nuBioAge
WELLNESS NETWORK

Clinical Application of Longevity Medicine

“Longevity Assessments, peptides, supplements and cellular medicine compounds”

Leonard Pastrana, PharmD
Co-Founder, nuBioAge

Peptide Optimization Framework

(Weight Loss, Metabolism, Longevity)

- **Improve body composition metrics**
  - Body Fat lbs
  - Muscle Mass
  - Visceral Fat
- **Improve cardiovascular risk factors**
- **Improve metabolic risk factors**
  - Glucose Dysregulation. Glucose/Insulin Dynamics
- **Improve exercise capacity**
  - Zone 2 Training
  - Aerobic Capacity VO2 max
- **Improve eating habits**
- **Improve immune/inflammation/Gut**
- **Improve sleep and stress management**

“A deep understanding of cellular medicine is essential in combining supplementation, small molecules and peptide therapy for optimal patient outcomes.”

Leveraging the Intelligence of the Cell

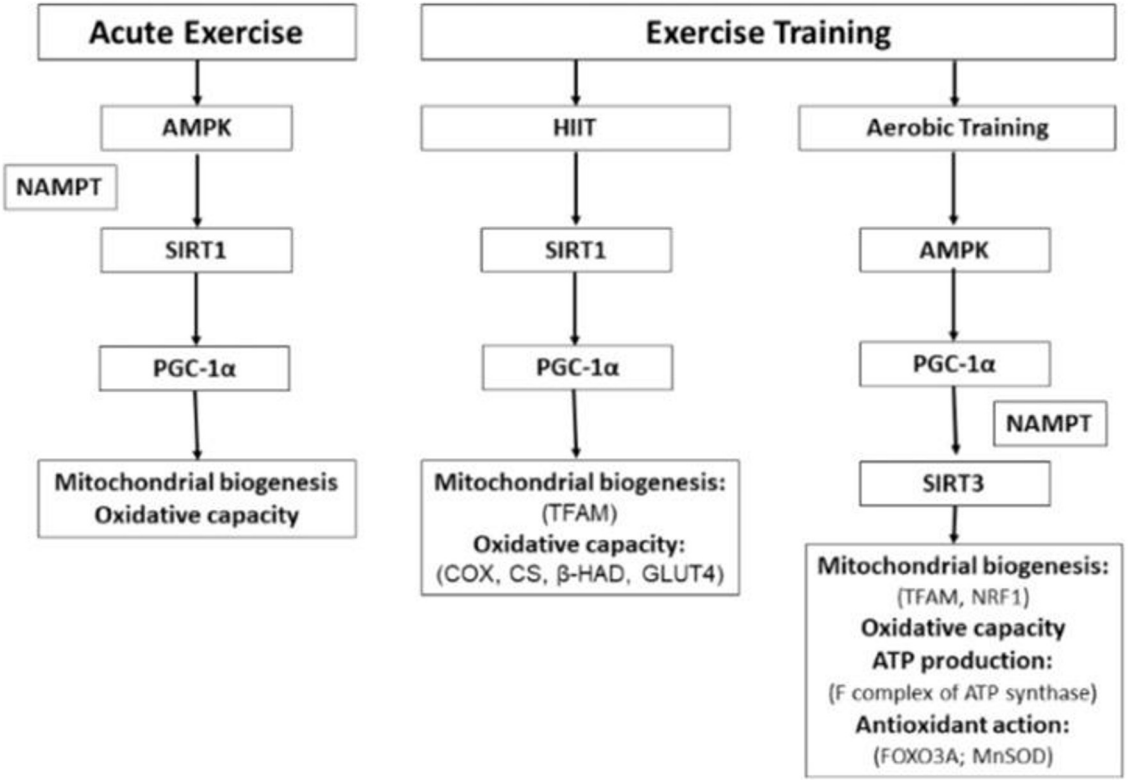
Weight Loss On A Cellular Level

Sirtuins and NAD+

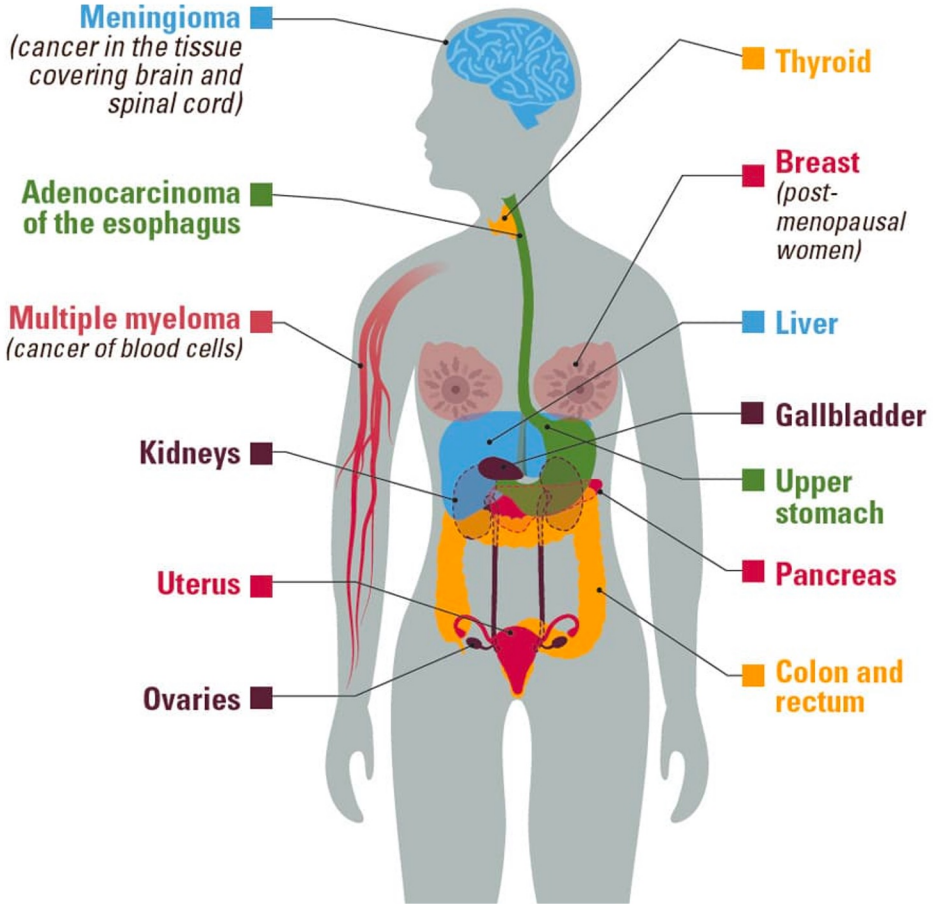
- Sirtuins are NAD+ dependent
- AMPK activates NAD+
- SIRT1- Activates gene transcription factors for cellular communication
- Regulates Metabolism
    - Fat Oxidation(PGC-1a)
    - Inflammation(NF-Kb)
    - Oxidative Stress(PGC-1a, FOXO3a)
    - Mitochondrial function(PPAR)

Vargas-Ortiz K, Pérez-Vázquez V, Macías-Cervantes MH. Exercise and Sirtuins: A Way to Mitochondrial Health in Skeletal Muscle. Int J Mol Sci. 2019 Jun 3;20(11):2717. doi: 10.3390/ijms20112717. PMID: 31163574; PMCID: PMC6600260.

Exercise's Influence on Nutrient Sensing Pathways



13 cancers are associated with overweight and obesity



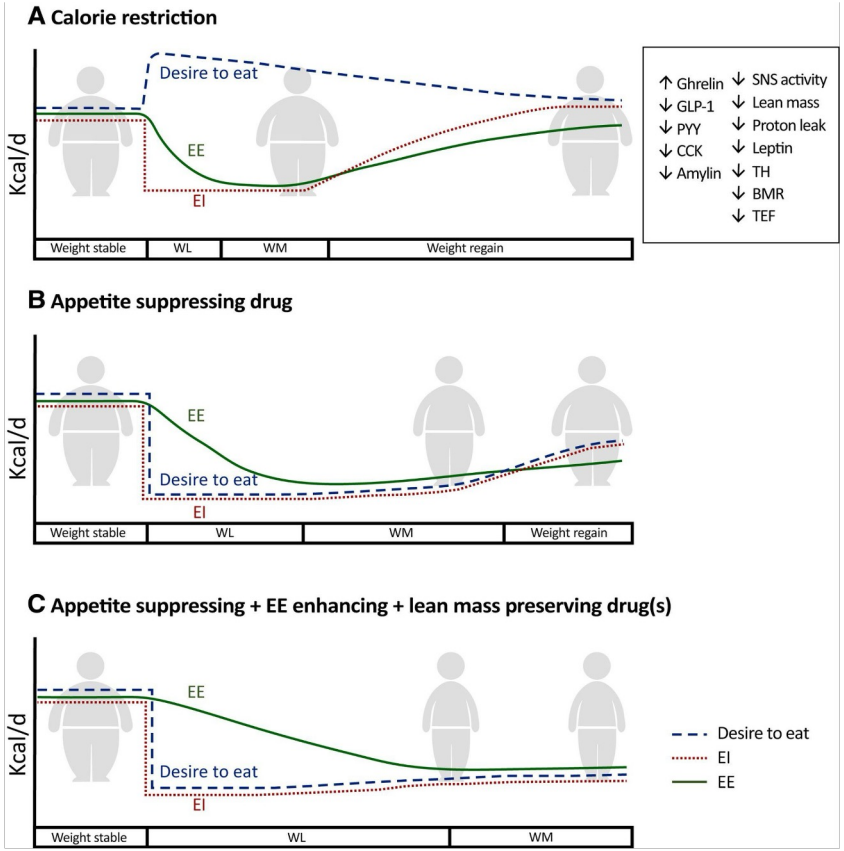
Do you have a weight loss program?

Or do you have:

- Metabolic Syndrome Prevention
- Cancer prevention program?
- CVD Prevention
- Neurodegenerative Prevention
- Longevity Program

(2021, March 10) Obesity and Cancer | CDC
https://www.cdc.gov/cancer/obesity/index.htm

The Next Era of Obesity Medicine



- Absolute Weight Loss vs Quality Weight Loss
- Focus should be on quality of weight loss and its maintenance
- Weight loss induction and weight loss maintenance require different treatment approaches.
- Regulation of energy expenditure, fat oxidation and preserving lean mass

Christoffersen BØ, Sanchez-Delgado G, John LM, Ryan DH, Raun K, Ravussin E. Beyond appetite regulation: Targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss. Obesity (Silver Spring). 2022 Apr;30(4):841-857. doi: 10.1002/oby.23374. PMID: 35333444; PMCID: PMC9310705.

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Metabolic Parameters **Predictive** of **Weight Regain**

Assessed under neutral energy balance conditions:

- Low resting and 24 hour energy expenditure while being sedentary
- Impaired fat oxidation, independent of energy expenditure
- Reduced sympathetic activity, which may underlie the two previous factors

*Both impaired fat oxidation and EE also cause resistance to weight loss

Christoffersen BØ, Sanchez-Delgado G, John LM, Ryan DH, Raun K, Ravussin E. Beyond appetite regulation: Targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss. Obesity (Silver Spring). 2022 Apr;30(4):841-857. doi: 10.1002/oby.23374. PMID: 35333444; PMCID: PMC9310705.

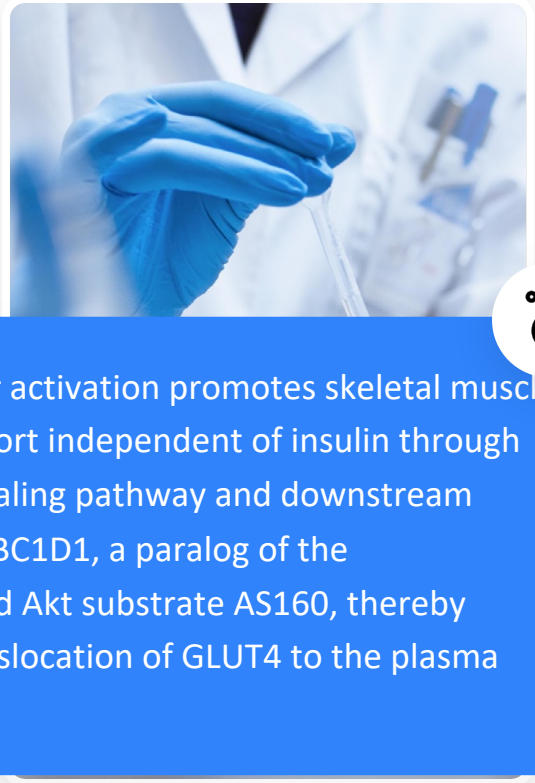
GLP-1

APPETITE/CRAVINGS

- Decreases orexigenic neuropeptide
- Increase anorexigenic neuropeptide
- Attenuation of neuronal activity in reward processing areas
- Stimulates serotonin receptor leading to reduction of appetite and hedonic feeding.

De Silva A, Salem V, Long CJ, et al. The gut hormones PYY 3-36 and GLP-1 7-36 amide reduce food intake and modulate brain activity in appetite centers in humans. *Cell Metab*. 2011;14(5):700-706. doi:10.1016/j.cmet.2011.09.010

GLP-1



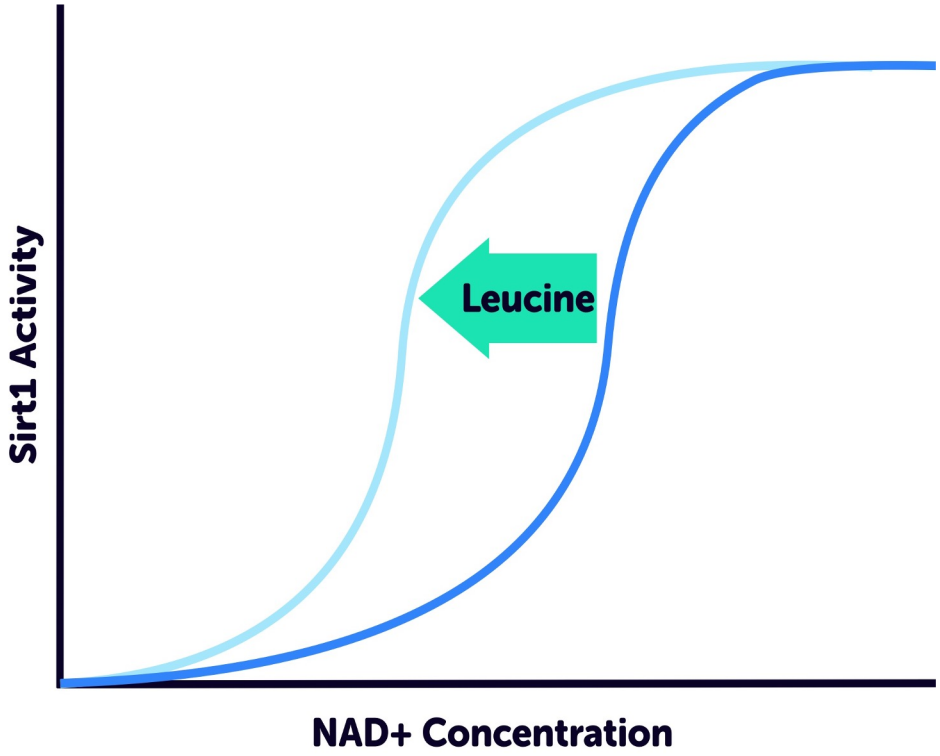
GLP-1 receptor activation promotes skeletal muscle glucose transport independent of insulin through the AMPK signaling pathway and downstream activation of TBC1D1, a paralog of the phosphorylated Akt substrate AS160, thereby leading to translocation of GLUT4 to the plasma membrane.

Andreozzi F, Raciti GA, Nigro C, et al. The GLP-1 receptor agonists exenatide and liraglutide activate Glucose transport by an AMPK-dependent mechanism. *J Transl Med*. 2016;14(1):229. Published 2016 Jul 30. doi:10.1186/s12967-016-0985-7

GLP-1 + Co-activating Compounds

Body Composition and Metabolic Risk Reduction Strategies

- Lose fat tissue and decrease visceral fat
- Minimize, maintain or gain muscle mass.
    - Under Muscle vs adequately muscled
- Improve insulin/glucose dynamics
    - Fasting insulin, HBA1C, FBG
- Improve cardiometabolic biomarkers
    - TG, LDL, APOb



SIRT1 and NAD+

SIRT1 is an NAD+ dependent deacetylase that relies on concentrations of NAD+ to activate the downstream targets of NAD+. (PGC-1a,PPAR,NF-kB,FOXO3a)

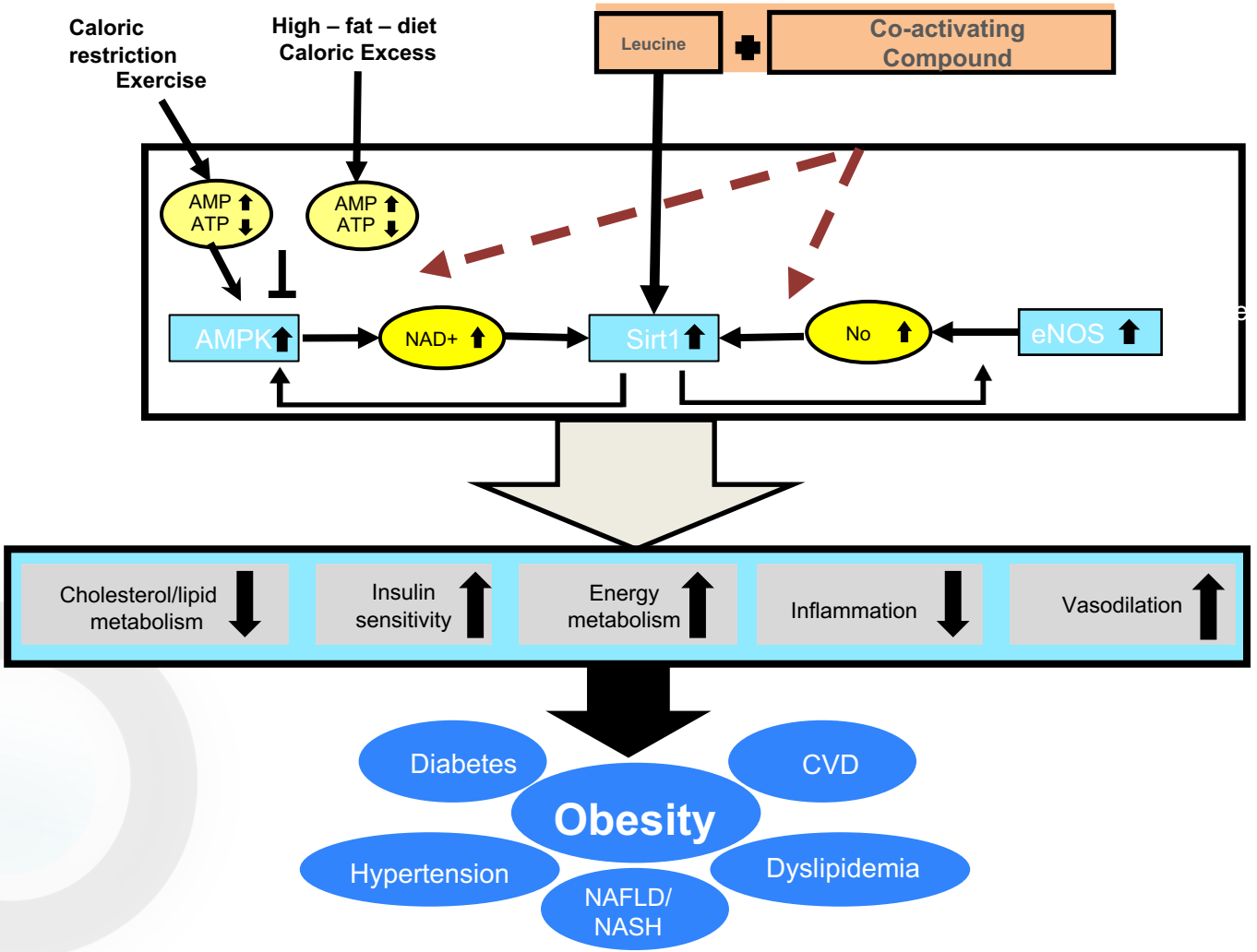
Leucine/NAD+/SIRT1

Leucine allosterically activates SIRT1, producing a leftward shift in SIRT1 activation response to NAD+. Enhancing endogenous NAD+ utilization by decreasing the kM of NAD+ by >50%

Leucine: Dose Specific Activations

0.5mM concentration of leucine was sufficient to activate SIRT1 **without concomitant mTOR activation.** Levels were achieved at Leucine dose of **1.0-1.5 grams.**

Zemel MB. Modulation of Energy Sensing by Leucine Synergy with Natural Sirtuin Activators: Effects on Health Span. J Med Food. 2020 Nov;23(11):1129-1135. doi: 10.1089/jmf.2020.0105. Epub 2020 Aug 4. PMID: 32758058.


Caloric restriction Exercise
High – fat – diet Caloric Excess
Leucine
Co-activating Compound
AMP ATP
AMP ATP
AMPK
NAD+
Sirt1
No
eNOS
Cholesterol/lipid metabolism
Insulin sensitivity
Energy metabolism
Inflammation
Vasodilation
Diabetes
CVD
Obesity
Hypertension
Dyslipidemia
NAFLD/ NASH

Leucine-Resveratrol Synergy

Human Pre-diabetic Subjects Randomized

- Leucine 1.1g + Resveratrol 50mg Twice Daily vs Placebo
  - OGTT and 60 minute glucose and insulin concentration
  - Reduced insulin resistance by 33%
  - Significant improvement and insulin/glucose dynamics

24-Week Trial in Obese Subjects

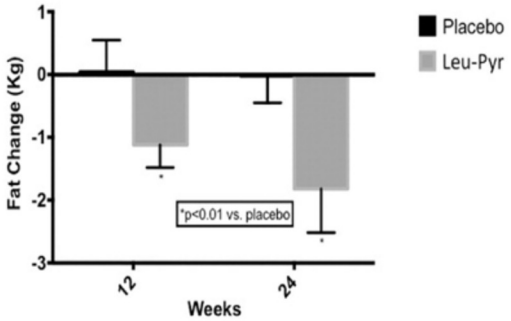
Leucine 1.1g + Pyridoxine 15 mg Twice Daily vs Placebo

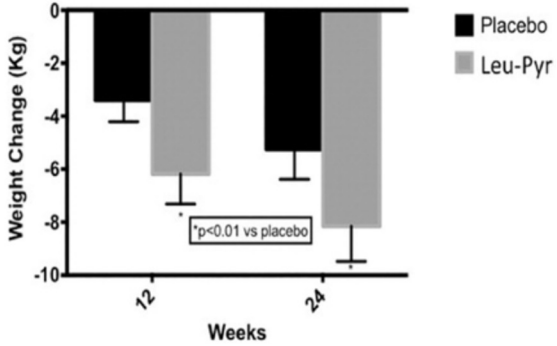
- Hypocaloric and weight maintenance study
- Significant loss of body fat using dexa scan
- Significant increase in insulin sensitivity

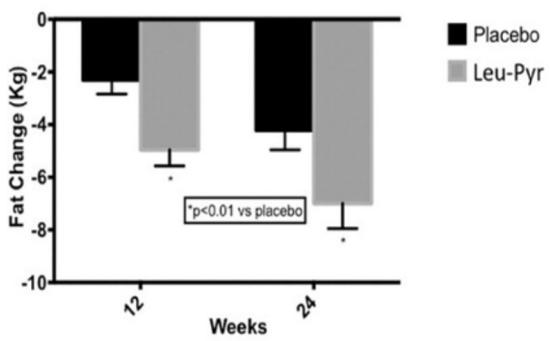
Leucine-Pyridoxine Synergy

Zemel MB, Bruckbauer A: Effects of a leucine and pyridoxinecontaining nutraceutical on fat oxidation, and oxidative and inflammatory stress in overweight and obese subjects. Nutrients 2012;4:529–541.

Weight Loss | Fat Oxidation | Insulin Sensitivity







Leu-Pyridoxine

- Leucine/B6 group lost 82% more weight than placebo at 12 weeks.
- Leucine/B6 group lost 2X fat tissue vs placebo
- Leucine/B6 group showed greater loss of waist circumference at 4 weeks
- Significant increase in insulin sensitivity

Zemel MB, Bruckbauer A: Effects of a leucine and pyridoxinecontaining nutraceutical on fat oxidation, and oxidative and inflammatory stress in overweight and obese subjects. Nutrients 2012;4:529–541.

Leusynergy + GLP-1 (Semaglutide) (Tirzepatide)

Insulin Independent Pathways for glucose disposal

- GLP-1 : Increase in GLUT4 expression by activating AMPK.
- LeuSynergy: Increase in GLUT4 expression through SIRT1 deacetylation of PGC-1a

Improved Fat oxidation

- GLP-1: Direct effects on hepatocytes by activating genes involved in beta-oxidation of fatty acids
- LeuSynergy: activation of PGC-1a and PPAR resulting in an increase in fatty acid oxidation and oxidative phosphorylation

Oxidative stress and pancreatic beta cell protection

- GLP-1: reduced oxidative stress in pancreatic islets. Increases β-cell mass by directly regulating cell kinetics and suppressing oxidative and ER stress, secondary to the amelioration of glucolipotoxicity.
- LeuSynergy: SIRT1 deacetylation and inhibition of NF-kB protecting beta cells from oxidative stress and inflammatory cytokines.

LeuSynergy™- Weight Loss and Body Composition

1. Leucine 1.1grams /Resveratrol 50mg/Pyridoxine 15mg
2. 2 capsules in the morning and 2 capsules 90 minutes after lunch.
3. Serving size is important SIRT1 activation happens at leucine dose of 1.0 to 1.5 grams.
4. Fat tissue loss, insulin/glucose control

Synergy: GLP-1s, CJC/Ipamorelin, 5-amino-1MQ, MOTS-c

ORIGINAL PAPER

Aging Cell WILEY

Glucagon-like peptide 1 infusions overcome anabolic resistance to feeding in older human muscle

Haitham Abdulla[1,3] | Bethan E. Phillips[1,2] | Daniel J. Wilkinson[1] | Marie Limb[1] | Tereza Jandova[1] | Joseph J. Bass[1] | Debbie Rankin[1] | Jessica Cegielski[1] | Mariwan Sayda[1] | Hannah Crossland[1] | John P. Williams[1,4] | Kenneth Smith[1,2] | Iskandar Idris[1,2,5] | Philip J. Atherton[1,2]

- Direct effect of GLP-1 at a cellular level in muscle
- **Greater increase in muscle blood flow** in response to feeding alongside GLP-1
- **Demonstrate and anabolic effect of GLP-1 in skeletal muscle** of older humans under fed-state conditions
- **GLP-1 infusions have clear translational potential in muscle mass attainment in settings where intentional weight loss is not the primary outcome being sought**

GLP-1 Reduce Thirst and Water Intake

- GLP-1 has also been shown to play a role in thirst and drinking behavior
- Primary polydipsia, characterized by excessive fluid intake, carries the risk of water intoxication and hyponatremia, but treatment options are scarce
- GLP-1 receptor agonists reduce fluid intake and thirst perception in patients with primary polydipsia and could therefore be a treatment option for these patients.
- Thus, the basic finding that GLP-1 receptor agonists decrease fluid intake could be especially important in clinical settings, especially with respect to geriatric patient populations that are already at risk for dehydration

McKay NJ, Kanoski SE, Hayes MR, Daniels D. Glucagon-like peptide-1 receptor agonists suppress water intake independent of effects on food intake. Am J Physiol Regul Integr Comp Physiol. 2011 Dec;301(6):R1755-64. doi: 10.1152/ajpregu.00472.2011. Epub 2011 Oct 5. PMID: 21975647; PMCID: PMC3233845.

Winzeler B, Sailer CO, Coynel D, Zanchi D, Vogt DR, Urwyler SA, Refardt J, Christ-Crain M. A randomized controlled trial of the GLP-1 receptor agonist dulaglutide in primary polydipsia. J Clin Invest. 2021 Oct 15;131(20):e151800. doi: 10.1172/JCI151800. PMID: 34473645; PMCID: PMC8516458.

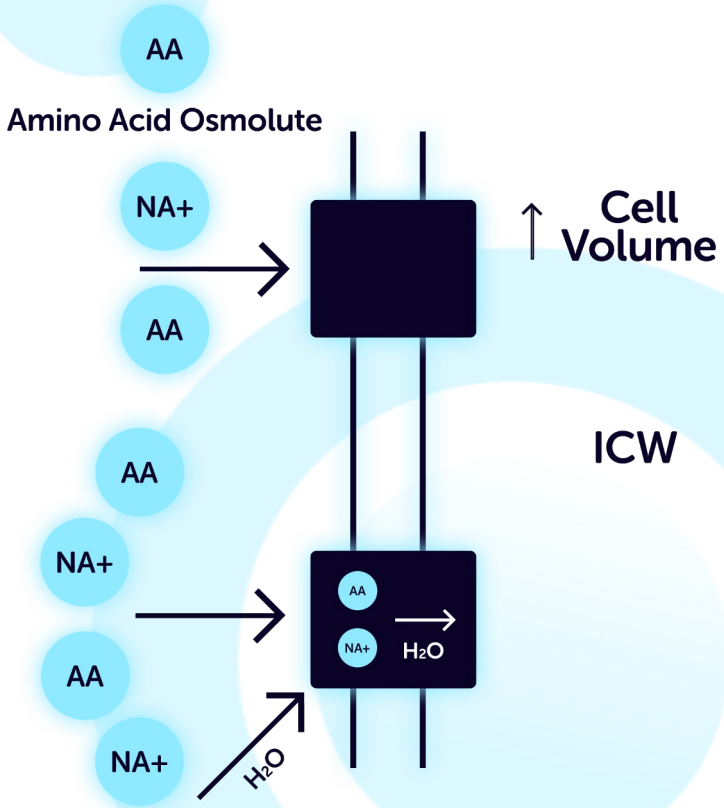
Cellular Hydration- Metabolic Control

Cellular Hydration State: Controls cellular protein turnover, protein synthesis and protein degradation

- An increase in cellular hydration (swelling) acts as an anabolic proliferative signal, whereas cell shrinkage is catabolic and antiproliferative

Modulating cellular hydration state by neutral amino acid osolytes

- Amino acids are taken up into the cell creating osmotically active amino acid gradients. (Causing water to come into the cell and lead to cell swelling)



Häussinger D, Roth E, Lang F, Gerok W. Cellular hydration state: an important determinant of protein catabolism in health and disease. Lancet. 1993 May 22;341(8856):1330-2. doi: 10.1016/0140-6736(93)90828-5. PMID: 8098459.

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Intracellular Water in Muscle Mass, Strength and Performance

> J Nutr Health Aging. 2019;23(1):96-101. doi: 10.1007/s12603-018-1129-y.

Total Body Water and Intracellular Water Relationships with Muscle Strength, Frailty and Functional Performance in an Elderly Population

M Serra-Prat [1], I Lorenzo, E Palomera, S Ramírez, J C Yébenes

Affiliations + expand

PMID: 30569076 DOI: 10.1007/s12603-018-1129-y

Observational Study > Int J Sports Med. 2014 Dec;35(13):1101-5.
doi: 10.1055/s-0034-1371839. Epub 2014 Jul 10.

Increases in intracellular water explain strength and power improvements over a season

A M Silva [1], C N Matias [1], D A Santos [1], P M Rocha [1], C S Minderico [1], L B Sardinha [1]

Affiliations + expand

PMID: 25009970 DOI: 10.1055/s-0034-1371839

- **In individuals with similar muscle mass, those with higher ICW had a better**
  - Functional performance
  - Lower risk of frailty
- **Young adult athletes**
  - ICW was the main predictor of leg strength and jump performance in highly trained athletes
  - Athletes who showed a decrease in ICW during training sessions were also found to have reduced power and grip strength

iCell Water

- Swell the cell- Optimize anabolic signaling and protect synthesis
- Based on neutral amino acids and creatine monohydrate that act as osmolytes to increase intracellular (ICW) or enhance cell volume
    - **L-Alanine 5 grams**
    - **Creatine Monohydrate 5 grams**
    - **Glycine 4g**
    - **L-Glutamine 3g**
    - **L-Leucine 3g**
- Meant to be sipped all day
    - **1 scoop in 2-4 liters of water**
    - **Make sure water is cold**

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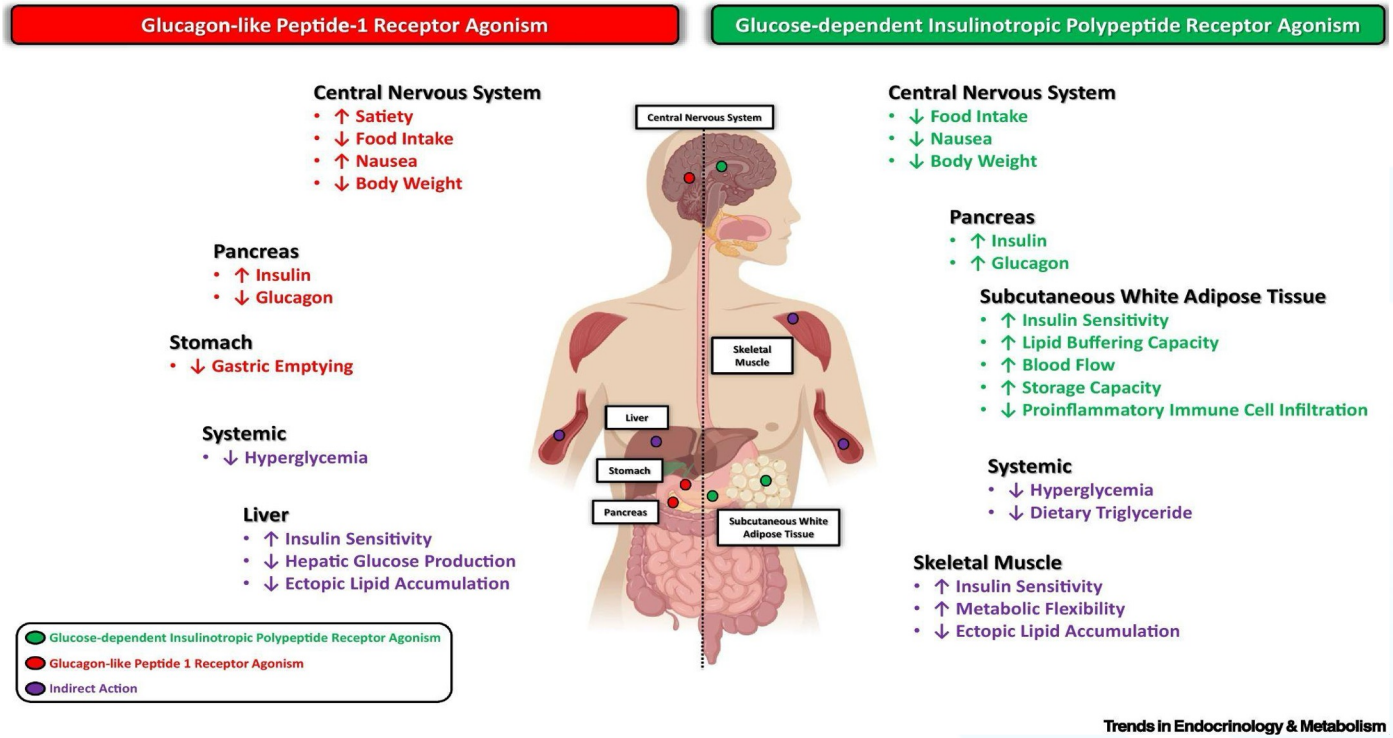
GLP-1s + Co-activating Peptides, Compounds and Supplements

- Low Dose Leucine Products: Leusynergy and Sytrinol LNA
- iCell Water: Hydration, Muscle Performance
- AKG Plus: ATP, Bone Mineral Density, Muscle
- GHRH/GHRP: Muscle, Sleep, Recovery
- Amlexanox: Energy Expenditure, inflammation, insulin sensitivity
    - GLucagon-FGF21 required for benefits of IKKe/TKB1 inhibition
- Mitochondrial Peptides: Energy Expenditure
- PPS: Inflammation
- Gut Health peptides: inflammation, immune dysregulation

GIP Enhanced the Therapeutic Efficacy of GLP-1



Samms RJ, Coghlan MP, Sloop KW. How May GIP Enhance the Therapeutic Efficacy of GLP-1? Trends Endocrinol Metab. 2020 Jun;31(6):410-421. doi: 10.1016/j.tem.2020.02.006. Epub 2020 Mar 16. PMID: 32396843.

Tirzepatide (Cardioprotection and Lipids)

GIP Enhancing Therapeutic Efficacy of GLP-1

- GIP enhances the lipid buffering capacity of WAT
  - Improves long term storage of lipids through healthy expancion WAT
  - Protection from spillover of dietary lipids that can cause ectopic lipid accumulation
- Surpass-2: Semaglutide vs Tirzepatide
  - Triglyceride: Tirzepatide>Semaglutide
  - VLDL: Tirzepatide>Semaglutide

Samms RJ, Coghlan MP, Sloop KW. How May GIP Enhance the Therapeutic Efficacy of GLP-1? Trends Endocrinol Metab. 2020 Jun;31(6):410-421. doi: 10.1016/j.tem.2020.02.006. Epub 2020 Mar 16. PMID: 32396843.

Tirzepatide + Sytrinol LNA

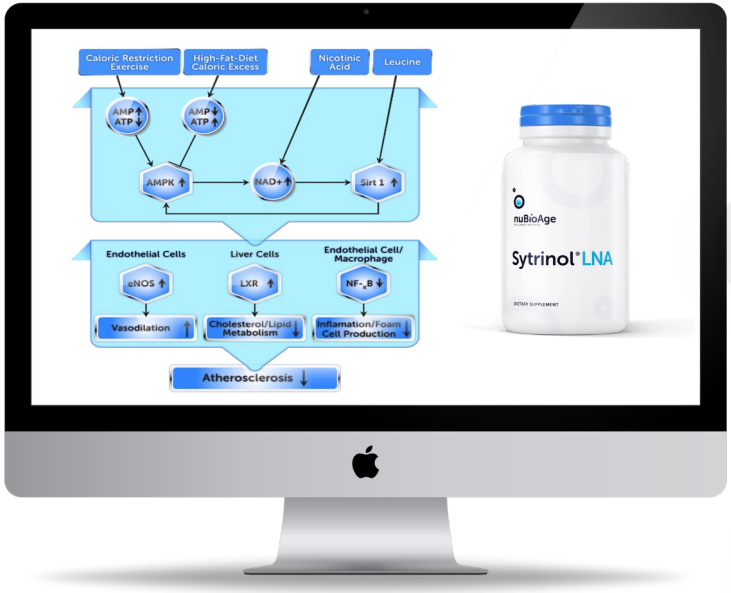
(Cardioprotection and Lipid Management)

Nicotinic Acid and Cardio protection

- Substrate for NAD+ biosynthesis, the cofactor for SIRT1.
- Used for decades as an effective treatment of dyslipidemias
- Lowers LDL-cholesterol, and triglycerides, and raises HDL
- Reduces atherosclerotic plaque progression
- Anti-inflammatory, anti-thrombotic, and antioxidant effects

Nicotinic Acid is Poorly Tolerated

- Therapeutic doses of 1-3 grams
- Severe vasodilation and flushing
- Potential hyperglycemic adverse effects.



Bruckbauer A, Banerjee J, Cao Q, Cui X, Jing J, Zha L, Li F, Xue B, Shi H, Zemel MB. Leucine-nicotinic acid synergy stimulates AMPK/Sirt1 signaling and regulates lipid metabolism and lifespan in Caenorhabditis elegans, and hyperlipidemia and atherosclerosis in mice. Am J Cardiovasc Dis. 2017 Apr 15;7(2):33-47. Erratum in: Am J Cardiovasc Dis. 2017 Jul 25;7(4):97. PMID: 28533928; PMCID: PMC5435603.

Amplifying Effects of Leucine and Nicotinic Acid

- Nicotinic Acid in the absence of Leucine
  - Human equivalent dose of 1500mg per day
    - Significant decrease in cholesterol and triglycerides
    - 50% reduction in atherosclerotic lesion size
  - Lowering the dose to 75mg
    - No independent effect

- In the presence of Leucine with Nicotinic Acid 75mg
  - Equivalent efficacy to therapeutic doses
    - Reducing circulating lipids
    - Regressing atherosclerotic plaque

Sytrinol

- A patented combination of polymethoxylated flavones and tocotrienols.
- Nobiletin was shown to increase hepatic fatty acid oxidation, decrease fatty acid synthesis and decrease inflammatory gene transcription factors.
- Nobiletin increases SIRT1 expression.
- Nobiletin was found to enhance circadian rhythms to protect against metabolic syndrome.
- Tocotrienol similar to statins work on HMG-CoA reductase.

Sytrinol Clinical Study Results

Measured Endpoints	Treatment Group	Sytrinol Clinical Study II % Change at 4 Weeks
Total Cholesterol	Sytrinol	-30%[b]
LDL	Sytrinol	-27%[b]
Triglycerides	Sytrinol	-34%[b]
HDL	Sytrinol	+4%[b]
LDL: HDL Ratio	Sytrinol	-29%[b]
Means + SEM. Statistical analysis by ANOVA plus post test by Dunnett's method		
B- Significantly different within same group, P ≤ 0.05 Source: SourceOne Global Partner		

Effect of citrus flavonoids and tocotrienols on serum cholesterol levels in hypercholesterolemic subjects

James M Roza1, Zheng xian-Liu, Najla Guthrie

Affiliations + Expand

PMD: 17985810

- Sytrinol significantly improved cardiovascular parameters compared to placebo in all groups.
- Significant reductions were shown in apolipoprotein B (21%

Sytrinol® LNA

Leveraging polymethoxylated flavones, Leucine and Nicotinic Acid Synergy

- Sytrinol 300mg (Nobiletin:Tangeretin 270 mg and Tocotrienols 30mg)
- Leucine 1.1 grams/Nicotinic Acid 75mg
- 3 capsules daily with dinner.
- Serving size is important SIRT1 activation happens at leucine dose of 1.0 to 1.5 grams of leucine
- Dyslipidemias, Atherosclerosis, Cardioprotection, Circadian Rhythm Disruptions
- When: (Non-optimal:TG, LDL, APOb), Liver Protection, Statin intolerance

Statin substitute?

- ❑ Tolerability/ Side effects
  - Nutrient depletion(CoQ10)
  - Muscle Pain
  - Patients not willing to take statins

Tirzepatide + Sytrinol LNA - (Cardioprotection and Lipids)

GIP Enhancing Therapeutic Efficacy of GLP-1

- GIP enhances the lipid buffering capacity of WAT
  - **Improves long term storage of lipids through healthy expansion WAT**
  - **Protection from spillover of dietary lipids that can cause ectopic lipid accumulation**
- Surpass-2: Semaglutide vs Tirzepatide
  - **Triglyceride: Tirzepatide>Semaglutide**
  - **VLDL: Tirzepatide> Semaglutide**
- Sytrinol
  - **Nobiletin shown to improve hepatic fatty acid oxidation and decrease inflammatory gene transcription factors.**
  - **Triglycerides: -34%**
  - **LDL: -24%**
  - **ApoB: -21%**

Mahmoud AM, Hernández Bautista RJ, Sandhu MA, Hussein OE. Beneficial Effects of Citrus Flavonoids on Cardiovascular and Metabolic Health. Oxid Med Cell Longev. 2019 Mar 10;2019:5484138. doi: 10.1155/2019/5484138. PMID: 30962863; PMCID: PMC6431442.

Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K; SURPASS-2 Investigators. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med. 2021 Aug 5;385(6):503-515. doi: 10.1056/NEJMoa2107519. Epub 2021 Jun 25. PMID: 34170647.

Case Study - Gaining Muscle while on GLP-1

42 Year old Male. Issue with over eating and controlling appetite.

- Adequate muscle mass
- Wants to improve body composition. Lose fat while maintaining muscle
- Looking to enhance strength and performance
- Improvement in apoB levels.
  - 98
  - Crp = 2.08
  - Family History of CVD

Treatment Plan

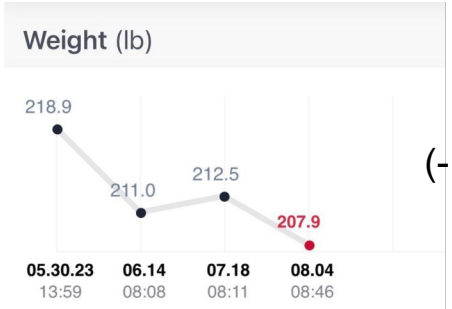
Month-1

- **Focus on protein intake and hydration**
- **Resistance training 4 days a week**
- Tirzepatide 2.5mg weekly
- Sytrinol LNA 3 caps PO BID

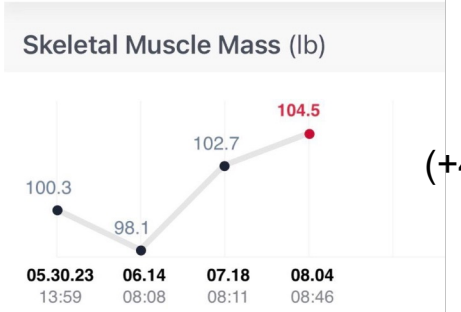
Month-2 Optimize Exercise Capacity

Add

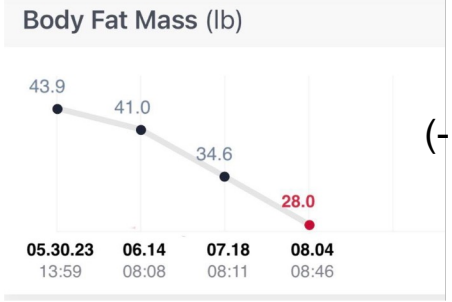
- CJC/Ipamorelin BID
- BPC 15 units BID
- MOTS-C 10mg 3 times per week
- **iCell Water (Amino Drink)- Daily**



(-11 lbs)

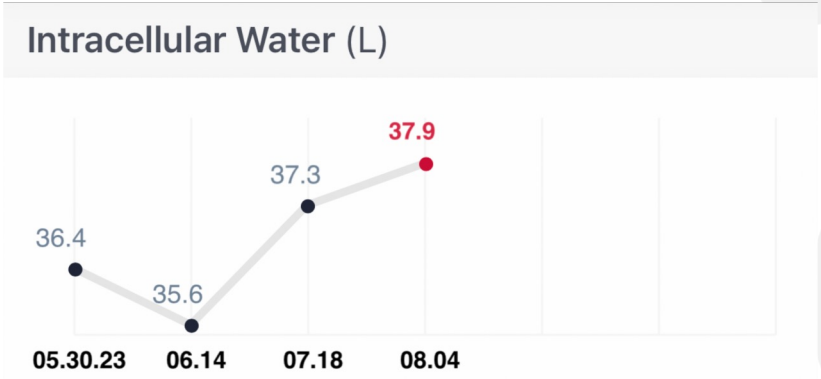


(+4.2 lbs)



(-15.9 lbs)

- **CRP**
  - **2.08→0.75**
- **Apolipoprotein B**
  - **98→80**
- **Increase Strength**
  - **(Grip,Bench,Squat)**



Treatment Plan

Month-1

- **Focus on protein intake and hydration**
- **Resistance training 4 days a week**
- Tirzepatide 2.5mg weekly
- Sytrinol LNA 3 caps PO BID

Month-2 Optimize Exercise Capacity

Add

- CJC/Ipamorelin BID
- BPC 15 units BID
- MOTS-C 10mg 3 times per week
- **iCell Water (Amino Drink)- Daily**

nuBioAge
WELLNESS NETWORK

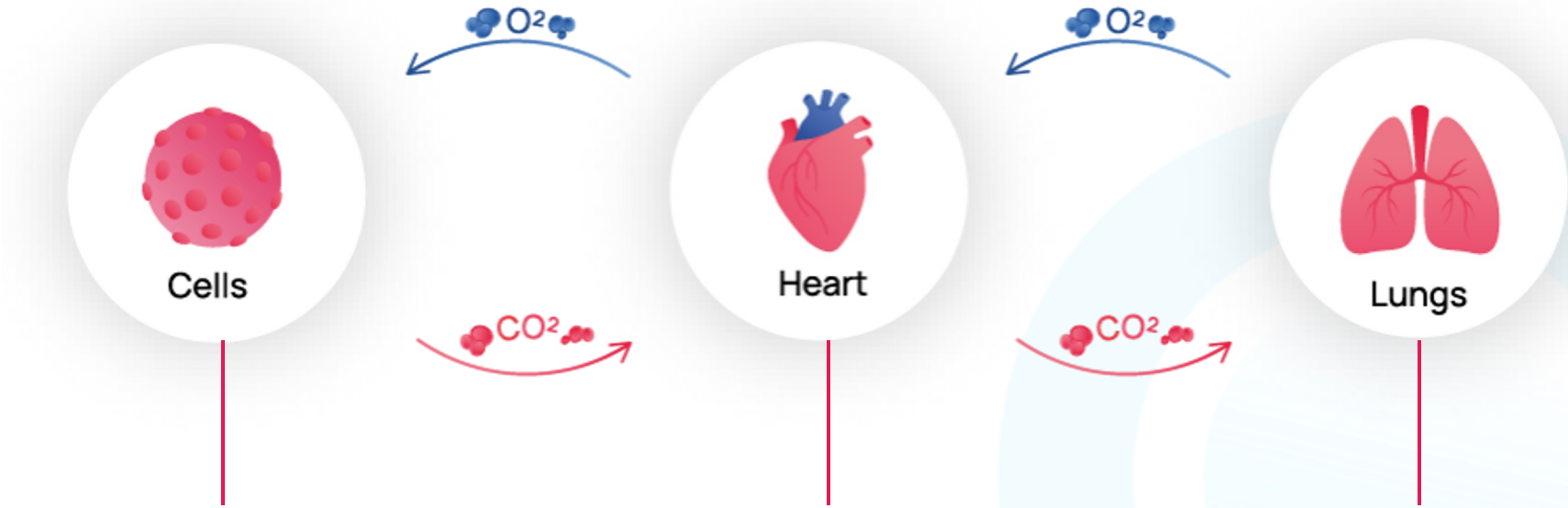
Science Backed Longevity Assessment Through Metabolic Breath Analysis

Leonard Pastrana, PharmD
Co-Founder, nuBioAge

Aerobic Metabolism & Breath Analysis

nuBioAge

OXYGEN CHAIN



Diabetes
Metabolic Disease
Neurodegenerative Disease

Ischemic Heart Disease
Heart Disease

COPD
Asthma

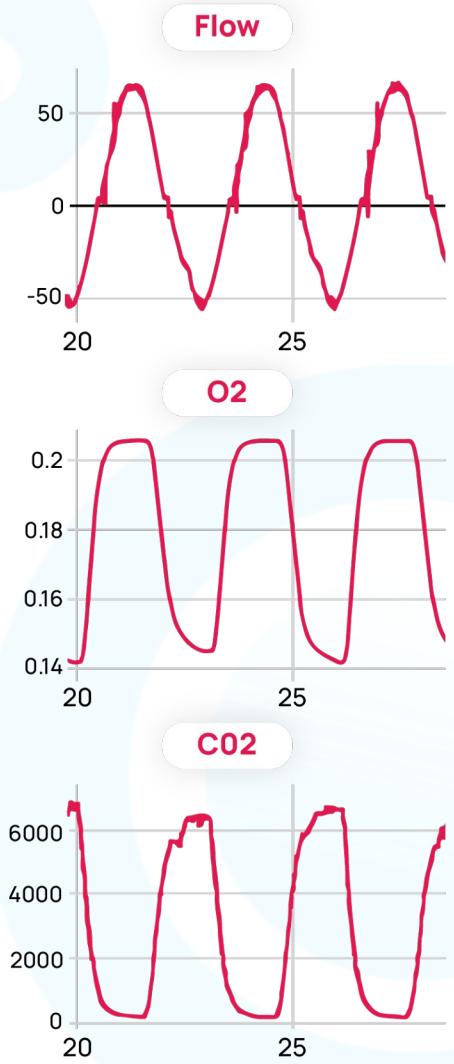
Today

Some History

PNOÉ

- Affordable, portable, easy to use hardware
- Automatic analysis without the need of specialized personnel
- Dedicated support for metabolic consultation, nutrition, exercise, and lifestyle planning

The Basic Principle



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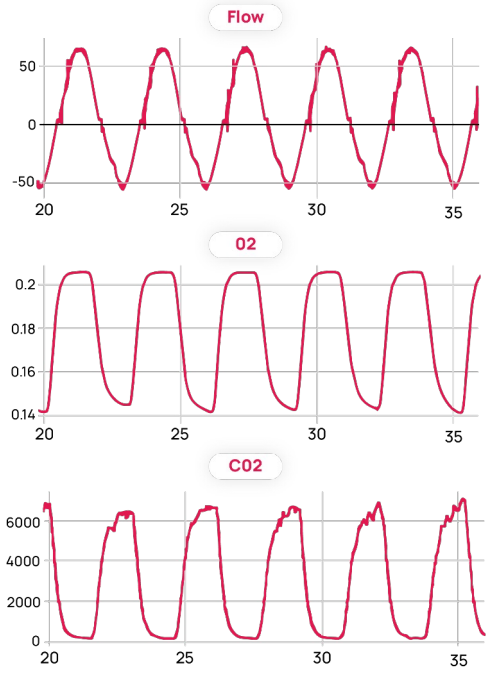
Breath Analysis Biomarkers



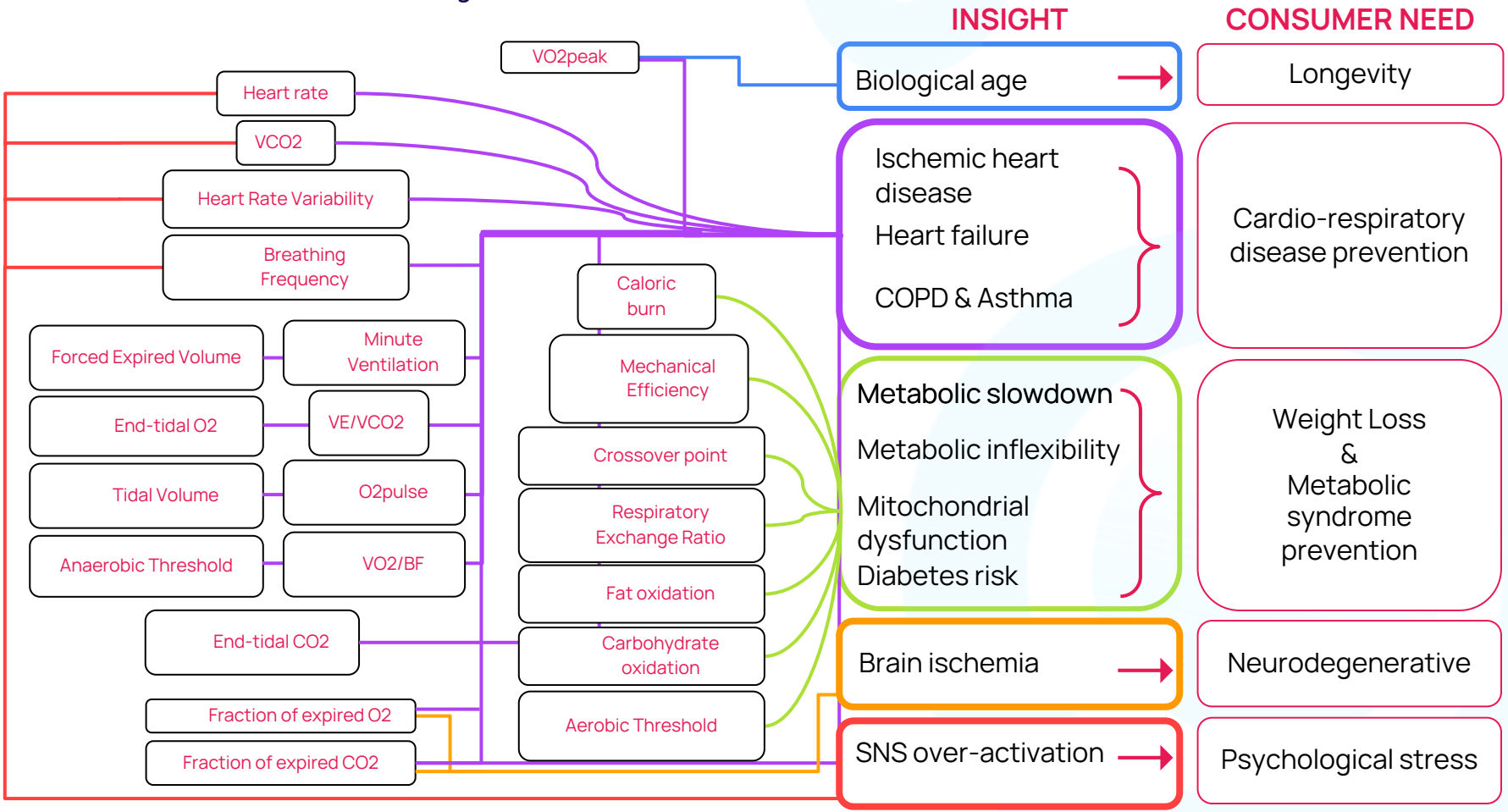
Heart Rate + Power output

23 BIOMARKERS

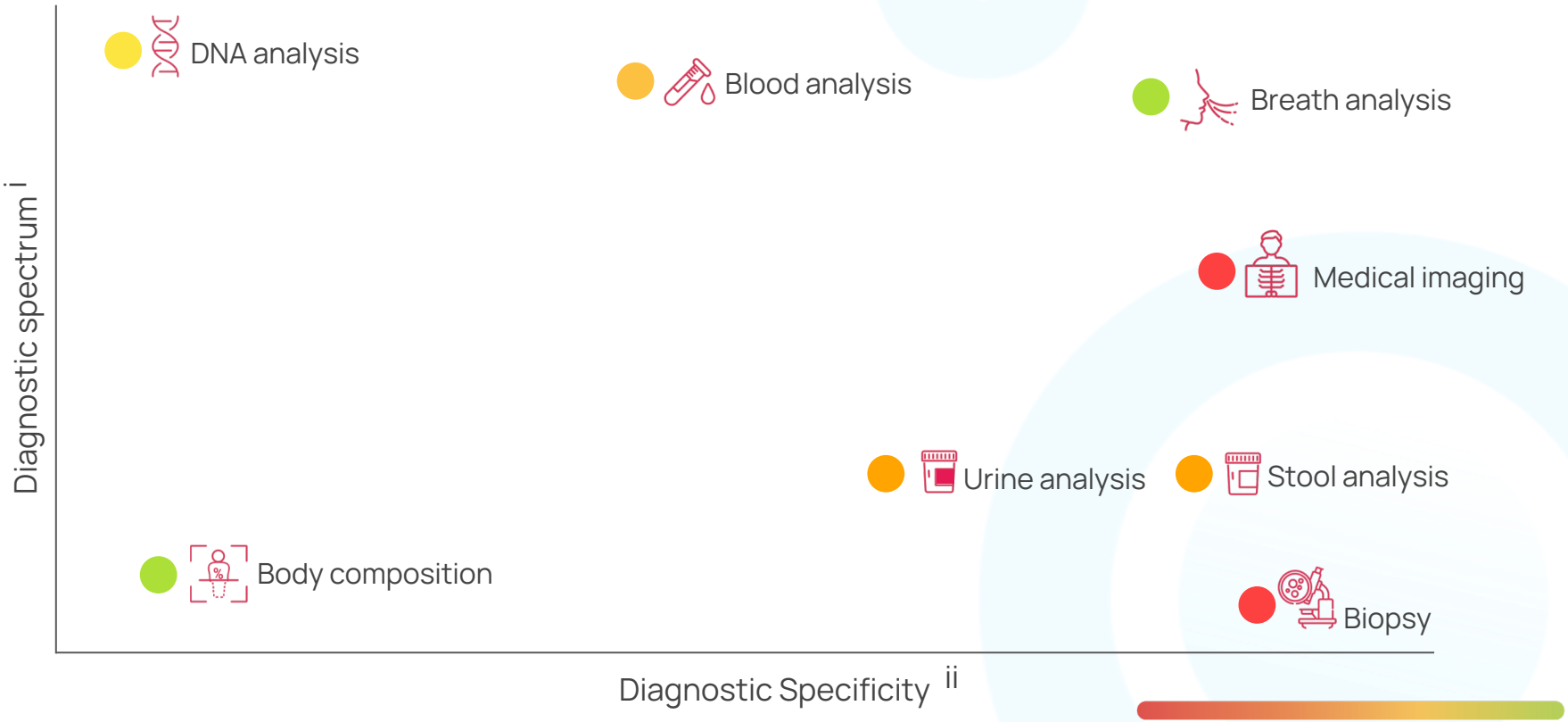
- VO2peak
- VCO2
- Respiratory Exchange Ratio
- Tidal Volume
- Breathing Frequency
- Minute Ventilation
- VE/VCO2
- O2 pulse
- VO2/BF
- End-tidal CO2
- End-tidal O2
- Heart rate
- Heart Rate Variability
- Forced Expired Volume
- Caloric burn
- Fat oxidation
- Carbohydrate oxidation
- Mechanical Efficiency
- Crossover point
- Aerobic threshold
- Anaerobic Threshold
- Fraction of expired CO2
- Fraction of expired O2

Age

From Biomarkers to Insights



Breath Analysis vs Other Assessments



i Spectrum of conditions method can detect

ii Ability to predict or detect a condition

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Detecting Metabolic Dysfunction Through Breath Analysis

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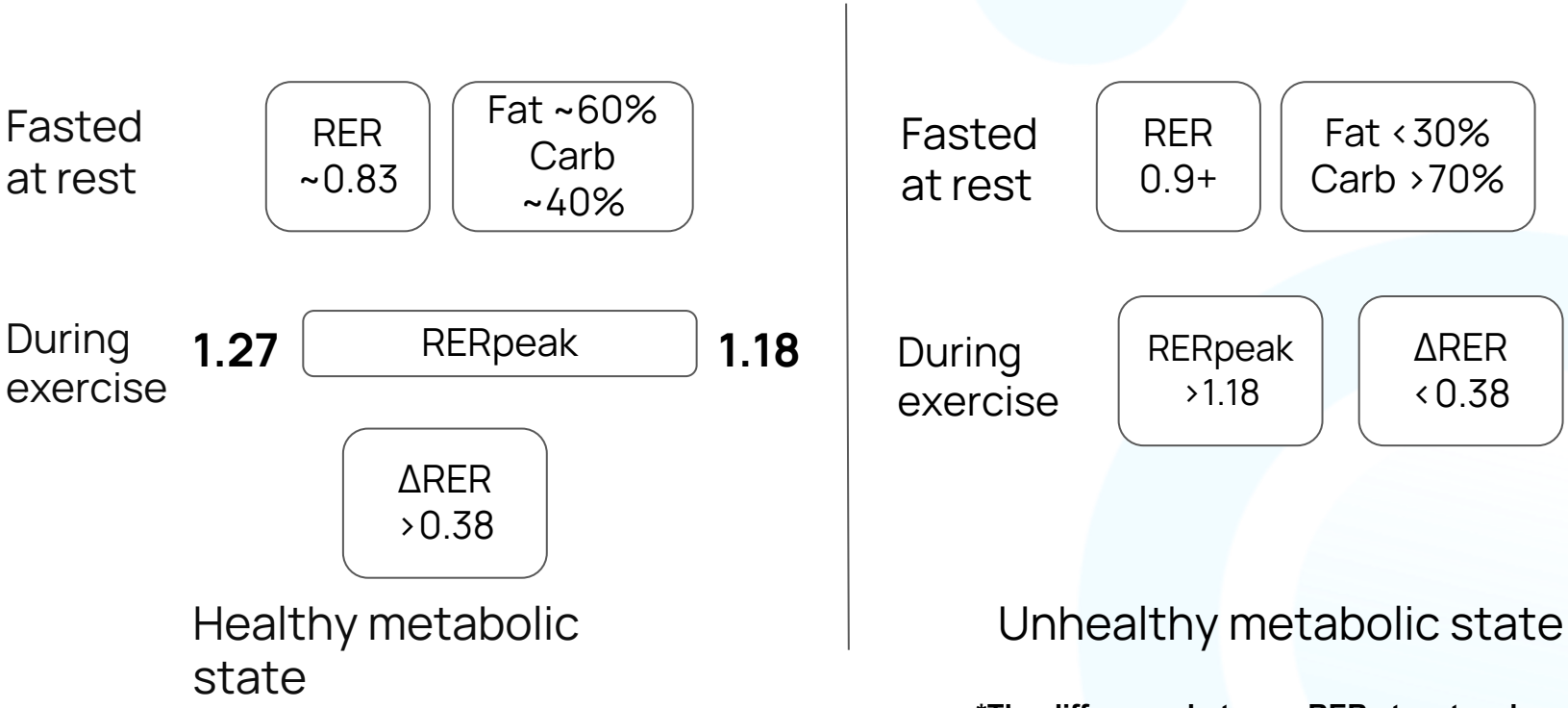
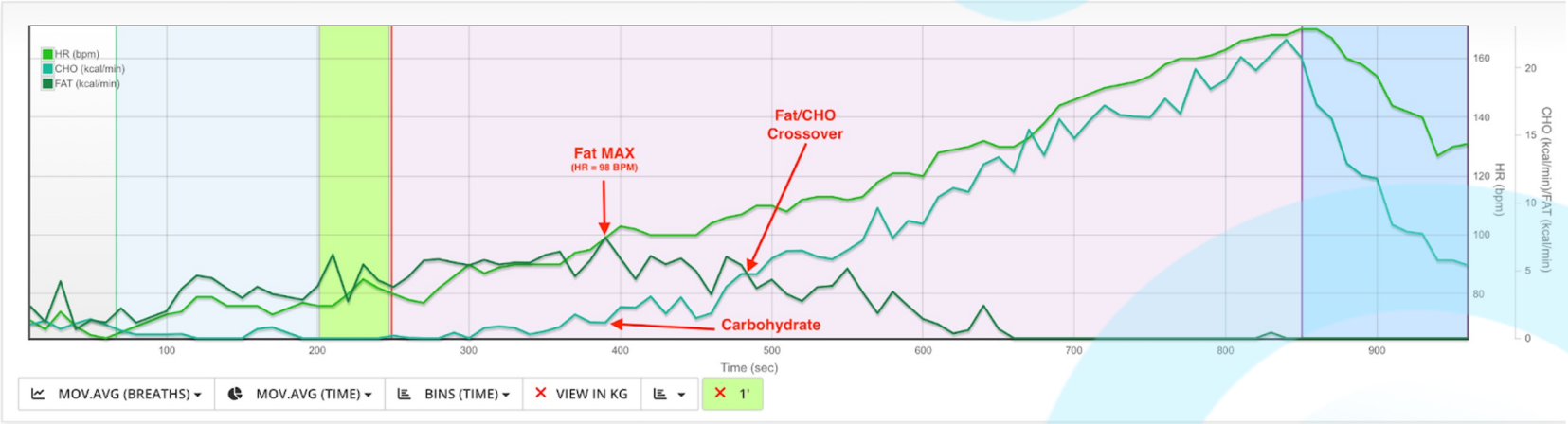


***The difference between RER at rest and peak exercise.**

Active - Metabolic Breath Analysis Test



- As exercise intensity increases our ability to oxidize fat effectively decreases and we rely more on glucose
- Metabolically inflexible patients rely on glucose earlier on in the process
- Fat oxidized in the mitochondria, therefore by measuring fat oxidation, we can indirectly see mitochondrial function.

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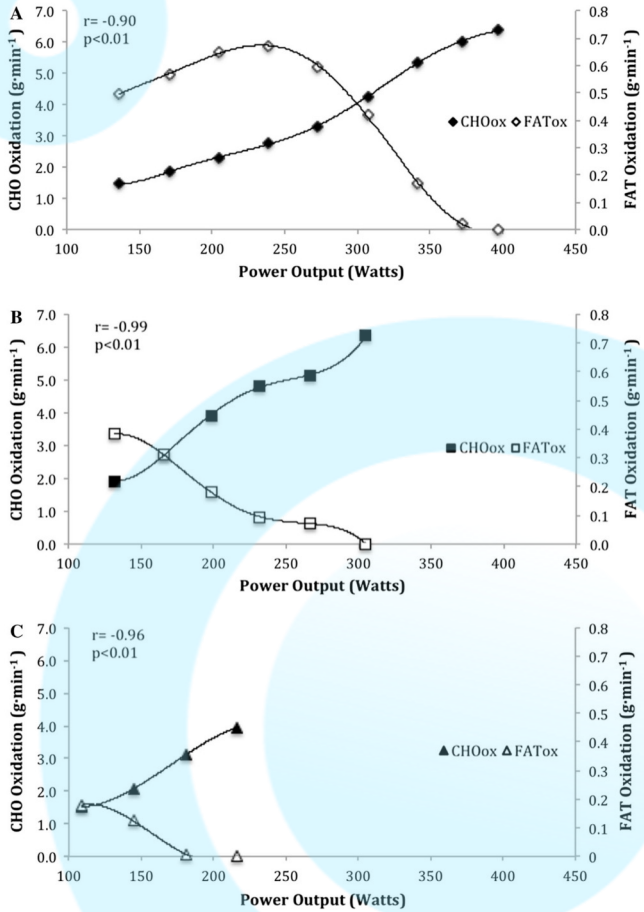
FATox vs CHOox

- Professional Athletes vs
- Moderate Active Healthy vs
- Metabolic Syndrome

Fig. 6 Relationship between the average FATox and CHOox rates as a function of exercise power output in **a** international-level professional endurance athletes, **b** moderately active healthy individuals, and **c** individuals with metabolic syndrome. *FATox* fat oxidation, *CHOox* carbohydrate oxidation



San-Millán I, Brooks GA. Assessment of Metabolic Flexibility by Means of Measuring Blood Lactate, Fat, and Carbohydrate Oxidation Responses to Exercise in Professional Endurance Athletes and Less-Fit Individuals. Sports Med. 2018 Feb;48(2):467-479. doi: 10.1007/s40279-017-0751-x. PMID: 28623613.

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Am J Respir Crit Care Med. 2022 Jan 1;205(1):126-129. doi: 10.1164/rccm.202108-1903LE.

Decreased Fatty Acid Oxidation and Altered Lactate Production during Exercise in Patients with Post-acute COVID-19 Syndrome

Esther de Boer [1 2], Irina Petrache [1 2], Nir M Goldstein [1], J Tod Olin [1], Rebecca C Keith [1 2], Brian Modena [1], Michael P Mohning [1 2], Zulma X Yunt [1 2], Inigo San-Millán [2 3], Jeffrey J Swigris [1 2]

Affiliations + expand

PMID: 34665688 PMCID: PMC8865580 DOI: 10.1164/rccm.202108-1903LE

Long Haul Covid Linked to Disruptions in Cellular Energy Metabolism

- Study showed increased levels of lactate early in exercise testing suggesting that the anaerobic energy production system kicked in early. The anaerobic energy production system produces less energy than the aerobic energy production system - and produces substances like lactate which, when they build up, produce symptoms like pain and fatigue.
- All the participants also showed evidence of impaired use of fatty acids to provide substrates for the mitochondria.

"Decreased Fatty Acid Oxidation and Altered Lactate Production during Exercise in Patients with Post-acute COVID-19 Syndrome." *American Journal of Respiratory and Critical Care Medicine*, 2022, 205(1), pp. 126–129

Covid Long Haul

40-Year old male, 6 months of chronic lung infections, sinus infections and post Covid complications. Multiple courses of antibiotic.

- **Metabolic Breath Analysis shows impaired fat oxidation and reduced mitochondrial function.**

	2/17/2021	5/9/2022	
VO2 Max	45	34	
Zone 2 Heart Rate	103-116	832-103	
Fat Max	103	82	

Zone 2 (Mitochondrial Focused Plan)

- MOTS-C 10mg twice weekly on days of toughest workout x 2 months
- Low Dose Leucine with NMN (Leu-NMN) 3 capsules every morning
- Zone 2 Training 45 minutes 4 days a week
- HIIT once weekly using zone 5 parameters
- Cont. resistance training

	2/17/2021	5/9/2022	7/10/2022
VO2 Max	45	34	43
Zone 2 Heart Rate	103-116	83-103	90-108
Fat Max	103	82	90

Measuring Cardiorespiratory Fitness

VO2 Max

- VO2 max is the strongest predictor of how long you are going to live.
- The maximum rate at which a person can utilize oxygen.
- The more oxygen your body is able to use, the higher your VO2max.
- Expressed in the volume of oxygen a person can use per kg of body weight per minute. ml/kg/min.

Original Investigation | Cardiology

JAMA Network | Open™

Association of Cardiorespiratory Fitness With Long-term Mortality Among Adults Undergoing Exercise Treadmill Testing

Kyle Mandsager, Md; Serge Harb, MD; Paul Cremer, MD; Dermot Phelan, MD,Phd; Steven E.Nissen MD; Wael Jaber, MD

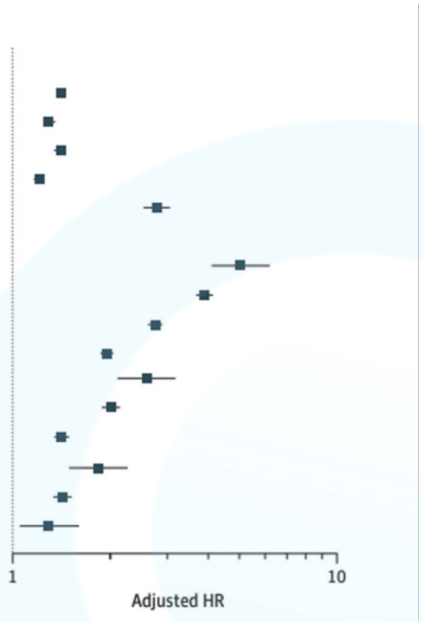
- 120,000 patients
- Cardiorespiratory fitness in inversely associated with long-term mortality with no observed upper limit benefit
- Cardiorespiratory fitness is a modifiable indicator of long-term mortality, and health care professionals should encourage patients to achieve and maintain high levels of fitness.

Quantifying Outcomes

C Comorbidities and performance groups

Variable	HR (95%CI)	P Value
Comorbidity		**<.001**
Smoking	1.41 (1.36-1.46)	<.001
CAD	1.29(1.24-1.35)	<.001
Diabetes	1.40(1.34-1.46)	<.001
Hypertension	1.21(1.16-1.25)	<.001
ESRD	2.78(2.53-3.05)	<.001
Group comparison		
Low vs Elite	5.04(4.10-6.20)	<.001
Low vs High	3.90(3.67-4.14)	<.001
Low vs Above Average	2.75(2.61-2.89)	<.001
Low vs Below Average	1.95(1.86-2.04)	<.001
Below Average vs Elite	2.59(2.10-3.19)	<.001
Below Average vs High	2.00(1.88-2.14)	<.001
Below Average vs Above Average	1.41(1.34-1.49)	<.001
Above Average vs Elite	1.84(1.49-2.26)	<.001
Above Average vs High	1.42(1.33-1.52)	<.001
High vs Elite	1.29(1.05-1.60)	.02

Adjusted hazard ratio (HRs) for all-Cause mortality compared with low performs in all patients (A) and by sex (B) (P values are for comparison with low performers). C, Adjusted HRs for comorbidities and between performance groups. Error bars indicate



95% CIs. Performance group classifications by cardiorespiratory fitness are defined in Table 2. CAD indicates coronary artery disease; and ESRD, end-stage renal disease

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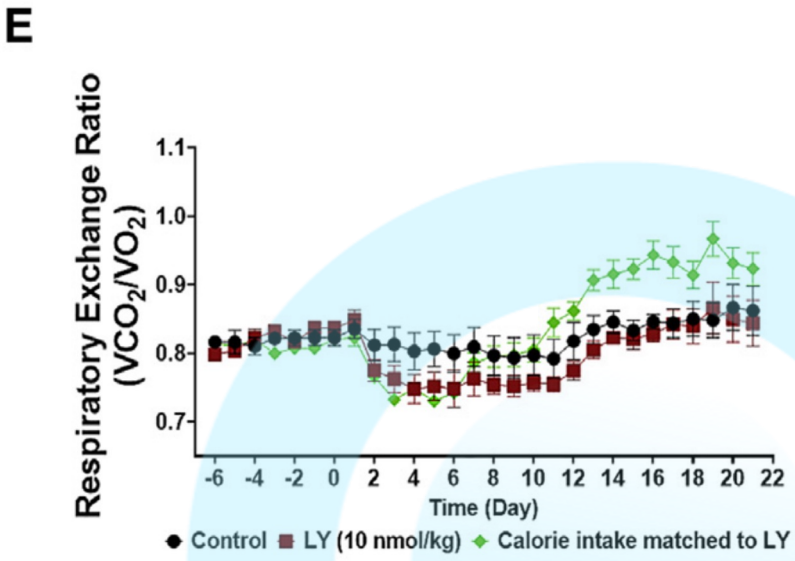
Metabolic Breath Analysis and GLP-1 Management

GLP-1 (Ozempic, Mounjaro, Semaglutide, Tirzepatide)

- Identifying patients with highest risk of weight regain
  - Metabolic Slowdown
  - Strategies to increase energy expenditure
- Maintaining muscle mass and strength
  - Protein Intake, exercise prescription, iCell Water
- Pivoting treatment plans
  - GLP-1 + co-activating compounds
    - Hormone replacement: Testosterone, GHRH/GHRP (Peptide Therapy)
    - Supplements-iCell Water AKG, Urolitin A)

Future GLP-1s: Triple Agonist

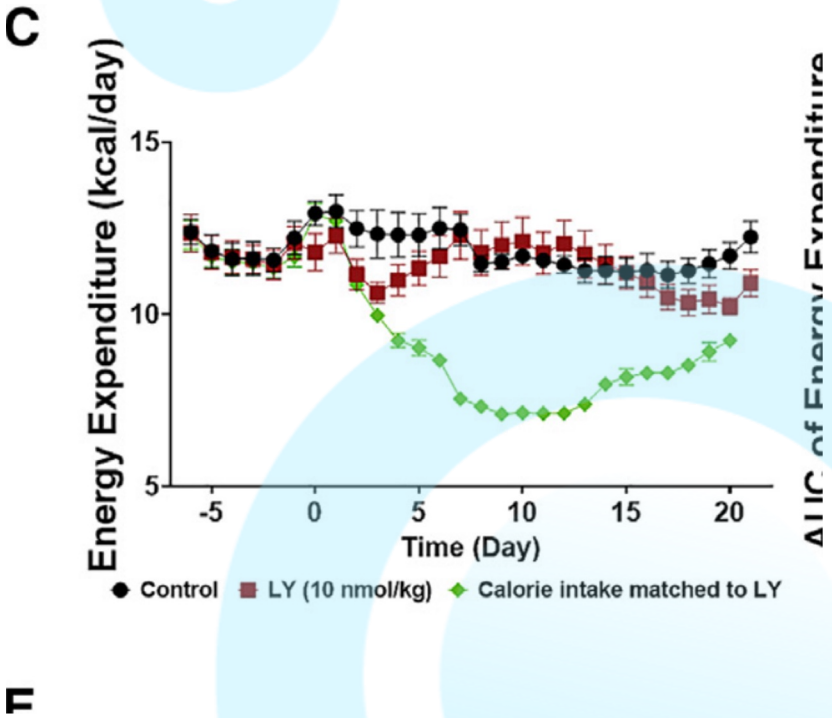
- Future drug development in weight loss, diabetes, metabolic optimization and Osteoarthritis are measuring RER.
- Looking at substrate utilization to determine lipid oxidation
- Retatrutide the next generation of GLP-1 agonist showed a decrease RER when calories were matched to placebo



Coskun T, Urva S, Roell WC, Qu H, Loghin C, Moyers JS, O'Farrell LS, Briere DA, Sloop KW, Thomas MK, Pirro V, Wainscott DB, Willard FS, Abernathy M, Morford L, Du Y, Benson C, Gimeno RE, Haupt A, Milicevic Z. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept. Cell Metab. 2022 Sep 6;34(9):1234-1247.e9. doi: 10.1016/j.cmet.2022.07.013. Epub 2022 Aug 18. PMID: 35985340.

Future GLP-1s: Triple Agonist

- Energy expenditure was substantially decreased with calorie restriction
- Retatrutide was able to maintain energy expenditure with calorie restriction
- This was done through glucagon receptor engagement



Coskun T, Urva S, Roell WC, Qu H, Loghin C, Moyers JS, O'Farrell LS, Briere DA, Sloop KW, Thomas MK, Pirro V, Wainscott DB, Willard FS, Abernathy M, Morford L, Du Y, Benson C, Gimeno RE, Haupt A, Milicevic Z. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept. Cell Metab. 2022 Sep 6;34(9):1234-1247.e9. doi: 10.1016/j.cmet.2022.07.013. Epub 2022 Aug 18. PMID: 35985340.

Potential Peptides and Supplements that influence Breath Analysis Biomarkers

- Growth hormone secretagogue (Sermorelin, CJC/Ipamorelin)
  - Fatty acid oxidation, muscle recovery, cellular efficiency
- Mitochondrial Peptides (MOTS-c, SS-31)
  - AMPK, Glucose disposal, Electron transport chain
- Amlexanox
  - Increased EE
- Methylene Blue
  - Electron transport chain
- iCell Water
  - Cell volume, intracellular water, protect from protein degradation, performance
- Alpha Keto Glutarate
  - TCA intermediate-ATP production
- Leusynergy, Sytrinol LNA
  - Exercise mimetics
- NAD precursors
- 1-Methyl Nicotinamide

Resistance To Weight Loss

Key drivers plateaus and non-responders

Gut Health

- Intestinal permeability
- Immune dysregulation
- Autoimmunity
- Food intolerance

Stress Management/ Sleep

- Elevated Cortisol
- Circadian Rhythm Dysregulation
- Impaired ability to recover
- Acute Cognitive decline. (Memory, Foggy Brain)

Sleep and Stress Management

Stress/cortisol management

- When you're under stress (physiologic or psychological), you're producing cortisol and that's going to exacerbate insulin resistance
- **Cortisol is catabolic to muscle and anabolic to fat.**
- Sleep debt has a harmful impact on carbohydrate metabolism and endocrine function.
    - Effects mimic aging and age-related chronic disorders
- Deprive people of sleep down to 4 hours per night for a period of two weeks there's an incredible deterioration in insulin signaling and glucose disposal

Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999 Oct 23;354(9188):1435-9. doi: 10.1016/S0140-6736(99)01376-8. PMID: 10543671.

Stress Management: Oxytocin

Oxytocin

- Inverse relationship between oxytocin levels and inflammatory markers like IL-10,IL-6 and TNF-a suggesting anti-inflammatory effect
- Potential enhances sleep quality and increase sexual desire
- Supports muscle health by promoting the activation and growth of muscle stem cells to prevent muscle aging
- **Reduces cortisol levels during physical stress, potentially lessening stress's impact.**

Li Y, Hassett AL, Seng JS. Exploring the mutual regulation between oxytocin and cortisol as a marker of resilience. Arch Psychiatr Nurs. 2019 Apr;33(2):164-173. doi: 10.1016/j.apnu.2018.11.008. Epub 2018 Nov 20. PMID: 30927986; PMCID: PMC6442937.
Inoue T, Yamakage H, Tanaka M, Kusakabe T, Shimatsu A, Satoh-Asahara N. Oxytocin Suppresses Inflammatory Responses Induced by Lipopolysaccharide through Inhibition of the eIF-2-ATF4 Pathway in Mouse Microglia. Cells. 2019 May 31;8(6):527. doi: 10.3390/cells8060527. PMID: 31159306; PMCID: PMC6627458.

Can Oxytocin reduce romantic rejection??

- Romantic rejection is an emotionally distressful experience profoundly affecting life, possibly leading to mental illness or suicide
- EEG recordings were obtained from 61 healthy participants in a double-blind, placebo-controlled study looking at the brain waves responses to romantic rejection
- In the placebo group, greater theta power was induced by romantic rejection, being associated with rejection distress. This pattern was not observed in the Oxytocin group
- **Oxytocin relieves social pain caused by romantic rejection**, reflected in decreased frontal-midline theta oscillations and a diminished connection between theta power and rejection distress

Zhang X, Li P, Otieno SCSA, Li H, Leppänen PHT. Oxytocin reduces romantic rejection-induced pain in online speed-dating as revealed by decreased frontal-midline theta oscillations. Psychoneuroendocrinology. 2021 Nov;133:105411. doi: 10.1016/j.psyneuen.2021.105411. Epub 2021 Sep 10. PMID: 34537623.

Zhang X, Li P, Otieno SCSA, Li H, Leppänen PHT. Oxytocin reduces romantic rejection-induced pain in online speed-dating as revealed by decreased frontal-midline theta oscillations. Psychoneuroendocrinology. 2021 Nov;133:105411. doi: 10.1016/j.psyneuen.2021.105411. Epub 2021 Sep 10. PMID: 34537623.

Nat Rev Endocrinol. Author manuscript; available in PMC 2018 Jun 1. *Published in final edited form as:* Nat Rev Endocrinol. 2017 Dec; 13(12): 700–709. Published online 2017 Sep 29. doi: 10.1038/nrendo.2017.115

PMCID: PMC5868755 | NIHMSID: NIHMS949823 | PMID: 28960210

The effects of oxytocin on eating behaviour and metabolism in humans

Elizabeth A. Lawson

- Oxytocin might affect appetite indirectly by **altering levels of other appetite-regulating hormones** (for example, increased levels of the anorexigenic hormones CCK and GLP 1
- Oxytocin might improve glucose homeostasis, independently of its effects on weight.
- Oxytocin works in the **brain** region critical for the regulation of food consumption
- **Oxytocin might inhibit food intake in part by modulating reward-related food motivation and/or impulse control** neurocircuitry.
- **This concept is in line with a study published in 2016 showing that a single intranasal dose of 24 IU oxytocin increased activation of brain circuitry involved in cognitive control.**
- Intranasal administration of oxytocin in humans reduces cortisol under basal and stress conditions.

Intranasal Oxytocin Improves Lean Muscle Mass and Lowers LDL Cholesterol in Older Adults with Sarcopenic Obesity: A Pilot Randomized Controlled Trial

Sara E. Espinoza, MD,[a,b,*] Jessica L. Lee, MD,[c] Chen-Pin Wang, PhD,[a,b,d] Vinutha Ganapathy, MD,[a,b] Daniel MacCarthy, BS,[a,b,d] Chiara Pascucci, MD,[e] Nicolas Musi, MD,[a,b] and Elena Volpi, MD, PhD[e]

Author information ▸ Copyright and License information PMC Disclaimer

- This was an 8-week double-blind, randomized, placebo-controlled trial
- 24 IU of oxytocin or placebo (3 spays to each nostril) 4 times a day (before meals and at bedtime)
- **Lean body mass increased after oxytocin administration compared with placebo**
- Oxytocin administration did not result in a decrease in total body mass in this study. This is explained by the increase in lean mass with a concomitant decrease in fat mass
- **We observed a trend toward a lower depression score in the oxytocin group**

DHH-B- Stress Management and Sleep

- DHH-B stands for dihydrohonokiol-B, (or DHH-B for short). It is a powerful extract from magnolia bark that is used as an anxiolytic and to facilitate sleep.
- Of all the analogs testes it was DHH-B that had the most potent anxiolytic effect after a single dose.
- Most importantly it did not show a significant change in motor activity or impaired balance or coordination in contrast to benzodiazepine anxiolytics.
- DHH-B
    - 15mg capsules
    - 1-2 capsules as needed for stress management.
    - Feel decrease in anxiety within 30 minutes

Kuribara H, Kishi E, Kimura M, Weintraub ST, Maruyama Y. Comparative assessment of the anxiolytic-like activities of honokiol and derivatives. Pharmacol Biochem Behav. 2000 Nov;67(3):597-601. doi: 10.1016/s0091-3057(00)00401-9. PMID: 11164091.

Stress Management Protocol

- Oxytocin Nasal Spray 20IU/Spray
  - 1-3 sprays twice daily as needed
    - May experience headache
- DHH-B
  - 1-2 capsules as needed
    - May be done 2-3 times daily

Weight Loss Resistance due to Gut Health

Gut Health

- Intestinal permeability
- Immune dysregulation
- Autoimmunity
- Food intolerance

Synergy-Combining Prescription Peptides with Supplements

Converging on similar pathways to improve patient outcomes

- Tributyrin
  - Tight junction, prevents gut inflammation, inflammatory cytokines (TNF-alpha)
- Larazotide:
  - Tight junction closure, inflammatory response from food sensitivities.
- BPC-157
  - Protecting the cells that line the GI tract from damage
  - Alter immune response to stress.
- KPV
  - Regulates inflammation once it has begun.
  - Inflammation can further worsen tight junction function

Guttides: BPC-157 + KPV Oral Nutraceutical

- BPC-157 500mcg + KPV 500mcg
- cGMP FDA registered manufacturer
- Practitioner only access
- Accessibility and Cost considerations
    - Typically $5.50/Capsule when compounded.
    - OTC will cost will be half the price.
- Dose: 1 capsule daily

nuButyrate- Butyrate supplementation as Tributyrin

- Tributyrin 500mg as Corebiome
  - Not all tributyrin is created the same
- Clinically substantiated bioavailability in the colon
- 48 hour study of GI model
  - Limited IL-6 and TNF-alpha
  - Epithelial function
  - Suggesting support of gut barrier function

Thank you

Contact

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