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Original Article

# Effects of long-term administration of omeprazole on bone mineral density and the mechanical properties of the bone☆

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ABSTRACT

*Objectives:* Epidemiological studies have shown a relationship between long-term use of proton pump inhibitors and bone metabolism. However, this relationship has not yet become established. The aim of the present study was to analyze the mechanical properties and bone mineral density (BMD) of rats that were subjected to long-term omeprazole use.

*Methods:* Fifty Wistar rats weighing between 200 and 240 g were divided equally into five groups: OMP300 (omeprazole intake at a dose of 300 μmoL/kg/day); OMP200 (200 μmoL/kg/day); OMP40 (40 μmoL/kg/day); OMP10 (10 μmoL/kg/day); and Cont (control group; intake of dilution vehicle). The solutions were administered for 90 consecutive days. After the rats had been sacrificed, their BMD, the mechanical properties of the dissected femurs and their serum Ca++ levels were analyzed.

*Results:* The BMD of the OMP300 group was lower than that of the controls ($p = 0.006$). There was no difference on comparing the OMP200, OMP40 and OMP10 groups with the controls. The maximum strength and rigidity of the femur did not differ in the experimental groups in comparison with the controls. The OMP300 group had a statistically lower serum Ca++ concentration than that of the controls ($p = 0.049$), but the other groups did not show any difference in relation to the controls.

*Conclusion:* Daily intake of 300 μmoL/kg/day of omeprazole decreased the BMD of the femur, but without changes to the rigidity and strength of the femur in adult rats.



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## Efeitos da administração em longo prazo do omeprazol sobre a densidade mineral óssea e as propriedades mecânicas do osso

*Palavras-chave:*
Osso
Densidade óssea
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RESUMO

*Objetivos:* Estudos epidemiológicos mostram uma relação entre o uso em longo prazo de inibidores de bomba de prótons e o metabolismo ósseo, porém essa relação ainda não está estabelecida. O objetivo deste estudo foi analisar as propriedade mecânicas e a densidade mineral óssea (DMO) de ratos submetidos ao uso de omeprazol em longo prazo.

*Métodos:* Cinquenta ratos Wistar, entre 200 e 240 g, foram divididos igualmente em cinco grupos: OMP300 (ingestão de omeprazol na dose de 300 μmoL/Kg/dia), OMP200 (200 μmoL/Kg/dia), OMP40 (40 μmoL/Kg/dia), OMP10 (10 μmoL/Kg/dia) e Cont (grupo controle; ingestão do veículo de diluição). A administração das soluções ocorreu durante 90 dias seguidos. Após a eutanásia, foram analisadas a DMO, as propriedades mecânicas dos fêmures dissecados e a dosagem de Ca++ sérico.

*Resultados:* A DMO do grupo OMP300 foi menor do que a do Cont (p = 0,006). Não houve diferença na comparação entre os grupos OMP200, OMP40 e OMP10 em relação ao Cont. A força máxima e rigidez do fêmur não foram diferentes nos grupos experimentais quando comparados ao Cont. O grupo OMP300 teve concentrações séricas de Ca++ estatisticamente menores do que o grupo Cont (p = 0,049) sem diferença entre os demais grupos em relação ao Cont.

*Conclusão:* A ingestão diária de 300 μmoL/Kg/dia de omeprazol diminuiu a DMO do fêmur, porém sem alterações na rigidez e na força do fêmur de ratos adultos.



## Introduction

Proton pump inhibitors (PPIs) are the main drugs used for treating diseases such as duodenal ulcers and reflux esophagitis.[1,2] Because these drugs present few adverse effects when administered correctly, they have come to be used not only for acute symptoms in clinical practice, but also for long-term purposes, even though such indications are highly debatable.[3–5]

PPIs act mainly toward suppressing gastric acid secretion by the parietal cells of the stomach, since they inhibit the enzyme H + K + ATPase, and this acid suppression may last for up to 48 h.[6]

Epidemiological studies have indicated that there is a relationship between prolonged use of PPIs and bone metabolism,[7–9] although this relationship is still not totally established. Yang et al.[4] reported that administration of omeprazole (20 mg/day), which is one of the most important PPIs, is capable of significantly diminishing bone mineral density (BMD). It is believed that the mechanism responsible for this consists of elevation of gastric pH, which would interfere with calcium absorption.[4,10,11] This occurs because some salts, such as calcium, are insoluble in basic pH and would therefore be absorbed less readily.[8] However, a study by Hyun et al.[3] suggested that using omeprazole would tend to diminish bone reabsorption and impede the progression toward osteoporosis. Therefore, the relationship between using PPIs and bone demineralization and the risk of fractures associated with prolonged use of omeprazole remains unclear.[9]

Given that there is evidence that prolonged use of PPIs may change the behavior of bone cells, our objective here was to analyze the bone mineral density and mechanical properties of rat femurs that were subjected to long-term use of omeprazole.

## Materials and methods

### *Type of study*

This was an experimental study using an animal model.

### *Animals*

The procedures used in this study followed the standards described by the Brazilian College for Animal Experimentation (COBEA) in 1991 and the International Guiding Principles for Biomedical Research Involving Animals[12] and were approved by the Ethics Committee for Animal Research of the University of Vale do Sapucaí.

Fifty male adult rats of Wistar lineage, weighing 200–240 g, were used in this study. The animals were kept under normal environmental and temperature conditions (21 ± 2 °C; humidity of 55–60%; and light/dark cycles of 12 h). They received water *ad libitum* and feed suitable for rats. Fasting of 6 h was maintained during the daytime period, before the daily protocol was started.

The rats were divided equally into five groups: (1) OMP300 – omeprazole intake at a dose of 300 μmol/kg; (2) OMP200