Metabolic Diseases: Update and Systemic Interventions

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Disclosures: Tracy Offerdahl, PharmD, FAAO

- **ALL relevant financial relationships have been mitigated**
  - Non-salaried affiliation agreement with NuSkin/Pharmanex

*Pending accreditor and third-party approvals.

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"Choose Your Parents Wisely"

Lifetime health
- **8% genetics**
  - ✶ DNA in our nucleus
  - Can't influence this by changing
- **92% epigenetics**
  - Lifestyle choices = we can influence
  - Turn on/off gene expression

Genes + Environment = GENE EXPRESSION

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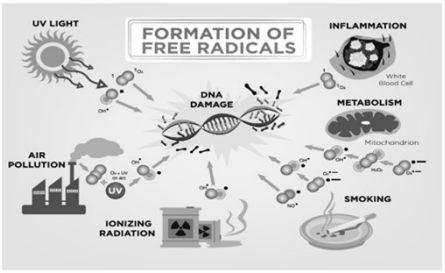
Endogenous and Exogenous Free Radical Formation



HIDDEN STRSSORS?!?

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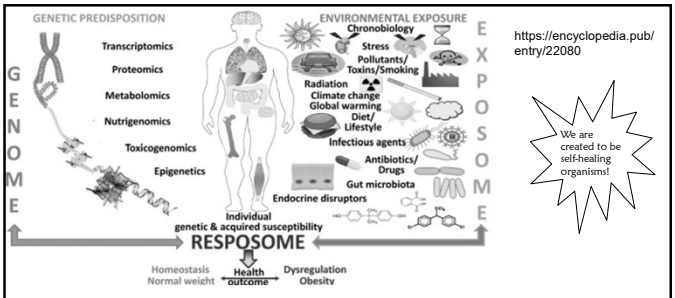

https://encyclopedia.pub/entry/22080

We are created to be self-healing organisms!

Above graphic shows how the genetic predisposition (**genome**) interacts with the environmental exposure (**"exposome"**) to influence an individual's genetic and acquired susceptibility shaping its responses (**resposome**) that yield the ultimate health outcome … **obesity** (in this case)

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Chronic inflammation is a long-term state of inflammation that can last for months or years. It's also known as a "slow burn" because it's a silent process that can have a significant impact on the body. Chronic inflammation is a hallmark of many chronic diseases and is linked to some leading causes of death in the United States

Some causes of chronic inflammation include:
- Lack of exercise
- Chronic stress
- Obesity
- Poor sleep
- Exposure to toxins
- Tobacco use
- An unhealthy gut microbiome

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Life Span versus Health Span

Today, slow death has surpassed fast death.

Most can expect to live to be their 80s, but suffer and die from chronic diseases and slow death

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Metabolic Disease

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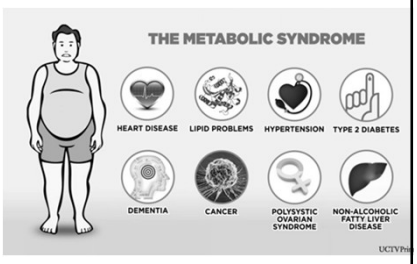
Metabolic Syndrome: The Cluster of Conditions

- **Elevated glucose**
  - **Insulin resistance**
  - ie >100 fasting or HbA1c >6.5
- **High blood pressure**
  - ie >120 systolic
- **Obese/overweight**
  - ie BMI >25
  - Abdominal obesity
- **Abnormal cholesterol/ratios, dyslipidemia**
  - High triglycerides ie > 150
  - Low HDL cholesterol ie <40
- **Proinflammatory and prothrombotic states**



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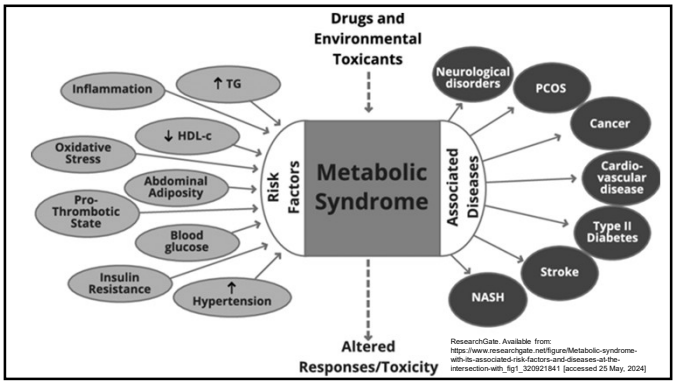

ResearchGate. Available from: https://www.researchgate.net/figure/Metabolic-syndrome-with-its-associated-risk-factors-and-diseases-at-the-intersection-with_fig1_320921841 [accessed 25 May, 2024]

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NORMAL isn't always OPTIMAL

- **Fasting insulin**: Standard range 2-25 µIU/mL (Optimal < 5µIU/mL
  - How hard your pancreas has to work to maintain normal blood sugar
  - One of the earliest signs of insulin resistance- present YEARS before high blood sugar
  - FIX: resistance training, 30+ grams protein/meal, ↓refined carbs. Improve sleep, berberine?
- **Homocysteine**: Standard range < 15µmol/L (Optimal < 8 µmol/L)
  - Impaired methylation + CV and neurological risk
  - Abnormal levels = independent risk factor for heart disease, stroke, and dementia
  - May indicate B-vitamin deficiency or MTHFR (methylenetetrahydrofolate reductase) gene variants
  - FIX: methylated B vitamins, dark leafy greens, lentils, reduce alcohol

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NORMAL isn't always OPTIMAL

- **HbA1c**: Standard range <5.7% (Optimal 4.8-5.2%)
  - 5.5-5.6% is "normal", but predicts diabetes YEARS in advance, along with fasting insulin
- **hsCRP**: < 3 mg/L (Optimal < 1 mg/L)
  - Systemic inflammation – marker of chronic disease; if high, this drives CVD, metabolic syndrome, neurodegeneration, and cancer
- **Vitamin D (25-OH)**: Standard range 30-100ng/mL (Optimal 50-80 ng/mL)
  - Critical for immunity, bone, metabolism; 30-35 is "normal", but it is associated with worse outcomes across nearly every disease category studied!
- **Omega-3 Index**: Standard range: not routinely tested (Optimal ≥ 8%)

  Most Americans are at 3-5% - low levels associated with higher rates of heart disease, inflammation, depression, cognitive decline

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Diabetes Mellitus Pathophysiology Reminder

- Type 1 DM
  - Pancreatic beta cells are destroyed = subsequent severe or absolute lack of insulin
- Type 2 DM
  - insulin resistance in tissue
  - AKA a decrease in insulin sensitivity

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Basic Mechanisms

- **Type 2 Patients** = primary dysfunction is hyperinsulinemia = insulin resistance
  - **Insulin and insulin-secreting meds** = hypoglycemia and weight gain
  - NEED MEDS that "re-teach" the body how to use the endogenous insulin that is already in the bloodstream!
  - All mechanism are NOT created equal!

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Biguanide

Metformin (Glucophage)

- Initial Drug of Choice / Cornerstone of Therapy
- Stimulation of glucose uptake in peripheral tissues
  - Decreases insulin resistance = improves insulin sensitivity

- Weight neutral/SMALL amount of weight loss
- B12 deficiency
- Maybe other vitamin deficiencies?
  - Vitamin D
  - Other than GI, it is well-tolerated and VERY BENEFICIAL

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Are you familiar with the Incretin System?

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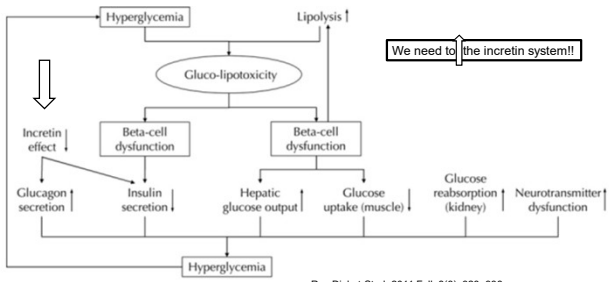
Pathogenesis of hyperglycemia and Type 2 Diabetes



Rev Diabet Stud. 2011 Fall; 8(3): 323–338.
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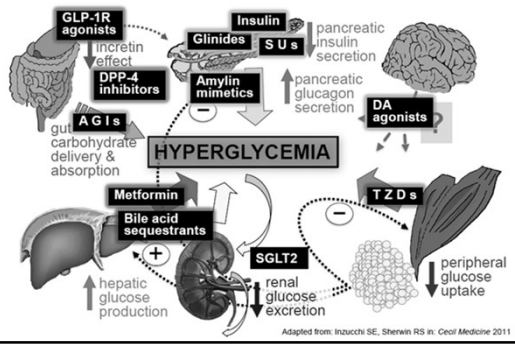

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Incretin mimetics (glucagon like peptide 1(GLP-1Agonists)

Liraglutide injection (Victoza)

Semaglutide (Ozempic) - SQ

Wegovy *brand name = weight loss – SQ*

Rybelsus *– T2DM – PO*

Wegovy Pill *– weight loss - PO*

Tirzepatide (Mounjaro/Zepbound)-S

Orforglipron (Foundayo) PO

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The Basics…

- **GLP-1 drugs** = foundation (diabetes + weight loss)
- **Dual agonists (like tirzepatide)** = more powerful metabolic effects
- **Triple agonists (like retatrutide)** = likely future standard

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GLP-1RA Use in the United States

As of 2024, 6% of U.S. adults are actively taking GLP-1RAs, with semaglutide use estimated in 15 million individuals.

- 12% of U.S. adults have used GLP-1RAs at some point
- Among users, 7% use these medications for chronic diseases and 5% for weight loss alone
- In Q4 of 2022, 9 million prescriptions for GLP-1RAs were filled highlighting their growing role (15 million in 2024) in chronic disease and weight management
- There is no published randomized controlled trial or evidence exhibiting higher rates of ophthalmic complications amongst the different GLP-1RAs

AMERICAN OPTOMETRIC ASSOCIATION 2 AOA.ORG | JUNE 2025

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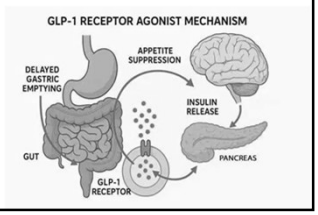
Mechanism of Action

- **Stimulate the GLP-1 receptor** –
  - enhances **glucose-dependent insulin secretion** by the pancreatic beta-cell (in response to high blood glucose levels)
  - suppresses secretion of glucagon after meals
  - **slows gastric emptying**
  - **appetite suppression and weight loss**



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Tirzepatide (Mounjaro, Zepbound)

- known as a **'twincretin',** is a 'first-in-class' and the only **dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptor agonist**

MOA:

- inactivated by dipeptidyl peptidase-4 **(DPP-4)**
- stimulate insulin secretion after an oral glucose load via the incretin effect
- pharmacological levels of GLP-1 can **revive insulin excretion**
- delayed gastric emptying
- **decrease pancreatic β-cell apoptosis** while promoting their proliferation
- **increased glucose uptake in the muscles**
- **decreased glucose production in the liver**

—**GIP** - **helps release insulin**, particularly after eating

- **enhances the effects of GLP-1**
  - **improving the overall therapeutic efficacy** of the drug

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Benefits

GLP-1 single, dual, and triple receptor agonists for treating type 2 diabetes and obesity: a narrative review

eClinicalMedicine
Part of THE LANCET Discovery Science

- ↓ systolic and diastolic blood pressure
- ↓ total cholesterol
- **improve** left ventricular ejection fraction, myocardial contractility, coronary blood flow, cardiac output, and endothelial function while reducing infarction size and overall risks for a cardiovascular events
- **Neuroprotection**
- **increased** satiety due to direct actions on the hypothalamus
- **lower** all-cause mortality and a hemoglobin A1c reduction of about 1% compared to control groups in patients with T2DM
- **reduce** new-onset in severe albuminuria
- ↓ non-alcoholic fatty liver disease (NAFLD) NOW called metabolic dysfunction-associated steatotic liver disease **(MASLD)**

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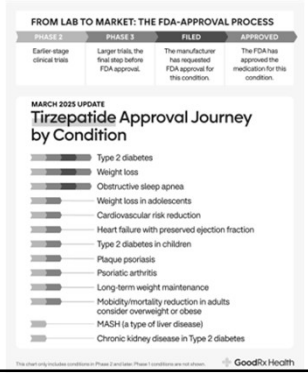

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Who might BENEFIT?

- **T2DM and obesity**
- **Obese adult patients**
  - **BMI ≥30**
  - Those who have tried to lose weight with appropriate lifestyle changes (exercise, eating, cognitive behavioral therapy), but who have been unsuccessful
    - have not lost at least 5% of body weight in 3-6 months
  - **BMI ≥27** who have obesity-related co- or multi-morbidities
    - **Cardiac**
      - ASCVD
      - Hypertension
      - dyslipidemia (eg. elevated triglycerides)
    - **GI**
      - GERD
    - **Functional/orthopedic**
      - Non-ambulatory
      - ambulatory with difficulty
    - **Cancer**

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Considerations & Limitations

- **Patient Suitability:** Comprehensive weight management plan is key for all patients
  - In many patients, the use of the injectable medications will be a **lifelong commitment**
    - With d/c of medications and without significant changes in behaviors, **most/all will gain the weight back** (+ additional weight in many cases)
  - Consideration: evidence supports **the longevity of the meds** are "effective" for up to 2 weeks in patients
    - Instead of weekly, might some continue to be successful if used every two weeks?
      - Time will tell
  - Importance of **Medical Supervision**
    - Necessary when patients use any weight loss medications
    - **Efficacy AND toxicity**

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Adverse Reactions

- **Nausea and vomiting**
  - WORSE with semaglutide (Ozempic, Wegovy) as compared to tirzepatide (Mounjaro, Zepbound)
  - GERD
- **Depression and suicidal ideation**
  - Important to screen and monitor
- **PREGNANCY**

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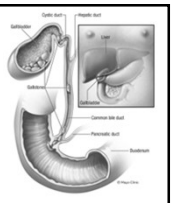
Adverse Reactions



- **Gallbladder** inflammation or stones
  - Handful of cases reported to FDA over 15 years
  - Risk seems to be higher over time
  - Severe, colicky pain – red flag
  - History of gallbladder disease (even if they had it removed) – biliary issues are still possible (stones)
- **Contraindicated in patients** with a personal or family history of medullary thyroid cancer or patients with multiple endocrine neoplasia type 2
- They can cause thyroid C-cell tumors in mice

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Adverse Reactions

Loss of skeletal muscle

- "Ozempic face"
- "Ozempic butt"

RECOMMEND:

- PROTEIN (1gm/lb)
- CREATINE (5-15 gm/day)
- Collagen Peptides
- BCAAs

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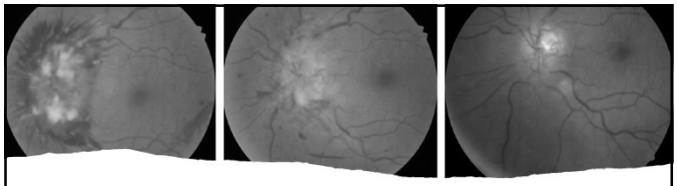

Adverse Reactions

- **Semaglutide AND tirzepatide**
  - **Worsening of diabetic retinopathy**?!
    - First seen and evaluated in 2018
  - AND… **nonarteritic anterior ischemic optic neuropathy**?!?
    - JAMA Ophthalmology (July, 2024) with T2DM or obesity – 4-fold increase in risk of NAION
      - Watch in history of NAION, low vision, monocular vision

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Diabetic Retinopathy – not surprising!

- We have seen **worsening of DR** in patients with T1D and T2D AND in patients undergoing weight loss surgery ("gastric bypass")
- **Drug therapy**: DR is seen in patients receiving insulin, sulfonylureas, thiazolidinediones, and now in the GLP-1 RAs

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MOA: association with RAPID IMPROVEMENT of hyperglycemia (& probably the severity of pre-existing diabetes-related retinopathy at baseline)

Hypoglycemia = the cells of central retina are not able to meet their metabolic demands due to decreased supply of glucose as well as decreased production of endogenous glucose by glycolytic pathways

Khan MI, Barlow RB, Weinstock RS. Acute hypoglycemia decreases central retinal function in the human eye. Vision Res. 2011 Jul 15;51(14):1623-6.

Reasonable scientific explanation: semaglutide causes faster HbA1c reduction compared to placebo =worsening of DR in the first **16 weeks**

Risk Factors:
- Diabetes
- Poorly controlled diabetes
- "disc at risk"

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Diabetic Retinopathy – not surprising!

- EVEN WITH THE POTENTIAL for initial progression of retinopathy, intensive improvement in glycemic control **reduces the risk for ONSET and PROGRESSION of DR over time**
- Patients with new onset T2D should have a **comprehensive eye exam**
  - Continue annually (or whatever you think is necessary)
  - Consider **retinopathy status** at time of initiation of treatment
    - **Follow guidelines** for monitoring patients with established retinopathy

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Clinical Report:

Glucagon-like Peptide-1 Receptor Agonists (GLP-1RAs) and Ocular Health: Guidance for Optometric Practice

American Optometric Association Evidence-based Optometry Committee

Diabetic Retinopathy (DR) Risks and GLP-1RAs

The **SUSTAIN-6 trial** found an increased rate of DR complications in patients using semaglutide (3.0%) vs placebo (1.8%). Events included:
- Vitreous hemorrhage
- Necessity for retinal laser or intravitreal therapy
- Vision loss

This was likely due to the rapid HbA1c reduction, a known contributor to early worsening of retinopathy. Patients with preexisting DR were especially vulnerable. Rapid glycemic improvement may transiently worsen DR, as noted in the United Kingdom Prospective Diabetes Study (UKPDS).

Emerging Risk: Neovascular AMD

A population-based study of 139,002 patients found:
- Risk of developing neovascular AMD was 0.2% in GLP-1RA users vs 0.1% in non-users
- The relative risk was more than 2x higher for those taking GLP-1RAs
- This accounts for a twofold increased risk of neovascular AMD among GLP-1RA users. Although the absolute risk is low, it warrants surveillance.

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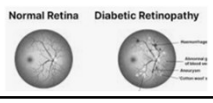
- **FOCUS trial (How Semaglutide Compared to Placebo Affects Diabetic Eye Disease in People With Type 2 Diabetes)**
  - seeks to further investigate the long-term effects of semaglutide on DR in patients with T2DM diabetes
  - measures the presence of early treatment diabetic retinopathy level progression in 1500 patients with an A1c between 7% and 10%
  - 1 mg of semaglutide or placebo subcutaneously every week
  - time frame of the trial is 5 years and is estimated to be completed in early 2027



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Emerging Ocular Risk:

Non-arteritic Anterior Ischemic Optic Neuropathy (NAION)

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common cause of acute optic neuropathy in individuals over 50 years of age. It results from ischemia due to impaired perfusion of the optic nerve head, primarily via the short posterior ciliary arteries. The resultant swelling in the confined space of the optic nerve canal leads to axonal compression and apoptosis of retinal ganglion cells. Optic nerve head drusen can also crowd the disc and should also be considered a risk in patients under 50 years of age.

Risk factors for NAION include:

- Diabetes mellitus
- Hypertension
- Hyperlipidemia
- Obstructive sleep apnea
- Small cup-to-disc ratio aka a "disc at risk" is the strongest risk factor for NAION

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Evidence Linking GLP-1RAs to NAION

A recent observational study titled "Risk of Non-arteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide" found an association between semaglutide, which is the most prescribed GLP-1RA, and NAION.

On June 6, 2025, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) concluded that NAION is a very rare side effect of semaglutide (up to 1 in 10,000 patients). Large epidemiological studies estimate that semaglutide use is associated with a two-fold increased risk of NAION, corresponding to just one additional case per 10,000 person-years.

The EMA has recommended updating semaglutide's product information to include NAION as a very rare side effect. Patients should be advised to report sudden or worsening vision changes, and semaglutide should be discontinued if NAION is confirmed.

EMA recommendations:

- List NAION as a "very rare" side effect
- Seek immediate care for sudden or worsening vision loss
- Discontinue semaglutide (or other GLP-1RAs) if NAION is confirmed

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Good direction…

- Until we get level 1 evidence from FOCUS trial
  - recommended for docs to screen patients for DR before initiating semaglutide
    - on the basis of the stage of retinopathy, eye physicians and retina specialists need to discuss the risk benefit ratio in initiating the treatment

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DPP4 Inhibitors (dipeptidyl-peptidase-4)

- **Sitagliptin (Januvia)** tablets
- **Sitagliiptin + metformin (Janumet)**
- **Saxagliptin (Onglyza) tablets**
- **Linagliptin (Tradjenta)** tablets
- **Mechanism of Action**
  - **I**nhibits the breakdown of glucagon-like peptide-1 (incretin)
  - ORAL agents
  - **THESE DO NOT CAUSE WEIGHT LOSS!!**

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Sulfonylureas

- **MOA: S**timulate release of insulin from functioning pancreatic beta cells
- **2nd Generation Agents (preferred):**
  - glyburide (DiaBeta, Micronase, Glynase)
  - **glipizide (Glucotrol, Glucotrol XL)**
  - **glimepiride (Amaryl)**

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Insulin Preparations

- Drug therapy of choice for all patients with type 1 DM and those with type 2 DM who cannot control their condition with diet, exercise, and 1st-line agents
  - Metformin
  - GLP-1 Agonists
  - DPP4 inhibitors
- **MOA: R**egulates glucose metabolism in the muscle and other tissues
- Semisynthetic "human" – identical amino acid composition to endogenous human insulin

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Sodium-Glucose Co-Transporter 2 SGLT2 Inhibitor

- **Canagliflozin (Invokana)**
- **Dapagliflozin (Farxiga)**
- **Empagliflozin (Jardiance)**

- **MOA**
  - Inhibition of the SGLT2
    - Reduced absorption of filtered glucose
    - Lowering of renal threshold for glucose
    - Increasing of urinary excretion of glucose

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Hypertension

- **Very common comorbid condition**
  - "compelling indication"
  - "JNC 8"
    - 8th Joint National Committee – prevention and treatment of hypertension
    - 2014

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Hyperlipidemia

- **LDL** – "bad cholesterol"
  - Drugs are usually the best choice
- **HDL** – "good cholesterol"
  - Protective
  - Exercise is the best treatment
- **Triglycerides**
  - Dietary changes and fish oil

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- **OTC AND Prescription Options**

- **Ethyl Ester:** DHA and EPA
  - It is ALL about the chemistry!
    - Ethyl-ester omega-3
    - Cheaper to make because it requires LESS purification to remove an alcohol side-chain
      - ALL RX products are this!
  - More likely to give "fishy" burps and aftertaste
  - We are learning that we might have to give a BIGGER dose of EE formulations to get the same "job" done as a lower dose of more PURE formulations or those that are the next BIOTRANSFORMATION step!

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Prescription and OTC Options Ethyl Ester Products

- Prescriptions options
  - Lovaza® (omega-3 ethyl esters) 4g/day
    - FDA-approved to lower triglyceride levels in hypertriglyceridemia
  - Vascepa ® (icosapent ethyl)- 4g/day
    - FDA-approved to lower trigylceride levels in hypertriglyceridemia
- Recommendations:
  - Typically given 1 capsule 3 – 4 times per day (with food)

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Fish oil is necessary for nutrients (carotenoids) to "do their job"!

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Additional Labs

ApoB: Standard range: < 130 mg/dL (Optimal < 80mg/dL)
You can have normal cholesterol and dangerous ApoB; More particles = more artery wall risk

Omega-3 Index: Standard range: not routinely tested (Optimal ≥ 8%)
Most americans are at 3-5% - low levels associated with higher rates of heart disease, inflammation, depression, cognitive decline

LP(a): Normal: < 75nmol/L**; Moderate:** 75-124 nmol/L**; High:** ≥ 125 nmol/L
increases risk of EARLY heart attack or stroke
90% INHERITED
NOT generally impacted by lifestyle, diet, exercise

Cardiac Calcium score: CT scan that measures calcified plaque in arteries
0: no identifiable plaque, very low risk
1-99: mild plaque build up
1**00-399**: moderate plaque burden, increased heart disease risk
400+: extensive plaque, high risk of significant CAD

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Functional Interventions

Immune System Support
Gut Microbiome Support

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But what if "healthy eating" ISN'T ENOUGH?!?

*** And how do we KNOW if it "isn't enough"?!?**

TERRAIN doesn't lie…

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Comprehensive Antioxidant Support

- **Cell membrane support**
- **Immune support**
- **Support the oxidative stress to the extracellular matrix**
- **Support to cell signaling**

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From Behavior-Changing Devices to Addiction-Interrupting Technology

- Behavior Disruption Devices
- Behavior Reset Technologies
- Physiologic Feedback Devices
- Metabolic Awareness Devices





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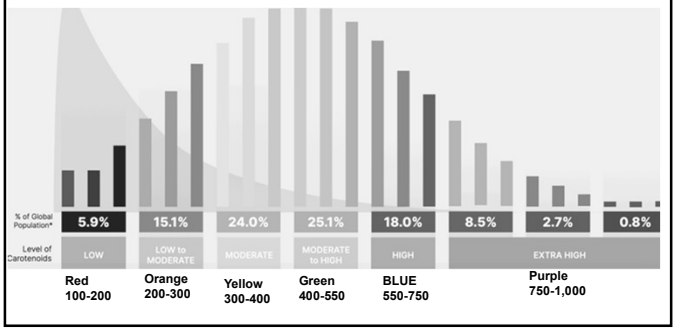

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Thank you!
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