Quintero-Platt G, González-Reimers E, Rodríguez-Gaspar M, Martín-González C, Pérez-Hernández O, Romero-Acevedo L, Espelosín-Ortega E, Vega-Prieto MJ, Santolaria-Fernández F. Alpha Klotho and Fibroblast Growth Factor-23 Among Alcoholics. Alcohol Alcohol. 2017 Sep 1;52(5):542-549. doi: 10.1093/alcalc/agx041. Erratum in: Alcohol Alcohol. 2020 Mar 19;55(2):235. PMID: 28651327.

**Alcoholism may be a cardiovascular risk factor. Osteocyte derived molecules such as fibroblast growth factor 23 (FGF-23) and soluble α Klotho have recently been associated with cardiovascular disease, but their role in alcoholics is unknown. We here analyze the behavior of FGF23 and α Klotho in alcoholics.**

**FGF-23 was higher in alcoholics than in controls, especially among cirrhotics, and soluble α Klotho levels were also higher among cirrhotics. Both were related to liver function impairment, independently of serum creatinine levels, and also showed significant associations with vascular risk factors, such as hypertension, diabetes or trunk fat amount in the case of FGF-23, or LVH or atrial fibrillation in the case of α Klotho.  We report increased values of fibroblast growth factor 23 (FGF-23) and soluble α Klotho in cirrhotic alcoholics. Both molecules are associated with liver function impairment, and with some cardiovascular risk factors such as diabetes, hypertension, increased body fat, left ventricular hypertrophy and atrial fibrillation independently of serum creatinine.**

Sanz B, Arrieta H, Rezola-Pardo C, Fernández-Atutxa A, Garin-Balerdi J, Arizaga N, Rodriguez-Larrad A, Irazusta J. Low serum klotho concentration is associated with worse cognition, psychological components of frailty, dependence, and falls in nursing home residents. Sci Rep. 2021 Apr 27;11(1):9098. doi: 10.1038/s41598-021-88455-6. PMID: 33907242; PMCID: PMC8079365.

**Serum alpha-klotho (s-klotho) protein has been linked with lifespan, and low concentrations of s-klotho have been associated with worse physical and cognitive outcomes. Although its significance in aging remains unclear, s-klotho has been proposed as a molecular biomarker of frailty and dependence. This study is a secondary analysis of data from a clinical trial performed in a population of 103 older individuals living in 10 nursing homes in Gipuzkoa (Spain). We aimed to elucidate associations between s-klotho (as measured by enzyme-linked immunosorbent assay) and body composition, physical fitness, and cognition, as well as frailty and dependence (determined using validated tests and scales). In addition, we investigated the association of s-klotho concentration with falls in the six months following the initial assessment. Low s-klotho levels were associated with a lower score in the psychological component of the Tilburg Frailty Indicator, a worse score in the Coding Wechsler Adult Intelligence Scale, and a greater dependence in activities of daily living. Moreover, participants with lower s-klotho concentrations suffered more falls during the 6 months after the assessment. Future translational research should aim to validate klotho's putative role as a biomarker that could identify the risk of aging-related adverse events in clinical practice.**

Ezquer F, Quintanilla ME, Moya-Flores F, Morales P, Munita JM, Olivares B, Landskron G, Hermoso MA, Ezquer M, Herrera-Marschitz M, Israel Y. Innate gut microbiota predisposes to high alcohol consumption. Addict Biol. 2021 Jan 28:e13018. doi: 10.1111/adb.13018. Epub ahead of print. PMID: 33508889.

**Gut microbiota is known to be transferred from the mother to their offspring. This study determines whether the innate microbiota of rats selectively bred for generations as high alcohol drinkers play a role in their alcohol intake. Wistar-derived high-drinker UChB rats (intake 10-g ethanol/kg/day) administered nonabsorbable oral antibiotics before allowing access to alcohol, reducing their voluntary ethanol intake by 70%, an inhibition that remained after the antibiotic administration was discontinued. Oral administration of Lactobacillus rhamnosus Gorbach-Goldin (GG) induced the synthesis of FGF21, a vagal β-Klotho receptor agonist, and partially re-invoked a mechanism that reduces alcohol intake.**

Wolf EJ, Chen CD, Zhao X, Zhou Z, Morrison FG, Daskalakis NP, Stone A, Schichman S, Grenier JG, Fein-Schaffer D, Huber BR; Traumatic Stress Brain Research Group, Abraham CR, Miller MW, Logue MW. Klotho, PTSD, and advanced epigenetic age in cortical tissue. Neuropsychopharmacology. 2021 Mar;46(4):721-730. doi: 10.1038/s41386-020-00884-5. Epub 2020 Oct 23. PMID: 33096543; PMCID: PMC8027437.

**This study examined the klotho (KL) longevity gene polymorphism rs9315202 and psychopathology, including posttraumatic stress disorder (PTSD), depression, and alcohol-use disorders, in association with advanced epigenetic age in three postmortem cortical tissue regions: dorsolateral and ventromedial prefrontal cortices and motor cortex. Using data from the VA National PTSD Brain Bank (n = 117), we found that rs9315202 interacted with PTSD to predict advanced epigenetic age in motor cortex among the subset of relatively older (>=45 years), white non-Hispanic decedents (corrected p = 0.014, n = 42). An evaluation of 211 additional common KL variants revealed that only variants in linkage disequilibrium with rs9315202 showed similarly high levels of significance. Alcohol abuse was nominally associated with advanced epigenetic age in motor cortex (p = 0.039, n = 114). The rs9315202 SNP interacted with PTSD to predict decreased KL expression via DNAm age residuals in motor cortex among older white non-Hispanics decedents (indirect β = -0.198, p = 0.027). Finally, in dual-luciferase enhancer reporter system experiments, we found that inserting the minor allele of rs9315202 in a human kidney cell line HK-2 genomic DNA resulted in a change in KL transcriptional activities, likely operating via long noncoding RNA in this region. This was the first study to examine multiple forms of psychopathology in association with advanced DNA methylation age across several brain regions, to extend work concerning the association between rs9315202 and advanced epigenetic to brain tissue, and to identify the effects of rs9315202 on KL gene expression. KL augmentation holds promise as a therapeutic intervention to slow the pace of cellular aging, disease onset, and neuropathology, particularly in older, stressed populations.**