Inulin significantly improves serum magnesium levels in proton pump inhibitor-induced hypomagnesaemia

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SUMMARY

Background
Proton pump inhibitors (PPI) are among the most widely prescribed drugs to treat gastric acid-related disorders. PPI-induced hypomagnesaemia, a defect in intestinal absorption of Mg²⁺, can be a severe side effect of chronic PPI use.

Aim
To restore serum Mg²⁺ concentrations in PPI-induced hypomagnesaemia patients by dietary supplementation with inulin fibres.

Methods
Eleven patients with PPI-induced hypomagnesaemia and 10 controls were treated with inulin (20 g/day). Each trial consisted of two cycles of 14-day inulin treatment followed by a washout period of 14 days. Patients continued to use their PPI. Serum Mg²⁺ levels served as the primary endpoint.

Results
Inulin significantly enhanced serum Mg²⁺ levels from 0.60 to 0.68 mmol/L in PPI-induced hypomagnesaemia patients, and from 0.84 to 0.93 mmol/L in controls. As a consequence 24 h urinary Mg²⁺ excretion was significantly increased in patients with PPI-induced hypomagnesaemia (0.3–2.2 mmol/day). Symptoms related to hypomagnesaemia, including muscle cramps and paraesthesia, were reduced during intervention with inulin.

Conclusion
Inulin increases serum Mg²⁺ concentrations under PPI maintenance in patients with PPI-induced hypomagnesaemia.
Proton pump inhibitors (PPIs) are used by millions of patients for treatment and prevention of peptic ulcers, gastro-oesophageal reflux disease and NSAID-induced mucosal damage.\textsuperscript{1, 2} There is accumulating evidence that PPIs induce hypomagnesaemia.\textsuperscript{3, 4} In 2011, the Food and Drug Administration issued a formal warning on PPI-induced hypomagnesaemia.\textsuperscript{5} A systematic review from 2012 on 36 cases concluded that PPI-induced hypomagnesaemia represents a class effect as it occurs with all PPIs but is absent with other gastric-suppressing agents such as histamine-2 receptor antagonists.\textsuperscript{6} The adverse effect results in a wide spectrum of symptoms including, but not limited to, fatigue, vertigo, lightheadedness, numbness and gastrointestinal complaints.\textsuperscript{6–8} PPI-induced hypomagnesaemia occurs after prolonged PPI use, resolves within days following interruption, but resumption of treatment inevitably results in recurrence.\textsuperscript{6, 9} Nevertheless, many patients are dependent on PPIs since they do not respond sufficiently to histamine-2 receptor antagonists.\textsuperscript{10}

Currently, there is no satisfying treatment strategy that resolves PPI-induced hypomagnesaemia while maintaining the desired acid suppressing effect of PPIs. Oral Mg\textsuperscript{2+} supplementation is not sufficient to treat PPI-induced hypomagnesaemia in 25% of PPI-induced hypomagnesaemia patients.\textsuperscript{5} This is the reason to search for alternative strategies that allow patients to continue PPI yet protect them against hypomagnesaemia. Mg\textsuperscript{2+} loss probably results from intestinal malabsorption of Mg\textsuperscript{2+} as renal Mg\textsuperscript{2+} retention is unaffected in PPI-induced hypomagnesaemia cases.\textsuperscript{11, 12} PPIs raise luminal pH which interferes with adequate Mg\textsuperscript{2+} uptake in the large intestine.\textsuperscript{13} A strategy that centres on acidification of colon might contribute to a more efficient intestinal absorption of Mg\textsuperscript{2+}.

Natural bacterial fermentation of carbohydrates and proteins generates short-chain fatty acids, which results in an acidic environment that promotes Mg\textsuperscript{2+} solubility and absorption.\textsuperscript{14} Inulin is a naturally occurring oligosaccharide that upon fermentation by colonic bacteria results in a decrease of pH.\textsuperscript{15–19} In experiments with rodents, inulin actually increased the intestinal uptake of Ca\textsuperscript{2+}.\textsuperscript{20} Therefore, inulin may serve to increase serum Mg\textsuperscript{2+} concentrations in patients with PPI-induced hypomagnesaemia.

In a series of n-of-1 crossover trials, we treated patients with PPI-induced hypomagnesaemia with inulin supplementation with the aim to evaluate changes in serum Mg\textsuperscript{2+} concentrations under continuous PPI use.
endpoints were serum Ca\(^{2+}\), K\(^{+}\) and Na\(^{+}\) concentrations at the indicated time points. We evaluated 24-h urinary Mg\(^{2+}\) and Ca\(^{2+}\) excretion in the PPI-induced hypomagnesemia group on days 27/28 and days 41/42 immediately prior to blood withdrawals. During each of the four treatment cycles of 14 days (inulin-washout-inulin-washout) patients were questioned for the presence of diarrhoea, flatulence, abdominal bloating, abdominal cramping, nausea, boborygmi (bowel sounds) and presence of soft stools.

Laboratory procedures
Serum Mg\(^{2+}\), Ca\(^{2+}\), K\(^{+}\) and Na\(^{+}\) levels were determined using a Hitachi Autoanalyzer according to the manufacturer’s protocol (Abbott Diagnostics, Ottignies/Louvain-La-Neuve, Belgium). Urinary Mg\(^{2+}\) concentrations were determined with a colorimetric xylidyl-II blue kit (Roche Diagnostics, Burgess Hill, UK) at 600 nm wavelength. Urinary Ca\(^{2+}\) concentrations were measured with a colorimetric chromogenic/buffer dual-component kit (Sigma Aldrich, Gillingham, UK) at 570 nm wavelength.

Statistical analysis
A mixed model analysis was performed using the SAS 9.2 software package (Cary, NC, USA). For each of the electrolytes (Mg\(^{2+}\), Ca\(^{2+}\), K\(^{+}\) and Na\(^{+}\)) the mixed model was used with fixed factors patient group (Control, Patients), treatment (Inulin addition, No addition) and their interaction. To deal with the correlation of the repeated measured outcome within a single patient, a random intercept was included in the model. The model assumes that the effect of treatment can be different for the two patient groups (interaction) and that correlations between two measurements within a patient is the same for each combination. Using the mixed model, the treatment effect, that is, the difference of the mean outcome using inulin minus the mean outcome without inulin, for both patient groups was estimated and tested. Averaged values were reported as mean ± S.E.M.

RESULTS
Demographics
Twenty-six patients (11 PPI-hypomagnesaemia patients and 15 healthy non-PPI using controls) were contacted for participation (Figure 1). All patients (6 male, 5 females, mean age 64 years-of-age, range 46-76 years-of-age) consented. We excluded five controls, due to intestinal complaints (n = 1), unwillingness to adhere to the study protocol (n = 1), intercurrent illness (n = 1) or loss of interest (n = 2). This resulted in a final study population of 11 cases and 10 healthy controls (Table 1). Patients with PPI-induced hypomagnesaemia used omeprazole (n = 6), pantoprazole (n = 3) or esomeprazole (n = 2) and the doses ranged from 20 to 60 mg/day. In all included patients, PPIs were temporarily stopped at one stage in their disease to show that hypomagnesemia is caused by PPI use. However, all of them reinitiated PPI treatment for gastrointestinal protection. During the study all patients continued their PPI treatment.

Inulin increases serum Mg\(^{2+}\) concentrations
Proton pump inhibitor-induced hypomagnesaemia patients had mean baseline serum Mg\(^{2+}\) concentration of 0.60 ± 0.03 mmol/L, which increased to 0.68 ± 0.03 mmol/L (P < 0.01) after the first course of 2 weeks of inulin supplementation (Figure 2a). Similarly, the second inulin course also enhanced serum Mg\(^{2+}\) concentrations from 0.61 ± 0.03 to 0.69 ± 0.03 mmol/L (P < 0.01). In controls, serum Mg\(^{2+}\) levels increased significantly during the second course of 2 weeks (0.84 ± 0.02 to 0.93 ± 0.03 mmol/L, Figure 2c). To determine a global treatment effect, we performed a mixed models analysis was performed that demonstrated that inulin
increased serum Mg\textsuperscript{2+} concentrations with 0.10 mmol/L (\(P < 0.01\)) in patients and with 0.06 mmol/L (\(P < 0.01\)) in controls.

**Inulin restores urinary Mg\textsuperscript{2+} excretion**

Urinary Mg\textsuperscript{2+} excretion analysis of PPI-induced hypomagnesaemia patients prior to and after the second inulin course demonstrated that eight cases had baseline urinary Mg\textsuperscript{2+} concentrations below the threshold of quantification (<0.2 mmol/L), while the remaining cases (\(n = 3\)) had a mean of 0.29 ± 0.05 mmol/24 h (Figure 2b). After 14 days of inulin urinary Mg\textsuperscript{2+} excretion increased to a mean of 2.20 ± 0.56 mmol/24 h (\(P < 0.01\)).

**Inulin and electrolyte homeostasis**

To determine the specificity of the effect of inulin supplementation on electrolyte homoeostasis, serum Ca\textsuperscript{2+}, Na\textsuperscript{+} and K\textsuperscript{+} levels were determined. During the first inulin course, serum Ca\textsuperscript{2+} concentrations increased in patients (2.27 ± 0.04 to 2.41 ± 0.04 mmol/L; \(P < 0.01\), Figure S1a). Similarly, the control group showed a significant increase in serum Ca\textsuperscript{2+} concentrations only in the second treatment period (\(P < 0.05\), Figure S1c). Mixed models analysis with data from both 2-week treatment courses demonstrated an increase in serum Ca\textsuperscript{2+} levels with 0.09 mmol/L in the PPI-induced hypomagnesaemia group. Urinary Ca\textsuperscript{2+} excretion increased significantly from 1.23 ± 0.30 to 2.40 ± 0.28 mmol/24 h in PPI-induced hypomagnesaemia patients (\(P < 0.01\), Figure S1b). Serum K\textsuperscript{+} levels increased in PPI-induced hypomagnesaemia cases during the second inulin course (Figure S2a). The overall mean treatment effects for inulin on serum K\textsuperscript{+} were significant for patients with a net increase in 0.26 mmol/L (\(P < 0.01\)), as determined by mixed models analysis (Figure S2a,b). Finally, inulin did not affect serum Na\textsuperscript{+} concentrations in both patients and control (Figure S2c,d).

**Symptoms**

Seven patients with PPI-induced hypomagnesaemia reported symptoms likely attributed to hypomagnesaemia (Table 2). Most frequently reported were paraesthesia in hands and feet, muscle cramps, generalised weakness,
tetany of hands, cardiac arrhythmia and nausea/vomiting. Inulin improved these symptoms. Three patients reported remission of paraesthesia in hands and feet, two patients found that muscle cramps improved or disappeared. Tetany of hands disappeared in a single patient, while weakness improved in another.

Introduction of inulin was associated with onset of intestinal symptoms such as bloating, increased flatulence (19 patients) and boborygmi (16 patients), which improved within the first week of therapy. Other commonly reported symptoms were soft stools and transient diarrhoea (Table 2). One control patient prematurely stopped treatment because of severe diarrhoea after 5 days of inulin use.

**DISCUSSION**

The primary finding of this study is that inulin increases serum Mg\(^{2+}\) concentrations in patients with PPI-induced hypomagnesaemia. Fourteen days of inulin supplementation was sufficient to raise Mg\(^{2+}\) levels in patients maintaining PPI intake. Inulin restored serum Mg\(^{2+}\) concentrations to the low-normomagnesemic range in PPI users. As a consequence, hypomagnesaemia-related symptoms improved. Inulin may thus represent an attractive treatment option in patients with PPI-induced hypomagnesaemia that cannot stop PPI use.

The typical approach of PPI-induced hypomagnesaemia consists of PPI withdrawal. However, alternative options such as histamine-2 receptor antagonists are
often ineffective. Oral Mg²⁺ supplementation results in side effects such as diarrhoea and are insufficient to raise Mg²⁺ levels in PPI users. Inulin is able to increase serum Mg²⁺ in PPI-induced hypomagnesaemia patients and in healthy controls, but the magnitude of increase in patients exceeded that of controls by a factor two. These results are in line with previous observations documenting that inulin fibres enhance Mg²⁺ absorption in human volunteers. The dose of 20 g/day is based on previously published studies that used inulin to increase intestinal absorption of Ca²⁺ or Mg²⁺. The commonly used dose in this type of experiments ranges between 10 and 40 g/day. Our dose of 20 g/day is in the centre of this spectrum.

The beneficial effects of inulin supplementation were not restricted to Mg²⁺ but extended to other electrolytes such as Ca²⁺ and K⁺. Although serum Ca²⁺ and K⁺ levels were in the normal range in our study population, there have been reports of hypocalcaemia and hypokalaemia associated with PPI use. We observed an increase in serum Ca²⁺ and K⁺ levels that stayed within the normal range.

In line with earlier studies in healthy patients using PPI, our PPI-induced hypomagnesaemia patients had marginally decreased 24-h urinary Ca²⁺ excretion. Low-serum Mg²⁺ suppresses parathyroid hormone secretion which reduces Ca²⁺ absorption and puts patients at risk for bone-fractures and/or osteoporosis. Inulin raised renal Ca²⁺ excretion in our population, resulting from stimulated intestinal Ca²⁺ absorption which is reflected in a net increase Ca²⁺ serum level. As such, this effect may contribute to the protection against osteoporosis in chronic PPI users.

The fact that inulin increases serum Mg²⁺, Ca²⁺ and K⁺ in this trial suggests a general mechanism of action. A plausible hypothesis proposes that colonic fermentation of inulin drives short-chain fatty acid production that lowers intestinal pH and ultimately improves the solubility of minerals. Ingestion of fermentable oligosaccharides increases true fractional Mg²⁺ and Ca²⁺ absorption in humans. Gut microbiota are present in the colon and caecum, overlapping with the main regions of Mg²⁺ absorption. Additionally, the main intestinal Mg²⁺ channel, TRPM6, is more active in acidic pH range. These findings may explain why the effects of inulin on Mg²⁺ absorption are stronger than on the uptake of other ions.

The use of inulin comes with gastrointestinal complaints such as flatulence and boborygmi. However, these side effects were mainly reported within the first 2–3 days after the start of the inulin treatment. These events reflect a transient adaptation to inulin treatment and disappeared with prolonged treatment. Therefore, we consider the 20 g/day dose as well-tolerated in PPI patients. This is supported by the fact that all the PPI-induced hypomagnesaemia patients completed the full 56-day trial period.

Our study comes with strength and limitations. The introduction-withdrawal design included two cycles of inulin-based treatment. Such a design delivers evidence-based results and is easily translatable to a large variety of settings within daily clinical practice. The clinical effect on Mg²⁺ serum levels during both cycles was highly reproducible in and between patients suggesting a true treatment effect. The washout time was determined on basis of a previous systematic review that indicated that the PPI-induced hypomagnesaemia is reversible in a few (<5) days. As such we avoided a carry-over effect that was documented by the finding that serum Mg²⁺

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<tr>
<th>Table 2</th>
<th>Symptoms of the participants</th>
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<td>Before inulin intake</td>
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<td></td>
<td>Patients (n = 11)</td>
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<tr>
<td>Muscle cramps</td>
<td>5</td>
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<tr>
<td>Paresthesia in hands/feet</td>
<td>4</td>
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<td>Generalised weakness</td>
<td>2</td>
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<td>Tetany of hands</td>
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<td>Cardiac arrhythmia</td>
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<td>Nausea/vomiting</td>
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<td>Flatulence</td>
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<tr>
<td>Boborygmi</td>
<td>–</td>
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<td>Soft stools</td>
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<td>Transient diarrhoea</td>
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Values represent number of patients.
Inulin improves PPI-induced hypomagnesemia

In conclusion, we demonstrated that inulin stimulates intestinal mineral uptake. Although not all patients reached normal serum Mg²⁺ levels after inulin treatment, serum Mg²⁺ levels increased sufficiently to improve hypomagnesemia-related symptoms. Therefore, inulin provides a novel treatment for patients with PPI-induced hypomagnesemia that do not respond to regular Mg²⁺ supplementation. Future randomised trials are necessary to examine the effects in larger patient groups. Its effect may extend to other hypomagnesemic populations such as type-2 diabetics.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Effects of inulin on serum Ca²⁺ and 24-h urinary Ca²⁺ excretion. The serum Ca²⁺ concentration is shown during 56 days in cases (a) and controls (c). The dotted line represents the lower cut-off value for normal serum Ca²⁺ levels. (B) The urinary excretion of Ca²⁺ before (day 27/28) and the end (day 41/42) of the second 14-day period of inulin supplementation (dotted line represents lower cutoff value for normal urinary Ca²⁺ excretion. Values depict means ± S.E.M. in mmol/L, with significant effects highlighted by *, with P < 0.01.

**Figure S2.** Effect of inulin treatment on serum K⁺ and Na⁺. The serum Na⁺ and K⁺ concentrations during the study period of 56 days are shown. The top row shows the values for K⁺ in cases (a) and controls (b). The dotted line represents the lower cut-off value for normal serum K⁺ levels. The bottom row shows the values for Na⁺ in controls (c) and cases (d) and the dotted line represents the lower cutoff value for serum Na⁺. Values depict means ± S.E.M. in mmol/L, with significant effects highlighted by *, with P < 0.01.

AUTHORSHIP

Guarantor of the article: Joost PH Drenth.

**Author contributions:** MH, JdB, MB, TB, JH, RB and JD were involved in study design. MH, MB, TB, BH and AT were involved in patient data acquisition. MH, JdB, JH, RB and JD were involved in data analysis and interpretation. MH, MB, TB, BH and AT were involved in clinical monitoring. MH, JdB, JH, RB and JD were involved in writing of the manuscript. JdB, JH, RB and JD were involved in supervision. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENTS

We are deeply indebted to the participants of the inulin trial. The authors thank the contributing physicians staff of the Radboud university medical center, namely F. Hoentjen MD, M. Goerres MD, J. Kersten MD, E. Klappe MD. We kindly thank A. Lameris, M. Blanchard, L. Bernts, D. Viering, J. Salomon, T. Wijnands and for their (technical) support and expertise.

**Declaration of funding interests:** This study was funded through a grant of the Radboud University Medical Center and was further supported by grants from the Netherlands Organization for Scientific Research (VICI 016.130.668) and the EURenOmics project from the European Union seventh Framework Programme (FP7/2007–2013, agreement no. 305608).

**Declaration of personal interests:** All authors declare that no financial and nonfinancial competing interests exist.

**Declaration of funding interests:** This study was funded through a grant of the Radboud University Medical Center and was further supported by grants from the Netherlands Organization for Scientific Research (VICI 016.130.668) and the EURenOmics project from the European Union seventh Framework Programme (FP7/2007–2013, agreement no. 305608).

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