A review of serum cholesterol and physical activity.

Cholesterol is a fat-like substance used to help build cell membranes, make some hormones, synthesize vitamin D, and form bile secretions that aid in digestion. Since fat can't mix with water, which is the main ingredient of blood, cholesterol's most important job is to help carry fat through your blood vessels. Before cholesterol can enter the bloodstream it is coated with a protein. These cholesterol-protein packages are referred to as lipoproteins.

Lipoproteins are transport vehicles in the circulation plasma that are composed of various lipids such as cholesterol, phospholipids, triglycerides, and proteins known as apoproteins. The major classes of lipoproteins are chylomicrons, very low-density lipoprotein cholesterol (VLDL-C), LDL-C, and HDL-C. Chylomicrons are the largest lipoproteins, consisting of approximately 85% triglycerides. Triglycerides are the main type of lipids found in adipose tissue and in the diet. Once the triglycerides are removed from the chylomicron at receptor sites in the body, the chylomicron remnant is returned to the liver for further metabolism. The principal lipid of VLDL-C is also triglycerides (60 - 70%).

LDL-C is the primary transport carrier of cholesterol in the circulation. About 50-60% of cholesterol is delivered to the cells by LDL-C. Evidence suggests that LDL-C may directly contribute to the cellular alterations of the inner walls of arteries which may ultimately lead to the development of atherosclerotic plaque (Scann, 1978). Thus, LDL-C is proposed to be more highly associated with CHD than total cholesterol (Manson et al., 1992).

On the other hand, HDL-C has an inverse relationship with coronary heart disease, offering a protecting mechanism against the development of CHD (Kannel, Castelli, & Gordon, 1971). HDL-C is considered to be the most powerful lipid parameter for predicting CHD in people of all ages (Gordon et al., 1977). The primary function of HDL-C is to transport cholesterol from the tissues and blood to the liver for excretion from the body or synthesis into bile acids. HDL-C also prevents the uptake of LDL-C at receptor sites in the body and participates in the metabolism of other lipoproteins.

HDL-C is predominantly composed of phospholipids and is separated into several subclasses, based on size and particle density. The major subclasses are referred to as HDL2 and HDL3. It is known that females have a higher content of HDL2 than males, which helps to protect women from developing CHD (Wood & Haskell, 1979).

The Role of Physical Activity on Lipid and Lipoprotein Levels

There is a variety of environmental and personal factors that may influence a person's cholesterol composition such as age, gender, level of body fat, dietary intake of fat, cholesterol, and carbohydrates, alcohol consumption, cigarette smoking, medication, menopausal status, and exercise. Because of complex interactions among these variables, it is difficult to assess how each of these factors independently affects cholesterol levels and composition.

Although total cholesterol levels are lower in persons with high aerobic fitness compared to low aerobic fitness, it has not been conclusively demonstrated that exercise training lowers total

cholesterol. Measurements made before and after exercise training have produced variable results with no clear consensus as to whether or not moderate or vigorous exercise can lower total cholesterol. In studies where total cholesterol has been significantly reduced, it appears that the activities were more dynamic and vigorous in nature, such as running programs. In contrast to the variable effects of exercise on total cholesterol, endurance exercise consistently lowers triglycerides (Martin, Haskell, & Wood, 1977). A physically active lifestyle may help to prevent the age-related rise in triglycerides normally observed in men. It also appears that endurance exercise lowers triglyceride levels more so in individuals having elevated initial baseline levels. Lower triglyceride concentrations in the blood have been attributed to increases in skeletal muscle and adipose tissue lipoprotein lipase activity resulting from aerobic training. Lipoprotein lipase is the key enzyme for the breakdown of triglyceride-rich lipoproteins. On a long-term basis, the decrease of body fat that often accompanies endurance training may be a contributing factor to this lowering effect of triglycerides due to exercise.

Like total cholesterol, the impact of habitual aerobic exercise on LDL-C appears to be quite variable. However, the majority of studies comparing endurance athletes to sedentary controls or the general population reported that athletes have lower LDL-C levels, with leaner athletes frequently having the lowest values. Although it appears that endurance training may decrease LDL-C, there is little information about the biochemical mechanism producing this change.

Endurance-trained athletes have much higher HDL-C values compared to sedentary populations (Haskell, 1984). Although it is not yet definitive, moderate and high-intensity aerobic exercise training appears to be associated with elevated HDL-C values. The primary reason for the elevation in HDL-C is an increase in lipoprotein lipase activity in response to exercise. Lipoprotein lipase accelerates the breakdown of triglycerides, resulting in a transfer of cholesterol and other substances to the HDL-C. It is interesting to note that healthy patients whose physical activity was restricted to bed rest for three to six weeks because of some type of traumatic fracture, showed a significant decrease in HDL-C levels (Nikkila, Kuusi, & Myllynen, 1980).

The term ‘lipid profile’ describes the varying levels of lipids in the blood, the most commonly reported ones being low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. High levels of LDL cholesterol indicate surplus lipids in the blood, which in turn increase the risk of cardiovascular complications. HDL cholesterol transports lipids back to the liver for recycling and disposal; consequently, high levels of HDL cholesterol are an indicator of a healthy cardiovascular system (Carroll MD,2009). Triglycerides in plasma are derived from fats eaten in foods or from other energy sources. An excess of triglycerides in plasma is positively and independently associated with cardiovascular disease (da Luz P, 2008). Very-low-density lipoprotein (VLDL) cholesterol—which is generally less frequently reported in the literature—has been shown to positively correlate with triglycerides and to be independently associated with cardiovascular risk, even in individuals who express normal LDL cholesterol levels (Ren J,2010). The most commonly used measure of cholesterol is arguably ‘total cholesterol’, a measure that includes LDL cholesterol and HDL cholesterol. However, given the different effects of LDL cholesterol and HDL cholesterol on health, total cholesterol can be a misleading metric. More sensitive measures report, for example, the total: HDL cholesterol ratio, or non-HDL cholesterol levels (i.e. all cholesterol variables that are positively associated with cardiovascular disease (Virani SS,2012)).

There is a direct relationship between chronically elevated cholesterol levels (dyslipidemia) and

coronary heart disease (CHD) (Lloyd-Jones DM,2004). In a meta-analysis of 170,000 participants (Baigent C,2010), it was reported that reductions in LDL cholesterol decreased the incidence of heart attacks and ischemic strokes. It has also been reported that individuals with elevated total cholesterol levels ((200 mg/dL/5.172 mmol/ L) have approximately twice the CHD risk of those with optimal levels (180 mg/dL/4.66 mmol/L) (Roger VL,2010). The US Centers for Disease Control and Prevention have suggested that this is the case for 71 million US adults, equating to 33.5 % of the population (Centers for Disease Control and Prevention (CDC), 2011). The prevalence of elevated total cholesterol is even higher in Europe, where 54 % of adults aged C25 years have total cholesterol levels above the recommended levels (World Health Organisation,2010). For over 10 years, the link between high cholesterol and ischaemic heart disease has been evident. Data from 2003 (Murray CJ, 2003) attributed one-third of all ischaemic heart disease globally to high cholesterol levels. While the age-adjusted prevalence of high cholesterol in the USA decreased from 26.6 % (in 1988–1994) to 25.3 % (in 1994–2004), recent data (Go AS,2013) have suggested that the proportion of the adult population using pharmacological cholesterol-lowering substances increased from 11.7 to 40.8 % during this period. It has long been recognized that reductions in serum cholesterol can reduce CHD risk—for example, reductions of around 0.6 mmol/L can reduce the incidence of ischaemic heart disease by 54 % at the age of 40 years, reducing to 19 % at 80 years (Law MR,2012). A reduction in total cholesterol is therefore still considered the gold standard in preventative cardiovascular medicine (Whayne TF,2011).

This highlights the importance of interventions aimed at reducing serum cholesterol levels. Furthermore, the advantage of early intervention has been demonstrated; long-term exposure to 1 mmol/L lower LDL cholesterol has been associated with a 55 % reduction in CHD risk, while treatment with statins starting in later life required a threefold reduction in LDL cholesterol to achieve the same magnitude of risk reduction (Ference BA,2012). Pedersen and Saltin, citing 13 meta-analyses, reported improvements in the lipid profile following exercise. They described this as Category A evidence that exercise can have a positive effect on the pathogenesis, symptomatology and physical fitness of individuals with dyslipidemia. In addition, Aadahl et al. reported a physical activity intervention based on lifestyle consultations in 1,693 sedentary men and women aged 33–64 years. Participants taking lipid-lowering medication were excluded from the analysis.

At 3-year follow-up, a significant positive association was observed between self-reported 24-h physical activity and HDL cholesterol levels ($p = 0.0001$), while a significant negative association was reported between physical activity and triglyceride levels ($p = 0.0001$). Overall, the data suggested a dose-response relationship between increases in physical activity and improvements in triglycerides and HDL cholesterol in previously sedentary populations. Five-year follow-up of a subsequent study by Aadahl et al. reported significant associations between physical activity and improvements in total cholesterol ($p = 0.006$), LDL cholesterol ($p = 0.007$), triglycerides ($p = 0.02$) and HDL cholesterol ($p = 0.01$) among 4,039 participants aged 30–60 years, although significant improvements in HDL cholesterol levels were found only in men. While the mechanisms underlying the effect of exercise on the lipid profile are unclear, exercise appears to enhance the ability of skeletal muscles to utilize lipids as opposed to glycogen, thus reducing plasma lipid levels (Earnest CP, 2013). The mechanisms may include increases in lecithin-cholesterol acyltrans (LCAT)—the enzyme responsible for ester transfer to HDL cholesterol (Calabresi L,2010), which has been shown to increase following exercise training (Riedl I,2010)—and increases in lipoprotein lipase activity, although the data in this instance are inconsistent (Harrison M,2012) and may depend upon the energy expenditure that is elicited.

Ferguson et al. reported that 1,100 kcal of energy expenditure is required to elicit increases in HDL cholesterol that coincide with significant increases in lipoprotein lipase activity. The process of cholesterol removal is known as ‘reverse cholesterol transport’. This process removes cholesterol from circulation for disposal as a result of increases in LCAT and reductions in cholesterol ester transfer protein (CETP)—the enzyme responsible for the transfer of HDL cholesterol to other lipoproteins—following acute and chronic exercise (Lira F,2010). This increased enzymatic activity increases the ability of muscle fibers to oxidize fatty acids originating from plasma, VLDL cholesterol or triglycerides (Shaw I,2009). This process is conceptualized by Kesaniemi et al. reviewed 51 papers describing physical activity interventions, and reported a mean increase in HDL cholesterol of 4.6 %. The effects on LDL cholesterol and triglycerides were reported as being inconsistent. The authors concluded that the most likely physical activity-induced improvement in the lipid profile is an increase in HDL cholesterol. 2 Physical Activity and Types of Exercise The terms ‘physical activity’ and ‘exercise’ are often used The terms ‘physical activity’ and ‘exercise’ are often used interchangeably in the literature. However, it is suggested that the two terms denote two different concepts (US Department of Health and Human Services, 1996). ‘Physical activity’ refers to any bodily movement produced by skeletal muscles that results in an expenditure of energy (expressed in kilocalories), and which includes a broad range of occupational, leisure and daily activities. ‘Exercise’ instead refers to planned or structured physical activity, performed for a reason, which can be aerobic exercise, resistance training or combined aerobic and resistance training.

The above data provide some support for the proposal that physical activity and exercise can be utilized to improve cholesterol levels. Regular physical activity has been shown to increase HDL cholesterol while maintaining, and theoretically offsetting increases in, LDL cholesterol and triglycerides. There appears to be a linear dose-response relationship between activity levels and HDL cholesterol levels. More intense activity, however, is required to elicit reductions in LDL cholesterol and triglyceride levels. Aerobic exercise at high intensities appears to be effective in improving the lipid profile, and the effects surpass those of physical activity by initiating clearance of plasma LDL cholesterol and triglycerides. The dose-response relationship between the lipid profile and energy expenditure seems to transcend the mode of exercise. Increases in calorific expenditure associated with aerobic exercise (via increased intensity and/or duration) have been shown to positively influence lipoprotein lipase activity, HDL cholesterol levels (Ferguson MA,198) and the lipid profile (Kraus W,2002).

During resistance training, it has been shown consistently that the increased volume of movement via increased numbers of sets and/or repetitions has a greater impact upon the lipid profile than increased intensity (e.g. via high-weight lower petition training) (Fett C,2003). Prolonged moderate-intensity aerobic exercise should be recommended as a starting point for those who have previously been sedentary or are new to exercise. Resistance training presents a viable alternative to aerobic exercise or is an effective intervention independently. High-intensity exercise ((85 % 1 RM) has been shown to be no more effective than moderate-intensity exercise (50–85 % 1 RM). The addition of resistance training to aerobic exercise will supplement—and possibly enhance—the effects on the lipid profile, although there is limited literature comparing the three modes of exercise, rendering definitive statements problematic. There will, however, be no reduction in the effect, and the additional physiological and psychological systems that are impacted may manifest additional benefits when aerobic exercise and resistance training are combined.

The data included in this review confirm the beneficial effects of regular physical activity on cholesterol levels. Such knowledge should aid in the prevention and management of dyslipidemia while reducing the risks of heart attacks, strokes and coronary artery disease. Having considered the baseline condition of their patients, clinicians should encourage as much physical activity as possible while, where feasible, highlighting the additional impact or appropriateness of aerobic exercise, resistance training or both to obtain optimal benefits in their patients.