Debates in Lifestyle Therapy

*Pro: Aerobic Physical Activity Lowers LDL*

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National Lipid Association Recommendations – Part 2

**National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2**

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"Contrasting" Physical Activity & Dyslipidemia Recommendations on LDL-C

3 to 4 sessions a week, lasting on average 40 minutes per session, and involving moderate-to-vigorous intensity physical activity

- **PA alone to reduce LDL-C independent of weight loss or dietary therapy**

Primary activity: aerobic exercise  
Intensity: 40-75% aerobic capacity (V02R)  
Frequency: 5 or more days a week  
Duration: 30-60 minutes

* Same as Rx for long-term weight control (≥2000 kcal/wk)

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2013 AHA/ACC Recommendations on physical activity:

They identified 14 studies with data on lipid outcomes, including 10 meta-analyses, and 4 systematic reviews.

- Evidence supporting the use of physical activity alone (i.e., not in combination with other interventions, such as dietary interventions or weight loss) versus no physical activity or other type of intervention for improvements in selected blood lipids (HDL–C, LDL–C, triglycerides, and non-HDL–C)

Among adults, aerobic physical activity, as compared to control interventions, reduces LDL–C 3.0 to 6.0 mg/dL on average.

Among adults, resistance training, as compared to control interventions, reduces LDL–C, TG, and non-HDL–C by 6 mg/dL to 9 mg/dL on average and has no effect on HDL–C

In general, advise adults to engage in aerobic physical activity to reduce LDL–C and non-HDL–C: 3 to 4 sessions a week, lasting on average 40 minutes per session, and involving moderate-to-vigorous intensity physical activity.
Cholesterol is not an exercise energy substrate

Oxidative Fuels for Exercise

% of maximal oxygen uptake
**LDL-C and Physical Activity**

Few controlled exercise trials have been conducted in subjects with dyslipidemia, with most evaluating individuals with normal or modestly elevated TG and/or LDL-C.

An often-quoted meta-analysis (of 13 studies) found a non-significant decrease of <1% in LDL-C, independent of changes in body weight. (Kelly 2005)

This analysis included a wide range of training modalities (running, swimming, stationary cycling, dance) and an average training stimulus of ~40 min/session, 3.9 times a week at the higher end of the range of what is considered moderate intensity exercise.

✓ This volume of exercise, ~1600 to 1800 kcal/week, is insufficient by current NLA & ACSM recommendations (≥2000 kcal/week) to demonstrate meaningful reductions in LDL-C.

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**LDL-C response to physical activity (NLA Review)**

Exercise programs have the best chance of reducing LDL-C when there is associated body fat reduction.

Most studies evaluating the total-C and/or LDL-C response to exercise training have found minimal to moderate decreases with sufficient exercise volume. Many studies have used an insufficient volume of exercise or energy expenditure, or failed to account for the effects of other variables such as changes in fat mass, plasma volume, dietary habits, or seasonal variation in cholesterol and lipoproteins.

✓ When changes in LDL-C and total-C have been reported, they are often associated with exercise training programs in which participants expended considerable more than 1200 kcal/week. (Durstine 2001)
The recommendations for accumulating sufficient physical activity to lower body fat and LDL-C differ from the more general public health PA guidelines. (Haskell ACSM/AHA 2007).

These guidelines recommend that all healthy adults aged 18 to 65 years should engage in moderate intensity aerobic (cardiorespiratory endurance) physical activity for a minimum of 30 min on 5 days each week (i.e., ≥150 min per week), or vigorous intensity aerobic physical activity for a minimum of 20 min on 3 days each week.

Combinations of moderate and vigorous intensity activity may be performed to meet this recommendation. The weekly volume of physical activity required to lower LDL-C and body weight is greater, i.e., ≥2000 kcal/week, which generally requires 200-300 min/week of moderate or higher intensity physical activity. (IAS, ACSM, ACE, NLA)

A greater amount of physical activity necessary for reducing LDL-C was also recommended by the 2008 Physical Activity Guidelines Advisory Committee. (Haskell HHS 2008) Thus, for management of body weight and LDL-C, the NLA recommendations are as follow:

- **Primary activity**: aerobic exercise
- **Intensity**: 40-75% aerobic capacity (oxygen uptake reserve)
- **Frequency**: 5 or more days a week
- **Duration**: 30-60 min per session
- **200-300 min/week of moderate or higher intensity physical activity (≥2000 kcal/week).**
Endurance exercise programs producing this level of caloric expenditure most effective at lowering total-C and LDL-C in previously untrained individuals, since trained individuals do not seem to respond, even with extreme increases in training volume.

✓ On average, the volume of exercise training associated with body fat loss (200-300 min per week of moderate intensity activity) will reduce LDL-C by 4 to 7%. *(Durstine 2001, Leon 2001)*

**The LDL-C response to exercise training appears to be greatest (> 7% red.) with higher baseline LDL-C, greater total energy expenditure of the exercise program, and more loss of fat mass.*

Example Graduated Weekly Exercise Energy Expenditures
(assumes 160- to 180-pound body weight; heavier patients expend more energy)

Protocol A (600-800 kcal/wk)
Monday, Wednesday, Friday: Walk 2 miles/day = 600 kcal*
Sunday: 20 min of low-level stationary cycling = 100 kcal

Protocol B (1,000-1,200 kcal/wk)
Monday, Wednesday, Friday: Walk 2 miles/day = 600 kcal
Tuesday: Walk 3 miles/day = 300 kcal
Sunday: Nine holes of golf or 30 minutes of singles tennis = 300 kcal

Protocol C (1,500-1,800 kcal/wk)
Monday, Wednesday, Friday: Walk 3 miles/day = 900 kcal
Tuesday & Thursday: 30 min of cycling (50% max VO2) = 300 kcal
Sunday: 60 min of singles tennis plus 2-mile walk = 500 kcal

Protocol D (2,000+ kcal/wk)
5 days a week average 300 kcal workout (e.g., 30 to 45-minute sustained aerobic session) = 1500 kcal;
1 day/week perform long, slow distance workout (e.g., two-hour moderate-to fast pace variable-terrain walk) = 600+ kcal
*walking at moderate pace (3.5-3.5mph)

LaForge, Lipid Spin, Summer 2014

Putative Mechanisms for Exercise Training Induced Changes in Lipids and Lipoproteins

- Lipoprotein lipase activity and LDL-R gene expression
- Total body adiposity
- PCSK9 modulation ??
- Nuclear receptor activation, e.g., PPAR α, δ, γ, ERRα
- NEFA oxidation
- Alterations in CETP and LCAT
- Alterations in LDL-C subspecies, e.g. increased particle size
- Intramuscular TG stores
- Net balance of VLDL-TG adding and removal
- VLDL-TG clearance rate
Exercise and TG

✓ The magnitudes of the decreases in plasma TG concentration after a single exercise session before and after training are similar, i.e., 15 to 50%.

✓ These observations suggest that chronic exercise, if not accompanied by reduced adiposity, does not have a sustained effect on the plasma TG concentration beyond that attributed to the repeated effects of acute exercise.

Hence exercise should be performed on a regular and uninterrupted basis to maintain a lower TG concentration. (Magkos 2009)

The magnitudes of changes in lipid and lipoprotein levels depend on a number of variables (see below) beyond the type, frequency, intensity, and duration of physical activity. These factors are important for clinicians to be aware of because they may influence, or interact with, the effects of exercise and contribute to variability in responses.

- Gender and menopausal status
- Race/ethnicity
- Nature and severity of the lipid/lipoprotein disorder
- Accompanying changes in diet (including alcohol intake)
- Changes in body fat
- Plasma volume changes
- Genetic factors (e.g., apo E and C isoforms, PCSK9)
- Seasonal and diurnal changes in lipoprotein lipid levels
My take on the AHA/ACC Recommendations on physical activity and LDL-C: (Nov. 13, 2013 NLA website)

“The AHA/ACC’s PA’s recommendation on PA and LDL-C serves no practical purpose from a patient recommendation and public health standpoint because virtually no clinician would advise using physical activity programming for managing dyslipidemia without some emphasis on fat weight loss and instituting dietary changes - certainly not in a lipid clinic. This is a misleading recommendation regarding the inference of using PA ALONE for managing LDL-C and serves no one from a practical patient recommendation standpoint.”

R. LaForge
Mechanisms?

Weight loss via a hypoenergetic diet and increased physical activity leads to a favorable lipid profile in overweight/obese women. The decrease in plasma TG, TC, and LDL-C can be explained in part by the increased gene expression of LPL and LDL-R.


**Impact of progressive resistance training on lipids and lipoproteins in adults: another look at a meta-analysis using prediction intervals.**

**OBJECTIVE:** Given recently developed prediction intervals (PIs) in which a random mean effect for a new study is estimated from meta-analytic data, we used the results from our previously published meta-analysis to calculate PIs for changes in lipids and lipoproteins as a result of progressive resistance training (PRT) in adults.

**METHODS:** Twenty-nine studies representing 1329 men and women (676 exercise, 653 control) were included. The primary outcomes included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), ratio of total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). Separate PIs (95%) were calculated for all lipids and lipoproteins.

**RESULTS:** The expected outcomes of a new study on this topic were as follows: TC, -5.5 (-24.0, 13.0) mg/dl; HDL-C, 0.7 (-8.9, 10.4) mg/dl; TC/HDL-C, -0.5 (-1.8, 0.8); non-HDL-C, -8.7 (-35.7, 18.3) mg/dl; LDL-C, -6.1 (-28.9, 16.4) mg/dl; TG, -8.1 (-34.5, 18.3) mg/dl.

**CONCLUSIONS:** Caution may be warranted in recommending that PRT improves TC, HDL-C, TC/HDL-C, non-HDL-C, LDL-C, and TG in adults. Future research should continue to examine the effects of PRT on lipids and lipoproteins in adults so as to determine optimal programs and populations in which PRT may have a positive effect.
Conclusions

Caution may be warranted in recommending that PRT improves TC, HDL-C, TC/HDL-C, non-HDL-C, LDL-C, and TG in adults.

Kelley GA 2009

For most individuals, the positive effects of regular exercise are exerted on blood lipids at low training volumes and accrue so that noticeable differences frequently occur with weekly energy expenditures of 1200 to 2200 kcal/wk.

✓ It appears that weekly exercise caloric expenditures that meet or exceed the higher end of this range are more likely to produce the desired lipid changes. This training volume threshold is slightly greater than what has been suggested previously for favorably altering blood lipids.

Quality and quantity of physical activity required to generate favorable lipid and lipoprotein changes

In order to reduce LDL-C, the quantity of physical activity needed is consistent with recommendations for long-term weight control (200-300 min/week of moderate intensity physical activity or ≥2000 kcal/week), which may be accumulated in repeated bouts of exercise of at least 10 min each.20

Use of well-engineered pedometers for recording walking step counts has been successfully employed in outpatient clinic settings as a means of tracking activity for managing dyslipidemia and promoting weight loss. In general, the amount of walking required to produce weight loss is ≥40,000 steps/week (beyond steps/activities of daily living), which is approximately equivalent to 2000 kcal/week energy expenditure (based on ~2000 steps/mile and ~100 kcal gross energy cost/mile).21,240

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TC & LDL and Exercise Training


Differential Effects of Aerobic Exercise, Resistance Training and Combined Exercise Modalities on Cholesterol and the Lipid Profile: Review, Synthesis and Recommendations

This review assesses the evidence from 13 published investigations and two review articles that have addressed the effects of aerobic exercise, resistance training and combined aerobic and resistance training on cholesterol levels and the lipid profile.

✓ The dose–response relationship between the lipid profile and energy expenditure seems to transcend the mode of exercise.

✓ Increases in caloric expenditure associated with aerobic exercise (via increased intensity and/or duration) have been shown to positively influence lipoprotein lipase activity, HDL cholesterol levels and the lipid profile [Kraus 2002] 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 low-repetition training) [Lira 2010, Fett 2009].

Reducing diet and/or exercise training decreases the lipid and lipoprotein risk factors of moderately obese women.

This study was designed to measure the influence of diet, exercise or both on serum lipids and lipoproteins in obese women.

METHODS: Obese subjects were randomly divided into one of four groups: diet alone (1,200-1,300 kcal/day, NCEP, Step I), exercise alone (five 45 minute sessions per week at 78.4+/-0.5% maximum heart rate), exercise and diet, and controls.

RESULTS: Cross-sectional comparisons at baseline showed obese subjects had significantly higher total cholesterol, triacylglycerol, total cholesterol/HDL-C and LDL-C values and lower HDL-C values. Prospective results showed that subjects in diet and exercise and diet lost 7.8+/-0.7 and 8.1+/-0.6 kg body mass, with no significant change for exercise relative to control. Serum cholesterol and triacylglycerol improved in both diet and in exercise and diet after 12 weeks of intervention, and was most strongly related to weight loss.

CONCLUSION: Weight loss is the most effective means of reducing lipid and lipoprotein risk factors in obese women.
Exercise and TG

The circulating TG level frequently declines with exercise training to a degree that depends upon several factors, including baseline value, exercise energy expenditure, and how soon TG values are measured after the last exercise session. Higher baseline values, greater energy expenditure and measurement closer to the time of the last exercise bout are all associated with larger reductions. In intervention trials, fasting TG have been lowered by 4 to 37% (approximate median reduction of 24%).244 TG generally decline immediately after a session of high-volume endurance exercise, and remain lower for up to 48 hours after the session.

The magnitudes of the decreases in plasma TG concentration after a single exercise session before and after training are similar, i.e., 15 to 50%. These observations suggest that chronic exercise, if not accompanied by reduced adiposity, does not have a sustained effect on the plasma TG concentration beyond that attributed to the repeated effects of acute exercise; hence exercise should be performed on a regular and uninterrupted basis to maintain a lower TG concentration.245 Changes in TG are highly correlated with changes in VLDL-C concentration.9,151 Thus, exercise training can help to lower the atherogenic cholesterol level by reducing VLDL-C, one of the two main components of non-HDL-C (non-HDL-C is mainly comprised of LDL-C and VLDL-C).

Nov. 2015 UPDATE (on file)

Iran Red Crescent Med J. 2015 April; 17(4): e26321. DOI: 10.5812/ircmj.17(4)2015.26321
Published online 2015 April 25. Research Article
The Effect of Regular Aerobic Exercise on Reverse Cholesterol Transport A1 and Apo Lipoprotein A-I Gene Expression in Inactive Women
Asghar Tofighi 1; Fatemeh Rahmani 2; Bahram Jamali Qarakhanlou 3; Solmaz Babaei

PLOS ONE | DOI:10.1371/journal.pone.0138853 October 21, 2015
High Intensity Interval- vs Moderate Intensity- Training for Improving Cardiometabolic Health in Overweight or Obese Males: A Randomized Controlled Trial
Gordon Fisher1,2,4*, Andrew W. Brown2,3 et.al.

Effect of resistance training on C-reactive protein, blood glucose and lipid profile in older women with differing levels of RT experience

Physical activity, sedentary behavior time and lipid levels in the Observation of Cardiovascular Risk Factors in Luxembourg study Georgina E Crichton and Ala’a Alkerwi. Lipids in Health and Disease (2015) 14:87
Update Continued.


Exercise/Physical Activity Questions

1. Based on known therapeutic effects of habitual physical activity, what would be the criteria (exercise intensity, duration, and frequency) for physical activity counseling for patients with dyslipidemia (i.e., 2013 International Atherosclerosis Society Global Recommendations for the Management of Dyslipidemia and the 2013 American College of Sports Medicine’s Guidelines for Exercise Testing and Prescription regarding the physical activity recommendations for persons with dyslipidemia)?

2. Does this ExRx differ in #1 for those adults who do not have dyslipidemia?

Answers on following slide
1. **ANSWER**

   Exercise intensity 40-75% aerobic capacity, 30-60+ minutes, ≥ 5 days/wk

   *This amount of physical activity is consistent with recommendations for long-term weight control: 200-300 minutes/wk mod. PA or ≥ 2,000 kcal/wk. This volume may be accumulated with repeated exercise bouts of ≥ 10 minutes.*

2. **ANSWER**


   2008 CDC: To promote and maintain health, all healthy adults aged 18 to 65 yr need moderate-intensity aerobic (endurance) physical activity for a minimum of 30 min on five days each week or vigorous-intensity aerobic physical activity for a minimum of 20 min on three days each week. (I (A)] Combinations of moderate- and vigorous-intensity activity can be performed to meet this recommendation

3. **Does the data suggest which specific type of physical activity training (aerobic vs. resistance training) is better for: a) ASCVD risk reduction; b) improvement in lipids; c) weight maintenance (or weight loss)?**

   **ANSWER:**

   Yes, in general those activities that exceed 1500-2000 Kcal per week are best for improving the overall lipid profile (e.g., reduction in LDL-C) and weight loss. Aerobic exercise is the preferred mode of physical activity in all consensus guidelines. Resistance exercise can and should play a supportive role. For ASCVD risk reduction a somewhat lower weekly energy expenditure is required – exercise (CDC 2008)
4. Does exercise decrease fasting triglycerides and/or hypertriglyceridemia?

ANSWER:

Depending on a number of variables TG can decrease from 4–37% (approximate mean change of 24%). Trejo-Gutierrez (2007)

**Variables influencing TG response to acute exercise and exercise training**

- Baseline TG
- Session energy expenditure
- Exercise intensity
- Apo C and E genotypes
- Fatty acid transporters
- VLDL clearance
- Muscle TAG stores
- Hepatic and lipoprotein lipase
- Post-prandial influences
- Gender *

* Women use more intra-muscular TAG as energy source during moderate-intensity exercise than men, possibly because they have higher baseline (i.e., resting) intra-muscular TAG content
5. How much exercise is required to increase HDL-C? Is there a consensus on this?

ANSWER:

There is a marked variability of HDL-C response between individuals with a small 3-5% increase in HDL-C.

6. Does resistance exercise training favorably alter the lipid profile – particularly in those with hyperlipidemia, i.e., elevated LDL-C and nonHDL-C?

ANSWER:

There is little if any reduction in LDL-C or nonHDL-C primarily because of inadequate exercise energy expenditure in most typical resistance exercise training sessions. That said, the greater number of muscle contractions (# of RT exercise reps and sets) can increase RT session energy expenditure and thus have a greater favorable impact on the lipid profile (TC, LDL, nonHDL, TG).
Does a single exercise session, eg. 45 minutes affect post prandial triglycerides and triglyceride-rich lipoproteins?

ANSWER

Yes. Over the past 15 years, there has been abundant research supporting the finding that sufficient exercise timed anywhere from one to 12 hours before a fat-rich meal will reduce postprandial lipemia by 25 to 40%. This is important because a reduction in PPL also is associated with a reduced exposure to atherogenic triglyceride-rich particles which include chylomicron and VLDL remnants.
8. Does physical activity have an impact on reducing nonHDL-C?

ANSWER: There is very little research that exclusively evaluated the response of nonHDL to exercise training. However at least one meta-analysis that retrospectively looked at nonHDL responsivity to walking exercise programs and found a decrease of approximately 6 mg/dL in response to training programs between 10 and 104 weeks. The same investigators also found significant reductions in nonHDL of ~8 mg/dL after resistance exercise training. The greatest nonHDL-C response apparently is observed when dietary and exercise interventions are combined.

AHA/ACC Guideline PA Literature Review


The threshold of energy that needs to be expended during continuous endurance exercise in order to evoke the metabolic changes in VLDL metabolism leading to hypotriacylglycerolemia lies near or above 500–600 kcal, but it is apparently much lower for resistance exercise and perhaps also for high-intensity aerobic interval exercise.

Recently, it has become apparent that the negative energy balance induced by exercise is an essential factor for exercise-induced hypotriacylglycerolemia to manifest.

Faidon Magkos  Prog Lipid Res, 2009
The mechanism of the exercise-induced reduction in serum triglyceride concentration is not clear. The decrease cannot be attributed solely to weight reduction, although this factor probably contributes to the change in some subjects.

Circulation 60, No. 6, 1979: p1220.

Low-intensity exercise equivalent to walking 11 miles/wk appears to reduce triglycerides by 25% in overweight/mildly obese, sedentary, middle-aged men and postmenopausal women (the percentage decrease was the same for normal and hypertriglyceridemic individuals; data not shown)
Physical Activity Guidelines Advisory Committee Report, 2008

- The response of serum lipoproteins to changes in habitual physical activity have been well studied. In general, both HDL cholesterol and serum TG reproducibly and favorably respond to changes in habitual physical activity, with increases in HDL cholesterol and decreases in serum TG, mostly related to the volume of exercise training and responding with threshold volumes in the range of 7 to 15 miles per week of regular exercise (equating to an approximate 600 to 800 MET-minutes or 700-1500 kcal/wk).

- LDL-C is generally found not to be responsive to exercise training interventions. However, in the few circumstances when LDL has been observed to be modulated by exercise, it requires approximately 12 MET-hours per week (~4 hours/wk) of exercise to favorably influence LDL.

- Recently, studies of the modulation of fractionated lipoproteins with exercise training have shown that HDL, TG, and LDL size and number are favorably modulated in a dose-response fashion to exercise training related to training volume and that 800 MET-minutes of exercise per week was required for an effect different from that of a sedentary control group, whose LDL parameters tended to worsen over time in the absence of other lifestyle changes (Slentz 2007).