

## OBSERVATIONS

## Vitamin B<sub>12</sub> Deficiency Associated With Concomitant Metformin and Proton Pump Inhibitor Use

**M**etformin and proton pump inhibitors have been implicated in decreasing levels of vitamin B<sub>12</sub> 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 B<sub>12</sub> 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 B<sub>12</sub> 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, H<sub>2</sub> blocker, or B<sub>12</sub> within 3 months of data collection. The vitamin B<sub>12</sub> levels were assessed using a competitive immunoassay with direct chemiluminescent technology. Deficiency was defined as vitamin B<sub>12</sub> levels <300 pg/mL. A  $\chi^2$  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 B<sub>12</sub> 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 B<sub>12</sub> 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 B<sub>12</sub> 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 B<sub>12</sub> deficiency have yielded conflicting results (3,4). Ting et al. (5) found no significantly increased risk for concurrent use of histamine H<sub>2</sub> receptor antagonist or proton pump inhibitor in the development of metformin-related B<sub>12</sub> deficiency. However, they did not separate out the use of H<sub>2</sub> blockers from proton pump inhibitors in calculating the risk of developing metformin-related B<sub>12</sub> deficiency.

Proton pump inhibitors and metformin alone were not associated with a significant difference in vitamin B<sub>12</sub> deficiency, but the combination was associated with a significant increase in vitamin B<sub>12</sub> deficiency. More studies are needed to elucidate the exact mechanisms by which proton pump inhibitors and metformin affect vitamin B<sub>12</sub> levels and relate these changes to clinical findings.

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