

## **DISLIPIDAEMIA &/OR HYPERCHOLESTEROLAEMIA**

### **Development of Atherosclerosis**

There are several stages in the development of atherosclerosis (15, 33). First, the arterial wall is injured by a variety of factors, including high blood pressure (hypertension), high blood cholesterol levels (hypercholesterolaemia), oxidized low-density lipoproteins (LDL), cigarette smoking, toxins and viruses, and blood flow turbulence. These injuries lead to a change or impairment in the normal function of the endothelium (the lining cells), and a chronic inflammatory response ensues (15). There is increasing evidence that inflammation and immunologic mechanisms play a major role in the formation of atherosclerosis (33). In response to the injury, monocytes and T cells (both are special types of immune cells) penetrate through the endothelium into the underlying intima (inner layer of the arterial wall) (24). The monocytes are then converted to macrophages, scavenger cells that ingest oxidized LDL and other substances. Key to the entire process is the malignant interaction of LDL particles, especially the oxidized form, with the endothelium and the monocytes (24).

A high intake of saturated fats and cholesterol, combined with a low fruit and vegetable intake, has been implicated in the formation of oxidized LDL. By accumulating large amounts of cholesterol from oxidized LDL, the macrophages are transformed into foam cells. In addition, oxidized LDL causes further injury to the endothelium, attracting even more monocytes, inducing a vicious cycle that leads to the development of a fatty streak, a precursor to plaque (24). The injured and impaired endothelial cells attract platelets and begin to release growth factors that stimulate the migration of smooth-muscle cells from the outer layers of the artery wall into the intima, where they proliferate abnormally. The macrophages and smooth-muscle cells begin to release collagen and other proteins, which form the fibrous component of atherosclerosis. The engorged foam cells then die and release cholesterol debris into the artery wall (28).

The mature plaque is made up of a complex mixture of foam cells, smooth-muscle cells, cholesterol debris, and fibrous proteins. Over time, the plaque may become hardened or calcified and then develop cracks and ulcers, prompting the formation of blood clots that can suddenly close up the narrowed artery lumen, causing a heart attack (1, 15, 33).

There is increasing evidence that atherosclerosis begins in childhood and progresses from fatty streaks to raised lesions in adolescence and young adulthood (14). In one autopsy study of 1,079 men and 364 women who had died from external causes between the ages of 15 and 34, researchers found dramatic differences in the severity of atherosclerosis, depending on blood LDL cholesterol levels and lifestyle habits such as smoking and fat-rich diets (14). Men and women who smoked and/or had elevated LDL cholesterol experienced the greatest amount of atherosclerosis. The researchers warned that teenagers and young adults place themselves at increased risk of early heart attack unless good lifestyle habits are practiced beginning in childhood.

## Description of Lipoproteins

To transport the cholesterol and triglycerides, the body utilizes various protein packets, called lipoproteins. Lipids are not water-soluble and consequently are transported through the plasma compartment as a lipoprotein. A lipoprotein is spherical in shape, made up of a lipid core that contains triglyceride, free and esterified cholesterol, and phospholipids and surrounded by an apoprotein to provide water solubility. The protein part of the lipoprotein is called apoprotein.

Lipoproteins differ slightly by their content of apoprotein, cholesterol (free and esterified), and triglyceride, resulting in differing density levels. There are three major lipoproteins in the fasting blood: high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low density lipoprotein (VLDL). HDL is the smallest and densest lipoprotein, being nearly half protein. LDL carries the most cholesterol (60-70% of all the serum cholesterol). VLDL is mostly triglyceride (7).

The HDL particle appears to act as a type of shuttle as it takes up cholesterol from the blood and body cells and transfers it to the liver, where it is used to form bile acids (10, 11, 20). The bile acids are involved in the digestion process, with some of them passing out with the stool, thus providing the body with a major route for excretion of cholesterol. HDLs have for this reason been called the “garbage trucks” of the blood system, collecting cholesterol and dumping it into the liver.

LDL, on the other hand, is formed after VLDL gives up its triglycerides to body cells. LDLs are high in cholesterol and take their cholesterol to various body cells, where it is deposited for cell functions. When LDL cholesterol is too high and becomes oxidized, it contributes to the buildup of atherosclerosis (27). HDL cholesterol (HDL-C) concentration is emerging as an important measure of heart disease risk, and the National Institutes for Health have urged that HDL-C determinations accompany measurements of total cholesterol when healthy individuals are being assessed for coronary heart disease risk (20, 27). Various studies have shown that a 1% rise in HDL-C reduces coronary heart disease risk 2-3%, and that people with the highest HDL-C have heart disease death rates 2-3 times lower than those with the lowest HDL-C levels (10). The National Cholesterol Education Program regards HDL-C levels below 40 mg/dl as an important risk factor, with optimal values rising above 60 mg/dl (27). Because of the importance of HDL-C, various ratios have been used to improve prediction of heart disease risk. HDL-C can be expressed as a percentage of the total cholesterol, or more commonly as (11, 26):

$$\frac{\text{total cholesterol}}{\text{HDL-C}}$$

This ratio has been extremely useful in estimating heart disease risk. In one study of 246 men who had suffered a heart attack versus 246 controls, risk of heart attack climbed sharply with increase in the ratio (26). A ratio below 3.0 is optimal, while 5.0 and above is considered high risk. For every unit the ratio falls (eg 5.0 to 4.0), risk of coronary heart disease decreases 53% (26).

## **Lifestyle Modification**

To have a favorable total cholesterol- HDL-C ratio, the total cholesterol and LDL-C must be lowered and the HDL-C elevated through an application of both dietary and lifestyle factors. Aerobic exercise, weight reduction, smoking cessation, and moderate alcohol consumption, each favorably affects HDL-C, while dietary changes and weight reduction lower LDL-C (32). As is emphasized in the role of exercise section below, aerobic exercise has little independent effect on LDL-C and on total cholesterol.

Improvements in lifestyle can have strong, relatively quick effects on total cholesterol, HDL-C, and LDL-C, depending on the initial levels and the degree of lifestyle change (3).

## **Diet Change**

It is recommended to consume less saturated animal fat and cholesterol and include more carbohydrates and fiber while moderating sodium, energy, and alcohol intake. These guidelines are based on extensive literature (3, 32). A wide variety of fruits and vegetables that provide “antioxidant” vitamins, are now thought to be crucial in reducing oxidized LDL.

The Pritikin Program is a 21-day residential program where high-risk individuals are put on an extremely low fat (<10% Calories), high-fiber, high-carbohydrate, primarily vegetarian diet, with 1-2 hours of daily moderate exercise (3). Major improvements are seen in total cholesterol and LDL-C (20-25% decreases), and triglycerides (20-40% decreases), with most of the changes occurring within the first 2 weeks of the 21 day program. Although the Pritikin diet is extreme for most people and probably can't be followed for extended periods, it does show what is possible when used therapeutically for several weeks.

## **Weight Loss**

Weight loss, in and of itself, has a powerful effect on blood fats and lipoproteins. With weight loss, the total cholesterol, LDL-C, and triglycerides decrease greatly, while HDL-C increases (but only when weight loss has been maintained and stabilized) (8). Some researchers have estimated that the total cholesterol drops about 1 mg/dl for every pound lost (decreases are greatest for those with the highest blood cholesterol levels) (19). In other words, if a subject changes weight from 180 to 160 pounds, blood cholesterol could be expected, on average, to decrease 20mg/dl (eg. from 205 to 185 mg/dl).

## **Role of Exercise**

In the 1970s, several published studies showed that low levels of HDL-C were related to coronary heart disease (7). About the same time, the first reports that exercise may be related to improved HDL-C levels were published (7, 31). In an early Stanford University study of male and female long-distance runners and sedentary controls, HDL-C was found to be substantially higher in the

runners (31). Total blood cholesterol, LDL-C, and triglycerides were reported to be much lower among the runners. In two more recent and larger studies of male and female runners, a dose-response relationship between miles run per week and HDL-C has been reported (29). In both of these studies, runners training the most had the highest HDL-C, and no evidence of a plateau or ceiling effect was seen. In other words, moderate amounts of running were better than little or none, while even more running was related to even higher HDL-C levels (9).

Studies show that weight loss and dietary changes can have dramatic effects on the blood lipids and lipoproteins. Often, when people begin exercise programs, improvements in dietary habits and body composition occur. Studies using randomized, controlled designs have carefully demonstrated that changes in blood cholesterol and fats with exercise training are very much affected by parallel changes in body weight and diet (8, 23).

A growing consensus among investigators is that when changes in body weight and dietary habits are controlled for, exercise training alone can be expected to increase HDL-C and to decrease triglyceride levels, with little or no effect on LDL-C (18, 19). In one study, changes in body weight and diet in both young and old men were minimized and controlled (23). After 6 months of training, aerobic fitness in the young and older subjects improved 18% and 22%, respectively. No significant changes in LDL-C were found (because diet and body weight were kept near pre-study levels), while HDL-C improved 14-15%. Triglycerides were low in the young subjects before starting the study, so exercise training had no further effect. For the older subjects, triglycerides fell strongly.

In a 12-week study of 90 overweight women, the participants were randomized to one of four groups: controls, walking (five 45-minute sessions per week, 60-75% maximum heart rate), diet (1,200- 1,300 Calories per day), and diet and walking (18). Subjects in the two diet groups lost an average of 17 pounds in 12 weeks, while the control and walking groups stayed within 2 pounds of their starting weight. The serum cholesterol did not change in the control or walking groups but decreased 20-25% in the two diet groups. Most of the improvement in serum cholesterol occurred within the first 3 weeks, of the 12 week study. How much exercise is necessary to improve the lipid profile? Most researchers agree that an exercise program equal to a moderate jog or brisk walk for at least 30 minutes per session, three to five times per week, is necessary before improvements in HDL-C can be measured (12, 31). In terms of energy expenditure, about 1,000 Calories per week of moderate-to-high intensity, aerobic-type exercise is required to produce favorable changes in blood fats and lipoproteins. At this basic, minimum exercise level, changes in HDL-C and triglyceride levels are sometimes small and variable, depending on the individual. Exercise programs with high duration (eg 45 minutes or longer), intensity, and frequency (ie near daily) produce the strongest effects on HDL-C and triglycerides. Total cholesterol and LDL-C, however, appear to be little affected by exercise training, even when it is intensive, unless body weight is decreased or dietary saturated fats are lowered at the same time.

Although there is increasing evidence that regular aerobic exercise increases HDL-C and lowers blood triglyceride levels, the exact mechanism explaining these positive changes is still being determined. At present, most researchers have concentrated their efforts on the interplay of important enzymes that regulate the breakdown and formation of HDL-C and triglycerides (30). Regular exercise alters the activity of the regulatory enzymes in a favorable manner.

The end result is that aerobically fit, compared to unfit, individuals appear to clear triglycerides from the blood more quickly, produce more HDL-C, and keep HDL-C in circulation longer.

Studies have shown that single bouts of aerobic exercise, especially when prolonged and intense, result in immediate and significant increases in HDL-C (4). This acute increase in HDL-C has been linked to the breakdown of triglycerides during exercise (4). As the exercise program is maintained on a regular basis, the acute changes in HDL-C and triglycerides, which persists for at least 24-48 hours, result in chronic improvement. In other words, the favorable lipid profiles of trained individuals may actually be related to short-term changes that occur during or immediately after a single bout of exercise, which over time add up to higher HDL-C and lower triglyceride levels.

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