Cholesterol and Skeletal Muscle Health

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Main Objective

To explain why individuals respond differently to identical exercise interventions

- Variable responses are explained by:
  - Genetics
  - Environment (nutrition)
Applications

- Sarcopenia: muscle loss with aging
- Muscle loss with space flight
- Cachexia: disease associated muscle loss (AIDS, cancer)
- Sport performance
Aging:
↑ fat
↓ Muscle
weight =

Sarcopenia

Young, active  Old, sedentary

Roubenoff, 2003
This study includes 60-69 year old men and women

Inclusion criteria: healthy, mobile, and able to perform exercise and testing

Exclusion criteria: CVD, blood pressure >160/100, atrial fibrillation, hernia, aortic aneurysm, cancer, kidney or lung disease
Orientation/Education

- 6 sessions / 2 weeks
  - Nutrition seminar (20-25 min)
  - Introduction to weight lifting
Training

- 12 weeks, 3 times per week
- 8 exercises, 3 sets of 8-12 repetitions
- Resistance @70% of maximal strength
- Post Exercise protein supplement
- 24 hour food log (>36 total), Nutribase software
- Pre/Post blood, DEXA for body composition
Protein Intake and Muscle Gain

Andrews, IJ SNEM, 2006

Protein Intake and Muscle Gain

Change in Lean Mass (kg)

N=9

N=19

N=15

N=8

GRAMS/ KG/TBW Mean Daily Protein Intake
Dietary Cholesterol and Muscle Gain

Riechman SE, J Gerontol, 2007
Blood Cholesterol and Muscle Gain

Riechman SE, J Gerontol, 2007
LDL and Muscle Gain

Riechman SE, J Gerontol, 2007
Statin and Muscle Gain

Riechman SE, J Gerontol, 2007
Regression

Change in lean mass: Dietary and blood cholesterol and statins

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Coefficient</th>
<th>p-value</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary (mg chol/kg)</td>
<td>0.5</td>
<td>&lt;0.001</td>
<td>0.29</td>
</tr>
<tr>
<td>Blood (low/high)</td>
<td>0.7</td>
<td>0.007</td>
<td>0.10</td>
</tr>
<tr>
<td>Statins (no,Ato/Sim, Pra/Lov)</td>
<td>0.8</td>
<td>0.020</td>
<td>0.09</td>
</tr>
<tr>
<td>Constant</td>
<td>-3.0</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

r² = 0.48

Riechman SE, J Gerontol, 2007
Dietary protein sources may have other micronutrients such as creatine that are highly correlated to dietary cholesterol and are responsible for the muscle effects.

Current dietary databases do not include creatine though creatine is well established as enhancing muscle performance with exercise training.
Possible Mechanisms

- Building Block
- Inflammatory Response
- Steroids
- Lipid Rafts
Lipid Rafts

- Cholesterol is essential to the formation of lipid rafts which function as platforms for the assembly of components of signaling pathways.

- Cholesterol depletion can induce protein missorting and reduced signal transduction.

- Lipid rafts have been implicated as essential for signaling through many pathways:
  - Src tyrosine kinases, Ras, NOS, PKCα, GPI-linked proteins, G-protein α subunits, insulin receptor, IGF1 receptor, TNFα, NF-κβ, PI3K, PKC, EGFR, PDGFR, IL6, ERK2, AKT1 and steroid hormone receptor.
Exercise & Muscle Hypertrophy

Cholesterol and Hypertrophy

Inflammation and Hypertrophy

Riechman SE, J Gerontol, 2007
Dietary Cholesterol and Muscle Damage

- 8 recreationally active subjects underwent a rigorous 100 repetition training session of eccentric knee flexion and extension on a Biodex Isokinetic Dynamometer

- Subjects performed two trials, one under restricted dietary cholesterol (<200 mg) and one with supplemental dietary cholesterol (600 mg, ~800 total)

- Hypothesis: Supplemental cholesterol will reduce markers of muscle damage suggesting faster recovery
Muscle Damage Study Design

-72                -48                   -24                        0   +4             +24                +48                  +72

Start chol<200, no exercise  
Start Supplement

Eccentric

Blood  Blood  Blood  Blood  Blood
DOMS   DOMS   DOMS   DOMS   DOMS
Strength  Strength  Strength  Strength  Strength
Soreness

Perceived Soreness (AU)

- **white**
- **whole**

Hours Post-Exercise

<table>
<thead>
<tr>
<th>Time</th>
<th>T0</th>
<th>T4</th>
<th>T24</th>
<th>T48</th>
<th>T72</th>
</tr>
</thead>
<tbody>
<tr>
<td>white</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Blood Creatine Kinase

Creatine Kinase (IU/ml)

White

Whole

* Indicates statistical significance.

Hours Post-Exercise

0 24 48 72
Blood Cholesterol

Cholesterol (mg/dl)

Hours Post Exercise

- White
- Whole

* Indicates significant difference
Strength Loss

- **Peak Torque (N-M)**
  - White
  - Whole

- **Hours Post-Exercise**
  - T0
  - T24
  - T48
  - T72

*Significant difference compared to initial value (T0).
Repeated Trial Strength

Baseline Strength

<table>
<thead>
<tr>
<th></th>
<th>Peak Torque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg white first</td>
<td>160</td>
</tr>
<tr>
<td>Whole egg first</td>
<td>140</td>
</tr>
</tbody>
</table>

Trial 1

Trial 2
Repeated Trial Soreness

Tentative Conclusion: Dietary Cholesterol exacerbates the short-term negative impact of an eccentric exercise bout but improves long term recovery
Resistance Training and Dietary Cholesterol

- Women and men, age 50-69, generally healthy, blood cholesterol <215 mg/dl
- 12 weeks of RET (same design as MERET II) using Keiser RET equipment

Funded by: U.S. Poultry and Egg Association
Resistance Training and Dietary Cholesterol

- Randomize N=36 to zero, ~200 or 600 mg supplemental cholesterol daily (N=12/group)

- Food cholesterol restricted to <200 mg

- Double-Blind administration in a protein drink

- Daily food intake log (Nutribase software)
Effect of Dietary Cholesterol on Whole Body Lean Mass Gain

<table>
<thead>
<tr>
<th>Cholesterol Group</th>
<th>Change in Lean Mass (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3</td>
</tr>
<tr>
<td>Average</td>
<td>4</td>
</tr>
<tr>
<td>High</td>
<td>5</td>
</tr>
</tbody>
</table>

P > 0.05, Covariates appearing in the model are: cohort, baseline fat percent
Effect of Dietary Cholesterol on Strength Gain

- **Cholesterol Group**
  - Control
  - Average
  - High

### Change in Strength (%)
- Control: 20 ± 5
- Average: 50 ± 10*
- High: 60 ± 15*

*P=0.05, Covariates appearing in the model are: protein/kg lean, cohort, gender, lean mass.
Thigh Muscle Gain

**Effect of Dietary Cholesterol on Thigh Lean Mass Gain**

<table>
<thead>
<tr>
<th>Cholesterol Group</th>
<th>Change in Thigh Lean Mass (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.0</td>
</tr>
<tr>
<td>Average</td>
<td>6.0</td>
</tr>
<tr>
<td>High</td>
<td>7.0</td>
</tr>
</tbody>
</table>

*P*=0.04. Covariates appearing in the model are: Cohort, age, baseline fat percent.
Effect of Dietary Cholesterol on Muscle Quality Gain

P > 0.05, Covariates appearing in the model are: protein/kg lean, gender, lean mass.
Testosterone

Change in Resting Testosterone with Training

Cholesterol Group

Low (N=9)  Medium (N=9)  High (N=9)

Change in Testosterone (ng/ml)

Men (N=10)  Women (N=17)
Effect of Dietary Cholesterol & RET on Resting Blood Cholesterol

- **Control**
  - Pretraining: 180 mg/dL
  - Posttraining: 200 mg/dL
  - p = 0.202

- **MED**
  - Pretraining: 190 mg/dL
  - Posttraining: 210 mg/dL
  - p = 0.149

- **HIGH**
  - Pretraining: 170 mg/dL
  - Posttraining: 190 mg/dL
  - p = 0.440

*p = 0.150 Between Groups*
Dietary Cholesterol and LDL

Effect of Dietary Cholesterol & RET on Resting LDL

<table>
<thead>
<tr>
<th>Cholesterol Group</th>
<th>LDL (mg/dL)</th>
<th>Pretraining</th>
<th>Posttraining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIGH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = .158 Between Groups
Cholesterol, Hypertrophy in Rats

**Purpose:** Develop a parallel model in rats to accelerate discovery of the mechanisms of cholesterol effects on muscle hypertrophy
Training Paradigm

- **Resistance Trained and Control**
  - operant conditioning
  - 15 training sessions (3/week)
  - Randomized to standard chow and standard chow + 10X cholesterol

- **Resistance Trained**
  - Progressive resistance training (80g – 410 g)
  - Start at 50 reps and decreased to 16 (final session)

- **Training Control**
  - Non-weighted vest
  - Matched reps and electrical stimulation as RT
Weight Gain

- High Cholesterol, Resistance Training
- High Cholesterol, Training Control
- Standard Chow, Resistance Training
- Standard Chow, Training Control

Change in Weight

Baseline Week 1 Week 2 Week 3 Week 4 Week 5 Post-Training

+4.9% lean
-0.7% lean
Rate of Muscle Protein Synthesis

Rate of Protein Synthesis

- Resistance training
- Training control

High Cholesterol
Standard Chow

Rate of Phe incorp. g-1 h-1

* Denotes significant difference
Fractional Muscle Protein Synthesis Rate

![Graph showing fractional synthesis rate (FSR) in different conditions.](image)

- Resistance Training
- Training Control
- Cage Control

High Cholesterol vs. Standard Chow

*Significant difference
New Studies

- Elite powerlifters: 8 weeks, ~10 whole eggs per day vs equivalent egg white
  - Mass and performance outcomes

- Muscle damage follow up with deuterium measures of protein synthesis
Conclusions

- Dietary Cholesterol positively affects muscle responses with resistance training in rats and humans

- The mechanism appears at least partly due to both increased protein synthesis and enhanced inflammatory response
Questions?

- Have cattle drives diminished over the years? What impact does sedentary cattle have on the nutritional value of the meat?
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