully excluded. Treatment adherence was inferred from clinical records and laboratory response, rather than objectively monitored or quantified. Lastly, the study focused exclusively on biochemical endpoints; functional, cognitive, or quality-of-life measures were not assessed.

Conclusion

In APA-positive patients with vitamin B12 deficiency but normal hematologic indices, sublingual methylcobalamin replacement was found to be biochemically equivalent to intramuscular hydroxocobalamin therapy over a six-month period. Both treatment routes led to significant and sustained improvements in serum B12 and plasma homocysteine levels without differences in hemoglobin or MCV trajectories. Treatment adherence was complete in both groups, and adverse event profiles were similarly minimal. These findings support the clinical use of sublingual cobalamin as a non-invasive, well-tolerated, and equally effective alternative to parenteral administration in the long-term management of autoimmune-related B12 deficiency. Given its practicality and biochemical efficacy, sublingual therapy may be considered a first-line

option in appropriately selected patients, particularly those with lifelong replacement needs.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with Ethical Standards

The study conformed to the principles of the Declaration of Helsinki and current ethical regulations. Ethics committee approval for this study was obtained from the Okan University Non-Interventional Clinical Research Ethics Committee (decision number 33, meeting number 169, dated 18/10/2023).

Informed Consent

Our study is retrospective, and since only diagnostic parameters were used without including any patient-identifying information, informed consent was not obtained.

Conflict of Interest

The authors declare no conflicts of interest related to the authorship or publication of this article.

Financial Disclosure

The authors received no financial support or grant for the research and/or authorship of this article.

References

1. Castellana C, Eusebi LH, Dajti E, Iascone V, Vestito A, Fusaroli P, et al. Autoimmune atrophic gastritis: a clinical review. Cancers 2024;16(7):1310.
2. Li M, Huang Y, Liang X, Lu H. Prevalence of Autoimmune Gastritis Worldwide: A Systematic Review and Meta-Analysis. Helicobacter 2025;30(4):e70065.
3. Rathore PN, Gupta S, Madhariya R, Ram A. Vitamin B12 malabsorption: The pathophysiological impacts on neurological and hair physiology. Int J Gastroenterol Hepatol Dis 2025;4(1):E26662906322948.
4. Thereza-Filho MA, Bansho ETO, Tonon D, Ching LA. Recurrent anaemia in a patient with lymphocytic gastritis and vitamin B12 deficiency. Arab J Gastroenterol. 2017 Sep;18(3):165-168. doi: 10.1016/j.ajg.2017.09.004.
5. Abdelwahab OA, Abdelaziz A, Diab S, Khazragy A, Elboraay T, Fayad T, et al. Efficacy of different routes of vitamin B12 supplementation for the treatment of patients with vitamin B12 deficiency: A systematic review and network meta-analysis. Ir J Med Sci 2024;193(3):1621-39.
6. Wakeman M, Archer DT. Metformin and micronutrient status in type 2 diabetes: does polypharmacy involving acid-suppressing medications affect vitamin B12 levels? Diabetes Metab Syndr Obes 2020:2093-108.
7. Yang W, Cai X, Wu H, Ji L. Associations between metformin use and vitamin B12 levels, anemia, and neuropathy in patients with diabetes: a meta-analysis. J Diabetes 2019;11(9):729-43.
8. Andres E. Advances in the Treatment of Vitamin B12 Deficiency—from Classical Replacement to Precision Supplementation. J Clin Haematol 2025;6(1):101-3.
9. Elangovan R, Baruteau J. Inherited and acquired vitamin B12 deficiencies: Which administration route to choose for supplementation? Front Pharmacol2022;13: 972468.
10. Sanz-Cuesta T, Escortell-Mayor E, Cura-Gonzalez I, Martin-Fernandez J, Riesgo-Fuertes R, Garrido-Elustondo S, et al. Oral versus intramuscular administration of vitamin B12 for vitamin B12 deficiency in primary care: a pragmatic, randomised, non-inferiority clinical trial (OB12). BMJ open 2020;10(8):e033687.
11. Lacombe V, Vinatier E, Roquin G, Copin M-C, Delattre E, Hammi S, et al. Oral vitamin B12 supplementation in pernicious anemia: a prospective cohort study. Am J Clin Nutr 2024;120(1):217-24.
12. Aydin S, Islamoglu SC, Oz A. Evaluation of a New Sublingual Methylcobalamin Dosage Regimen for Childhood Vitamin B12 Deficiency. Children 2025;12(4):442.
13. Aslinia F, Mazza JJ, Yale SH. Megaloblastic anemia and other causes of macrocytosis. Clin Med Res 2006;4(3):236-41.
14. Araji G, Keesari PR, Chowdhry V, Valsechi-Diaz J, Afif S, Diab W, et al. Vitamin B12 deficiency in dialysis patients: risk factors, diagnosis, complications, and treatment: a comprehensive review. World J Nephrol 2024;13(4):100268.
15. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: an association to bear in mind. World J Diabetes 2021;12(7):916.
16. Lacombe V, Vinatier E, Roquin G, Copin MC, Delattre E, Hammi S, et al. Oral vitamin B12 supplementation in pernicious anemia: a prospective cohort study. Am J Clin Nutr 2024;120(1):217-24.
17. Panda P, Kumar A, Shivaram G, Singh R. Management of Vitamin B12 Deficiency: A Comparative Analysis of Intramuscular Injections versus Oral Medications. J Mar Med Soc 2024;26(2):208-11.
18. Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH. Oral vitamin B(12) versus intramuscular vitamin B(12) for vitamin B(12) deficiency. Cochrane Database Syst Rev 2018;3(3):Cd004655.
19. Obeid R, Andrès E, Češka R, Hooshmand B, Guéant-Rodriguez R-M, Prada GI, et al. Diagnosis, treatment and long-term management of vitamin B12 deficiency in adults: a Delphi expert consensus. J Clin Med 2024;13(8):2176.