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"DIABETES AND HYPERTENSION: UPDATE"

THURSDAY, December 3, 2009

UCLA Faculty Center – Hacienda Room
405 Hilgard Ave., Los Angeles

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References


39. Ehrhart-Bornstein M, Arakelyan K, Krug AW, Scherbaum WA, Bornstein SR. Fat cells may be the obesity-hypertension link: human adipogenic factors stimulate aldosterone secretion from adrenocortical cells. Endocr Res. 2004;30:

40. Review: Emerging Clinical Implications of the Role of Aldosterone


Renin and Aldosterone: the other RASS Components

James R. Sowers, MD
Director, Diabetes and Cardiovascular Center
Professor of Medicine and Physiology
University of Missouri and Truman VA
CV Disease: Patients at Risk

- 125 million with high cholesterol
- 75 million with hypertension
- 50 million with CMS
- 21 million with diagnosed diabetes
  + 8 million undiagnosed

One death every 33 sec
JNC 7: CVD Risk Factors

- Hypertension*
- Cigarette smoking
- Obesity* (BMI \(>30 \text{ kg/m}^2\))
- Physical inactivity
- Dyslipidemia*  
  *Components of CMS.
- Diabetes mellitus*
- Microalbuminuria
- Estimated GFR \(<60 \text{ ml/min}\)
- Age (men \(>55 \text{ yo}\), women \(>65 \text{ yr}\))
- Family history of premature CVD 
  (men \(<55 \text{ yo}\), women \(<65 \text{ yr}\)

Who Is Insulin Resistant?

- 90% of patients with type 2 diabetes mellitus
- 30% of the US population, age 40–74 yr
- 60% of all patients with CVD
- 50% of patients with confirmed CHD and no prior history of diabetes
- 50% of patients with HTN
- 85% of people with low HDL and high TG

Mechanism of Insulin Resistance in Hypertension

• ↓ Nonoxidative glucose metabolism by skeletal muscle
• Postreceptor defect
  – Increased redox sensitive serine kinase activation
  – decreased insulin-mediated glucose transport

• Altered skeletal muscle fiber type
  – decreased insulin-sensitive slow twitch fibers

• ↓ Delivery of insulin and glucose to skeletal muscle
  – vascular rarefaction
  – vascular hypertrophy
  – increased vasoconstriction

Tyr P vs Ser P - IRS-1

Serine Kinases

PO₄

Glucose transport

AKT

NOS gene / expression & increased glucose transport

NADPH Oxidase ROS/Ser Kinases

Mitogenesis, hypertrophy & remodeling

Ang II/ Aldosterone

Insulin receptor

Mitogenesis, hypertrophy & remodeling
MR Blockade and Renin Inhibition in a Tg ANG II/MR Induced CMS Model

- **Tg Ren 2** Overexpresses mouse renin transgene in:
  - Kidneys
  - Heart
  - Vessels
  - Skeletal muscles

- **Ren 2** and SD Treated – **MR antagonist or Aliskerin** - 3 wks

- Insulin Sensitivity, Proteinuria
- Soleus Muscle Glucose Uptake, Signaling and ROS
- **Sk Muscle**, vasculature Heart and kidney
- NADPH oxidase: ROS ,
- Insulin signaling
Role of Aldosterone in CVD Injury and metabolism

ALDOSTERONE

- Epithelial Effects
- Non-Epithelial Effects

Kidneys  Skeletal muscle  Brain  Heart  Vascular

Skeletal muscle
Increased oxidative stress and TNF-α in soleus muscles from Ren2 Transgenic rats
Angiotensin II Receptor Blockade and Glucose Transport in Skeletal Muscle

Soleus muscle treated Val INS for 20 min, and incubated with [3H] 2DG INS for another 20 min.

INS=insulin mediated; AT1B = ARB
Soleus Glucose Transport: Role of MR

(Continued)
Systemic effects of Aldosterone on Insulin Sensitivity and Hypertension.

MR Antagonism Prolongs Survival and Protects Against Stroke in Saline-Drinking SHRSP

Systolic Blood Pressure

<table>
<thead>
<tr>
<th>mm Hg</th>
<th>Vehicle</th>
<th>Eplerenone</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
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</table>

Survival

% Surviving

Age (weeks)

Begin treatment

P < 0.001

Combined treatment with a MR antagonist and an ACE-I has additive protective effects on endothelial function and atherosclerosis.

Imanishi, T et al. Hyp 2008;51:734
Large Artery Compliance Correlates Inversely with Plasma Aldosterone

Plasma Aldosterone Levels in patients with STEMI (24-96 hours post-mi)

- Aldosterone levels post-mi (within the normal range) are independent predictors of survival and hospitalization for Heart Failure over a 5 year follow up period

Effects of RAAS on Insulin signaling in the Heart

Micro-PET determination of myocardial GLU uptake - INS

18F-FDG Cardiac Imaging

Control

Insulin

Function/metabolic effects of INS in heart

Micro-PET TM

Gated MRI

Micro-PET TM
Cardiac Glu (3wks ROS Inhibition)
Change in Serum PIIINP (Marker of ECM Turnover) in EPHESUS and RALES

[NOTE: Dissimilar Units]

*P=0.002.

*P=0.004.
MR Activation Induces Vascular Inflammatory Injury in the Heart

Coronary Injury

Macrophage Infiltration

Aldosterone/NaCl Rats

MR Blockade

- Effect in hypertensive patients with diastolic HF

- MR blockade improves diastolic function independent of changes in blood pressure

Superoxide Production in the Kidney of Mineralocorticoid Hypertensive Rats

MR Activation Induces Renal Injury

Aldosterone/NaCl-Treated Hypertensive Rats

Glomerular Injury Score (0-4)

Renovascular Injury Score (0-4)

Albuminuria (mg/day)

Systemic effects of Aldosterone on Insulin Sensitivity and Hypertension.

Aliskiren: Renin Inhibitor

Potential Effects related to decreases in RAAS

- Insulin resistance
- Endothelial function
- Vascular compliance
- Ventricular remodeling post MI
- Urinary albuminuria
- Inflammatory cytokines
- Progression of atherosclerosis
Blocking Renin

- Angiotensinogen
Skeletal Muscle NADPH Oxidase Activity

SD-C  SD-A  Ren2-C  Ren2-A
mOD/min/mg

SD-C  SD-A  Ren2-C  Ren2-A
mOD/min/mg
Role of the NADPH Oxidase and Ang II/MR Generation of ROS

ANG=angiotensin; ROS=reactive oxygen species.
Soleus/Aliskiren/NADPH Oxidase Subunits

Nox2

Soleus/Aliskiren

Rac

Average Gray Scale Intensities

Soleus/Aliskiren

gp91

Rac

SDC

SDA

R2C

R2A

**
Direct renin inhibition improves IRS-1, Akt, and GLUT-4 in soleus of Ren2 rat.
Aliskiren/3-Nitrotyrosine (Islets)

Pancreas/3-Nitrotyrosine

Average Gray Scale Intensities

SDC SDA R2C R2A

Ren2-C Ren2-A

SDC SDA R2C R2A
## Microalbuminuria and Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Chronic Kidney Disease</th>
<th>Microalbuminuria</th>
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<tbody>
<tr>
<td><strong>Components</strong></td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>4</td>
<td>4.2</td>
</tr>
<tr>
<td>5</td>
<td>5.9</td>
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</tbody>
</table>

Adjusted for age, race or ethnicity, sex, nonsteroidal anti-inflammatory drug use in past month, high school education, physical inactivity, and current or former smoking.

*Compared with those with 0 or 1 component of the metabolic syndrome.

OR=odds ratio.

Microalbuminuria: A Manifestation of Diffuse Endothelial Cell Injury

Systemic Vasculature

Interstitial Albumin Leak

Injured Endothelium

Cardiovascular Risk Factors
- Age
- Diabetes
- Hypertension
- Smoking
- Absent nocturnal BP dipping
- Salt sensitivity
- Left ventricular hypertrophy
- Dyslipidemia
- Central obesity
- Insulin resistance
- Elevated CRP
- Sympathetic dysfunction
- Hyperuricemia

Renal Vasculature

Microalbuminuria
Microalbuminuria Predicts CV Risk at Levels Below Current Definition

*Microalbuminuria assessment in patients with hypertension and diabetes improves CV risk stratification.*

<table>
<thead>
<tr>
<th>Quintile of urine A/C ratio (mg/g)</th>
<th>Adjusted hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6.9</td>
<td>0</td>
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<tr>
<td>≥6.9 – &lt;17.2</td>
<td>0.5</td>
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<tr>
<td>≥17.2 – &lt;45.0</td>
<td>1.5</td>
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<tr>
<td>≥45.0 – &lt;149.4</td>
<td>2.5</td>
</tr>
<tr>
<td>≥149.4</td>
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</tbody>
</table>

**LIFE Study: Composite Endpoint**

Quintile of urine A/C ratio (mg/g) among 1,063 hypertension patients with diabetes.
Proteinuria in Ren 2 Rats

Whaley-Connell A et al. AJP 2006
Renal ROS
Kidney Tissue Malondialdehyde

μM MDA: mg protein

SD control  Ren-2  Ren2+Aliskerin

\( P < .05 \)

A: SD-C

SD-A

B: 3-Nitrotyrosine

Ren2-C

Ren2-A

Average Gray Scale Intensities

SD-C    SD-A    Ren2-C  Ren2-A
Summary

• Ang II and Aldo stimulates production of ROS in skeletal muscle, Cardiovascular, and Kidney.

• NADPH Oxidase is a source of Renin, Ang II and Adosterone generated ROS in Vascular, Skeletal Muscle, and Renal Tissue.

• RAAS Stimulated ROS - a common mechanism of Structural and Functional abnormalities.

• Blocking MR and Inhibiting Renin Improve Glucose Metabolism and reduce Cardiovascular and Kidney disease.