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Use of Statins and Hip Fracture Risk: a Case-Control Study

Užívání statinů a riziko zlomeniny proximálního femuru: případová studie

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ABSTRACT

PURPOSE OF THE STUDY
To evaluate a possible association between hip fracture and statin use.

MATERIAL AND METHODS
In this case-control study we compared the use of statins between two groups of 210 patients: the first group (case group) included patients hospitalized for hip fractures while the second group (control group) included patients who did not suffer femur bone injuries. The two groups were matched for age, sex, year of hospitalization and possible confounding factors. Inside the group of cases, we also evaluated the differences in terms of fracture type, presence of previous fragility fracture and mortality between statin users and non-users.

RESULTS
The use of statins was most common among patients without previous fractures (OR=0.54; 95% CI=0.33–0.89; p=0.0138), especially in older patients (OR=0.40; 95% CI=0.22–0.76). We did not find any significant difference in statin intake between men and women in the control group. In the case group, those who did not use statins were more likely to undergo a medial hip fracture (28.5% vs 16.1%). Patients from case group also presented a greater mortality (27.9% vs 19.35%) and an higher percentage of previous hip fractures (20.11% vs 9.7%). However, they didn't presented a significant higher rate of fragility fractures in other sites.

DISCUSSION AND CONCLUSIONS
Our study suggests a reduced hip fracture risk, especially in cases aged 80 or more, a different fracture pattern (lower percentage of medial fractures) and a reduced mortality at 9 months in patients treated with HMG-CoA reductase inhibitors, confirming the previous evidences reported in literature.

Key words: statin, hip fractures, fracture risk, osteoporosis.

INTRUDUCTION

In western world countries and other states with elevated life expectancy, hip fractures can be considered both an important issue both from an epidemiological and an economical point of view. The annual incidence of hip fractures is about 1,6 million and it is expected to rise to 6,3 million in 2050, due to the general population ageing that will dramatically increase the percentage of people aged 85 or more (6, 17, 20). Total annual costs exceed the billion of euros in Italy, a burden similar to the ones represented by acute myocardial infarction and ischemic stroke (21). 1-year mortality after hip fracture is about 20% and a certain percentage of patients could never recover the ability to walk independently after the fracture and the injury (20, 5).

However, in the last years epidemiological studies testified a slightly reduced incidence of hip fractures; this fact can be explained by the diffusion of effective strategies introduced for the prevention and treatment of osteoporosis (4, 30).

Treatment for osteoporosis is mainly based on antiresorptive drugs (such as bisphosphonates) and an appropriate income of calcium and vitamin D (9, 11, 12). However, also due to the major importance of fragility fractures in modern days clinical practice, several other classes of drugs have been proposed as therapeutic approaches to prevent or treat osteoporosis (27). HMG-CoA reductase inhibitors, also known as statins are mainly used to treat hypercholesterolemia (7, 25), but their potential use to decrease the risk of osteoporosis is actually under examination. Several in vitro and in vivo studies indicated a possible link between statin use and the secretion of BMP-2 (bone morphogenetic protein-2), a cytokine involved in osteoblasts differentiation and activation (3, 18). As a result, the effect of statins on bone mineral density has been investigated and statin users were found with a statistically significant higher bone mass density (BMD) of proximal femur and lumbar spine compared to general population (14, 28). Many studies have been carried out to evaluate the effect of statins on fracture risk. Although on one hand some of them found a negative correlation between the use of statins and fracture risk (10, 19, 24), describing these drugs as a protective treatment, on the other hand some other studies did not find any significant association (31, 33).

The first aim of our work was to observe whether there was or not a relationship between statin use and

fractures involving proximal femur in our institution. Our second aim was to highlight eventual differences in fracture's features and clinical outcome between patients who used statins and those who did not.

MATERIAL AND METHODS

This single-center case-control study was approved by our local ethical committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave written consent.

We evaluated co-morbidities and drug therapies of 210 patients (46 men 164 women) hospitalized for hip fracture in our institution between January 2016 and December 2017.

We also carried out radiological evaluation of each patient's fractures, classifying them according to the AO/OTA classification (15). A partition of our population in consideration of cases' age and fracture type is reported in Table 1.

In parallel, we selected other 210 patients as a control group. These patients were recruited from admissions carried out between January 2016 and December 2017 at the Operative Unit of Internal Medicine of our hospital using a simple randomization. Exclusion criteria were 65 or more years of age and a medical history of previous fragility fractures involving femur, distal radius, proximal humerus, or vertebrae. We examined the medical records of all the 210 patients included in the control group, with a particular focus on statin use, in order to compare the incidence of statin utilization with the case group. Eventual differences in sex and age distribution of statin users were also evaluated.

Using the chi-squared test, we also evaluated and compared the use of glucocorticoids, bisphosphonates, cholecalciferol and calcium in order to exclude they could have a role as confounding factors. The same was made taking into consideration patients' comorbidities: rates of diabetes, hypertension, Parkinson's disease, COPD, kidney failure, ischemic heart disease and hypotiroidism were compared as well.

Inside the group of patients with hip fracture (case group), we also compared statin users and non-users to establish if the use of HMG-CoA reductase inhibitors could be somehow associated with the fracture type (classified according to the AO/OTA classification), with a medical history of previous fragility fractures in other sites or with cases' mortality at 9 months.

Statistical analysis was performed using Stata SE 13 (StataCorp LLC, College Station, TX). Statistical significance was set at 0.05 for all endpoints.

Table 1. Subdivision of patients (according to age group) and fractures (according to AO/OTA classification)

Number of patients	Age group
21	55–69
40	70–79
101	80–89
48	90 or more
Number of fractures	AO/OTA
7	subcapital (31B1)
36	transcervical (31B2)
13	basicervical (31B3)
83	simple pertrochanteric (31A1)
51	multifragmentary pertrochanteric (31A2)
10	intertrochanteric (31A3)
10	subtrochanteric (32A)

Table 2. Mean age and standard deviation of the two groups

	Case group	Control group
Sample size	210	210
Mean age	82.61	83.15
S.D. mean age	9.0754	7.8463
Men	46	46
Mean age men	83.51	82.57
S.D. mean age men	9.39	7.29
Women	164	164
Mean age women	82.39	83.32
S.D. mean age women	9.00	8.01

RESULTS

Demographic characteristics of case group and control group are highlighted in Table 2. No significant discrepancy was observed.

Likewise, the use of glucocorticoid, bisphosphonates, cholecalciferol and calcium, was not significantly different between the two groups. Diabetes, Parkinson's disease and COPD were significantly more frequent in

Table 3. Drugs and comorbidities differences between the two groups

	Case group (210)	Control group (210)	P value
Bisphosfonates use	10	8	0.63
Glucocorticoids use	10	12	0.66
Colecalciferol use	31	35	0.59
Calcium use	5	4	0.74
Diabetes	57	48	0.12
Hypertension	114	130	0.11
Parkinson‘s disease	11	8	0.48
COPD	22	16	0.31
Kidney failure	17	26	0.14
Ischemic heart disease	34	40	0.44
Hypothyroidism	18	20	0.73

the case group. Hypertension, kidney failure and ischemic heart disease, for their part, were significantly more frequent in the control group. Results involving drug use and comorbidities are summarized in Table 3.

We then quantified the use of statins into the two groups: users among case group were 31 (14.76%), while the control group included 51 users (24.3%). Using the chi-square test, we could testify that the use of statins was significantly lower in the case group compared to the control group (p=0.0138). OR was 0.54 with a 95% confidence interval (CI) of 0.33–0.89. Considering only patients aged 80 years or more, the OR was 0.40 with a 95% CI of 0.22–0.76.We therefore identified an association between statin use and hip fracture risk. We could not find any major difference between men and women (Table 4).

Simvastatin and atorvastatin resulted as the most used active substances (respectively 42 and 33 patients). Pravastatin, pitavastatin and lovastatin were less represented, being used by a total of 7 patients.

Regarding the 210 patients hospitalized for hip fracture, statin users and non-users showed the fracture pattern reported in Table 5:

A different distribution of medial (femoral neck) and lateral (peri-trochanteric) fractures was detected. Medial fractures accounted for 16.1% of fractures between users and 28,5% between non-users. Lateral fractures instead represented respectively 83.9 and 71.5% of fractures in the two groups.

Those who did not use statins showed a larger proportion of additional hip fractures (20.11% vs 9.7%). Fragility fractures in other sites (distal radius, proximal humerus, vertebrae) were similarly distributed in the two groups (Table 6).

Table 4. Statin use in the two groups

	Case group	Control group
Total	31 on 210 (14.76%)	51 on 210 (24.3%)
Men	11 on 46 (23.91%)	15 on 46 (31.61%)
Women	20 on 164 (12.19%)	36 on 164 (21.95%)
Aged 79 or less	14 on 61 (22.9%)	15 on 61 (24.6%)
Aged 80 or more	17 on 149 (11.41%)	36 on 149 (24.16%)

Table 5. Fracture's characteristics in patients hospitalized for hip fracture

	Statin users	Non-users
Total fractures	31	179
Subcapital fractures	0 (0%)	7 (3.91%)
Transcervical fractures	3 (9.76%)	33 (18.44%)
Basicervical fractures	2 (6.45%)	11 (6.15%)
Simple pertrochanteric fractures	14 (45.16%)	70 (39.11%)
Multifragmentary pertrochanteric fractures	8 (25.81%)	42 (23.46%)
Intertrochanteric fractures	2 (6.45%)	8 (4.47%)
Subtrochanteric fractures	2 (6.45%)	8 (4.47%)

Table 6. Further fragility fractures

	Statin users	Non users
Total patients	31	179
Further hip fractures	3 (9.7%)	36 (20.11%)
Other fragility fractures	7 (22.58%)	52 (29.05%)

Finally, mortality after 9 months was found to be higher in patients who did not use statins (27.9% against 19.35% for those who used them).

DISCUSSION

In-vitro and in-vivo studies proved an upregulation of BMP-2 gene (cytokine involved in osteoblasts activation) and a subsequent increase in bone mineral density (BMD) linked to exposure to statins (14, 18). On that basis, many case-control studies and meta-analysis found a lower risk of fragility fractures in statin users (3, 10, 19). Similar results were also found in studies concerning specifically hip fractures (1, 23). Statin's effect on BMD and fracture risk seems vary in consideration of the various anatomical regions. Statin's intake seem to be particularly effective on the femoral neck, leading to a marked BMD increasement and consequentially to a reduced risk of hip fracture (2, 32, 34). Their effectiveness has also shown to be greater in patients aged 80 or more (1). To our knowledge, there is instead no solid evidence that statins could cause a similar effect in other skeletal sites (22).

Our findings are consistent with these evidences, as we found the use of statins was statistically associated with a reduction of hip fracture risk (OR= 0.54; 95% CI=0.33–0.89; p=0.0138), particularly in elder people (OR=0.40; 95% CI= 0.22-0.76). This finding suggests a protective effect of the HMG-CoA reductase inhibitors on acute bone injuries of proximal femur. Previous studies and meta-analysis found a higher efficacy in male patients; such a gender difference could not be found in our population (2).

In clinical practice, it is important to consider that femoral neck fractures, especially in the Ward triangle, are more closely related to osteoporosis than trochanteric fractures (8, 16, 29, 35). This evidence is consistent with our finding of a lesser percentage of medial hip fractures among statin users (16.1% vs 28.5%), among the lines of what already shown by Safaei et al. in 2007, who reported an increased BMD in the Ward triangle but not in the trochanter zone after introduction of statins (26).

The lesser mortality after hip fracture among statin users observed in our study (19.35% vs 27.9%) had already been detected also by Juliebo et al. in 2010. This effect might be attributable to statin's systemic anti-inflammatory effect, which probably improves body's response to the fracture and its surgical treatment and indirectly increases the long-term survival rate (11).

We are conscious our study has some limitations. A larger population size could have enhanced the statis-

tical power of the study enabling a deeper evaluation of all the different variables. Moreover, observed results could have been affected by confounding factors different from those taken into consideration through our examination. These aspects should be considered and possibly overcame in order to continue and extend the study, with the aim to obtain even more reliable and definitive results.

CONCLUSIONS

In conclusion, we detected a reduced hip fracture risk (more evident in people aged 80 or more), a different fracture pattern (less medial fractures) and a reduced mortality at 9 months in patients treated with HMG-CoA reductase inhibitors, confirming the previous evidences reported in literature. Additional fragility fractures, in particular hip fractures, were more common in those cases who did not use statins.

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