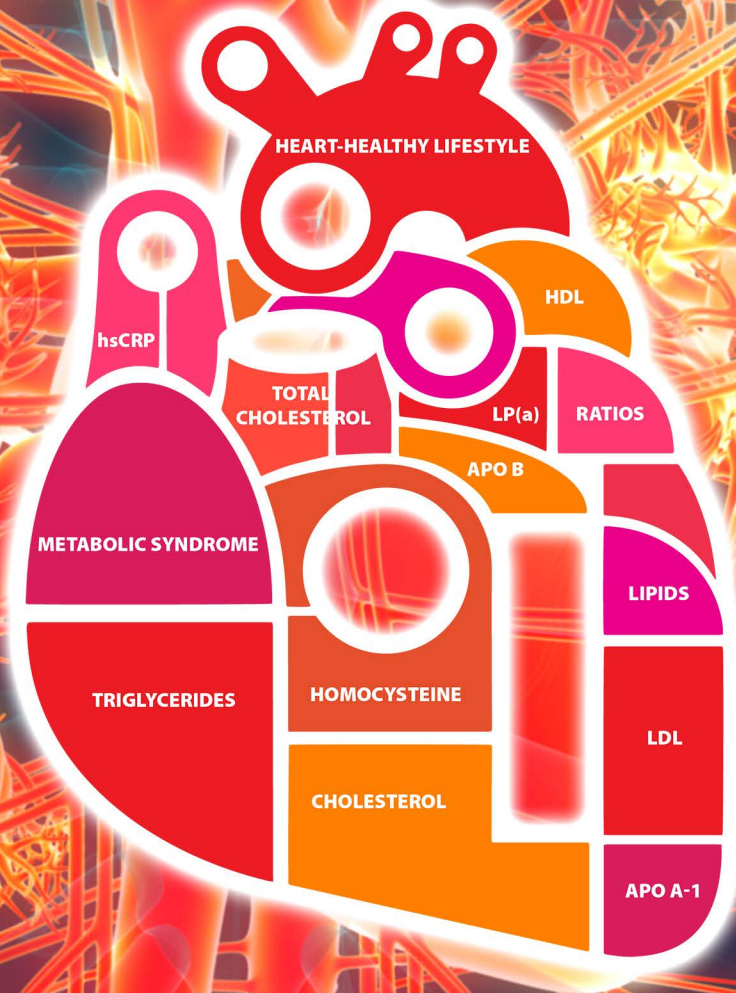
CardioCheck SUPPORT GUIDE



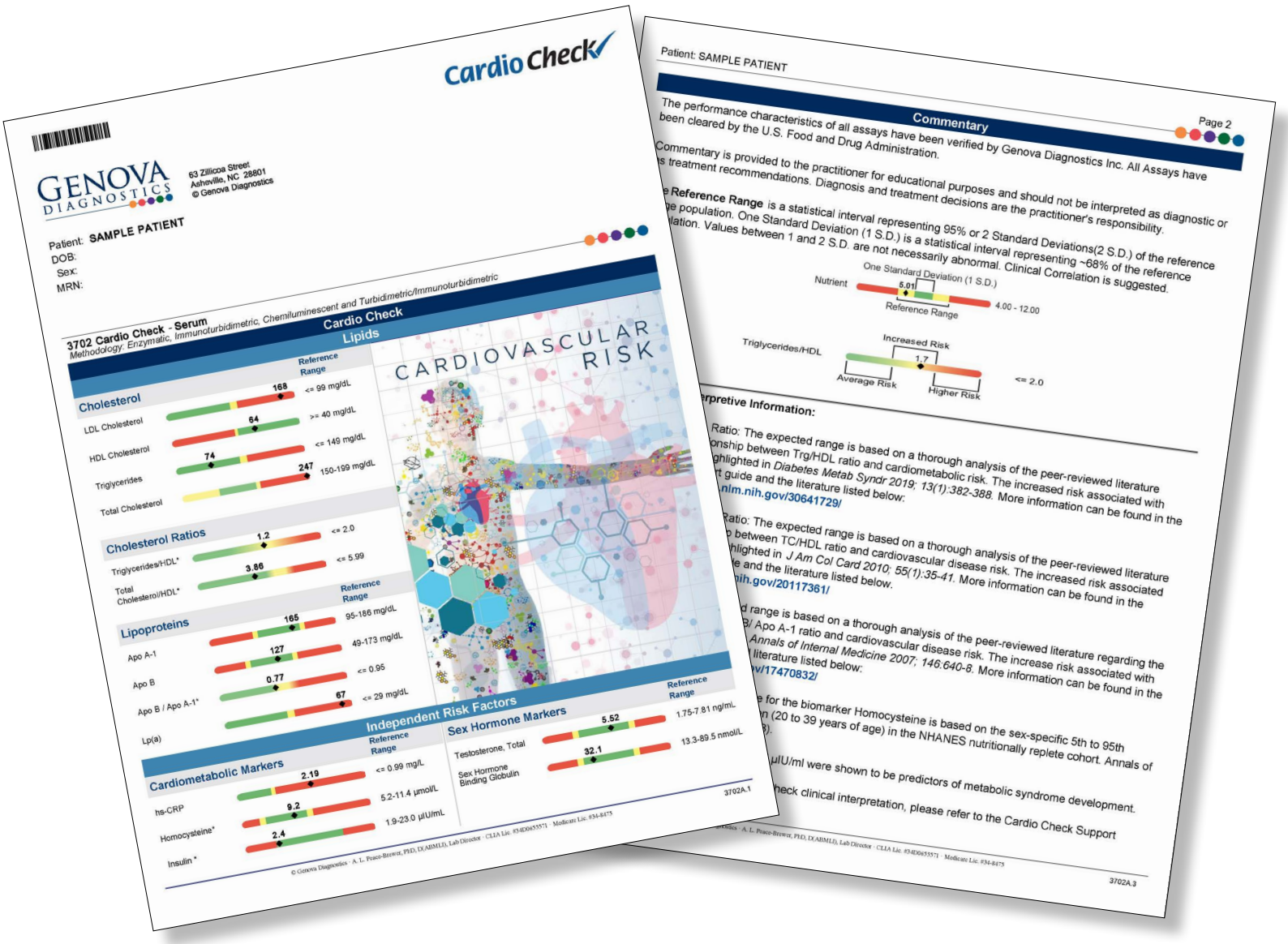
GENOVA DIAGNOSTICS

CONTENTS

Cardio Check

The Cardio Check Profile is an advanced blood assessment of lipids and cardiometabolic analytes that provides insight regarding cardiovascular risk. By combining the best of both conventional and novel biomarkers, it offers a broader look at cardiometabolic health to guide therapeutic strategies.
The Cardio Check results are arranged into two functional categories:

- **Lipids**
  - » **Standard cholesterol markers**
  - » **Cholesterol ratios**
  - » **Lipoproteins**
- **Independent Risk Factors**
  - » **Cardiometabolic Markers**
  - » **Sex Hormone Markers**



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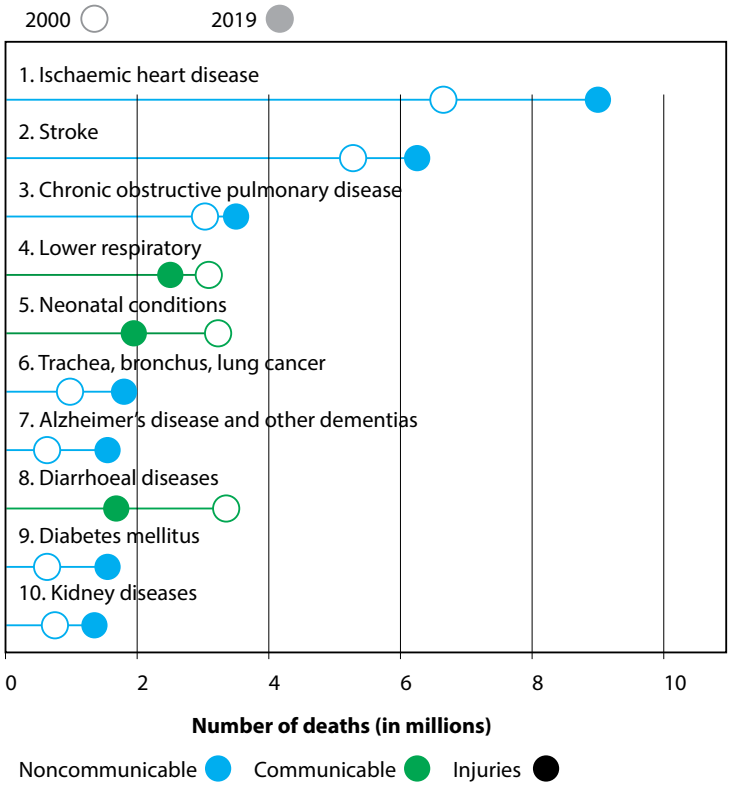
INTRODUCTION

Cardiovascular disease (CVD) refers to the group of illnesses including coronary heart disease (CHD), hypertension (HTN), cerebrovascular disease (stroke), heart failure, rheumatic heart disease, congenital heart disease, cardiomyopathies, and peripheral vascular disease. The pathological processes of these diseases have the progression of atherosclerosis as a common precursor. Atherosclerosis is a chronic inflammatory disorder that begins in childhood and results in arterial plaque formation and arterial stiffness, often presenting as CVD later in life.[5] Abnormal cholesterol metabolism is one of the primary causal risk factors for atherosclerosis and CVD. Approximately 38% of American adults have elevated cholesterol.[6] A standard lipid panel assesses total cholesterol, high-density lipoprotein - cholesterol (HDL-C), low-density lipoprotein - cholesterol (LDL-C) and triglycerides (TG) and is often the first step clinicians will take in either screening the general population or managing patients with symptoms of CVD. LDL-C reduction remains the primary focus of lipid management for CVD reduction, mainly due to the abundance of clinical trials studying this marker. However, even when LDL-C and traditional risk factors are addressed, residual CVD risk remains in many patients. Focusing on LDL-C reduction alone neglects other important aspects of lipoprotein metabolism.[7-9] Atherosclerosis does not simply result from the accumulation of lipids – inflammation, oxidative stress, and other factors play an important role in its pathogenesis and must be taken into consideration.[1,10]

Other contributing lipid and nonlipid biomarkers have been proposed for assessing risk and initiating different therapies. However, mainstream testing algorithms are only now beginning to incorporate these important markers. Some guidelines suggest measuring these analytes mainly in "select patients" or for secondary versus primary prevention, when a patient already has serious progressive CVD.[7,8,11] Testing indications for these advanced markers may not be straightforward for busy clinicians to implement in practice. However, it is clear that advanced cardiovascular panels may provide more clinical insight and help tailor therapies by including apolipoproteins, inflammatory markers such as high sensitivity C-reactive protein (hs-CRP), homocysteine, among others.[2,12]

Leading Causes of Death Globally



Source: WHO Global Health Estimates

Testing Guidelines

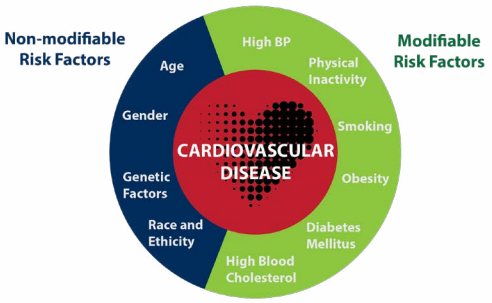
Several organizations worldwide have guidelines to address cardiovascular risk factors, including lipid modification, and these guidelines continue to evolve. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) guidelines are a widely used tool for assessing risk and have been updated over the years. NCEP began in 1985 and was facilitated by the National Heart, Lung, and Blood Institute (NHLBI). In 2013, the American Heart Association/American College of Cardiology (AHA/ACC) released guidelines designed to update the previous ATP III guidelines from 2001 with input from the NHLBI. These guidelines were loosely referred to as ATP IV, however, expert organizations are beginning to move away from this framework.[13-18] In 2018 the AHA, ACC, and several other societies released joint evidence-based Guidelines on the Management of Blood Cholesterol for reducing risk of atherosclerotic cardiovascular disease (ASCVD). An online risk-assessment tool helps clinicians to determine whether intervention is necessary. These and other association guidelines are beginning to incorporate other biomarkers in addition to the standard lipid panel as part of cardiovascular risk assessment.[8] For example, both the 2021 Canadian Cardiovascular Society (CCS) Guidelines and 2019 European Atherosclerosis Society/ European Society of Cardiology (ESC/EAS) Guidelines recommend a once per lifetime Lp(a) measurement for screening, and Apo B measurement as an alternative to LDL-C for screening.[11,19] These updated testing guidelines help to tailor therapies.

Although several organizations offer screening and treatment guidelines, ultimately treatment decisions are at the discretion of the clinician based on an individual's clinical presentation and risk factors.

- National Lipid Association (NLA) 2018 Guideline on the treatment of high blood cholesterol (summary of AHA/ACC Guidelines): **https://www.lipid.org/sites/default/files/nla_clinicianhandout_2018cholgl.pdf**
- American Heart Association/American College of Cardiology (AHA/ACC) 2018 Guidelines (full report): **https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625**
- Canadian Cardiovascular Society (CCS) 2021 Guidelines: **https://www.onlinecjc.ca/article/S0828-282X(21)00165-3/fulltext**
- European Atherosclerosis Society/ European Society of Cardiology (EAS/ESC) 2019 Guidelines: **https://academic.oup.com/eurheartj/article/41/1/111/5556353**
- ACC Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator Plus (online risk calculation tool): **https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/**

Of note, in the past, fasting lipid panels were exclusively recommended, but recent guidelines no longer require fasting. Studies have shown the ability to predict ASCVD is similar when fasting versus non-fasting lipid panels are compared.

Heart-Healthy Lifestyle

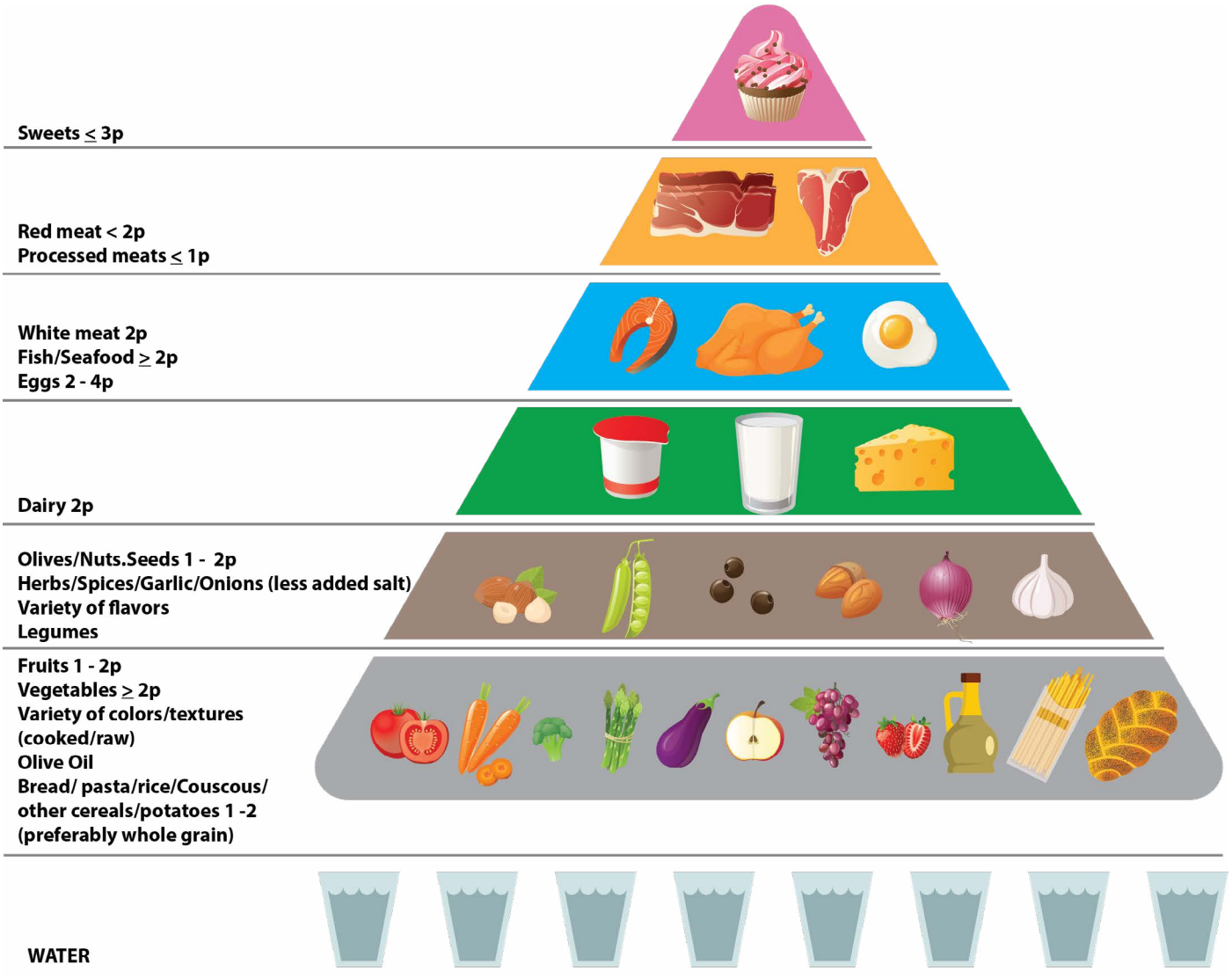


Risk factors for CVD include both modifiable and non-modifiable factors.[7] Addressing modifiable factors can profoundly impact risk. Emphasis on a heart-healthy lifestyle is a core recommendation for the public and for patients at risk for ASCVD. Being that the development of atherosclerotic plaque begins in childhood, these recommendations can be followed early on and throughout life for prevention.[5] The need for pharmaceutical or more intensive therapies should be determined for individuals based on overall risk. Even in patients using cholesterol-lowering drug therapies, lifestyle modification is crucial. In general, all guidelines focus on healthy diet and lifestyle modification as foundational for preventing and addressing CVD.[8,11,20-27]

- **Diet**: While there continues to be ongoing debate both in the scientific literature and in the public forum regarding the most effective dietary strategy for cardiometabolic health, there are some well-researched general guidelines that can be used to aid in a personalized dietary intervention for many patients.
  - » **Reduction in high-glycemic foods:** this includes dramatic reduction in refined carbohydrates, sugary foods/sweets, sweetened beverages, and even starchy vegetables such as white potatoes.
  - » **Incorporation of whole foods:** focus on items such as fruits, vegetables, whole grains, nuts, legumes, and healthy fats and protein. This dietary strategy is akin to diets such as **The Mediterranean Diet** that has been well-studied for its therapeutic value in CVD, metabolic syndrome, and T2D.
  - » **Ensure adequate dietary fiber intake:** diets higher in fiber aid in regulation of blood glucose, help support the gut microbiome, and can lower cholesterol. Sources of fiber include whole grains, nuts, seeds, legumes, and some fruits and vegetables.
  - » **Balance the fats:** The Standard American Diet (SAD) is often rich in inflammatory fats that can promote cardiovascular risk. These include hydrogenated fats and trans fats such as those found in fried and/or processed foods. Furthermore, there has been a shift in the consumption of Omega-6s compared to Omega-3s. Swapping out these fats for more cardioprotective fats are recommended, such as those found in oily fish, olive oil, and nuts.
  - » **Adjust for calorie requirements**
  - » **Adjust for personal and cultural food preferences**
  - » **Nutritional therapy for other medical conditions (i.e., diabetes)**
    - >It should also be noted that specific nutrient insufficiencies have been associated with abnormal lipid profiles. Additionally, targeted nutrient supplementation may improve lipid levels. For example, zinc supplementation has been shown to reduce total cholesterol, LDL cholesterol, and triglycerides. In non-healthy patients, zinc supplementation increased levels of HDL cholesterol.[28,29] Supplementation with CoQ10, amino acids, magnesium, and vitamin C have also shown promise as adjunct therapeutic strategies to optimize lipid profiles and improve cardiovascular risk.[30-34]
- **Activity**:
  - » **Aerobic physical activity** 3-4 sessions per week lasting average 40 minutes per session and involving moderate-to-vigorous-intensity
- **Weight loss** if appropriate to achieve a healthy BMI
- **Smoking cessation**
- **HPA axis balance/Stress Management:** There is an abundance of literature examining the effects of both acute and chronic stress in the development of cardiovascular disease. Personalized interventions to manage stress and HPA axis function can help lower the deleterious impact of stress on cardiovascular health.

Several expert organizations offer educational information on therapeutics both for clinicians and patients.Institute for Functional Medicine

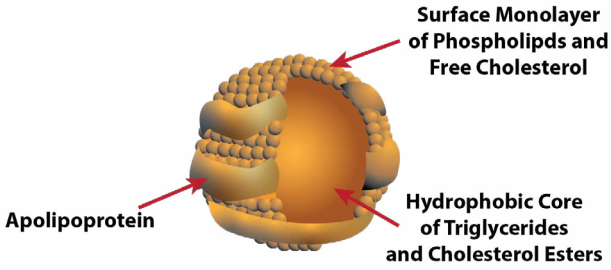
- National Lipid Association (NLA) patient and clinician tear sheets: https://www.lipid.org/TearSheets
- American College of Cardiology (ACC) CardioSmart health information: https://www.cardiosmart.org/About
- American Heart Association (AHA) Life's Simple 7 information: https://www.heart.org/en/professional/workplace-health/lifes-simple-7



The Mediterranean Diet Pyramid is recommended as a healthy eating plan.[35,36] The PREDIMED study supported the beneficial effect of the Mediterranean diet for the primary prevention of CVD.[25]

LIPIDS

Lipids, such as cholesterol and triglycerides, are insoluble in water. Therefore, they must be transported in association with proteins (lipoproteins) in the circulation. Each lipoprotein contains a mixture of cholesterol, protein, and triglyceride, but in varying amounts unique to each type of particle. The relative proportions of protein and lipid determine the density of these lipoproteins. These lipoproteins include lipoprotein a [Lp(a)], HDL, intermediate-density lipoprotein (IDL), LDL, very low-density lipoprotein (VLDL), chylomicrons, and chylomicron remnants. HDL is anti-atherogenic while the other lipoproteins are pro-atherogenic. Apolipoproteins are surface proteins of lipoprotein particles and serve as ligands that recognize specific receptors on cell membranes, thus helping to determine fat distribution throughout the body. While lipids are important for health, abnormal blood concentrations can be harmful and put patients at risk for cardiovascular diseases.[3,37]



The basic structure of a lipoprotein: phospholipid, free cholesterol and protein constitute the outer surface of the lipoprotein particle; the inner core contains mostly esterified cholesterol and triglycerides.[3]

Cholesterol

Cholesterol is a lipophilic molecule necessary for normal cellular function. It contributes to the structural makeup of cell membranes and modulates membrane fluidity. Additionally, cholesterol is a precursor to vitamin D, cortisol, aldosterone, sex steroid hormones, and bile.[37] Cholesterol can be synthesized de novo in the liver and intestines or obtained from the diet. De novo synthesis involves several steps including the enzyme HMG-CoA reductase, which is also the site of action for statins.[38] Most circulating cholesterol is synthesized by the liver with a small contribution from diet.[39]

LDL Cholesterol

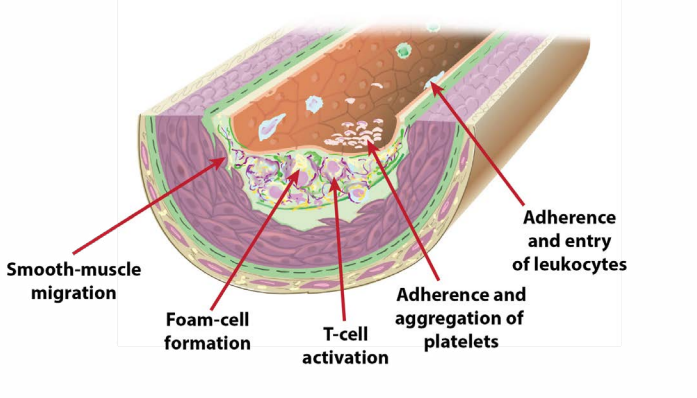
Low-density lipoprotein cholesterol (LDL-C) is the form of cholesterol that can deposit in plaques in the arteries leading to atherosclerosis. About 60-70% of cholesterol in the body is carried as LDL-C in the blood.[40] LDL oxidation dramatically increases the proatherogenic effect of LDL, therefore antioxidants and HDL (which possesses antioxidant properties) are important for preventing pro-inflammatory LDL oxidation.[41]

There is controversy in the literature regarding LDL measurement. The widely used Friedewald equation developed in 1972 estimates LDL-C as total cholesterol minus HDL-C minus triglycerides/5 in mg/dL. The controversy lies in the fact that elevated TG values can skew the formula, resulting in an underestimation of LDL-C.[42,43] Since that time, other equations have been proposed including the Martin-Hopkins Formula and Sampson's Equation which show more accuracy.[44-47] The concept of LDL-C accuracy is extremely important, considering LDL-C management is often the primary focus of risk and treatment guidelines. This concept may also explain discordance among biomarkers in clinical studies, where other markers such as Apo B and non-HDL-C may be better markers for risk, as compared to Friedewald-estimated LDL-C.[43] Genova uses a direct measurement of LDL-C versus a calculation for better accuracy.

LDL-C and non-HDL-C levels are strongly correlated to and associated with an increased risk of ASCVD. Non-HDL-C is easily calculated by subtracting HDL levels from total cholesterol. Non-HDL-C targets are normally 30 mg/dL higher than the LDL-C targets, and appear to be a better predictor of risk.[44] Several studies have confirmed that other parameters are better predictors of risk as compared to LDL-C, which is why it is important to assess other lipid and non-lipid markers. Non-HDL-C, TG levels, or an elevated TC/HDL-C ratio predict CHD independent of the LDL-C level.[48]

High Levels:

Elevated LDL cholesterol has been associated with an increased risk of atherosclerosis, which can lead to coronary artery disease, stroke, and peripheral artery disease. Contributing factors for increased LDL include genetics, diet, stress, sedentary lifestyle, medications, and disorders such as nephrotic syndrome and hypothyroidism. Diets high in saturated fat and trans-fat can lead to elevated cholesterol levels, while dietary cholesterol itself has not been shown to contribute significantly to LDL levels.[37,49,50] Certain medications are associated with elevated LDL levels including retinoids, cyclosporine A, phenothiazines, steroids, progestins, and androgens.[40,51] Additionally, not fasting prior to testing may cause a false elevation,[40] although this guideline has been challenged and several organizations are no longer requiring fasting prior to lipid testing, as previously discussed.



LDL-C remains the primary target of cholesterol-lowering therapy, with statins being the cornerstone drug treatment. Lipid-lowering therapy should be tailored to the individual based on overall risk factor assessment. In addition to statins, treatments for lowering elevated LDL include proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, ezetimibe, bile acid sequestrants, niacin, red yeast rice, and phytosterols.[8,23,52-55] Therapeutic considerations and additional educational resources for lipid management can be found in the Heart-Healthy Lifestyle section.

Preventing LDL oxidation may be another therapeutic consideration. LDL oxidation is counteracted by the body's antioxidant defense enzymes including superoxide dismutase, catalase and glutathione peroxidase, as well as ascorbate, urate, bilirubin, α-tocopherol, and ubiquinol.[41]

Low Levels:

Low levels may be observed in patients actively being treated for hypercholesterolemia. Additionally, decreased LDL levels occur in the following conditions: hypolipoproteinemia, type 1 hyperlipidemia, Apo C-II deficiency, hyperthyroidism, chronic anemias, hepatocellular disease, Reye's syndrome, acute stress (burns, illness), inflammatory joint disease, and chronic pulmonary disease. Decreased LDL may be seen in patients taking oral estrogen.[40] LDL-C levels <70 mg/dL and low triglycerides are associated with increased risk of hemorrhagic stroke in women.[56]

HDL Cholesterol

High-density lipoprotein (HDL) has anti-inflammatory, antioxidant, and anti-thrombotic activities and promotes reverse cholesterol transport.[57] HDL carries LDL cholesterol away from the arteries and back to the liver, where LDL is broken down and excreted as bile. For this reason, higher HDL is considered protective against heart disease and is termed "good cholesterol".[22] Cholesterol cannot be metabolized and used as an energy source in the human body, so excretion through bile is the only way the body can get rid of excess cholesterol. Apolipoprotein A-1 helps HDL accomplish this.[58]

HDL's antioxidant properties help to prevent LDL oxidation. However, the antioxidant capacity is diminished in inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, renal disease, iron deficiency anemia, polycystic ovarian syndrome, and in postmenopausal women.[59]

High Levels:

A higher HDL concentration is correlated with a decreased risk of atherosclerotic plaque formation.[37] Some medications are known to increase HDL including estrogens, androgens and related steroids, and insulin. Conditions associated with increased HDL include familial hyper-α-lipoproteinemia, chronic liver disease (cirrhosis, alcoholism, hepatitis), and long term aerobic or vigorous exercise.[40]

Low Levels:

Low HDL can increase the risk of ASCVD when LDL is high. However, clinical trials targeting increasing HDL levels have yielded null results. For this reason, the major treatment focus is on lowering LDL levels.[37,60] Therapies that support HDL functionality versus levels may be a better therapeutic target. Diet and exercise beneficially impact the antioxidative activity of HDL, whereas smoking impairs it. Additionally, a variety of medications have been studied that have variable effects on HDL's antioxidant function including statins, fibrates, niacin, Infliximab, and others.[41] Consumption of saturated fat reduces the anti-inflammatory potential of HDL whereas PUFAs increase the anti-inflammatory potential. However, replacing saturated fat with PUFAs or MUFAs may lower HDL levels slightly. Carbohydrates and trans fats also lower HDL cholesterol.[22] Therapeutic considerations and additional educational resources for lipid management can be found in the Heart-Healthy Lifestyle section.

Low HDL is part of the diagnostic criteria for metabolic syndrome.[51] Several medications are known to decrease HDL-C including progestins, androgens, antihypertensive agents, thiazides, beta-blockers, and anabolic steroids.[40,51]

Decreased HDL-C occurs in the following conditions: familial hypo-α-lipoproteinemia, Apo C-III deficiency, α-β-lipoproteinemia, familial hypertriglyceridemia, poorly controlled diabetes mellitus, hepatocellular diseases, cholestasis, chronic renal failure, uremia, nephrotic syndrome, anorexia, obesity, smoking, and stress/recent illness.[40,57]

Metabolic Syndrome

Metabolic syndrome is a group of five factors that can lead to heart disease, diabetes, stroke and atherosclerosis.[61] Metabolic syndrome is defined by having 3 out of 5 of the following criteria:[51]

- HDL cholesterol: < 40 mg/dL (men) or < 50 mg/dL (women)
- Triglycerides: ≥ 150 mg/dL
- Glucose: ≥ 100 mg/dL
- Obesity: Waist circumference ≥102 cm (men) or 88 cm (women)
- Blood pressure: ≥130/85 mmHg

Each of these factors is a risk factor for CVD, however the chance of developing a serious cardiovascular condition is doubled with three or more of these factors.[17,61]

Triglycerides

Triglycerides (TG) are the most common type of fat in the body. They store excess energy obtained from the diet. Triglycerides account for >90% of dietary intake and comprise 95% of fat in stored tissues.[40] Triglyceride-rich lipoproteins include chylomicrons and VLDL. Dietary TG is transported in intestinally-derived chylomicrons, while endogenously synthesized TG circulates in hepatically-derived VLDL.[62]

Triglycerides are a well-established independent marker of CVD risk, atherosclerotic disease risk, and part of the diagnostic criteria for metabolic syndrome.[51] Triglyceride levels may increase in the fed state depending on the amount of fat consumed and time since the last meal. If triglyceride levels are markedly elevated with a non-fasting panel, the lipid panel should be repeated while fasting.[44] Some studies suggest utility of a non-fasting TG level to reflect metabolic abnormalities.[48,63]

High Levels:

Even in the presence of controlled LDL-C, elevated TGs are strongly associated with CHD, and this risk is compounded if HDL-C is low.[9,22]

Alcohol and food intake prior to testing may cause a transient increase. Many medications may lead to elevated triglyceride levels including corticosteroids, thiazides, beta-blockers, oral estrogen, tamoxifen, bile acid sequestrants, cyclophosphamide, antiretroviral drugs, and antipsychotic agents.[40,62,64]

Increased triglycerides occur with the following conditions: hyperlipoproteinemia type I, Iib, III, IV and B, liver disease, alcoholism, nephrotic syndrome, renal disease, hypothyroidism, poorly controlled diabetes mellitus, pancreatitis, glycogen storage disease (von Gierke's disease), myocardial infarction, gout, Werner's syndrome, Down syndrome, anorexia nervosa, systemic lupus erythematosus, HIV infection, Cushing's syndrome, growth hormone deficiency, acute illness (cold/flu), pregnancy, obesity, physical inactivity, smoking, and with oral contraceptive use.[40,62,65]

Lipid-lowering therapy should be tailored to the individual based on collective risk factor assessment. The two major goals of treating hypertriglyceridemia are the prevention of CVD and pancreatitis.[65]

Elevated TGs are treated with lifestyle interventions, fibrates, niacin, and omega-3 fatty acids. The main intervention includes weight loss as one of the most important and effective approaches to lowering elevated TGs. Elevated TGs can be reduced by lifestyle interventions much more effectively than elevated LDL-C. Several of the drugs used to lower LDL-C, including statins, also lower TG to an extent. Research on newer drugs is evolving.[65,66] Replacing saturated fats with PUFAs or MUFAs lowers triglycerides, whereas carbohydrates raise triglyceride levels. Additionally, trans fats elevate triglycerides.[22] Therapeutic considerations and additional educational resources for lipid management can be found in the **Heart-Healthy Lifestyle section.**

Low Levels:

Generally, low TG levels do not contribute to CV risk. Many medications may lead to decreased triglyceride levels.[40] Several of the drugs used to lower LDL-C, including statins, also lower TG to an extent.[65]

Decreased triglyceride levels may occur with the following conditions: congenital α-β-lipoproteinemia, malnutrition/malabsorption, hyperthyroidism, hyperparathyroidism, brain infarction, and chronic obstructive lung disease.

Total Cholesterol

Total cholesterol (TC) includes LDL, VLDL, and HDL cholesterol.

High Levels:

Elevated total cholesterol correlates with ASCVD and is associated with elevated BMI and smoking.[63] LDL-C and TG are closely correlated with elevated TC.[67] Elevated cholesterol levels occur in the following conditions: type II familial hypercholesterolemia, hyperlipoproteinemia types I, IV, and V, cholestasis, hepatocellular disease, biliary cirrhosis, nephrotic syndrome, glomerulonephritis, chronic renal failure, pancreatic and prostatic malignancies, hypothyroidism, poorly controlled diabetes mellitus, alcoholism, glycogen storage disease (von Gierke's disease), Werner's syndrome, high fat diet, obesity, and pregnancy.[40]

Ratios such as the TC/HDL-C and TG/HDL ratios are better predictors of risk and should be evaluated in addition to TC levels alone.[67] Lipid-lowering therapy should be tailored to the individual based on overall risk factor assessment. LDL-C is the primary target of cholesterol-lowering therapy. Therapeutic considerations and additional educational resources for lipid management can be found in the **Heart-Healthy Lifestyle section.**

Low Levels:

Low levels may be observed in patients actively being treated for hypercholesterolemia. Low cholesterol has been associated with an increased risk of cancer, hemorrhagic stroke, and mortality, however it is unknown whether the relationship is causal.[68-73] Estrogen supplementation is known to decrease plasma cholesterol levels.[40]

Decreased cholesterol may be seen in the following conditions: hypo-α-lipoproteinemia, severe hepatocellular disease, myeloproliferative diseases, hyperthyroidism, malabsorption/malnutrition, megaloblastic or sideroblastic anemia, severe burns, inflammation, acute illness/infection, chronic obstructive pulmonary disease, and mental retardation.

Cholesterol Ratios

Lipid ratios are helpful for assessing risk versus looking at lipids individually and may help adjust therapeutic interventions. Multiple epidemiological studies have shown that lipoprotein ratios have a greater correlation with CVD and are therefore better predictors than individual lipid measurements.[67]

When interpreting expected ranges for lipid ratios, it is helpful to consider odds ratios (OR) and hazard ratios (HR). Statistically, these ratios are used to compare two variables in a dataset. The lipid ratio is one variable, and the OR and HR gives the association between the lipid ratio and CVD. An OR or HR equal to 1 indicates there is no association. A finding greater than 1 indicates an increased association and can be used to show the magnitude for the outcome.[74,75]

Triglycerides/HDL

The triglyceride/HDL (TG/HDL) ratio has been shown to predict both metabolic and cardiovascular risk and is associated with insulin resistance. High triglycerides and low HDL-C contribute to heart disease risk. The TG/HDL-C ratio is a better CV risk predictor versus LDL-C and a good parameter for deciding on the intensity and need for therapeutic intervention with different lipid patterns.[67]

High Levels:

An elevated ratio shows that a patient is both at increased metabolic risk and cardiovascular risk. The ratio predicts CHD and CVD mortality in men.[76] Additionally, a high ratio is suggestive of risk of insulin resistance, metabolic syndrome, and diabetes mellitus. Metabolic risk factors such as abdominal obesity, hypertension, and dysglycemia should be addressed.[76-79] In patients with insulin resistance, the ratio is able to predict CVD.[80] Interventions that address insulin resistance may be helpful for lowering the TG/HDL level.[81] See section on high triglycerides for more considerations. Therapeutic considerations and additional educational resources for lipid management can be found in the **Heart-Healthy Lifestyle section.**

Low Levels:

There are no known clinical associations with a low ratio. Assess overall lipid levels. See sections on high HDL and low triglycerides, if appropriate.

Total Cholesterol/HDL

The total cholesterol/HDL ratio (TC/HDL ratio), also known as the Castelli risk index-1, or cardiac risk ratio (CRR) provides more information than either value alone.[82] The ratio was developed using Framingham Study data and was shown to be a better predictor of CHD compared to individual lipid values.[83,84] The ability of this ratio to predict CHD has been confirmed in multiple subsequent studies, including longitudinal studies such as the large EPIC-Norfolk cohort.[48,67,84-86] Because the ratio reflects the formation of coronary plaques and is a good predictor of carotid intima-media thickness, it performs comparably to the Apo B/Apo A-1 ratio for prediction of CHD.[67,82,87] Total cholesterol correlates with CVD, whereas HDL has a protective effect. The higher the total-to-HDL ratio, the greater the risk for developing atherosclerosis.[40,67]

High Levels:

An elevated total-to-HDL ratio suggests increased risk for atherosclerosis and CHD.[48,67,84,88] Therapeutic considerations and additional educational resources for lipid management can be found in the **Heart-Healthy Lifestyle section**. The expected range for the TC/HDL ratio is based on risk stratification for future coronary heart disease risk as outlined by Arsenault et al. Below is a table highlighting the hazard ratios associated with the TC/HDL ratio. A ratio >5 correlates to roughly a 66% increase risk for CHD (Hazard ratio = 1.66), and a ratio >6 correlates to greater than 2x increased risk for CHD.[89]

Low Levels:

A low ratio indicates relatively higher HDL, which has a protective cardiovascular effect. It is important to assess overall concentrations of cholesterol, in addition to evaluating ratios. If total cholesterol is slightly elevated, it may be less problematic when HDL is elevated, and the total-to-HDL ratio is low.

TC/HDL-C	<4.00	4.00 - 4.99	5.00 - 5.99	>6.00
Total, person-yrs	89,089	61,443	42,140	42,354
HR	1.00	1.36 (1.20 - 1.56)	1.66 (1.45 - 1.91)	2.14 (1.88 - 2.44)
Men, person-yrs	23,007	27,914	22.833	26,632
HR	1.00	1.32 (1.09 - 1.58)	1.74 (1.45 - 2.09)	2.15 (1.81 - 2.56)
Women, person-yrs	66,041	33,546	19,311	15,722
HR	1.00	1.40 (1.16 - 1.69)	1.46 (1.18 - 1.81)	2.02 (1.65 - 2.48)

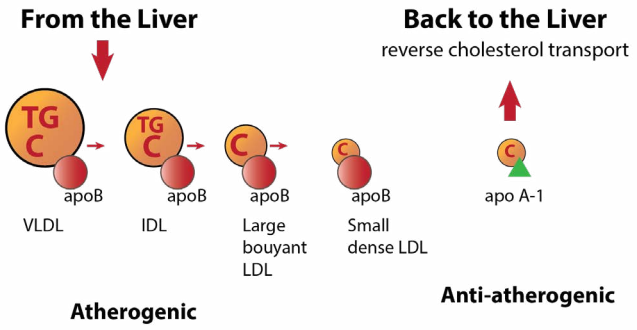
HR = Hazard Ratio

Lipoproteins

Apolipoproteins are surface proteins involved in lipoprotein metabolism. Examples include Apo A1, Apo B, and Apo (a), among others. Apolipoproteins have four major functions, including:[3]

1. serving a structural role
2. serving as ligands that recognize specific receptors on cell membranes, thus helping to determine fat distribution throughout the body
3. guiding the formation of lipoproteins
4. serving as activators or inhibitors of enzymes involved in lipoprotein metabolism

Testing apolipoproteins is important in the study of atherosclerosis and helps to evaluate the risk for CAD.[7,40] Abnormalities of apolipoproteins are referred to as dyslipoproteinemias. Apolipoproteins are acute-phase reactants and may be elevated in ill patients (acute stress, burns, major illness, inflammatory diseases).[40] Although the necessity of fasting lipids is debated, a benefit of measuring apolipoproteins as compared to standard lipids is that a fasting specimen is not required.[90]



There is one Apo B per atherogenic lipoprotein particle. Apo A-1 is the main apolipoprotein in HDL particles. Abbreviations: triglycerides (TG), cholesterol (C), very low density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL)

Apolipoprotein A-1

Apolipoprotein A-1 (Apo A-1) is the main structural component of HDL accounting for approximately 70% of HDL protein.[3,7,40] Cholesterol cannot be metabolized and used as an energy source in the human body, so excretion through bile is the only way the body can get rid of excess cholesterol. Apo A-1 helps HDL accomplish this, owing to its protective anti-atherogenic effect. Many studies have suggested that Apo A-1 and Apo B levels may be more accurate predictors of CAD, especially in patients with low or normal LDL-C levels.[58] Apo A-1 has antioxidant and anti-inflammatory effects. It stimulates nitric oxide and release of prostacyclin from the endothelium which protects vascular function.[91]

High Levels:

Elevated Apo A-1 is associated with a decreased risk of atherosclerosis.[3] Certain medications are associated with increased levels including carbamazepine, furosemide, gemfibrozil, nisoldipine, OCPs, phenobarbital, phenytoin, and prednisolone.[40]

Increased Apo A-1 is also associated with familial hyper-α-lipoproteinemia.

Low Levels:

Patients with low Apo A-1 are more likely to have CVD than those with high concentrations.[7] Factors that lower Apo A-1 include diets high in trans fats and PUFAs, smoking, and lovastatin.[22,40] Apo A-1 content in HDL tends to be reduced in metabolic and inflammatory diseases.[41]

Decreased Apo A-1 is associated with the following conditions: genetic/hereditary lipoproteinemias, familial amyloidosis polyneuropathy, hypertriglyceridemia, poorly controlled diabetes, premature CHD, hepatocellular disease, nephrotic syndrome, malnutrition, and renal failure.[40,92,93] Therapeutic considerations and additional educational resources for lipid management can be found in the **Heart-Healthy Lifestyle section.**

Apolipoprotein B

Apolipoprotein B (Apo B) is the main component of atherogenic lipoprotein particles, i.e. chylomicron remnants, LDL, IDL, VLDL, and Lp(a).[4,40,44,91,94] It is involved in the metabolism and transport of lipids. Apo B is present in two forms within the body. Intestinal Apo B-48 is essential for the formation of chylomicrons and serves in the absorption of dietary fats from the intestines. Hepatic Apo B-100 is necessary for the assembly of VLDL in the liver and also serves as a ligand for LDL receptor mediated clearance of LDL particles from the blood into the tissues.[4,90] Some researchers suggest that the risk of vascular disease is not related to the plasma concentration of cholesterol or triglycerides as much as it is the number, composition, and size of the Apo B particles.[95] Each atherogenic particle contains one molecule of Apo B. More than 90% of all Apo B in blood is from LDL.[4]

Apo B is a stronger indicator of atherogenicity than LDL-C alone.[8,44] Both Apo B and non-HDL-C have a similar ability to predict ASCVD.[44] Studies have shown that Apo B may be more strongly related to CHD risk than non-HDL-C.

Consensus reports from the American Diabetes Association and the American College of Cardiology suggest that Apo B measurements be added to standard cholesterol panels in patients with high cardiometabolic risk.[7] The Canadian Cardiovascular Society Guidelines recommend that either non-HDL-C or Apo B could be used as alternate targets to LDL-C because it provides a more accurate assessment of the total concentration of atherogenic particles than LDL-C.[11] Apo B measurement improves CVD risk prediction in patients with diabetes and metabolic syndrome.[90] Many studies have suggested that Apo A-1 and Apo B levels may be more accurate predictors of CAD, especially in patients with low or normal LDL levels.[58]

High Levels:

Increased Apo B is thought to be more atherogenic and is associated with an increased risk of atherosclerosis and CVD.[3] There are many medications associated with increased levels of Apo B including amiodarone, atenolol, chlorthalidone, conjugated estrogens, cyclosporine, estrogen/progestin therapy, etretinate, furosemide, gemfibrozil, isotretinoin, levonorgestrel, methyclothiazide, metoprolol, oral contraceptives, phenobarbital, radioactive iodine, simvastatin, and stanozolol.[40] Dietary trans-fat and saturated fat can raise Apo B.[22,49]

Increased Apo B is associated with the following conditions: hyperlipoproteinemia types IIa, IIb, and V, premature CHD, diabetes mellitus, insulin resistance, hypothyroidism, nephrotic syndrome, renal failure, hepatic disease and obstruction, dysglobulinemia, porphyria, Cushing's syndrome, pregnancy, and Werner's syndrome.[40,96-98]

Newer clinical trials include treating lipids using antisense oligonucleotides to target mRNA of proteins involved in cholesterol metabolism. These medications have shown a 50% reduction in Apo B levels, 30% reduction in LDL levels and decreased cardiovascular risk, however may cause liver dysfunction.[90] Other treatments studied for lowering elevated Apo B include niacin and statins.[4,52] Therapeutic considerations and additional educational resources for lipid management can be found in the **Heart-Healthy Lifestyle section**.

Low Levels:

Decreased Apo B may be seen in patients being treated for hypercholesterolemia. In addition to cholesterol-lowering medications, several anti-hypertensives and other medications used to treat CVD are associated with decreased levels. Other medications that may result in decreased levels include conjugated estrogens, indomethacin, interferon alpha-2a, interferon beta-1b, ketoconazole, levothyroxine, low molecular weight heparins, neomycin, phenytoin, prednisolone, psyllium, raloxifene and tacrolimus. Lower levels are also seen with high dietary intake of PUFAs and lower cholesterol intake.[40]

Decreased Apo B is associated with the following conditions: genetic/hereditary lipoproteinemias, type I hyperlipidemia, hyperthyroidism, Reye's syndrome, liver disease and malnutrition/malabsorption.[40,93,99-101]

Apo B/Apo A-1

The Apo B/Apo A-1 ratio has been shown in multiple studies to have a higher predictive ability for metabolic syndrome, CVD, obesity, insulin resistance, diabetes, MI, and early atherosclerosis as compared to standard lipid evaluations.[91,102-107] In fact, combining this ratio with markers like non-HDL-C levels or Lp(a) showed even greater predictive value for coronary and valvular heart diease.[7,40,58,108-110]

The results of the AMORIS study (Apolipoprotein-related MOrtality RISk) demonstrated specificity of this ratio for ischemic and atherosclerotic CV events, as compared to risk for other diseases such as non-ischemic CV events, cancer, and dementia.[111] Additionally, the landmark INTERHEART study of acute myocardial infarction (AMI) across 52 countries showed that globally 50% of AMI is predicted by the Apo B/ApoA-1 ratio, though smoking and other risk factors also account for MI risk to a lesser extent.[4,112]

High Levels:

A higher ratio indicates that more atherogenic particles are circulating leading to atherosclerosis and higher risk of CVD events.[4,88] It is important to assess overall levels of apolipoproteins, therefore, review the sections on high levels of Apo B and low levels of Apo A-1.

The expected range for the Apo B/Apo A-1 ratio is based on risk stratification for future coronary heart disease risk as outlined by Wim A van der Steeg et al.[113] Below is a table highlighting the odds ratios associated with the Apo B/Apo A-1 ratio. A ratio >.7 correlates to roughly a 33% increase risk for CHD (Odds ratio = 1.33), and a ratio >.9 correlates to 78% increased risk for CHD.[113]

Low Levels:

A lower ratio indicates relatively higher Apo A-1, which is considered anti-atherogenic. The lower the Apo B/ Apo A-1 ratio, the lower the risk.[4] See section on Apo A-1 if applicable.

ApoB/A-1					
Median	0.56	0.72	0.88	1.10	
Range	0.25 - 0.65	0.65 - 0.79	0.79 - 0.96	0.96 - 2.55	
OR (95% CI)	1.00	1.33 (1.01 - 1.77)	1.78 (1.37 - 2.32)	2.64 (2.04 - 3.42)	<0.001

OR= Odds Ratio, CI = Confidence Interval

Lp(a)

Lipoprotein(a), [Lp(a)] is composed of an LDL-like particle in which Apo B is covalently bound by a disulfide bond to apolipoprotein (a) (Apo (a)). Lp(a) carries the atherogenic risk of LDL particles, including the ability to oxidize after entry into the vessel wall, creating proinflammatory oxidized LDL. The Apo (a) component of Lp(a) contributes to risk via multiple mechanisms: it potentiates atherothrombosis via inflammation through its content of oxidized phospholipids, acts through lysine binding sites allowing accumulation in the arterial wall, and has antifibrinolytic effects by inhibiting plasminogen activation.[94]

Lp(a) is a highly prevalent genetic risk factor for CVD and calcific aortic valve disease. Circulating Lp(a) levels are primarily genetically determined by the LPA gene and are not significantly influenced by dietary or environmental influences.[94] Single nucleotide polymorphisms in the LPA gene are strongly associated with Lp(a) levels.[114]

Indications for measuring Lp(a) vary among many expert organizations. The 2021 Canadian Cardiovascular Society (CCS) Guidelines and 2019 European Atherosclerosis Society/ European Society of Cardiology (ESC/EAS) Guidelines recommend measuring Lp(a) once in a person's lifetime as a part of initial lipid screening for primary prevention.[11] Other organizations recommend measuring in patients with premature CVD, intermediate or high CVD risk patients, patients with inherited dyslipidemias, family history of premature CVD and/ or elevated Lp(a), patients with premature vascular disease, recurrent CVD despite statin treatment, or a 3% 10-year risk of fatal and/or 10% 10-year risk of fatal and nonfatal CHD.[7,94]

High Levels:

Because levels are largely genetically determined, diet and environmental influences have minimal impact.[94] However, trans fatty acid consumption specifically has been shown to raise Lp(a) levels.[115] Statins may lead to elevated Lp(a).[116,117] The kidney plays a role in Lp(a) clearance, therefore kidney disease is associated with delayed clearance and elevated Lp(a) levels.[3] Additionally, inflammation can increase Lp(a).[44]

There are no approved medications that directly target Lp(a). Niacin is used in broader populations, whereas PCSK9 inhibitors, mipomersen, cholesterol ester transfer protein inhibitors, and estrogen are used in limited populations. Antisense oligonucleotides (ASOs) show promise in clinical trials, however these are not yet approved for use. While these therapeutics have shown reduction in Lp(a) levels, most have not significantly impacted clinical outcomes.[94,114,118,119] Individuals with very high baseline Lp(a) concentrations and large reductions in Lp(a) may benefit the most from treatment.[114] Apheresis, a blood filtering process similar to dialysis, is the most effective therapy for high Lp(a) and is considered for select patients, however the procedure is costly and cumbersome.[94] Natural products have been studied, showing reduction in Lp(a) levels, although, demonstration of clinical benefit is minimal. L-carnitine, coenzyme Q10, and xuezhikang (red yeast rice) were shown to significantly decrease Lp(a) levels in patients, while other products showed a lesser reduction, including pectin, Ginkgo biloba, flaxseed, red wine, resveratrol, and curcuminoids.[114]

There is an association between elevated Lp(a) and venous thromboembolism, CAD, PAD, cerebrovascular disease, abdominal aortic aneurysm, aortic valve calcification and stenosis, and with risk of cardiovascular death, non-fatal MI, and ischemic stroke.[7,114] Lp(a) is estimated to be elevated in approximately 20% to 30% of the world's population using <30 mg/dL as a cutpoint.[7,94] According to the 2021 CCS Guidelines, in the setting of primary prevention, a Lp(a) ≥ 50 mg/dL warrants more intensive health behavior modification and management of other ASCVD risk factors.[11] In the setting of controlled LDL-C, Lp(a) still presents risk.[94]

INDEPENDENT RISK FACTORS

In addition to lipids and apolipoproteins, other cardiometabolic biomarkers may identify risk. Cardiovascular disease pathology can be attributed to dyslipidemia as well as inflammation and disturbances in the methylation pathway.[1] For this reason, hsCRP and homocysteine are included to assess inflammation and methylation, respectively.

Cardiometabolic Markers

hsCRP

High-sensitivity C-Reactive Protein (hsCRP) is an acute-phase response protein produced by the liver as well as extrahepatic tissues such as vascular smooth muscle, atherosclerotic plaques, cardiac tissue, and possibly adipose tissue.[120,121] It is triggered by interleukin-6 (IL-6), IL-1β, tumor necrosis factor (TNF), and other pro-inflammatory stimuli.[120] The marker CRP assesses non-specific inflammation from infections, inflammatory disorders, and endocarditis. Because inflammation is ubiquitous in the atherothrombotic process, a high sensitivity (hs) CRP test is more specific for cardiovascular related conditions such as atherosclerosis.[122]

High Levels:

hsCRP levels are strongly correlated to the severity of coronary atherosclerosis.[123] In patients with previous myocardial infarction, peripheral artery disease, or diabetes, elevated hsCRP was a strong predictor of subsequent major adverse cardiovascular events and death.[124–126] Elevated hsCRP levels may also be associated with risk of type 2 diabetes and all-cause mortality.[127–129] hsCRP elevations can be seen in post-menopausal women taking oral estrogens (but not topical estrogens), insulin resistance, and obesity.[129] Smoking, including secondhand smoke, is associated with higher levels of hsCRP and worse measures of subclinical atherosclerosis.[130]

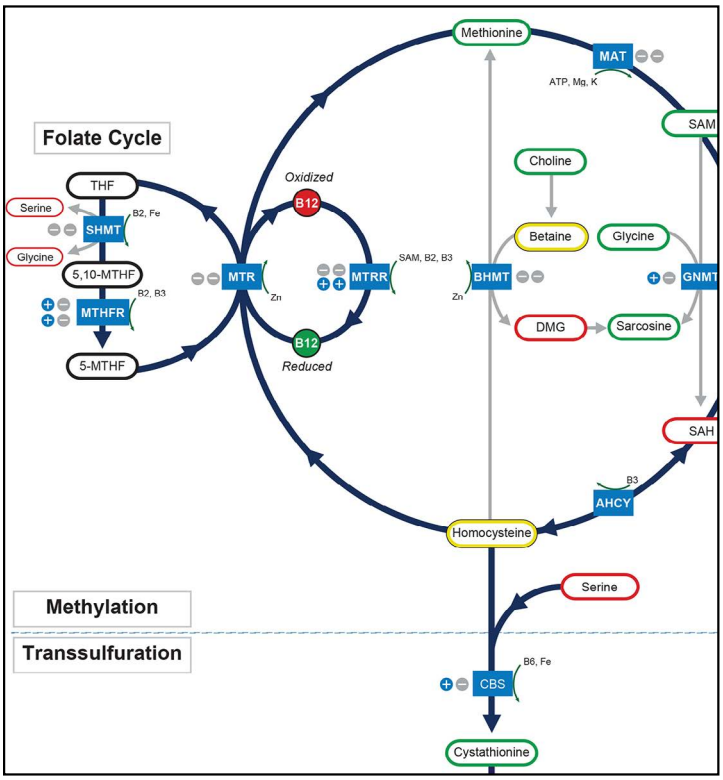
Fortunately, hsCRP is a modifiable risk factor for cardiovascular disease. Multiple dietary and lifestyle factors may augment CRP levels including extra virgin olive oil, omega-3 fatty acids, low glycemic index foods, fiber, exercise, weight reduction, and smoking cessation.[107,121,130–132] The Mediterranean and Paleolithic diets may be associated with lower levels of inflammation (including lower hsCRP) and oxidative stress.[117,133] Therapeutic considerations and additional educational resources can be found in the **Heart-Healthy Lifestyle section.**

Medications, such as aspirin, have also been shown to improve hsCRP levels.[122,129] Additionally, the JUPITER trial showed that patients who did not qualify for statins according to their LDL-C levels but did qualify for statins by having elevated hsCRP, had fewer heart attacks and strokes.

Levels of hsCRP[121]	
<1 mg/L	Low systemic inflammatory status, low vascular risk
1-3 mg/L	Moderate vascular risk
>3 mg/L	Higher vascular risk in context of other risk factors
>10 mg/L	Unspecified inflammation; may reflect transient infection or other acute phase response; repeat in 2-3 weeks

Homocysteine

Homocysteine (Hcy) is regarded as a risk factor for non-coronary atherosclerosis and coronary artery disease.[134] Hcy is toxic to the endothelium, prothrombotic, increases collagen production, and decreases the availability of nitric oxide – factors that promote ASCVD.[1] Hcy is a type of amino acid, but not a classic amino acid found in dietary protein. Homocysteine's only source in humans is the demethylation of s-adenosylmethionine (SAM). Homocysteine is a major branch point in the methylation pathway. It can be metabolized via two pathways: degraded irreversibly through the transsulfuration pathway or re-methylated back to methionine. These two pathways are greatly affected by vitamin and mineral cofactor availability and enzymatic SNPs.[135]



Transsulfuration is the main route for irreversible Hcy disposal. Transsulfuration begins when Hcy is converted to cystathionine, using the cystathionine β-synthase enzyme (CBS). This reaction requires nutrient cofactors, such as vitamin B6 and iron.[136]

Alternatively, Hcy can be re-methylated back to methionine.[134] Two distinct routes exist for Hcy remethylation. The first reaction is dependent on folate and vitamin B12. The second route for Hcy remethylation is independent of folate but requires betaine. The betaine pathway for Hcy remethylation is a salvage pathway when folate metabolism abnormalities are present or in folate deficiency.[135] Under normal conditions, the body will remethylate Hcy several times before allowing irreversible transsulfuration.[137]

Whereas SAM-dependent methylation occurs in nearly all tissues, the transsulfuration pathway and Hcy remethylation occur primarily in the liver and kidneys.[138]

High Levels:

Several factors can affect Hcy metabolism causing hyperhomocysteinemia. These include B-vitamin deficiencies, impaired renal excretion, advanced age, sex (male), stress, smoking, alcohol, and genetic enzyme deficiencies.[134,139-146] Modifiable factors should be addressed. Medications can increase Hcy levels including methotrexate, metformin, cholestyramine, and antiepileptics.[147-152] Dietary nutrient cofactors are important for metabolizing Hcy, including vitamins B6, B12 and folate, as well as iron, and choline.[136,153] Dietary supplementation with folate, vitamin B12, and SAM has been shown to effectively lower plasma homocysteine levels and improve outcomes.[134,154,155] Refer to the **Heart Healthy Lifestyle** in the introduction to this document for therapeutic considerations and additional educational resources.

Elevated homocysteine levels have many clinical implications.

- Hyperhomocysteinemia is regarded as a risk factor for non-coronary atherosclerosis and coronary artery disease. Elevated homocysteine enhances vascular smooth-muscle cell proliferation, increases platelet aggregation, and acts on the coagulation cascade and fibrinolysis, causing normal endothelium to become more thrombotic. The mechanism may be related to elevations in S-Adenosylhomocysteine (SAH), due to the reversible nature of Hcy formation.[134] SAH has been shown to be a more sensitive marker in many diseases.[156,157]
- Diabetes, both type 1 and type 2, initially causes hypohomocysteinemia, due to renal hyperperfusion early in the diabetic nephropathy disease process. This progresses to hyperhomocysteinemia as renal function becomes compromised.[134,158]

- Elevated homocysteine levels have also been implicated in gastrointestinal disorders such as inflammatory bowel disease and colon cancer.[134,159] Hyperhomocysteinemia may be partially due to nutrient malabsorption (methyl donor and B-vitamin deficiency). Subsequently, elevated Hcy has been shown to induce inflammatory cytokines and contribute to disease progression.[159]
- Homocysteine status is associated with the severity of hypothyroidism and levothyroxine treatment is associated with a reduction in plasma Hcy levels.[160-162] Increased Hcy in hypothyroidism may be due to the effect of thyroid hormone on Hcy metabolism in the liver and clearance in the kidney. Thyroid hormone deficiency decreases hepatic levels of enzymes involved in remethylation of Hcy to methionine.[163]
- Homocysteine can impair bone health by interfering with osteoclast activity. The increased Hcy impairs the cellular and molecular mechanism of bone marrow-derived osteoclasts by causing imbalance between phosphorylation and de-phosphorylation of various protein kinases that modulate bone cell remodeling.[164]
- Homocysteinemia contributes to neurodegenerative diseases (Alzheimer's and Parkinson's diseases) and mood disorders.[154,165,166] Elevated Hcy increases CNS phosphorylated tau protein leading to increased neurofibrillary tangle formation, seen in Alzheimer's dementia.[167] Hyperhomocysteinemia related to mood disorders may be multifactorial. Elevated Hcy causes elevations in SAH, which interferes with many methyltransferase reactions involved in neurotransmitter synthesis and metabolism. Hcy may also have direct neurotoxic effects. Research is ongoing regarding the exact mechanisms regarding Hcy and psychiatric disorders.[168,169]

Low Levels:

Low levels may be seen in patients taking methylation support formulas. Literature is evolving regarding low Hcy. There is an association with low Hcy and peripheral neuropathy.[170] There are a few animal studies looking for implications, physiologic impacts, and treatment strategies to correct hypohomocysteinemia, but currently no human studies exist.[171,172]

However, because Hcy is used to make glutathione and is remethylated to maintain methionine levels, the theoretical importance of low Hcy exists. Without Hcy, glutathione production is compromised. Excessive oxidative stress may accelerate the transsulfuration pathway toward glutathione production, which can lower Hcy. A SNP in the CBS enzyme accelerates homocysteine transsulfuration, which may result in a low Hcy.[173,174] Additionally, if there is a defect in the enzyme AHCY that converts SAH to Hcy, or a lack of vitamin B3 which is a cofactor for this enzyme, then Hcy may be lower.[175]

Insulin

Insulin is an important hormone secreted by the beta cells of the pancreas in response to elevated blood glucose following a meal. Insulin binds to insulin receptors on target cells and helps to transport glucose from the blood into the cells, thus helping to regulate blood glucose levels. Insulin's major target tissues include skeletal muscle, liver, and white adipose tissue. In skeletal muscle, insulin promotes glucose utilization and storage by increasing glycogen synthesis. In the liver, insulin activates glycogen synthesis, increases lipogenic gene expression, and decreases gluconeogenic gene expression. In white adipose tissue, insulin suppresses lipolysis and increases glucose transport and lipogenesis.[176]

Fasting insulin levels are used as a surrogate or compensatory reaction of insulin resistance. Insulin resistance is the pathological state between insulin synthesis and reduced tissue sensitivity to insulin. This results in impaired glucose homeostasis and increasing blood glucose levels. Target tissues are unable to coordinate a normal glucose-lowering response and insulin secretion increases to compensate. Over time, prolonged exposure to high insulin could be detrimental to islet and beta cell function, resulting in decreased insulin secretion.[176,177] In addition to increased insulin secretion, insulin resistance can feature a decrease in the insulin clearance rate which may also contribute to hyperinsulinemia.[178] Lipid accumulation in sites other than adipose tissue, including liver and skeletal muscle is associated with insulin resistance and is considered metabolically harmful.[176]

It has been hypothesized that elevated insulin levels can precede type 2 diabetes (a cardiovascular risk factor) and are also associated with adverse cardiovascular disease risk profile. Whether insulin itself is an independent risk factor is still being debated. Meta-analyses and prospective cohort studies are ongoing and suggest a positive association between fasting insulin concentrations and the risk of hypertension and coronary heart disease.[179]

Insulin can act as an inotropic agent and may increase cardiac output and blood volume by stimulating vasopressin secretion and renal sodium retention. It can also increase vascular tone and vasoconstriction, stimulate the renin-angiotensin system, and stimulate secretion of other important vasoconstrictors like endothelin-1.[179]

Insulin resistance is associated with endothelial dysfunction, platelet aggregation, and increased reactive oxygen species in the vessel wall. Insulin resistance can affect adipocytes, resulting in elevations of systemic inflammatory mediators such as C-reactive protein and complement.[179]

High Levels:

Elevated fasting insulin can reflect insulin resistance as outlined above. Multiple pathologic changes accompany insulin resistance including glucose intolerance, dyslipidemia, endothelial dysfunction, elevated procoagulant factors, hemodynamic changes, elevated inflammatory markers, abnormal uric acid metabolism, increased ovarian testosterone secretion, and sleep-disordered breathing.[180] Insulin resistance is associated with many clinical conditions including obesity, type 2 diabetes, metabolic syndrome, CVD, polycystic ovarian syndrome, nonalcoholic fatty liver disease, dyslipidemia, acanthosis nigricans, certain cancers, sleep apnea, Cushing's disease, pregnancy, cirrhosis, acromegaly, and lipodystrophy.[176,180,181]

A number a pharmaceutical agents are associated with inducing insulin resistance including diuretics, β-blockers, corticosteroids, oral contraceptives, nicotinic acid, antipsychotic agents, and anti-retrovirals.[180]

Elevated insulin may also be seen in pancreatic tumors (insulinomas), or with excess administered exogenous insulin which causes hypoglycemia. A normal insulin level does not exclude an insulinoma, and proinsulin levels have been suggested as being diagnostic of insulinoma.[182]

Hyperinsulinemia and insulin resistance results from several dietary and lifestyle factors including chronic excess calorie consumption, high fat diets, physical inactivity, stress, sleep deprivation, and obesity. The rate of insulin secretion is lower when low glycemic index foods are consumed. Dietary fiber and resistant starches improve post-prandial glucose and insulin responses.

Moderate alcohol intake can increase postprandial insulin secretion but may decrease fasting insulin in nondiabetics. The effects of alcohol on insulin levels have been shown to vary between men and women with women having lower insulin levels. However, alcohol can increase or decrease insulin secretion which may result in inadequate pancreatic response to blood sugar, leading to insulin resistance and risk of developing type 2 DM.[183-185]

Micronutrients that can influence insulin secretion and physiologic action include zinc, boron, calcium, magnesium, and chromium.[186] Addressing these nutritional and lifestyle factors can improve insulin resistance. Pharmaceutical therapeutics to modulate insulin include sulfonylureas, metformin (a biguanide), thiazolidinediones, and others.[180]

Low Levels:

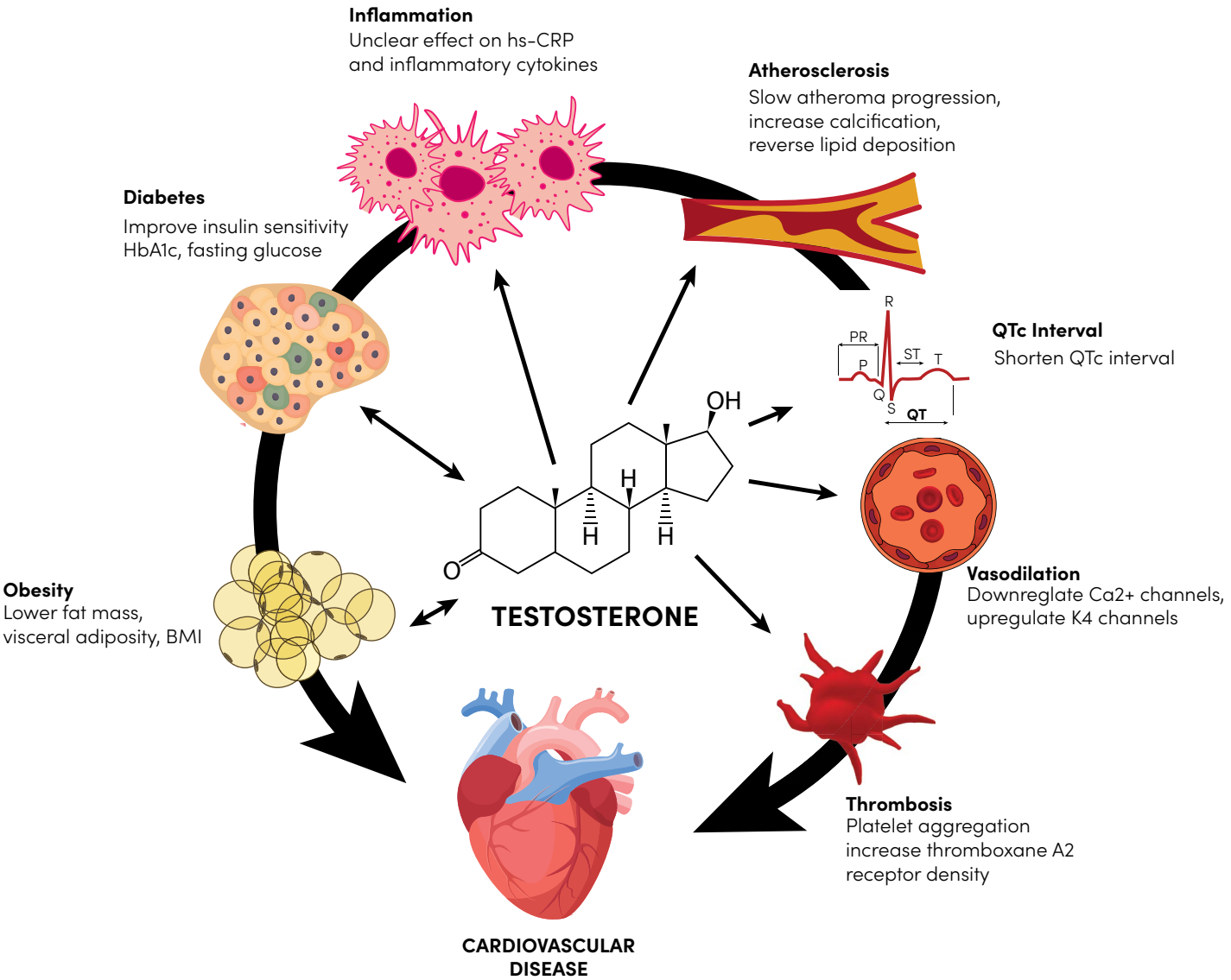
Fasting insulin is expected to be lower in healthy individuals. Insulin deficiency is seen in type 1 and some type 2 diabetics due to destruction or failure of the pancreatic beta cells, whereby patients become dependent on exogenous insulin.[177] Additionally, other pancreatic diseases such as chronic pancreatitis, cystic fibrosis, and pancreatic cancer can also be associated with insulin deficiency or insufficiency.[187,188] Low insulin may also be present in hypopituitarism.[40]

SEX HORMONE MARKERS

Testosterone

Testosterone is the principal male hormone secreted by the testes in men, and the ovaries and adrenal glands in men and women. 98-99% of testosterone is transported systemically bound to sex hormone binding globulin and albumin. The unbound, free testosterone exhibits the more potent biological activity. Testosterone can be acted on by the enzyme 5α-reductase to form dihydrotestosterone (DHT) which is the most biologically active form of testosterone. Testosterone can also be aromatized to estradiol peripherally. In addition to causing androgenic sex characteristics, it is responsible for anabolic functions like increasing muscle mass and bone density.

Testosterone has been shown to regulate nitric oxide (NO) and the NO/cyclic guanosine monophosphate (cGMP) pathway which can influence vasodilation and endothelial function.[189] It also has been shown to affect platelet aggregation, cardiac electrophysiology, lipid metabolism, and insulin sensitivity.[190]



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https://www.cjcopen.ca/article/S2589-790X(21)00133-5/fulltext

There are observational and epidemiological studies to suggest higher all-cause mortality in men with low testosterone, even after accounting for age and comorbid disease.[191-193] Several studies, including the Rotterdam Study found that men with higher levels of testosterone had less atherosclerosis and cardiovascular disease.[194-196]

High Levels:

Testosterone secretion does have a circadian rhythm and is higher in the morning. Elevated testosterone can be seen in the presence of glandular tumors like the testes, adrenal glands, and ovaries, or any disorders of these glands. High testosterone is found in women with polycystic ovarian syndrome (PCOS). Elevations can also be seen in patients taking exogenous hormonal supplementation.

High testosterone may present with symptoms of virilization, such as increased muscle mass, excess body hair, elevated libido, and deepening of the voice.

Addressing the underlying cause, assessing detoxification pathways, optimizing methylation, and balancing the microbiome may be helpful strategies to treat high testosterone.

Low Levels:

Testosterone levels fall with advancing age. It can also be seen with any disorder of the hypothalamus, pituitary, or testes. The hypothalamic-pituitary-testes (HPT) axis can also be suppressed in some chronic medical conditions such as metabolic syndrome, diabetes, dyslipidemia, hypertension, renal disease, and malignancy which can result in low testosterone.[197]

Medications such as opioids, anabolic steroids, and glucocorticoids, as well as alcohol and marijuana use have been shown to cause a functional hypogonadism and lower testosterone levels.

Obesity is also associated with lowering testosterone and weight loss can recover endogenous testosterone production. Systemic illnesses, sleep disorders, end-stage renal disease, and some nutritional insufficiencies (low-fat diets and lack of vitamin D), are also associated with secondary hypogonadism and lower testosterone levels.[198-200]

Clinical signs of testosterone deficiency include decreased hair growth, central obesity, sarcopenia, low libido, impotence, and decreased bone density.

Addressing underlying metabolic causes and nutritional insufficiencies, sleep, weight loss, medication review, cessation of alcohol and cannabis use are important treatment strategies to increase testosterone. Weight bearing exercise and high intensity interval training (HIIT) have also been shown to increase endogenous testosterone levels.[201,202]

Herbal supplements, such as mucuna and ashwagandha, can be useful to raise testosterone. Additionally, there are herbs that can inhibit aromatase and the enzyme 5-α-reductase, such as stinging nettles, saw palmetto, chaste tree berry and others.

Bioidentical testosterone replacement therapies are increasingly being prescribed. Despite decades of research, there is still controversy and a host of conflicting studies regarding the role of exogenous testosterone supplementation as it relates to cardiovascular risk.[190,203]

Sex Hormone Binding Globulin (SHBG)

Sex hormone binding globulin (SHBG) is a protein produced mainly in the liver that binds and transports testosterone, dihydrotestosterone, and estrogen to tissue receptors for biologic action. It does have a greater affinity for androgens. Not only does it transport hormones, it's been shown that SHBG can regulate hormone bioavailability, affinity, and access to target tissues.[204] Because most hormones are bound to SHBG or albumin, changes in SHBG can greatly affect interpretation of measured hormone levels and their clinical effects due to bioavailability. A complete hormonal evaluation should include levels of sex hormones as well as SHBG.

When SHBG is high, there is less bioavailable hormone which can cause symptoms of hormone deficiencies. In the case of testosterone for example, high SHBG causes symptoms of testosterone insufficiency. At the same time, those low testosterone levels stimulate the production of SHBG further worsening the clinical situation.

Levels of SHBG are influenced by many factors including nutrition, metabolism, hormonal balance, and lifestyle habits.

High Levels:

SHBG levels rise with aging, stress, alcohol use, smoking, and with various clinical conditions such as cirrhosis, hepatitis, HIV, and hyperthyroidism. Levels in women can vary within the menstrual cycle and elevate during ovulation and throughout pregnancy.[205-208]

Adiponectin, a protein produced in white adipose tissue which is inversely correlated to body mass and weight, can increase levels of SHBG through molecular signalling.[204]

Some medications, such as carbamazepine, phenytoin, thiazolidinediones, and oral contraceptives induce the liver to produce higher levels of SHBG.[204]

There are also dietary influences on SHBG. For example, diets low in protein and vegetarian diets are associated with higher SHBG levels.[209] Dietary oleic acid has been show to increase SHBG production[210]

Because high SHBG can cause decreased testosterone bioavailability, it can present with symptoms of low testosterone (sarcopenia, central obesity, low libido etc.). For this reason, some clinicians may consider strategies to lower it. These strategies might include higher protein intake, medication review, stress management, and smoking and alcohol cessation.

Low Levels:

Obesity, PCOS, hypothyroidism, systemic inflammation, and non-alcoholic fatty liver are well known to be associated with lower levels of SHBG.[204,205,211,212] Smoking has also been shown as a risk factor for low SHBG in men and women.[213] Because secretion of SHBG is suppressed by insulin, low levels are observed in insulin resistance and have been studied as a potential predictor of developing metabolic syndrome and type 2 DM, both cardiac risk factors.[204,214]

Having low SHBG can potentially present clinically with virilization since it accounts for elevated bioavailable testosterone. Addressing underlying clinical conditions, evaluation for insulin resistance, weight loss, smoking cessation, and exercise are potential therapeutic options.[215]

APPENDIX

Terminology Used in Cardiology	
Apolipoprotein	Surface proteins of lipoprotein particles that serve as ligands to recognize specific receptors on cell membranes, ultimately determining fat distribution throughout the body. Examples include Apo A-1 and Apo B.
Dyslipidemia	Abnormal cholesterol and/or triglyceride levels
Dyslipoproteinemias	Abnormal apolipoprotein levels
Lipoprotein	A transport particle that contains a mixture of cholesterol, triglyceride, and protein, but in varying amounts unique to each type of particle. Lipoprotein particles include HDL, IDL, LDL, VLDL, and chylomicrons, in order of decreasing density.
Primary Prevention	Screening and intervening before clinical disease manifestations occur
Secondary Prevention	Screening to identify additional risk, and to prevent progression in patients with established CVD

Abbreviations and Acronyms Used in Cardiology	
ACC	American College of Cardiology
AMI	Acute myocardial infarction
AHA	American Heart Association
Apo A-1	Apolipoprotein A-1
Apo B	Apolipoprotein B
ASCVD	Atherosclerotic Cardiovascular Disease
ATP	Adult Treatment Panel
CAD	Coronary Artery Disease
CBS	Cystathionine β-synthase (enzyme)
CCS	Canadian Cardiovascular Society
CDC	Centers for Disease Control
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
Hcy	Homocysteine
HDL-C	High-density lipoprotein cholesterol
HMG CoA-Reductase	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
HTN	Hypertension
IDL	Intermediate-density lipoprotein
JUPITER	Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
MI	Myocardial infarction
MUFA	Monounsaturated fatty acid
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung, and Blood Institute
NLA	National Lipid Association
Non-HDL-C	A simple calculation of total cholesterol minus HDL-C
PCSK9	Proprotein convertase subtilisin/kexin type 9
PREDIMED	Prevention with Mediterranean Diet (trial)
PUFA	Polyunsaturated fatty acid
SAM	S-Adenosylmethionine
SAH	S-Adenosylhomocysteine
SNP	Single nucleotide polymorphism
TC	Total cholesterol
TG	Triglyceride
VLDL	Very-low-density lipoprotein
WHO	World Health Organization

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