Review

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Review

A Review of the Literature on "The Effects of Exercise, Diet and Resistance Training on Lipoprotein Particle Subfractions"

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Abstract: Cardiovascular disease is the number one cause of death in the United States, and accounts for one-third of all deaths worldwide. 1 In the United States, 43.9% of the adult population is projected to have some form of Cardiovascular Disease, CVD, by the year 2030. 2 The increasing trend of cardiovascular mortality is ever increasing especially for low and middle-income countries. 3 Some common risk factors that drive this trend include tobacco smoking, lack of physical activity, and unhealthy diet. 4 Fortunately, some of the risk factors for CVD can be clinically assessed and treated medically through blood lipid profiles. Previously, this has been done through lipoprotein-cholesterol (LDL-C) reduction, however, a closer look at the LDL subclasses or particle size distribution has revealed that it may be the size and not the number of lipoprotein particles that are a more powerful predictor of CVD. 5. It appears that small, less dense particles have a greater susceptibility to oxidation and permeability to the endothelial wall in the coronary vessels. 2 Furthermore, small, dense LDL particles also circulate longer in the blood stream and are likely to undergo numerous atherogenic modifications such as desialylation, glycation, and oxidation, increasing their atherogenicity. 6 Similar findings have been found with HDL particle sizes where small HDL particles have been associated with increased CVD risk. Conversely, the concentration of large HDL particles has been shown to be negatively correlated with CVD risk, however, the size of the HDL particle and its cardioprotective functions has not been clearly established in the literature and the mechanisms need further study. 7,8 Therefore, the purpose of this review is to discuss the effect of exercise (both aerobic & resistance training) and diet on HDL and LDL particle size.

Keywords: particle size; subfractions; HDL; LDL

Introduction

Cardiovascular disease is the number one cause of death in the United States, and accounts for one-third of all deaths worldwide. [1] In the United States, 43.9% of the adult population is projected to have some form of Cardiovascular Disease, CVD, by the year 2030. [2] The increasing trend of cardiovascular mortality is ever increasing especially for low and middle-income countries. [3] Some common risk factors that drive this trend include tobacco smoking, lack of physical activity, and unhealthy diet. [4] Fortunately, some of the risk factors for CVD can be clinically assessed and treated medically through blood lipid profiles. Previously, this has been done through lipoprotein-cholesterol (LDL-C) reduction, however, a closer look at the LDL subclasses or particle size distribution has revealed that it may be the size and not the number of lipoprotein particles that are a more powerful predictor of CVD. [5]. It appears that small, less dense particles have a greater susceptibility to oxidation and permeability to the endothelial wall in the coronary vessels. [2] Furthermore, small, dense LDL particles also circulate longer in the blood stream and are likely to undergo numerous atherogenic modifications such as desialylation, glycation, and oxidation, increasing their atherogenicity. [6]

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Similar findings have been found with HDL particle sizes where small HDL particles have been associated with increased CVD risk. Conversely, the concentration of large HDL particles has been shown to be negatively correlated with CVD risk, however, the size of the HDL particle and its cardioprotective functions has not been clearly established in the literature and the mechanisms need further study. [7],[8] Therefore, the purpose of this review is to discuss the effect of exercise (both aerobic & resistance training) and diet on HDL and LDL particle size.

The Effect of Aerobic Exercise on HDL and LDL Particle Size

Exercise has been shown to increase lipoprotein particle sizes even though the mechanisms are still not fully understood. Some studies found HDL and LDL particle sizes to increase following high intensity, 65 to 80% of peak oxygen consumption. [9,10] However, other studies have reported that LDL particle size increased significantly with moderate intensity aerobic training 60-65% of age-predicted maximum heart rate. [11] Other studies reported that after just three consecutive days of aerobic training at 65% of peak oxygen consumption, HDL particle size increased but LDL particle size did not increase. [12] Furthermore, other researchers reported that it took 12 weeks of aerobic exercise (running) at 60-75% peak oxygen consumption, for 45-60 minutes, three days a week for HDL particle size to increase, while LDL particle size remained unchanged. [8] A detailed look at why such variations exist is needed and may be explained based on the type, mode, duration and intensity of exercise.

It is well known that aerobic exercise reduces CVD risk by decreasing triglycerides and total cholesterol while increasing HDL-C. [13] However, the specific parameters of aerobic exercise especially pertaining to the particle size of HDL and LDL cholesterol still needs to be clearly defined. In this section, the effect of the volume of exercise (intensity X duration) will be considered.

A few studies have examined the impact of exercise volume particularly through Studies of Targeted Risk Reduction Interventions through Defined Exercise (STRRIDE) which are multi-cite, randomized, controlled clinical trials. This particular study design involved assessing cardiovascular risk factors using a graded exercise regimen with different volumes of cardiovascular exercise. In this type of study, subjects who were classified as overweight, Body Mass Index, (BMI: 25-35 kg/m^2) with mild to moderate dyslipidemia (LDL cholesterol of 130-190 mg/dL or HDL cholesterol of <40 mg/dL for men and <45 mg/dL for women) were randomly prescribed a high intensity of 65-80% of their maximum heart rate and placed in either a 32km per week or 19 km per week jogging group. A third group was exercised at a moderate intensity of 40-55% of maximum heart rate for 19km per week. [9] In this study by Krauss et al. (2002), it was reported that exercise performed at a high intensity 65-80% of maximum oxygen consumption accompanied with 32km per week of jogging resulted in an increase in HDL particle size and also resulted in the greatest reduction in small LDL particle sizes. [9] In another STRRIDE study, sedentary, n=240 overweight subjects were randomized to a 6 month control group or a high-amount/vigorous-intensity group, a low-amount/vigorous-intensity exercise group or a low-amount/moderate exercise group. Exercise was prescribed using treadmills, elliptical trainers and stationary cycles and was based on the number of minutes to expend 14kcal·kg body wt^{-1}·wk^{-1} for both the low-amount groups and 23 kcal·kg body wt^{-1}·wk^{-1} for the high-amount group. The high-amount group showed the siginificant improvements in HDL cholesterol, HDL particle size that were sustained for 15 days after the cessation of exercise. [10]

In a study that used n=20 Thai women, whom had normal lipid levels, it was reported that moderate intensity exercise, 60% of maximum heart rate reserve carried out 3 times a week on a stationary cycle for 12 weeks caused a significant drop in small LDL particles. [14] The authors noted that a plausible mechanism explaining how moderate intensity exercise leads to reduction in small LDL particle size could be explained as a result of a decrease in Cholesteryl Ester Transfer Protein (CETP) which is responsible for the core lipid transfer between vLDL and LDL particles. Furthermore, the decreased number of small, LDL particle sizes also could be due to the reduction in plasma Triglycerides (TG's) which are cleared upon with exercise. [14]

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Other researchers also have proposed alternate mechanisms explaining that reductions in small LDL particles could be due to changes in interactions of LDL's with their receptors or endothelial cells. [11] In this study, running and calisthenics at a moderate intensity exercise 60-65% of maximum heart rate for 45-60 minutes carried out 3 times a week conferred significant increases in LDL particle size compared to a higher exercise intensity of 75-80% of maximum heart rate. [11] This further supports the argument that moderate intensity exercise may be sufficient. Furthermore, the difference between high versus medium intensity exercise could also lie on their subsequent interactions on hepatic triglyceride lipase (HTGL) activity although the precise mechanism of how this happens is still not known. The two previously described studies [11,14] were carried out on normolipidemic adults (plasma cholesterol levels <230 mg/dL and plasma TG<150 mg/dL). Perhaps baseline lipoprotein particle size might have contributed to the results.

In another study that looked at the effects of HDL and LDL particle sizes on exercise and exercise with weight loss, those who lost weight and exercised had greater improvements in lipoprotein profile HDL and LDL particle size compared to the group that did not report significant weight loss with exercise. Therefore, it may be important for monitor and encourage weight loss with exercise to enhance HDL and LDL particle sizes. [16]

Unfortunately, there is no consensus on the exact volume of exercise, (Duration X intensity) that is the most beneficial for reducing HDL and LDL particle sizes. This may be because in many of the studies referenced, the modality of the exercise varied. In general, it appears that exercise durations between 19-32 km per week and intensities between 40-80% maximum heart rate appear to positively effect HDL and LDL particle sizes.

The Effect of Resistance Training on HDL and LDL Particle Size

The research involving resistance training and its effect of HDL and LDL particle sizes is very limited. One study that examined resistance training and its effect on the metabolism of an LDL-like nanoemulsion and on the lipid transfer to HDL, which is an important step of HDL metabolism. Thirty healthy, normolipidemic men who were previously engaged in resistance training for at least one year (n=15), were compared against a similar group of sedentary men (n=15) who did not engage in resistance training exercise for at least one year. [17] The resistance training program was reported to consist of 3-4 sets of 8-12 reps for 3-4 exercises for each muscle group, carried out 4-5 times a week. Although the size of LDL particles was not directly measured, the researchers demonstrated that accelerated removal of LDL-like nanoemulsion particles comprised of free and esterified cholesterol components in the resistance training group, indicating that the LDL pool was renewed more rapidly. The increased LDL turnover means less LDL circulates in plasma and is less subjected to lipid, therefore improving endothelial function. However, the diameter of HDL particles was the same in resistance training group as in sedentary group. The study presented limitations though as exact pre-training resistance training data was not collected. Future studies are needed to explore if resistance training results in variations on HDL and LDL particle sizes.

The Effect of Diet on HDL and LDL Particle Sizes

In addition to exercise, diet plays a major role in reducing cardiovascular risk factors. In this section, the effects of how diet effects HDL and LDL particle sizes along with a comparison to exercise will be discussed. Furthermore, the effect of different macro- and micro-nutrients on HDL and LDL particle sizes will be examined.

Dietary restriction regimens and alternate day fasting have been considered to be one of the ways to help obese individuals lose weight and lower their risk of CVD. [18] Previous studies that involved diet interventions have reported favorable effects on LDL particle sizes. In a 2006 study, n=30 hypercholesterolemic obese women (BMI: 25-39.9kg/m^2) participated in a low fat weight loss diet AND moderate exercise designed to evaluate any changes in LDL particle sizes. This study design consisted of a 2-week pre-stabilization phase, combined with a 20-week weight loss phase,

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followed by a 2-week post-stabilization phase. The low fat diet consisted of <30% fat, 50-60% carbohydrate and 20% protein accompanied with 40 minutes of moderate endurance training 3 days a week. This resulted in a significant mean weight loss of 14.8%, significant reductions in total cholesterol (8.9%), LDL cholesterol (7.5%), and triacylglycerol concentrations (27.15). High-density lipoprotein concentrations significantly increased by 9.9%. LDL peak or LDL integrated particle size did not show a significant change. [19] The authors concluded that weight loss combined with a low fat diet and moderate endurance exercise had minimal effects on LDL particle size and distribution. Another study compared the effects of Caloric Restriction, (CR), Alternate Day Fasting, (ADF) and exercise and on LDL and HDL particle sizes in obese adults. [8] Body weight and plasma LDL cholesterol significantly decreased, while HDL cholesterol showed a significant increase. Furthermore, the LDL particle sizes increased with ADF only, while large HDL particles increased with endurance exercise and minimal weight loss. The authors went on to conclude that none of the interventions increased both HDL and LDL particle sizes.

In a similar study, a 12-week randomized, controlled trial with n=64 obese individuals (BMI: 30-39kg/m^2) studied the effects of Alternate Day Fasting, (ADF), plus exercise, and each intervention alone with a control group, to see if superior changes occurred in plasma lipid levels. Subjects were divided into four groups: 1) exercise only at 60-75% of heart rate maximum on elliptical machines and stationary bikes three days a week. 2) ADF, consuming 25% of baseline energy on fasting days alternated with an ad-libitum day. 3), a combined group with both diet and exercise, or 4) and a control group. The authors reported that low-density lipoprotein (LDL) cholesterol significantly decreased and high-density lipoprotein (HDL) cholesterol significantly increased in the combination group only. LDL particle size increased ($P < 0.001$) in the combination group and ADF groups, respectively. The proportion of small HDL particles decreased ($P < 0.01$) in the combination group only. The authors concluded that the combination of exercise and ADF produced superior results when compared to individual treatments. [20]

Another author did a study that involved Alternate Day Fasting, ADF with a low fat and high fat diets for ten weeks, and their effects on LDL and HDL particle sizes. [21] In this study, 35 obese subjects were randomized into either a ADF high fat or ADF low fat group. In both groups, LDL particle size significantly increased, while HDL particle size remained unchanged in both groups. Overall, it appears that alternate day fasting with either a high or low fat diet, is an effective dieting strategy for increasing LDL particle size, although studies with larger sample sizes need to be carried out before firm conclusions are reached.

On the other hand, there are also studies stating that exercise still confers changes in HDL and LDL particle size independent of diet. [22] In this study 100 sedentary, healthy subjects 50-75 years of age were put on an endurance exercise program for 24 weeks at 50% of their VO_2 max for 20 minutes progressing to 70% of VO_2 max for 40 minutes via various types of training equipment: bikes, treadmill, elliptical machines, skier machines, stepping machines, and rowers. Both groups reported a significant reduction in HDL and LDL particle sizes showing that 24 weeks of endurance exercise independent of diet and body fat changes may be enough to favorably effect HDL and LDL particle sizes.

Dietary patterns were examined in another study to see if changes in lipoprotein particle size along with different intensities of exercise are affected by dietary patterns. [23] A z-score for diet was calculated comparing dietary intake results for total, saturated, and trans-fat; cholesterol; omega-3 fatty acids; and fiber respective to the intake recommendations by the American Heart Association (AHA). The researchers found that even though the overall diet z- score deviated from the ideal score of zero z-score, HDL and LDL particle size increased from just performing exercise alone. However, it should be noted that other dietary factors such as carbohydrate intake were not included in the z-score calculation, so the results are not entirely conclusive for all dietary components. Moreover, the above two studies were not dietary interventions but simply dietary records to ensure that the subjects remained weight stable.

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With regards macronutrients, high carbohydrate diets, especially those with refined sugars and high glycemic indexes have been found to be associated with an increased concentration of small, dense LDL particles. [24] In another similar study involving a cross-sectional study on normal and overweight 6–14-year-old Swiss children it was reported that higher intakes of dietary fructose were associated with reduced LDL particle size and lower HDL cholesterol. [25] Furthermore, the mechanism of reduced LDL particle size with diets high in refined carbohydrates such as glucose and fructose may result from the elevation of post-prandial triglycerides as well as fasting LDL cholesterol content [26] It is generally agreed that aerobic exercise combined with a diet low in refined carbohydrates, high in fiber and low in fat will increase LDL particle size.

Several other studies have demonstrated the benefits of restricting carbohydrates while increasing the intake of fats on LDL particle size. This was demonstrated in the study by Chiu et al. [27] where a high fat DASH diet of (40% fat, 43% carb, 18%protein) was compared to the DASH diet of (27% fat, 55% carb, 17% protein). The high fat dash diet significantly reduced triglycerides and large and medium very-low-density lipoprotein (VLDL) particle concentrations and increased LDL peak particle diameter compared with the DASH diet. The DASH diet reported a reduction in large LDL particles, and LDL peak diameter. Both groups were classified as the Dietary Approach to Stop Hypertension (DASH) diets which is composed mainly of fruits and vegetables, low-fat dairy foods, and whole grains.

In another carbohydrate related study, a fat controlled diet that was 30% fat, 50% carb, 20% protein was compared to a diet lower in fat and higher in carbohydrate, 30% fat, 50% carb, 20% protein. Larger, more buoyant LDL particles were seen in the higher fat diet.[28] In another study the same results were reported. This study included obese insulin-resistant subjects, who were given either a high fat diet, of 45% fats, 40% carbs, 15% fats or a higher carbohydrate diet, 25% fats, 60% carbs, 15% protein. The subjects with the diets higher in fat reported greater increases in LDL particle sizes.[29]

However other authors have not come to the same conclusions. In contrast, a randomized, controlled, interventional trial reported that HDL and LDL particle diameter did not alter during a 12-week intervention with participants given either a Carbohydrate Restriction Diet (CRD) with 20-25% carbohydrates, 25-30% protein, 45-50% fat for 12 weeks, or a combined diet composed of CRD for 6 weeks followed by the American Heart Association (AHA) diet for an additional 6 weeks with 55% carbohydrates, 15-20% protein, <30% fat.[30] Furthermore, the study concluded that the number of medium and small LDL particles decreased in all subjects, and that the CRD diet had a better effect on atherogenic VLDL and HDL when compared to the low fat diet recommended by the AHA.

In a randomized, crossover study it was demonstrated that a low carbohydrate diet with lower saturated fats, 38% fat, 8% SFA, 21% MUFA, and 31% carbohydrate significantly reduced small, dense LDL particles compared to a low carbohydrate diet with higher saturated fats 38% fat, 15% SFA, 15% MUFA, and 31% carbohydrates[31].

A similar study also showed that 3 weeks of a low carbohydrate, high saturated fat diet, 38% fat, 15% SFA, 15% MUFA, and 31% carbohydrate increased the concentration of small dense LDL particles compared to a low carbohydrate, low saturated fat diet 38% E fat, 8% SFA, 21% MUFA, and 31% carbohydrates[32].

On the other hand, levels of atherogenic lipids were studied following the consumption of diets high and low in saturated fats containing red meat compared to similar amounts of protein derived from white meat or non-meat sources.[33] The authors concluded that LDL cholesterol and apolipoprotein B were higher with the red and white meat diets compared to the non-meat diet, independent of saturated fat content. However, the higher concentration of LDL cholesterol was due primarily to an increase in large LDL particles. The authors went on to conclude that small and medium LDL particles and total/high density lipoprotein cholesterol were unaffected by protein source and that based on lipid and lipoprotein effects, there was no evidence for choosing white over red meat for reducing the risk of heart disease.

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Another author named Chiu, et. al 2017, studied the effects of apolipoprotein B, small, medium, large particle sizes and total LDL in phenotype B individuals placed on either a high or low saturated fat diet.[34] The high saturated fat diet resulted in an overall increase in total cholesterol, plasma concentrations of apolipoprotein B, medium LDL particles, and LDL cholesterol, while large and very small LDL particle size concentrations were unchanged.

Nevertheless, a series of studies have shown that mono- and poly-unsaturated fats have been shown to be favorable for increasing LDL particle size. When the Mediterranean, a diet high in Monounsaturated fatty acids (21%MUFA), was compared to a diet high in mono-unsaturated fats (20% MUFAs) were compared against a Western diet high in SFAs (19% SFAs) in individuals at risk of developing metabolic syndrome, only the MUFA rich diet and Mediterranean diet reduced the subclass of small, dense LDL particles.[35]

The antiatherogenic properties of MUFAs are also demonstrated in a randomized, crossover study in overweight and obese subjects (BMI: 25-35kg/m^2) where consumption of 1 Haas avocado a day (34% fats, 6% SFAs, 17% MUFAs, 49% carb) decreased the number of small, dense LDL particles, unlike in a low-fat diet (24% fats, 7% SFAs, 11% MUFAs, 59% carb), or a diet high in saturated fats (34% fats, 13% SFAs, 12% MUFAs, 51% carb).[36]

In patients with metabolic syndrome, PUFA rich sunflower oil diets lower in fat and higher in carbohydrates and diets high in MUFA's were found to increase LDL particle size and a resulted in a favorable alteration of LDL phenotype B to A. In total, four diets were compared: 1) A diet high in saturated fats (38% fats), 2) A diet high in MUFAs (38% fats), 3) A diet that is low in fat and rich in complex carbohydrates with 1.24g/day of sunflower oil or Polyunsaturated Fatty Acids (PUFA's), (28% fats), and 4) A diet that is low in fat and rich in complex carbohydrates with 1.24g/day of PUFAs.[37] Furthermore, increases in LDL density was reported in the high saturated fat diet.

In another related study, no differences in LDL particle size were seen in subjects with impaired glucose tolerance, who consumed MUFA diets of (40% fats, 19% MUFAs) or PUFA diets with (34% fats, 10% PUFA) diets for 8 weeks.[38] In another study, in contrast, dietary intake of PUFAs was associated with smaller LDL size in a cross-sectional cohort study conducted on subjects with type II diabetes and impaired glucose metabolism.[39]

When a low fat, high carbohydrate diet of 22%-25% energy from fat, 7-8% energy from monounsaturated fats and 55-60% carbohydrate was compared to a higher fat monounsaturated enriched sunflower oil diet that contained 40-42% energy from fat, 26-28% from monounsaturated fat and 40-45% of energy from carbohydrate, LDL particle size was not significantly different.[40] Overall, the effect of unsaturated fats on LDL size, relative to saturated fats needs further clarification.

As for protein, a low fat, high protein diet (32% fat, 37% carb, 31% protein) was found to increase LDL particle size compared to a lower protein diet (30% fat, 55% carb, 15% protein) in twelve abdominally obese men with a Body Mass Index, BMI of 28 – 33 kg/m^2 and an average waist circumference of 117.4cm.[41]

In another study involving protein, a randomized, double-blind study reported that soy-protein, independent of isoflavone content, increased LDL size compared to animal protein constituting of milk and meat.[42]

Other than the important variables like diet and exercise, it is also crucial for future studies to control variables like age, gender, ethnicity, and BMI. This was demonstrated in a study where ethnicity-specific genes like APOE alleles were shown to influence the effect of aerobic exercise on mean HDL particle size. In this study, black postmenopausal women with APOE2/3 alleles displayed significant improvements in lipoprotein profiles unlike in whites after 24 weeks of endurance training, when compared to whites who were maintained on a AHA step 1 low-fat diet.[43] Finally, it is important to note that in another related study, women had lower levels of small and medium LDL particle sizes, medium VLDL, large VLDL and small HDL with a much higher concentration of large HDL particles compared to men. Furthermore, whites had significantly more IDL, small LDL, medium VLDL, and large VLDL with lower levels of large LDL particles than blacks with HDL and LDL particle sizes being larger among blacks and women.[44]

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Training Applications & Future Directions

From the studies that compared the effect of different exercise volumes, (intensity X duration) on HDL and LDL particle size, high amounts (32 km per week) accompanied with high intensity of (65-80% of maximum oxygen consumption), performed 3 times a week for 24 weeks or more were found to increase HDL and LDL particle size especially in overweight/obese individuals with mild to moderate dyslipidemia. However, lower amounts of exercise (19 km per week) at a moderate intensity of (40-55% of maximum oxygen consumption) also could lead to improvements in HDL particle size if weight loss occurred. Furthermore, in normolipidemic, sedentary individuals, lower amounts of exercise (19 km per week) and moderate exercise at 40-55% of maximum oxygen consumption may be enough to increase HDL and LDL particle size.

Early research even suggests that alternate day fasting has been found to be effective for improving HDL and LDL particle sizes among obese individuals. Lower carbohydrate diets (37-74% fats, 6-50% carb) as well as diets high in MUFAs and PUFAs may be effective for lowering CVD risk through increasing HDL and LDL particle as well. However, additional well-controlled studies are needed to form conclusive results.

Conclusions

It is evident that aerobic exercise reduces atherogenicity of LDL particles and improves the function of HDL particles. However, the specific intensity, duration, and or volume and even modality necessary to induce changes for each population requires additional study. The effect resistance training has on LDL and HDL particle sizes also requires more study. Overall, high intensity and duration seem to be the most effective especially for individuals at a greater risk for CVD. It is important that obese and overweight individuals prioritize weight loss including fat loss from both diet and exercise. Strict considerations need to take place for future studies as lipoprotein particle changes depend not only on the lifestyle interventions but also on genetic and anthropometric characteristics.

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