Effect of long-term proton pump inhibitors on bone mineral density

Baisse de la densité minérale osseuse lors de la prise des Inhibiteurs de la Pompe à Protons au long cours

Hayfa Romdhane [1,2], Shema Ayadi [1,2], Nour Elleuch [1,2], Kawther Abdelghani [3,2]

1 : Service de gastroentérologie, Hôpital Mongi Slim Tunis, Tunisie
2 : Faculté de Médecine de Tunis, Université Tunis El Manar
3 : Service de rhumatologie, Hôpital Mongi Slim, Tunis Tunisie

RÉSUMÉ

Introduction : Les Inhibiteurs de la pompe à protons (IPP) sont actuellement largement prescrits. Un traitement au long cours exposerait à une diminution de la densité minérale osseuse (DMO) avec augmentation du risque de fractures.

Objectif : Etait d'établir la prévalence de l'ostéopénie et de l'ostéoporose au cours d'un traitement prolongé par les IPP et de rechercher les facteurs de risque qui y sont associés.

Méthodes : Etude prospective incluant consécutivement des patients sous IPP depuis au moins un an. La DMO a été évaluée par une ostéodensitométrie. Le risque de fracture ostéoporotique était évalué par le score FRAX.

Résultats : Nous avons inclus 52 patients avec un âge moyen de 49,5 ans et un sexe ratio H/F de 0,48. Les IPP étaient pris pour une durée moyenne de 45 mois et principalement pour un reflux gastro-oesophagien (75%). Un apport calcique insuffisant était fréquent (94%). Au moins trois facteurs de risque d'ostéoporose ont été retrouvés chez près de 50% de la population. L'ostéopénie et l'ostéoporose était observées dans respectivement 52% et 19%. Les facteurs prédictifs d'une DMO basse étaient l'âge ≥50 ans, la ménopause, l'apport calcique ≤550mg/j et une durée de prise des IPP ≥30 mois. Le score FRAX était significativement plus élevé lorsque la DMO était basse. L'analyse multivariée n'a pu être faite en raison de la colinéarité des facteurs.

Conclusion : La prise des IPP au long cours expose à une baisse de la DMO surtout chez des patients déjà à risque.

Mots-clés

Inhibiteurs de la pompe à protons, densitométrie osseuse, ostéoporose, ostéopénie

SUMMARY

Background: Proton pump inhibitors (PPIs) are widespread nowadays. Recent concerns have emerged about possible bone complications of their long-term use, as low bone mineral density (BMD) and an increased risk of fractures.

Aim: To evaluate the effect of long-term use of PPIs on bone by estimating the frequency of osteopenia and osteoporosis, and determining the risk factors associated to these complications.

Methods: A prospective study including consecutive patients taking PPI for at least one year. All patients underwent bone densitometry, and FRAX score was calculated to estimate the risk of osteoporotic fracture.

Results: We included 52 patients with a mean age of 49.5 years and a male-female ratio of 0,48. Mean duration of PPI intake was 45 months. The most frequent indication was gastroesophageal reflux disease. PPI prescription was appropriate in 94% of cases. The calculated daily calcium intake was in majority insufficient (94%). Approximately half of patients had at least three risk factors. Osteopenia and osteoporosis were observed in 52% and 19% respectively. Predictive factors of low BMD were an age ≥50 years, menopause, calcium intake ≤550mg/day and a PPI use duration≥30 months.

FRAX score was significantly higher when BMD was lower. The multivariate analysis could not be undertaken because of co linearity of the factors.

Conclusion: Long-term PPI use is associated with risk of bone complications, especially among patients at risk for osteoporosis. It seems reasonable to be more vigilant in prescribing PPIs and to use the lowest effective dose for patients with appropriate indications.

Key-words

Proton pump inhibitors, bone densitometry, osteoporosis, osteopenia.

Proton pump inhibitors (PPI) are one of the most long-term prescribed drugs worldwide [1]. This widespread use of PPI can be explained by their high efficacy for the treatment and prevention of gastroesophageal reflux disease (GERD) and peptic ulcer disease, and by their reputation for being well tolerated and unlikely to lead to long-term complications [2-4].

But, recent concerns have emerged about possible bone complications of long-term use of PPI, such as low bone mineral density (BMD) and increased risk of fractures. In fact, PPI affect bone mineral density by a variety of possible mechanisms such as reducing calcium absorption or by leading to hypergastrinemia and thereby to hyperparathyroidism [5-10]

The aim of our study was to evaluate the effect of long-term use of PPI on bone by measuring the BMD in order to estimate the frequency of osteopenia and osteoporosis, and to determine the risk factors associated to these complications.

METHODS

Study Design and population

This was a prospective study including consecutive patients admitted to a Tunisian gastroenterology department for the period between June 2014 and June 2015. We recruited consecutive patients aged 18 years and more, and who were taking PPI at long-term. Long-term PPI use was defined by taking of at least simple dose of PPI, for a period of 12 months at minimal. Patients with chronic conditions that may affect bone density, such as a renal disorder, chronic hepatic disease, malabsorption-related disease, inflammatory rheumatic disease, were excluded. We also excluded patients who have been taken medications that were known to modify bone metabolism such as corticosteroids and patients for whom X-Ray was contraindicated like pregnancy.

Data collection

For all patients, epidemiological data were noted as well as personal history of fragility fracture or parental history of menopause fracture. Other personal risk factors for fracture and osteoporosis such as smoking and alcohol intake, menopause status, sedentary lifestyle, disthyroidism and calcium daily-intake were precised. Nutritional condition was evaluated by anthropometric measures (Body Mass Index (BMI), waist size (WS), triceps skinfolds (TS), brachial circumference (BC) and muscular brachial circumference (MBC). Denutrition was defined by anthropometric values less than the fifth percentile compared to a population reference [11]. The type, daily-dose and the intake total duration of PPI were noted. PPI indication was also reviewed, according to the 2013 guidelines of the American College of Gastroenterology for GERD and to Maastricht V recommendations for the other indications.

All patients underwent bone densitometry measurements using dual-energy X-ray absorptiometry at the lumbar spine and femur neck. T sore was precised. Osteoporosis, osteopenia and normal bone density were defined according to WHO definition (T score <-2,5 DS, -2,5< T-score < -1 DS, T score> -1DS respectively) [12].

Patients were divided into two groups: BMD (-) for patients with osteopenia or osteoporosis, and BMD (+) for those with normal bone densitometry.

Finally we calculated FRAX score in patients aged 40 years and more, in order to estimate the 10 years risk for major osteoporotic fracture and the risk for femur neck fracture.

Statistical analysis

Statistical analyses were performed using SPSS v19.0. We compared patients who had normal BMD (BMD+) with those who had a decrease in bone mineral density (BMD -) in order to identify the risk factors associated with a decrease in BMD.

T student test was used for comparison of means between two independent groups. The Chi-square test was used to compare the Percentage on independent series.

A univariate study was carried out to identify risk factors by calculating the Odds Ratio (OR) after transforming the quantitative variables into qualitative variables with two modalities according to the threshold values identified by the ROC curves.

The multivariate study could not be undertaken because of co linearity of the factors.

The observed differences were considered significant when the result of P-value was <0.05.

Ethical Considerations

Oral informed consent was obtained from all participants

Conflict of interest

We have no conflict of interest to declare

RESULTS

General characteristics

Fifty-two subjects were enrolled in this study represented by 17 males and 35 females (67%). Mean age of patients was 49,5 years and more than 50% of patients were aged more than 50 years. Patients general characteristics are displayed in Table 1.

Risk factors for osteopenia and osteoporosis (RFO)

In our series, RFO were frequently observed. Indeed, approximately half patients had 3 RFO at least (3, 4 and 5 RFO in respectively 17%, 19% and 8%). These factors are described in Table 2.

Characteristics of long-term PPI intake

Omeprazole was the most prescribed PPI (84%). Other PPI used were represented by Lansoprazole (8%) and

Esomeprazole (32%). Mean duration of intake was 45,4 months [12-240]. GERD was the principal indication (75%). PPI prescription was adequate in majority of cases (94%).

Table 1: Patients general characteristics

Age in years (mean±s.d.)	**49,5± 14,55**
Female (%)	67
History of Non-traumatic fracture (%)	
- Personal Hx	21
- Family Hx	23
BMI kg/m 2 (mean±s.d.)	28,2 ± 5,9
Percentage with BMI ≥25 kg/m 2	67
Other Anthropometric measures (mean±s.d)	
- WS (mm)	42 ± 12
- TS (mm)	312 ± 48
- BC (mm)	178 ± 48
- MBC (cm)	96,9 ± 12,4
(Percentage of Values < 5 percentile)	
- WS	-
- TS	0
- BC	4
- MBC	46

Hx: history, WS: waist size, TS: triceps skinfold, BC: Brachial circumference, MBC: muscular brachial circumference

Table 2: Risk factors of osteopenia and osteoporosis

Risk Factors of Osteoporosis	Number	Percentage
Menopause	20/35	57
Smoking	13	25
Alcohol	6	12
Sedentary lifestyle	22	42
Disthyroidism	3	6
Insufficient Calcium intake	49	94
History of Non-traumatic fracture		
- Personal Hx of fragility fracture	11	21
- Family Hx of menopause fracture	5	23

Hx: history

Bone Densitometry Data

According to T score, osteopenia and osteoporosis was observed respectively in 52 and 19% of cases, most frequently in women (Table 3).

Frax score

Mean Frax score in patients aged more than 40 was 1,08 % ± 0,84 for major osteoporotic fracture and 0,26 % ± 0,29 for femur neck. All these patients were under therapeutic limen (30% for major osteoporotic fracture and 7% for femur neck).

Table 3: BMD results according to gender

	Male	Female	Total
Normal BMD	3 (20%)	12 (80%)	15 (29%)
Osteopenia	10 (37%)	17 (63%)	27 (52%)
Osteoporosis	4 (40%)	6 (60%)	10 (19%)

BMD: Bone mineral density

Analytic study

Pathological findings in BMD was correlated with age (>50 years), menopause, calcium intake (<550 mg/day). Osteopenia and osteoporosis were significantly correlated with higher levels of Frax score (p< 0,05). Patients with a PPI intake more than 30 months had an OR of 6,5 to develop osteopenia or osteoporosis, while PPI type and dose (simple or double) were not correlated abnormal BMD (Table 4).

Table 4: Factors correlated with pathological findings in BMD

	BMD (+)	BMD (-)	P
Age (mean, years)	40,1	53,3	0,002
Gender (%)			
- M	20	38	0,33
- F	80	62	
Anthropometric Data			
- BMI	27,62 ± 4,29	28,38 ± 6,48	0,678
- WS	96,92 ± 12,26	96,88 ± 12,75	0,993
- TS	45,23 ± 8,41	41,06 ± 13,94	0,322
- BC	308,33 ±31,21	313,55 ± 53,79	0,755
- MBC	164,15 ± 25,65	184,3 ± 53,98	0,225
Sedentary Lifestyle	5 (33%)	7 (46%)	0,404
Calcium Intake (mg/d)	504 ± 215	721 ± 485	0,029
Smoking	6 (40%)	7 (19%)	0,112
Dysthyroidism	2 (13%)	1 (3%)	0,196
Menopause	2 (13%)	18 (78%)	<0,0001
Personal History of fragility fracture	1 (6, 7%)	11 (29,7%)	0,74
Family history of osteoporotic fracture	3 (20%)	8 (21,6%)	0,897
Omeprazole	14 (93%)	28 (80%)	0,407
Lansoprazole	1 (6,5%)	3 (8,5%)	0,820
Esomeprazole	3 (20%)	13 (37%)	0,328
Intake duration >30months	3 (20%)	23 (62%)	0,006 (OR 6,6)
PPI simple dose	15 (100%)	36 (97%)	1

BMD: Bone mineral density, F: female, M: male, BMI: Body mass index, WS: waist size, TS: triceps skinfold, BC: Brachial circumference, MBC: muscular brachial circumference

DISCUSSION

In our series, female sex was predominant. Approximately half of patients had at least 3 risk factors for osteoporosis. Mean PPI intake duration was 45 months, principally for GERD. The PPI prescription was adequate in 94% of cases.

Osteopenia was observed in 50% of cases and osteoporosis in 21%. Higher Frax score was associated with lower BMD. In univariate analysis, low BMD was correlated with an age> 50 years, menopause, calcium intake (<550mg/d) and PPI intake duration more than 30 months. Multivariate analysis was not possible because of co linearity between variables.

PPI are one of the most prescribed therapeutic class in the world. In 2013, annual cost of PPI use was 26 milliard dollars all over the world [1].They are frequently prescribed as a long-term therapy. Nevertheless, an inadequate prescription is observed between 25 and 70% of cases [13].The cost of this inappropriate use of PPI is estimated to 1,5 million US dollars [14]. In our study, the PPI prescription was inadequate in only 6% of cases. New concerns had emerged about the safety of use of this therapeutic class because of the increasing consumption and its new availability as “over the counter” drug. In fact, PPI are already known as a safe drug, and severe side effects are rare [13]. However, some authors revealed new side-effects of PPI as low bone density and increasing risk of fracture. Odzil and al had shown, in a prospective study, a significant bone density decrease at both femoral and spinal lumbar site, in patients after 6 months of PPI intake [15]. Gray and al had demonstrate likewise, that PPI consumption more than 3 years decreased bone density, but only in femoral site [16].

However, data about this subject are conflicting. In osteoporotic patients, Targowink and al didn’t find significant association between PPI long-term use and osteoporosis. There was no significant decrease in bone densitometry after 1 year of PPI intake [17]. In the largest study assessing the influence of long-term PPI use on bone health, there was no significant differences in BMD, bone turnover, or indices of bone strength between persons with PPI use of 5 years or greater and those with no history of PPI use within the previous 5 years [18]. In our series, PPI intake for 30 months and more was associated significantly with a lower BMD. However, it was based on a single measure in patients with long-term PPI intake, without comparing with a control group and without screening the evolution of BMD over the treatment. Data reported regarding the relation of PPI medications with bone fractures are also conflicting. A meta-analysis demonstrated that there was a significant increase in bone fracture risk in patients with long-term use of PPI [19], while other authors failed to show similar findings in recent reports [20]. In our study, we hadn’t evaluate the risk of fracture under long-term PPI use because of the impossibility of prolonged follow.

Several hypotheses had been advocated to explain the PPI effects on BMD. First, it may pass by reducing calcium absorption as gastric acidity is necessary to calcium absorption [21]. Secondly, gastric acid suppression leads to a hypergastrinemia and thereby to hyperparathyroidism. This will be responsible of increasing bone resorption and a lower BMD as a consequence [9, 22].Thirdly, PPI effects on BMD may pass by inducing vitamin B12 deficit which unbalance bone metabolism [23], and also by inducing hypomagnesaemia which will be responsible of bone depletion for magnesium leading to bone fragility [24,25]. Finally, some authors demonstrated that PPI block, in vitro, a bone proton pomp which is necessary to the bone resorption. Alteration of bone resorption will not affect BMD but will induce bone micro architectural disorders that enhance the fracture risk [26]. However data are still conflicting [27]. Few studies exist about the treatment of bone complications under PPI. There are no specific recommendations for their treatment. It is clear that a good calcium intake (alimentary calcium in preference) should be assured, especially for patients with high risk for osteoporosis (elderly patients taking long-term PPI at high doses) [28].

Stopping PPI in these patients is not recommended if the indication is adequate. However, it will be preferable to indicate the shorter treatment duration and the minimal doses if long-term treatment is necessary [29].

This study have some limitations which may affect the interpretability of the findings: the absence of a control group, small number of patients included, the impossibility of multivariate analysis and the absence of prolonged follow to evaluate the real risk of fracture.

CONCLUSION

The long-term PPI use is associated to the risk of bone complications, especially among patients with other risk factors of osteoporosis. It seems reasonable to be more vigilant in prescribing PPI, to use the lowest effective dose for patients with appropriate indications, and to screen these complications if necessary.

REFERENCES

1. IMS. IMS Health Report. In IMS heath reports 2013.
2. Kahrilas PJ, Shaheen NJ, Vaezi MF. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. Gastroenterology. 2008; 135(4):1392–413, 1413.e1–5.
3. Yeomans ND, Tulassay Z, Juhasz L, Rácz I, Howard JM, van Rensburg CJ et al. A comparison of omeprazole with ranitidine for ulcers associated with non steroidal anti inflammatory drugs. Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group. N Engl J Med. 1998; 338(11):719–26.
4. Hawkey CJ, Karrasch JA, Szczepanski L,Walker DG, Barkun A, Swannell AJ et al. Omeprazole compared with misoprostol for ulcers associated with non steroidal anti inflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group.N Engl J Med. 1998; 338(11):727–34.
5. Mazziotti G, Canalis E, Giustina A. Drug-induced osteoporosis: mechanisms and clinical implications. Am J Med. 2010; 123(10):877–84.
6. Graziani G, Badalamenti S, Como G, Gallieni M, Finazzi S, Angelini C et al. Calcium and phosphate plasma levels in dialysis patients after dietary Ca–P overload. Role of gastric acid secretion. Nephron. 2002; 91(3):474–9.
7. O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. Am J Med. 2005; 118(7):778–81.
8. Yang YX. Proton pump inhibitor therapy and osteoporosis. Curr Drug Saf. 2008; 3(3):204-9
9. Gagnemo-Persson R, Samuelsson A, Hâkanson R, Persson P. Chicken parathyroid hormone gene expression in response to gastrin, omeprazole, ergocalciferol, and restricted food intake. Calcif Tissue Int. 1997; 61(3):210-5.
10. Tuukkanen J, Vaananen HK. Omeprazole, a specific inhibitor of H+/K+ATPase, inhibits bone resorption in vitro. Calcif Tissue Int. 1986; 38(2):123–5.
11. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr. 1981;34(11):2540-5.
12. Organisation mondiale de la santé. Evaluation du risque de fracture et son application au dépistage de l'ostéoporose post-ménopausique. Genève: OMS;1994.
13. Macaigne G. Inhibiteurs de la pompe a protons : pourquoi des recommandations de bonne pratique sont-elles necessaires? Hepato Gastro. 2016; 23(6):538-51.
14. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. Am J Manag Care. 2010; 16(9):228-34
15. Ozdil K, Kahraman R, Sahin A, Calhan T, Gozden EH, Akyuz U, et al. Bone density in proton pump inhibitors users: a prospective study. Rheumatol Int. 2013; 33(9):2255-60.
16. Gray SL, LaCroix AZ, Larson J, Robbins J, Cauley JA, Manson JE, et al. Proton pump inhibitor use, hip fracture and change in bone density in postmenopausal women; results from the women's health initiative. Arch of Intern Med. 2010;170(9):765–71.
17. Targowink LE, Lix LM, Leung S, Leslie WD. Proton-pump inhibitor use is not associated with osteoporosis or accelerated bone mineral density loss. Gastroenterology. 2010; 138(3):896–904.
18. Targownik LE, Goertzen AL, Luo Y, Leslie WD. Long-term proton pump inhibitor use is not associated with changes in bone strength and structure. Am J Gastroenterol. 2017 Jan; 112(1):95-101.
19. Eom CS, Park SM, Myung SK, Yun JM, Ahn JS. Use of acid-suppressive drugs and risk of fracture: a meta-analyse of observational studies. Ann Fam Med. 2011; 9(3): 257-67.
20. Reyes C, Formiga F, Coderch M, Hoyo J, Ferriz G, Casanovas J, et al. Use of proton pump inhibitors and risk of fragility hip fracture in a Mediterranean region. Bone. 2013; 52(2):557-61.
21. Sipponen P, Härkönen M. Hypochlorhydric stomach: a risk condition for calcium malabsorption and osteoporosis? Scand J Gastroenterol. 2010;45(2):133-8.
22. Yang YX. Chronic proton pump inhibitor therapy and calcium metabolism. Curr Gastroenterol Rep. 2012; 14(6):473-9.
23. Valuck RJ, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. J Clin Epidemiol. 2004; 57(4):422–8.
24. Faulhaber GA, Furlanetto TW. Could magnesium depletion play a role on fracture risk in PPI users? Arch Intern Med. 2010; 170(19):1776.
25. Kuipers MT, Thang HD, Arntzenius AB. Hypomagnesaemia due to use of proton pump inhibitors – a review. Neth J of Med. 2009; 67(5):169–72.
26. Mizunashi K, Furukawa Y, Katano K, Abe K. Effect of omeprazole, an inhibitor of H+K+ ATPase, on bone resorption in humans. Calcif Tissue Int. 1993; 53(1):21-5.
27. Hansen KE, Jones AN, Lindstrom MJ, Davis LA, Ziegler TE, Penniston KL, et al. Do proton pump inhibitors decrease calcium absorption? J Bone Miner Res. 2010; 25(12):2786-95.
28. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006; 296(24):2947-53.
29. Johnson DA, Oldfield EC. Reported side effects and complications of long-term proton pump inhibitor use: dissecting the evidence. Clin Gastroenterol Hepatol. 2013; 11(5):458-64.