AGING, INSULIN RESISTANCE AND THE METABOLIC SYNDROME

Kitt Falk Petersen, M.D.
Yale University School of Medicine
Prevalence of Diabetes and Glucose Intolerance

## Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Young (n=13)</th>
<th>Elderly (n=15)</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27±2</td>
<td>71±4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>71±4</td>
<td>70±3</td>
<td>NS</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24±1</td>
<td>25±1</td>
<td>NS</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>28±3</td>
<td>29±2</td>
<td>NS</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>20±2</td>
<td>20±2</td>
<td>NS</td>
</tr>
<tr>
<td>Lean Body Mass (kg)</td>
<td>54±5</td>
<td>49±3</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting Glucose (mg/dL)</td>
<td>90±3</td>
<td>94±3</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting Insulin (µU/ml)</td>
<td>9±1</td>
<td>10±1</td>
<td>NS</td>
</tr>
</tbody>
</table>

_Petersen et al, Science 300:1140, 2003_
Oral Glucose Tolerance Test - Glucose

![Graph showing glucose levels over time for young and elderly individuals. The graph illustrates the rise and fall of glucose levels with time, with distinct curves for each group.]
Oral Glucose Tolerance Test - Insulin

![Graph showing Insulin levels over time for Young and Elderly groups.](image-url)
Rates of Insulin Stimulated Whole Body Glucose Uptake

$P=0.002$

$\mu\text{mol} / (\text{kg LBM-min})$

Young

Elderly

Petersen et al, Science 300:1140, 2003
$^1$H spectrum of the soleus muscle of a lean subject

Diabetologia 1999;42:113-116
$^1$H MRS Spectrum of Liver

Coil
Voxel

H$_2$O
Lipid

(ppm)

6 5 4 3 2 1 0
Intramyocellular and Hepatic Triglyceride Content

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramyocellular Triglyceride (%)</td>
<td>0.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Hepatic Triglyceride (%)</td>
<td>1.2</td>
<td>0.8</td>
</tr>
</tbody>
</table>

P < 0.006

P < 0.03

Petersen et al, Science 300:1140, 2003
Muscle

- PI 3 kinase
- GLUT 4
- AKT
- nPKC
- IRS-1 serine/threonine phosphorylation
- IRS-1 tyrosine phosphorylation
- serine/threonine kinase cascade
- fatty acyl CoA
- diacylglycerol
- plasma glucose
- plasma fatty acid

Insulin

Shulman JCI 2000, Savage, Petersen et al. Physiological Reviews 2007
Insulin

IRS-2 tyrosine phosphorylation

PI 3 kinase

GLYCOGEN

GS

DAG

TAG

PKCε

serine/threonine kinase cascade

Liver

plasma glucose

plasma fatty acid

Increased Fatty Acid Delivery and/or Decreased Fatty Acid Oxidation?

Petersen et al, Science 300:1140, 2003
Rates of Whole Body Glycerol Turnover

Petersen et al, Science 300:1140, 2003
Potential Role of Mitochondrial Dysfunction
$^{31}$P NMR measurement of ATP synthase flux

Petersen et al, Science 300:1140, 2003
\(^{13}\text{C}\) NMR measurement of TCA cycle

- Acetate \(^{13}\text{C}2\)
- Acetyl CoA
- \(^{13}\text{Citrate}\)

**TCA Cycle Flux**

- \(\alpha\text{KG} \leftrightarrow \text{Glu}^{13}\text{C}4\)
- \(\text{Glu}^{13}\text{C}2\) on the 2\(^{nd}\) turn
Mitochondrial Oxidative-Phosphorylation Activity

TCA Flux Rates

- Young: 100 nmol/g/min
- Elderly: 60 nmol/g/min

ATP Synthesis Rates

- Young: 8.00 µmol/g/min
- Elderly: 4.00 µmol/g/min

P<0.006

P<0.004

Petersen et al, Science 300:1140, 2003
Mitochondrial Oxidative-Phosphorylation Activity is Reduced in the Elderly

Petersen et al, Science 300:1140, 2003
The Road to Insulin Resistance

- Defects in Adipocyte Fatty Acid Metabolism
- Acquired (aging) or Inherited (IR Offspring) Defects in Mitochondrial Metabolism
- Caloric Intake
Effects of Aging on Neuronal Mitochondrial Metabolism
$^{13}$C MRS Studies of Brain Metabolism

N=8 young: 27±3 years

N=7 elderly: 76±3 years

Neuronal TCA Activity: [1-$^{13}$C]glucose

Boumezbeur et al. J Cerebral Blood Flow & Metab., 2009
Neuronal TCA Cycle Flux

(µmol per gram per min)

Young  Elderly

P = 0.01
28%

Boumezbeur et al. J Cerebral Blood Flow & Metab. 1-11, 2009
Brain Composition and Atrophy with Aging

Boumezbeur et al. J Cerebral Blood Flow & Metab. 1-11, 2009
Can Overexpression of Catalase in the Mitochondria Prevent Age-Associated Muscle Insulin Resistance?
MCAT mice are protected from age-associated mtDNA damage in skeletal muscle.
MCAT mice are protected from age-associated reduction in mitochondrial activity

**In Vitro**
State III oxygen consumption

**In Vivo**
Muscle ATP synthesis by $^{31}$P MRS

Lee et al. Cell Metabolism 12, 668–674, 2010
MCAT mice are protected from age-associated muscle insulin resistance

Rates of Glucose Uptake (mg/[kg/min])

- Young WT
- Young MCAT
- Old WT
- Old MCAT

P< 0.01

P= 0.01

Lee et al. Cell Metabolism 12, 668–674, 2010
Offspring of Patients With Type 2 Diabetes

- 40% lifetime risk of developing type 2 diabetes
- Insulin resistance is the best predictor

Insulin Sensitivity Index (n=\sim 200)

In the chart, "Insulin Resistant (+FHx)" and "Insulin Sensitive" are represented by bars. The number of subjects is indicated on the y-axis, ranging from 0 to 30. The x-axis represents values from 1.5 to 10.0.

The Metabolic Syndrome

Type 2 diabetes

Atherosclerosis

Hypertension

Hypertriglyceridemia

Impaired glucose tolerance

Decreased fibrinolytic activity

Decreased HDL

Inflammation

Polycystic ovarian syndrome

Hyperuricemia

Insulin Resistance or Abdominal Obesity?
Hypothesis

Insulin resistance in muscle promotes the development of atherogenic dyslipidemia by changing the pattern of energy deposition.
MRI Slices of Intra-Abdominal Fat
3-D Reconstruction of Intra-Abdominal Fat
Intra-Abdominal Fat Content

Volume (mL)

Insulin Sensitive

Insulin Resistant
Protocol

6am     12pm     6pm     12am     6am

$^1$H MRS

Meals*

D$_2$O

DNL

*Liquid Meals: 125% of daily total energy requirements (+ 25% additional sucrose)
% 64 carbohydrate, % 28 fat, & % 8 protein
Plasma Insulin Concentrations

Meal 10 A.M.
Meal 2:30 P.M.

No difference
TNFα
RBP-4
HMW adiponectin
IL-6
Resistin

Petersen et al. PNAS (2007)
### Change in Muscle and Liver Glycogen

**Muscle**

- **Insulin Sensitive**
- **Insulin Resistant**

<table>
<thead>
<tr>
<th>(mmol/L)</th>
<th>P=0.003</th>
<th>60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Sensitive</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Insulin Resistant</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Liver**

- **Insulin Sensitive**
- **Insulin Resistant**

<table>
<thead>
<tr>
<th>(mmol/L)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Sensitive</td>
<td>80</td>
</tr>
<tr>
<td>Insulin Resistant</td>
<td>60</td>
</tr>
</tbody>
</table>
Change in Muscle and Liver Triglyceride Content

**Intramyocellular**

- **Insulin Sensitive**
  - Value: 0.0
- **Insulin Resistant**
  - Value: 0.1

**Liver**

- **Insulin Sensitive**
  - Value: 0.4
- **Insulin Resistant**
  - Value: 0.6

**P<0.05**

- Difference: 0.2

**140%**
De Novo Lipogenesis by $^{2}\text{H}_2\text{O}$

![Graph showing De Novo Lipogenesis comparison between Insulin Sensitive and Insulin Resistant groups.](Image)

- **Petersen et al. PNAS (2007)**

  - **Insulin Sensitive**
    - **Insulin Resistant**
  
  - **P = 0.00005**
  - **220%**
Fasting Plasma Lipids

Triglyceride

P < 0.009

HDL

P = 0.01

Petersen et al. PNAS (2007)
Glucose

Glycogen

De novo lipogenesis

Insulin Sensitive

Insulin Resistant

Triglyceride

HDL

NAFLD

Glycogen

Glycogen

Glucose

De novo lipogenesis

Insulin Resistant

NAFLD
Can this abnormal pattern of energy storage be reversed by a single bout of exercise?
Effects of Exercise on Insulin-Stimulated Muscle Glycogen Synthesis

**μmol** (liter muscle · min)

Pre-Training

Post-Training

IR OFFSPRING

CONTROLS

100%

Mechanisms by which exercise reverses insulin resistance

AMPK

Plasma glucose

GLUT 4

Glucose

Exercise

PLasma glucose

GLUT 4

Glucose

Exercise

AMPK

ACC
Postprandial Increase in Muscle Glycogen

Rabøl et al. PNAS 2011
Postprandial Change in Liver Triglyceride

Rabøl et al. PNAS 2011
Hepatic De Novo Lipogenesis

Rest  Exercise

(Percent)

P<0.01

30%

Rabøl et al. PNAS 2011
Insulin Resistant

Single-Bout of Exercise

Liver TG Content

de novo lipogenesis

Glucose

Exercise

Glycogen

Liver TG Content
de novo lipogenesis

Glycogen
Can this muscle insulin resistance be reversed by modest weight reduction?
IMCL Before and After Weight Reduction

Intramyocellular Lipid Content (%)

Post Weight Loss

Pre Weight Loss

P=0.045

Petersen et al. PNAS, 2012
Effects of Modest Weight Reduction on Muscle Insulin Sensitivity

Petersen et al. PNAS, 2012
Cellular Mechanisms of Insulin Resistance

- Defects in Adipocyte Fatty Acid Metabolism
- Caloric Intake
- Acquired (aging) or Inherited (IR Offspring) Defects in Mitochondrial Metabolism
Collaborators

Tiago Alves
Douglas Befroy
Kevin Behar
Fawzi Boumezbeur
Sylvie Dufour
Clare Flannery
Rina Garcia
Anne Impellizeri
Silvio Inzucchi

Yanna Kosover
Martin Krssak
Vincent Lebon
Graeme Mason
Gianluca Perseghin
Rasmus Rabøl
Varman Samuel
Jun Shen
Irina Smolgovsky
Shin Yonemitsu
Xian-Man Zhang

Howard Hughes Medical Institute
Gerald I. Shulman

Yale-Diabetes Endocrine Research Center
Gary W. Cline (Stable Isotope Core)

Yale-Magnetic Resonance Center
Douglas Rothman

Yale-Center for Clinical Investigation
Gina Solomon
Catherine Parmelee
Mikhail Smolgovsky

ADA Distinguished Clinical Scientist Award,
NIH R01 AG-23686, R01 NS-087568, R24 DK-085638