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Adiponectin Is a Candidate Biomarker of Lower Extremity Bone Density in Men With Chronic Spinal Cord Injury

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Abstract

Adipose tissue is a major regulator of bone metabolism and in the general population obesity is associated with greater bone mineral density (BMD). However, bone-fat interactions are multifactorial, and may involve pathways that influence both bone formation and resorption with competing effects on the skeleton. One such pathway involves adipocyte production of adipokines that regulate bone metabolism. In this study we determined the association between BMD, walking status, and circulating adipokines (adiponectin and leptin) in 149 men with chronic spinal cord injury (SCI). Although adipokine levels did not vary significantly based on walking status, there was a significant inverse association between adiponectin and BMD in wheelchair users independent of body composition. We found no association between adiponectin and BMD in the walkers and no association between leptin and BMD in either group. These findings suggest that for subjects with chronic SCI, walking may mitigate the effect of adiponectin mediated bone loss. For wheelchair users, adipose-derived adiponectin may contribute to SCI-induced osteoporosis because the osteoprotective benefits of obesity appear to require mechanical loading during ambulation.

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Keywords

OSTEOPOROSIS; ADIPONECTIN; BIOMARKER; SPINAL CORD INJURY; REHABILITATION MEDICINE

Introduction

A complex system of cross-regulation exists linking fat and bone metabolism.[1,2] Adipocyte-derived hormones regulate bone cell activities[3–12] while the bone-derived protein osteocalcin stimulates expression of the adipokine adiponectin.[13,14] The role of adipokines in bone metabolism has been examined in vitro,[3,7–13] in animal models,[4,10,15] and in epidemiological studies,[16–31] with much of the focus on leptin and adiponectin. Leptin was originally described as the product of the obesity gene and the observed link between obesity and bone mineral density (BMD) led to the investigation of leptin's role in bone.[32] Long considered to signal via both central nervous system[33] and peripheral pathways,[34] more recent evidence suggests that leptin mediates bone metabolism primarily via the peripheral pathway to stimulate bone formation.[35] The leptin receptor is expressed on osteoblasts[36] and has been shown to promote osteoblast over adipocyte differentiation in bone marrow stromal cells.[37] Leptin has also been shown to inhibit in vitro differentiation of human peripheral blood mononuclear cells (PBMC) into mature, functional osteoclasts.[7] Similarly, adiponectin is a polypeptide hormone produced by osteoblasts and adipocytes in both visceral and marrow fat depots.[3,38] Circulating levels of adiponectin are inversely associated with central adiposity and increase significantly with age.[39] Signaling via active receptors expressed on bone-forming cells,[3] adiponectin can directly stimulate osteoblastogenesis and indirectly inhibit osteoclastogenesis. It has been suggested that adiponectin may be a biomarker of both bone loss and fracture risk.[23,39–41] Higher adiponectin levels were associated with greater bone loss at the lumbar spine over the course of 1 year in 35 physically active older women.[22]

In general, greater body fat is associated with greater BMD[42,43] and this is often attributed to mechanical loading of the skeleton by fat mass and modulation of bone turn over by adipokines. Spinal cord injury (SCI) is a condition characterized by both obesity and severe osteoporosis, suggesting a disruption of the mechanisms linking fat mass and BMD. No information exists regarding the impact of paralysis on bone-fat interactions. Therefore, in this study we examined the association between circulating adiponectin or leptin levels and BMD based on the ability to walk in chronic SCI.

Materials and Methods

Subjects

We studied participants with chronic SCI who were enrolled in the Boston SCI-Health Study.[44,45] Subjects were recruited from veterans who receive care at our Veterans Affairs (VA) Medical Center facility, by advertisement in SCI consumer magazines, and by direct mail. Direct mail recruitment was sent to (1) persons who previously received medical care at our non-VA acute rehabilitation facility, (2) New England subscribers of New Mobility Magazine, and (3) members of the National Spinal Cord Injury Association. Participants were eligible if they were 22 years of age or older, 1 or more years after injury, were not ventilator dependent, did not have a tracheostomy, and had no other neuromuscular disease. A total of 196 participants with SCI were enrolled in the Boston SCI-Health Study between August 2009 and January 2011. For this study, we excluded females (n=29) and only included those who were 5 years or more postinjury, for a total of 149 participants.

Motor score

Motor level and completeness of injury were confirmed by physical exam at study entry by a trained rater according to the American Spinal Injury Association Impairment Scale (AIS). Participants were classified as AIS A or B (motor complete, no motor function below the neurological level of injury); AIS C (motor incomplete, motor function preserved below the neurological level, and more than half the key muscles below the neurological level are not strong enough to overcome gravity); or AIS D (motor incomplete, motor function preserved below the neurological level, and more than half the key muscles below the neurological level strong enough to overcome gravity). Injury severity was then classified in two categories: motor complete SCI (AIS A/B) or motor incomplete SCI (AIS C or D).

Dual X-ray absorptiometry for bone mineral density and body composition

We used a fifth-generation GE Healthcare Lunar (Madison, WI, USA) iDXA dual X-ray absorptiometry (DXA) scanner with enCore configuration version 12.3 to determine BMD and to assess body composition. Total fat mass (kg) and total lean mass (kg) were calculated by the system software from whole-body scans based on body weight measured at the time of scanning. Fractures are most common at the knee (distal femur or proximal tibia) after SCI. Therefore, BMD was determined at both SCI-specific (proximal tibia, distal femur) and standard (hip, radius) skeletal sites as described.[46] Unless there was a prior fracture or instrumentation, the nondominant lower extremity and radius were scanned. For the distal femur, the proximal edge of the region of interest (ROI) was set at 20% of the femur length (measured from the lateral femoral condyle), and the distal edge was set at the visible intersection between the patella and the femur, excluding the patella from the ROI. For the proximal tibia, the proximal edge was set at the most proximal point of contact between the tibia and fibular head sites, avoiding regions of overlap between the fibula and the tibia. Scans were obtained in triplicate at the proximal tibia and distal femur and averaged. Customized research software supplied by General Electric was used to determine BMD at the knee. As a standard procedure, a quality assurance phantom supplied by the manufacturer was measured at least every 2 days to confirm accuracy of the densitometer.

For subjects age 50 years or older, *T*-score was used to classify hip bone density (total hip and femoral neck) according to the World Health Organization (WHO) definitions of normal (*T*-score≥−1), osteopenia (*T*-score<−1 and>−2.5), and osteoporosis (*T*-score≤−2.5). For subjects under the age of 50 years, *Z*-score was used to classify hip BMD as normal (*Z*-score>−2) or as lower than expected for age and sex (*Z*-score≤−2).

Biochemical analyses

Subjects were asked to undergo testing in a fasting state and efforts were made to collect samples in the morning before a meal. For subject safety, individuals were advised to have a light meal or snack if fasting could worsen a medical condition (orthostatic hypotension). In all cases information was collected on time since last meal or snack. Plasma samples were drawn into an EDTA tube and immediately delivered to the core blood research laboratory at our facility. The samples were centrifuged for 15 minutes at 2600 rpm (1459*g*) at 4°C and stored at −80°C until batch analysis. All biochemical analyses were performed at the Clinical & Epidemiologic Research Laboratory, Department of Laboratory Medicine at Children's Hospital in Boston (Boston, MA, USA), a state-of-the-art reference laboratory that specializes in microanalysis. Assays were performed in duplicate and any duplicate with >10% coefficient of variation (CV) was repeated. Total adiponectin was quantified by ELISA assay (Alpco Diagnostics, Salem, NH, USA) with a detection limit of 0.075 ng/mL. Leptin was quantified by ultrasensitive ELISA assay (R&D Systems, Minneapolis, MN, USA) with a detection limit of 7.8 pg/mL. Total osteocalcin was measured as an indicator of bone formation by electrochemiluminescence immunoassay on a 2010 Elecsys autoanalyzer

(Roche Diagnostics, Indianapolis, IN, USA) with a detection limit of 0.50 ng/mL. C-telopeptide was measured as an indicator of bone resorption by electrochemiluminescence immunoassay on a 2010 Elecsys autoanalyzer (Roche Diagnostics) with a detection limit of 0.01 ng/mL. The amount of 25-hydroxyvitamin D (25 OH vitamin D) was quantified by enzyme immunoassay (Immunodiagnostic Systems Inc., Fountain Hills, AZ, USA) with a detection limit of 2.0 ng/mL. One wheelchair user had an osteocalcin level of 87.8 ng/mL. One walker and one wheelchair user had leptin levels of 122,358.5 and 91,812.2 pg/mL, respectively. These values were considered to be outliers and were removed from subsequent osteocalcin or leptin analyses.

Variable definition

Information regarding SCI, medical history, medication use, and fracture history was obtained by questionnaire at the time of DXA scan. Participants were weighed and supine length measured for the calculation of body mass index (BMI). In subjects with severe joint contractures, length was self-reported (n=14). Usual mobility mode (more than 50% of the time) was considered in the following two categories: wheelchair use (motorized wheelchair or hand-propelled wheelchair) or walking (with aid such as crutch, cane or walk without assistance). For fracture history, information was collected on timing (before SCI, at time of SCI, or after SCI), and location. Fractures were categorized as osteoporotic (ie, those occurring from standing height or less or in the absence of trauma) or traumatic fracture. Digit and rib fractures were excluded. When available, medical records were used to confirm self-reported fracture history (20/40 fractures). Osteoporotic fractures that occurred after SCI were considered in the analysis. Bisphosphonate use was assessed as ever/never. Hip BMD was used to categorize osteoporosis status as normal bone density, osteopenia, or osteoporosis/BMD lower than expected for age. For body composition, total lean mass (kg) and total fat mass (kg) were included in the analyses.

Statistical analysis

All analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA). Statistical t tests or χ^2 tests were used to compare subject characteristics as appropriate. General linear models (PROC GLM) were applied to assess associations between adiponectin and osteocalcin. To account for the multiple measurements of bone density measured within the same person at the four sites below the level of injury (total hip, femoral neck, proximal tibia, and distal femur), a mixed model procedure with repeated measures and unstructured correlation was used to assess predictors of BMD. Factors with a p value of <0.10 in the univariate mixed models, as well as factors that were deemed clinically significant (body composition), were included in the multivariable models assessing the association of BMD and adiponectin or leptin (PROC MIXED). Factors with a p value of <0.05 were considered statistically significant and any factor with a p value of >0.05 was removed from the model. Linear trend p values for the BMD of each quartile of adiponectin among the walkers and wheelchair users were derived using an ordinal variable coded based on the median of each quartile.

Results

Subject characteristics

Subject characteristics are presented in Table 1. All participants were male and the majority were white. Ages ranged from 27.1 to 87.6 years, and injury duration ranged from 5.1 to 60.8 years. A total of 54 subjects walked independently or with an assistive device and 95 subjects used a wheelchair. Those who walked were significantly older than those who used a wheelchair (62.6 versus 51.3 years old, p<0.0001). Years since injury did not vary between the two groups (p=0.63). Participants who walked had a significantly higher lean mass

($p<0.0001$) and BMI ($p=0.01$) than those who used a wheelchair. There was no difference in bisphosphonate use or levels of vitamin D, cross-linked C-telopeptide (CTX), osteocalcin, adiponectin, or leptin between the two groups ($p=0.08$–0.87). A majority of subjects (77%) had not consumed anything for at least 8 hours prior to testing. Adiponectin and leptin levels did not vary significantly based on time since last meal or snack ($p=0.27$ for adiponectin and $p=0.88$ for leptin).

BMD could not be determined in 1 subject at the distal femur, 2 subjects at the proximal tibia, 8 subjects at the hip, and 2 subjects at the radius due to knee/hip replacement, fixation rods, heterotrophic ossification, spasms, or contractures preventing proper scan positioning. Lower extremity BMD (distal femur, proximal tibia, total hip and femur neck) was significantly lower in the wheelchair users compared to the walkers ($p<0.0001$), but there was no significant difference in radius BMD between the 2 groups ($p=0.97$). Walkers were more likely to have their hip BMD classified as normal compared to wheelchair users. Wheelchair users were more likely to be classified as osteoporotic/low BMD ($p<0.0001$) and to report post-SCI osteoporotic fractures ($p=0.01$).

Clinical factors associated with lower extremity BMD

Factors associated with BMD varied according to the ability to walk. There was no significant association between BMD and age, injury duration, vitamin D level or status, or total fat mass ($p=0.12$–0.99; Table 2). For the walkers, BMD was positively associated with body weight ($p=0.01$), BMI ($p=0.03$), and lean mass ($p=0.0008$). There was no association between BMD and CTX ($p=0.36$) or osteocalcin ($p=0.16$). Adiponectin and leptin were not significantly associated with BMD in the walkers and remained nonsignificant after adjusting for lean mass ($p=0.36$, Table 3A, $p=0.14$, Table 3B, respectively). These results remained unchanged when also adjusting for BMI or when excluding active bisphosphonate users from the analyses. There was no significant linear trend in mean BMD among the quartiles of adiponectin and mean BMD in the walkers after adjusting for lean mass ($p=0.87$, Table 4).

For wheelchair users, there was no association between BMD and body weight or BMI ($p=0.07$–0.11, Table 2). BMD was positively associated with lean mass ($p=0.03$) and negatively associated with CTX ($p=0.01$) and osteocalcin ($p=0.02$). BMD was negatively associated with adiponectin ($p=0.0005$) and remained significant after adjusting for lean mass ($p=0.004$, Table 3A). Leptin was not significantly associated with BMD ($p=0.82$) and remained nonsignificant after adjusting for lean mass ($p=0.20$, Table 3B). These results remained unchanged when adjusting for BMI or when excluding active bisphosphonate users from the analyses. There was an inverse linear trend in BMD level with adiponectin quartiles that remained significant after adjusting for lean mass ($p=0.002$, Table 4). A similar analysis demonstrated no consistent relationship between leptin quartiles and BMD in either walkers or wheelchair users (results not shown).

Adiponectin and history of post-SCI osteoporotic fracture

Fifteen fractures occurred during high-impact events including motor vehicle accidents, falls down flights of stairs, and skiing accidents. These fractures were considered traumatic and were not included in the analysis. There was no association between adiponectin and post-SCI osteoporotic fracture history in either group (walkers $p=0.1$, wheelchair users $p=0.08$). When considering only those who reported a history of fracture, there was no association between adiponectin and time since fracture (walkers $p=0.82$, wheelchair users $p=0.77$).

Association between osteocalcin and adiponectin

For walkers, osteocalcin was positively associated with adiponectin (p=0.01) and this remained significant after adjusting for age and fat mass (p=0.02, R^2=0.32; Fig. 1A, B). For wheelchair users, the association between osteocalcin and adiponectin was not significant (p=0.19, age and fat mass adjusted p=0.20). These results remained unchanged when excluding active bisphosphonate users from the analyses.

Discussion

We examined BMD and circulating adipokine levels based on walking status in 149 men with chronic SCI. There was a significant inverse relationship between adiponectin and BMD in wheelchair users independent of body composition. We found no association between adiponectin and BMD in walkers and no association between leptin and bone density in either group. Wheelchair users also had lower BMD at the knees (distal femur and proximal tibia) and hips (total hip and femur neck), were more likely to have osteoporosis at the hip, and were more likely to report a history of osteoporotic fracture compared to those who walk. BMD at the radius was not significantly different between the two groups. Adiponectin and leptin levels also did not vary significantly based on walking status. We found no association between age, vitamin D level, or vitamin D status (normal versus deficient) and BMD in either walkers or wheelchair users. We found that lower extremity BMD increased with lean mass in both groups. Body weight and BMI were positively associated with BMD in walkers but not in wheelchair users.

Our findings are in agreement with previous reports of a negative association between BMD and adiponectin in men that is independent of body composition.[40] In the current study, we detected this association in paralyzed men with chronic SCI. We found no association between adiponectin and bone in subjects who walk. Although we found no association between adiponectin and bone in subjects who walk, it is possible that differences in study population and design could account for this finding. Other studies have found associations in the elderly, and included men generally older than in our cohort.[39–41] Associations have been reported between adiponectin and lumbar spine BMD,[23] a site that we did not study because spinal instrumentation or arthritic changes are common after SCI, making reliable spine imaging difficult. Furthermore, the lumbar spine is not a clinically relevant skeletal site in this population because compression fractures rarely occur after SCI. In addition, other studies in the general population included a much larger numbers of subjects. Therefore, it is possible that a weaker association exists between bone and adiponectin in men with SCI who walk that we could not detect.

SCI has been considered a model of accelerated aging because it prematurely leads to reduced mobility.[45] In this respect, it is possible that wheelchair users have bone-fat interactions that are more similar to elderly men than younger men with SCI who walk. Adipose tissue may serve a dual role in the context of bone-fat interactions: (1) contributor to total body weight and therefore a source of mechanical loading; and (2) an endocrine organ that produces adipokines. Motor complete SCI results in pure mechanical unloading. In this case adipose tissue functions as an endocrine organ without the accompanying mechanical loading. It is possible that elderly men have changes in functional status associated with less mobility than younger, healthy males. In this case, bone-fat interactions in elderly men may more resemble wheelchair users. Most studies do not address walking status when examining adipokines and bone. The Swedish based MrOs study assessed physical activity in the week prior to testing and found adiponectin levels were greater in subjects who were more physically active, suggesting a relationship between mechanical loading and adipokine production.[39] This is in contrast to our finding that adipokine levels did not vary based on the ability to walk.

A negative association has been demonstrated between adiponectin and BMD in healthy older men, postmenopausal women,[17,18,20,25,28,31] adolescents,[20] and people with metabolic syndrome.[47] In some studies this relationship is mediated by body mass, fat mass, lean mass, or BMI and does not remain significant after adjusting for these factors.[18,20,23,28,48] Adiponectin has also been implicated in the development of osteoporosis.[23,39–41] Adiponectin was associated with fracture risk in elderly men participating in the MrOS study (Sweden) and in the Health ABC study (USA).[39,41] There was no relationship between adiponectin and fracture in elderly women in the Health ABC study, suggesting a gender effect. The relationship between adipokine levels and bone loss or fracture risk is unknown in SCI. In this study we found no association between adiponectin levels and history of osteoporotic fracture occurring after SCI. Future work is needed to determine if adiponectin levels are predictive of incident osteoporotic fractures in this population.

It has been suggested that BMI does not accurately reflect changes in body composition after SCI. In one report participants with SCI were 13% fatter per unit of BMI compared to age and sex matched controls.[49] Our data are consistent with this finding in that wheelchair users had greater total fat and a lower BMI than the walkers. Even though it underestimates adiposity, BMI is still recommended for body composition assessment in SCI clinical trials with epidemiological, neurological, and functional outcomes.[50] In this study we did not use BMI to identify individuals with SCI who were overweight or obese. Instead, we considered BMI to reflect mechanical loading of bone during ambulation due to total body mass. We did find that relationships between bone and body composition differ based on walking status. Body mass and BMI are positively associated with BMD in men with chronic SCI who walk, and this finding is in agreement with reports in the general population. In contrast, we observed a dissociation between body weight and BMD in paralyzed men that is not unexpected given that obesity and fractures are both common in this population. Osteocalcin is a marker of bone formation and is thought to link bone and fat metabolism by regulating adiponectin expression.[13,14] In the current study we also found a significant association between osteocalcin and adiponectin in the walkers only. These findings suggest that the mechanical loading associated with walking is critical for cross-regulation of bone and fat metabolism.

Despite the widely held belief that obesity is osteoprotective, many studies have suggested detrimental effects of obesity on bone. In the general population, obesity in adolescence causes decreased bone strength relative to body weight, and fractures may be more common in both obese children[51] and obese adults.[52] Although not directly assessed, decreased physical activity and therefore decreased mechanical loading may account for the findings reported in these studies. It is possible that, in the absence of mechanical loading to stimulate bone formation, adipokine-mediated bone resorption predominates promoting bone loss. This is supported in the current study by the significant inverse association between markers of bone turnover and BMD in the wheelchair users only.

In this study we found no independent relationship between leptin and BMD after adjusting for body composition. Leptin has been studied in the context of SCI but none have focused on associations between leptin and bone.[53–59] Leptin is reportedly greater in men with SCI compared to age- and BMI-matched controls and is positively correlated with fat mass. In contrast to leptin, there is a significant inverse relationship between adiponectin and BMD in wheelchair users independent of body composition.

In this study ambulatory status is closely related to the severity of neurological injury. Bone is densely innervated and it is possible that loss of neural input contributes to bone loss in the setting of chronic SCI. Similarly, there are other putative signaling pathways that may

work separately or synergistically with adiponectin to influence bone metabolism following paralysis. Future work focused on differences in myokine or inflammatory cytokine expression based on ambulatory status is warranted. Furthermore, additional work is required to assess adiponectin as a biomarker of fracture risk and to determine if adiponectin contributes to bone loss in motor complete SCI or other conditions associated with decreased mechanical loading of the lower extremity, including cerebral palsy, prolonged bed rest, or microgravity.

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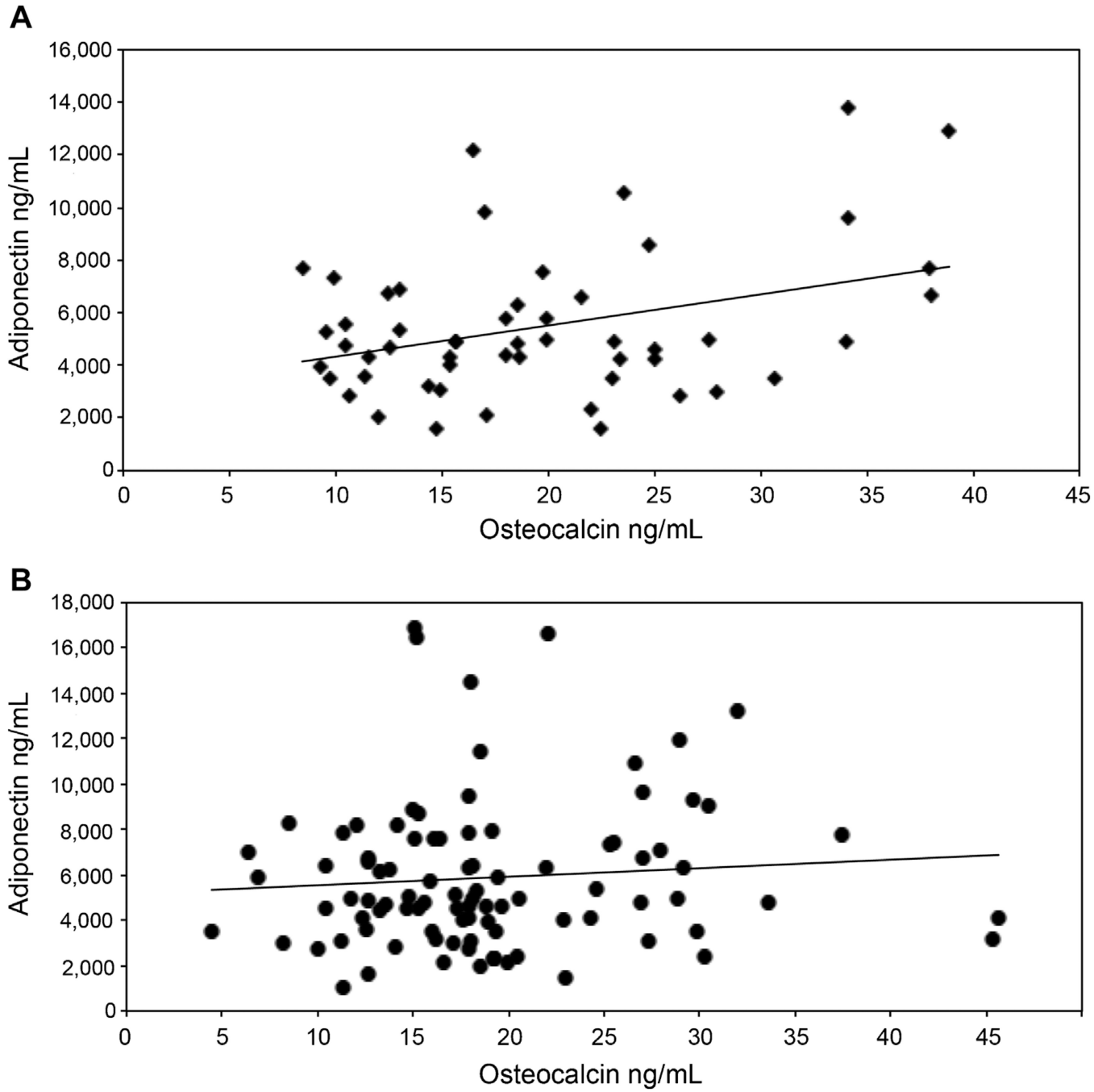

Fig. 1.

Association between adiponectin and osteocalcin by walking status. Greater osteocalcin levels are significantly associated with greater adiponectin levels (*A*) in subjects with SCI who walk (p=0.02, R^2=0.32), (*B*) but not those who use a wheelchair (p=0.38). These relationships did not change when excluding subjects taking a bisphosphonate.

Table 1

Participant Characteristics

Variable	Walkers (*n* ± 54)	Wheelchair users (*n* ± 95)
Demographics		
Age (years) (mean ± SD)	62.6 ± 12.0	51.3 ± 12.5*
Years since injury (mean ± SD)	22.1 ± 13.2	21.1 ± 11.8
White, *n* (%)	47 (87.0 %)	87 (91.6 %)
Injury severity, *n* (%)		
Motor complete SCI	2 (3.7 %)	74 (77.9 %)
Motor incomplete SCI	52 (96.3 %)	21 (22.1 %)
Body composition (kg) (mean ± SD)		
Weight	88.53 ± 16.50	83.76 ± 20.35
Total lean mass	55.80 ± 80.02	49.95 ± 82.35*
Total fat mass	29.69 ± 10.71	31.20 ± 14.04
BMI (kg/m^2) (mean ± SD)	28.5 ± 5.0	26.1 ± 5.7**
25 OH vitamin D (ng/mL) (mean ± SD)	23.8 ± 12.7	23.5 ± 8.0
Normal (≥20 ng/mL)	31 (57.4 %)	62 (65.3 %)
Deficient (<20 ng/mL)	23 (42.6 %)	33 (34.7 %)
BMD (g/cm^2) (mean ± SD)		
SCI-specific skeletal sites		
Distal femur	0.91 ± 0.18	0.64 ± 0.19[b],*
Proximal tibia	1.02 ± 0.21	0.63 ± 0.22[c],*
Traditional sites		
Total hip	0.99 ± 0.19[a]	0.73 ± 0.20[d],*
Femur neck	0.93 ± 0.15[a]	0.75 ± 0.20[d],*
Radius	0.98 ± 0.12	0.98 ± 0.10[c]
Hip bone density classification, *n* (%)[e]		
Normal	26 (48.1 %)	12 (12.6 %)*
Osteopenia	19 (35.2 %)	9 (9.5 %)
Osteoporosis/BMD lower than expected for age	8 (14.8 %)	67 (70.5 %)
Hip BMD not available	1 (1.9 %)	7 (7.4 %)
Bisphosphonate use, *n* (%)	5 (9.3 %)	18 (19.0 %)
Post SCI osteoporotic fracture history, *n* (%)	9 (16.7 %)	31 (32.6 %)**
Markers of bone turnover (ng/mL) (mean ± SD)		
Osteocalcin	19.5 ± 8.1	19.0 ± 7.6[b]
C-telopeptide	0.31 ± 0.13	0.36 ± 0.22
Adiponectin (ng/mL) (mean ± SD)	5730.9 ± 3355.8	5849.2 ± 3283.2
Leptin (pg/mL) (mean ± SD)	13517.1 ± 13480.0[a]	13016.6 ± 11796.5[b]

SCI=spinal cord injury; BMI=body mass index; BMD=bone mineral density.

[a] *n*=53.

[b] n=94.

[c] n=93.

[d] n=88.

[e] Based upon Z-score or T-score at the total hip or femoral neck.

* Significantly different from walkers, $p<0.0001$.

** Significantly different from walkers, $p<0.0001$.

Table 2

Univariate Factors Associated With BMD (g/cm^2) Based on Walking Status

	Walkers (*n*=54)		Wheelchair users (*n*=95)	
Variable	**β ± SE**	***p***	**β ± SE**	***p***
Age (years)	−0.0023 ± 0.0015	0.12	0.0011 ± 0.0012	0.37
Injury duration (years)	0.00080 ± 0.0014	0.56	−0.0019 ± 0.0015	0.19
Weight (kg)	0.0028 ± 0.0010	0.01	0.0015 ± 0.00084	0.07
Lean mass (kg)	0.0074 ± 0.0021	0.0008	0.0046 ± 0.0020	0.03
Fat mass (kg)	0.0022 ± 0.0017	0.20	0.0013 ± 0.0012	0.29
BMI (kg/m^2)	0.0076 ± 0.0034	0.03	0.0049 ± 0.003	0.11
25 OH vitamin D (ng/mL)	−0.00028 ± 0.04	0.85	−0.0013 ± 0.002	0.53
Markers of bone turnover (ng/mL)				
C-telopeptide	0.13 ± 0.14	0.36	−0.19 ± 0.076	0.01
Osteocalcin	0.0031 ± 0.0022	0.16	−0.0054 ± 0.0022	0.02
	Mean BMD ± SE	***p***	**mean BMD ± SE**	***p***
25 OH vitamin D		0.99		0.52
Normal (≥20 ng/mL)	0.875 ± 0.027		0.684 ± 0.021	
Deficient (<20 ng/mL)	0.875 ± 0.023		0.708 ± 0.029	

Bone density was obtained from a repeated measures regression model based on proximal tibia, distal femur, total hip, and femoral neck BMD.

BMD=bone mineral density; BMI=body mass index.

Table 3

Association Between Adipokines and Bone Density Based on Walking Status

	β ± SE	*p*
(*A*) Adiponectin, BMD (g/cm^2) per mg/dL		
Walkers (*n*=54)		
Unadjusted	−0.00764 ± 0.0532	0.89
Fully adjusted[a]	−0.0460 ± 0.0496	0.36
Wheelchair users (*n*=95)		
Unadjusted	−0.179 ± 0.0494	0.0005
Fully adjusted[a]	−0.159 ± 0.0532	0.004
(*B*) Leptin, BMD (g/cm^2) per mg/dL		
Walkers (*n*=54)		
Unadjusted	0.0242 ± 0.0133	0.08
Fully adjusted[a]	0.0186 ± 0.0122	0.14
Wheelchair users (*n*=95)		
Unadjusted	−0.00276 ± 0.0123	0.82
Fully adjusted[a]	−0.0168 ± 0.0132	0.20

Bone density was obtained from a repeated measures regression model based on proximal tibia, distal femur, total hip, and femoral neck BMD.

BMD=bone mineral density.

[a]Adjusted for lean mass (kg).

Table 4

Mean Bone Density by Adiponectin Quartile Based on Walking Status

	Walkers		Wheelchair users	
	Mean BMD (g/cm^2) ± SE	***p* for trend**	**Mean BMD (g/cm^2) ± SE**	***p* for trend**
Adiponectin quartiles (mg/dL)		0.87*		0.002*
Quartile 1 (≤0.3350)	0.897 ± 0.032		0.776 ± 0.033	
Quartile 2 (0.3350 to ≤0.4916)	0.901 ± 0.031		0.703 ± 0.035	
Quartile 3 (0.4916 to ≤0.7336)	0.852 ± 0.031		0.703 ± 0.032	
Quartile 4 (>0.7336)	0.910 ± 0.035		0.616 ± 0.032	

Mean bone density was obtained from a repeated measures regression model based on proximal tibia, distal femur, total hip, and femoral neck BMD. Adiponectin quartiles based on its distribution in the entire cohort.

BMD=bone mineral density.

*Adjusted for lean mass (kg).