Casual Friday Presents

Patients on Medication Pt II
Statins

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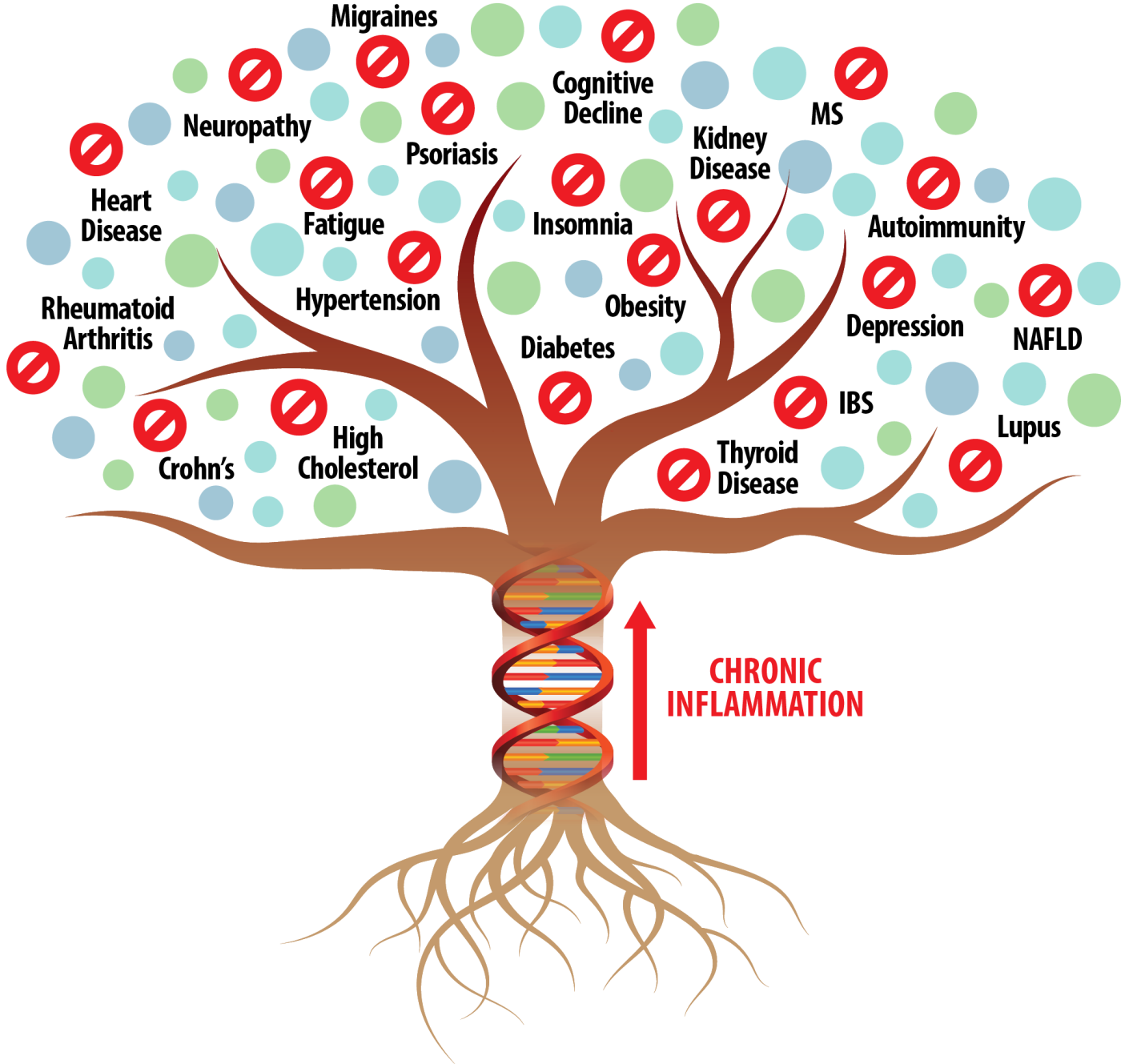
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Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Crohn's
High Cholesterol
Lupus
Thyroid Disease
CHRONIC INFLAMMATION

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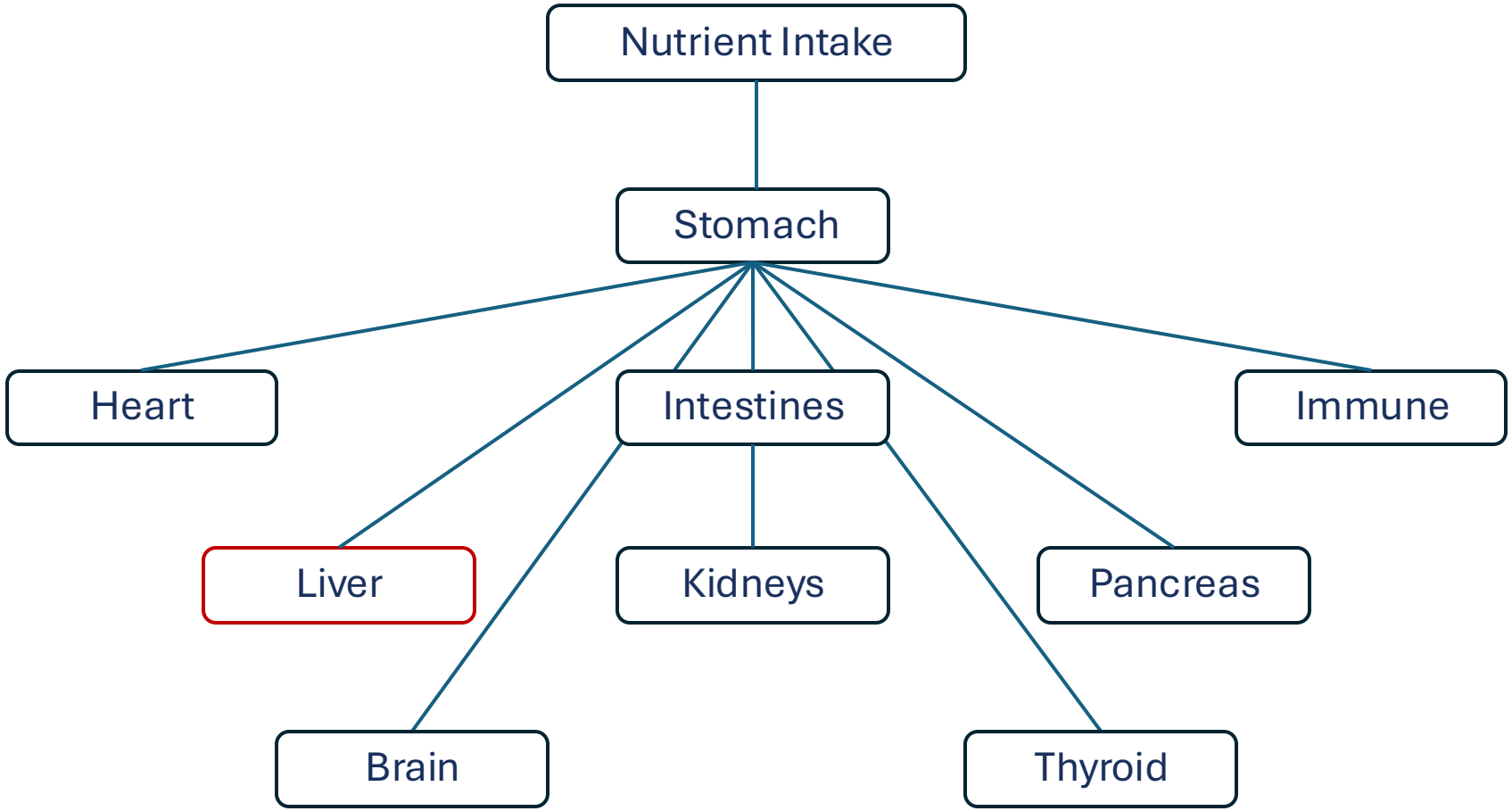
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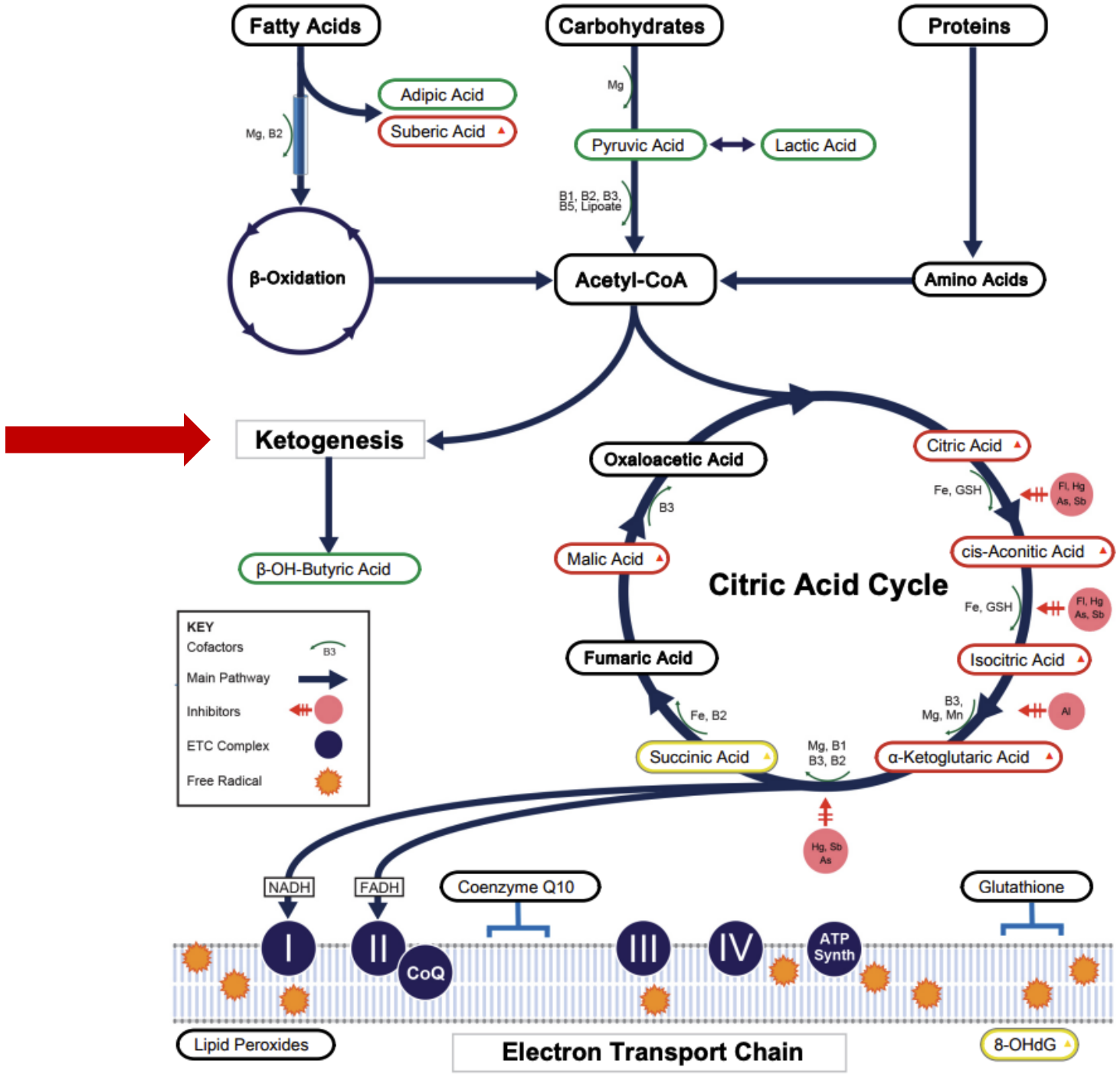
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β-Oxidation
Acetyl-CoA
Amino Acids
Ketogenesis
β-OH-Butyric Acid
Oxaloacetic Acid
B3
Malic Acid
Citric Acid
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ETC Complex
Free Radical
NADH
FADH
Coenzyme Q10
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ATP Synth
Lipid Peroxides
Electron Transport Chain
8-OHdG

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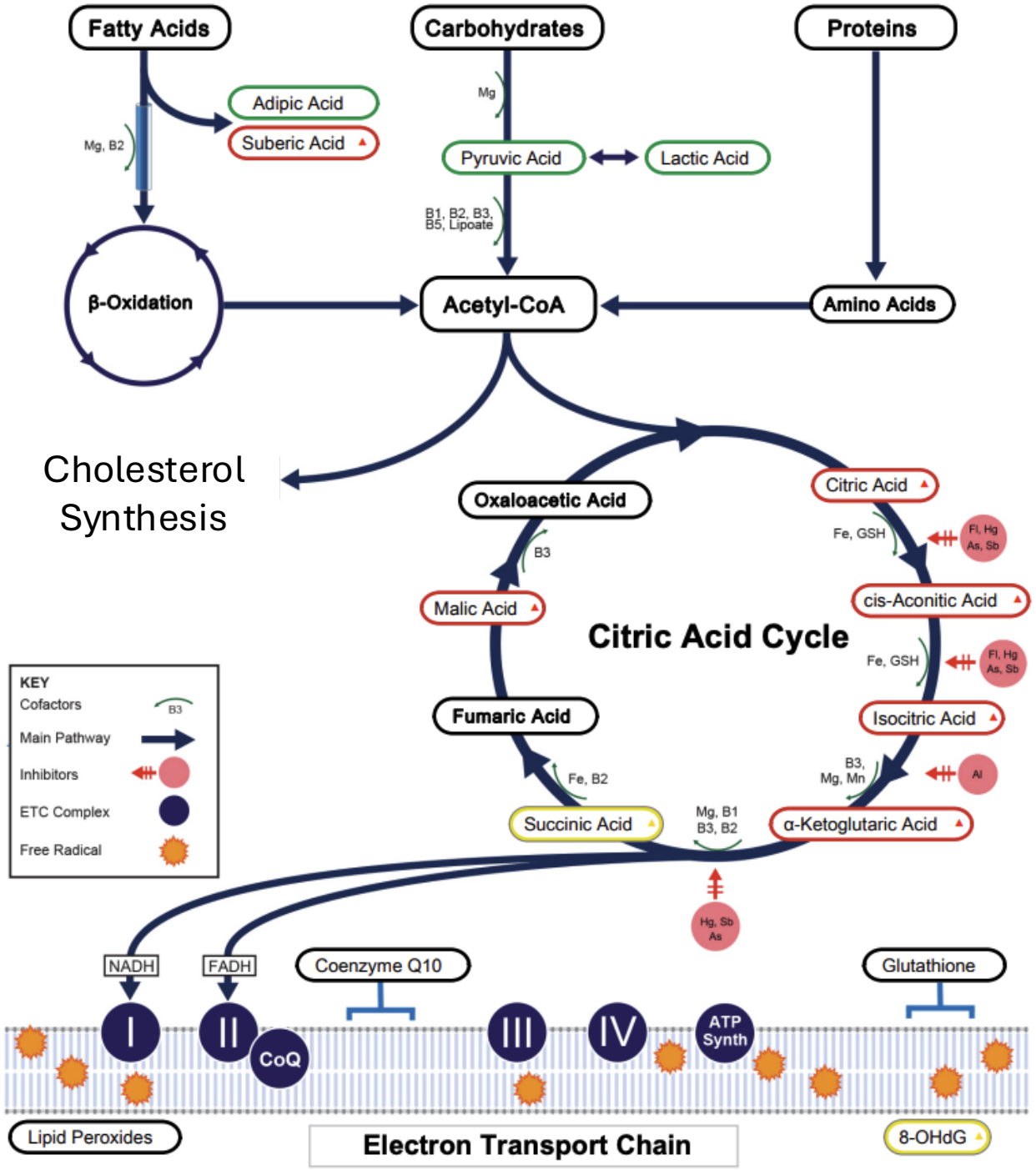
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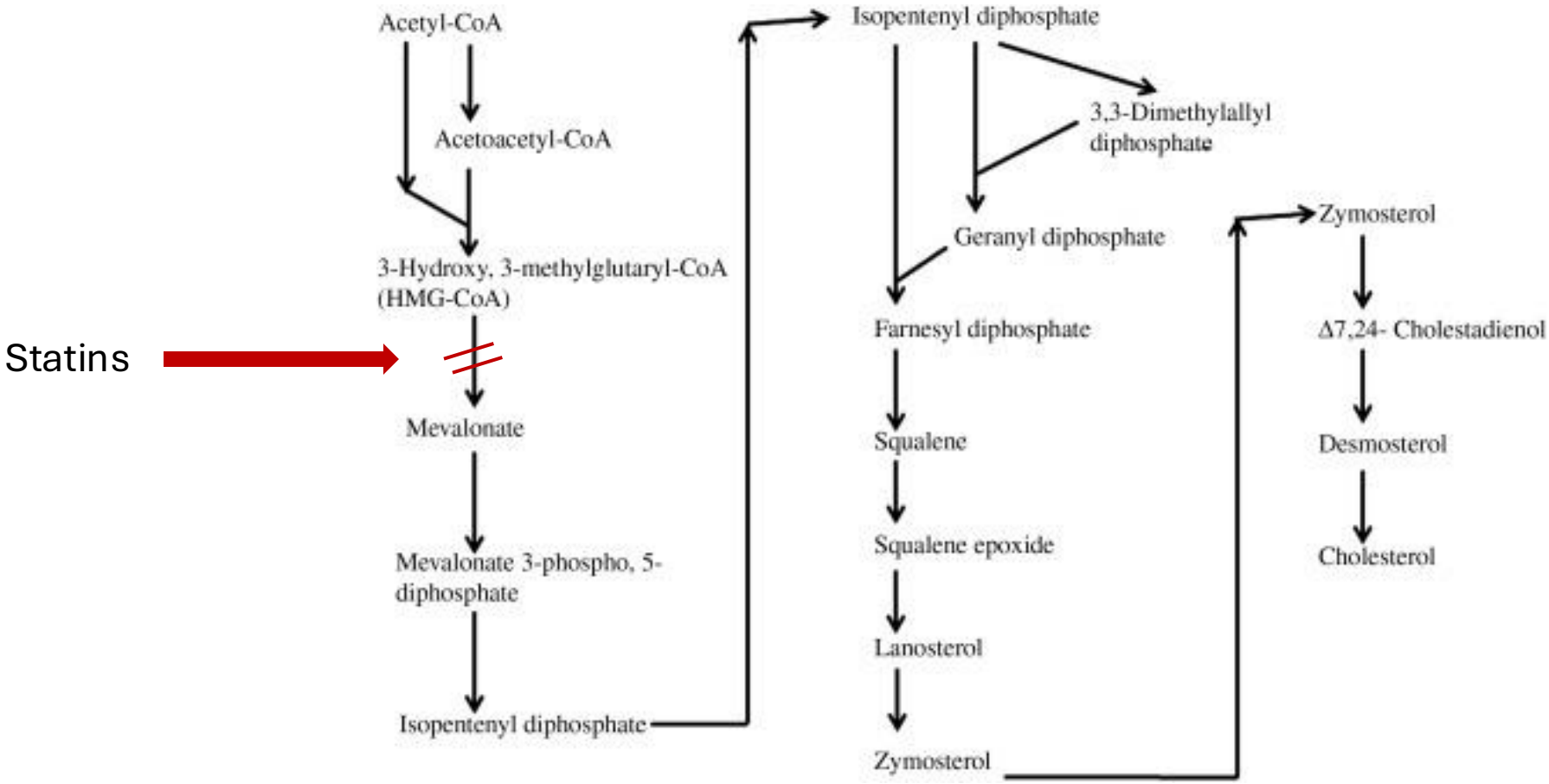
Cholesterol Synthesis Pathway



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Statins are a selective, competitive inhibitor of hydroxymethylglutaryl-CoA (HMG-CoA) reductase, the enzyme responsible for converting HMG-CoA to mevalonate in the cholesterol synthesis pathway. By reducing hepatic cholesterol synthesis, an upregulation of LDL receptors and increased hepatic uptake of LDL-cholesterol from the circulation occurs. Statin treatment reduces the hepatic production rate of apo B100 containing lipoproteins, leading to a decrease in both cholesterol and triglyceride concentrations. Drug responses may also differ according to genetic factors, such as the ATP binding cassette G2, lipoprotein(a), and apo E genes [32]. The RhoA gene may play an important role in statin's LDL-C response.[13]

HMG CoA reductase inhibitors have pleiotropic effects. Statins inhibit the synthesis of isoprenoid intermediates required for activating intracellular or signaling proteins (Ras, Rho, Rab, Rac, Ral, or Rap). Consequently, statins have anti-inflammatory, antioxidant, antiproliferative, and immunomodulatory effects. In addition, they promote plaque stability and prevent platelet aggregation. This pleiotropic effect is the class effect of statins. The COSMOS (coronary atherosclerosis study measuring the effects of rosuvastatin using intravascular ultrasound in Japanese subjects) trial results indicated that patients treated with rosuvastatin had a substantial decrease in plaque volume independent of LDL-C reduction.[14]

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Absorption: Absorption is faster for lipophilic drugs like atorvastatin, simvastatin, fluvastatin, pitavastatin, and lovastatin than hydrophilic statins like rosuvastatin or pravastatin. Atorvastatin is completely absorbed after oral administration, but atorvastatin undergoes extensive first-pass metabolism; the bioavailability is about 12%. The bioavailability of pitavastatin is highest (>60%), followed by rosuvastatin (20%), while simvastatin has <5% bioavailability.[15] Simvastatin and lovastatin are prodrugs converted to an active form by hydrolysis.[16]

Distribution: Protein binding affects drug distribution and the pharmacological efficacy of drugs because only the unbound or free drug can elicit targeted effects. All statins have high plasma protein binding (PPB) except pravastatin (PPB ~50%). Lipophilic statins can penetrate cells by passive diffusion and are widely distributed in different tissues. Hydrophilic statins pravastatin and rosuvastatin are attached to the polar surface of the cell membrane and require protein transporters to inhibit the HMG-CoA reductase.[17]

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Metabolism: CYP3A4 plays a crucial role in the metabolism of atorvastatin, lovastatin, and simvastatin. CYP2C9 metabolizes fluvastatin. Rosuvastatin is metabolized to a lesser degree by CYP2C9 and CYP2C19. OATPB1 (organic anion-transporting polyprotein) plays a role in eliminating atorvastatin, rosuvastatin, simvastatin, pitavastatin, and pravastatin, while OATPB3 is involved in the elimination of rosuvastatin, fluvastatin, and pravastatin. Atorvastatin and lovastatin are both substrates and inhibitors of P-gp (permeability glycoprotein).[18]

Excretion: Statins are extensively metabolized, and the amount of statin excreted in its unchanged form through renal elimination is comparatively less. Rosuvastatin does not undergo extensive metabolism and is primarily excreted unchanged in urine and feces. Fluvastatin, lovastatin, pravastatin, and simvastatin have a relatively short half-life. These drugs should be administered in the evening or as an extended-release formulation (for fluvastatin or lovastatin) to maximize their efficacy. In contrast, atorvastatin and rosuvastatin have longer half-lives and can be administered at any time of the day. HMG-CoA reductase inhibitors are excreted into bile and feces.[19]

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Hepatic impairment: All statins are contraindicated in active liver disease. Statins are associated with mild-to-moderate serum aminotransferase elevations during therapy that are temporary, asymptomatic, and usually resolve without dose adjustment. Statins with minimal hepatic metabolism, such as pravastatin and rosuvastatin, are preferred in chronic liver disease.[28] NAFLD (nonalcoholic fatty liver disease), now also known as metabolic dysfunction-associated steatotic liver disease (MASLD), is a known risk factor for cardiovascular disease. According to American Gastroenterological Association guidelines, statins benefit patients with MASLD.[29] According to a recent study, in chronic liver disease with atherosclerotic cardiovascular disease, high statin intensity therapy is associated with a reduced risk of mortality.[30] The significant concern is atorvastatin in cases of decompensated cirrhosis due to an 11-fold increase in Cmax and a 16-fold increase in area under the curve. Rosuvastatin and pravastatin demonstrate pharmacokinetics resembling baseline levels due to minimal metabolization before biliary excretion in compromised liver function.[31][30]

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Renal impairment: Statins with minimal kidney elimination should be preferred as GFR declines. Atorvastatin appears to be the statin of choice in CKD stages 4–5. After appropriate dose adjustments, fluvastatin may also be used for advanced CKD.[32] According to KDIGO (Kidney Disease Improving Global Outcomes) guidelines, statin therapy is recommended for adults >50 years with CKD stages 1 and 2. For stage 3 to stage 5 CKD (not on HD), a statin+ezetemibe combination is recommended. Statin therapy is recommended for patients between 18 to 49 years (stage 1 to 5) of age with 1 risk factor (known coronary artery disease, diabetes mellitus, prior ischemic stroke, the estimated 10-year incidence of coronary death, or non-fatal MI >10%). In adult patients with dialysis-dependent CKD, statins should NOT be initiated; however, statins can be continued if the patient is already being administered statins at the time of dialysis initiation.[33] A network meta-analysis demonstrated that high doses of atorvastatin and fluvastatin 20 mg/ezetimibe 10 mg significantly prevented eGFR decline and proteinuria. Dose adjustment is required with other statins in patients with stage 4 CKD (creatinine clearance < 30 mL/min).[34]

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Elevated hepatic transaminases can occur. This elevation is usually transient and resolves with continued therapy or after a brief therapy interruption. Patients with statin-induced hepatotoxicity have hepatocellular rather than cholestatic or mixed liver injury. The cholestatic or mixed hepatic injury appeared more predominant in patients administered atorvastatin.[40] The FDA no longer supports liver function tests for monitoring the use of these medications without symptoms of hepatotoxicity, such as unusual weakness or fatigue, jaundice, or dark-colored urine.[41][42][43]

Statin-associated cognitive dysfunction is a rare adverse drug reaction; changing lipophilic to hydrophilic statins may resolve cognitive impairment.[44] Statin therapy is also associated with an increased risk of developing new-onset diabetes mellitus.[45] Concerns exist regarding hemorrhagic stroke with statins; however, a large cohort study found no evidence that HMG-Co-A-reductase inhibitors increase the risk of intracerebral hemorrhage in individuals with a history of stroke.[46] Statin-associated immune-mediated necrotizing myopathy is due to the development of antibodies against the HMG-CoA reductase enzyme. Symmetrical, proximal muscle weakness with significantly increased CPK persists for months after discontinuation of statins, which is common in statin-associated immune-mediated necrotizing myopathy.[47]

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Report

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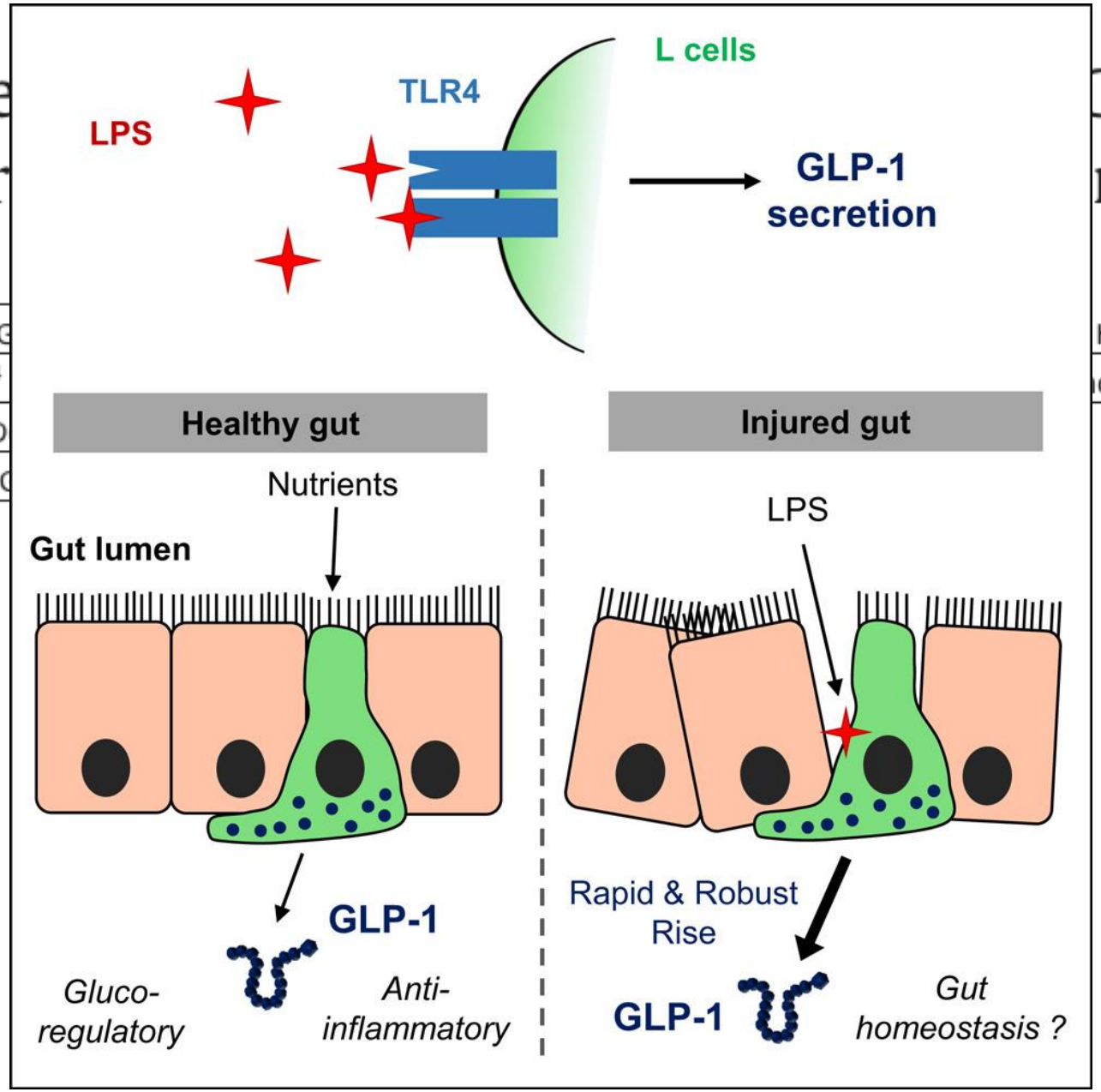

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Nutrients. 2025 Feb 21;17(5):765. doi: 10.3390/nu17050765

The Cholesterol Paradox in Long-Livers from a Sardinia Longevity Hot Spot (Blue Zone)

Alessandra Errigo [1], Maria Pina Dore [1,2], Michele Portoghese [3], Giovanni Mario Pes [1,4,*]

Cardiovascular disease, the leading cause of mortality in high-resource countries, is often attributed to several risk factors, (including sex, family history, hypertension, cigarette smoking, obesity, and dyslipidemia [1]), which independently increase the probability of atherosclerosis development. The notion that high blood cholesterol is one of the primary factors for cardiovascular risk owes much to the work of Alexander Ignatowski, Nikolai Anichkov, and Semen Chalatov in the first two decades of the last century, when cholesterol-fed rabbits were shown to develop accelerated atherosclerosis [2]. In 1910, Adolf Windaus, a Nobel Prize winner for Chemistry in 1928, reported that the cholesterol concentration in the aortic plaques of patients affected by atherosclerosis was 20-fold higher compared to that in normal aortas [3]. Despite these early reports, it was not until the early 1950s that the association between increased lipid-transporting protein levels and the development of cardiovascular disease was acknowledged [4]. Since then, numerous epidemiological studies, including the NIH-funded Framingham Heart Study [5] and the Seven Countries Study [6], have supported a link between high blood cholesterol levels and accelerated atherosclerosis

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Editor: Benedict C Albensi

[7]. Ancel Keys disseminated the idea that cholesterol levels were primarily determined by diet, suggesting that populations following a lipid-rich diet schedule were at higher risk of hypercholesterolemia and subsequent onset of premature atherosclerosis. Later, the discovery of effective cholesterol-lowering drugs (e.g., statins), which act by reducing the endogenous production of cholesterol in the liver, further strengthened the "cholesterol hypothesis" by reinforcing the mainstream view that hypercholesterolemia was responsible for atherosclerosis and cardiovascular disease. Evidence from all randomized clinical trials on statin therapy attests that cholesterol is an essential cause of coronary heart disease, regardless of age [8,9,10,11]. The notion that long-term cholesterol lowering increases lifespan and longevity has recently been strengthened by a Mendelian randomization study [12].

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However, in more recent times, the link between chronically elevated cholesterol levels and cardiovascular mortality has been seriously questioned by several lines of research. Various animal models have been created to mimic hypercholesterolemia in humans [13], although no animal model entirely reproduces human lipoprotein metabolism [14]. Notably, although they exhibit hypercholesterolemia, LDL receptor knock-out mice do not develop spontaneous atherosclerosis [15].

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Not all epidemiological studies in Western and Eastern populations have supported the direct relationship between hypercholesterolemia and cardiovascular disease. For instance, studies conducted in Japan have revealed that high blood cholesterol is associated with an increased risk for coronary artery disease but not with stroke [16]. Furthermore, the association between cholesterol levels and the risk for cardiovascular disease was not consistent across all age groups, tending to fade in older individuals, although the cholesterol hypothesis does not predict this attenuation. A collaborative meta-analysis of 61 studies published in The Lancet in 2007, which collected individual records from 892,337 eligible participants without previous cardiovascular disease, reported 55,000 deaths during nearly 12 million person-years of follow-up. This analysis revealed that after age 80, the risk for cardiovascular disease attributable to high cholesterol levels was minimal [17]. Dr. Uffe Ravnskov has published a series of controversial articles and books arguing that in older individuals, high cholesterol levels do not significantly increase the risk for cardiovascular disease and that treatment with statins has little, if any, value [18,19]. A systematic review by this author attempted to test the cholesterol/cardiovascular disease relationship by eliminating the confounding effect of HDL cholesterol (HDL-C), which is regarded as an important protective factor against cardiovascular disease [20]. The results of this study revealed a lack of direct association between LDL cholesterol (LDL-C) and cardiovascular mortality in nearly 80% of individuals over 60 years of age, and even a statistically significant inverse relationship between cholesterol and all-cause mortality [20].

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(ii) Cholesterol is a precursor of steroid hormones such as cortisol, estrogen, progesterone, and testosterone. These hormones are critical for several functions in the elderly, including metabolism and immune response. Higher cholesterol levels may sustain hormone synthesis, whereas low cholesterol, also induced by cholesterol-lowering drugs such as statins and PCSK9 inhibitors, may exacerbate age-related hormonal deficiency [76]. (iii) Cholesterol is a precursor in the synthesis of vitamin D in sunlight-exposed skin. Vitamin D plays a crucial role in immune system function, bone health, and overall well-being in elderly individuals [77], and higher levels have been reported to promote longevity [78]. (iv) Higher cholesterol levels may increase the production of specific molecules that are part of the immune system's function [79]. It has been reported that high cholesterol content in the cell membranes of cytotoxic T lymphocytes and natural killer cells can protect them from accidental perforin lysis, which causes apoptosis of target cells [80]. Some evidence indicates that higher cholesterol levels in later life might imply a stronger immune system and improved resilience to infections and diseases [81,82], which could contribute to greater longevity. (v) Cholesterol is vital for brain health as it is involved in forming synapses and supporting neurotransmission. In particular, low cholesterol levels have been associated with cognitive decline and conditions such as Alzheimer's disease [83].

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In conclusion, our analysis of the cholesterol profiles in a population that has achieved extreme longevity indicates that older subjects with higher cholesterol levels tend to survive longer, regardless of the influence of other lipids and confounding factors evaluated. However, further studies are necessary to clearly establish whether it is advisable to administer cholesterol-lowering medications to hypercholesterolemic individuals beyond a certain age.

Mediterranean Diet

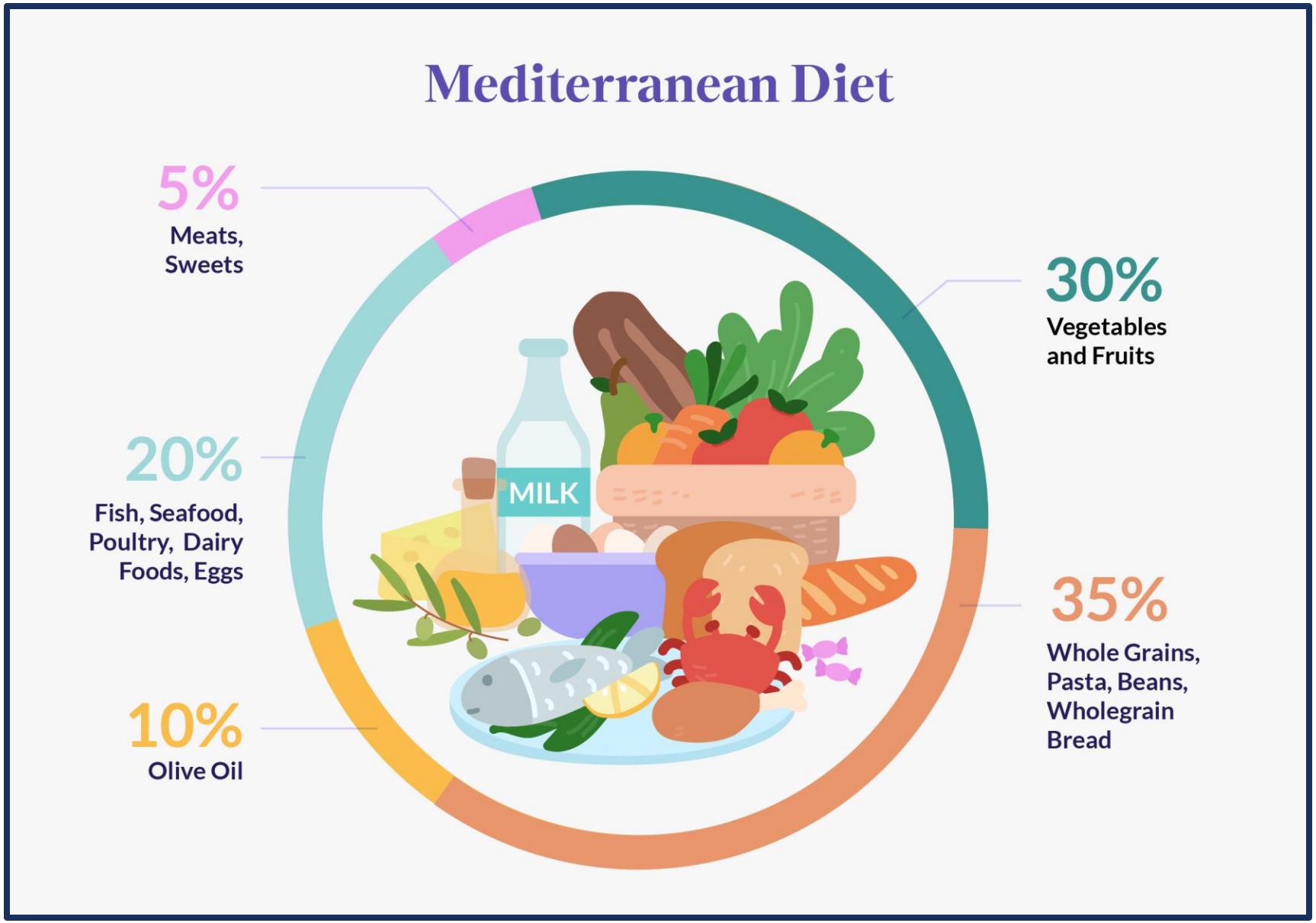

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Table 5.

Correlation between food consumption frequency and lipid parameters in the 168 study participants.

Foods	Lipid Profile							
	TC	HDL-C	LDL-C	Non-HDL-C	VLDL-C	TG	TG/HDL	LDL/HDL
Meat	0.243 *	0.249	0.115	0.076	−0.078	−0.024	−0.163	−0.089
Fish	0.121	0.095	0.134	0.106	−0.137	−0.140	−0.183 *	0.005
Legumes	0.012	0.087	0.069	0.135	0.133	0.117	0.059	−0.012
Greens	0.107	0.076	0.167	0.193	0.127	0.126	0.088	0.090
Cereals	0.194 *	−0.115	0.199 *	0.241 *	0.184 *	0.118	0.161	0.147
Potato	−0.123	0.001	0.025	0.018	0.044	0.036	0.058	−0.010
Fruit	0.234	0.141	0.214	0.205	0.022	0.016	−0.041	0.083
Sweets	−0.070	0.081	−0.077	−0.041	0.119	0.114	0.016	−0.097
Olive oil	−0.187	−0.015	−0.098	−0.156 *	−0.017	−0.007	−0.025	−0.054
Dairy food	−0.072	−0.023	−0.034	−0.029	0.104	0.110	0.069	−0.022
Coffee	−0.011	0.204 *	−0.116	0.025	−0.113	−0.099	0.064	−0.163
Wine	−0.157	0.036	−0.094	−0.107	−0.111	−0.101	−0.078	−0.094

Items to Consider when supporting Patients on statin therapies:

1. Is the high cholesterol food driven (high fat content)?
2. Is the high cholesterol food driven (high inflammatory impact)?
3. Is the high cholesterol genetic (proven)?
4. Any external drivers?

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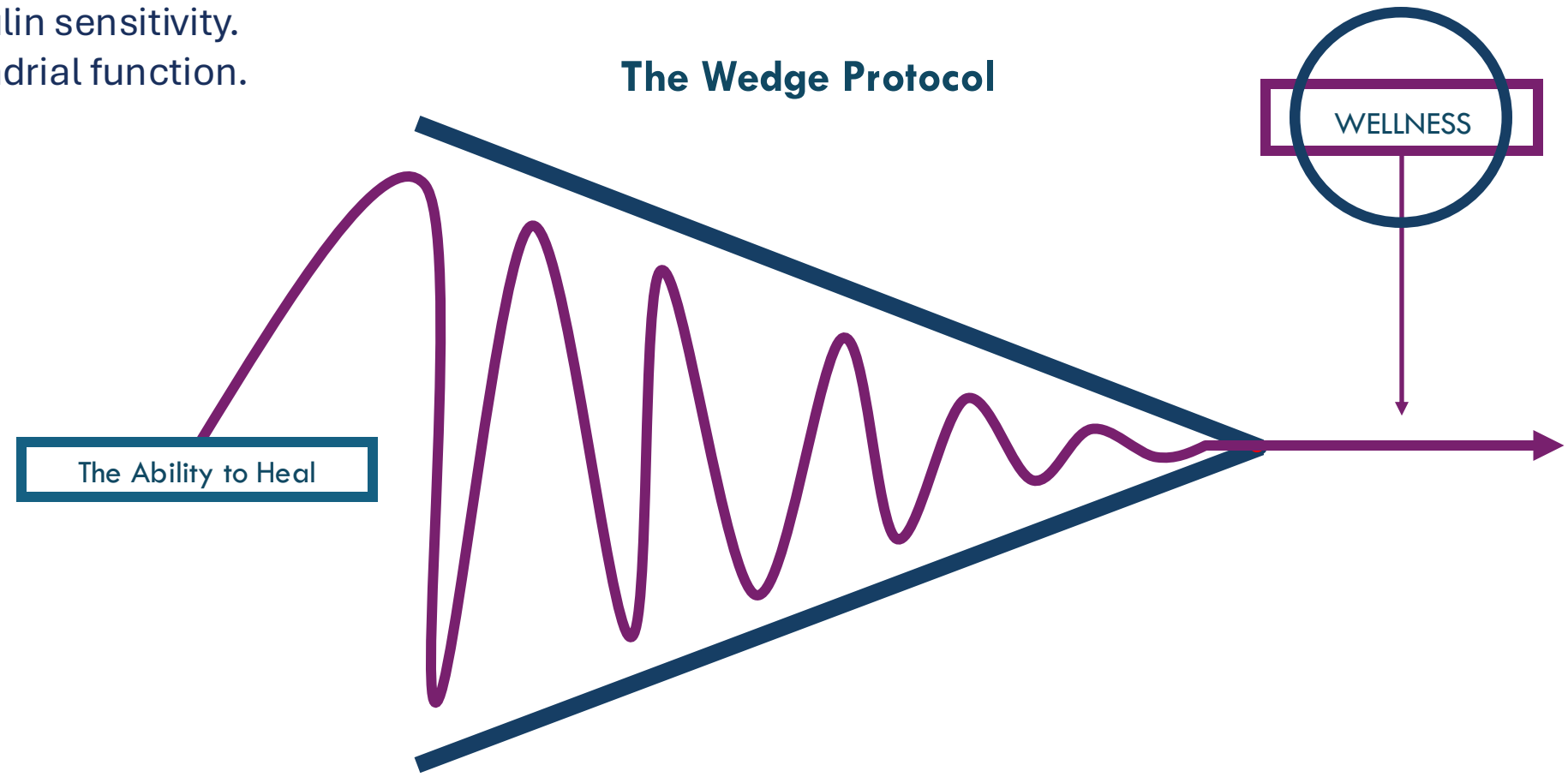
The Strat:

1. Slow enteroendocrine injury.
2. Decrease systemic inflammatory drivers.
3. Support ideal insulin sensitivity.
4. Support mitochondrial function.



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