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Research Article

Circulating Dkk1 and TRAIL Are Associated With Cognitive Decline in Community-Dwelling, Older Adults With Cognitive Concerns

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Abstract

Background: Osteoporosis and Alzheimer's disease are common diseases of aging that would seem to be unrelated, but may be linked through the influence of bone-derived signals on brain function. The aim of the current study is to investigate the relationship between circulating levels of bone-related biomarkers and cognition.

Methods: The population included 103 community-dwelling older individuals with memory concerns but without cognitive impairment. A global cognition summary measure was collected at baseline and 6, 12, and 18 months post-enrollment by converting raw scores from 19 cognitive function tests to *z*-scores and averaging. Baseline plasma concentrations of bone-related biomarkers, including undercarboxylated, carboxylated, and total osteocalcin, parathyroid hormone, C-terminal telopeptide of collagen 1 (CTX-1), procollagen type 1 amino-terminal propeptide, osteoprotegrin, osteopontin, Dickkopf WNT signaling pathway inhibitor 1 (Dkk1), sclerostin, and amyloid β peptides ($A\beta_{40}$ and $A\beta_{42}$), were measured.

Results: Using sex, age, and education-adjusted mixed-effects models, we found that baseline levels of TNF-related apoptosis-inducing ligand (TRAIL; $p < .001$), Dkk1 ($p = .014$), and CTX-1 ($p = .046$) were related to the annual rate of change of global cognition over the 18 month follow-up. In cognitive domain-specific analysis, baseline TRAIL was found to be positively related to the annual rate of change in episodic ($p < .001$) and working memory ($p = .016$), and baseline Dkk1 was positively related to semantic memory ($p = .027$) and negatively related to working memory ($p = .016$).

Conclusions: These results further confirm the link between bone and brain health and suggest that circulating levels of bone-related biomarkers may have diagnostic potential to predict worsening cognition.

Keywords: Osteoporosis, Cognitive decline, Biomarkers, Dkk1, TRAIL.

Osteoporosis and Alzheimer's disease (AD) are common, chronic diseases of aging resulting in significant morbidity and mortality. Although it would seem that the two diseases are unrelated but co-occurring, several epidemiological studies have demonstrated an association between low bone mineral density (BMD) and cognitive decline (1–4) with AD patients having lower BMD than age-matched controls (4). Furthermore, patients with the lowest BMD have a twofold increased risk of developing AD (5) and two large prospective studies have reported increased odds of AD development in patients with deteriorating BMD (6, 7).

The factors linking osteoporosis and AD remain unclear, although the strong associations between active bone loss and AD progression (6, 7) point to bone remodeling. Indeed, patients with AD have elevated circulating biomarkers of bone remodeling (8).

Bone remodeling is a dynamic process controlled by proteins, such as parathyroid hormone (PTH), osteoprotegrin (OPG), Dickkopf WNT signaling pathway inhibitor 1 (Dkk1), and sclerostin that release factors into the circulation such as C-terminal telopeptides of type I collagen (CTX-1) and osteocalcin.

Bone is now recognized to be an endocrine organ (9), with osteocalcin, in particular, controlling both glucose and testosterone metabolism (10). Osteocalcin also has been reported to cross the blood-brain barrier and exert direct control of neurological function by improving anxiety, depression, and memory in mouse models of AD (11). More recently, a cross-sectional study of participants with obesity found that lower serum osteocalcin was associated with worse cognitive function and alterations to the brain microarchitecture (12). Taken together, these findings suggest that bone-related proteins affect brain function and may be implicated in AD development.

The current study was designed to investigate the relationship between circulating bone-related peptides and cognition in a patient population with self-reported memory concerns, which has been related to the development of dementia due to AD development and AD pathology (13–15). Both cross-sectional and longitudinal approaches were taken to determine whether baseline biomarker levels were correlated with baseline cognitive scores and the annual rate of change in cognition over the 18 month observation period.

Methods

Patient Demographics

Between March 2008 and September 2009, participants enrolled in a 6 month, single site, randomized, double-blind clinical trial of a medical food on inflammatory blood markers in older, community-dwelling persons with memory complaints receiving a standard daily multivitamin (NCT 00597376) with an open-label 12 month extension phase in addition to a data and specimen repository approved by the Rush University Medical Center Institutional Review Board (16). All individuals provided written consent. Participants were eligible based on positive responses to questions regarding memory complaints, including "Do you think you have memory problems?" and "Has there been a decline in your memory over the last 10 years?" Exclusion criteria included confirmed clinical diagnosis of stroke, Parkinson's disease, mild cognitive impairment (MCI), vascular dementia, or AD; history of renal stones or peptic ulcer disease; current use of an approved AD drug; current use of a daily vitamin containing more than 400 mcg of folic acid within past 2 months; vitamin B_{12} injection within past 6 months; use of an investigational agent within 1 month of screening; or medical history, physical exam, or blood work findings requiring evaluation. A standardized Mini–Mental State Exam (MMSE) was performed at baseline and all patients were evaluated for dementia using previously published methods (17).

Cognition Scores

A global cognition summary measure, defined as the global cognition score, was used as the primary outcome to variable. Briefly, global cognition was constructed by converting raw scores of 19 individual tests to *z*-scores, using the baseline mean and standard deviation, and averaging the *z*-scores to yield the composition global cognitive score. Based in part on a factor analysis of the individual tests at baseline, we also constructed composition measures of five specific cognitive domains. The 19 tests included tests for episodic memory (Word List Memory, Recall, and Recognition, immediate and delayed recall of the East Boston Story, Story A from Logical Memory), working memory (Digit Span Forward, Digit Span Backward, Digit Ordering), semantic memory (a 20-item version of the Boston Naming Test, Verbal Fluency, a 15-item form of Extended Range Vocabulary, a 20-item form of the National Adult Reading Test), perceptual orientation (a 15-item form of Judgment of Line Orientation, and a 17-item form of Standard Progressive Matrices), and perceptual speed (Symbol Digit Modalities Test, Number Comparison) (18, 19). Further information on the individual tests and the global and specific composition scores is published elsewhere (20). Global cognition was assessed at baseline, 6, 12, and 18 months after enrollment.

Biomarker Analysis

Non-fasting blood was collected at baseline, processed to obtain plasma, and stored at −80°C until analyses. Enzyme-linked immunosorbent assays (ELISA) were used to measure $A\beta_{42}$ (Wako Chemicals USA, Inc.) and $A\beta_{40}$ (Invitrogen Corporation), undercarboxylated (Glu-OC, Takara) and carboxylated osteocalcin (Gla-OC, Takara), and soluble receptor activator of nuclear factor κ-B ligand (RANKL, Immundiagnostik AG). DKK1, OPG, osteopontin (OPN), sclerostin (SOST), interleukin 1 beta (IL-1β), PTH, and TNF-related apoptosis-inducing ligand (TRAIL) were assayed using a multiplex assay (EMD Millipore). CTX-1 or crosslaps, procollagen type 1 amino-terminal propeptide (PINP), and total osteocalcin were measured using an electrochemiluminescence immunoassay measured on the Cobas e411 Elecsys (Roche Diagnostics Corporation).

Statistical Analysis

To characterize the cohort, the means and standard deviations were determined for demographic variables (age and education). The majority of the biomarkers were non-normally distributed; distributions were more symmetric after log transformation. The parent study found no effects of Cerefolin treatment on global cognition (16); therefore, there were no treatment terms and both treatment groups were included in all models. Pairwise Pearson correlations were obtained to assess the associations of biomarker concentration with global cognition and demographics. Mixed-effects regression models were constructed to examine the relationship of baseline biomarker levels to the annual rate of change in global cognition over the 18 month follow-up period with terms to control for the effects of age, sex, and the level of education on baseline level and on rate of change. Similar mixed-effects models were constructed for each cognitive domain specifically (episodic memory, working memory, semantic memory, perceptual orientation, and perceptual speed). The effects of repeated cognitive testing were assessed using a separate mixed-effects model that adjusted for the number of visits. Lastly, a sensitivity analysis was conducted by repeating the mixed effects model after excluding all participants that developed clinical dementia concerns over the follow-up period. Results from the mixed-effects models are presented as the annual rate of change of cognition. All statistical analyses were programmed in SAS, version 9.3 (SAS Institute, Inc.).

Results

A total of 103 participants (88 females and 15 males) were recruited, with a mean age of 80.3 years (*SD* = 7.7), 15 years of education (*SD* = 3), and a mean MMSE score of 28.3 (*SD* = 1.7). Of these

103 participants, 93 were followed longitudinally, with at least two measurements made over an 18 month period. The patients followed longitudinally included 79 females and 14 males, with a mean age of 80.2 (*SD* = 7.8) and 15 years of education (*SD* = 3). Nine of the 93 patients developed likely dementia over the course of 18 month follow-up period. The overall average change in global cognition was 0.17, indicating a general cohort improvement in cognitive function over 18 months. Baseline and 18 month *z*-scores for each of the cognitive function tests are presented in Supplementary Table 1.

Table 1 shows the geometric means and standard deviations for each of the tested biomarkers. Biomarker associations with sex and age were assessed with pairwise correlations. Biomarkers were not significantly associated with sex. $A\beta_{40}$ (ρ = .216, p = .029), OPG (ρ = .497, p < .001), OPG/TRAIL (ρ = .337, p = .001), and OPG/RANKL (ρ = .359, p = .002) levels were significantly correlated with age, whereas $A\beta_{42}$ and sclerostin concentrations were not correlated with age.

Correlations of the *z*-score of global cognition at baseline as a function of log-transformed biomarker levels were significant for the $A\beta_{40}$ and $A\beta_{42}$ concentrations (Supplementary Table 2). Several bone-related biomarkers also were significantly correlated with cognition, including sclerostin and OPG, as were the ratios of OPG to TRAIL and RANKL. The other baseline bone-derived biomarkers were not significantly associated with cognition. As global cognition is also influenced by demographics, we developed mixed-effects models that adjusted for age, sex, and education. In these adjusted models, none of the biomarkers were found to be significantly associated with baseline cognition (Table 2), nor were there any significant biomarker-demographic interactions (data not shown).

Mixed-effects models adjusted for age, sex, and education assessed the relationship between baseline biomarker concentrations and the annual rate of change in cognition over the 18 month observational period (Table 2). Baseline Dkk1 was negatively related to the annual rate of change in cognition (p = .014) with a parameter estimate of –0.168, signifying that every increase in one log unit of Dkk1 is related to a 0.168 annual decrease in *z*-score. Baseline CTX-1 was negatively related to the annual rate of cognition change (p = .046). Baseline TRAIL was positively related to the rate of cognition change (p < .001), whereas the OPG/TRAIL ratio was negatively related (p = .003).

Additional mixed-effects models were run to test the effects of the number of visits on the relationships between baseline biomarkers and rate of cognitive change (Supplementary Table 3). Although adjusting for the number of visits reduced the parameter estimate, the relationship between cognitive change and TRAIL, OPG/TRAIL, Dkk1, and CTX-1 remained significant.

A total of nine patients met criteria for dementia over the course of the follow-up period. To test the sensitivity of our findings to clinical dementia, mixed-effects models were run excluding these patients (new sample size of 84). After removing patients with dementia, the relationships between baseline biomarker levels and rate of cognition change remained significant for TRAIL (p = .002) and the OPG/TRAIL ratio (p = .019), but the relationship with baseline Dkk1 (p = .197) and CTX-1 (p = .087) was no longer significant (Supplementary Table 4). Baseline PTH (p = .047) and RANKL (p = .002) were significantly related to the rate of cognition change in the patient population excluding those with dementia concerns.

Cognitive domain-specific analyses were performed for the biomarkers with significant relationships with global cognition, TRAIL, OPG/TRAIL ratio, Dkk1, and CTX-1 (Table 3). Baseline TRAIL was positively related to the annual rate of change in both episodic (p < .001) and working memory (p = .016). The OPG/TRAIL ratio was negatively related to the annual rate of change in episodic memory (p = .002), but not significantly related to working memory. Baseline Dkk1 was positivity related to the annual rate of change in semantic memory (p = .027) and negatively related to the change in working memory (p = .023). Despite the significant relationship between baseline CTX-1 and global cognitive change, there were no significant relationships between CTX-1 and the change in any of the cognitive domains. There was also a significant negative relationship between baseline Aβ42 and the annual rate of change in episodic memory (p = .034), a negative relationship between baseline undercarboxylated osteocalcin and the annual rate of change in semantic memory (p = .043), and a negative relationship between total osteocalcin and the annual rate of change in working memory (p = .046, Supplementary Table 5).

Table 1. Descriptive Biomarker Statistics

Biomarker	Geometric means (*SD*)†
$A\beta_{40}$, pmol/L	72.20 (2.06)
$A\beta_{42}$, pmol/L	2.21 (1.66)
Sclerostin, pg/mL	4,433.75 (1.53)
OPG, pg/mL	734.38 (1.72)
OPG/TRAIL ratio	10.43 (2.30)
OPG/RANKL ratio	0.02 (5.61)
DKK1, pg/mL	2,518.08 (1.42)
TRAIL, pg/mL	69.97 (1.90)
RANKL, pg/mL	41,340.17 (4.91)
CTX-1, ng/mL	0.23 (1.66)
PINP, ng/mL	48.10 (1.61)
Total osteocalcin, ng/mL	18.62 (1.44)
Undercarboxylated osteocalcin, ng/mL	7.32 (2.35)
Carboxlyated osteocalcin, ng/mL	8.41 (2.14)
Osteopontin, pg/mL	8,439.77 (2.11)
PTH, pg/mL	99.62 (2.19)

Note: †Geometric means and standard deviations are computed as the exponential of the means and SDs of logarithmically transformed values.

Discussion

Emerging evidence has linked osteoporosis and AD. The current study investigated circulating bone-related biomarkers in elderly individuals with memory concerns but without clinically diagnosed asymptomatic AD. There is growing interest in possible common disease mechanisms associated with osteoporosis and AD. Demographic studies have consistently identified a relationship between lower BMD and poorer cognition (1–7). Although several studies have investigated the association between circulating bone-related biomarkers and cognition, the analyses have been cross-sectional. Our goal was to determine whether circulating bone-related biomarker levels are related to a short-term change in global cognition. After evaluating 14 bone-related biomarkers, we determined that the baseline levels of TRAIL, the OPG/TRAIL ratio, Dkk1, and CTX-1 were significantly related to the annual rate of change in global cognition. The relationship between OPG/TRAIL and cognitive decline was largely driven by TRAIL, whereas CTX-1 was not found to be related to any of the cognitive domain-specific analyses. Of the biomarkers evaluated, TRAIL and Dkk1 demonstrated the most potential to predict cognitive decline.

Table 2. Association of Baseline Biomarker Concentration With 18 Month Change in Global Cognition in All 93 Patients Evaluated

	Biomarker (baseline cognition)		Biomarker × Time (annual rate of change of cognition)	
Biomarker	Parameter estimate† (*SE*)	*p*-Value	Parameter estimate† (*SE*)	*p*-Value
TRAIL	0.082 (0.152)	.589	0.114 (0.030)	**<.001**
OPG/TRAIL	−0.146 (0.126)	.247	−0.074 (0.024)	**.003**
Dkk1	−0.248 (0.280)	.376	−0.168 (0.068)	**.014**
CTX-1	0.074 (0.188)	.693	−0.078 (0.038)	**.046**
PINP	−0.208 (0.202)	.307	−0.070 (0.042)	.096
PTH	−0.002 (0.016)	.855	0.040 (0.028)	.159
Total osteocalcin	−0.202 (0.264)	.443	−0.068 (0.052)	.194
Osteopontin	0.072 (0.134)	.596	−0.028 (0.030)	.350
Sclerostin	−0.316 (0.238)	.190	0.022 (0.050)	.658
$A\beta_{40}$	−0.076 (0.134)	.576	−0.012 (0.030)	.712
Undercarboxylated osteocalcin	0.124 (0.114)	.283	0.008 (0.024)	.742
OPG/RANKL	−0.052 (0.072)	.472	0.004 (0.016)	.827
RANKL	0.028 (0.076)	.712	−0.002 (0.016)	.855
Carboxlyated osteocalcin	−0.224 (0.128)	.082	−0.002 (0.026)	.912
OPG	−0.256 (0.212)	.232	−0.004 (0.044)	.926
$A\beta_{42}$	−0.196 (0.184)	.286	−0.000 (0.040)	.980

Note: †The effect of a log unit change in biomarker concentration on annual rate of change in cognition from mixed-effects model adjusted for age, sex, and education. Significant associations are bolded for clarity.

Table 3. Association of Baseline Concentrations ofTRAIL, OPG/TRAIL, Dkk1, and CTX-1 With 18 Month Change in Domain-Specific Cognition

	Biomarker (baseline cognition)		Biomarker × Time (annual rate of change of cognition)	
Biomarker	Parameter estimate† (*SE*)	*p*-Value	Parameter estimate† (*SE*)	*p*-Value
Episodic memory				
TRAIL	−0.045 (0.104)	.669	0.113 (0.031)	**<.001**
OPG/TRAIL	−0.002 (0.086)	.977	−0.076 (0.024)	**.002**
Dkk1	−0.139 (0.192)	.469	−0.076 (0.064)	.241
CTX-1	0.109 (0.131)	.406	−0.034 (0.041)	.408
Semantic memory				
TRAIL	0.142 (0.087)	.106	−0.003 (0.030)	.919
OPG/TRAIL	−0.135 (0.071)	.062	0.006 (0.024)	.806
Dkk1	−0.356 (0.158)	.027	0.123 (0.055)	**.027**
CTX-1	0.032 (0.110)	.772	−0.021 (0.038)	.574
Working memory				
TRAIL	−0.031 (0.107)	.769	0.092 (0.038)	**.016**
OPG/TRAIL	−0.026 (0.088)	.767	−0.048 (0.029)	.104
Dkk1	−0.152 (0.194)	.434	−0.165 (0.072)	**.023**
CTX-1	0.027 (0.132)	.838	−0.074 (0.049)	.133
Perceptual orientation				
TRAIL	0.194 (0.105)	.069	0.029 (0.047)	.539
OPG/TRAIL	−0.162 (0.086)	.064	−0.012 (0.036)	.732
Dkk1	−0.127 (0.196)	.519	−0.148 (0.088)	.093
CTX-1	−0.113 (0.138)	.415	−0.009 (0.063)	.885
Perceptual speed				
TRAIL	−0.041 (0.027)	.124	0.057 (0.034,)	.098
OPG/TRAIL	−0.059 (0.091)	.521	−0.041 (0.027)	.124
Dkk1	0.041 (0.203)	.839	−0.114 (0.069)	.098
CTX-1	0.026 (0.139)	.853	−0.042 (0.044)	.342

Note: †The effect of a log unit change in biomarker concentration on annual rate of change in each cognitive domain from mixed-effects model adjusted for age, sex, and education. Significant associations are bolded for clarity.

The brain is known to exert control over the skeleton through serotonin production (21), but with bone emerging as an endocrine organ (9), it is possible that bone-derived signals also may influence brain function. For example, the bone-derived hormone osteocalcin has been reported to cross the blood brain barrier in mouse models, where it influences mood, anxiety, and depression (11). In mouse models, it is the undercarboxylated form that is thought to be active in the brain, whereas several recent cross-sectional human studies

have concluded that total osteocalcin is positively associated with cognition scores (22) and brain microstructural organization (12). In the current study, we investigated both total osteocalcin and the active undercarboxylated form and found no significant relationship with the rate of cognition change. It is not clear why our cross-sectional results did not mirror the positive associations previously reported; however, it is worth noting that these previous reports were only noted in relatively homogeneous patient populations, either older women (22) or obese patients (12).

OPG controls the bone remodeling process by antagonizing the interaction of soluble receptor activator to NF-κ B ligand (RANKL) and the RANK receptor on the surface of preosteoclasts or bone resorbing cells (23). OPG is also expressed in cerebrospinal fluid (24) where it is thought to antagonize the action of the apoptosis factor TRAIL (25), which is elevated in the brains of patients with confirmed AD (26). OPG has been studied as a biomarker of cognition with plasma OPG found to be an independent predictor of AD and vascular dementia after accounting for age, gender, and APOE ε4 allele in one study (27) but was not found to be significantly elevated in either MCI or AD patients compared with healthy controls in another study (8). Our study similarly noted no significant associations between OPG and cognition in either the cross-sectional or longitudinal models.

Due to the antagonistic action of OPG on the RANK/RANKL signaling pathway, it is common to report the OPG/RANKL ratio in studies investigating skeletal remodeling (28). OPG similarly antagonizes the interaction of TRAIL (29) with its receptors (death receptors 4 (30) and 5 (31)); therefore, we investigated the ratios of both OPG/RANKL and OPG/TRAIL. The OPG/TRAIL ratio was associated with the annual rate of change in global cognition, but this relationship was driven by the strong association with baseline TRAIL. Baseline TRAIL was positively associated with rate of change in cognition, suggesting that high TRAIL levels are protective for subsequent cognitive decline. This finding is surprising considering the increased levels of TRAIL in the brains of patients with confirmed AD (26) and because antagonizing the TRAIL receptor appears to be protective for amyloid-induced neurotoxicity (32, 33). Despite what appears to be a causal role in AD progression in the brain, circulating TRAIL has been reported to be decreased in patients with AD (34) and one other study has demonstrated a positive cross-sectional association with circulating TRAIL and cognitive scores (35). Our study builds on these findings demonstrating a demographic-adjusted relationship between TRAIL and the rate of change in cognition, pointing to potential divergent roles of brain and circulating TRAIL. The finding that baseline TRAIL level was significantly related to episodic memory points to the potential utility of this biomarker as an AD-predictive molecule, as early deficits in episodic memory have been shown to predict subsequent AD diagnosis (36–38).

Wnt proteins are important regulators of bone remodeling with antibodies to the circulating Wnt antagonists sclerostin and Dkk1 currently in development as osteoporosis treatments (39). Wnt signaling has also been recognized for its neuroprotective effects and suppression of Wnt appears to play a critical role in neurodegeneration including in the progression of AD (40, 41). Therefore, it is not surprising that Dkk1, an antagonist to Wnt signaling, was negatively associated with cognition change. Sclerostin, another antagonist to the Wnt pathway, was not related to cognition change, which is likely due to the fact that sclerostin is almost exclusively expressed in the skeleton. The expression of Dkk1 is more ubiquitous and has been shown to be expressed in the brain and deletion of Dkk1 in the brain has protective effects on age-related memory loss in mouse models (42). Our data suggest that the relationship between baseline Dkk1 and cognitive decline is likely due to the relatively strong relationship between Dkk1 and semantic memory, which, similar to episodic memory, declines early in the progression of AD (38, 43). Interestingly, the relationship between rate of cognitive decline and baseline Dkk1 appeared to be strongly influenced by the development of clinical dementia, as the associations between models excluding patients who developed dementia during follow-up were no longer significant. The sample size of current study is not large enough to further investigate the associations between Dkk1 and dementia development, but these preliminary results may suggest that Dkk1 is more predictive of dementia pathologies than cognitive decline.

It is currently unclear whether any of the biomarkers related to cognition in the current study are able to cross the blood–brain barrier. Although expression patterns of Dkk1 and TRAIL suggest that these proteins likely exist in both the brain and in circulation, it is not clear whether serum levels are reflective of brain levels. Further work is necessary to determine whether the relationships noted in the current study indicate cross barrier mechanisms or whether changes in circulating protein levels are indicative of downstream effects caused by pathological changes in the brain.

The limitations of the current study include the relatively small sample size, which was primarily female, and narrow ranges of both age and cognition scores. The narrow demographic distributions were likely the cause for a lack of significance in the biomarker levels and participant age and sex. Furthermore, although this study included change in cognition as an outcome, the timeframe is relatively short. Additionally, as patients were provided the same cognitive tests during the follow-up period, there was potential for the learning effect influencing the cognitive outcomes. A comparison of the mixed-effects models with and without adjustment for the number of visits suggests that this effect was likely relatively small as the relationships between cognitive decline and TRAIL, OPG/TRAIL, Dkk1, and CTX-1 remained significant. This finding was consistent with previous findings that have suggested that accounting for the effects of retesting had little impact on the association of risk factors with the rate of cognitive change (44).

The patient recruitment strategy did not account for individuals with diagnosed osteopenia or osteoporosis or whether these patients were taking bone remodeling modifying treatments. As designed, our study used circulating bone-related biomarkers as the independent variable but was not able to determine whether upstream factors influencing the circulating levels may independently contribute to cognition change. Future research on larger cohorts is necessary to account for this potential covariant. Furthermore, the study was not designed to make longitudinal bone mass measurements, such as a BMD with dual energy x-ray absorptiometry (DEXA); therefore, it is not clear how the biomarker levels related to the quantity of bone.

An additional limitation relates to the plasma collection strategy, which did not require participant fasting and the collection was not constrained to a particular time of day. Therefore, it is possible that diurnal effects may have masked some associations. CTX-1(45), PTH (46), and osteocalcin (47) are particularly sensitive to diurnal effects, whereas PINP has been shown to be relatively insensitive to diurnal fluctuations (48). To the best of our knowledge, there have been no formal evaluations of the diurnal fluctuations for TRAIL, Dkk1, OPG, or sclerostin. Although we did not note any patterns in the biomarker concentrations over time (data not shown), we cannot rule out diurnal effects on the current results.

In the current study, we evaluated the relationship between circulating concentrations of bone-related biomarkers and the annual rate of change in global cognition scores. We report that circulating baseline total TRAIL, the OPG/TRAIL ratio, Dkk1, and CTX-1 were all significantly related to the annual rate of change in cognition over the 18 month follow-up period. However, subsequent follow-up, including analysis of domain-specific cognition change, suggests that TRAIL and Dkk1 demonstrated the most potential to predict cognitive decline. Interestingly, the relationship between cognitive decline and TRAIL appeared to be relatively insensitive to dementia, whereas the relationship between cognitive decline and Dkk1 was lost when patients with probable dementia were removed from the model. Future work is needed to establish the role of clinical dementia in the relationships between these biomarkers and cognition. The current work provides further evidence of a connection between bone and brain health and should serve to motivate future studies to determine whether bone-derived biomarkers have potential to predict or influence cognitive decline.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of interest

None declared.

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