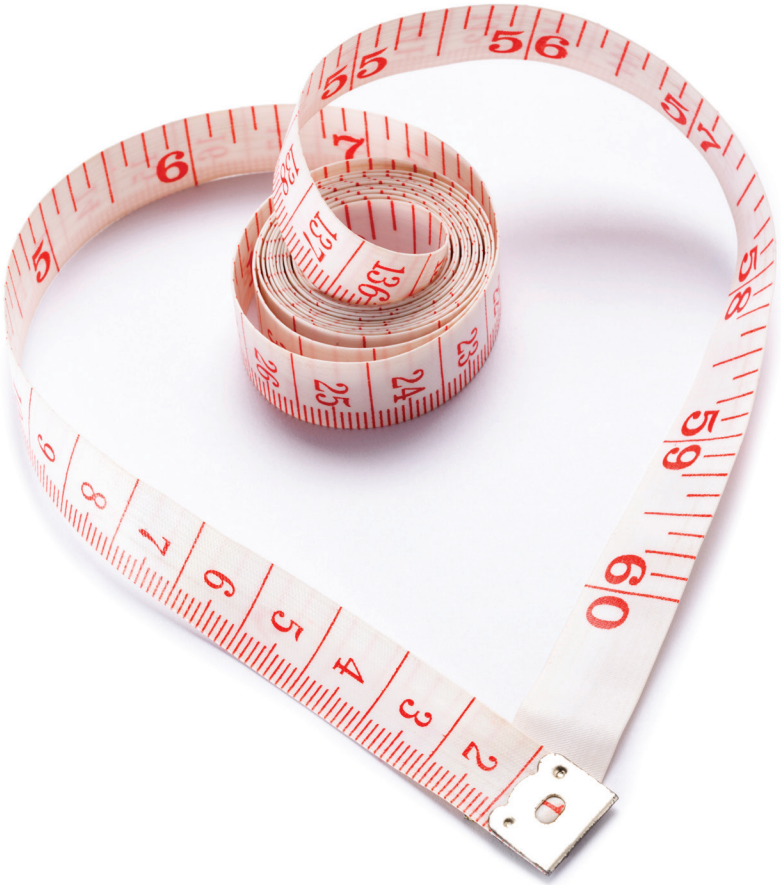
Effective Clinical Evaluation of Atherosclerosis and other Cardiovascular Diseases



Nordic Laboratories

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Effective Clinical Evaluation of Atherosclerosis and Other Cardiovascular Diseases

A major contributor to global mortality is cardiovascular disease (CVD). WHO estimates that 17.3 million people died from CVDs in 2008[1], and moreover it is estimated that 20 million people will die from CVDs in 2015[2]. Metabolic Syndrome is a major risk factor for CVD, and is even suggested to be a precursor hereof[3].

Cardiometabolic risk has been identified as "the cluster of modifiable risk factors and markers that identify individuals at increased risk for cardiovascular disease (myocardial infarction, stroke, peripheral arterial disease) and type 2 diabetes."[4]. The National Cholesterol Education Program (NCEP)'s Adult Treatment Panel III (ATP III) has suggested the characteristics for Metabolic Syndrome as follows[5]:

- Hypertension/elevated blood pressure
- Abdominal obesity
- Atherogenic dyslipidemia (low HDL cholesterol, elevated triglycerides, elevated LDL cholesterol)
- Prothrombotic/pro-inflammatory state
- Insulin resistance/glucose intolerance

In addition, NCEP ATP III has identified several modifiable nonlipid risk factors for coronary heart disease (CHD) – one form of CVD – including hypertension, cigarette smoking, thrombogenic state, diabetes, obesity, physical inactivity and an atherogenic diet[5].

For decades we have been taught to believe that the primary cause of heart disease simply is high cholesterol levels, and that diets high in saturated fat and cholesterol are major contributors to heart disease. Additionally, the conventional medical establishment has endorsed the widespread use of statins, which may cause a number of side effects. Relying on standard lipid panels for risk assessment of CVDs may fail to detect a great number of individuals at actual risk, and it has become increasingly apparent that more reliable approaches must be considered.

Cholesterol readings and lipoproteins

Historically, direct measures and quantification of total cholesterol, lipoproteins (HDL/LDL) and triglycerides have been used as standard markers of atherosclerosis and related CVDs[6]. However, it is known that nearly 50% of people, who have suffered from heart attack, have presented with cholesterol values within the normal reference range[7]. Evidence suggests that subclasses of LDL-particles characterized by density are clinically useful and important in the risk assessment of cardiovascular diseases[8]. Predominance of small, dense LDL particles (sd-LDL) is independently associated with increased risk of coronary artery disease[9].

Besides predominance of sd-LDL in patients with CVD, some studies also suggest that predominance is present to some extent in patients with DM2 and those with low HDL-C, high triglyceride levels and other characteristics of insulin resistance and Metabolic Syndrome[10].

With such improved and detailed understanding of potential pathological influences, intervention protocols and preventative strategies for CVD may be more accurately tested, efficient and precisely targeted. Strategies of advanced lipid testing acknowledge the importance of lipoprotein size, as well as testing the modified and proatherogenic form of LDL – oxidised LDL – allowing for a more comprehensive risk assessment than a conventional lipid profile.

Triglycerides

Triglycerides are complexes of three fatty acid groups attached to a glycerol backbone, and function as dense storage lipids important for our energy and metabolism. The fatty acids in each triglyceride can be different in structure, thus there are many possible structures of triglycerides. High triglyceride levels are an indicator of dyslipidemia and are associated with DM2 and obesity, as well as CVDs[5].

Cholesterol

Cholesterol is a steroid lipid-containing molecule that has many essential functions in our body. It serves as a major component of cellular membranes, where it keeps optimal fluidity and prevents any unwanted leakage of molecules. These functions play a critical role throughout the body. An example is our peripheral and central nervous system, where the cholesterol-rich myelin sheaths insulate the neurons; another example is the major role cholesterol plays as a precursor in the production of steroid hormones. Additionally, cholesterol is a precursor to vitamin D and contributes to the synthesis of bile acids. Cholesterol therefore, is essential for health. Cholesterol travels in the blood in lipoprotein particles; low density lipoproteins (LDL) (commonly referred to as "bad" cholesterol), high-density lipoproteins (HDL) (commonly referred to as "good" cholesterol), very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL).

Lipoproteins

Low-dense lipoprotein (LDL) is composed of esterified cholesterol and triglyceride in a core of the lipid molecule, as well as unesterified cholesterol and phospholipids on the surface. Additionally, a structural apolipoprotein is attached to the surface, e.g. ApoB and ApoA1. These are typically measured for determining plasma levels of LDL and HDL particles, respectively. These apolipoproteins assist the transport of the lipoproteins. LDL particles carry cholesterol from the liver to the cells, whereas HDL particles removes excess cholesterol from the arteries and cells, and transports it back to the liver, where it can be reabsorbed or used for the formation of bile salts. VLDL functions as a precursor for LDL; when releasing some of its triglycerides to fat cells, it transforms into LDL particles. LDL has long been identified by NCEP as the primary atherogenic lipoprotein and target for cholesterol-lowering treatment[5], however, all LDL particles are not created equal, and the atherogenic role LDL plays in disease risk is rather more complex.

Nordic Laboratories assays for cardiovascular health

Lipoprotein and subfraction analysis: Liposcan

The total level of LDL particles reported in conventional lipid profiles is a non-differentiated measure of all particle sizes, both HDL and LDL. However, LDL particles are divided into subclasses according to their subfraction size. The subfraction size and density depends on the amount of lipid in the core of the particle – the smaller the size the denser the particle. These subfractions are represented from largest to smallest, 1-7. Thus, LDL subfractions 1-2 are larger and more buoyant, whereas LDL subfractions 3-7 are smaller and denser. LDL subfractions 3-7 are considered more atherogenic because of their increased susceptibility to oxidation and increased permeability through the endothelial barrier[10]. The Liposcan laboratory test serves as a comprehensive lipid test, measuring the size and density of the LDL particles by electrophoretic separation. Such advanced testing gives detailed insight into potential risk factors of CVDs, because Liposcan provides direct and subclassified measures of LDL-C.

Analytes measured with Liposcan (measured in mmol/l)

- Cholesterol
- Triglycerides
- HDL, LDL, LDL/HDL, VLDL, IDL
- LDL subfractions 1-7 (non-pathogenic LDL1 & LDL2 vs pathogenic LDL3-7)

Advantages of Liposcan

- Identifies potentially pathogenic lipoprotein subfractions.
- Identifies and quantifies cholesterol fractions (HDL, LDL, VLDL, IDL) and LDL subfractions.
- Identifies and differentiates the size and pathogenicity of ApoB containing fractions (LDL).
- The detailed information eliminates the implementation of unwanted therapies
- Indication of Type A versus Type B.
- A Liposcan report provides visual and simple evaluation: The results outside the reference ranges are marked in red, and are also presented in a color-coded chart.

When to use Liposcan

- For screening and treating patients with lipid disorders associated with risk for CVDs
- For potential detection of residual risk in patients (patients who may experience CVD events despite treatment with cholesterol-lowering drugs)[11]
- For a detailed risk assessment enabling practitioner to determine the atherogenic risk of patient
- For targeted therapy and guided treatment decisions: interventions may be more precisely monitored
- For screening for those at hereditary risk

Clinical pearls

- The results offers insight into two specific patterns related to cholesterol readings; Type A versus Type B pattern is an expression of atherogenic risk. Type A is characterized by a predominance of large, buoyant LDL particles, whereas type B is characterized by a predominance of sd-LDL particles. Patients expressing type B pattern may therefore be at greater risk for CVDs
- Studies have suggested that lifestyle change and pharmacologic treatment can alter the LDL particle distribution, and such shift is often accompanied by changes in HDL-C and triglyceride levels[10]

LIPOSCAN (+ Oxidised LDL)	CONVENTIONAL LIPID PANEL
Cholesterol	Included
HDL, LDL, LDL/HDL, VLDL,	Included
IDL	Not routinely included as a separate marker, only non-differentiated in total cholesterol
Triglycerides	Included
LDL subfractions non-pathogenic LDL1 & LDL2	**Not included**
LDL subfractions pathogenic LDL3 - LDL 7	**Not included**
(Oxidised LDL)	**Not included**

Preanalytics

- 12 hours fasting serum (1 SST tube)
- Centrifugation: optional (recommended for patients outside Europe).
- Uncentrifuged: Draw on a Monday or Tuesday - must reach Nordic laboratories next day.
- Centrifuged: Must reach Nordic Laboratories within 7 days of draw.
- Keep at ambient temperature or refrigerated.
- Freezing of sample is not recommended.
- Laboratory method: Polyacrylamide gel electrophoresis.

Oxidised LDL analysis: Oxidised LDL (can be combined with Liposcan)

LDL particles are very susceptible to oxidative damage, small dense LDL particles in particular. When the fatty acid components of the LDL particles are exposed to free radical substances, they become oxidised. These LDL particles are known to play a significant role in atherogenesis, and they are suggested to play a pathogenic role in the initiation of atherosclerosis and in lesion exacerbation[12]. An increase in plasma LDL levels causes an increased number of circulating monocytes and macrophages to adhere to the arterial endothelial cells, and several substances found in the arterial lesion sites oxidize the LDL particles, and these become modulated in their structure. When LDL is to a certain extent, it may become unrecognizable by LDL receptors, and rather be recognized by scavenger receptors[12]. This causes immune cells to release cytokines as an inflammatory response, and continuous recruitment of immune cells to the lesion sites, resulting in a vicious cycle of more inflammation, and in turn more oxidization of LDL particles. Such inflammation in the walls of the arteries contributes to the plaque formation and rupture of the arteries. It is thought to be the oxidised LDL rather than the native (non-) LDL causing problems in the blood vessels[12]. LDL is thought to be involved in the formation of foam cells, which may be a result of interaction between modified forms of LDL and macrophages. A build up of foam cells indicate atherosclerosis[12].

Besides playing a pathogenic role in CVDs, it has become increasingly acknowledged that LDL may also play a pathogenic role in other diseases such as DM2. It has even been suggested to play a role in the pathogenicity in certain autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE)[12]. Additionally, high concentrations of circulating LDL have been associated with the incidence of metabolic syndrome[13] and the presence of CHD[14].

When to use the oxidised LDL test

- When contributions to overall detailed risk assessment of CVD, metabolic syndrome and acute myocardial infarction is needed
- When wanting to add further knowledge to the Liposcan assay, as small dense LDL particles are more prone to oxidation
- When targeted intervention is needed at a more specific level

Clinical pearls

- LDL levels may present as abnormal, even though direct cholesterol and LDL evaluation present as normal
- Assessment of LDL may help determine the true risk for CVD
- Measurement of native (non-) LDL particles does not necessarily serve as precise risk assessment, as many people who have suffered from CVDs have normal LDL levels[7]
- LDL may serve as a predictive marker in sub-clinical development of CVDs[15]

Preanalytics

- 12 hours fasting serum (1 SST tube)
- Centrifugation: optional (recommended for patients outside Europe)
- Uncentrifuged: Draw on a Monday or Tuesday - must reach Nordic laboratories next day.
- Centrifuged: Must reach Nordic Laboratories within 7 days of draw.
- Keep at ambient temperature or refrigerated.
- Laboratory method: ELISA

Cardiometabolic Profile I

Whilst the incidence of CVDs is sharply increasing, so too is obesity and type 2 diabetes (DM2). The primary clinical outcome of metabolic syndrome has been identified as CVD. Furthermore, it has been found that most people with Metabolic Syndrome have insulin resistance[16], which in turn increases the risk for DM2. In sharing many of the same risk factors with CVD, a clear link exists between the conditions, and identifying these risk factors in an overall cardiometabolic risk assessment may help structure preventative lifestyle modifications.

If blood draws are not possible for the liposcan and oxidsed LDL analysises, another test that Nordic Laboratory offers is the Cardiometabolic Profile I. It is a simple blood spot test and the patient can easily collect at home, fasting. The test offers insight into the insulin resistance/DM2 area.

Analytes measured with the Cardiometabolic Profile I

- High-sensitive C-Reactive Protein (hs-CRP) – Reference range < 3
- Hemoglobin A1C (HbA1c) - Reference range < 6%
- Fasting Insulin (In) - Reference range 1-15 (optimal 2-6)
- Fasting Triglycerides (Tg) – Reference range < 150 mg/dL
- Total Cholesterol (CH) - Reference range < 200 mg/dL
- LDL Cholesterol (LDL) - Reference range < 130 mg/dL (optimal < 100)
- HDL Cholesterol (HDL) - Reference range 40 mg/dL or higher
- Very low-density Cholesterol (VLDL) Reference range < 30 mg/dL

High-sensitive C-Reactive Protein (hs-CRP)

CRP is considered a most important biomarker in assessing the risk of CVDs[17]. It is a protein produced in the liver and is an established key indicator of inflammation in the body. CRP levels increase in acute inflammatory states, but some elevation is also seen in the Metabolic Syndrome - a high-sensitivity assay is designed to detect smaller rises[18] (thus referred to as hs-CRP). Overweight, obese, diabetic or insulin resistant patients tend to have elevated CRP[19]. Increased levels have been associated with polycystic ovarian syndrome[20] and have been suggested to predict the development of DM2[21].

Hemoglobin A1C (HbA1c)

HbA1c is a measure of red blood cell hemoglobin glycation and serves as an indication of the mean glycemia during the previous three months (lifespan of circulating red blood cells). This is considered a more reliable indicator of high blood sugar than occasional fasting blood glucose levels. It may find that glucose tolerance is impaired even though fasting blood glucose is normal[22].

Fasting Insulin

Fasting blood insulin measures the degree of insulin resistance. With insulin resistance present, circulating levels of insulin in the blood will increase, because the cells do not respond optimally. Whether or not the patient shows glucose tolerance, high fasting insulin may indicate the presence of insulin resistance. Additionally, high blood sugar levels from a result of insulin resistance may lead to changes in blood lipids, and may intensify glycation reactions, leading to exacerbation of LDL oxidation[12].

Fasting Triglycerides

High levels of triglycerides are an established indicator of atherogenic dyslipidemia, and are furthermore associated with DM2 and obesity[5]. Additionally, it is one of the diagnostic criteria for Metabolic Syndrome, and has been shown to increase the risk of CVDs[5].

Total Cholesterol (CH), LDL Cholesterol (LDL), HDL Cholesterol (HDL), Very low-density Cholesterol (VLDL)

Dyslipidemic abnormalities in these markers are some of the most important in CVD risk assessment[5]. Total cholesterol, LDL and VLDL above the reference ranges as well as low levels of HDL are some diagnostic criteria of CVDs and metabolic syndrome[5]. These serve as basic lipid markers, but may be much more efficiently predictive and diagnostic in conjunction with other mentioned parameters in the risk assessment.

Advantages of Cardiometabolic Profile I

- Blood spot – non-invasive testing
- Convenient for both practitioner and patient; sample collection can be done at home
- Sample keeps stable for several weeks at room temperature
- Dried blood spots carry little infection risk (infectious agents inactivated when dry)
- Great correlation with serum and plasma assays

When to use Cardiometabolic Profile I

- Early detection of major indicators associated with Metabolic Syndrome and insulin resistance
- Screening profile to allow clinicians to target treatment interventions appropriately and precise
- Risk assessment for reducing the overall risk of CVD and DM2 (along with clinical assessment)
- Patients with risk factors; overweight, obese, advanced age (above 45 y for men and 55 y for women), family history or premature coronary heart disease, infections, oxidative stress and cigarette smoking
- Regular testing may be used for monitoring and assessing patients with DM2
- Elevated levels of CRP in individuals with polysystic ovarian syndrome may serve as an early marker of CVD risk in these patients[20]

Preanalytics

- Blood-spot
- A simple finger stick provides the few drops of blood required, which are collected on the filter paper provided
- 12 hours fasted sample
- Take in the morning upon 30 minutes of waking (before eating or drinking)
- Laboratory method: EIA, ITA, Enzymatic

Clinical pearls

- Lifestyle modification (exercise, weight loss, no smoking) may decrease CRP levels[20]
- High fasting insulin levels are indicators of insulin resistance, meaning impaired cellular response to insulin and impaired ability of glucose utilization
- High HbA1c may reflect hyperglycemia (elevated glucose) for the previous 3 months
- Insulin resistance and high blood sugar levels may exacerbate glycation reactions, which may influence oxidation of LDL-particles
- Elevated CRP levels may predict the development of DM2, and very high levels may indicate an acute inflammatory event (such as infection)

Management of lipid disorders and metabolic syndrome

Conventional approaches to the management of lipid disorders

Conventional medical approaches to lowering the risk of developing CVDs include lowering LDL as the primary target of therapy[5]. NCEP ATP III has identified optimal LDL cholesterol levels at < 100 mg/dL to be optimal[5]. Inhibition of cholesterol production or prevention of reabsorption of cholesterol from the gut is one of the desired outcomes of cholesterol-lowering drug agent, e.g. statins (HMG-CoA reductase inhibitors), bile acid sequestrants or fibrates. Thus it reduces the amount of available cholesterol to the cells, and the cells will in turn have to acquire the cholesterol from the blood. Additionally, an increase in breakdown of fatty acids in the liver is also one of the objectives from prescribing lipid-lowering drugs. Nicotinic acid (niacin) at high doses is also used for reduction of LDL cholesterol levels while increasing HDL cholesterol levels in both conventional and integrative medicine[23].

Conventional medicine is mostly focused on the suppression of symptoms, whereas there is less focus on investigating the root cause of the increase in lipid markers. Although conventional medicine acknowledges the existence of non-lipid risk factors modifiable by lifestyle modifications, such as cigarette smoking, diabetes, obesity, atherogenic diet (high carbohydrate and saturated fat intake) and physical inactivity, much emphasis is put on the lipid-lowering drugs.

However, the efficacy of statins may be more modest than the NCEP ATP III[5] lipid management indicates, not to mention the harmful adverse effects these drugs may have. An evaluation of a large meta-analysis by David Newman, examined the use of statins for 5 years among people with pre-existing heart disease[24]. He found the following:

- 96% saw no benefit at all
- 1.2% (1 in 83) had their lifespan extended (were saved from a fatal heart attack)
- 2.6% (1 in 39) were helped by preventing a repeat heart attack
- 0.8% (1 in 125) were helped by preventing a stroke
- 0.6% (1 in 167) were harmed by developing diabetes
- 10% (1 in 10) were harmed by muscle damage

David Newman also evaluated the use of statins for 5 years among people without pre-existing heart disease, and found the following[25]:

- 98% saw no benefit at all
- 1.6% (1 in 60) were helped by preventing a heart attack
- 0.4% (1 in 268) were helped by preventing a stroke
- 1.5% (1 in 67) were harmed by developing diabetes
- 10% (1 in 10) were harmed by muscle damage

Statins and lipid-lowering drugs have their place in the treatment of CVD, but a decision on whether to include them in the individual patient's therapy should be based on a comprehensive risk assessment, alongside considering the impact of diet and lifestyle.

Integrative approaches to management of lipid disorders

Dietary modifications and therapeutic nutritional approaches may reduce the risk for CVDs in several ways, and it has been suggested that 9 out of 10 of the biggest risk factors for heart disease is modifiable by diet and lifestyle modifications[26]. A therapeutic nutritional intervention must depend on the individual patient's symptoms and risk assessment, but the following are some parameters to consider in the treatment of risk reduction. Other lifestyle modifications such as exercise and stress management plays important roles in the risk reduction as well.

Dietary influences

Total calorie intake is important to assess in that excessive calorie intake leads to obesity, even though the type of food is considered healthy.

An optimal **macronutrient distribution** with an ideal balance of fats, carbohydrates and proteins should be approached along with the elimination of highly refined and processed foods. Both the **quantity** but also the **quality** of nutrients is essential for proper absorption and utilization. A Mediterranean diet is an example of a nutritional approach typically associated with management of risk reduction in CVDs[27]. Such diet is characterized by increased intake of unrefined monounsaturated fats in substitute for saturated and trans fats, increased consumption of omega-3 fats and increased intake of vegetables and nuts, and less high glycemic fruits and vegetables[27].

High-carbohydrate diets, with high intakes of refined and simple carbohydrates can cause problems through effects on insulin resistance, altered LDL, VLDL and HDL particle sizes and triglycerides[28]. Excessive intake of alcohol is known to be a cause of elevated triglycerides, and no more than a moderate intake is recommended (maximum two drinks for men and one drink for women per day)[5].

High-fat diets, fats primarily from refined and rancid sources such as refined vegetable oils, margarine and trans fats, should be avoided. Healthy, unmodified fats should still be eaten in balanced amounts, though an increased intake of monounsaturated compared to saturated fats may be recommended. Recent research suggest that mono- and polyunsaturated fats have a beneficial impact on serum lipids and CVD risk, and that focusing solely on the intake of the dietary cholesterol and intake of saturated fats may have less impact on serum lipids[28]. Animal fats from grass fed and pasture-raised animals provides a healthier fat profile including less total fat and more omega-3 fats compared to grain fed animals[29].

Healthy omega-3 fats, especially from cold-water, fatty fish is a great source of EPA and DHA. These long-chain omega-3 fats have shown to have many benefits on cardiovascular health[27]. Certain nuts and seeds may also serve as sources of precursors to essential omega-3 fatty acids, however not as abundant as in marine sources. Studies have confirmed reductions of 30 mg/dL triglycerides in serum at an average intake of 3.35 grams EPA and DHA over 24 weeks[30]. Omega-3 fatty acids are anti-inflammatory and have been seen to lower blood pressure[30].

Studies have suggested that consumption of nuts may reduce the risk of CVDs[31,32]. Nuts such as almonds, macadamia and hazelnuts may be recommended, due to their lower contents of omega-6 fats.

"Eat the rainbow" Antioxidants play important, protective roles against CVDs because of their function as our major defense against oxidative damage. Eating a variety of foods rich in antioxidants has significant health benefits, and helps protect against the inflammation occurring in CVDs. Fruits and vegetables, especially dark leafy greens and berries are rich in antioxidants. The colour in many fruits and vegetables comes from polyphenols and flavonoids, which are classes of antioxidant plant molecules in foods such as green tea, extra-virgin olive oil, dark chocolate, coffee, citrus fruits, turmeric, blueberries, hibiscus and many herbs and spices. However, not only plant foods contain antioxidants. Other foods such as organ meats contain CoQ10 and retinol (vitamin A).

Dietary fibers, particularly the water-soluble type found in fruits and vegetables like carrots, sweet potatoes,

squash, brussel sprouts, asparagus, oranges, pears, mangoes, has been independently associated with a lower risk of CVDs[33]. The soluble fibers are non-digestible and fermentable carbohydrates. They bind bile acids or cholesterol and thereby prevent absorption, increasing the clearance of LDL, inhibiting fatty acid synthesis and increase satiety[34], and are suggested to lower total cholesterol and LDL-C[27]. Studies have focused on soluble fibers such as oats, psyllium, guar gum and pectin[27]. Consumption of a mixture of soluble fibers at a dose of at least 10g daily is recommended for patients with lipid disorders to lower total cholesterol and LDL-C[27]. Additionally, they can help stabilize blood sugar levels.

Prebiotics are a subset of soluble fibers (e.g. inulin and dextrin), which are fermented into short-chain fatty acids (acetate, butyrate, propionate) and can help inhibit cholesterol synthesis in the liver. This requires sufficient amounts of **probiotics** to serve as the mechanism that ferments the prebiotics.

Long-term consumption of **probiotics** have been shown in both animal and human studies to have some effect on lowering serum lipids, including reduction in total cholesterol, LDL-C and triglycerides[27]. Some of the bacteria strains include *Lactobacillus acidophilus, Bifidobacterium, Streptococcus thermophilus and L delbrueckii*[27]. In addition there are other beneficial nonlipid effects such as increasing antioxidant potential and lowering blood pressure[27].

Non-dietary Lifestyle Modifications

Exercise has been shown to reduce levels of LDL particles independently of diet patterns[35]. Not only does exercise independently reduce LDL-C - it has also been shown to reduce levels of oxidised LDL[42]. One study showed decreased levels of oxidised LDL levels in both men and women after a 10-month program of 3-5 hours of weekly exercise. The subjects were sedentary prior to the intervention. In addition, the exercise program also showed to increase HDL-C levels in the subjects (15% in men and 5% in women)[42]. This indicates the great importance of regular exercise benefits for improving CVD health and overall lipid profiles. Moreover, exercise promotes weight loss or maintenance of weight as well as insulin sensitivity. Thus, exercise aids in preventing development of atherosclerosis, or exacerbating the development of people that already have CVD.

30-60 minutes of daily exercise varying between aerobic and resistance training has been shown to be beneficial[27]. Exercise has also shown to modify high levels of CRP[36].

Getting enough sleep

High blood pressure is a strong independent risk factor for CVDs. Epidemiological studies show that bad sleep quality, and less than optimal duration, is associated with impaired blood pressure[37]. A study looking into sleep duration and risk of coronary heart disease in women showed that those who slept fewer than 5 hours at night had 38% greater risk of coronary heart disease compared to women sleeping for 8 hours[38].

Stress

The risk of CVDs are increased with elevated stress levels in many ways, whether the stress originates from physical, emotional or mental forms. Stress contributes to inflammation and has been shown to increase circulating inflammatory markers associated with heart disease, like C-reactive protein (CRP) and interleukin-6 (IL-6)[39]. Additionally, it contributes to gastrointestinal dysfunctions, impaired immune function and blood sugar control. Stress management, e.g. including mediation, is important in obtaining a significant reduction in risk of CVDs. An adrenal stress test for measuring adrenal function may be relevant.

"Anne Catherine Færgemann is a registered dietician, holds a master in nutritional medicine and is at the moment working on her PhD education. She has been working in the Functional Medicine field since 1998 and has written a couple of books and holds lectures for both the public and practitioners. In her clinic she supports both adults and children with complications such as weight loss, cardiovascular, behavioral, gut, fatigue, hormonal and optimal performance (work and sport) issues. In this material she shares some of her clinical considerations in relation to the use of supplements."

Nutraceuticals (supplements)

Omega-3 (EPA/DHA): Several mechanisms in relation to omega-3 fats are thought to influence CVD risk reduction, including modifying eicosanoid biosynthesis and impacting membrane fluidity. Furthermore, anti-inflammatory effects of omega-3 fats are thought to be due to alterations in gene expression and inflammatory cytokines[27]. Doses of 3 g per day of combined EPA and DHA at a ratio 3:2 may be recommended. To reduce lipid oxidation, the EPA/DHA can be combined with 100 IU of gamma,delta and alpha tocopherols (gamma/delta should make up 80% and alpha 20% of the total tocopherols) per 3 g of EPA and DHA[27]. Another source of omega-3 is krill oil, which is phospholipid-derived fatty acids. Some studies have suggested that the bioavailability of phospolipid-derived fatty acids from krill oil are better absorbed than those derived from ethyl ester or triglycerides – however a recent study has suggested that the fatty acids derived from all three sources are equally bioavailable [43].

Eicosamax liquid, ProThera. High-potency, ultra-pure fish oil containing over 70% omega-3 fatty acid content. Advanced molecular distillation processing super-concentrates the amount of EPA and DHA from fish oil into a 2910 mg amount per teaspoon for added convenience and enhanced benefit. Removal of environmental toxins, including mercury, PCBs, and dioxins, is achieved through careful purification processes. Natural lemon oil flavor has been added to the oil, lending a pleasant, light lemon scent and taste. (Capsules are also available, but with different amounts of omega-3).

Omegacare, Biocare. OmegaCare is a potent and highly concentrated fish oil derived from anchovies and sardines, flavoured with natural orange oil. This great tasting liquid can be taken neat or mixed with water or juice and provides EPA and DHA in amounts of 1800mg per teaspoon.

Super EPA Fish Oil Concentrate, Allergy Research Group. Prepared from fish oil from cold water fish such as sardines, anchovies and mackerel. Each batch is molecularly distilled and tested to insure purity and the absence of heavy metals and other contaminants. 2 capsules contain 1200 mg EPA/DHA.

Real Krill, Doctors Best, 350 mg. This is a 100 percent authentic product from sustainably harvested Antarctic Krill. It provides omega-3 EPA and DHA linked into phospholipids, together with the versatile protective carotenoid astaxanthin. These nutrients are vital lipids, building blocks for the cell membrane systems that manage most of the important life functions.

CLINICAL COMMENT from Anne Catherine:

"I may use a dosage of up to 5000mg EPA/DHA combined for periods when I monitor my patients. It is an amazing anti-inflammatory agent."

Tocotrienols: Vitamin E is a cluster of lipid-soluble phenols, tocopherols and tocotrienols with antioxidant properties. It is the suggested to have LDL- and TC-lowering effects[27]. However, the tocopherols should make up less than 20% of the total vitamin E consumed per day, and alpha-tocopherol should make up no more than 20% of the total tocopherols as well (gamma and delta)[27].

Tocomin SupraBio® Tocotrienols, Allergy Research Group. A pure palm mixed tocotrienol complex, with a natural ratio of alpha, beta, gamma, and delta-tocotrienols. It is extracted and concentrated from fresh, virgin red palm oil. A patented self-emulsifying composition enhances absorption compared to regular tocotrienol extracts.

CardiE, Nutri Ltd. Cardi-E is an innovative, patent-pending preparation of vitamin E containing a mixture of natural tocopherols, all of which act as antioxidants. Alpha-tocopherol is more protective against reactive oxygen species, while gamma-tocopherol is more protective against reactive nitrogen species (e.g. peroxynitrite). A combination of natural, mixed tocopherols provides the broadest possible antioxidant protection for fat-soluble molecules and organelles.

CLINICAL COMMENT from Anne Catherine:

"We mainly get alpha tocopherols from our diet, so when advising vitamin E supplements, it is important to evaluate the quality of the product and add diversity in the tocopherols rather than supplementing with more alpha."

Niacin: Vitamin B3. It is important to emphasize that it is the nicotinic acid and not niacinamide. Niacin has been shown to have a dose-related effect in reducing triglycerides, LDL, total cholesterol as well as increasing levels of large type A LDL particle size from small dense type B subfractions[23,27]. Additionally, it has been shown to increase levels of HDL-C[28]. Mechanisms of niacin include inhibiting LDL oxidation and platelet function, decreasing cytokines and increase triglyceride lipolysis in adipose tissue[28]. Doses of niacin ranging from 500-4000 mg daily has been shown to have some effect[27,28].

Niacin Vitamin B3, **Allergy Research Group**. Contains 250 mg per capsule. Also known as nicotinic acid, niacin is an essential nutrient, positioned at the core of NAD/NADH and NADP/NADPH, which are major redox-active "electron storage" compounds. One or both of these "redox pairs" is involved in every major biochemical pathway.

CLINICAL COMMENT from Anne Catherine:

"The patient should be informed that niacin can cause skin flushing and tingling – this is called 'niacin flush' and will pass within a short while. The dosage should be increased slowly."

Coenzyme Q10 (ubiquinone): CoQ10 has crucial functions in mitochondrial metabolism and ATP production. It is a lipid soluble antioxidant, and protects against oxidation, and is therefore suggested to protect against the oxidation of LDL (27). Statins suppress blood levels of CoQ10, thus patients taking statins should also supplement with CoQ10.

High Absorption CoQ10 (100 mg), Doctor's Best. Contains pure, vegetarian coenzyme Q10 plus BioPerine®. BioPerine®, a standardized herbal extract derived from black pepper fruit, promotes absorption of nutrients in the GI tract.

Best CoQ10 (100 mg), Doctor's Best. Contains pure, fermented, USP grade coenzyme Q10.

CLINICAL COMMENT from Anne Catherine:

"I often allow the patient to work with the dosage when recommending Q10. I ask them to start on a lower dosage and then up it to perhaps 400mg per day. Often they feel a difference in their energy level when getting the optimal amount."

Anti-inflammatory remedies: Reducing inflammation is crucial in reducing the risk of CVDs. Anti-inflammatory remedies may assist in reducing lipid peroxides and thereby lipid oxidation (oxidation of LDL) - elements contributing to the progression of atherosclerosis. Curcumin (active component of tumeric) has demonstrated lipid-lowering effects based on its impact on expression of genes involved in cholesterol synthesis (such as HMG-CoA reductase), and a small study found that it increases HDL and lowered total cholesterol with a daily intake of 500mg[27].

Best Curcumin w/Bioperine, Doctor's Best (500mg). Contains a standardized extract of Curcuma longa root, commonly known as "Turmeric." Curcuma C3 Complex supplies 95% total curcuminoids, including curcumin, bisdemethoxy curcumin and demethoxy curcumin. Bioperine is an extract of Black Pepper fruit that contains 95-98% piperine. Bioperine is added as a natural bioenhancer to promote absorption of the product.

CLINICAL COMMENT from Anne Catherine:

"At some stage my patients seem to get tired of the curcumin added to their food (all gets yellow and all gets this dry taste). Best curcumin has added pepper for greater bioavailability, so it's a perfect alternative to the dietary source."

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