

# Metformin plus proton pump inhibitors therapy: the cobalamin deficiency challenge

F. PURCHIARONI, G. GALLI, B. ANNIBALE

Department of Digestive and Liver Disease, "Sapienza" University of Rome, Rome, Italy

**Abstract. – OBJECTIVE:** It is known in literature that metformin and proton pump inhibitors (PPIs) are associated to cobalamin levels reduction independently but still very little is known about the combination of the two drugs in cobalamin levels decrease. Currently there are no published data concerning the management of patients with cobalamin deficiency related to the concomitant use of the aforementioned drugs.

**CASE REPORT:** We present the case of a 65 year-old white man with an history of renal cell carcinoma, melanoma and hepatic nodular sclerosis Hodgkin's lymphoma, who was under treatment with metformin because of diabetes and with pantoprazole because of Barrett's esophagus. He came to our attention because of a progressive reduction of cobalamin levels without related anemia. We decided to continue metformin and pantoprazole therapy and we treated the patient with intramuscular injection of cobalamin to avoid the vitamin deficiency consequences.

**DISCUSSION:** Up to now no published data are available concerning the management of patients with cobalamin deficiency related to the concomitant use of metformin and PPIs. Our case report faces this clinical problem in terms of therapeutic management.

*Key Words:*

Combined therapy, Metformin, Proton pump inhibitors, Cobalamin deficiency, Cobalamin replacement.

## Introduction

Metformin and proton pump inhibitors (PPIs) have been associated to vitamin B12 (or cobalamin) levels reduction independently. Different studies concerning cobalamin levels decrease in patients with type 2 diabetes mellitus (DM2) treated with metformin have shown an association both with the dose of the drug<sup>1</sup> and the treatment duration<sup>2,3</sup>.

Other studies<sup>4,5</sup> have investigated the link between acid suppression by PPIs and cobalamin deficiency and showed that malabsorption of protein-bound B12 may occur with the PPIs dosage normally used in clinical practice.

Currently there is a poor knowledge of the association between the two drugs in cobalamin levels reduction; in this respect, one retrospective study<sup>6</sup> demonstrated that said combination is associated with a significant increase in vitamin B12 deficiency.

To our best knowledge, no published data are available concerning the management of patients with cobalamin deficiency related to the concomitant use of metformin and PPIs, with specific regards to patients for whom treatment continuation is recommended.

## Case Report

We hereby present the case of a 65 year-old white man who came to our attention because of a progressive reduction of cobalamin and ferritin levels without related anemia (Table I). The patient showed neither neurological symptoms nor other clinical manifestations of cobalamin deficiency. Accurate gastrointestinal evaluation, including gastroscopy with gastric and duodenal biopsies and total colonoscopy, excluded malabsorption and bleeding causes for the observed combined deficiency. Moreover, the patient was not vegetarian and did not undergo bowel resection.

The patient had an history of renal cell carcinoma, melanoma and hepatic nodular sclerosis Hodgkin's lymphoma; he had been completely cured from all said neoplasms years before. Moreover, for many years he suffered from DM2 and had been treated with metformin 850 mg three times/day plus repaglinide 1 mg twice/day.

Furthermore, three years ago, the patient was endoscopically and histologically diagnosed with Barrett's esophagus (one centimeter of intestinal metaplasia) and from then on he has been treated with pantoprazole 40 mg once/day.

**Table I.** Progressive reduction in cobalamin levels and other relevant laboratory values.

	Hemoglobin (g/dl)	Mean corpuscular volume (fl)	Red cell distribution width (%)	Vitamin B12 (pg/ml)	Ferritine (ng/ml)	Homocysteine (mmol/l)
March 2013	13.2	78.3	13.8	132	10.8	25
April 2013	13.4	77.5	13.8	129	10.2	23
June 2013	13.3	77.3	14.1	98	9.2	22
October 2013*	14	85	13.2	600	10.2	12

\*After four months of intramuscular cobalamin injection.

In order to avoid cobalamin deficiency consequences, we treated the patient with intramuscular injection of cobalamin with an initial loading dose of 4 mg; the dose was then decreased to 2 mg/month for life.

As far as metformin therapy is concerned, even if some authors<sup>7</sup> suggest drug discontinuation in diabetic patients with cobalamin deficiency, we continued the drug administration, as suggested by other authors<sup>3</sup>.

With respect to PPIs treatment, in order to minimize the negative effect on cobalamin and iron absorption, we decided to administer pantoprazole 40 mg every other day. We then monitored hematochemical values after four months and we found that cobalamin levels were within the normal range, ferritin serum concentration remained steadily low and hemoglobin was still at normal levels (Table I).

## Discussion

Up to now there are no published data in literature regarding the management of patients with cobalamin deficiency related to the concomitant use of metformin and PPIs.

In our case, given the clinical history of the patient, we decided to maintain metformin and pantoprazole therapy, administering the latter every other day. Moreover, to avoid vitamin deficiency consequences, we started to treat our patient with intramuscular injection of cobalamin every month for life. We found that cobalamin serum levels returned to normal range.

Our report demonstrates that, even if our patient is under treatment with drugs that led to cobalamin deficiency, Vitamin B12 replacement

is effective, it prevents cobalamin deficiency consequences and allows the patient to continue metformin and PPIs treatment.

## Conflict of Interest

The authors have no conflict of interest/personal interest. The authors did not receive any funding that supported this study.

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