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Physical Activity Associations with Bone Mineral Density and Modification by Metabolic Traits

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Objective: To assess the relationship of physical activity with bone mineral density (BMD) at various sites and examine potential modifying metabolic factors.

Methods: Responses from physical activity questionnaires were used to determine total physical activity (PA), moderate physical activity (mod-PA), and sedentary time. Regression analyses were performed to evaluate association of activity traits with insulin sensitivity by euglycemic clamp, adiponectin, C-reactive protein (CRP), and plasminogen activator inhibitor-1 (PAI-1) in 741 healthy subjects.

Results: The cohort was relatively sedentary. Activity level was associated with arm, pelvis, and leg BMD in univariate analyses. In multivariate association analyses of arm BMD, only female sex (β = -0.73, P < 0.0001) and adiponectin (β = -0.076, P = 0.0091) were significant. Multivariate analyses of pelvis BMD found independent associations with body mass index (BMI) (β = 0.33, P < 0.0001), adiponectin (β = -0.10, P = 0.013), female sex (β = -0.18, P < 0.0001), sedentary time (β = -0.088, P = 0.034), PA (β = 0.11, P = 0.01), and mod-PA (β = 0.11, P = 0.014). Age (β = -0.10, P = 0.0087), female sex (β = -0.63, P < 0.0001), BMI (β = 0.24, P < 0.0001), and mod-PA (β = 0.10, P = 0.0024) were independently associated with leg BMD.

Conclusions: These results suggest that BMD increases with physical activity in the arms, legs, and pelvis and is inversely related to sedentary time in the pelvis and legs; these associations may be modified by age, sex, BMI, and adiponectin, depending on the site, with physical activity being more important to pelvis and leg BMD than arm BMD and sedentary time being important for pelvis BMD. Moreover, we demonstrated that CRP, PAI-1, and insulin sensitivity play a minor role in BMD.

Abbreviations: BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; DXA, dual energy x-ray absorptiometry; GEE, generalized estimating equation; I, steady-state insulin level; M, glucose infusion rate; MET, metabolic equivalent; mod-PA, modified physical activity; PA, physical activity; PAI-1, plasminogen activator inhibitor-1; VIF, variance inflation factor.

Physical activity is known to play a significant role in bone mineral density (BMD). Multiple studies have shown positive correlations between both resistance and aerobic training exercise with improved BMD [1–4]. In a meta-analysis of 32 randomized clinical control trials, both premenopausal and postmenopausal women demonstrated improved lumbar spine BMD in aerobic and resistance training groups [5]. Data also suggest that increased activity level in young women and minimizing sedentary behavior in older women are independently associated with improved lumbar spine and femoral neck BMD across a woman's lifespan [6]. Others have reported positive effects on BMD of increased activity level and reduced sedentary time in both men and women [7, 8]. Screen-based sedentary time has been noted to have a particularly deleterious impact on BMD [8].

Moreover, seemingly disparate activities, sports, and exercise regimens have demonstrated improved BMD [9–11]. One study noted improved BMD in both men and women with swimming, a nonimpact sport, over a 9-month follow-up period, though prolonged periods of engagement appeared to negatively affect these gains, independent of sex [11]. Basketball, karate, judo, ballet, and water polo have also all demonstrated improved BMD compared with control [9, 10, 12]. The benefits of exercise on BMD have even been seen in the context of weight loss [13, 14].

Interestingly, serum osteoprotegerin and receptor activator of nuclear factor kappa B ligand levels have not shown significant change in response to exercise, which may suggest alternative metabolic pathways mediating effects of exercise on BMD [15]. Exercise has been independently associated with changes in metabolic markers such as C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), insulin sensitivity, and adiponectin [16–19]. Increased physical activity and reduced sedentary time have been shown to reduce CRP levels [20, 21]. Several studies have also shown similar associations between PAI-1 and exercise, whereas increases in adiponectin and improved insulin sensitivity have been associated with exercise [22–26].

However, data are currently limited regarding whether metabolic parameters such as CRP, PAI-1, insulin sensitivity, and adiponectin may modulate the effects of physical activity on BMD. Gaining a better understanding of this potential link may prove valuable in the context of clinical practice, counseling patients, and improving bone health. Our aim was to establish the relationship of physical activity level with BMD assessed by dual energy x-ray absorptiometry (DXA) and determine whether metabolic traits modify or mediate associations between physical activity and BMD.

Materials and Methods

Subjects

Metabolic, physical activity, and anthropometric parameters were assessed in subjects participating in the University of California Los Angeles/Cedars-Sinai Mexican-American Coronary Artery Disease (MACAD) project, a study of Mexican-American families living in Los Angeles [27]. To qualify for the study, subjects had to report at least 3 grandparents of Mexican origin. In the current analyses, 741 subjects from 197 families with BMD values and physical activity questionnaires were included, consisting of adult offspring of probands with coronary artery disease (determined by evidence of myocardial infarction on electrocardiogram or hospital record, angiographic evidence of atherosclerosis, or record of angioplasty or coronary artery bypass graft) and the spouses of those offspring. To avoid potential confounding factors, those with overt endocrine or cardiovascular disease, major illness, or those taking glucocorticoids or antihyperglycemic agents were excluded from phenotyping. Although 17% of the subjects reported current smoking, smoking was not associated with reduced BMD in this cohort and therefore was not considered further.

Phenotyping

Study subjects underwent a phenotyping protocol that included anthropometry, biomarkers, glucose homeostasis indices, and physical activity assessments. On different days, subjects gave fasting blood, underwent the euglycemic-hyperinsulinemic clamp, and had a DXA scan.

During the euglycemic-hyperinsulinemic clamp, a priming dose of human insulin (Novolin; Novo Nordisk, Clayton, NC) was given and followed by infusion for 120 minutes at a constant rate (60 mU·m^{-2}·min^{-1}) to achieve and maintain a plasma insulin concentration of 100 µIU/mL or greater [28, 29]. Blood was sampled every 5 minutes, and 20% dextrose was co-infused with the rate adjusted to maintain plasma glucose concentrations at 95 to 100 mg/dL. Over the last 30 minutes of steady-state insulin and glucose concentrations, the glucose infusion rate (M; given in milligrams per meters squared per minute) approximates glucose uptake by all body tissues (primarily insulin-mediated glucose uptake in muscle) and thus reflects tissue insulin sensitivity [29]. By dividing M by the steady-state insulin level (I), an insulin sensitivity index can be calculated (M/I), which is what we used as the measure of insulin sensitivity herein.

Fasting biomarkers included adiponectin, CRP, and PAI-1 levels, whereas anthropometric indices included height and weight (yielding body mass index [BMI]). Bone density was evaluated with whole-body DXA scans, which were obtained primarily to assess body fat distribution, including fat and lean mass. Though whole-body scans focus on regions more commonly used for body composition assessment, they also yield accurate BMD assessments [30]. In comparable sites, regional BMD generated from whole-body DXA scans have been shown to compare well with site-specific DXA [31, 32]. In particular, arm subregion and total wrist BMD, lumbar spine subregion and anteroposterior spine are highly correlated, whereas there is a similar but less pronounced association of both leg and pelvis regional BMD to femoral neck BMD [33, 34]. In this study, we evaluated total arm BMD (average of right and left arms including hands), total leg BMD (average of right and left legs including feet), and total pelvis BMD, defined superiorly as the region horizontally demarcated by the upper boundaries of the iliac crests and inferiorly by 2 angled lines through the femoral necks. Lumbar spine (T12-L1 disk space to pelvis line) and thoracic spine (C7-T1 disk space to T12-L1 disk space) BMD were also assessed.

Physical activity was assessed based on the 12-item multiple choice Morgenstern physical activity questionnaire [35]. Responses from participant questionnaires were used to determine physical activity scores: total physical activity score (PA), moderate physical activity score (mod-PA), and overall sedentary time. Each question was assigned a score associated with its average metabolic equivalents (METs), which is the ratio of energy expenditure in a particular activity to the energy expenditure at rest for an individual [36]. Activity, measured by number of hours per week, was codified using midpoints of 8 different response categories: 0 (none), 0.5 (<1), 1.5 (1-2), 4 (3-5), 7.5 (6-9), 14.5 (10-19), 24.5 (20-29), and 35 (≥35). A sum of hours in each category weighted by its corresponding MET value was used to assess the total physical activity score. Moderate physical activity was calculated in a similar manner but included only those activities requiring moderate energy expenditure of MET > 4.5. Sedentary time (including sleep, MET = 1) was calculated by subtracting the number of hours spent in each category from the total number of hours in a week [35]. The cohort was found to be relatively sedentary.

Data analysis

We used logtransformed (BMI, CRP, adiponectin, mod-PA) or squareroottransformed (PAI-1, insulin sensitivity, PA) variables as necessary to normalize distribution for statistical analyses. T-tests for quantitative traits and χ^2 tests for categorical traits were used to compare traits between men and women.

Generalized estimating equations (GEE) were used to assess the effects of single traits (univariate analyses) or joint effects of multiple traits (multivariate analyses) on BMD, adjusting

for familial relationships. The weighted GEE1 [37] was computed assuming an exchangeable correlation structure and using the sandwich estimator of the variance to account for familial correlation present in family data. GEE was used to derive standardized regression coefficients, which in any 1 regression equation are measured on the same scale, with a mean of 0 and an SD of 1. They are then directly comparable to one another, with the largest coefficient indicating which independent variable has the greatest association with the dependent variable.

Correlation analyses were carried out in several stages. Using GEE to adjust for familial relationships, univariate simple regression analysis was first conducted with age, sex, BMI, metabolic traits (insulin sensitivity, CRP, PAI-1, and adiponectin) and physical activity measures as separate independent variables versus each site-specific BMD as the dependent variable.

To determine whether physical activity trait associations with site-specific BMD were modified by metabolic and anthropometric parameters, multivariate analyses were next conducted using GEE. Within body sites with more than 1 variable significantly ($P < 0.05$) associated with BMD (and at least one being a physical activity trait), multiple regression analyses were conducted for BMD (dependent variable) only including traits that were significant in the univariate analyses as independent variables. When undergoing multivariate analysis for site-specific BMD, separate models were constructed for each statistically significant activity level domain (sedentary time, total physical activity, and moderate physical activity). To assess for collinearity within the multiple regression models, variance inflation factors (VIFs) were calculated. VIFs less than 5 are acceptable, whereas VIFs above 10 indicate poorly estimated regression coefficients because of collinearity.

Post hoc power calculations found that the sample size of 741 could detect (at 80% power and alpha of 0.05) low coefficients of association between activity traits and site-specific BMD, ranging from 0.002 to 0.003 for total physical activity, 0.01 to 0.02 for moderate physical activity, and 0.0003 to 0.0005 for sedentary time.

Results

Table 1 displays clinical characteristics of the cohort. Neither activity nor sedentary time was correlated with lumbar spine or thoracic spine BMD in univariate analysis (Table 2). Activity and sedentary time were associated with both pelvis and leg BMD, with sedentary time showing an inverse relationship to pelvis and leg BMD. Though activity was correlated with arm BMD, sedentary time did not show an association with arm BMD. In addition to sex and BMI, metabolic traits such as adiponectin, CRP, PAI-1, and insulin sensitivity were also significantly associated with site-specific BMD (Table 2).

In multivariate analyses of arm BMD (Table 3), only sex and adiponectin were significant, with sex exhibiting the strongest effect. In contrast to trends seen in univariate analysis, multivariate analysis found no statistically significant association of PA, mod-PA, CRP, or insulin sensitivity with arm BMD.

Multivariate analyses of pelvis BMD (Table 4) found independent associations with BMI, sex, adiponectin, PA, and mod-PA, and sedentary time. Standardized coefficients demonstrate relative strengths of these relationships to BMD. BMI showed the strongest relative correlation with pelvis BMD. There were no significant associations with CRP, PAI-1, or insulin sensitivity.

Age, sex, BMI, and mod-PA were independently associated with leg BMD (Table 5). Sex showed the strongest relative correlation with leg BMD. Unlike pelvis and arm BMD, adiponectin did not show a significant association with leg BMD. Similarly, there were no independent associations with CRP or PAI-1.

Discussion

In the present study, we demonstrated that physical activity level was associated with BMD at several sites, including arm, pelvis, and leg. Notably, there was no association of physical

Table 1. Clinical Characteristics of Study Cohort

Traits	Men (n = 319)	Women (n = 422)	*P* Value
Age (years)	34.0 (27.8-41.0)	34.0 (28.0-41.0)	0.78
BMI (kg/m^2)	28.7 (26.1-31.5)	28.3 (25.3-32.1)	0.67
Metabolic indices			
Adiponectin (μg/mL)	6.1 (4.6-7.9)	7.6 (5.4-10.0)	<0.0001
Insulin sensitivity (mg·m^{-2}·min^{-1}·μIU^{-1}·mL)	1.93 (1.17-1,93)	1.66 (1.11-2.34)	0.0084
CRP (mg/L)	1 (0.5-1.7)	1.9 (0.9-3.3)	<0.0001
PAI-1 (ng/mL)	33.1 (22.2-52.6)	30.9 (19.2-46.7)	0.07
BMD (g/cm^2)			
Total arm BMD	0.86 (0.82-0.89)	0.72 (0.70-0.75)	<0.0001
Total leg BMD	1.29 (1.22-1.35)	1.12 (1.06-1.18)	<0.0001
Pelvis BMD	1.28 (1.19-1.39)	1.24 (1.15-1.33)	<0.0001
Lumbar spine BMD	0.99 (0.92-1.07)	1.01 (0.93-1.09)	0.11
Thoracic spine BMD	0.90 (0.84-0.97)	0.87 (0.82-0.94)	0.0043
Physical activity (MET/hours/week)			
Total physical activity	207.1 (135.9-289.9)	155.3 (85.5-244.6)	<0.0001
Moderate physical activity	49.3 (12.9-217.1)	7.5 (2.4-29.3)	<0.0001
Sedentary time	117 (95.5-128.0)	116 (92.9-138.6)	0.24

Quantitative traits are presented as median (interquartile range).
Abbreviations: BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; MET, metabolic equivalent; PAI-1, plasminogen activator inhibitor-1.

activity level with lumbar spine BMD. This is in contrast to studies that found a positive correlation with exercise and lumbar spine BMD [6, 38, 39]. However, other data suggest that lumbar spine BMD is less responsive to exercise, including ground force activity, such as running or walking, and joint reactive activity, such as resistance or weight training, which may in part explain our findings [40].

Though several authors suggest a negative correlation between sedentary time and BMD, in the present study, sedentary time negatively and independently correlated only with pelvis BMD, and had a limited role in BMD at other sites [7, 8]. Our data demonstrated that only moderate intensity of physical activity level is associated with leg BMD, whereas sedentary time, total physical activity level, and moderate intensity of physical activity are correlated with pelvis BMD. Additionally, we found that sex and BMI played an important role in BMD and tended to modify the effects, of sedentary time on leg BMD. However, this is not surprising because the associations of BMD with BMI and sex are well described in the literature.

To our knowledge, this is one of the few studies to examine whether activity associations with BMD are modified by metabolic parameters. Several authors have demonstrated that adiponectin levels increase with exercise and activity levels [41, 42]. Some have even suggested a role for adiponectin in bone metabolism and osteoporosis, with studies reporting lower levels of adiponectin correlating with higher BMD [43, 44]. In our study, adiponectin also demonstrated an inverse association with arm and pelvis BMD but not leg BMD in multivariate models. Physical activity associations with arm BMD lost significance in multivariate models including adiponectin, raising a hypothesis for future study that adiponectin may modify physical activity associations with arm BMD but has an independent role in pelvis BMD.

In the current body of literature, improved insulin sensitivity and decreased inflammatory markers such as CRP have been associated with increased physical activity, independent of weight loss [16, 45, 46]. Studies have also demonstrated that increased insulin resistance is associated with lower BMD and strength indices [47, 48]. Similar, though somewhat conflicting, evidence regarding the association of exercise and PAI-1 exists in the literature [26, 49]. One recent study found that higher levels of PAI-1 were associated with

Table 2.   Univariate Associations of Activity and Metabolic Traits with Arm, Pelvis, Leg, and Spine BMD

Trait	Association with Arm Average BMD	Association with Pelvis BMD	Association with Leg Average BMD	Association with L-spine BMD	Association with T-spine BMD
Total PA	**0.20 (<0.0001)**	**0.10 (0.0048)**	**0.20 (<0.0001)**	0.005 (0.89)	-0.014 (0.67)
Moderate PA	**0.37 (<0.0001)**	**0.10 (0.0042)**	**0.33 (<0.0001)**	-0.021 (0.55)	0.04 (0.24)
Sedentary time	-0.056 (0.13)	**-0.083 (0.018)**	**-0.087 (0.009)**	-0.018 (0.60)	0.025 (0.43)
Age	-0.036 (0.37)	-0.039 (0.39)	**-0.080 (0.029)**	**-0.11 (0.026)**	0.091 (0.065)
BMI	0.049 (0.20)	**0.35 (<0.0001)**	**0.20 (<0.0001)**	0.054 (0.12)	**0.29 (<0.0001)**
Sex	**-0.78 (<0.0001)**	**-0.16 (<0.0001)**	**-0.65 (<0.0001)**	0.059 (0.11)	**-0.11 (0.0016)**
Adiponectin	**-0.22 (<0.0001)**	**-0.21 (<0.0001)**	**-0.18 (0.0002)**	0.027 (0.53)	**-0.10 (0.019)**
CRP	**-0.22 (<0.0001)**	**0.14 (0.002)**	**-0.12 (0.0028)**	0.060 (0.17)	**0.13 (0.0023)**
PAI-1	0.059 (0.15)	**0.16 (0.0007)**	**0.14 (0.0016)**	0.003 (0.95)	**0.15 (0.0031)**
Insulin sensitivity	**0.14 (0.0008)**	**-0.19 (<0.0001)**	0.042 (0.30)	0.023 (0.53)	**-0.15 (<0.0001)**

Data are standardized coefficients (P value), with significant associations in bold.

Abbreviations: BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; MET, metabolic equivalent; PAI-1, plasminogen activator inhibitor-1.

Table 3.   Multivariate Analysis of Arm BMD

Model/Traits	Standardized Coefficient (β)	Standard Error	95% Confidence Interval		P Value
Model 1 ($R^2 = 0.60$)					
Total PA	0.023	0.030	-0.035	0.081	0.43
Sex (M-F mean difference)	**-0.73**	**0.027**	**-0.78**	**-0.68**	**<0.0001**
Adiponectin	**-0.076**	**0.029**	**-0.13**	**-0.019**	**0.0091**
CRP	-0.0091	0.031	-0.070	0.052	0.77
Insulin sensitivity	0.054	0.030	-0.0050	0.11	0.073
Model 2 ($R^2 = 0.61$)					
Moderate PA	0.051	0.031	-0.0099	0.11	0.10
Sex (M-F mean difference)	**-0.71**	**0.029**	**-0.77**	**-0.66**	**<0.0001**
Adiponectin	**-0.074**	**0.029**	**-0.13**	**-0.017**	**0.011**
CRP	-0.0079	0.031	-0.069	0.053	0.80
Insulin sensitivity	0.048	0.031	-0.012	0.11	0.12

For each activity trait, results for all independent variables included in the multivariate model are displayed. Significant predictors are in bold. Overall R^2 for each model is provided. Variance inflation factors ranged from 1.1 to 1.2 for model 1 and from 1.2 to 1.4 for model 2.
Abbreviations: BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; F, female; M, male; PA, physical activity.

Table 4.   Multivariate Analysis of pelvis BMD

Model/Traits	Standardized Coefficient (β)	Standard Error	95% Confidence Interval		P Value
Model 1 ($R^2 = 0.20$)					
Total PA	**0.11**	**0.041**	**0.025**	**0.19**	**0.01**
BMI	**0.33**	**0.053**	**0.22**	**0.43**	**<0.0001**
Sex (M-F mean difference)	**-0.18**	**0.046**	**-0.27**	**-0.088**	**0.0001**
Adiponectin	**-0.010**	**0.040**	**-0.18**	**-0.021**	**0.013**
PAI-1	-0.015	0.048	-0.11	0.078	0.75
CRP	0.033	0.054	-0.072	0.14	0.54
Insulin sensitivity	-0.025	0.049	-0.12	0.071	0.61
Model 2 ($R^2 = 0.20$)					
Moderate PA	**0.11**	**0.046**	**0.022**	**0.20**	**0.014**
BMI	**0.34**	**0.053**	**0.23**	**0.44**	**<0.0001**
Sex (M-F mean difference)	**-0.15**	**0.051**	**-0.25**	**-0.051**	**0.0032**
Adiponectin	**-0.088**	**0.040**	**-0.17**	**-0.0092**	**0.029**
PAI-1	-0.023	0.048	-0.12	0.072	0.63
CRP	0.030	0.054	-0.076	0.14	0.58
Insulin sensitivity	-0.037	0.049	-0.13	0.060	0.46
Model 3 ($R^2 = 0.20$)					
Sedentary time	**-0.088**	**0.042**	**-0.17**	**-0.0068**	**0.034**
BMI	**0.33**	**0.053**	**0.23**	**0.43**	**<0.0001**
Sex (M-F mean difference)	**-0.19**	**0.047**	**-0.28**	**-0.10**	**<0.0001**
Adiponectin	**-0.10**	**0.040**	**-0.18**	**-0.022**	**0.012**
PAI-1	-0.015	0.048	-0.11	0.078	0.75
CRP	0.028	0.054	-0.077	0.13	0.60
Insulin sensitivity	-0.021	0.049	-0.12	0.076	0.68

For each activity trait, results for all independent variables included in the multivariate model are displayed. Significant predictors are in bold. Overall R^2 for each model is provided. Variance inflation factors ranged from 1.1 to 1.6 for model, from 1.2 to 1.6 for model 2, and from 1.0 to 1.6 for model 3.
Abbreviations: BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; F, female; M, male; PA, physical activity; PAI-1, plasminogen activator inhibitor-1.

improved bone density in postmenopausal diabetic patients [50]. Though our univariate analysis suggested a role for insulin sensitivity, CRP, and PAI-1 in site-specific BMD, none of these metabolic parameters were found to be independently associated with site-specific

Table 5.   Multivariate Analysis of Leg Average BMD

Model/Traits	Standardized Coefficient (β)	Standard Error	95% Confidence Interval		P Value
Model 1 (R^2 = 0.52)					
Total PA	0.049	0.033	-0.016	0.11	0.14
Age	**-0.11**	**0.040**	**-0.18**	**-0.026**	**0.0091**
BMI	**0.22**	**0.042**	**0.14**	**0.31**	**<0.0001**
Sex (M-F mean difference)	**-0.67**	**0.039**	**-0.74**	**-0.59**	**<0.0001**
Adiponectin	0.0041	0.026	-0.047	0.056	0.88
PAI-1	0.015	0.034	-0.052	0.083	0.66
CRP	-0.012	0.044	-0.099	0.074	0.78
Model 2 (R^2 = 0.52)					
Moderate PA	**0.10**	**0.035**	**0.037**	**0.17**	**0.0024**
Age	**-0.10**	**0.040**	**-0.18**	**-0.027**	**0.0087**
BMI	**0.24**	**0.041**	**0.16**	**0.32**	**<0.0001**
Sex (M-F mean difference)	**-0.63**	**0.041**	**-0.71**	**-0.55**	**<0.0001**
Adiponectin	0.0059	0.027	-0.047	0.059	0.83
PAI-1	0.0082	0.035	-0.061	0.077	0.82
CRP	-0.012	0.044	-0.098	0.073	0.78
Model 3 (R^2 = 0.51)					
Sedentary time	-0.027	0.034	-0.093	0.039	0.42
Age	**-0.11**	**0.041**	**-0.19**	**-0.027**	**0.0086**
BMI	**0.26**	**0.042**	**0.14**	**0.31**	**<0.0001**
Sex (M-F mean difference)	**-0.67**	**0.040**	**-0.75**	**-0.59**	**<0.0001**
Adiponectin	0.0055	0.026	-0.046	0.057	0.83
PAI-1	0.015	0.035	-0.053	0.083	0.67
CRP	-0.015	0.044	-0.10	0.071	0.74

For each activity trait, results for all independent variables included in the multivariate model are displayed. Significant predictors are in bold. Overall R^2 for each model is provided. Variance inflation factors ranged from 1.1 to 1.5 for model 1, from 1.1 to 1.5 for model 2, and from 1.0 to 1.5 for model 3.
Abbreviations: BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; F, female; M, male; PA, physical activity; PAI-1, plasminogen activator inhibitor-1.

BMD in multivariate analysis. The univariate associations between insulin sensitivity and arm and pelvis BMD may be explained by the correlation between insulin sensitivity and physical activity [51, 52]. With the notable exception of adiponectin, overall, these findings suggest a modest role for metabolic traits in modulating the effects of physical activity on BMD.

Though these results are thought provoking, our findings should be considered carefully. Our study was limited to a cross-sectional design. We can identify associations but cannot demonstrate causality. Because the cohort consisted of relatively sedentary Mexican-Americans, our results may not be generalizable to a more physically active population or other ethnic groups. It is possible that a more active population would have different baseline metabolic traits and relatively different associations with sedentary behaviors and physical activity. Additionally, DXA imaging was primarily used to assess body fat mass distribution, and not BMD; therefore, we used regional BMD. For this reason, DXA did not directly assess femoral BMD, which is an important site for osteoporosis-related fractures and an important therapeutic target. Physical activity data relied on a self-reported questionnaire by study participants and may not have reflected actual physical activity participation. In some cases, there may been overestimations and underestimations of physical activity and sedentary behaviors, respectively. The Morgenstern physical activity questionnaire was selected because it captures multiple aspects of physical activity. To our knowledge, it has not been validated against other physical activity questionnaires in current use, such as the International Physical Activity Questionnaire. Another limitation is that our analyses were limited to biomarkers that were previously measured in the cohort.

In conclusion, physical activity plays an important role in BMD. Although adiponectin appears to modulate these effects in the arm and was an independent correlate of BMI in the pelvis, the other metabolic characteristics studied herein appear to play a limited role. Our findings suggest that BMD increases with the physical activity in the arms, legs, and pelvis and is inversely related to sedentary time in the pelvis and legs. We demonstrated that these associations may be modified by age, sex (female sex being a strong negative predictor of BMD), BMI, and adiponectin, depending on the site, with physical activity being more important to pelvis and leg BMD than arm BMD and sedentary time important for pelvis BMD. This study is one of the first to demonstrate the limited effects of sedentary time on BMD and that metabolic traits such as CRP, PAI-1, and insulin sensitivity play a minor role on BMD. Additional studies using objective measures of physical activity and DXA scans performed specifically for BMD are warranted to further explore these findings.

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Additional Information

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Disclosures Summary. The authors have no disclosures.

Data Availability: Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

References and Notes

1. Duncan CS, Blimkie CJ, Cowell CT, Burke ST, Briody JN, Howman-Giles R. Bone mineral density in adolescent female athletes: relationship to exercise type and muscle strength. *Med Sci Sports Exerc.* 2002;**34**(2):286-294.
2. Howe TE, Shea B, Dawson LJ, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev* 2011(7):CD000333.
3. Martyn-St James M, Carroll S. High-intensity resistance training and postmenopausal bone loss: a meta-analysis. *Osteoporos Int.* 2006;**17**(8):1225-1240.
4. Waltman NL, Twiss JJ, Ott CD, et al. The effect of weight training on bone mineral density and bone turnover in postmenopausal breast cancer survivors with bone loss: a 24-month randomized controlled trial. *Osteoporos Int.* 2010;**21**(8):1361-1369.
5. Wallace BA, Cumming RG. Systematic review of randomized trials of the effect of exercise on bone mass in pre- and postmenopausal women. *Calcif Tissue Int.* 2000;**67**(1):10-18.
6. Braun SI, Kim Y, Jetton AE, Kang M, Morgan DW. Prediction of bone mineral density and content from measures of physical activity and sedentary behavior in younger and older females. *Prev Med Rep.* 2015;**2**:300-305.
7. Chastin SF, Mandrichenko O, Helbostadt JL, Skelton DA. Associations between objectively-measured sedentary behaviour and physical activity with bone mineral density in adults and older adults, the NHANES study. *Bone.* 2014;**64**:254-262.
8. Chastin SF, Mandrichenko O, Skelton DA. The frequency of osteogenic activities and the pattern of intermittence between periods of physical activity and sedentary behaviour affects bone mineral content: the cross-sectional NHANES study. *BMC Public Health.* 2014;**14**:4.
9. Matthews BL, Bennell KL, McKay HA, et al. Dancing for bone health: a 3-year longitudinal study of bone mineral accrual across puberty in female non-elite dancers and controls. *Osteoporos Int.* 2006;**17**(7):1043-1054.

10. Andreoli A, Monteleone M, Van Loan M, Promenzio L, Tarantino U, De Lorenzo A. Effects of different sports on bone density and muscle mass in highly trained athletes. *Med Sci Sports Exerc.* 2001;**33**(4):507-511.

11. Ribeiro-Dos-Santos MR, Lynch KR, Agostinete RR, et al. Prolonged practice of swimming is negatively related to bone mineral density gains in adolescents. *J Bone Metab.* 2016;**23**(3):149-155.

12. Agostinete RR, Lynch KR, Gobbo LA, et al. Basketball affects bone mineral density accrual in boys more than swimming and other impact sports: 9-mo follow-up. *J Clin Densitom.* 2016;**19**(3):375-381.

13. Shah K, Armamento-Villareal R, Parimi N, et al. Exercise training in obese older adults prevents increase in bone turnover and attenuates decrease in hip bone mineral density induced by weight loss despite decline in bone-active hormones. *J Bone Miner Res.* 2011;**26**(12):2851-2859.

14. Armamento-Villareal R, Aguirre L, Napoli N, et al. Changes in thigh muscle volume predict bone mineral density response to lifestyle therapy in frail, obese older adults. *Osteoporos Int.* 2014;**25**(2):551-558.

15. Marques EA, Wanderley F, Machado L, et al. Effects of resistance and aerobic exercise on physical function, bone mineral density, OPG and RANKL in older women. *Exp Gerontol.* 2011;**46**(7):524-532.

16. Vasconcellos F, Seabra A, Cunha F, et al. Health markers in obese adolescents improved by a 12-week recreational soccer program: a randomised controlled trial. *J Sports Sci.* 2016;**34**(6):564-575.

17. Ramel A, Geirsdottir OG, Jonsson PV, Thorsdottiri I. C-reactive protein and resistance exercise in community dwelling old adults. *J Nutr Health Aging.* 2015;**19**(7):792-796.

18. Duggan C, Xiao L, Wang CY, McTiernan A. Effect of a 12-month exercise intervention on serum biomarkers of angiogenesis in postmenopausal women: a randomized controlled trial. *Cancer Epidemiol Biomarkers Prev.* 2014;**23**(4):648-657.

19. Racil G, Ben Ounis O, Hammouda O, et al. Effects of high vs. moderate exercise intensity during interval training on lipids and adiponectin levels in obese young females. *Eur J Appl Physiol.* 2013;**113**(10):2531-2540.

20. Falconer CL, Cooper AR, Walhin JP, et al. Sedentary time and markers of inflammation in people with newly diagnosed type 2 diabetes. *Nutr Metab Cardiovasc Dis.* 2014;**24**(9):956-962.

21. Martins RA, Neves AP, Coelho-Silva MJ, Veríssimo MT, Teixeira AM. The effect of aerobic versus strength-based training on high-sensitivity C-reactive protein in older adults. *Eur J Appl Physiol.* 2010;**110**(1):161-169.

22. Ahmadizad S, Ghorbani S, Ghasemikaram M, Bahmanzadeh M. Effects of short-term nonperiodized, linear periodized and daily undulating periodized resistance training on plasma adiponectin, leptin and insulin resistance. *Clin Biochem.* 2014;**47**(6):417-422.

23. Ahmadizad S, Haghighi AH, Hamedinia MR. Effects of resistance versus endurance training on serum adiponectin and insulin resistance index. *Eur J Endocrinol.* 2007;**157**(5):625-631.

24. Araiza P, Hewes H, Gashetewa C, Vella CA, Burge MR. Efficacy of a pedometer-based physical activity program on parameters of diabetes control in type 2 diabetes mellitus. *Metabolism.* 2006;**55**(10):1382-1387.

25. Papp ME, Lindfors P, Nygren-Bonnier M, Gullstrand L, Wändell PE. effects of high-intensity hatha yoga on cardiovascular fitness, adipocytokines, and apolipoproteins in healthy students: a randomized controlled study. *J Altern Complement Med.* 2016;**22**(1):81-87.

26. Boyle LJ, Nagelkirk PR. The effects of whole body vibration and exercise on fibrinolysis in men. *Eur J Appl Physiol.* 2010;**110**(5):1057-1061.

27. Goodarzi MO, Taylor KD, Guo X, et al. Variation in the gene for muscle-specific AMP deaminase is associated with insulin clearance, a highly heritable trait. *Diabetes.* 2005;**54**(4):1222-1227.

28. Goodarzi MO, Guo X, Taylor KD, et al. Lipoprotein lipase is a gene for insulin resistance in Mexican Americans. *Diabetes.* 2004;**53**(1):214-220.

29. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol.* 1979;**237**(3):E214-E223.

30. Bazzocchi A, Ponti F, Albisinni U, Battista G, Guglielmi G. DXA: technical aspects and application. *Eur J Radiol.* 2016;**85**(8):1481-1492.

31. Franck H, Munz M. Total body and regional bone mineral densitometry (BMD) and soft tissue measurements: correlations of BMD parameter to lumbar spine and hip. *Calcif Tissue Int.* 2000;**67**(2):111-115.

32. Hammami M, Koo MW, Koo WW, Thomas RT, Rakhman D. Regional bone mass measurement from whole-body dual energy X-ray absorptiometry scan. *J Clin Densitom.* 2001;**4**(2):131-136.

33. Hangartner TN, Skugor M, Landoll JD, Matkovic V. Comparison of absorptiometric evaluations from total-body and local-regional skeletal scans. *J Clin Densitom.* 2000;**3**(3):215-225.

34. Melton LJ 3rd, Looker AC, Shepherd JA, et al. Osteoporosis assessment by whole body region vs. site-specific DXA. *Osteoporos Int.* 2005;**16**(12):1558-1564.

35. Rubenstein JH, Morgenstern H, Kellenberg J, et al. Validation of a new physical activity questionnaire for a sedentary population. *Dig Dis Sci.* 2011;**56**(9):2678-2687.

36. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc.* 1993;**25**(1):71-80.

37. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics.* 1986;**42**(1):121-130.

38. Maddalozzo GF, Widrick JJ, Cardinal BJ, Winters-Stone KM, Hoffman MA, Snow CM. The effects of hormone replacement therapy and resistance training on spine bone mineral density in early postmenopausal women. *Bone.* 2007;**40**(5):1244-1251.

39. Glenn JM, Gray M, Vincenzo JL. Differences in regional adiposity, bone mineral density, and physical exercise participation based on exercise self-efficacy among senior adults. *J Sports Med Phys Fitness.* 2015;**55**(10):1166-1173.

40. Kelley GA, Kelley KS, Kohrt WM. Effects of ground and joint reaction force exercise on lumbar spine and femoral neck bone mineral density in postmenopausal women: a meta-analysis of randomized controlled trials. *BMC Musculoskelet Disord.* 2012;**13**:177.

41. Wang X, You T, Murphy K, Lyles MF, Nicklas BJ. Addition of exercise increases plasma adiponectin and release from adipose tissue. *Med Sci Sports Exerc.* 2015;**47**(11):2450-2455.

42. Belalcazar LM, Lang W, Haffner SM, et al.; Look AHEAD (Action for Health in Diabetes) Research Group. Improving adiponectin levels in individuals with diabetes and obesity: insights from look AHEAD. *Diabetes Care.* 2015;**38**(8):1544-1550.

43. Al-Osami MH, Hameed EK. Serum adiponectin level in osteoporotic postmenopausal women with type 2 diabetes mellitus. *Diabetes Metab Syndr.* 2018;**12**(6):939-942.

44. Fuggle NR, Westbury LD, Syddall HE, et al. Relationships between markers of inflammation and bone density: findings from the Hertfordshire Cohort Study. *Osteoporos Int.* 2018;**29**(7):1581-1589.

45. Hawkins M, Braun B, Marcus BH, Stanek E 3rd, Markenson G, Chasan-Taber L. The impact of an exercise intervention on C-reactive protein during pregnancy: a randomized controlled trial. *BMC Pregnancy Childbirth.* 2015;**15**:139.

46. Balducci S, Zanuso S, Nicolucci A, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutr Metab Cardiovasc Dis.* 2010;**20**(8):608-617.

47. Yang J, Hong N, Shim JS, Rhee Y, Kim HC. Association of insulin resistance with lower bone volume and strength index of the proximal femur in nondiabetic postmenopausal women. *J Bone Metab.* 2018;**25**(2):123-132.

48. Kalimeri M, Leek F, Wang NX, et al. Association of insulin resistance with bone strength and bone turnover in menopausal Chinese-Singaporean women without diabetes. *Int J Environ Res Public Health.* 2018;**15**(5):889.

49. Rokling-Andersen MH, Reseland JE, Veierød MB, et al. Effects of long-term exercise and diet intervention on plasma adipokine concentrations. *Am J Clin Nutr.* 2007;**86**(5):1293-1301.

50. Canecki-Varžić S, Prpić-Križevac I, Bilić-Ćurčić I. Plasminogen activator inhibitor-1 concentrations and bone mineral density in postmenopausal women with type 2 diabetes mellitus. *BMC Endocr Disord.* 2016;**16**:14.

51. Temple KA, Tjaden AH, Atkinson KM, et al.; RISE Consortium. Association of habitual daily physical activity with glucose tolerance and β-cell function in adults with impaired glucose tolerance or recently diagnosed type 2 diabetes from the restoring insulin secretion (RISE) study. *Diabetes Care.* 2019;**42**(8):1521-1529.

52. Dauriz M, Bacchi E, Boselli L, et al. Association of free-living physical activity measures with metabolic phenotypes in type 2 diabetes at the time of diagnosis. The Verona Newly Diagnosed Type 2 Diabetes Study (VNDS). *Nutr Metab Cardiovasc Dis.* 2018;**28**(4):343-351.