Lipoprotein Apheresis Reduces Circulating Galectin-3 in Humans
Presenter

Isaac Eliaz, MD, MS
Medical Director
Amitabha Medical Clinic and Healing Center
Santa Rosa, California

www.amitabhaclinic.com

An integrative medical center focusing on innovative, individualized treatments for cancer and chronic illness
Co-authors

Isaac Eliaz MD, MS¹, Elaine Weil NP¹, Julie-Ann Dutton MS, RD², Audrey E McCalley BS³, Barbie Nolte RN³, Patrick M Moriarty MD²,³

¹Amitabha Medical Clinic and Healing Center, Santa Rosa, CA

²University of Kansas Medical Center, Atherosclerosis and Lipid-Apheresis Center, Kansas City, KA

³University of Kansas Medical Center, Department of Internal Medicine, Kansas City, KA
• Dr. Isaac Eliaz is the Medical Director of Amitabha Medical Clinic.

• Apheresis procedures are offered as part of Amitabha Medical Clinic’s treatment options.

• Dr. Eliaz is engaged in researching the role and possible development of new targeted apheresis approaches.
Galectin-3

Role of galectin-3 in cancer, and chronic cardiovascular & inflammatory diseases
What is Galectin-3 (Gal-3)?

- Widely expressed
- Multifunctional
- $\beta$-galactoside binding lectin
- Regulatory roles in cancer, inflammation, fibrosis, immunology
- In nucleus, cytoplasm, mitochondria, cell surface, extracellular space, and circulation
Gal-3 Plays a Role in Numerous Diseases

- Serum marker for high risk of mortality
- Known to promote pathology
  - Metastasis, inflammation, fibrosis
- Predicts clinical outcome
Gal-3 and Cancer
Elevated Gal-3 Promotes

- Cell adhesion
- Aggregation of cancer cells
- Tumor growth
- Metastasis
- Angiogenesis
- Inhibition of apoptosis
- Immune evasion


Serum Gal-3 as a Tumor Marker
Selected Research

Gal-3 and Cardiovascular Disease

Active biomarker linking inflammation, remodeling, and progression in heart failure
Gal-3 & Cardiovascular Disease Research Review


- Gal-3 is therapeutic target in heart failure
- Most studied Gal-3 blocker is Modified Citrus Pectin
The PREVEND Study
(Prevention of Renal and Vascular End-stage Disease)

Galectin-3 Levels & All-Cause Mortality in the General Population

- Quintile-1: 7.7
- Quintile-2: 9.4
- Quintile-3: 10.9
- Quintile-4: 12.6
- Quintile-5: 15.6

Overall Average: 11.9 ng/ml

N = 7,968 Subjects
### Galectin-3 in General Population: PREVEND (N = 7,968)

<table>
<thead>
<tr>
<th>Median Gal-3 (ng/ml)</th>
<th>TOTAL 11.9</th>
<th>QUINTILE-1 7.7</th>
<th>QUINTILE-2 9.4</th>
<th>QUINTILE-3 10.9</th>
<th>QUINTILE-4 12.6</th>
<th>QUINTILE-5 15.6</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM%</td>
<td>3.6</td>
<td>2.3</td>
<td>2.3</td>
<td>3.1</td>
<td>4.3</td>
<td>6.1</td>
<td>0.000</td>
</tr>
<tr>
<td>MI</td>
<td>3.7</td>
<td>1.8</td>
<td>2.4</td>
<td>2.7</td>
<td>4.2</td>
<td>7.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33.4</td>
<td>22.2</td>
<td>26.6</td>
<td>31.1</td>
<td>39.7</td>
<td>47.9</td>
<td>0.000</td>
</tr>
<tr>
<td>Stroke %</td>
<td>0.9</td>
<td>0.8</td>
<td>0.6</td>
<td>0.6</td>
<td>1.3</td>
<td>1.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>129.2±20.2</td>
<td>125.0±18.1</td>
<td>126.6±19.0</td>
<td>128.6±19.6</td>
<td>131.3±20.6</td>
<td>134.9±22.5</td>
<td>0.000</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>74.0±9.7</td>
<td>72.1 ±9.4</td>
<td>73.3±9.8</td>
<td>74.1±9.6</td>
<td>75.2±9.8</td>
<td>75.4±9.8</td>
<td>0.000</td>
</tr>
<tr>
<td>Median Gal-3 (ng/ml)</td>
<td>TOTAL 11.9</td>
<td>QUINTILE-1 7.7</td>
<td>QUINTILE-2 9.4</td>
<td>QUINTILE-3 10.9</td>
<td>QUINTILE-4 12.6</td>
<td>QUINTILE-5 15.6</td>
<td>P-value</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>CRP, ng/ml</td>
<td>1.29 [0.56-3.00]</td>
<td>0.89 [0.39-2.16]</td>
<td>1.04 [0.49-2.40]</td>
<td>1.33 [0.58-2.92]</td>
<td>1.53 [0.71-3.42]</td>
<td>1.98 [0.85-4.28]</td>
<td>0.000</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>5.66±1.12</td>
<td>5.41±1.05</td>
<td>5.56±1.10</td>
<td>5.68±1.11</td>
<td>5.79±1.11</td>
<td>5.91±1.17</td>
<td>0.000</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>3.69±1.05</td>
<td>3.47±1.00</td>
<td>3.60±1.01</td>
<td>3.71±1.04</td>
<td>3.77±1.05</td>
<td>3.90±1.06</td>
<td>0.000</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>1.27 [1.03-1.56]</td>
<td>1.32 [1.07-1.62]</td>
<td>1.28 [1.04-1.57]</td>
<td>1.25 [1.03-1.55]</td>
<td>1.24 [1.03-1.53]</td>
<td>1.24 [0.99-1.52]</td>
<td>0.000</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>1.16 [0.85-1.68]</td>
<td>1.02 [0.75-1.43]</td>
<td>1.11 [0.82-1.59]</td>
<td>1.17 [0.86-1.69]</td>
<td>1.23 [0.89-1.78]</td>
<td>1.31 [0.95-1.92]</td>
<td>0.000</td>
</tr>
</tbody>
</table>
COACH (Coordinating Study on Outcomes of Advising and Counseling in Heart Failure)

Multicenter, randomized, controlled trial conducted in The Netherlands. A prospective sub-study evaluated Gal-3 in patients with chronic heart failure. Gal-3 levels were measured in 582 banked EDTA-plasma samples.
Gal-3 All-Cause Mortality (1 Year) in Chronic Heart Failure Patients

<table>
<thead>
<tr>
<th>Galectin-3 Levels (ng/mL)</th>
<th>% Died within 365 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 17.8</td>
<td>12.57%</td>
</tr>
<tr>
<td>17.8 - 25.9</td>
<td>19.69%</td>
</tr>
<tr>
<td>&gt; 25.9</td>
<td>36.51%</td>
</tr>
</tbody>
</table>
Gal-3 Plays Key Roles in Fibrosis

- Activates macrophages which in turn activate myofibroblasts
- Promotes myofibroblast activation and differentiation, and increases collagen-I synthesis
- Scar tissue and adverse remodeling in:
  - Heart failure, hypertension, cancer, arthritis, asthma, diabetes, kidney, liver & lung disease
Gal-3 & Fibrosis Selected Research

ELISA assay measures plasma Gal-3. Elevated Gal-3 levels are a risk factor in chronic heart failure.
Lipoprotein Apheresis Reduces Circulating Galectin-3 in Humans

A retrospective study in conjunction with the University of Kansas Medical Center Atherosclerosis and Lipid Apheresis Center
Purpose

To compare the clinical utility of two FDA approved lipoprotein apheresis (LA) systems in reducing plasma Gal-3
Blood samples collected pre- and post-apheresis from familial hypercholesterolemia patients (FHC) (n=10/group) undergoing therapeutic LA at the University of Kansas Medical Center, Atherosclerosis and Lipid-Apheresis Center
LA Systems Compared

• Heparin-induced extracorporeal LDL precipitation (HELP; Plasmat® Futura; B. Braun Medical Inc., Bethlehem, PA)

• Dextran sulfate-adsorption (DSA; Liposorber®; Kaneka Corp., Osaka, Japan)
Patient Characteristics

- Twenty FHC patients undergoing LA every 2 weeks to manage disease
- n=10 patients per LA system
- HELP group median age 64 years (range 45–71)
  - 40% females
- DSA group median age 64 years (range 51–76)
  - 30% females
Galectin-3 ELISA Assay

• Gal-3 plasma levels assessed by validated ELISA
  – Galectin-3 ELISA kit; BG Medicine Inc., Waltham, MA
  – Assayed by Health Diagnostic Lab Inc., Richmond, VA
Results

• Mean baseline plasma Gal-3 concentrations
  • HELP: 14.3±5.1 ng/ml (range 6.6–22.8)
  • DSA: 14.5±2.8 ng/ml (range 10.6–19.8)
  ➢ Gal-3 % reduction between devices was insignificant. (p=0.53)

• Post-apheresis Gal-3 levels (p=very significant)
  • HELP reduced by 19.4% (p=0.0094)
    – Levels: 11.3±3.7 ng/ml (range 4.5–16.3)
  • DSA reduced by 22.7% (p=0.0027)
    – Levels: 11.3±3.8 ng/ml (range 7.5–20.7)
Pre/Post Apheresis
Individual Plasma Gal-3 Levels

A. HELP

B. DSA
Pre/Post Apheresis Mean Values
Conclusions

• We report for the first time that the two FDA-approved LA systems reduced plasma Gal-3 levels in humans

• Reduction was statistically significant, but not clinically optimal
Therapeutic Potential of Gal-3 Reduction

- Gal-3 promotes diverse inflammatory, cardiovascular, and neoplastic disorders
- Our approach can be the foundation of new therapeutic strategies, by reducing Gal-3, additional galectins, and other cancer and inflammation promoting factors (CIPFs)
Cardio-protective clinical benefits of LA in FHC patients may be due to concomitant extraction of inflammatory Gal-3, CRP, fibrinogen and other CIPFs, along with targeted LDL and LP(a)
• Study limitations include relatively small cohort size; however, investigation was sufficiently powered to evaluate the basic premise of this proof-of-concept study
Study Limitations

- Patients were not treatment naïve and underwent LA every 2 weeks for variable durations prior to plasma analysis.
- May have underestimated baseline plasma Gal-3 levels due to lowering of baseline levels during previous apheresis sessions.
Future Directions

• Optimize Gal-3 reduction to maximize therapeutic effects
• Reduction of Gal-3, CRP, fibrinogen, and other CIPFs via LA and other apheresis methods warrants further investigation for combined clinical benefit
We are currently studying a new cohort of LA treatment naïve patients to evaluate reduction of Gal-3 and other CIPFs, as well as rebound kinetics following apheresis in patients with cancer and other inflammatory conditions.
Future Directions

• New apheresis technologies being developed to enhance apheresis utility by selectively lowering circulating Gal-3 and CIPF levels

• Strategy may provide important therapeutic benefit in cancer and other pathologies promoted by excessive plasma Gal-3 and CIPFs
Acknowledgements

We would like to thank the following contributors

Patrick M. Moriarty, MD, University of Kansas Medical Center, Department of Internal Medicine, Atherosclerosis and Lipid-Apheresis Center, Kansas City, KA.

Elaine Weil, NP, Amitabha Medical Clinic and Healing Center, Santa Rosa, CA.

Julie-Ann Dutton, MS, RD, University of Kansas Medical Center, Atherosclerosis and Lipid-Apheresis Center, Kansas City, KA.

Audrey E. McCalley, BS, University of Kansas Medical Center, Department of Internal Medicine, Kansas City, KA.

Barbie Nolte, RN, University of Kansas Medical Center, Department of Internal Medicine, Kansas City, KA.
Thank You!

Amitabha Medical Clinic and Healing Center

www.amitabhaclinic.com
(707) 542-5900