Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Osteocalcin

Evidence Summary

Only observational and preclinical studies exist for osteocalcin and the evidence is mixed on whether low or high levels are predictive of better health.

Neuroprotective Benefit: Higher osteocalcin levels are associated with better cognitive functions but also with Alzheimer's disease; neuroprotective potential of osteocalcin has only been demonstrated in mice so far.

Aging and related health concerns: Only observational studies exist for humans. Both low and high levels of osteocalcin have been associated with increased risk for mortality; and high levels are also seen in some cancers.

Safety: Osteocalcin is a protein hormone naturally present in osteoblasts and dentin, but there have not been any studies testing its therapeutic potential in humans.

What is it? Osteocalcin is a noncollagenous protein and hormone synthesized in osteoblasts and odontoblasts (in dentin). Osteocalcin levels in the blood are often used as a biomarker of bone formation and turnover, particularly in treatment paradigms for osteoporosis or other conditions affecting bone formation. Some observational as well as preclinical studies have suggested that osteocalcin has functions beyond bone formation, including regulation of cognitive, metabolic, and cardiovascular functions (Kanazawa, 2015; Levinger et al., 2017). But therapeutic potentials of osteocalcin have only been tested in rodents so far.

Neuroprotective Benefit: Higher osteocalcin levels are associated with better cognitive functions but also with Alzheimer's disease; neuroprotective potential of osteocalcin has only been demonstrated in mice so far.

Types of evidence:

- 3 observational studies examining the association between blood osteocalcin levels and cognitive functions
- 3 observational studies examining the association between osteocalcin levels and ApoE genotype
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Only observational studies exist to date. In a cross-sectional study of 225 old and 134 young people, plasma osteocalcin levels were positively associated with measures of executive functioning and global cognition in older non-demented women (Bradburn et al., 2016). There was also an association between higher osteocalcin levels and better working memory function in older women, but this failed to reach statistical significance after controlling for multiple analyses. It is unclear why the association was specific to older women, but it is possible that this population is more susceptible to problems with bone formation/turnover, especially with increased risk of osteoporosis after menopause. However, no associations were found between whole body bone mineral density and cognitive functions (episodic memory, working memory, executive functioning, or global cognition) in young or old, women or men. A smaller cross-sectional study in 44 people reported that lower osteocalcin concentrations were associated with higher Iowa Gambling Task (IGT) scores, which indicate worse cognitive function (Puig et al., 2016).

Human research to suggest benefits to patients with dementia:
No studies have tested osteocalcin as a treatment for dementia. One observational study including 20 Alzheimer's patients, 19 with mild cognitive impairment (MCI), 7 with osteoporosis, and 8 cognitively healthy controls reported that blood levels of osteocalcin is significantly *higher* in Alzheimer's disease (by 76%) and non-significantly higher in osteoporosis (by 63%) compared to controls (Luckhaus et al., 2009). People with MCI had osteocalcin levels comparable to those in cognitively healthy controls. The authors suggest that the increased osteocalcin levels observed in Alzheimer's is related to increased bone catabolism. It is currently unknown whether manipulating osteocalcin levels would be beneficial or harmful to dementia patients.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Several studies in mice have shown neuroprotective effects from osteocalcin treatment. A study from 2013 showed that osteocalcin crosses the blood-brain barrier, binds to neurons of the brainstem, midbrain, and hippocampus, enhances the synthesis of monoamine neurotransmitters, inhibits GABA synthesis, prevents anxiety and depression, and promotes learning and memory independently of its metabolic functions (Oury et al., 2013). They also showed that maternal osteocalcin crosses the placenta during pregnancy and prevents neuronal apoptosis before embryos synthesize this hormone. Osteocalcin knockout mice had severe neuroanatomical defects and learning and memory deficits but delivering osteocalcin to pregnant osteocalcin-knockout mothers rescued these abnormalities in their progeny. The method of delivery for osteocalcin-knockout mice was an Alzet micro-osmotic pump surgically implanted subcutaneously, which released 300 ng/hour of uncarboxylated osteocalcin. In rescue experiments, 10 ng/hour of osteocalcin was delivered via intracerebroventricular infusion.

A 2017 study from the same group sought to define the mechanisms underlying the cognitive effects of osteocalcin (Khrimian et al., 2017). Peripheral delivery of osteocalcin improved memory and decreased anxiety-like behaviors in old mice. The method of delivery was the same micro-osmotic pump described above, which released 90 ng of uncarboxylated osteocalcin per hour. They discovered that osteocalcin modulates cognitive function through its interaction with Gpr158, an orphan G protein-coupled receptor expressed in hippocampal neurons. They also found that osteocalcin treatment increases BDNF expression in wild-type mice but not in mice where Gpr158 is deleted.

APOE4 interactions: It is unknown whether osteocalcin treatment will be more or less effective in ApoE4 carriers. An observational study in 413 postmenopausal women reported that ApoE3 carriers had higher bone mineral densities and higher serum concentrations of osteocalcin compared to non-carriers (Souza et al., 2017). The ApoE4 allele was associated with lower bone mineral density as well as higher levels of

biomarkers for bone resorption (serum C-terminus collagen peptide and urinary deoxipyridinolines). It is possible that the ApoE4 allele may be associated with lower bone formation as well as increased risk of osteoporosis and bone fractures, whereas ApoE3 appears to be protective. However, a larger observational study of 1,406 people reported that while the presence of ApoE4 was associated with lower bone mineral density, bone markers (osteocalcin, urinary deoxypyridinolines) and fractures were not associated with ApoE4 in men or women (Pluijm et al., 2002).

Aging and related health concerns: Only observational studies exist for humans. Both low and high levels of osteocalcin have been associated with increased risk for mortality; and high levels are also seen in some cancers.

Types of evidence:

- 6 meta-analyses examining the associations between blood osteocalcin levels and age-related conditions
- 4 observational studies examining the associations between blood osteocalcin levels and age-related conditions and/or mortality
- Numerous laboratory studies and reviews

Mortality: MIXED. In a prospective cohort study of 3,542 community-dwelling elderly men (70-89 years old), a U-shaped relationship was found between total osteocalcin levels and all-cause mortality (Yeap et al., 2012). People with the lowest (HR=1.36; 95% CI, 1.02-1.80) and highest quintile (HR=1.53; 95% CI, 1.18-1.98) of osteocalcin levels had increased all-cause mortality compared to those in the second quintile. People with the lowest (HR=1.35) and highest quintile (HR=1.69; 95% CI, 1.09-2.64) of osteocalcin also had significantly increased risks of cardiovascular disease-related mortality. The "optimal" range of total osteocalcin levels associated with lower mortality in older men corresponded to the middle three quintiles with osteocalcin levels ranging from 13.5 to 26.0 µg/L. Higher osteocalcin levels in elderly men may be a reflection of increased bone turnover and act as a biomarker for poorer health outcomes and frailty.

In contrast, a smaller prospective cohort study of 774 older men (51-85 years old) reported that higher osteocalcin levels were associated with lower 10-year all-cause mortality; an increase of 10 ng/mL of total osteocalcin was associated with a 38% reduction in risk of all-cause mortality (HR=0.62, 95% CI, 0.44-0.86)(Confavreux et al., 2013). Subjects in this cohort were on average younger than the study described above and may have included fewer men with high bone turnover and/or frailty.

Because both studies were observational, it is unknown whether manipulating osteocalcin levels would have any impact on longevity. No preclinical studies have tested the effects of osteocalcin on lifespan.

Cardiovascular: MIXED. A 2017 meta-analysis of 46 observational studies suggested that there is no definitive association between blood osteocalcin levels and vascular calcification or atherosclerosis (Millar et al., 2017). No significant differences between osteocalcin levels were detected between patients with atherosclerosis and controls. However, in studies using histological staining for osteocalcin, the presence of osteocalcin-positive cells was associated with calcification and atherosclerosis. This meta-analysis found 26 positive, 17 negative, and 29 neutral relationships, with ethnicity potentially playing a role (more negative relationships in Asian compared to European studies).

A longitudinal study of 1280 middle-aged men (not included in the above meta-analysis) also reported that serum total osteocalcin level was not associated with the development of cardiovascular disease after adjusting for other risk factors (Hwang et al., 2015). No differences were observed across osteocalcin tertiles in the prevalence of hypertension, stroke, coronary heart disease, or cardiovascular disease.

However, a prospective cohort study of 774 older men (51-85 years old) showed that higher baseline osteocalcin levels were associated with lower progression rates of abdominal aortic calcification; an increase of 10 ng/ml of osteocalcin was associated with a 26% reduction in progression rate (OR=0.74; 95% CI, 0.57-0.97)(Confavreux et al., 2013). This reduction also translated to lower all-cause mortality in the study.

A study using ApoE knockout mice showed that a daily intraperitoneal injection of osteocalcin (30 µg/kg body weight) for 12 weeks showed improved endothelium-dependent relaxation, which is protective against atherosclerosis (Dou et al., 2014). Osteocalcin may be mediating this effect by signaling through the PI3K/Akt/eNOS pathway.

Osteoporosis: NO HARM. A meta-analysis of 5 case-control studies including 300 adult males reported that there were no significant differences between people with osteoporosis and controls in serum osteocalcin levels (Liu et al., 2017).

In a huge meta-analysis of 33 studies (total of 1,663,665 people) evaluating the effects of statins on risk of fractures, the use of statins was associated with increased bone mineral density and higher levels of

osteocalcin (An et al., 2017). This study suggested that statins may have a greater effect on these measures in men compared to women.

Weight: POTENTIAL BENEFIT. In a meta-analysis of 25 case-control or cohort studies, there was a significant inverse association between serum osteocalcin levels and BMI (r = -0.161; 95% CI, -0.197-0.124) such that higher osteocalcin levels were linked to lower BMI (Kord-Varkaneh et al., 2017). These associations were most pronounced in studies with metabolic syndrome patients.

Diabetes: POTENTIAL BENEFIT. In a meta-analysis of 24 observational studies, total osteocalcin level was significantly lower among type 2 diabetes patients than controls, and high total osteocalcin level was significantly and independently associated with decreased risk of diabetes (OR=0.70; 95% CI, 0.56-0.88) (Liu et al., 2015). A different meta-analysis of 39 observational studies totaling 23,381 subjects reported that blood osteocalcin levels (uncarboxylated or total) were inversely correlated with fasting plasma glucose and glycated hemoglobin A1c (Liu et al., 2015). These inverse correlations were more pronounced in men than in women.

Several mouse studies have shown that daily injections of osteocalcin improved glucose tolerance and insulin sensitivity while preventing the development of obesity (Ferron et al., 2008; Dou et al., 2014). Cell-based studies have shown that osteocalcin regulates the expression of insulin and proliferation markers in beta cells. Osteocalcin also affects adiponectin and Pgc1α expression in white and brown adipocytes, respectively.

Cancers: POTENTIAL HARM. Osteocalcin is expressed in several solid tumors, including osteosarcoma and ovarian, lung, brain, and prostate cancers (Koeneman et al., 2000). A cross-sectional study in 239 pre- and postmenopausal women reported that osteocalcin levels were associated with high-risk pattern mammograms and this association was most pronounced in obese postmenopausal women (Vega et al., 2017). In the study, osteocalcin levels were increased in postmenopausal women. Neither of these studies was designed to determine whether higher osteocalcin levels are causal to tumor formation or growth.

Safety: Osteocalcin is a protein hormone naturally present in osteoblasts and dentin, but there have not been any studies testing its therapeutic potential in humans.

Types of evidence:

- Numerous observational studies examining the associations between blood osteocalcin levels and health conditions

There are no studies that have tested osteocalcin as a therapeutic in humans. But it is a protein hormone naturally present in the body, particularly in osteoblasts and dentin. Some studies described above have associated higher blood levels of osteocalcin with better health, while others have associated higher levels with Alzheimer's disease and cancer (Luckhaus et al., 2009; Koeneman et al., 2000). It is possible that manipulating levels of osteocalcin may alter dementia/cancer risk or progression. However, it is equally possible that changes in osteocalcin levels are merely a consequence of dementia/cancer or of old age and not associated with increased risk and/or disease progression.

Drug interactions: Unknown.

Sources and dosing: No studies have tested osteocalcin as a therapy in humans. A mouse study that showed cognitive benefits with osteocalcin used uncarboxylated osteocalcin at 30 ng/hr and 90 ng/hr for 12- and 16-month-old mice, respectively (Khrimian et al., 2017). Osteocalcin was administered via Alzet microosmotic pumps that were surgically installed subcutaneously in the back of the mice. A different study reported that a daily intraperitoneal injection of osteocalcin (30 µg/kg body weight) for 12 weeks improved lipid metabolism, glucose tolerance, and insulin sensitivity in APOE knockout mice (Dou et al., 2014). The human equivalent dose is 2.44 µg/kg/day.

Research underway: Based on ClinicalTrials.gov, there are no studies that are testing osteocalcin as a therapy in humans. Dr. Gerard Karsenty, an investigator at Columbia University, has received a program project grant from the NIH to study the effects of osteocalcin on cognitive functions in mice as they age (P01 AG032959). He is the senior author on two mouse studies discussed in the Neuroprotective Benefit section (Oury et al., 2013; Khrimian et al., 2017).

Search terms:

Pubmed, Google: Osteocalcin

- + cognitive, + Alzheimer's, + meta-analysis, + systematic review, + ApoE, + mortality, + lifespan, + toxicity, + cancer

Websites visited for osteocalcin:

- Clinicaltrials.gov
- NIH RePORTER
- DrugAge (0)
- Geroprotectors (0)

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.