Revista de Nutrición Clínica y Metabolismo

Review

Impact of exercise on lipid metabolism and dyslipidemia

Impacto del ejercicio sobre el metabolismo de los lípidos y la dislipidemia

Impacto do exercício sobre o metabolismo dos lípidos e da dislipidemia

Eitan A. Scher-Nemirovsky[1], Daniel Ruiz-Manco[1], Carlos O. Mendivil[1,2*]

Received: 16 July, 2019. Accepted: 5 August, 2019
https://doi.org/10.35454/rncm.v2n2.004

Summary

The chronic practice of exercise induces a series of cellular and organismal adaptations that modify the way the human body metabolizes all macronutrients, including lipids. Endurance exercise and resistance exercise elicit different responses that result in differential effects on lipid and lipoprotein metabolism. These effects are quantitatively and qualitatively different, and mediated by distinct signaling pathways. In this review, we summarize relevant evidence on the impact of exercise on lipid and lipoprotein metabolism, and finalize with some practical recommendations on exercise practice for patients with dyslipidemia in the primary care setting.

Keywords: Lipids; Physical activity; Primary attention.

Resumen

La práctica crónica del ejercicio induce una serie de adaptaciones celulares y orgánicas que modifican la forma en que el cuerpo humano metaboliza todos los macronutrientes, incluidos los lípidos. El ejercicio de duración y el ejercicio de resistencia provocan diferentes respuestas que resultan en efectos diferenciales sobre el metabolismo de los lípidos y las lipoproteínas. Estos efectos son cuantitativa y cualitativamente diferentes y mediados por distintas vías de señalización. Esta revisión, resume la evidencia pertinente sobre la repercusión del ejercicio en el metabolismo de los lípidos y las lipoproteínas, y finaliza con algunas recomendaciones sobre la práctica del ejercicio para los pacientes con dislipidemia en el ámbito de la atención primaria.

Palabras clave: lípidos, actividad física, atención primaria.

Resumo

A prática crônica de exercício induz uma série de adaptações celulares e orgânicas que modificam a maneira pela qual o corpo humano metaboliza todos os macronutrientes, incluindo os lipídios. O exercício de duração e o exercício de resistência provocam diversas respostas que resultam em efeitos diferenciais no metabolismo de lipídios e lipoproteínas. Estes efeitos são quantitativa e qualitativamente distintos e mediados por diferentes vias de sinalização. Nesta revisão, se resume as evidências relevantes sobre o impacto do exercício no metabolismo de lipídios e das lipoproteínas e conclui, com algumas recomendações sobre a prática de exercícios para pacientes com dislipidemia no campo da atenção primária.

Palavras-chave: lipídios, atividade física, atenção primária.

INTRODUCTION

During evolution, only the fittest managed to survive and pass on their genes to the next generation. In an era where resources were scarce, the fittest humans were those who could withstand long hours of hunting or laboring. This meant that genes encoding efficient energy storage and metabolism were favored and passed down generation after generation until now. However, in modern times of plentiful resources and mechanized production, an overabundance of energy and low expenditure are the norm. Such physical inactivity increases the incidence of at least 17 unhealthy conditions and related chronic diseases, whereas a low exercise capa-

1 School of Medicine, Universidad de los Andes, Bogotá, D.C., Colombia.

2 Section of Endocrinology, Fundación Santa Fe de Bogotá, Bogotá, Colombia

Correspondence: *Carlos O. Mendivil, MD, PhD.
cmendivi@uniandes.edu.co

city is an independent predictor of all-cause mortality and morbidity[1]. One of the demonstrated effects of sedentary behavior is metabolic dysfunction, characterized by increased plasma triglyceride levels, decreased levels of high-density lipoprotein (HDL) cholesterol, and decreased insulin sensitivity[2]. All these undesirable consequences of physical inactivity warrant an understanding of the physiological pathways by which physical activity confers its metabolic benefits.

PHYSICAL ACTIVITY, EXERCISE AND SPORT

Physical activity (PA) is considered any kind of corporal movement produced by conscious contraction of skeletal muscle that demands the use of energy[3]. Meanwhile, exercise is a type of physical activity that is planned, structured, repetitive and purposeful in the sense that the objective is an improvement or maintenance of one or more components of physical fitness[4]. While every time you exercise you do PA, not necessarily every time you are physically active means you are doing exercise. Finally, sport means all forms of PA which, through casual or organized participation, aim at expressing or improving physical fitness and mental well-being, forming social relationships or obtaining results in competition at all levels.

The capacity of coordination and adaptation of a full range of physiological and cognitive qualities determines the physical fitness. This term is further divided into 3 components that can be enhanced through continuous training. These are cardiorespiratory fitness, muscle fitness and speed/coordination. Cardiorespiratory fitness is the overall capacity of the cardiovascular and respiratory systems to carry out prolonged strenuous exercise. Aerobic capacity, is defined by the American College of Sports Medicine as the product of the capacity of the cardiorespiratory system to supply oxygen and the capacity of the skeletal muscles to utilize oxygen[5]. The maximal oxygen consumption (VO_2max) attained during a graded maximal exercise to voluntary exhaustion has long since been considered the single best indicator of cardiorespiratory fitness. Muscle fitness is the capacity to carry out work against a resistance. The maximum force that can be generated depends on several factors including the size and number of muscles involved, the proportion of muscle fibers called into action, and the coordination of the muscle groups. The main health-related muscular fitness components are maximal strength (isometric and dynamic), explosive strength, endurance strength and isokinetic strength[6]. Speed is the ability to move the body (or some parts of the body) as fast as possible. Agility is the ability to move quickly and change direction while maintaining control and balance. Consequently, agility is a combination of speed, balance, power and coordination[6].

PHYSIOLOGICAL RESPONSE TO PHYSICAL ACTIVITY

To support the constant demands of PA, the body responds with a multisystem adaptation that maintains the supply of oxygen and metabolic substrates to the skeletal muscle. The chronic adaptations that optimize the generation, oxidation and consumption of substrates, and/or cellular changes will be discussed further below. The acute responses to exercise are:

- Cardiovascular: Blood flow to active skeletal muscle can increase 100-fold above basal levels, accounting for up to 80%–90% of cardiac output. The tremendous increase in skeletal muscle blood flow is accomplished largely by increased cardiac output by means of the skeletal muscle pump which promotes venous return during dynamic exercise, but also in part by diverting flow away from the kidneys and the splanchnic organs. Notably, there is only a modest (20%) increase in mean arterial blood pressure (MAP), whereas values for arterial PO_2, PCO_2, and pH remain essentially identical to rest until maximal exercise intensities are reached[1]. MAP stability is mainly maintained due to the decrease in total peripheral resistance caused by metabolic vasodilator accumulation and decreased vascular resistance in the active skeletal muscle which is a pressure-lowering disturbance that elicits a strong increase in sympathetic activity through the arterial baroreceptor reflex. Static exercise (i.e., isometric) presents a much different disturbance on the cardiovascular system than does dynamic exercise. As discussed in the previous section, dynamic exercise produces large reductions in total peripheral resistance because of local metabolic vasodilation in exercising muscles. Static efforts, even of moderate intensity, causes a compression of the vessels in the contracting muscles and a reduction in the blood flow through them. Thus, total peripheral resistance may increase significantly. Cardiovascular effects of static exercise include increases in the heart rate, cardiac output, and arterial pressure[7].
- Respiratory: The critical functions of the pulmonary system are to maintain arterial oxygenation and to

facilitate the removal of CO_2 produced during oxidative metabolism by increasing ventilation in proportion to exercise intensity[8].

- Skeletal Muscle: ATP is not stored in any large quantity inside skeletal muscle. Because of its limited availability, ATP is resynthesized at a rate for meeting the metabolic demands placed upon the cell. The most immediate substrate source for ATP resynthesize in skeletal muscle is phosphocreatine (PCr). Skeletal muscle has enough PCr to sustain the maximum ATP turnover rate for about 7–10 s. Skeletal muscle also utilizes both fat and carbohydrate as substrates for ATP resynthesizes. The rates at which FFA and carbohydrates can replenish muscle ATP are significantly lower than that from either PCr or ADP. However, the amount of ATP they can produce from a single molecule from either of them is significantly greater. Increasing exercise duration is achieved at the expense of the rate of ATP turnover. The lower rate of ATP turnover can be matched by oxidative phosphorylation that employs a combination of glucose/glycogen and fatty acids as substrates[9].
- Lipid metabolism: The sources of energy during exercise have been known since the 1960s[10]. At workloads below 30% of VO_2max, the main energy source is fatty acids, between 40 and 65% of VO_2max there is approximately a 50:50 balance between carbohydrate and fat oxidation, and beyond 70% of VO_2max there is an exponential rise in carbohydrate oxidation with a concomitant decrease in fat oxidation[9]. The relative contribution of fat oxidation to total energy expenditure changes very little up to intermediate levels of exercise intensity[11]. However, as exercise intensity is further increased up to 75 % VO_2max, substrate utilization changes markedly, total body fat oxidation rate decreases while muscle glycogenolysis becomes the primary source of energy (Figure 1).

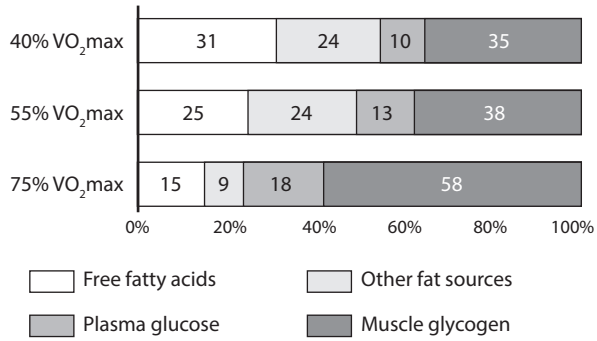

Figure 1. Percent of total energy obtained from each energy source according to exercise intensity. Numeric data from[11].

CHRONIC ADAPTATIONS TO EXERCISE

There are 3 known subgroups of fibers in human muscles: Fast-twitch glycolytic (FG), fast-twitch oxidative (FO), and slow-twitch oxidative (SO)[12]. The FG are predominantly anaerobic fibers, they have a high glycogen concentration and high phosphorylase, lactate dehydrogenase and alpha-glycerophosphate dehydrogenase activities. FG fibers have a fast contraction and explosive rate, at the expense of fast fatigability. Meanwhile, SO fibers rely predominantly on aerobic metabolism, have a low glycogen concentration and low phosphorylase, lactate dehydrogenase, and mitochondrial alpha-glycerophosphate dehydrogenase activities. The properties of FO fibers are midway in between those of FG and SO fibers, with high rate of both oxidation and glycogenolysis[13].

When considering chronic physiological adaptations to exercise, there are two main pathways that activate very distinct responses at the cellular level. It's important to note that each pathway is activated by different kinds of training. In the case of endurance training, it favors the pathway that stimulates the formation of new mitochondria, thus enhancing the development of SO fibers. On the other hand, resistance training favors the hypertrophic pathway enhancing the development of FG fibers.

AMPK pathway

Aerobic, endurance training acutely increases the AMP/ATP ratio, which activates the AMPK pathway. AMPK is an important sensor of decreased energy charge in cells and subsequently acts to increase catabolic reactions and decrease anabolic reactions, particularly to increase glucose uptake through GLUT4 expression, increase fatty acid oxidation, and decrease glycogen synthesis[14]. AMPK requires Peroxisome Proliferator-Activated Receptor gamma (PPAR-gamma) Coactivator 1-alpha (PGC-1) for many of its effects on gene expression in skeletal muscle. AMPK binds to and activates PGC-1 in muscle by direct phosphorylation on two critical residues, threonine-177 and serine-538[15]. PGC-1 is a critical regulator of transcription of many genes involved in energy homeostasis, particularly fuel oxidation and mitochondrial biology.

These AMPK-mediated phosphorylations induce PGC-1alpha to activate a transcriptional cascade that ends in mitochondrial biogenesis and the stoichiometric assembly of multi-subunit protein complexes into a functional respiratory chain. Nuclear respiratory factor-1 and 2, targets of PGC-1, directly regulate the expression of nuclear-encoded mitochondrial genes and can stimulate the expression of mitochondrial transcription factor A (Tfam), a mitochondrial matrix protein essential for the replication and transcription of mitochondrial DNA[16].

mTOR pathway

Resistance training activates a completely different intracellular signaling response, elicited chiefly by the secretion of growth hormone[17]. Several heavy resistance exercise protocols have been proven to elevate the post exercise concentration of GH[17]. GH regulates important physiological processes, including somatic growth and development, as well as carbohydrate and lipid metabolism, directly through the activation of specific GH receptors, or indirectly through insulin-like growth factor 1 (IGF-1), which is produced mainly in the liver in response to GH stimulation[18]. Hypertrophy of myotubes induced in vitro by IGF-1 depended on a pathway initiated by Phosphoinositide 3-kinase (PI3K) and the PI3K-regulated kinase Akt, which in turn led to activation of the rapamycin-sensitive kinase known as mTOR, whose downstream targets, p70S6K and PHAS-1/4E-BP1, have been shown to promote protein synthesis through increases in translation initiation and elongation[19]. Phosphorylation of p70S6K (a downstream effector of mTOR) increases the phosphorylation of ribosomal protein S6 and facilitates the synthesis of some ribosomal proteins, initiation factors, and elongation factors that play important roles in protein synthesis[20]. An *in-vivo* study in human volunteers further confirmed this effect: following 8 weeks of resistance training, human skeletal muscle hypertrophy was associated with an increase in the amount of phosphorylated Akt and mTOR[21].

HOMEOSTASIS OF LIPIDS AND LIPOPROTEINS

The term lipids encompasses a large group of hydrophobic compounds that cannot travel efficiently in a polar solvent like human plasma. For them to be transported to the various tissues and organs for utilization and storage, nonpolar lipids (triacylglycerol and cholesteryl esters) need to be associated with amphipathic lipids (phospholipids and cholesterol) and proteins to make water-miscible lipoproteins[22] Plasma lipids comprise triacylglycerols - also called triglycerides- (16%), phospholipids (30%), cholesterol (14%), cholesteryl esters (36%) and a much smaller fraction of unesterified long-chain fatty acids (or free fatty acids - FFAs) (4%)[23] .

Since fat is less dense than water, the density of a lipoprotein decreases as the proportion of lipid to protein increases. Four major groups of lipoproteins have been identified that are important physiologically and clinically. These are (1) chylomicrons, derived from intestinal absorption of triacylglycerol and other lipids; (2) VLDL, synthesized by the liver for the export of triacylglycerol; (3) low-density lipoproteins (LDL), representing a final stage in the catabolism of VLDL; and (4) high-density lipoproteins (HDL), involved in cholesterol transport and also in VLDL and chylomicron metabolism[24]. Every class of lipoprotein contains apolipoproteins that define its structure and function. The most important apolipoproteins are summarized in Table 1[22].

Metabolism of chylomicrons

Once absorbed into intestinal epithelial cells, dietary TG are secreted into the bloodstream within chylomicrons. The assembly of chylomicrons requires apoB-48 as structural apolipoprotein. Once chylomicrons access the bloodstream, the triglycerides in their core are hydrolyzed into free fatty acids and glycerol by lipoprotein lipase-1 (LPL-1) (present in the surface of most endothelial cells) with apolipoprotein C-II as a cofactor. This process yields smaller chylomicron remnants[25]. These remnants are later removed primarily by a chylomicron remnant receptor on the liver, known as the LDL-like receptor protein-1 (LRP-1)[24].

Metabolism of VLDL

VLDL suffer a process quite similar to that of chylomicrons, but with different actors. Triglyceride-rich VLDL are synthesized and secreted by the liver, a process that requires apoB-100 instead of apoB-48. In plasma, the triglycerides in VLDL are broken down to free fatty acids and glycerol by lipoprotein lipase with participation of apoC-II, just like it happens to chylomicrons. This results in the production of smaller VLDL remnants and IDL (intermediate-Density Lipoproteins). Some of the IDL particles are removed through the interaction of apolipoprotein E with the LDL receptor

Table 1. Main apolipoproteins, their functions and location.

Type of apolipoprotein	Apolipoprotein	Function	Present in
Structural	apoB (ApoB-48 and apoB-100)	Backbone of lipoproteins	Chylomicrons, VLDL, and LDL
Enzymatic cofactors/ inhibitors	ApoC-II	Lipoprotein lipase coactivator	HDL, chylomicrons and VLDL
	ApoA-I	Coenzyme of lecithin:cholesterol acyltransferase (LCAT)	Mainly HDL, may also be found in chylomicrons
	ApoC-I	Inhibitor of cholesteryl ester transfer protein (CETP)	Mainly HDL, seen in other lipoproteins in postprandial state
	ApoA-II	Inhibitor of lipoprotein lipase	HDL
Ligands	ApoE	Binds to LDL receptor and LDL-receptor–related protein-1, enabling lipoprotein removal from circulation	HDL, chylomicrons, VLDL and LDL,
	ApoC-III	ApoE antagonist, blocks removal of circulating lipoproteins	VLDL, LDL

on the surface of the liver, while some others can be further hydrolyzed by hepatic lipase to produce LDL. LDL is normally removed by the interaction of apolipoprotein B-100 with the LDL receptor. ApoB comprises 23.8% of the weight of the LDL particle and is the protein determinant for cellular recognition and catabolism of LDL[26]. When LDL are oxidized, they can be more easily phagocytosed by macrophages through the scavenger receptors CD36 and SR-A[24].

Metabolism of HDL

HDL, synthesized and secreted from both liver and intestine, are complex particles. As of today, over 110 individual polypeptides have been identified in HDL by various approaches[27]. A major function of HDL is to act as a repository for the apoC and apoE required for the metabolism of chylomicrons and VLDL. HDL is originally secreted as a phospholipid-rich, cholesterol-poor nascent particle, that later acquires additional phospholipids and cholesterol via cellular efflux, as well as by transfer of surface components from chylomicrons and VLDL during intravascular lipolysis[28]. The class B scavenger receptor B1 (SR-B1) has been identified as an HDL receptor with a dual role. In the liver and in steroidogenic tissues, it binds HDL via apo A-I, and cholesteryl ester is selectively delivered to the cells, although the HDL particle itself is not taken up. In other tissues, SR-B1 mediates the acceptance of cellular cholesterol by HDL, which then esterifies free cholesterol and transports it to the liver for biliary excretion[29]. Plasma concentrations of HDL show a strong independent inverse relationship with the risk of atherosclerotic cardiovascular disease. Although HDL has antioxidant, anti-inflammatory, vasodilating and antithrombotic properties, the central anti-atherogenic activity of HDL is likely to be its ability to remove cholesterol and oxysterols from macrophage foam cells, smooth muscle cells and endothelial cells in the arterial wall[30].

After going through all the transport required to reach cells, fat reaches the mitochondria in the form of free fatty acids. Inside the mitochondria, fatty acid breakdown continues in a four-step process called the β-oxidation cycle, a reiterative process which removes two carbons from the fatty acid with each cycle[22]. This process is inhibited by insulin during the postprandial period[31]. As mentioned previously, a cycloergometry study in human volunteers[11] showed that the relative contribution of fat oxidation to total energy expenditure is reduced only when as exercise intensity approaches 75% of VO_2max. This means that fat oxidation becomes saturated with high-intensity PA. Nonetheless, the capacity to oxidize fat can be enhanced by means of endurance PA, which induces in muscle tissue: i. Augmented expression of fatty acid transporters in the plasma membrane, ii. Greater density of mitochondria ii. Proliferation of capillaries and iii. Faster fatty acid transport from cytosol to mitochon-

dria. All these effects jointly result in enhanced fatty acid delivery and oxidation[32].

Quantitative effect of exercise practice on plasma lipids and lipoproteins

The positive effects of both physical activity and exercise on cardiovascular protection have been extensively validated. Each 1 MET increase in exercise performance confers a reduction in total mortality of approximately 12%[33]. An important proportion of such benefit is mediated by lipid metabolism, including positive impacts on plasma triglycerides, LDL, HDL Lp(a), and even apolipoproteins like apoC-III.

Impact of exercise on plasma triglycerides

Plasma triglycerides are one of the components of the lipid profile most amenable to change through lifestyle modifications. In a large epidemiological study in Brazil, the regular practice of at least 150 min/week of vigorous physical activity was associated with significantly higher HDLc and lower triglyceride levels[34]. In the Health Professionals Follow-up Study (HPFS), a prospective cohort study of US men, the difference in TG/HDLc ratio between the top and bottom quintiles of physical activity practice was −26%[35].

In individuals with obesity, a Cochrane meta-analysis including 43 studies with 3476 participants found that a physical activity intervention lasting at least 12 weeks induced a mean decrease in fasting TG of 18 mg/dL, independent of nutritional modifications[36]. Another meta-analysis of regular endurance training among men, including 49 studies and 2990 participants, found a mean TG decrease of 9% and a positive correlation between TG lowering and exercise intensity[37].

Overall, current evidence suggests that exercise and physical activity do impact plasma triglycerides, and their effect is largely related to the intensity and frequency of practice.

Impact of exercise on plasma HDLc

Some studies have focused on the effect of exercise and physical activity and exercise on HDLc in children. A cross-sectional study of 1731 adolescents aged 12-19 years analyzed accelerometer-measured physical activity in order to find the minimal intensity that would confer health benefits. After adjusting for potential confounders, each additional hour/day of light-intensity activity was associated with 1.5 mg/dL (0.03 to 2.6) higher plasma HDLc[38]. Another study of 3984 youngsters aged 6-17 from the National Health and Nutrition Examination Survey (NHANES 2003-2006) found that for every additional 1% of time in moderate-to-vigorous physical activity, plasma triglycerides were lower by 2.08 mg/dL (-3.89 to -0.27) and HDL-C was higher by 0.47 mg/dL (0.25 to 0.69)[39].

The impact of exercise on HDL is not limited to HDLc concentrations, but also to the size of the lipoproteins, which has been shown to shift towards larger, presumably more functional particles. The quantitative effect of regular aerobic exercise on plasma HDLc has been estimated as a 10-15% increase[40].

Impact of exercise on plasma LDL cholesterol

The relationship between physical activity levels and LDLc is much less pronounced than for HDLc or triglycerides. In a prospective, 8-month study of 109 participants, vigorous physical activity (up to 75 min/week) significantly reduced LDLc levels, but the numeric reduction was modest (from 115 +/- 33.4 to 109.8 +/- 31.7 mg/dL, p=0.04)[41]. Other studies have shown even less of an effect: Eight trials investigated the effect of aerobic exercise on LDLc, showing strong evidence for heterogeneity (I^2=86%, p<0.001). After compilation of the results using a random effects model in a meta-analysis, the pooled estimate of LDLc change with aerobic exercise was not significantly different from zero (weighted mean difference versus control group: -0.52, 95% CI: -7.97 to 6.92)[42].

These results confirm what is known about LDLc physiology, namely that hepatic cholesterol production has a heavy genetic influence, is modestly influenced by diet, and not influenced much by exercise.

Impact of exercise on non-HDL cholesterol

Non-HDL cholesterol or atherogenic cholesterol (i.e., the sum of VLDL cholesterol, LDL cholesterol, remnant lipoprotein cholesterol and Lp(a)-cholesterol), is considered a robust and consistent cardiovascular risk factor[43]. Most evidence specifically assessing the association between physical activity and non-HDL cholesterol comes from studies in young populations. In a study that followed 108 teens who had undergone bariatric surgery for 3 years, a greater volume of physical activity correlated with greater absolute decreases in non-HDL-C, despite low absolute step counts and slow cadence[44]. A cohort study including 880 Norwegian schoolchildren with a mean age of 10.2 years showed that replacing

30 minutes a day of sedentary time with 30 minutes of moderate-to-vigorous physical activity (>2296 accelerometer counts/min) was inversely associated with the concentration of non-HDL-cholesterol[45].

Impact of exercise on plasma apolipoprotein C-III

ApoC-III has been identified as an independent cardiovascular risk factor because of its antagonism to the LDL receptor and hindrance of the protective functions of HDL[46-48]. In a cross-sectional study involving 3631 participants, each additional 20 MET-hours per week of physical activity were associated with 0.9 (-1.7 to -0.1) lower concentrations of HDL containing apoC-III[49].

Impact of exercise on plasma lipoprotein(a)

Several large cohort and mendelian randomization studies have shown that plasma lipoprotein(a) -Lp(a)-, exhibits a negative and at least partially causal association with cardiovascular risk[50]. A negative association between Lp(a) and physical activity seems to be particularly striking among children: A large multicenter follow-up study of 2464 children and young-adults (age 9 to 24) found that plasma Lp(a) was significantly correlated only with physical activity level, but not age, gender or other known cardiovascular risk factors. A similar cross-sectional study in 1340 adults correlated physical activity levels in the IPAQ (International Physical Activity Questionnaire) with plasma Lp(a). Lp(a) concentrations in participants with low, moderate and high physical activity levels were respectively 29.2 +/- 13.7, 26.3 +/- 12.9, and 24.5 +/- 11.4 mg/dL with significant differences between groups[51]. These results suggest that, unlike LDLc, Lp(a) tends to be responsive to exercise and physical activity in a dose-response fashion.

Differential effects of exercise modalities on plasma lipids

In general, the health effects of physical activity depend on its volume (the product of exercise intensity and exercise time), frequency (amount of training units per week or month) and its modality (aerobic, resistance or combined)[52].

ENDURANCE EXERCISE

Both intermittent (short periods at high intensities) and continuous aerobic exercise decrease total cholesterol and increase HDL cholesterol in sedentary subjects[53]. A threshold for aerobic exercise-induced HDLc increase has been estimated at about 1000 kcal of running or a similar aerobic exercise per week[54]. In a meta-analysis of 51 interventions involving 4700 patients who underwent aerobic exercise programs during at least 12 weeks, HDLc, TG and LDLc changed on average +4.6%, -3.7% and -5%, respectively, without changes in total cholesterol. HDLc was the lipid profile component most prone to change with aerobic exercise, even a 10-week program (three times a week at 85% the maximal heart rate) induced a 13% increase in HDLc. Prolonged aerobic exercise (150 min/week) was superior at improving lipid parameters compared to an intense interval running protocol (40 min/week).

RESISTANCE EXERCISE (RE)

Findings on the effect of resistance exercise on blood lipids have been more conflicting than for aerobic exercise[52]. A recent study in adult women found a remarkable impact of only 12 weeks of resistance exercise using the participant´s own body weight, reducing TG by 14.3% while increasing HDLc by 7.9%[55]. A separate small study restricted to postmenopausal women only, reported also significant reductions in LDLc with 150 min/week of resistance exercise[56]. In men, two small studies have specifically examined the impact of resistance exercise on plasma lipids. In one of them, the acute (72-h) effect of 75% of maximum repetitions on plasma TG was estimated at -11.0 mg/dL[57]. In a second study, patients taking part in a moderate (45-55% of maximum repetitions) or high-intensity (80-90% of repetitions maximum) resistance exercise program experienced significant reductions in LDLc (-12.2 to -13.5 mg/dl). The high-intensity group also saw significant increases in HDLc (+5.5 mg/dl)[58].

COMBINED MODALITIES

Combining aerobic and resistance exercise would be expected to provide the cumulative benefits of both modalities, but data on combined intervention protocols have shown inconsistent effects on plasma lipids (59). In general, the impact of interventions combining both modalities is comparable to that obtained from aerobic exercise, in all major lipid subfractions[60].

Exercise prescription in patients with dyslipidemia

Evidence-based, grade A recommendations concerning physical activity among patients with dyslipidemia can be summarized as follows[61]:

- LDLc goals depend on the patient's global cardiovascular risk (GCVR) status[62]:
  - <130 mg/dL for low-risk patients (no prior cardiovascular events, no cardiovascular risk factors and estimated GCVR <10%)
  - <100 mg/dL for moderate or high-risk patients (no prior cardiovascular events, 1-2 cardiovascular risk factors and/or estimated GCVR 10-20%, or diabetes or chronic kidney disease without additional risk factors).
  - <70 mg/dL for very high-risk patients (prior cardiovascular event, or estimated GCVR >=20%, or familial hypercholesterolemia, or diabetes or chronic kidney disease plus one or more uncontrolled risk factors).
  - <55 mg/dL for extreme risk patients (prior cardiovascular event + diabetes or chronic kidney disease, or progressive cardiovascular disease despite LDLc below 70 mg/dL, or cardiovascular disease before 55y in men or before 65y in women).
- Exercise sessions should last > 40 min, the training program should last > 40 weeks.
- If possible, it is desirable to perform resistance exercise of at least 5 large muscle groups, as 8-10 repetitions, each series at 70-85% of maximum repetitions.
- Exercise in dyslipidemic patients should be prescribed together with adequate lipid-lowering pharmacotherapy and dietary modifications.

Recommendations can be further adjusted to the general condition of the patient; these recommendations are summarized in Table 2[59].

CONCLUSION

Physical activity and exercise have the potential to positively impact plasma lipids, especially triglycerides, HDL cholesterol and to a lesser degree LDL cholesterol, Lp(a) and probably apoC-III. However, the overall impact of exercise on cardiovascular risk goes beyond its impact on plasma lipids.

Conflicts of interest

The authors manifest no conflict of interest to report.

Funding

The authors received no specific funding for the writing of this article.

Authorship statement

EASN, DRM, COM participated in the concept, design, analysis, writing, and revision of the manuscript. All the authors approved of the version of the manuscript to be published.

Table 2. Summary of recommendations for exercise practice in patients with dyslipidemia according to overall mobility. Adapted from[59].

Patient status	Targets	Physical activity recommendations
Mobile, no dyslipidemia	Maintain low LDLc and TG levels, increase HDLc	>30 min/day, 5 times /week of aerobic exercise at 70-80% of the heart rate reserve, combined with resistance exercise at 50% of maximum repetitions.
Mobile, dyslipidemia	Reduce LDLc and TG, increase HDLc	>30min/day, 5 times/week of aerobic exercise at 70-80% of the heart rate reserve, progressing to 85% of the heart rate reserve, combined with resistance exercise at 75-85% of maximum repetitions.
Limited mobility (disabled, elderly), dyslipidemia	Reduce LDLc and TG, increase HDLc	Increase physical activity as much as feasible, progressing in resistance exercise from 50 to 75% of maximum repetitions in major muscle groups.

References

1. Hawley JA, Hargreaves M, Joyner MJ, Zierath JR. Integrative Biology of Exercise. Cell. 2014;159(4):738-49.
2. Tremblay MS, Colley RC, Saunders TJ, Healy GN, Owen N. Physiological and health implications of a sedentary lifestyle. Appl Physiol Nutr Metab. 2010;35(6):725-40.
3. Organización Mundial de la Salud. Actividad física [*online*]. 2019. [Accessed 4 Jun. 2019]. Available at: https://www.who.int/dietphysicalactivity/pa/es/
4. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985; 100(2): 126-31.

5. Ferguson B. ACSM's Guidelines for Exercise Testing and Prescription 9th Ed. 2014. J Can Chiropr Assoc. 2014;58(3):328.
6. Ortega FB, Ruiz JR, Castillo MJ, Sjöström M. Physical fitness in childhood and adolescence: a powerful marker of health. Int J Obes (Lond). 2007; 32(1): 1-11.
7. Mohrman DE, Heller LJ. Cardiovascular physiology. 9th edition. New York: McGraw-Hill; 2018.
8. Dempsey JA, Blain GM, Amann M. Are type III-IV muscle afferents required for a normal steady-state exercise hyperpnoea in humans? J Physiol. 2014;592(3):463-74.
9. Ball D. Metabolic and endocrine response to exercise: sympathoadrenal integration with skeletal muscle. J Endocrinol. 2015;224(2):R79-95.
10. Havel RJ, Naimark A, Borchgrevink CF. Turnover rate and oxidation of free fatty acids of blood plasma in man during exercise: studies during continuous infusion of palmitate-1-C14. J Clin Invest. 1963; 42(7):1054-63.
11. Van Loon LJ, Greenhaff PL, Constantin-Teodosiu D, Saris WH, Wagenmakers AJ. The effects of increasing exercise intensity on muscle fuel utilisation in humans. J Physiol. 2001; 536(Pt1): 295-304.
12. Scott W, Stevens J, Binder–Macleod SA. Human skeletal muscle fiber type Classifications. Phys Ther. 2001;81(11): 1810–6.
13. Peter JB, Barnard RJ, Edgerton VR, Gillespie CA, Stempel KE. Metabolic profiles of three fiber types of skeletal muscle in guinea pigs and rabbits. Biochemistry. 1972;11(14):262-33.
14. Hardie DG. AMP-activated protein kinase: A key system mediating metabolic responses to exercise. Med Sci Sports Exerc. 2004; 36(1): 28-34.
15. Jäger S, Handschin C, St-Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. Proc Natl Acad Sci USA. 2007;104(29):12017-22.
16. Lin J, Handschin C, Spiegelman BM. Metabolic control through the PGC-1 family of transcription coactivators. Cell Metab. 2005;1(6):361-70.
17. Wideman L, Weltman JY, Hartman ML, Veldhuis JD, Weltman A. Growth hormone release during acute and chronic aerobic and resistance exercise. Sports Med. 2002; 32(15):987-1004.
18. Perrini S, Laviola L, Carreira MC, Cignarelli A, Natalicchio A, Giorgino F. The GH/IGF1 axis and signaling pathways in the muscle and bone: mechanisms underlying age-related skeletal muscle wasting and osteoporosis. J Endocrinol. 2010; 205(3): 201-10.
19. Bodine S, Stitt TN, Gonzalez M, Kline WO, Stover GL, Bauerlein R, et al. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. Nat Cell Biol. 2001; 3(11): 1014-9.
20. Liu Z, Jahn LA, Wei L, Long W, Barrett EJ. Amino acids stimulate translation initiation and protein synthesis through an Akt-independent pathway in human skeletal muscle. J Clin Endocrinol Metab. 2002; 87(12): 5553-8.
21. Léger B, Cartoni R, Praz M, Lamon S, Dériaz O, Crettenand A, et al. Akt signalling through GSK-3beta, mTOR and Foxo1 is involved in human skeletal muscle hypertrophy and atrophy. J Physiol. 2006; 576(Pt 3): 923-33.
22. Janson LW, Tischler ME. The Big Picture: Medical Biochemistry. New York: McGraw-Hill; 2018.
23. Nikkari T, Luukkainen P, Pietinen P, Puska P. Fatty acid composition of serum lipid fractions in relation to gender and quality of dietary Fat. Ann Med. 1995; 27(4): 491-8.
24. Kwiterovich PO Jr. The metabolic pathways of high-density lipoprotein, low-density lipoprotein, and triglycerides: a current review. Am J Cardiol. 2000; 86(12A): 5L-10L.
25. Redgrave TG. Chylomicron metabolism. Biochem Soc Trans. 2004; 32(Pt 1): 79-82.
26. Cladaras C, Hadzopoulou-Cladaras M, Nolte RT, Atkinson D, Zannis VI. The complete sequence and structural analysis of human apolipoprotein B-100: relationship between apoB-100 and apoB-48 forms. EMBO J. 1986; 5(13): 3495-507.
27. Vaisar T. Proteomics investigations of HDL: challenges and promise. Curr Vasc Pharmacol. 2012; 10(4): 410-21.
28. Lewis GF. Determinants of plasma HDL concentrations and reverse cholesterol transport. Curr Opin Cardiol. 2006; 21(4): 345-52.
29. Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA, et al. Harper's Illustrated Biochemistry. 31st edition. New York: McGraw-Hill; 2018.
30. Tall AR. Cholesterol efflux pathways and other potential mechanisms involved in the athero-protective effect of high density lipoproteins. J Intern Med. 2008; 263(3): 256-73.
31. Coyle EF, Jeukendrup AE, Wagenmakers AJ, Saris WH. Fatty acid oxidation is directly regulated by carbohydrate metabolism during exercise. Am J Physiol. 1997; 273(2 Pt 1): E268-75.
32. Horowitz JF, Klein S. Lipid metabolism during endurance exercise. Am J Clin Nutr. 2000; 72(2 Suppl): 558S-63S.
33. Ruegsegger GN, Booth FW. Health Benefits of Exercise. Cold Spring Harb Perspect Med. 2018; 8(7): pii: a029694.
34. Silva RC, Diniz Mde F, Alvim S, Vidigal PG, Fedeli LM, Barreto SM. Physical Activity and Lipid Profile in the ELSA-Brasil Study. Arq Bras Cardiol. 2016;107(1):10-9.
35. Lee DH, de Rezende LFM, Eluf-Neto J, Wu K, Tabung FK, Giovannucci EL. Association of type and intensity of physical activity with plasma biomarkers of inflammation and insulin response. Int J Cancer. 2019;145(2):360-9.
36. Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. Cochrane Database Syst Rev. 2006;(4):CD003817.
37. Fikenzer K, Fikenzer S, Laufs U, Werner C. Effects of endurance training on serum lipids. Vascul Pharmacol. 2018;101: 9-20.

38. Carson V, Ridgers ND, Howard BJ, Winkler EA, Healy GN, Owen N, et al. Light-intensity physical activity and cardiometabolic biomarkers in US adolescents. PLoS One. 2013; 8(8): e71417.
39. Jenkins GP, Evenson KR, Herring AH, Hales D, Stevens J. Cardiometabolic Correlates of Physical Activity and Sedentary Patterns in U.S. Youth. Med Sci Sports Exerc. 2017;49(9): 1826-33.
40. Woudberg NJ, Mendham AE, Katz AA, Goedecke JH, Lecour S. Exercise intervention alters HDL subclass distribution and function in obese women. Lipids Health Dis. 2018; 17(1):232.
41. Sponder M, Campean IA, Dalos D, Emich M, Fritzer-Szekeres M, Litschauer B, et al. Effect of long-term physical activity on PCSK9, high- and low-density lipoprotein cholesterol, and lipoprotein(a) levels: a prospective observational trial. Pol Arch Intern Med. 2017;127(7-8):506-11.
42. Cai M, Zou Z. Effect of aerobic exercise on blood lipid and glucose in obese or overweight adults: A meta-analysis of randomized controlled trials. Obes Res Clin Pract. 2016;10(5):589-602.
43. Millán J, Hernández-Mijares A, Ascaso JF, Blasco M, Brea A, Díaz Á, et al. The real measurement of non-HDL-cholesterol: Atherogenic cholesterol. Clin Investig Arterioscler. 2016; 28(6): 265-70.
44. Price PH, Kaizer AM, Daniels SR, Jenkins TM, Inge TH, Eckel RH. Phisical Activity Improves Lipid and Weight-Loss Outcomes After Metabolic Bariatric Surgery in Adolescents with Severe Obesity. Obesity (Silver Spring). 2019;27(6):989-96.
45. Jones PR, Rajalahti T, Resaland GK, Aadland E, Steene-Johannessen J, Anderssen SA, et al. Associations of PA and sedentary time with lipoprotein subclasses in Norwegian schoolchildren: The Active Smarter Kids (ASK) study. Atherosclerosis. 2019. pii: S0021-9150(19)30447-2.
46. Mendivil CO, Zheng C, Furtado J, Lel J, Sacks FM. Metabolism of very-low-density lipoprotein and low-density lipoprotein containing apolipoprotein C-III and not other small apolipoproteins. Arterioscler Thromb Vasc Biol. 2010;30(2):239-45.
47. Mendivil CO, Rimm EB, Furtado J, Chiuve SE, Sacks FM. Low-density lipoproteins containing apolipoprotein C-III and the risk of coronary heart disease. Circulation. 2011; 124(19):2065-72.
48. Jensen MK, Rimm EB, Furtado JD, Sacks FM. Apolipoprotein C-III as a Potential Modulator of the Association Between HDL-Cholesterol and Incident Coronary Heart Disease. J Am Heart Assoc. 2012; 1(2): pii: jah3-e000232.
49. Koch M, Furtado JD, Jiang GZ, Gray BE, Cai T, Sacks F, et al. Associations of anthropometry and lifestyle factors with HDL subspecies according to apolipoprotein C-III. J Lipid Res. 2017; 58(6):1196-203.
50. Wilson DP, Jacobson TA, Jones PH, Koschinsky ML, McNeal CJ, Nordestgaard BG, et al. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol. 2019; 13(3):374–92.
51. Bermúdez V, Aparicio D, Rojas E, Peñaranda L, Finol F, Acosta L, et al. An elevated level of physical activity is associated with normal lipoprotein(a) levels in individuals from Maracaibo, Venezuela. Am J Ther. 2010;17(3):341-50.
52. Vanhees L, Geladas N, Hansen D, Kouidi E, Niebauer J, Reiner Z, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR. Part II. Eur J Prev Cardiol. 2012;19(5):1005-33.
53. Altena TS, Michaelson JL, Ball SD, Guilford BL, Thomas TR. Lipoprotein subfraction changes after continuous or intermittent exercise training. Med Sci Sports Exerc. 2006; 38(2):367-72.
54. Wood PD, Haskell WL, Blair SN, Williams PT, Krauss RM, Lindgren FT, et al. Increased exercise level plasma lipoprotein concentrations: a one-year, randomized, controlled study in sedentary middle-aged men. Metabolism. 1983;32(1):31-9.
55. Zapata-Lamana R, Cigarroa I, Diaz E, Saavedra C. Resistance exercise improves serum lipids in adult women. Rev Med Chil. 2015;143(3):289-96.
56. Prabhakaran B, Dowling EA, Branch JD, Swain DP, Leutholtz BC. Effect of 14 weeks of resistance training on lipid profile and body fat percentage in premenopausal women. Br J Sports Med. 1999;33(3):190-5.
57. Lira FS, Yamashita AS, Uchida MC, Zanchi NE, Gualano B, Martins E Jr, et al. Low and moderate, rather than high intensity strength exercise induces benefit regarding plasma lipid profile. Diabetol Metab Syndr. 2010;2:31.
58. Sheikholeslami Vatani D, Ahmadi S, Ahmadi Dehrashid K, Gharibi F. Changes in cardiovascular risk factors and inflammatory markers of young, healthy, men after six weeks of moderate or high intensity resistance training. J Sports Med Phys Fitness. 2011; 51(4):695-700.
59. Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. Sports Med. 2014; 44(2):211-21.
60. Shaw I, Shaw BS, Krasilshchikov O. Comparison of aerobic and combined aerobic and resistance training on low-density lipoprotein cholesterol concentrations in men. Cardiovasc J Afr. 2009;20(5):290-5.
61. Hansen D, Niebauer J, Cornelissen V, Barna O, Neunhäuserer D, Stettler C, et al. Exercise Prescription in Patients with Different Combinations of Cardiovascular Disease Risk Factors: A Consensus Statement from the EXPERT Working Group. Sports Med. 2018; 48(8):1781-97.
62. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract. 2017;23(Suppl 2):1-87.