

A4M | MEDICINE REDEFINED

CLINICAL WEIGHT MANAGEMENT Certification Program



 **IPS** THE PREMIER EDUCATIONAL RESOURCE
FOR SAFE & ADVANCED PEPTIDE THERAPY

EDUCATIONALLY
PARTNERED WITH

A4M

Insulin Resistance IR and Type II Diabetes T2D

James LaValle, RPh, CCN, DHM, DPh, MT,DM

- Chief Science Officer, Lifetime Fitness/Miora.....
- Founder and CEO, Metabolic Code Enterprises
- Academic Co-Chair, A4M
- Chair International Peptide Society IPS
- LaValle Performance Health Center

.....

.....



Copyright © 2025 James B. LaValle. All rights reserved.

No part of this material may be used or reproduced in any manner whatsoever, stored in a retrieval system, or transmitted in any form, or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior permission of the author.

This material is provided for educational and informational purposes only to licensed health care professionals. This information is obtained from sources believed to be reliable, but its accuracy cannot be guaranteed. Herbs and other natural substances are very powerful and can occasionally cause dangerous allergic reactions in a small percentage of the population. Licensed health care professionals should rely on sound professional judgment when recommending herbs and natural medicines to specific individuals. Individual use of herbs and natural medicines should be supervised by an appropriate health care professional. The use of any specific product should always be in accordance with the manufacturer's directions.

Diabetes and IR Statistics

Diabetes

- 37.3 million people in the US have diabetes (11.3% of population)
- 28.7 million diagnosed
- 8.5 million undiagnosed

Insulin Resistance (IR)

- 96 million in US over 18 years have pre-diabetes (38% of population)
- 26.4 million people 65 and older have prediabetes

www.cdc.gov Centers for Disease Control and Prevention CDC, accessed August 2023.

Current Diabetes Epidemic

- On top of this – COVID reported to increase risk of T2D by up to 22%
- ADA estimates up to 70% of individuals with prediabetes/IR will eventually develop diabetes

Tabak AG, et al. Prediabetes: a high-risk state for developing diabetes. *Lancet*. 2012;379(9833):2279-90.
Naveed Z, et al. Association of COVID-19 infection with incident diabetes. *JAMA Network Open*. 2023;6(4):e238866.

Weight Gain and Insulin Resistance

- Association between adult weight gain and insulin resistance at middle age largely mediated by both visceral fat and liver fat
- Approx. 1 in 4 people in the US have IR

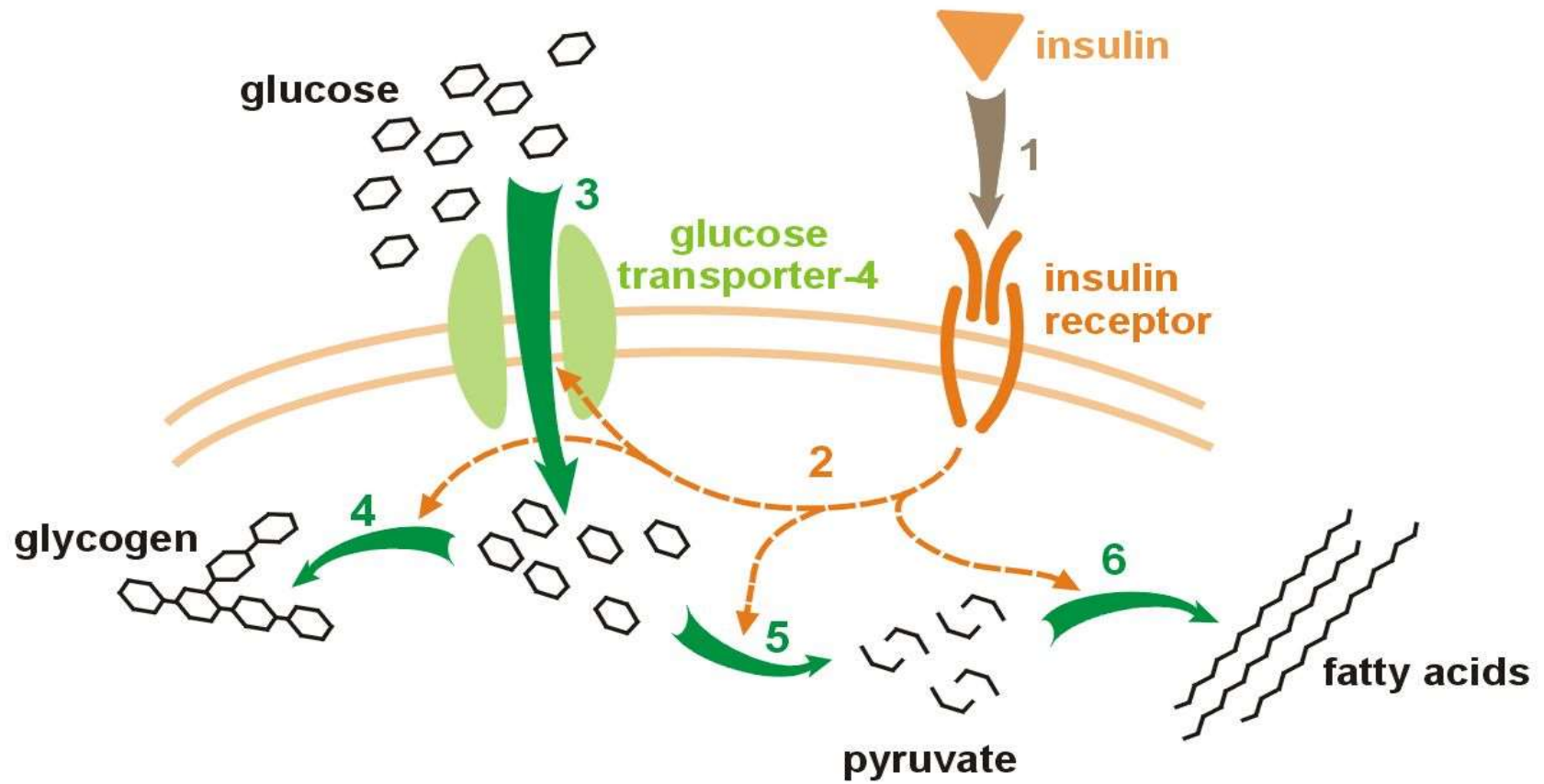
**Insulin Resistance is The Number 1 Metabolic Factor
that Keeps Us Overweight**

American Diabetes Association (ADA). www.diabetes.org

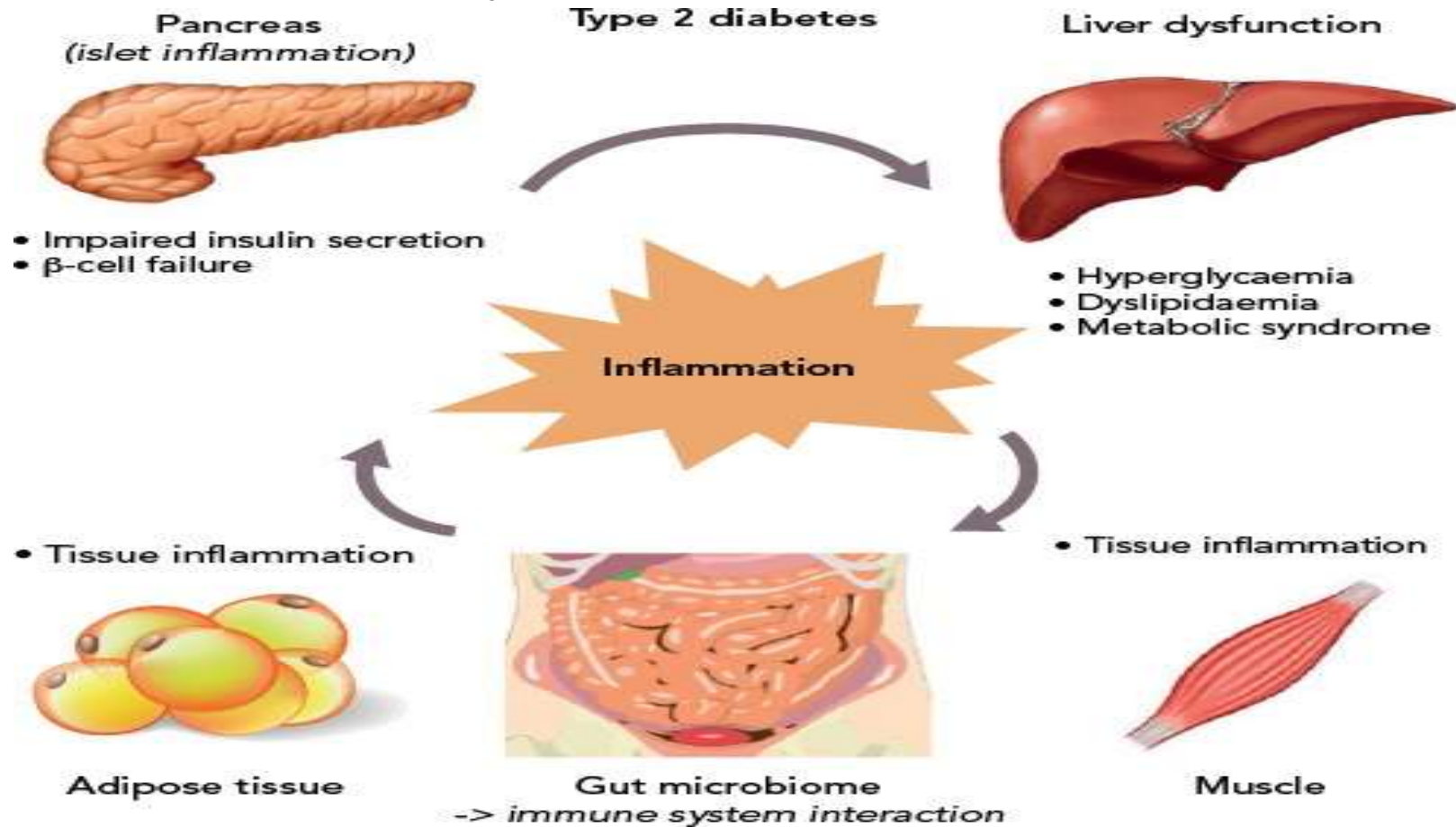
Weight Gain and Metaflammation

- Chronic inflammation = increased circulating cytokines level and C-reactive protein (CRP)
- Adipokine production driven by increased adipocytes and adipose tissue infiltration with inflammatory cells
- Reduction of body fat following both controlled diets or gastric surgery help reduce pro-inflammatory cytokines

Bianchi VE. Weight loss is a critical factor to reduce inflammation. Clin Nutr ESPEN. 2018;28:21-35.



Inflammatory Mediators in Diabetes



Tsalmandris S, et al. The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. Eur Cardiol. 2019;14(1):50-59.

Frontiers in Diabetes

Editors: M. Porta, F.M. Matschinsky

Vol. 19

Diabetes and Cancer

**Epidemiological Evidence and
Molecular Links**

Editors

K. Masur

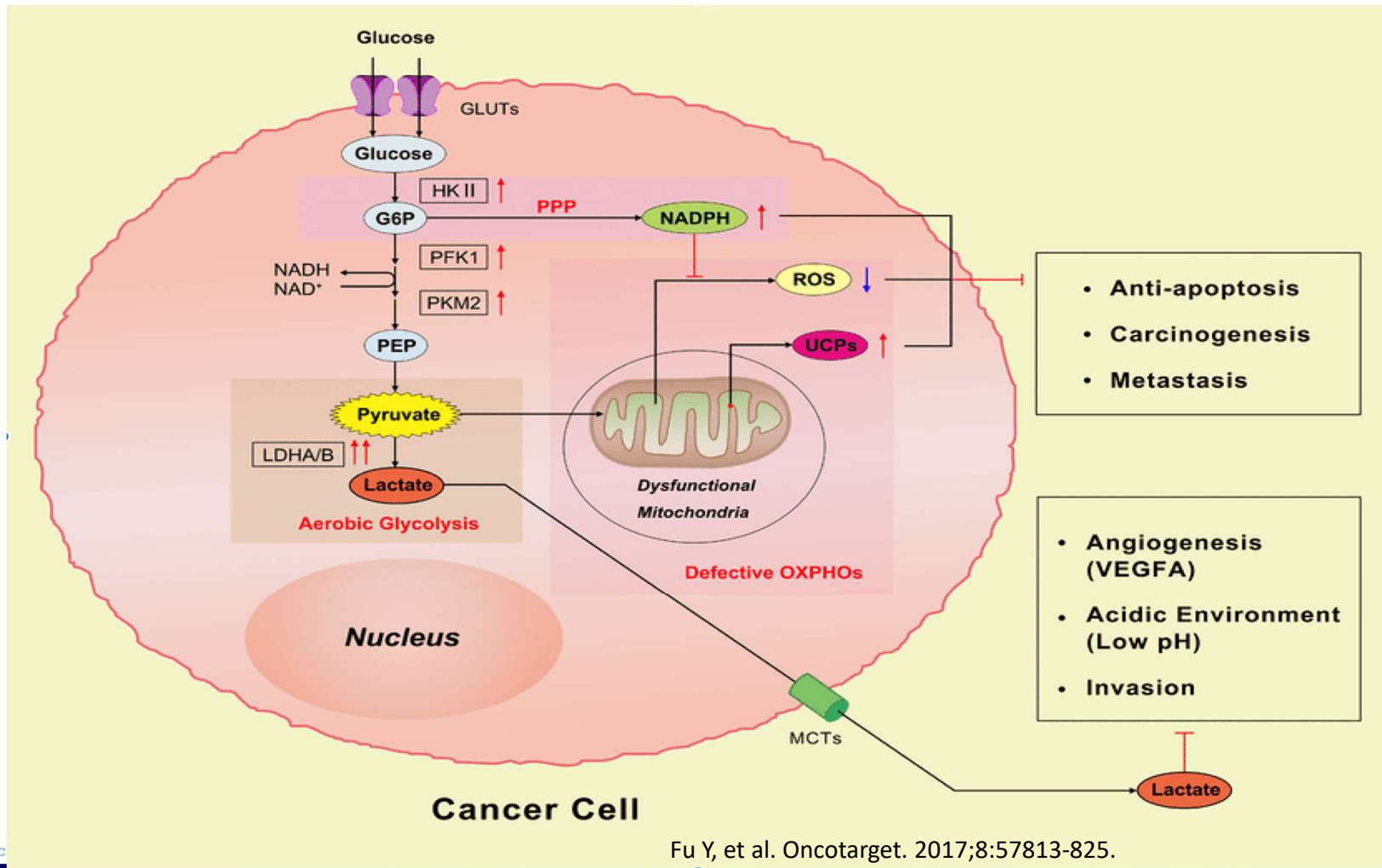
F. Thévenod

K.S. Zänker

KARGER

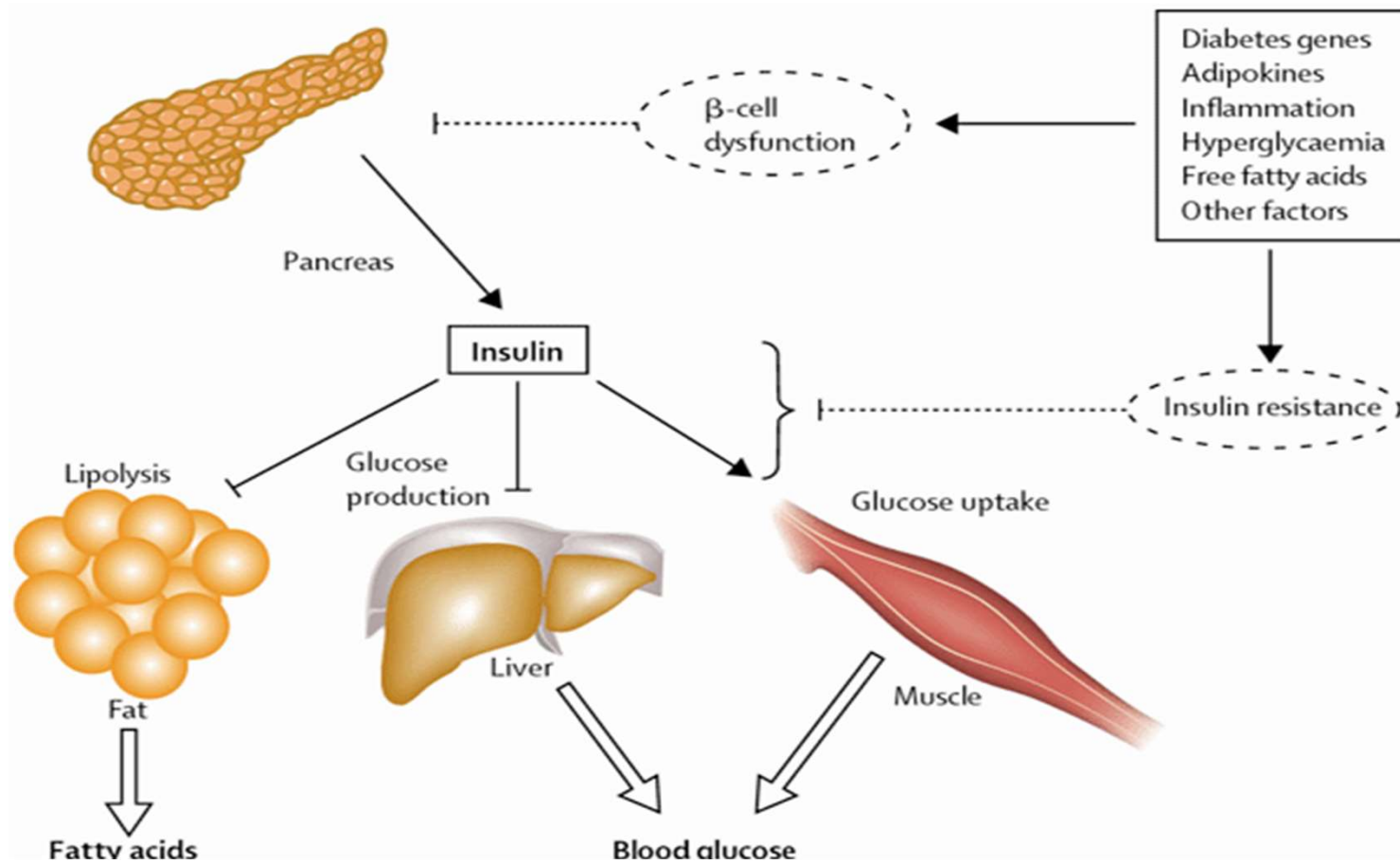


Warburg Effect



Fu Y, et al. Oncotarget. 2017;8:57813-825.

Actions of Insulin



2008 Insulin Resistance Study

- 46,578 members of Kaiser Permanente Northwest
- FPG levels < 100 mg/dL (Jan '97-Dec 2000)
- No previous diagnosis of diabetes or impaired fasting glucose
- Subjects assigned to 1 of 4 categories (<85, 85-89, 90-94, or 95-99 mg/dL)
- Followed until developed diabetes, died, left the health plan, or until April 30, 2007
- Cox regression analysis--estimated risk of incident diabetes, adjusted for age, sex, body mass index, blood pressure, lipids, smoking, cardiovascular disease, and hypertension

Nichols GA, Hiller TA, Brown JB. Normal Fasting Plasma Glucose and Risk of Type 2 Diabetes Diagnosis. Am J Med. 2008;121(6). 519-524.

Study Results and Conclusions

- Every glucose rise of 1 point above 84, was correlated with a 6% increased risk of developing Type 2 diabetes
- **Insulin resistance, which leads to Type 2 diabetes, is developing at least a decade before detection by traditional lab markers**

Nichols GA, Hiller TA, Brown JB. Normal Fasting Plasma Glucose and Risk of Type 2 Diabetes Diagnosis. Am J Med. 2008;121(6). 519-524.

Fasting Plasma Glucose and T2D Risk – Updated Study

- 2022 long-term retrospective study
- N= 37,148 Japanese individuals w/ normal plasma glucose
- In 10 years, 1,028 patients developed T2D
- Cox regression analyses reveal:
 - Risk for onset of T2D increased by 9.0 % per 1mg/dL increase in fasting plasma glucose from 90 – 99 mg/dL

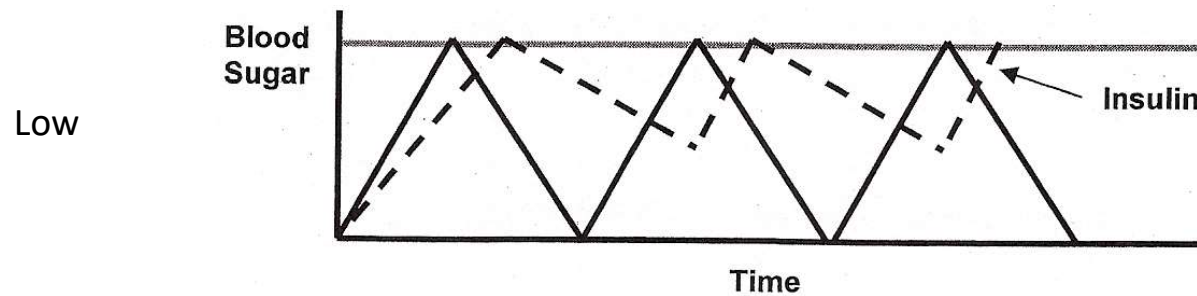
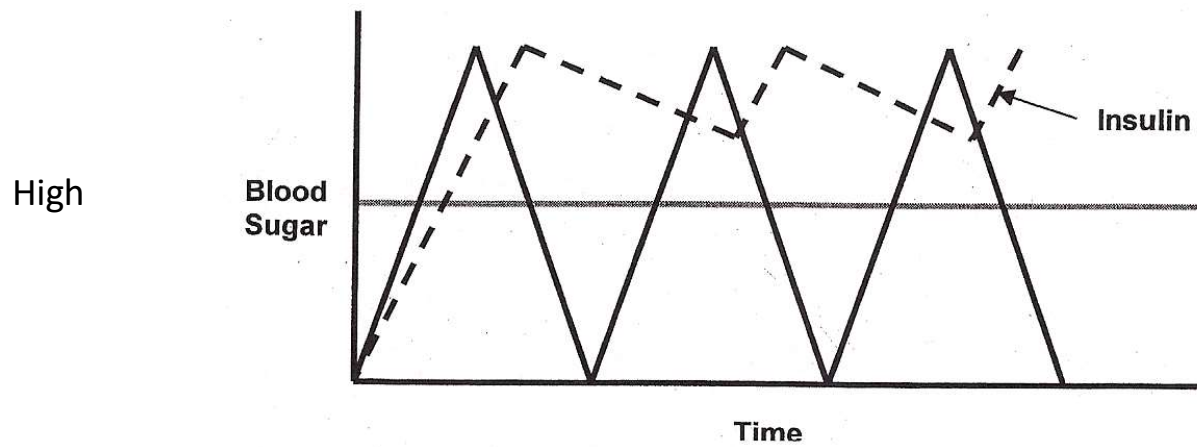
Munekawa C, et al. J Diabetes Invest. 2022;13:453-59.

Bottom Line

- RISK of T2D increases by 9 % for every point above 90mg/dL fasting plasma glucose

Munekawa C, et al. J Diabetes Invest. 2022;13:453-59.

Blood Sugar & Insulin in High/Low Glycemic Meals



What is Insulin Resistance (IR)

- Profile of Patient Exhibiting Signs of IR:
 - Elevated Waist-to-Hip ratio
 - May or may not be overweight
 - FPG 90 – 100 mg/dL or more
 - FASTING INSULIN +10
 - Post-prandial insulin elevated
 - Lipids and trig's elevated with suboptimal HDL
 - Elevated Blood Pressure
 - Reduced Mg/K
 - Increase LDH
- IR associated with:
 - Obesity
 - Diabetes
 - Metabolic dysfunction-associated fatty liver disease (MAFLD)
 - Cardiovascular disease(s)
 - Polycystic ovary syndrome (PCOS)
 - Other abnormalities

IR Contributing Factors

- Genetic polymorphisms
- Decreased muscle mass
- Physical inactivity
- Increased belly fat/oxidative stress/inflammation
- Chronic stress
- Sleep quality
- Chronic hyperglycemia from excessive intake of high GI foods and/or fructose
- Overtraining Syndrome
- Bowel terrain imbalances
- Leptin and Adiponectin alterations
- Increased Resistin (hormone secreted by fat cells)
- Endocrine Disruption – often from environmental toxicity (heavy metals and organic solvents)
- Micronutrient - inadequate intake
- Low Vitamin D status

Inflammation as a Cause of IR

- Excessive production of inflammatory compounds in the body can cause IR
- Inflammatory substances damage and/or inactivate insulin receptors.
- Contributes to breakdown of one or more factors needed to complete the process of glucose transport

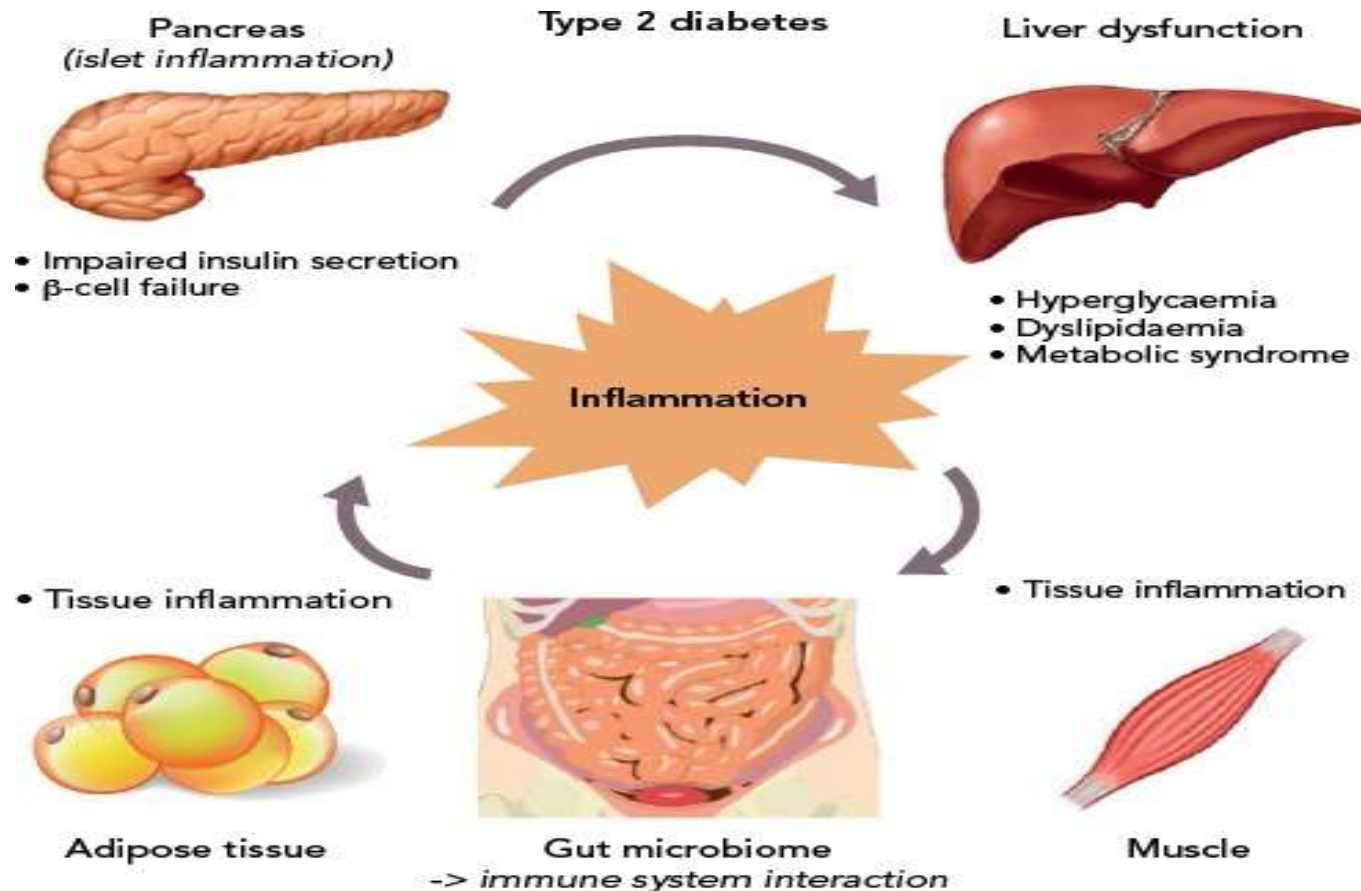
Wu H, et al. Metabolic inflammation and insulin resistance in obesity. *Circ Res.* 2020;126(11):1549-64.

...and IR is a Cause of Inflammation

- IR leads to ↑ inflammatory markers
- Including ferritin, uric acid, white cell counts, fibrinogen, CRP and IL-6
- insulin resistance in adipocytes results in production of the chemokine monocyte chemoattractant protein 1 (MCP1)
- This recruits monocytes and activates proinflammatory macrophage
- Insulin resistance is correlated with reduced insulin/mTORC2 signaling and elevated MCP1 production in visceral adipose tissue

Shimboyashi M, et al. Insulin resistance causes inflammation in adipose tissue. *J Clin Invest.* 2018;128(4):1538-50.

Inflammatory Mediators in Diabetes



T2D Inflammation

- T2D is an inflammatory disease
- T2DM promotes increased levels of pro-inflammatory cytokines including TNF α and IL-6
 - Involved in the development of insulin resistance in skeletal muscle

Perry BD, et al. Muscle atrophy in patients with Type 2 Diabetes Mellitus: roles of inflammatory pathways, physical activity and exercise. *Exerc Immunol Rev.* 2016;22:94-109.

T2D Inflammation

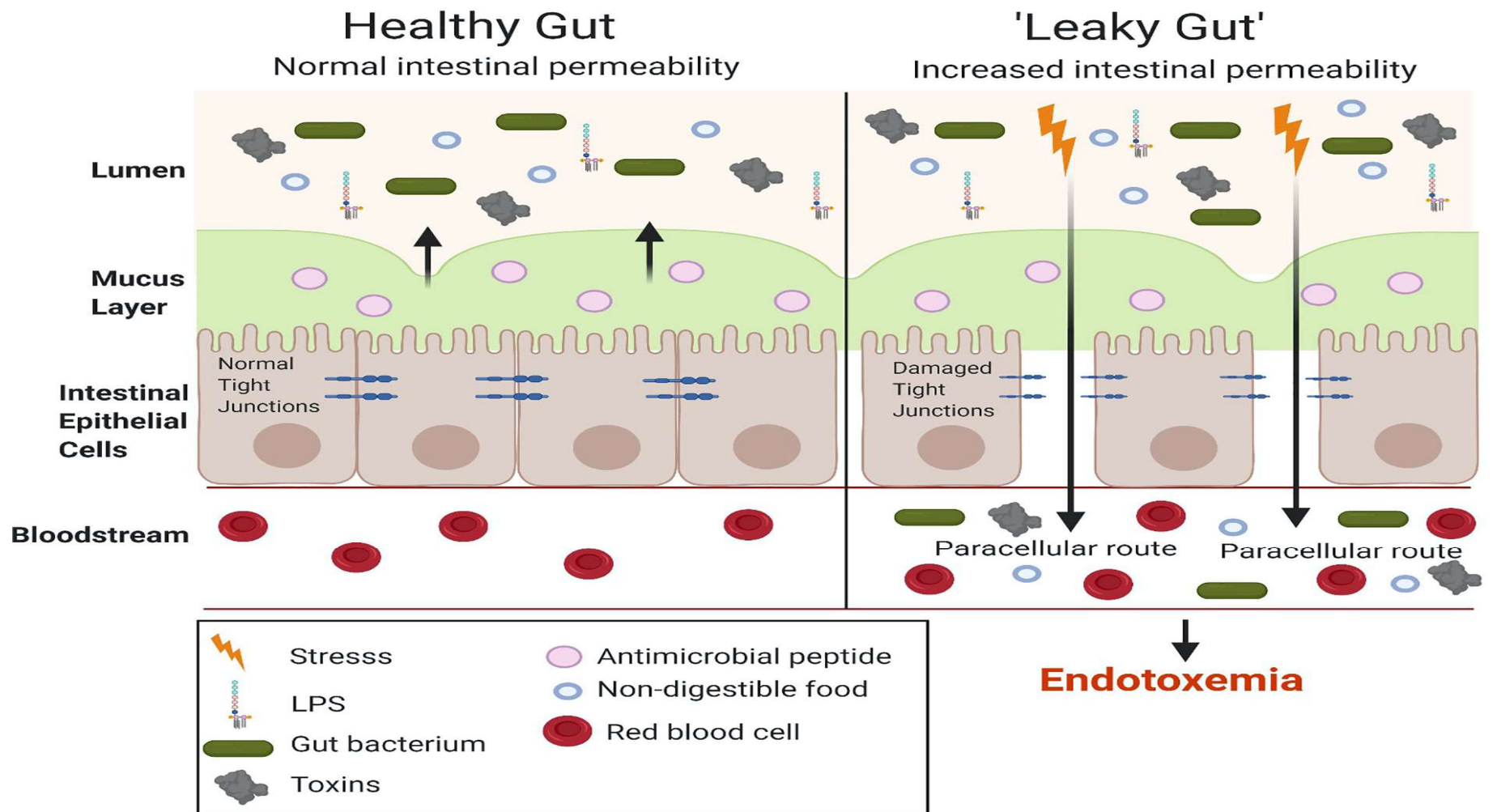
- Studies report inflammatory pathways in muscle - in particular, NF- κ B - contributes to T2DM-mediated muscle atrophy
- 2016 cohort of obese patients with T2DM compared to age-matched controls
 - Demonstrated patients with T2DM have 60% higher skeletal muscle expression of the atrophy transcription factor FoxO1

Perry BD, et al. Muscle atrophy in patients with Type 2 Diabetes Mellitus: roles of inflammatory pathways, physical activity and exercise. *Exerc Immunol Rev.* 2016;22:94-109.

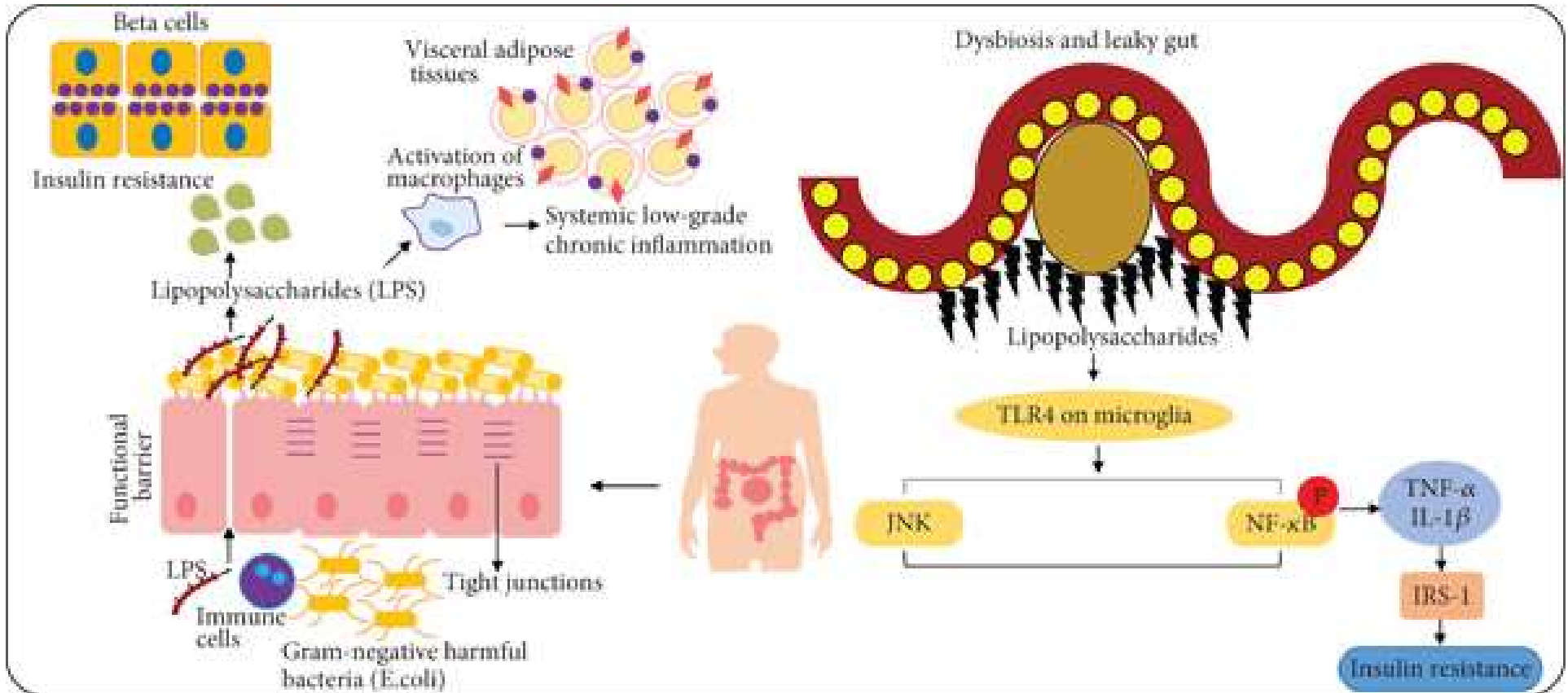
Metabolic Endotoxemia and Diabetes Risk

- 537 subjects with prevalent diabetes
- Mean serum endotoxin level statistically higher
- Endotoxin activity was significantly associated with increased risk for incident diabetes with a hazard ratio
- Endotoxin score correlated with CRP, cholesterol, triglyceride - correlation with HDL

Pussinen P.J et al Endotoxemia Is Associated With an Increased Risk of Incident Diabetes. *Diabetes Care* 2011;34:392-397.



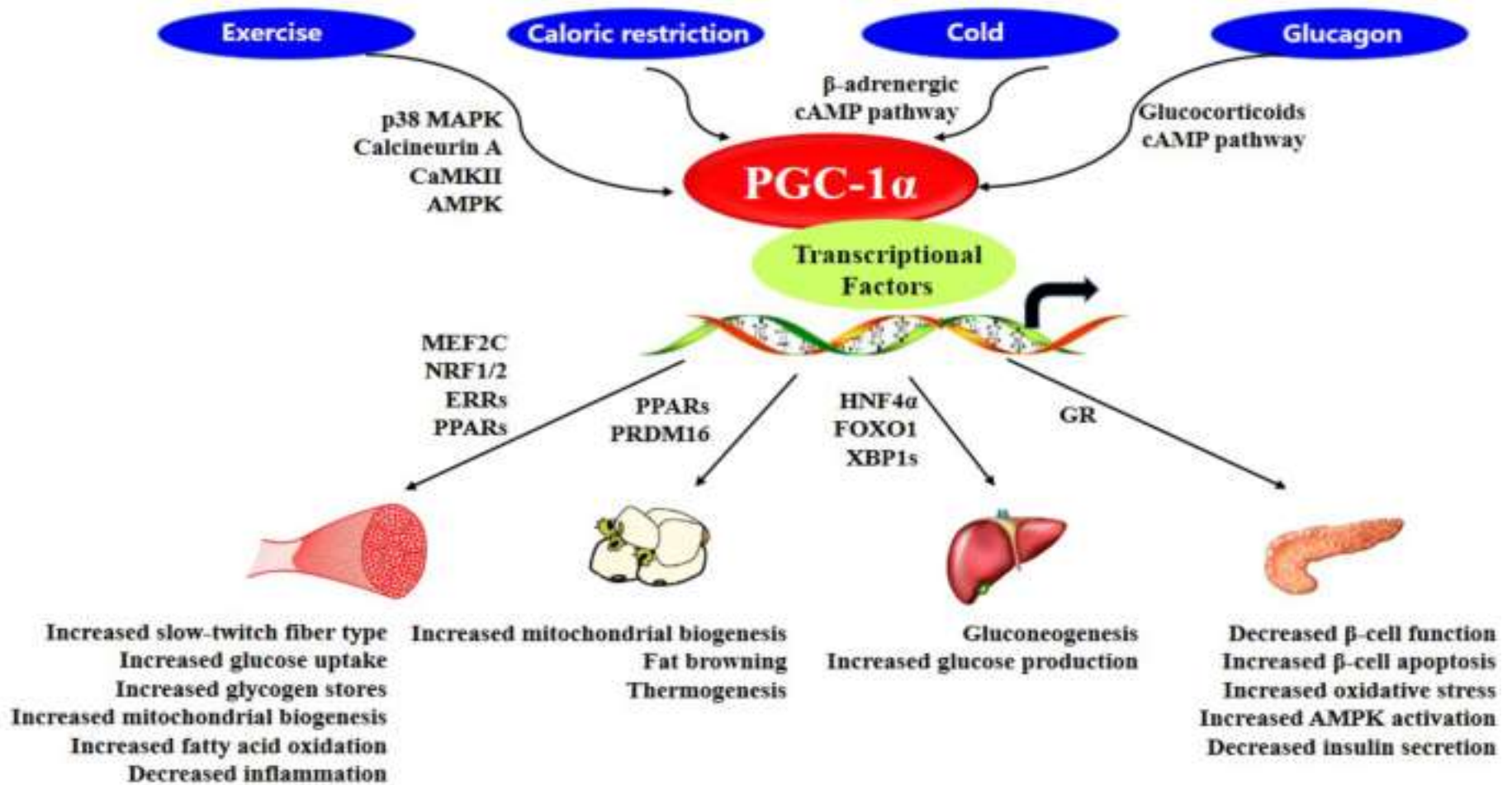
Dysbiosis, Leaky GUT, LPS → IR



Khan MS, et al. Pathology, Risk Factors, and Oxidative Damage Related to Type 2 Diabetes-Mediated Alzheimer's Disease and the Rescuing Effects of the Potent Antioxidant Anthocyanin. *Ox Med Cell Longev.* 2021;4051207.

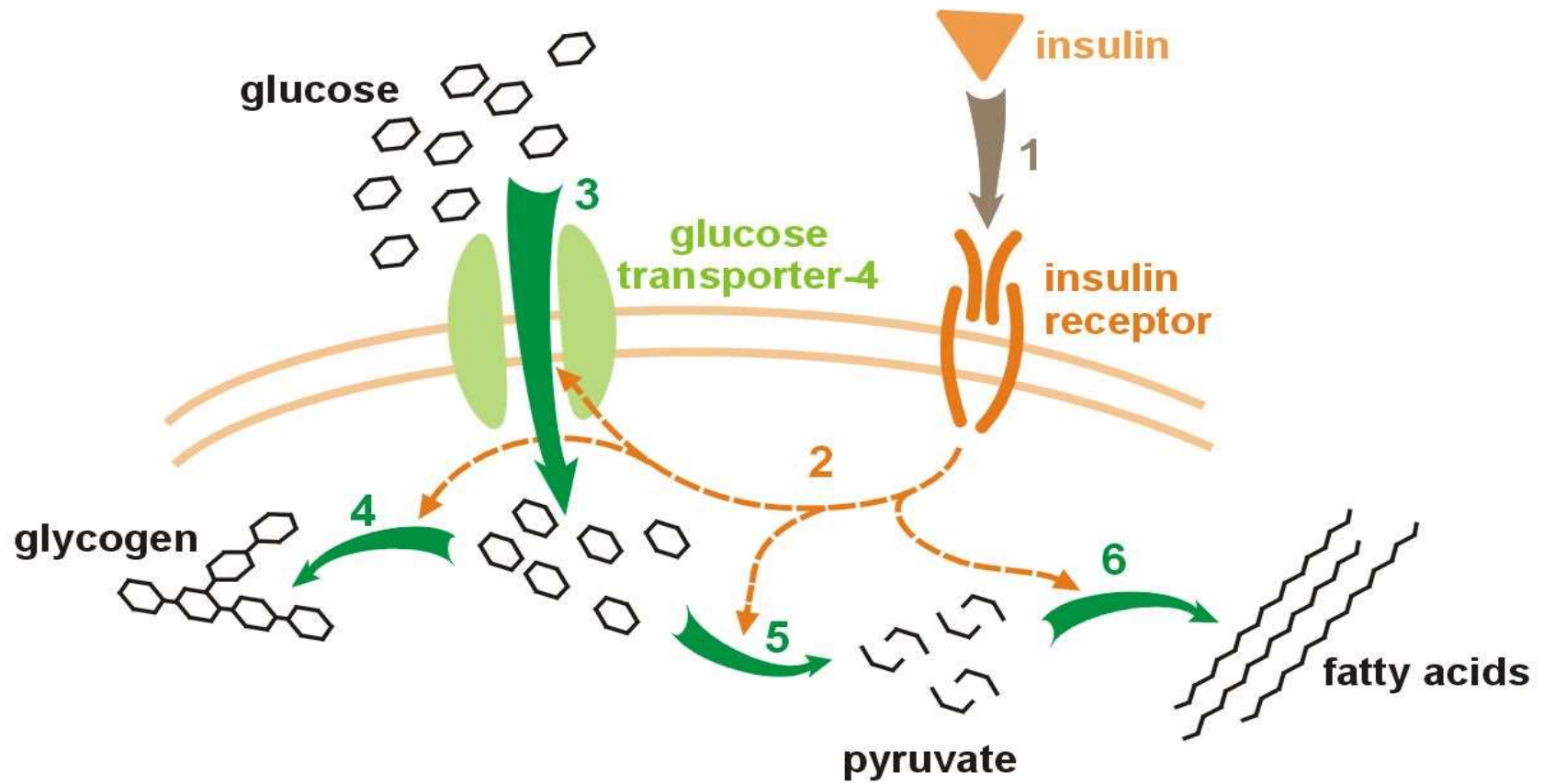
Peroxisome proliferator-activated receptor (PPAR) coactivator PGC-1 α

- Co-activator for neurotransmitter/hormonal sites
- Regulation of cellular energy metabolism and adaptive thermogenesis
- Stimulates mitochondrial biogenesis
- Glucose/fatty acid metabolism
- Reduces reactive oxygen species (ROS)
- Promotes remodeling of muscle tissue to a fiber-type composition
 - Metabolically more oxidative
 - Less glycolytic



Nutrients That Promote PGC1- α

- L-Citrulline
- Thai ginseng (*Kaempferia parviflora*) root polymethoxyflavones
- Resveratrol
- Quercetin
- Dihydroquercetin
- Astragaloside IV
- Fisetin
- Alpha Lipoic Acid
- Green Tea / EGCG





GLUT 4 Glucose Transporter

- Glucose transporter type 4 - Hexose transporter system
- Uses ATP-independent, facilitative diffusion mechanism
- Mediates insulin-stimulated glucose transport in fat and muscle
- Predominantly expressed in skeletal muscle and adipocytes
- Failure of GLUT4 to translocate to the plasma membrane in response to insulin
 - An early step in the development of insulin resistance and type 2 diabetes

Leto D, et al. Regulation of glucose transport by insulin: traffic control of GLUT4. *Mol Cell Bio.* 2012;13:383-396

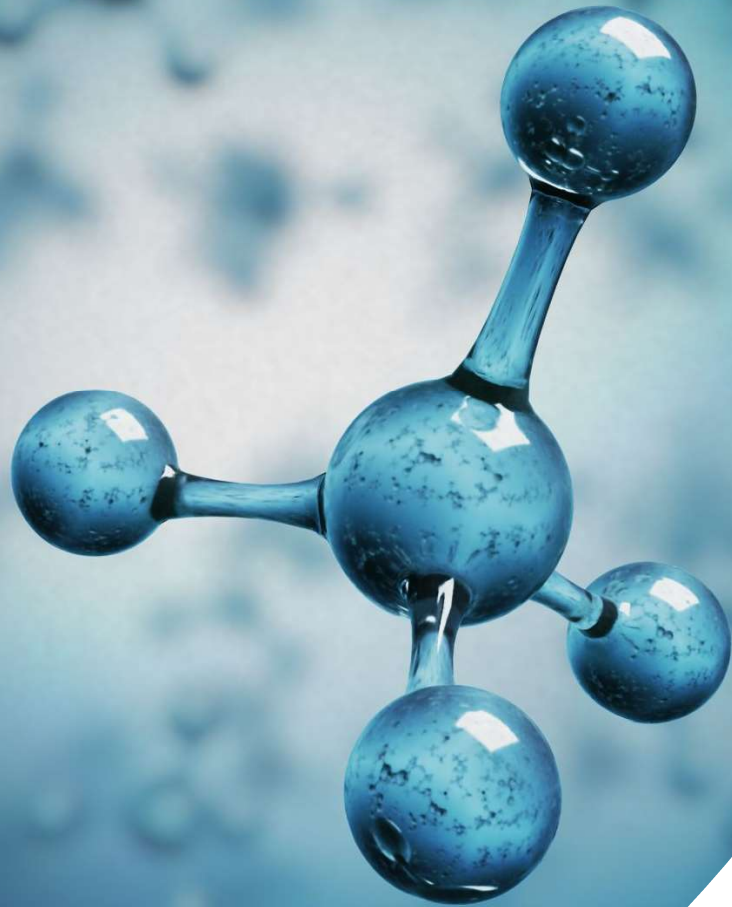
Glut 1 Dominated Transport

- Leads to Increase RNA, DNA, NAD + FAD
- Increases the Pentose Pathway
- Regenerates its own glutathione (NADPH)
- GLUCOSE THROUGHPUT 
- LACTATE PRODUCTION 
- Intracellular pH reduced H⁺ ions pumped into intracellular space creating necrotic space

Klepper J, et al. Autosomal dominant transmission of GLUT1 deficiency. Hum Mol Genet. 2001;10(1):63-8.

Gal-3 - Diabetes

- Gal-3 levels elevated in chronic inflammatory diseases including obesity, diabetes and its complications
- Gal-3 levels significantly higher in T2D patients
- **Elevated Gal-3 levels associated w/ increased HbA1c, FPG and hsCRP**
- Study findings suggests Gal-3 may play a role in the progression of prediabetes stage to diabetes stage



Supplements and Peptides for Glucose/Insulin Management



Basic BS/Insulin Management

FBS>90/↑IR/↑Cortisol

- Trace Minerals and Vitamins – quality multi
- Mag 300-600 chelate per day divided doses
 - Berberine 97% 60mg BID oral liposomal or 250-500mg BID 98%
 - Bitter melon 10% charantins 500mg BID or 50mg BID oral liposomal
 - GTF Chromium 400mcg BID oral liposomal or 500mcg BID
 - ALA 600-1,200mg BID
 - PQQ 10-40mg BID oral liposomal
 - Vanadium up to 50mg or 2mg oral liposomal
 - Resistant starch

IR (>22)/↑Cortisol

Magnolia/Phellodendron if
cravings + stress 250mg TID
Use adaptogens if no cravings

Prediabetes

ADD to above: Amansarate build to 2 caps 2 times a day

If no improvement in 60 days add: GLP-1s or GLP-1/GIP

Supplements for Stress/HPA Axis

- Adaptogens – rhodiola (250mg BID std. 3-5% rosavins), holy basil (300mg BID std 2.5% ursolic acid), Cordyceps (500mg BID hot water extract)
- L-Theanine – calming amino acid from green tea – 200mg TID
- Adrenal glandular – supports low or trending low cortisol levels
 - 2x 200mg AM, 200mg early afternoon
 - use whole adrenal when no anxiety, if anxiety use adrenal cortex
 - Use New Zealand or Argentinian glandulars only
- Magnolia/Phellodendron combo – stress with anxiety and stress-induced eating issues; 250mg TID
- Peptide – Sermorelin
 - Synthetic GHRH (growth hormone releasing hormone)
 - 100-300mcg SQ 5 out of 7 nights of the week before bedtime on an empty stomach

GUT Microbiome Protocol

- GUT support :
 - Berberine 97% 400mg/day + Cat's claw 500mg std. 3% alkaloids BID combo for Microbiome stabilization and immune/mucosal support
 - Add grapefruit seed extract for further antibacterial/anticandida support
 - Probiotics – 50-60 billion CFU daily
 - Digestive enzymes – 1 w/ meals; use HCL if no GUT sensitivity and meat eater
 - If leaky GUT suspected, combo glutamine + Zinc carnosine + DGL licorice + Aloe/marshmallow
 - Peptides - BPC-157 oral (250mcg BID)) + KPV oral (250mcg BID) – chew/swallow
- Immune support:
 - Plant sterols/sterolins – 1 cap BID (30mg sterols/0.3mg sterolins per cap)



Fish Polypeptides

Innovations in natural compounds

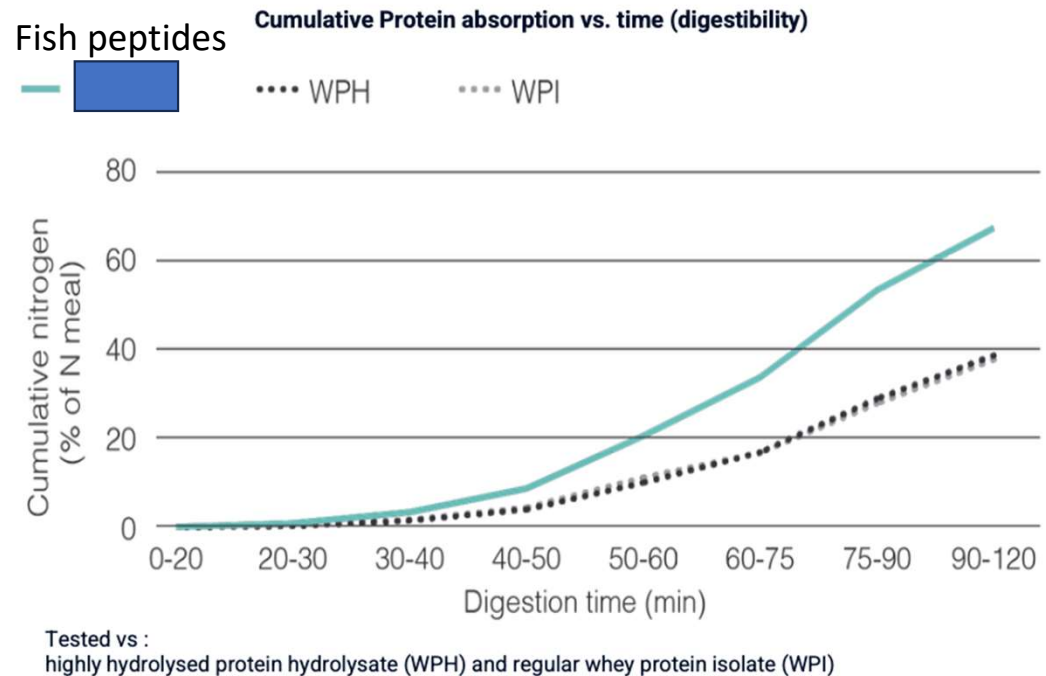
Fish Polypeptides

- Bioactive peptide mix derived from fresh Atlantic salmon – salmon protein hydrosylate
- Dosage 4-16gm daily ; highly bioavailable, up to 67.5% more absorption than hydrolyzed whey protein
- Improves iron metabolism
- GLP-1 and GIP effects
- Protects muscle mass
- Metabolic support
- Anti-inflammatory – decreases neuroinflammation
- Weight loss protocols
- Skin wrinkling

Fish Polypeptides

Faster Absorbability for Recovery

- Up to pure 100% protein with type I & III collagen
- Patent-protected and trade secrets
- **+67.5% more absorption than highly hydrolysed whey protein (which is not even commercially available) over just 2 hours**
- **Higher bioavailability**
- **Better digestibility**
- **Light stomach feel**
- **Hypo-allergenic**



Hofseth Biocare ASA Confidential & Proprietary Information

Polypeptides

Unique Health Benefits & Mode of Action

- GLP-1, GIP - Metabolic Health
- Boosting Energy levels & Quality of Life
- Protecting Muscle Mass
- New and unique health claims

→ **Advanced Science:** Powerful Gene Expression Modulation

>3x FTH1 upregulation

Effects:

- Improves iron absorption from the daily diet
- Enhances energy levels
- None of the adverse effects of iron supplementation

>3x HMOX1 upregulation

Effects:

- Supports GI health via important targeted protective pathways
- Provides antioxidant benefits

>3x ALOX-12 downregulation

Effects:

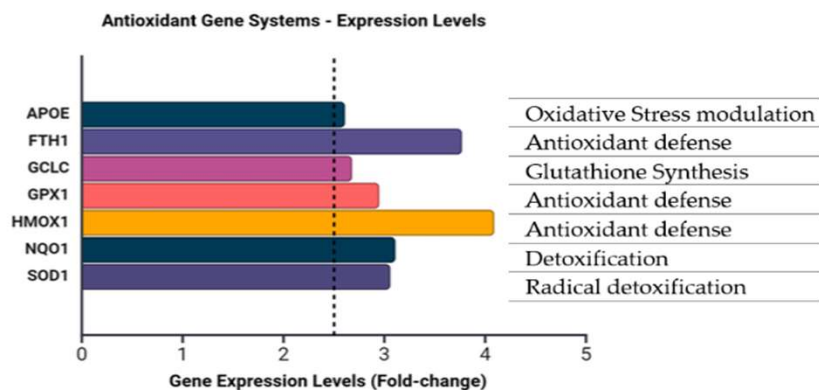
- Increases fat burn
- Increases insulin sensitivity
- Better body profile and weight control

Hofseth Biocare ASA Confidential & Proprietary Information

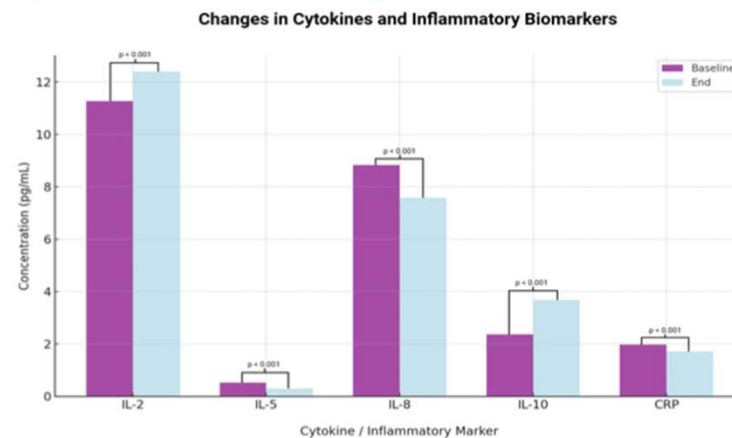
Gene Expression

Clinical Study: 4g clinical study demonstrates very strong antioxidant and anti-inflammatory effects

By Day 128 of SPH supplementation, the expression levels of antioxidant-related genes were analyzed, revealing significant changes in the expression of seven genes



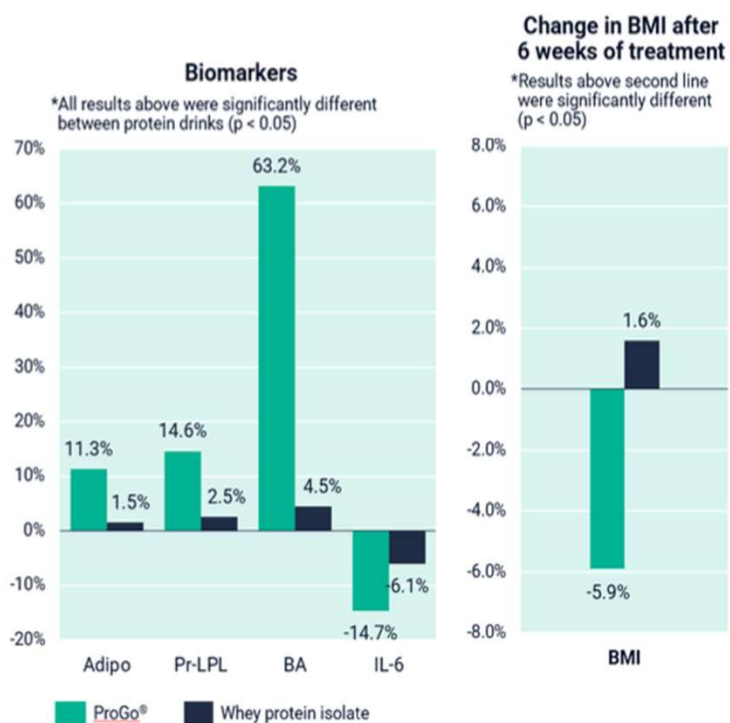
This data highlights the differential expression of select antioxidant genes, with positive changes more than a 2.5-fold change reflecting a significant response to SPH supplementation.



Illustrated above are of cytokines and inflammatory markers that exhibited statistically significant changes from baseline (Day 0) to the end of the study (Day 128).

Fat Loss

Bioactive Peptides Clinical Trial		
48 overweight subjects	16g/day	6 weeks



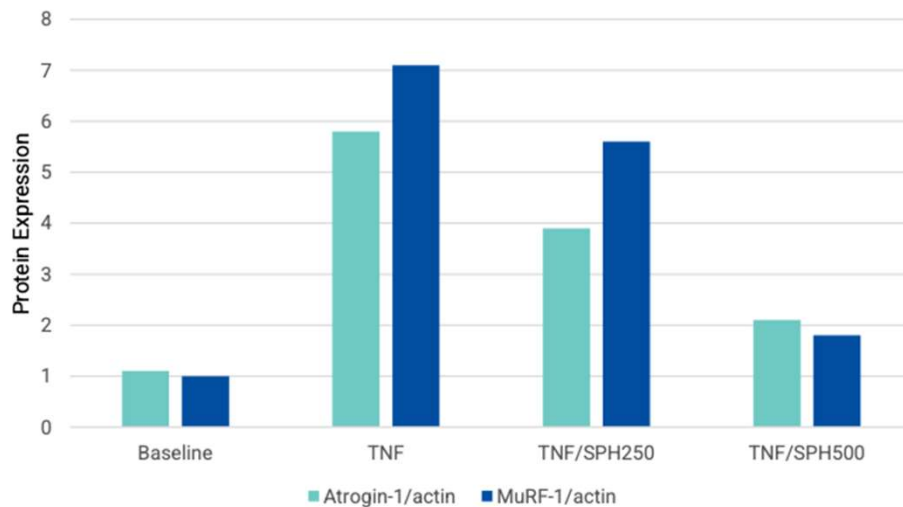
- **Confirmatory -6% BMI reduction** in just 6 weeks
- **Further pro-metabolic efficiency gains** seen through key markers of improved insulin sensitisation (adiponectin) & reduced blood cholesterol (lipoprotein lipase)
- **Significant bile acid (BA) boost** (remaining within healthy limits) boosting fat burn
- **Significant reductions in inflammation:** IL-6, an important driver of ill health, reduced by 15%

Published:
Framroze et. al. **A placebo-controlled, randomized study on the impact of dietary salmon protein hydrolysate supplementation on body mass index in overweight human subjects.** J. of Obesity & Weight Loss Therapy 2016

Hofseth Biocare ASA Confidential & Proprietary Information

Protection against Muscle Cell Inflammation driven wasting

TNF-induced muscle damage



An invitro model of induced skeletal muscle cell inflammation-driven wasting

Atrogin-1 and MuRF-1 are proteolytic proteins and major players in skeletal muscle wasting (particularly contractile protein loss)

Actin, and myosin, are the contractile proteins of skeletal muscle and therefore the basis of muscle function and strength

The ~6-7-fold increase in Atrogin and MuRF-1 expression (relative to actin) reflects significant muscle wasting which was reduced 3-4-fold by SPH at the higher 500µg/ml level

This suggests SPH has the potential to support muscle health against a common driver of inflammation and muscle damage

Cultured human skeletal muscle cell expression of atrogin-1 and MuRF-1 when exposed to inflammatory cytokine TNF

SPH 250 & 500 = 250µg/ml and 500µg/ml respectively

The Iron-Ferritin Alignment

1. Energy - boosts iron absorption by directly improving iron metabolism

Bioactive Peptides Clinical Trial		
48 subjects with iron deficiency anemia	16g/day	6 weeks

Clearly defined mode of action via FTH1 gene expression boost over 3-fold

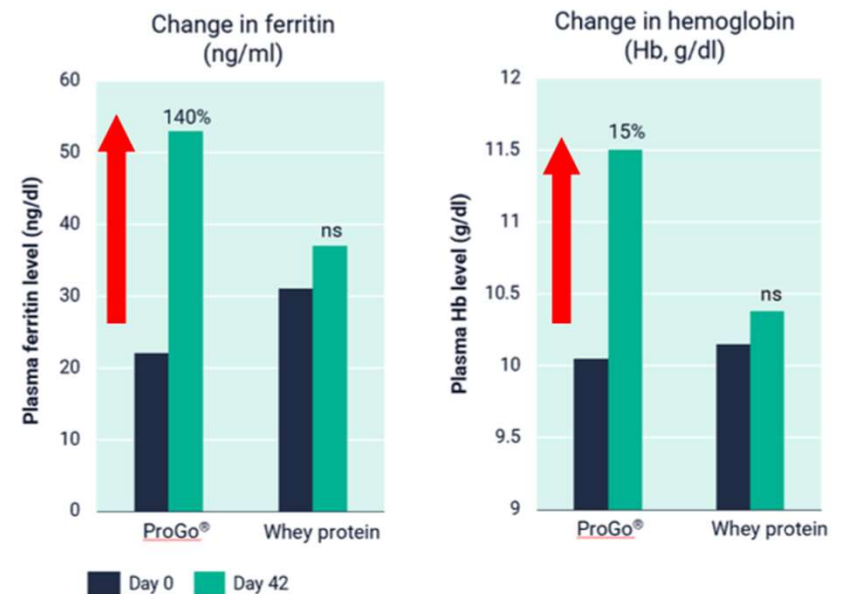
Directly boosts ferritin production that directly increases red blood cell (hemoglobin) production

Boosts iron absorption without any gut irritation

Enhanced energy levels

Resulting in New Qualified Health & Structure Function claims

Change in hemoglobin & serum ferritin after 6 weeks of treatment



Published:

Framroze et. al. A placebo-controlled study of the impact of dietary salmon protein hydrolysate supplementation in increasing ferritin and hemoglobin levels in iron-deficient anemic subjects. Nutrition and Food Sciences 2015

Hofseth Biocare ASA Confidential & Proprietary Information

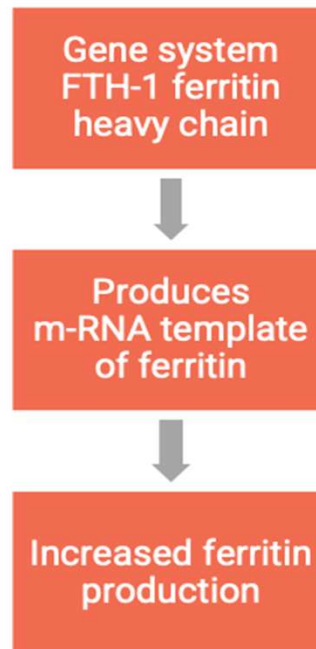
Iron-Ferritin

FTH-1 Upregulation mode of action explained

Context

- Iron is vital for efficient body function
- Iron is difficult to absorb: only 5-10% of iron is absorbed from the diet
- Increased need for iron in children, premenopausal women & physically active.
- Iron deficiency is common with fatigue, poor concentration, reduced fertility & impaired wound healing as a consequence
- A low circulating level of serum Ferritin is often used as an early indicator of iron deficiency

FTH-1 action



Effects of FTH-1 upregulation

- Increased iron uptake from the daily diet
- Increased iron storage as shown by normalized levels of serum ferritin
- Improved iron delivery to cells
- Improved hemoglobin blood levels
- Improved red cell distribution width (RDW)

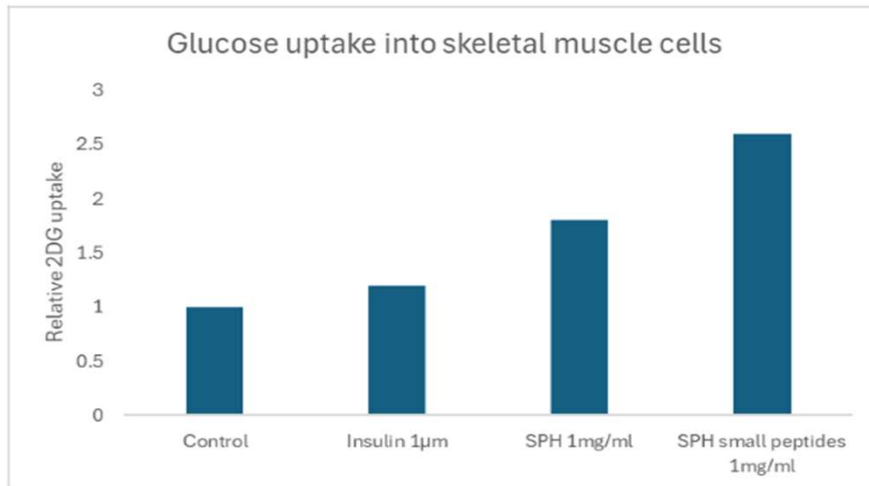
Outcomes

- Improved iron metabolism
- Increased energy, vitality & wellbeing
- Reduced stress on the body
- Optimized health & wellness
- Improved recovery from ill health

Glucose Uptake

has consistently shown a 3-6% reduction in fasting blood glucose and improved energy levels in clinical studies

delivers >100% increase in glucose uptake directly into the muscle cells



This provides:

1. Increased energy for an active lifestyle
2. Better regulation of blood glucose levels
3. Better metabolic health with lower inflammatory levels and less stress on the body



Article

Glucoregulatory Properties of a Protein Hydrolysate from Atlantic Salmon (*Salmo salar*): Preliminary Characterization and Evaluation of DPP-IV Inhibition and Direct Glucose Uptake In Vitro

Christian Bjerknes ^{1,*}, Sileshi Gizachew Wubshet ², Sissel Beate Ronning ², Nils Kristian Afseth ², Crawford Currie ¹, Bomi Framroze ¹ and Erland Hermansen ^{1,3}

¹ Hofseth Biocare ASA, Keiser Wilhelms Gate 24, 6003 Ålesund, Norway; cc@hofsethbiocare.no (C.C.); bf@hofsethbiocare.no (B.F.); ebe@hofsethbiocare.no (E.H.)

² Nofima AS, Osloveien 1, 1433 Ås, Norway; sileshiwubshet@nofima.no (S.G.W.); sissel.beate.ronning@nofima.no (S.B.R.); nils.kristian.afseth@nofima.no (N.K.A.)

³ Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Larsgårdsvegen 2, 6009 Ålesund, Norway
* Correspondence: chbj@hofsethbiocare.no

Abstract: Metabolic disorders are increasingly prevalent conditions that manifest pathophysiologically along a continuum. Among reported metabolic risk factors, elevated fasting serum glucose (FSG) levels have shown the most substantial increase in risk exposure. Ultimately leading to insulin resis-

Pleiotropic Effect

Clinical Study: demonstrating very strong Energy data

Bioactive Peptides Clinical Study Safety study for Health Canada QHCs

20 healthy subjects

4g/day

128 days

↑ **57%**

anti-inflammatory
IL-10 levels

↓ **7%**

red cell
variability

↑ **Vitality**

p=0.005

↑ **4.2x**

HMOX-1 gene
expression

↓ **9%**

oxidative
stress

↑ **Waking up
energized**

p=0.004

↑ **3.8x**

FTH-1 gene
expression

↓ **Irritability**

p=0.001

- Improved metabolic efficiency at lower doses
- Anti-inflammatory effects via significant increase in IL-10
- Less red blood cell variability demonstrating less stress on the body
- Significant HMOX1 increase for protecting gut health
- Better overall wellbeing
- The same benefits from 4g to 16g doses

Article
Soluble Protein Hydrolysate Ameliorates Gastrointestinal Inflammation and Injury in 2,4,6-Trinitrobenzene Sulfonic Acid-Induced Colitis in Mice

Jingjing Wei ^{1,2}, Guozhong Tao ^{1,2}, Ruihui Xu ^{1,2}, Kewei Wang ^{1,3}, Junlin Liu ^{1,4}, Chih-Hsin Chen ¹, James C. Y. Dunn ^{5,6}, Crawford Currie ^{5,6}, Bomi Fransmore ^{1,3} and Karl G. Sylvestre ^{1,4}

¹ Department of Surgery, Stanford University School of Medicine, Stanford, CA 94304, USA
² Department of Pediatrics, Shantou Medical University, Taishan 524001, China
³ Department of Gastrointestinal Surgery, The First Hospital of China Medical University, Shenyang 110001, China
⁴ Department of General Surgery, The People's Hospital of Linying City, Linying 410000, China
⁵ R&D Department, Helsebæ BioCare AS, 4010 Askland, Norway
⁶ Correspondence: gcurrie@stanford.edu (G.C.); kgs@stanford.edu (K.G.S.)

Abstract: Inflammatory bowel diseases (IBD) are chronic, recurring gastrointestinal diseases that severely impact health and quality of life. Although therapeutic options have significantly expanded in recent years, there is no effective therapy for a complete and permanent cure for IBD. Well tolerated dietary interventions to improve gastrointestinal health in IBD would be a welcome advance especially with anticipated favorable tolerability and affordability. Soluble protein hydrolysate (SPH) is produced by the enzymatic hydrolysis of commercial food industry salmon offcuts (consisting of the head, backbone and skin) and contains a multitude of bioactive peptides including those with anti-oxidant properties. This study aimed to investigate whether SPH ameliorates gastrointestinal injury in 2,4,6-trinitrobenzene sulfonic acid (TNBS) induced mouse colitis model. Mice were randomly assigned to four groups: Control (no colitis), Colitis, Colitis/CP (with control peptide treatment), and Colitis/SPH (with SPH treatment). Colitis was induced by cutaneous sensitization with 1% TNBS on day -8 followed by 2.5% TNBS enema challenge on day 0. Control peptides and SPH were provided to the mice in the Colitis/CP or Colitis/SPH group respectively by drinking water at the final concentration of 2% w/v daily from day -10 to day 4. Then, the colon was harvested on day 4 and examined macro- and microscopically. Relevant measures included disease activity index (DAI), colon histology injury, immune cell infiltration, pro- and anti-inflammatory cytokines and anti-oxidative gene expression. It was found that SPH treatment decreased the DAI score and colon tissue injury when compared to the colitis-only and CP groups. The protective mechanisms of SPH were associated with reduced infiltration of CD4⁺ T, CD8⁺ T and B220⁺ B lymphocytes but not macrophages, downregulated pro-inflammatory cytokines (tumor necrosis factor- α and interleukin-6), and upregulated anti-inflammatory cytokines (transforming growth factor- β 1 and interleukin-10) in the colon tissue. Moreover, the upregulation of anti-oxidative genes, including ferritin heavy chain 1, heme oxygenase 1, NAD(P)H quinone oxidoreductase 1, and superoxide dismutase 1, in the colons of colitis/SPH group was observed compared with the control peptide treatment group. In conclusion, the protective mechanism of SPH is associated with anti-inflammatory and anti-oxidative effects as demonstrated herein in an established mouse model of colitis. Clinical studies with SPH as a potential functional food for the prevention or as an adjunct therapy in IBD may add an effective and targeted diet-based approach to IBD management in the future.

Keywords: soluble protein hydrolysate; IBD; TNBS; anti-inflammatory; anti-oxidative

check for updates
 Citation: Wei, J.; Tao, G.; Xu, R.; Wang, K.; Liu, J.; Chen, C.H.; Dunn, J.C.Y.; Currie, C.; Fransmore, B.; Sylvestre, K.G. Soluble Protein Hydrolysate Ameliorates Gastrointestinal Inflammation and Injury in 2,4,6-Trinitrobenzene Sulfonic Acid-Induced Colitis in Mice. *Biomolecules* **2022**, *12*, 1207. <https://doi.org/10.3390/biom12041207>

Academic Editor: Peter Gerner
 Received: 2 August 2022
 Accepted: 5 September 2022
 Published: 10 September 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

Biomolecules **2022**, *12*, 1207. <https://doi.org/10.3390/biom12041207>

<https://www.mdpi.com/journal/biomolecules>

1. Introduction
 Inflammatory bowel diseases (IBD) affect more than 1.5 million Americans, with over 70,000 new cases diagnosed annually (<https://www.crohnscolitisfoundation.org/>).

Gut Health

upregulates anti-oxidative gene expression to support gut health & protect against inflammation

A standard mouse model of inflammatory bowel disease (IBD)

Three groups with chemically-induced IBD were treated with

- (1) Water
- (2) Collagen peptides or bioactive peptides.

Fourth group acted as control & therefore had no bowel disease

provided faster recovery for the gut and overall health via an increase in HMOX1 and FTH1

This was NOT a nutritional effect supporting healing – the control peptides had no benefit for gut health or overall health

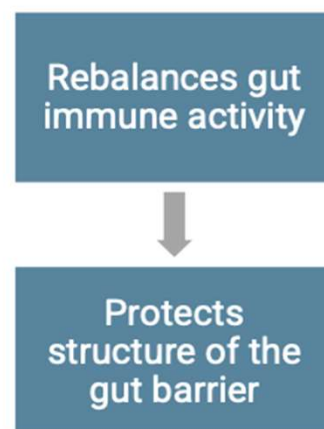
Gut Protection

HMOX-1 Upregulation mode of action explained

Context

- HMOX-1 antioxidant gene system sustains GI health
- The gut has a difficult balancing act — to take nutrients in and to keep bacteria out. HMOX-1 activity is pivotal in enabling the gut to achieve this dual action
- From lab to clinic (4g daily), ProGo® has consistently raised HMOX-1 activity >4-fold

HMOX-1 action



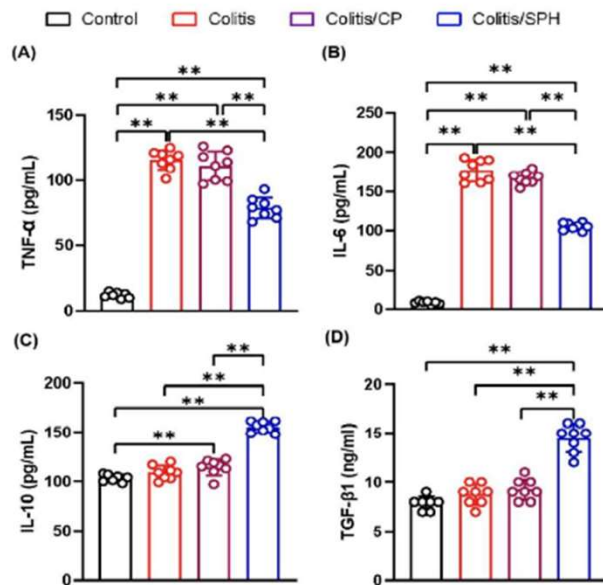
Effects of HMOX-1 upregulation

- Improved support of a healthy interaction between the microbiota and the mucosal immune compartment
- Improved blood flow
- Enhanced support for GI barrier function

Outcomes

- Healthier gut and body
- Healthier inflammatory profile
- Enhanced energy and vitality
- Healthier GI immune function profile and better overall health

Gut Inflammation signaling profile



The impact of **HMOX1** and **FTH1** upregulation on gut inflammation...

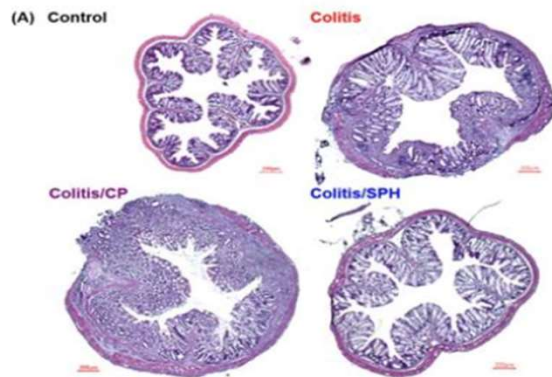
- **TNF** and **IL-6** are pro-inflammatory cytokines central gut inflammation & were significantly reduced by ProGo
- These are the target of the major treatments of IBD: anti-TNF monoclonal antibodies and JAK inhibitors (which have multi-billion \$ sales)
- **IL-10** and **TGFβ** are anti-inflammatory and involved in maintaining gut health
- This change results in an environment supporting healing and sustained gut health

- TNF-α and IL-6 - major pro-inflammatory cytokines
- IL-10 and TGF-β1 - major anti-inflammatory cytokines
- A healthier immune response via HMOX1 & FTH1 activity with ProGo®

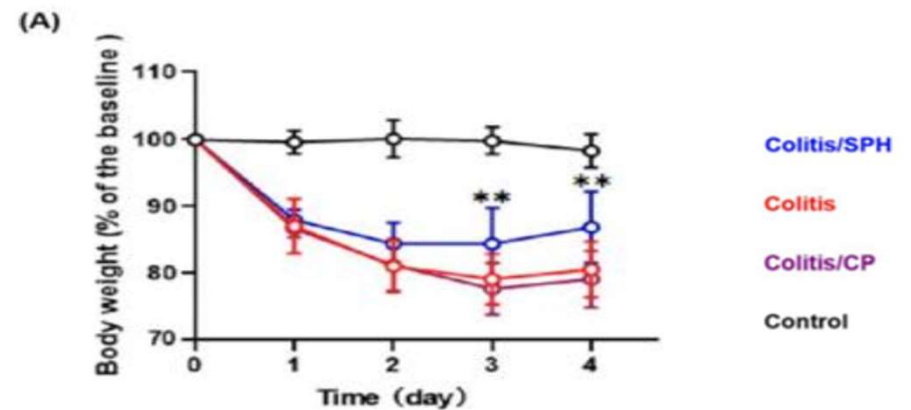
Gut Health

Improved GI & Overall Health

Normal structure of the gut protected indicating better gut function maintained



Protecting gut function led to a significantly improved recovery as indicated by the weight profile



helped to reduce swelling, maintain the gut lining and reduce stress on the body enabling faster weight recovery – weight loss is an important marker of disease severity and weight regain on the effectiveness of treatment in inflammatory bowel disease

The group fed bovine collagen peptides suffered severe damage to the gut, with gross swelling and damage indicating significant loss of bowel function reflected in the very weak recovery

J Wei, G. Tao, K Sylvester et al. Soluble protein hydrolysate ameliorates GI inflammation and injury in 2,4,6 TNBS-induced colitis in mice, *Biomolecules* 2022, 12,1287.

Inflammatory and Metabolic Markers

	Inflammation markers*				Antioxidant marker
	C-Reactive Protein CRP marker of inflammation	cytokine IL-6 major pro-inflammatory cytokines	cytokine IL-8 major pro-inflammatory cytokines	cytokine IL-10 anti-inflammatory cytokines	TNF
4g	▼ 19%		▼ 15%	▲ 57%	▼ 9%
12g		▼ 14.4%	▼ 22.3%		▼ 16.4%
16g	▼ 15%	▼			

	Metabolic biomarkers				
	BMI	Body fat	Bile acids	Adiponectin	Pre-heparin lipoprotein lipase
4g					
12g	▼ 6.97%	▼ 10.8%			
16g	▼ 5.9%		▲	▲	▲

Impact of observed metabolic biomarker changes

- Elevated serum bile acid increases “fat burn”
- Elevated adiponectin is associated with reduced inflammation and improved cardiac health
- Elevated serum levels of lipoprotein lipase (LPL) reflect increased insulin sensitivity
- Lowered human interleukin 6 (IL-6) associated with improvement in underlying health
- Consistent BMI reduction and better body profiling associated with fat reduction

Consistent >3x gene expression modulation in human trials

Fish Oil IR/T2D

- Omega-3s (especially EPA, DHA) can reduce inflammation, oxidative stress, endoplasmic reticulum (ER) stress, and lipotoxicity in tissues
 - Includes adipose, liver, muscle
- They may improve:
 - Mitochondrial function
 - Upregulate mitochondrial biogenesis factors (PGC1 α , NRF1)
 - Shift substrate handling toward better fatty acid oxidation rather than ectopic lipid deposition.

Fish Oil IR/T2D

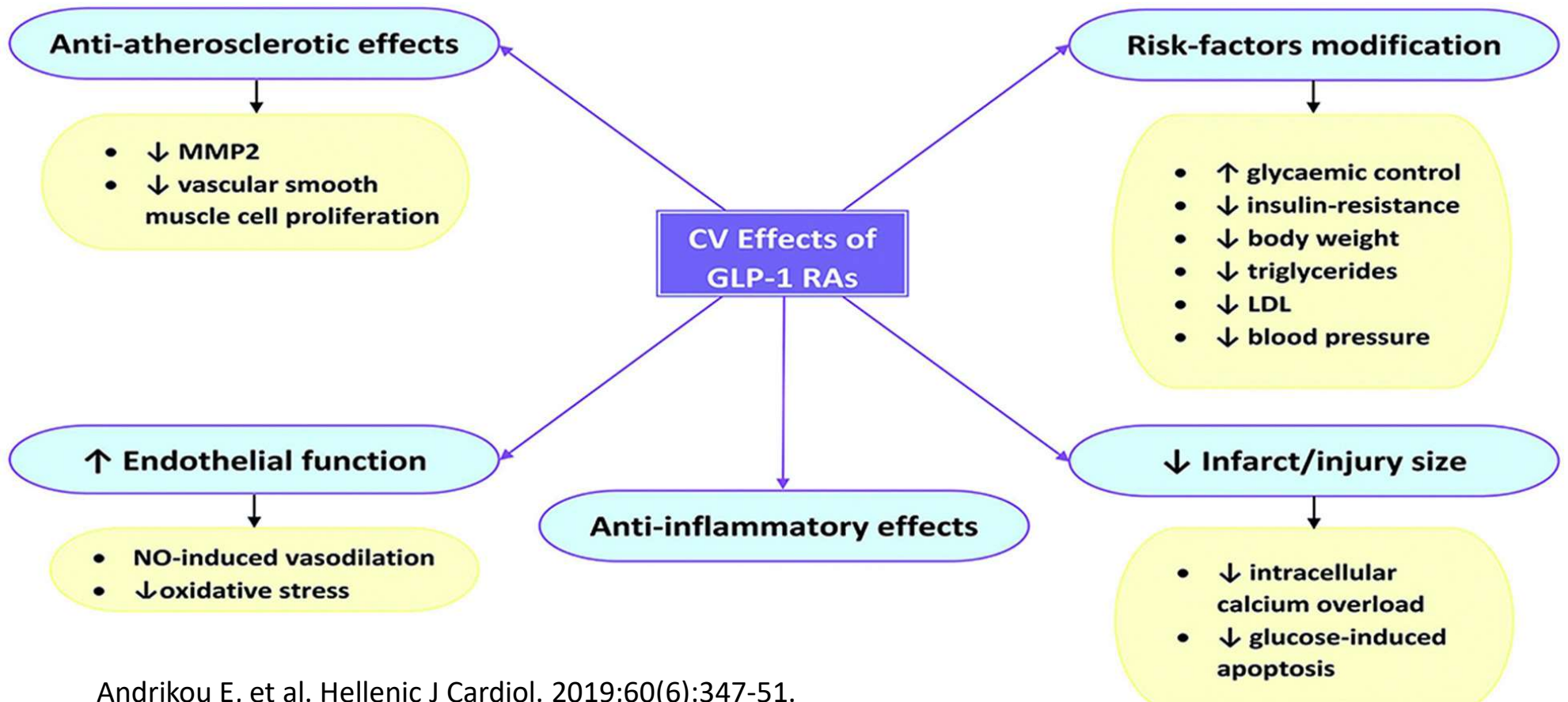
- Omega-3s can reduce a “lipotoxic burden” that impairs insulin signaling
 - By lowering circulating triglycerides, nonesterified fatty acids, and improving lipid partitioning
- Omega-3s can modulate gut microbiome / endotoxin translocation (LPS) and systemic low-grade inflammation, which is implicated in IR

GLP-1 Agonists

- Incretin-mimetics
- GLP-1 secreted by the small intestine in response to nutrient ingestion
- Enhances insulin secretion from pancreatic β -cells, and decreases glucagon release from pancreatic α -cells
- Increased resistance to enzymatic degradation by DPP-4
- Useful for improving glycemic control and atherosclerosis-related parameters
- Short-acting GLP-1 receptor agonists primarily slow gastric emptying
 - Exert their main effect on postprandial blood glucose levels
- Long-acting compounds have insulinotropic and glucagonostatic actions
 - Exert their main effect on fasting glucose levels

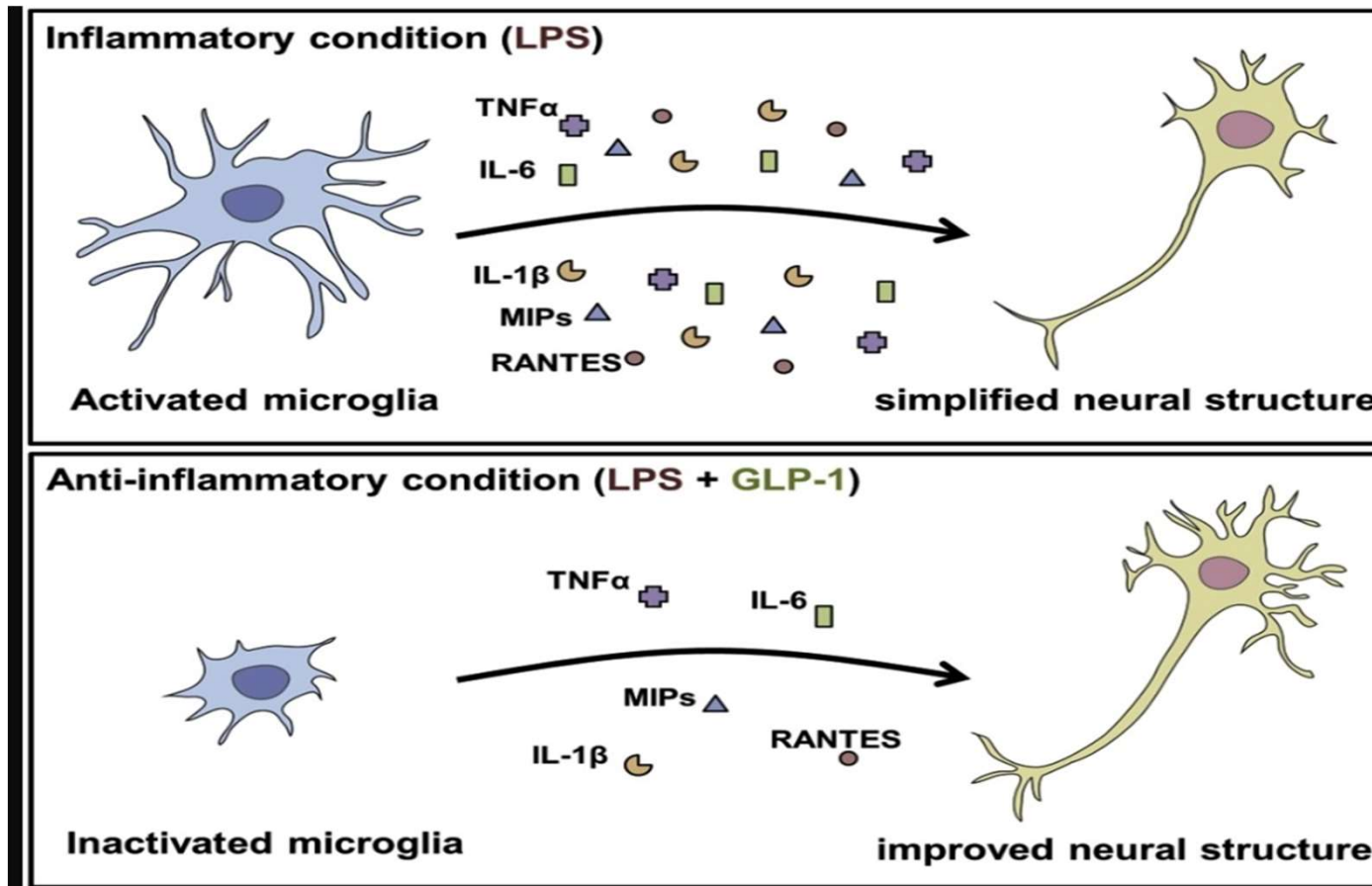
Neumiller JJ, et al. Clinical pharmacology of incretin therapies for type 2 diabetes mellitus: implications for treatment. Clin Ther. 2011;33(5):528-76.

Cardiovascular Effects of GLP-1 Agonists



Andrikou E, et al. Hellenic J Cardiol. 2019;60(6):347-51.

GLP-1 Effect on Neuroinflammation



Yoon G, et al. Pharmacological Res. 2020;152:104615.

New Research – GLP-1 and Neuroprotection

- Helps regulate memory
 - Activation of autophagy
 - Decreased neuroinflammation
 - Inhibits hippocampal neuronal loss
 - Inhibiting neuronal cell death
 - Promotes neurogenesis
- Brain derived GLP-1 also reported to improve glucose metabolism and insulin resistance in the brain
- Potential uses in Parkinson's and Alzheimer's

Yoon G, et al. Glucagon-like-peptide-1 suppresses neuroinflammation and improves neural structure. *Pharmacological Res.* 2020;152:104615.

GLP-1 – General

- **GLP-1 controls insulin secretion and body weight through activation of its receptor, GLP1R**
- **Large-scale functional analysis of 60 *GLP1R* genetic variants revealed that loss-of-function (LoF) phenotypes, in particular of cell surface expression, are associated with impaired glucose control and increased adiposity**

Gao W, et al. Nature Metabolism. 2023;5:1654-55.

GLP-1 Agonist SEs – General

- GLP-1 receptor agonists appear to have a favorable safety profile
- **NOT FOR USE IN PREGNANCY – discontinue med at least 2 months before a planned pregnancy**
- Most common SE = GI symptoms, mainly nausea; headache
- Injection site reactions – redness, swelling, pruritus
- Severe SE's include – pancreatitis, allergic reactions, thyroid C-cell carcinoma
- Several cases report acute kidney injury, primarily through hemodynamic derangement due to nausea, vomiting, and diarrhea

Filippatos TD, et al. Adverse effects of GLP-1 receptor agonists. Rev Diabet Stud. 2014;1`1(3):202-230.

GLP-1 Agonist SEs – General

- GLP-1 receptor agonists have no reported negative effects on the cardiovascular risk of patients with T2
- **Contraindicated in Medullary thyroid carcinoma (MTC) and Multiple Endocrine Neoplasia syndrome type 2 (men)**
- **Not known whether GLP-1 agonists can be used in patients w/ a history of pancreatitis**

Filippatos TD, et al. Adverse effects of GLP-1 receptor agonists. Rev Diabet Stud. 2014;1`1(3):202-230.

FROM THE SOCIETY · [Volume 122, Issue 1, P344-367, July 2025](#) · [Open Access](#)

 [Download Full Issue](#)

Nutritional priorities to support GLP-1 therapy for obesity: a joint Advisory from the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and The Obesity Society

[Dariush Mozaffarian](#) ¹  · [Monica Agarwal](#)² · [Monica Aggarwal](#)³ · ... · [Deepa Sannidhi](#)¹⁸ · [Fatima Cody Stanford](#)^{19,20} · [Emily A Callahan](#)¹ ... [Show more](#)

Supplementing the Diet while on GLP-1s - Fiber

- Why Fiber? – Sunfiber – partially hydrolyzed guar gum
 - GLP-1 slows gastric emptying and can reduce bowel motility. Many people experience constipation as a side effect.
 - Soluble and insoluble fibers add bulk, soften stools, and promote more regular bowel movements
 - Fiber also enhances satiety
 - GUT microbiome benefits
 - Lipid and metabolic effects
 - 18gm daily
- Johnson B, et al. Investigating nutrient intake during use of glucagon-like peptide-1 receptor agonist: a cross-sectional study. *Front Nutr.* 2025;12:1566498.

Supplementing the Diet while on GLP-1s - Magnesium

- Why Magnesium? Mag Bisglycinate chelate 400-600mg daily
- Nausea/vomiting can lead to Mag depletion
- Low mag worsens constipation, already common in GLP-1 patients
- Supports CV protection of GLP-1
- Supports sleep/stress
- GLP-1s improve insulin sensitivity and lower glucose
 - But if magnesium is low, this effect is blunted
 - Overweight/obese generally low in Mag

Johnson B, et al. Investigating nutrient intake during use of glucagon-like peptide-1 receptor agonist: a cross-sectional study. *Front Nutr.* 2025;12:1566498.

Supplementing the Diet while on GLP-1s - Artichoke

- Why Artichoke? 250 Artichoke leaf std. 10-12% chlorogenic acid
BID
- Improves liver, gallbladder function
- improves bile production and flow
- helps fat digestion, reduces dyspepsia, and supports gallbladder/liver function
 - Especially important since rapid weight loss on GLP-1s increases gallstone risk
- Lipid lowering effects
- Improves GUT microbiome and GUT motility

Johnson B, et al. Investigating nutrient intake during use of glucagon-like peptide-1 receptor agonist: a cross-sectional study. *Front Nutr.* 2025;12:1566498.

Supplementing the Diet while on GLP-1s - Protein

- Why Protein?
- Low allergenic protein – contains organic hemp seed, watermelon seed and pumpkin seed proteins + full spectrum BCAAs + resistant starch (Solnul)
- 1.6gm/kg protein a day
- Protein helps preserve lean muscle mass
- Improves satiety
- Improves glucose/insulin control
- Improves recovery
 - Protein supports mitochondrial repair, hormone production, and tissue recovery

Johnson B, et al. Investigating nutrient intake during use of glucagon-like peptide-1 receptor agonist: a cross-sectional study. *Front Nutr.* 2025;12:1566498.

Semaglutide

- GLP-1 agonist
- Indications:
 - An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
 - To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease
 - Approved for Weight loss maintenance
 - Not for Type 1 Diabetes

Semaglutide

- 2021 randomized, n=803 obese/overweight participants
- 20-week weekly SQ semaglutide, 2.4 mg
- Mean weight loss of 10.6%
- Randomized to continued treatment with subcutaneous semaglutide vs placebo for an additional 48 weeks
- At the end of additional 48 wks, mean weight change was -7.9% vs $+6.9\%$, respectively



Rubino D, et al. Effect of subcutaneous semaglutide on body weight in adults with obesity. *JAMA*. 2021;325(14):1414-1425.

Semaglutide Inj Dosage

- Ozempic, Rybelsus, Wegovy
- Ozempic - start at 0.1 mg once weekly X 2 WEEKS
- Weeks 3-4 go to .25mg unless GI issues then go up by 5 units evaluate weight loss at 4 weeks if losing 1-4 pounds a week maintain dose. Go up by 5 unit increments based on weight loss standstill
- Most patients will lose weight at the dose to 0.5 mg once weekly.
- If after at least 4 weeks additional glycemic control is needed, increase to 1 mg once weekly(rarely needed if working diet and exercise)
- Administer once weekly at any time of day, with or without meals 0.5 - 1mg weekly for T2D
- Wegovy - 2.4mg SQ once weekly for weight loss
 - Start w/ 1mg SQ weekly, then dose must be increased gradually over 16 to 20 weeks to 2.4 mg once weekly to reduce gastrointestinal side effects

Oral Semaglutide

- Adults with an average starting A1C of 8.3% lowered their A1C by an average of:
- -1.0% on 7 mg of semaglutide oral
- -1.3% on 14 mg of semaglutide oral

Rybelsus® [package insert]. Plainsboro, NJ:
Novo Nordisk Inc; January 2020.

New Research – GLP-1 and Muscle Loss

- Muscle atrophy is common in T2D
- GLP-1 receptor agonists ameliorate muscle wasting
 - by suppressing MSTN and muscle atrophic factors
 - enhancing myogenic factors through GLP-1R-mediated signaling pathways
- GLP-1 regulates skeletal muscle remodeling to enhance exercise endurance
 - via GLP-1R signaling-mediated phosphorylation of AMPK

Fan D, et al. Hypoglycemic drug liraglutide alleviates low muscle mass by inhibiting the expression of MuRF1 and MAFbx in diabetic muscle atrophy. *J Chin Med Assoc.* 2023;86(2):166-75.

Wu L, et al. GLP-1 regulates exercise endurance and skeletal muscle remodeling via GLP-1R/AMPK pathway. *Biochim Biophys*

Information Class *Acta Mol Cell Res.* 2022;1869(9):119300.

Semaglutide Lean Muscle Loss?

- STEP1 Study – semaglutide primary clinical trial
 - Subset of patients (n=140) underwent DXA scans for body composition
 - Participants on semaglutide lost an average of 10.4% of their fat mass and 6.9% of their lean body mass
 - Placebo lost an average of 1.2% of their fat mass and 1.5% of their lean body mass
- Although total lean body mass decreased in absolute terms (kg), the proportion of lean body mass relative to total body mass increased with semaglutide

Wilding JPH, et al. Once-weekly semaglutide in adults with overweight or obesity. NEJM. 2021;384:989-1002.

Semaglutide Lean Muscle Loss?

- Subset of SUSTAIN 8 Phase IIIB Trial using semaglutide in diabetes treatment
- N = 178 patients, body composition tested using DXA scan
- Semaglutide 1mg or Canagliflozin or placebo
- Total fat mass was reduced by 3.4 kg and 2.6 kg with semaglutide and canagliflozin, respectively
- Although total lean mass was also reduced by 2.3 kg and 1.5 kg with semaglutide and canagliflozin, respectively , the proportion of lean mass increased by 1.2%- and 1.1%-point, respectively
- Changes in visceral fat mass and overall changes in body composition (assessed by the fat to lean mass ratio) were comparable between the two treatment groups

Wilding JPH, et al. Once-weekly semaglutide in adults with overweight or obesity. NEJM. 2021;384:989-1002.

Semaglutide - Cardiovascular Events

- 2023 study – 17,604 patients in 41 Countries
- Semaglutide reduced cardiovascular events by 20% in adults with overweight or obesity
- Risk reductions similar in men and women and across different ethnicities, patient ages and baseline levels of bodyweight
- Patients were with pre-existing CVDs and overweight or obesity BUT without diabetes
 - Weekly injections of semaglutide 2.4 mg reported superior to placebo in reducing the risk of death from cardiovascular causes, nonfatal heart attack, or nonfatal stroke over an average follow-up of 40 months
- In the trial, patients treated with semaglutide lost an average of 9.4% of their body weight
- Also experienced improvements in other risk factors for cardiovascular disease – HTN, lipids, vascular dysfunction
- #1 adverse event was GI symptoms – nausea, diarrhea

Lincoff AM, et al. N Engl J Med. 2023;[epub ahead of print].

Semaglutide

Dosages

- Oral dosage (adult):
 - Initially 3 mg once a day for 30 days
 - Then increase to 7mg once daily for 30 days
 - Then 14 mg once a day target dosage if warranted
 - Swallow whole on an empty stomach, at least 30min before eating
 - No dosage adjustment in hepatic or renal impairment
- Oral semaglutide can be initiated 7 days after the last dose of injectable semaglutide administered
 - There is no equivalent dose of oral semaglutide for subcutaneous semaglutide 1 mg weekly per manufacturer
- Can add Vitamin B12 or B6 - reduces nausea and GI side effects

Ecnoglutide

- Long acting GLP-1 agonist used in T2D and obesity
- Ecnoglutide is a modified GLP-1 (7–37) peptide
 - Contains an alanine to valine substitution at position 8, as well as an 18-C fatty acid conjugation at the lysine 30 side chain
 - Improves peptide stability and activity
- Ecnoglutide (natural amino acids) is easier to manufacture vs. semaglutide (contains synthetic moieties)
- Ecnoglutide valine substitution also biases GLP-1 receptor signaling towards cyclic adenosine monophosphate (cAMP) induction
 - Over β -arrestin recruitment and receptor internalization like semaglutide
 - Tirzepatide – dual agonist – does show cAMP bias also

Zhu D, et al. Efficacy and safety of GLP-1 analog ecnoglutide in adults with type 2 diabetes: randomized, double-blind, placebo-controlled phase 2 trial. Nature Comm. 2024;15:8408.

Ecnoglutide

- In preclinical models, ecnoglutide reported significant improvements in glucose control and body weight reduction compared to the analog semaglutide

Zhu D, et al. Efficacy and safety of GLP-1 analog ecnoglutide in adults with type 2 diabetes: randomized, double-blind, placebo-controlled phase 2 trial. Nature Comm. 2024;15:8408.

Ecnoglutide SubQ

- Phase II randomized, double-blind, placebo-controlled study
- N=145 adults w/ T2D
- 0.4, 0.8 or 1.2mg ecnoglutide once-weekly SubQ x 20wks
- Primary endpoint was improvement in HbA1c
 - Also looked at lipids, weight, glucose AND safety
- 0.4, 0.8 and 1.2mg all produced significant reductions in HbA1c from baseline (-1.81%, -1.90% and -2.39% respectively) compared to -0.55% placebo
- At end of treatment, 71.9% of the 1.2 mg group had HbA1c \leq 6.5% versus 9.1% on placebo
- 33.3% had body weight reductions \geq 5% versus 3.0% for placebo
- Ecnoglutide SubQ was generally safe and well tolerated

Zhu D, et al. Efficacy and safety of GLP-1 analog ecnoglutide in adults with type 2 diabetes: randomized, double-blind, placebo-controlled phase 2 trial. Nature Comm. 2024;15:8408.

Oral Ecnoglutide Study

- Phase 1 randomized, double-blind, placebo-controlled multiple ascending dose study- oral formulation of ecnoglutide
- 42 healthy (Cohorts 1-3) and 14 healthy obese (Cohort 4) participants
 - Placebo or ecnoglutide oral tabs – 7mg, 15mg and 30mg - once daily x 2 weeks (the healthy groups)
- Cohort 4 study as 30mg oral ecnoglutide once daily x 6 weeks

Results:

- Adverse events included: nausea, headache, diarrhea, vomiting, and decreased appetite
 - All mild-moderate

Oral Ecnoglutide Study Results

- In Cohorts 1-3, treatment with doses up to 7, 15, or 30 mg Ecnoglutide once-daily for 2 weeks resulted in body weight changes of -3.6%, -3.4%, and -6.6%, respectively
 - Placebo change in weight was -0.9%
- In obese participants (Cohort 4), treatment with doses up to 30 mg ecnoglutide once-daily for 6 weeks resulted in -6.8% body weight loss at end of treatment
 - Compared to -0.9% for the placebo group

Oral Ecnoglutide Study Conclusions

Conclusions:

- *Oral ecnoglutide was safe and well tolerated with gastrointestinal side effects as the most commonly reported adverse events*
- *Study participants receiving up to 30 mg oral ecnoglutide once-daily for 6 weeks achieved a mean body weight reduction of -6.8% from baseline, compared to -0.9% for the placebo group*
- *The study remains ongoing to evaluate additional dosing regimens including once-weekly oral administration*

Ecnoglutide

- Dosage = 30mg ORALLY once daily x 6 weeks

Tirzepatide GIP/GLP-1

- Dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist
- 39 amino acids
- Approved for use in tx of T2D
 - Reduces HbA1c
 - Weight control
 - Improves cardiovascular risk factors

Frias JP, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. NEJM. 2021;285:503-

Tirzepatide Dosage

- Mean half-life of ~5 days
 - Enables once-weekly dosing
- 2.5 – 5mg SubQ weekly
- Side effects reported in at least 5% of patients:
 - nausea, diarrhea, decreased appetite, vomiting, constipation, indigestion (dyspepsia), and stomach (abdominal) pain
- BOX Warning regarding thyroid C-cell tumors
- Tirzepatide contraindicated in patients with:
 - a personal or family history of medullary thyroid carcinoma OR
 - In patients with Multiple Endocrine Neoplasia syndrome type 2

Overview of the SURPASS Studies – Phase III Trials

- Tirzepatide Phase III use demonstrates greater reduction in A1C vs semaglutide 1 mg, degludec, and glargine
- Tirzepatide is associated with greater reduction in body weight
- Compared with semaglutide 1 mg, treatment with tirzepatide is associated with greater reduction in cardiovascular risk factors of A1C, weight, BP, and greater improvements in TG and HDL-C
- Reductions in LDL-C were significant, but similar to semaglutide 1 mg
- Gastrointestinal side effects were similar to GLP-1 RA, but were numerically greater with tirzepatide compared with semaglutide 1 mg

Frias JP, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. NEJM. 2021;285:503-

Tirzepatide Dosage

For T2D or pre-diabetes - SubQ

- Start at 2.5 mg SQ once weekly.
- After 4 weeks, increase the dose to 5.0 mg once weekly.
- If after at least 4 weeks additional glycemic control is needed, increase dosage by 2.5mg until desired effects achieved.
- Maximum dosage = 15mg once weekly
- Administer with or without meals; any time of day.

For Weight Loss - SubQ

- Start at 2.5 mg SQ once weekly.
- After 4 weeks, increase the dose to 5.0 mg once weekly.
- Titrate until desired effects are seen; if stalls, then increase by 2.5mg weekly until maximum of 15mg once weekly is achieved.
- Administer with or without meals; any time of day.

Retatrutide (LY3437943)

- Phase III development
- Triple hormone receptor agonist for obesity
 - Glucose-dependent insulinotropic peptide receptor (GIPR) agonist
 - GLP-1 receptor agonist
 - Glucagon receptor (GCGR) agonist
- Induces lipolysis in adipocytes > native GIP
- Delays gastric emptying
- Effective for weight management

Jastreboff AM, et al. N Engl J Med. 2023;389;514-26.

Retatrutide (LY3437943)

- 2023 randomized, double-blind, placebo-controlled phase 2 study
- N = 338 adults BMI 30 or > OR BMI 27 or > w/ one weight-related condition
- Dose 1mg, 4mg, 8mg, 12mg SubQ, Q week x 24 and 48 wks

• <u>RESULTS (wt loss):</u>	<u>24wk</u>	<u>48wk</u>
• 1mg wt loss =	- 7.2%	- 8.7%
• 4mg =	- 12.9%	-17.1%
• 8mg =	- 17.3%	- 22.8%
• 12mg =	- 17.5%	- 24.2%
• Placebo =	- 1.6%	- 2.1%

Jastreboff AM, et al. N Engl J Med. 2023;389;514-26.

Retatrutide

- Treatment associated w/ improvements in cardiometabolic measures at 24 and 48wks including:
 - Systolic and diastolic BPs
 - Triglycerides
 - LDL-cholesterol
 - Total cholesterol
 - HbA1c
 - Fasting glucose and insulin
- Most common side effects = GI
 - Nausea/vomiting
 - Diarrhea or constipation
 - Dose-related
- Can add pyridoxine to help decrease GI SE's

Jastreboff AM, et al. N Engl J Med. 2023;389;514-26.

Clinical Trial > N Engl J Med. 2023 Aug 10;389(6):514-526. doi: 10.1056/NEJMoa2301972.

Epub 2023 Jun 26.

Triple-Hormone-Receptor Agonist Retatrutide for Obesity – A Phase 2 Trial

Ania M Jastreboff ¹, Lee M Kaplan ¹, Juan P Frías ¹, Qiwei Wu ¹, Yu Du ¹, Sirel Gurbuz ¹, Tamer Coskun ¹, Axel Haupt ¹, Zvonko Milicevic ¹, Mark L Hartman ¹;

Retatrutide Phase 2 Obesity Trial Investigators

Lilly's phase 2 results published in The New England Journal of Medicine show retatrutide achieved up to 17.5% mean weight reduction at 24 weeks and up to 24.2% at 48 weeks in adults with obesity and overweight

Jastreboff AM, et al. N Engl J Med. 2023;389;514-26.

Retatrutide NAFLD

- Nearly 24% Americans have NAFLD
- The retatrutide Phase 2 study we discussed also reported a profound benefit in patients with NAFLD
- Findings: amount of fat in 9 out of 10 patients normalized after tx w/ retatrutide 8 or 12mg subQ weekly
- > 85% of patients had NAFLD completely resolve after retatrutide tx

Jastreboff AM, et al. N Engl J Med. 2023;389;514-26.

Retatrutide Dosage

Doses	Initial Dose
1 mg	1 mg
4 mg	2 mg or 4 mg
8 mg	2 mg or 4 mg
12 mg	2 mg

- Start with initial dose
- IF WEIGHT LOSS IS SATISFACTORY MAINTAIN DOSE
- increase dosage every other week to max dosage depending on tolerability
- 48 weeks total therapy
- T_{1/2} = 6 days – weekly dosing

Jastreboff AM, et al. N Engl J Med. 2023;389;514-26.



ANY QUESTIONS ?

