Lifestyle Changes and HDL

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## Select Lifestyle Interventions and HDL-C

<table>
<thead>
<tr>
<th>Therapeutic Intervention</th>
<th>Increase in HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic exercise</td>
<td>5-10%</td>
</tr>
<tr>
<td>Tobacco cessation</td>
<td>5-10%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0.35 mg/dL per kg weight lost</td>
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<tr>
<td>Alcohol consumption</td>
<td>5-15%</td>
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<tr>
<td>Dietary factors (n-3, n-6 PUFA, MUFA)</td>
<td>0-5%</td>
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</tbody>
</table>

PUFA = polyunsaturated fatty acids  
MUFA = monounsaturated fatty acids

Reverse Cholesterol Transport and HDL Metabolism: Lipid Efflux

Reverse Cholesterol Transport and HDL Metabolism: Lipid Efflux

Excess cholesterol stored in macrophages in arterial walls contributes to atherogenesis. In reverse cholesterol transport, cholesterol ester hydrolase (CEH) releases free cholesterol from cholesterol ester (CE) stores.

The ABCA1 transporter facilitates the efflux of cellular cholesterol to lipid-poor apo A-I to form nascent pre-β-HDL. Apo A-I is produced in the liver and intestine, and is also generated upon catabolism of mature HDL.
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Lecithin-cholesterol acyltransferase (LCAT) esterifies free cholesterol in nascent pre-β-HDL to cholesterol ester, converting nascent β-HDL to mature α-HDL (HDL₃ and HDL₄).

Reverse Cholesterol Transport and HDL Metabolism: Lipid Efflux

Reverse Cholesterol Transport and HDL Metabolism: Cholesterol Uptake

Reverse Cholesterol Transport and HDL Metabolism: Cholesterol Uptake

Exercise and HDL-C

• Frequent aerobic exercise: ↑HDL-C by ~5% as early as 2 months from start of regular exercise in sedentary, otherwise healthy people.

• To increase HDL-C levels optimally:
  – 5 x 30-minutes brisk aerobic exercise/week
  – Total duration of exercise >120 minutes per week is strongest determinant of increased HDL-C levels.

Exercise and HDL-C: Clinical Trials

Exercise and HDL-C: Clinical Trials

- Meta-analysis of 25 clinical trials
- Mean net change in HDL-C level was modest (+2.53 mg/dL; P.001).
- Threshold exercise for increasing HDL-C level was >900 kcal of energy expenditure or 120 minutes of exercise per week.
- Every 10-minutes of exercise per session was associated with an approximately 1.4-mg/dL increase in HDL-C.
- No significant association between exercise frequency or intensity.
- Subjects with a BMI < 28 and TC ≥ 220 mg/dL experienced an approximately 2.1-mg/dL larger increase in HDL-C level than those with a BMI ≥28 and TC < 220 mg/dL.

**Effects of Chronic Exercise on HDL Level**

- Dose-response relationship between aerobic exercise (running) and HDL levels in men:

<table>
<thead>
<tr>
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<th>HDL (mg/dL)</th>
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<tbody>
<tr>
<td>Nonrunner</td>
<td>47.3</td>
</tr>
<tr>
<td>5 mi/wk (n = 685)</td>
<td>48.7</td>
</tr>
<tr>
<td>9 mi/wk (n = 512)</td>
<td>50.6*</td>
</tr>
<tr>
<td>17 mi/wk (n = 602)</td>
<td>53.0**</td>
</tr>
<tr>
<td>31 mi/wk (n = 396)</td>
<td>56.3***</td>
</tr>
</tbody>
</table>

*P < 0.001 vs nonrunners; †P < 0.01 vs nonrunners and 5 mi/wk;
‡P < 0.01 vs all other groups

Exercise and HDL

- Increases pre-β HDL
- Promotes reverse cholesterol transport
- Upregulates LPL
- Increases atheroprotective HDL subpopulations

Tobacco and HDL-C

- Tobacco, smoked and smokeless, reduces HDL-C levels.
- Tobacco smoke also is a source of oxidative stress that can lead to HDL dysfunction.
- Meta-analysis: HDL-C levels increase by approximately 4 mg/dL following smoking cessation without significant changes in LDL-C, TC, or TG.
- Tobacco cessation should be aggressively promoted via a multidisciplinary approach of counseling and pharmacological agents, as appropriate.

Smoking Cessation Increases HDL-C

Summary, 1 year clinical trial of 5 different smoking cessation regimens

HDL-C and "Passive Smoking"

- In a twin study, twins with a family history of CVD had lipid profiles measured.
- Twins exposed to passive smoking had a 3 mg/dL lower HDL than twins not exposed (45 mg/dL vs 48 mg/dL).

Tobacco and HDL-C

• Increases LCAT
• Promotes reverse cholesterol transport
• Decreases CETP

NHANES II: BMI and HDL-C

Weight Loss and HDL-C

• Weight loss generally increases HDL-C levels in overweight or obese patients.
• During active weight loss, HDL-C levels decrease slightly; however, when a stable weight is achieved, HDL-C levels increase by 0.35 mg/dL per kilogram lost.
• Weight loss, achieved by lifestyle modifications with or without pharmacological support, has been associated with improved cardiometabolic risk factors.
• Overweight and obese should aim to achieve a BMI<25 (<24 if Asian), at a rate of 2 kg/month.

Caloric Restriction Acutely Lowers HDL-C Level

• Trials of very-low-calorie diets show that HDL-C levels decrease by 2–12 mg/dL during acute caloric restriction.

• After 12 wks, HDL-C returned to pretreatment range, and this trend was still apparent at 1 yr.

• Therefore, benefits of weight-loss programs should not be assessed during acute caloric restriction.

Meta-Analysis of Atkins’ vs. Low Fat Diet

• 5 dietary comparison trials met criteria
  – Low carbohydrate arm
    • No specific instruction on calorie restriction
    • Maximum intake of carbohydrate = 60 gm
  – Low Fat arm
    • <30% of calories from fat
    • Calorie restriction 500-1,000 kcal/d

• At 6 months: low carb produced more weight loss but at 12 months, no differences seen

Weighted Mean Differences In LDL-C After 6 (A) And 12 (B) Months Of Follow-up

Weighted Mean Differences In HDL-C After 6 (A) And 12 (B) Months Of Follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted Mean Difference, mg/dL (95% CI)</th>
<th>% Weight Favors Low Carb</th>
<th>% Weight Favors Low Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foster et al., 2003</td>
<td>7.0 (2.7 to 11.2)</td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td>Samaha et al., 2003</td>
<td>1.2 (-0.8 to 3.1)</td>
<td>30.2</td>
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<tr>
<td>Yancy et al., 2004</td>
<td>7.0 (3.1 to 12.0)</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>Dansinger et al., 2005</td>
<td>5.4 (2.3 to 8.5)</td>
<td>26.6</td>
<td></td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>4.6 (1.5 to 8.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity P = .01 Inconsistency $I^2 = 75%$ (95% UI, 29%-91%)</td>
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<td>Foster et al., 2003</td>
<td>7.0 (2.7 to 11.2)</td>
<td>27.7</td>
<td></td>
</tr>
<tr>
<td>Stern et al., 2004</td>
<td>0.0 (-2.3 to 2.3)</td>
<td>37.8</td>
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<tr>
<td>Dansinger et al., 2005</td>
<td>3.9 (0.8 to 7.0)</td>
<td>34.5</td>
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<tr>
<td>Overall (95% CI)</td>
<td>3.1 (-0.8 to 7.0)</td>
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<td></td>
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<tr>
<td>Heterogeneity P = .01 Inconsistency $I^2 = 79%$ (95% UI, 31%-93%)</td>
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Besides Weight Loss

- Low Carb diets
  - Significant -2.4 mm Hg systolic and -3.7 mm Hg diastolic improvements in BP at 6 months dissipated to nonsig changes of -1.3 and -.04 mm in trials lasting 12 months
  - Significant 22 mg/dL lower TG at 6 months that was sustained at 31 mg/dL in trials lasting 12 months

...However..

• Low Fat diets significantly lowered LDL-C by 5.4 mg/dL at 6 months and this benefit was sustained in trials lasting 12 months (-(-7.7 mg/dL)

• Low Fat, calorie restricted diets also raised HDL-C by 4.6 mg/dL at 6 months; although improvement was also seen in trials lasting 12 months (3.1 mg/dL), the results were not statistically significant

Mediterranean Diet

A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)

- Med diet, EVOO: hazard ratio, 0.70 (95% CI, 0.53–0.91); P=0.009
- Med diet, nuts: hazard ratio, 0.70 (95% CI, 0.53–0.94); P=0.02

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Years</th>
<th>Control diet</th>
<th>Med diet, EVOO</th>
<th>Med diet, nuts</th>
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</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td></td>
<td>2450</td>
<td>2268</td>
<td>2020</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2268</td>
<td>2486</td>
<td>2320</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2020</td>
<td>2320</td>
<td>2093</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1583</td>
<td>1987</td>
<td>1657</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1268</td>
<td>1687</td>
<td>1389</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>946</td>
<td>1310</td>
<td>1031</td>
</tr>
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</table>

Lipoprotein Changes After One Year of Lifestyle Intervention

Men

Women

Weight Loss and HDL

- Increases LCAT
- Upregulates LPL
- Promotes reverse cholesterol transport

Sleep Duration: Another Variable

HDL –C levels according to self reported duration of sleep

Alcohol Consumption

- Intake of moderate amounts of alcohol (30-40 g [1-3 drinks] per day) ↑HDL-C and is independently associated with ↓risk of CHD.
- The link between moderate alcohol consumption and ↓cardiovascular risk may reflect the “sick quitter” effect.
- Ingestion of 30-40 g of alcohol per day for 3 weeks ↑HDL-C levels by as much as 12%, irrespective of the type of alcohol.
- Current guidelines advise no more than 2 drinks per day for men and no more than 1 drink per day for women.
- Persons who do not drink should not be encouraged to initiate regular alcohol consumption.

Clinical Trials of Alcohol Intake and HDL-C

• Meta analysis of 42 intervention trials

• 4 week daily ingestion of 40g/d ethanol increased HDL-C 5 mg/dL

Alcohol and HDL

- Increases ABCA1
- Increases Apo A-1
- Increases paraoxonase
- Decreases CETP activity

Dietary Fat Type and HDL-C

• Diets rich in saturated FA’s and trans-FA’s can ↑HDL-C but also ↑LDL-C and HDL-induced expression of proinflammatory endothelial CAM’s.

• Substituting dietary saturated FA’s and trans-FA’s with monounsaturated fatty acids and polyunsaturated FA’s ↓LDL-C: HDL-C ratio.

• Ingestion of n-3 polyunsaturated FA’s has been associated with ↑HDL-C and cardiovascular benefits; however, studies of the cardiovascular effects of n-6 polyunsaturated FA’s are lacking.

• Replacing saturated FA’s and trans-FA’s with low–glycemic index carbohydrates may improve HDL-C profile, but the data are limited.

• Patients should be advised to replace dietary saturated FA’s and trans-FA’s with monounsaturated and polyunsaturated FA’s sources such as plant oils (olive, canola, soy, mustard, flaxseed), nuts (almonds, peanuts, walnuts, pecans), and marine foods (salmon, tuna, mackerel, marine oils).
Soy Protein

- Meta-analysis of controlled studies assessing ≤65 (median 30)g of daily soy protein intake
  - HDL-C ↑3.2% (p < 0.007) with soy vs control

Other Supplements/Diets Associated with Modest Increase in HDL-C

- Black tea
- Strawberry powder
- Mediterranean diet
- Sesame seed oil
- Soybean oil
- Low-glycemic index products
- High-fat diet
Reported Lack of Association with Changes in HDL-C

- Fruit/vegetable intake
- Probiotics
- Resveratrol
- Soluble fiber
- Brown rice
- Eggs
- Green tea
Under Normal Circumstances, HDL is Anti-Inflammatory

- Inhibition of MCP-1 expression by endothelial cells
- Inhibition of LDL oxidation
- Lipid efflux
- Lipid-laden macrophage
- To liver
Inflammatory/Anti-Inflammatory HDL-C

Results: Characterization

MCA

1.0

NA | LDL | LDL+HDL

- Green: Anti-inflammatory
- Pink: Pro-inflammatory

www.lipid.org
Effect of Intensive Lifestyle Intervention On HDL Anti-Inflammatory Function

- **Subjects:**
  - Metabolic Syndrome, n=22
  - Mean BMI = 33

- **Diet:**
  - High-fiber grains (≥5 serv/d)
  - Vegetables (≥4 serv/d)
  - Fruits (≥3 serv/d)
  - Protein: Plant, fish based
  - Fats: Minimal saturated

- **Supervised Exercise:**
  - 45-60 minute walk/day

- **Follow-up at 21 days:**
  - BMI: 33.1 → 32.1
  - LDL-C: 126 → 93.8
  - HDL-C: 43.7 → 39.4
  - TG: 219 → 155

Effect of Dietary Fat Type on HDL Anti-Inflammatory Function

Expression of ICAM-1 (A) and VCAM-1 (B) in human endothelial cells after incubation with HDL isolated following meal with polyunsaturated or saturated fat.

Summary

• Changes in lifestyle make significant, but relatively modest changes in HDL-C, however may contribute to greater changes in CVD risk.
• Increased HDL-C reflects only part of the benefits of lifestyle change.
• Simultaneous lifestyle improvements may yield greater HDL-C increases.
• Lifestyle changes may also favorably impact HDL functionality.