REVIEW

The Unraveling

Cardiac and Musculoskeletal Defects and Their Role in Common Alzheimer Disease Morbidity and Mortality

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Alzheimer disease (AD) is characterized by deterioration of cognitive capabilities with an estimated 44 million individuals worldwide living with it. Beyond memory deficits, the most common AD co-morbidities include swallowing defects (muscle), fractures (bone, muscle), and heart failure. The underlying causes of these co-morbidities and their role in AD pathophysiology are currently unknown. This review is the first to summarize the emerging picture of the cardiac and musculoskeletal deficits in human AD. We present the involvement of the heart, characterized by diastolic heart failure, the presence of amyloid deposits, and electrophysiological changes, compared with age-matched control subjects. The characteristic musculoskeletal defects in AD come from recent clinical studies and include potential underlying mechanisms (bone) in animal models. These studies detail a primary muscle weakness (without a loss of muscle mass) in patients with mild cognitive impairment, with progression of cognitive impairment to AD associating with ongoing muscle weakness and the onset of muscle atrophy. We conclude by reviewing the loss of bone density in patients with AD, paralleling the increase in fracture and fall risk in specific populations. These studies paint AD as a systemic disease in broad strokes, which may help elucidate AD pathophysiology and to allow for new ways of thinking about therapeutic interventions, diagnostic biomarkers, and the pathogenesis of this multidisciplinary disease. (*Am J Pathol* 2020, 190: 1609–1621; <https://doi.org/10.1016/j.ajpath.2020.04.013>)

Alzheimer disease (AD), the most common type of dementia, is a progressive disorder of the brain characterized by cell death, memory loss, and cognitive decline. The Centers for Disease Control and Prevention estimates that approximately 121,404 individuals died of AD in 2017,¹ based on the death certificate listing of AD as the cause of death (“the disease or injury which initiated the train of events leading directly to death”^{2,pp.23}).³ Between 2000 and 2017, AD deaths increased 145% in contrast to those from heart disease, the most common cause of death in the United States, which decreased 9%. AD is now the sixth leading cause of death in the United States. In 2019, AD and other dementias are estimated to cost \$290 billion, increasing to an estimated \$1.1 trillion by 2050.^{1,4,5} Common complications in severe dementia include immobility, swallowing disorders, and malnutrition, which increase the risk of

serious acute conditions that can cause death, such as pneumonia (lung infection).⁶ Pneumonia is the most common cause of death in patients with AD (and other dementias),^{7,8} with >50% of individuals with AD having respiratory system diseases as their immediate cause of death. Because death certificates often list pneumonia and other acute conditions as the primary cause of death instead of AD, these numbers likely underestimate AD as a cause of death.^{9–11} Diseases of the circulatory system closely follow lung complications, with approximately 25% dying of cardiovascular complications according to one autopsy study.⁷ Cardiovascular involvement in AD, often attributed to the

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advanced age of these patients, may instead have deeper pathogenic roots in the presence of amyloid beta (A β) deposits in the myocardium.¹² Early in the progression of clinical AD, skeletal deficits also emerge in ways that cannot be explained by co-incident factors, including aging, female sex, mobility status, falls, or genetics.¹³ Despite the fact that AD is primarily a brain disease, how the immediate causes of death and co-morbidities are linked to the heart, skeletal muscle, and bone are not clearly understood.

The current review summarizes the PubMed-indexed literature on AD manifestations in the heart, skeletal muscle, and bone, which have recently emerged as distinct phenotypes during the prodromal spectrum of disease, from mild cognitive impairment to development of dementia (AD). Studies that diagnose the prodromal early impairments, as well as dementia itself (AD), using standard neuropsychological evaluations as well as autopsy-confirmed diagnoses were included. None of the studies presented use only biomarker definitions of AD. The first section reviews the cardiac manifestations in patients with AD, including the overlapping risk factors that are shared between AD and cardiovascular disease (CVD). The second section examines the progressive changes in skeletal muscle during the AD prodromal period through dementia, illustrating an initial decrease in muscle strength, which later develops into an accelerated loss of muscle mass. The final section summarizes what is known about the changes that occur in the bone in patients with AD, characterized by a decrease in bone mineral density (BMD) and increased bone fractures during the progression of the disease, linking directly to the common co-morbidities and mortality in these patients. Although the existing literature seems to imply that the extraneuronal manifestations (ie, heart, skeletal muscle, bone) of AD are a result of the underlying pathophysiology, reports of A β in the heart,¹² for example, leave the possibility of primary AD occurring in non-brain tissues. If this is the case, future considerations of cross-talk between organs are critical, as systemic inflammation (among other things) may contribute back to the brain; this topic remains to be reported and is outside the scope of the current review.

AD and the Heart

Overlapping Risk Factors for Heart Failure and AD

Both dementia and heart failure contribute to the growing social, economic, and health care problems we face today. In 2010, an estimated 35 million individuals worldwide had dementia, which is anticipated to double every 20 years¹⁴ due to the aging population and increasing prevalence of risk factors for dementia.¹⁵ Other risk factors for dementia include a family history, hypertension and hypotension, high cholesterol level, low levels of physical activity, less education, obesity, and the prevalence of the apolipoprotein E (ApoE4) gene.^{16–18} The presence of heart failure has been

proposed as an additional risk factor¹⁹ causing low perfusion to the brain.

The most common cause of death in the United States and worldwide is CVD.²⁰ Risk factors associated with CVD in expansive clinical trials include hypertension, physical inactivity, cigarette smoking, obesity, diabetes, and dyslipidemia.²⁰ These risk factors have a mechanistic relationship to the broad pathogenesis of CVD: atherosclerosis. Chronic inflammation, homocysteine levels, and ApoE4 are other risk factors that play a role in the pathogenesis of CVD and contribute to microvascular dysfunction, which also affects brain perfusion.

Anatomic Evidence for the Overlap of CVD and AD in the Brain

The association between atherosclerosis (CVD) and AD in the brain has been studied in nine published autopsy series, as reviewed elsewhere.¹⁵ Four of these studies identified a relationship between atherosclerosis and the presence of A β plaques and neurofibrillary tangles,^{21–24} including one that identified a relationship to cerebral amyloid angiopathy, particularly in women.²⁴ Conversely, four other studies found no relationship between atherosclerosis and AD pathology,^{25–28} and one identified a relationship between atherosclerosis and A β plaques but not neurofibrillary tangles.²⁹ Both AD and heart failure have considerable overlap of risk factors related mechanistically to atherosclerosis (ie, the basis of CVDs, including heart failure). Whereas atherosclerosis has been universally accepted as the basis of many CVDs, including heart failure, there is no consensus for the pathogenic contribution of atherosclerosis in the brain and AD. Overall, the overlap between AD and CVD risk factors may: i) be co-incident because they are both common diseases and may not be mechanistically linked; ii) be linked in a subset of patients by a single shared mechanism (eg, inflammation); or iii) may result from independent mechanisms that have a common and/or transient initiating event (eg, A β proteotoxicity).

Genome-Wide Association Studies of CVD and AD

A known CVD-related locus linked to an increased risk for late-onset AD is the E4 apolipoprotein E gene encoding a transporter involved in cholesterol metabolism.³⁰ In addition, genome-wide association studies in late-onset AD have identified single nucleotide polymorphisms (SNPs) involved in lipid/cholesterol metabolism, including CLU and ABCA7.^{31–33} These associations are interesting because CVD has long had strong associations with plasma lipids (eg, low-density lipoprotein, total cholesterol, high-density lipoprotein, triglycerides). Systemic review of the literature using stringent *P* value thresholds for AD SNPs identified a 100-fold, 75-fold, 65-fold, and 25-fold enrichment using low-density lipoprotein, total cholesterol, high-density lipoprotein, and triglycerides, respectively.³⁴ No enrichment

was found with body mass index (BMI), type 2 diabetes, coronary artery disease, or waist-to-hip ratio.³⁴ After excluding the long-range loci disequilibrium associated with the APOE/TOMM40 region, 90 SNPs jointly associated with CVD and AD, including multiple loci involved in cholesterol/lipid function [eg, ATP Binding Cassette Subfamily G Member 5 (ABCG5), ATP Binding Cassette Subfamily A Member 1 (ABCA1), Apolipoprotein A4 (APOA4)].^{34,35} Replication studies that included 68 of the 90 SNPs found that 20 were significant, including novel variants within MINK1 (Misshapen like Kinase 1), MBLAC1 (Metallo-Beta-Lactamase Domain Containing 1), and DDB2 (Damage Specific DNA Binding Protein 2).³⁴ Investigations of these SNPs in healthy populations found significant effects of the differential expression of MINK1, SPI1 (Spi-1 Proto-Oncogene), DDB2, and MBLAC1 compared with those in patients with AD.

How these four SNPs are related to either CVD or AD is unknown, and their gene functions have not been linked to lipid/cholesterol metabolism to date. However, these proteins have known functions in other tissues and/or disease processes that may offer some insight into their roles in the pathogenesis of CVD and AD. The MINK1 protein is a serine/threonine kinase in the germinal center kinase family whose expression is increased in mouse cerebral development, and its function is linked to c-Jun N-terminal kinase and p38 signaling pathways. The SPI1 gene encodes with ETS-domain transcription factor activity linked to the differentiation/activation of macrophage or B cells and may modulate pre-mRNA splicing. The DDB2 gene encodes a protein involved in DNA damage, similar to proteins with nucleotide excision repair activity that forms a complex to mediate histone H3 and histone H4 ubiquitination to facilitate the cellular response to UV-mediated DNA damage. The MBLAC1 encodes for a protein that regulates the expression of glial glutamate transporters involved in multiple brain disorders, from neurodegenerative disease to addiction.³⁶ MBLAC1 has also been described in cancer cells to selectively process replication-dependent histone pre-mRNA during the S phase.³⁷ The association of these four novel gene SNPs expands the functions of AD/CVD-associated genes beyond lipid and cholesterol metabolism to fundamental processes involved in MAPK signaling (MINK1), pre-mRNA processing (SPI1 and MBLAC1), and the cellular response to DNA damage (DDB2). These are interesting findings given the established role(s) of MAPK signaling,^{38–40} pre-mRNA processing,^{41,42} and DNA damage^{4,43} in the pathogenesis of CVD and heart failure, which, for example, may be common to that observed in AD.

Presence of Cardiac A β and the Phenotype of AD Heart Failure

The co-existence of common risk factors in heart failure and AD (eg, hyperlipidemia, diabetes, decreased vascular blood

flow), in addition to the emerging genetic overlap discussed above (*Genome-Wide Association Studies of CVD and AD*), has led to clinical studies investigating heart failure in AD patient populations. One study investigated the prevalence of heart failure in AD and if the presence of amyloid deposits composed of the amyloid precursor protein (APP) proteolytic fragments (A β) were present in the heart and brain parenchyma.¹² The study identified the presence of A β deposits in the myocardium from patients with a clinical diagnosis of AD, confirmed by pathology. The clinical correlate was tested in a retrospective cross-sectional study of a cohort of patients with AD and age-matched control subjects exhibiting echocardiographic and Doppler evidence of diastolic dysfunction.

Twenty-five patients with a clinical diagnosis of AD were compared with 35 age-, sex-, and ethnicity-matched control subjects with no risk factors or clinical evidence of cardiac dysfunction.¹² Cardiac function assessment by Doppler analysis of the mitral valve E/A ratio found significantly decreased diastolic function in patients with AD in the first and second tertiles of age due to alterations in compliance (relaxation) (Figure 1, A–D).¹² Patients in the third tertile of age did not significantly differ from age-matched control subjects and may represent diastolic changes that occur with age. As seen with cardiac amyloidosis, hearts from patients with AD had an increased left ventricular wall thickness, which was significant only in elderly subjects but not in those from the first age tertile. Together, these findings identified for the first time a diastolic dysfunction in the younger AD age tertile and a left ventricular wall thickening in the oldest age tertile compared with age-matched control subjects. With this clinical association of heart failure in patients with AD, the underlying mechanistic links between AD and heart failure were next investigated.

Cardiac tissue from four patients with AD (aged 58, 70, 84, and 91 years) with a medical history of AD maintained on life support before organ harvesting was analyzed post-mortem by using structural staining of A β in the myocardium and brain.¹² Immunogold transmission electron microscopy staining using anti-A β_{42} antibodies and/or A β_{42} /pre-amyloid oligomer structural VIA antibodies (recognizing the last 3 amino acids Val40-Ile41-Ala42 of A β_{42}) was performed on AD and control patient cardiac tissue (Figure 1E).¹² Positive VIA immunogold staining was detected within the sarcomere structures and interstitial tissues, suggesting the presence of A β_{42} . Quantification of A β_{40} and A β_{42} peptides was identified in the heart and brain of patients with AD by using enzyme-linked immunosorbent assay and immunoblot. Enzyme-linked immunosorbent assay confirmed that A β_{40} and A β_{42} peptides were present in the heart and brain, albeit at much higher levels in the brain of patients with AD. Furthermore, A β_{40} and A β_{42} peptides were both increased in patients with AD compared with control subjects. Overall, these studies highlight the involvement of the heart in terms of the pathologic A β proteins associated with AD disease pathogenesis. The

Figure 1 Crude means of cardiac ultrasound parameters for age tertiles and groups corresponding to the linear regression. **A:** The graph shows how the value of the mitral valve E/A ratio is lower in younger subjects with Alzheimer disease (AD) and progressively overlaps with the control subjects at advanced ages. The mean value of the mitral valve E/A ratio of patients with AD in the first tertile appears intermediate between the value of the first and the second tertile of control subjects. An analogous pattern is shown for patients with AD in the second tertile. **B:** Notably, the atrial (A) component alone shows no differences in any group, suggesting that left ventricular compliance is the main contributor to the diastolic dysfunction in patients with AD. **C and D:** Increased left ventricular septal and inferior wall thickness, respectively, in the older subjects with AD. **E:** Quantification of the levels of amyloid beta₄₀ (Aβ₄₀) and Aβ₄₂ in AD and donor samples by enzyme-linked immunosorbent assay, showing increased levels of both fragments in the heart and brain of patients affected by AD. Control subjects were grouped by age (<50 years, >50 years). A one-way analysis of variance was also performed in all groups, followed by Bonferroni post hoc analysis. Analysis of variance was significant for Aβ₄₀ ($P < 0.0001$) and Aβ₄₂ ($P < 0.05$). Posttest for Aβ₄₀ was significant ($P < 0.001$) by age group comparisons; $P = 0.074$ for all groups for Aβ₄₂. The Levene test was performed for equal variances. A larger sample size may be necessary to establish the significance of the differences. The axis of ordinates is separated to better visualize the control values. yo, years of age. Reprinted with permission from Elsevier Science and Technology Journals.¹² * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.005$ versus AD (t-test).

presence of aggregate prone peptides outside of the brain may illustrate the mechanistic overlap that AD and CVD share resulting from parallel risk factors related in yet-to-be determined ways.

With the identification of Aβ aggregates found within cardiomyocytes or the cardiac interstitium of patients with AD at autopsy and the clinical evidence of diastolic dysfunction,⁴⁴ a subsequent study confirmed the findings in a replication cohort. Patients were evaluated clinically by using ECG, echocardiography, and Doppler analysis of the heart; they underwent genetic analysis for gene alleles associated with early-onset AD [Presenilin 1 (*PSEN1*), *PSEN2*, *APP* (Aβ), and *APOE*]. A single missense *PSEN2* mutation was observed in a female patient with late-onset AD; two subjects were homozygous for the *APOE* E4 allele, and 10 subjects were heterozygous. Patients with AD had a higher prevalence of low-voltage QRS complexes according to ECG (28% versus 3% in control subjects; $P = 0.0004$) and a decreased voltage/mass ratio ($P = 0.05$). Echocardiography identified a greater echocardiographic interventricular septum and a greater wall thickness. Doppler analysis found a twofold higher prevalence of diastolic dysfunction (70% versus 35%; $P = 0.007$). The authors of this study hypothesize a common disease mechanism whereby misfolded proteins (eg,

Aβ) in the brain and heart drive a common pathologic mechanism. However, no evidence for this is given beyond the findings in previous studies in four patients at autopsy summarized above.

Muscle Atrophy and Strength Correlations with AD Severity

AD progression has been correlated with skeletal muscle mass, strength, and function.^{45,46} Skeletal muscle dysfunction appears early in disease and may perhaps be a predictor of cognitive decline in AD before the onset of neurologic symptoms, in specific clinical scenarios.⁴⁵ Given the critical role of skeletal muscle in insulin activity and systemic glucose regulation, targeting muscle tissue might be a promising therapeutic strategy in AD,⁴⁷ which indirectly contributes to worsening central nervous system disease.

Sarcopenia and Dynapenia in Patients with AD

A link between the severity of AD and muscle mass has emerged in recent clinical studies. Patients with AD have a higher risk for fractures and falls,⁴⁸ which muscle strength and mass may contribute to. At least two types of muscle

remodeling occur with age and are exacerbated in AD. The first is sarcopenia, defined as loss of skeletal muscle mass associated with aging. The second is dynapenia, which describes the loss of muscle strength, function, and quality in the absence of muscle mass loss. Both sarcopenia and dynapenia increase the risk of falls, physical impairment, poor quality of life, and mortality.⁴⁹ Although muscle functions and physical performance decrease with aging, these functions further decrease in the early stage of AD^{45,49} and may contribute to patients' increased risk of falls. Patients with AD have higher rates of sarcopenia, even in the early stages.⁴⁵ Initial studies identified alterations in body composition in patients with dementia and AD. Burns et al⁵⁰ reported reduced lean mass in individuals with early AD, suggesting an association of sarcopenia with AD. Other studies identified weight loss before the diagnosis of AD as being associated with faster clinical progression of AD.⁵¹ Moreover, this study identified a significant negative correlation between BMI and severity of AD.⁵²

Recent studies have identified a relationship between muscle strength and the risk of developing AD. When muscle function was measured by grip strength tests and assessments of gait speed, greater muscle strength was associated with a decreased risk of developing AD.⁵³ Furthermore, muscle strength was associated with the rate of cognitive decline: patients with greater strength at baseline exhibited a considerably slower rate of decline.⁴⁵ Low muscle strength was associated with the risk of developing mild cognitive impairment, the earliest manifestation of cognitive impairment, and AD.⁵⁴ Similarly, a prospective cross-sectional study of 127 patients with AD versus 279 healthy control subjects recently reported that patients with AD had an increased prevalence of dynapenia.⁴⁹ When the 127 enrolled patients with AD were analyzed, increased sarcopenia and dynapenia were associated with increased AD disease stage.⁴⁹ In a longitudinal study aimed at studying the association of sarcopenia and dynapenia with cognitive impairment and dementia, sarcopenia was associated with verbal fluency, whereas dynapenia was associated with cognitive impairment in multiple dimensions.⁵⁵ Overall, these data show that greater muscle strength is associated with a decreased risk of developing AD and suggest that common pathogenesis may underlie the loss of muscle strength and cognition in AD.

The link between quantitative gait markers of preclinical dementia has been studied for its utility in predicting dementia onset.⁵⁶ To determine the relationship between gait and dementia, a prospective community-based aging cohort study of 427 subjects (aged ≥ 70 years) was performed. Quantitative gait assessments were conducted over 5 years, with 399 of these patients dementia free at baseline. Over a 5-year period, 33 subjects developed dementia. Factor analysis revealed that a 1 point increase in the rhythm factor (gait analysis) correlated with further memory decline (by 107%). The pace factor associated with a decrease in executive function as measured by digit symbol substitution

(29% decline) and letter fluency (92% decline). When adjusted for age, sex, and education, a 1 point increase in rhythm and variability scores associated with increased dementia risk, indicating the utility of quantitative gait measures to predict the risk of future cognitive decline and dementia in older adults without dementia. Subsequent studies have identified poor gait as a prodromal feature of cognitive decline and dementia. Darweesh et al⁵⁷ recently reported that the specific aspects of poor gait might be independently associated with cognitive decline. Using quantitative gait and cognitive assessments, Darweesh et al studied 30 gait parameters in >4000 dementia-free participants and dementia patients from the population-based Rotterdam Study. When these 30 gait parameters were summarized into seven mutually independent gait domains and a Global Gait score, three (Base of Support, Pace, and Rhythm) gait domains and the Global Gait score associated with cognitive decline. The association between gait and cognitive decline and incident dementia was only present in patients who had been unimpaired cognitively at baseline, indicating their diagnostic utility. These studies illustrate the physical manifestations of AD in gait, which may be manifesting the primary brain disease in the neuronal regulatory components of gait in addition to the possible direct effects AD has on skeletal muscle strength.

Dysfunction of Specific Muscle Groups as an Early Preclinical Predictor in AD

Identifying muscle defects in patients with AD led to the hypothesis that decreased muscle mass and/or function might be used as an early predictor of AD before cognitive decline. Indeed, reduced muscle strength without loss of muscle mass in the upper or lower extremities appears to be an early noncognitive feature of AD progression.⁴⁵ Surprisingly, the alterations in muscle function in the upper and lower extremities differed between female and male patients at different stages of AD (Figure 2).⁴⁵ At early AD stages, female patients displayed reduced muscle strength in both arms and legs, whereas male patients exhibited a significant reduction in muscle strength in legs but not in arms. Even at later stages of AD, men appear to display a lesser impact on the muscle strength in upper extremities. Thus, muscle function should be measured in a sex-specific manner when using dynapenia as an early predictor for AD, with measurements of muscle functions in the lower extremity being more sensitive for detecting physical disability than those in the upper extremity in male patients with AD. Importantly, these differences in muscle strength were not accompanied by sarcopenia at these early stages of AD, suggesting that muscle strength is lost earlier and at a substantially faster rate than muscle mass in AD (Figure 2).⁴⁵ Therefore, it seems that dynapenia, but not sarcopenia, is an early symptom during AD progression, with a significant reduction in gait speed considered to be one of the more universal and frequent early symptoms observed in AD.

Figure 2 Differences in average values of body mass index (BMI), skeletal muscle index (SMI), muscle strength, and muscle mass in the upper and lower extremities, and gait speed at various stages of Alzheimer disease (AD) compared with these values in the normal cognition (NC) group. The y axis indicates reduction from the mean values of the parameters in the NC group. Values in the early, mild, and moderate AD groups are normalized to the mean of the NC group. Reprinted with permission under the Creative Commons Attribution License (CC-BY).⁴⁵

Association of Clinical Myopathies with AD

The association between AD and muscle symptoms begs the question of whether similar molecular pathologies exist in the brain and muscle of patients with AD. Sporadic inclusion-body myositis (s-IBM) is the most common aging-associated myopathy, leading to progressive muscle weakness and atrophy in specific muscle groups.⁵⁸ s-IBM shares several pathologic features with AD and can co-exist with AD. Skeletal muscles of patients with s-IBM show accumulation and deposition of beta-amyloid, abnormalities in the gamma-secretase complex, hyperphosphorylation of tau protein, and increased inflammation, all hallmarks of AD.⁵⁹ These observations suggest that the pathologic molecular abnormalities observed in the brain of patients with AD also exist in other tissues, where they can lead to similar atrophy phenotypes. It is unclear whether there is a causative relationship between AD and s-IBM. It is also unknown whether cytotoxic proteins in AD can be distributed systemically from the brain in a metastatic fashion, or whether atrophy disease phenotypes originate in muscle by endogenous expression of AD-associated cytotoxic proteins. In this aspect, future studies of animal models of AD will be critical to elucidating the precise mechanisms by which AD can lead to skeletal muscle atrophy.

Motor Defects in AD Animal Models

Preclinical studies of transgenic AD mouse models variably recapitulate the neuropathologic features of AD^{60,61} and may offer ways to study the pathogenesis of disease over

time. The assessment of motor function in these mouse models has produced conflicting results, depending on the genetic alterations and transgenes expressed in these animals.⁶² One of the models considered to provide an accurate reflection and aggressive presentation of human AD is the 5XFAD transgenic (5XFAD Tg⁺) mouse model.⁶³ These mice express human *APP* and *PSEN1* transgenes with a total of five AD-linked mutations: the Swedish (K670N/M671L), Florida (I716V), and London (V717I) mutations in *APP*, and the M146L and L286V mutations in *PSEN1*.⁶⁴ The 5XFAD Tg⁺ mice developed motor impairments starting at 9 months of age.^{63,64} Specifically, they exhibited an abnormal gait, traveled shorter distances, moved slower in an open field test, and fell off a rotarod, balance beams, and metal grids significantly faster than wild-type animals.⁶³ 5XFAD Tg⁺ mice also had a slower swimming speed in a Morris water maze compared with control mice. Although these findings suggest that 5XFAD Tg⁺ mice have declining muscle function with age, not all muscle functions were different from those of wild-type mice. For example, muscle function by isometric tension recordings and twitch force tracings of the soleus muscle in 5XFAD Tg⁺ mice did not differ from those of wild-type mice. Peak tension did not differ significantly between 5XFAD Tg⁺ mice and wild-type control mice, suggesting that at least some aspects of muscle function were not affected in the 5XFAD Tg⁺ mice. The development of AD-related pathology of the pyramidal and extrapyramidal motor systems within the brain and spinal cord likely contributes to the observed impaired motor ability in 5XFAD Tg⁺ mice. A more detailed analysis of the underlying mechanisms in the 5XFAD Tg⁺ (and

other) mice is needed along with human correlations to appreciate how the underlying brain disease and potentially skeletal muscle and neuromuscular junction pathology is occurring; the goal is to identify the contributions of both the central nervous system disease and potentially intrinsic skeletal muscle defects that contribute to the established motor dysfunction in patients with AD.

Therapeutic Potential of Targeting Muscle Mass and Function in AD

Regular exercise has the most consistent promise in both the prevention and treatment of AD but also cardiovascular and, evidently, skeletal myopathy.⁴⁷ In contrast, AD drug interventions have shown mixed effectiveness in attenuating disease progression,⁶⁵ whereas nonpharmacologic treatment of AD using cognitive training and cognitive stimulation have shown inconsistent benefits. Barnes and Yaffe⁶⁶ estimated that more than one-half of AD risk factors might be preventable, and Norton et al⁶⁷ found that the highest attributable risk for AD was physical inactivity. Hamer and Chida⁶⁸ found that physical activity reduces the risk of AD by 45%. Smith et al⁶⁹ reported significant improvements in attention and processing speed, executive function, and memory improvement in the exercise groups. In a meta-analysis of randomized controlled trials of drug and exercise treatment of AD and mild cognitive impairment, Ströhle et al⁶⁵ found that exercise had a moderate to strong pooled effect size for AD, whereas drug treatments (cholinesterase inhibitors and memantine, an antagonist of the *N*-methyl-D-aspartate receptor believed to be involved in glutamate excitotoxic activity in neurodegeneration) resulted in a small effect on cognition for AD. Moreover, the discontinuation rate for medications was high, although much lower than the discontinuation rate found in the exercise regimen studies. This meta-analysis suggests that preventing skeletal muscle atrophy by regular exercise can have positive effects on the prevention and treatment of AD. These studies should be interpreted carefully, as the end point for many of these trials is cognitive function by testing, which is related to, but not identical to, cognitive function in everyday life. These studies were also relatively short, making the long-term outcomes of exercise (and other interventions) limited as the long-term consequences of AD are particularly difficult. These studies provide evidence that exercise and AD are correlated, highlighting the importance of a brain–skeletal muscle axis communication.

The causal relationship between cognitive deficits and skeletal muscle defects has not been resolved to date. The use of animal models that recapitulate parts of the AD phenotype may allow us to begin to appreciate the mechanisms linking the brain–skeletal muscle axis to regulate skeletal muscle mass, strength, and even insulin resistance. One recent example is a 2019 publication on the AD *APP/PSEN1* Tg⁺ mouse model.³⁴ An increase in the skeletal muscle expression of myostatin, a potent modulator of both

muscle atrophy and neurologic symptoms in AD, has been identified in the *APP/PSEN1* Tg⁺ mouse.⁷⁰ In addition, these studies identified a significant correlation between skeletal muscle atrophy and cognitive decline. To determine the mechanistic link in this correlation, the investigators used shRNA knockdown to block the *APP/PSEN1* Tg⁺ gastrocnemius myostatin elevation *in vivo*. Blocking myostatin not only increased muscle mass and grip strength but also improved neurologic parameters, including memory, in the *APP/PSEN1* Tg⁺ mouse. Although the underlying mechanisms in the *APP/PSEN1* Tg⁺ mouse skeletal muscle are not clear at the molecular level, nor are their relationship to human disease known, these studies provide direct evidence that preventing AD-associated molecular changes in muscle can give feedback to the brain to positively affect the neurologic symptoms of AD.

Clinical Correlations and Disease Mechanisms across AD and Bone

Patients with AD are more susceptible to falls and fractures, which may be due to bone loss. In addition to the involvement of the skeletal muscle, several other common factors are associated with dementia and falls, including aging, exercise, alcohol consumption, smoking, ApoE4, vitamin D deficiency, and reduced gastrointestinal absorption of calcium.^{71,72} Patients with AD have decreased circulation of vitamin D, which might be linked to the increased risk for falls. Elevated levels of parathyroid hormone may contribute to the pathogenesis of AD by impairing cognitive abilities.

The sympathetic nervous system and parasympathetic nervous system are part of the autonomous nervous system and regulate body homeostasis; each plays a distinct role in regulating the bone in addition to participation in balance and risk of falls *per se*. The SNS is involved in bone loss by suppressing osteoblast-derived bone formation and enhancing osteoclast-mediated resorption. In contrast, the parasympathetic nervous system plays a role in bone formation by enhancing osteoblast-mediated mineral deposition and suppressing osteoclast activity.⁷³

Effect of Donepezil on AD and Bone

A case-control study found that donepezil, a commonly used acetylcholinesterase inhibitor in AD, was associated with reduced hip fractures, in addition to treating AD by improving cognitive performance.⁷⁴ In this study, 80 case patients aged >75 years with AD were compared with 2178 patients with AD without hip fracture between January 2004 and December 2008 (Figure 3).⁷⁴ Patients with AD treated with acetylcholinesterase inhibitors had a fracture-adjusted odds ratio (OR) of 0.42 (95% CI, 0.24–0.72), with those taking rivastigmine having an OR of 0.22 (95% CI, 0.10–0.45) and those taking donepezil having an OR of

0.39 (95% CI, 0.19–0.76) adjusted for BMI, fall risk, smoking habits, cognition, dependence, degree of AD, comorbidity score, treatment with SSRIs, age, and sex (Table 1).⁷⁴ Subsequent *in vitro* studies investigated the potential mechanisms. Donepezil, which crosses the blood–brain barrier, prevented receptor activator of nuclear factor- κ B ligand–induced bone loss by inhibiting bone resorption (Figure 4). Specifically, donepezil blocked acetylcholinesterase activity in bone cells.⁷⁵ Acetylcholinesterase was found to be involved in osteoblast differentiation and in promotion of osteoclast differentiation.⁷⁶ Osteoblasts secrete acetylcholinesterase *in vitro* to mediate osteoblast adhesion in bone.⁷⁷ Together, these studies identify an association between acetylcholine and osteoblast function and osteoclast differentiation, which may be linked mechanistically to differences in bone fractures in patients with AD (Figure 4).

AD Risk Correlates with Lower BMD and Increased Bone Fractures

A longitudinal observational study of dementia patients biennially evaluated for their risk of bone fractures also showed an association between AD and bone health.⁷⁸ Of the 5209 participants (2336 men, 2873 women) in this study, 987 participants of the total had BMD measurements; thus, these 377 men and 610 women were included in this study, which included a mostly white American population. Women with lower femoral BMD were two times more risk-prone to develop AD than women with higher BMD. This observation was found to be independent of various risk factors of AD such as smoking, ApoE mutations, stroke, estrogen replacement therapy, age, baseline homocysteine levels, age, and education. However, in male subjects, no proper correlation was observed for lower BMD as a risk factor for AD. Furthermore, women who did not have dementia but lower BMD were found to have a more severe cognitive decline.

A Canadian National Population Health Survey of 408 men and 1105 women looked into the risk factors, demographic characteristics, medication use, health, and socioeconomic status and falls.⁷⁹ The investigators found that all of the hip fractures were due to falls, although not more than 3.7% of the falls led to hip fracture. Individuals with a sustained hip fracture later ended up with heart disease, osteoporosis, and also AD. A Chinese clinical study with 1380 control subjects and 345 patients with AD revealed that fall-related fractures increased the number of hospitalizations for patients with AD, which elevated the health care costs.⁸⁰ Patients with osteoporosis were found to be more prone to falls if they had AD, which was independent of the age-related falls in AD patients. However, AD was not found to have an impact on the fracture location. There are also independent factors that increased hospitalization, as indicated by women being hospitalized more than men, and more hospital admissions in the winter in elderly populations than the rest of the year. Another study from a Chinese cohort involving 946 men and women aged 60 to 75 years who underwent bone density analysis [dual-energy X-ray absorptiometry (DEXA)] found that individuals with lower BMD were found to develop cognitive impairment over the years.⁸¹ Yet another study from the same age group, but in the Chongqing cohort of China who were followed up for 6 years, identified that female patients with osteoporotic fractures were more prone to AD. The osteoporotic fractures were attributed to several factors, including smoking, AD, 25-hydroxyvitamin D levels, drinking, and stroke.⁸²

The risk of bone fractures increases with the diagnosis of AD. A study in Rochester with 543 individuals revealed that there was no incidence of fracture risk detected before the diagnosis of AD.⁸³ However, after the onset of AD, as noted in the clinics, the risk for fractures was found to be increased by twofold and was not found to increase after that. In another study of 485 subjects aged 85 years, hip fracture was associated with AD and vascular dementia in women

Figure 3 Identifying the association between Alzheimer disease (AD), acetylcholinesterase inhibitors, and bone fracture risk: overview of the case and control subject selection process. Reprinted with permission from John Wiley and Sons Books.⁷⁴

Table 1 Use of AChEIs and Fracture Risk (versus Nonuse)

Characteristic	Cases (<i>n</i> = 80)*	Controls (<i>n</i> = 21.78)*	Crude OR (95% CI)	Adjusted OR (95% CI) [†]	<i>P</i>
Nonuse of AChEIs	37 (46.3)	450 (20.7)	1.00	1.00	-
Use of AChEIs	43 (53.8)	1728 (79.3)	0.30 (0.19–0.48)	0.42 (0.24–0.72)	0.002
Rivastigmine	11 (13.8)	900 (41.3)	0.20 (0.11–0.37)	0.22 (0.10–0.45)	<0.001
Donepezil	15 (18.8)	630 (28.9)	0.29 (0.16–0.54)	0.39 (0.19–0.76)	<0.002
Galantamine	9 (11.3)	82 (8.4)	0.68 (0.33–1.39)	1.67 (0.63–4.45)	0.305

From: Tamimi et al. *J Bone Miner Res* 2012; 27:1518-1527.⁷⁴ (Used with Permission from John Wiley and Sons Books.)

*Values are *n* (%); percentages may not sum to 100% due to rounding.

[†]Adjusted to the following categorical parameters: age, sex, body mass index, clinical dementia rating scale, Blessed dementia scale, Mini-Mental State Examination, Fall Risk Assessment Tool, institutionalization, Charlson comorbidity score, smoking, selective serotonin reuptake inhibitor use, and fracture history.

AChEIs, acetylcholinesterase inhibitor; CI, confidence interval; OR, odds ratio.

but not in men.⁸⁴ The fracture rate was twice that in women with dementia compared with the general population (32.7% versus 13.6%). Bone density was not associated in this study with hip fracture or dementia. Multiple factors were associated with the increased probability of hip fracture in these women, including BMI (lower in women with dementia and those with hip fracture). Hip fractures were also increased in patients taking psychotropic drugs (eg, tricyclic antidepressants). Multiple regression analysis identified that the use of antidepressants and patient sex independently contributed to hip fracture risk. The increased risk of hip fractures may be the result of defective neuromuscular junctions, gait apraxia, antidepressant use, lower BMI, and systemic/cerebral hypoperfusion postsurgery/anesthesia exposure. In a cross-sectional observational study of 2041 women, AD and dementia associated with age, being more common with increasing age; for example, 0% had AD/dementia in the group aged <55 years, and 29.7% had AD/dementia in the group aged 85 to 89 years.⁸⁵ This study found that the most common fracture was to the proximal femora (77%), followed by the wrist (13%) and proximal humerus (10%). The prevalence of AD/dementia was higher

in postmenopausal women with severe osteoporosis, especially if they had proximal femoral fractures. These two studies show the correlation between AD and bone fractures in women, with evidence that the bone loss correlates with AD/dementia severity.

Only a few clinical studies have reported correlations between AD and bone loss. In 2009, a clinical study of 71 patients with early-stage dementia and 69 participants without dementia identified a correlation between decreased BMD using DEXA analysis and AD.⁸⁶ They also found that female patients with AD had significantly more BMD loss compared with male subjects. This reduced BMD was additionally correlated with both the amount of brain atrophy and decline in cognitive performance in the group with early-stage dementia. In a 2020 study, the relationship of low bone mass (osteopenia) on regional cortical blood flow areas affected by AD was identified.⁸⁷ Nineteen female patients with osteopenia (>65 years old) and 12 aging outpatients without dementia underwent a single-photon emission computed tomography brain scan and a DEXA scan. The mean *z* scores of cerebral subregions most often affected by AD were significantly lower in patients with AD

Figure 4 The acetylcholinesterase inhibitor donepezil used to treat Alzheimer disease (AD) is associated with a decreased risk of fractures possibly related to acetylcholinesterase activity in osteoblasts and osteoclasts. As described in the text (*Effect of Donepezil on AD and Bone*), published clinical and translational studies report that donepezil is associated with reduced fracture risk in patients with AD compared with age-matched control subjects.^{74–77} Acetylcholinesterase signaling leads to receptor activator of nuclear factor- κ B ligand (RANKL)-mediated osteoclast differentiation *in vitro*. This may suggest that the observed acetylcholinesterase inhibition with donepezil reduces AD bone loss by suppressing bone resorption to reduce fractures. In addition, RANKL was found to contribute to increases in endogenous levels of acetylcholinesterase levels in osteoblasts, wherein it was found to mediate osteoblast adhesion to the matrix *in vitro*. Direct mechanistic links between acetylcholinesterase activity in AD osteoblasts and osteoclasts have not yet been established.

compared with the group without dementia, indicating the first correlations between bone loss and brain hypoperfusion. Together, these studies show how AD correlates to bone loss and may offer insight for the higher risk that patients with AD have for fractures and falls.⁴⁸

Bone Phenotypes Developing in Preclinical AD Mouse Models

What we understand about AD–bone interactions mechanistically comes from animal studies of disease. The human studies described in the previous section are uniformly observational, with only circumstantial evidence for the underlying mechanisms (eg, the correlation between AD and an increased circulating parathyroid hormone level).^{88–90} One example of how animal studies have been useful in studying mechanisms not easily obtained in patients is the identification of APP expression in bone marrow stromal cells, which is ubiquitously expressed in osteoblasts and osteoclasts.^{91,92} The *Tg2576* model, one of the well-characterized and widely used preclinical models of AD, overexpresses human *APP695* with double Swedish mutations at *KM670/671NL* (*APP_{swe}*).⁹¹ These mice have elevated levels of A β and develop amyloid plaques from 11 to 13 months. Reduced bone formation was observed in *Tg2576* mice compared with wild-type mice as young as 1 month. In another study, *APP_{swe}* mutations were introduced in osteoblasts; decreased osteogenesis and bone mass were observed in these *TgAPP_{swe}-Ocn* (osteoblast-lineage expression under the control of osteocalcin-driven Cre) mice.⁹² *Tg2576* mice with ubiquitous expression (under the prion-promoter control) also had an age-related decrease in osteoblast genesis and bone formation, increased bone marrow fat, and an increase in the osteoclast genesis and related bone resorption. At a young age, the *Tg2576* mice exhibited increased osteoclast numbers that the authors attribute to A β oligomer interaction with RAGE (receptor for advanced glycation end products) in bone marrow macrophages, contributing to the inflammatory process. As these mice age, a reduced osteoclast number and increased soluble RAGE levels were identified that led to altered bone remodeling and increased bone fractures.⁹¹ Unexpectedly, when mice were put on a high-fat diet, the deteriorated bone microarchitecture and mechanical properties in female *APP_{swe}/PSEN1dE9* (*APP/PSEN1*) transgenic mice improved.⁹³ These studies uniquely illustrate the possible pathogenic role of APP in bone cells regulating the bone turnover directly, independent from outside toxic mediators from the brain in ways that cannot be delineated in humans.

Conclusions

AD is a disease primarily affecting the central nervous system that additionally has extraneuronal effects that significantly alter bone and skeletal muscle strength and

mass, and, as determined more recently, cardiac function. To date, no specific mechanistic links between the brain and the heart–skeletal muscle–bone axis in AD are known. Direct neuronal disease may underlie the observed skeletal muscle, cardiac, and even bone defects because each has significant neuronal innervation. In contrast, indirect mechanisms may be responsible for extraneuronal disease via cross-talk with the brain. This cross-talk may occur via systemic circulating small molecules (eg, inflammation, proteotoxic proteins, miRNA, circulating metabolites originating from the brain), including exosomes. It is also unknown whether cytotoxic proteins in AD can be distributed systemically from the brain in a metastatic fashion, or whether cardiac dysfunction or bone and muscle atrophy phenotypes originate by endogenous expression of AD-associated cytotoxic proteins.

A better understanding of the fundamental and precise mechanisms of the brain–cardiac–skeletal muscle–bone axis must be addressed in the pathogenesis of AD to guide how to best study AD as a systemic disease and at all translational levels. Whether the clinical manifestations in the heart, muscle, and the bone are endogenously only neuronal, systemic, and/or metastatic in AD warrants investigation despite potential disruption of dogma as the systemic nature and cross-communication of tissues in disease continues to emerge throughout medicine; it may even be worth considering given the challenge of AD therapies to date and the focus on central nervous system being the only source of pathology. Considering the critical role of skeletal muscle and heart in glucose regulation and inflammation in general, it is possible that they are an unseen contributing source to the central nervous system disease not currently being considered. Although outside the scope of this review, skeletal muscle may be critically affected given the insulin resistance and impaired lipid metabolism seen in AD, suggesting links between diabetes and AD.^{94–97} Lastly, the cardiac–skeletal muscle–bone axis may offer multiple additional biomarkers that could be associated with disease presence, progression, and response to AD therapy. Those might be important to consider in addition to other emerging brain and circulating biomarkers that could improve the quality of life in patients with AD, heart failure, skeletal myopathy, and bone diseases.

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