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Going Deeper: Addressing Cardiometabolic Cases with a Functional Medicine Approach

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Disclosures

- Hartzler
  - Speaker’s Bureau for Novo Nordisk & Abbott
- Zakaria
  - Nothing to disclose

Objective

- Apply knowledge of cardiometabolic pathophysiology, clinical work-up, and interventions to patient cases.

Case 1

Hypertension/ASCVD Risk Focus

Case 1

- 47-year-old male
- HTN, HLP, DM
- HbA1c 9.5%
- Recent car accident
- Diet Recall
  - 2 L of Mt Dew per day, also drinks milk daily
  - Frozen entrees for lunch
  - Dinners: lasagna, spaghetti, chicken alfredo, mashed potatoes, green beans/corn/peas
  - Snacks Swiss cake rolls
- Active at job (25-35K steps per day) but no formal exercise plan
- BP was 142/88 , Pulse of 86
- Car accident last year
- FH: All men in family have died of MI (not less than 50)
- Has trouble with costs and wants as much to be covered on insurance as possible

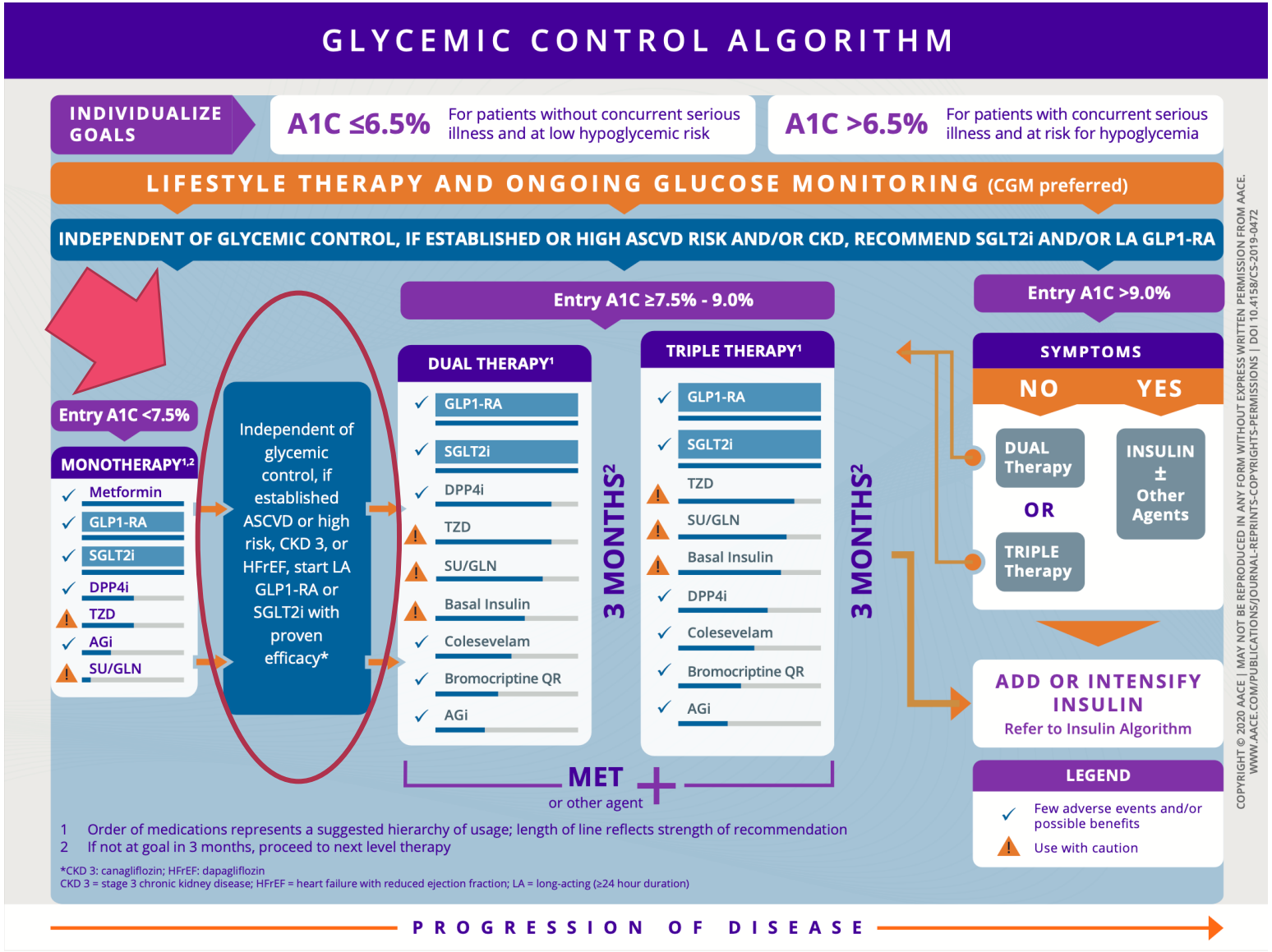
Case 1: Current Medications

- Glimepiride 4 mg tablet, take one by mouth twice a day
- Empagliflozin10 mg tablet, take one by mouth once a day
- Lisinopril 20 mg-hydrochlorothiazide 25 mg tablet take one by mouth once a day
- Metformin 1,000 Mg Tablet, take one by mouth twice a day
- Alogliptin 25 mg tablet, take one by mouth once a day
- Simvastatin 10 Mg Tablet, take one by mouth every evening\
- Ibuprofen 800 mg tablet, take one by mouth three times a day with food
- Amlodipine 5 mg tablet, take one by mouth once a day
- Methocarbamol 750 mg tablet, one PO before bed for neck pain
- Sumatriptan 100 mg tablet, one PO onset migraine, may repeat in 2 hours (max 200mg in 24 hours)

Low Hanging Fruit.. Where do we start?

Polling Question

1. What intervention do you see best to focus on first?
    a. Dietary
    b. Medication Changes
    c. New Supplements
    d. Exercise
    e. More than one of the above



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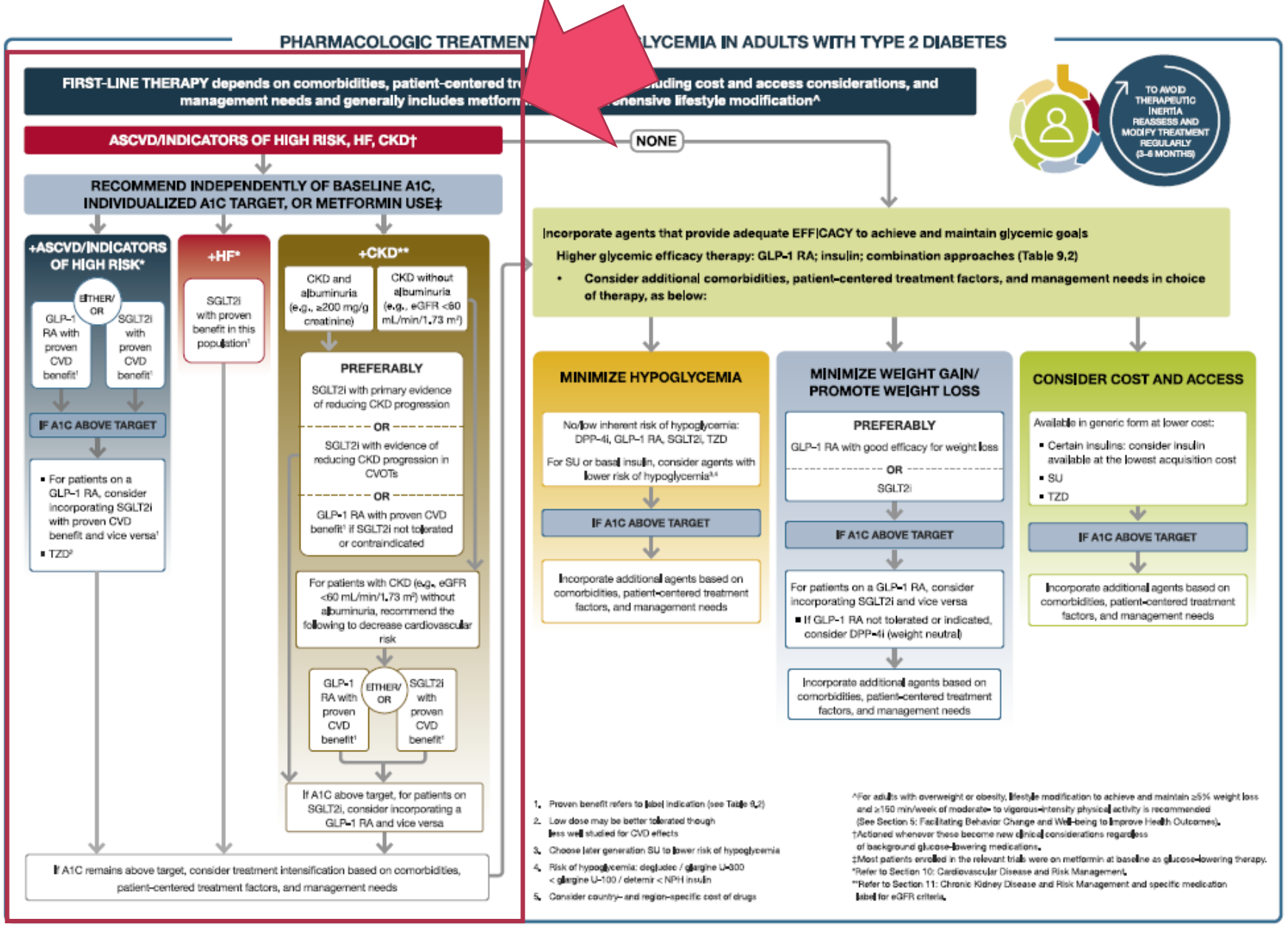

Figure 9.3—Pharmacologic treatment of hyperglycemia in adults with type 2 diabetes. 2022 ADA Professional Practice Committee (PPC) adaptation of Davies et al. (43) and Buse et al. (44). For appropriate context, see **Fig. 4.1**. The 2022 ADA PPC adaptation emphasizes incorporation of therapy rather than sequential add-on, which may require adjustment of current therapies. Therapeutic regimen should be tailored to comorbidities, patient-centered treatment factors, and management needs. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

Glucose-lowering Medication in Type 2 Diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al. and Buse et al.

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2022. Diabetes Care* 2022;45(Suppl. 1):S125-S143

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Initial Plan

- Restart metformin 1000 mg twice daily and Jardiance 10 mg once daily; stop glimepiride.
- Start semaglutide 0.25 mg once weekly for 4 weeks then increase to 0.5 mg weekly.
- Stop simvastatin; start rosuvastatin 5 mg once daily
- Start CoQ10 100 mg daily
- Increase Empagliflozin to 25 mg
- **Make dietary changes:**
  - Nix daily milk intake. Recommended protein shakes in its place – ideally as a breakfast option to jumpstart daily metabolism and develop regular eating routine.
  - Nix soda
  - Substitute spaghetti and lasagna noodles with zucchini/spaghetti squash or eggplant
  - Increase daily intake of green leafy vegetables, limiting intake of corn and peas.
- Start exercising more regularly by going to Anytime Fitness more routinely (30 min per day 5x/wk).
- Consider curcumin 500 mg up to 4 times a day for pain/inflammation instead of NSAIDS like aspirin or ibuprofen so frequently

4-month follow-up

- HbA1c 6.5%
- HTN uncontrolled (amlodipine bumped to 10 mg 2 weeks prior)
  - Stress with family
  - Lost father due to Cardiac arrest
  - BP 162/110, pulse 95
- Start Carvedilol 3.125 mg twice daily.
- Referrals to Cardio and Pulmonology
- Go to ER if Chest Pain, Headache, call office if BP doesn't come down.
- Labs

Refractory HTN Considerations

- Medication non-adherence
- White Coat
- Inaccurate measurements
- Sleep Apnea
- Hypercortisolism/HPA-axis dysfunction)
- Renal disease
- Nutrient depletions (minerals, Coq10)

Acelajado MC, et al. Circ Res. 2019 Mar 29;124(7):1061-1070.
Gouaref et al. Ann Biol Clin (Paris). 2016 Mar-Apr;74(2):233-43.
Houston MC. Expert Rev Cardiovasc Ther. 2007 Jul;5(4):681-91

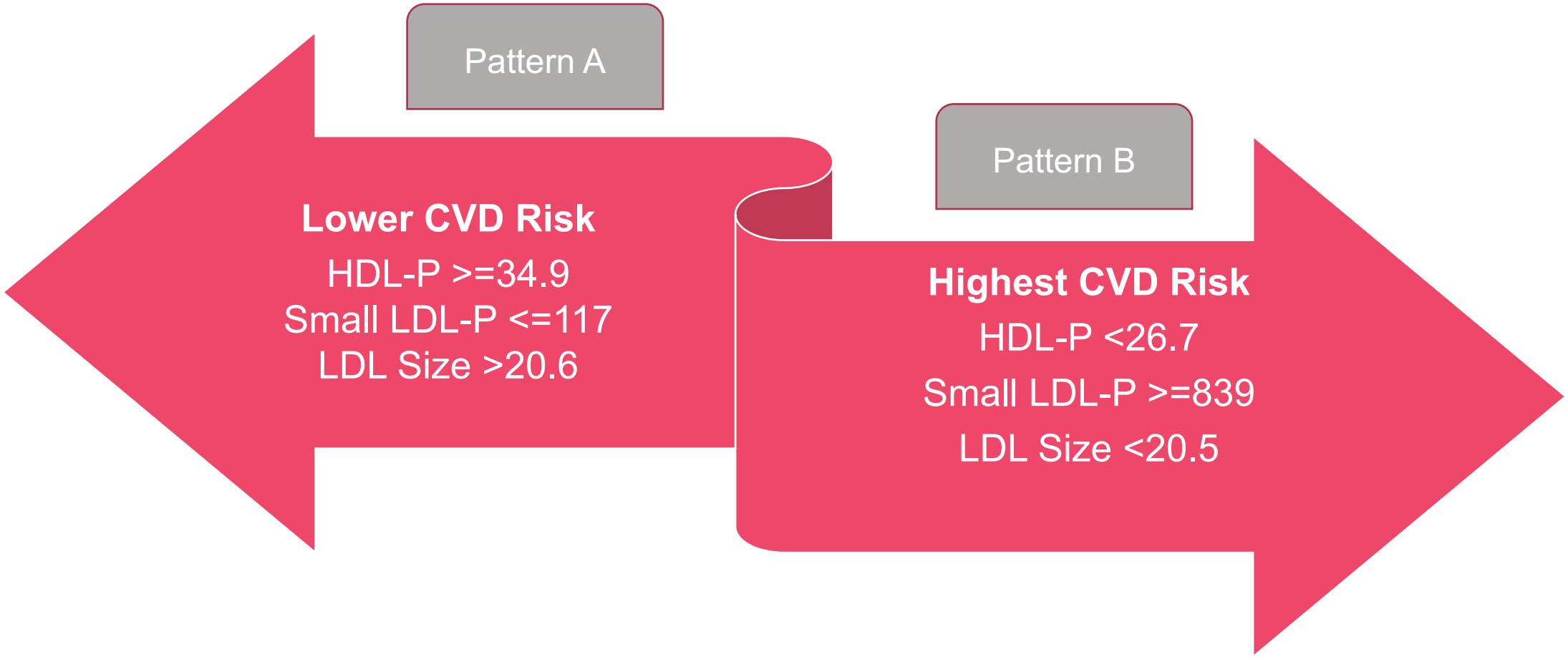
Labs

- Adiponectin <0.2 ug/ml (2.4-17.9)
- Apo A1 126 mg/dl (101-178)
- Apo B 78 mg/dl (<90)
- ApoA1/Apo B Ratio 0.6 (0-0.7)
- CRP <1 mg/L (0-10)
- CBC WNL
- Glucose 126 mg/dl, HbA1c 6.5%
- Bilirubin 1.2 mg/dl (0-1.2), otherwise CMP WNL
- Homocysteine 10.4 umol/L (0-14.5)
- Lipoprotein (a) Lp(a) 218.4 nmol/L (<75)
- Myeloperoxidase (MPO) 332 pmol/L (0-469)

Adiponectin is a hormone your adipose (fat) tissue releases that helps with insulin sensitivity and inflammation

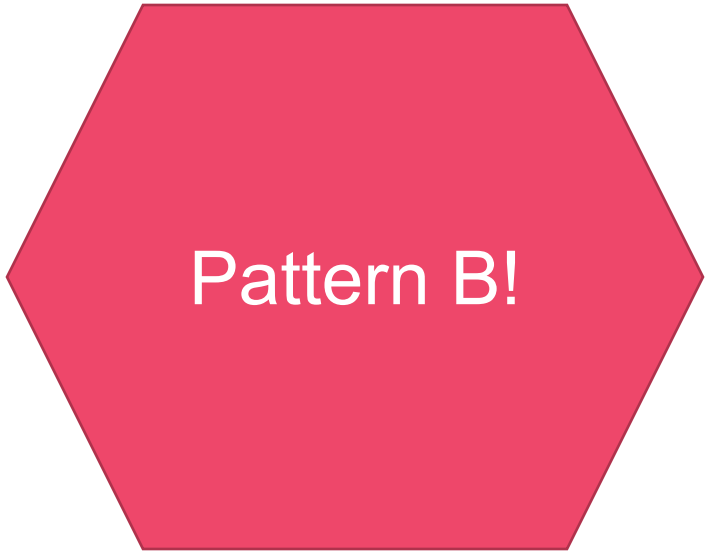
Lp(a) is an independent risk factor for heart disease.

Particle Size Evaluations



Labs

- Particle Size Lipid Panel
  - LDL-P 1163 nmol/L (<1,000)
  - LDL-c 74 mg/dl (0-99)
  - HDL-C 35 mg/dl (>39)
  - TG 194 mg/dl (0-149)
  - Total Cholesterol TC 142 (100-199)
  - HDL (p) (total) 31 umol/L (>=30.5)
  - Small LDL-p 762 nmol/L (<=527)
  - LDL Size 20.00 nm (>20.5)
  - Lp-ir Score 79 (<=45)
- Oxidized LDL 39 ng/ml (10-170)
- Thyroid Panel WNL
- Vitamin D 14.8 ng/ml (30-100)



Where do we go next? Recommendations? Put them in the chat!

Lipoprotein (a)

- Lp(a) blocks plasminogen by attaching to lysine and proline in damaged collagen in vascular wall. This binding during clot formation results in inhibition of fibrinolysis
  - Major carrier of oxidized LDL
- 1 to 16 increase in CVD morbidity/mortality/SD (Jupiter, AIMHIGH)
- Data
  - Niacin 2 grams/day (lowers 21-40%)
    - May be dependent on apolipoprotein(a) phenotype
  - N-acetyl cysteine 1-2 grams/day (mixed results)
  - COQ10 100mg/day
  - ASA 81 mg/day (decreases 80%)
  - Other anti-inflammatory/antioxidant considerations
    - Flax, omega-3, berberine, vitamin C, etc.
  - PSK9 Inhibitors (does have outcomes data lowering of Lp(a) and MACE but not directly looking at them together.)

Artemeva NV et al. Dependent on apolipoprotein(a) phenotype. Atheroscler Suppl. 2015 May;18:53-8
Ooi EM, et al. Arterioscler Thromb Vasc Biol. 2015 Dec;35(12):2686-93.
Rouhi H, et al. *J Nephropathol*. 2013;2(1):61-66.
Gavish D et al. Lancet. 1991 Jan 26;337(8735):203-4.
Sahebkar A, et al. Pharmacol Res. 2016 Mar;105:198-209.
Akaike M et al. Clin Chem. 2002 Sep;48(9):1454-9. PMID: 12194922.
Bonaca MP et al. Circulation. 2018 Jan 23;137(4):338-350.
Cao YX, et al. Am J Cardiovasc Drugs. 2019 Feb;19(1):87-97.

Case 1 Follow-up

- Increased Carvedilol to 6.25 mg twice daily
- Start Niacin 500 mg ER once daily and work up to 4 tablets a day
- Start ASA 81 mg
- Start Vitamin D 10,000 IU once daily with K2
- Consider icosapent ethyl if affordable/tolerable
- Goals
  - Decrease inflammation
  - Reduce Lp(a) and overall cardiac risk
  - Vitamin D above 40

What else would we do from a functional approach?

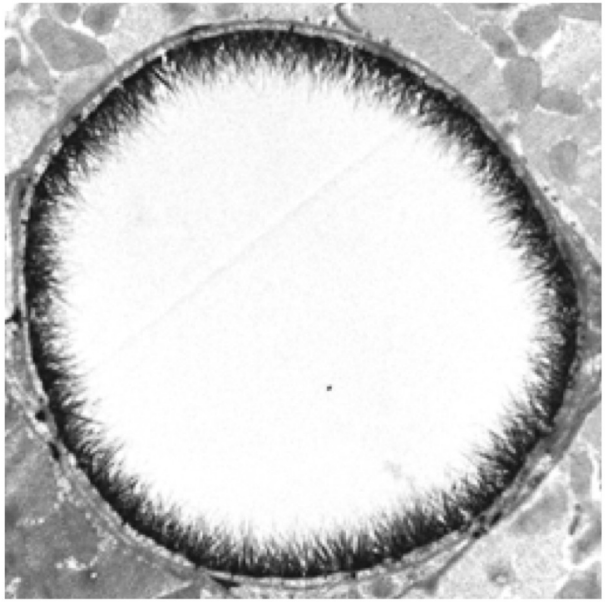
If this was a patient committed to diet/lifestyle and natural products, how would the plan change?

Something Else to Consider…

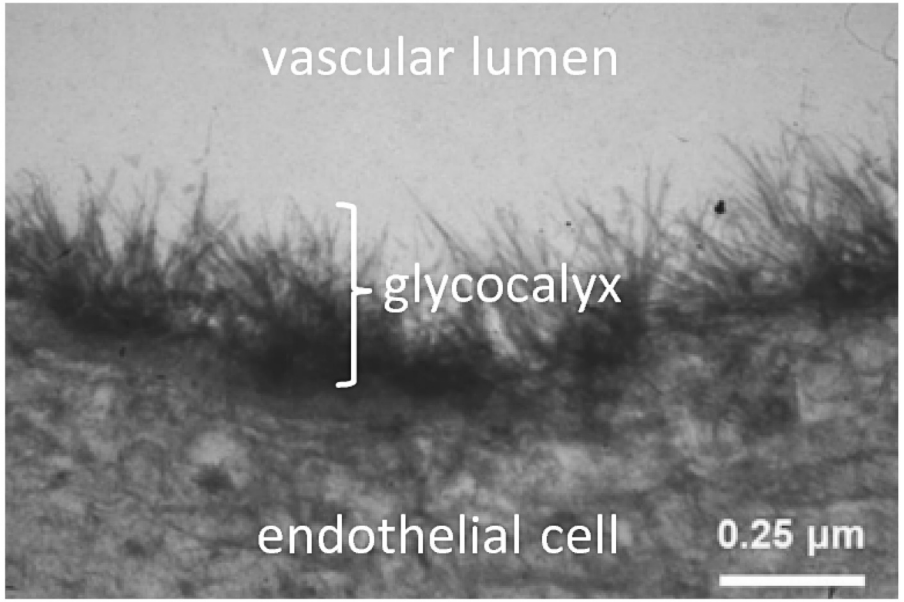
The Endothelial Glycocalyx

The glycocalyx is a micro-thin gel covering the endothelial surface of every artery, vein and capillary. It protects the endothelium and regulates the following functions:

- Transduces blood shear to induce nitric oxide (NO) production
- Houses extra-cellular superoxide dismutase
- Acts as a selectively permeable barrier for molecules and cells such as LDL and leukocytes
- Inhibits platelet aggregation
- Harbors coagulation regulatory factors
- Prevents leukocyte adhesion



van den Berg, et al. Circ Res 2003 & Endothelial Biomedicine ed., W.C. Aird, 2007



Wiesinger A, Peters W, Chappell D, Kentrup D, Reuter S, Pavenstädt H, et al. (2013) Nanomechanics of the Endothelial Glycocalyx in Experimental Sepsis. PLoS ONE 8(11): e80905

Directions: Take 2 capsules daily, preferably one in the morning and one in the evening, with a meal, or as directed by your healthcare practitioner.

Supplement Facts

Serving Size: 2 Capsules
Servings Per Container: 30

	Amount Per Serving	% Daily Value
Proprietary Blend containing:	900mg	†
Green Seaweed (Monostroma sp.) extract, grape (seed and skin) extract, green tea (leaf) extract, grape pomace (fruit) extract, tomato (fruit), carrot (root) juice, bilberry (fruit), broccoli (aerial parts), green cabbage (leaf), onion (bulb), garlic (bulb), grapefruit (fruit), asparagus (stalk), papaya (fruit), pineapple (fruit), strawberry (fruit), apple (fruit), apricot (fruit), cherry (fruit), orange (fruit), blackcurrant (fruit), olive (fruit) extract, and cucumber (fruit) extract.		

† Daily Value Not Established

- Early Data on:
  - Carotid Plaque Regression
  - Glycocalyx Regeneration
  - Leukocyte Adhesion
  - Arterial Elasticity
  - Hypertension
  - Neuropathy

https://f.hubspotusercontent20.net/hubfs/7072026/Arterosil%20Research%20Study%20Summary.pdf

Case 2

Nutraceutical Approach to Hyperlipidemia

Case 2

- 33 y/o white male
- No medications
- No significant PMH other than genetic high total bilirubin
- Regular exercise
  - Mix of cardio and CrossFit, weightlifting, etc.
- 6’3”, 210 lbs
- Diet
  - Probably more sugar/sweets than he should eat but eats a wide variety of veggies and adequate protein. Did Paleo for a period.

2017 Labs

- TC 282 mg/dl
- TG 72 mg/dl
- HDL Cholesterol 61 mg/dl
- LDL Cholesterol 207 mg/dl
- VLDL 14 mg/dl
- CBC WNL
- Lipoprotein fractionation
  - LDL particle number- high
  - LDL medium high
  - Size good
  - Pattern A

2019 Labs

- TC 258 mg/dl
- HDL 60.3 mg/dl
- LDL 181 mg/dl
- TC 79 mg/dl
- LDL/HDL ratio 3
- Total Bilirubin 1.28 mg/dl (0.10-1.2 mg/dl)
- LFTs WNL

What do we recommend?

- Drug Therapy?
- Supplements?
- Nutrition?
- Lifestyle?

Patient started taking…

- Omegas
- Bergamot 800 mg with Amla Extract 600 mg daily
- Vitamin C with flavonoids
- Multi w/o iron
- Magnesium
- K2/D3 5,000 IU per day
- Zinc Glycinate
- Probiotic
- Detox caps (milk thistle, pomegranate extract, milk thistle, MSM, CDG, Green tea extract, ALA, NAC, Artichoke, B12, Folate, B6)

2022 Labs

- Adiponectin 2.9 ug/ml (2.0-19.3)
- Iron Studies (TIBC, UIBC, IRON, ISAT, Ferritin) all WNL
- Vitamin B12 949 pg/ml (232-1245)
- Folate 13.2 ng/ml (>3.0)
- CBC WNL
- Apo A1 120 mg/dl (101-178)
- Apo B 107 mg/dl (<90)
  - Ratio 0.9 (0-0.7)
- BMP WNL
- CRP <1 mg/L (0-10)

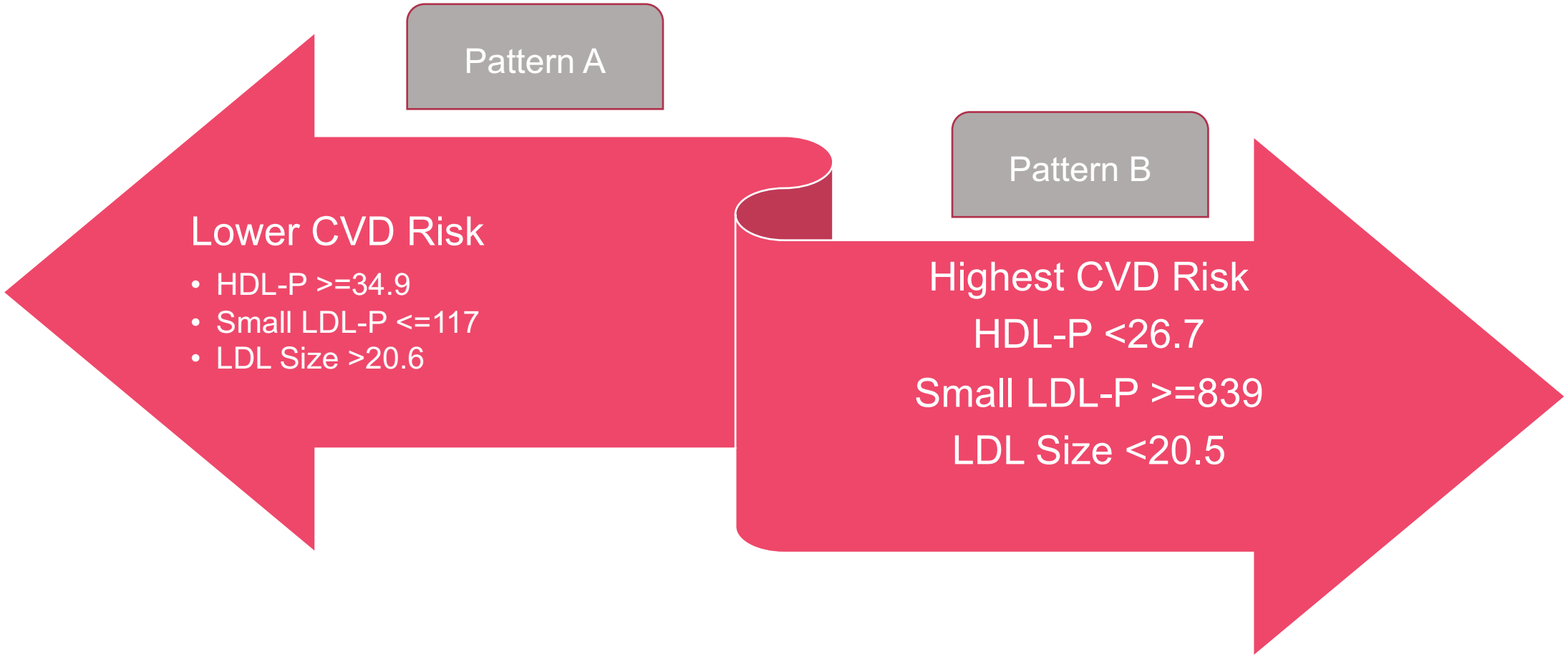
Case 2 Labs

- CoQ10 Serum or Plasma 99 ug/dl (69-132)
- HbA1c 5.3%
- Hepatic Panel WNL except total Bilirubin 1.4 mg/dl (0-1.2)
- Leptin 8.1 ng/ml
- Lipoprotein (a) 21.1 nmol/L (<75)
- Magnesium RBC 5.4 mg/dl (4.2-6.8)
- Myeloperoxidase 279 pmol/L (0-469)

Case 2 Labs

- Particle Size Lipid Panel
  - LDL-p 1580 nmol/L (<1,000)
  - LDL-c 149 mg/dl (0-99) (down from 181)
  - HDL-c 47 mg/dl (>39)
  - TG 89 mg/dl (0-149)
  - TC 212 mg/dl (100-199
  - HDL-p (total) 24.7 (>=30.5)
  - Small LDL-p 423 nmol/L (<=527)
  - LDL Size 21.6 nm (>20.5)
  - Lp ir Score 40 (<=45)
- Oxidized LDL 380 ng/ml (10-170)
- Vitamin D 42.7 ng/ml (30-100)
- TSH 1.5 uIU/ml (0.450-4.5)
- Free T4 1.18 ng/dl (0.82-1.77)

Particle Size Evaluations



What do we consider now?

Red Yeast Rice

- Effectiveness is directly related to the amount of monacolin K within the extract (up to 10 mg/day)
  - Consuming monacolin K daily reduces low-density lipoprotein (LDL) cholesterol plasma levels between 15% and 25% within 6 to 8 weeks
  - Similar reduction in total cholesterol, non-high-density lipoprotein cholesterol, plasma apolipoprotein B, matrix metalloproteinases 2 and 9, and high-sensitivity C-reactive protein.
- Small RCT of combo RYR and olive extract
  - 10.82 mg of monacolins and 9.32 mg of hydroxytyrosol
  - Reductions in OxLDL (20%) and lipoprotein-associated phospholipase A2 (Lp-PLA2) (7%) were associated with each other ($r = 0.740$, $p < 0.001$).

Cicero AFG, et al. Methodist Debakey Cardiovasc J. 2019 Jul-Sep;15(3):192-199.
Hermans N, et al. Trials. 2017 Jul 3;18(1):302.

Other thoughts on this case?

Case 3

Dyslipidemia and Metabolic Syndrome

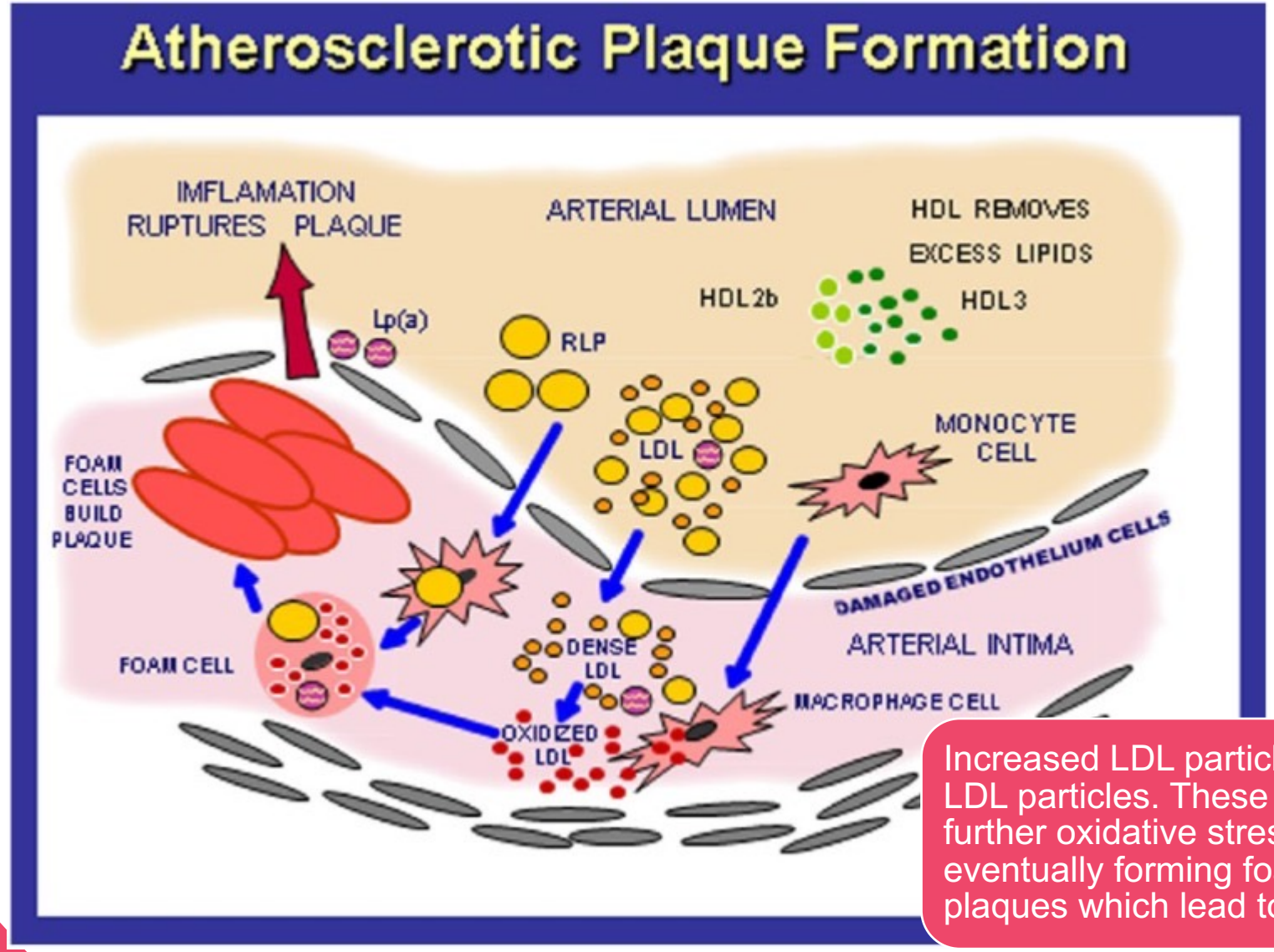
Dyslipidemia: Testing

A serum lipid panel is a good screening tool but limited

Patients with dyslipidemia should be evaluated using advanced lipid profiles to determine treatment and predict individual CHD risk more accurately.

- Lipoprotein fractionation
- Nuclear magnetic resonance (NMR) Quest CardioIQ and Boston Heart Lab

Quality vs Quantity



Increased LDL particle number leads to increased oxidation of LDL particles. These are taken up by macrophages and induce further oxidative stress, inflammation, immune dysfunction – eventually forming foam cells, fatty streaks and coronary artery plaques which lead to cardiovascular events.

Ther Adv Cardiovasc Dis. 2018;12(3):85-108.

Ellen

- 57 y/o woman
- Struggled with her weight throughout her adult life
  - Mostly carries weight around waist (elevated hip to waist ratio)
  - Dyslipidemia and FBS slowly rising over the last 2-3 years
  - BP within normal range
  - Hip pain significantly limits mobility
- Fall 2021 BMI 51
  - Reduced to BMI 48 Winter 2022
  - Goal BMI < 40 (hip surgery)
- Currently not on any medication for metabolic Dz
  - Primary would like her to initiate statin, but she'd like to try diet and lifestyle first
  - Meloxicam 7.5mg to manage hip pain PRN

Metabolic Syndrome

Defined when 3+ of the following are met:

- Increased waist circumference (>40in for men or >35in for women)
- Elevated TG (>150 mmol/L)
- Low HDL (<40 mg/dL in men and <50 mg/dL in women)
- HTN (>130/85 mm Hg)
- Elevated FBS or insulin resistance (>100 mg/dL)

https://www.mayoclinic.org/diseases-conditions/metabolic-syndrome/diagnosis-treatment/drc-20351921

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Standard testing 2018

Test Name	In Range	Out Of Range	Reference Range
CHOLESTEROL, TOTAL		**202 H**	<200 mg/dL
HDL CHOLESTEROL	92		> OR = 50 mg/dL
TRIGLYCERIDES	96		<150 mg/dL
LDL-CHOLESTEROL	91		<100 mg/dL (calc)
GLUCOSE	96		65-99 mg/dL

Fasting reference interval

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Standard Lab 2019 (cholesterol)

LIPID PANEL WITH REFLEX TO DIRECT LDL			
CHOLESTEROL, TOTAL	**216 H**	<200 mg/dL	NL1
HDL CHOLESTEROL	**41 L**	> OR = 50 mg/dL	NL1
TRIGLYCERIDES	**178 H**	<150 mg/dL	NL1
LDL-CHOLESTEROL	**144 H**	mg/dL (calc)	NL1

Reference range: <100

Desirable range <100 mg/dL for primary prevention;
<70 mg/dL for patients with CHD or diabetic patients
with > or = 2 CHD risk factors.

LDL-C is now calculated using the Martin-Hopkins
calculation, which is a validated novel method providing
better accuracy than the Friedewald equation in the
estimation of LDL-C.
Martin SS et al. JAMA. 2013;310(19): 2061-2068
(http://education.QuestDiagnostics.com/faq/FAQ164)

CHOL/HDLC RATIO	**5.3 H**	<5.0 (calc)	NL1
NON HDL CHOLESTEROL	**175 H**	<130 mg/dL (calc)	NL1

For patients with diabetes plus 1 major ASCVD risk
factor, treating to a non-HDL-C goal of <100 mg/dL
(LDL-C of <70 mg/dL) is considered a therapeutic
option.

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Standard Lab 2019 (BS)

Test Name	In Range	Out Of Range	Reference Range	Lab
COMPREHENSIVE METABOLIC PANEL				NL1
GLUCOSE		**100 H**	65-99 mg/dL Fasting reference interval	
HEMOGLOBIN A1c	4.7		<5.7 % of total Hgb	NL1
For the purpose of screening for the presence of diabetes: <5.7% Consistent with the absence of diabetes 5.7-6.4% Consistent with increased risk for diabetes (prediabetes) > or =6.5% Consistent with diabetes				
INSULIN	10.1		2.0-19.6 uIU/mL	NL1
This insulin assay shows strong cross-reactivity for some insulin analogs (lispro, aspart, and glargine) and much lower cross-reactivity with others (detemir, glulisine).				

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Standard Lab 2019 (Vit D)

Test Name	Result	Reference Range	Lab
QUESTASSURED 25-OH VIT D, (D2,D3)			AMD
VITAMIN D, 25-OH, TOTAL	21 L	30-100 ng/mL	
VITAMIN D, 25-OH, D3	<17	ng/mL	
VITAMIN D, 25-OH, D2	<4	ng/mL	

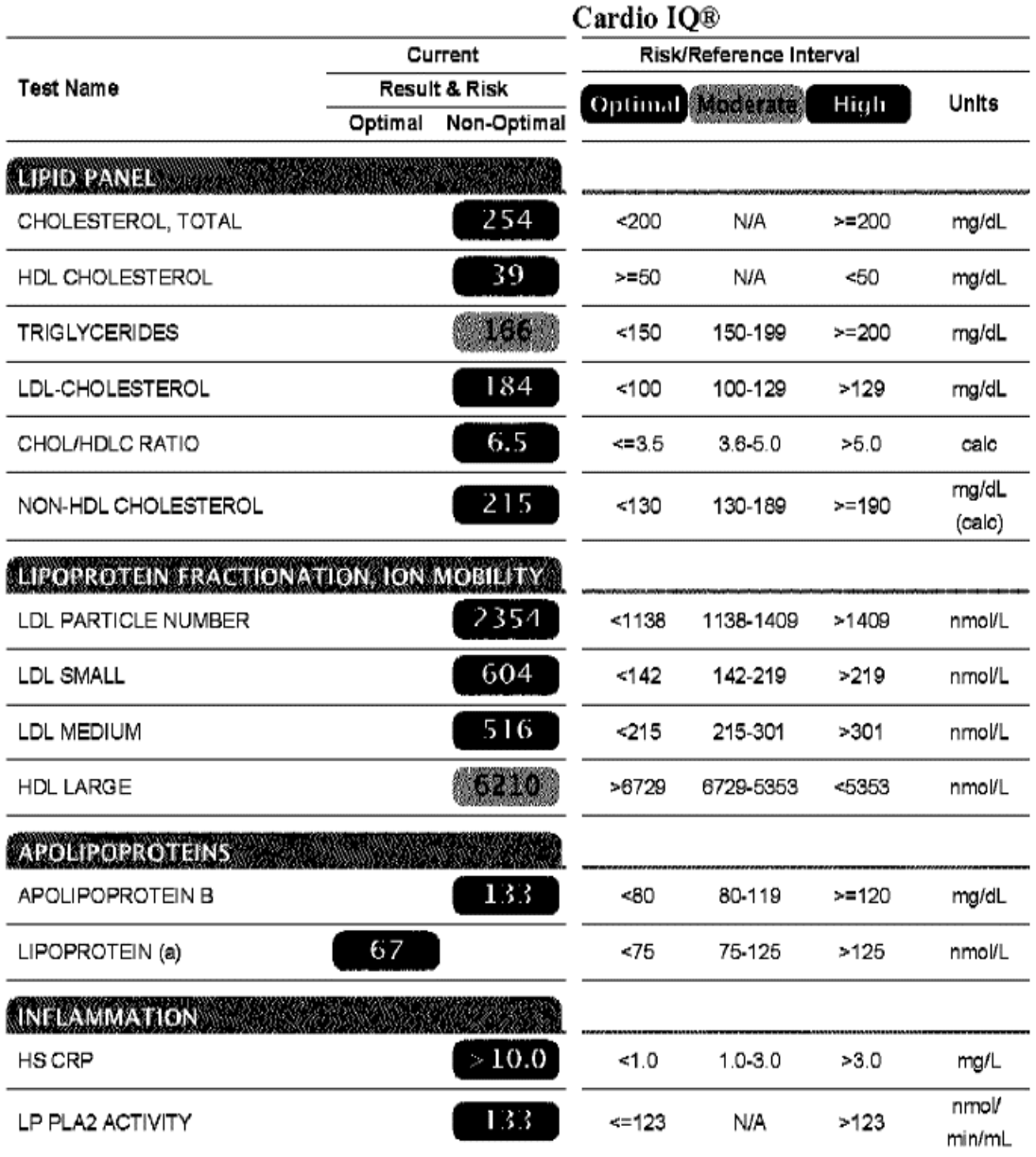
25-OHD3 indicates both endogenous production and supplementation. 25-OHD2 is an indicator of exogenous sources such as diet or supplementation. Therapy is based on measurement of Total 25-OHD, with levels <20 ng/mL indicative of Vitamin D deficiency while levels between 20 ng/mL and 30 ng/mL suggest insufficiency. Optimal levels are > or = 30 ng/mL.

For additional information, please refer to http://education.questdiagnostics.com/faq/FAQ163

(This link is being provided for information/ educational purposes only.)

This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute Chantilly, VA. It has not been cleared or approved by the U.S. Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

Fall 2020 Advanced Metabolic Panel



Cardio IQ®

Test Name	Current Result & Risk		Risk/Reference Interval			Units
	Optimal	Non-Optimal	Optimal	Moderate	High	
LIPID PANEL						
CHOLESTEROL, TOTAL		254	<200	N/A	>=200	mg/dL
HDL CHOLESTEROL		39	>=50	N/A	<50	mg/dL
TRIGLYCERIDES		166	<150	150-199	>=200	mg/dL
LDL-CHOLESTEROL		184	<100	100-129	>129	mg/dL
CHOL/HDLC RATIO		6.5	<=3.5	3.6-5.0	>5.0	calc
NON-HDL CHOLESTEROL		215	<130	130-189	>=190	mg/dL (calc)
LIPOPROTEIN FRACTIONATION, ION MOBILITY						
LDL PARTICLE NUMBER		2354	<1138	1138-1409	>1409	nmol/L
LDL SMALL		604	<142	142-219	>219	nmol/L
LDL MEDIUM		516	<215	215-301	>301	nmol/L
HDL LARGE		6210	>6729	6729-5353	<5353	nmol/L
APOLIPOPROTEINS						
APOLIPOPROTEIN B		133	<80	80-119	>=120	mg/dL
LIPOPROTEIN (a)	67		<75	75-125	>125	nmol/L
INFLAMMATION						
HS CRP		>10.0	<1.0	1.0-3.0	>3.0	mg/L
LP PLA2 ACTIVITY		133	<=123	N/A	>123	nmol/ min/mL

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2020 Advanced Metabolic Panel

Compare to 2019

- TC 216
- HDL 41
- TG 178
- LDL 144
- Chol/HDLC 5.3
- nonHDL 175

Cardio IQ®

Test Name	Current Result & Risk		Risk/Reference Interval			Units
	Optimal	Non-Optimal	Optimal	Moderate	High	
LIPID PANEL						
CHOLESTEROL, TOTAL		254	<200	N/A	>=200	mg/dL
HDL CHOLESTEROL		39	>=50	N/A	<50	mg/dL
TRIGLYCERIDES		166	<150	150-199	>=200	mg/dL
LDL-CHOLESTEROL		184	<100	100-129	>129	mg/dL
CHOL/HDLC RATIO		6.5	<=3.5	3.6-5.0	>5.0	calc
NON-HDL CHOLESTEROL		215	<130	130-189	>=190	mg/dL (calc)
LIPOPROTEIN FRACTIONATION, ION MOBILITY						
LDL PARTICLE NUMBER		2354	<1138	1138-1409	>1409	nmol/L
LDL SMALL		604	<142	142-219	>219	nmol/L
LDL MEDIUM		516	<215	215-301	>301	nmol/L
HDL LARGE		6210	>6729	6729-5353	<5353	nmol/L
APOLIPOPROTEINS						
APOLIPOPROTEIN B		133	<80	80-119	>=120	mg/dL
LIPOPROTEIN (a)	67		<75	75-125	>125	nmol/L
INFLAMMATION						
HS CRP		>10.0	<1.0	1.0-3.0	>3.0	mg/L
LP PLA2 ACTIVITY		133	<=123	N/A	>123	nmol/ min/mL

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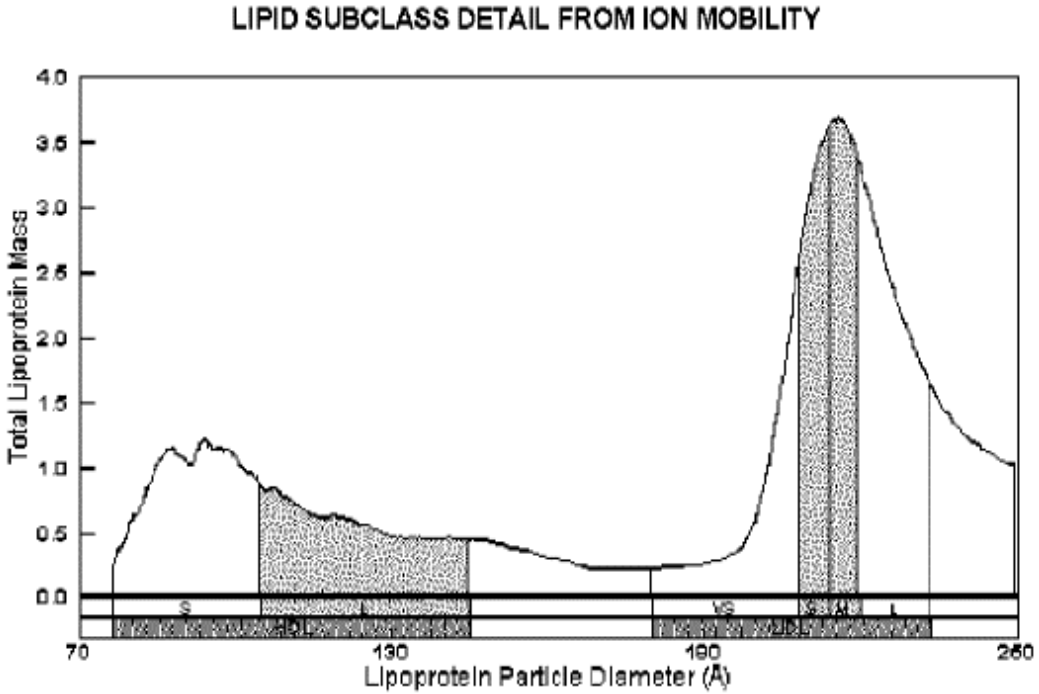
LDL Pattern & Size



Test Name	Current Result & Risk: Optimal	Current Result & Risk: Non-Optimal	Risk/Reference Interval: Optimal	Moderate	High	Units
LIPOPROTEIN SUBFRACTIONS						
LDL PATTERN		B	A	N/A	B	Pattern
LDL PEAK SIZE		213.4	>222.9	222.9-217.4	<217.4	Angstrom

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Interventions

Dietary changes

- MedD, lower carbohydrate with a focus on whole foods, good sources of protein, anti-inflammatory fat, color (eat the rainbow) and fiber
- Fasting mimicking and TRE

Nutraceuticals

- Berberine + ALA 1000mg/day in divided doses
- Bergamot 2g/day
- Fish oil 2g/day
- Antioxidants and CoQ10
- NAC and milk thistle
- Fiber (with arabinogalactan, pectin, green tea phytosome)

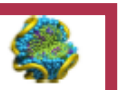
Advanced Panel 2022

Lipid Tests

Total Cholesterol		227	
	<200	200-240	>240 mg/dL
Direct LDL-C		160	
	<100	100-160	>160 mg/dL
HDL-C			36
	>60	50-60	<50 mg/dL
Triglycerides	129		
	<150	150-200	>200 mg/dL
Non-HDL-C			191
	<130	130-190	>190 mg/dL
ApoB			134
	<80	80-120	>120 mg/dL
LDL-P[1]			2688
	<1200	1200-1800	>1800 nmol/L
HDL-P[1]			31.8
	>44.0	34.0-44.0	<34.0 umol/L
sdLDL-C		39	
	<20	20-40	>40 mg/dL
%sdLDL-C		24	
	<20	20-30	>30 %
VLDL-C		31	
	<30	30-40	>40 mg/dL
Lp(a)	29		
	<30	30-50	>50 mg/dL
ApoA-I			109.1
	>180	140-180	<140 mg/dL

Lipid Ratios

TC/HDL-C			6.3
	<4	4-6	>6
VLDL-C/TG		0.24	
	<0.2	0.2-0.3	>0.3
ApoB/ApoA-I			1.23
	<0.6	0.6-0.9	>0.9
HDL-C/TG		0.28	
	>0.5	0.25-0.5	<0.25

α-1			26.6	
	>45	35-45	<35 mg/dL	
α-2			44.4	
	>65	55-65	<55 mg/dL	
α-3	15.6			
	<20	20-25	>25 mg/dL	
α-4	12.6			
	<20	20-25	>25 mg/dL	
preβ–1	8.1			
	<20	20-25	>25 mg/dL	

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Fall 2020 Inflammation Profile

Test Name	Current Result & Risk		Risk/Reference Interval			
	Optimal	Non-Optimal	Optimal	Moderate	High	Units
INFLAMMATION						
HS CRP		> 10.0	<1.0	1.0-3.0	>3.0	mg/L
LP PLA2 ACTIVITY		133	<=123	N/A	>123	nmol/min/mL

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Winter 2022 Inflammation Profile

hsCRP 2020 10.1 → 5.8

- Better but not ideal
- Hip pain

LpPLA2 133 → 199*

- Got worse!
- Note different reference ranges

Insulin slightly worse at 11 (from 10)

- Impact of cortisol and pain?

Inflammation and Oxidation Tests

hs-CRP			**5.8**		
	<1.0	1.0-3.0	**>3.0 mg/L**		
$LpPLA_2$ Activity		**199**			
	<180	**180-224**	≥225 nmol/min/mL		

Interpretation: Current studies reveal increased risk of stroke when both $LpPLA_2$ and hs-CRP are elevated. Elevated $LpPLA_2$ and hs-CRP may indicate arterial wall inflammation, plaque instability and reduced endothelial function. HIGH hs-CRP may indicate inflammation and may be associated with increased CVD risk. BORDERLINE $LpPLA_2$ may indicate vascular inflammation, plaque instability and may be associated with increased CVD risk.

Consideration: Consider evaluating potential contributing CVD risk factors. Identify and treat underlying causes such as atherogenic lipoproteins and metabolic markers. If indicated, control blood pressure, encourage smoking cessation and weight reduction.

Metabolic Tests

Insulin[3]		**11**		9	
	<10	**10-15**	>15 µU/mL		

Consideration: Consider encouraging dietary modification supported by education. If indicated encourage weight reduction, smoking cessation, increased activity and control blood pressure.

Fatty Acid Panel Winter 2022

Saturated Fatty Acid Index	28.8			Saturated FA Index is OPTIMAL.		
	<30.0	30.0-33.0	>33.0 %			
Trans Fatty Acid Index	0.33			Trans FA Index is OPTIMAL.		
	<0.50	0.50-0.70	>0.70 %			
Unsaturated/Saturated Ratio	2.43			Unsaturated/Saturated Ratio is OPTIMAL.		
	>2.25	2.00–2.25	<2.00			
Omega-3 Fatty Acid Index	8.58			Omega-3 FA Index is OPTIMAL. Eicosapentaenoic Acid (EPA) level is OPTIMAL. Docosahexaenoic Acid (DHA) level is OPTIMAL. Maintain current level of dietary and/or supplemental intake of Omega-3 fatty acids.		
	>4.50	2.50-4.50	<2.50 %			
EPA	119.7					
	>50.0	20.0-50.0	<20.0 µg/mL			
DHA	167.4					
	>100.0	60.0-100.0	<60.0 µg/mL			
ALA		26.1		Alpha Linolenic Acid (ALA) level is BORDERLINE. Higher levels of ALA have been associated with a lower risk of CVD. Consider recommending increasing intake of walnuts, chia seeds, ground flaxseeds, or flaxseed oil.		
	>30.0	14.0–30.0	<14.0 µg/mL			
EPA/AA Ratio	0.45			EPA/AA Ratio is OPTIMAL. Some authorities indicate that an EPA/AA ratio of >0.75 is optimal, usually only achieved with supplementation.		
	>0.17	0.07-0.17	<0.07			
AA/EPA Ratio	2.24			AA/EPA Ratio is OPTIMAL. Some authorities indicate that an AA/EPA ratio of <1.33 is optimal, usually only achieved with supplementation.		
	<5.88	5.88-14.29	>14.29			

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Fatty Acid Panel Winter 2022 (cont)

	Low	Mid	High			
Monounsaturated Fatty Acid Index		**20.0**		Values are reported according to the lowest, middle and highest thirds of our reference population. Dietary monounsaturated fats from plant sources reduce heart disease risk; however, blood levels of monounsaturated fats do not necessarily correlate closely with dietary intake. More data are needed on the complex effects of omega-6 fatty acids on cardiovascular risk.		
	<20.0	20.0-23.0	>23.0 %			
Omega-6 Fatty Acid Index		**41.0**				
	<39.0	39.0-43.0	>43.0 %			
Linoleic Acid (LA)		**1073.1**				
	<930.0	930.0-1150.0	>1150.0 µg/mL			
Arachidonic Acid (AA)		**268.4**				
	<250.0	250.0-320.0	>320.0 µg/mL			
Omega-3/Omega-6 Ratio			**0.23**			
	<0.07	0.07-0.10	>0.10			

Interpret with caution!

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Case 4

Diabetes & NAFLD

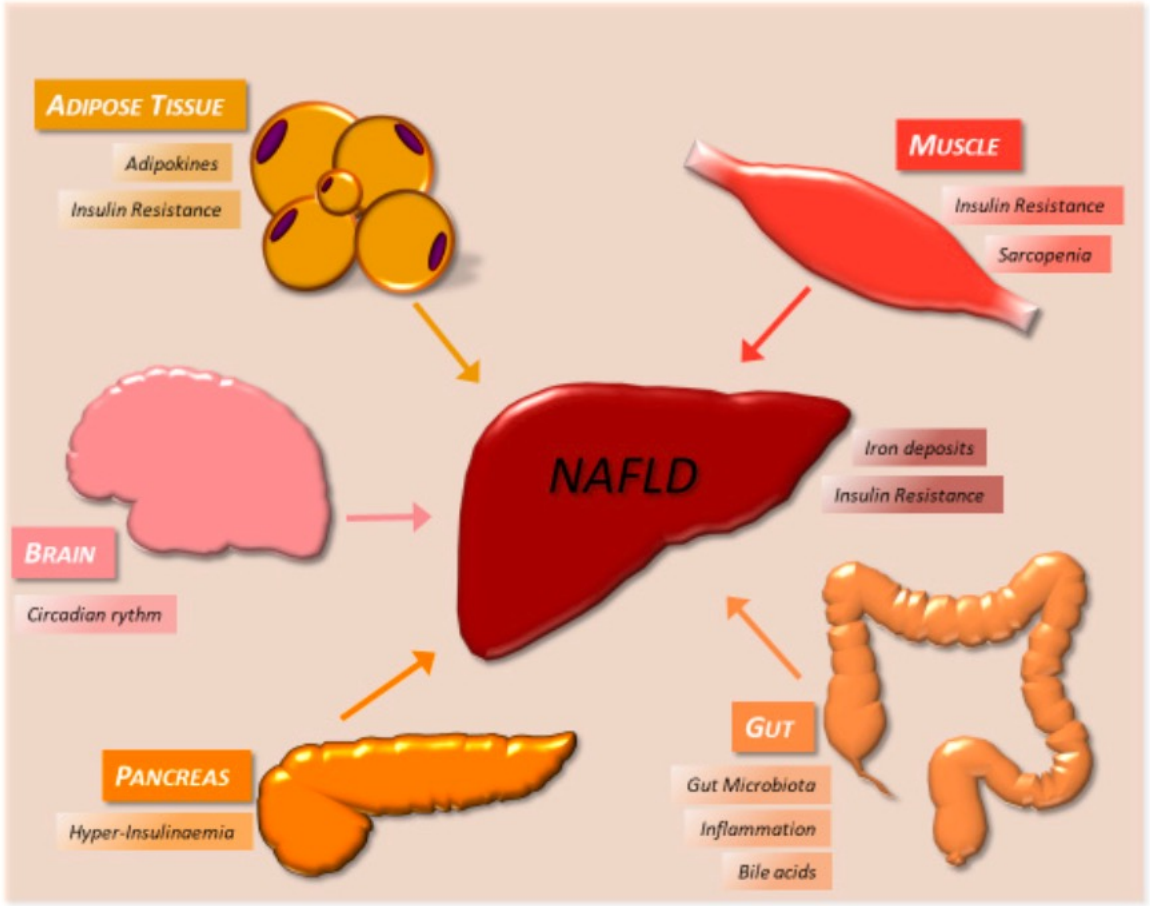
HPI/ROS

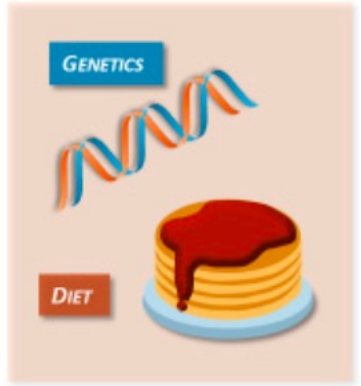
- 47 y/o Female with Type 2 Diabetes
  - On insulin pump
  - NAFLD (liver enzyme elevations x 5 years)
  - HbA1c 10.2
  - 5 years post hysterectomy (menopause)
- Fatigue (poor sleep, wakes after a few hours of sleep)
- Family Hx (Cardiac events grandmother, doesn't know biological dad)
- Yeast infection Hx with SGLT-2i's.
- No gallbladder, stomach problems since childhood
  - + Diarrhea and NV this week
- BP 116/78, pulse of 88

Pertinent Labs 12-2019

- Ferritin 730 ng/ml (range 15-150)
- Vitamin B12 1685 (232-1245)
- Hgb 16.6 g/dl (11.1- 15.9
- Hct 49.1 % (34-46)
- Alk Phos 122 IU/L (39-117)
- AST 121 IU/L (0-40)
- ALT 160 IU/L (0-32)
- Glucose 258 mg/dl (70-100)
- HbA1c 10.2%
- Thyroid Panel WNL except T3 uptake low
- Vitamin D 18.8 ng/ml (30-100)

Nonalcoholic Fatty Liver Disease (NAFLD)





Marchisello S, et al. *Int J Mol Sci*. 2019;20(8):1948.

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Nonalcoholic Fatty Liver Disease (NAFLD)

- Liver steatosis in the absence of secondary causes of hepatic fat accumulation (ie alcohol abuse)
- Liver biopsy is gold standard for diagnosis
  - MRI/CT imaging is also used
- Other differential dx: hepatitis C, autoimmune hepatitis, celiac disease, Wilson's disease, hemochromatosis, a/hypo-betalipoproteinemia, and other rare causes of liver steatosis
- Leading cause of liver disease in western countries

Marchisello S, et al. *Int J Mol Sci*. 2019;20(8):1948.

Nonalcoholic Fatty Liver Disease (NAFLD)

- Overlap with pathophysiological components of Type 2 DM
  - Insulin resistance (although NAFLD can proceed IR and worsen as well)
  - Oxidative stress
  - ATP depletion (Mitochondrial dysfunction)
  - Endotoxins
- All leads to fibrosis and eventually cancer
- Hallmark feature is TG accumulation in the liver due the the imbalanced fatty acid (FA) influx and efflux.

Marchisello S, et al. *Int J Mol Sci*. 2019;20(8):1948.

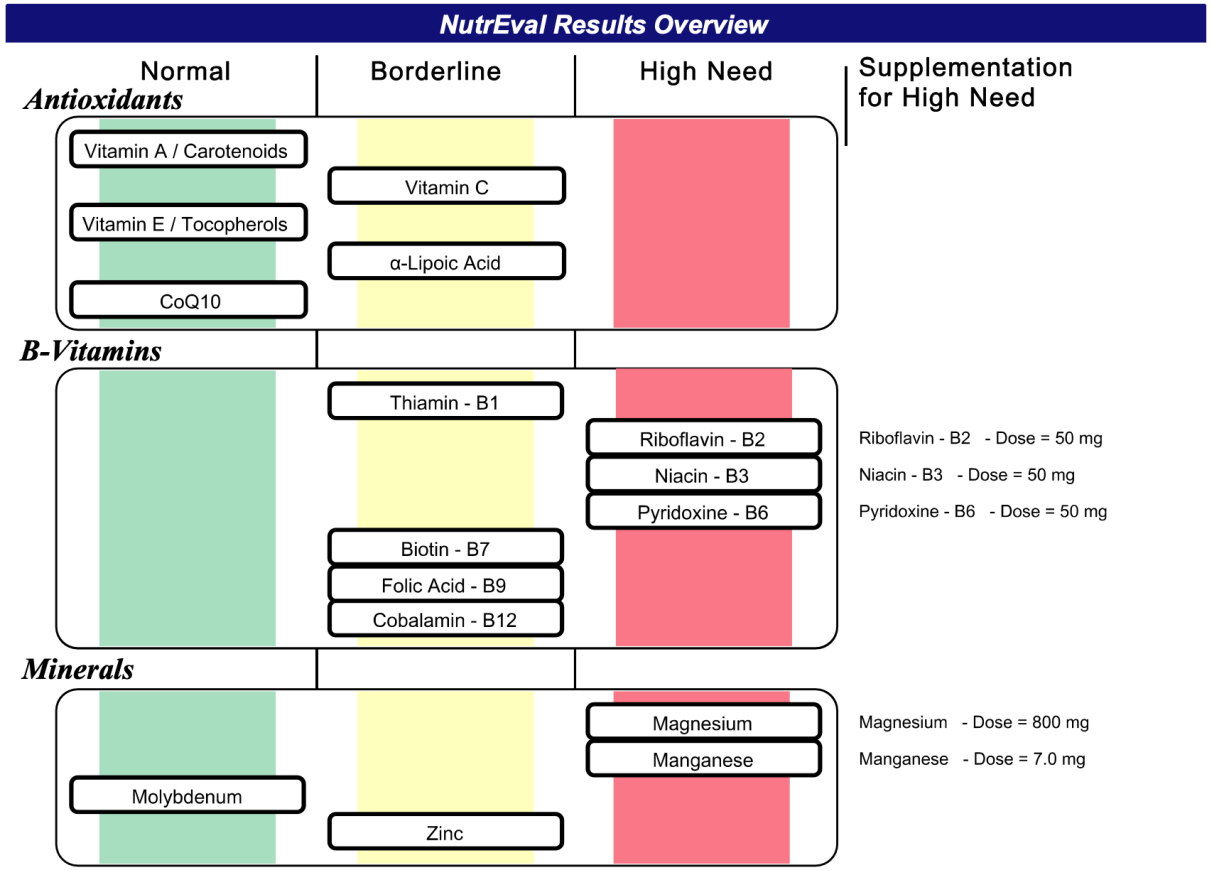
Follow-up 12-2019

- Hepatitis Screen Negative
- Abdominal US confirms NAFLD
- Recommended
  - Probiotic (Women's Flora blend)
  - Vitamin E
  - Berberine
  - Curcumin
- Stool testing/micronutrient testing discussed patient declined at this time.
- New medications (initial insulin rate decrease by 20%)
  - Semaglutide 0.25 mg once weekly (goal to titrate from here to 0.5 mg, then 1 mg)
  - Pioglitazone 15 mg once daily
- Vitamin D 50,000 IU once per week

Follow-up 2020

- Jan 2020
  - Patient had started Vitamin E, CoQ10, berberine, fish oil, probiotic and cinnamon.
  - Tolerating semgaglutide and pioglitazone
  - Titrated semaglutide to 1 mg at the visit
  - Cinnamon was causing GI upset, ok to stop.
- Feb 2020
  - Hepatic panel on 02-12-20
    - ALK Phos: WNL, AST 43 IU/L, ALT 34 IU/L
- May 2020
  - HbA1c 5.6%
- June 2020
  - Hepatic panel all WNL
  - Vitamin D up to 42 ng/ml
  - Off all insulin
  - Lipid Panel Pattern B (small dense particles) high TG, high insulin resistance score

Follow-up 2020- Nutrient Testing



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Metabolic Analysis Markers (Urine)

All biomarkers reported in mmol/mol creatinine unless otherwise noted.

Malabsorption and Dysbiosis Markers

Malabsorption Markers

		Reference Range
Indoleacetic Acid (IAA)	4.4	<= 4.2
Phenylacetic Acid (PAA)	0.23	<= 0.12

Bacterial Dysbiosis Markers

		Reference Range
Dihydroxyphenylpropionic Acid (DHPPA)	1.4	<= 5.3
3-Hydroxyphenylacetic Acid	<dl	<= 8.1
4-Hydroxyphenylacetic Acid	18	<= 29
Benzoic Acid	0.18	<= 0.05
Hippuric Acid	<dl	<= 603

Yeast / Fungal Dysbiosis Markers

		Reference Range
Arabinose	64	<= 96
Citramalic Acid	8.4	<= 5.8
Tartaric Acid	<dl	<= 15

Cellular Energy & Mitochondrial Metabolites

Carbohydrate Metabolism

		Reference Range
Lactic Acid	<dl	1.9-19.8
Pyruvic Acid	<dl	7-32
β-OH-Butyric Acid (BHBA)	1.7	<= 2.8

Energy Metabolism

Citric Acid	736	40-520
Cis-Aconitic Acid	23	10-36
Isocitric Acid	73	22-65

Neurotransmitter Metabolites

		Reference Range
Vanilmandelic Acid	<dl	0.4-3.6
Homovanillic Acid	<dl	1.2-5.3
5-OH-indoleacetic Acid	11.9	3.8-12.1
3-Methyl-4-OH-phenylglycol	<dl	0.02-0.22
Kynurenic Acid	11.2	<= 7.1
Quinolinic Acid	<dl	<= 9.1
Kynurenic / Quinolinic Ratio	NR	>= 0.44

Vitamin Markers

		Reference Range
α-Ketoadipic Acid	1.2	<= 1.7
α-Ketoisovaleric Acid	<dl	<= 0.97
α-Ketoisocaproic Acid	<dl	<= 0.89
α-Keto-β-Methylvaleric Acid	<dl	<= 2.1
Formiminoglutamic Acid (FIGlu)	<dl	<= 1.5
Glutaric Acid	0.60	<= 0.51
Isovalerylglycine	2.8	<= 3.7
Methylmalonic Acid	<dl	<= 1.9
Xanthurenic Acid	0.50	<= 0.96
3-Hydroxypropionic Acid	12	5-22
3-Hydroxyisovaleric Acid	<dl	<= 29

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Essential and Metabolic Fatty Acids Markers (RBCs)

Omega 3 Fatty Acids

Analyte	(cold water fish, flax, walnut)	Reference Range
α-Linolenic (ALA) 18:3 n3	0.16	>= 0.09 wt %
Eicosapentaenoic (EPA) 20:5 n3	0.28	>= 0.16 wt %
Docosapentaenoic (DPA) 22:5 n3	1.34	>= 1.14 wt %
Docosahexaenoic (DHA) 22:6 n3	2.8	>= 2.1 wt %
% Omega 3s	4.6	>= 3.8

Omega 9 Fatty Acids

Analyte	(olive oil)	Reference Range
Oleic 18:1 n9	13	10-13 wt %
Nervonic 24:1 n9	2.7	2.1-3.5 wt %
% Omega 9s	15.5	13.3-16.6

Saturated Fatty Acids

Analyte	(meat, dairy, coconuts, palm oils)	Reference Range
Palmitic C16:0	20	18-23 wt %
Stearic C18:0	17	14-17 wt %
Arachidic C20:0	0.27	0.22-0.35 wt %
Behenic C22:0	1.01	0.92-1.68 wt %
Tricosanoic C23:0	0.20	0.12-0.18 wt %
Lignoceric C24:0	3.1	2.1-3.8 wt %
Pentadecanoic C15:0	0.13	0.07-0.15 wt %
Margaric C17:0	0.29	0.22-0.37 wt %
% Saturated Fats	42.8	39.8-43.6

Methodology: GCMS

Omega 6 Fatty Acids

Analyte	(vegetable oil, grains, most meats, dairy)	Reference Range
Linoleic (LA) 18:2 n6	13.7	10.5-16.9 wt %
γ-Linolenic (GLA) 18:3 n6	0.12	0.03-0.13 wt %
Dihomo-γ-linolenic (DGLA) 20:3 n6	1.99	>= 1.19 wt %
Arachidonic (AA) 20:4 n6	17	15-21 wt %
Docosatetraenoic (DTA) 22:4 n6	2.61	1.50-4.20 wt %
Eicosadienoic 20:2 n6	0.22	<= 0.26 wt %
% Omega 6s	35.9	30.5-39.7

Monounsaturated Fats

Omega 7 Fats		Reference Range
Palmitoleic 16:1 n7	0.27	<= 0.64 wt %
Vaccenic 18:1 n7	0.78	<= 1.13 wt %
Trans Fat		
Elaidic 18:1 n9t	0.29	<= 0.59 wt %

Delta - 6 Desaturase Activity

	Upregulated Functional Impaired	
Linoleic / DGLA 18:2 n6 / 20:3 n6	6.9	6.0-12.3

Cardiovascular Risk

Analyte		Reference Range
Omega 6s / Omega 3s	7.8	3.4-10.7
AA / EPA 20:4 n6 / 20:5 n3	61	12-125
Omega 3 Index	3.1	>= 4.0

The Essential Fatty Acid reference ranges are based on an adult population.

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Oxidative Stress Markers

Oxidative Stress Markers

Reference Range

Methodology: Colorimetric, thiobarbituric acid reactive substances (TBARS), Alkaline Picrate, Hexokinase/G-6-PDH, LC/MS/MS, HPLC

Glutathione (whole blood)	870	>=669 micromol/L
Lipid Peroxides (urine)	6.9	<=10.0 micromol/g Creat.
8-OHdG (urine)	<DL	<=15 mcg/g Creat.
Coenzyme Q10, Ubiquinone (serum)	0.84	0.43-1.49 mcg/mL

The Oxidative Stress reference ranges are based on an adult population.
The performance characteristics of the Oxidative Stress Markers have been verified by Genova Diagnostics, Inc. Unless otherwise noted with ◆ they have not been cleared by the U.S. Food and Drug Administration.

Elemental Markers

Nutrient Elements

Element	Reference Range	Reference Range
Copper *(plasma)*	91.6	75.3-192.0 mcg/dL
Magnesium *(RBC)*	40.2	30.1-56.5 mcg/g
Manganese *(whole blood)*	9.1	3.0-16.5 mcg/L
Potassium *(RBC)*	2,388	2,220-3,626 mcg/g
Selenium *(whole blood)*	172	109-330 mcg/L
Zinc *(plasma)*	88.4	64.3-159.4 mcg/dL

Toxic Elements*

Element	Reference Range	Reference Range
Lead	0.35	<= 2.81 mcg/dL
Mercury	0.60	<= 4.35 mcg/L
Arsenic	0.8	<= 13.7 mcg/L
Cadmium	0.11	<= 1.22 mcg/L
Tin	<DL	<= 0.39 mcg/L

* All toxic Elements are measured in whole blood.
Methodology: ICP-MS

The Elemental reference ranges are based on an adult population.
The performance characteristics of the Elemental Markers have been verified by Genova Diagnostics, Inc. They have not been cleared by the U.S. Food and Drug Administration.

Elemental testing performed by Genova Diagnostics, Inc. 3425 Corporate Way, Duluth, GA 30096 - Robert M. David, PhD, Lab Director - CLIA Lic. #11D0255349 - Medicare Lic. #34-8475

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Functional Medicine Recommendations

- Recommended by FxMed CNP
  - High Quality MV Packets with Omega 3 FA
  - Green Smoothies with different fibers

Polling Question

1. What intervention do you see best to focus on first?
    a. Dietary
    b. Medication Changes
    c. New Supplements
    d. Exercise
    e. More than one of the above

Hormone Labs- 2021

- Estradiol <5.0 pg/ml
- Estrogens Total 80 pg/ml
- Progesterone 0.1 ng/ml
- SHBG 85.5 nmol/L (24.6-122)
- Testosterone Serum 4 ng/dl (4-50)
- Free testosterone 5.3 pg/ml (0-4.2)
- DHEA 100 ng/dl (31-701)

How do hormones impact CVD risk?

Hormone Connections to Cardiometabolic

- Estrogen
  - Decreases plaque formations
  - Helps maintain the elasticity of arteries
  - Dilates small arteries
  - Increases blood flow
  - Decreases LDL and prevents its oxidation
  - Decreases lipoprotein(a)
  - Acts as a natural calcium channel blocker to keep arteries open
  - Decreases coronary artery calcification

NeLobo RA et al. Obstetrics and Gynecology. 1994 Dec;84(6):987-995ed Citation
Walsh BW, et al. N Engl J Med. 1991 Oct 24;325(17):1196-204.
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HHS Public Access
Author manuscript
N Engl J Med. Author manuscript; available in PMC 2016 September 30.

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N Engl J Med. 2016 March 31; 374(13): 1221–1231. doi:10.1056/NEJMoa1505241.

Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol

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M.D., **Matthew J. Budoff, M.D.**, **Juliana Hwang-Lev**
M.D., **Laurie Dustin, M.S.**, **Naoko Kono, M.P.H.**, **Fra**
M.S., **Stanley P. Azen, Ph.D.**, and **the ELITE Resea**
Atherosclerosis Research Unit (H.N.H., W.J.M., J.H.-
the Departments of Medicine (H.N.H.), Preventive Me
S.P.A.), Molecular Pharmacology and Toxicology (H.N
Gynecology (D.S., F.Z.S.), Keck School of Medicine,
Angeles, the Departments of Health Research and P
Neurological Sciences, Stanford University, Stanford

METHODS—A total of 643 healthy postmenopausal women were stratified according to time since menopause (<6 years [early postmenopause] or ≥10 years [late postmenopause]) and were randomly assigned to receive either oral 17β-estradiol (1 mg per day, plus progesterone [45 mg] vaginal gel administered sequentially [i.e., once daily for 10 days of each 30-day cycle] for women with a uterus) or placebo (plus sequential placebo vaginal gel for women with a uterus). The primary outcome was the rate of change in carotid-artery intima– media thickness (CIMT), which was measured every 6 months. Secondary outcomes included an assessment of coronary atherosclerosis by cardiac computed tomography (CT), which was performed when participants completed the randomly assigned regimen.

CONCLUSIONS—Oral estradiol therapy was associated with less progression of subclinical atherosclerosis (measured as CIMT) than was placebo when therapy was initiated within 6 years after menopause but not when it was initiated 10 or more years after menopause. Estradiol had no significant effect on cardiac CT measures of atherosclerosis in either postmenopause stratum. (Funded by the National Institute on Aging, National Institutes of Health; ELITE ClinicalTrials.gov number, NCT00114517.)

Menopausal Hormone Therapy and Type 2 Diabetes Prevention

- Large, randomized controlled trials suggest that menopausal hormone therapy (MHT) using estrogens delays the onset of type 2 diabetes in women.
- MHT improves *β*-cell insulin secretion, glucose effectiveness, and insulin sensitivity, as measured in clinical settings.
- Lower premenopausal E2 levels during the early menopausal transition were associated with 47% higher risk of developing diabetes
- In the meta-analysis by Salpeter *et al.*
  - MHT reduced the HOMA-IR in women with diabetes by an average of 36%, a greater reduction than that observed in postmenopausal women without known diabetes

Mauvais-Jarvis, Franck et al.. *Endocr Rev*. 2017;38(3):173-188. doi:10.1210/er.2016-1146
Salpeter SR, et al. *Diabetes Obes Metab*. 2006;8(5):538–554

Case 4

- Initiated
  - Biest 80/20 0.5 mg per gram, 1 gram topically per day
  - Oral micronized progesterone 100 mg capsule once daily in the evening
- Within a few weeks sleeping 7 hours a night
- Improved hair growth
- Glucose time in range improving *(note there were several other changes in diabetes targeted therapy around the same time, so it wasn't this alone)*

Take-Aways

1. Patients with dyslipidemia should be evaluated using advanced lipid profiles to determine treatment and predict individual CHD risk more accurately.
2. Nutrient depletions, inflammation markers, and hormone levels should be evaluate and used to formulate treatment in patients with cardiometabolic conditions.