

# VITAMIN B12 DEFICIENCY INDUCED BY THE USE OF GASTRIC ACID INHIBITORS: CALCIUM SUPPLEMENTS AS A POTENTIAL EFFECT MODIFIER

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**Abstract:** *Objective:* Use of gastric acid inhibitors has emerged as a risk factor of vitamin B12 deficiency, especially in older adults. Calcium supplements could be an effect modifier of this relationship by its role in the absorption process of vitamin B12. The aim of this study is to examine whether the use of calcium supplements could be an effect modifier of the association between gastric acid inhibitors and vitamin B12 deficiency. *Design:* Cross-sectional study based on medical chart reviews. *Setting:* Geriatric Assessment Unit (GAU) of a university-affiliated hospital. *Participants:* The study included 172 patients discharged from the GAU between 2008 and 2012. *Measurements:* Cases of vitamin B12 deficiency were identified as those who had received a diagnosis of vitamin B12 deficiency, and/or were receiving a treatment for vitamin B12 deficiency. Use of gastric acid inhibitors and calcium supplements at admission was determined from the pharmacist report. Associations between medications and vitamin B12 status were investigated using logistic regression models. *Results:* Seventy-one patients (41%) had vitamin B12 deficiency. At admission, 42% were taking gastric acid inhibitors and 45% calcium supplements. After adjustment for covariates, analyses revealed that vitamin B12 deficiency was more likely among users of gastric acid inhibitors who did not concomitantly received calcium supplements [OR=3.12; P=0.01]. Conversely, no significant association was observed in patients using both, gastric acid inhibitors and calcium supplements [OR=1.30; P=0.59]. *Conclusions:* The present study provides the very first evidence that the use of calcium supplements could be an effect modifier of the association between gastric acid inhibitors and vitamin B12 deficiency. Failure to consider calcium supplements as an effect modifier could have led to biased risk estimates in previous published studies.

**Key words:** Gastric acid inhibitors, proton pump inhibitors, vitamin B12 deficiency, calcium supplements.

## Introduction

Vitamin B12 malabsorption can occur from hypochlorhydria induced by the use of gastric acid inhibitors, specifically proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs). Basically, these drugs alter the release of vitamin B12 from its food-protein carriers, which prevents its liaison to the intrinsic factor (IF) (1-7). Accordingly, observational studies have reported an increased risk for vitamin B12 deficiency among long-term users of gastric acid inhibitors (8-13). However, risk estimates were inconsistent across studies, fluctuating from 0.92 to 4.45. This variability can arise from differences in studies' samples and designs, potential biases, and residual confounding. Another explanation can stem from failure to account for potential effect modifiers, notably calcium supplementation.

Existing data from pioneer studies do suggest that calcium supplements can restore vitamin B12 absorption in various conditions such as steatorrhea (14) and hypoparathyroidism (15). More recently, calcium supplements were also shown to reverse vitamin B12 malabsorption induced by metformin, an oral antidiabetic (16). This effect of calcium supplements could relate to the role of calcium ions in the absorption process of vitamin B12 (17). To our knowledge, whether calcium supplements could also reverse the effect of gastric acid inhibitors on vitamin B12 absorption remains unknown.

Vitamin B12 deficiency is common in older adults, with prevalence of 5-15% in community-dwellers (18-21) and up to 42% in hospitalized patients (22-25). Moreover, gastric acid inhibitors and calcium supplements are known to be widely-prescribed drugs in aged individuals. For instance, a recent report from the Public Drug Insurance Plan in Quebec (Canada) revealed that 34.1% of individuals aged 65 or older were PPI users in 2010 (26). Accordingly, the relationship between gastric acid inhibition and the risk of vitamin B12 deficiency is primary investigated in older adults.

In Quebec we benefit from an in-hospital program named the Geriatric Assessment Unit (GAU), where community-dwelling aged and vulnerable patients with acute conditions are admitted for comprehensive assessment and short-term care. In the present cross-sectional study, we performed a chart review of 172 GAU patients to examine whether the use of calcium supplements could be an effect modifier of the association between gastric acid inhibitors and vitamin B12 deficiency.

## Methods

This retrospective cross-sectional study is based on data collected from hospitalization records of patients discharged from the GAU of the Institut universitaire de gériatrie de Montréal (IUGM), between January 1st, 2008 and March 31st, 2012. During this period, there were 565 discharges from which

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212 hospitalisation records (37.5%) were randomly selected. Thirteen hospitalisation records could not be reviewed because the charts were either purged from detailed information (n=5) or not available at the Medical Records Department at the time of data collection (n=8). We further excluded 27 hospitalization records of patients admitted for a very short stay ( $\leq 5$  days), which was mostly due to admission for a specific procedure (eg, investigation of sleep apnea, administration of intravenous antibiotics) so that no comprehensive clinical assessment was performed. The final sample included thus 172 hospitalizations. The study was approved by the medical director and the research ethics committee of the IUGM.

Hospitalization records were reviewed by a registered dietitian. Data were collected from the hospital administrative database, the Summary Hospitalization Sheet filled at discharge by the attending physician, and the Feuille d'ordonnance médicale de départ, which is a discharge prescription form, filled by the pharmacist and the attending physician, and describing the prescription regimen at admission and discharge (27).

**Outcome:** Cases of vitamin B12 deficiency have been identified as the ones who had received a diagnosis of vitamin B12 deficiency (based on the list of diagnoses of the Summary Hospitalization Sheet), and/or were receiving a treatment for vitamin B12 deficiency. For each patient, we have also noted if the complete blood count and the measurement of serum vitamin B12 have been performed at admission. Of note, tests for functional biomarkers of vitamin B12 status, namely serum methylmalonic acid and homocysteine, are not routinely available at the IUGM and consequently, were not performed in any of the hospitalizations reviewed.

**Gastric acid inhibitors and calcium supplements:** The use of prescription PPIs, H2RAs, and calcium supplements upon GAU admission was determined. The specific molecule used and the daily dose were noted. Patients with "on-demand" (pro re nata) prescription of PPIs or H2RAs were not considered as PPI/H2RA users. We identified patients who were ongoing an intensive gastric acid inhibition treatment as follows: patients with a daily dose of PPIs or H2RAs higher than the standard daily dose, or patients taking both classes, H2RA and PPI, concomitantly.

**Covariables:** Age at admission, sex, patient's origin at admission, and destination at discharge were determined from the hospital administrative database. Reason of admission and comorbidities were collected from the Summary Hospitalization Sheet. The number of prescribed drugs at admission has been determined. This number excludes "on-demand" (pro re nata) medication, topical medication, and eye drops.

In order to account for potential confounders, patients with other conditions that could lead to vitamin B12 deficiency were identified, including atrophic gastritis, Crohn's disease, coeliac disease, total or partial gastrectomy, gastric surgery, pancreatectomy, pancreatitis, and ileal resection. We

also identified those who were taking metformin, an oral antidiabetic drug that could also alter vitamin B12 absorption (28). The nursing notes and the dietitian consultation sheet (when available) have been checked to determine if any patient has reported following a vegetarian or vegan diet. Falsely elevated serum vitamin B12 levels can be observed in chronic kidney disease, liver diseases, alcoholism, and cancer (29, 30), which could preclude or delay the diagnosis of vitamin B12 deficiency. Therefore, patients with any of these conditions have been identified. Similarly, we have identified patients who have reported taking over-the-counter (OTC) supplements, and those with conditions that could be indications for gastric acid inhibition.

**Statistical analyses:** Student's *t* tests, Fisher's exact tests, and  $\chi^2$  were used for crude comparison of patients' characteristics between cases of vitamin B12 deficiency and non-cases. Logistic regression models have been used to examine the association between gastric acid inhibitors and vitamin B12 deficiency. In Model 1, the OR was estimated without taking into account the use of calcium supplements. In Model 2, the use of calcium supplements was included as an effect modifier. The two logistic regression models were adjusted for age and sex, in addition to covariates which have been found to be associated with vitamin B12 deficiency in crude analyses. Analyses were conducted using IBM SPSS Statistics 22;  $P < 0.05$  was considered significant.

## Results

Hospitalization records pertained to 57 men and 115 women aged 61.8 to 100.8 years (Table 1). Main reasons for admission were neurodegenerative diseases (26.7%), functional decline and deconditioning (18.0%), and falls/mobility disabilities (18.0%). Prevalent use of PPIs was common (42.4%), most patients receiving pantoprazole (63.0%) or esomeprazole (24.7%). Typically, PPI users received the standard daily dose (87.7%), while 9 patients had twice the standard dose daily. Only 3 patients were prevalent users of H2RAs, all three being also prevalent users of PPIs. Prescribed calcium supplements were also widespread (44.8%). All were calcium carbonate and doses varied from 250 to 1,500 mg daily with 81.8% of patients receiving  $\geq 1,000$  mg/day.

Seventy-one patients (41.3%) were found with vitamin B12 deficiency (Table 2). Of note, investigation of the vitamin B12 status was quite systematic at the GAU with serum vitamin B12 concentration and complete blood count determined at admission in 94.8% and 100% of hospitalizations, respectively. In crude analyses, there was slightly more patients ongoing gastric acid inhibition among cases of vitamin B12 deficiency, although the difference was not significant (Table 2). However, marginally significant difference was found when the intensity of the treatment is considered. Significant difference was also observed when concomitant use of prescribed calcium supplements was accounted for.

**Table 1**

Description of the 172 frail older adults admitted at the Geriatric Assessment Unit of the Institut universitaire de g  riatrie de Montr  al and included in the present study

| Characteristics                              | Values <sup>1</sup> |
|--|---------------------|
| Female, %                                    | 66.9                |
| Age, y                                       | 81.2±8.0            |
| Origin at admission, %                       |                     |
| Home, with or without in-home care           | 80.2                |
| Transfer from another hospital unit          | 18.0                |
| Long-term care unit or nursing homes         | 1.7                 |
| Destination at discharge, %                  |                     |
| Home, with or without in-home care           | 84.3                |
| Transfer to another hospital unit            | 6.4                 |
| Long-term care unit or nursing homes         | 7.0                 |
| Death during the GAU stay                    | 2.3                 |
| Comorbidities, %                             |                     |
| Chronic kidney disease                       | 27.9                |
| Chronic obstructive pulmonary diseases       | 11.6                |
| Coronary artery diseases and atherosclerosis | 36.1                |
| Diabetes                                     | 25.6                |
| Falls and/or mobility disabilities           | 35.5                |
| Heart failure                                | 14.0                |
| Inflammatory arthritis                       | 26.7                |
| Malnutrition                                 | 30.8                |
| Neurodegenerative diseases                   | 46.5                |
| Number of prescribed drugs at GAU admission  | 8.9±4.3             |

GAU, Geriatric Assessment Unit; 1. Values are in percentages or mean ± SD.

Logistic regression analyses: Both models 1 and 2 revealed a significant relationship between the use of gastric acid inhibitors and vitamin B12 deficiency. In Model 1, an OR=2.04 has been found (95%CI: 1.04-3.99; P=0.039). However, Model 2 revealed calcium supplements as a strong effect modifier (Table 3). Indeed, only patients who used gastric acid inhibitors without concomitant use of calcium supplements showed an increased likelihood of vitamin B12 deficiency. The two logistic regression models were adjusted for sex, age, and ‘diseases related to falsely elevated serum vitamin B12 levels’, the latter being the only relevant covariate identified in crude analyses (Table 1). We did not adjust the model for ‘the use of OTC supplements’ as the number of OTC supplement users was very small (n=10). Further adjustment for ‘gastroesophageal reflux disease/dyspepsia’ reduced slightly the risk estimate from 3.12 to 2.69 [95%CI: 1.07-6.78]; P=0.036).

## Discussion

The present study provides the first evidence that calcium supplements could be an effect modifier of the relationship between gastric acid inhibitors and vitamin B12 deficiency. Incidentally, we revealed an increased likelihood of vitamin B12 deficiency only in patients who underwent PPI therapy without concomitant use of calcium supplements, while no effect has been observed in patients with both treatments. These results shed a new light on previous published data and give new insights on how prescription drugs may affect vitamin B12 status in older adults.

Our findings are in line with published reports where vitamin B12 status improved following oral administration of calcium in steatorrhea (14), and hypoparathyroidism (15). Calcium supplementation as an effect modifier have also been studied in one small trial examining vitamin B12 malabsorption induced by metformin (16). In the latter, 14 diabetic patients treated with sulfonylureas have been transferred to metformin. After 3 months, these patients showed a significant decrease of two biomarkers of vitamin B12 status, serum vitamin B12 and holotranscobalamin II. Oral calcium carbonate (1,200 mg daily) was then started for one month, which resulted in an increase of 53% of the holotranscobalamin II, while serum vitamin B12 remained stable.

The mechanism that could explain such an effect of calcium supplements against PPI-induced vitamin B12 deficiency is likely related to the existing role of calcium ions in the absorption process of vitamin B12 (17). In fact, chelating calcium from the intestinal environment caused inhibition of vitamin B12 absorption in both, in vitro and in vivo animal models (31-35), and in human (35-37). To our knowledge, there is no evidence that PPIs could chelate calcium ions. Furthermore, two recent clinical trials showed that gastric acid suppression with PPIs did not affect intestinal absorption of calcium in young adults and in postmenopausal women, respectively (38, 39). How PPIs, calcium and vitamin B12 interact in gut still remains to be clarified.

Our findings surely raise questions as for the “true” risk of vitamin B12 deficiency among PPI users. In fact, risk estimates published so far fluctuate from 0.92 to 4.45 (8-12). However, no study has accounted for effect modification by calcium supplements. Failure to account for this effect modifier can have led to biased risk estimates, which would have been underestimated as much as the study sample included users of calcium supplements. Underestimation is all the more probable as most studies’ samples were predominated by older adults. In light of our findings, further research on gastric acid inhibition and vitamin B12 status should from now on, account for this effect modifier and when possible, vitamin B12 and calcium intakes from diet.

Study limitations: In addition to its cross-sectional design, this study has limitations to acknowledge. For instance, cases of vitamin B12 deficiency were identified based on diagnosis made by the patient’s physician so that we cannot

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**Table 2**

Characteristics of patients according to their vitamin B12 status as determined during their stay at a Geriatric Assessment Unit (n=172)<sup>1</sup>

| Characteristics   | Vitamin B12 deficiency |            | P <sup>2</sup> |
|---|------------------------|------------|----------------|
|   | Yes (n=71)             | No (n=101) |                |
| Female, %   | 62.0                   | 70.3       | 0.25           |
| Age, y  | 81.9±7.5               | 80.8±8.4   | 0.36           |
| Conditions that could lead to vitamin B12 deficiency,% <sup>3</sup> | 19.7                   | 18.8       | 0.88           |
| Atrophic gastritis  | 1.4                    | 0.0        | 0.41           |
| Crohn's disease   | 1.4                    | 0.0        | 0.41           |
| Coeliac disease   | 0.0                    | 2.0        | 0.51           |
| Pancreatectomy, Pancreatitis  | 2.8                    | 0.0        | 0.17           |
| Vegetarian or vegan diet  | 0.0                    | 1.0        | 1.00           |
| Metformin use   | 16.9                   | 15.8       | 0.85           |
| Metformin use w/o use of calcium supplements                        | 11.3                   | 9.9        | 0.77           |
| Diseases related to falsely elevated vitamin B12 levels, %          | 28.2                   | 43.6       | 0.040          |
| Chronic kidney disease  | 19.7                   | 33.7       | 0.045          |
| Liver diseases  | 4.2                    | 7.9        | 0.53           |
| Alcoholism  | 2.8                    | 6.9        | 0.31           |
| Cancer  | 9.9                    | 12.9       | 0.54           |
| Use of over-the-counter supplements, %                              | 1.4                    | 8.9        | 0.048          |
| Multivitamins   | 1.4                    | 8.9        | 0.048          |
| Vitamin B12   | 0.0                    | 1.0        | 1.00           |
| Calcium   | 0.0                    | 2.0        | 0.51           |
| Use of prescribed calcium supplements, %                            | 39.4                   | 48.5       | 0.24           |
| Potential indications for gastric acid inhibition <sup>4</sup>      | 66.2                   | 58.4       | 0.30           |
| Gastroesophageal reflux disease, dyspepsia                          | 19.7                   | 9.9        | 0.07           |
| Gastritis, esophagitis, peptic ulcer                                | 5.6                    | 6.9        | 0.73           |
| Use of drugs that could require cytoprotection                      | 62.0                   | 52.5       | 0.22           |
| Gastric acid inhibition, %  | 47.9                   | 38.6       | 0.23           |
| Proton pump inhibitors  | 47.9                   | 38.6       | 0.23           |
| Histamine-2 receptor antagonists                                    | 2.8                    | 1.0        | 0.57           |
| Intensive gastric acid inhibition treatment <sup>5</sup>            | 11.3                   | 4.0        | 0.08           |
| PPI/H2RA use w/o calcium supplements                                | 31.0                   | 16.8       | 0.029          |

1. Values are in percentages or mean ± SD; 2. Data were analyzed by  $\chi^2$ , Fisher's exact test, or t test as appropriate; 3. No patient has been found with gastrectomy, gastric surgery, or ileal resection; 4. No patient has been found with *Helicobacter pylori* infection, Zollinger-Ellison syndrome, or gastrinoma; 5. Concomitant use of H2RA and PPI, or daily PPI dose twice the standard dose.

ascertain whether or not the same diagnosis criteria had been used. Nonetheless, missed cases are not likely since physical examination, complete blood count, and measurement of serum vitamin B12 are quite systematic in the GAU. Moreover, the prevalence observed in the present study is similar to that recently reported in a sample of older adults admitted in a rehabilitation unit (24). As data collection depended exclusively on hospitalization records, some relevant information was not available or cannot be consistently and reliably extracted from charts such as dietary data or use of OTC calcium-based antacids. Notably, we cannot estimate the duration of PPI/H2RA exposure prior admission at the GAU. Consequently, residual confounding may remain. Also, the lack of statistical power impedes accounting for intensive gastric acid inhibition, the dosage of calcium supplements, and the use

of OTC supplements in our analyses. Finally, generalizability can be limited to vulnerable older adults.

In conclusion, the present study provides evidence that calcium supplements could be an effect modifier of the association between gastric acid inhibitors and vitamin B12 deficiency. Our results are biologically plausible and consistent with previous reports. Failure to account for calcium supplementation in previous studies can have biased their risk estimates. Further research should thus account for this potential effect modifier.

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**Table 3**

Results from the logistic regression model examining the effect modification by calcium supplements of the association between the use of gastric acid inhibitors and vitamin B12 deficiency<sup>1</sup>

| Usage of gastric acid inhibitors and calcium supplements           | OR [95% CI]      | P     |
|--|------------------|-------|
| No use of either drugs   | 1.00             | ---   |
| Use of calcium supplements only                                    | 1.06 [0.44-2.55] | 0.90  |
| Use of gastric acid inhibitors only                                | 3.12 [1.26-7.71] | 0.014 |
| Concomitant use of calcium supplements and gastric acid inhibitors | 1.30 [0.50-3.38] | 0.59  |

1. Results are based on Model 2. ORs are adjusted for sex, age, and diseases related to falsely elevated vitamin B12 levels.

*Conflict of interest:* Authors have no conflict of interest.

*Ethical Standards:* The study procedures comply with the current ethical standards for investigation involving human participants in Canada.

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