Article 4

Association between osteoporotic fractures and statin use – A review of literature and results of a preliminary case control study done at National Hospital of Sri Lanka.

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Abstract

Osteoporosis and related fractures are a major health problem all over the world. Several studies have shown that statin use is associated with a reduced risk for osteoporotic fractures among older population.

A case control study was conducted among elderly patients presenting to NHSL accident service. A hundred patients aged more than 60 years who presented with newly diagnosed neck of femur, distal radial and vertebral body wedge fractures following minor trauma were recruited from April 2021 to July 2021. Patients who had previous osteoporotic fractures and previous hip, distal radius and spine surgery were excluded from the study. An additional group of 100 patients who were matched for age and sex presenting to the same unit following minor trauma without osteoporotic fractures were selected as the control group with the same exclusion criteria. Use of statins for more than 4 months and other sociodemographic and lifestyle factors were compared among the two groups.

As no other independent variable was found to be significantly related to osteoporotic fracturs between the two groups, univariable analysis was done. The odds of current statin use in cases with osteoporotic fracture (45.2%) were lower than the odds of current statin use (54.8%) in subjects without osteoporotic fractures adjusted OR 0.74, 95% CI 0.42, 1.32) (p=0.304).

According to our results there might be a protective effect in statin use against osteoporotic fractures although a statistical significance was not demonstrated. However further studies using larger sample size and randomized control studies are suggested to ascertain a statistically significant result.

Key words – osteoporosis, osteoporotic fractures, statins

Introduction

Osteoporotic fractures or fragility fractures are a major health problem having a considerable socio-economic burden all over the world [1]. It affects the elderly population by increasing their morbidity and mortality while diminishing the quality of life. It affects a country's economy as the financial burden incurred on the health system to manage these fractures are considerably high.

In Sri Lanka with the increase of the elderly population the social and economic burden of osteoporosis

related fractures are expected to rise. Due to its significance, prevention of these injuries is as important as finding out novel treatment strategies to manage them.

The osteoprotective effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are currently well established in in vitro and animal studies. However only a handful of clinical studies have been done to establish its effect in preventing osteoporotic fractures of the elderly.

Literature Review

Osteoporosis affects 75 million people in Japan, Europe and USA [2]. Epidemiological data with regard to incidence and prevalence of osteoporotic fractures in Sri Lanka are lacking in published literature.

Osteoporosis is defined as a general disorder of the skeleton characterised by low bone mass and deterioration in the microarchitecture of the bone tissue, which is translated into a deterioration of bone resistance predisposing to fractures [3].

According to the definition, the key clinical fact is fragility fracture. Therefore, the presence of osteoporosis without fracture makes diagnosis difficult. Thus, the diagnosis is based on the confirmation of low bone mineral density (BMD) on dual-energy x-ray absorptiometry (DEXA) scan. Therefore, in 1994 the WHO agreed on an operative definition based on cut-off points of BMD for postmenopausal women. The normal level for BMD was set at a value higher than -1 standard deviation (SD) relative to the average for young adults. For osteopenia, values of BMD between -1 and -2.5 SD was set. Osteoporosis was defined to be set at values of BMD lower than -2.5 SD. Established osteoporosis was defined when, along with these conditions, were associated one or more osteoporotic fractures [4]. It has been recommended that the same cut-off values be used for osteoporosis in males [5]. Even though BMD is the most quantifiable risk factor of future fracture, many other clinical risk factors come in to play with regard to the occurrence of fractures. As a solution, WHO recently introduced the FRAX algorithm to help clinicians in therapeutic decision making. FRAX is a web-based calculator which, apart from BMD, accommodates multiple clinical risk factors in estimating fracture risk. Since its implementation, FRAX has undergone many alterations and many country-specific FRAX models have been developed. (http://www.shef.ac.uk/FRAX).

In accordance with the WHO criteria, the estimated prevalence of osteoporosis in white women over 50 years of age is 15% when one of the three usual locations (spine, hip or writs) is considered, and 30% when measured in all of them [6]. The prevalence increases with age from 15% for the period between 50 and 59 years of age, up to more than 80% in ages over 80 years [7]. In males, the prevalence of osteoporosis is lower, 8% according to the NHANES study [8].

Approximately 1.6 million hip fractures (neck of femur) annually occur worldwide and this figure is estimated to reach 4.5-6.3 million by 2050 [9, 10]. According to the International Osteoporosis Foundation, the incidence of neck of femur (NOF) fractures in Sri Lanka is estimated to rise from the 2006 figure of nearly 2700 to 4900 in 2020 and 6900 in 2041. However according to the growth rate of elderly sector of the population these figures could become higher [11]. Fracture NOF is the most feared osteoporosis-related fracture owing to the financial burden it incurs and the associated mortality and morbidity. It is estimated that the mortality of NOF fractures during the first year is 20-25% [12]. The increased mortality could persist up to five years after a NOF fracture. It also has profound effects on physical independence. Nearly 40% of hip fracture survivors have walking disability while 60% require assistance to maintain day to day physical activities [13]. Furthermore, a third of NOF

fracture patients are totally physically dependent or require nursing home placement

at one year following fracture [14]. Vertebral fractures present with its own set of characteristics different from NOF fractures. Only one third of them are symptomatic [15]. Therefore, most of the vertebral fractures are detected as an incidental finding. They are also associated with acute and chronic backache, loss of mobility and functions. Furthermore, they lead to more vertebral fractures and non-vertebral fractures in later years [16, 17]. Forearm fractures behave different to other osteoporotic fractures. It lacks the classical exponential rise with advancing age [18] seen with typical osteoporosis-related fractures such as NOF and vertebrae. They also tend to occur in relatively young people [19]. Although no increased mortality is seen following distal forearm fractures, increased incidence of pain and numbness of affected hand is reported.

Most preventative and curative drugs currently used for osteoporosis such as raloxifene, denosumab, bisphosphonates, and calcitonin work by the anti-resorptive mechanism. [20–23] Alendronate and risedronate are the main oral bisphosphonates used in Sri Lanka to treat patients with osteoporosis and a high fracture risk. Zoledronic acid is becoming popular due to its reduced frequency of administration. The inconvenience of injections and prohibitive cost make teriparatide a reserve drug to treat osteoporosis. Upper gastro-intestinal adverse events associated with oral bisphosphonates are the most common side effects seen among patients. Myalgia, bone pain and arthralgia are also unwanted side effects. They can be severe enough to result in discontinuation of oral bisphosphonates in some people [24].

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are widely used as a mainstay in preventing and treating cardiovascular disease (CVD). According to recently published studies they also appear to be potentially promising drugs for osteoporosis. The mechanisms of statin's effects on the bone have been examined by a number of researchers. The current literature agrees that the effects of statins on the bone may involve a number of mechanisms including proliferation, differentiation and protection of osteoblasts while reducing osteoclastogenesis [25]. As a result, statins which are both anti-resorptive and anabolic agents may play a major role in the clinical management of osteoporosis.

To that end several case-control studies have been published showing that statin use is associated with a reduced risk for osteoporotic fractures among older population [26-28]. Other studies have concluded that bone mass is higher among patients taking statins [29, 30]

After analysing results of 4 large prospective studies [31-34] and cumulative Meta-analysis of observational Studies and controlled trials published until 2002, Bauer et al concluded that statins were associated with a consistent and clinically meaningful reduction in hip and vertebral fractures. They also suggested the necessity of carefully controlled specifically designed Clinical trials to test the effects of statins on skeletal metabolism [35] A meta-analysis published by An et al in 2017 also indicates that statin treatment could be associated with a decreased risk of overall fractures and hip fractures with an increased BMD at the hip and lumbar spine. It also showed that statin treatment may have a greater effect on males than females [36]. A study conducted in Australia on a medical population showed a dose dependant relationship between the diagnosis of osteoporosis and statins [37] In a population-based case control study published in 2017, Cheng et al concluded 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 in elderly in Taiwan. [38]. The most recently published population-based study we could find was also done in Taiwan by Chen et al among patients with COPD. They demonstrated a beneficial effect of statins in patients with COPD against the occurrence of NOF fractures at 10 years follow

up [39]. Clinical studies done in south asian cohorts in this regard have been lacking so far and we were not able to find any studies done in Sri lanka.

The Accident & Orthopaedic Service of the National Hospital of Sri Lanka being the Level 1 Trauma Care Centre in Sri Lanka treats about 300 patients per day, averaging about 100,000 patients per year. About 30,000 patients are treated as in ward [40]. Out of that a significant proportion of patients belong to the elderly group presenting with low energy fragility fractures. From our study we hoped to establish the association between statin use and osteoporotic fractures when it comes to a clinical setting among patients presenting to a trauma unit.

Materials and Methods

Patients above the age of 60 years who present to accident service NHSL within 48hrs of low energy trauma having clinically and radiologically confirmed fragility fractures were recruited to the study starting from April 2021 to July 2021. These included necks of femur fractures, distal radial fractures and vertebral body wedge fractures. The patients who have previously sustained above fractures, those with pathological fractures, those diagnosed with rheumatoid arthritis and those who had undergone previous surgery in the hip radius and spine were excluded from the study. A hundred such cases were collected consecutively. Age and sex matched patients who presented to NHSL accident service with low energy trauma with no clinical or radiological evidence of osteoporotic fractures were recruited using the same inclusion and exclusion criteria until 100 controls were collected. Age was matched by selecting controls within 5 years of the year of birth of the cases. Data collection was done using an interviewer administered questionnaire.

Ethical approval was taken for this study from the Ethical review committee at NHSL (AAJ/ETH/COM//2021/MAR). Statistical analysis was performed through IBM SPSS 23 statistics package.

Results

The study group included 200 patients (100 cases and 100 controls.) Among the cases and controls 69 were females and 31 were males in each group. The cases had a mean age of 72.86 years with a range of 60 - 92 years (SD – 9.18) The mean age of the control group was 71.06 years with an age range of 60 – 96 years. (SD – 8.49) Among the study participants 69% were females and 31% were males. Among the patients with fragility fractures fulfilling the inclusion criteria, 92% had NOF fractures. Distal radius fractures and vertebral body wedge fractures that fulfilled the criteria were 6% and 2% respectively.

Among the 33 cases who were currently on statins for more than 4 months, all of them were on atorvastatin. Among the 40 controls who were on statins 35 was on Atorvastatin and while 3 subjects were on simvastatin and 2 were on Rosuvastatin.

We compared the distributions of the sociodemographic characteristics, lifestyle factors and comorbidities between osteoporotic 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 fracture cases and controls (tables 1 and 2). No statistically significant difference was observed among cases and controls with regard to the above. ($p<0.05$). As no other independent variable was found to be significantly related to osteoporotic fractures in the univariable analysis, we did not perform the multivariable logistic regression model. The univariable logistic regression showed that the odds of current statin use in cases with osteoporotic fracture (45.2%) were lower than the odds of current statin use (54.8%) in subjects without hip fracture (adjusted OR 0.74, 95% CI 0.42, 1.32) ($p=0.304$). Our results suggest that there may be a negative association between statin use and osteoporotic fractures (i.e. statins may have a protective affect against osteoporotic fractures) in the studied population although a statistical significance was not demonstrated. ($p<0.05$)

	Overall	Cases	Control	P value	Test
Mean Age	71.96 (60-96) Median 70.00	72.86 (60-92)	71.06 (60-96)	0.152	Independent sample t test
Marital status					
Married	192 (96.0%)	96 (96.00%)	96 (96.00%)	0.565	Chi Square
Single	7 (3.5%)	3 (3.00%)	4 (4.0%)		
Separated/Widowed	1 (0.5%)	1 (1.00%)	0		
Functional Status					
Independent	175 (87.5%)	92 (92.0%)	83 (83.0%)	0.054	Chi Square
Dependent	25 (12.5%)	8 (8.0%)	17 (17.0%)		
Occupational Status					
Working	38 (19.0%)	20 (20.0%)	18 (18.0%)	0.843	Chi Square
Retired	74 (37.0%)	38 (38.0%)	36 (36.0%)		
Unemployed	88 (44.0%)	42 (42.0%)	46 (46.0%)		
Physical Activity Level					
Mild	38 (19.0%)	16 (16.0%)	23 (23.0%)	0.364	Chi Square
Moderate	64 (32.0%)	34 (34.0%)	30 (30.0%)		
High	97 (49.0%)	50 (50.0%)	47 (47.0%)		
Smoking Status					
Smoking	48 (24.0%)	22 (22.0%)	26 (26.0%)	0.427	Chi Square
Non-Smoking	152 (76.0%)	78 (78.0%)	74 (74.0%)		
Alcohol consumption					
Yes	46 (23.0%)	24 (24.0%)	22 (22.0%)	0.737	Chi Square
No	154 (77.0%)	76 (76.0%)	78 (78.0%)		

Table 1 – Analysis of the association between demographic and lifestyle factors among cases and controls

	Overall	Cases	Control	P value	Test
Diabetes Mellitus					
Yes	98 (49.0%)	50 (50.0%)	48 (48.0%)	0.777	Chi Square
No	102 (51.0%)	50 (50.0%)	52 (52.0%)		
Hypertension					
Yes	104 (52.0%)	46 (46.0%)	58 (58.0%)	0.103	Chi Square
No	96 (48.0%)	54 (54.0%)	42 (42.0%)		
Ischaemic Heart Disease					
Yes	32	14 (14.0%)	18 (18.0%)	0.440	Chi Square
No	168	86 (86.0%)	82 (82.0%)		
Dyslipidaemia					
Yes	57 (28.5%)	30 (30.0%)	27 (27.0%)	0.638	Chi Square
No	143 (71.5%)	70 (70.0%)	73 (73.0%)		
Cerebrovascular Disease					
Yes	12 (6.0%)	4 (4.0%)	8	0.373	Chi Square
No	188 (94.0%)	96 (96.0%)	92		

Table 2 – Analysis of the association between co morbidities among cases and controls

	Value	95% confidence interval	
		Lower	Upper
Odds Ratio for Cases or controls (Cases / Controls)	0.739	0.415	1.317
For cohort Usage of statin = Yes	0.825	0.571	1.192
For cohort Usage of statin = No	1.117	0.904	1.379
N of valid cases	200	0.415	1.317

Table 3 – Risk estimate for cases and controls for statin use

Discussion

The main conclusion of the present study is that oral statin use might have a protective effect against osteoporotic factors. This is in keeping with all the previous published studies done in this regard. However, all previous studies had been done as population-based cohort or case control studies. According to our knowledge this is the only single centre case control study done regarding the association between statins and osteoporotic fractures. One of the main drawbacks of population-based case control studies is the potential explanation of its results by the healthy drug user effect. The population receiving preventive oral statins for the cardiovascular disease or dyslipidaemia may exhibit certain behaviours that put them at lower risk of osteoporotic fractures. This may include better health insight and help-seeking behaviour which put them at a lower risk of sustaining falls and other minor trauma leading to fractures. Since both our cases and controls were recruited from among patients presenting to a trauma centre with minor trauma, healthy drug user effect is minimised. DEXA scans were not performed on our patients to confirm the osteoporosis unlike other studies due to the lack of facilities. Collecting data regarding osteoporotic fractures is difficult in the Sri Lankan population as we lack a functional database or a registry of patients who are affected.

So far, we are lacking a nationwide program for the prevention of osteoporotic fractures. Also, DEXA scans are not routinely performed as a means of diagnosing osteoporosis due to the unavailability of scan machines and the cost. Consequently, in most of these patients the first indication of established osteoporosis maybe an occurrence of a low energy fragility fracture. Therefore, within the framework of the Sri Lankan health system with its financial and practical constraints, the occurrence of fragility fractures in the elderly population can be used as an indirect indication of the presence of osteoporosis.

Statins are widely used in the Sri Lanka for the treatment of cardiovascular and cerebrovascular diseases as well as dyslipidaemia. As the above diseases are prevalent in the same age group where osteoporotic fracture risk is increased, the osteoprotective effects of statins may be a blessing in disguise for these patients. If these effects are properly established from extensive studies, statins may in fact be indicated in the future in its own right for the prophylaxis and treatment of osteoporotic fractures.

One of the main limitations of this study compared to other published studies is the small number of cases and controls. This study was conducted during the Covid-19 pandemic. Therefore, the number of cases which could be obtained in the stipulated time period was difficult. Also, the study was conducted only at NHSL. A larger sample size and a more statistically significant result could have been obtained had the study been a multicentre one.

We suggest further population based observational and randomised studies using larger samples to establish the connection between statin use and osteoporotic fractures. Multicentre studies could be conducted in

trauma centers using a larger population with the same methodology. It should also be emphasised regarding the necessity of creating a patient database with regard to osteoporotic fractures at institutional and national level in Sri Lanka which will make the data accessible to researchers

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