Acetylcholinesterase inhibitors and healing of hip fracture in Alzheimer’s disease patients: a retrospective cohort study

H. Eimar1,‡, A. Perez Lara2,4‡, I. Tamimi3, P. Márquez Sánchez2, I. Gormaz Talavera3, F. Rojas Tomba3, T. García de la Oliva3, F. Tamimi1

1Faculty of Dentistry, McGill University, Montreal, Quebec, H3A 0C7, Canada; 2Radiology Department, Hospital Regional Universitario Carlos Haya, Malaga, 29002, Spain; 3Traumatology and Orthopedic Surgery Department, Hospital Regional Universitario Carlos Haya, Malaga, 29017, Spain; 4Hospital Punta de Europa, Algeciras, Cádiz, 11207, Spain; ‡The first two authors contributed equally to this work

Abstract

Objectives: This study was designed to assess effects of cholinergic stimulation using acetylcholinesterase inhibitors (AChEIs), a group of drugs that stimulate cholinergic receptors and are used to treat Alzheimer’s disease (AD), on healing of hip fractures. Methods: A retrospective cohort study was performed using 46-female AD patients, aged above 75 years, who sustained hip fractures. Study analyses included the first 6-months after hip fracture fixation procedure. Presence of AChEIs was used as predictor variable. Other variables that could affect study outcomes: age, body mass index (BMI), mental state or type of hip fracture, were also included. Radiographic union at fracture site (Hammer index), bone quality (Singh index) and fracture healing complications were recorded as study outcomes. The collected data was analyzed by student’s-t, Mann-Whitney-U and chi-square tests. Results: No significant differences in age, BMI, mental state or type of hip fracture were observed between AChEIs-users and nonusers. However, AChEIs-users had better radiographic union at the fracture site (relative risk (RR),2.7; 95%confidence interval (CI),0.9-7.8), better bone quality (RR,2.0; 95%CI,1.2-3.3) and fewer healing complications (RR,0.8; 95%CI,0.7-1.0) than nonusers. Conclusion: In elderly female patients with AD, the use of AChEIs might be associated with an enhanced fracture healing and minimized complications.

Keywords: Fracture Healing, Bone, Acetylcholine, Acetylcholinesterase Inhibitors, Parasympathetic Nervous System

Introduction

The central nervous system affects bone remodeling through the adrenergic and cholinergic branches of the autonomous nervous system1-4. Adrenergic activity has been associated with bone resorption and drugs that inhibit this activity have been found to increase bone accrual, reduce the risk of hip fractures and accelerate fracture healing5,6. In contrast, cholinergic activity has been recently found to have a positive effect on bone accrual7-10, however, this physiological mechanism has never been explored as potential therapy for bone diseases such as osteoporosis and fracture healing.

One way of stimulating cholinergic activity is by administration of cholinergic agonists such as acetylcholinesterase inhibitors (AChEIs)11. AChEIs are a group of drugs that cause stimulation of cholinergic receptors by inhibiting the action of acetylcholinesterase; thus, increasing the levels of acetylcholine in the synaptic space. These drugs are widely used to treat Alzheimer’s disease (AD) and other forms of dementia since the mid-1990s12.

Alzheimer’s disease (AD) is characterized by a degradation of the hypothalamus, a brain structure that encloses cholinergic components13. Surprisingly, AD patients suffer from a low bone mineral density that is highly correlated with the cholinergic degradation of the hypothalamus14,15. Due to the reduced bone density, it has been shown that AD patients are more prone to bone fractures, particularly hip fractures, compared...
Healing of hip fractures in AD patients is usually slow and often results in delayed-union, non-union, need for re-intervention, or even death. Previously, we have demonstrated that AD patients who are receiving AChEIs, are associated with lower risk of hip fracture. However, the potential effect of these drugs on fracture healing has not been explored yet.

We hypothesize that the administration of AChEIs may have a beneficial effect on bone regeneration that could accelerate fracture healing. In order to test this hypothesis, we have designed a retrospective cohort study in which we compared the healing of hip fractures in a group of AD patients under AChEI treatment with another group of AD patients receiving no AChEIs. In this paper, we provide evidence for a potential approach to enhance fracture healing and reduce clinical complications, through stimulation of cholinergic activity by AChEIs.

Materials and methods

Study design

Approval from the ethical committee at Carlos Haya Hospital, in Malaga, Spain, was obtained to carry out a retrospective cohort study on AD patients who sustained hip fracture injuries at the same hospital. Patients records were identified in the computerized database of the Department of Traumatology, and the original hardcopy files were retrieved for manual examination. The overall study period was 8 years, between January 1, 2004 and December 31, 2012. All the hip fractures in AD patients that occurred within the study period were reviewed.

Patients, who were female, aged between 75 and 95 years at the date of the fracture, were included in this study. Our study did not include male patients since the number of male patients who satisfied our inclusion and exclusion criteria was too low. Accordingly, our study excluded male patients to control the number of parameters (variables) that could affect the study outcomes. Patients who were smokers or previously diagnosed with any of the following diseases, which are known to substantially affect bone metabolism and fracture healing, were excluded: osteomalacia, paget disease, Vitamin D deficiency, hyperthyroidism, Cancer [excluding non-melanoma skin cancer], Alcoholism, patients on corticosteroids, patients on anti-epileptic drugs, patients on bisphosphonates. Patients were also excluded if their five-week postsurgical radiographs were missing.

Hip fractures were defined according to the International Classification of Diseases (Tenth Revision, Codes 72.0-72.2) as a fracture of the proximal femur ranging from the femoral neck (intracapsular) to the subtrochanteric (extracapsular) region. The analyses included the first six months after operation.

A total of 135 AD patients who suffered hip fractures were identified in our health care area during the study period; among these patients 80 fulfilled our medical inclusion criteria (Figure 1). Due to missing radiographs, 34 patients were excluded; and therefore, 46 patients were included in our final assessment model (Figure 1).

Study variables

The following parameters which may affect the study outcomes were retrieved from the patients’ files, computerized records and standardized questionnaires: patient age, body mass index (BMI), Charlson comorbidity score (CCS) and the grade of AD according to the clinical dementia rating scale (CDR). In addition, information about type of hip fracture: intracapsular or extracapsular fractures were retrieved. The presence of AChEIs was considered as the predictor variable.
**Study outcomes**

**Degree of calcification and bone quality**

Five weeks-post-surgical plain pelvic radiographs (antero-posterior), taken as part of the routine follow-up, showing the fractured hip and non-fractured hip of the AD patients were retrieved. All of the retrieved radiographs were performed at our department using a digital conventional hip x-rays machine (General Electric Corporation, Milwaukee, WI) with an adjusted X-ray exposure to match the anatomy of patient being examined. The retrieved radiographs were examined by two experienced musculoskeletal radiologists blinded to the patient treatment group. Inter-observer agreement among the two radiologists was significantly high (κ=0.824; 95% CI=0.691-0.957; p<0.001).

The following parameters were retrieved from the radiographs: the degree of calcification (radiographic union) at the fracture site and the bone quality at the non-fracture site.

Degree of radiographic union at the fracture site was assessed following the criteria proposed by Hammer et al.\(^2\)\(^4\). Hammer et al classified the degree of radiographic union of bone fracture into 5 grades; from grade 1 (corresponding to a complete calcification) to grade 5 (corresponding to a fracture without any evidence of calcification), based on the quality of the bridging callus and the presence or absence of a fracture line (Hammer union index)\(^2\)\(^5\).

Bone quality at the non-fracture site was assessed following the criteria proposed by Singh et al.\(^2\)\(^5\). Singh et al classified bone quality into 6 grades; from grade 1 (corresponding to a poor bone quality) to grade 6 (corresponding to a normal bone quality), based on the trabeculae morphology and distribution at the proximal femur (Singh index)\(^2\)\(^5\).

**Healing complication**

Fracture healing complications that occurred within 6 months from the date of hip fracture were retrieved from the patients’ files. The investigated complications included the presence of infection, delayed-union, new hip fractures and surgical re-intervention.

**Statistical analyses**

Inter-observer agreements for the evaluations of the degree of bone calcification (radiographic union) of the fracture site and bone quality using radiographs were done by Kappa Test (κ). The value ranged from +1, with perfect agreement, to -1, which corresponds to absolute disagreement.

Clinical outcomes (degree of fracture calcification, bone quality and fracture healing complications) as a function of patients’ characteristics (age, BMI, CCS, CDS and type of hip fracture) were tested using unpaired Student T-test and Mann-Whitney U test. AD Patients’ characteristics and clinical outcomes as a function of the presence of AChEIs treatment were tested using unpaired Student T-test and chi-square test. Ratios of the probabilities (relative risk) of the study outcomes were presented with 95% confidence intervals (CIs), and accompanied p values. Values of p were two-sided and considered statistically significant if less than 0.05.

Sample sizes calculation to reject the null hypothesis, that states the study outcomes in AChEIs users and non-users are equal, were conducted using the chi-square test based on the following inputs: (i) expected fair radiographic union at the fracture site (hammer index ≤3) at the 5th-week in 100% of AChEIs users versus 60% in nonusers (controls)\(^2\)\(^6\), (ii) type I error probability (α) equals to 0.05. It was determined that at least fifteen patients in each group would be needed to reach a power of 80%. In addition, Post-hoc power calculations (following Fleiss test), to reject our null hypothesis, were conducted based on the following inputs: (i) number of included AChEIs users; (ii) ratio between AChEIs nonusers to AChEIs users; and (iii) probabilities of each outcome in AChEIs users and non-users\(^2\)\(^7\).

**Results**

**Study outcomes distribution in AD patients**

Degree of radiographic union (calcification)

Analyses of the retrieved radiographs demonstrated that 3 hip fractures had grade 2, 11 hip fractures had grade 3, 10 hip fractures had grade 4 and 11 hip fractures had grade 5 on fracture healing scale (Hammer union index). Degree of calcification of the fracture site could not be evaluated in 11 radiographs since the hip fracture was treated with a hip hemiarthroplasty.

Due to the small number of hip fractures in each grade, we categorized them into 2 groups: hip fractures that showed grade 3 or less (fair healing) and hip fractures that showed higher than grade 3 (poor healing) on fracture healing scale. The distribution of these two groups as function of AD patients’ characteristics is shown in Table 1. AD patients who showed calcification of the fracture site of grade 3 or lower did not have significant differences in age, BMI, mental state or type of hip fracture compared to those who had degree of calcification higher than grade 3 (Table 1). Moreover, degree of radiographic union at the fracture site was not significantly related to bone quality measured at the non-fracture hip (RR,1.5; 95%CI, 0.9-2.7; p=0.129).

Degree of bone quality

Analyses of the retrieved radiographs demonstrated that 10 non-fracture hips had grade 2, 19 non-fracture hips had grade 3, 10 non-fracture hips had grade 4, 3 non-fracture hips had grade 5 based on bone quality scale (Singh index). Bone quality could not be evaluated in 4 radiographs due to the poor quality of radiographs showing the non-fracture hip.

Due to the small number of non-fracture hips in each grade, we categorized them into 2 groups: non-fracture hips that showed grade 3 or less (poor bone quality) and non-fracture hips that showed higher than grade 3 (fair bone quality) on bone quality scale. The distribution of these two groups as function of AD patients’ characteristics is shown in Table 1. AD patients who showed bone quality higher than grade 3 at
the non-fracture site did not have significant differences in age, BMI, mental state or type of hip fracture compared with those who had bone quality of grade 3 or less (Table 1).

Healing complications

The distribution of healing complications observed at the fracture site as function of AD patients’ characteristics is shown in Table 1. AD patients with fracture healing complications did not have significant differences in age, BMI or mental state compared with those without complications (Table 1). However, all of the reported complications at the fracture site were observed in patients who had poor bone qualities (bone quality index ≤3) (RR, 1.5; 95%CI, 1.2-1.9; p=0.159).

Three, out of four complications, were observed in patients who suffered from intracapsular hip fractures and the forth complication was in a patient who suffered from an extracapsular hip fracture (RR=0.8; 95%CI, 0.7-1.0; Power=0.56; p=0.152; Table 1). The reported complications were 2 cases of post-surgical infections, 1 case of new hip fracture at a nearby site and 1 delayed-union case. Both infection cases occurred in patients who were previously treated with a hip hemiarthroplasty. These cases who suffered from infections were retreated.
with Gridlestone osteotomy, however, one of them died 4 months following the operation, while second patient survived for more than 5 years. Patient with the delayed-union of the hip fracture was retreated with Gridlestone osteotomy; due to high risk of surgical complications and low mobility demand.

**AChEIs distribution in AD patients and study outcomes**

Among the patients included, 24 were AChEIs users and 22 were non-users. Out of 24 AChEIs users, 10 patients had been treated with rivastigmine 3-12 mg/day for 12-48 months, 7 patients had been treated with donepezil 5-10 mg/day for 12-36 months and 7 patients had been treated with galantamine 6-24 mg/day for 12-48 months prior to enrolment.

The distribution of the presence of AChEIs in the study group as a function of age, BMI, CDR, CCS and type of hip fracture is shown in Table 2. Users of AChEIs did not have significant differences in age, BMI, mental state or type of hip fracture compared with AChEIs non-users (Table 2).

Interestingly enough, users of AChEIs were associated with a better degree of calcification at the fracture site (fracture healing index ≤3) and a better bone quality (bone quality index >3) than nonusers (Figure 2 and Table 3). Moreover, patients using AChEIs had no complications following hip fracture fixation than nonusers.

**Discussion**

In this study we provided the first clinical evidence for the previously unexplored potential role of cholinergic stimulation on fracture healing. Based on our cohort study, AD patients receiving AChEIs such as rivastigmine, donepezil or galantamine expressed accelerated radiographic union (calcification) at the fracture site, better bone quality and less postoperative comorbidity compared to AChEIs-nonusers.

Healing of hip fractures in elderly, such as AD patients, is slow and usually requires a long-term immobilization of the fracture ends leading to greater morbidity and mortality. Accordingly, several studies were conducted to find new therapeutic approaches to accelerate bone regeneration and fracture healing. Nowadays, the only approved drugs that are commonly prescribed to improve fracture healing are parathyroid hormone (PTH) analogs. However, even though PTH analogs are successful therapies for fracture healing, their use is limited due to the high cost and side effects. In our study, we show that AChEIs might accelerate the radiographic union at the fracture sites, which may enhance the healing process. Accordingly, future in vivo and longitudinal clinical studies should be conducted in order to investigate the positive effect of AChEIs on bone quality and fracture healing.

**AChEIs accelerate calcification at the fracture site**

In this study, healing of hip fractures was evaluated radiographically, by two radiologists who showed a high level of agreement, following criteria proposed by Hammer et al. This method has been previously used to evaluate radiographic union of the fracture in several clinical studies with a moderate overall general agreement.

In this study, AD patients who showed a high degree of calcification of their hip fractures (grade 3 or less on fracture healing index) had similar demographic characteristics to those patients who showed a poor calcification degree (higher than grade 3 on fracture healing index). Moreover, our study illustrated that types of hip fracture (intracapsular and extracapsular) or quality of bone (assessed by Singh index) did not significantly influence the radiographic union of the hip fracture. However, our results indicated that most hip fractures showing higher degree of calcification or radiographic union...
were observed in AD patients receiving AChEIs (Table 3), indicating that more bone regeneration might have occurred in these patients. These findings represent the first clinical evidence demonstrating that administration of AChEIs might be associated with an enhanced hip fracture healing. However, future research will have to be performed in order to assess whether the administration of these drugs are also associated with faster stability of the fracture site.

**AChEIs favor bone mass**

This study investigated the bone quality at non-fracture sites using Singh index as described by Sernbo et al.\(^40\). This method has been previously used to evaluate bone mineral density in clinical studies, and it has been shown to have a good correlation with results obtained from Dual-energy X-ray Absorptiometry (DXA), the most popular tool to measure bone mineral density\(^41-45\).

In this study, AD patients with bone quality higher than grade 3 based on bone quality index had similar patients’ characteristic to those with bone quality of grade 3 or below. However, our results indicated that AChEIs users had better bone quality (bone quality index >3) than non-users. These results are aligned with our previous clinical study, in which it has been shown that users of AChEIs were associated with a lower risk of hip fracture\(^5\), and it might open a new insight to treat bone diseases such as osteoporosis and minimize bone fractures.

Singh index refers to the architectural quality of trabecular network which is affected mainly by bone resorption rather than bone formation. The higher Singh index score observed in AChEIs users compared to nonusers might be related to the fact that these drugs would suppress bone resorption rate by promoting osteoclasts (bone-resorbing cells) apoptosis\(^4\), independently or in addition to their potential role in promoting the proliferation of osteoblasts (bone-forming cells)\(^4\). However, future research will have to be performed to confirm these hypotheses.

**AChEIs minimize healing complications**

Healing complications following hip fractures in elderly patients are common. A metaanalysis study reported that healing complications might occur in 49% of patients who suffered hip fractures\(^46\). Hip fracture typically results in a 1.8-year decrease in life expectancy\(^31,32\). Most of deaths due to hip fractures occur within the first 3-6 months following the event\(^31,32\). The remaining mortality beyond the initial 6 months is associated with institutionalization and new deficits that are only indirectly related to the fracture itself\(^31,32\).

In this study, we detected four healing complications that occurred within 6 months after the hip fracture fixation procedure. Healing complications were not associated with patient’s age, gender, BMI, or with their mental status. Interestingly, our study illustrated that all complications at the fracture site were observed in patients who were not AChEIs users, indicating a potential positive effect of AChEIs on minimizing the fracture healing complications. However, healing complications were also found in patients who showed poor bone quality as assessed by Singh index. Accordingly, the observed complications at the fracture sites might not be solely dedicated to the un-usage of AChEIs.

**Table 3. Study outcomes as a function of AChEIs treatment.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Users of AChEIs (n=24)</th>
<th>Nonusers of AChEIs (n=22)</th>
<th>Crude RR (95% CI)</th>
<th>Power</th>
<th>p-value(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture healing index(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 (Poor)</td>
<td>9 (38%)</td>
<td>12 (56%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(\leq 3) (Fair)</td>
<td>11 (46%)</td>
<td>3 (14%)</td>
<td>2.7 (0.9-7.8)</td>
<td>0.56</td>
<td>0.036</td>
</tr>
<tr>
<td>Missing(^b)</td>
<td>4 (16%)</td>
<td>7 (32%)</td>
<td>0.9 (0.5-1.6)</td>
<td>0.05</td>
<td>1.000</td>
</tr>
<tr>
<td>Bone quality index(^c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 3) (Poor)</td>
<td>9 (37%)</td>
<td>20 (91%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt;3 (Fair)</td>
<td>11 (46%)</td>
<td>2 (9%)</td>
<td>2.0 (1.2-3.3)</td>
<td>0.92</td>
<td>0.001</td>
</tr>
<tr>
<td>Missing(^d)</td>
<td>4 (16%)</td>
<td>0 (0%)</td>
<td>0.31 (0.2-0.5)</td>
<td>0.04</td>
<td>0.018</td>
</tr>
<tr>
<td>Healing complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24 (100%)</td>
<td>18 (82%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0%)</td>
<td>4 (18%)</td>
<td>0.8 (0.7-1.0)</td>
<td>0.56</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Values are mean (95% confidence interval).
Abbreviation: AD: Alzheimer’s disease; AChEIs: acetylcholinesterase inhibitors; RR: Relative Risk.
\(^a\) Measured based on criteria proposed by Hammer et al.\(^19\)
\(^b\) Missing data: degree of fracture healing could not be evaluated for 4 AChEIs users and 7 AChEIs nonusers since their hip fractures were treated with a hip hemiarthroplasty.
\(^c\) Measured based on criteria proposed by Singh et al.\(^20\)
\(^d\) Missing data: Singh index could not be evaluated for 4 AChEIs users since the radiographs showing the non-fractured hip were poor.
\(^e\) p-value was calculated by chi-square test.
three AChEIs: rivastigmine, donepezil and galantamine, that are capable to stimulate cholinergic receptors: nicotinic and muscarinic, located peripherally and within the central nervous system\(^7\). Cholinergic activity is known to favor bone mass either indirectly through suppression of the adrenergic activity and/or directly through suppression of osteoclasts proliferation\(^1,7\). Also, substantial observations pointed toward a possible direct up-regulation of osteoblasts by cholinergic activity\(^4,8,10\).

**Limitations and future directions**

One limitation of this study was the small number of patients included. Despite this, we found that there is a strong association with a good power between radiographic union of hip fractures, bone quality and healing complications in one hand and the use of AChEIs on the other hand. Another limitation in our study was the use of X-rays radiography to assess the effect of AChEIs on bone healing and bone quality. Analysis of radiographs is subjective; however, it was conducted by two radiologists who were blinded to the treatment patient group, and yet showed a high inter-observer agreement among their results.

One more limitation in this study is that Hummer index was applied to assess the radiographic union of hip fractures from radiographs recorded in an antero-posterior view. Ideally, in order to assess the degree of radiographic union of bone fracture using Hummer index, two radiographs (antero-posterior and lateral radiographs) taken from perpendicular positions is recommended\(^24\). Another limitation present in our study is that the radiographic union assessment of the fracture site did not include 4 AChEIs users and 7 AChEIs non-users, since their hip fractures were fixed by prostheses. However, those missing participants did not significantly affect the results of radiographic union of the fracture site (Table 3). We also could not assess the bone quality for other 4 AChEIs users due to the poor quality of radiographs showing the non-fracture sites (Table 3). However, comparing the characteristics, radiographic union of the fracture site and fracture healing complications of these excluded AChEIs users versus the rest of participants were not significant (Table Supplementary 2), indicating a small potential effect of these patients on bone quality results reported in this study.

An additional limitation of this study is that the relationship of rivastigmine, donepezil and galantamine dosages and durations with the study outcomes could not be assessed for statistical significance due to the small number of participants who used these drugs. In Table supplementary 1, we assessed the association of each of the included AChEI with the study outcomes.

One more limitation in this study is the missing information about the recovery process that patients received after the hip fracture fixation procedure which might affect the study outcomes. A further limitation in this study was the missing information about the criteria used by physicians to prescribe AChEIs for AD patients\(^9\). It has been found that physicians are less likely to prescribe AChEIs for patients with high number of comorbidities\(^9\), which could affect our results. Nevertheless, the comorbidity grades, based on CCS, of the AD patients included in our study were not associated with the study outcomes: fracture healing, bone quality and healing complication.

For all of these reasons, future large-scale prospective randomized clinical trials, adjusted to all possible variables that might influence study outcomes, will have to be performed in order to confirm the findings of this study. Moreover, in vivo and clinical studies assessing biochemical bone markers, bone density measurements, and bone microarchitecture will have to be performed to explore the effect of AChEIs on bone structure and mineral content.

**Conclusion**

To the best of our knowledge this is the first clinical evidence demonstrating that the administration of AChEIs might be associated with a faster calcification (radiographic union) of hip fracture and a better bone quality in female, aged between 75 and 95 years AD patients. These findings might help identify new therapeutic approaches to accelerate bone regeneration and fracture healing, although additional clinical studies are needed to confirm these potentially important findings.

**References**


### Supplementary Tables

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Fracture healing index&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Bone quality index&lt;sup&gt;c,d&lt;/sup&gt;</th>
<th>Healing complication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤3 (n=14)</td>
<td>&gt;3 (n=21)</td>
<td>RR (95%)</td>
</tr>
<tr>
<td>No Drug</td>
<td>3 (12)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>4 (4)</td>
<td>1.6</td>
<td>0.156</td>
</tr>
<tr>
<td>Donepezil</td>
<td>4 (2)</td>
<td>2.4</td>
<td>0.064</td>
</tr>
<tr>
<td>Galantamine</td>
<td>3 (3)</td>
<td>1.6</td>
<td>0.198</td>
</tr>
</tbody>
</table>

Abbreviation: AChEIs: acetylcholinesterase inhibitors; RR: Relative Risk.

<sup>a</sup> Measured based on criteria proposed by Hammer et al.<sup>19</sup>

<sup>b</sup> Missing data: degree of calcification at the fracture site could not be evaluated for 7 AChEIs nonusers, 2 Rivastigmine, 1 donepezil and 1 neostigmine users since their hip fractures were treated.

<sup>c</sup> Measured based on criteria proposed by Singh et al.<sup>20</sup>

<sup>d</sup> Missing data: Singh index could not be evaluated for 2 Rivastigmine, 1 donepezil and 1 neostigmine users since the radiographs showing the non-fractured hip were poor.

<sup>e</sup> p-value was calculated by chi-square test.

### Table Supplementary 1. Study outcomes as a function of AChEIs treatment (no treatment, Rivastigmine, Donepezil and Galantamine).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with missing information</th>
<th>Rest of the patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84.5±5.4</td>
<td>82.9±3.5</td>
<td>0.405&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>27.8±4.4</td>
<td>25.3±4.2</td>
<td>0.266&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>CDR&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.5±0.6</td>
<td>2.0±0.7</td>
<td>0.224&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>CCS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.6±2.2</td>
<td>2.2±1.6</td>
<td>0.018&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fracture healing&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Poor</td>
<td>1</td>
<td>20</td>
<td>0.193&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>4</td>
<td>0.686&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviation: BMI: body mass index; CDR: clinical dementia rating scale; CCS: Charlson comorbidity score.

<sup>a</sup> Values are expressed as the mean and standard deviation.

<sup>b</sup> Measured as weight in kilograms divided by the square of height in meters.

<sup>c</sup> Measured based on criteria proposed by Hammer et al.<sup>18</sup>

<sup>d</sup> p-value was calculated with Mann-Whitney U test for independent samples.

<sup>e</sup> p-value was calculated by chi-square test.

### Table Supplementary 2. Characteristics of patients who had their bone quality not evaluated (missing data) vs. Characteristics of rest of patients who had their bone quality assessed.