

World Journal of *Orthopedics*

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World Journal of Orthopedics
Volume 8 Number 5 May 18, 2017

ABOUT COVER

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WJO covers topics concerning arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthritis, bone tumors and osteoporosis, minimally invasive therapy, diagnostic imaging. Priority publication will be given to articles concerning diagnosis and treatment of orthopedic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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INDEXING/ABSTRACTING

World Journal of Orthopedics is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central and Scopus.

FLYLEAF

I-III Editorial Board

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NAME OF JOURNAL
World Journal of Orthopedics

ISSN
ISSN 2218-5836 (online)

LAUNCH DATE
November 18, 2010

FREQUENCY
Monthly

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7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
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Help Desk: <http://www.fjpublishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLICATION DATE
May 18, 2017

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Dementia and osteoporosis in a geriatric population: Is there a common link?

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Author contributions: Downey CL and Young A contributed equally to this work; Downey CL and Tsiridis EM designed the research; Downey CL, Young A and Burton EF performed the research and wrote the paper; Graham SM, Macfarlane RJ and Tsiridis EM provided significant contributions in drafting the paper and revising it critically for important intellectual content; Tsapakis EM provided expert review.

Conflict-of-interest statement: The authors confirm that there are no potential conflicts of interest. There is no financial support to declare.

Data sharing statement: None.

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Manuscript source: Invited manuscript

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Received: December 5, 2016

Peer-review started: December 6, 2016

First decision: January 16, 2017

Revised: February 8, 2017

Accepted: February 28, 2017

Article in press: March 2, 2017

Published online: May 18, 2017

Abstract

AIM

To determine the existence of a common pathological link between dementia and osteoporosis through reviewing the current evidence base.

METHODS

This paper reviews the current literature on osteoporosis and dementia in order to ascertain evidence of a common predisposing aetiology. A literature search of Ovid MEDLINE (1950 to June 2016) was conducted. The keywords "osteoporosis", "osteoporotic fracture", "dementia" and "Alzheimer's disease" (AD) were used to determine the theoretical links with the most significant evidence base behind them. The key links were found to be vitamins D and K, calcium, thyroid disease, statins, alcohol and sex steroids. These subjects were then searched in combination with the previous terms and the resulting papers manually examined. Theoretical, *in vitro* and *in vivo* research were all used to inform this review which focuses on the most well developed theoretical common causes for dementia (predominantly Alzheimer's type) and osteoporosis.

RESULTS

Dementia and osteoporosis are multifaceted disease processes with similar epidemiology and a marked increase in prevalence in elderly populations. The existence of

a common link between the two has been suggested despite a lack of clear pathological overlap in our current understanding. Research to date has tended to be fragmented and relatively weak in nature with multiple confounding factors reflecting the difficulties of *in vivo* experimentation in the population of interest. Despite exploration of various possible mechanisms in search for a link between the two pathologies, this paper found that it is possible that these associations are coincidental due to the nature of the evidence available. One finding in this review is that prior investigation into common aetiologies has found raised amyloid beta peptide levels in osteoporotic bone tissue, with a hypothesis that amyloid beta disorders are systemic disorders resulting in differing tissue manifestations. However, our findings were that the most compelling evidence of a common yet independent aetiology lies in the APOE4 allele, which is a well-established risk for AD but also carries an independent association with fracture risk. The mechanism behind this is thought to be the reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele which may be amplified by the nutritional deficiencies associated with dementia, which are known to include vitamins K and D. The vitamin theory postulates that malnutrition and reduced exposure to sunlight in patients with AD leads to vitamin deficiencies.

CONCLUSION

Robust evidence remains to be produced regarding potential links and regarding the exact aetiology of these diseases and remains relevant given the burden of dementia and osteoporosis in our ageing population. Future research into amyloid beta, APOE4 and vitamins K and D as the most promising aetiological links should be welcomed.

Key words: Osteoporosis; Fracture; Dementia; Thyroid disease; Alzheimer's disease; Elderly; Vitamin D; Vitamin K; Calcium; Statins; Alcohol; Sex steroids

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Core tip: A potential pathological link between osteoporosis and dementia has been explored in observational studies, but there exists a lack of large scale randomised controlled trials. We hypothesise that dementia and osteoporosis have common yet independent aetiologies. The most compelling evidence lies in the APOE4 allele, a well-established risk factor for Alzheimer's disease. APOE4 is associated with fracture, independent of dementia and falling. The mechanism behind this is postulated to be reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele. This may be augmented by the nutritional deficiencies associated with dementia, known to include vitamins K and D.

Downey CL, Young A, Burton EF, Graham SM, Macfarlane RJ, Tsapakis EM, Tsiridis E. Dementia and osteoporosis in a geriatric population: Is there a common link? *World J Orthop* 2017; 8(5): 412-423 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i5/412.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i5.412>

INTRODUCTION

Dementia and osteoporosis are complex disease processes with similar epidemiology. Alzheimer's disease (AD) is the most common form of dementia and increases from 16% in 75-year-old to 84-year-old to 48% in over-85s^[1]. Osteoporosis affects 25% of women and 10% of men over 60^[2]. The two diseases co-exist in a subsection of the population, especially amongst females^[3]. Indeed, an odds ratio of 6.9 for fracture prevalence between people with and without AD has been reported^[4]. Thus a common link has been suggested despite no apparent pathological overlap.

The pathogenesis of AD lies in three complex mechanisms^[5]. The development of amyloid senile plaques causes neuronal death and phosphorylation of Tau proteins. Tau disassembles the microtubules resulting in neurofibrillary tangles and ultimately neuronal degeneration. Amyloid and Tau localise in the synapses, causing excessive calcium entry into post-synaptic neurons, necrosis and apoptosis. Despite extensive research into the disease, current treatment options are limited by their cost and efficacy. Their action lies in palliation of symptoms and most are only effective in a subsection of AD sufferers.

Osteoporosis is a progressive skeletal disease characterised by reduced bone density and micro-architectural bone destruction. This leads to increased bone fragility and susceptibility to fracture. Like dementia, the pathophysiology of osteoporosis is multifactorial and extends far past the traditional theory of nutritional calcium depletion. Indeed, both diseases have been associated with a number of other metabolic disturbances such as decreased vitamin D concentration and elevated serum parathyroid hormone, in addition to postulated common genetic variations such as the APOE4 allele^[2].

The burden of elderly care is a significant challenge to healthcare systems throughout the world and will only continue to grow in the coming decades. AD is the leading cause of loss of autonomy and independency in the elderly, and is associated with a number of comorbidities^[6]. Osteoporotic fractures have huge impact in terms of morbidity and mortality. Both diseases form part of the frailty syndrome, a collection of signs and symptoms associated with significant disability and public expenditure^[7]. Here we hypothesize that osteoporosis and dementia share a common predisposing aetiology. We propose that this is multifactorial, involving genetic, metabolic, endocrine and environmental factors. Elucidation of a common link between the two diseases could prove vital in the development of novel treatments for these complex medical and social problems.

MATERIALS AND METHODS

A comprehensive literature search of Ovid MEDLINE (1950

to June 2016) was conducted. The keywords “osteoporosis”, “osteoporotic fracture”, “dementia” and “Alzheimer’s disease” were used initially to determine the theoretical links with the most significant evidence base behind them. From manual study of key papers the lead investigators selected these to be vitamins D and K, calcium, thyroid disease, statins, alcohol and sex steroids. These subjects were searched in combination with the previous terms. Manual examination of titles and abstracts was used to exclude irrelevant articles. Theoretical, *in vitro* and *in vivo* research were all used to inform this review which focuses on the most well developed theoretical common causes for dementia (predominantly Alzheimer’s type) and osteoporosis.

RESULTS

Vitamin D

Approximately 1 billion adults are vitamin D deficient worldwide, and the prevalence is especially marked in older people, ranging from 50%-80%^[5]. Vitamin D has long been known for its effects on phosphocalcic metabolisms and bone^[5], thus vitamin D deficiency is well established as a risk factor for the development of osteoporosis^[8]. In contrast, the association between vitamin D and dementia requires clarification.

In 1995, Kipen *et al*^[8] found significantly lower vitamin D in women with dementia compared to cognitively-intact controls. A subsequent cross-sectional study found a vitamin D deficiency of < 10 ng/mL doubled the risk of cognitive impairment^[9]. A similar association between severe vitamin D deficiency (here defined as < 25 nmol/L at baseline) and mild cognitive impairment has been seen in elderly subjects over 65 years of age^[10].

A recent large Danish prospective study looked at participants who were free of cognitive impairment at enrolment and found that a decline in serum levels of vitamin D were associated with increased risk of participants developing AD^[11]. A more diverse American prospective study with a shorter length of follow up also found an association between baseline vitamin D deficiency (defined by the authors as serum levels < 50 nmol/L) and likelihood of participants developing AD and other all-cause dementias, an association that remained despite adjustment for mediators such as diabetes and hypertension^[12]. Both these studies looked at healthy participants who were ambulatory at enrolment^[11,12]. However reduced exposure to sunlight in patients with AD has been implicated as the main cause of vitamin D deficiency in patients with dementia^[13]. Patients with dementia are often immobile or housebound, and may be unable to gain sufficient sunlight exposure. Furthermore, generalised malnutrition either due to changes in functional ability, appetite disturbance, or disease may compound this problem.

In addition to environmental and functional changes, a decline in renal function accompanies the process of aging with the incidence of chronic kidney disease quoted as up to 35.8% in the geriatric population^[14].

Chronic renal disease results in impaired 1,25 dihydroxycholecalciferol production, the physiologically active metabolite within the body. Patients with suboptimal production of 1,25 dihydroxycholecalciferol may have this confirmed by low serum levels, and evidence of a secondary hyperparathyroidism^[15].

Aside from well-established physiological effects on bone metabolism, vitamin D has been found to play a pivotal role in both the normal function and protection of the central nervous system (CNS). As a neurosteroid hormone, vitamin D receptors are found in the neurons and glial cells of the CNS^[5]. The binding of 1,25 dihydroxycholecalciferol to these receptors results in a number of neuroprotective mechanisms. These can be categorised as direct, immune and homeostatic.

Directly, vitamin D inhibits the synthesis of nitric oxide synthase, an enzyme which promotes neuron alterations, and increases the synthesis of neurotrophic agents such as nerve growth factor^[5]. In addition, neuron-glial cell cultures treated with vitamin D show increased expression of genes known to limit the progression of AD^[16]. Vitamin D is also known to increase the number of macrophages and leukocytes in the brain. *In vitro* studies of macrophages from AD patients showed that stimulation with vitamin D increased phagocytosis and clearance of amyloid^[17]. Vitamin D plays an important role in the homeostasis of calcium and the avoidance of hyperparathyroidism by upregulating calcium channels and the synthesis of calcium-binding proteins^[5]. The importance of calcium and parathyroid status is discussed later.

Despite evidence *in vitro*, conclusive evidence of a link between vitamin D and dementia in patients is lacking (Table 1). In cross-sectional studies, vitamin D deficiency has been shown to double the risk of presenting with cognitive impairment^[9]. However, the nature of cross-sectional studies means that no cause and effect link can be made. Clearly, dementia may be the cause of reduced mobility and therefore reduced exposure to sunlight. A recent BMJ editorial criticised the perceived reliance on cross-sectional studies in relation to vitamin D as an aetiological factor in AD. It cited “a range of interpretational difficulties” such as reverse causality, confounding, classification bias and differences in assay methods^[18].

Nevertheless, in longitudinal studies, low baseline vitamin D levels have been found to predict incident cognitive decline in the elderly. A study of 858 Italians over the age of 65 showed that those who were “severely deficient” in vitamin D had a 1.6-fold increased risk of a substantial cognitive decline over 6 years, thus providing a temporal association^[19]. Another longitudinal study looking at time to progression to AD along with vitamin D treatment status, found that time to progression was longer in those treated with vitamin D (5.4 ± 0.4 years, $P = 0.003$) than in those who were not supplemented (4.4 ± 0.16 years, $P = 0.003$) but only in those who went on to develop severer manifestations of the disease^[20]. This study however was limited again by an observational

Table 1 Studies investigating the association between vitamin D and cognition

Study design	Ref.	Population	Results
Cross-sectional study	[88]	80 community-dwelling women 40 with mild AD 40 cognitively-intact	Vitamin D deficiency was associated with impairment on two of four measures of cognitive performance
	[89]	32 community-dwelling patients	Significant positive correlation between vitamin D concentrations and MMSE scores
	[90]	9556 community-dwelling patients	Lower 25(OH)D levels were not associated with impaired performance on various psychometric measures
	[91]	225 older outpatients diagnosed as having probable AD	Significant positive association between MMSE test scores and serum 25-hydroxyvitamin D(3) levels
Case-control study	[92]	5596 community-dwelling women	Significant positive association between vitamin D intakes and cognitive performance
	[93]	69 community-dwelling patients	A significant negative correlation between dietary intake of vitamin D and poor performance on cognitive tests
	[94]	148 community-dwelling patients	No significant positive association between cognitive performance and serum 25-hydroxyvitamin D(3) levels
Longitudinal study	[95]	1138 community-dwelling men	Independent association between lower vitamin D levels and odds of cognitive decline
	[19]	175 community-dwelling patients	1.60-fold risk of losing at least 3 points on MMSE in 6 yr with low baseline vitamin D
Pre-post study	[96]	63 frail nursing home residents 25 in intervention group 38 in control group	No treatment-induced improvement in ambulation, cognition or behaviour was observed
	[21]	13 community-dwelling patients with mild to moderate AD	Significant improvement in ADAS-cog score
Randomised controlled trial	[21]	32 community-dwelling patients with mild to moderate AD 16 in intervention group 16 in control group	Neither cognition nor disability changed significantly after high-dose D

AD: Alzheimer's disease.

study design and exclusion of some confounders from analysis, for example treatment with psychotropic medication^[20]. Pre-post studies, where cognitive function was measured before and after supplementation of vitamin D, found an improvement in cognition concomitant with the increase in vitamin D concentrations^[5]. There is only one, small randomised controlled trial on this topic, where 32 individuals with mild to moderate AD received low-dose vitamin D supplementation for 8 wk, before being randomised to either continue with the low dose (plus placebo) or to receive an additional high-dose supplement for a further 8 wk. Cognition was tested using a number of validated scales. Despite promising results from a smaller pilot study, the authors found that supraphysiological doses of vitamin D were no better than physiological doses at improving cognition or disability in this group, but acknowledge the limitations of such a small sample size^[21].

Vitamin K

Vitamin K is the collective term for a group of fat-soluble vitamins responsible for gamma-carboxylation of glutamate at various sites in the body. In the liver, vitamin K plays a vital role in the modification of prothrombin and other proteins responsible for haemostasis^[1]. In addition, vitamin K promotes bone health by means of site-specific carboxylation of osteocalcin (a marker of bone formation) and other bone matrix proteins such as matrix Gla-protein and protein S^[22]. In vitamin K deficiency,

undercarboxylated osteocalcin is associated with osteoporosis and increased risk of fracture^[1]. A meta-analysis of 3 trials involving patients with neurological disease (AD, stroke and Parkinson's Disease) showed that when vitamin K is replaced, there is a decreased risk of fractures compared to non-treatment^[23].

As with vitamin D, the link between vitamin K and osteoporosis is well-established, whilst any connection to dementia remains both multifactorial and largely theoretical. Numerous observational studies from Japan have indicated that vitamin K deficiencies contribute to reduced bone mineral density in patients with AD^[22]. A number of reasons have been postulated for the association between vitamin K deficiency and dementia including that of reverse causality.

It is plausible that, rather than vitamin K deficiency causing dementia, it is the dementia which affects vitamin K levels through malnutrition. Suboptimal dietary intake is evident even in the early stages of AD compared to cognitively intact age-matched controls^[24]. In humans, vitamin K₁ is dietary, whilst K₂ is synthesised by gut bacteria^[3]. In a cross-sectional study of 100 women with varying degrees of AD, BMI, bone mineral density and vitamin K₁ levels were significantly lower in severe AD compared to mild AD^[3]. However, vitamin K₂ levels were not significantly decreased, indicating a nutritional cause. Another study analysed the dietary vitamin K intakes of 31 patients with mild AD, compared to 31 controls.

Vitamin K intakes were significantly less in patients with AD, even after adjusting for energy intake^[25].

Nevertheless, vitamin K does also appear to have a direct effect on the brain. Vitamin K-dependent gamma-carboxylation of glutamate in the liver and bone has already been discussed. This process is also apparent in the brain, by which growth-arrest-specific gene (*Gas6*) is biologically activated. Yagami *et al.*^[26] investigated the effect of *Gas6* in primary cultures of rat cortical neurons. *Gas6* was shown to protect against AD by the rescue of cortical neurons from amyloid-induced apoptosis^[26]. In addition, vitamin K is involved in sphingolipid synthesis. Sphingolipids are an important constituent of the myelin sheath and the neuron cell membrane, and alterations in sphingolipid metabolism have been identified in the brains of patients with mild AD^[25].

Alternatively, dementia and vitamin K deficiency may share a common cause. As previously discussed, apolipoprotein E4 (APOE4) is an allele that has been well-established as a risk factor for AD^[3]. APOE is found in chylomicrons which bind to vitamin K in plasma^[1]. APOE binds to a hepatic LDL receptor and LDL receptor-related protein (LRP); the variant APOE4 binds particularly quickly, thus reducing plasma vitamin K levels^[1]. The concentration of vitamin K is therefore lower in the circulating blood of APOE4 carriers^[1] and women expressing the APOE4 allele have been shown to have a significantly increased risk of osteoporotic hip fractures compared with those with other APOE genotypes^[27]. Another genotype, consisting of two copies of the apolipoprotein allele E2, has also been associated with increased frequency of vertebral fractures, suggesting further that apolipoprotein polymorphisms may play a role in bone mineral density and fracture risk^[28].

Although the association between vitamin K and dementia appears strong, there is little outside of cell work to prove a causal relationship. The evidence thus far lies in observational studies^[22] and a small number of randomised controlled trials in which vitamin K supplementation has been proven to reduce the risk of fractures in patients with neurological disease^[23]. This effect is assumed to be bone-mediated, and the possibility of improved cognitive function is not explored.

Calcium and hyperparathyroidism

Calcium has long been known to contribute to bone health. In combination with vitamin D, calcium promotes osteoblast differentiation and formation of mineralised bone, thus impairment in calcium signalling can contribute to the pathophysiology of osteoporosis^[29]. Likewise, the role of calcium homeostasis in the pathophysiology of dementia has been extensively investigated for almost three decades. The "calcium hypothesis" of the late 1980s^[30] postulates that "in the aging brain, transient or sustained increases in the average concentration of intracellular free calcium contribute to impaired function, eventually leading to cell death". This hypothesis was supported by a range of animal and human studies, the earliest of which have been well-described by Disterhoft *et al.*^[30]. For example, administration of magnesium, a

calcium channel antagonist, to aging rats was shown to reduce calcium influx in hippocampal neurons and reverse functional and learning difficulties. Similarly, nimodipine, an isopropyl calcium channel antagonist that readily crosses the blood-brain barrier, was found by a recent Cochrane review to be of "some benefit in the treatment of patients with features of dementia due to unclassified disease or to AD, cerebrovascular disease, or mixed Alzheimer's and cerebrovascular disease" although the authors stressed this benefit could only be applied to short-term outcomes^[31].

The role of calcium in the pathophysiology of impaired cognition is complex. Calcium is required for the function of all cells in the body, including neurons. The neurons of aged animals have been found to exhibit enhanced calcium activity compared to their younger counterparts^[32]. This has been attributed to an excess of calcium influx *via* voltage-gated calcium channels. Indeed, an increased density of these channels has been positively correlated with cognitive decline in animals. Further, in humans, enhanced intracellular calcium release from the endoplasmic reticulum has been found in the ageing brain, and research into this phenomenon continues^[32].

To propose that changes in calcium transport and metabolism forms the basis of link between osteoporosis and dementia seems counterintuitive, as the former may result from falling calcium levels, whilst the latter has been attributed to high intracellular calcium. One possible mechanism is that calcium deficiency and the resultant secondary hyperparathyroidism results in bone loss whilst shifting calcium from the skeleton to the soft tissue, and from the extracellular to the intracellular compartments^[33]. Indeed a recent cross-sectional study has found association between high levels of PTH with low bone mineral density, which persisted even in participants where serum calcium levels were not overtly deficient^[34].

Increased parathyroid activity is well known to be associated with impaired cognitive function. Moreover, a recent 10-year longitudinal prospective study found that elevated PTH concentrations are associated with a five-year cognitive decline in a general aged population, although this was found to be independent of calcium concentrations^[35]. Further investigation would be required to establish a common role for calcium as a contributing factor to both osteoporosis and cognitive decline.

Thyroid disease

Overt thyroid disease is well known to be a reversible cause of cognitive impairment and altered bone metabolism^[36]. Subclinical thyroid disease - whereby normal levels of thyroxine (T4) and tri-iodothyronine (T3) are coupled with a deranged level of thyroid stimulating hormone (TSH) - is being increasingly recognised as a cause of significant morbidity and mortality within the elderly population^[37].

Subclinical hyperthyroidism: Subclinical hyper-

thyroidism (levels of T3 and T4 that are towards the top of the reference range coupled with reduced TSH, without symptoms of thyrotoxicosis) has been associated with various pathologies, and affects both bone mineral density and cognition^[38]. This may be due to exogenous causes, *i.e.*, excessive replacement with levothyroxine in hypothyroid patients; or endogenous causes such as Grave's disease^[37].

There is considerable debate as to whether it is the level of TSH or of T4 itself that results in the physiological effects of thyroid hormone excess. A prospective study in Rotterdam found that individuals with subclinical hyperthyroidism had a greater than threefold increase in risk of developing dementia; with higher levels of T4 conferring greater risk. It is worth noting that none of these patients had a T4 level above the reference range^[36]. This finding is supported by a further retrospective study, which also demonstrated an association between elevated thyroid hormone levels and dementia, not related to the concentration of TSH. It therefore seems likely that the level of T4 is the important determinant^[39]. Furthermore, in a prospective cohort study of 665 Japanese-American men, followed-up for development of dementia after thyroid function was recorded, subsequent autopsy of one fifth of the cohort-including both healthy and demented patients-demonstrated that at higher levels of T4, more numerous intracerebral tangles and plaques are seen, as well as clinical dementia^[40].

Data regarding any association between osteoporosis and subclinical hyperthyroidism is unclear. Some studies show low levels of TSH appear to result in slightly reduced bone mineral density in men and post-menopausal women, but the protective effect of oestrogens means this does not generally apply in pre-menopausal women^[41]. The fifth Tromso population study in Norway, conducted in 2001, compared bone mineral density levels of TSH whilst adjusting for possible confounding factors such as weight and smoking. It discovered that, if TSH was normal, there was no relationship to bone mineral density; however, low TSH was seen in subjects with lower bone mineral density^[42]. T4 levels that are within the normal range are correlated with a lower level of bone mineral density at both the higher and lower ends of the spectrum - that is, in the region of subclinical thyroid disease^[36,43]. These hormone derangements are also associated with increased risk of fracture^[44].

Subclinical hypothyroidism: Subclinical hypothyroidism is a significant problem within the elderly population, and is more common than overt hypothyroidism^[45]. Despite the above discussion relating subclinical hyperthyroidism to cognitive impairment and dementia, patients with subclinical hypothyroidism have also been shown to be more likely to develop such attributes^[46]. This may be due to the effect of T4 itself, or reduced hormone concentration within the brain, resulting in slower information processing and increased susceptibility to cognitive dysfunction^[47]. It is also worth noting that treatment with levothyroxine has

been shown to reduce cognitive impairment and improve mood in patients with mild hypothyroidism^[48]. Currently, although there is evidence that both states can cause cognitive decline, subclinical hyperthyroidism appears to have a stronger association with the development of dementia. A small scale study of 59 patients with multi-diagnosis dementia found a slight increase in TSH serum levels patients with AD compared to other diagnosis dementia patients and with healthy controls, along with a decrease in cerebrospinal fluid (CSF) total T4 levels in both patients with AD and those with other diagnoses compared to healthy controls^[49]. The CSF total T4 levels correlated positively with MMSE test scores and negatively with markers of axonal damage, which the authors hypothesized may mean that central levels of T4 are functionally important in AD^[49].

Despite the association between subclinical hypothyroidism and cognitive impairment, osteoporosis has not specifically been linked to subclinical hypothyroidism. Overtreatment of these patients with thyroxine has in fact been shown to lead to reduced bone mineral density and an increased rate of osteoporosis^[50,51]. This represents an important clinical disadvantage, and clinicians should exert caution in deciding whether or not to treat subclinical hypothyroidism^[51]. Subclinical thyroid disease is common in the elderly population, and has been shown to be associated with a number of co-morbidities including osteoporosis and dementia in the case of subclinical hyperthyroidism. Additional work is required to establish if age-related changes in thyroid hormone concentrations represent a common factor in the aetiology of both conditions. Furthermore, investigating the treatment of subclinical disease, and whether or not it results in a lower rate of dementia and osteoporosis in the elderly, represents an exciting avenue for research in the future.

Alcohol

Excessive alcohol use is well known to result in low bone mineral density and increased risk of fracture^[52]. This has been thought to be due to a direct deleterious effect on osteoblast activity and subsequently a decrease in bone formation^[53], however this mechanism is not likely to be related to the development of dementia. Recently it has been suggested that lower levels of vitamin D in chronic alcoholics may be related to hepatic insufficiency and subsequently impaired metabolism of the substance^[54]. This could in turn affect bone formation. It must be remembered that low to moderate levels of alcohol intake does not reduce bone density; however, there has been no protective effect demonstrated either.

Whilst chronic excessive alcohol use leads to unique forms of dementia (*i.e.*, Korsakoff's syndrome) this is secondary to vitamin deficiencies, especially thiamine. Ethanol toxicity has been shown in rats to cause hippocampal and cortical cell loss, as well as loss of proteins required for neuronal survival^[55]. However, at low to moderate levels of intake there appears to be a protective effect against developing dementia^[56,57]. Interestingly, there was no protective effect seen in individuals with the

APOE4 gene^[56]. The reasons for this protective effect are currently unclear.

It is difficult to assess whether alcohol intake is related to an increased risk of osteoporosis and dementia, especially given the likely protective effect of a moderate alcohol intake against dementia. The multiple comorbidities often experienced by chronic alcoholics (most notably nutrient deficiency) means studies are affected by a number of confounding factors. Varying patterns in form and frequency of alcohol abuse also make analysis difficult. Any link that were to be demonstrated would possibly be due to a secondary impact on another aspect of physiology (such as vitamin D deficiency), as opposed to an innate property of ethanol itself.

Statins

Statins (HMG CoA reductase inhibitors) are currently the target of a large volume of research given their supposed pleiotropic effects. As well as treating dyslipidaemia, statins have been proposed as being effective against malignancy, nephropathy, cataract formation and macular degeneration as well as against osteoporosis and dementia^[58].

The role of statins in reducing the risk of dementia was classically thought to be due to their role in reducing plaque formation, hence reducing vascular insults to the brain and the risk of ischaemic neuronal loss^[59]. Newer studies have proposed a systemic reduction in the inflammatory response, as evidenced by the ability of statins to reduce levels of C-reactive protein^[60]. Statins act on the mevalonate pathway, inhibiting conversion of HMG-CoA to mevalonate^[61]. Mevalonate is a precursor of the interleukin-6 group of cytokines which are implicated in systemic inflammation^[60]. It is possible that a reduction in systemic inflammation by inhibiting this pathway may help to prevent the development of dementia^[62].

Given the interest in the proposed mechanisms, Cochrane reviews have been held into randomised controlled trials of both the prevention and treatment of dementia by statins. They have found that despite marked reductions in serum low density cholesterol levels, statin use neither improves cognitive function in those with dementia nor does it reduce the incidence. The reviews conclude that there is insufficient evidence to recommend statins as either a prophylactic against, or treatment for, dementia^[63,64].

New theories on the development of osteoporosis hold that the mechanism is similar to that whereby lipids are oxidised^[65]. If statins were shown to act directly on this mechanism then a beneficial effect in osteoporosis would also be likely. *In vitro* studies investigating mechanisms by which statins stimulate osteoblast differentiation have demonstrated that they exert their effects *via* the SMAD and the bone morphogenetic protein-2 (BMP-2) signalling pathways^[66]. A recent review of *in vitro* and *in vivo* data suggests that statins also act *via* the RANKL pathway, which has been implicated in both adipogenesis and in changing osteoclastic activity, leading to osteoporosis^[67].

Whilst there are theoretical benefits of statins in both dementia and osteoporosis, they have yet to be demonstrated in clinical studies. A large meta-analysis of hip bone mineral density showed a small but statistically significant benefit in patients taking statins^[68]. However, this advantage does not translate into a decreased risk of fracture, according to a systematic review of studies observing fracture incidence in patients taking statins^[69]. A recent RCT has also failed to demonstrate the benefit of specific statins in decreasing fracture risk^[70]. Further evidence is required before routine statin use can be recommended for the prevention or treatment of either condition.

Androgens and oestrogens

Sex steroids play important roles in reproductive function, and in recent years receptors for these hormones have been identified in a range of body tissues, including bone and the nervous system^[71]. The relationship between ageing, falling levels of sex steroids, and the subsequent reduction in bone mineral density is well described and a cause of much morbidity in the elderly population. Reduction in oestrogen levels in women is known to result in increased osteoclast activity and bone resorption^[72]. The androgens are also known to be important in maintaining bone mineral density, both through intrinsic activity and as a result of aromatization to oestrogens^[73]. Androgen activity gradually reduces in later male life, hence the resulting increase in rates of osteoporosis in older men. Whilst administration of endogenous sex steroids in the form of hormone replacement therapy in post-menopausal women does reduce the risk of fracture, it is no longer recommended for the prevention of osteoporosis due to cardiovascular side-effects^[74]. Newer theories propose that oxidative stress holds an important role in the development of osteoporosis, and that sex steroids are important in protecting against this^[65]. This would represent a possible therapeutic target with statin agents, if such a mechanism is proven.

Androgens and oestrogens have been suggested as being protective against AD, given that cognitive impairment is associated with a decrease in testosterone levels^[75]. Animal studies have shown increased neuronal activity when testosterone supplements are administered, but the data from clinical trials is disappointingly inconclusive^[75]. Additionally, the role of oestrogen in both preventing cognitive decline in intellectually normal women, and in maintaining cognitive function in patients with AD, has been the subject of a number of systematic reviews. Insufficient evidence for any beneficial effect was found for oestrogen administration in all studies reviewed^[76,77]. Moreover, one review of long-term hormone replacement therapy found that in healthy women aged over 65 there was an increased incidence of dementia^[74], although this is unlikely to be due to a direct effect of hormone replacement, and may simply be a result of an increase in frequency of cardiovascular events, a known independent risk factor for developing dementia.

There has been recent animal work looking at the effects of sex steroid analogues, so called selective androgen receptor agonists (SARMs) and selective estrogen receptor agonists, which are thought to allow for the beneficial effects of the sex steroids in protecting against neurodegenerative disorders whilst avoiding detrimental cardiovascular tissue effects which may also contribute to development of dementia^[78]. Such analogues are thought to interfere in the progression of AD by aiding clearance of amyloid beta peptides from neurological tissue^[78]. In the treated mice there were decreased levels of amyloid beta, along with increased levels of amyloid beta clearing enzymes and improved long term memory^[78].

The evidence surrounding changes in sex steroid levels and dementia is inconclusive. There is no firm evidence for a beneficial effect of androgen administration, and the increase in frequency of cardiovascular events causes significant morbidity and may increase the prevalence of dementia itself. This may be due to the significant increase in cholesterol levels associated with falling androgen levels^[79]. Additionally, the low levels of androgens demonstrated in some men with dementia may be unrelated or may be secondary to the disease itself.

DISCUSSION

Despite various possible mechanisms for a link between the two pathologies, it is also quite possible that these associations are coincidental and not related to a common aetiological factor. Only one such investigation into common aetiologies exists in a 2014 study which found raised amyloid beta peptide levels in osteoporotic bone tissue compared to age matched controls in female patients^[80]. The level of amyloid beta expression negatively correlated with bone density levels in this study^[80]. Amyloid beta was found to also have an impact on osteoclast differentiation and activation, implying it may play a role in the pathological processes of osteoporosis^[80]. Authors hypothesized amyloid beta disorders to be systemic disorders resulting in differing tissue manifestations^[80], yet robust evidence remains to be produced regarding this link and regarding the exact aetiology of amyloid beta in AD.

People with dementia are more prone to falls and fractures due to cognitive and behavioural disorders, visual and motor problems, gait and balance disturbances, malnutrition, and the adverse effects of medication^[81]. Thus there may be a higher pick-up rate for osteoporosis amongst this group. However, a population-based study of more than 2600 elderly people found that those with dementia received less preventative treatment for osteoporosis compared to people without dementia^[82]. In patients who have received the appropriate prescription, efficacy may be diminished in patients with dementia due to factors such as medical comorbidities, polypharmacy, lack of adherence, substance abuse, delirium and inadequate social support^[83].

Nevertheless, we hypothesise that dementia and osteoporosis have common aetiologies as significant

counterevidence exists in recent literature. There remains a significant increased prevalence of osteoporosis in AD sufferers in large scale observational studies compared to the general population, with an odds ratio for femoral fracture amongst a French female population the same as that of other severe systemic illnesses (OR = 4, $P < 0.0001$). The mortality and morbidity associated with such fractures in elderly populations prompts continued interest in this area of research^[84]. Furthermore, following femoral neck fracture treatment and subsequent inpatient stays, this subsection of the population has been found to have poor return to previous functional states as measured by residential status, along with poor 30-d mortality compared to patients without dementia^[85]. Other very large scale observational studies have had compelling results in favour of a potential link, with Chang *et al.*^[86] finding a 1.46-fold and 1.39-fold higher risk of dementia (95%CI: 1.37-1.56) and AD (95%CI: 0.95-2.02) in osteoporosis patients studied, whilst adjusting for potential confounders such as comorbid disease. This Taiwanese cohort also demonstrated a negative correlation between treatment for osteoporosis (such as bisphosphonates) and the risk of dementia, with the most marked negative correlation found in those taking bisphosphonates and oestrogens^[86]. However, patients with dementia have repeatedly been found to be least likely to be prescribed osteoporosis treatments which may have such protective effects both in terms of fracture risk and cognitive health^[87]. Despite these recent findings, the same limitations to such large scale retrospective studies apply and further RCTs would be required to provide higher quality evidence of such links despite the varied evidence explored in this paper.

The most compelling evidence for a common aetiology is the APOE4 allele, a major cholesterol carrier, and a well-established genetic risk factor for AD *via* its binding to Amyloid beta peptide and its potential role in deposition of senile plaques^[3]. APOE4 has also been found to be associated with fracture, independent of dementia and falling^[27]. The mechanism behind this effect on fracture risk is postulated to be the reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele, which binds vitamin K in the plasma and promotes its uptake into the liver more rapidly than other APOE variants. Women who express this allele have a higher risk of osteoporotic fractures than other APOE genotypes found in the general population^[1]. This may be multifactorial in its effect and augmented by the nutritional deficiencies associated with dementia, which are known to include vitamins K and D. In particular, vitamins D and K are known to play a role in the both bone matrix stability and neuronal protection in the CNS. The vitamin theory postulates that malnutrition and reduced exposure to sunlight in patients with AD leads to vitamin deficiencies.

Robust evidence of an underlying pathophysiological link between osteoporosis and dementia would potentially transform the care of the older adult. Research to date has tended to be fragmented and of a relatively weak

nature with multiple confounding factors reflecting the difficulties of *in vivo* experimentation in the population of interest. A suggestion for future work would include randomised controlled trials of vitamin supplementation vs placebo, stratified for APOE4 and hormone status. As our understanding of the molecular basis of osteoporosis and dementia improves, new therapeutic targets should become apparent.

COMMENTS

Background

Dementia and osteoporosis are diseases processes with similar epidemiology and increasing prevalence in the elderly, where the two coexist in a subsection of the population especially amongst females. The burden of elderly care continues to be a significant challenge to healthcare systems globally. Alzheimer's disease (AD) is the leading cause of loss of independence and autonomy in the elderly and osteoporotic fractures have a huge impact in this patient population in terms of morbidity and mortality. An odds ratio of 6.9 for fracture prevalence between people with and without AD has been reported. In current understanding of the disease aetiologies no pathological overlap has been identified but a common link has been postulated to exist. The pathogenesis of AD is currently understood to involve development of amyloid plaques causing neuronal death and subsequent phosphorylation of Tau proteins, which ultimately cause further neuronal degeneration and the localisation of these two abnormal proteins in the synapses causes post-synaptic neuronal death via calcium influx. Despite extensive research into AD and its multifactorial pathophysiology, current treatments are limited by cost and efficacy and their action lies in palliation of symptoms. Osteoporosis in contrast is a progressive skeletal disease characterised by reduced bone density and micro-architectural bone destruction leading to increased susceptibility to fracture. Both diseases have multifactorial pathophysiology and have been associated with other metabolic disturbances including decreased vitamin D levels and elevated parathyroid hormone. Other genetic variants such as the APOE4 allele have also been postulated to link their pathophysiology.

Research frontiers

Both osteoporosis and AD form part of frailty syndrome, a collection of signs and symptoms associated with significant disability in the elderly population and increased public expenditure in healthcare and social care systems. This paper hypothesizes that both diseases share a common predisposing aetiology, which may be multifactorial and involve genetic, metabolic, endocrine and environmental factors.

Innovations and breakthroughs

Many studies have been conducted in the last 60 years exploring various aspects of the pathophysiology of both osteoporosis and dementia as both diseases represent significant burdens upon the affected populations. However very few have been higher tier research designs such as randomised control trials or specifically examined an aetiological link as addressed by the research question of this paper. The authors' key findings were that the most compelling evidence of a common yet independent aetiology lies in the APOE4 allele, which is a well-established risk for AD but also carries an independent association with fracture risk and so osteoporosis. The mechanism behind this is thought to be the reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele which may be amplified by the nutritional deficiencies associated with dementia, which are known to include vitamins K and D. The vitamin theory postulates that malnutrition and reduced exposure to sunlight in patients with AD leads to vitamin deficiencies which are then well associated with increased risk of fracture.

Applications

Discovery of a common aetiological link between the two may prove key in development of novel treatments for these complex medical and social problems. This study found that research to date on this topic has tended to be fragmented and of a relatively weak nature with multiple confounding factors, which may reflect inherent difficulties of *in vivo* experimentation in the

population of interest. Despite many theoretical links between the two diseases, there is a lack of systematic high level evidence and as such the link between the two remains theoretical. This study may help direct design of future large scale studies or RCTs in the affected population groups.

Peer-review

This is an interesting study, and what is reviewed is well done.

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P- Reviewer: Gonzalez-Reimers E, Lee YK, Li JX **S- Editor:** Ji FF
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