



Vitamin B12 Deficiency on Long-Term Metformin and Proton Pump Inhibitors: A Case for Scheduled Testing

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Abstract

The two drugs named in the title do not carry equal evidence. Metformin is established: it reduces serum B12 in 10 to 30 per cent of users, a regulator has reclassified low B12 as a common side effect affecting up to one in ten, and in a study of 231 matched pairs deficiency was present in 22.5 against 7.4 per cent, persisting at 17.9 against 5.6 per cent after acid-suppressant users were excluded. For proton pump inhibitors the evidence conflicts: one systematic review found no difference in serum B12 between users and controls, with a standardised mean difference of 0.01 ($p = 0.92$), while an earlier meta-analysis of acid-lowering drugs reported a hazard ratio of 1.83 using inconsistent deficiency criteria. Testing meanwhile is uncommon: in 104 patients taking both agents, 13.5 per cent had a documented level and none was deficient.

Keywords: Vitamin B12; Metformin; Proton pump inhibitors; Monitoring; Polypharmacy

Introduction

Metformin and proton pump inhibitors are first-line treatments for type 2 diabetes and for acid-related disease respectively, and both are taken for years [1,2]. Each has been associated with reduced absorption of vitamin B12, and the two are frequently co-prescribed [1,3].

Deficiency is prevalent yet often underdiagnosed, particularly in older patients, because the clinical manifestations are subtle while the potential complications, haematological and neuropsychiatric, are serious [3,4]. Deficiency has been linked to cognitive decline, neuropathy, impaired bone mineralisation, fracture, muscle weakness and falls [5].

This review examines what is established for each drug separately, where the evidence conflicts, how much testing actually happens, and what would have to be true for scheduled testing to be worthwhile.

Objective

This review sets out to establish four things from the published literature. First, the strength of evidence linking metformin to B12 deficiency. Second, whether the evidence for proton pump inhibitors supports the same conclusion. Third, what monitoring is currently performed and what it finds. And fourth, at what duration and in which patients guidance places the threshold for testing.

Literature Review

The metformin evidence: Metformin has been shown in multiple studies to reduce serum B12 in 10 to 30 per cent of patients [1]. Reported prevalence of deficiency in metformin-treated patients with diabetes ranges from approximately 6 to 50 per cent across studies [6]. A regulator concluded in 2022 that the effect occurs more frequently than previously thought, that low B12 should now be considered a common side effect particularly with high-dose or long-term use, affecting up to one in ten people, and required an update to the product information for all metformin-containing medications [6].

A controlled comparison: A cross-sectional study compared 231 patients with type 2 diabetes taking metformin against 231 controls, defining biochemical deficiency as serum B12 below 180 pg/mL. Deficiency was more frequent in the metformin group at 22.5 against 7.4 per cent, and the difference persisted after excluding users of proton pump inhibitors and H2 antagonists at 17.9 against 5.6 per cent (Figure 1) [7]. The factors interfering with serum B12 were use of acid suppression and metformin duration of ten years or more, with acid-suppressant use associated with deficiency at an odds ratio of 2.60 (95% CI 1.34 to 5.04) [7].

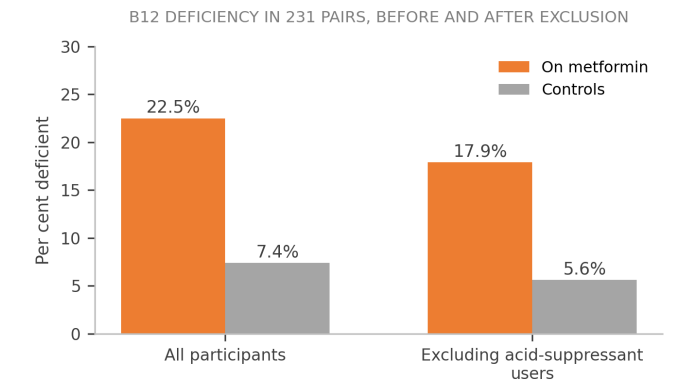


Figure 1: B12 deficiency in 231 matched pairs, before and after exclusion [7]

Where the acid-suppression evidence conflicts: A systematic review and meta-analysis of long-term proton pump inhibitor therapy found no difference between users and controls in serum total vitamin B12, with a standardised mean difference of 0.01 (95% CI -0.14 to 0.16, p = 0.92), nor in total homocysteine at 0.05 (-0.02 to 0.11, p = 0.17) (Figure 2) [8]. An earlier meta-analysis of five studies of acid-lowering drugs reported an association with deficiency at a hazard ratio of 1.83 and recommended monitoring, but its criteria for what constituted deficiency were not consistent between the included studies [8].

Table 1: Evidence by agent and duration, as published

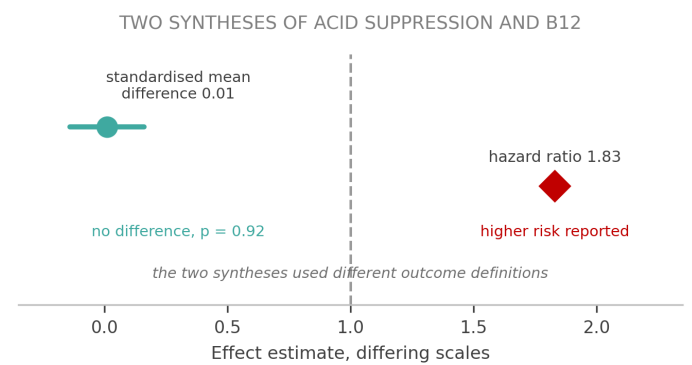


Figure 2: Two syntheses of acid suppression and vitamin B12 [8]

A mechanistic asymmetry: Metformin interferes with five different pathways of vitamin B12 absorption, whereas proton pump inhibitors principally reduce gastric acid production, which has been offered as an explanation for why metformin presents the greater risk (Figure 3) [9]. Short-term proton pump inhibitor use has been shown to decrease B12 levels over a two-week period, while studies of long-term use have yielded conflicting results [1].

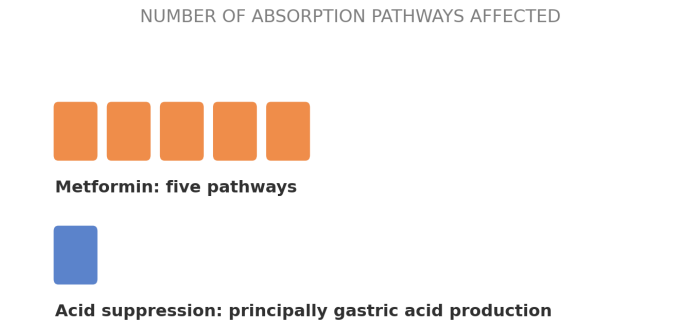


Figure 3: Absorption pathways affected by each drug class [1,9]

Agent	Strength of association	Basis
Metformin	Established	10 to 30% reduction in serum B12 [1]
Metformin, long duration	Stronger	Ten years or more [7]
Acid suppression, short term	Reduction shown	Over two weeks [1]
Acid suppression, long term	Conflicting	No difference against a hazard ratio of 1.83 [8]

Longer-term acid suppression in polypharmacy: A systematic review of long-term use of six months or more in older adults on polypharmacy identified five studies including 693 participants and reported a 12 to 18 per cent reduction in serum vitamin B12 over twelve months of use [5]. The same review notes that medications frequently co-prescribed in this population, including metformin, independently impair absorption of key micronutrients and may act synergistically when combined [5].

How much testing happens: A retrospective analysis at a single health centre identified 104 patients receiving concomitant metformin and proton pump inhibitor therapy, most commonly for one to four years. Fourteen patients, or 13.5 per cent, had a

documented B12 level, none was categorised as deficient, and seven were prescribed a supplement during the study period (Figure 4) [10]. The authors concluded that their data did not support routine monitoring for patients with four years of therapy or less, while noting it may matter for those on longer-term therapy or with symptoms [10].

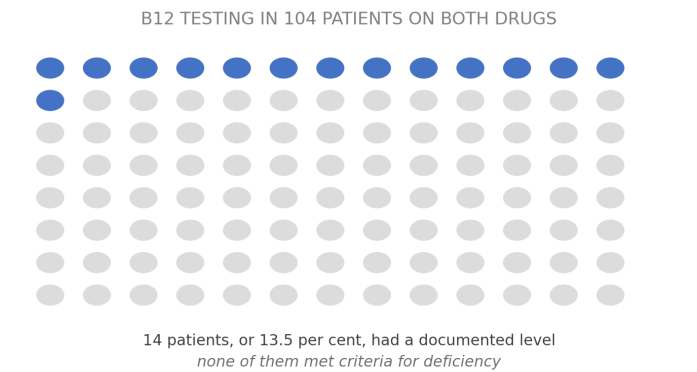


Figure 4: Documented B12 testing in 104 patients taking both drugs [10]

What guidance says: Professional guidance recommends periodic monitoring for patients on metformin, particularly beyond four years of therapy or with additional risk factors, since the B12-lowering effect increases with time, though a frequency has not been agreed (Figure 5) [11,12]. There are no specific guidelines on screening modalities in this population [6]. Consensus reported in one quality improvement study holds that screening is encouraged with long-term metformin and is not typically recommended for long-term acid suppression, though it may be considered in high-risk or symptomatic patients [9].

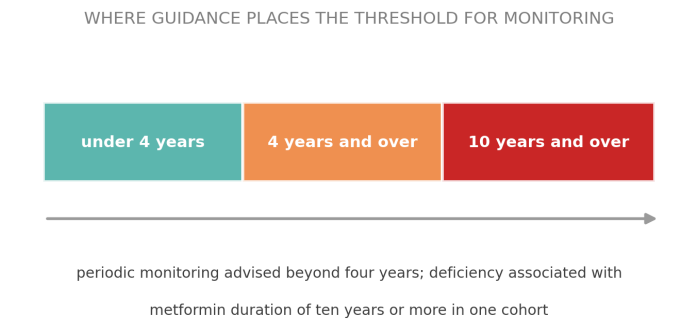


Figure 5: Where guidance places the threshold for monitoring [7,11,12]

What a test would have to measure: Each single biomarker has limitations, and there is general agreement that deficiency should be diagnosed using a combination of two or more markers, drawn from serum vitamin B12, homocysteine, methylmalonic acid and holotranscobalamin (Figure 6) [8]. The reviewing authors note a lack of studies using multiple biomarkers, which makes it difficult to recommend monitoring in low-risk patients on chronic acid suppression, and call for future studies to include at least two markers alongside serum folate, calcium and dietary intake across age brackets and dosages [8].

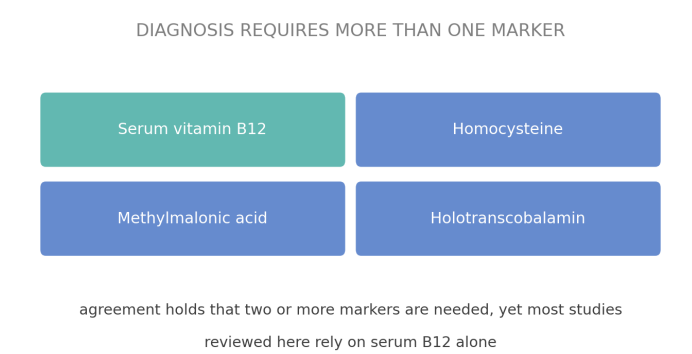


Figure 6: Markers proposed for diagnosis [8]

Table 2: Summary of the reviewed evidence

Consideration	What the evidence shows
Prevalence on metformin	Approximately 6 to 50% across studies [6]
Regulatory position	Common side effect, up to one in ten [6]
Acid suppression alone	Conflicting between syntheses [8]
Combined therapy, 1 to 4 years	No deficiency found in one audit [10]
Testing performed	13.5% of eligible patients [10]

The randomised and long-term metformin evidence: A randomised placebo-controlled trial of long-term metformin in type 2 diabetes examined risk of B12 deficiency directly [13], and post hoc analysis of a 4.3-year randomised trial followed methylmalonic acid as well as serum B12 [19]. Long-term use and deficiency were examined in a large prevention programme outcomes study [12]. Risk factors in metformin recipients have been identified [14], and biochemical deficiency related to both therapy and supplement use in national survey data [15]. Systematic review and meta-analysis have since pooled the association [16,17], with dose examined separately [18] and associations with anaemia and neuropathy assessed together [33]. The long-term association has been reviewed as a standing clinical concern [34].

The acid-suppression literature in more detail: A large study examined both proton pump inhibitor and H2 receptor antagonist use in relation to deficiency [21], and the meta-analysis reporting a hazard ratio drew on five such studies [22]. Earlier case-control work assessed the question in older adults [23], and a cohort examined long-term use and B12 status in elderly individuals [24]. Expert review has weighed the risks and benefits of long-term use [25], and the wider question of vitamin and mineral depletion on these drugs has been reviewed with its clinical implications [26]. The stomach itself is identified as a commonly overlooked contributor to micronutrient deficiency [27].

Recognising and treating the deficiency: National guidelines exist for the diagnosis and treatment of cobalamin and folate disorders [28], and clinical reviews set out recognition and

management [29,31]. The condition presents in many forms, which is part of why it is missed [30,32], and its consequences have been described comprehensively [4,32]. These accounts bear on what a positive test would lead to, which is the question any monitoring proposal has to answer [28,31].

Table 3: What is and is not established about monitoring on these drugs

Question	What the evidence supports
Does metformin lower B12?	Yes, established across designs [1,13,16]
Do acid suppressants?	Conflicting between syntheses [8,22]
Does duration matter?	Yes, effect increases with time [11,12]
Is testing performed?	13.5% in one audit [10]
Can one marker diagnose it?	No, two or more advised [8,28]

Method

Search strategy: PubMed and the archives of the major diabetes, gastroenterology, pharmacy and geriatric medicine journals were searched for studies of vitamin B12 status in users of metformin and acid-suppressing drugs. Search terms combined vitamin B12 deficiency with metformin, proton pump inhibitor, monitoring, duration of therapy and polypharmacy. Reference lists of the acid suppression meta-analysis [8] and the monitoring audit [10] were screened by hand for primary sources.

Eligibility: Studies were included if they reported vitamin B12 status in defined populations exposed to either drug class, examined monitoring practice, or issued recommendations. Regulatory statements are cited for their content and identified as such. Where a study did not separate acid-suppressant classes, that is stated.

Data extraction and handling: Population, drug and duration of exposure, the definition of deficiency applied and the biomarker used were extracted as published. The biomarker and threshold are stated alongside every prevalence figure, because reported prevalence in metformin users spans approximately 6 to 50 per cent and the reviewing authors of the acid suppression evidence attribute much of the conflict between syntheses to inconsistent deficiency criteria. This review reports published findings and does not constitute guidance on prescribing, monitoring, supplementation or deprescribing for any individual patient, all of which are matters for the treating clinician. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis of published literature and was not registered as a systematic review.

Concluding Remarks

The title pairs two drugs whose evidence is not comparable, and separating them is the first useful step. For metformin the association is established across multiple lines: reduction in serum B12 in 10 to 30 per cent of users, a controlled comparison showing 22.5 against 7.4 per cent deficiency that survived exclusion of acid-suppressant users, and a regulatory reclassification of the effect as common [1,6,7].

For proton pump inhibitors the position is genuinely unsettled. One systematic review found a standardised mean difference of 0.01 with a p value of 0.92, which is as close to no signal as a result can be; an earlier meta-analysis reported a hazard ratio of 1.83 [8]. The reviewing authors attribute the discrepancy to inconsistent deficiency criteria between the included studies, which is a methodological explanation rather than a biological one [8].

The mechanistic account supports the asymmetry rather than merely rationalising it. Metformin interferes with five separate absorption pathways; acid suppression works principally through reduced gastric acid [9]. Two interventions with different numbers of points of action on the same pathway would not be expected to produce equivalent effects, and the data are consistent with that.

The monitoring audit is the most awkward result for the case the title makes. In 104 patients on both drugs, 13.5 per cent had a documented level and none of those tested was deficient [10]. Two readings are available and the study cannot distinguish them: either deficiency is genuinely rare at one to four years of combined therapy, or the 13.5 per cent who were tested were selected in a way that missed it. The authors take the first reading and confine their negative recommendation to that duration [10].

Duration is where the evidence converges. Deficiency was associated with metformin use of ten years or more in the controlled study, guidance places its threshold beyond four years, and the audit finding of no deficiency covers a population whose typical exposure was one to four [7,10,11]. Those three observations are consistent with a time-dependent effect and with testing being unrewarding early and worthwhile later.

A measurement problem sits underneath all of it. Agreement holds that diagnosis requires two or more biomarkers, and most of the studies reviewed here rely on serum B12 alone [8]. A test that cannot reliably establish the outcome will produce exactly the pattern seen in this literature: wide prevalence ranges, conflicting syntheses, and difficulty issuing a recommendation. The call for studies using at least two markers is the specific thing the field needs [8].

Three limitations belong with these conclusions. The controlled comparison is cross-sectional, so duration of metformin use and deficiency are measured at the same moment and causal direction is inferred rather than demonstrated [7]. The

monitoring audit involves 104 patients at one centre with only 14 tested, so the absence of deficiency rests on a very small denominator [10]. And several studies do not separate proton pump inhibitors from H2 antagonists when calculating risk, which limits what can be said about either class individually [1,8,20]. The regulatory advice that prompted the change in product information addressed metformin specifically and does not extend to acid suppression [20].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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