ADME in NAFLD: Genes and Big Jeans Increase the Risk of Adverse Drug Reactions

Nathan J. Cherrington, Ph.D.

Drug-Induced Liver Injury
Dec 11th, 2003 The Economist

Obesity: An Increasing Health Crisis

Obesity Trends* Among U.S. Adults
BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Obesity Trends* Among U.S. Adults
BRFSS, 1986
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data           <10%        10%–14%

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/

Obesity Trends* Among U.S. Adults
BRFSS, 1987
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data           <10%        10%–14%

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Obesity Trends* Among U.S. Adults
BRFSS, 1988
(*BMI ≥ 30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data           <10%        10%–14%

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/

Obesity Trends* Among U.S. Adults
BRFSS, 1989
(*BMI ≥ 30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data           <10%        10%–14%

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Obesity Trends* Among U.S. Adults
BRFSS, 1990
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

Obesity Trends* Among U.S. Adults
BRFSS, 1991
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1992
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/

Obesity Trends* Among U.S. Adults
BRFSS, 1993
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Obesity Trends* Among U.S. Adults
BRFSS, 1994
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data  <10%  10%–14%  15%–19%

Obesity Trends* Among U.S. Adults
BRFSS, 1995
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data  <10%  10%–14%  15%–19%

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Obesity Trends* Among U.S. Adults
BRFSS, 1996
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

Obesity Trends* Among U.S. Adults
BRFSS, 1997
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1998
(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

No Data          <10%         10%–14%         15%–19% ≥20%

Obesity Trends* Among U.S. Adults
BRFSS, 1999
(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

No Data          <10%         10%–14%         15%–19% ≥20%
Obesity Trends* Among U.S. Adults
BRFSS, 2000
(*BMI ≥30, or ~ 30 lbs. overweight for 5’4” person)

No Data  <10%  10%–14%  15%–19%  ≥20%

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/

Obesity Trends* Among U.S. Adults
BRFSS, 2001
(*BMI ≥30, or ~ 30 lbs. overweight for 5’4” person)

No Data  <10%  10%–14%  15%–19%  20%–24%  ≥25%

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Obesity Trends* Among U.S. Adults
BRFSS, 2002
(*BMI ≥30, or ~ 30 lbs. overweight for 5’4” person)

No Data          <10%         10%–14%         15%–19%          20%–24%          ≥25%

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/

Obesity Trends* Among U.S. Adults
BRFSS, 2003
(*BMI ≥30, or ~ 30 lbs. overweight for 5’4” person)

No Data          <10%         10%–14%         15%–19%          20%–24%          ≥25%

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Obesity Trends* Among U.S. Adults
BRFSS, 2004
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

Obesity Trends* Among U.S. Adults
BRFSS, 2005
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Obesity Trends* Among U.S. Adults
BRFSS, 2006
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/

Obesity Trends* Among U.S. Adults
BRFSS, 2007
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Obesity Trends* Among U.S. Adults
BRFSS, 2008
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

Obesity Trends* Among U.S. Adults
BRFSS, 2009
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Obesity Trends* Among U.S. Adults
BRFSS, 2010
(*BMI ≥30, or ~30 lbs. overweight for 5’ 4” person)

Prevalence of Nonalcoholic Fatty Liver Disease in U.S.

308 million

Prevalence of Nonalcoholic Fatty Liver Disease in U.S.

- Metabolic Syndrome in the liver is manifested as Nonalcoholic Fatty Liver Disease


Prevalence of Nonalcoholic Fatty Liver Disease in U.S.

Prevalence of Nonalcoholic Fatty Liver Disease in U.S.

- **Healthy**: 180-210 million
- **Steatosis**: 40-105 million
- **Steatohepatitis**: 15-50 million
- **Diagnosed**: 300,000

NAFLD Comprises a Spectrum of Pathologic Severity

Healthy liver  Steatosis  NASH w/fat  NASH not fatty (Cirrhosis)

- benign
- reversible
- steatosis
- inflammation
- irreversible scarring
- end-stage
- progressive fibrosis

NAFLD = Nonalcoholic Fatty Liver Disease
NASH = Nonalcoholic Steatohepatitis
The Liver is the Major Organ of Drug Metabolism and Elimination

HEPATOCYTE

SINUSOIDAL BLOOD

Phase I Drug Metabolism
- Cytochrome P450s

Phase II Drug Conjugation

Phase III Transport

BILE

HEPATOCYTE

HEPATOCYTE
Drug Metabolizing Enzyme Protein Expression in NAFLD Patients

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Steatosis</th>
<th>NASH (fatty liver)</th>
<th>NASH (not fatty)</th>
<th>Densitometry Statistics</th>
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</thead>
<tbody>
<tr>
<td>CYP1A2</td>
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<td></td>
<td></td>
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<td>↓ Trend (*p&lt;0.001)</td>
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<tr>
<td>CYP2A6</td>
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<td>↑ Trend (*p&lt;0.020)</td>
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<tr>
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<td>↓ Trend (*p&lt;0.010)</td>
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<tr>
<td>CYP2C19</td>
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<td></td>
<td></td>
<td>↑ Trend (*p&lt;0.008)</td>
</tr>
<tr>
<td>CYP2D6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ Trend (*p&lt;0.010)</td>
</tr>
<tr>
<td>CYP2E1</td>
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<td></td>
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<td>↑ Trend (p=0.112)</td>
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<tr>
<td>CYP3A4</td>
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<tr>
<td>GAPDH</td>
<td></td>
<td></td>
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</tbody>
</table>

* Indicates significant trend with progressive disease states (p < 0.05)


Drug Metabolizing Enzyme Activity in NAFLD Patients

- Phenacetin O-Dealkylation: ↓ Trend p = 0.001
- Hydroxytiobutamide Metabolism: ↑ Trend p = 0.004
- Testosterone 6β-Hydroxylase Metabolism: ↓ Trend p = 0.180
- Diclofenac Metabolism: ↑ Trend p = 0.0001

Nrf2 Activation in All Stages of NAFLD

The Affect of NAFLD on NQO1

Ref: Hardwick et al. DMD. 2010: 38(12):2293-301
Global Gene Expression

All genes

DMEs

Overexpression

No change

Downregulation

Ref: Lake et al. DMD. 2011: 39(10):1954-60

33,252 genes-Affymetrix Genechip Human 1.0 ST Array

Ref: Lake et al. DMD. 2011: 39(10):1954-60
Global Gene Expression

Ref: Lake et al. DMD. 2011: 39(10):1954-60
Global Gene Expression

Uptake Transporters

Ref: Lake et al. DMD. 2011: 39(10):1954-60

NAFLD Alters BSP Clearance

Figure 5 Functional BSP Disposition in NASH

The Liver is the Major Organ of Drug Metabolism and Elimination

Hepatocyte Sinusoidal Blood Bile

Phase I Drug Metabolism - Cytochrome P450s
Phase II Drug Conjugation

OH

COO\(^{-}\)H

OH

OH

O

Efflux Transporter Protein Expression

<table>
<thead>
<tr>
<th>Protein</th>
<th>Normal</th>
<th>Steatosis</th>
<th>NASH (fatty)</th>
<th>NASH (not fatty)</th>
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<td>ABCC1</td>
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<td>Pan-Cadherin</td>
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<td><img src="image31.png" alt="Image" /></td>
<td><img src="image32.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Ref: Hardwick et al. DMD. 2011: Epub ahead of print
**ABCC3 Immunohistochemistry**

Normal
Steatosis
NASH (fatty)
NASH (not fatty)

Ref: Hardwick et al. DMD. 2011: Epub ahead of print

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**Cellular Localization of ABCC2**

Normal
Steatosis
NASH (fatty)
NASH (not fatty)

Ref: Hardwick et al. DMD. 2011: Epub ahead of print
Cellular Localization of ABCC2

Normal NASH (not fatty)

Ref: Hardwick et al. DMD. 2011: Epub ahead of print

Normal Steatosis NASH (fatty) NASH (not fatty)

ABCC2

Cadherin

Ref: Hardwick et al. DMD. 2011: Epub ahead of print

APAP Elimination in Normal Liver

BLOOD LIVER BILE

APAP-Gluc APAP-Sulf
APAP Elimination in Normal Liver

BLOOD  LIVER  BILE

APAP-GLuc  APAP-Sulf

APAP Elimination in NASH

BLOOD  LIVER  BILE

APAP-GLuc  APAP-Sulf
APAP Elimination in NASH

APAP = Acetaminophen

*p < 0.05 significant vs. Control

APAP Disposition

**Rat Plasma**

- APAP (nmol/ml)
- APAP-Glu (nmol/ml)
- APAP-Sulf (nmol/ml)

**Human Plasma**

- APAP (nmol/ml)
- APAP-Glu (nmol/ml)
- APAP-Sulf (nmol/ml)

**Ref:** Lickteig et al. DMD, 2007: 35(10):1970-8

*APAP = Acetaminophen

* $p < 0.05$ significant vs. Control

**Ref:** Merrell et al. unpublished data

*APAP = Acetaminophen

* $p < 0.05$ significant vs. Control
Ezetemibe Disposition

Liver

- EZE
- EZE-GLUC

Small Intestine

Abcc2 and Abcb1 Localization

Control

MCD

Abcc2

Abcb1

Ref: Hardwick et al. unpublished data
EZE and EZE-Gluc Disposition

Plasma

Ref: Hardwick et al. unpublished data

Drug-Induced Liver Injury

Minimal Toxicity

Toxicity

Exposure
Summary

- Drug Metabolizing Enzyme and Transporter expression changes occur during the transition from simple fatty liver to NASH
- Mechanisms of regulating DME and Transporter function during NASH may be controlled at the transcription, post-translational modification, and cellular localization levels
- Changes in the expression of the ADME battery of genes results in altered disposition and exposure of numerous drugs and xenobiotics
- Understanding inter-individual variation in drug metabolism may help lead to “personalized medicine”

Acknowledgments

- Cherrington Lab
  Andrew Lickteig, Ph.D.
  Craig Fisher, Ph.D.
  Lisa Augustine
  Matthew Merrell, Ph.D.
  Rhiannon Hardwick
  Lisa Beilke, Ph.D.
  Jonathan Jackson, Ph.D.
  April Lake
  Mark Canet
  David Klein
- Jose E. Manautou, Ph.D.
  Sarah Campion, Ph.D.
  - University of Connecticut
- Angela Slitt, Ph.D.
  - University of Rhode Island
- Lauren Aleksunes, Ph.D.
  - Rutgers University
- Michael Goedken, Ph.D.
  - Merck
- Steven Ferguson, Ph.D.
  - Invitrogen
- Walter Klimecki, Ph.D.
- Dean Billheimer, Ph.D.
- Robert P. Erickson, M.D.
- H. Hesham A-Kader, M.D.
- Petr Novak, Ph.D.
- Leif Abrell, Ph.D.
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Funding:
- HRAA
- NICHD HD062489
- NIDDK DK068039
- NIAID AI083927
- NIEHS ES011646, ES007091, ES006694