**Table. Best ‘Univariate’ Predictors of Insulin Sensitivity**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>t Ratio</th>
<th>Pr &gt;</th>
<th>p2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>-0.020</td>
<td>-11.47</td>
<td>&lt;0.0001</td>
<td>0.37</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.062</td>
<td>-12.77</td>
<td>&lt;0.0001</td>
<td>0.40</td>
</tr>
<tr>
<td>Head % Fat</td>
<td>-0.040</td>
<td>-12.52</td>
<td>&lt;0.0001</td>
<td>0.41</td>
</tr>
<tr>
<td>Upper Body Fat</td>
<td>-0.044</td>
<td>-12.50</td>
<td>&lt;0.0001</td>
<td>0.41</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>-0.087</td>
<td>-12.78</td>
<td>&lt;0.0001</td>
<td>0.42</td>
</tr>
</tbody>
</table>

* Age and gender were forced into every model.

**T124-198**

Impact of Elevated Age and Sex-Adjusted Body Mass Index in School Age Children on Insulin Resistance and Lipoprotein Subfractions

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**Background:** The Wausau SCHOOL Project is a community-based effort to assess the frequency of cardiovascular risk factors in students in the Wausau School District. **Objective:** Define the incidence of elevated BMI and determine its relationship to standard lipid profiles, homeostatic model assessment of insulin resistance (HOMA-IR), LDL particle size and number. **Methods:** Age and sex adjusted BMI (zBMI), fasting plasma insulin, glucose levels and nuclear magnetic resonance lipid profiles (LipoScience®) were measured in 225 randomly selected students (110 in 2nd grade and 125 in 11th grade). **Results:** Overweight was defined as zBMI > 85th percentile based on 2000 CDC norms. **Conclusions:** Overweight rates were significantly higher for 11th graders than for 2nd graders (2.18±2.65 vs. 1.22±1.07, p<0.01). HOMA-IR values were also significantly higher for females than for males (2.04±2.66 vs. 1.33±3.94, p<0.05). These data suggest that elevated BMI may influence the statin response. The CYP7A1 enzyme in bile acid biosynthesis, may influence the statin response.

**T124-199**

Additive Gene-Gene Interaction Between CYP7A1 and Apolipoprotein E as Genetic Determinants of Low-Density Lipoprotein Cholesterol-Lowering Response to Atorvastatin

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**Background:** The mechanisms responsible for interindividual variation in response to statin therapy remain uncertain. Bile acid biosynthesis is one of the determinants of intracellular cholesterol and, in turn, cholesterol synthesis rate in hepatocytes. This raises the hypothesis that variation in the cholesterol 7a-hydroxylase gene (CYP7A1), a key enzyme in bile acid biosynthesis, may influence the statin response. **Methods and Results:** In order to test this hypothesis, we examined a promoter polymorphism (A–290C) in CYP7A1 in 324 hypercholesterolemic patients treated with atorvastatin 10mg. The CYP7A1 polymorphism was significantly and independently associated with poor LDL cholesterol response. Mean reductions were -39% in wild type allele homozygotes, -37% in variant allele heterozygotes, and -34% in variant allele homozygotes, respectively (p<0.001 for linear trend). The effects of this polymorphism were more striking in men than in women and were enhanced by the coexistence of common variants of the apolipoprotein E gene (APOE), rs4 and rs4. In subjects having wild type alleles at both loci, the mean reduction in LDL cholesterol was -46%, while in subjects having two CYP7A1 variant alleles and at least one variant APOE allele, the mean reduction in LDL cholesterol was -51% (p<0.0001). In addition, combination analysis of these two polymorphisms more accurately predicted the achievement of goal LDL cholesterol, than did both single polymorphism analysis. **Conclusions:** The CYP7A1 A–290C polymorphism was significantly and independently associated with poor response to atorvastatin. The effects of this polymorphism were additive, when common variants in another locus, APOE, coexisted.
Apolipoprotein A1 Mimetic Peptide Reduces Cholesterol

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BACKGROUND: Apo-A1 mimetic peptide (DWFKAFYDVKAEKFKEAF or D4F) reduces diet-induced aortic atherosclerosis. Whether D4F is effective in reducing accelerated atherosclerosis in vein grafts is unknown. We studied the effect of intraperitoneal (IP) administration of D4F on accelerated atherosclerosis in a murine vein graft bypass model.

METHODS: Right carotid artery of hypercholesterolemic apoE(-/-) mice were grafted with a segment of IVC from donor mice at 16 weeks of age. Treatment group (n=10) received IP injection of 50 mcg D4F peptide daily for 4 weeks after surgery whereas control group (n=7) received saline injections. The grafts, heart, and aorta were harvested and sectioned for morphometric and immunohistochemical analysis and plasma collected for cholesterol and D4F levels and lipoprotein fractionation analysis.

RESULTS: D4F treatment significantly reduced plaque size in the vein graft but not in the aortic sinus or aorta. D4F also reduced lipid content in the vein graft but not in the aortic sinus plaques (Table). There were no difference in cholesterol levels or lipoprotein fractionation or plaque phenotypes in the vein graft or aortic sinus plaques between the groups.

CONCLUSION: Four week treatment of Apo A1 mimetic peptide reduces accelerated atherosclerosis in vein graft but has no effect on native spontaneous atherosclerosis in apoE(-/-) mice.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cholesterol (mg/dl)</th>
<th>Lipid content in vein graft (%)</th>
<th>Aortic sinus plaque size (mm²)</th>
<th>Lipid content in aortic sinus (%)</th>
<th>O-4F conc. (pmol/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1424±467</td>
<td>0.96±2.03</td>
<td>12.4±6.5</td>
<td>39.3±12</td>
<td>17.5±2.6</td>
</tr>
<tr>
<td>D4F</td>
<td>1273±294</td>
<td>5.05±0.37</td>
<td>6.4±3.8</td>
<td>50.5±0.9</td>
<td>18.0±6.6</td>
</tr>
</tbody>
</table>

*: p<0.05, by t-test

Bach1 Is a Key-Repressor of Heme Oxygenase-1 and Regulates Cell Proliferation

Shintaro Omura, Jiaying Sun, Hiroshi Suzuki, Kazuhiko Igarashi, Hiroshima University, Hiroshima-City, Japan

Background: Heme oxygenase-1 (HO-1) protects cells from various insults including oxidative stress and its transcriptional induction by various stresses provides an important cellular adaptive defense mechanism. Recently we found that Bach1 is a physiological repressor of HO-1 (EMBO J., 2002). Though some investigators reported that HO-1 protects against vascular proliferation, the role for Bach1 in cell growth is poorly understood.

Methods: We have developed bach1 knockout (KO) mice and isolated aortic smooth muscle cells (SMC), macrophages, and embryonic fibroblasts (EF). Using RT-PCR method, western blotting and immunofluorescence staining, we analyzed the expression of HO-1 comparing them with that in wild type (WT) cells. Using retrovirus system we method, western blotting and immunofluorescence staining, we analyzed the expression of Bach1 and HO-1 and evaluated their effect on cell proliferation.

Results: Expression of HO-1 was increased in KO SMC, macrophages and EF as compared to WT cells (1.9-fold and p<0.05; 3.6-fold and p<0.01, respectively). Bach1 is a key-repressor of HO-1 in KO cells or not. We also investigated expression of Bach1 in vivo using BrdU labeling assay and BrdU labeling assay in vivo. In KO EF, Bach1 is significantly decreased in cell counting and in BrdU labeling assay. In 3% O2 KO EF proliferates as well as WT cells. When cultured in 20% O2, KO EF underwent senescence more frequently than WT cells.

Conclusion: Inactivation of Bach1 leads to increased expression of HO-1 and anti-proliferative effect. Bach1 is an important molecule for the response of oxidative stress. Bach1 may represent a novel molecular target in anti-atherosclerotic therapy.

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