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Research Article

Association between statin use and fractures among dialysis patients in the north of the West Bank in 2021

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ABSTRACT

Introduction: Hip fractures are associated with higher morbidity and mortality among dialysis patients than among the general population. Statins reduce the risk of hip and bone fractures. However, this protective effect has not been studied in dialysis patients.

Methods: Hemodialysis patients from hemodialysis centers located in the north of the West Bank were recruited (N = 713) in a cross-sectional study in 2021. A statin user is a patient who has used statin for at least one year. The patient's medical records and an interview-administered structured questionnaire were used. Adjusted multiple logistic regression examined the association between statin use and fractures. A p-value less than 0.05 was considered statistically significant.

Results: The final sample size was 529 patients, 184 were excluded, 60.7% were males, 54.4% were statin users, 76.1% were always adherent to their statin, and 75.3% used moderate-intensity statin. Statin users who were always adherent to their dose had a significantly lower risk of hip fractures (OR = 0.090, p-value = 0.026) than rarely adherent patients. In addition, patients who were always adherent with their statin dose (OR = 0.188, p-value = 0.007) or sometimes adherent (OR = 0.171, p-value = 0.022) had a significantly lower risk of having other bone fractures after dialysis than the rarely adherent counterparts. There were no differences between high and moderate-intensity statins regarding hip fracture effects (p-value >0.05). Moreover, the increased duration of dialysis significantly increased the risk of hip fractures (OR = 1.349, p-value = 0.003).

Conclusion: The results of this study suggest that adherence to statin therapy was associated with decreased risk of hip fractures and other bone fractures among hemodialysis patients. These results could be the initial evidence of the protective effect against a vital health hazard among dialysis patients. This might ultimately contribute to re-considering the current statins prescription practice for dialysis patients. Further studies are recommended.

1. Introduction

Hip fractures are a significant health risk for the elderly as the incidence of fractures increases significantly with age.[1] There is a decrease in bone mineral density and muscle strength with aging and an increase in the risk of falls and injuries related to falls.[2] An accidental fall of an elderly person occurs most commonly at home, sustaining a fracture around the hip joint, either with pre-existing medical problems or without any previous comorbidity.[3] Dialysis patients have accelerated bone loss, leading to osteoporosis and osteopenia.[4] They have a significantly higher risk for bone fractures, ranging from 1.5-fold to 8-folds, than the general population.[5] They have a four-fold increase in hip fractures in that range compared to the general population.[6] This increased risk is attributed to their comorbid hypogonadism, diabetes, inactivity, frailty, and cardiovascular disease, predisposing them to an increased risk of falls and fractures.[7] In addition, chronic kidney disease patients have different bone pathophysiology than the general population, including urea build-up, metabolic acidosis, disturbances in vitamin D metabolism, and PTH secretion.[6] Moreover, dialysis patients have increased all-cause mortality following hip fractures more than the general population.[2,8,9]

Statins are a group of drugs used to treat dyslipidemia and inhibit the

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effect of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the main enzyme in cholesterol synthesis.[10,11] Statins are among the most prescribed type of drugs worldwide.[10] In addition, many patients have received statins as primary or secondary prophylaxis for cardiovascular diseases in all developed countries.[10] Several studies involving a non-dialysis population have shown that statins use was significantly associated with decreased risk of hip fracture.[12–15] Moreover, patients taking statins have a higher femoral bone density than those who do not.[16] A meta-analysis of many observational studies has shown that statins use was significantly associated with decreased risk of bone fractures, including hip fractures.[17] This protective effect of statins probably originates from their impact on bone mineral density and the molecular structures of the bone.[13] Statins enhance osteoblastic proliferation in bone by promoting the expression of bone morphogenic protein-2 (BMP-2), alkaline phosphatase, type 1 collagen, osteocalcin, bone sialoprotein, and the vascular endothelial growth factor.[14,18–20] Moreover, statins were found to suppress the genetic expression of the collagenase-1 and collagenase-3 genes, which involve bone remodelling.[14,18–20]

Many studies have demonstrated that statins reduce the risk of hip fractures. However, this effect has not been shown in kidney transplant patients.[6] Kidney transplant patients are at increased risk for hip fractures compared to dialysis patients.[6] Although there are similarities between kidney transplant patients and dialysis patients, transplant patients are clinically treated differently from dialysis patients.[21–23] The protective effect of statins is yet to be studied on dialysis patients.[5–7] This study aimed to determine the association between statin use and hip fractures in specific, and bone fractures, in general, among dialysis patients in the north of the West Bank, Palestine, in 2021. The prevalence of dialysis in the West Bank increased in 2020 (305 per million) compared to 2013 (204 per million).[9,24] It was demonstrated that 42.8% of Palestinian end-stage renal disease patients had osteoporosis, and 40.2% had osteopenia.[25] This study will help the scientific community better approach hip fractures, mainly their impact on morbidity and mortality in dialysis patients. The results will give a better insight into the protective effect of statins when investigated on high-risk groups (i.e., dialysis patients) and might ultimately contribute to changing the current guidelines for statin use among dialysis patients. Finally, the results will lead to new research potential among the scientific community.

2. Materials and methods

2.1. Study design and setting, population

A cross-sectional study was conducted in 2021 involving all dialysis centers (6 centers) in the north of the West Bank. The total number of dialysis patients in the north of the West Bank in 2021 upon conducting this study was 713 patients.[9,26] Patients were included if they were aged >18 and gave informed consent and excluded if they had a history of malignancy to avoid bone metastasis.

2.2. Research tool

An interview-administered structured questionnaire was used for basic sociodemographic characteristics. In addition, medical records were used for past medical history (including bone mineral disease and other chronic diseases), drug history (including type, dose, and duration), statins use history (type, dose, duration, drug adherence and time of ingestion), dialysis process (duration and frequency of dialysis), hip and other bones fractures (age and location of fracture).

2.3. Variables and operational definitions

A statin user is a patient who has used statins for at least one year. Adherence to statin therapy is defined as the extent to which a patient takes his or her statin medications as prescribed. It was categorized into always, sometimes, and rarely adherent. The intensity of statins found in the West Bank is divided into high-intensity and moderate-intensity statins.[26] A current smoker is a patient who smoked at least during the last 30 days.[27] Diseases that can affect or are associated with fractures are atherosclerosis and coronary artery disease, peripheral vascular disease, and cerebrovascular disease.[28,29] Other diseases include bone mineral disease,[30] diabetes,[28] hypertension,[28] chronic obstructive pulmonary disease,[31] and vitamin D and calcium therapy.[32]

2.4. Data analysis

Statistical Product and Service Solutions (SPSS) (version 22, IBM Corporation) were used for data entry and analysis. Participants' characteristics were described using means, standard deviations, percentages, or median and interquartile range (IQR) wherever appropriate. A p-value less than 0.05 was considered statistically significant. T-test (for parametric) and Mann-Whitney (for nonparametric) were used to compare means. Adjusted multiple logistic regression was used to test the association between statin use and hip fractures. Kolmogorov-Smirnov test was used to test the normality of continuous variables distribution.

2.5. Ethical considerations

Approval was taken from An-Najah University's Institutional Review Board (IRB). Patients were given informed consent stating that their part was voluntary without coercion. Full settings of privacy and confidentiality were considered to protect the collected data.

3. Results

3.1. General characteristics of dialysis patients

Out of 713 recruited patients, 184 were excluded for the following reasons: 61 patients had significant cognitive or language disabilities that interfered with their language comprehension or expression, 107 patients refused to participate in the study, and 16 patients had incomplete medical records. The final sample size in this study was 529 patients, 60.7% were males, 28.7% were current smokers, 86.2% were married, 53.3% were from villages, 38.8% from cities, 7.9% were refugees, 19.3% with higher education, and 68.6% had been educated up to high school. The median age (IQR) was 58.5[18] years, with no significant differences between males (58[17]) and females (60[20]) years (p-value 0.774) (Table 1-Part 1).

There were 15 patients (2.8%) who had a hip fracture after dialysis, compared to 6 patients (1.1%) before dialysis, with no significant differences between males and females in hip fractures (p-value >0.05). Only one patient had a hip fracture before and after dialysis. Fifty-four patients (10%) had other fractures after dialysis, compared to 115 (21.7%) before dialysis, with no significant difference between males and females (p-value> 0.05) (Table 1-Part 2).

The most prevalent diseases were hypertension (77.9%) and diabetes mellitus (50.9%), with no significant difference between males and females (p-value >0.05). On the other hand, the bone mineral disease had a total prevalence of 11.7% and was significantly higher in females (18.75%) than in males (7.1%) (p-value <0.001) (Table 1-Part 3).

3.2. General clinical characteristics of statins use among dialysis patients

Most of the patients (54.4%) had used statins for ≥1 year, 3.8% had used statins for less than one year, 41.8% did not use statins at all, 75.3% of statins users had used a moderate-intensity statin, and 76.1% were always adherent to their dose (Table 2).

Table 1
General characteristics of dialysis patients.

		Total n(%)	Females n(%)	Males n(%)	P-value
Part 1- Sociodemographic data					
Residency	City	205(38.8)	78(37.5)	127(39.6)	0.195
	Village	282(53.3)	108(51.9)	174(54.2)	
	Camp	42(7.9)	22(10.6)	20(6.2)	
Marital status	Single	73(13.8)	36(17.3)	37(11.5)	0.06
	Married	456(86.2)	172(82.7)	284(88.5)	
Educational level	Illiterate	63(11.9)	41(19.7)	22(6.9)	<0.001
	Up to high school	363(68.8)	138(66.3)	225(70.3)	
	undergraduate degree	97(18.4)	28(13.5)	69(21.6)	
	Postgraduate studies	5(0.9)	1(0.5)	4(1.3)	
Smoking status	Current smoker	152(28.7)	17(8.2)	135(42.1)	<0.001
	Ex-smoker	127(24.0)	22(10.6)	105(32.7)	
	Never smoked	250(47.3)	169(81.3)	81(25.2)	
Part-2 The prevalence of hip and other fractures after and before dialysis					
Hip fracture after dialysis	Yes	15(2.8)	8(3.8)	7(2.2)	0.260
Hip fracture before dialysis	Yes	6(1.1)	2(1.0)	4(1.2)	0.763
Other fractures after dialysis	Yes	54(10.2)	25(12.0)	29(9.0)	0.268
Other fractures before dialysis	Yes	115(21.7)	42(20.2)	73(22.7)	0.519
Part 3- The prevalence of various comorbidities					
Bone mineral disease	Yes	62(11.7)	39(18.8)	23(7.2)	<0.001
Diabetes Mellitus	Yes	269(50.9)	110(52.9)	159(49.5)	0.451
Hypertension	Yes	412(77.9)	162(77.9)	250(77.9)	0.999
Deep vein thrombosis	Yes	6(1.1)	2(1.0)	4(1.2)	0.763
Chronic obstructive pulmonary disease	Yes	20(3.8)	8(3.8)	12(3.7)	0.949
Malignant Tumors	Yes	10(1.9)	4(1.9)	6(1.9)	0.965

Table 2
General clinical characteristics of statin use among dialysis patients.

		Total	Females	Males
Statin users n(%)	Yes (≥1 year)	288(54.4)	109(52.4)	179(55.8)
	No	241(45.6)	99(47.6)	142(44.2)
Adherence to statin therapy n(%)	Always	217(76.1)	86(78.9)	131(74.4)
	Sometimes	47(16.5)	14(12.8)	33(18.8)
	Rarely	21(7.4)	9(8.3)	12(6.8)
Statin intensity n(%)	High intensity	53(17.4)	18(16.5)	35(11.2)
	Moderate intensity	217(75.3)	81(40.9)	136(42.5)
	Missing	18(6.3)	10(4.8)	8(2.5)
Statin use duration in years	Median(IQR)	0.85(6.0)	0.25(6.0)	1.0(7.0)
	Minimum-Maximum	0–33	0–30	0–33

3.3. Logistic regression models for the association between statins use and fractures

3.3.1. Model 1: Adjusted logistic regression for the association between statins use and hip fractures among dialysis patients

Statin users who were always adherent to their dose had a significantly decreased risk of hip fractures (11.1 times reduced risk) compared to those who are rarely adherent (OR = 0.090, p-value = 0.026). No significant differences were found between high and moderate intensities statins on their effect on decreasing hip fracture (p-value >0.05). Moreover, the increased duration of dialysis significantly increased the risk of hip fractures (OR = 1.349, p-value = 0.003). No significant differences were found between patients diagnosed with the bone mineral disease before dialysis and those not diagnosed with bone mineral disease (p-value >0.05). Age, gender, smoking, diabetes, hypertension, and calcium & vitamin D supplements after dialysis did not significantly affect the risk of hip fractures after dialysis (p-value >0.05) (Table 3).

3.3.2. Model 2: Adjusted multiple logistic regression for the association between statins use and bone fractures, except hip fractures, among dialysis patients

Patients who were always adherent with their statin therapy (OR = 0.188, p-value = 0.007) or sometimes adherent (OR = 0.171, p-value = 0.022) had a significantly lower risk of having any bone fracture after dialysis than the rarely adherent patients. Moreover, the duration of dialysis was significantly associated with an increased risk of other fractures after dialysis (OR = 1.256, p-value <0.001). However, age, time of statin use, statin dose, gender, bone mineral disease, and fracture before dialysis had no significant associations with the risk of having any fracture after dialysis (p-value >0.05) (Table 4).

Table 3
Adjusted logistic regression for the association between hip fractures after dialysis and statin use.

Hip fracture after dialysis Yes[a]	Variables	Reference category	Odds ratio	95% CI	P-value
Age			1.052	0.963–1.148	0.263
Statin duration in years			1.057	0.955–1.171	0.284
Duration of dialysis in years			1.349	1.108–1.643	0.003*
Statin intensity	High	Moderate	0.748	0.093–6.027	0.785
Statin adherence	Always	Rarely	0.090	0.011–0.752	0.026*
	Sometimes		0.130	0.010–1.703	0.120
Atherosclerosis	Yes	No	5.396	0.814–35.771	0.081
Bone mineral disease before dialysis	Yes	No	9.028	0.851–95.722	0.068

[a] Reference group of Hip fracture after dialysis is No.

4. Discussion

Hip fractures are conditions that carry high morbidity and mortality among dialysis patients. Dialysis patients have increased incidence, morbidity, and mortality from hip fractures than the general population.[6,8] However, to our knowledge, this association has yet to be previously studied among dialysis patients. Therefore, this study aimed to investigate the association between statin use and the risk of hip fractures among dialysis patients in the West Bank, Palestine.

This study indicated that statin is a protective factor against fractures in general and hip fractures, specifically in dialysis patients in the West Bank. However, the results showed that the protective effect among

Table 4
Adjusted logistic regression for the association between other fractures after dialysis and statin use.

Other fractures after dialysis Yes[a]	Variables	Reference category	Odds ratio	95% CI	P-value
Age			0.982	0.947–1.018	0.317
Statin duration in years			1.019	0.960–1.082	0.530
Dialysis duration in years			1.256	1.127–1.400	<0.001*
Statin intensity	High	Moderate	0.630	0.218–1.823	0.394
Statin Adherence	Always	Rarely	0.188	0.056–0.628	0.007*
	Sometimes		0.171	0.037–0.778	0.022*
Gender	Female	Males	1.159	0.513–2.618	0.723
Atherosclerosis	Yes	No	0.899	0.245–3.298	0.873
Bone mineral disease before dialysis	Yes	No	3.663	0.870–15.426	0.077
Fracture before dialysis	Yes	No	1.023	0.384–2.728	0.963

[a] Reference group is a Hip fracture after dialysis is No.

dialysis patients is associated with adherence to statin therapy. Patients who were always adherent to statins were 11 times less likely to risk hip fractures than rarely adherent statin users among dialysis patients. Moreover, dialysis patients who were always adherent to their statin dose had decreased risk of other bone fractures after dialysis compared to the rarely adherent group.

This study indicated that adherence to statin therapy decreases the incidence of bone fractures among dialysis patients. However, no association was found between the dose intensity of statins and the risk of fractures. These results agree with previous study results on the general population.[33,34] In addition, it was demonstrated previously that the efficacy of statins to lipid profile and serum HMG-CoA reductase levels in dyslipidemic patients might be lost or vary with the reduction in compliance but not with the increasing intensity of statins therapy.[33] Therefore, improving compliance with existing adherence therapy is appropriate rather than switching to higher-intensity statin therapy.

Moreover, evidence from the literature suggests a decreased risk of bone mineral disease among statin users in the general population.[34–36] However, a previous Australian study involving the general population suggested that high-intensity statin use was associated with an increased risk of bone mineral disease (with more potent effects in females than males) than low-intensity statins.[34] This effect of increased bone mineral disease risk among female patients might be explained by the HMG-CoA-reductase inhibitory impact on sex hormone production.[34] The same protective association could not be determined whether low-intensity statins share, as the dialysis patients in this study only used moderate and high-intensity statins. Further research involving low-intensity statins in terms of their effect on hip fractures compared to moderate and high intensities is recommended. Given the high risk and consequences of hip fractures on dialysis patients, the results of this study could be the initial evidence of the protective effect against a vital health hazard among dialysis patients.[6,8] This could lead to re-considering the current practice of statin prescription for dialysis patients.

Although the results of this study indicated that statin adherence was associated with decreased risk of other fractures among dialysis patients, these findings differ from studies on the general population where statins were not significantly associated with a reduced risk of fractures.[37,38] Moreover, to our knowledge, no currently published studies on statins' effect on non-hip bone fractures among dialysis patients. It is unclear why there is a discrepancy in results involving non-hip fractures between dialysis patients in this study and non-dialysis patients in other studies. However, a possible explanation could be the difference in the pathophysiology of bone disease between dialysis patients and the general population.[6] Further research involving dialysis patients from other ethnicities might give more definitive insight into the effect of statins on non-hip fractures. Moreover, further research concerning the general Palestinian population is recommended to explore the possible consequences of statins on hip fractures among non-dialysis patients.

A study involving kidney transplant patients in the USA, who have an even higher risk of hip fractures than dialysis patients, found that high adherence to statin use did not significantly decrease the risk of hip fractures.[6,39] The lack of statins' protective effect on hip fractures in kidney transplant patients compared to dialysis patients might be due to the adverse effects on bone of high-dose corticosteroids (especially in first stages post-transplant) and various other immunosuppressants, as well as their interaction with statin metabolism.[37,40–42] Another contributing factor could be post-operative immobility among these patients, followed by a relatively higher level of physical activity.[39] These factors contributed to offsetting the protective effect of statins on hip fractures among kidney transplant patients. Further research involving bone pathology differences between dialysis and kidney transplant patients is warranted.

The effects of different predictors associated with hip fractures were tested in this study. In a survey of elderly women, severe atherosclerosis was associated with advanced bone mineral disease in the hip. Therefore, diagnosing bone mineral disease might be alert for hip fractures.[43] Another study highlighted a link between carotid atherosclerosis and bone mineral disease in postmenopausal women.[44] Moreover, a meta-analysis found a significant relationship between peripheral arterial disease (PAD) and hip fractures.[45] Since statins decrease the progression of atherosclerotic changes, this relationship between atherosclerosis and hip fracture could explain the protective effect of statins against hip fractures.[46] Further research is recommended to investigate the association between atherosclerosis and hip fractures among dialysis patients. Diabetic patients in this study did not have a significantly increased risk of hip fractures than non-diabetic (p-value >0.05). This result contradicts a French research study, where there was an association between diabetes and an increased risk of hip fractures among dialysis patients.[47] This discrepancy might be partially attributed to ethnic differences. However, more research involving this association is warranted. Likewise, hypertension was not significantly associated with an increased risk of hip fractures in this study. A study involving non-dialysis chronic kidney disease patients found an association between hypertension and an increased risk of hip fractures; however, further research is needed to investigate this association among dialysis patients.[48] Additionally, calcium and vitamin D supplementations were not associated with decreased risk of hip fractures. To the best of our knowledge, there is no precise data in the literature about the direct relationship between the supplementation of vitamin D and calcium and the risk of hip fractures in dialysis patients. Moreover, a meta-analysis involving the general population found that vitamin D supplementation did not lead to a decrease in hip fracture risk.[49] However, further studies on the relationship between vitamin D, calcium, and hip fractures in dialysis patients are recommended.

4.1. *Strength & limitations*

As with any study, this study has some limitations. For example, the study's cross-sectional design does not establish a cause-effect relationship between statins and hip fractures. Moreover, some details needed to be included in the medical records, such as the DEXA scan reports limiting our patients' ability to get accurate data about the bone mineral disease. Another area for improvement involving the records was the inconsistency of conducting tests involving parathyroid hormone, calcium, and phosphate levels, limiting their utility to this study. Moreover, an interventional study is recommended to control for the current study's limitations. Despite these limitations, it is worth noticing that this is the first local and international study to investigate the association between

statins and hip fractures among the Palestinian population. In addition, this multi-centred study includes almost all dialysis patients in the north of the West Bank, who account for about half of all dialysis patients in the West Bank.

5. Conclusion

This study found that high adherence to statins was significantly associated with decreased risk of hip fractures, a condition linked with increased morbidity and mortality among dialysis patients. These results could be the initial evidence of the protective effect against a vital health hazard among dialysis patients. This might ultimately contribute to re-considering the current statins prescription practice for dialysis patients. Further research involving low-intensity statins in terms of their effect on hip fractures compared to moderate and high intensities is recommended.

Data availability

Most data generated or analyzed during this study are included in this manuscript. Other data supporting this study's findings and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Informed consent

The Ethics Committee of the Institutional Review Board "IRB" approval at An-Najah National University (ANNU) was obtained. All procedures followed the ethical standards of the responsible.

Author contribution

AF, ST, SA, and AS performed data collection. AF wrote the first draft of the article. KI, MH, ZH, NK, BD critically reviewed the drafts. BD performed data analysis. All authors contributed to the article and approved the submitted version.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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