Effect of an increased dosage of statins on spinal degenerative joint disease: a retrospective cohort study

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ABSTRACT

Objectives It has been proven that statin can protect synovial joints from developing osteoarthritis through its anti-inflammatory effects. However, studies on the effect of statins on spinal degenerative joint diseases are few and limited to in vitro studies. Therefore, we investigated the relationship between the statin dosage and the development of spinal degenerative joint diseases.

Design A retrospective cohort study.

Setting Patients registered in Taiwan National Health Insurance Research Database.

Participants Patients aged 40–65 years old from 2001 to 2010 were included. Those who received statin treatment before 2001, were diagnosed with spinal degenerative joint diseases or received any spinal surgery before 2004 or had any spinal trauma before 2011 were excluded. A total of 7238 statin users and 164,454 non-users were identified and followed up for the next 7 years to trace the development of spinal degenerative joint disease.

Outcome measures The incident rate of spinal degenerative joint diseases and HRs among the groups treated with different statin dosages.

Results A higher dosage of statins was associated with a significantly lower risk of developing spinal degenerative joint disease in patients with hypercholesterolaemia. Compared with the group receiving less than 5400 mg of a statin, the HR of the 11 900–28 000 mg group was 0.81 (95% CI 0.68 to 0.97), and that of the group receiving more than 28 000 mg was 0.81 (95% CI 0.68 to 0.97). Results of subgroup analysis showed a significantly lower risk in men, those aged 50–59 years and those with a monthly income less than US$600.

Conclusions Our study’s findings clearly indicated that a higher dosage of statins can reduce the incidence of spinal degenerative joint disease in patients with hypercholesterolaemia, and it can be beneficial for people with a higher risk of spine degeneration.

INTRODUCTION

Low back pain is a common symptom that occurs in up to 80% of people during their lifetime,1 and it may significantly impact one’s quality of life and work efficiency. Although the exact pathological source for low back pain cannot be definitely diagnosed in most patients, spinal degenerative joint disease (DJD) is traditionally believed to be an important source of low back pain.2 Spinal DJD is the degenerative change in the three-joint complex of the spine (ie, one intervertebral disc and two posterior facet joints), which can be observed as decreased joint space and spur formation on plain radiographs.3 It is primarily caused by ageing-related disc change, repetitive microtrauma and axial loading stress. In addition, increased oxidative stress and inflammatory responses also play a significant role in the senescence mechanism of intervertebral disc degeneration.4 It has been proven that statins mitigate inflammatory responses and oxidative stress by inhibiting a variety of proinflammatory cytokines.5 As previously mentioned, oxidative stress and inflammatory responses may contribute significantly to the pathogenesis of spinal DJD; therefore, it aroused our curiosity if statins could also be...
also been related to a decreased incidence of osteoarthritis. It is worth noting that statin use was associated in Taiwan since 1

Insurance Research Database (NHIRD), which was
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tion, including the diagnoses of diseases by the

their monthly income, living area and medical informa-

as subjects' date of birth, sex, insured amount relating to

the epidemiology in Taiwan extensively. Therefore, we

databases in the world, and it has been used to analyse

recorded anonymously. The database we analysed was

modifications (ICD-9-CM) codes, medication dosages and

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January 2004. Because the cumulative dosage of statins

were recorded anonymously. The database we analysed was

composed of systematically sampled one million people from all the beneficiaries in the year 2010 in the insurance

programme, and there were no statistically significant
differences in age, gender or healthcare costs between the

sample group in the database and all beneficiaries

under the programme. It is one of the largest medical
databases in the world, and it has been used to analyse

the epidemiology in Taiwan extensively. Therefore, we

recruited our subjects from this database to obtain the

most representative data in Taiwan to analyse the rela-
tionship between the dosage of the statin and incidence

of spinal DJD.

Case selection and study design

Informed consent of our study subjects could not be
obtained because all data were recorded anonymously

in the NHIRD. We intentionally selected subjects aged

between 40 and 65 to include the onset of spinal DJD,
because the prevalence of radiographic change due to

spinal DJD was higher in people aged more than 65 years

in our database. Those who received any statin treatment

before 1 January 2001, who had been diagnosed as having

spinal DJD (ICD-9 codes: 721.0–721.4) before 1 January

2004, who received any surgical intervention of the spine

(1) before 1 January 2004 and those who had been diagnosed

as having spinal trauma (ICD-9 codes: 721.7, 805.0–805.9,

806.0–806.9, 839.00–839.59, 847.0–847.9, 952.0–952.9

and 953.0–953.9) at any time during the study period

were excluded. For the remaining subjects, those who

started to receive any type of statin from 1 January 2001

to 31 December 2003 were identified, and the summed

dosage of all types of statins prescribed in the first 3 years

was transformed into the equivalent simvastatin dose.

The statin users were then divided into four groups

according to the prescribed dosage of statins while

maintaining a similar number of people per group. The
dosages of statins used to divide the four groups were

5400 mg, 11900 mg and 28000 mg, which were designated

as Q1, Q2 and Q3, respectively. Therefore, the four statin

users groups were defined as statin prescribed <5400 mg,

5400–11900 mg, 11900–28000 mg and >28000 mg. On

the other hand, those who did not receive any statin

therapy from 1 January 2001 to 31 December 2003 were

also included since 1 January 2004. The development of

spinal DJD was followed over the next 7 years since 3 years

after starting statin therapy in the statin users, and the

same outcome was followed in the statin non-users since

1 January 2004. Because the cumulative dosage of statins

were counted in the first 3 years since first prescription

and the outcome was followed in the next 7 years only,

there should be no collinearity between time and cumu-

lative dosage of statins in our study, as shown in the online

supplementary figure. To ensure that the diagnosis of

spinal DJD was accurate, only those who had at least three
times of coding 721.0–721.4 as the main outpatient diag-
nosis by different doctors after radiological examination

were counted as having spinal DJD, and the first coding
time was counted as the onset of spinal DJD. Other poten-
tial confounders, including age, sex the Charlson Comor-
bidity Index, monthly income and living area, were all

recorded, and they were considered in further statistical

adjustment during calculation of the HR.

Statistical analysis

We used Statistical Package for Social Sciences software

package for Windows, V17.0 (SPSS) for data analysis.

Kruskal-Wallis test, χ² tests and one-way analysis of vari-

 ance (ANOVA) were used to assess statistical differences

in age, sex, the Charlson Comorbidity Index, monthly

income and living area among the statin users groups

and the non-users. Kaplan-Meier survival analysis was

then performed to generate the cumulative incidence of

spinal DJD for the four groups of statin users and

non-users. Cox proportional hazard regression analysis

was performed to calculate the HR of the development

of spinal DJD with reference to the group with a statin

prescription less than 5400 mg after adjusting for age, sex,

the Charlson Comorbidity Index, monthly income and

living area. Furthermore, stratified analysis of different

age, sex and monthly income groups was performed to

examine the HR of developing spinal DJD in patients

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Statistical analysis

We used Statistical Package for Social Sciences software package for Windows, V17.0 (SPSS) for data analysis. Kruskal-Wallis test, χ² tests and one-way analysis of variance (ANOVA) were used to assess statistical differences in age, sex, the Charlson Comorbidity Index, monthly income and living area among the statin users groups and the non-users. Kaplan-Meier survival analysis was then performed to generate the cumulative incidence of spinal DJD for the four groups of statin users and non-users. Cox proportional hazard regression analysis was performed to calculate the HR of the development of spinal DJD with reference to the group with a statin prescription less than 5400 mg after adjusting for age, sex, the Charlson Comorbidity Index, monthly income and living area. Furthermore, stratified analysis of different age, sex and monthly income groups was performed to examine the HR of developing spinal DJD in patients.
with a cumulative dosage of statins more than Q1 with reference to less than Q1. A P value <0.05 was considered statistically significant in our study.

RESULTS
Overall, 7238 statin users and 164454 non-users were identified in our database, and the statin users were divided into four groups according to the dosage of statins in the first 3 years: group 1, <5400 mg; group 2, 5400–11 900 mg; group 3, 11 900–28 000 mg; and group 4, >28 000 mg. There were 1810 subjects in group 1, 1818 in group 2, 1841 in group 3 and 1769 in group 4. A flow chart of our subject selection and group assignment is shown in figure 1. A comparison of age, sex, the Charlson Comorbidity Index, monthly income and living area among the four groups and statin non-users is shown in online supplementary table 1. Nearly all characteristics were significantly different among the five groups in Kruskal-Wallis test, χ² tests and one-way ANOVA.

During the next 7 years of the follow-up period, 14633 subjects developed spinal DJD. The incident rates of spinal DJD were 1.25, 2.57, 2.4, 2.19 and 2.15 per 100 person-years in groups non-user, 1, 2, 3 and 4, respectively. The comparison of cumulative incidence of spinal DJD between statin users and non-users according to Kaplan-Meier analysis is shown in figure 2A, and that of the four statin users groups is shown in figure 2B. To elucidate the HR among the four groups, further Cox proportional hazard regression analysis was performed with reference to group 1. The HR of the development of spinal DJD in group 2 was 0.93 (0.79–1.10) versus group 1, which did not achieve statistical significance. However, statistically significant higher HRs were noted in group 3 and group 4, which were 0.83 (95% CI 0.70 to 0.99) and 0.81 (95% CI 0.68 to 0.97), respectively. The HR of the statin non-users was 0.66 (95% CI 0.58 to 0.74). Detailed data are shown in table 1.

To clarify the effect of the statin dosage in different age, sex and monthly income subgroups, stratified analysis of the HR was performed. As shown in figure 3, taking more than 5400 mg of a statin in the first 3 years was shown to have a lower risk of developing spinal DJD within the 7-year follow-up period (HR 0.84, CI 0.74 to 0.97, P=0.014). The protective effect was observed in all subgroups despite differences in age, sex and monthly income, and statistical significances were achieved in those aged between 50 and 59 years, men and those with an income less than US$600 per month.

DISCUSSION
Our study’s findings clearly showed a protective effect against the development of spinal DJD with a higher dosage of statins compared with a lower dosage of statins in patients with hypercholesterolaemia. Statin dosages more than 5400 mg in the first 3 years significantly reduced the incidence of spinal DJD in the next 7 years.

Figure 1  Study design. The flow chart illustrates how the statin users were selected and assigned to groups according to the different dosages of statins used in our study. Q1: Statin dosage of 5400 mg, Q2: statin dosage of 11 900 mg, Q3: statin dosage of 28 000 mg. DJD, degenerative joint disease; NHIRD, National Health Insurance Research Database.
This is the first large-scale population-based cohort study on the relationship between the statin dosage and spinal DJD, and it can be corroborated by previous findings in vivo studies.

Hu et al.\(^1\) performed an interesting study on the effect of an intradiscal injection of lovastatin on iatrogenically induced spine disc degeneration in rats. They discovered that a higher concentration of lovastatin (10 µM) produced more significant phenotypic disc repairs than lower concentrations (0.1, 1 and 5 µM). In contrast, Than et al.\(^1\) reported that degenerative discs injected with 5 mg/mL of simvastatin in a hydrogel carrier demonstrated more improved radiographic and histological features compared with discs treated at higher doses (10 and 15 mg/mL). Based on the aforementioned two studies, the exact dosage of a statin injected intradiscally that brought the most beneficial disc changes could not be determined since it was the lowest concentration in one study and the highest concentration in the other study. Nevertheless, they were still both impressive studies that demonstrated the dramatic effect of an intradiscal injection of a statin on disc degeneration. Statins are mostly taken up by the liver after oral administration and undergo first-pass metabolism, and their bioavailability may be greatly reduced in synovial joints and discs. Therefore, an important review article summarised that the protective effects on animal models of inflammatory and DJDs are less probative in clinical trials adopting oral administration of statins.\(^2\) Our study, however, still showed that the oral intake of a statin could also have a protective effect on the development of spinal DJD in patients with hypercholesterolaemia. Figure 2B clearly shows the dose-dependent response of a statin on the incidence of spinal DJD. Although the log-rank P value was 0.128, which was not statistically significant, we still observed a significantly decreased HR in those taking 11 900–28 000 mg (group 3) or more (group 4) compared with those taking less than 5 400 mg of a statin (group 1). As shown in figure 3, when we calculated the HR in those taking more than 5 400 mg of a statin (groups 2, 3 and 4 combined) versus group 1, it was still significantly decreased (HR 0.84, CI 0.74 to 0.97). This result indicated that taking between 5400 mg and 11 900 mg of a statin may be the cut-off point for the statin’s beneficial effect on preventing the development of spinal DJD. However, the exact dosage should still be validated by further prospective, randomised, controlled studies in the future. Furthermore, alternative routes of administration of statin other than oral intake, such as intradiscal, intra-articular or transdermal, should be developed to increase the effectiveness of statin in joint diseases while preventing the adverse effects of high oral statin doses.

The complete mechanism underlying how statins can prevent discs from degeneration is still under investigation. Current evidence supports that statins can facilitate bone morphogenetic protein-2, aggrecan and type II collagen gene expression by inhibiting the production of mevalonate.\(^3\) As the nucleus pulposus of the disc is mainly composed of a mixture of aggrecan and type II collagen,\(^4\) statins could potentially reverse wear and tear due to ageing and repetitive microtrauma during everyday work. In addition to the anabolic effect of statins on the composition of the disc, statins could also prevent disc degeneration through its anti-inflammatory pathway. A past study showed that simvastatin can inhibit interleukin-6 and interleukin-8 production in isolated chondrocytes and cartilage explants in a significant dose-dependent manner on stimulation by interleukin-1ß and tumour

![Figure 2](image-url)

**Figure 2** Cumulative incidence of spinal degenerative joint disease (DJD). (A) In each of the statin users and non-users, the cumulative incidence rates of spinal DJD are shown during the next 7 years of follow-up by the Kaplan-Meier method. (B) The cumulative incidence of spinal degenerative joint diseases are shown in each of the four statin users groups.
Another study also showed that simvastatin can reduce the matrix metalloproteinase-3 level in interleukin-1β-stimulated human chondrocyte culture. As an increased level of matrix metalloproteinases has been proven to be associated with disc degeneration, statins, which exert action on anti-inflammation and the reduction of matrix metalloproteinases, may also protect discs from degeneration. Our study revealed that non-statin users had a lower incidence of spinal DJD. In Taiwan, the cost of statin prescription is reimbursed by National Health Insurance programme if a patient has hypercholesterolaemia. In the past literature, hypercholesterolaemia was evidenced to enhance the inflammatory status in human bodies, which is detrimental to chondrocytes in joints. Therefore, it could be expected that non-statin users, who had never been diagnosed as hypercholesterolaemia, had a lower incidence of spinal DJD in our study.

In the subgroup analysis, our study had an interesting finding that the protective effect of statins was significantly observed in men, those aged 50–59 years and those with a monthly income less than US$600. In other subgroups, especially those who were women and aged 40–49 years, a statin dosage more than 5400 mg in the first 3 years had only a mildly decreased risk without statistical significance (HRs: women, 0.93; those aged 40–49 years, 0.95). A previous study showed that the protective effect of statins was not equal regarding sex, showing that statin therapy reduced the risk of coronary

| Statin dosage     | No. of DJD events | Person-years | Incident rate† | Adjusted HR (95% CI) | P value |
|-------------------|-------------------|--------------|----------------|-----------------------|---------|
| Statin non-users  | 13572             | 1 084 974    | 1.25           | 0.66 (0.58 to 0.74)   | <0.001* |
| ≤Q1†              | 290               | 11 289       | 2.57           | 1.00                  |         |
| Q1–Q2‡            | 276               | 11 514       | 2.40           | 0.93 (0.79 to 1.10)   | 0.382   |
| Q2–Q3‡            | 255               | 11 643       | 2.19           | 0.83 (0.70 to 0.99)   | 0.035   |
| >Q3‡              | 240               | 11 166       | 2.15           | 0.81 (0.68 to 0.97)   | 0.019   |

| Age (years)       | No. of DJD events | Person-years | Incident rate† | Adjusted HR (95% CI) | P value |
|-------------------|-------------------|--------------|----------------|-----------------------|---------|
| 40–49             | 6374              | 666 085      | 0.96           | 1.00                  |         |
| 50–59             | 5503              | 338 763      | 1.62           | 1.59 (1.53 to 1.65)   | <0.001* |
| 60–65             | 2756              | 125 741      | 2.19           | 1.99 (1.89 to 2.08)   | <0.001* |

| Gender            | No. of DJD events | Person-years | Incident rate† | Adjusted HR (95% CI) | P value |
|-------------------|-------------------|--------------|----------------|-----------------------|---------|
| Female            | 8670              | 548 130      | 1.58           | 1.00                  |         |
| Male              | 5963              | 582 460      | 1.02           | 0.66 (0.64 to 0.68)   | <0.001* |

| Comorbidity       | No. of DJD events | Person-years | Incident rate† | Adjusted HR (95% CI) | P value |
|-------------------|-------------------|--------------|----------------|-----------------------|---------|
| Diabetes mellitus | 1128              | 55 434       | 2.03           | 0.79 (0.74 to 0.85)   | <0.001* |
| Hyperlipidaemia   | 1070              | 47 835       | 2.24           | 1.14 (1.07 to 1.22)   | <0.001* |
| Cardiovascular    | 3632              | 165 865      | 2.19           | 1.31 (1.26 to 1.37)   | <0.001* |
| Chronic kidney    | 74                | 3518         | 2.10           | 0.80 (0.63 to 1.01)   | 0.061   |

| CCI               | No. of DJD events | Person-years | Incident rate† | Adjusted HR (95% CI) | P value |
|-------------------|-------------------|--------------|----------------|-----------------------|---------|
| 0                 | 9103              | 861 293      | 1.06           | 1.00                  |         |
| 1                 | 3303              | 178 008      | 1.86           | 1.54 (1.47 to 1.60)   | <0.001* |
| 2                 | 1352              | 58 422       | 2.31           | 1.83 (1.72 to 1.94)   | <0.001* |
| ≥3                | 875               | 32 866       | 2.66           | 2.03 (1.88 to 2.20)   | <0.001* |

| Monthly income (US$) | No. of DJD events | Person-years | Incident rate† | Adjusted HR (95% CI) | P value |
|---------------------|-------------------|--------------|----------------|-----------------------|---------|
| ≤600                | 7320              | 543 565      | 1.35           | 1.00                  |         |
| 600–1400            | 2140              | 430 205      | 0.50           | 0.99 (0.94 to 1.05)   | 0.707   |
| >1400               | 3676              | 156 820      | 2.34           | 0.89 (0.85 to 0.94)   | <0.001* |

*P<0.05.
†Per 100 person-years.
‡Q1, statin dosage of 5400 mg; Q2, statin dosage of 11 900 mg; Q3, statin dosage of 28 000 mg.
CCI, Charlson Comorbidity Index; DJD, degenerative joint disease.
heart diseases in men without prior cardiovascular disease, but not in women. Coidentally, our study also demonstrated a significant protective effect on the development of spinal DJD in men, but not in women. Past studies have also established strong evidence for the benefits of statins in the primary and secondary prevention of cardiovascular disease in those aged 40–75 years. For those less than 40 years old, statins are primarily reserved for treating severe hypercholesterolaemia only. Similarly, our study also showed only a borderline protective effect on the development of spinal DJD in the youngest group. Our study's findings further showed a significantly protective effect of statins in those with a monthly income less than US$600, but the association between the beneficial effect of statins and one's socioeconomic status has never been explored before. Furthermore, the relationship between cardiovascular protection and preventative effects of statins on DJD deserves further investigation in the future.

Our study's findings clearly showed the protective effect of statins on the development of spinal DJD in patients with hypercholesterolaemia. One strength of our study is the population-based retrospective cohort design and use of the largest medical database in Taiwan, because it enabled us to follow the development of spinal DJD in all statin users without any loss of follow-up. Furthermore, the large sample size contributed to sufficient statistical power in elucidating the relationship between statin dosages and the incidence of spinal DJD. However, there are at least six limitations in our study. First, we could only record the prescription time and dosage of medications in our database; thus, we could not ensure whether the patients took these pills after they went home. Polypharmacy has been identified as a factor in poor medication adherence. We can assume that patients with a higher Charlson Comorbidity Index who took a higher dosage of a statin in our study had a lower medication compliance. Even so, they still had a lower incidence of spinal DJD, although the actual dosage of the statin they took may be less than that recorded. Another issue was that the statin dosage in our study was the summed dose in the first 3 years, and we could not identify whether the patients took all the drugs in the first few months or took them averagely during the 3 years, which may influence the homogeneity in each groups in our study. Second, the degree of degenerative changes shown on a plain radiograph was required to establish a diagnosis of spinal DJD, which may have been different among doctors. For example, a radiograph considered to show mild degenerative changes of the spine for one doctor may still be deemed as within normal range for another doctor. To prevent arbitrary diagnoses made by one doctor, a diagnosis of spinal DJD was counted only if it was listed as a main diagnosis three times at different outpatient visits in our study. Third, some patients may acquire spinal DJD without seeking medical help, such as those with lower socioeconomic status, older age or with other comorbidities. However, Taiwan is a small island with easily assessed medical services. Furthermore, the existence of National Health Insurance enables patients to get medical help with extremely low costs. Therefore, this

![Figure 3](http://bmjopen.bmj.com/)

Figure 3  Results of the stratified subgroup analysis. The HR of the development of spinal degenerative joint disease in statin users with a dosage more than 5400 mg was compared with those with a dosage less than 5400 mg in different age, sex and monthly income subgroups. USD, US$.
limitation could be of less concern in our study using the NHIRD. We further statistically adjusted for age, sex, the Charlson Comorbidity Index, monthly income and living area during Cox regression analysis to reduce the impact of this limitation. Fourth, the time patients seek medical help may not represent the onset of spinal DJD. The study results would be strengthened if all patients were clinically assessed on the onset of spinal DJD. Fifth, the major risk factor of spinal DJD is considered to be axial loading during work and daily activities. However, the information of occupation and working properties could not be obtained in our database, and we could only take monthly income and living area into statistical adjustment instead. Finally, the subjects we analysed in our study were mainly Taiwanese; thus, the study results may not be extrapolated to other racial groups. However, our findings can still serve as a valuable reference for physicians of Asian countries.

CONCLUSIONS
A higher dosage of statins can reduce the incidence of spinal DJD in patients with hypercholesterolaemia according to the results of our study. Thus, physicians have another clinically significant reason, in addition to cardiovascular benefits, to recommend their patients to take statins at a higher dosage under the consideration of the possible side effects such as liver and muscle damage, elevated blood sugar, memory loss or confusions. Further prospective case-controlled studies should be done to validate our study results in the future.

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Patient consent Detail has been removed from this casedescription/these case descriptions to ensure anonymity. The editors andreviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval The Institutional Review Committee of Taichung Veterans General Hospital in Taiwan (No. CE13152).

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