Inflammation and Nutrition: Rheumatoid Arthritis and anti-TNF Therapy as a Case Study

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Vice President and Translational Medicine Head, Musculoskeletal Disorders, Novartis Institutes for Biomedical Research (after 9/21), Cambridge, MA

Adjunct Professor of Nutrition and Associate Professor of Medicine, Tufts University & Tufts Medical Center, Boston
RA is the Most Common Inflammatory Arthritis

People Die Faster With (OF??) RA

Nutritional Complications of RA

- Macronutrients
  - Rheumatoid cachexia
  - Cachectic obesity
- Micronutrients
  - B6 deficiency
  - Folate deficiency
  - Oxidative stress
Rheumatoid Cachexia

- Loss of body cell mass - predominantly in skeletal muscle - that occurs in RA.
- Compromises strength and functional capacity, and is accompanied by:
  - TNF-α & IL-1β (systemic)
  - REE
  - Whole-body protein catabolism
- Excess fat mass and low physical activity.
Body Composition in RA

Roubenoff et al. JCI 1994; 93: 2379
PBMC Production of IL-1$\beta$ and TNF-$\alpha$ in RA and Matched Controls
Rheumatoid Cachexia and Functional Class

TBK (g/knee ht (cm))

Control RA Class IA RA Class IB RA Class III

*p < 0.05; **p < 0.01 vs. control

Roubenoff et al., J Clin Invest 1994
Body Cell Mass and Prednisone History in RA

Body Cell Mass (g TBK/Knee Ht (cm))

Mean ± S.E.; p < 0.01
RA vs. Control

Prednisone Use

Control | RA Never Pred | RA Former Pred | RA Pred Now

1.7 | 1.8 | 1.9 | 2.0

Prednisone Use
Hypermetabolism: REE per g TBK in RA vs. Matched Controls

Δ = RA; o = control

Roubenoff et al., J Clin Invest 1994
Whole-Body Protein Metabolism in RA and Aging

Rall et al., *Arthr Rheum* 1996

* p < 0.05

Leucine flux, ug/g TBK/hr

Control | Elderly | RA | Young
--- | --- | --- | ---
Baseline | Trained | Baseline | Trained

Group

* *
Methotrexate Normalizes Accelerated Protein Breakdown in Rheumatoid Cachexia

Lean Body Mass Declines with Duration of Rheumatoid Arthritis

Duration of Rheumatoid Arthritis, yrs

Lean Body Mass Index, LBM kg/m²

Controls:
\[ r = -0.68, \quad P = 0.06 \]

Body Cell Mass and Spontaneous PBMC TNF-α and IL-1β Production

TNF-α

- Controls: $r = -0.002, P = 0.99$
- Patients: $r = -0.51, *P = 0.03$

IL-1β

- Controls: $r = -0.03, P = 0.93$
- Patients: $r = -0.43, P = 0.08$

Total Energy Expenditure is Reduced in RA due to Lower Physical Activity

Δ = 321 kcal/d

Δ = 247 kcal/d

p < 0.02

p < 0.04

In Vivo Rate of Mixed Skeletal Muscle Protein Synthesis

Skeletal Muscle Quality in RA (strength per unit mass)

36% lower in RA

Gene Expression in Skeletal Muscle of RA Patients vs. Controls

Rate of Skeletal Muscle Protein Synthesis

Healthy Controls

**Catabolic**
- TNF-α
- TGF-β
- IL-1β
- IL-15
- IGF-1
- MyoD

**Anabolic**
- CD18

Index of leukocyte infiltration

RA Patients

**Rate of Skeletal Muscle Protein Synthesis**

- TNF-α: 3.0x
- TGF-β: 4.0x
- IL-1β: 1.4x
- IL-15: 1.5x
- IGF-1: 1.8x
- MyoD: 4.2x
- CD18: 3.0x

*p < 0.05

25%, *P < 0.04

Effect of TNF inhibition on cachexia: Disappointing!

Marcora et al. Am J Clin Nutr 2006; 84:1463

Metsios et al. Rheumatology 2007; 46: 1824
Could TNF inhibition support LBM gain *in the setting of weight gain*?

FIGURE 3. Mean (±SE) effect of treatment with etanercept or methotrexate on the composition of body mass gained [% of fat-free mass (FFM)] in the 12 patients with early rheumatoid arthritis who had a significant increase in body weight over the 6-mo follow-up period. □, Fat mass; ■, FFM. Data were analyzed by unpaired *t* test.

Marcora et al. Am J Clin Nutr 2006; 84:1463
Both TNF & IL-1 Blockade are Needed to Inhibit Soleus Atrophy in Rat Adjuvant Arthritis

Hamada et al., FASEB J, 2000
IL-6 and Aging...
IL-6 Predicts All-Cause Mortality: Framingham Heart Study

IL-6 Production in the Elderly: The Framingham Heart Study

Roubenoff et al., *J Gerontol* 1998
IL-1Ra Production in the Elderly: The Framingham Heart Study

Roubenoff et al., J Gerontol 1998
Determinants of 2-yr changes in fat-free mass
Framingham Study n=539, 72-94 yrs

<table>
<thead>
<tr>
<th></th>
<th>$\beta$</th>
<th>SE</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>-.02</td>
<td>.02</td>
<td>.40</td>
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<tr>
<td>FFM (kg) at baseline</td>
<td>-.04</td>
<td>.01</td>
<td>.0001</td>
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<tr>
<td>Cell. Il-6 (ng/ml)</td>
<td>-.21</td>
<td>.10</td>
<td>.04</td>
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</table>

Adj. $R^2 = .04$, p=.001

Predictors of Death in the Elderly: Framingham Heart Study

- 4-year all cause mortality, ages 72-92
  - High serum IL-6
  - High PBMC TNF-alpha
  - Low serum IGF-1
  - Greater loss of fat-free mass

(Adjusted for smoking, diabetes, CVD, arthritis, high CRP, being bedridden)
Effect of Acute Exercise on Serum IL-6 in Young and Old Men

![Graph showing the effect of acute exercise on serum IL-6 in young and old men.](image)

- Young
- Old

Lines indicate means ± 1 SD, N = 15 per group.

- *p < 0.02; **p < 0.001

Effect of Acute Exercise on TNF-α, IL-1β, and IL-6 mRNA Levels in Vastus Lateralis from Young and Old Men

Hamada et al., *FASEB J* 19: 264-266, 2005
Effect of Acute Exercise on TGF-β₁ and MSTN mRNA Levels in Vastus Lateralis from Young and Old Men

Hamada et al., FASEB J 19: 264-266, 2005

*P < 0.05 vs. Pre-EX; ** P < 0.01 vs. Pre-EX; # P < 0.05 vs. Y.
Effect of Acute Exercise on IL-15, IGF-I and MGF mRNA Levels in Vastus Lateralis from Young and Old Men

* $P < 0.05$ vs. Pre-EX; # $P < 0.05$ vs. Y.

Hamada et al., FASEB J 19: 264-266, 2005
### Table 3. Correlations between changes in cytokine and CD18 mRNA levels within age groups

<table>
<thead>
<tr>
<th></th>
<th>CD18</th>
<th>TNF-α</th>
<th>IL-1β</th>
<th>IL-6</th>
<th>TGF-β1</th>
<th>MSTN</th>
<th>IL-15</th>
<th>IGF-I</th>
<th>MGF</th>
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<tr>
<td><strong>CD18</strong></td>
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<tr>
<td></td>
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<td>&lt;.001</td>
<td>0.01</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
<td>0.89</td>
<td>0.61</td>
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<td><strong>TNF-α</strong></td>
<td>0.62</td>
<td>0.01</td>
<td>0.22</td>
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<td>&lt;.001</td>
<td>0.92</td>
<td>0.86</td>
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<td></td>
<td>0.02</td>
<td>&lt;.001</td>
<td>0.98</td>
<td></td>
<td>0.76</td>
<td>0.68</td>
<td>0.74</td>
<td>0.09</td>
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<tr>
<td><strong>IL-1β</strong></td>
<td>-0.13</td>
<td>0.65</td>
<td>0.45</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.01</td>
<td>-0.07</td>
<td>0.74</td>
<td>0.09</td>
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<tr>
<td></td>
<td>-0.22</td>
<td>0.45</td>
<td>0.75</td>
<td></td>
<td>0.01</td>
<td>-0.09</td>
<td>0.77</td>
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<td><strong>IL-6</strong></td>
<td>0.45</td>
<td>0.09</td>
<td>-0.31</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.01</td>
<td>-0.09</td>
<td>0.89</td>
<td>0.47</td>
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<td>-0.07</td>
<td>0.27</td>
<td>0.75</td>
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<td>-0.12</td>
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<td><strong>TGF-β1</strong></td>
<td>0.60</td>
<td>0.02</td>
<td>0.66</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.01</td>
<td>-0.12</td>
<td>0.46</td>
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<td></td>
<td>-0.27</td>
<td>0.33</td>
<td>0.33</td>
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<td>0.01</td>
<td>-0.12</td>
<td>0.39</td>
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<td><strong>MSTN</strong></td>
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<td>0.02</td>
<td>0.68</td>
<td>0.58</td>
<td>0.39</td>
<td>-0.12</td>
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<td></td>
<td>0.15</td>
<td>0.94</td>
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<td><strong>IL-15</strong></td>
<td>0.18</td>
<td>0.54</td>
<td>0.26</td>
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<td>0.01</td>
<td>-0.55</td>
<td>-0.38</td>
<td>0.59</td>
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<tr>
<td></td>
<td>-0.05</td>
<td>0.44</td>
<td>0.65</td>
<td></td>
<td>0.01</td>
<td>-0.16</td>
<td>0.58</td>
<td>0.02</td>
<td>&lt;.01</td>
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<tr>
<td><strong>IGF-I</strong></td>
<td>-0.13</td>
<td>0.66</td>
<td>-0.08</td>
<td>0.79</td>
<td>0.48</td>
<td>0.20</td>
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<td>-0.22</td>
<td>0.44</td>
<td>0.11</td>
<td></td>
<td>0.81</td>
<td>0.48</td>
<td>0.58</td>
<td>0.76</td>
<td>0.02</td>
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<tr>
<td><strong>MGF</strong></td>
<td>-0.27</td>
<td>0.34</td>
<td>0.00</td>
<td>1.00</td>
<td>0.74</td>
<td>0.10</td>
<td>-0.09</td>
<td>0.69</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>0.42</td>
<td>0.68</td>
<td>0.68</td>
<td></td>
<td>0.76</td>
<td>0.42</td>
<td>0.76</td>
<td>0.16</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

The gray blocks indicate significant correlations. 

- **P < 0.001, Y vs. O**
- **P < 0.06, Y vs. O**
Muscle Anabolics in Aging
Assessing the Role of Nutrition and Exercise in Preventing Muscle Wasting

N. Brooks et al. 2008
Bed Rest Mitigation: Thigh Muscle and Fat Areas

Mid-Thigh Muscle Area (CT)  Mid-Thigh Fat Area (CT)

A

B

N. Brooks et al. 2008

AA only  RT only  AA + RT
Mitigation of Bedrest Weakness

Lower Body Strength

Upper Body Strength

AA only
RT only
AA + RT

N. Brooks et al. 2008
Roles of GH and T in Sarcopenia

Hyposomatotropic, Low Eugonadal
65-90 Year Old Men
n=122 Randomized*

5 g/day Testosterone
n=58 Randomized

10 g/day Testosterone
n=54 Randomized

0 µg/kg/day rhGH
n=19

3 µg/kg/day rhGH
n=19

5 µg/kg/day rhGH
n=20

0 µg/kg/day rhGH
n=20

3 µg/kg/day rhGH
n=17

5 µg/kg/day rhGH
n=17

HORMA Investigators: JCEM, 2009
T > GH Effect

Figure 3: Line Plot of % Change in Appendicular LBM by Time and Treatment

HORMA Investigators: JCEM 2009
Activin Inhibition of Myostatin-Induced Muscle Wasting

Lee et al., PNAS 102:18117-18122, 2005
Micronutrients in RA: Vitamin B6 as a Case Study
B6, B12, and Folate Metabolism

Homocysteine Elevation and PLP Depression are Common in RA

Vitamin B6 is an Acute Phase Reactant in RA

$r = -0.52, \ p < 0.002$

NHANES: Relationship between Plasma PLP and Serum CRP concentrations

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Plasma Pyridoxal-5-Phosphate (nmol/L) by CRP Category.</th>
<th>P-Trend$^2$</th>
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<tbody>
<tr>
<td></td>
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<td>CRP 1 (≤0.1mg/dL)</td>
<td>CRP 2 (0.11-0.3mg/dL)</td>
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<tr>
<td>All</td>
<td>6013</td>
<td>54.74$^a$ (52.12, 57.49)</td>
<td>45.42$^b$ (43.21, 47.74)</td>
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<tr>
<td>Males</td>
<td>2982</td>
<td>63.30$^a$ (59.66, 67.16)</td>
<td>52.74$^b$ (49.53, 56.15)</td>
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<tr>
<td>Females</td>
<td>3031</td>
<td>47.45$^a$ (43.83, 51.38)</td>
<td>39.13$^b$ (36.21, 42.28)</td>
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</tbody>
</table>

Not shown: No effect of supplement use.

Geometric Means (95% confidence interval) adjusted (or stratified) by sex, age, race, BMI smoking status, alcohol use, vitamin B6 intake, protein intake, and plasma/serum levels of folate, vitamin B12, homocysteine, albumin, creatinine and hormone use in women.

Sakakeeny et al. 2009 in press
Prevalence of Low PLP by CRP status is Independent of Vitamin B6 Intake

Sakakeeny et al. 2009 in press
Relationship between plasma PLP and Inflammatory Biomarkers in the Framingham Offspring Study

| Inflammatory Biomarker Quintiles | 1 (77.4±(72.4, 82.6)) | 2 (72.8±(68.4, 77.6)) | 3 (70.3±(66.1, 74.9)) | 4 (62.0±(58.3, 65.9)) | 5 (57.6±(54.0, 61.3)) | p-trend
<table>
<thead>
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<tr>
<td>CRP</td>
<td>77.4±(72.4, 82.6)</td>
<td>72.8±(68.4, 77.6)</td>
<td>70.3±(66.1, 74.9)</td>
<td>62.0±(58.3, 65.9)</td>
<td>57.6±(54.0, 61.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CD40 Ligand</td>
<td>70.0±(65.6, 74.7)</td>
<td>74.3±(69.7, 79.2)</td>
<td>65.4±(61.4, 69.6)</td>
<td>65.2±(61.1, 69.4)</td>
<td>61.9±(58.2, 65.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>72.8±(68.0, 77.9)</td>
<td>70.0±(65.5, 74.8)</td>
<td>69.9±(65.6, 74.4)</td>
<td>68.2±(65.3, 71.9)</td>
<td>60.8±(57.3, 64.5)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Interleukin-6 (IL-6)</td>
<td>65.1±(61.2, 69.2)</td>
<td>68.1±(64.0, 72.5)</td>
<td>66.7±(62.7, 71.1)</td>
<td>67.3±(63.1, 71.9)</td>
<td>67.4±(63.2, 71.9)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Intracellular adhesion molecule-1 (ICAM-1)</td>
<td>77.9±(72.8, 83.2)</td>
<td>69.5±(65.2, 74.1)</td>
<td>70.0±(65.7, 74.5)</td>
<td>62.6±(58.9, 66.7)</td>
<td>59.6±(55.9, 63.4)</td>
<td>&lt;0.0001</td>
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<td>Lipoprotein Phospholipase-A2 Activity</td>
<td>66.9±(62.6, 74.6)</td>
<td>72.6±(68.1, 77.4)</td>
<td>70.3±(66.0, 75.0)</td>
<td>65.7±ab(61.7, 70.0)</td>
<td>61.1±b(57.4, 65.1)</td>
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<tr>
<td>MCP-1</td>
<td>66.7±(62.5, 71.2)</td>
<td>66.1±(62.0, 70.6)</td>
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<td>65.4±(61.4, 69.6)</td>
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<td>Myeloperoxidase</td>
<td>65.5±(62.4, 70.8)</td>
<td>69.9±(65.6, 74.5)</td>
<td>68.9±(64.6, 73.4)</td>
<td>65.5±(61.6, 69.7)</td>
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<td>Osteoprotegerin</td>
<td>70.8±(66.2, 75.7)</td>
<td>69.9±ab(65.6, 74.6)</td>
<td>67.4±ab(63.2, 71.9)</td>
<td>65.3±ab(61.4, 69.5)</td>
<td>63.1±b(59.1, 67.2)</td>
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<td>P-selectin</td>
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<td>67.9±ab(63.7, 72.4)</td>
<td>67.4±ab(63.3, 74.8)</td>
<td>66.8±ab(62.7, 71.1)</td>
<td>63.6±b(59.8, 67.6)</td>
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<td>Tumor Necrosis Factor Receptor 2</td>
<td>76.5±(71.5, 81.8)</td>
<td>73.8±ab(69.3, 78.5)</td>
<td>68.8±bc(64.6, 73.2)</td>
<td>64.2±(60.3, 68.3)</td>
<td>56.5±d(52.9, 60.3)</td>
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<td>Tumor Necrosis Factor-α</td>
<td>72.9±(67.6, 78.6)</td>
<td>70.1±ab(65.1, 75.5)</td>
<td>70.0±ab(65.1, 75.3)</td>
<td>63.9±bc(75.4, 68.7)</td>
<td>61.5±c(57.1, 66.3)</td>
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<td>Resistin</td>
<td>68.1±(63.5, 73.2)</td>
<td>71.9±(67.1, 77.1)</td>
<td>69.5±(64.8, 77.1)</td>
<td>67.4±ab(62.8, 72.3)</td>
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<td>Adiponectin</td>
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<td>67.1±(62.5, 72.0)</td>
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<td>70.2±(65.2, 75.6)</td>
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1 Geometric means (95% confidence intervals) adjusted for sex, age, BMI, plasma homocysteine, folate, vitamin B12, creatinine, total cholesterol, vitamin B6 intakes, protein intakes, calories, NSAID use, Cigarette use, and multivitamin use.

Sakakeeny et al. 2009 in press
Effect of Vitamin B6 Restriction on Tissue PLP in a Mouse Obesity Inflammation Model

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Fat</th>
<th>High Fat</th>
<th>High Fat, 50% B6</th>
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<tr>
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<td>Plasma PLP (nmol/L)</td>
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<tr>
<td></td>
<td>223.3 (77.8)a</td>
<td>215.5 (49.1)a</td>
<td>73.3 (24.0)b</td>
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<td>Liver PLP (pmol/g)</td>
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<td></td>
<td>23852.3 (5670.4)</td>
<td>24387.1 (5490.6)</td>
<td>19459.1 (4331.3)</td>
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<td>Adipose PLP (pmol/g)</td>
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<td></td>
<td>420.8 (20.1)a</td>
<td>380.0 (102.9)a</td>
<td>163.7 (16.1)b</td>
</tr>
</tbody>
</table>

No effect of Low Vitamin B6 on the recruitment of macrophages, T-Cells, and NK cells to Adipose Tissue

Sakakeeny et al. 2009 in press

Table values are presented as unadjusted means (standard deviation). Different superscripts by column indicate a p-value < 0.05.
Free-Fatty Acids and LPS bind to TLR2 and TLR4/CD14 resulting in inflammation and insulin resistance.

Chemokines involved in Macrophage Chemotaxis which are increased in obesity.

Costimulatory molecules involved in T-cell activation which are associated with obesity.
Nutritional Impact of Inflammation in RA: Signposts for Aging

- Cachexia is common and persists even when inflammation is controlled.
- Increased fat mass and reduced lean mass (sarcopenic obesity) is common.
- Overlapping cytokine effects are probably driving rheumatoid cachexia.
- Plasma PLP is reduced in RA and age-related inflammation, independently of Vitamin B6 intake.
- The effect of PLP reduction on inflammation is unclear.
Back-Up Slides
# PLP and Inflammation in NHANES III: Population Characteristics by CRP Category

<table>
<thead>
<tr>
<th></th>
<th>CRP 1 (≤0.1mg/dL)</th>
<th>CRP 2 (0.11-0.3mg/dL)</th>
<th>CRP 3 (0.31-1.0mg/dL)</th>
<th>CRP 4 (≥1.0mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (48.7)</td>
<td>50.9</td>
<td>27.9</td>
<td>16.8</td>
<td>4.3</td>
</tr>
<tr>
<td>Females (51.2)</td>
<td>43.6</td>
<td>23.4</td>
<td>22.7</td>
<td>10.4</td>
</tr>
<tr>
<td><strong>Ages (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-19 (27.4)</td>
<td>77.3</td>
<td>12.8</td>
<td>7.3</td>
<td>2.7</td>
</tr>
<tr>
<td>20-44 (36.4)</td>
<td>40.7</td>
<td>28.3</td>
<td>22.3</td>
<td>8.8</td>
</tr>
<tr>
<td>&gt;45 (36.2)</td>
<td>29.0</td>
<td>33.4</td>
<td>27.6</td>
<td>9.9</td>
</tr>
<tr>
<td><strong>Race (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White (69.7)</td>
<td>46.1</td>
<td>26.8</td>
<td>20.1</td>
<td>7.0</td>
</tr>
<tr>
<td>Non-Hispanic Black (12.6)</td>
<td>47.6</td>
<td>22.2</td>
<td>19.1</td>
<td>11.1</td>
</tr>
<tr>
<td>Mexican American (9.2)</td>
<td>47.6</td>
<td>24.9</td>
<td>20.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Other Race- Including Multi-Racial (4.6)</td>
<td>58.3</td>
<td>21.6</td>
<td>16.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Other-Hispanic (4.1)</td>
<td>51.5</td>
<td>19.6</td>
<td>21.8</td>
<td>7.1</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22.8 (22.6-23.0)</td>
<td>27.2 (27.0-27.5)</td>
<td>30.1 (29.8-30.4)</td>
<td>32.6 (32.1-33.1)</td>
<td></td>
</tr>
<tr>
<td>78.6 (77.5-79.7)</td>
<td>82.3 (80.9-83.8)</td>
<td>81.1 (79.5-82.8)</td>
<td>74.9 (72.3-77.6)</td>
<td></td>
</tr>
<tr>
<td>1.88 (1.85-1.91)</td>
<td>1.87 (1.83-1.91)</td>
<td>1.80 (1.75-1.85)</td>
<td>1.64 (1.56-1.71)</td>
<td></td>
</tr>
<tr>
<td><strong>Plasma/Serum (95%CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLP (nmol/L)</td>
<td>49.8 (48.2-51.4)</td>
<td>46.0 (44.2-47.8)</td>
<td>35.7 (34.2-37.3)</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.034 (.033-.035)</td>
<td>0.181 (.177-.185)</td>
<td>0.514 (.501-.528)</td>
<td></td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>7.0 (6.9-7.1)</td>
<td>8.3 (8.2-8.4)</td>
<td>8.2 (8.1-8.3)</td>
<td></td>
</tr>
<tr>
<td>B12 (pmol/L)</td>
<td>391.9 (385.9-398.0)</td>
<td>351.6 (345.1-358.2)</td>
<td>342.8 (335.6-350.2)</td>
<td></td>
</tr>
<tr>
<td>Folate (nmol/L)</td>
<td>28.4 (27.9-28.9)</td>
<td>27.7 (27.2-28.3)</td>
<td>27.1 (26.4-27.7)</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>44.3 (44.2-44.4)</td>
<td>43.1 (43.0-43.2)</td>
<td>41.6 (41.4-41.7)</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.838 (0.829-0.846)</td>
<td>0.876 (0.866-0.885)</td>
<td>0.849 (0.839-0.860)</td>
<td>0.827 (0.810-0.843)</td>
</tr>
</tbody>
</table>

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