Overmedicated and Undernourished: A Recipe for Immune Disaster - Drug-Induced Immune Dysfunction

presented by :

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Disclosures

- Nothing to Disclose

Objectives

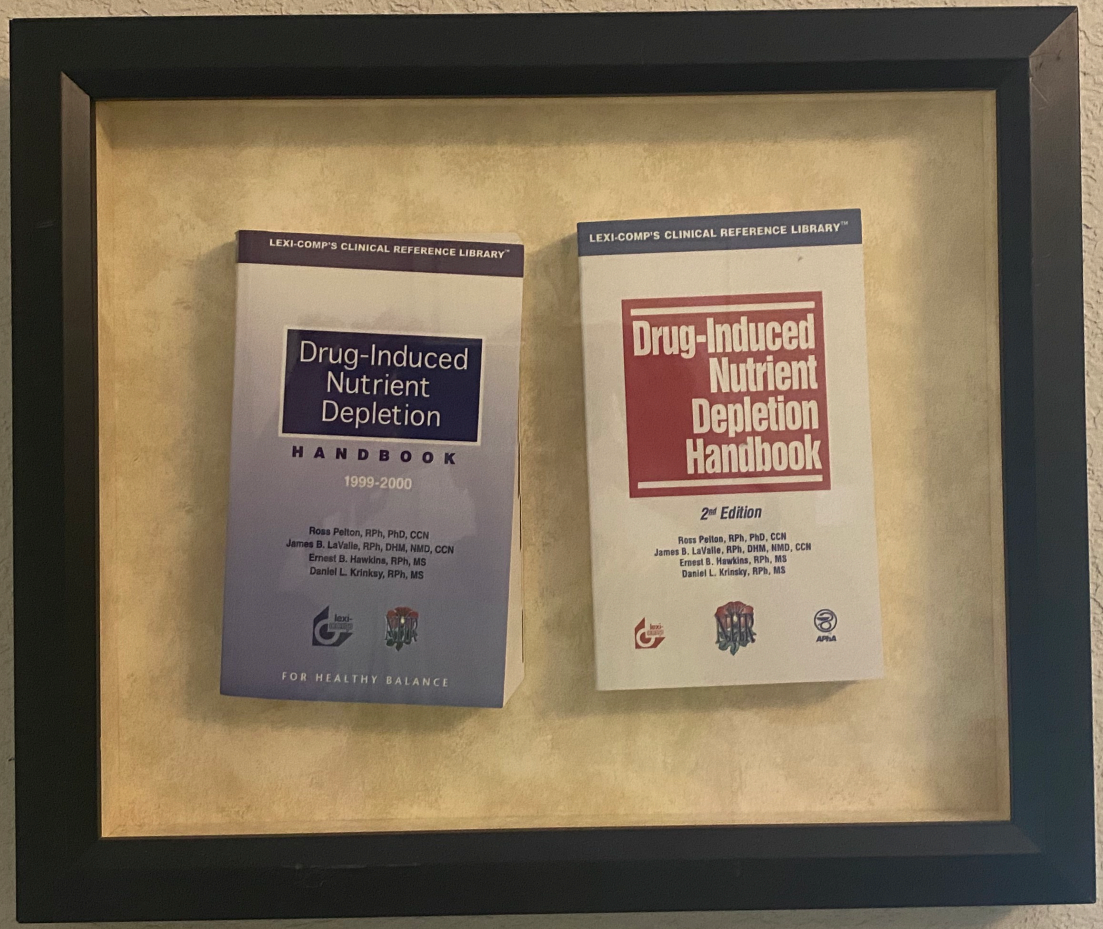
Pharmacists:

- Discuss how polypharmacy contributes to immune challenges
- Understand how the Standard American Diet is not fulfilling dietary needs to support a healthy immune system.
- Explore the micronutrient inadequacies leading to immune dysfunction

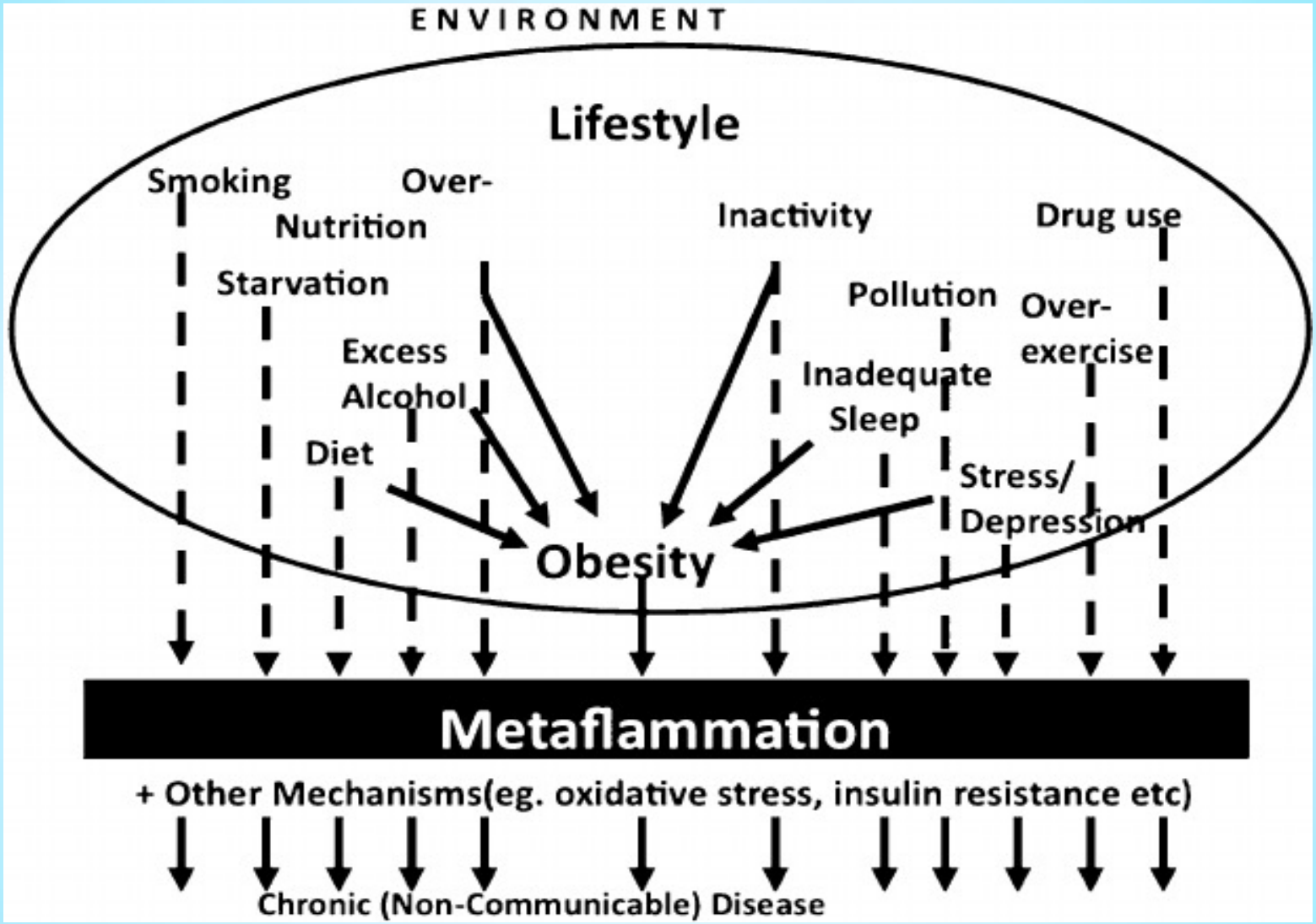
Technicians:

- Review the negative impact of the Standard American Diet on the immune system.
- Discuss micronutrient depletions that impair immune function.

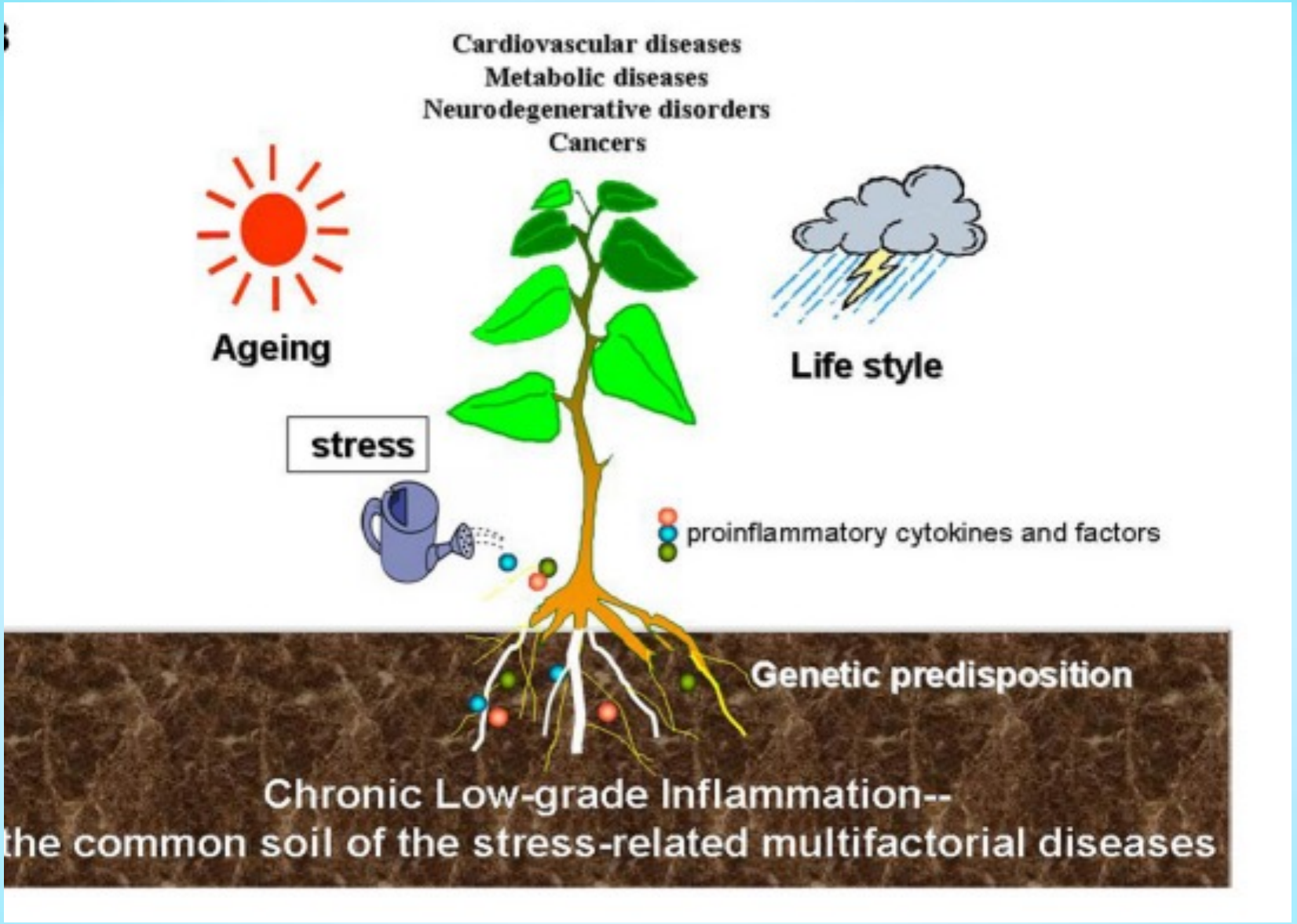
It all started here:



Metaflammation Constructs

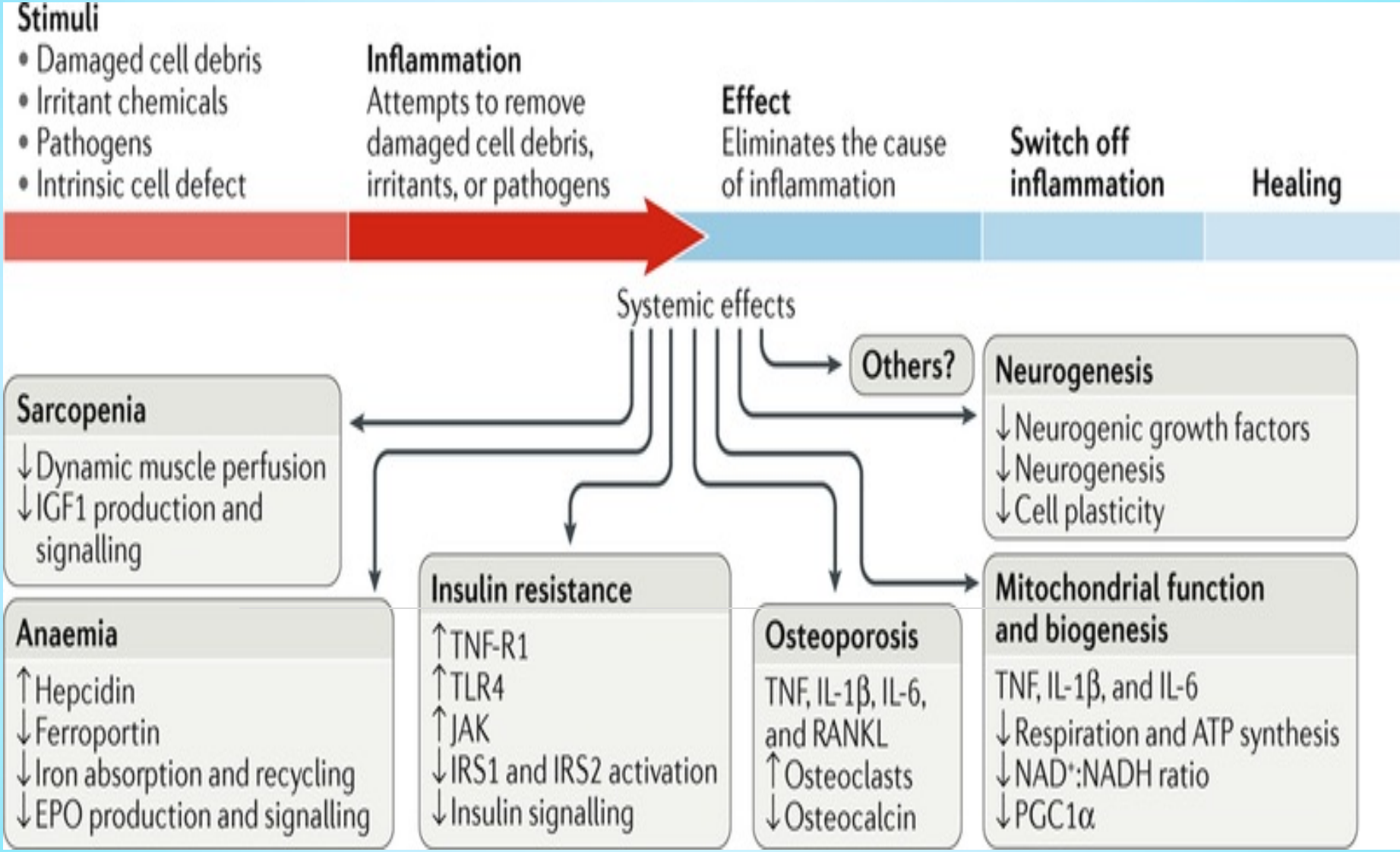


Egger G, et al. Obesity Reviews. 2008;10(2):237-49.



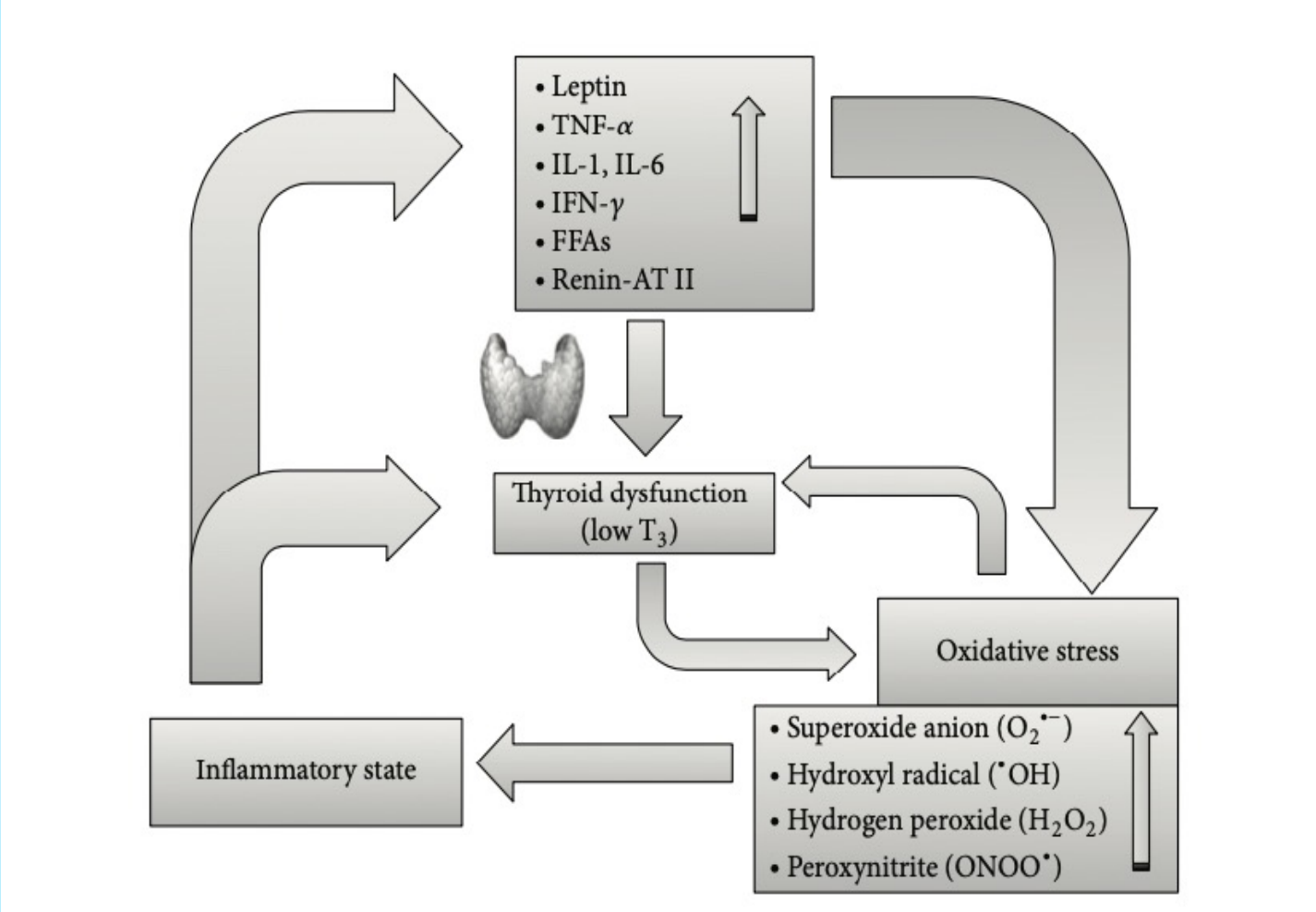
Liu YZ, et al. Inflammation: the common pathway of stress-related diseases. Front Human Neurosci. 2017;2017:00316.

Metaflammation Induces Catabolic State



Ferruci L, et al. Inflammageing: chronic inflammation in ageing, cardiovascular disease and frailty. Nat Rev Cardiol. 2018;15(9):505-22.

Oxidative Stress, Metaflammation and Thyroid Dysfunction



Mancini A, et al. Thyroid hormones, oxidative stress and metaflammation. Mediator Inflamm. 2016: 6757154.

Mitochondria and Metaflammation

- Increased pro-inflammatory mediators alter mitochondrial

function

- Increases mitochondrial oxidative stress = dysfunction
- Uncontrolled generation of ROS overwhelms cellular antioxidant protection of mitochondria
- Vicious cycle of inflammation
- Increased aging

Lopez-Armada MJ, et al. Mitochondrial dysfunction and the inflammatory response. Mitochondrion. 2013;13(2):106-118.

Mitochondrial Dysfunction

- Mitochondrial dysfunction activates the redox-sensitive factor NF-κB pathway

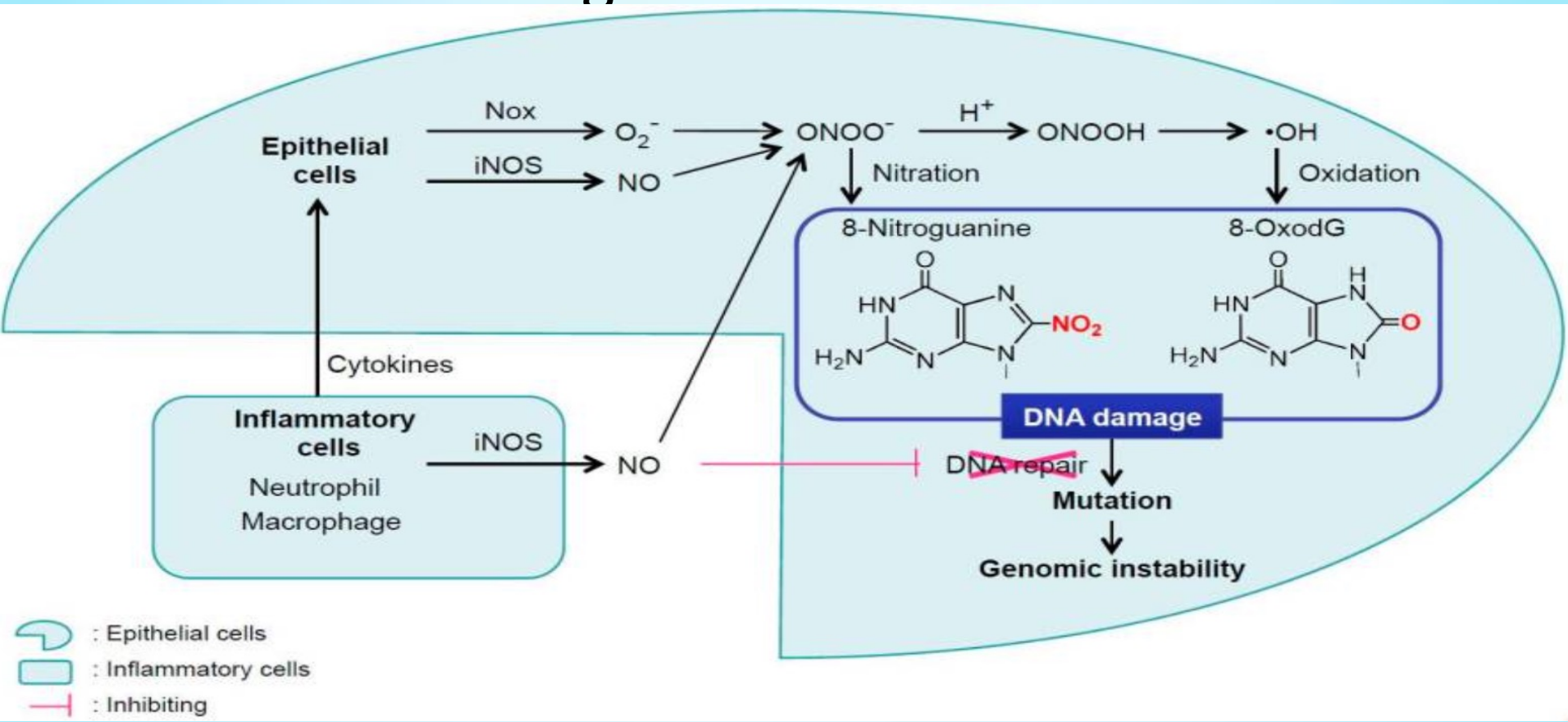
- Induces NLRP3 inflammasome activation

- NLRP3 inflammasome/NF-kB pathways work together to activate inflammatory cytokines

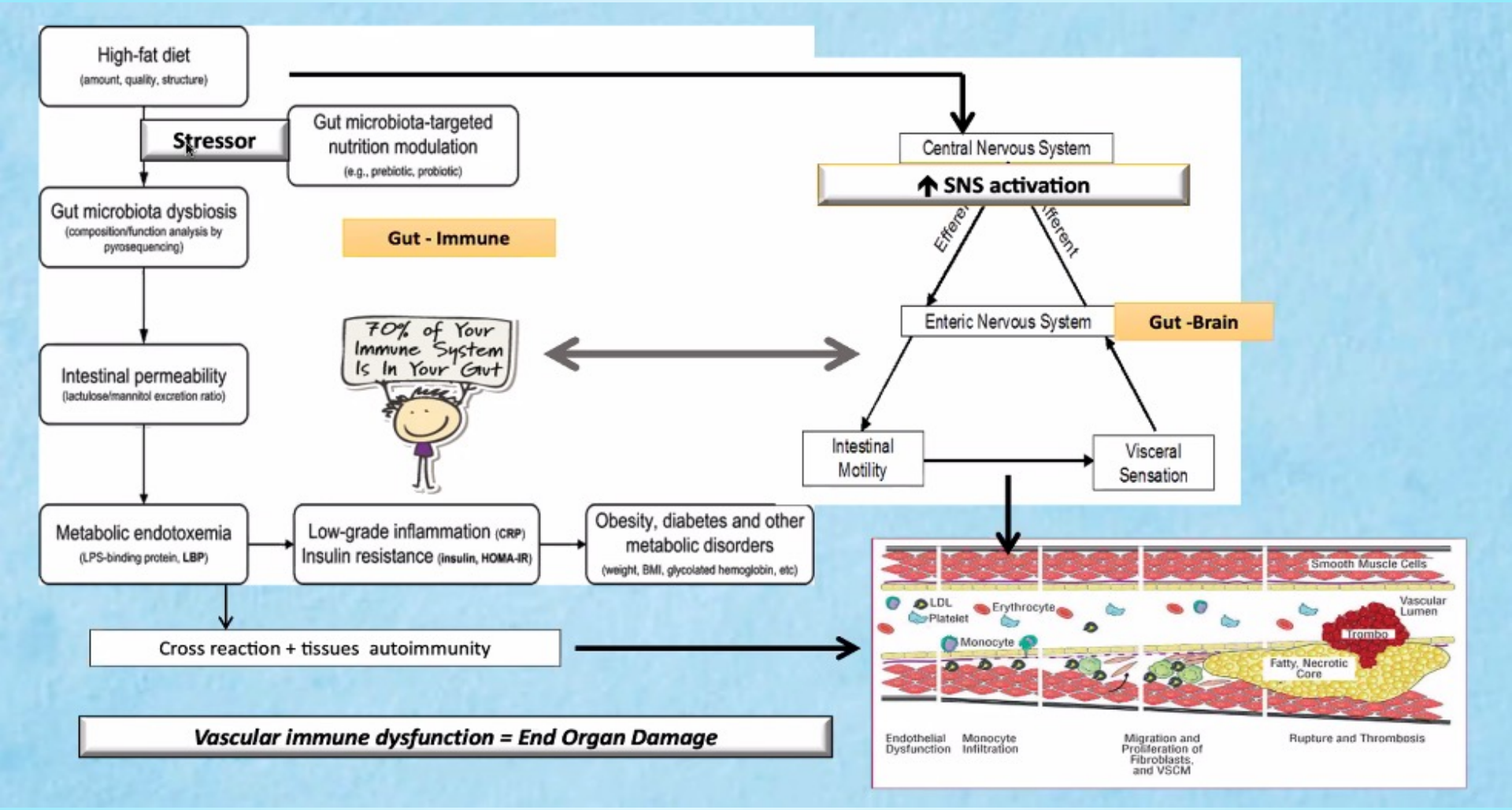
- Inflammatory mediators induce mitochondrial dysfunction.

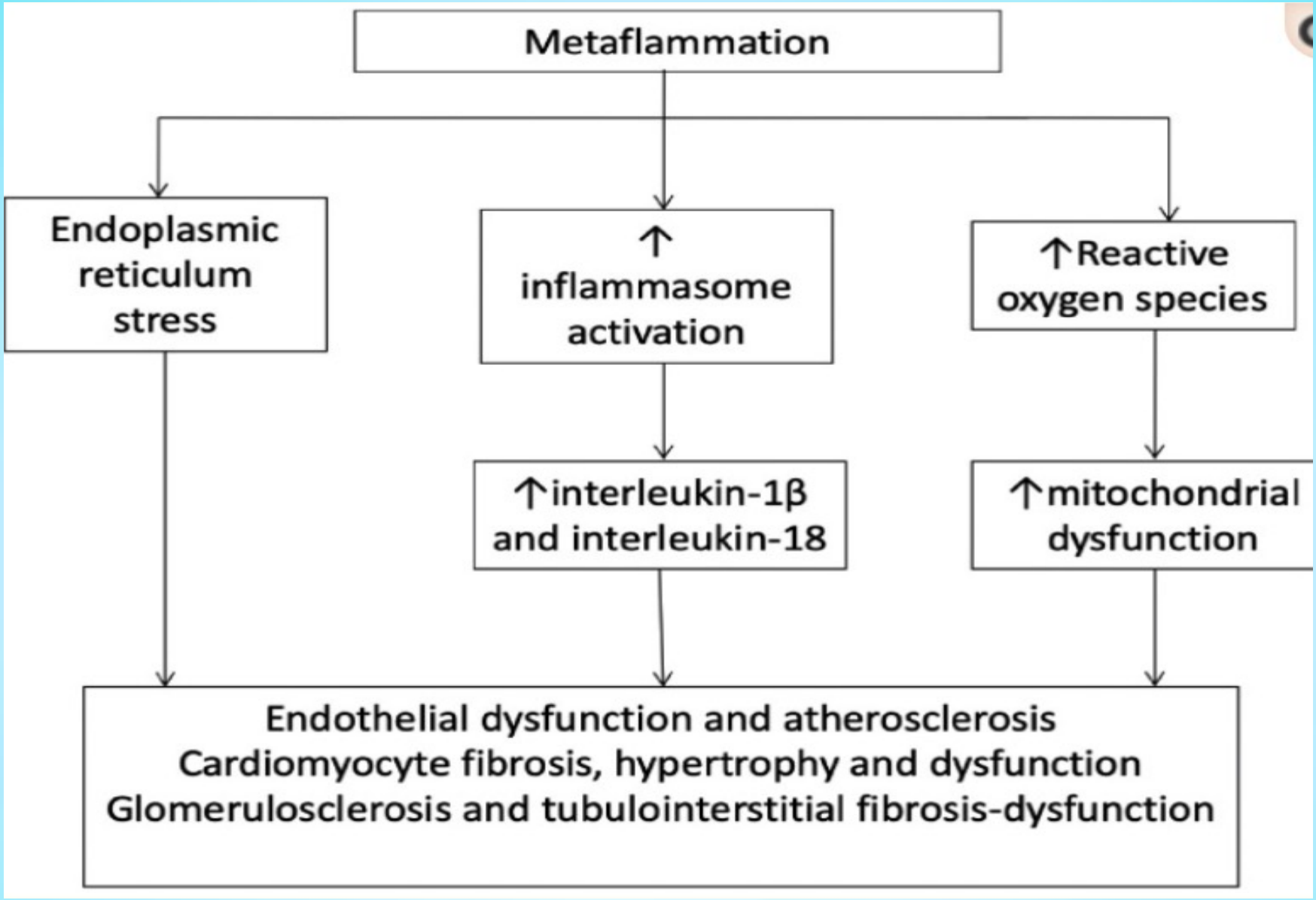
Lopez-Armada MJ, et al. Mitochondrial dysfunction and the inflammatory response. Mitochondrion. 2013;13(2):106-118.

DNA Damage and Metaflammation



Why does *polypharmacy* escalate?





Kanbay M, et al. A journey from microenvironment to macroenvironment: the role of metaflammation and epigenetic changes in cardiorenal disease. Clin Kidney J. 2019;12(6):861-70.

Write down these numbers

- How many people come into your practice that are on:
- Statins
- H2 Blockers and PPI's
- Diabetes Med's
- Metformin
- Blood Pressure medication including Diuretics
- Anxiety and Sleep disturbances

Drug-Induced Nutrient Depletions

- Drugs can inhibit nutrient absorption, synthesis, transport, storage, metabolism, or excretion
- Health problems are multi-factorial & complex
- Tremendous opportunity to improve health outcomes and reduce risk of polypharmacy and adverse events.

Susceptibility to Drug Induced Nutrient Depletions a mixture of:

- Lifelong dietary habits
- Individual Stress Levels
- Presence or absence of lifestyle factors like exercise and smoking
- Environmental exposures
- Genetic predisposition

A “RARE” EXAMPLE: JOE

35 year
old “Joe”

- ✓ Elevated lipids and triglycerides
- ✓ 40 pounds overweight (visceral fat)
- ✓ Blood pressure 135/95
- ✓ Blood Glucose 106
- ✓ GFR 65
- ✓ GERD
- ✓ Poor dietary & Exercise habits
- ✓ Smoker
- ✓ Stressful job, doesn’t sleep well
- ✓ Prides himself on being a Beer Conasueir

Metaflammation and Obesity

- Altered homeostasis of nutritionally overloaded cells in obesity
- Elevated expression of pro-inflammatory cytokines from M1 macrophages in white adipose tissue – TNFalpha, IL-6, CRP, IL-1b etc…
- Decrease in anti-inflammatory cytokines from M2 macrophages – IL-10, IL-Ra, adiponectin, etc..
- Macrophage-like Kupffer cells increase pro-inflammatory cytokines
  - In response to transducer signals produced by white adipose
  - Leads to necroinflammation
  - “Cycle” of inflammation leading to tissue and cell death

Debnath M, et al. Obesity induced metaflammation: pathophysiology and mitigation. J Cytokine Biol. 2016;1:1.

Metaflammation and Obesity

- Adipose tissue over-expression of chemoattractant CCL2 leads to macrophage infiltration, IR and hepatosteatosis
- Adipocytes under stress activate mTOR pathway
- Downregulation of AMP-activated protein kinase (AMPK) and SIRT pathways
- Muscle fibers suffer from decreased glycogen synthesis
- HPA axis dysregulation
- Insulin signaling issues

- Debnath M, et al. Obesity induced metaflammation: pathophysiology and mitigation. J Cytokine Biol. 2016;1:1.
- Li et. . Suppression of the mTORC1/STAT3/Notch1 pathway by activated AMPK prevents hepatic insulin resistance induced by excess amino acids. Am. J. Physiol. Endocrinol. Metab. 2014;306:E197–E209. (2014)

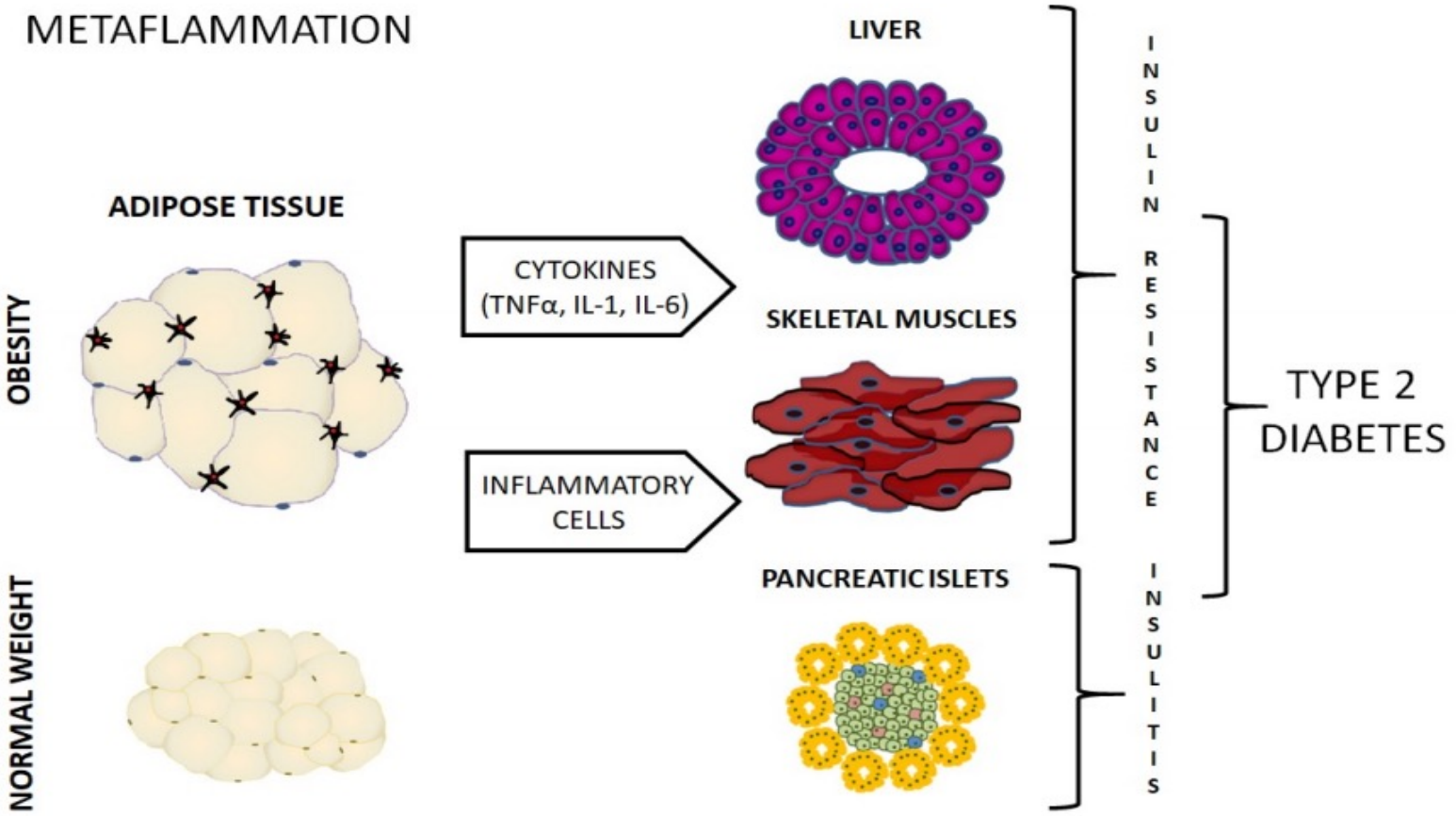


Figure 1. A schematic presentation of the concept of metaflammation.

Metaflammation and Chronic Heart Disease

- Increased CRP directly interferes with NO formation by increasing endothelin-1
  - Increased endothelial dysfunction
  - Increased atherogenesis

- TNF and IL-1β downregulate Ca^{+2}-related gene expression, including sarcoplasmic reticulum Ca^{+2} ATPase and Ca^{+2} release channels

- Impairs the efficiency of gap junction mechanisms

- Leads to dysregulated electrical conduction and unsynchronized contraction

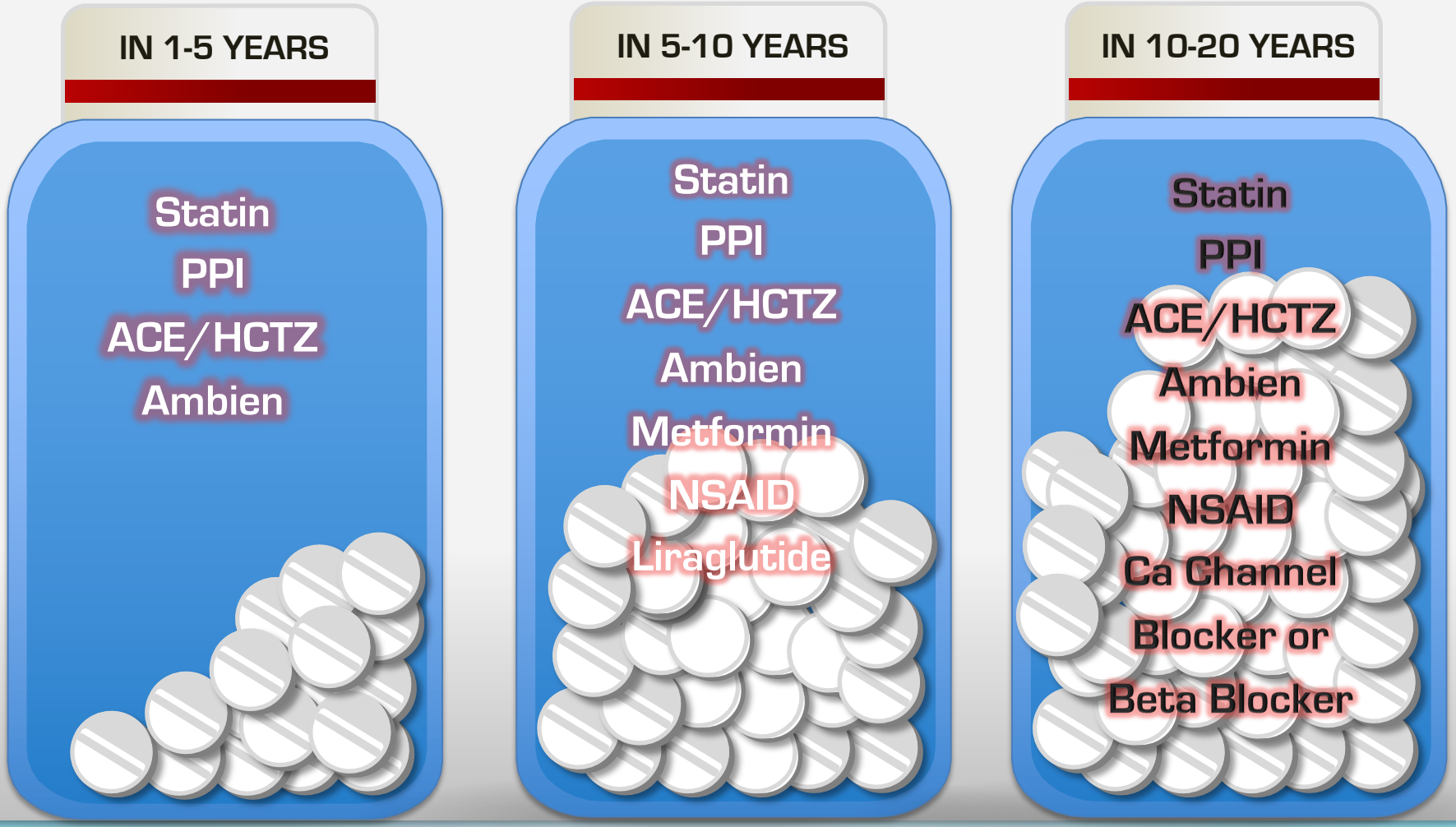
Kanbay M, et al. A journey from microenvironment to macroenvironment: the role of metaflammation

Metaflammation and Chronic Heart Disease

- Negative inotropic effect on myocytes,
- Eccentric cardiomyocyte hypertrophy, myocardial fibrosis, ventricular dilation and ultimate CHF
- CKD-driven Klotho deficiency also contributes to cardiomyopathy
- GUT microbiota alterations also links metaflammation and CHD/CKD

Kanbay M, et al. A journey from microenvironment to macroenvironment: the role of metaflammation and epigenetic changes in cardiorenal disease. Clin Kidney J. 2019;12(6):861-70.

WHERE IS JOE HEADED?



National Cholesterol Education Program Diagnostic Criteria - Combination of 3 or more of the following:

Elevated waist circumference:

Men — Equal to or greater than 40 inches (102 cm)

Women — Equal to or greater than 35 inches (88 cm)

Elevated triglycerides:

Equal to or greater than 150 mg/dL

Reduced HDL (“good”) cholesterol:

Men — Less than 40 mg/dL

Women — Less than 50 mg/dL

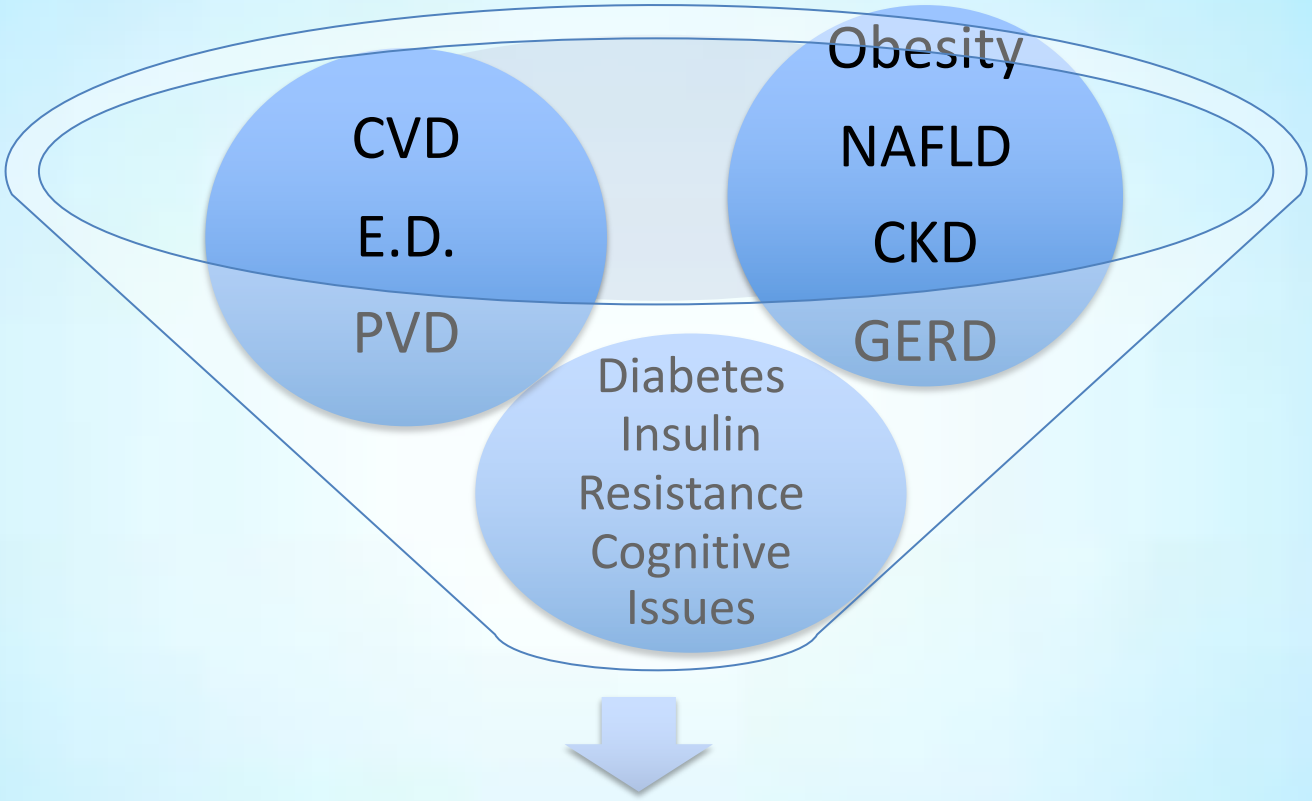
Elevated blood pressure:

Equal to or greater than 130/85 mm Hg

Elevated fasting glucose:

Equal to or greater than 100 mg/dL

Metabolic Syndrome and it's Complications



Obesity and Cancer Deaths

- Meta analysis of 203 studies, n= 6.3 million participants
- Results Obesity (BMI > 30) associated with:
  - increased overall and cancer-specific mortality in patients with obesity and breast, colorectal, or uterine cancers.
  - Cancer mortality was increased in breast, colorectal, prostate, and pancreatic cancers.
  - Relapse rate was increased in breast, colorectal, prostate and gastroesophageal cancers.
  - However, some studies reported that patients w/ obesity had better survival than those without in renal cell carcinoma, lung cancer and melanoma – *** this data was only from 12 of the studies**

*next page

Petrelli F, et al. Association of obesity with survival outcomes in

Obesity and Cancer Deaths

- Authors admit the study had several limitations
  - They combined data for patients with obesity and compared their prognosis with patients with different weights (ie, normal weight or normal weight and overweight)
  - Accurate measures of self-reported weight and height are always a challenge in observational studies

Petrelli F, et al. Association of obesity with survival outcomes in patients with cancer. JAMA Netw Open. 2021;4(3):e213520.

Obesity and Diabetes

- Obesity is a major risk factor for T2D
- Both obesity and diabetes are important independent risk factors for the development of cardiovascular disease
- Women with a BMI of 30 kg/m^2 have a 28 x greater risk of developing diabetes than do women of normal weight
  - The risk of diabetes is 93 x greater if the BMI is 35 kg/m^2

- Petrelli F, et al. Association of obesity with survival outcomes in patients with cancer. JAMA Netw Open. 2021;4(3):e213520.

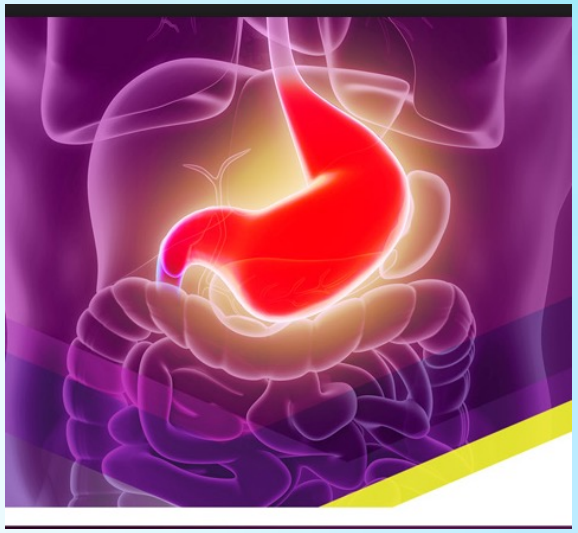
Glucose Regulation and Alzheimer's

- Being overweight and having Type 2 diabetes can increase the risk of developing Alzheimer's disease
- Insulin Receptors 80% lower in Alzheimer pt vs normal
- Insulin and IGF 1 lose ability to bind to receptors
- Acetylcholine deficiency is directly linked to loss of insulin and IGF-1 in the brain
- Evidence Growing That Alzheimer's is **Type 3 Diabetes**
- **Lab studies report APOE4 variant associated with IR**

De la Monte SM, et al. Alzheimer's disease is type 3 diabetes-evidence reviewed. J Diab Sci Technol. 2008;2(6):1101-1113.
Zhao N, et al. Apolipoprotein E4 impairs neuronal insulin signaling by trapping

Drug Induced Microbioime Disruption (DIMD)

- Prescription and non-prescription drugs can alter the microbiome
- Potentially disrupting metabolic pathways
- DIMD can lead to metaflammation if not corrected
- Affects all facets of metabolism
  - Nutrient absorption
  - GUT-IMMUNE-BRAIN axis
    - GUT dysbiosis, leaky GUT
    - Impairs immunity
    - Neuroinflammation
  - Blood glucose balance/insulin resistance
  - Hormonal balance – sex / thyroid / appetite
  - Sleep

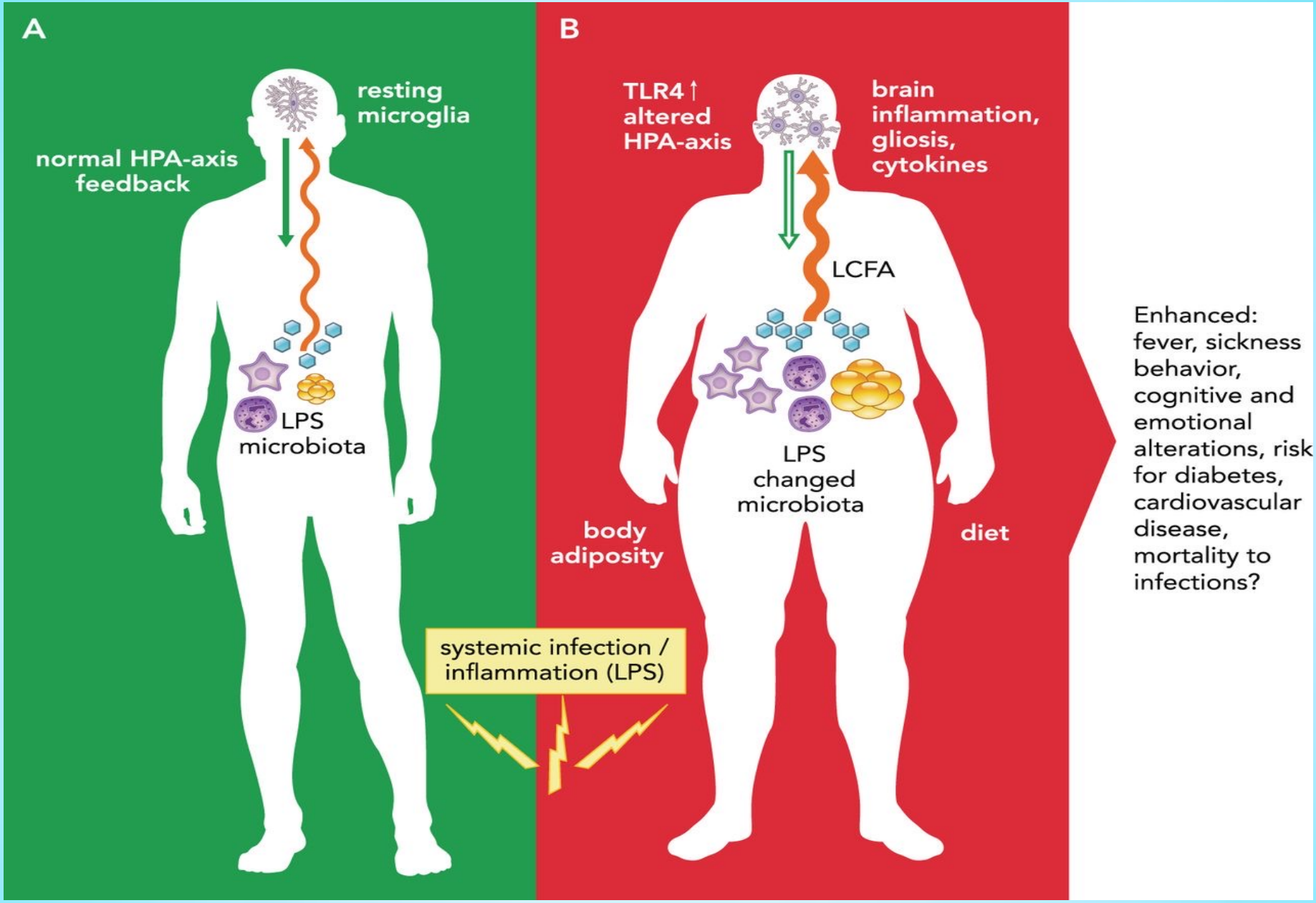


Bastard QL, et al. Systematic review: human gut dysbiosis induced by

What Drugs Commonly Affect the Microbiome

- Antibiotics
- NSAIDs
- Corticosteroids
- OCs/HRT
- PPIs / H2 blockers
- Metformin
- Statins
- Antisychotics
- Opioids
- OTHERS not studied??

Bastard QL, et al. Systematic review: human gut dysbiosis induced by non-antibiotic prescription medications. Aliment Pharmacol Ther. 2018;47(3):332-45.



Rummel C, et al. Obesity impacts fever and sickness behavior during acute systemic

The Drugs: Nutrient Depletions that Impact Metabolic Signaling

- DIND = Drug Induced Nutrient Depletion
- Often overlooked mechanisms of drugs that lead to nutrient depletions
- Has great impact on short- and long-term side effect profiles of drugs
- Understanding these potential DINDs and making supplement recommendations can improve metabolic signaling and decrease side effect profiles of drugs

Cholesterol Lowering Drugs

HMG-CoA Reductase Inhibitors "statins	CoQ10, Vitamin D, total testosterone Vitamin E, Omega-3, Carnitine, Zinc, Selenium, Copper, K2, DHEA
The "fibrates"	CoQ10, Vit D, E, DHEA
Bile Acid Sequest.	Co10, A, D, E, K, B12, Ca, Mg, Phosphorus Zn, Fe, Folic Acid, beta-carotene

Aberg, et al. "Gemfibrozil-induced decrease in serum ubiquinone and alpha- and gamma-tocopherol levels in men with combined hyperlipidemia," Eur J Clin Invest. 1998; 28: 235-42.

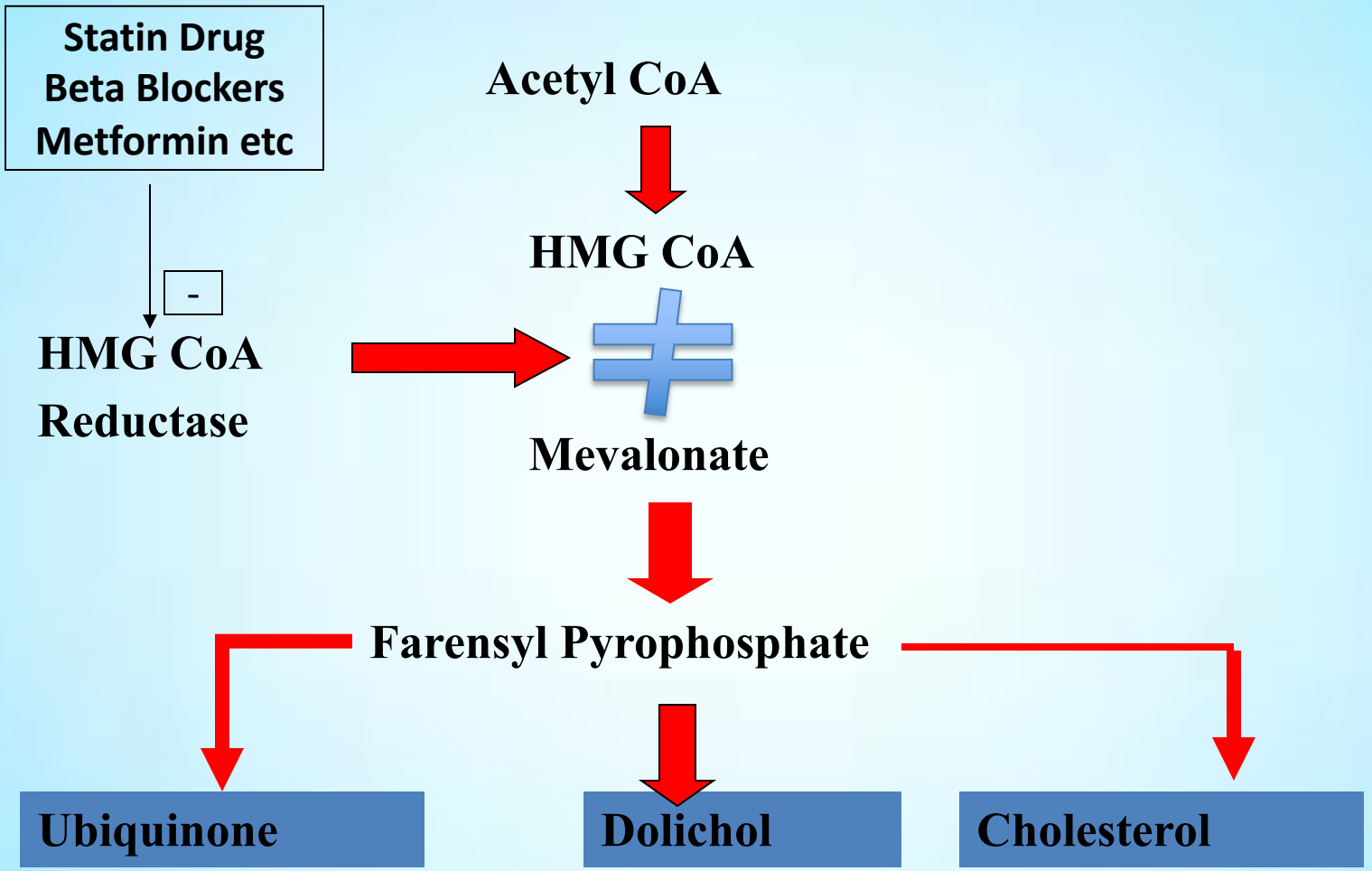
Hoppner & Lampi, "Bioavailability of folate following ingestion of cholestyramine in the rat," Int J Vitamin Nutr Res. 1991; 61: 130-4.

Mortensen SA, Leth A, Agner E, Rhode M. Dose-related decrease of serum coenzyme Q10 during treatment with MG-CoA reductase inhibitors. Mol Aspects Med 1997; 18(suppl):S137-44.

Associated Research

- Qu H, et al. The effect of statin treatment on circulating coenzyme Q10 concentrations: an updated meta-analysis of randomized controlled trials. Eur J Med Res. 2018;23:57.
- Bargossi AM, Grossi G, Fiorella PL, et al. Exogenous CoQ10 supplementation prevents plaxma ubiquinone reduction induced by HMG-CoA reductase inhibitors. Mol Aspects Med 1994;15(suppl):s187-93.
- Langsjoen PH, Langsjoen, AM. The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications. Biofactors 2003;18 (1-4); 101-11.
- Garnett WR. Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors. Am J Health Syst Pharm 1995; 52:1639-45.
- Mabuchi H, Higashikata T, Kawashiri M, et al. Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients. J Atheroscler Thromb. 2005;12(2):111-119. (PubMed)
- Hargreaves IP, Duncan AJ, Heales SJ, Land JM. The effect of HMG-CoA reductase inhibitors on coenzyme Q10: possible biochemical/clinical implications. Drug Saf. 2005;28(8):659-676. (PubMed)

HMG CoA Synthesis Pathways



Study - Statins May Lower Testosterone

- Study on 3484 men with ED
- Avg age 51 followed 7 years 2002-09
- 244 (7%)atorvastatin or simvastatin
- Total Testosterone, Free Fraction and unbound in serum
- Men on statins 2X as likely to have low testosterone

Corona G, et al. The effect of statin therapy on testosterone levels in subjects consulting for erectile dysfunction. J Sexual Med. 2010;7(4 pt1):1547-56.

Study - Statins May Lower Testosterone

- 2013 meta-analysis of placebo-controlled randomized trials of statins to test hypothesis that statins lower testosterone
- 11 studies eligible
- In 5 homogenous trials of 501 men, mainly middle aged with hypercholesterolemia, statins lowered testosterone by -0.66 nmol/l
- In 6 heterogeneous trials of 368 young women with polycystic ovary syndrome, statins lowered testosterone by -0.40 nmol/l
- Overall statins lowered testosterone by -0.44 nmol/L
- **CONCLUSION: Statins may partially operate by lowering testosterone**

Corona G, et al. The effect of statin therapy on testosterone levels in subjects consulting for erectile dysfunction. J Sexual Med.

Low Testosterone Linked:

- Immune issues
- Obesity
- Metabolic Syndrome
- Insulin resistance
- Diabetes
- CVD
- Poor performance – loss of strength

Ji H, et al. Review of health risks of low testosterone and testosterone administration. World J Clin Cases. 2015;3(4):338-44.

Low Testosterone Immune Dysfunction

- "Low testosterone predisposes men to a less effective immune response against infectious agents"
- 2020 study, n=31 male SARS-CoV-2 patients w/ pneumonia
- A steep increase in ICU transfer and mortality occurred in men with low TT and FT
- Male hypogonadism may be a trigger for cytokine dysfunction and poor COVID-19 prognosis

Rastrelli G, et al. Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients. Andrology. 2020;9(1):88-98.

Low Testosterone Linked to Early Death from Heart Disease and All Cause

- Important study
- 930 Men all with CVD
- Tracked 7 years
- 25% defined as hypogonadism low bio-T
- 2X higher death rate in men with low T
- Borderline low levels also denoted risk

Chris J Malkin, Peter J Pugh, Paul D Morris, Sonia Asif, T Hugh Jones, Kevin S Channer. **Low serum testosterone and increased mortality in men with coronary heart disease**. *Heart*, 2010; DOI: 10.1136/hrt.2010.195412

Ronald C W Ma, Peter C Y Tong. **Testosterone levels and cardiovascular disease**.

Low Testosterone and Sleep

- 1 Week of Short sleep (5hrs) = 10-15% drop in testosterone lowest levels 2-10 pm on restricted sleep days
- Self reported decline in mood corresponded to the dip in testosterone

R. Leproult, E. Van Cauter. **Effect of 1 Week of Sleep Restriction on Testosterone Levels in Young Healthy Men**. *JAMA: The Journal of the American Medical Association*, 2011; 305 (21): 2173 DOI:

- 2008 study, n= 1312 men aged 65 and >=, community-dwelling from 6 facilities in US
- Followed by 72 hr actigraphy and 1 night of in-home polysomnography
- RESULTS: Men with lower testosterone levels had lower sleep efficiency
  - Also Increased nocturnal awakenings
  - less time in slow-wave sleep
  - higher apnea-hypopnea index

Barrett-Connor E, et al. he Association of Testosterone Levels with Overall Sleep Quality, Sleep Architecture, and Sleep-Disordered Breathing. J Clin Endocrinol Metab. 2008;93(7):2602-09.

CoQ10 Statins

- Statins reported to deplete CoQ10
- Statins associated with mild-moderate statin-associated muscle symptoms (SAMS)
- <1% incidence in industry-funded research
- Independent studies - > 60% muscle symptoms present in those taking statins

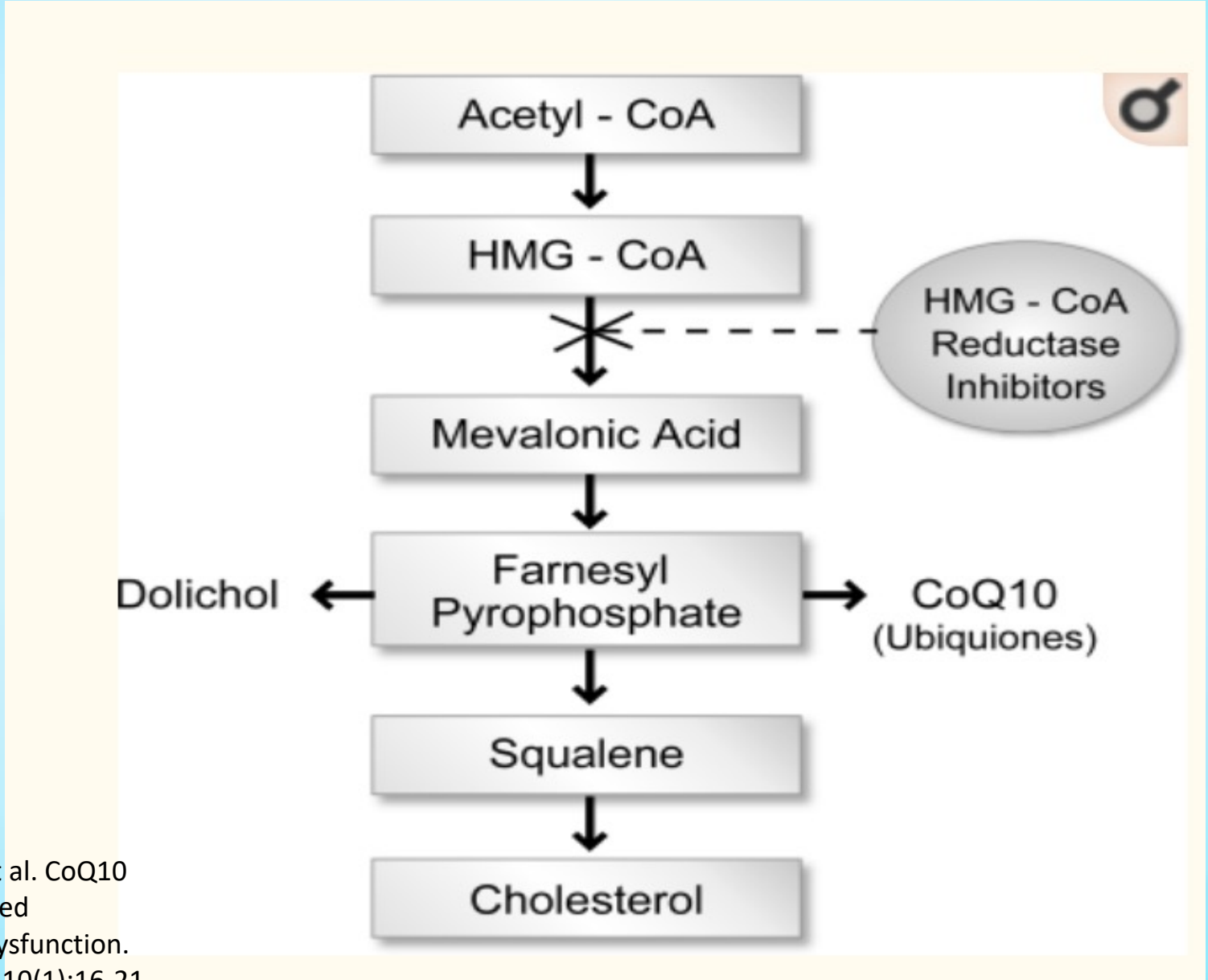
Cohen JD, et al. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol.* 2012;6(3):208–15

.

- Leads to a high rate of non-compliance

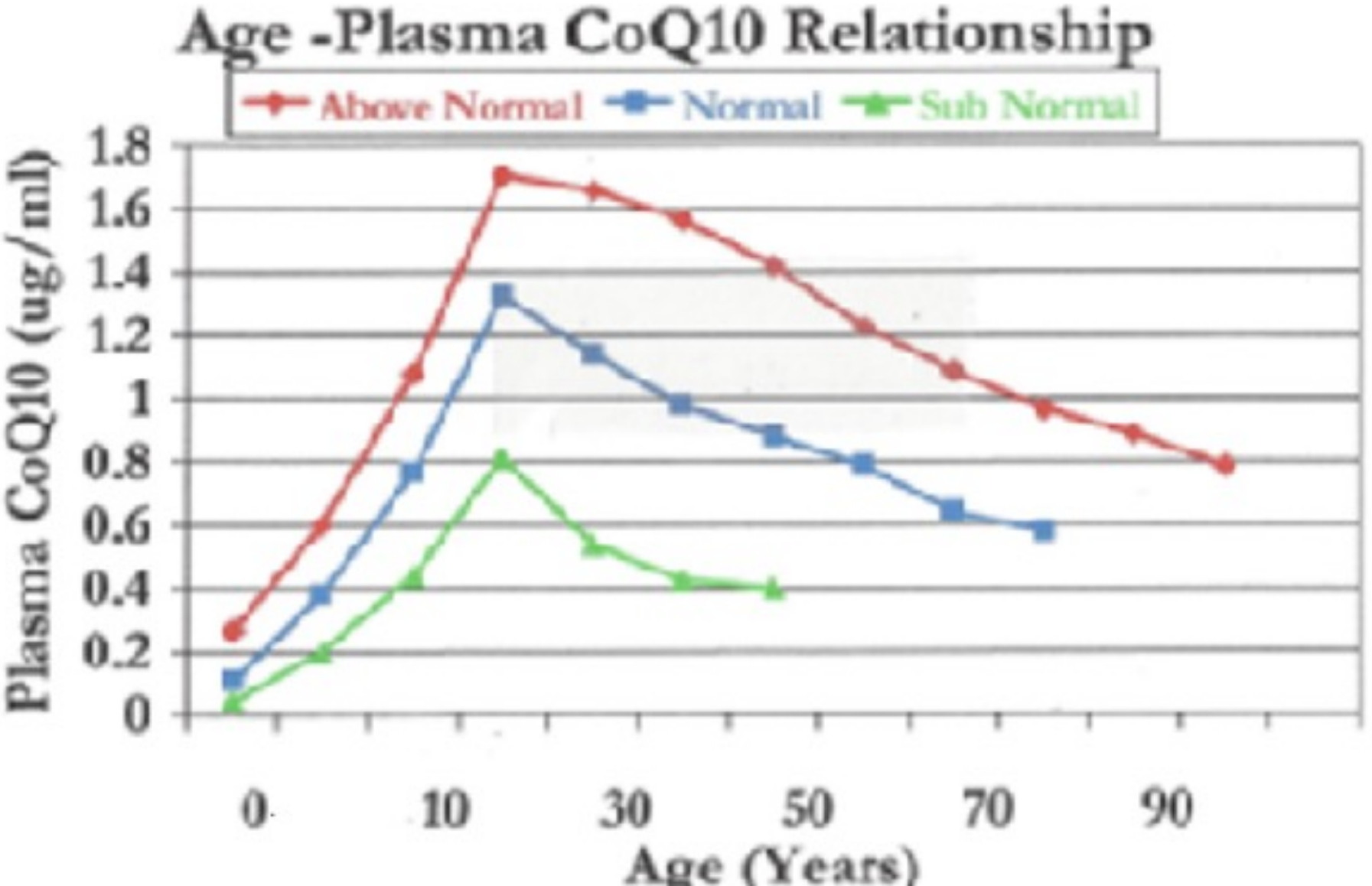
- Morrison JT, et al. Effect of rosuvastatin on plasma coenzyme Q10 in HIV-infected individuals on antiretroviral therapy. HIV Clin Trials. 2016;17(4):140-46.
- Qu H, et al. The effect of statin treatment on circulating coenzyme Q10 concentrations: an updated meta-analysis of randomized controlled trials. Eur J Med

Statin Effects on CoQ10 Synthesis In Vivo



Deichmann R, et al. CoQ10 and statin-induced mitochondrial dysfunction. Ochsner J. 2010;10(1):16-21

CoQ10 Declines with Age



CoQ10 Immunity

- An important feature of mitochondria is it can regulate activation, differentiation, and survival of immune cells
- In addition, it can also release signals such as mitochondrial DNA (mtDNA) and mitochondrial ROS (mtROS) to regulate transcription of immune cells
- CoQ10 very important in immune support

Angajala A, et al. Diverse Roles of Mitochondria in Immune Responses: Novel Insights Into Immuno-Metabolism. Front Immunol. 2018;9:1605.

CoQ10 Immunity

- CoQ10's: cellular energy supply via oxidative phosphorylation - affects immunity
- Immune responses intensive energy consumers
- Antioxidant support affects immunity
  - phagocytic cells destroy invading pathogens via the production of free radicals
  - the antioxidant activity of CoQ10 may protect phagocytic cells from self-destruction caused by generation of free radicals
- CoQ10 reported to have an anti-inflammatory role via its ability to repress inflammatory gene expression
- CoQ10 also been reported to play an important function within the lysosome - an organelle central to the immune response

Angajala A, et al. Diverse Roles of Mitochondria in Immune Responses: Novel Insights Into Immuno-Metabolism. Front Immunol. 2018;9:1605.

CoQ10 Immunity

- Several clinical studies have linked depleted CoQ10 levels to an increased susceptibility to infection
- Clinical studies report CoQ10 supplementation in athletes can improve immune function
- Prevention of excessive pro-inflammatory cytokine release

Simpson RJ, et al. Exercise and the regulation of immune functions. Prog. Mol. Biol. Transl. Sci. 2015;135:355–380.

Chase M, et al. Coenzyme Q10 in acute influenza. Influenza Other Respir. Viruses. 2019;13:64–70.

CoQ10 Immunity – SARS-CoV-2

- 2 Case control cohort studies – n=6202 and n=6919 (patients hospitalized w/ COVID-19 , ages 18-95)
- intake of CoQ10 is associated with a significantly reduced risk of hospitalization from SARS-Co
- RNA viruses such as SARS-CoV-2 are known to require cholesterol both to enter cells and for viral replication
- Authors of this study considered the possibility that supplemental CoQ10 prevents the virus from hijacking the mevalonate pathway to produce cholesterol

Israel A, et al. Large population study identifies drugs associated with reduced COVID-19 severity. *MedRxiv*. 2020 doi: 10.1101/2020.10.13.20211953.

CoQ10 as Mitochondrial Catalyst

- Co Q10 is an essential component to the Electron transport Chain (Complex I and II) in the mitochondria.
- Multiple categories of Drugs deplete CoQ10
- Mitochondrial deficiencies have been correlated to energy level, immune issues, cognitive issues, obesity, insulin resistance and T2D

CoQ10 Clinical Effects

CoQ_{10} administration in different conditions.

Zozina V, et al. CoQ10 in cardiovascular and metabolic diseases: current state of the problem. Curr Cardiol Rev. 2018;14(3):164-74.

Condition	Possible Effects	References
Hypertension	Scavenging of ROS Vasodilatation Angiotensin effect adjustment Aldosterone level reducing	[27-29]
T2DM	Protection against ROS Antioxidant Fatty acid oxidation enhancement	[130-132]
Metabolic syndrome	Protection against ROS Antioxidant Tissue-protective The increase in triglyceride-rich lipoproteins (VLDL)	[115, 133]
Overall role in cardiovascular disease	Antioxidant Protection against ROS Bioenergetic Anti-inflammatory	[14, 18, 19]

JAHA
Journal of the American Heart Association

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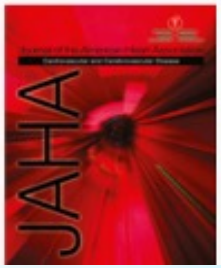
Effects of Coenzyme Q10 on Statin-Induced Myopathy: An Updated Meta-Analysis of Randomized Controlled Trials

Hua Qu, Ming Guo, Hua Chai, Wen-ting Wang, Zhu-ye Gao, and Da-zhuo Shi

Originally published 25 Sep 2018 | https://doi.org/10.1161/JAHA.118.009835 | Journal of the American Heart Association. 2018;7



- 2018 meta-analysis – J Am Heart Assoc.
- 12 randomized controlled trials; n=575
- Conclusion: CoQ10 supplementation ameliorated statin-associated muscle symptoms, implying that CoQ10 supplementation may be a complementary approach to manage statin-induced myopathy.

Qu H, et al. Effects of Coenzyme Q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials. JAHA. 2018;7(19):

2020 Study - Athletes CoQ10 Antioxidant Status

- N= 31 well trained college athletes
- Randomly assigned to CoQ10 300mg/day or placebo x 12 wks
- RESULTS: Higher WBC CoQ10 levels correlate with:
  - Significantly lower erythrocyte Malondialdehyde (MDA)
  - Better glycemic control
  - Lower HOMA-IR
  - Higher erythrocyte TAC (total antioxidant capacity) and QUICKI (quant. Insulin sensitivity check)
- CONCLUSION: Athletes have better antioxidant capacity when taking CoQ10

Ho C, et al. Ubiquinone Supplementation with 300 mg on Glycemic Control and Antioxidant Status in Athletes: A Randomized, Double-Blinded, Placebo-Controlled Trial. Antioxidants (Basel).

CoQ10 Diabetes

- Randomized controlled clinical trials have reported that supplementation with CoQ10 can significantly improve glycemic control, as well as improve vascular dysfunction
- Supplementation with CoQ10 may be of particular importance in type 2 diabetics prescribed antidiabetic meds (metformin/sulfonylureas), statins and in those with fatty liver disease
- The importance of product quality and bioavailability cannot be over-emphasized

Mantle D. Coenzyme Q10 supplementation for diabetes and its complications: an overview. Br J Diabetes. 2017;17(4):145-148.

Oxidative Burden in Prediabetic and Diabetic Patients and CoQ10

- 2015 study, n= 156 subjects
- Serum CoQ10 and vitamin E measured
- ROS determine by free oxygen radicals testing (FORT)
- Also tested: Glutaredoxin (Grx) activity, oxidized LDL cholesterol (oxLDLc), high sensitive CRP (hsCRP), HbA1c, urine albumin, serum creatinine, serum cystatin C, and plasma lipids
- **RESULTS:** Serum CoQ10 higher than in nondiabetics.
- HbA1c, fP-glucose, hyperlipidemia, inflammation (hsCRP), and increased BMI associated with signs of oxidative stress as increased levels of FORT, Grx activity and/or increased levels of oxLDLc
- Oxidative stress strongly correlated with prevalence of cardiovascular disease (CVD) and peripheral sensory neuropathy (PSN)

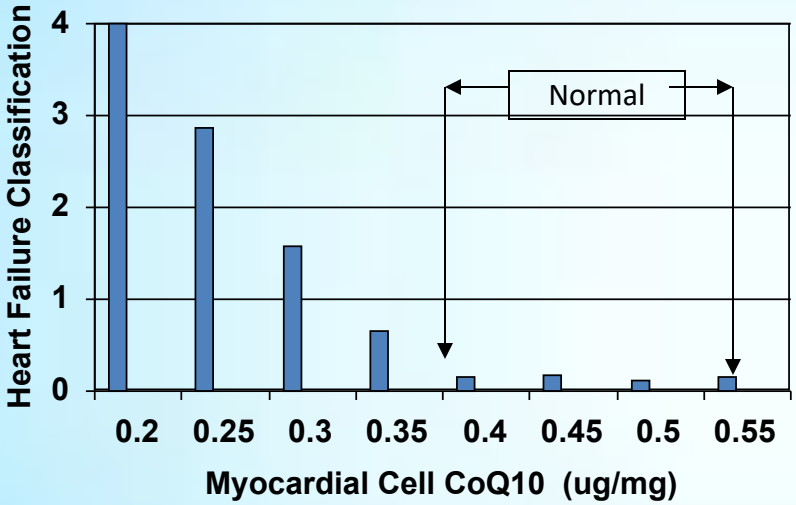
Forsberg E, et al. Coenzyme Q10 and oxidative stress, the association with peripheral sensory neuropathy and cardiovascular disease in type 2 diabetes mellitus. J Diabet Complications. 2015;29(8):1152-8.

Oxidative Burden in Prediabetic and Diabetic Patients and CoQ10

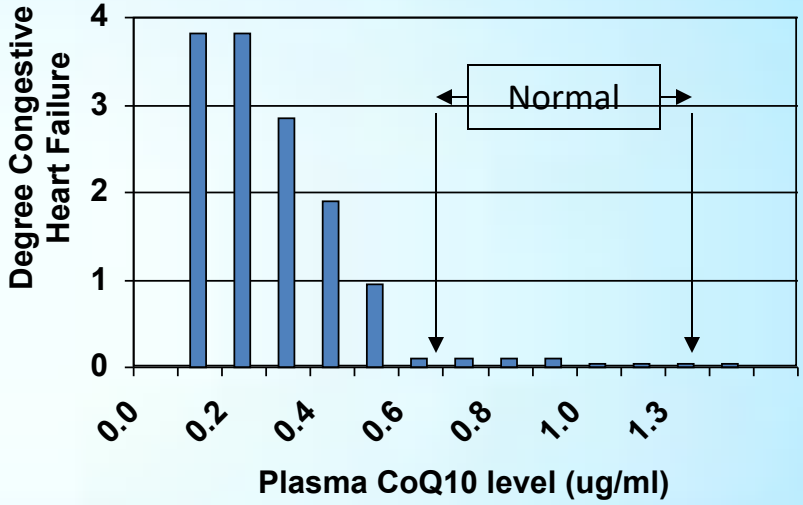
- In both gender groups there were positive correlations between CoQ10 and oxLDLc
- Also between BMI and the ratio CoQ10/chol.
- Grx activity was inversely correlated to oxLDLc and CoQ10
- Women with CVD and PSN had higher waist index, oxLDLc, and FORT levels compared to men but lower CoQ10 levels.
- Men had worse kidney function and lower vitamin E.
- Multiple regression analysis showed increased levels of CoQ10 to be significantly correlated with increased levels of cholesterol, triglycerides, vitamin E, fB-glucose and BMI.
- **Conclusions:** Hyperlipidemia, hyperglycemia and inflammation/metaflammation are associated with oxidative stress, which is correlated to the prevalence of diabetes complications
- CoQ10 levels are increased in response to oxidative stress
- There are gender differences in the risk factors associated with diabetes complications

Forsberg E, et al. Coenzyme Q10 and oxidative stress, the association with peripheral sensory neuropathy and cardiovascular disease in type 2 diabetes mellitus. J Diabet Complications

Plasma and Heart Cells CoQ10 Levels and Degree of Congestive Heart Failure



Mortensen 1983
Biomedical and Clin. Aspects of CqQ10
Vol 3 1983 Elsiver



Littarru and Folkers 1972
Biomedical and Clincial Asp. of CoQ10 Vol1
1980

CoQ10 Lab Testing

- CoQ10 Total Reference range (QUEST) 0.37-2.20 ug/ml
- CPT Code 82542
- Desired levels in trials is above 0.6 ug/ml in plasma
- Dosing for clinical condition + depletion will result in a 100-300 mg dosage range in most cases
- 100mg daily is generally sufficient for exogenous support

Anti-ulcer Drugs

H-2 Receptor Antagonists:	B12, folic acid, D, Ca ,Fe, Zn, protein
Proton Pump Inhibitors:	Ca, Vitamin D, B12, Fe, folic acid, vit C, Zn, magnesium, protein

Heidelbaugh JJ, Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. Ther Adv Drug Saf. 2013;4(3):125-133.

OLDER STUDIES

Odes HS, et al. "Effect of cimetidine on hepatic vitamin D metabolism in humans," 1990; 46(2): 61-4.

Sturniolo GC, et al. "Inhibition of gastric acid secretion reduces zinc absorption in man," J Am Coll Nutr. 1991; 10(4): 372-5.

Russell RM, et al. "Effect of antacid and H2 receptor antagonists on the intestinal absorption of folic acid," J Lab Clin Med. 1988; 112(4): 458-63.

Force & Nahata, "Effect of histamine H2-receptor antagonists on vitamin B12 absorption," Ann Pharmacother. 1992; 26: 1283-86.

Marcuard, et al. "Omeprazole therapy causes malabsorption of cyanocobalamin," Ann Int Med. 1994;

PPIs and Bone Loss

- Mechanisms:
  - Increased gastrin production
  - Induction of hypochlorhydria, PPIs may interfere with Ca absorption
  - Inhibition of osteoclastic vacuolar proton pumps - may reduce bone resorption
- 2019 Meta Review concluded: PPIs are positively associated with elevated fracture risk in multiple studies (*n* = 14)
- CONCLUSION: patients on long-term PPI treatment should pay attention to bone health status and consider prophylaxis to decrease fracture risk

Thong BKS, et al. Proton pump inhibitors and fracture risk: a review of current evidence and mechanisms involved. Int J Environ Res Public Health. 2019;16(9):1571/

PPI's and WHI

130,000 women in the WHI on current PPI's

- 47% more likely to have spine fracture
- 26% more likely for forearm fracture
- 25% more likely for any type fracture

Gray, S.L. *Archives of Internal Medicine*, May 10, 2010; vol 170: pp 765-771.

PPIs and Hip Fracture Risk

- 2018 meta-analysis - studies 1990 – 2018
- Only included large (n> 500) observational studies w follow up of at least 1 yr
- Total n = 2,103,800 (million) people
- Quantify the magnitude of association of PPIs to hip fx risk
- Bottom Line and Overall Results: Patients with PPIs have a greater risk of hip fracture than those without PPI therapy

Poly TN, et al. Proton pump inhibitors and risk of hip fracture: a meta-analysis of

PPIs Clostridium Infection

- 2017 meta analysis - Jan 1990 – March 2017
- 56 studies involving 356,683 patients
- RESULTS: direct association w/ PPI use and *Clostridium difficile* infection – CDI

Trifan A, et al. Proton pump inhibitors therapy and risk of Clostridium difficile infection: Systematic review and meta-analysis. World J Gastroenterol. 2017;23(35):6500-6515.

PPIs Dementia

- Two German prospective, cohort studies reported statistically significant increased risks of dementia in patients taking PPIs

Haenisch B, et al. Risk of dementia in elderly patietns with the use of proton pump inhibitors. Eur Arch Psychiatry Clin Neurosci. 2015;265(5):419-28.

- Risk in Asian population – 15,726 participants – PPI significantly increase risk of dementia

Tai SY, Chien CY, Wu DC, et al. Risk of dementia from proton pump inhibitor use in Asian population: a nationwide cohort study in Taiwan. PLoS One. 2017;12(2):e0171006.

- However, a 2019 systematic review and meta-analysis

Of 6 cohort studies

- RESULTS: meta-analysis suggests that there was no statistical association between PPIs use and increased risk of dementia or AD.

Li M, et al. Proton pump inhibitor use and risk of dementia. Medicine (Baltimore). 2019;98(7):e14422.

Vitamin D

- 42% US population low in vitamin D

  Forest KY, et al. Prevalence and correlated of vitamin D deficiency in US adults. Nutr Res. 2011;31(1):48-54.

- Levels > 30 ng/ml 25OHD associated with
  - Increased mucosal immunity
  - Decreed inflammation

- Low levels of vitamin D reported associated with increased risk of infectious processes:
  - Tuberculosis TB
  - Respiratory tract infections
  - Influenza
  - COPD exacerbations
  - Cystic fibrosis
  - Sepsis
  - HIV

Kearns MD, et al. The impact of vitamin D on infectious disease: a systematic review of controlled trials. Am J Med Sci. 2015;349(3):245-262.

Vitamin D Mortality

- Low levels also reported to increase risk in general population of: **all-cause** and **infection-related mortality** in general population

  Melamed ML, et all. Arch Int Med. 2008;168(15):1629-37.

- 15 year follow-up in a cohort of 9,548 adults aged 50–75 years from Germany
- Vitamin D insufficiency and deficiency were common (44% and 15%, respectively)
- Compared to those with sufficient vitamin D status, participants with vitamin D insufficiency and deficiency had strongly increased respiratory mortality
- Overall, 41% of respiratory disease mortality attributed to vitamin D insufficiency or deficiency

Brenner H, et al. Vitamin D Insufficiency and Deficiency and Mortality from Respiratory Diseases in a Cohort of Older Adults: Potential for Limiting the Death Toll during and beyond the COVID-19 Pandemic? Nutrients.

Vitamin D - IR

- Circulating Vitamin D inversely related to insulin resistance
- Vitamin D is protective of potential Type 2 diabetes risk
- Vitamin D gene expression may interact with insulin receptor conformation

Szymczak-Pajor I, et al. The Molecular Mechanisms by Which Vitamin D Prevents Insulin Resistance and Associated Disorders. Int J Mol Sci. 2020;21(18):644.

Vitamin D Respiratory Tract Infections

- 2013 meta-analysis and systematic review
- 25OHD levels and respiratory tract infections
- 11 randomized, double-blind placebo-controlled trials included n = 5,660 patients
- REULTS:
  - Vitamin D3 supplementation decreased risk of developing respiratory tract infections
  - Av. Dose studied was 1,600 IU daily

Bergman P, et al. Vitamin D and respiratory tract infections: a systematic review and meta analysis of randomized controlled trials. PLoS One. 2013;8(6):e65835.

D3 Range - Dosage

- 25-hydroxyvitamin D (D3)
- 2,000 – 10,000 IU (50- 250 mcg) daily
- D3 levels optimal 50-80ng/ml
- 30-50 trending low
- 1,300 people participating in the Longitudinal Aging Study Amsterdam. People with blood levels of vitamin D (serum 25-hydroxyvitamin D) lower than 50 ng/ml were likelier to have metabolic syndrome than those whose vitamin D levels exceeded 50 ENDO Society 92 annual meeting 2010 Annual Meeting

Blood Pressure Meds

Hydralazine:	B6, CoQ10
Loop:	Ca, Mg, K, Na, Zn, B1, B6, C, Zn
Thiazides:	Mg, K, Zn, CoQ10, P, Na
Potassium-sparing:	Ca, Zn, FA, Mg
Beta-blockers:	CoQ10, melatonin, testosterone
Clonidine/Methyldopa:	CoQ10
ACE/ARB:	Zn
Chlorthalidone:	Zn, Na, P, K

Golik, et al. "Effects of captopril and enalapril on zinc metabolism in hypertensive patients," J Am Coll Nutr. 1998; 17: 75-8.

Stoschitzky K, et al. "Influence of beta-blockers on melatonin release," Eur J Clin Pharmacol. 1999 Apr; 55(2): 111-15.

Golik A, Zaidenstein R, Dishi V, et al. Effects of captopril and enalpril on zinc metabolism in

hypertensive patients. J Am Coll Nutr. 1998; 17:75-80.

Paparrigopoulos T. Melatonin response to atenolol administration in depression: indication of beta-adrenoceptor dysfunction in a subtype of depression. Acta Psychiatr Scand. 2002 Dec; 106(6):440-5.

Bioenergetics in Clinical Medicine. III. Inhibition of Coenzyme Q10-enzymes by Clinically used Anti-hypertensive Drugs

- Propranolol: ↓ CoQ10-succinoxidase and CoQ10-NADH-oxidase
- Metoprolol, HCTZ, hydralazine and clonidine inhibit CoQ10-NADH-oxidase
- Methyldopa: weak succinoxidase inhibit

Kishi H, et al. Research Communication Chemical Pathology Pharmacol. 1975 Nov; 12(3): 533-40.

Sarter B. Coenzyme Q10 and cardiovascular disease: a review. J Cardiovasc Nurs. 2002 Jul;16(4):9-20

Lanoxin (digoxin)

- Calcium, magnesium, phosphorus via increased urinary excretion

- Magnesium deficiencies increase likelihood of cardiac dysrhythmias and atrial fibrillation

Crippa, et al. "Magnesium and cardiovascular drugs: interactions and therapeutic role," Ann Ital Med Int. 1999; 14: 40-45.

Kupfer S, et al. "Effects of cardiac glycosides on renal tubular transport of calcium, magnesium, inorganic phosphate and glucose in the dog," J Clin Investig. 1965; 44: 1143.

Magnesium and Loop Diuretics

- Loop diuretics increase Mg excretion and inhibit passive Mg absorption

- Loss of intracellular Mg++

Quamme GA, "Renal magnesium handling: new insights in understanding old problems." Kidney Int. 1997; 52(5): 1180-95.

Compare side effects of Thiazide Diuretics and Mg Depletion

Magnesium Depletion

- Muscle cramps and spasms, including vasospasm
- Migraines
- Anxiety, nervousness, and insomnia
- Low energy/fatigue
- Increased BP
- Arrhythmia and heart palpitations
- Depression
- Kidney Stones
- Osteoporosis
- Constipation
- Blood sugar disturbances

Thiazide Diuretic Side Effects

- Muscle pain, weakness or cramps
- Low back pain
- Headache
- Unusual tiredness or weakness
- Irregular heartbeat
- Mood changes
- Constipation
- Glucose intolerance

- Source Facts&Comparisons

Magnesium - PPI Use

- PPI exposure is associated with a nearly 3-fold increased risk for hypomagnesemia,
  - Especially among those greater than 65 years old
- Over 10 human clinical studies since 2010 support PPI use depletes magnesium
- 11,000 critically ill PPI use associated with hypomagnesemia; PARTICULARLY among diuretic users
- PPI + diuretic = 54% increased risk of low Mg++
- These studies also looked at SERUM Mg, not RBC Mg

Danziger J, William JH, Scott DJ, et al. Proton-pump inhibitor use is associated with low serum magnesium concentrations. Kidney Int. 2013 ; 83 : 692 – 699.

Magnesium Deficiency: Pathophysiologic and Clinical Review

- Cofactor for ATP, critical in energy production, protein synthesis and anaerobic phosphorylation
- If Mg is depleted, bone stores contribute to Extracellular Fluid
- "The serum Mg can be normal in the presence of intracellular Mg depletion, and the occurrence of a low serum level usually indicates significant Mg deficiency."

Al-Ghamdi SM, Am J Kidney Disease. 1994 Nov; 24(5): 737-52.

Magnesium Immunity

- Magnesium reported as a co-factor in immunity for:
  - immunoglobulin synthesis
  - C’3 convertase
  - immune cell adherence
  - antibody-dependent cytolysis
  - IgM lymphocyte binding
  - macrophage response to lymphokines and T helper–B cell adherence

Tam M, et al. Possible roles of magnesium on the immune system. Eur J Clin Nutr. 2003;57:1193-97.

Magnesium

4637 Americans 18-30 free of MetS and Diabetes

15 year follow up 608 cases MetS.

-Studies suggest magnesium intake may be inversely related to risk of hypertension and type 2 diabetes mellitus:

-Higher intake of magnesium may decrease blood triglycerides and increase high-density lipoprotein (HDL) cholesterol levels..

s***Circulation***: Epidemiology: Magnesium Intake and Incidence of Metabolic Syndrome Among Young Adults *2006; 113: 1675-1682* Published online before print March 27, 2006, doi: 10.1161/CIRCULATIONAHA.105.588327

Magnesium cont'd

- Magnesium intake inversely related to individual component of the metabolic syndrome and fasting insulin levels.

- ***Conclusions—*** "Our findings suggest that young adults with higher magnesium intake have lower risk of development of metabolic syndrome".

Magnesium Intake and Risk of Type 2 Diabetes in Men and Women

- 85,600 women and 42,872 men no Hx diabetes CVD or cancer at baseline
- Magnesium Intake eval q2yr
- 18 yr follow up women 4,085 cases
- 12 year follow men 1,333 cases
- Relative Risk 0.66 in women ($P<0.001$)
- Relative Risk 0.67 in men ($P<0.001$)
- Comparing the highest to lowest quintile of intake

Magnesium and Type 2 Diabetes Risk

- Conclusion:—”Our findings suggest a significant inverse association between magnesium intake and diabetes risk. This study supports the dietary recommendation to increase consumption of major food sources of magnesium, such as whole grains, nuts, and green leafy vegetables.”

- **Diabetes Care** *January 2004 vol. 27 no. 1 134-140*
- doi: 10.2337/diacare.27.1.134

Magnesium Intake

- Gallup poll 2004 commissioned by Purdue Products (makers of Slo Mag®)
  - 80% not getting RDA just from diet
  - 35% getting RDA between diet and supplements

  July 21, 2004 PRNewswire

- Low levels found in obese/overweight individuals

  Huerta MG, et al. Magnesium deficiency is associated with insulin resistance in obese children.Diabetes Care. 2005 May;28(5):1175-81

- NHANES study 1999-2000 68% got less than RDA, 19% consumed less than 50%. Low Mg increases CRP and heart disease

  JACN, Vol. 24, No. 3, 166-171 (2005)

Magnesium and Risk of Heart Disease

- 2018 prospective cohort study
- 85,293 Japanese subjects 45-74 yrs
- Free of cardiovascular disease and cancer from 1995-1998
- Followed until 2009-2010 in Cohorts 1 and 2
- After 1,305,738 (million) subjects
- Bottom line: Higher dietary magnesium intake was associated with a reduced risk of CHD in Japanese men

Kokubo Y, et al. Dietary magnesium intake and risk of incident coronary heart disease in men: a prospective cohort study. Clin Nutr. 2018;37(5):1602-8.

Magnesium and Stroke Risk

Meta Analysis

- 7 studies pooled
- For every 100mg increase intake magnesium meant a 8-9% decreased total and ischemic stroke risk.

Larsson, N, Orsini, Wolk, A. Dietary magnesium intake and the risk of stroke: a meta analysis of prospective studies; AmJClinNutr:2012;95(2):362-6.

Repletion of Magnesium

- 300 to 800 mg/day Range: **elemental** Mg++ per day
- Better absorbed forms:
  - Magnesium citrate
  - Magnesium glycinate
  - Magnesium taurate
  - Magnesium malate
- Magnesium carbonate and oxide not effective
- Watch citrate forms – diarrhea
- Percent Daily value at 300mg/per day
- 7.5-10mg/kg/day

Magnesium Blood Levels

- Serum 1.5-2.5 mg/dL, optimal = 2.2—2.4
- RBC 4-6.4 mg/dL, optimal = 5.7-6.2

- True measurement of magnesium tissue status is problematic as the serum level is not reflective of tissue levels
- RBC status may improve on this to some degree but it may still be an issue in interpreting true tissue magnesium status

Source Laboratory tests for the Assessment of Nutrition Status Author: Howerde E Suberlich

NSAIDs

- NSAIDs are one of the most commonly prescribed classes of medication for pain and inflammation
- 5-10% of all meds prescribed annually
- The prevalence of NSAID use in patients over 65 years old is as high as 96% in the general practice setting

Centers for Disease Control (CDC). www.cdc.gov. Accessed August 2021

NSAIDs

- Nutrients Depleted :
  - Folic Acid
  - Melatonin
  - Zinc
  - DHEA
- Indomethacin = Iron (aplastic anemia after prolonged use of indomethacin)
- NSAIDs – carprofen - reported to impair immune response in heart failure
  - Triggers metaflammation in kidney and heart damage
- NSAIDs also damage GUT microbiome and mucosa – leads to metaflammation and immune dysfunction

Kornberg A, et al. Aplastic anemia after prolonged ingestion of indomethacin. Acta Haematol. 1982;67(2):136-8.
Baggot JE, et al. Inhibition of folate-dependent enzymes by non-steroidal inflammatory drugs. Biochem J. 1992;282(pt1):197-202.
Krishnan V, et al. Pretreatment of carprofen impaired initiation of inflammatory- and overlapping resolution response and

Corticosteroids – Nutrients Depleted

- Calcium
- CoQ10
- DHEA
- Folic acid
- Magnesium
- Potassium
- Selenium
- Vitamin C
- Chromium
- Vitamin D
- Vitamin B6
- Vitamin B12
- Vitamin E
- Zinc

Skversky AL, et al. Association of Glucocorticoid Use and Low 25-Hydroxyvitamin D Levels: Results from the National Health and Nutrition Examination Survey (NHANES): 2001–2006. J Clin Endocrinol Metab. 2011;96(12):3838-45.

Corticosteroids – Nutrients Depleted

- Immunosuppressive effects
- HPA axis disruption
- Increased IR due to action on glucose metabolism
- Bone resorption effects and decreased Ca absorption in GUT
- Important immune nutrients depleted – selenium, magnesium, vitamin D, C, E, Zinc, CoQ10
- Also think GUT involvement – microbiome/ mucosal integrity

Skversky AL, et al. Association of Glucocorticoid Use and Low 25-Hydroxyvitamin D Levels: Results from the National Health and Nutrition Examination Survey (NHANES): 2001–2006. J Clin Endocrinol Metab. 2011;96(12):3838-45.

Hardy RS, et al. Glucocorticoids and Bone: Consequences of Endogenous and

Anti-diabetic Drugs

Sulfonylureas: deplete CoQ10

Biguanides: deplete CoQ10, B12, FA

Pongchaidecha, et al. "Effect of metformin on plasma homocysteine, vitamin B12 and folic acid: a cross-sectional study in patients with type 2 diabetes mellitus," J Med Assoc Thai. 2004; 87: 780-87.

Wulffele, et al. "Effects of short-term treatment with metformin on serum levels of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized placebo-controlled trial," J Intern Med. 2003; 254: 455-63.

Malabsorption of Vitamin B12 and Intrinsic Factor Secretion during Biguanide Therapy

- 46 diabetic patients: 30% had malabsorption of vitamin B12
- Withdrawal normalized absorption in only half of those with malabsorption
- Biguanides can induce malabsorption by 2 different mechanisms: 1 is temporary and unrelated to intrinsic factor; other causes permanent ↓ in intrinsic factor secretion

Adams JF, et al. Diabetologia. 1983 Jan; 24(1): 16-18.
Liu Q, et al. Vitamin B12 status in metformin treated patients: a systematic review. PLoS

2015 Systematic Review – B12 Metformin

- Database search from 1950 – June 2013
- 26 clinical trials included
- A majority of the studies reported statistically significantly lower vitamin B_{12} levels in those patients on metformin

Chapman LE, et al. The association between biguanide drug metformin and vitamin B12 deficiency in diabetic patients: a systematic review. PNS Cambridge. 2015;74(OCE1):14-17.

Metformin Increases Total Serum Homocysteine Levels

- Non-diabetic males with CVD
- 60 males open randomized trial 40 wk
- Results in significant increase in homocysteine with metformin administration
- B12 and folate levels were decreased

Carlsen SM, et al. "Metformin increases total serum homocysteine levels in nondiabetic male patients with coronary artery disease," Scand J Clin Lab Invest. 1997; 57(6): 521-7.

Metformin Diabetic Neuropathy

- Metformin associated with:
- B12 (Cbl) depletion
- Homocysteine elevation
- Methylmalonic acid elevation
- PT 6mth on Metformin n=59 w/o n=63
- **RESULTS**
  - Metformin-treated patients had depressed Cbl levels and elevated fasting MMA and Hcy levels.
  - Clinical and electrophysiological measures identified more severe peripheral neuropathy in these patients;
  - the cumulative metformin dose correlated strongly with these clinical and paraclinical group differences.

Wile and Toth Association of Metformin, Elevated Homocysteine, Methlmalonic Acd Levels

Diabetic Neuropathy

- **CONCLUSIONS** — Metformin exposure may be an iatrogenic cause for exacerbation of peripheral neuropathy in patients with type 2 diabetes. Interval screening for Cbl deficiency and systemic Cbl therapy should be considered upon initiation of, as well as during, metformin therapy to detect potential secondary causes of worsening peripheral neuropathy.

- Wile and Toth Association of Metformin, Elevated Homocysteine, Methlmalonic Acd Levels and The Clinically Worsened Diabetic peripheral Neuropathy ***Diabetes Care*** **33:156–161, 2010**

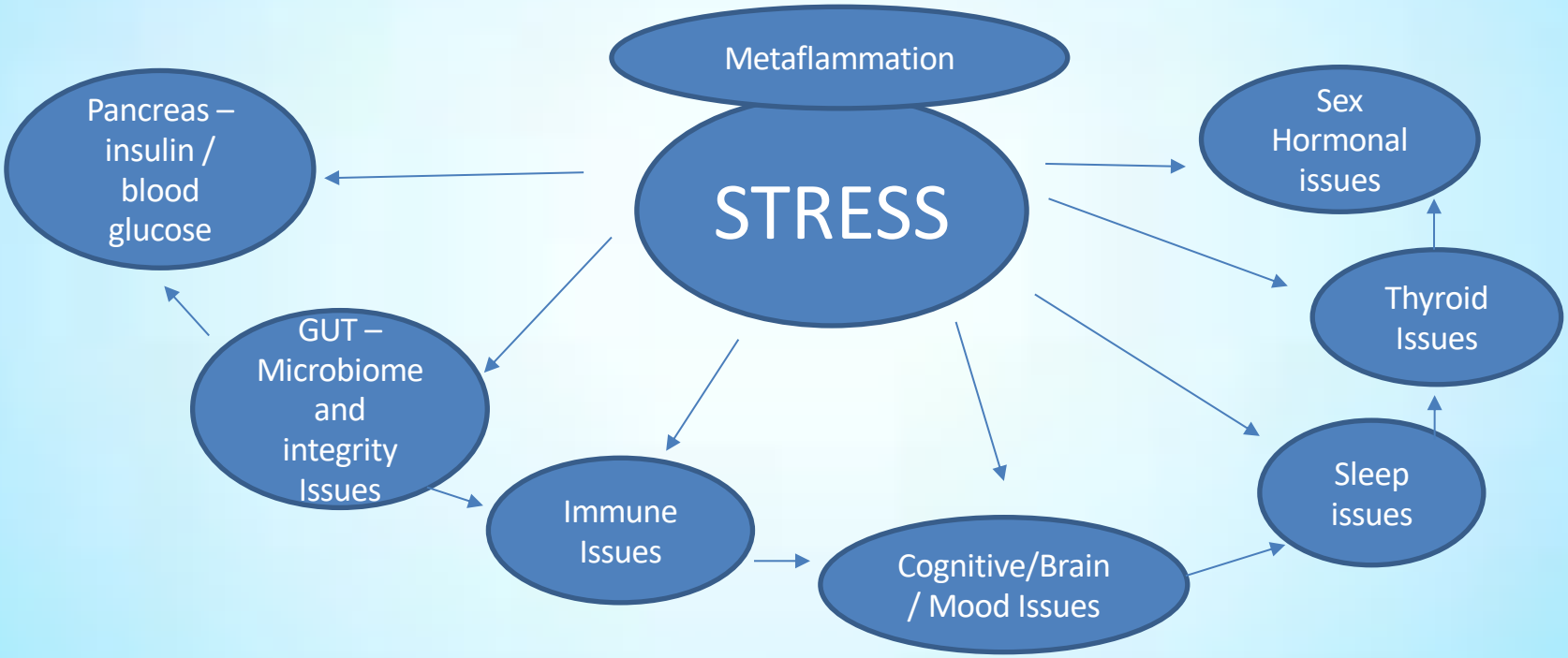
Metformin Immunity

- Metformin may **suppresses immune responses**
- Mainly through direct effect on the cellular functions of immune cell types by induction of AMPK and subsequent inhibition of mTORC1
- By inhibition of mitochondrial ROS production
- By DIMD – microbiome disruption

Bryrup T, et al. Metformin-induced changes of the gut microbiota in healthy young men: results of a non-blinded, one-armed intervention study. Diabetologia. 2019;62(6):1024-35.

Systems Biology Approach to Metaflammation

- Optimizing Inter-relationship of organ systems important in treatment



So What Do We Do As Pharmacists?

- When patients are prescribed drugs with DIND or DIMD implications, intervention should be taken
- Familiarize yourself with a reputable DIND Chart – have it handy as reference and/or drug nutrient depletion software intervention
- Generally, DIND can be remedied w recommending:
  - a quality multiple vitamin mineral daily – look at vitamin/mineral daily amounts and make sure the depleted nutrient for your patient is covered adequately (i.e Mg, Cr, Zn); if not add other nutrient support
  - Other nutrient depletions not contained in most multiples such as iron (check labs), CoQ10, DHEA (check labs 1st), protein, probiotics, melatonin, glutathione
- If metabolic imbalances are present, what nutrient support