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Original Article

# Does omeprazole cause functional hypoparathyroidism?

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## Abstract

Proton pump inhibitors are widely used worldwide and are misused classes of drugs, especially in developing countries. Several case reports, case series, and review studies suggest proton pump inhibitors may cause hypomagnesemia hypoparathyroidism. Therefore, the goal of this case-control study is to determine whether there is a link between omeprazole and functional hypoparathyroidism, and this case-control study is the first study on animal models regarding this project. Twenty mature male rabbits were randomly divided into two groups (10 rabbits/group); Group 1 – the control group, was given distilled water (1ml/kg/day for 45 days) via intraperitoneal (I/P) injection and Group 2 – treated with omeprazole (PPI) (1 ml/kg/day for 45 days) I/P injection to induce hypoparathyroidism. The serum used in the PTH and electrolyte studies was obtained from blood samples taken through cardiac puncture. The results show a significant decrease in PTH, $Mg^{2+}$ and $Ca^{2+}$ concentration in the treated group compared to the control group. Omeprazole (PPI) induced hypomagnesemia, a potential cause for functional hypoparathyroidism.

**Keywords:** hypomagnesemia, hypoparathyroidism, proton pump inhibitor (PPI), parathyroid hormone resistance.

## Introduction

Hypoparathyroidism is defined as a deficiency or absence of parathyroid hormone secretion [1]. Resorption of soluble calcium by the skeleton slows down and the osteoclasts go into near-total hibernation when parathyroid glands do not release enough parathyroid hormone (PTH). As a result, there is less calcium in the blood and other bodily fluids because calcium reabsorption from the bones is greatly reduced [2]. The blood calcium level lowers from 9.4 mg/dl to 6 or 7 mg/dl within 2 to 3 days after parathyroid gland removal, while the blood phosphate concentration may quadruple during this time. In the event that calcium levels drop to this, tetany symptoms appear. The laryngeal muscles are particularly susceptible to tetanic spasms. This muscular spasm obstructs breathing and is the typical cause of mortality in tetany in the absence of adequate therapy [3].

Peptic ulcer disease, gastroesophageal reflux disease, and conditions associated with increased gastric acid secretion are all treated with Proton pump inhibitors (PPIs) (*e.g.*, omeprazole) and PPIs are also used to prevent gastric ulcers in patients who need to take nonsteroidal anti-inflammatory drugs or corticosteroids for extended periods of time [4]. PPIs work by inhibiting the gastric $H^+/K^+$-ATPase by binding to cysteine residues in the proton pump, hence decreasing acid production in the stomach [5]. However, the recommended treatment period for acute gastric and duodenal ulcers is 4 to 8 weeks. A 2–3 week treatment sessions per year are the maximum the U.S. Food and Drug Administration (FDA) recommends [6].

Growing evidence suggests that PPIs, especially when used for longer periods of time, may have a role in the onset of hypomagnesemia hypoparathyroidism [7]. In 2006, the first cases of hypomagnesemia hypoparathyroidism caused by proton pump inhibitors

were reported [8], then a series of reviews and case reports [9]. Hypomagnesemia may be caused by variants of Transient Receptor Potential Melastin 6/7 (TRPM 6/7) in vulnerable people; TRPM 6/7 is an active transcellular channel found in the intestines and kidneys that transports magnesium and calcium into the cells. Mutations in genes involved in the regulation of magnesium reabsorption in the kidneys, which might lead to a continuous magnesium leak via the kidneys, are also conceivable in individuals who develop hypomagnesemia while receiving proton pump therapy [10].

The synthesis of magnesium-dependent cyclic adenosine monophosphate (cAMP) is impaired in hypomagnesemia, and this prevents the parathyroid gland from releasing PTH and preventing the end-organ impact of PTH (PTH resistance) [11]. This leads to decreased calcium reabsorption from the kidneys, decreased parathyroid hormone-mediated calcium release from the bones, and decreased vitamin D3 production, resulting in decreased calcium absorption via the gastrointestinal system [12].

This study aimed to determine if PPI-induced hypomagnesemia increases the risk of developing hypoparathyroidism.

## Material and Methods

### Ethical approval

The study was approved by the scientific committee of the Department of Physiology, Pharmacology and Chemistry, College of Veterinary Medicine, University of Basrah, ID: 1203, at the first meeting dated 5–11/10/2021, checking that the concurrent experiment did not hurt the animals' rights.

### Animals

Twenty local male rabbits were employed, all of which were purchased from a Basrah City market and ranged in age from 15 to 18 months and in weight from 1,300 to 1,600 grams. The animals were kept in laboratory cages with a regulated temperature of 25±2˚C, a light/dark cycle of 12 hours per day, and food and drink ad libitum were provided daily. The animals were allowed two weeks to acclimatize to the experimental facility.

### Chemicals

Omeprazole (PPI) was obtained from (KONTAM Pharmaceuticals Co. LTD- China) (1ml/kg/day for 45 days) I/P injection to induce hypoparathyroidism [13]. Doses of administered drugs according to Plumb's Veterinary Drug Handbook, 6$^{th}$ edition, 2008, as therapeutic doses [14].

### Experimental design

The male rabbits were randomly divided into two groups, each containing 10 rabbits. Group 1 – control group was given distilled water (1ml/kg/day for 45 days) I/P injection. Group 2 – treated with Omeprazole (PPI) (1ml/kg/day for 45 days) I/P injection to induce hypoparathyroidism.

### Blood sampling

Blood samples were collected via cardiac puncture by using a 5ml disposable syringe. Following blood collection in a plan tube, centrifugation at 3000 rpm for 15 minutes separates the serum, which is then divided among many Eppendorf tubes and frozen at -20˚C for later use in PTH and electrolyte assays.

### Laboratory analysis

For the accurate quantitative detection of rabbit parathyroid hormone (PTH) in serum, there was used BT LAB sandwich kit (Bioassay Technology Laboratory, China, Cat. No. E0195Rb, 2022) ELISA kit [15]. At the same time, the serum magnesium concentration used QuantiChromTM Magnesium Assay Kit (DIMG-250, Bioassay Systems, USA, 2021). Quantitative colorimetric magnesium determination at 500 nm [16] and calcium assay kit for rabbit serum (Colorimetric Assay Kit,

Table 1: Effect of Omeprazole on PTH, $Ca^{2+}$, and $Mg^{2+}$ concentration in mature male rabbits (mean±S.D.) n=10.

| Parameters / Groups | PTH (pg/ml) | $Ca^{2+}$ (mg/dl) | $Mg^{2+}$ (mg/dl) |
|---|---|---|---|
| **Control group** | 5.70±3.32 [a] | 14.16±0.39 [a] | 3.71±0.35 [a] |
| **Hypo PTH group** | 2.34±0.80 [b] | 13.46±0.94 [b] | 2.83±0.52 [b] |

Note: Significant differences at the (P≤0.05) level are denoted by values in small letters.


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Table 2: Effect of Omeprazole on $Ca^{2+}$, $PO_4^{3}$ and $Na^{2+}$ concentration in mature male rabbits (mean±SD) n=10.

| Parameters / Groups | $Ca^{2+}$ (mg/dl) | $PO_4^{3-}$ (mmol/L) | $Na^{2+}$ (mg/dl) |
|---|---|---|---|
| **Control group** | 14.16±0.39 [a] | 3.83±0.97 [a] | 141.30±5.01 [a] |
| **Hypo PTH group** | 13.46±0.94 [b] | 2.09±1.63 [b] | 115.90±27.44 [b] |

Note: Significant differences at the (P≤0.05) level are denoted by values in small letters.

Elabscience, USA, Biochemical Assay Kit, Catalog No: E-BC-K103-M, 2022) [17].

## Statistical analysis

In this study, all the recorded and calculated data were analyzed for ANOVA analysis one way using complete randomized design (CRD) with the help of the computer package program SPSS (Version 26, SPSS Inc., Chicago, Illinois, USA). The data were expressed as mean±standard deviation (M±S.D.). P≤0.05 was considered significant [18].

## Results

The results of the current study show that $Mg^{2+}$ concentrations are significantly decreased in the treated group (hypoparathyroidism group) (2.83±0.52 mg/dl) compared to the control group (3.71±0.35mg/dl) and the PTH levels are significantly decreased in the treated group (2.34±0.80pg/ml) compared to the control group (5.70±3.32pg/ml). However, in the hypoparathyroidism treated group, the $Ca^{2+}$ serum concentration was significantly decreased than in the control group (13.46±0.94 mg/dl), (14.16±0.39 mg/dl) respectively (Table 1). While other electrolytes PO3- and $Na^{2+}$, significantly decreased in the treated group (2.09±1.6 mmol/L, 115.90±27.44 mg/dl), respectively, compared to the control group (3.83±0.97 mmol/L, 141.30±5.01 mg/dl) (Table 2).

Regarding the results of B.W. changes and B.W. gain, there is significant weight gain (P≤0.05) in the hypoparathyroidism group and control group as compared to the initial body weight (Table 3).

## Discussion

Results showed significantly decreased PTH, $Ca^{2+}$, $Mg^{2+}$, $PO_4^{3-}$ and $Na^{2+}$ in the treatment group compared to the control group. The specific pathophysiological pathways of proton pump inhibitor-induced hypomagnesemia hypoparathyroidism remains unknown; however, it is believed that renal and intestinal magnesium processing is to blame. Hypomagnesemia may be a consequence of proton pump inhibitor-induced hypochlorhydria. "Low gastric pH is important because $Mg^{2+}$ binds to ligand sites on dietary fibers and may be displaced by hydrogen ions, which promotes intestinal absorption. Also, waves of acidity entering the small intestine from the stomach may aid in keeping $Mg^{2+}$ salts in the solution until they are absorbed [19] or altered in the expression of TRPM 6/7 [20]. The intraluminal acid-base balance controls the activity of TRPM 6/7, with an acidic environment increasing its activity [21]. PPIs reduce the activity of TRPM 6/7, causing a reduction in intestinal magnesium absorption and causing hypomagnesemia [20, 21].

The results of the current study revealed a highly significant decrease of PTH in the treated group (hypoparathyroidism), and this finding agreed with Adam *et al.* [11], who showed that hypomagnesemia is produced by PPI [10]; which affected the parathyroid gland's ability to secrete PTH and with PTH's effect on target organs (PTH resistance) by inhibiting cAMP

Table 3: Effect of Omeprazole on final Body Weight (B.W.) and B.W. gain (mean±S.D.) n=10.

| Parameters / Groups | Body weight (g) | | |
|---|---|---|---|
| | Initial B.W. (g) | Final B | B.W. (g) B.W. gain (g) |
| **Control group** | 1141.66±49.15 [B b] | 1283.33±40.82 [A a] | 100.65±26.36 [A] |
| **Hypo PTH group** | 1191.66±42.80 [A b] | 1265±223.04 [B a] | 80.77±23.58 [B] |

Note: Capital letters denote significant differences between groups P≤0.05 *vs.* control. Small letters denote differences within groups P≤0.05.

production which requires magnesium and calcium reabsorption from the kidneys, parathyroid hormone-mediated calcium release from the bones, and vitamin D3 production are all reduced. This leads to decrease calcium absorption from the intestines and disagrees with Chowdhry *et al*. [22], who concluded in their research that the magnesium levels were unaffected by proton pump inhibitors. Due to intestinal pH variations that affect channel activity (active transport) or because sensitive patients are heterozygous carriers of TRPM6 mutations, omeprazole and other proton pump inhibitors cause hypomagnesemia by reducing magnesium absorption in the intestine [23]. These findings agreed with Delgado *et al*., Florentin & Elisaf and Gan *et al*. [9, 24, 25]. They found a dose response between the PPI use and development of hypomagnesemia.

Furthermore, the findings of a significant increase in weight gain in the hypoparathyroidism group agree with Yoshikawa *et al*. [26], who found that long-term treatment with various PPIs was associated with weight gain in patients with gastroesophageal reflux disease (GERD) since untreated patients with reflux symptoms find it difficult to eat large meals because doing so tends to exacerbate their symptoms.

Therefore, the cure of reflux symptoms by PPI medication increases food consumption and weight gain, and these findings disagree with Cui *et al*. [27], which was shown to suppress body weight gain and bone mineralization in young male rats with omeprazole treatment.

## Conclusion

Results conclude that hypomagnesemia caused by omeprazole (PPI) increases vulnerability to hypoparathyroidism and support the conclusions of the previous case reports, case series and meta-analyses. Therefore, patients on proton-pump inhibitors should thus have their magnesium levels monitored. Future research with a larger sample size, greater omeprazole dosages, and longer follow-up times for patients taking the drug might more accurately establish this association.

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## Conflict of interest

The authors declare no conflict of interest.

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