Observational Study

Medicine®

OPEN

Case-control study examining the association between hip fracture risk and statins therapy in old people

Kao-Chi Cheng, MD, MS[a,b,c], Kuan-Fu Liao, MD, PhD[d,e], Cheng-Li Lin, MS[a,f], Cheng-Chieh Lin, MD, PhD[a,b,g], Shih-Wei Lai, MD[a,b,*]

Abstract

A population-based case-control study investigated possible association between statin use and risk of hip fracture among the elderly in Taiwan.

The Taiwan National Health Insurance Program database was used to identify 7464 subjects aged 65 years or older with newly diagnosed hip fracture in 2000 to 2013. An additional 7464 subjects aged 65 years or older without hip fracture were randomly selected as the control group. Hip fracture cases and controls were matched for sex, age, comorbidities, and index year of hip fracture diagnosis. Statin use was defined as "current," "recent," or "past" if the patient's statin prescription was respectively filled <3, 3 to 6, or ≥6 months before the date of the hip fracture. The odds ratio (OR) and 95% confidence interval (CI) for hip fracture associated with statin use was estimated using the logistic regression model.

The logistic regression analysis demonstrated that the odds of current statin use in cases with hip fracture were lower than the odds of current statin use in subjects without hip fracture (adjusted OR 0.73, 95% CI 0.65, 0.82).

The odds of current statin use in cases with hip fracture were lower than the odds of current statin use in subjects without hip fracture in elderly people in Taiwan.

Abbreviations: CI = confidence interval, *ICD-9* code = *International Classification of Diseases, 9th Revision, Clinical Modification*, OR = odds ratio; statins = hydroxymethylglutaryl-coenzyme A reductase inhibitors.

Keywords: case-control studies, elderly, hip fracture, osteoporosis, statins

1. Introduction

Considerable research has focused on the effect of hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins), including simvastatin, pravastatin, and lovastatin, in reducing coronary heart disease in patients with or without the history of ischemic heart disease.[1–4] However, less attention has been paid to the relationship between statin use and hip fractures. Furthermore, data of hip fractures resulting from osteoporosis were particularly lacking in Taiwan previously.

Osteoporosis is a major public health issue, with >200 million sufferers worldwide, according to the World Health Organization estimate.[5] Osteoporosis is commonly seen in East and Western countries.[6,7] In addition, the number of people living with osteoporosis and cardiovascular disease is growing as populations continue to age, particularly in rapidly aging countries such as China, Hong Kong, Japan, and Taiwan.[8,9]

Correlation between osteoporosis and population aging has been examined in several East Asian countries.[7,10,11] The relationship between hip fracture resulted from osteoporosis and cardiovascular disease resulted from atherosclerosis, although scare, was occurred in other countries.[12,13] We could hypothesis that lower the incidence of atherosclerosis maybe lower the risk of hip fracture. In other words, statins might have an impact on blood vessels and blood vessel "health" may be related to bone health. However, this issue has been largely overlooked in Taiwan. The present study seeks to explore possible correlations between statin use and hip fractures among elderly people.

Editor: Abdelouahab Bellou.

This study was supported in part by the Ministry of Health and Welfare in Taiwan (MOHW108-TDU-B-212-133004), China Medical University Hospital in Taiwan (DMR-107-192 and DMR-108-089), Academia Sinica Stroke Biosignature Project (BM10701010021), and MOST Clinical Trial Consortium for Stroke (MOST 108-2321-B-039-003). These funding agencies did not influence the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors have no conflicts of interest to disclose.

[a] College of Medicine, [b] Department of Family Medicine, China Medical University Hospital, [c] Department of Food and Nutrition, Providence University, [d] Division of Hepatogastroenterology, Department of Internal Medicine, Taichung Tzu Chi General Hospital, Taichung, [e] College of Medicine, Tzu Chi University, Hualien, [f] Management Office for Health Data, China Medical University Hospital, [g] Department of Healthcare Administration, College of Health Science, Asia University, Taichung, Taiwan.

[*] Correspondence: Shih-Wei Lai, Department of Family Medicine, China Medical University Hospital, No 2, Yuh-Der Rd, Taichung City 404, Taiwan (e-mail: wei@mail.cmuh.org.tw).

How to cite this article: Cheng KC, Liao KF, Lin CL, Lin CC, Lai SW. Case-control study examining the association between hip fracture risk and statins therapy in old people. Medicine 2019;98:41(e17476).

Received: 24 December 2018 / Received in final form: 21 August 2019 / Accepted: 12 September 2019

http://dx.doi.org/10.1097/MD.0000000000017476

2. Methods (the statistic analysis was performed in 2017)

2.1. Data source

Launched in March 1995, Taiwan's National Health Insurance Program covers 99% of Taiwan population of 23 million.[14–17] Details of the program and patient database can be found in previous studies.[18–22] The present study was approved by the Institutional Review Board of China Medical University (CMUH-104-REC2-115).

2.2. Sampled subjects and comorbidities

We identified subjects aged 65 years or older with hip fracture [*International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9* code 820)] newly diagnosed from 2000 to 2013, with diagnosis defined as the index date. Subjects aged 65 years or older without hip fracture were randomly selected from the same database as the control group. Both cases and controls were matched for sex, age (5-year intervals), and comorbidities. Comorbidities which could be potentially related to hip fracture before the index date were included as follows: alcohol-related diseases, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, hypertension, and osteoporosis. Based on the *ICD-9* codes, the diagnosis accuracy of comorbidities has been well examined in previous studies.[9,23–27]

2.3. Measurements of statin use and nonstatin lipid-lowering drugs use

The following statins are available in Taiwan: atorvastatin, lovastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin. To explore the association between statin use and risk of hip fracture, prescription history of statins before the index date was collected. To reduce bias, subjects whose final statin prescriptions were filled >12 months before the index date were excluded. In Taiwan, prescriptions for chronic diseases are refilled every 3 months. Therefore, following previous studies, statin use was categorized according to the final statin prescription being filled within 3 months ("current use"), between 3 and 6 months ("recent use"), and between 6 and 12 months ("past use") before the index date. Subjects who never received a statin prescription were defined as never use of statins. Prescription history of nonstatin lipid-lowering drugs before the index date was also collected. Subjects who never had a prescription of nonstatin lipid-lowering drugs were defined as never use. Those who ever had a prescription of nonstatin lipid-lowering drugs were defined ever use.

2.4. Statistical analysis

We compared the distributions of the demographic status, statin use, nonstatin lipid-lowering drug use, and comorbidities between hip fracture cases and controls using the Chi-square test for categorized variables. Student *t* test was used to examine the difference of mean age between hip fracture cases and controls. Univariable and multivariable unconditional logistic regression analyses were used to calculate odds ratio (OR) and 95% confidence interval (CI) for the association between hip fracture and statin use. We further analyzed the dose-dependent effect among those with current statin use. An average daily statin dose of 15 mg was calculated by dividing total statin prescription quantity by total number of days supplied. Daily dose was then categorized as either <15 or ≥15 mg. All analyses were performed using SAS statistical software (version 9.2; SAS Institute Inc, Cary, NC). The results were considered statistically significant when 2-tailed *P* values were <.05.

3. Results

3.1. Characteristics of the study population

We identified 7464 cases with hip fracture newly diagnosed in 2000 to 2013, along with 7464 controls without hip fracture (Table 1). The hip fracture cases and the controls had similar distributions for sex and age. The mean age (standard deviation) was 80.1 (7.19) years in the hip fracture cases and 80.1 (7.50) years in the controls, without statistical significance (*t* test, $P = .88$). The controls were more likely to have a higher proportion of current statin use than the hip fracture cases (11.0% vs 8.27%, Chi-square test, $P < .001$). The 2 groups showed no significant difference for nonstatin lipid-lowering drug use or for comorbidities (Chi-square test, $P > .05$ for all).

3.2. Association between hip fracture and statin use

Because no other variable was found to be significantly related to hip fracture in the univariable analysis, we did not perform the multivariable unconditional logistic regression model. The univariable unconditional logistic regression model demonstrated that the odds of current statin use in cases with hip fracture were lower than the odds of current statin use in subjects without hip fracture (adjusted OR 0.73, 95% CI 0.65, 0.82) (Table 2).

3.3. Association between hip fracture and average daily dose of current statin use

We conducted an analysis on the dose-dependent effect among those with current statin use. The odds of average daily statin dose of <15 mg among cases with hip fracture were lower than among subjects without hip fracture (adjusted OR 0.75, 95% CI 0.65, 0.88). The odds of average daily dose of ≥15 mg among cases with hip fracture were lower than among subjects without hip fracture (adjusted OR 0.71, 95% CI 0.61, 0.82) (Table 3). Otherwise, analysis of trend tests was performed using a Cochran-Armitage trend test for enhancement the dose effect in our manuscript. Thus, there seems to be a dose-dependent effect of statin use on the risk of hip fracture.

3.4. Association between hip fracture and cumulative duration of current statin use

We conducted an analysis of risk of hip fracture associated with cumulative duration of current statin use. The odds of cumulative duration of statin use <12 months among cases with hip fracture were lower than among subjects without hip fracture (adjusted OR 0.68, 95% CI 0.56, 0.83). The odds of cumulative duration of statin use ≥12 months among cases with hip fracture were lower than among subjects without hip fracture (adjusted OR 0.75, 95% CI 0.66, 0.86) (Table 4).

4. Discussion

As in previous studies, we found that oral statin use may potentially protect against hip fracture in patients with

Table 1

Characteristics of hip fracture cases and controls in older people.

	Hip fracture				
	No N = 7464		Yes N = 7464		
Variable	n	(%)	n	(%)	P*
Sex					.56
Female	4393	58.9	4428	59.3	
Male	3071	41.1	3036	40.7	
Age group, yr					.11
65–74	1719	23.0	1619	21.7	
75–84	3529	47.3	3551	47.6	
≥85	2216	29.7	2294	30.7	
Age, yr, mean (standard deviation)†	80.1	7.50	80.1	7.19	.88
Statin use					<.001
Never use	6383	85.5	6603	88.5	
Current use	817	11.0	617	8.27	
Recent use	97	1.30	97	1.30	
Past use	167	2.24	147	1.97	
Nonstatin lipid-lowering drug use					.26
Never use	6322	84.7	6371	85.4	
Ever use	1142	15.3	1093	14.6	
Comorbidities before index date					
Alcohol-related diseases	235	3.15	219	2.93	.46
Cardiovascular disease	4960	66.5	4931	66.1	.62
Chronic kidney disease	682	9.14	680	9.11	.95
Chronic obstructive pulmonary disease	3210	43.0	3149	42.2	.31
Diabetes mellitus	1701	22.8	1659	22.2	.41
Hyperlipidemia	1992	26.7	1890	25.3	.06
Hypertension	5830	78.1	5750	77.0	.12
Osteoporosis	2420	32.4	2447	32.8	.64

Data are presented as the number of subjects in each group with percentages given in parentheses, or mean with standard deviation given in parentheses.
CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus.
* Chi-square test
† *t* Test comparing subjects with and without hip fracture.

Table 2

Odds ratio and 95% confidence interval of association between hip fracture and statin use, nonstatin lipid-lowering drug use, and comorbidities in older people.

Variable	Crude* OR (95% CI)
Sex (male vs female)	0.98 (0.92,1.05)
Age (per 1 year)	1.00 (0.99, 1.01)
Statin use (never use as a reference)	
Current use	0.73 (0.65, 0.82)
Recent use	0.97 (0.73, 1.28)
Past use	0.85 (0.68, 1.07)
Nonstatin lipid-lowering drug use (never use as a reference)	
Ever use	0.95 (0.87, 1.04)
Comorbidities before index date (yes vs no)	
Alcohol-related diseases	0.93 (0.77, 1.12)
Cardiovascular disease	0.98 (0.92, 1.05)
Chronic kidney disease	1.00 (0.89, 1.11)
Chronic obstructive pulmonary disease	0.97 (0.91, 1.03)
Diabetes mellitus	0.97 (0.90, 1.05)
Hyperlipidemia	0.93 (0.87, 1.00)
Hypertension	0.94 (0.87, 1.02)
Osteoporosis	1.02 (0.95, 1.09)

CI = confidence interval, CKD = Chronic kidney disease, COPD = Chronic obstructive pulmonary disease, DM = Diabetes mellitus, OR = odds ratio.
* Because no other variable was significantly related to hip fracture in the univariable model, we did not perform the multivariable unconditional logistic regression model.

hypercholesterolemia.[4,10,11,28,29] Other populations (e.g., postmenopausal women[30–32] and some rodents[6] showed a similar protect effect for osteoporosis. Furthermore, our results confirmed those of a previous study which noted a clear use-response relationship and dose-dependent effect.[28]

Statins are widely prescribed drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase and decrease hepatic cholesterol biosynthesis, thereby reducing plasma cholesterol levels and the incidence of cardiovascular events, including myocardial infarction.[3,33] Although many studies have examined the relationship between cardiovascular events and statin use, few have emphasized on the association of statin use with fractures resulting from elderly osteoporosis patients.

Incidence of hip fracture increases markedly with age. Osteoporosis is characterized by low bone mass and structural deterioration of bone architecture, leading to fragility and thus increasing risk of hip fracture. Recently developed drugs have been found to inhibit bone resorption, but there remains a clear need for nontoxic anabolic agents to increase bone formation and protect from hip fracture. However, for example, few such drugs [Teraperitide, romasuvamab, and abaloparatide (Tymlos)] has yet been approved for this indication. But most of them mentioned above were not on the market in Taiwan when designing our article. Therefore, the results of the present study may provide a valuable reference for further treatment to osteoporosis.

Table 3

Association between hip fracture and average daily dose of current statin use in older people.

Variable	Case number/control number	Crude odds ratio*	(95% CI)
Never use of statin as a reference	6603/6383	1.00	(reference)
Average daily dose of current use of statin			
<15 mg	313/402	0.75	(0.65, 0.88)
≥15 mg	304/415	0.71	(0.61, 0.82)
P for Cochran-Armitage Trend Test			<.001

CI = confidence interval.
* Because no other variable was significantly related to hip fracture in the univariable model, we did not perform the multivariable unconditional logistic regression model.

Table 4

Association between hip fracture and cumulative duration of current use of statin in older people.

Variable	Case number/control number	Crude odds ratio*	(95% CI)
Never use of statin as a reference	6603/6383	1.00	
Cumulative duration of current use of statin			
<12 mo	176/250	0.68	(0.56, 0.83)
≥12 mo	441/567	0.75	(0.66, 0.86)

CI = confidence interval.
* Because no other variable was significantly related to hip fracture in the univariable model, we did not perform the multivariable unconditional logistic regression model.

One potential explanation for the protective effect of statins might be confounding by a healthy drug user effect. That is, the population who receive preventive oral statins treatment to lower cardiovascular incidents usually exhibit certain behaviors that put them at lower risk of hip fracture, including better health insight and good care-seeking behaviors.[4,29] Those who take better care of themselves will generally be more aware of fall risk and the potential for fractures, including hip fracture. In addition, decreased risk of dementia has been found to be associated with statin use, and this could also possibly be explained by increased health awareness.[34]

It is also noteworthy that many studies have found lower risk of hip fracture among statin users, likely due to the statins protective effect being confounded by obesity or body weight.[29,35] Obesity is commonly seen in hypercholesterolemia patients, and is associated with lower risk of hip fracture.[10,36] The protective effect of adiposity on risk of hip fracture could be explained by the likelihood of abundant adipose tissue increasing bone density, along with the local shock-absorbing capacity of fat.[37] In other words, patients taking oral statins for hyperlipidemia tend toward obesity, which reduces the risk of hip fracture compared to nonobese populations.

The precise mechanism by which statins act remains unclear, but they indeed decrease the production of mevalonate, a precursor of cholesterol production, by inhibiting the enzyme HMG-CoA reductase.[38] This mechanism is also very important in the action of certain bisphosphonates, such alendronate, which is used to treat osteoporosis.[39] These similar mechanisms differ only in terms of the action site and the enzyme in the mevalonic acid pathway.[6] Therefore, statins might provide a protective effect against hip fractures by increasing bone-mineral density.

Some strengths of the present study should also be noted. Comorbidities based on *ICD-9* codes have been carefully reviewed in previous studies.[9,23–26] The study design and statistical models are well conducted. The results are reasonable and provide updated evidence on this issue.

5. Limitation

The present study acknowledges certain limitations. First, the National Health Insurance (NHI) database provides no measure of bone-mineral density, and we are thus unable to definitely evaluate the level of osteoporosis and osteoporosis patients might potentially be excluded from the sample population, introducing bias or resulting in underestimation in the evaluation of hip fracture risk.

Second, diagnosis of osteoporosis and dyslipidemia might require relatively long-term observation for clinical manifestation and multiple plasma serum cholesterol level tests, and intermittent or interrupted observation may be insufficient to estimate osteoporosis and hyperlipidemia risk.

6. Conclusion

The odds of current statin use in cases with hip fracture were lower than the odds of current statin use in subjects without hip fracture in elderly people in Taiwan, with a pronounced dose-dependent effect. Future work should focus on observational studies or randomized trials to provide a better understanding of these correlations between statin use and hip fracture in elderly people worldwide.

Author contributions

Conceptualization: Kao-Chi Cheng.
Data curation: Kuan-Fu Liao.
Formal analysis: Cheng-Li Lin.
Supervision: Cheng-Chieh Lin, Shih-Wei Lai.
Writing – original draft: Kao-Chi Cheng.
Writing – review and editing: Kao-Chi Cheng, Shih-Wei Lai.

References

[1] Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.

[2] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333:1301–8.
[3] Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998;279:1615–22.
[4] Ray W, Daugherty J, Griffin M. Lipid-lowering agents and the risk of hip fracture in a Medicaid population. Inj Prev 2002;8:276–9.
[5] Uzzan B, Cohen R, Nicolas P, et al. Effects of statins on bone mineral density: a meta-analysis of clinical studies. Bone 2007;40:1581–7.
[6] Mundy G, Garrett R, Harris S, et al. Stimulation of bone formation in vitro and in rodents by statins. Science 1999;286:1946–9.
[7] Jin S, Jiang J, Bai P, et al. Statin use and risk of fracture: a meta-analysis. Int J Clin Exp Med 2015;8:8269–75.
[8] Yong V, Saito Y. National long-term care insurance policy in Japan a decade after implementation: some lessons for aging countries. Age Int 2012;37:271–84.
[9] Lai SW, Liao KF, Liao CC, et al. Polypharmacy correlates with increased risk for hip fracture in the elderly: a population-based study. Medicine 2010;89:295–9.
[10] Scranton RE, Young M, Lawler E, et al. Statin use and fracture risk: study of a US veterans population. Arch Intern Med 2005;165:2007–12.
[11] Pasco JA, Kotowicz MA, Henry MJ, et al. Statin use, bone mineral density, and fracture risk: Geelong Osteoporosis Study. Arch Intern Med 2002;162:537–40.
[12] Barzilay JI, Buzkova P, Cauley JA, et al. The associations of subclinical atherosclerotic cardiovascular disease with hip fracture risk and bone mineral density in elderly adults. Osteoporos Int 2018;29:2219–30.
[13] Fujihara Y, Nawata H, Honda M, et al. Comparative study of the correlation between atherosclerosis and osteoporosis in women in Japan and Mongolia. J Gen Fam Med 2017;18:237–43.
[14] Database NHIR. Taiwan. Available at: http://nhirdnhriorgtw/en/indexhtml [cited in February 1, 2017, English version]. Accessed February 1, 2017.
[15] Liao KF, Lin CL, Lai SW. Association between colorectal cancer and thiazolidinediones administration in a case-control study. Biomedicine (Taipei) 2019;9:4.
[16] Yang J-S, Peng Y-R, Tsai S-C, et al. The molecular mechanism of contrast-induced nephropathy (CIN) and its link to in vitro studies on iodinated contrast media (CM). Biomedicine 2018;8:1.
[17] Pan CC, Huang HL, Chen MC, et al. Lower risk of end stage renal disease in diabetic nurse. Biomedicine (Taipei) 2017;7:25.
[18] Cheng KC, Chen YL, Lai SW, et al. Risk of esophagus cancer in diabetes mellitus: a population-based case-control study in Taiwan. BMC Gastroenterol 2012;12:177.
[19] Liao KF, Lai SW, Li CI, et al. Diabetes mellitus correlates with increased risk of pancreatic cancer: a population-based cohort study in Taiwan. J Gastroenterol Hepatol 2012;27:709–13.
[20] Chen HY, Lin CL, Lai SW, et al. Association of selective serotonin reuptake inhibitor use and acute angle-closure glaucoma. J Clin Psychiatry 2016;77:e692–6.
[21] Hung SC, Lai SW, Tsai PY, et al. Synergistic interaction of benign prostatic hyperplasia and prostatitis on prostate cancer risk. Br J Cancer 2013;108:1778–83.
[22] Kuo SC, Lai SW, Hung HC, et al. Association between comorbidities and dementia in diabetes mellitus patients: population-based retrospective cohort study. J Diabetes Complications 2015;29:1071–6.
[23] Lai SW, Liao KF, Lai HC, et al. Risk of major osteoporotic fracture after cardiovascular disease: a population-based cohort study in Taiwan. J Epidemiol 2013;23:109–14.
[24] Mei-Ling S, Kuan-Fu L, Sung-Mao T, et al. Herpes zoster correlates with pyogenic liver abscesses in Taiwan. Biomedicine (Taipei) 2016;6:22.
[25] Liao KF, Lin CL, Lai SW, et al. Sitagliptin use and risk of acute pancreatitis in type 2 diabetes mellitus: a population-based case-control study in Taiwan. Eur J Intern Med 2016;27:76–9.
[26] Liao KF, Cheng KC, Lin CL, et al. Etodolac and the risk of acute pancreatitis. Biomedicine (Taipei) 2017;7:4.
[27] Lin H-F, Lai S-W, Liao K-F, et al. Synergistic interaction between alcoholism and polypharmacy on the risk of falls in the elderly. Int J Gerontol 2013;7:122–3.
[28] Wang PS, Solomon DH, Mogun H, et al. HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. JAMA 2000;283:3211–6.
[29] Toh S, Hernández-Díaz S. Statins and fracture risk. A systematic review. Pharmacoepidemiol Drug Saf 2007;16:627–40.
[30] Edwards C, Hart D, Spector T. Oral statins and increased bone-mineral density in postmenopausal women. Lancet 2000;355:2218–9.
[31] Gotoh M, Mizuno K, Ono Y, et al. Fluvastatin increases bone mineral density in postmenopausal women. Fukushima J Med Sci 2011;57:19–27.
[32] Yamaguchi T, Sugimoto T, Yano S, et al. Plasma lipids and osteoporosis in postmenopausal women. Endocr J 2002;49:211–7.
[33] Rossouw JE, Lewis B, Rifkind BM. The value of lowering cholesterol after myocardial infarction. N Engl J Med 1990;323:1112–9.
[34] Jick H, Zornberg GL, Jick SS, et al. Statins and the risk of dementia. Lancet 2000;356:1627–31.
[35] Van Staa T-P, Wegman S, De Vries F, et al. Use of statins and risk of fractures. JAMA 2001;285:1850–5.
[36] Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. N Engl J Med 1995;332:767–74.
[37] Schwartz AV, Capezuti E, Grisso JA. Falls as risk factors for fractures. Aging, Place, and Health. Michael Brown: United States of America; 2017.
[38] Alberts A, Chen J, Kuron G, et al. Mevinolin: a highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterol-lowering agent. Proc Natl Acad Sci U S A 1980;77:3957–61.
[39] Fisher J, Rogers M, Halasy J, et al. Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro. Proc Natl Acad Sci U S A 1999;96:133–8.