스타틴이 폐경기 여성의 골밀도 혹은 골절위험에 미치는 효과
-보고된 임상연구결과 분석을 중심으로-

방준석 Pharm.D.
LG생명과학㈜

Efficacy of Statins on BMD or Fracture Risk in Postmenopausal Women

Joon Seok Bang, Pharm.D.

Pharmaceutical Division, LG Life Sciences, Ltd., Seoul, Korea

스타틴이 골형성을 자극하며 골밀도를 개선한다는 다수의 동물실험과 임상보고에 의해, 스타틴을 폐경기 이후 노령의 여성 고지혈증 환자에게 골다공증의 예방 혹은 치료적 용도로 사용할 수 있는가에 대한 관심이 고조되어 왔다. 하지만, 보고된 문헌들이 예방 혹은 치료효과를 제시하거나 해석됨에는 아직도 실험결과가 상이하거나 의견이 상충되고 있다. 본 연구는 폐경기 이후의 고지혈증을 지닌 골다공증 환자에게 처방된 스타틴이 실질적으로 골다공증 혹은 골절위험을 경감시키는 예방적 또는 치료적 효과를 지니는지 규명하고자, 1990년부터 2005년 사이에 MEDLINE에 등재된 데이터베이스 중에서 6개의 키워드를 사용하여 인체대상 연구보고서를 cross-sectional study, prospective cohort study 및 case-control study의 연구유형별로 수집, 분류하여 각각의 결과를 비교, 평가하였다. 각 연구결과들은 골다공증 평가에 이용하는 다수의 측정지표들에 대하여 공히 인정될 만한 수준의 유의성 여부를 제공하기에는 곤란했는데, 이는 연구디자인이 부적절했거나 실험대상 환자들이 보유한 각종 질병요소들과 치료상황이 복잡한 상호관계를 지녔기 때문이다. 따라서 대규모의 잘 계획된 이중맹검형 다국가 임상시험을 통해서 임상적 효과 유무가 입증되기 전에는 스타틴을 고지혈증을 보유한 폐경기 이후 노령 여성의 골다공증의 예방 혹은 치료적 용도로 사용하는 것은 아직 시기상조로 사료된다.

□ Key words – HMG-CoA Reductase Inhibitor, Statin, Bone Mineral Density, Postmenopausal Women, Fracture Risk, Osteoporosis

Are statins a prophylactic or therapeutic option for osteoporosis in postmenopausal women?

Osteoporosis (OP) affects 20% of women older than 50 years of age and an even larger proportion of elderly women. Fractures attributable to OP occur in approximately 1.5 million Americans annually.[1,2] According to some animal studies[3,4] and clinical reports,[7,10,11,13,18], statins might stimulate bone formation activities and may also be a potential OP treatment option for elderly women with hyperlipidemia.

Many clinical reports show that the use of statins is associated with significant effects on reduction of fracture risk at various sites by increasing bone mineral density (BMD) or affecting other bone metabolic biochemical markers. However, it is not yet clear whether these in vitro studies and observed effects on BMD have clinical relevance in preventing bone fractures and thus potentially useful implications for the care of elderly patients. There are conflicting evidences and different interpretations regarding the preventive or therapeutic effects of statin use on OP. The purpose of this article is to evaluate literature to elucidate whether statins should be used as treatment to increase BMD levels and reduce fracture risk in the postmenopausal women.

Correspondence to : 방준석
LG 생명과학㈜

Tel: 02-3773-7021, Fax: 02-3773-3132
E-mail: bjb0191@hotmail.com

LITERAURE REVIEW

In a cross-sectional survey, Solomon et al found that BMD was higher in women who had used statins com-

pared those who had never used statins.[5] They examined a relationship between statin use and BMD among 339 postmenopausal women (162 were statin-users, and 177 were not; mean age 62 yrs.). Among the statin-users, there are 120 subjects on atorvastatin (65%), 15 on fluvastatin (8%), 33 on lovastatin (18%), 43 on pravastatin (23%), and 32 on simvastatin (17%). The median duration of treatment was 32 months and many women had taken multiple statins. They found that statin use was associated with a significantly higher t-score at the total hip (-0.53±0.17; adjusted mean±SD BMD t-score) compared with non-users (-0.83±0.18; p=0.02). At the lumbar spine, there was a trend toward higher t-scores in statin users (-0.91±0.24) compared with non-users (-0.21±0.23; p=0.08). However, no relationship between duration of treatment and BMD was observed. Thus, longer-term use of statins may not necessarily be associated with a linear increase in BMD.

In the other study by Rejnmark et al, statins affected the function of bone cells, but did not BMD.[6] They measured BMD, biochemical markers of bone turnover, and plasma levels of PTH in 140 postmenopausal women (mean age 62 yrs.) who had been treated with a statin such as atorvastatin (15% of the sample), cerivastatin (0.7%), fluvastatin (5%), lovastatin (8.6%), pravastatin (5.7%), and simvastatin (65%) with usual anti-hyperlipidemic doses for a median duration of treatment of 4 years compared with 140 control subjects who did not receive a statin. The adjusted mean±SEM of BMD in the statin group versus the control group was as following, respectively: At lumbar spine (0.89±0.01 vs. 0.90±0.01; p=0.34), total hip (0.84±0.01 vs. 0.85±0.01; p=0.71), total forearm (0.46± 0.01 vs. 0.45±0.01; p=0.62), and whole body (0.99±0.01 vs. 1.00±0.01; p=0.45). There was no correlation between BMD at any site and duration of use. However, there was a positive correlation between doses (median: 20 mg; range: 10-40 mg) of simvastatin and BMD at the mid-forearm (R=0.25, p<0.04), total forearm (R=0.25, p=0.04), and the arms (R=0.36, p=0.002; R=regression coefficient). Statin dosages and duration of therapy were not mentioned; these could affect the study outcomes.

Another study showed a 60% reduction in fracture risk associated with the use of statins; the risk reduction was not explained by the effects of changes in BMD.[7] It involved 1,375 women aged 50-95 years from the same community of Southeastern Australian, 573 with incident fractures and 802 without incident fractures. Odds ratios (OR) for fracture associated with statin use have been expressed with 95% confident intervals (CI) before and after adjusting for BMD, age, weight, dietary calcium, alcohol use, smoking, activity levels, exposure to HRT, glucocorticoids, and Ca/Vit.D supplements. The unadjusted OR for fracture associated with statin use was 0.4 (CI: 0.23-0.71). Adjusting for BMD at the femoral neck, spine, and whole body increased the OR to 0.45 (CI: 0.25-0.80), 0.42 (CI: 0.24-0.75) and 0.43 (CI: 0.24-0.78), respectively. In this study, statin users tended to be younger and heavier within the fracture cohort; it might affect fracture outcome because younger age is often associated with more mental alertness and acuity and therefore a decreased chance of falls; bones might be more cushioned in heavier patients. The study did not account for dosage and duration of statin use; it suggested that the reduction in fractures might be due to statin-induced changes to bone surfaces rather than by increases in BMD.

In a prospective cohort study, LaCroix et al found that statin use neither improves fracture risk or BMD nor prevents or treats OP.[8] Among 93,716 women in the total cohort (50-79 yrs., 40 institutions in the US), no statistically significant differences were observed in BMD at the posterior-anterior spine or of the total body regardless of duration of use or potency of statin. Use of other lipid-lowering medications was not associated with changes in BMD at any skeletal site.

Another study by Schoofs et al showed the adjusted the relative risk (RR) for incident vertebral fracture statin users (compared with non-users) was 0.58 (95% CI: 0.34-0.99)[9]; the RR decreased with higher cumulative use to 0.52 (95% CI: 0.28-0.97) for use more than 365 days during the study period. The study sample was 3,469 men and women ≥55 years of age. This study showed that the use of pravastatin and non-statin cholesterol-lowering drugs were not significantly associated with decreases in vertebral fracture risk. Statin use was not associated with significant changes in lumbar spine BMD.

According to 4 different case-controlled analyses of Wang[10], Meier[11], Rejnmark[12], and Chan[13], exposure to statins was associated with a decrease risk of bone fractures in elderly patients including postmenopausal women. Wang et al enrolled a total of 6,110 patients (≥65 yr.; 1,222 case patients and 4,888 control patients) and measured adjusted OR of hip fracture by statin use in the 180 days and 3 years prior to the index date (ID, the earliest date of admission for surgical repair on hip fracture)[10]. The adjusted OR for demographic, clinical characteristics, and health care utilization showed use of statins in either the prior 180 days (adjusted OR=0.50; 95% CI: 0.33-0.76) or 3 years prior (OR=0.57; 95% CI: 0.40-0.82) was associated with a significant reduction in the risk of hip fracture. After adjusting for extent of statin use in the prior 3 years, current use (on the ID) was associated with a 71% reduction in risk (adjusted OR=0.29; 95% CI, 0.10-0.81).

Meier et al enrolled 91,611 patients (≥50 yr.; 3,940 case patients and 23,379 control patients from the UK-based General Practice Research Database) and measured adjusted OR of fracture risk statin users compared with non-users (OR=0.55; 95% CI, 0.44-0.69).[11] Current use of fibrates (OR=0.87; 95% CI, 0.70-1.08) or other lipid-lowering drugs (OR=0.76; 95% CI, 0.41-1.39) was not related to a significantly decreased fracture risk.

Rejnmark's study[12] (6,660 subjects with hip fracture and 33,274 gender- and age-matched; 50-69, and ≥70 yrs.) showed that statin treatment was associated with a reduced risk of hip fracture (OR=0.68; 95% CI: 0.5-0.93) for those subjects who had redeemed more than or equal to 4 prescriptions for a statin. Duration of statin treatment was not specified.

A study by Chan et al used data from 6 health-maintenance organizations in different regions of the USA.[13] Upon investigation of 928 cases and 2,747 controls of women aged 60 years or older, the results showed a decreased risk of non-pathological fracture in women with 13 or more fractures during the previous 2 years (OR= 0.48; 95% CI: 0.27-0.83 after adjustment of age, number of hospital admissions during the previous year, chronic disease score, and use of non-statin lipid-lowering drugs).

Berthold et al conducted a prospective study on 49 post-

Table 1. The summary of the retrieved study data to evaluate the preventive or therapeutic efficacy of statins on patients with osteoporosis.

Type of Study	Investigator	Remark	Methods	Results
Cross Sectional Study (Evaluative, observational study)	Solomon et al[5]	Relationship between statin use and BMD	■ 339 postmenopausal women (162 were multi-statin users, and 177 were not; mean age 62 years and median duration of treatment was 32 months)	■ BMD was higher in statin users compared with non-users. ■ No relationship between duration of treatment and BMD was observed.
	Rejnmark et al[6]	BMD in the statin group vs. the control group	■ 140 postmenopausal women (mean age 62 years for a median duration of treatment of 4 years) compared with 140 control subjects who not received a statin	■ Statins affected the function of bone cells, but did not BMD. ■ No correlation between BMD at any site and duration of use
	Pasco et al[7]	Patient enrolled from the same community of Southeastern Australian	■1,375 women aged 50-95 years. (573 with incident fractures and 802 without incident fractures) ■ Did not account for dosage and duration of statin use	■ 60% reduction in fracture risk associated with the use of statins. ■ Risk reduction was not explained by the effects of changes in BMD.
Prospective Cohort Study (Evaluative, observational, and follow-up study)	LaCroix et al[8]	Patient enrolled from 40 institutions in the US	■ 93,716 women in the total cohort (50-79 years)	■ Statin use neither improves fracture risk or BMD nor prevents or treats osteoporosis.
	Schoofs et al[9]		■ 3,469 men and women ≥55 years of age for more than 365 days	■ Statin use was not associated with significant changes in lumbar spine BMD. ■ The use of statin was not significantly associated with decreases in vertebral fracture risk.

Table 1. Continued

Type of Study	Investigator	Remark	Methods	Results
Case-controlled Study (Evaluative, observational, and retrospective study)	Wang et al[10]		▪ 6,110 patients (≥65 year.; 1,222 case patients and 4,888 control patients)	▪ Associated with a significant reduction in the risk of hip fracture
	Meier et al[11]	Patients enrolled from the UK-based General Practice Research Database	▪ 91,611 patients (≥50 year.; 3,940 case patients and 23,379 control patients) ▪ Measured adjusted OR of fracture risk statin users compared with non-users	▪ OR=0.55; 95% CI, 0.44-0.69
	Rejnmark et al[12]		▪6,660 subjects with hip fracture and 33,274 gender- and age-matched; 50-69, and ≥70 years. Duration was not specified	▪ Statin treatment was associated with a reduced risk of hip fracture (OR=0.68; 95% CI: 0.5-0.93).
	Chan et al[13]	Used data from 6 health-maintenance organizations in different regions of the USA	▪ 928 cases and 2,747 controls of women aged 60 years or older	▪ A decreased risk of non-pathological fracture in women with 13 or more fractures during the previous 2 yrs (OR=0.48; 95% CI: 0.27-0.83 after adjustment of confounding factors).
Clinical Research (Experimental, clinical trial)	Berthold et al[14]	Prospective study	▪ 49 postmenopausal women (mean age: 61±8.8 years); divided into the group of 24 women given atorvastatin 20 mg daily and the group of 25 women. ▪ Study last for 8 weeks.	▪ No statistically significant effect of atorvastatin on either the bone formation markers or on the bone resorption markers. But there were age-dependent effects on biochemical markers of bone turnover.
	Rejnmark et al[15]	One-year randomized controlled trial	▪ 82 postmenopausal women group given simvastatin (40 mg/day, for 1.5 year) vs. placebo group	▪BMD t-score changes on lumbar spine as -2.1 (-2.5 to -1.6, n=41) vs. -2.0 (-2.8 to -1.4, n=41); p= 0.97 and on total hip as -1.4 (-1.9 to -0.9, n=41) vs. -1.4 (-1.7 to -0.8, n=41); p=0.46.
	Reid et al[16]	The LIPID study	▪9,014 elderly patients (17% women, mean age 62 years) using 40 mg pravastatin daily for 6 years	▪ The RR of hip fracture in statin users was 0.3 (95% CI, 0.08-1.08). ▪ No real trend towards lower fracture numbers for all non-vertebral fractures 0.83 (95% CI, 0.61-1.15).
	Lupattelli et al[17]	Longitudinal study	▪ 40 hypercholesterolemic women who were given simvastatin 40mg daily and 20 hypercholesterole-mic women who treated only with diet for 2 years	▪ Simvastatin treatment exerted a beneficial effect on BMD.

Abbreviations: BMD (Bone Mineral Density); OR (Odds Ratio); CI (Confident Interval); The LIPID Study (The Long-term Intervention with Pravastatin in Ischaemic Disease Study); RR (Relative Risk Ratio)

menopausal women (mean age: 61±8.8 years); they were divided into 2 groups. The first group includèd of 24 women and was given atorvastatin 20 mg daily. The second group or matching placebo group included 25 women. Both groups were studied for 8 weeks. There were no statistically significant effects of atorvastatin on either the bone formation markers (intact osteocalcin, bone specific alkaline phosphatase) or on the bone resorption markers

(C-telopeptide, intact PTH). But there were age-dependent effects on biochemical markers of bone turnover.[14]

One-year randomized controlled trial in the 82 postmenopausal women group given simvastatin (40 mg/day, for 1.5 year) vs. placebo group by Rejnmark et al showed BMD t-score changes on lumbar spine as -2.1 (-2.5 to -1.6, n=41) vs. -2.0 (-2.8 to -1.4, n=41); p=0.97 and on total hip as -1.4 (-1.9 to -0.9, n=41) vs. -1.4 (-1.7 to -0.8, n=41); p=

0.46.[15] Similarly, the LIPID study by Reid et al on 9,014 elderly patients (17% women, mean age 62 years) using 40 mg pravastatin daily for 6 years showed the RR of hip fracture in statin users was 0.3 (95% CI, 0.08-1.08). The study found no real trend towards lower fracture numbers for all non-vertebral fractures 0.83 (95% CI, 0.61-1.15).[16]

A longitudinal study by Lupattelli et al on 40 hypercholesterolemic women who were given simvastatin 40mg daily and 20 hypercholesterolemic women who treated only with diet for 2 years indicated simvastatin treatment exerted a beneficial effect on BMD. In the group treated with simvastatin, both the spine BMD (baseline: 0.878 ± 0.133; 8 months: 0.893 ± 0.130; 24 months: 0.907 ± 0.132, p <0.001) and femoral hip BMD (baseline: 0.840 ± 0.101; 8 months: 0.854 ± 0.101; 24 months: 0.863 ± 0.10, $p < 0.001$) showed a significant increase after 8 and 24 months, respectively; there was a percentage increase of 1.7% after 8 months and 3.3% after 24 months at the spine; at the femoral hip, BMD increase 1.6% after 8 months and 2.7% after 24 months.[17]

SUMMARY

There are 3 different hypotheses on how statins may affect bones, through promoting bone formation, inhibiting bone resorption or through anti-inflammatory effect.[17] In the 3 cross-sectional studies above, one showed increase BMD at hip and spine, one showed increase BMD only at mid-forearm and one showed that the risk reduction in fractures is not explained by the changes in BMD[5,6,7] however, all 3 studies showed a decrease in risk of fracture associated with statins. In the 2 prospective cohort studies, one showed the use of statins was not associated with BMD at any skeletal site or decreasing the risk of fracture, and the other showed statins except pravastatin decreased in risk of vertebrate fracture but not affecting lumbar spine BMD.[8,9] All of case-control studies indicated reduction in fracture risk but did not provide any data regarding BMD. 2 of the randomized, controlled studies showed no significant reduction in fracture risk as well as statins' effects on BMD.[11,13] Finally, one longitudinal study showed statin use reduced fracture risk and increased BMD.[17]

Among the conflicting results shown above, even when statin use was shown to increase BMD, it does not seem to account for the reduction in fracture risk. There may be different ways that statins affect bone other than those hypotheses proposed above. Many studies seem to agree that pravastatin does not have any effect on bone.[9] Some studies suggested that the reason statins did not achieve clinically significant increases in BMD in some studies, is due to the low affinity of statins on bone; statins are designed to act in the liver therefore their effective concentration in extrahepatic tissue is low.[9,15]

The limitations to those studies discussed above. Many studies did not account for the change of lifestyle while subjects' were on statins. Increases in weight bearing exercise and changes in diet might affect BMD and thus reduce risk of fractures. Mental alertness and vision acuity might prevent falls from occurring; many statin-users in the studies were young so the risk of fractures from falls would be decreased. Almost all of the studies failed exclude patients with neurological problems. During study periods, many subjects may have been started on drugs for diseases that usually occur with aging which could cause drowsiness and lead to falls. The sample sizes used in some of the trials were small and the duration of treatment and follow up might not have been long enough to see clinically relevant results.

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