

## Decreased hemoglobin concentration associated with PPI and metformin treatment among geriatric patients

### Obniżone stężenie hemoglobiny związane ze stosowaniem PPI i metforminy wśród pacjentów geriatrycznych

Martyna Bziukiewicz-Walendzik<sup>1</sup>, Krzysztof Wilczyński<sup>2</sup>

<sup>1</sup> Student researchgroup at the Department of Geriatrics, Upper Silesian Medical Center, Katowice, Poland

<sup>2</sup> Department of Geriatrics, Upper Silesian Medical Center, Katowice, Poland

#### Abstract

**Introduction.** We examined the influence of combined metformin and proton pump inhibitor treatment on hemoglobin levels among geriatric inpatients. **Materials and methods.** This was a retrospective study based on the analysis of medical records of 314 randomized patients (219 women and 95 men) admitted to a geriatric ward. Mean patient age was 80.27 years. We analyzed the following: vitamin B<sub>12</sub> concentration, age, sex, mean corpuscular volume-MCV, level of hemoglobin, the use of proton pump inhibitors (PPIs) and metformin. **Results.** Among patients treated with metformin and PPI(D), the mean Hb concentration was 11.9 g/dl. In contrast, among patients not treated with neither metformin or a PPI (N), the mean Hb concentration was 12.9 g/dl. Analysis of variance revealed a statistical significance between groups D and N and Hb concentration ( $p = 0.004$ ). The U Mann-Whitney test revealed a statistically significant difference in Hb concentration between the D and N groups ( $p = 0.002$ ,  $Z = -3,05310$ ). **Conclusions.** In comparison to patients treated with metformin, a PPI or neither, combination therapy with PPI and metformin was associated with reduced Hb concentration in our study population. (Gerontol Pol 2019; 27; 97-99)

**Keywords:** metformin, PPIs, hemoglobin, MCV, anemia, vitamin B12, iron, geriatric population

#### Streszczenie

**Wstęp.** Zbadaliśmy wpływ skojarzonej terapii metforminą i inhibitorami pompy protonowej na poziom hemoglobiny w populacji geriatrycznej. **Materiały i metoda.** Było to badanie retrospektywne i opierało się na analizie dokumentacji medycznej 314 losowo wybranych pacjentów (219 kobiet i 95 mężczyzn) z Oddziału Geriatrycznego. Średni wiek pacjenta wynosił 80,27 lat i przeanalizowaliśmy następujące dane: stężenie witaminy B12, wiek, płeć, średnia objętość krwinek-MCV, poziom hemoglobiny, zastosowanie inhibitorów pompy protonowej (PPI) i metforminy. **Wyniki.** W grupie pacjentów stosujących metforminę z PPI (D) średnie stężenie Hb wynosiło 11,9 g/dl. Natomiast w grupie, w której nie stosowano żadnego z tych leków (N), średnie stężenie Hb wynosiło 12,9 g / dl. Analiza wariancji wykazała istotność statystyczną między grupami D i N i stężeniem Hb,  $p = 0,004$ . Test U Manna-Whitneya ujawnił istotną statystycznie różnicę w stężeniu Hb między grupami D i N,  $p = 0,002$ ,  $Z = -3,05310$ . **Wnioski.** W porównaniu do pacjentów leczonych metforminą, PPI lub nieleczonych tymi lekami, leczenie skojarzone z PPI i metforminą wiązało się ze zmniejszonym stężeniem Hb w badanej populacji. (Gerontol Pol 2019; 27; 97-99)

**Słowa kluczowe:** metformina, PPI, hemoglobina, MCV, anemia, witamina B 12, żelazo, populacja geriatryczna

#### Introduction

We analyzed the effect of metformin and proton pump inhibitors (PPI) on hemoglobin concentration in geriatric patients. Both drugs are recognized in the medical literature as possible causes of vitamin B 12 deficiency and

also, in the case of PPI use, iron deficiency [1,2]. The combined use of metformin and PPIs is common in the geriatric population partly due to multimorbidity prevalent among the geriatric demographic, but also may be due to a side effect of metformin therapy – gastroesophageal reflux [3]. Both drugs, by various mechanisms,

Correspondence address: ✉ Martyna Bziukiewicz-Walendzik; Department of Geriatrics, GCM, 45/47, Ziółowa St., 40-635 Katowice ☎ (+48 32) 359 81 74  
✉ martbziu@interia.pl

can reduce vitamin B 12 concentration [3]. Metformin decreases secretion of intrinsic factor (IF), which is necessary for absorption of vitamin B 12 from the gastrointestinal tract [3]. Metformin affects the motility of the small intestine, which may result in bacterial overgrowth [4]. Prolonged metformin therapy may interact with the ileal endocytic receptor – Cubilin, which in turn impairs calcium availability and leads to the inhibition of the calcium dependent absorption of the vitamin B12-IF complex at the terminal ileum [5]. PPIs inhibit acid secretion by gastric parietal cells and in this way disturb cleavage of dietary vitamin B 12 [6]. In addition, PPIs are cation transport inhibitors, thereby increasing the plasma concentration of metformin [7]. Therefore, attention was paid to the increased risk of anemia among patients taking these medications at the same time.

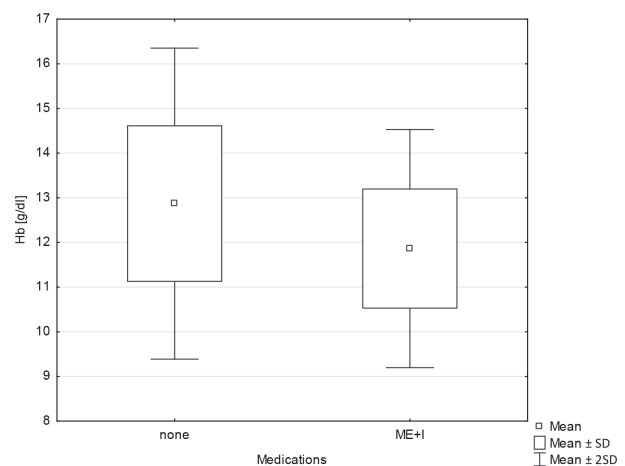
## Materials and methods

A retrospective study based on the analysis of 314 randomized patients (219 female and 95 male) admitted to the Department of Geriatrics at University Hospital No 7 SUM, Uppersilesian Medical Center, in Katowice, Poland. We examined patient records of patients between the ages of 60 and 97 years old (mean 80.27 years old), vitamin B<sub>12</sub> concentration, age, sex, mean corpuscular volume-MCV, level of hemoglobin, use of proton pump inhibitors (PPIs) and metformin. Laboratory tests were carried out at the UMC laboratory. Hb level was determined by the colorimetric method, the coefficient of variation was 0.82%, total error LAB UMC 1.4%, standard 12.00 (13.00)-16.00(16.50) g/dl. The concentration of vitamin B 12 was determined by enhanced, competitive chemiluminescence using streptavidin and biotin, coefficient of variation was 4.49%, total error LAB UMC 7.4%, functional sensitivity 150 pg /ml, standard 191- 663pg / ml. The MCV was measured using the impedance method, coefficient of variation of 0/63%, total error LAB UMC 1%. Data was analyzed using Statistica software. The following statistical analyzes were used: Kolmogorov-Smirnov test, U Mann-Whitney test, variance analysis, T- test and descriptive statistics.

## Results

69 patients used a PPI (I), 41 patients used metformin (M), 22 patients used combined therapy (PPI with metformin- D), 182 people used neither metformin nor a PPI (N). Mean hemoglobin concentration was 12.7 g/dl. In the metformin group the, mean Hb was 12.9 g/dl. Among patients using PPIs, the mean Hb concentra-

tion was 12.2 g/dl. In contrast, in the group of patients using metformin with a PPI, the mean Hb concentration was 11.9 g /dl and in the group of patients using neither metformin nor PPI, the mean Hb concentration was 12.9 g/dl. Variance analysis showed statistical significance between patient groups receiving PPIs, metformin, PPIs with metformin (D), taking neither metformin nor a PPI (N) and Hb concentration ( $p = 0.004$ ). The U Mann-Whitney test showed significant statistical difference in Hb concentration between the D and N groups,  $p = 0.002$ ,  $Z = -3.05310$  (Figure 1). Mean MCV values for patients treated with metformin and a PPI were 89.1 fl and 88.2 fl, respectively. Among patients that used neither metformin or PPI, mean MCV was 90.3 fl.



**Figure 1. Average hemoglobin concentration among patients taking metformin and PPI and among patients not taking any of these drugs**

Average vitamin B12 concentration in the patient group not using metformin or a PPI (N) was 390,6 pg/ml, and among patients using PPIs (I) 447.8 pg/ml, and among patients using metformin( M) 347.8 pg/ml. In contrast, among patients using PPI and metformin (D), the vitamin B12 concentration was 433.7 pg/ml.

In the study population no statistically significant correlation was found between the concentration of vitamin B 12 and the concentration of Hb and MCV. No statistically significant difference in vitamin B12 concentration or MCV was observed among patient groups I, M, D, or N. A lower concentration of vitamin B 12 was seen in patients taking metformin.

## Discussion

A reduction of Hb levels was observed with combination therapy of metformin and a PPI while no reduction in Hb levels was observed with patients treated with metformin, PPI or neither. Reductions in Hb due to vita-

min B12 deficiency would be associated with an increase in MCV, however, MCV among our patient group taking metformin or metformin with PPI was lower than in the group of patients not taking these drugs.

Iron deficiency may result in a reduction in hemoglobin levels and decreases in MCV. Gastric acid assists absorption of non-heme iron from food by converting it from its ferrous form to the ferric form [2]. PPI suppression of gastric acid secretion may lead to non-heme iron malabsorption [2]. With age, the intake of meat, the main source of heme iron, is often reduced. Elderly people are at greater risk of chronic internal bleeding due to peptic ulcer disease or chronic therapy with nonsteroidal anti-inflammatory drugs, which may also lead to

iron deficiency. We cannot rule out that iron deficiency has a greater role in the development of anemia than vitamin B 12 insufficiency.

## Conclusions

Combined use of metformin and PPI significantly reduced the Hb concentration in our geriatric patient group. As such, care should be taken when prescribing metformin with a PPI for geriatric patients.

Conflict of interest

None

## References

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