

OBSERVATIONS

Vitamin B₁₂ Deficiency Associated With Concomitant Metformin and Proton Pump Inhibitor Use

Metformin and proton pump inhibitors have been implicated in decreasing levels of vitamin B₁₂ independently. The purpose of this study was to evaluate the effect of concomitant use of metformin and proton pump inhibitors on the incidence of vitamin B₁₂ deficiency.

A retrospective chart review was done using the computerized patient record system at the Memphis VA Medical Center for 614 patients with type 2 diabetes and previously collected vitamin B₁₂ levels. Patients were excluded if they were over the age of 60 years; on a vegetarian diet; had been diagnosed with pernicious anemia, documented by a positive Schilling test or anti-intrinsic factor antibody, or pancreatic exocrine insufficiency; had undergone a gastrectomy or bowel resection; or had been treated with supplemental calcium, H₂ blocker, or B₁₂ within 3 months of data collection. The vitamin B₁₂ levels were assessed using a competitive immunoassay with direct chemiluminescent technology. Deficiency was defined as vitamin B₁₂ levels <300 pg/mL. A χ^2 test was used to compare patients taking metformin or proton pump inhibitors alone and those taking both with a control population taking neither medication.

Mean \pm SD age was 65.08 \pm 9.23 years, with a majority of male patients (96.3%). African Americans comprised 40.07% of the study population and Caucasians 50.33%; 9.6% had "other" listed for race. The incidence of vitamin B₁₂ deficiency was found in 48 (22.2%) of the 216 control subjects. This was not significantly different compared with 32 (21.91%) of the 146 metformin subjects or

33 (25.58%) of the 129 proton pump inhibitor alone subjects ($P = 0.9454$ and 0.4763). However, there was a significant difference found in 42 (34.15%) of the 123 concomitant metformin and proton pump inhibitor subjects compared with the control group ($P = 0.0096$).

Metformin is a first-line medication used in the treatment of type 2 diabetes but has also been shown in multiple studies to reduce serum B₁₂ levels in 10–30% of patients (1). Proton pump inhibitors are also commonly used medications for the treatment of gastroesophageal reflux disease and peptic ulcer prevention and treatment and, short-term, have been shown to decrease B₁₂ levels from 3.4 to 0.4% ($P < 0.05$) in a 2-week period (2). However, studies looking at long-term proton pump inhibitor use and vitamin B₁₂ deficiency have yielded conflicting results (3,4). Ting et al. (5) found no significantly increased risk for concurrent use of histamine H₂ receptor antagonist or proton pump inhibitor in the development of metformin-related B₁₂ deficiency. However, they did not separate out the use of H₂ blockers from proton pump inhibitors in calculating the risk of developing metformin-related B₁₂ deficiency.

Proton pump inhibitors and metformin alone were not associated with a significant difference in vitamin B₁₂ deficiency, but the combination was associated with a significant increase in vitamin B₁₂ deficiency. More studies are needed to elucidate the exact mechanisms by which proton pump inhibitors and metformin affect vitamin B₁₂ levels and relate these changes to clinical findings.

AMANDA N. LONG, DO¹
CHRISTOPHER L. ATWELL, BS¹
WONSUK YOO, PHD²
SOLOMON S. SOLOMON, MD¹

From the ¹Memphis VA Medical Center and University of Tennessee Health Science Center, Memphis, Tennessee; and the ²Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, Tennessee.

Corresponding author: Solomon S. Solomon, ssolomon@uthsc.edu.

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