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.

FGF 21

Evidence Summary
Interesting lifespan and metabolic data, but current drugs have potential side effects (bone loss).

**Neuroprotective Benefit:** Some data suggests that FGF21 may be neuroprotective, but there is no data that treatment with FGF21 could improve Alzheimer’s disease.

**Aging and related health concerns:** Interesting preclinical studies suggesting that FGF21 can increase lifespan in preclinical models and improve metabolic status in humans, but current drugs have potential side effects.

**Safety:** Some evidence for bone loss in preclinical and clinical studies. Next generation of drugs may have a better safety profile.
What is it?
Fibroblast growth factors are a set of 22 factors critically involved in many cellular functions. Most are autocrine and paracrine factors that bind to FGF receptors 1-4 via interaction with heparin sulphate glycosaminoglycans. The endocrine FGFs (FGF19, FGF21, and FGF23) are different from most FGFs in that they do not require heparan sulfate in the extracellular matrix and can thus be secreted and act in an endocrine fashion. They bind to β-Klotho in a complex with FGF receptor (FGFR) 1c, 2c, or 3c (but not FGFR4). They are important for whole-body homeostasis – governing bile acid, glucose and lipid metabolism – they modulate vitamin D and phosphate homeostasis, and they induce metabolic adaptation in response to fasting (Degiroamo et al, 2015). FGF21 is a reportedly pro-longevity hormone released by the liver, and, when an organism has an energy deficit, it supports survival by increasing ketogenesis and fuel utilization through mitochondrial fatty acid oxidation (Xie and Leung, 2017). In addition to its metabolic effect, FGF21 is reported to be involved in the browning of white adipose tissue, stimulation of the hypothalamic-pituitary-adrenal axis, and the regulation of circadian rhythm during fasting (FGF21 levels show a correlation with the circadian rhythm, increasing at midnight, peaking in the early morning, and decreasing in the early afternoon – Degiroamo et al, 2015).

FGF21 levels vary widely (250-fold in a study of 76 healthy individuals). FGF21 was induced by prolonged fasting (7 days but not 2 days) by 74% and increased by fibrate treatment (due to stimulation of PPARα, 3-week treatment with fenofibrate increased FGF21 by 28%) (Galman et al, 2008). It may also be increased by exposure to cold temperatures in thermogenic adipose tissue (Degiroamo et al, 2015).

Determining the beneficial/detrimental effects of FGF21 by circulating levels is difficult, as patients with obesity, T2DM, NAFLD, coronary heart disease (CAD), and other metabolic diseases have increased levels of circulating FGF21. This apparent paradox – beneficial metabolic effects of exogenous FGF21 but increased levels in disease – could be due to FGF21 resistance (similar to insulin resistance) in patients with metabolic syndrome. In fact, obese mice have reduced expression of FGFR1 and β-Klotho (Xie and Leung, 2017).

Also, some rodent data conflicts with primate data. For instance, while rodents lose weight despite eating the same amount after FGF21 treatment, weight loss in non-human primates is primarily due to less food consumption. Similarly, while FGF21 reduces glucose levels in rodents, the glucose-lowering effect in humans is not as significant (Sonoda et al, 2017).
Recombinant FGF21 has a short half-life, so the development of therapeutics for humans has focused on FGF21 mimetics that stay in circulation longer.

**Neuroprotective Benefit:** Some data suggests that FGF21 may be neuroprotective, but there is no data that treatment with FGF21 could improve Alzheimer’s disease.

**Types of evidence:**
- 1 study suggesting FGF21 can cross the blood brain barrier in mice
- 5 preclinical studies suggesting FGF21 may be neuroprotective

**Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?**
Labeled FGF21 was reported to enter the mouse brain 10 minutes after intravenous bolus injection (Hsuchou et al, 2007). Additionally, FGF21 was reported to be in human CSF at 40% of levels found in plasma, suggesting it is either produced locally or can cross the blood brain barrier (Tan et al, 2011).

**Human research to suggest benefits to patients with dementia:**
None

**Mechanisms of action for neuroprotection identified from laboratory and clinical research:**

*In vitro* studies suggest that FGF21 increases the expression of peroxisome proliferator activated receptor γ coactivator 1a (PGC-1α – a transcriptional coactivator important for mitochondrial biogenesis), increased the expression of SIRT1, increased the NAD/NADH ratio, and enhanced the mitochondrial respiratory capacity in human dopaminergic neurons (Makela et al, 2014). These results are reflected in another *in vitro* study where human brain vascular smooth muscle cells (hBVSMCs) were exposed to Ang II to induce an aging phenotype (increased expression of β-gal staining, p53, and reduced complex IV activity). Coadministration with FGF21 attenuated the Ang II-induced aging phenotype. FGF21 was thought to act through AMPK activation, as coadministration with an AMPK inhibitor abolished the beneficial FGF21 effects (Wang et al, 2016). In human neuroblastoma cells, FGF21 improved survival after Aβ-induced toxicity (interestingly it was most effective at the lowest doses), reduced ROS generation, reduced caspase 3 activity (a marker of apoptosis), and reduced expression of NF-kβ (Amiri et al, 2018).
In a mouse model of toxin-induced demyelination, FGF21-KO mice had increased demyelination and there was a decrease in oligodendrocyte precursor cell (OPC) proliferation when βKlotho was knocked out of OPC cells, suggesting that peripheral FGF21 is important to remyelination. Additionally, the same group found that βKlotho expression was increased in the spinal cord of patient with MS (Kuroda et al, 2017).

In a mouse model of aging where D-galactose was administered with or without FGF21 for 8 weeks, animals administered FGF21 had improved cognition, reduced hippocampal neuron loss, reduced levels of ROS, advanced glycation end products, markers of lipid peroxidation, pro-inflammatory cytokines, and reduced expression of NF-kB. Additionally, treated animals had increased expression of anti-oxidant enzymes SOD and catalase (Yu et al, 2015). Long-term caloric restriction was also reported to increase FGF21 brain and plasma levels, FGFR downstream signaling, and reduce mTOR phosphorylation. However, whether these effects were due to FGF21 or some other effects of caloric restriction were not investigated (Ruhlmann et al, 2016).

APoe4
Unknown

**Aging and related health concerns:** Interesting preclinical studies suggesting that FGF21 can increase lifespan in preclinical models and improve metabolic status in humans, but current drugs have potential side effects.

**Types of evidence:**
- 2 preclinical genetic studies on lifespan and thymus involution
- 4 clinical studies on FGF21 mimetics for metabolic disease

**Lifespan**
Zhang et al (2012) reported that mice that overexpress FGF21 in hepatocytes (to levels 5-10x seen during prolonged fasting) live 36% longer than control mice (with more benefits in females than males; in fact, at 44 months, >30% of the females were still alive). FGF21 mice weighed less but had similar levels of food consumption, physical activity, and oxygen consumption as control mice. FGF21 mice had higher levels of ketones, lower triglycerides (in females), lower IGF-1, lower glucose, and increased insulin sensitivity, but also decreased bone mass. These effects were thought to be largely independent of AMPK, mTOR, and sirtuin pathways (contrary to some other studies). Bone-loss was also seen in
younger mice treated with FGF21 for 2-weeks. These effects were thought to be mediated by PPARγ, as FGF21 knockout prevented rosiglitazone-induced bone loss (Wei et al, 2012).

In another study, despite the fact that expression of Fgfr1 and β-Klotho mRNA increased in mice with age in the thymus, expression of Fgf21 mRNA decreased, an effect that was reversed with caloric restriction. In addition, although FGF21 overexpressing mice (with 50-100x more circulating FGF21) had decreased body weight, size, and thymic size – when adjusting for body weight these mice had increased relative thymic size, improved thymic morphology, decreased white adipose tissue, and increased brown adipose tissue, suggesting that FGF21 overexpression reduced thymic involution with age. FGF21 also improved the thymic microenvironment and increased T-cell diversity. Opposing effects were seen in FGF21 knockout mice (Youm et al, 2015).

In theory, FGF21 may be a pro-longevity hormone as it acts through many aging-related pathways. Administration of FGF21 to adipocytes in vitro enhanced AMPK-SIRT1-PGC1a signaling and mitochondrial oxidative capacity (Chau et al, 2010). However, because of the potential negative effects on bone density, it is still to early to consider taking it as a drug.

**Diabetes/Obesity**

Pfizer tested a long-acting FGF21 analogue (PF-05231023) with an increased half life in obese individuals with or without T2DM for 28 days at doses ranging from 5-150mg once or twice per week. At higher doses, PF-05231023 improved lipid profiles (triglycerides ~50%, LDL-c ~20%, HDL-c ~+20%), increased adiponectin (~1500%), decreased body weight (~4%), but increased levels of IGF-1 (though they remained within the normal range). There were no changes in insulin resistance or glucose control. The drug slightly increased blood pressure and heart rate. There were changes in circulating levels of bone markers that may be indicative of bone loss, but these results could be confounded by weight loss (as weight loss and caloric restriction may lead to some bone loss). Long-term studies with measurements of bone mineral density will be required to determine whether FGF21 may increase the risk of fractures. The bone marker measurements returned to normal after a 20-day washout period. PF-05231023 also reduced weight in obese monkeys, but this may be due to a decrease in food intake, as food intake and weight returned to normal after a washout period. The most common adverse effect was diarrhea (~30% of patients) (Talukdar et al, 2016; Dong et al, 2015; Kim et al, 2017).

An RCT with another FGF21 mimetic (LY2405319) reported similar results in obese patients with T2DM over 28 days. LY2405319 reduced LDL-c and ApoB (~25%), increased HDL-c (~17%), reduced ApoC3 (~35%), reduced triglycerides (~45%), did not change glucose levels, reduced fasting insulin (~40%),
increased adiponectin (~83%), increased beta-hydroxybutyrate (~105%), and decreased weight (~1.5%). There were no serious adverse events (Gaich et al, 2013).

The main side effect of FGF21, bone loss, is thought to be due to signaling through PPARγ. FGF21 treatment in mice promotes the differentiation of bone marrow mesenchymal cells into adipocytes rather than osteoclasts (Degirolamo et al, 2016). Future drugs are being developed to target the FGFR1c-βklotho receptor complex that could avoid these side effects as βklotho has lower expression in the bone marrow. Some of the early drugs used the FGF21 epitope that could bind to FGFR1 without βklotho, so FGFR1c-βklotho receptor complex targeted therapeutics may have a larger therapeutic window. A recent study using FGF21 gene therapy reported similar metabolic benefits without bone-loss side effects and might be useful in future studies (Jimenez et al, 2018).

**Safety:** Some evidence for bone loss in preclinical and clinical studies. Next generation of drugs may have a better safety profile.

**Types of evidence:**
- 2 preclinical studies
- 3 short clinical trials

Preclinical studies suggest that increased FGF21 may induce bone loss, thus increasing the risk of bone fracture (Zhang et al, 2012; Wei et al, 2012). Human studies suggest that FGF21 could change circulating biomarkers of bone turnover, but there are no long-term studies using FGF21 analogues (Talukdar et al, 2016; Dong et al, 2015; Kim et al, 2017). The most common side effect is diarrhea (~30%). Long-term studies are needed to determine whether certain FGF21 analogues do not induce bone loss.

**Drug interactions:**
Not known. However, given the mechanism of action, FGF21 may interact with diabetes drugs (such as metformin or pioglitazone) and fibrates.

**Sources and dosing:**
Recombinant FGF21 has a short half life and may increase the risk of bone loss. FGF21 analogues are currently in clinical trials and are currently unavailable.
Research underway:
Other FGF21 analogues in development:

- **BMS-986036** – pegylated FGF21 in a phase 2, 24 week, clinical trial for Non-Alcoholic Steatohepatitis
- **BIO89-100** – pegylated FGF21 in a phase 1 for NASH
- **LLF-580** – FGF21 fusion protein in a 12-week phase 1 in obese individuals
- **AKR-001** – FGF analog soon to go into phase 2 for NASH

Search terms:
- Pubmed
- FGF 21 + aging, alzheimer, longevity, [articles in Nature Reviews Drug Discovery]

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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.