Non-alcoholic Fatty Liver Disease in PCOS

Walter Futterweit, M.D., F.A.C.P., FACE
Clinical Professor of Medicine
Division of Endocrinology
Mount Sinai School of Medicine

Liver Histology: the Hepatocyte

- Arranged into cords which are separated by vascular sinusoids
- Mostly bright pink hepatocyte cytoplasm
- They are separated by the clear space of sinusoids
Non-alcoholic Fatty Liver Disease is Common - NAFLD & NASH pathology

Population Prevalence:
NAFLD 16-23%
NASH 2-6%
(varies by ethnicity, BMI, age and gender globally)

NASH has more ballooning of hepatocytes -> PMN Neutrophilic and LC infiltrates, cellular lobular necrosis, Mallory bodies, some fibrosis


Increasing Severity of NAFLD -> NASH

Hepatocyte ballooning with hyaline Mallory bodies, Pericellular and perisinusoidal fibrosis & collagen
Spectrum of NAFLD

- Simple hepatic steatosis (NAFLD) is most frequent, usually benign, and asymptomatic.

- 10% have or develop liver injury and necroinflammation which is nonalcoholic steatohepatitis (NASH) and up to 20% of NASH subjects may progress to more advanced liver disease.

- Cirrhosis may occur in ~ 30% of NASH patients and some may develop hepatocellular carcinoma (increased 2-3 fold in T2DM).

Browning JD et al. Hepatology 2004;40:1387
**Spectrum of NAFLD (cont’d)**

- The increased incidence of global obesity is distinctly a NAFLD contributing factor associated with a higher IR & MS prevalence.

- A large 2,287 multi-ethnic population-based study in the USA found a 34% prevalence of hepatic steatosis, NL ALT in 79%. Caucasian males had almost 2-fold increase of NAFLD than women (42% vs 24% in women). Highest incidence was in Hispanic obese IR women with hepatic steatosis in 45%. Lowest incidence was in African Americans (24%) and higher in women.

Browning JD et al. Hepatology 2004;40:1387

---

**NAFLD: DX and Imaging**

- Liver biopsy is the “gold standard” for diagnosis (when to Bx)
- US: sensitivity 60-99%
  - specificity 84-95%
  - 100% sensitive in detecting >33% fat on biopsy
- Imaging generally underestimates presence of steatosis
- No imaging modality allows staging of NAFLD
- CT scanning reveals low density hepatic parenchyma with occasional focal areas which may be misread as masses. MRI can differentiate masses and may allow a more quantitative assessment of fatty infiltration of liver
- No reliable serum markers have been found to stage NAFLD

**Link of NAFLD to Metabolic Syndrome**

**NAFLD**
- 70% of obese population
- USA prevalence 23-34%
- Risk factors similar to those of NASH & central obesity
- Obesity predisposes to the frequent presence of MS-> ~50% have IGT or T2DM, and/or dyslipidemia (TG)
- Nondiabetics with MS and increased data suggestive IR have a prevalence of NAFLD > those with lower IR indices

**NASH**
- Risk factors: obesity, type 2 DM, hyperlipidemia (mostly hypertriglyceridemia): the MS
- Treatment with TZD may reduce hepatic acute phase reactants -> improved insulin sensitivity & inflammation. ? Metformin helpful as well. Confirmatory tests of liver pathology not done as yet with TZDs or metformin
- 10-11% wgt loss and exercise may reverse NASH. Biopsy Dx pre and post-biopsy reported in PCOS case report

Angelico F et al. JCEM 2006;90:1578

**Non-alcoholic Fatty Liver Disease and the Metabolic Syndrome**

- **NAFLD:** Obesity 60-95%
  - DM 21-55%
  - hTG 20-92%
- **Morbidly obese:** >95% NAFLD
  - 25% NASH (biopsy)

NAFLD: The Hepatic Component of the Metabolic Syndrome?

- Association with biochemical manifestations of IR

- Is NAFLD a predictor of MS in general population? In a study of 326 subjects -> 29% NAFLD, 13% MS. Those with the MS had an NAFLD prevalence of 71%. and also had significantly higher glucose, insulin, TG, serum ALT, BMI and central obesity than non-NAFLD subjects

- Pts with T2DM and NAFLD have a 2-3 fold higher incidence of acute MI than those without NAFLD independent of BMI. NAFLD likely marker of CHD?


NAFLD: The Hepatic Component of the Metabolic Syndrome? (cont’d)

- NAFLD in lean and overweight Korean population demonstrated 16% and 23% prevalence, respectively (increased CHO intake). NAFLD was associated with IR in both the lean and overweight subjects

Central obesity was signif correlated with NAFLD in the lean. Its association with MS variables were similar to overweight without NAFLD

NAFLD and Insulin Resistance

- Frequently present in peripheral IR such as T2DM and obesity. Severity NAFLD ~ increased IR in nondiabetics.
- Hepatic IR likely plays a role in the pathogenesis and progression of NAFLD, and increases with age (M~F).
- Excessive triglyceride accumulation in liver.
- IR association with increased hepatic iron levels.
- Decreased plasma adiponectin (exclusion of T2DM) is associated men>women with increased fat content and necroinflammation in NAFLD and may->NASH. These may be related to reduced hepatic insulin sensitivity.

Bugianese E et al. JCEM 90:3498   Targher G et al 2004;Clin Endocrinol 61:700

Multiple “Hits” to NASH

- Normal liver
- Simple steatosis
- NASH
- Cirrhosis HCC

Insulin resistance
- ↑ FFA synthesis
- ↑ FFA delivery to liver
- ↓ FFA degradation
- ↓ TG release from liver
- ↑ TG in hepatocytes

Oxidative stress
Cytokines
FFAs, low adiponectin
Increased Iron
Leptin? Increased-> fibrosis
TNF-alpha cytokine

Adapted from Collantes R, Ong JP, and Younossi ZM, Cleveland Clinic Journal of Medicine 2004; 71(8):657.
Global Prevalence of NAFLD: US

- **ALL**: 76%
- **OVT**: 34%
- **LEAN**: 16%
- **OBS**: 16%

**China (1)**
**India (2)**
**Japan (3)**
**Italy (4)**
**Korea (5)**

3) Omagari K et al. *J of Gastroenterology and Hepatology* 2002; 17:1098.

---

**PCOS and the MS**

- PCOS is the most common cause of the MS and related disorders in young women
- Prevalence is about 7-fold higher than that of a female population of similar age in the USA
- Changes in BMI in many countries compared to those in the USA reduces its prevalence ~ 4-fold that of a young female population of similar age

**Apronidze T et al. J Clin Endocrinol Metab 2005;90:1929**
**Carmina E. J. Hepatology 2007;47:313**
AIMS of Study of NAFLD in PCOS

- Prevalence of NAFLD in women with PCOS by US criteria

- Predictors of NAFLD in women with PCOS

METHODS

- Retrospective study
- Study population: • 88 consecutive pre-menopausal women with PCOS from 4/04 to 11/04 (office setting)
  • ≥18 yo (median 31.4yrs)
  • PCOS: menstrual dysfunction, hyperandrogenism, and the exclusion of other causes (1990 NIHC)
- Exclusion criteria: (PCOS women with regular menses)
  • Heavy alcohol use (>1-2 drinks, or >20g EtOH/day)
  • Known liver disease


METHODS: Data

- Clinical history
- Blood pressure
- Height and weight
- Fasting glucose and insulin
- Fasting lipid profile
- 75g oral glucose tolerance test
- Liver chemistries
- Abdominal and Pelvic US
METHODS: Data

- Body mass index (BMI):
  - “Lean” BMI < 25 kg/m²
  - “Overweight” BMI ≥ 25 but < 30 kg/m²
  - “Obese” BMI ≥ 30 kg/m²
- HOMA-IR (fasting insulin x fasting glucose / 405)
  - Homeostasis model assessment: a surrogate insulin resistance measure
- Severity of hepatic steatosis (US): graded as
  - none
  - mild
  - moderate
  - severe


RESULTS: % Women on PCOS Therapy

- 36%
- 27%
- 11%
- 25%

- Neither
- Metformin
- OCP
- Both
Grading of Hepatic Steatosis

a: **ABSENT**: the echogenicity of the liver parenchyma is slightly greater or equal to that of the renal cortex; clear visualization of the diaphragm and intrahepatic vessels

b: **MILD**: slight diffuse increase in fine echoes in the liver parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders

c: **MODERATE**: moderate diffuse increase in fine echoes in the liver parenchyma with slightly impaired visualization of intrahepatic vessels and diaphragm

d: **SEVERE**: marked increase in fine echoes with poor or non-visualization of the intrahepatic vessel borders, diaphragm and posterior or deep portion of the right lobe of the liver.

RESULTS:
PCOS Subjects by BMI Group

<table>
<thead>
<tr>
<th>Percent</th>
<th>Obese</th>
<th>Overweight</th>
<th>Lean</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=88

Courtesy of Hsu-Chong Yeh, MD (MSSM)
**RESULTS**

**Prevalence of Steatosis by BMI Group**

- **Overall** 70% *p<0.01 vs. lean population estimates

**Prevalence of Steatosis by HOMA-IR Quartile**

- *p<0.05 vs. Quartile I
### RESULTS: Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects</th>
<th>Steatosis Absent</th>
<th>Steatosis Present</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>31.4 (N=88)</td>
<td>29.0 (N=40)</td>
<td>32.0 (N=48)</td>
<td>0.280</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ashkenazi Jewish</td>
<td>33 (38%)</td>
<td>13 (33%)</td>
<td>20 (42%)</td>
<td>0.208</td>
</tr>
<tr>
<td>- Other White</td>
<td>48 (55%)</td>
<td>25 (63%)</td>
<td>23 (48%)</td>
<td></td>
</tr>
<tr>
<td>- Hispanic</td>
<td>4 (5%)</td>
<td>0 (0%)</td>
<td>4 (8%)</td>
<td></td>
</tr>
<tr>
<td>- Asian</td>
<td>2 (2%)</td>
<td>1 (3%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>- African-American</td>
<td>1 (1%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>26.9 (N=88)</td>
<td>24.3 (N=40)</td>
<td>31.1 (N=48)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mm Hg</strong></td>
<td>111 (N=88)</td>
<td>110 (N=40)</td>
<td>115 (N=48)</td>
<td>0.108</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mm Hg</strong></td>
<td>68 (N=88)</td>
<td>67 (N=40)</td>
<td>70 (N=48)</td>
<td>0.123</td>
</tr>
</tbody>
</table>

All data are medians or counts with proportions of the column using fasting laboratory specimens unless otherwise noted. P-values reflect Mann-Whitney U tests or chi-square tests, as appropriate. Percentages may not total to 100% due to rounding.

###RESULTS: Laboratory Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects</th>
<th>Steatosis Absent</th>
<th>Steatosis Present</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting glucose, mg/dL</strong></td>
<td>86 (N=79)</td>
<td>86 (N=36)</td>
<td>86 (N=43)</td>
<td>0.159</td>
</tr>
<tr>
<td><strong>Fasting insulin, mIU/L</strong></td>
<td>2.7 (N=79)</td>
<td>2.9 (N=36)</td>
<td>12.6 (N=43)</td>
<td>0.059</td>
</tr>
<tr>
<td><strong>HOMA-IR, mmol mIU/L²</strong></td>
<td>2.04 (N=79)</td>
<td>1.50 (N=36)</td>
<td>3.53 (N=43)</td>
<td>0.033</td>
</tr>
<tr>
<td><strong>OGTT, 2hr glucose, mg/dL</strong></td>
<td>93 (N=65)</td>
<td>93 (N=27)</td>
<td>101 (N=38)</td>
<td>0.315</td>
</tr>
<tr>
<td><strong>OGTT, 2hr insulin, mIU/L</strong></td>
<td>46.3 (N=62)</td>
<td>42.0 (N=25)</td>
<td>53.9 (N=37)</td>
<td>0.248</td>
</tr>
<tr>
<td><strong>Presence of IFG, IGT, or DM</strong></td>
<td>36 (42.9%) (N=67)</td>
<td>2 (7.7%) (N=26)</td>
<td>13 (34.3%) (N=41)</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Total cholesterol, mg/dL</strong></td>
<td>193 (N=88)</td>
<td>195 (N=40)</td>
<td>187 (N=48)</td>
<td>0.443</td>
</tr>
<tr>
<td><strong>HDL cholesterol, mg/dL</strong></td>
<td>60 (N=87)</td>
<td>64 (N=40)</td>
<td>52 (N=47)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>LDL cholesterol, mg/dL</strong></td>
<td>105 (N=85)</td>
<td>105 (N=40)</td>
<td>105 (N=45)</td>
<td>0.792</td>
</tr>
<tr>
<td><strong>Triglycerides, mg/dL</strong></td>
<td>97 (N=88)</td>
<td>92 (N=40)</td>
<td>107 (N=48)</td>
<td>0.155</td>
</tr>
<tr>
<td><strong>ALT, U/L</strong></td>
<td>17 (N=88)</td>
<td>25 (N=40)</td>
<td>20 (N=48)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>GGT, U/L</strong></td>
<td>7 (N=81)</td>
<td>14 (N=35)</td>
<td>19 (N=46)</td>
<td>0.023</td>
</tr>
<tr>
<td><strong>Elevated ALT or GGT</strong></td>
<td>9 (10.2%) (N=88)</td>
<td>2 (5.0%) (N=40)</td>
<td>7 (14.6%) (N=48)</td>
<td>0.139</td>
</tr>
</tbody>
</table>

All data are medians or counts with proportions of the column using fasting laboratory specimens unless otherwise noted. P-values reflect Mann-Whitney U tests or chi-square tests, as appropriate. Percentages may not total to 100% due to rounding.
Prevalence of Elevated ALT or GGT in PCOS Study Group

**BMI Category**

- Lean: 3%
- Overweight: 8%
- Obese: 19%*
- Overall: 10%

* *p<0.05 vs. lean

**Grade of Steatosis**

- Absent: 5%
- Mild: 10%
- Moderate: 0%
- Severe: 31%*
- Present: 15%

*p<0.01 vs. absent
p<0.05 vs. moderate

Prevalence of Elevated ALT in PCOS

**Subjects by BMI Group**

- Lean: 20%
- Overweight: 10%
- Obese: 63%

N=70

63% Hispanic, 17% White, 10% Black, 10% Asian

**Elevated ALT**

- 30%

Prevalence of Unexplained Elevation in ALT or AST in the US (NHANES III) (no detectable liver disease or excessive alcohol consumption)


PCOS & persistently elevated LFT’ s may already have NASH

- Persistently elevated aspartate (AST) and/or alanine aminotransferase levels (ALT) U/L > 60U/L suggest the presence of nonalcoholic steatohepatitis (NASH)

- The above were present in 29/200 young women with PCOS (15%) in a Duke University study (Dr. Ann Brown’s Group)

- Liver Bx in 6 such women had Bx-demonstrated evidence of NASH with fibrosis. MS signs were higher in this group than those without liver Bx and nl LFT’s. Mean levels of AST and ALT were 143 and 144 U/L, respectively.

*Setji TL et al. J Clin Endocrinol Metab* 2006;91:1741
### RESULTS: Imaging

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects</th>
<th>Steatosis Absent</th>
<th>Steatosis Present</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of splenomegaly</td>
<td>6 (6.8%) (N=88)</td>
<td>1 (2.5%) (N=40)</td>
<td>5 (10.4%) (N=48)</td>
<td>0.142</td>
</tr>
<tr>
<td>Presence of hepatomegaly</td>
<td>4 (4.5%) (N=88)</td>
<td>0 (0%) (N=40)</td>
<td>4 (8.3%) (N=48)</td>
<td>0.062</td>
</tr>
<tr>
<td>Presence of PCO morphology</td>
<td>64 (72.7%) (N=87)</td>
<td>28 (30.0%) (N=40)</td>
<td>36 (76.6%) (N=47)</td>
<td>0.487</td>
</tr>
</tbody>
</table>

All data are medians or counts with proportions of the column using fasting laboratory specimens unless otherwise noted. P-values reflect Mann-Whitney U-tests or chi-square tests, as appropriate. Percentages may not total to 100% due to rounding.

### Steatosis in Non-obese PCOS Subjects Compared to Controls

Comparing STEATOSIS in PCOS Patients with that in Controls
All Patients and Controls are Lean or Overweight (Obese patients are excluded)

<table>
<thead>
<tr>
<th>BMI</th>
<th>Number</th>
<th>Steatosis Grade (Number, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCOS patients</td>
<td></td>
</tr>
<tr>
<td>BMI&lt;25</td>
<td>38</td>
<td>23 (61%)</td>
</tr>
<tr>
<td>Controls</td>
<td>10</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>BMI 25-30</td>
<td>PCOS patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>6 (46%)</td>
</tr>
<tr>
<td>Controls</td>
<td>12</td>
<td>10 (83%)</td>
</tr>
</tbody>
</table>

The grade of steatosis differs significantly between PCOS patients and controls, p<0.02 by Mantel-Haenszel test for ordered outcomes, stratifying on BMI category.
**US study of NAFLD Prevalence in PCOS (Cerda ’07)**

- A recent study of 41 Chilean women with PCOS (mean age 24.6 and BMI 30.3) noted an US prevalence of NAFLD in 41.5% compared to 19% of 31 controls.
- 9 of 17 with NAFLD (64%) had ALT levels >25 (mean 27.8 IU/L) vs 15.5 in controls (?? Increased NASH).
- 17 PCOS women with steatosis had mean ALT of 38.9 vs 20.0 IU/L in the 24 nonsteatotic PCOS subjects.
- IR was noted in 63% (Insulin, HOMA index) vs 35.5% of nonsteatotic PCOS.
- Similarly, increased WHR was increased in women with NAFLD.

*Cerda C et al, J Hepatology 2007;47:412*

**CONCLUSIONS**

- NAFLD is common in PCOS regardless of BMI.
- Obesity and insulin resistance are important associated factors (as has been shown in other population studies).
- Despite established hepatic steatosis, elevated liver chemistries are relatively uncommon in PCOS.
- As non-alcoholic steatohepatitis may be a risk factor for the development of cirrhosis, hepatic failure and infrequent hepatocellular carcinoma, the high prevalence of hepatic steatosis in young obese and non-obese women with PCOS and frequent normal liver chemistries is of concern.
- Further data are needed to establish the role of lifestyle modification, metformin, TZD’s, & others in its treatment.
Collaborators

- Sanjiv V Kinkhabwala
- Maya Gambarin
- Thomas D Schiano
- Carol A Bodian
- Hsu-Chong Yeh
Comparison of HOMA-IR values between non-obese PCOS Subjects and Controls

<table>
<thead>
<tr>
<th>PCOS Women (nonobese)</th>
<th>Normal Controls (nonobese)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 47</td>
<td>N=18</td>
</tr>
<tr>
<td>Median HOMA-IR= 1.40</td>
<td>= 1.30</td>
</tr>
<tr>
<td>Min, Max = 0.35, 9.50</td>
<td>= 0.62, 2.30</td>
</tr>
</tbody>
</table>

No statistical comparison of HOMA-IR was possible in these 2 groups due to too few controls.

The HOMA-IR values for 3 steatosis controls were a Median value of 1.43 with a range of 1.14-2.06. The 15 controls without steatosis had a Median and Range of 1.17 and 0.62-2.27. (No HOMA-IR data in 4 of the 22 control subjects).
Should NAFLD be Included in the Definition of Metabolic Syndrome?

- HOMA-IR >2, oxidative stress, and circulating adipokines were correlated to ATP III criteria, and to NAFLD in 197 healthy nonobese nondiabetics
- NAFLD more accurately predicted IR then ATP III criteria (including studies of circulating adipokines)
- Adding NAFLD to ATP criteria significantly improved diagnostic accuracy for IR, independent of adiposity, or any feature of the MS in IR subjects

Musso G et al, Diabetes Care 2008;31:562

Future Investigations for Rx NAFLD

- Insulin sensitizers
  - Metformin
  - TZD' s- piagliitazone

Cochrane Database System Review
2007 (1-24-07), Angelico F et al (Rome)
Prevalence of Elevated ALT in PCOS

Subjects by BMI Group

- Obese
- Overweight
- Lean

N=70

Elevated ALT

30%

Adapted from Schwimmer JB, Khorram O, Chiu V, and Schwimmer WB. *Fertility and Sterility* 2005; 83(2):494-497
Table: Prevalence and severity of steatosis by BMI group.

<table>
<thead>
<tr>
<th>BMI group</th>
<th>N</th>
<th>None %</th>
<th>Mild %</th>
<th>Moderate %</th>
<th>Severe %</th>
<th>Overall Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean</td>
<td>33</td>
<td>61</td>
<td>26</td>
<td>11</td>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td>Overweight</td>
<td>13</td>
<td>46</td>
<td>23</td>
<td>15</td>
<td>15</td>
<td>54</td>
</tr>
<tr>
<td>Obese</td>
<td>37</td>
<td>30</td>
<td>22</td>
<td>14</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>45</td>
<td>24</td>
<td>13</td>
<td>38</td>
<td>55</td>
</tr>
</tbody>
</table>
Prevalence and Grade of Steatosis in Overweight and Lean PCOS Women Compared to Control Subjects

The proportion of patients with steatosis differs significantly between PCOS patients and controls, p<0.05 by Mann-Whitney U test for ordered outcome, stratifying on BMI category.

Age and the MS: PCOS and Women of NNANES III

Fig. 1

Fig. 1. Age-specific prevalence of the MS among 126 women with PCOS compared with the prevalence of MS among a representative sample of U.S. women (NHANES III, 1988-1994). Results are expressed as percentage (95%) CI. The prevalence of MS was different across 4 age groups of women with PCOS (Cochran-Armitage trend test, P < 0.001). Reproduced with permission J Clin Endocrinol Metab 2003;88:1169-1185. Copyright © 2010, The Endocrine Society. All rights reserved.

Prevalence of Steatosis by BMI of PCOS Women

Table: Prevalence and severity of steatosis by BMI group.

<table>
<thead>
<tr>
<th>BMI group</th>
<th>N</th>
<th>None %</th>
<th>Mild %</th>
<th>Moderate %</th>
<th>Severe %</th>
<th>Overall Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean</td>
<td>38</td>
<td>61</td>
<td>26</td>
<td>11</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Overweight</td>
<td>13</td>
<td>45</td>
<td>23</td>
<td>15</td>
<td>35</td>
<td>54</td>
</tr>
<tr>
<td>Obese</td>
<td>37</td>
<td>30</td>
<td>22</td>
<td>14</td>
<td>35</td>
<td>70</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>45</td>
<td>24</td>
<td>13</td>
<td>38</td>
<td>55</td>
</tr>
</tbody>
</table>
**RESULTS:** Prevalence of Steatosis by BMI Group (off Rx)

Higher BMI group was associated with increasing grade of steatosis, stratifying on treatment with OCP, metformin, neither, or both (Mantel-Haenzsel test, p=0.0005).

**MS and NAFLD in 4400 Japanese Patients**

- A longitudinal study of 4,401 Japanese men and women (aged 21-80 yrs, mean age 47 yrs, BMI 23-25 kg/m2), a causal relationship between the MS and NFLD was noted.
- US evidence of NAFLD was found initially in 18% of participants. After 15 months re-exam -> additional 10% was noted where no NAFLD was present previously.
- 1/3 met the ATP III criteria for the MS, and observed that MS had a 4-11 fold higher risk for NAFLD. In this ethnic group a small increase in weight of 2-3 Kg exerted significant metabolic effects.
- They also demonstrated that minimal weight loss and lifestyle modification was associated with a regression NAFLD in almost all with no prior MS. Conclusion: NAFLD is hepatic expression of MS.