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Higher Sclerostin Reduces Bone Mineral Density in Non-Ambulatory Stroke Patients

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Introduction

Reduced mobility and bone load are major contributors to bone loss mechanism, with bone loss being a serious clinical manifestation in chronic stroke patients.
There is strong association between ambulation and bone mineral density. BMD at paretic side fell significantly more than non-affected side, and correlated with motor impairment in stroke patients.

Sclerostin is a protein expressed by the SOST gene in osteocytes, and is a key mechanosensor in osteocytes. Sclerostin binds to Wnt Lrp5/Lrp6 receptors and inhibits Wnt/b-catenin signaling, decreasing bone formation. Sclerostin shows a higher elevation in non-ambulatory stroke patients due to lack of weight-bearing.

Patients with mutation in the SOST gene shows high bone mass, and SOST knock out mice also showed increased BMD, high bone mass, and bone formation. In sone studies, by mechanical stimulation in the rodent ulna, SOST/sclerostin levels were reduced.

Some previous studies investigated correlation between sclerostin and BMD, but mainly in hemodialysis patients, patients who have calcific atherosclerosis or post-menopausal women. Unlike previous studies, this study shows non-ambulatory stroke patients have higher sclerostin levels, leading to low BMD score. Gaudio, Agostino, et al. showed long-term immobilized patients present higher sclerostin levels associated with reduced bone formation, and lower BMD, but did not serially follow up BMD.

Sclerostin antibodies including romosozumab, blosozumab are new promising anabolic treatment for osteoporosis. Romosozumab lowered risk of vertebral fracture and increased bone mineral density at lumbar spine, total hip, and femoral neck in post-menopausal women with osteoporosis. Some studies showed that rebuilding the bone foundation with romosozumab before transitioning to antiresorptive therapy like denosumab can be beneficial to patients with osteoporosis.

The aim of this study is to examine the association of mechanical unloading and sclerostin levels in stroke patients and elucidate the consequence of high sclerostin concentration on bone mineral density (BMD) in stroke patients over a 3 years follow-up period.

Keywords: *Stroke, BMD, sclerostin, ambulatory status, weight-bearing*

Method

Total of 26 stroke patients were gathered for this study. We allocated these patients into two subgroups by their ambulatory status: ambulator group (n=11) and non-ambulator group (n=15).

Ambulatory status is based on MBI (Modified barthel index) ambulation score. Patients who have MBI ambulation score 8 or more allocated into ambulator group. Patients who have MBI ambulation score 0 or 3 allocated into non-ambulator group, which means that these patients need constant presence of one or more assistant during ambulation or are dependent in ambulation.

Initial serum sclerostin concentration was measured. BMD at lumbar spine, hip, and femur were obtained by computed tomography (QCT). BMD was measured twice, at the beginning and at 3 years follow-up period. Serum bone markers including parathyroid hormone (PTH), C-telopeptide of type I collagen (CTx), 25-hydroxyvitamin D, creatinine, calcium, bone ALP and P1NP, were also obtained in the initial assessment stage.

Results

Non-ambulatory stroke patients showed significantly higher level of sclerostin (310.66±27.23 pg/mL) compared to ambulatory stroke patients (197.95±13.25 pg/mL) (p=0.001) (Table 1). Regression analysis showed that older patients or non-ambulatory patients had a higher serum sclerostin level, suggesting that serum sclerostin level was associated with age (p=0.027), ambulatory status (p=0.038) (Table 2).

There was no statistical difference in the initial T-score of BMD between ambulatory and non-ambulatory groups. After 3 years, BMD T-score of hip total, hip trochanter, femur intertrochanter decreased in the non-ambulatory group. BMD score of hip total and femur trochanter showed a greater decrease in the non-ambulatory group than in the ambulatory group (Figure 1).

BMD Z-score of hip total, femur neck, femur trochanter, femur intertrochanter significantly decreased in the non-ambulatory group after 3 years while BMD Z-score of the ambulator group did not show any change over 3 years (Figure 1).

Table 1. Baseline characteristics in hemiplegic patients with stroke

Parameter	Ambulator	Non-ambulator	P-value
Sclerostin concentration(pg/mL)	197.95±13.25	310.66±27.23	0.001*
Age(Years)	46.66±10.20	61.05±4.72	0.155
Sex(male %)	0.66	0.45	0.372
BMI(kg/m²)	23.43±2.08	19.73±0.95	0.074
PTH(pg/mL)	35.86±5.65	28.49±2.07	0.119
CTx(ng/mL)	1.30±0.21	0.84±0.11	0.058
25-hydroxyvitaminD(ng/mL)	21.46±5.89	31.11±4.90	0.299
Creatinine(mg/dL)	0.56±0.09	0.61±0.04	0.542
Calcium(mg/dL)	9.25±0.19	9.12±0.15	0.665
Bone ALP	122.00±12.28	104.20±14.56	0.515
P1NP	134.96±54.67	134.27±28.43	0.991

Note. Data are presented as mean±SEM, <.05 Significant difference by independent T-test.

Table 2. Linear regression analysis for predicting sclerostin levels from clinical variables

Parameter (Reference)	Univariate analysis				Multivariate analysis[A]				
	Unstandardized Coefficient		t	P-value	Unstandardized Coefficient		Standardized Coefficient	t	P-value
	B	SE			B	SE			
Age	2.299	0.984	2.337	0.028*	2.157	0.916	0.404	2.355	0.027*
Sex (male)	-13.660	45.970	-0.298	0.769	-0.128			-0.609	0.549
BMI	3.603	5.208	0.692	0.496	0.215			1.072	0.295
Ambulatory status (non-ambulatory)	-108.512	49.965	-2.172	0.040*	-100.855	45.930	-0.377	-2.196	0.038*

*p<0.05, **p<0.01, ***p<0.001, Note A. adjusted R2 = 0.268, Durbin-Watson = 1.851, F(p) = 0.011

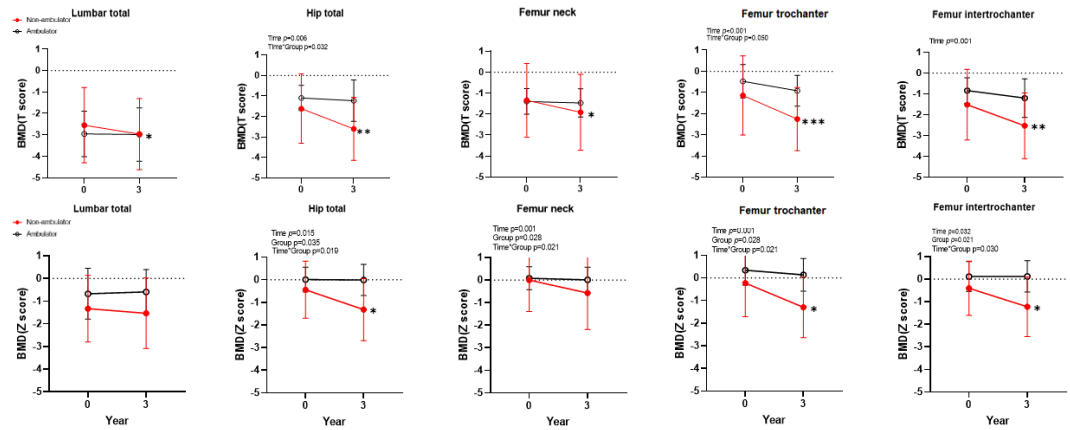

Figure 1. BMD Z-score and T-score of lumbar total, hip total, femur neck, femur trochanter, femur intertrochanter between non-ambulatory and ambulatory group over a 3-year period. p <.05, p<.01, p<0.001 significant effect by two-way repeated measures ANOVA ,*p <.05, **p<.01, ***p<0.001 significant difference by paired T-test

Conclusion

This study suggests that low BMD is associated with elevated sclerostin level in hemiplegic patients with stroke. This may serve as a potential basis of therapeutic effect of anti-sclerostin medication in non-ambulatory stroke patients with bone loss.

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