



Chronic Oral Alendronate Use is Associated with Gastrointestinal Reflux Disease and Voice Alterations Irrespective of the Presence of Esophagitis

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This study aimed to compare the presence of atypical symptoms and signs of gastroesophageal reflux disease (GERD) in postmenopausal women with osteoporosis on long-term oral alendronate (ALN).

Methodology: One hundred and eighteen postmenopausal women, 59 on oral alendronate (cases) and 59 without using bisphosphonates (controls) were evaluated using a questionnaire of symptoms of gastroesophageal reflux and voice changes; voice capture using the Auditory Perceptive Assessment of Voice and Acoustic Evaluation of Voice. The voice was assessed by the GRBASI Scale and the acoustic measurement of voice by VoxMetria Software.

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Results: The median age was 66.87 ± 7.78 years (cases 68.83 ± 7.55 and control 64.91 ± 8.01 , $p = 0.0073$) ranging from 52 to 85 years. The median body mass index was 27.38 ± 4.63 , and there was no significant difference between groups (cases 26.64 ± 4.81 and control 28.13 ± 4.46 $p = 0.0833$). A greater frequency of typical clinical manifestations of Gastro-esophageal reflux disease (GERD) was observed (98, 83.05%), in the case group (52; 88.14%) in the control group (46; 77.97%), but there was no statistically significant difference ($p = 0.146$). Although, there was a trend towards more esophagitis in the control group (9 / 15.25% vs 2/ 3.39%; $p = 0.042$), atypical symptoms of the globus pharyngeal, dysphagia, discomfort in the upper airways (UA) and odynophagia had significantly more referrals in the ALN group. The presence of voice changes (96; 81.36%), was more frequent in the cases (53; 89.83%) than in controls (43; 72.88%; $p = 0.022$).

Conclusion: In conclusion, we found an independent association between voice disorders and gastroesophageal reflux independent of the presence of esophagitis, with the long-term use of oral alendronate.

Keywords: Voice; gastroesophageal reflux; alendronate; bisphosphonate.

1. INTRODUCTION

Oral alendronate is commonly used in the prolonged treatment of postmenopausal osteoporosis. It can induce gastrointestinal (GI) side effects mainly esophagitis, in about 20% of patients [1-3]. In general this drug is well tolerated, have low toxicity and few side effects if administered properly. Otherwise, it can cause changes, especially in the digestive tract, such as esophagitis, esophageal and gastric ulcers [4]. Patients who receive daily bisphosphonate are more likely to discontinue treatment due to gastrointestinal events [1,5,6,7,8,9].

GERD has two clinically recognized manifestations, classical or typical form, which presents with gastrointestinal manifestations, and laryngopharyngeal reflux (LPR), and atypical form, which presents with respiratory and/or laryngeal symptoms [10]. GERD is usually diagnosed by typical GI symptoms such as pyrosis and regurgitation, and upper GI endoscopy is usually performed to assess complications such as esophagitis. PH monitoring, although a cumbersome test, can also be used [11].

Sex hormones directly influence the voice and menopause can cause dysphonia, edema and lowering of the fundamental frequency (Fo). Aging also leads to changes in the voice mechanism and phonoaudiology can intervene to promote a better use of voice, improving individual communication skills [12]. GERD maybe associated with otorhinolaryngological symptoms such as dysphonia and studies on GERD and dysphonia show statistically

significant correlations between reflux and the presence of vocal edema and subsequent hypertrophy of the vocal cords [13]. Laryngopharyngeal reflux (LPR) as a manifestation of GERD, can compromise the well-being and quality of life of patients, but its prevalence is underestimated [14,15].

Therefore, this study aims to evaluate the presence of atypical signs and symptoms of gastroesophageal reflux disease (GERD) related to voice disorders in post-menopausal patients and the relationship between them and the use of alendronate.

2. STUDY POPULATION AND METHODS

This is a cross sectional study in which 59 postmenopausal women on long-term ALN were compared to a control group of 59 postmenopausal women not treated with oral bisphosphonates, who were recruited from an elderly catholic association. Data were collected in a period of one year.

The inclusion criteria was postmenopausal women on oral weekly alendronate for the treatment of osteoporosis, constituting the ALN group. For the control group, a population of women who did not use bisphosphonates was selected. The exclusion criteria, were as follows: previous significant gastrointestinal (GI) tract disease, tobacco use and/or alcohol, or drugs that could cause GI alterations.

After signing the informed consent, the patients answered a questionnaire to collect clinical data, had a voice capture for perceptive auditory and acoustic evaluation, and bone densitometry

(BMD) measurements. Upper GI endoscopy was performed to assess for the presence of esophagitis.

The atypical manifestations of GERD were identified through symptoms such as heartburn, sensation of heartburn that can reach up to the neck, acidic or food regurgitation. The evaluation of atypical GERD signs; global voice abnormality perceived during phonation of the patient was assessed by a speech therapist based on the international scale GRBASI to perceptual voice evaluation [12].

2.1 Statistical Analysis

The descriptive analysis of the study population was carried out by means of frequency distribution for categorical variable type, and the average with a standard deviation for quantitative type variable. Normality was verified applying the Komogorov-Smirnov test. In the analysis of associations Pearson’s chi-square test was used for independent variable type categorical, and Student t test for quantitative type variable. The measure of association was estimated by measuring the odds ratio, with their respective confidence intervals. For modeling of the factors related to the use of medication the multivariate logistic regression technique was applied of the stepwise method with the introduction of variables with statistical significance in the bivariate analysis below 20% (p<0.2). They remained in the model variables with statistical significance below 10% (p <0.1). Data was analyzed using Stata version 11.0.

3. RESULTS

The sample consisted of 118 women, 59 (50%) for each group, aged between 52-85 years (median 66.87±7.78 years), in the ALN group the age range from 57-85 years (median 68.83±7.55) and control 52-84 years (median 64.91±8.01). The mean age of menopause was 45.35 ±7.04 (Table 1).

Most of the patients (67.79%) had an abnormal endoscopic examination, and a history of proton pump inhibitor (PPI) use, but none were on PPI at the time of inclusion in this study. The typical signs of the GER disease were identified through endoscopy in 67.79% of patients. In considering the groups separately it was observed that 82.69% in the case group and 82.22% in the control group had typical manifestations of GERD with no statistically significant differences between them. Esophagitis was significantly more frequent in the control group than in the ALN group, 24.32% and 4.65% respectively (p = 0.050) (Table 2).

GERD was more likely to occur in the ALN group, but this was not statistically significant. Cases were more likely to have globus pharyngeous and odynophagia than controls (55.93 vs 33.90%; p=0.017 and 22.03 vs 8.47%; p= 0.048, respectively) (Table 2).

Using the acoustic perceptual vocal evaluation scale (GRBASI) dysphonia and hoarseness were more common in ALN group (OR 2.8, 95% CI 1.17-7.12; p=0.021) (Table 3).

Table 1. Baseline clinical characteristics of participants

	Median	n(%)	Cases	Controls	p-value
Age(years)	66.68 ± 7.78	118	68.83 ± 7.55	64.94 ± 8.01	0.0073*
Menopause (age)	45.35 ± 7.04	118	45.35 ± 6.54	45.35 ± 7.55	1.0000
BMI(kg/m ²)	27.38 ± 4.63	118	26.64 ± 4.81	28.13 ± 4.46	0.0833
<25	-	42 (35.59%)	26 (44.07%)	16 (27.12%)	0.055
25-29.9	-	40 (33.89%)	18 (31.03%)	22 (37.29%)	0.476
≥ 30	-	36 (30.50%)	15 (25.42%)	21 (36.21%)	0.206
BMD (g/m²)					
L1-L4	0.888 + 0.177	-	0.86 ± 0.12	0.91 ± 0.20	0.0867
Femoral neck	0.777 + 0.121	-	0.76 ± 0.11	0.78 ± 0.12	0.4507
Total hip	0.859 + 0.135	-	0.82 ± 0.12	0.89 ± 0.14	0.0113*
Osteoporosis treatment					
Ca or Vit. D	-	78 (66.10%)	55 (93.22%)	23 (38.98%)	<0.001*
Ca + Vit. D	-	65 (55.08%)	50 (84.75%)	15 (25.42%)	<0.001*
Alendronate	-	59 (50%)	59 (100%)	-	-

Table 2. Clinical Manifestation of Gastroesophageal Reflux Disease (GERD) and alterations on Upper Gastrintestinal Endoscopy (UGE)

	n(%)	Cases	Controls	OR IC(95%)	p-value
Typical	98 (83.05%)	52 (88.14%)	46 (77.97%)	2.09 (0.77-5.71)	0.146
Regurgitation	78 (66.10%)	41 (69.49%)	37 (62.71%)	-	0.437
Pyrosis	72 (61.01%)	38 (64.41%)	34 (57.63%)	-	0.451
Esophagitis	11 (9.32%)	2 (3.39%)	9 (15.25%)	5.13 (1.02-24.86)	0.042*
Atypical	115 (97.46%)	58 (98.31%)	57 (96.61%)	-	0.566
Hoarseness	70 (59.32%)	32 (54.24%)	38 (64.41%)	-	0.262
Chest discomfort	63 (53.39%)	36 (61.02%)	27 (45.76%)	-	0.098
Ear discomfort	59 (50.00%)	28 (47.46%)	31 (52.54%)	-	0.581
Oral discomfort	54 (45.76%)	28 (47.46%)	26 (44.07%)	-	0.712
Globus pharyngeal	53 (44.92%)	33 (55.93%)	20 (33.90%)	-	0.017*
Vocal fatigue	51 (43.22%)	26 (44.07%)	25 (42.37%)	-	0.853
Throat discomfort	46 (38.98%)	26 (44.07%)	20 (33.90%)	-	0.258
Nausea / vomit	42 (35.59%)	25 (42.37%)	19 (42.37%)	-	0.126
Constant cough	41 (34.75%)	21 (35.59%)	20 (33.90%)	-	0.847
Dysphagia	35 (29.66%)	21 (35.59%)	14 (23.73%)	-	0.160
Upper airways discomfort	21 (17.80%)	14 (23.73%)	7 (11.86%)	-	0.098
Odynophagia	18 (15.25%)	13 (22.03%)	5 (8.47%)	-	0.048*
UGE	97 (82.20%)	52 (88.14%)	45 (76.27%)	-	0.098
Normal	17 (14.40%)	9 (17.31%)	8 (17.78%)	-	0.793
Abnormal					
Gastritis	63 (53.38%)	35 (81.40%)	28 (75.68%)	-	0.198
Hiatal hernia	38 (32.20%)	19 (44.19%)	19 (51.35%)	-	1.000
Esophagitis	11 (9.32%)	2 (3.39%)	9 (24.32%)	4.86(1.00-23.58)	0.050

There was a positive association between the use of oral alendronate and the occurrence of voice alterations after adjustments for potential confounders (OR 4.4; 95% CI 1.48-13.1, $p=0.008$). Voice disturbances were more frequently reported in the ALN group when GERD was present (OR 2.32, 95% CI 1.02-5.31; $p=0.045$) (Table 4).

4. DISCUSSION

In the present study, although the number of cases of esophagitis was higher in the control group, GERD presented more often in ALN group. Data in the literature suggest that gastrointestinal events among women treated with osteoporosis therapy are more common in patients with a prior history of gastrointestinal events, confirming the importance of conducting research on GERD before the start of therapy [16].

Regarding atypical symptoms related to GERD, the group treated with alendronate showed more chance in presenting them, when compared to the control group. Thoracic discomfort, vocal fatigue, throat discomfort, nausea/vomiting and constant cough were seen more often in the

treatment group, as well as *globus* pharyngeus, dysphagia, upper airways discomfort and sore throat, with significant differences between the groups.

In general, bisphosphonates have low toxicity and few adverse effects, if properly administered in adequate doses. Due to its low intestinal absorption, a standardized management is recommended, with a full glass of water, fasting before and after taking the medicine, and not to lie down after administration. Stability minimizes the toxicity of the treatment, and optimises the results [17-20]. Gastrointestinal side effects attributed to the use of bisphosphonates, have been associated with esophageal irritation and ulceration, resulting from direct exposure esophageal mucosa to the drug associated with an acid environment, due to GERD; resulting in heartburn, chest and abdominal pain, and nausea, and may happen in the first weeks of therapy [14].

In this study, voice alterations, were more common in the ALN group despite being younger than those with no voice alterations. The most commonly reported symptoms were dysphonia/hoarseness, coughing, *globus pharyngeus*,

laryngitis, asthma, heartburn and dysphagia. LPR is a manifestation of GERD, and may lead to a decrease in psychological well-being and the quality of life [16].

The average grade of dysphonia, based on GRBASI scale, was more common in ALN group and these results are in accordance with previous report on GERD and voice disturbance.

Jitter and Shimmer scores were significantly higher in patients with voice alterations and the presence of GERD, and this confirm the variability of F0 and the lack of vibration control of the vocal folds (instability of the laryngeal wave). The presence of this variability of F0 corresponds to reduced glottic resistance and are correlated to the presence of emission noise and soprosity [12,21,22,23].

Table 3. Distribution of patients for the presence of vocal disturbances and the profile of acoustic and perceptual vocal evaluation

	Media	n (%)	Cases	Controls	OR IC (95%)	p-value
Voice disturbances	-	96 (81.36%)	53 (89.83%)	43 (72.88%)	-	0.022*
Hoarseness	-	85 (72.03%)	46 (77.97%)	39 (66.10%)	-	0.154
Afonia	-	4 (3.39%)	3 (5.08%)	1 (1.69%)	-	0.332
Vocal fatigue	-	42 (35.59%)	26 (44.07%)	16 (27.12%)	-	0.056
Difficulty in speaking	-	27 (22.28%)	18 (30.51%)	9 (15.25%)	-	0.052
Difficulty to sing	-	21 (17.80%)	13 (22.03%)	8 (13.56%)	-	0.233
Thicker voice	-	9 (7.62%)	4 (6.78%)	5 (8.47%)	-	0.729
Vocal disturbances and GERD						
GERD presente	-	84 (85.71%)	47 (79.66%)	37 (62.71%)	2.32 (1.02-5.31)	0.045*
GERD absent	-	12 (60%)	6 (10.17%)	6 (10.17%)	1 (0.30-3.29)	1.000
Acoustic and perceptual vocal evaluation						
G-GRBASI	0.86±0.59	118 (110%)	1.15±0.66	0.57±0.53	2.8 (1.17-7.12)	0.021*
0 = Normal	-	35 (29.66%)	9 (15.25%)	26 (44.07%)		
1 = Mild	-	64 (54.24%)	32 (54.24%)	32 (54.24%)		
2 = Moderate	-	19 (16.10%)	18 (30.51%)	1 (1.69%)		
3 = Severe	-	0 (0.00%)	0 (0.00%)	0 (0.00%)		

Table 4. Association between use of alendronate and the occurrence of GERD and voice disturbances adjusted for potential confounders

	OR IC (95%)	p-value
Age (years)	1.07 (1.02-1.12)	0.006*
GERD	2.56 (0.88-7.42)	0.083
Voice disturbances	4.40 (1.48-13.1)	0.008*

Aging brings changes in the voice mechanism and speech therapy can intervene promoting its better use by improving the communication of people. The F0 is the speed at which the sound wave is repeated per unit of time, in *Hertz* (Hz), biodynamic characteristic of the vocal folds and subglottic pressure. Auditory Perceptual Assessment of Voice is subjective, and observes the cultural, emotional and social aspects of dysphonia of individuals, and the acoustics assessment, performs objective measurements of voice sounds. Aging or healthy senescence presents gradual changes in functional adaptation process without disruption while maintaining quality of life. Physiological changes can modify the natural process of speech production. Patients with complaints of laryngeal disorders may have an underlying cause of GERD, and the treatment of related dysphonia requires joint and complementary action between doctors and speech therapists, treatment together is essential for a successful outcome [10]. Vocal and laryngeal abnormalities are commonly associated with GERD, the voice may have hoarseness, throat clearing (discomfort), coughing, vocal fatigue, and this is mentioned and considered as a cofactor for the development of vocal fold carcinoma [24].

5. CONCLUSION

In conclusion, we found that the long-term use of oral alendronate had an independent association with voice disturbances and GERD irrespective of the presence of esophagitis.

ETHICAL APPROVAL

The study was approved by the Ethics in Research Committee of the Agamenon Magalhães Hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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