Adding Klotho to your GDF11 Regimen

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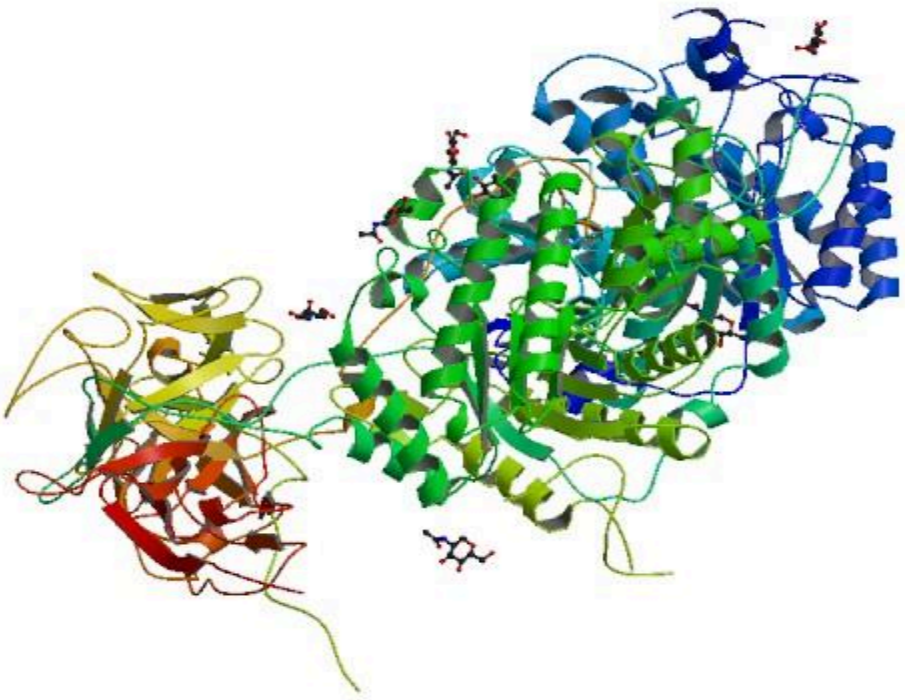

Above is Klotho's Molecular Structure

Molecular Weight: 58,600 Daltons 2.6 times the size of Human Growth Hormone and must be injected

Produced in: Kidneys and brain

Circulating levels: 472 pg/ml, total about 2360 ng. For comparison, note that GDF11 levels at age 40 are about 1000 ng, so dosing Klotho is in the same magnitude/neighborhood as GDF11.

Metabolic MOA: Klotho is an essential component of endocrine fibroblast growth factor (FGF) receptor complexes, as it is required for the high-affinity binding of FGF19, FGF21 and FGF23s.

- **FGF21 is a starvation hormone that stimulates glucose uptake in adipocytes but not in other cell types. FGF21 is additive to the activity of insulin. Increased FGF21 results in increased energy expenditure, fat utilization and lipid excretion.**
- **FGF19 is a satiety hormone that promotes metabolic responses to feeding.**
- **FGF23 is a phosphaturic hormone; increased FGF23 levels in patients with early-stage chronic kidney disease or elderly individuals is indicative of excess phosphate intake relative to the residual nephron number.**

Observations of Klotho levels in humans from Klotho.com:

Natural human Klotho is associated with improved cognitive performance in humans. In fact, 25% of the population naturally produces higher levels of Klotho. In these people, executive thinking is measurably better and parts of the brain measurably bigger than the normal population. That is, an 85 year old who has higher levels of Klotho has similar brain size and thinking ability to someone over 10 years younger. Lifespan is affected too. In animal studies, overexpression of Klotho leads to 20-30% longer lives than those with normal Klotho levels.

Klotho levels are associated with insulin production in human and animal studies. The Centers for Disease Control indicate that >29 million Americans are living with diabetes, and 86 million are living with prediabetes, which significantly increases their risk of type 2 diabetes and other chronic diseases. Human and animal research show that Klotho levels are decreased in the pancreatic islets in diabetics and lack of Klotho is associated with decreased insulin production. When diabetic mice were treated with Klotho for 2 weeks, blood glucose levels declined significantly, accompanied by significant increases in insulin levels3

Klotho also plays a role in cancer, a disease that kills more than 500,000 Americans every year. Several studies show that Klotho levels are decreased in certain types of human tumor cells/tissues and reduced Klotho expression in liver

cancer patients was associated with decreased survival. In addition, multiple animal studies have shown that Klotho can improve survival rates, reduce metastasis and reduce cancer cell resistance to chemotherapeutic agents.

Klotho plays a major role in kidney disease as much of the Klotho protein circulating in the blood is produced in the kidneys. Klotho levels are known to decline in chronic kidney disease (CKD) and may be an early marker of this disease. Klotho deficiency may be one of the causes for CKD progression and resulting complications including cardiovascular disease. Klotho has also been shown to play a role in acute kidney injury. In animal studies, Klotho reduced the size of the kidney injury and promoted healing.

Peer Reviewed Klotho Papers

Below are some of my favorites. Note that like GDF11, whose MOA is stem cell DNA repair, Klotho also has a profound effect on stem cells:

Klotho, stem cells, and aging

"Klotho is an antiaging gene encoding a single-pass transmembrane protein, klotho, which serves as an aging suppressor through a wide variety of mechanisms, such as antioxidation, anti-senescence, anti-autophagy, and modulation of many signaling pathways, including insulin-like growth factor and Wnt. Klotho deficiency activates Wnt expression and activity contributing to senescence and depletion of stem cells, which consequently triggers tissue atrophy and fibrosis. In contrast, the klotho protein was shown to suppress Wnt-signaling transduction, and inhibit cell senescence and preserve stem cells."

Stem cells and anti-aging genes: double-edged sword-do the same job of life extension

"Stem cells, together with anti-aging genes such as Klotho, play a crucial role in delaying the aging process. Stem cells in combination with anti-aging genes make a complex and protective shield, which stand against the eroding effects of aging.

Increased wear and tear of the stem cells, as well as Klotho deficiency, is expected to heavily increase cellular damage and accelerate the process of aging."

Klotho enhances brain function and resilience in both young and aging mice.

"α-klotho protein fragment (αKL-F), administered peripherally, surprisingly induced cognitive enhancement and neural resilience despite impermeability to the blood-brain barrier in young, aging, and transgenic α-synuclein mice. αKL-F treatment induced cleavage of the NMDAR subunit GluN2B and also enhanced NMDAR-dependent synaptic plasticity. GluN2B blockade abolished αKL-F-mediated effects. Peripheral αKL-F treatment is sufficient to induce neural enhancement and resilience in mice and may prove therapeutic in humans."

Secreted αKlotho isoform protects against age-dependent memory deficits

"This study demonstrates for we believe the first time in vivo that 6 months after a single injection of s-KL into the central nervous system, long-lasting and quantifiable enhancement of learning and memory capabilities are found. More importantly, cognitive improvement is also observable in 18-month-old mice treated once, at 12 months of age. These findings demonstrate the therapeutic potential of s-KL as a treatment for cognitive decline associated with aging."

Klotho rejuvenates muscle healing in old mice

"In young animals, Klotho expression soars after a muscle injury, whereas in old animals, it remains flat. By raising Klotho levels in old animals, or by mitigating downstream effects of Klotho deficiency, the researchers could restore muscle regeneration after injury."

Klotho expression is a prerequisite for proper muscle stem cell function and regeneration of skeletal muscle

"...muscle stem cell numbers are significantly decreased in klotho hypomorphic mice. Furthermore, we show that muscle stem cell function is also severely impaired upon loss of klotho expression, in culture and during regeneration in vivo. Moreover, we demonstrate that addition of recombinant Klotho protein inhibits aberrant excessive Wnt signaling in aged muscle stem cells thereby restoring their functionality."

Recombinant Klotho protein enhances cholesterol efflux of THP-1 macrophage-derived foam cells via suppressing Wnt/β-catenin signaling pathway

"The Recombinant-Klotho-induced up-regulation of reverse cholesterol transport capacity promotes cholesterol efflux and reduces lipid accumulation by suppressing the Wnt/β-catenin pathway in foam cells."

Klotho ameliorates the onset and progression of cataract via suppressing oxidative stress and inflammation in the lens in streptozotocin-induced diabetic rats

"...Cataract formation and scores were significantly less in klotho-treated diabetic rats than vehicle-treated diabetic rats….
...Klotho treatment can ameliorate the onset and progression of diabetic cataract via enhancing Nrf2-mediated antioxidant defense and suppressing NF-κB-mediated inflammatory responses. Klotho in the lens may be a novel therapeutic target for prevention of cataract formation in diabetes."

Antiaging Factor Klotho Retards the Progress of Intervertebral Disc Degeneration through the Toll-Like Receptor 4-NF- κ B Pathway

"Antiaging protein Klotho exhibits impressive properties of anti-inflammation, however is declined early after intervertebral disc injury, making Klotho restoration an attractive strategy of treating intervertebral disc inflammatory disorders."

Association between serum levels of Klotho and inflammatory cytokines in cardiovascular disease

"Decrease in soluble anti-aging Klotho protein levels is associated to cardiovascular disease (CVD). Diverse studies have shown a bidirectional relationship between Klotho and inflammation, a risk factor for the development of CVD. … Multiple logistic regression analysis showed that age, smoking and the neutrophil-to-lymphocyte ratio (NLR) constituted risk factors for the presence of CVD, while Klotho was a protective factor.In conclusion, in patients with established CVD, the reduction in soluble Klotho is associated with a pro-inflammatory status marked by lower IL10 concentrations and higher TNFα/IL10 ratio and CRP levels."

Klotho and the Treatment of Human Malignancies

"Emerging research has also demonstrated a potential therapeutic role for Klotho in cancer biology, which is perhaps unsurprising given that cancer and ageing share similar molecular hallmarks. In addition to functioning as a tumour suppressor in numerous solid tumours and haematological malignancies, Klotho represents a candidate therapeutic target for patients with these diseases, the majority of whom have limited treatment options."

FLI-1 mediates tumor suppressor function via Klotho signaling in regulating CRC

"Klotho is a tumor suppressor, and its expression is aberrant in CRC. In this study, the roles of the FLI-1 gene in regulating Klotho gene expression and Klotho-associated signaling, as well as the effects of FLI-1 on colony formation, invasion, and apoptosis were investigated in CRC cell lines."

My Experience With Klotho - Positive Effects

Klotho functions as a cofactor essential for FGF21 activity. If you understand the MOA of FGF21, you'll understand the observable MOA of Klotho. Once again, note the Wikipedia entry for FGF21 says:

"FGF21 stimulates glucose uptake in adipocytes but not in other cell types. This effect is additive to the activity of insulin. Increased FGF21 results in increased energy expenditure, fat utilization and lipid excretion".

Needless to say, Klotho lowers blood sugar, often rapidly. Therefore, it is recommended you have a CGM (continuous glucose monitor), such as Abbott Libre, in your arm before starting on Klotho.

And since FGF21 (whose efficacy increases under Klotho supplementation) is additive to the effects of insulin, it is quite effective for weight loss. Another probable reason for weight loss is that increased FGF21 levels, once again brought on by Klotho supplementation, do increase energy expenditure as per above.

Increasing FGF21 levels does improve skin elasticity, tightness and overall skin glow. After all, FGF21 stands for fibroblast growth factor 21. A fibroblast is a type of biological cell that synthesizes the extracellular matrix and collagen, produces the structural framework (stroma) for animal tissues, and plays a critical role in wound healing. Fibroblasts are the most common cells of connective tissue in animals.

Klotho also improves cognition - see my recent cognitive biomarkers on this sie under "Actual Biomarkers". Below are several MOA's behind its cognitive improvement:

Neuroprotective Effects

Klotho has been shown to have neuroprotective properties, meaning it helps protect neurons in the brain from damage and degeneration. This protection can help maintain

the structural integrity and function of brain cells, ultimately supporting better cognitive function.

Anti-Inflammatory Actions

Chronic inflammation in the brain can have detrimental effects on cognition. Klotho has been found to possess anti-inflammatory properties, reducing inflammation in the brain. By mitigating inflammation, Klotho may help preserve cognitive abilities.

Regulation of Ion Channels and Neurotransmitters

Klotho has been shown to interact with various ion channels and neurotransmitter systems in the brain. By modulating these channels and neurotransmitters, Klotho may influence neuronal communication and synaptic plasticity, which are crucial for learning, memory, and overall cognitive function.

Antioxidant Activity

Klotho exhibits antioxidant effects, helping to reduce oxidative stress in the brain. Oxidative stress, caused by an imbalance between the production of harmful free radicals and the body's ability to neutralize them, can damage brain cells and impair cognition. Klotho's antioxidant activity may help counteract this oxidative damage, promoting better cognitive performance.

It is strongly recommended that you take a CNS Vital Signs test before starting on Klotho as well as after 3 months so that you can quantify your cognitive improvement.

My Experience With Klotho - Negative/Side Effects

The side effects of GDF11 are a walk in the park compared to Klotho. After 9 years and hundreds of people, dogs and cats who have tried GDF11, we know the side effects of GDF11, which are insomnia, GERD and dyspnea, are relatively innocuous. The only side effect of GDF11 that is dangerous is arrhythmia which is easily preventable with proper HRV monitoring.

At the end of the day, Klotho is a metabolic hormone which makes it as difficult to work with as insulin or thyroid hormone. And most likely equally dangerous in excess amounts.

Between Klotho's effects on FGF21 and FGF19, the first thing you may notice is feeling full after a small meal.

However, if your Klotho levels get too high, a half sandwich suddenly feels like you ate a big Thanksgiving dinner with a stomach ache to match.

If you keep taking Klotho at this point, then you'll experience tachycardia (rapid heartbeat) which can be dangerous and take at least an hour to subside.

And if you for some reason don't take a break and cut the dose after all the above, the next level of side effects is what feels like constriction/tightening of the throat. This probably has something to do with the Klotho/FGF21 effect on the thyroid. This is a scary side effect and if you experience it, you surely will have the good sense to take at least a month off from Klotho and cut the dose substantially.

<u>Dosing Klotho</u>

Given the side effects of Klotho, an extremely conservative approach to dosing is warranted.

I recommend you take it very slowly and start with .2 pg/day. Being a metabolic hormone, daily dosing is recommended. You certainly can't take insulin or thyroid once or twice/week and the same holds true here. My current dose is .5 pg/day and almost everyone in the GDF11 cohort takes this dose.

Until you perfect your dose, do not take Klotho on an empty stomach or while fasting. Hypoglycemia will result which can be dangerous. If you experience this, drink fruit juice, or eat something ASAP.

Unlike GDF11, you can titrate your Klotho dose to how you feel as well as the readings from your CGM. Needless to say, if you feel any of the side effects above, take a two week break and cut the dose.

Also, excess Klotho will raise BP and pulse (no surprise here given the side effects), so keep an eye on the trending of these biomarkers.

Note that the latest thinking on the GDF11 maintenance dose is there is no maintenance dose. We just look at GDF11ers Emfit HRV and reaction time and when these biomarkers start to go south, we recommend a 3 zeptogram to 1 attogram "booster" shot based on biomarker trending.

Your feedback is welcome here which will help us refine the dosing strategy, just like we did with GDF11. Please send your dose/observations to steve@stevegperry.com.

In summary, please be careful with Klotho and repeat after me:

Less is MORE

Less is More

Less is More!

Looking forward to hearing your Klotho experiences and dosing recommendations.

Tnx.

Steve Perry

Also, a special thanks to Marcello Bergamo, a fellow GDF11er, who took the initial plunge with Klotho. Marcello did an excellent job of determining starting

dose which is a key piece of information when working powerful peptide like Klotho. Marcello can be reached in the GDF11 Slack community or at Marcello.Bergamo@hotmail.com