*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.*

# Insulin-like Growth Factor (IGF-1)

**Evidence Summary**
IGF-1 is a double-edged sword—increasing IGF-1 may improve cognitive and muscle health but may also promote some cancers and potentially shorten lifespan.

**Neuroprotective Benefit:** Higher IGF-1 levels are associated with better cognitive function, but evidence is limited to observational and preclinical studies.

**Aging and related health concerns:** Higher IGF-1 signaling or levels are associated with shorter lifespan and increased risks of some cancers, though some harmful associations are also seen with low IGF-1 levels, including cardiovascular disease risk.

**Safety:** IGF-1 treatment can cause hypoglycemia, which may be prevented with co-infusion of the binding protein, IGFBP-3. IGF-1 treatment should not be used in people with known or suspected cancer as it may promote its growth.

**What is it?** IGF-1 is a hormone similar in structure to insulin. It is produced primarily in the liver, delivered to different parts of the body through the bloodstream, and can enter the brain by crossing the blood-brain-barrier (Benarroch, 2012). It is also synthesized and released in the brain. Bioavailability of IGF-1 is regulated by IGF binding proteins (IGFBP), but when unbound, IGF-1 binds to IGF-1 receptor (IGF1R), IGF/insulin hybrid receptor, or insulin receptor (lower affinity). IGF-1 binding to a receptor initiates multiple signaling cascades, including the PI3K/Akt pathway and the RAS/ERK pathway, which together stimulate protein translation and proliferation while inhibiting oxidative stress and apoptosis.

Most of the effects of growth hormones are mediated through IGF-1, which plays a particularly important role in childhood growth. Synthetic IGF-1 is used for treating growth failure in children. IGF-1 levels increase until puberty, remain high until about 50 years old, then decrease thereafter (Junnila et al., 2013). Growth hormone and IGF treatments are popular among athletes and bodybuilders for their purported effects on supporting muscle growth, endurance, and joint health.

**Neuroprotective Benefit:** Higher IGF-1 levels are associated with better cognitive function, but evidence is limited to observational and preclinical studies.

*Types of evidence:*
- 1 meta-analysis based on 13 observational studies in healthy elderly
- 2 meta-analyses based on 9 and 7 observational studies in Alzheimer's disease patients
- 1 prospective study linking IGF-1 levels and decline in cognitive function in AD patients
- 1 observational study examining the link between IGF-1 levels and cognitive performance
- 1 observational study examining the link between IGF-1 polymorphism and dementia risk
- 2 observational studies examining IGF levels in Alzheimer's patients
- Numerous laboratory studies

*Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?*
No studies have tested the effects of IGF-1 treatment on cognitive function. IGF-1 appears to benefit cognitive function, though all evidence comes from observational studies of endogenous levels. A meta-analysis of 13 observational studies examining a total of 1,981 healthy older subjects showed that higher IGF-1 levels correlate with better cognitive functioning, with a medium-to-large effect size (0.6) (Arwert et al., 2005). Studies showed that higher IGF-1 levels were associated with faster perceptual motor speed (Papadaki et al., 1995) and mental processing speed (Aleman et al., 1999). Thus, increasing levels

of IGF-1 in the brain may potentially prevent cognitive decline and dementia. While IGF-1 crosses the blood-brain-barrier (Pan and Kastin, 2000), having too much IGF-1 in the periphery can be harmful (e.g., cancer). To potentially achieve cognitive benefits, IGF-1 levels in the brain may need to be increased in ways other than increasing total levels of IGF-1.

_Human research to suggest benefits to patients with dementia:_  No studies have evaluated the effects of IGF-1 treatment in dementia patients. Some studies suggest a link between low IGF-1 levels and Alzheimer's disease (AD), though the evidence is mixed. One meta-analysis of 9 observational studies (1,639 people) reported an absence of a relationship between serum IGF-1 levels and AD (Ostrowski et al., 2016). Another meta-analysis of 7 studies (1,342 people) showed that IGF-1 levels are lower in AD patients compared to controls, though this difference only emerged after excluding some studies to remove variability (Hu et al., 2016). In a prospective study that followed AD patients for 2 years, the decline in cognitive function (MMSE score) was steeper among those with lower IGF-1 levels (Vidal et al., 2016). In another observational study, higher serum IGF-1 levels correlated with better cognitive performance in AD patients, and scores on "recall", "verbal fluency", and "attention and calculation" positively correlated with IGF-1 levels (Kimoto et al., 2016).

_Mechanisms of action for neuroprotection identified from laboratory and clinical research:_ IGF-1 infusion improves working memory in aged rats (Markowska et al., 1998). In rat hippocampal neurons, IGF-1 significantly protects against neurotoxicity induced by Aβ peptides, even when neurons are exposed for up to 4 days before treatment (Dore et al., 1997). However, in older AD mice (11-15 months) that exhibit significant pathology, reducing IGF-1 signaling decreases behavioral deficits, inflammation, and neuronal loss (Cohen et al., 2009). These results suggest that IGF-1 may potentially be harmful in the later stages of AD when significant degeneration has already taken place.

IGF-2, another type of insulin-like growth factor, has also received attention recently due to its positive effects on memory. A seminal study reported that IGF-2 is essential for memory consolidation, which requires IGF-2 receptors and new protein synthesis (Chen et al., 2011). Increasing IGF-2 in the brain improves memory in aged rats (Steinmetz et al., 2016) and in AD mouse models (Pascual-Lucas et al., 2014). Some reported mechanisms of action include increased adult neurogenesis (Iwamoto and Ouchi, 2014), increased levels of choline acetyltransferase and neurotrophic factors (BDNF, NGF), and decreased amyloid plaques in APP mice (Mellott et al., 2014). Overall, less is known about IGF-2 compared to IGF-1, as the association between IGF-2 and cognitive function was discovered relatively recently (Chen et al., 2011).

*APOE4 interactions:*  The evidence on interactions between IGF-1 and ApoE status is limited and inconclusive. One observational study in 794 Han Chinese people reported that a certain allele of the IGF-1 gene had a 1.16-fold risk for late-onset AD compared with those with another allele (Wang et al., 2012). After accounting for ApoE status, this polymorphism was only associated with late-onset AD in non-ApoE4 carriers. Mice with ApoE4 have lower levels of IGF-1 in the brain compared to those with ApoE2 or ApoE3 (Keeney et al., 2015), suggesting that different ApoE isoforms may differentially affect IGF signaling.

**Aging and related health concerns:**  Higher IGF-1 signaling or levels are associated with shorter lifespan and increased risks of some cancers, though some harmful associations are also seen with low IGF-1 levels, including cardiovascular disease risk.

*Types of evidence:*
- 6 meta-analyses of observational studies on endogenous levels
- 1 meta-analysis of 21 genome-wide association studies (GWAS's)
- 1 DBRCT in patients with osteoporosis after hip surgery
- 2 genetic studies examining common variants and mutations in genes regulating the insulin/IGF-1 signaling pathway
- 1 prospective study examining the links between IGF-1 levels, longevity, and cancer history
- Numerous laboratory studies

*Longevity*: HARM. Low levels of IGF-1 or IGF-1 activity are associated with longevity. A 2016 meta-analysis of 21 GWAS's identified an IGF-1-decreasing allele that was associated with lower adiposity and higher likelihood of survival beyond 90 years (Teumer et al., 2016). A functional mutation in the IGF-1 receptor gene, which confers partial IGF-1 resistance, was more prevalent in centenarians as compared to controls without familial longevity (Suh et al., 2008). However, another observational study of nonagenarians (mean age 93.4 years old) reported that familial longevity may be linked to insulin sensitivity (glucose handling), and not necessarily with levels of IGF-1, IGFBP-3, or insulin (Rozing et al., 2009).

The protective effects of low serum IGF-1 levels appear to be more pronounced in women. In a prospective study of 184 nonagenarians, females with lower IGF-1 levels had a significantly longer survival compared to those with higher levels, and this association persisted after controlling for age,

HDL, cardiovascular disease, and type II diabetes (Milman et al., 2014). This survival advantage was not observed in males and it is currently unknown why men and women respond differently to IGF-1.
*Cancers*: HARM. A meta-analysis of 96 studies including a total of over 110,000 people reported that higher IGF-1 levels were associated with increased risk of cancer (OR, 1.15, 95% CI, 1.03-1.29), especially among prostate, premenopausal breast, and colorectal cancers (Chen et al., 2009). Higher concentrations of IGFBP-3, which bind to and regulate IGF-1, are associated with a 56% decreased risk of advanced prostate cancer. In contrast, a meta-analysis showed that in women under 55 years old, higher circulating IGF-1 levels were correlated with decreased ovarian cancer risk (Li et al., 2016). In people with a history of cancer, low IGF-1 levels predicted longer survival (Milman et al., 2014).

*Cardiovascular disease*: MIXED. A meta-analysis of 12 observational studies (total of 14,938 people) reported that both low and high IGF-1 levels are associated with increased risk of cardiovascular disease (Jing et al., 2015). However, these associations were absent in women. The mechanisms underlying the association between IGF-1 and cardiovascular disease, or the interactions with sex, are currently unclear.

*Osteoporosis*: BENEFIT. In a small double-blind RCT of 30 osteoporotic patients who underwent hip surgery, subcutaneous infusion of IGF-1/IGFBP-3 (1.0 mg/kg/day) was associated with increased bone mass and better functional recovery compared to controls (Boonen et al., 2002).

**Safety:** IGF-1 treatment can cause hypoglycemia, which may be prevented with co-infusion of the binding protein, IGFBP-3. IGF-1 treatment should not be used in people with known or suspected cancer as it may promote its growth.

*Types of evidence:*
- 3 double-blind RCTs, 1 in children with growth failure, 1 in patients with osteoporosis, and 1 in patients with acute renal failure
- 4 open-label clinical trials, 2 in children with growth failure, 1 in preterm infants, and 1 in myotonic dystrophy
- 1 case study in a baby with Donohue syndrome (congenital insulin resistance)
- 3 review articles

*Details.* IGF-1 should not be used if you have known or suspected cancer as it may promote tumor growth (Milman et al., 2016). IGF-1 may also lower blood sugar levels (Clark, 2004). In diabetes patients,

co-administering IGF-1 with IGFBP-3 (mecasermin rinfabate, iPlex™), appears to result in fewer side effects such as hypoglycemia when compared to using IGF-1 alone (Kemp et al., 2006).

Most clinical studies testing the effects of IGF-1 therapy have been carried out in children with growth failure. In a small RCT of 17 children with growth hormone receptor deficiency, children receiving recombinant human IGF-1 (rhIGF-1) experienced increased growth rate (Guevara-Aguirre et al., 1995). However, one subject in the rhIGF-1 group developed papilledema (optic disc swelling due to increased intracranial pressure), which resolved spontaneously. In open-label trials of children with growth failure, the most common adverse events were headache, vomiting, and hypoglycemia (Midyett et al., 2010; Bang et al., 2015).

Older osteoporotic patients who received infusion of IGF-1/IGFBP-3 did not experience hypoglycemia or other side effects, though the RCT was small (Boonen et al., 2002). A small open-label clinical trial in patients with myotonic dystrophy type I reported that IGF-1/IGFBP-3 treatment for 24 weeks increased lean body muscle mass, metabolism, HDL levels, and testosterone in men (Heatwole et al., 2011). However, some side effects included mild transient hypoglycemia, transient papilledema, and lightheadedness.

**Sources and dosing:** Currently available IGF-1 treatments are not ideal because they will increase levels in the periphery, which comes with significant risks to cancer and possibly decreased longevity. Some experimental approaches might be able to decrease levels only in the periphery but they have not been promising in clinical studies.

Currently available recombinant human IGF-1 (rhIGF-1, mecasermin, Increlex™) is typically administered subcutaneously or intravenously, sometimes in combination with rhIGFBP-3, a binding protein that regulates IGF-1 (mecasermin rinfabate, iPlex™). IGF-1 is used to treat children with stunted growth (Bang et al., 2015), growth hormone insensitivity (Camacho-Hubner et al., 2006), or growth hormone receptor deficiency (Guevara-Aguirre et al., 1995). In adults, rhIGF-1 has been used in patients with diabetes (Williams et al., 2008), osteoporosis (Boonen et al., 2002), and myotonic dystrophy type 1 (Heatwole et al., 2011). Doses range from 40-120 µg/kg/day (Guevara-Aguirre et al., 1995; Midyett et al., 2010) in children and up to 200 µg/kg/day in adults (Hirschberg et al., 1999).

Supplements containing IGF-1 are available commercially, though IGF-1 in pill form will likely be broken down in the gut before reaching the bloodstream. Sublingual formulations (placed under the tongue)

and oral sprays are also sold and likely have better bioavailability. No research has directly compared the effects of different products and brands.

**Research underway:** An ongoing clinical trial (RESUS-AMI) is testing the safety and efficacy of IGF-1 (mecasermin) in patients who experienced a heart attack (NCT01438086). This study was scheduled to be completed in August 2016, but is still recruiting participants. Another clinical trial is testing the effects of IGF-1 in patients with autism spectrum disorder (NCT01970345).

**Search terms:**
Pubmed, Google:  IGF-1, insulin-like growth factor 1, IGF-2
- + meta-analysis, + cognitive, + dementia, + Alzheimer's, + ApoE4, + meta-analysis, + clinical trial, + safety, + cancer, + cardiovascular

Clinicaltrials.gov
- insulin-like growth factor 1, IGF-1, mecasermin

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