Vascular Aging

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What is antiaging medicine?

- It depends on who you ask. Often, patients seeking age management tend to be more interested in cosmetic appearances. Testosterone for big muscles, hair implants, skin peels, laser treatments, hormone replacement, and supplements.
- I believe more emphasis should be placed on the causes of biological aging. Prevention of serious diseases such as heart attack, stroke, and cancer often gets sidelined because of less sex appeal. Skin treatments and hormone replacement will not do us any good we die of a stroke or heart attack next week!
- Optimal, slowed aging occurs from the inside out. NDs know this but it is often under emphasized by conventional antiaging providers.
- It spans a continuum from skin treatments into preventive medicine and then going beyond that into hormone replacement, glucose control, fasting, hot and cold therapy and then fiddling with all mechanisms of aging.

Vascular aging

- Vascular aging as an important consideration in antiaging and longevity medicine. Cardiovascular disease remains the leading cause of morbidity and mortality in the United States and other industrialized countries. Slowing aging is an important field.
- The human life and health span has been proposed to be approximately 120 years, Depending on what scientist you listen to. However, depending on biomedical advances, the lifespan could be possibly longer.
- Without proper blood for perfusion organs like the brain, eyes, heart, kidneys and the skin will fail.
- This thought is well represented by the axiom that “a man is only as old as his arteries” coined by the Canadian Sir William Ostler, MD in 1894.

Vascular Age

- Atherosclerosis is important, but its role may be overstated, while arterial stiffening, endothelial dysfunction, thickening, and pathological remodeling are often underrecognized. These processes mark the true onset of arterial disease—long before hospitalization, where outcomes may be uncertain.
- An emerging concept is that vascular age may be a better predictor of cardiovascular events than chronological age. Thanks to advances in technology, we can now assess vascular age more accurately using tools like carotid intima-media thickness (CIMT) via ultrasound, pulse wave velocity testing, and a range of new serum inflammatory biomarkers.
- Although arterial stiffening increases with age, it can be significantly slowed—and even reversed. Just as arterial plaque can regress, arterial stiffness can improve. Simple interventions such as regular exercise, arginine supplementation, and consumption of dietary nitrates (from leafy greens and beets) enhance nitric oxide delivery. More advanced strategies will be explored later.

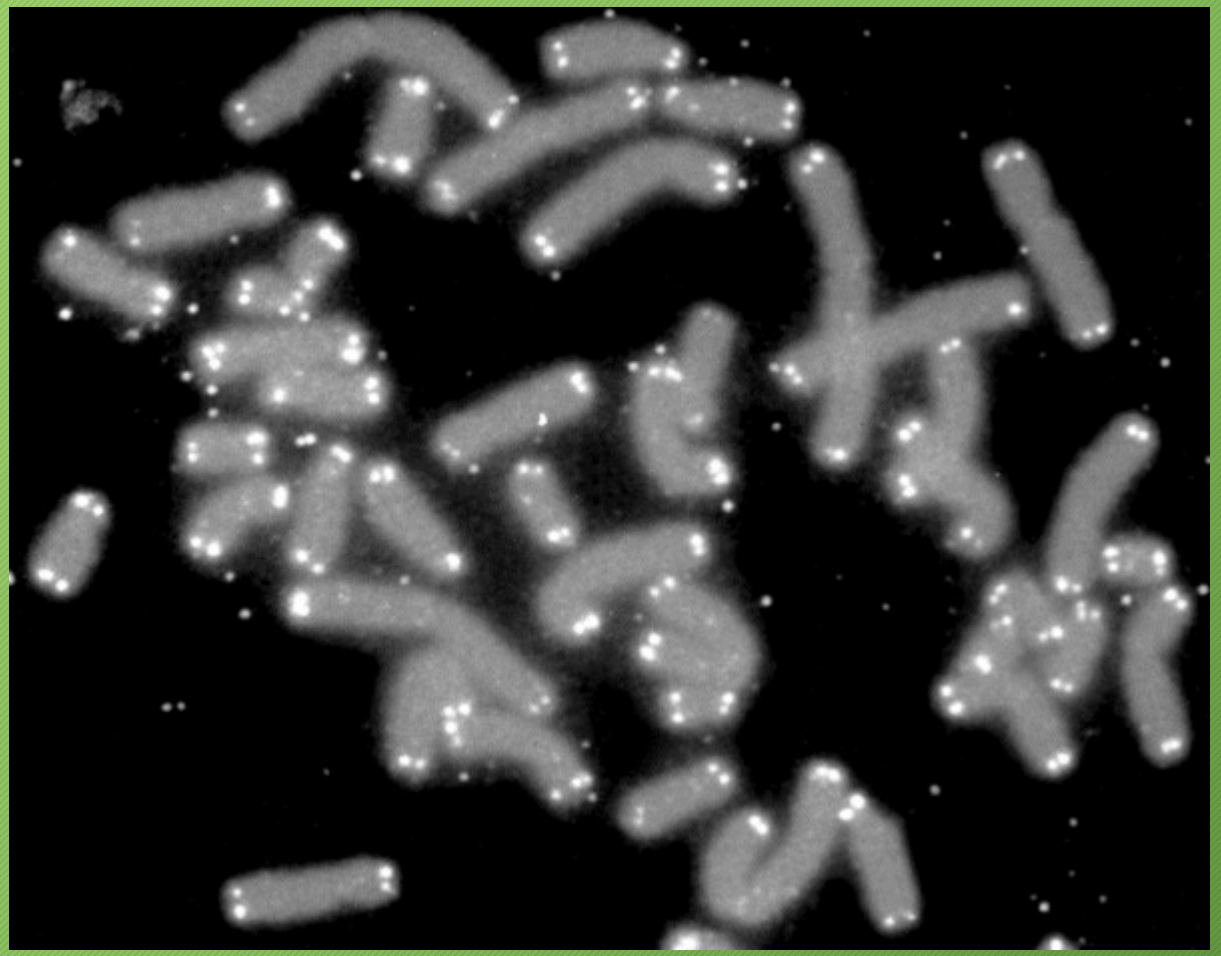
Current considerations on modifiable causes of aging:

- **Genomic instability from DNA damage:** DNA damage accelerates epigenetic aging and the loss of information at the epigenetic level and the genetic level causing genomic instability. Epigenetics is generally defined as heritable changes in gene activity and expression that occur without alteration in DNA sequence. Breaking a chromosome is the best way to accelerate aging. Even just a few DNA breaks can accelerate aging of any human tissue.
- **Deregulated nutrient sensing:** As we age there is a decline in nutrient sensing involving amino acids, glucose, insulin and sirtuin gene expression, which in turn ages the cells. Type 2 Diabetes, which is a bad for aging, is probably the worst one for arteries.
- **Mitochondrial dysfunction:** Both exercise and calorie restriction boost mitochondrial activity. Mitochondria that don't work well are a source of oxidative stress with age. Mitochondria accumulate ROS-induced damage and become dysfunctional. With time, the function of cells declines causing more aging and subsequent death.
- **Misfolded proteins:** What people can do for that is to fast. Fasting a little bit is good, fasting for three days is even better at reversing misfolded proteins and inducing chaperone-mediated autophagy [cellular regeneration], which helps maintain cellular proteostasis.
- **Telomere shortening:** This will happen naturally as cells divide but will also be accelerated by free radicals and DNA damage. Fasting and high intensity exercise have been shown to help. Supplements like resveratrol or an NAD-boosters to try to get sirtuins more active may slow down telomere shortening.

Current considerations on modifiable causes of aging cont.

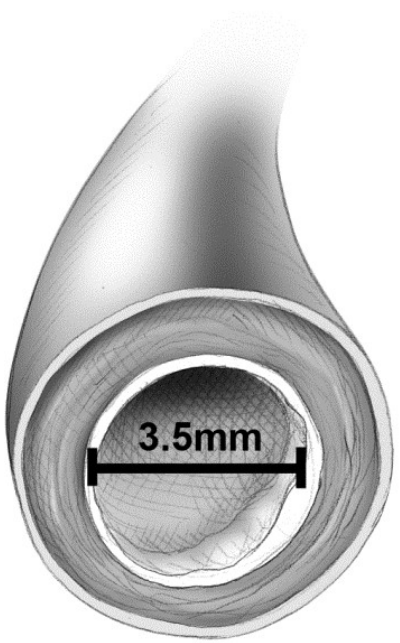
- Loss of information
- **Cellular senescence:** is a state where cells permanently stop dividing but remain metabolically active, typically in response to stressors like DNA damage, oxidative stress, or telomere shortening. While it helps prevent cancer by halting the spread of damaged cells, senescent cells can accumulate with age and release inflammatory factors (SASP), contributing to chronic inflammation, tissue dysfunction, and age-related diseases.



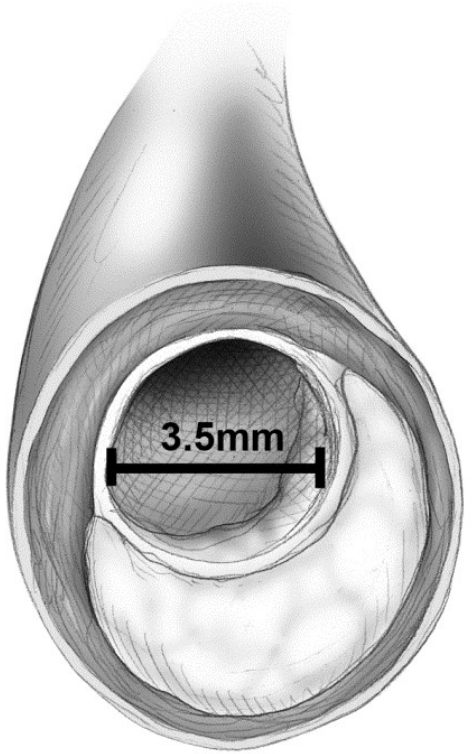


Inflammation/ immune/ lipids

- The balance between pro- and anti-inflammatory cytokines is the major factor that determines the stability of atherosclerotic plaque.
- Experimental data obtained from mouse models of atherosclerosis has shown that inhibition of pro-inflammatory cytokines suppresses atherosclerosis development and progression.
- LDL cholesterol and HDL cholesterol balance may or may not be the first assault on the endothelium. Once endothelial dysfunction happens it drives the process.

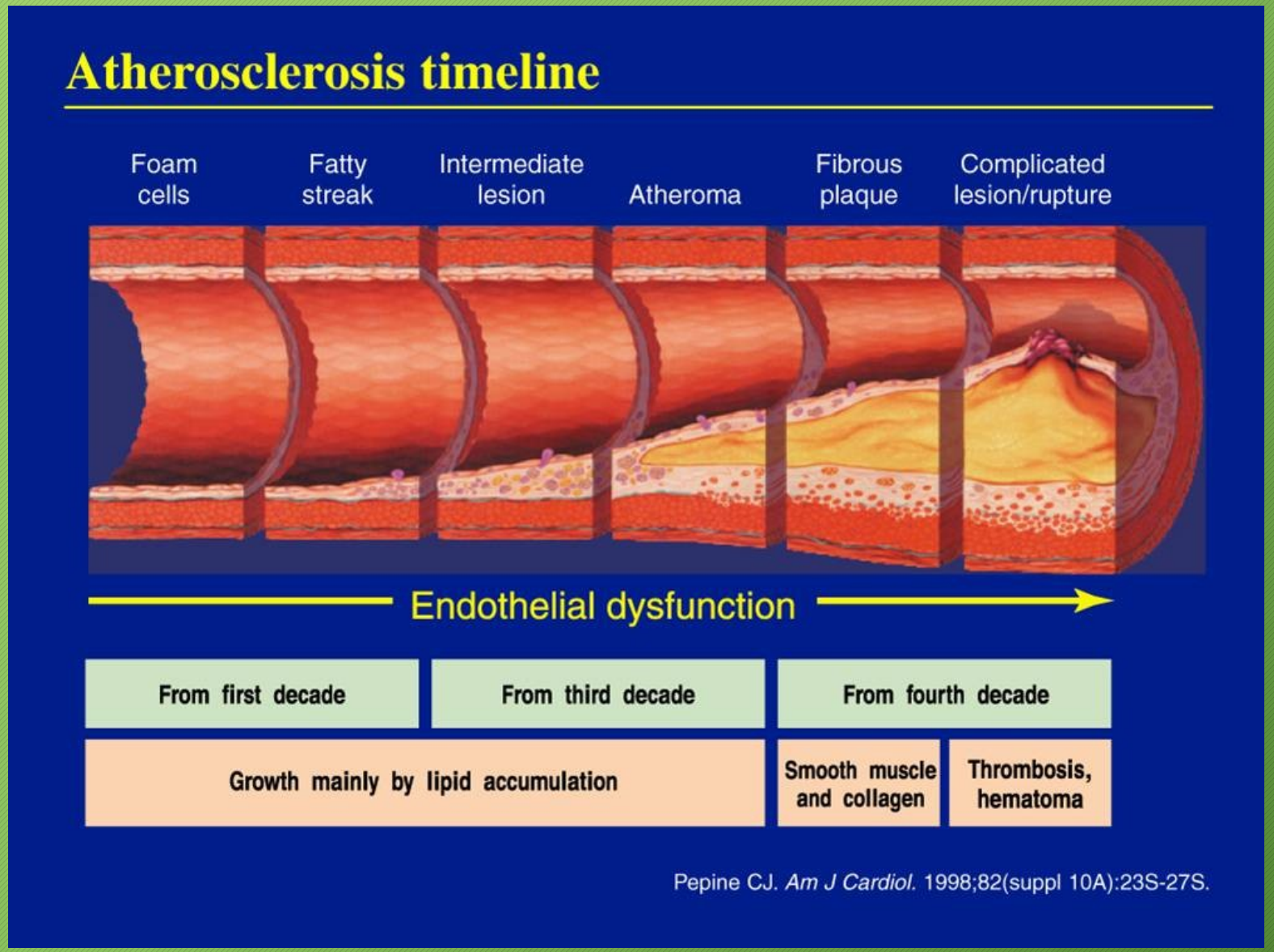


Early atherosclerosis



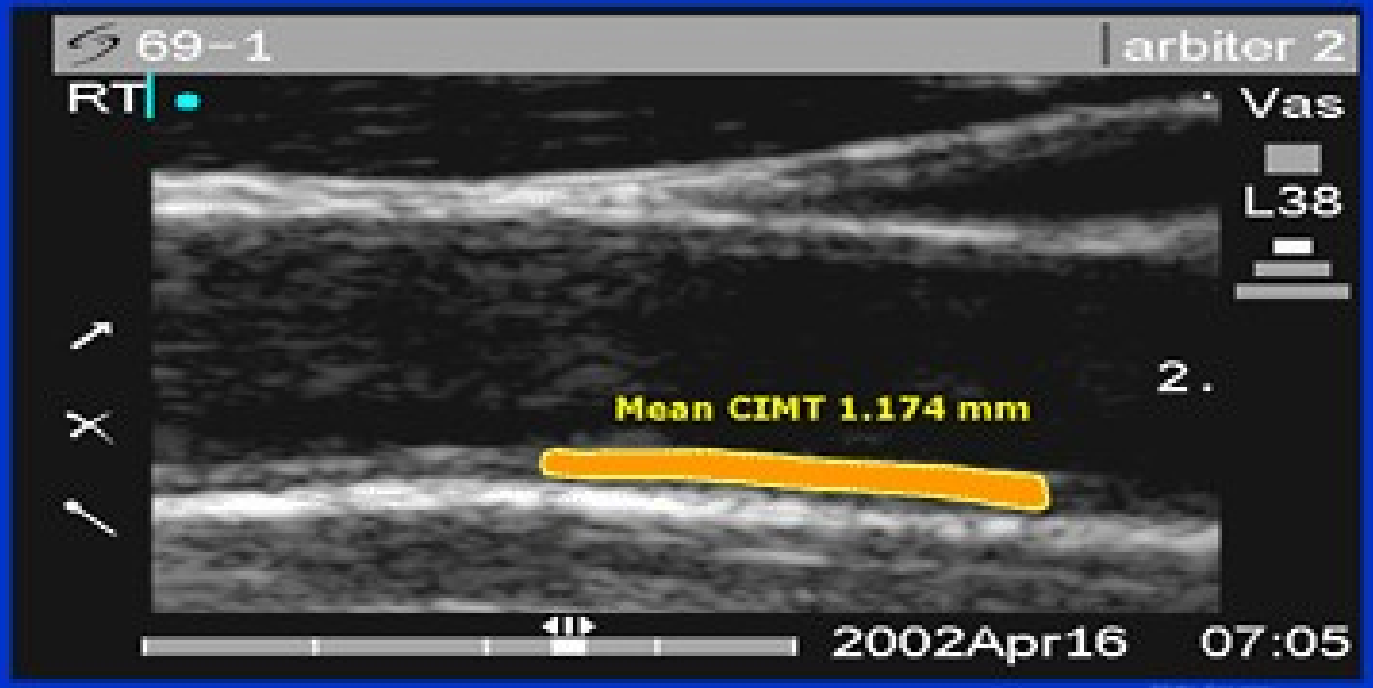
Advanced atherosclerosis - artery expands outward, outside diameter of artery increases, inside diameter stays the same.

Intima-media thickness

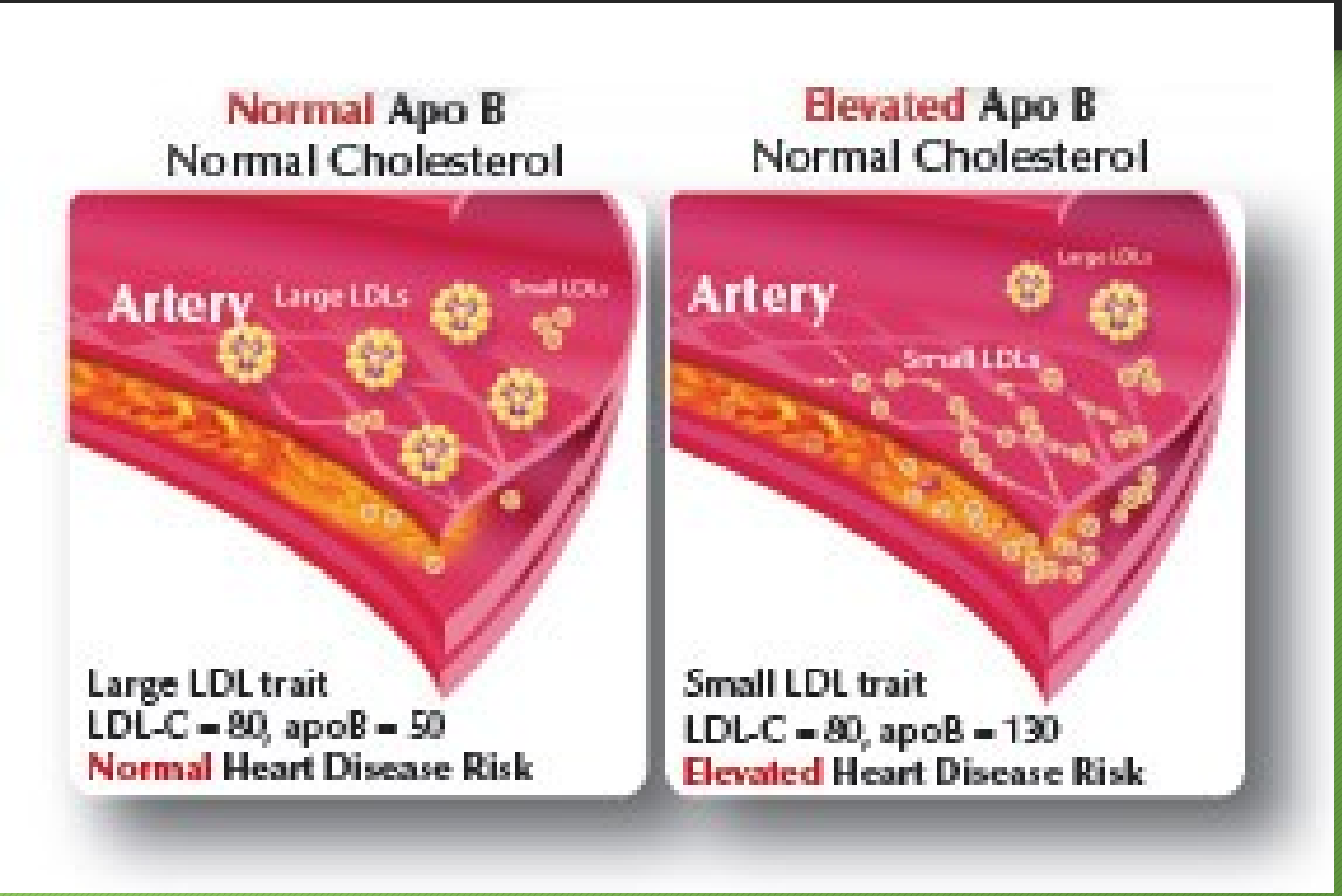


CIMT

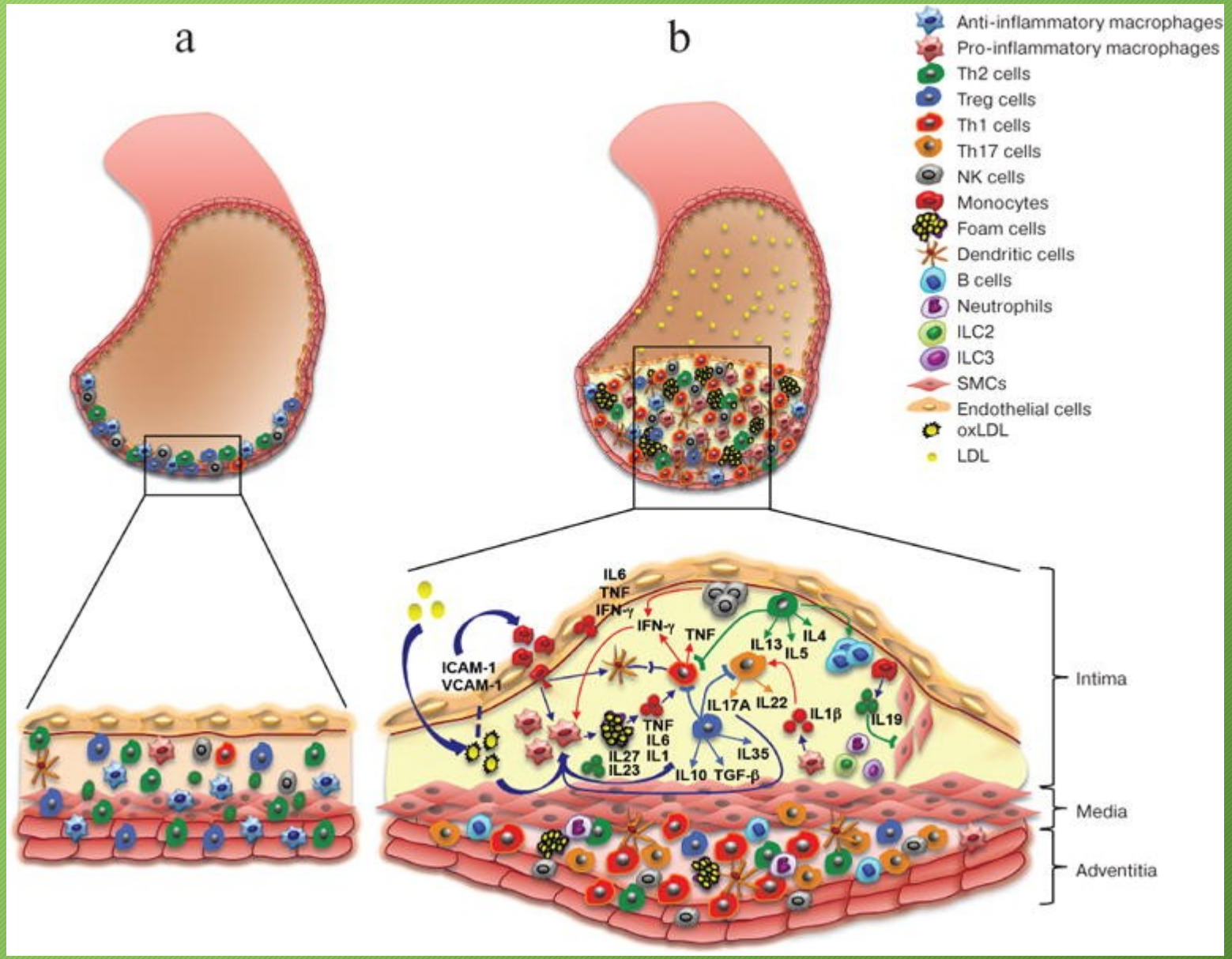
What is Carotid Intima–Media Thickness (CIMT)?



Like Adding Cheese to a Sandwich

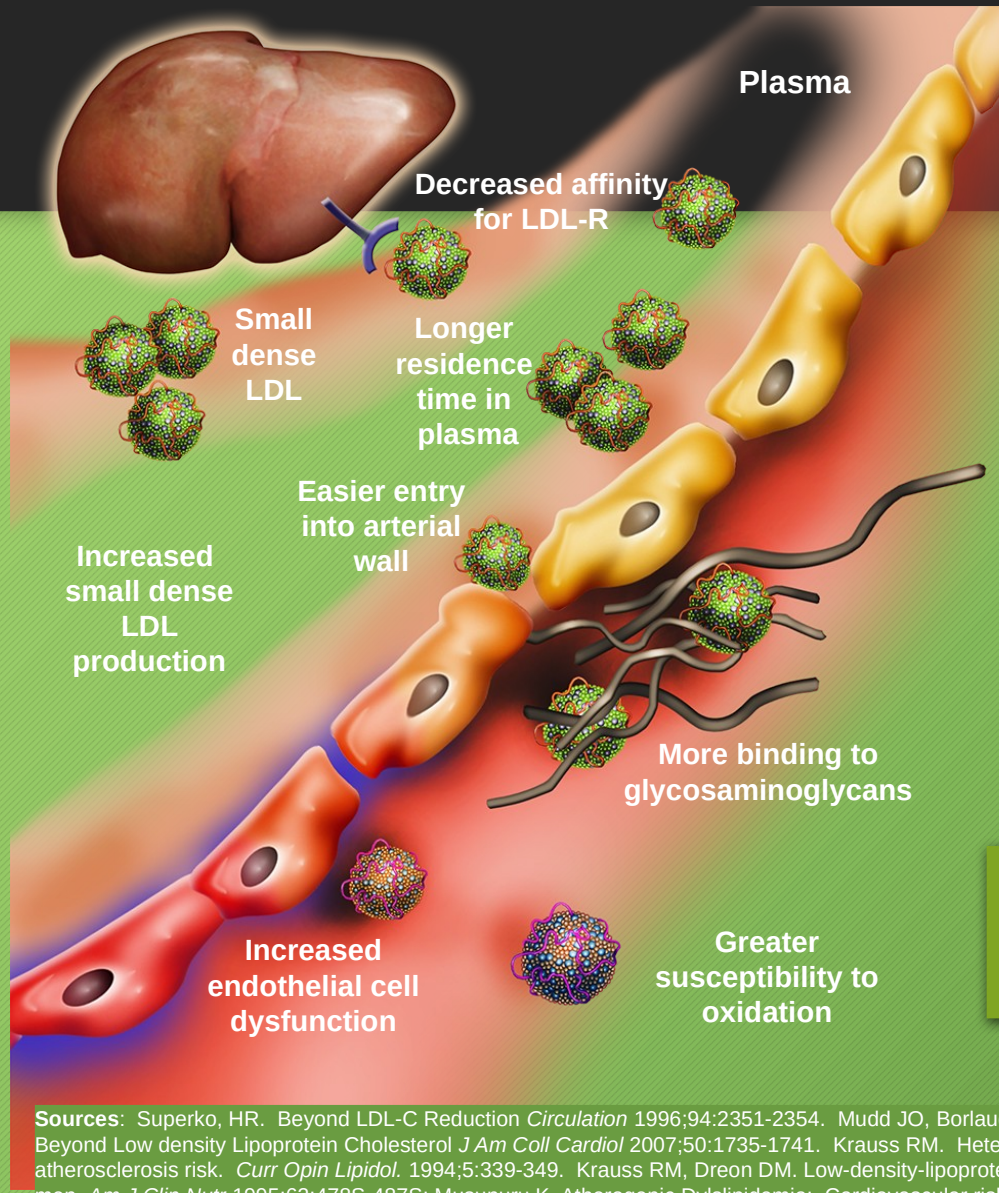


Inflammation drives atherosclerosis



What is happening here?

LIPID PANEL					
CHOLESTEROL, TOTAL	245	<200	N/A	>=200	mg/dL
HDL CHOLESTEROL	49	>=50	N/A	<50	mg/dL
TRIGLYCERIDES	164	<150	150-199	>=200	mg/dL
LDL-CHOLESTEROL	165	<100	100-129	>129	mg/dL (calc)
CHOL/HDLC RATIO	5.0	<=3.5	3.6-5.0	>5.0	calc
NON-HDL CHOLESTEROL	196	<130	130-189	>=190	mg/dL (calc)
LIPOPROTEIN FRACTIONATION, ION MOBILITY					
LDL PARTICLE NUMBER	1876	<1138	1138-1409	>1409	nmol/L
LDL SMALL	517	<142	142-219	>219	nmol/L
LDL MEDIUM	474	<215	215-301	>301	nmol/L
HDL LARGE	5559	>6729	6729-5353	<5353	nmol/L
LDL PATTERN	B	A	N/A	B	Pattern
LDL PEAK SIZE	213.9	>222.9	222.9-217.4	<217.4	Angstrom
APOLIPOPROTEINS					
APOLIPOPROTEIN B	141	<90	90-119	>=120	mg/dL
LIPOPROTEIN (a)	<10	<75	75-125	>125	nmol/L
INFLAMMATION					
HS CRP	4.7	<1.0	1.0-3.0	>3.0	mg/L
LP PLA2 ACTIVITY	134	<=123	N/A	>123	nmol/ min/mL



- LDL particle number may increase due to:
  - Increased production of small dense LDL-P
  - Decreased LDL-receptor affinity
  - Long residence time in plasma
- When LDL particle number increases:
  - Smaller LDL particles cross arteries, bind proteoglycans, and are oxidized more easily – **promoting atherogenesis and plaque vulnerability**
  - Endothelial cells are induced to produce more PAI-1 and thromboxane A2

LDL particle number (LDL-P) offers valuable prognostic information beyond traditional factors

Sources: Superko, HR. Beyond LDL-C Reduction *Circulation* 1996;94:2351-2354. Mudd JO, Borlaug BA, Johnston et al. Cannon CP, Deedwania PC, et al. Beyond Low density Lipoprotein Cholesterol *J Am Coll Cardiol* 2007;50:1735-1741. Krauss RM. Heterogeneity of plasma low-density lipoproteins and atherosclerosis risk. *Curr Opin Lipidol.* 1994;5:339-349. Krauss RM, Dreon DM. Low-density-lipoprotein subclasses and response to a low-fat diet in healthy men. *Am J Clin Nutr* 1995;62:478S-487S; Musunuru K. Atherogenic Dylslipidemia: Cardiovascular risk and Dietary Intervention. *Lipids* 2010;45:907-914.

Arteries get less elastic and thickened with age. This leads to arterial stiffness.

- Increased artery thickness is a hallmark of aging. Artery thickness can be predicted as a population ages despite aggressive treatment for established risk factors such as hypertension and hypercholesterolemia. Age itself causes not only arterial thickening but also other changes to arteries such as atherosclerosis, arterial stiffening and remodeling. Morphological changes occur in all layers of the vasculature.
- These changes mainly involve **intimal thickening** as well as sclerotic changes all resulting in increased vascular stiffness. Vascular stiffness, in turn, causes increased systolic blood pressure and pulse pressure with a decrease in diastolic blood pressure and a higher central blood pressure.
- Like the skin, arteries contain **elastin and collagen**. Arteries such as the aorta have more elastic properties than distal aspects of the vasculature. The stiffness of an artery is related to how much collagen compared to elastin is in the vessel wall.
- As we age other proteins buildup inside the artery wall and cause degradation of elastin, more collagen. The vascular smooth muscle cells also change their morphology from cells mainly involved contraction to cells causing thickening.
- The trajectory to dysfunction, however, can be modulated with diet, lifestyle, exercise and certain very targeted nutraceuticals.

Vascular age can be stabilized

Carotid-IMT (Carotid Intima Media Thickness)

Your Carotid-IMT was significantly abnormal, at > 0.800 mm. Talk with your doctor about treating this abnormal Carotid-IMT with medications that may reverse arterial wall thickness. Lifestyle adjustments may help support this effort, as well. A C-IMT of >1.000mm is most significant from a preventive cardiology perspective, and should receive aggressive medical attention.

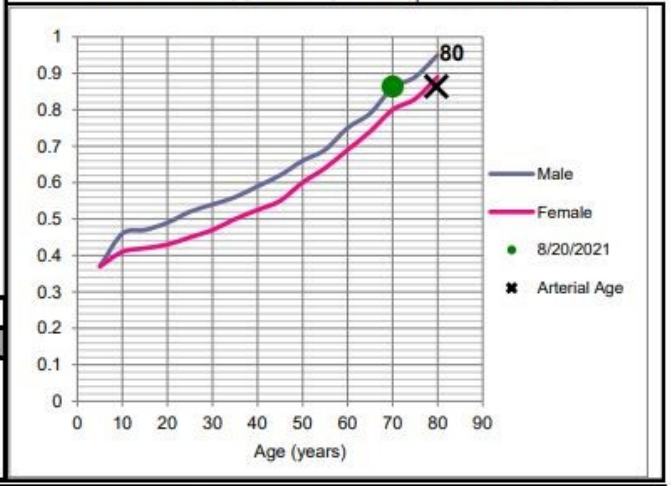


Date	8/20/2021	8/21/2020	2/21/2020
CIMT	0.864	0.922	0.863

An IMT measurement of less than 0.600 mm is generally considered healthy

Age	70	69	68
Arterial Age	80	85	80

Mean Distal 1 cm CCA IMT of General Population Without CAD



Thyroid Incedental Findings		
Location	Type	Notes

Carotid Plaque Assessment and Characterization

Left Carotid	Plaque		Right Carotid	No Plaque	
Max Velocity	65.7	cm/s	Max Velocity	39.3	cm/s

Atherosclerotic plaque was present in the carotid arteries of your neck. Medication strategies to treat this atherosclerotic plaque will need to be considered. Optimal exercise, nutrition, weight control, and stress management strategies will also help. Also, please discuss the use of daily Aspirin therapy with your doctor. The presence of carotid artery plaque is to be taken seriously, as it places you at higher risk for serious cardiovascular disease during the next 10 years.

Plaque	Current Test			Last Test			Previous Test		
Year-to-Year Comparison	8/20/2021			8/21/2020			2/21/2020		
Plaque Location	Type	Ht(mm)	Approx %	Type	Ht(mm)	Approx %	Type	Ht(mm)	Aprrox %
LT BULB	Soft	2.185	20%	Soft	1.796		Soft	1.102	
				Soft	1.524		Soft	1.717	
							Soft	1.455	

The data graphed above has been gathered from many known studies. This information should be used in conjunction with you physician as a estimate of your overall cardiovascular health. "Arterial Age" is equivalent to the 50th percentile of C-IMT values in a general population of patients at the aforementioned age with no history of coronary artery disease. The observed repeatability of IMT scores when using a standardized scanning and measuring protocol of 6 to 12 ultrasound images is within 4% with 95% confidence. This test is for screening purposes only. Your physician should interpret this IMT result in conjunction with your other risk factors. Medical decision-making must take a multitude of factors into account, and risk factor modification should be made only in

Arterial stiffness cont.

- Like epidermal cells the vasculature is also subject to cross-linking from **advanced glycation end products** (AGEs) and glucose. AGE related cross-linking occurs from a non-enzymatic reaction between reducing sugars proteins such as collagen and resulting in increased arterial stiffness. Arterial stiffness is a sensitive early measure of vascular health. It can be measured noninvasively by measuring pulse wave velocity. Sugar=aging
- Arterial stiffness is itself a disease that propagates in a feed forward cycle leading to higher systolic blood pressure, end organ damage from high pulsatile pressure, microvascular disease affecting the brain, eye and kidney as well as further endothelial dysfunction. The heart muscle is also affected.
- Increased stiffness increases heart afterload increasing the risk of pathologic remodeling such as left ventricular hypertrophy, overcompensation, diastolic dysfunction, heart failure and volume overload.

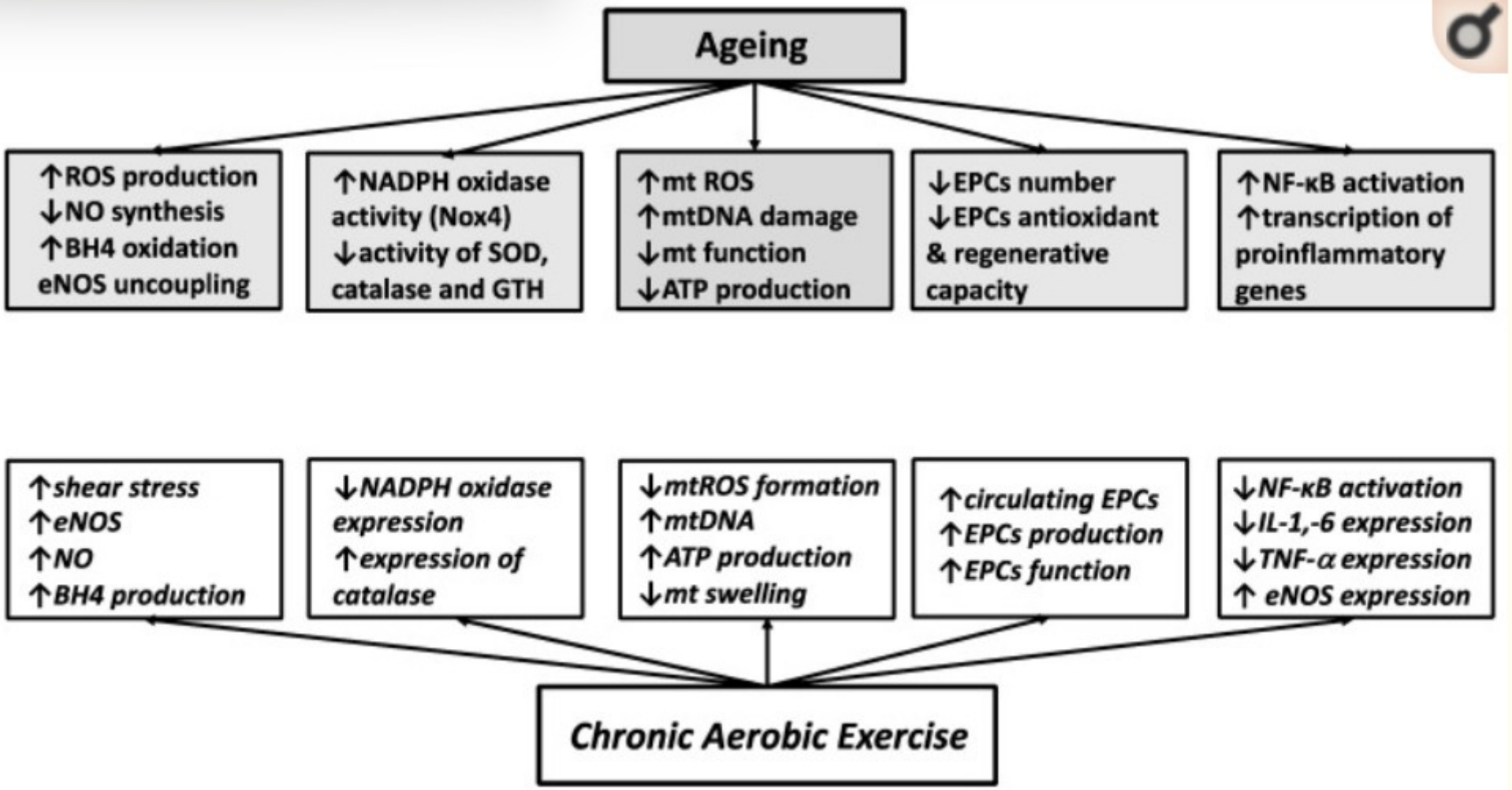
Pulse pressure

- Pulse pressure is the difference between systolic and diastolic blood pressure.
  - For example, if systolic blood pressure is 120 mm Hg and your diastolic blood pressure is measured as 80 mm Hg, then pulse pressure would be 40 mm Hg. Optimal pulse pressure is between 40 and 60. Lower is better. A high pulse pressure causes increased mechanical stress on the vasculature.
  - Elevated pulse pressure causes greater stretch of arteries, induces fatigue and fracture of elastic elements more quickly, is more likely to hasten development and ultimate rupture of aneurysms.
  - High PP is also more likely to hasten development of the intimal damage that leads to atherosclerosis and thrombotic events.

Exercise

- Regular exercise reduces arterial pressure and heart rate. It reduces the amount of strain at each cycle and the total amount of cycles. Optimal blood pressure is still around 120/80 or less. The key word here being optimal. The lower the better.
- Exercise should be prescribed from 30 minutes of walking a day to 90 to 120 minutes a day of moderate to vigorous exercise. More exercise is usually better and most of us don't get enough for optimal health. The body can handle much more than most of us realize and the fitter you are the less relative risk you have for most diseases.
- Most experts agree that 60-90 minutes of moderate to vigorous physical activity almost every day is optimal. As primates, we simply were not designed to walk for 30 minutes and spend the rest of the time sitting.
- Analysis of the intersection between cardiovascular mortality and hours of exercise demonstrates progressive reduction of risk with more exercise.

- Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ*. 2006;174(6):801–809. doi:10.1503/cmaj.051351Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ*. 2006;174(6):801–809.


Ageing
↑ROS production
↓NO synthesis
↑BH4 oxidation
eNOS uncoupling
↑NADPH oxidase activity (Nox4)
↓activity of SOD, catalase and GTH
↑mt ROS
↑mtDNA damage
↓mt function
↓ATP production
↓EPCs number
↓EPCs antioxidant & regenerative capacity
↑NF-κB activation
↑transcription of proinflammatory genes
↑shear stress
↑eNOS
↑NO
↑BH4 production
↓NADPH oxidase expression
↑expression of catalase
↓mtROS formation
↑mtDNA
↑ATP production
↓mt swelling
↑circulating EPCs
↑EPCs production
↑EPCs function
↓NF-κB activation
↓IL-1,-6 expression
↓TNF-α expression
↑ eNOS expression
Chronic Aerobic Exercise

Exercise

- Exercise is critical for longevity.
- Increases the endogenous antioxidant system.
- Improves nitric oxide functionality and endothelial function.
- Strengthens the heart muscle which lowers heart attack risk. Health span is greater and cardiovascular morbidity and mortality is lower than those who exercise.
- Lowers cholesterol and triglycerides, lowers blood pressure.
- Lower risk of dementia.
- Improves mood.
- Optimizes glucose metabolism and preserves skeletal muscle.

Inflammation and the Endothelium

- Inflammation plays a part. Specifically, inflammatory cytokines, chemokines and other molecules encourage pathologic remodeling of the artery through chemoattractant and pro-oxidative forces.
- Endothelial cells also lose their protective capacity and experience decreased nitric oxide production locally. The cytokine storm seen with COVID-19 is a good example of an infection causing inflammation induced endothelial dysfunction leading to arterial disease/vasculitis.
- Footnote: entire books have been written about the role of the endothelium but, in short, it is a line of defense participating in all aspects of vascular homeostasis and responsible for processes like thrombosis vascular remodeling, regulation of vascular tone, coagulation and fibrinolysis, and blood vessel formation.
- Don’t forget about the endothelial glycocalyx.

Enough of the depressing stuff what can we do?

- While we will all get arterial stiffening as we age it is possible to slow it down considerably and even reverse it. Just like arterial plaque may regress arterial stiffness can improve as too.
- Simple measures work such as increasing nitric oxide delivery through exercise or arginine supplementation and ingestion of nitrates found in leafy greens and beets. M
- All human systems depend on optimal blood flow delivering oxygen and nutrients. As we try to increase the **health span** of our patients many of us now die associated with old age. Vascular aging is often an unseen, asymptomatic progression. The following are some clinically relevant, easy to implement strategies to use with patients.

Testing (why guess when you can know)

- Carotid intima thickness testing. Use the same company for all repeat testing. Verify that technicians are trained adequately and that the best software is being utilized.
- A routine carotid ultrasound can be somewhat helpful but not as sensitive as carotid intima thickness testing.
- Coronary calcium scoring
- Blood testing through conventional labs with insurance first:
  - hsCRP, CBC, CMP, homocysteine, Lip(a), OXLDL, PLA2, TMAO, lipid subfractions, ADMA, myeloperoxidase, ferritin, MTHFR, vitamin D, uric acid, hs troponin, ProBNP and A1C. There are more.
  - There are also special tests available through “outside labs” they can do advanced testing if you live in an underserved or rural area.

Treatment goals

- Optimize cholesterol: This can be done through many means and include plant-based diet, exercise and addition of super foods and supplements. Foods that “improve” cholesterol include but are not limited to almonds, cashews, Brazil nuts, ground flaxseed, soy, Whole grains, dietary fiber in general and green tea.
- Lower inflammation: Implement a plant based (80/20 rule) **anti-inflammatory diet**. If the patient is unable to follow such a restrictive diet add antioxidants such as resveratrol, Green tea, coenzyme Q 10, curcumin, EPA, DHA, lipoic acid, etc.
- Recheck inflammation markers to make sure treatments are working. And exactly what are these markers? Other than cytokines which can be expensive and difficult to obtain. Some Readily available good ones are high-sensitivity C-reactive protein and PLA2. There are urine tests as well to measure oxidative stress.

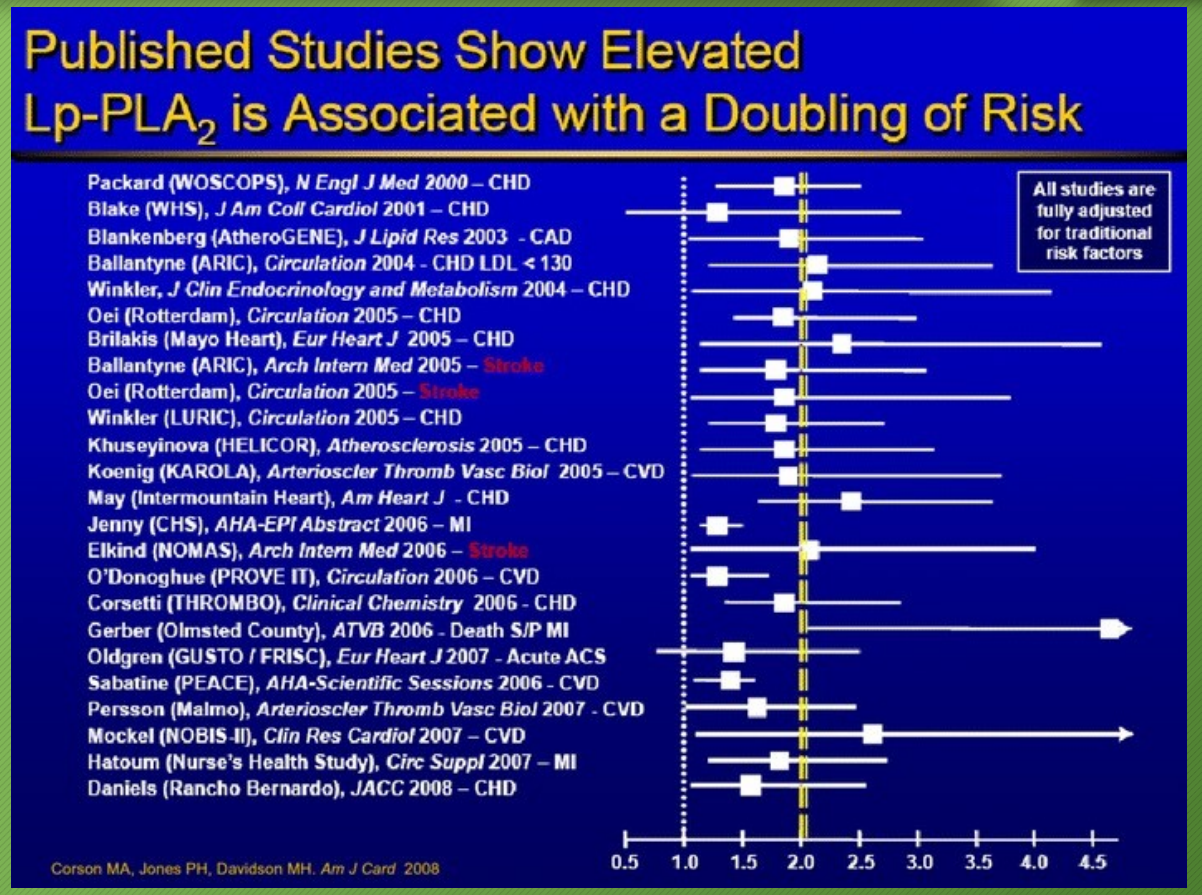
PLA2

- An enzyme thatplays a mechanistic role in atherogenesis; serum levels reflect intravascular inflammation and the presence of unstable plaque; increased expression of the enzyme within plaque associated with more complex and advanced lesions; treatment will lower it, increased serum levels associated with progressive elevation in risk for cardiovascular events.

- Colley KJ, Wolfert RL, Cobble ME. Lipoprotein associated phospholipase A(2): role in atherosclerosis and utility as a biomarker for cardiovascular risk. EPMA J. 2011 Mar;2(1):27-38. doi: 10.1007/s13167-011-0063-4. Epub 2011 Mar 10. PMID: 21654904; PMCID: PMC3084931.

PLA2

More than two dozen clinical studies demonstrate the utility of Lp-PLA2 and are peer-reviewed and published



Colley KJ, Wolfert RL, Cobble ME. Lipoprotein associated phospholipase A(2): role in atherosclerosis and utility as a biomarker for cardiovascular risk. EPMA J. 2011 Mar;2(1):27-38.

Treatment goals: NO

- Nitric oxide is critical for healthy endothelial function. Nitric oxide addresses vascular homeostasis by acting as an antioxidant, modulating vascular tone, regulating cell proliferation, protecting against toxic insult and mechanical and chemical damage.
- Dietary approaches to increasing nitric oxide production include the ingestion of leafy greens especially arugula, kale and spinach.
- Nuts contain copious arginine.
- Sustained-release arginine if under 50 Nitrate if over 50.
- Unfortunately, there is no truly accurate test for measuring nitric oxide production in a patient but improvements in erectile dysfunction and blood pressure and circulation are good markers. Also, one can run an asymmetric dimethyl arginine test (ADMA). If the patient is positive for this, they need extra nitric oxide support.
- Exercise also greatly increases endogenous nitric oxide production.

Optimize blood pressure

- Optimal blood pressure is (120/80) or less with pulse pressure less than 40): High blood pressure regardless of cause leads to mechanical stress on arteries…… like stretching skin constantly.
- Damage to the endothelial occurs and then its easy for cholesterol particles to get in and build plaque.
- With more mechanical stress and more plaque, the arteries get stiffer which in turn leads to higher blood pressure in a vicious cycle.
- Diet, exercise, nutraceuticals and prescriptions all should be employed to optimize blood pressure.

Heavy metal toxins

- Address toxic metals: Naturopaths are trained in environmental medicine so we should not miss this. Lead, cadmium and mercury the big players for cardiovascular health. Lead can cause high blood pressure and displaces calcium in bone.
- Mercury has been demonstrated to increase oxidative stress within arteries. Possible biological effects of mercury exposure include hypertension, coronary artery disease, heart attack heart rhythm disturbances controlled by the autonomic nervous system and direct neurotoxic effects.
- The main mechanism appears to be an increase in oxidative stress and the resultant increase in free radicals and reduction in the activity of antioxidant enzymes such as glutathione peroxidase.

- Zheutlin AR, Hu H, Weisskopf MG, Sparrow D, Vokonas PS, Park SK. Low-Level Cumulative Lead and Resistant Hypertension: A Prospective Study of Men Participating in the Veterans Affairs Normative Aging Study. *J Am Heart Assoc*. 2018;7(21)
- Farkhondeh, T., Afshari, R., Mehrpour, O. *et al.* Mercury and Atherosclerosis: Cell Biology, Pathophysiology, and Epidemiological Studies. *Biol Trace Elem Res* (2019).

Metals cont.

- Cadmium: Proposed mechanisms and associations of cadmium include up regulation of cytokines and resultant increased endothelial cell permeability and dysfunction, increased oxidative stress, hypertension, carotid artery disease, ischemic heart disease and peripheral arterial disease.
- Iron: Hemochromatosis can be homozygous or heterozygous there are many individuals who have never been checked and are running a high ferritin in the 400s to 600s and they are usually heterozygous. Homozygous individuals can have even higher levels and typically have other health problems by the time they are 40. Elevated iron greatly promotes systemic oxidative stress. A ferritin with serum iron and total iron binding capacity should be performed. Ferritin may also be elevated due to liver disorders, so both need to be done together.
- Do a provoked toxic metal test preferably with IV calcium EDTA given with DMPS or oral DMSA. The DMSA dose is 30 mg/kg, DMPS is 3-5 mg/kg and the standard calcium EDTA dose is 3 mg/kg. Hair tests and blood tests are virtually useless. The former is not sensitive enough and the latter only checks for acute exposure. Extensive information exists within the intravenous therapy naturopathic continuing education courses.

Avoid AGEs

- Advanced glycation end products and food (AGEs): Created by the Maliard reaction, AGEs bind to proteins and DNA causing cross-linking, and arterial aging. High heat especially in the presence of marinades containing sugar and sauces are the worst. High heat alone like flame broiling is also bad.
- If you are cooking meat cook it with the lowest heat possible, or even better, steam it. The #1 worse food on the AGEs list was fried bacon. Barbecued chicken breast with skin was the second worst. This is because of the heat and the fact that barbecue sauce contains sugar.
- In general meat, cheese and highly processed foods contain the highest age content of AGEs and grains, beans, bread, vegetables, fruits and milk have the least. Try to avoid roasted nuts as they have a high content too. Eat raw nuts only. Nuts contain healthy fats, minerals, vitamins, fiber and protein!
- Diabetes is a disease that causes accelerated aging because of the high blood sugar reacts with proteins in the body creating AGEs and tissue damage.

Avoid

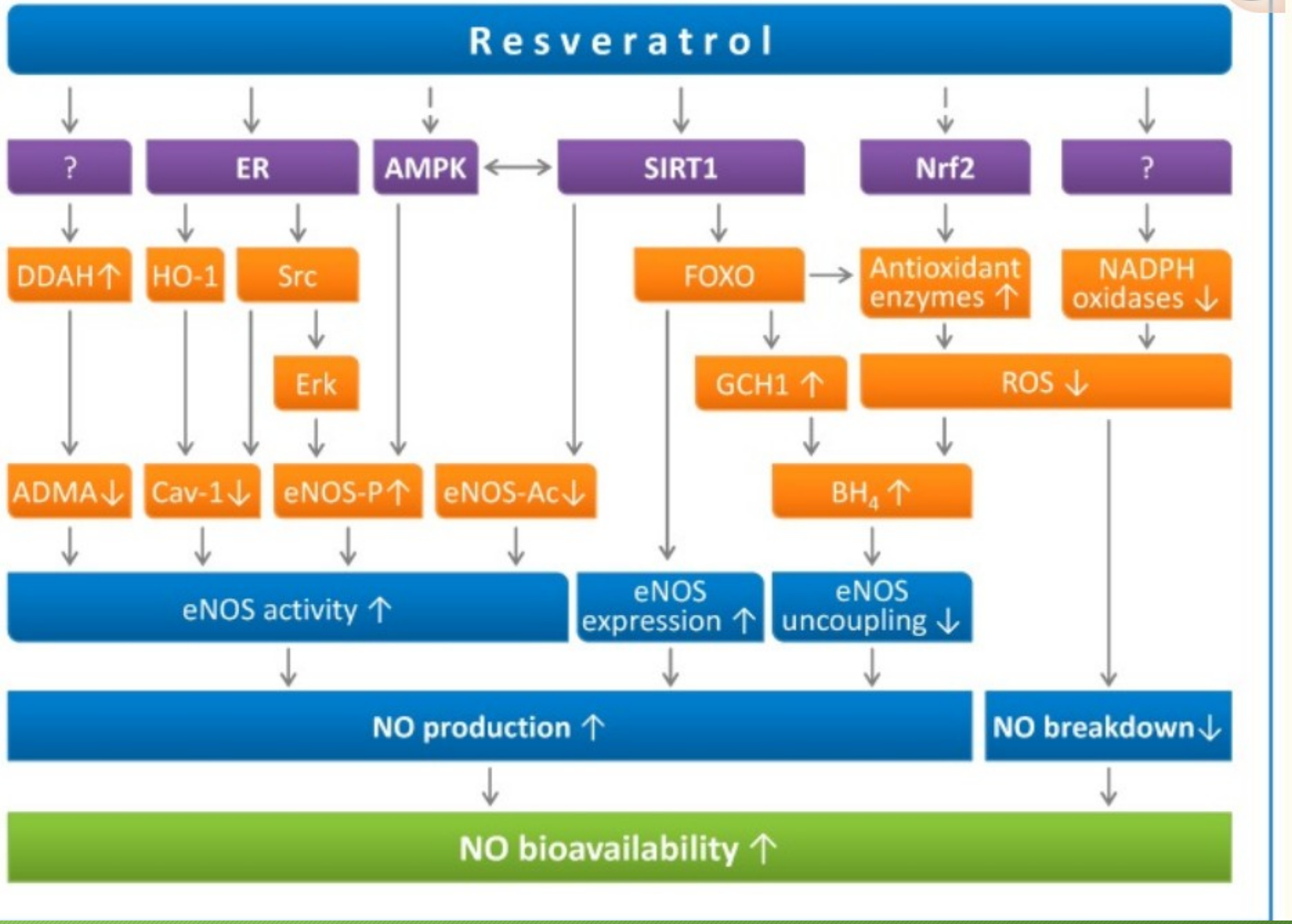
- Poly-cyclic aromatic hydrocarbons (PAHs). Ubiquitous in the environment, at least 90% of exposure occurs through the diet. Meat cooking methods such as roasting, grilling barbecuing and smoking of generate these. PAHs cause oxidative stress, increased blood pressure and endothelial injury.
- Heterocyclic amines (HCAs). Heterocyclic amines are a major class poisonous compounds produced during the broiling and frying creatine containing foods such as meats. They are genotoxic eventually bringing about mutagenicity and carcinogenicity in addition to endothelial injury.

Avoid

- Eliminate trans fatty acids: Found and fully hydrogenated as well as partially hydrogenated vegetable oil and to a much lesser extent animal fat trans fatty acids (TFFAs) should never be consumed.
- Trans fatty acids increase triglycerides, reduce LDL particle size, reduce HDL and increase LDL. They also increase systemic inflammation demonstrated by many studies and manifesting as increased tumor necrosis factor interleukin-6, and C-reactive protein.
- TFFAs cause endothelial dysfunction as demonstrated by reduced brachial flow mediated vasodilation of up to 30%. They also been shown to increase visceral fat and insulin resistance.

Supplements

- The typical ones protect DNA, lower cholesterol, reduce blood sugar, improve insulin response, lower blood pressure and act as antioxidants. Examples include green tea, garlic, omega 3, resveratrol, NAD+, curcumin, arginine, magnesium, berberine, pomegranate extract and many more.
- Resveratrol increases production of nitric oxide by up regulating endothelial nitric oxide synthetase and prevents its degradation. Resveratrol can reduce oxidative stress in endothelial cells and reduce pathological vascular remodeling and stiffness. It also helps reduce the immune cell mediated entry of immune cells into the artery wall.
- RX: There is also interesting data on metformin, rapamycin, methylene blue and angiotensin receptor blockers (losartan).


Resveratrol
?
ER
AMPK
SIRT1
Nrf2
?
DDAH↑
HO-1
Src
FOXO
Antioxidant enzymes ↑
NADPH oxidases ↓
Erk
GCH1 ↑
ROS ↓
ADMA↓
Cav-1↓
eNOS-P↑
eNOS-Ac↓
BH4 ↑
eNOS activity ↑
eNOS expression ↑
eNOS uncoupling ↓
NO production ↑
NO breakdown↓
NO bioavailability ↑

Tea

- Tea: contains numerous bioactive substances such as alkaloids, free amino acids, polyphenols.
- Multiple benefits have been seen in the studies and include anti-oxidation, immune regulation, anti-cancer, cardiovascular prevention, anti-inflammatory effects, improved glucose control, weight control and even liver health.

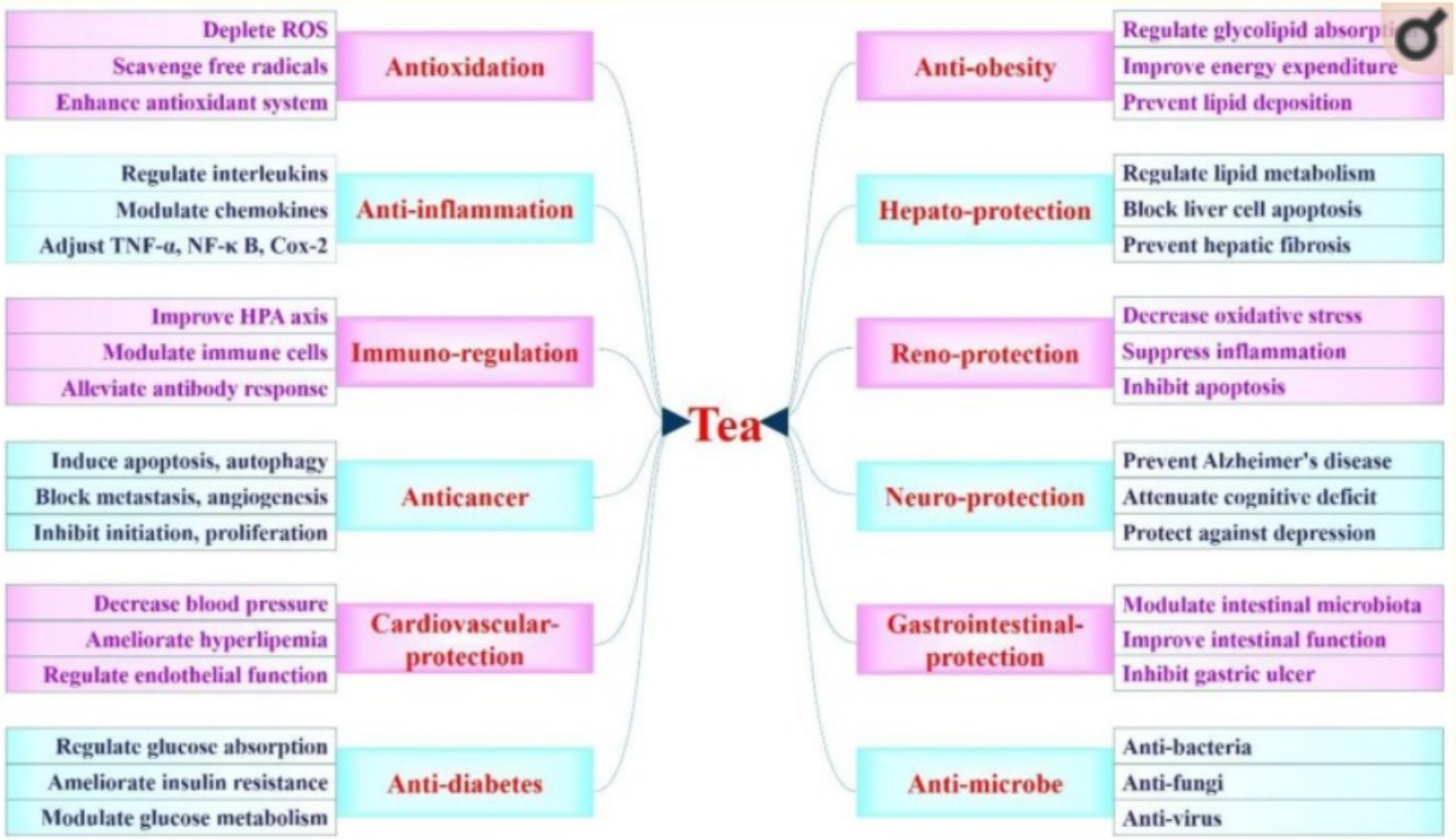


Figure 1

The main health functions of tea.

Tang G-Y, Meng X, Gan R-Y, Zhao C-N, Liu Q, Feng Y-B, Li S, Wei X-L, Atanasov AG, Corke H, et al. Health Functions and Related Molecular Mechanisms of Tea Components: An Update Review. International Journal of Molecular Sciences. 2019; 20(24):6196. https://doi.org/10.3390/ijms20246196

NAD+

- Increasingly strong evidence demonstrates that with advancing age there is less availability of NAD+. It is postulated that this can be a contributor to aging. This notion is supported by the fact that increasing NAD+ levels can extend lifespan of worms, flies and yeast as well as improving general health and longevity and mice. NAD+ works in part by improving mitochondrial function and decreasing oxidative stress which, in turn, also improve vascular function. Trials are currently ongoing looking at a variety of clinical uses.
- NAD precursors can be given orally. NAD+ can also be given orally, intramuscularly and intravenously. Niacin works too.

Food for blood pressure (WFPBD)

- A Whole food plant-based diet (WFPBD) is good for blood pressure. Also Med and DASH diet.
- Naturally occurring nitrates are great for a blood pressure. Beets and leafy greens especially arugula are high in them. The body converts nitrates to nitric oxide (NO) a molecule that helps relax arteries, improve circulation and lower blood pressure. Athletes use shots of beet juice to improve exercise performance because of this. Nitric oxide and works as an antioxidant in addition to opening up arteries.
- The top 10 sources of healthy plant sources of nitrates starting with foods highest are: Arugula, rhubarb, cilantro, butter leaf lettuce, beet greens, oak leaf lettuce, Swiss chard and beets. Drinking beet juice prior to exercise can improve performance.
- So, to clarify, eating animal products with added nitrates and nitrates should be avoided. Naturally occurring nitrates found in plant foods are very beneficial for cardiovascular health. Nitrosamines ocurr when nitrate/nitrite are added to meat. Think beets not beef.

How exactly does a WFPBD work to slow the progression of coronary artery disease and lower cholesterol?

- Cholesterol intake goes down because plants do not contain cholesterol. Dietary cholesterol “can” reduce hepatic LDL receptor function. This leads to decreased clearance of LDL and increased production of LDL by the liver.
- It should be noted that 70-80 percent of the cholesterol is made in the liver. Individuals with familial hypercholesterolemia inherited the ability to make excessive amounts even on a plant-based diet. Additionally, some individuals are more sensitive to dietary cholesterol than others.
- The monosaturated and polyunsaturated fats in raw nuts, olives and avocado are neutral on cholesterol whereas saturated fat increases cholesterol.

Plant based

- Saturated fat intake typically goes down significantly.
- Saturated fat of animal origin “can be” pro-inflammatory when overconcumed and can like in the arterial toxin causing arterial constriction within hours of a high saturated animal fat meal. Saturated fat is also the main driver of cholesterol production by the liver. Aracidonic and palmitic acids are fatty acids largely responsible for pro-inflammatory activity.
- Palm oil and coconut oil are rich in saturated fat too and will raise both HDL and LDL. There is an additional problem with palm oil. It contains palmitic acid which boosts inflammation, diabetes and cardiovascular disease. It is pervasive in the food industry and is the main ingredient in no stir nut butters.

Plant based

- Intake of the amino acid carnitine and the nutrient choline also decrease by avoiding animal products. This is important because these nutrients can be converted into an unpleasant substance called trimethylamine-N-oxide or TMAO. The research on TMAO and atherosclerosis is quite clear to date. Vegetarian diets decrease TMAO. Can pure vegetarians get a carnitine deficiency?
- Vegetarians who are adapted to a low carnitine diet developed increased bioavailability of carnitine compared to meat eaters. Because carnitine is a conditionally essential amino acid it can be synthesized from lysine and methionine. How do strict vegetarians get choline then if they are not eating animal foods? Plant foods contain choline too. Plant foods rich in choline include tofu, soy nuts, soy milk, cruciferous vegetables, beans, quinoa, peanuts, and peanut butter.

Plant based

- Plant nitrate consumption goes up. Leafy greens and beets promote increased nitric oxide levels which lower blood pressure and improve circulation. One shot of beet juice improves time to exhaustion from 9 min 43 seconds to 10:57 and 11 min 15 seconds in one study.
- Also, sodium goes down, fiber goes up and disease preventing phytonutrients intake goes way up phytonutrients or molecules that include Beta-carotene, lycopene, soy isoflavones, prebiotics, lutein, resveratrol and lignans.

Plant based

- Added phosphates are avoided with a plant-based diet. Red meat and colas and other processed foods have phosphates added to enhance or preserve color. In addition, phosphates prevent seepage of fluid from the meat. We have all seen meat that has been there for a few days that has weird juice in the package. Phosphate helps prevent this.
- Phosphates are **vascular toxins** and cause vascular calcification. The recommended daily maximum intake is 700 mg. Daily intake can be double or triple that when processed foods are eaten. High phosphate intake is more prevalent in underserved, poorly educated and impoverished populations. Taking extra magnesium, niacin, vitamin K, and vitamin D can help mitigate the effects of phosphates on calcification.

Vascular disease (ASVD)

- The importance of healthy vasculature cannot be over emphasized. Health span and life span is limited by blood supply.
- In addition to increased heart attack, hypertension and stroke risk ASVD also contribute to increased risk of dementia, Alzheimer's, muscle wasting, kidney and eye disease. High LDL is moderately associated.
- A decrease in capillary density also known as microvascular rarefaction contributes to a decrease in tissue perfusion. Additionally vascular disease can contribute to risk of falling and even osteoarthritis.

Summary

- Preventive, holistic, and integrative-minded providers are well-positioned to do more for vascular aging than other specialties.
- Our ability to prescribe highly targeted prescription-strength nutraceuticals in addition to detailed diet and lifestyle counseling provides an opportunity for the best outcome.
- Integrating prescriptions may be needed in some cases.
- Much of this type of thing is not covered by health insurance. Therefore, it is even more important for you because no one else can do it!
- You do not find it if you do not look for it. Be data driven.

Summary

- Do comprehensive blood tests.
- Check blood pressure carefully.
- Do a complete family history.
- Do a detailed diet intake.
- Get a clear understanding of exercise.
- Good understanding of the patient's stress level.
- Do a complete medication and supplement review.
- Get coronary artery calcium scoring, and/or CCTA and carotid artery ultrasounds.
- High blood pressure must be worked up carefully it can be a sign of advanced arterial aging and stiffness especially if other causes such as excessive salt or stress hormones is ruled out. Renal hypertension. Aldosterone, rennin, angiotensin.