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.

Irisin

Evidence Summary

Preclinical evidence for neuroprotection is compelling. But irisin levels are increased or decreased depending on various age-related conditions, so safety as therapy is unclear. No studies exist in humans.

Neuroprotective Benefit: In humans, CSF irisin levels are decreased in Alzheimer's disease and correlate with cognitive function, CSF BDNF, and CSF Aβ42 levels. Irisin treatment in rodent models of Alzheimer's improved cognitive function while increasing BDNF.

Aging and related health concerns: In humans, both higher and lower circulating irisin levels have been associated with disease and mortality. No studies have tested irisin as a therapeutic intervention in humans.

Safety: No studies have tested irisin as a therapy in humans. Levels are increased or decreased depending on different age-related conditions, so safety as a therapy is unclear. It is a natural circulating hormone/myokine, so it is likely safe at physiological levels.

Availability: Not available; research grade only	**Dose**: Not established. In mice, doses have ranged from 10-500 µg/kg via i.v. or i.p.	**Chemical formula:** N/A **MW**: 12 kDa (undergoes glycosylation and dimerization, so the apparent molecular weight is likely higher, ~39-48 kDa)
Half life: less than 1 hour	**BBB**: Peripheral FNDC5/irisin can affect brain FNDC5/irisin levels. Irisin is also locally induced in the hippocampus.	
Clinical trials: none	**Observational studies**: Irisin has been studied in numerous meta-analyses (including thousands of people total) as a serum or plasma biomarker.	

What is it? Irisin was discovered in 2012 for its role in stimulating adipocyte browning, energy expenditure, and thermogenesis by enhancing mitochondrial uncoupling protein 1 (UCP1) expression (Bostrom et al., 2012). Since then, irisin has been shown to have wider ranging effects on many tissues to regulate energy metabolism, such as promoting glucose and lipid uptake by skeletal muscles and increasing glucose and lipid metabolism in the liver (Pignataro et al., 2021).

Irisin is a 112-amino-acid hormone/myokine that is proteolytically cleaved from the membrane protein fibronectin type III domain containing protein 5 (FNDC5; 212 amino acids) in skeletal muscle cells prior to being secreted into the blood circulation. This cleavage is regulated by the peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), and both PGC-1α and FNDC5 are induced by exercise training. Once cleaved, irisin is secreted by skeletal and cardiac muscle cells (Askari H et al., 2018). Currently, receptors for irisin have not been fully identified, but it has been proposed that integrins, specifically αV/β5, could be its receptor (Pignataro et al., 2021). Irisin exerts its biological effects via MAPK, AMPK, PI3K/AKT, STAT3, and cAMP/PKA/CREB signaling pathways. Irisin is also an upstream mediator of BDNF expression (Wrann et al., 2013).

Beyond skeletal and cardiac muscles, irisin/FNDC5 is also highly expressed in the brain. Irisin has been studied most extensively as a biomarker. It has not been used as a treatment in humans, but its role in neuroprotection has been studied in preclinical models (e.g., Lourenco et al., 2019).

Neuroprotective Benefit: In humans, CSF irisin levels are decreased in Alzheimer's disease and correlate with cognitive function, CSF BDNF, and CSF Aβ42 levels. Irisin treatment in rodent models of Alzheimer's improved cognitive function while increasing BDNF.

Types of evidence:

- 0 clinical trials
- 5 clinical observational studies examining blood levels of irisin
- Numerous laboratory studies

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

There have not been any studies in humans that have tested irisin as an intervention for preventing dementia or cognitive decline. However, several studies have probed whether circulating levels of irisin might be associated with cognitive function.

In 21 middle-aged and older adults who underwent high-intensity interval training (30 minutes) and moderate-intensity continuous exercise (30 minutes), working memory accuracy rates were significantly increased only after the moderate-intensity continuous exercise intervention (Tsai et al., 2021). However, both types of exercise improved reaction time and increased event-related potential P3 amplitudes. Circulating irisin levels increased significantly with high-intensity interval training (pre- vs. post-intervention: 622.23 ± 151.81 ng/mL vs. 674.32 ± 150.08 ng/mL; p=0.003). With moderate-intensity continuous exercise, irisin levels approached statistical significance when pre- and post-intervention levels were compared (pre- vs. post-intervention: 629.77.19 ± 111.76 ng/mL vs. 657.81 ± 113.25 ng/mL; p=0.076). Serum BDNF levels were significantly increased after both types of exercise. Changes in irisin and BDNF levels were not correlated with changes in neurocognitive performance, with the exception of a correlation between irisin levels and reaction times with moderate-intensity continuous exercise.

In 26 endurance athletes and 10 sedentary men, cognitive scores (measured by MSSE and Isaac's Set Test of Verbal Fluency) and irisin levels were higher in endurance athletes than sedentary individuals (Belviranli et al., 2016). Irisin levels in were 3.25 ± 0.70, 6.16 ± 0.99, and 6.58 ± 1.09 µg/mL in the sedentary, orienteers, and pentathletes, respectively. Irisin levels were inversely correlated with body fat and positively correlated with cognitive function (MMSE, Isaac's Set Test) and BDNF levels ($p<0.05$ for all).

In a pilot human study of stroke patients, CSF irisin levels were lower than those from control subjects (Jin et al., 2021). CSF irisin levels in control subjects, stroke patients at acute stage, and stroke patients after recovery were 3.92 ± 0.23 ng/ml, 2.12 ± 0.25 ng/ml, and 2.83 ± 0.29 ng/ml, respectively. In stroke patients, there was a positive correlation between CSF irisin levels and cognitive function (measured by MoCA).

Human research to suggest benefits to patients with dementia:
There have not been any studies in humans that have tested irisin as an intervention for dementia. However, several studies have probed whether circulating levels of irisin might be associated with mild cognitive impairment or dementia.

In a postmortem study of brains from 26 controls, 14 mild cognitive impairment, 14 Alzheimer's disease, and 13 Lewy body dementia, CSF and hippocampal levels of irisin were significantly reduced in late-stage Alzheimer's patients compared to age-matched early Alzheimer's patients, people with mild cognitive impairment, or cognitively normal subjects (Lourenco et al., 2019). Lewy body dementia patients also had reduced CSF levels of irisin. In contrast, no significant changes were seen in plasma levels of irisin in Alzheimer's or Lewy body dementia patients compared to non-demented controls. CSF irisin levels positively correlated with age in non-demented controls, but not in Alzheimer's patients (Lourenco et al., 2019).

In an observational study of 14 Alzheimer's patients and 25 non-demented controls, CSF irisin levels positively correlated with cognitive function (MMSE score), CSF BDNF, and CSF Aβ42, but not with CSF total tau (Lourenco et al., 2020). Higher irisin levels correlating with higher CSF Aβ42 suggests that there is less Aβ42 deposition in the brain.

In an observational study of 40 Alzheimer's patients and 20 age-matched healthy controls, serum irisin levels were slightly elevated in Alzheimer's patients with agitation/aggression (by 10.0%, $p<0.05$), which correlated with the duration of agitation/aggression ($r=0.74$; $p<0.03$)(Conti et al., 2019). However, serum irisin (and BDNF) levels were unchanged when considering the whole sample of Alzheimer's patients compared to age-matched controls. Serum irisin levels failed to correlate with sex, age, disease duration, Neuropsychiatric Inventory-10 scores, MMSE scores, or medication use (AChEi or memantine).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
One of the first studies to report neuroprotective actions of irisin was in a 2013 Cell Metabolism paper (Wrann et al., 2013). This study showed that FNDC5 is induced with exercise and cleaved and secreted

as irisin in mice. Endurance exercise (using a free running wheel) also increased irisin levels in the hippocampus of mice. In primary cortical neurons, overexpression of FNDC5 increased BDNF expression. Most interestingly, peripheral delivery of FNDC5 to the liver via adenoviral vectors (10^{11} adenoviral particles per animal, i.v., sacrified 7 days later) resulted in elevated blood irisin levels and increased expression of BDNF and other neuroprotective genes in the hippocampus. While this study did not prove that irisin crosses the blood-brain barrier, peripheral FNDC5 was sufficient to produce neuroprotective effects in the brain.

The following high-profile publication on irisin's neuroprotective role was a 2019 Nature Medicine paper (Lourenco et al., 2019). In this study, they first showed that FNDC5 and irisin levels are reduced in the hippocampus and CSF of Alzheimer's patients (described above) and in experimental models of Alzheimer's disease. Knockdown of brain FNDC5/irisin impaired synaptic plasticity (measured by long-term potentiation) and novel object recognition memory in mice. In contrast, boosting brain levels of FNDC5/irisin (by hippocampal infusion of recombinant irisin, 75 pmol/site) rescued synaptic plasticity and memory in two mouse models of Alzheimer's disease (APPswe/PSEN1ΔE9 mice and mice infused with Aβ oligomers). An exercise protocol (daily swimming, 1 hour/day, 5 days/week) for 5 weeks protected mice from Aβ oligomer-induced memory impairment while also preventing the decrease in FNDC5 and irisin levels (mRNA and protein). Thus, irisin appears to be a novel mediator of the beneficial effects of exercise on synaptic function and memory in models of Alzheimer's disease.

Intriguingly, peripheral overexpression of FNDC5/irisin (via AdFNDC5 administration into the caudal vein of mice) also increased FNDC5 and irisin levels in the hippocampus and rescued memory impairment in mice infused with Aβ oligomers (Lourenco et al., 2019). In these mice, hippocampal levels of FNDC5/irisin were decreased but intravenous AdFNDC5 administration prevented this decrease.

In contrast, inhibition of either peripheral or brain FNDC5/irisin attenuated the neuroprotective actions of physical exercise on synaptic plasticity and memory in these mice.

The most recent follow-up of this line of work was published this month (August 2021) in Nature Metabolism (Islam et al., 2021). In this study, the authors showed that irisin is sufficient to confer the benefits of exercise on cognitive function. This was demonstrated with use of a global Fndc5-knockout mice. These mice exhibited impaired cognitive functions (e.g., pattern separation) but this deficit could be rescued by delivering irisin directly into the hippocampal dentate gyrus. Additionally, peripheral delivery of irisin via AAV overexpression in the liver (tail vein injection of AAV8-Irisin-FLAG, $1x10^{10}$ genome copies) resulted in increased irisin levels in the brain, which was sufficient to improve cognitive

functions in two mouse models of Alzheimer's disease (APP/PS1, 5xFAD mice). Although this does not definitively prove that irisin penetrates the blood-brain barrier, these results demonstrate that peripheral irisin increases brain irisin protein levels and improves cognitive function.

In transgenic htau mice, irisin treatment (recombinant human irisin protein, 100 µg/kg weekly, i.p.) beginning at presymptomatic age (4 months old) significantly reduced p-tau and the proinflammatory cytokine, TNF-α, in the hippocampus and serum of females compared to vehicle-treated controls (Bretland et al., 2021). However, irisin treatment did not alter p-tau levels in male htau mice and appeared to increase both neural and systemic TNF-α levels. P-tau in prefrontal cortex, brainstem and hypothalamus did not statistically change with irisin treatment in female or male htau mice. In this study, exogenous treatment with recombinant irisin did not alter neural FNDC5/irisin levels in mice, while serum levels of irisin were doubled in all animals.

Irisin treatment showed cognitive improvements in several mouse models. In a mouse model of diabetes (induced by streptozotocin), irisin treatment (0.5 mg/kg/day, prepared in normal saline, i.p.) improved cognitive function (measured by Y-maze, novel object recognition) while also preventing the elevation of inflammation biomarkers (IL-1β, IL-6, GFAP) and the loss of a synaptic protein (synaptophysin)(Wang et al., 2019). Irisin also inhibited the activation of p38, STAT3, and NFκB proteins. In a mouse model of cerebral ischemia (middle cerebral artery occlusion), pretreatment with exogenous irisin (10 µg/kg, i.v.) prevented cognitive impairment while upregulating protein expressions of klotho, MnSOD, and FOXO3a, and reducing reactive oxygen species generation (Jin et al., 2021).

In aged rats (20 months old), exercise training (voluntary free wheel running exercise) for 90 days significantly improved spatial memory and increased protein expressions of BDNF, FNDC5, PGC-1α, mTOR, ARC, c-fos, ERK, SIRT, and FOXO in the hippocampus compared to aged rats that did not exercise (Belviranli and Okudan, 2018).

Several studies in culture systems further validated irisin's mechanisms of neuroprotection. In rat hippocampal culture as well as in cultured human adult cortical slides, exposure to Aβ oligomers resulted in reductions of FNDC5 and irisin both at the mRNA and protein levels (Lourenco et al., 2019). In cultured hippocampal neurons exposed to Aβ oligomers, treatment with recombinant irisin prevented dendritic spine loss and reduced Aβ oligomer binding to neurons. In human cortical slices and in mouse hippocampal slices, treatment with recombinant irisin stimulated the cAMP/PKA/CREB pathway that is important for memory formation. In a cell culture study of astrocytes and hippocampal neurons exposed to Aβ, irisin pretreatment attenuated the release of IL-6 and IL-1β from astrocytes and decreased the

expression of COX-2 and p-AKT (Wang et al., 2018). Neuroprotective benefits of irisin were mediated by inhibition of astrocytic release of IL-6 and IL-1β.

APOE4 interactions: Unknown.

Aging and related health concerns: In humans, both higher and lower circulating irisin levels have been associated with disease and mortality. No studies have tested irisin as a therapeutic intervention in humans.

Types of evidence:

- 10 meta-analyses or systematic reviews of observational studies examining circulating irisin levels
- 0 clinical trials
- 8 observational studies examining circulating irisin levels
- 1 genetic SNP study of centenarians and non-centenarians
- Numerous laboratory studies

There have not been any studies in humans that have tested irisin as an intervention for preventing age-related diseases. However, numerous studies have probed whether circulating levels of irisin might be associated with disease versus health.

Cancer: IRISIN LEVELS LOWER IN SOME AND HIGHER IN OTHER CANCERS
In an observational study of 101 women with ductal breast cancer and 51 healthy controls, serum irisin levels were lower in breast cancer patients compared to controls (2.47 ± 0.57 and 3.24 ± 0.66 μg/ml, respectively; $p<0.001$)(Provatopoulou et al., 2015). In this study, irisin could discriminate breast cancer patients at a cut-off point of 3.21 μg/ml, with 62.7% sensitivity and 91.1% specificity.

In an observational study of 75 bladder cancer patients and 75 healthy controls, serum irisin levels were significantly lower in bladder cancer patients compared to controls (1.07 μg/ml vs 1.80 μg/ml)(Esawy et al., 2020). In this study, irisin had 74.7% sensitivity and 90.7% specificity at a cutoff point of ≤1.2 μg/mL. Serum irisin levels also could predict bladder cancer stages, when adjusted for BMI and serum cholesterol level. Patients with low serum irisin levels also had a higher mortality rate when compared to those with high irisin levels (38.2% vs 5%).

In an observational study of 138 patients with metastatic solid tumors who were followed up for a median duration of 13.8 months, overall survival was significantly correlated with CRP, activin, and myostatin, but irisin was not associated with overall survival (Kim et al., 2019).

It is still unclear how irisin functions in cancerous tissues as observational and preclinical data have been mixed. Although irisin levels are lower in some cancers as described above (e.g., breast, bladder), studies report higher irisin levels in other cancers (e.g., gastric, colon, ovarian and hepatocellular)(Askari et al., 2018). Irisin could potentially suppress cancer by exerting apoptotic effects in malignant cells (activation of caspase 3 and 7), reducing migration, proliferation, and invasion of cancer cells by inhibiting the PI3K/AKT pathway, and retarding cell proliferation by promoting hyperthermia and reduction of ATP synthesis (Askari et al., 2018). However, other *in vitro* studies have reported that irisin did not regulate cell adhesion, proliferation, or malignancy in endometrial, colon, thyroid, and esophageal cancer cell lines (Moon et al., 2014).

***Cardiovascular diseases*: MIXED; IRISIN LEVELS LOWER IN CAD, HIGHER IN MYOCARDIAL INFARCTION; HIGHER IRISIN LEVELS MAY BE ASSOCIATED WITH HIGHER OR LOWER MORTALITY DEPENDING ON DISEASE**

In a meta-analysis of 7 case-control studies involving 867 patients with coronary artery disease and 700 controls, irisin levels were lower in coronary artery disease patients compared with controls (Guo et al., 2020). The pooled data showed that irisin levels were lower by -18.10 ng/mL in patients with cardiovascular disease or atherosclerosis.

In a longitudinal study of 517 people with coronary artery disease who were followed up for 12 months, serum irisin levels were lower in people with coronary artery disease (Pan et al., 2021). Serum irisin levels in people with acute coronary syndrome, stable coronary artery disease, nonobstructive coronary artery disease and normal coronary arteries were 196.62±72.05 ng/ml, 216.81±79.69 ng/ml, 245.26±77.92 ng/ml and 300.17±76.74 ng/ml, respectively. Additionally, serum irisin levels showed high areas under the curve (AUC) for coronary lesions (AUC=0.799), coronary artery disease (AUC=0.734), and acute coronary syndrome (AUC=0.681). Patients with higher irisin levels exhibited a higher event-free survival rate in both stable coronary artery disease and acute coronary syndrome groups after percutaneous coronary intervention.

In an observational study of 324 Chinese patients with first-ever acute ischemic stroke who were followed for 3 months, lower serum levels of irisin predicted the risk of poor functional outcomes and mortality (Wu et al., 2019). Irisin remained significantly associated with poor outcomes even after

controlling for CRP or IL-6, suggesting that the effect of irisin on prognosis was independent of its association with inflammation. In a similar observational study of 1,530 Han Chinese patients with acute ischemic stroke who were followed for 6 months, poor outcome across the irisin quartiles ranged from 54.5% (first quartile) to 21.7% (fourth quartile), and mortality rate ranged from 39.3% (first quartile) to 6.3% (fourth quartile)(Tu et al., 2018).

In a cohort study of 399 patients with acute myocardial infarction, elevated risks of cardiovascular mortality, stroke, heart failure, and revascularization were seen among those with the highest concentrations of irisin, with concentrations higher than the 75th percentile of the overall distribution having a 4-fold increase in risk (HR=3.96; 95% CI, 1.55 to 10.11; p<0.01)(Hsieh et al., 2018).

Based on Kaplan–Meier curves, higher serum irisin concentration (> 0.6 μg/mL) was associated with increased risk for early adverse cardiovascular events. However, no association between irisin concentrations and total cholesterol, HDL cholesterol, or LDL cholesterol was seen. (Hsieh et al., 2018).

In an observational study of 161 Chinese patients with acute heart failure who were followed for 1 year, serum irisin levels were higher in patients who were deceased at the one-year follow-up (Shen et al., 2017). Kaplan-Meier survival analysis showed that acute heart failure patients with higher serum irisin had significantly higher mortality (OR=1.287; p<0.001).

In preclinical studies, irisin may improve cardiovascular problems by inhibiting inflammatory mediators, protecting cardiomyocytes from apoptosis in ischemic conditions, stabilizing mitochondrial membrane potential, and attenuating myocardial damage in ischemia-reperfusion injury by increasing antioxidative defenses (SOD, GPX, catalase) (Pan et al., 2021). Irisin may also exert anti-atherosclerotic actions by reducing the recruitment of inflammatory cells like T lymphocytes and macrophages to atherosclerotic lesions (Zhang et al., 2016).

Inflammation: INCONCLUSIVE
In a meta-analysis of 14 observational studies including a total of 2,530 participants, there was no overall significant correlation between irisin and CRP levels (Eslampour et al., 2019). However, subgroup analyses showed significant positive, but weak, correlations between CRP and irisin levels in studies conducted among healthy participants, studies in which the male-to-female ratio was less than 1, in overweight or obese subjects, and in studies with a sample size of at least 100 participants.

Lifespan: HIGHER IRISIN LEVELS MAY BE ASSOCIATED WITH HIGHER OR LOWER MORTALITY DEPENDING ON DISEASE; HIGHER IRISIN LEVELS CORRELATE WITH TELOMERE LENGTH
In a longitudinal study of people with coronary artery disease who were followed up for 12 months, patients with higher irisin levels exhibited a higher event-free survival rate in both stable coronary artery disease and acute coronary syndrome groups after percutaneous coronary intervention (Pan et al., 2021). In contrast, in an observational study of 161 Chinese patients with acute heart failure who were followed for 1 year, patients with higher serum irisin levels were more likely to be deceased at the one-year follow-up (Shen et al., 2017). Kaplan-Meier survival analysis showed that acute heart failure patients with higher serum irisin had significantly higher mortality (OR=1.287; p<0.001).

There are 2 single-nucleotide polymorphisms (SNPs) in the FNDC5 gene, rs16835198 and rs726344, which are associated with insulin sensitivity. However, in a study of 175 centenarians and 347 healthy non-centenarians from Spain, Italy and Japan, there were no differences between genotype/allele frequencies of the two SNPs in centenarians versus controls in any of the cohorts (Sanchis-Gomar et al., 2014). In a gene reporter activity study, the rs726344 SNP had functional significance, with the A-allele having higher luciferase activity compared with the G-allele (p=0.04). For the rs16835198 SNP, the T-allele tended to show higher luciferase activity compared with the G-allele, but the difference was not statistically significant (p=0.07).

In 81 healthy non-obese people (average age, 43), plasma irisin levels were significantly correlated with log-transformed relative telomere length (Rana et al., 2014).

Nonalcoholic fatty liver disease (NAFLD): IRISIN LEVELS ARE HIGHER IN NAFLD IN ASIANS
NAFLD is one of the most common causes of chronic liver disease and ranges from mild hepatic steatosis (fat deposition) to aggressive forms like NASH (nonalcoholic steatohepatitis), characterized by inflammation and oxidative damage (Askari et al., 2018). In a meta-analysis of 5 case-control studies with a total of 1,087 participants, circulating irisin levels did not show significant differences between NAFLD patients and healthy controls (Hu et al., 2020). However, subgroup analyses showed that irisin levels were higher in NAFLD patients compared to healthy controls in Asians, and higher in mild NAFLD patients compared to moderate-to-severe NAFLD patients. It is not known whether or how irisin might affect the pathology of NAFLD.

In preclinical studies, irisin treatment has anti-inflammatory effects and reduces inflammatory mediators including TNF-α, IL-6, phosphorylated NF-κB, phosphorylated p-38, and COX-2 in hepatocytes, while also reducing oxidative stress (Askari et al., 2018).

Osteoporosis: IRISIN LEVELS ARE LOWER WITH OSTEOPOROSIS
In a meta-analysis of 7 studies including a total of 1,018 middle-aged and older participants, those with osteoporosis had decreased irisin levels (mean difference, -87.91)(Zhou et al., 2019). A subgroup analysis revealed an even lower level of irisin in postmenopausal women and in those with a history of fractures. Irisin levels were weakly and positively correlated with femoral neck or lumbar spine bone mineral density. Preclinical studies have shown that irisin treatment promoted osteoblast differentiation and proliferation, while inhibiting the differentiation of osteoclast precursor cells (Zhang et al., 2017; Ma et al., 2018).

Obesity: IRISIN LEVELS ARE HIGHER IN OVERWEIGHT/OBESE PEOPLE
In a meta-analysis of 18 case-control studies including a total of 2,247 participants, circulating irisin levels in overweight/obese people were higher than those in healthy controls (p=0.003)(Jia et al., 2019). In a subgroup analysis by ethnicity, irisin levels were higher in overweight/obesity people in Africa but not in European, Asian, or American populations. Also a subgroup analysis by age showed that obese children exhibited a higher irisin level than age-matched controls but irisin levels in adult patients were not significantly different from controls.

Thyroid dysfunction: IRISIN LEVELS ARE LOWER IN HYPOTHYROIDISM
In a meta-analysis of 11 observational studies including 1,210 participants, irisin levels were significantly lower in patients with hypothyroidism (mean difference, -10.37)(Shan et al., 2020). A subgroup analysis showed an even lower level of irisin in patients with clinical-type hypothyroidism (mean difference, -17.03) and hypothyroidism caused by autoimmune disease (mean difference, -19.38). There were no differences in irisin levels between patients with hyperthyroidism and controls. A possible inverse correlation was found between irisin and TSH and positive correlations between irisin and both free T3 and free T4. Irisin was also correlated with TSH receptor antibodies. It is not known whether or how irisin might affect the pathology of hypothyroidism.

Type 2 diabetes mellitus (T2DM): IRISIN LEVELS ARE LOWER IN T2DM
In a meta-analysis of 26 case-control or cross-sectional studies involving a total of 3,667 participants, irisin levels were significantly lower in patients with T2DM compared to non-diabetic individuals (Song et al., 2021). This was true in both the plasma and serum. The ethnic subgroup analysis showed that irisin levels were significantly lower in patients with T2DM in Asia, Europe, and Turkey.

In a meta-analysis of 17 studies enrolling 1,912 participants who are non-diabetic (3 randomized trials, others are case-control or cross-sectional observational studies), circulating irisin levels were inversely

associated with insulin sensitivity (r=-0.17); however, this association was small (Qiu et al., 2016). A larger correlation coefficient between circulating irisin and insulin resistance was observed in a subpopulation of people with abnormal fasting glycemia (fasting blood glucose ≥ 6.1 mmol/L and < 7.0 mmol/L) compared to those with normal fasting blood glucose. These findings are counterintuitive but may be explained by the fact that this increase in irisin with insulin resistance may be compensatory to restore glucose metabolism or metabolic disturbances in non-diabetic people. There could be a compensatory oversecretion of irisin prior to the development of diabetes, followed by a failure of irisin secretion once diabetes develops. Also, elevated irisin levels are associated with higher carbohydrate intake and increased levels of inflammatory markers such as IL-6, TNF-α, and CRP, which play roles in the development of insulin resistance. Because of the associations between diet, exercise, and irisin levels, further studies are needed to validate these relationships. A large-scale epidemiological study that analyzes the association between irisin and insulin resistance while properly controlling for many confounding factors, such as glycemic status, diet, exercise, race, sex, and others is needed.

In a mouse model of type 2 diabetes (high-fat diet), irisin treatment (0.5 mg/kg/day) for 2 weeks improved vascular function (Zhu et al., 2015). This improvement was through reduction of oxidative and nitrative stress (e.g., superoxide and peroxynitrite).

Safety: No studies have tested irisin as a therapy in humans. Levels are increased or decreased depending on different age-related conditions, so safety as a therapy is unclear. It is a natural circulating hormone/myokine, so it is likely safe at physiological levels.

Types of evidence:

- 2 meta-analyses of clinical trials using exercise as the intervention and irisin as the biomarker
- Numerous observational studies of circulating irisin levels in health and disease
- Several laboratory studies

No clinical trials have tested the efficacy of irisin in any disease indication. Numerous observational studies have measured the levels of circulating irisin in blood (serum, plasma) and the CSF in health and disease. While causation is unknown, irisin is increased in numerous conditions, including obesity, metabolic syndrome, coronary artery disease, gastrointestinal cancers, and others (Askari H et al., 2018), and it is possible that these conditions may be worsened with irisin therapy.

The safest way to increase endogenous levels of irisin is through exercising. In a meta-analysis of 7 randomized controlled trials including a total of 282 adults, resistance training for at least 8 weeks increased circulating irisin levels, though the overall analysis did not achieve statistical significance (Cosio et al., 2021). Subgroup analyses showed significant increases in irisin for older adults ($p< 0.001$) and when training was demanding, and its intensity was progressive ($p=0.03$). Interventions that resulted in greater increases in irisin levels had shorter durations (8–12 weeks). Most studies used machine-based exercises for resistance training and one study used elastic bands.

The findings above are in line with an older meta-analysis of 12 studies (3 randomized controlled trials and 9 non-randomized studies) of chronic exercise training (Qiu et al., 2015). The 3 randomized controlled trials showed that chronic exercise training was associated with a moderate and significant overall effect in decreasing circulating irisin levels compared with the control. Subgroup analyses showed that chronic endurance exercise training had a non-significant effect in decreasing circulating irisin compared with the control, while chronic resistance exercise training showed a significant effect in decreasing circulating irisin compared with the control. In the 9 non-randomized studies, chronic exercise was associated with a non-significant overall effect in decreasing circulating irisin levels compared with baseline.

Drug interactions: Irisin has not been used as an intervention in humans, and therefore, drug interactions are unknown.

Sources and dosing: No studies have tested irisin as a therapeutic intervention in humans. Irisin is available in research-grade form. Irisin has also been studied as a circulating biomarker in health and disease. In mouse studies, irisin doses have ranged from 10-500 µg/kg via i.v. or i.p. (Wang et al., 2019; Jin et al., 2021; Bretland et al., 2021).

To measure circulating irisin levels, robust measurement methods such as mass spectrometry is recommended; in many studies, ELISA kits are often used but these have not been the most reliable (Cosio et al., 2021).

Research underway: There are currently no clinical trials testing the efficacy of an irisin intervention, based on ClinicalTrials.gov. However, there are several trials using irisin expression as biomarkers (Clinicaltrials.gov). Several NIH grants have been awarded to Christiane Wrann, DVM, PhD, at Massachusetts General Hospital for exploring irisin as a novel target for Alzheimer's disease in preclinical models (R21 AG062904; R56 AG064580). The most efficient protocol to increase irisin in humans is not

clear; while acute exercise protocols in humans increase plasma irisin levels, there is no consensus on the ideal protocol to consistently raise irisin levels (de Freitas et al., 2020).

Search terms:

Pubmed, Google: irisin

- + cognitive, + memory, + dementia, + meta-analysis, + Cochrane, + mortality, + safety

Websites visited for irisin:

- Clinicaltrials.gov
- NIH RePORTER
- Examine.com
- DrugAge (0)
- Geroprotectors (0)
- PubChem (0)
- DrugBank.ca (0)
- Cafepharma (0)
- Pharmapro.com (0)