Changes in HDL Particle Traits in Response to Regular Exercise: Results from the HERITAGE Family Study

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FINANCIAL DISCLOSURE:
No relevant financial relationship exists
BACKGROUND

• Plasma HDL particles (HDL-P) are highly heterogeneous in their physiochemical properties, metabolism, and biological functions (Kontush and Chapman. Pharmacol Rev. 2006; 58(3):342-374)
  – Plasma HDL-C concentration does not necessarily represent the subfraction(s) that play the most important roles in cardioprotection

• Refined analyses of lipoprotein subfractions may lead to further improvements in CVD risk evaluation and in the identification of appropriate targets for therapeutic intervention in individual patients (Krauss RM. Curr Opin Lipidol 2010;21:305-11. Mackey et al. J Am Coll Cardiol 2012;60:508-16)

• Thus, there is a need to investigate other features of HDL and how they respond to various preventive interventions
• On average endurance exercise training increases plasma HDL-C levels in both men and women
  – Average increases range from 2 to 8 mg/dl, or 4 to 22% (Durstine JL et al. *Sports Medicine*. 2001;31(15):1033-1062)

• The effect of regular endurance exercise on the concentration and size of HDL-P subfractions has been less well studied
The purpose of our study was to examine the effects of regular endurance exercise on HDL-P traits in the HERITAGE Family Study.
METHODS
• Subjects recruited and exercise-trained at four Clinical Centers:
  – Indiana Univ., Laval Univ., Univ. of Minnesota, Univ. of Texas

• Subjects were sedentary, but otherwise healthy at baseline
  – Parents were <65 yrs, Offspring ranged from 17-41 yrs

• Standardized, supervised exercise training program:
  – Subjects exercised at 55-75% of VO₂max for 30-50 min three times/wk for 20 weeks on computer controlled cycle ergometers

• 469 White subjects and 246 Black subjects completed the exercise training program (100% compliance) and had available data for the present study
HDL-P TRAITS

• Baseline and post-exercise training plasma samples were measured via NMR spectroscopy (LipoScience, Inc.)

• Change ($\Delta$) was calculated as post-training value – baseline value and examined in the following HDL-P traits:
  — Concentration (µmol/L) of Total, Large, Medium, and Small HDL-P
  — Mean HDL-P size (nm)
  — Cholesterol-per-HDL-P: calculated by dividing HDL-C (mmol/L) by total HDL-P (mmol/L)
• Baseline and post-training values for HDL-P traits were compared using paired t-tests
  – Analyses were run in the total sample and stratified by race and sex

• ANOVA used to compare mean changes in HDL-P traits across combined race, sex groups

• Familial aggregation tests:
  – ANCOVA was used to compare the between-family to the within-family variances for HDL-P trait responses controlling for age, sex, and baseline BMI and baseline trait value.
RESULTS
## Basic Characteristics of Total Sample

<table>
<thead>
<tr>
<th>Trait</th>
<th>Baseline (N=715)</th>
<th>Change (N=695)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>35.2 13.7</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5 5.3</td>
<td>-0.12 0.8</td>
<td>0.0002</td>
</tr>
<tr>
<td>VO₂max (mL/kg/min)</td>
<td>31.3 8.8</td>
<td>5.31 2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>40.7 10.6</td>
<td>1.56 4.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL₂-C (mg/dL)</td>
<td>13.7 7.5</td>
<td>1.08 4.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL₃-C (mg/dL)</td>
<td>27.0 5.3</td>
<td>0.48 4.0</td>
<td>0.002</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>112.2 67.1</td>
<td>-0.02 0.4</td>
<td>0.12</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>114.0 30.9</td>
<td>0.37 14.2</td>
<td>0.50</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>170.8 35.9</td>
<td>0.04 0.4</td>
<td>0.009</td>
</tr>
</tbody>
</table>

p-value indicates significance of the paired t-test between baseline and post-exercise program.
## Changes in HDL-P traits in Total Sample (N=715)

<table>
<thead>
<tr>
<th>Delta HDL-P Trait</th>
<th>Mean</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total HDL-P (µmol/L)</td>
<td>-0.08</td>
<td>3.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Large HDL-P (µmol/L)</td>
<td>0.21</td>
<td>1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medium HDL-P (µmol/L)</td>
<td>-0.17</td>
<td>4.3</td>
<td>0.28</td>
</tr>
<tr>
<td>Small HDL-P (µmol/L)</td>
<td>-0.11</td>
<td>3.9</td>
<td>0.45</td>
</tr>
<tr>
<td>HDL-P size (nm)</td>
<td>0.003</td>
<td>0.3</td>
<td>0.76</td>
</tr>
<tr>
<td>Cholesterol-per-HDL-P</td>
<td>1.49</td>
<td>5.22</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
# Changes in HDL-P traits

## Stratified by Race or Sex

<table>
<thead>
<tr>
<th>HDL-P trait</th>
<th>Whites (N=469)</th>
<th>Blacks (N=246)</th>
<th>Males (N=322)</th>
<th>Females (N=393)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean  SD   p-value</td>
<td>Mean  SD   p-value</td>
<td>Mean  SD   p-value</td>
<td>Mean  SD   p-value</td>
</tr>
<tr>
<td>Total HDL-P</td>
<td>0.10  3.5  0.52</td>
<td>-0.43  3.4  0.053</td>
<td>-0.22&lt;sup&gt;b&lt;/sup&gt;  3.1  0.20</td>
<td>0.04&lt;sup&gt;b&lt;/sup&gt;  3.8  0.85</td>
</tr>
<tr>
<td>Large HDL-P</td>
<td>0.20  1.3  &lt;0.0001</td>
<td>0.22  1.3  &lt;0.0001</td>
<td>0.10&lt;sup&gt;b&lt;/sup&gt;  1.2  0.12</td>
<td>0.29&lt;sup&gt;b&lt;/sup&gt;  1.4  &lt;0.0001</td>
</tr>
<tr>
<td>Medium HDL-P</td>
<td>-0.06  4.4  0.78</td>
<td>-0.40  4.0  0.12</td>
<td>-0.30&lt;sup&gt;b&lt;/sup&gt;  3.8  0.16</td>
<td>-0.07&lt;sup&gt;b&lt;/sup&gt;  4.6  0.75</td>
</tr>
<tr>
<td>Small HDL-P</td>
<td>-0.03&lt;sup&gt;a&lt;/sup&gt;  4.0  0.86</td>
<td>-0.26&lt;sup&gt;a&lt;/sup&gt;  3.6  0.26</td>
<td>-0.02&lt;sup&gt;b&lt;/sup&gt;  3.4  0.91</td>
<td>-0.19&lt;sup&gt;b&lt;/sup&gt;  4.3  0.39</td>
</tr>
<tr>
<td>HDL-P Size</td>
<td>-0.01  0.3  0.48</td>
<td>0.02  0.3  0.14</td>
<td>-0.02  0.3  0.28</td>
<td>0.02  0.3  0.16</td>
</tr>
<tr>
<td>Cholesterol per HDL-P</td>
<td>1.37  5.1  &lt;0.0001</td>
<td>1.74  5.5  &lt;0.0001</td>
<td>1.41&lt;sup&gt;b&lt;/sup&gt;  4.3  &lt;0.0001</td>
<td>1.56  5.9  &lt;0.0001</td>
</tr>
</tbody>
</table>

<sup>a</sup>P=0.047 for mean difference between ethnic groups.  <sup>b</sup>P≤0.001 for mean difference between sexes.
Changes in HDL-P Traits by Race & Sex Groups

**Large HDL-P**

- Black Males: 90
- Black Females: 156
- White Males: 232
- White Females: 237

* P = 0.003 for trait response to regular exercise within group.

**Total HDL-P**

- Black Males: 90
- Black Females: 156
- White Males: 232
- White Females: 237

* P = 0.04 for trait response to regular exercise within group.

a P = 0.03 for mean difference between groups b P = 0.004 for mean difference between groups

**Small HDL-P**

- Black Males: 90
- Black Females: 156
- White Males: 232
- White Females: 237

**HDL-P size**

- Black Males: 90
- Black Females: 156
- White Males: 232
- White Females: 237

* P = 0.006 for trait response to regular exercise within group.

a Mean value significantly different (P<0.03) from all other groups
Familial Aggregation of HDL-P Trait Responses to Regular Exercise

- We found significant evidence of familial aggregation for the exercise-induced changes in HDL-P traits in both races.

<table>
<thead>
<tr>
<th>HERITAGE Whites: N=469, 98 families</th>
<th>HERITAGE Blacks: N=246, 101 families</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delta HDL-P Trait</strong></td>
<td><strong>Delta HDL-P Trait</strong></td>
</tr>
<tr>
<td>F-value</td>
<td>p-value</td>
</tr>
<tr>
<td>Total HDL-P</td>
<td>1.4</td>
</tr>
<tr>
<td>Large HDL-P</td>
<td>1.5</td>
</tr>
<tr>
<td>Medium HDL-P</td>
<td>1.2</td>
</tr>
<tr>
<td>Small HDL-P</td>
<td>1.6</td>
</tr>
<tr>
<td>HDL-P size</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Models adjusted for age, sex, baseline BMI, and baseline trait value.
CONCLUSIONS

• The HDL-P subclass profile favorably responded to regular exercise in previously sedentary Black and White adults, highlighted by increases in the concentration of large HDL-P, and may be influenced by a significant genetic component
  – Results differed by sex and race

• We provide evidence that regular exercise could potentially be used as a therapy designed to target beneficial HDL subfractions
The response of HDL-P traits to regular exercise needs to be examined in larger, more diverse populations, including diseased individuals.

Future work will need to address whether the raising/lowering of specific HDL subfractions via regular exercise leads to tangible health benefits (e.g., reduction in risk for diabetes, CVD, etc).

The potential association of genetic factors with these responses needs to be explored.
Sources of Funding:

• Study funded by:
  – 1 U54 GM104940: NIH/NIGMS Louisiana Clinical and Translational Science Center (LA CaTS) Pilot Grants Program (PI: MA Sarzynski)
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QUESTIONS/COMMENTS?

WELL BEYOND THE EXPECTED.
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