“Health is the thing that makes you feel that now is the best time of the year”

Franklin Pierce Adams

Liver
Liver and Biliary System

Right Hepatic Duct
Left Hepatic Duct
Liver
Pancreas
Stomach
Common Hepatic Duct
Cystic Duct
Common Bile Duct
Duodenum

Gallbladder
Food
Why this topic!

- Wrong topic!
- Heart of the liver is:
  - Gut
  - Bone Marrow
  - Bile
  - Pancreas – Insulin, Glucagon
- What Does Liver Do!
  - What is Central for body!
What Does Liver Do!
What Does Liver Do!

Best tolerogenic organ

Liver functions:
- Synthesis and storage of amino acids, proteins, vitamins, and fats
- Detoxification
- Blood glucose regulation
- Bile drainage
- Blood circulation and filtration

- Iron
- Clotting
- Double blood supply
Liver: Seat of Energy homeostasis

Nutrient-related signals (e.g. FFA) → Glucose production → Energy balance (Food intake vs. Energy expenditure) → Body fat mass

Circulating nutrients → Nutrient availability

Adiposity-related signals (leptin, insulin) → Liver

“Heart of the Liver”

Energy Balance
Outline

• Why the topic
• Liver
• Energy Balance
• Fatty Liver
• Test your Liver
• Excess energy – NAFLD, DM, HT
• Treatment
Human Evolution

19th Century Starvation

21st Century Excess
Liver: The 1st stop of Fat Metabolism

Intestine Fat ++

Liver
Metabolize

++

Adipose Tissue

ADIPOSE TISSUE BUFFER ACTIVE!

Accumulation of blood vessel macrophages
Foamy Cells

Other organs
What Causes Liver Injury!
75.5% linked it with unhygienic food

<table>
<thead>
<tr>
<th>Causes of Liver Diseases</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaking Hands</td>
<td>15</td>
<td>1.5</td>
</tr>
<tr>
<td>Eating Unhygienic Food</td>
<td>761</td>
<td>75.5</td>
</tr>
<tr>
<td>Smoking</td>
<td>121</td>
<td>12.0</td>
</tr>
<tr>
<td>Drinking Alcohol</td>
<td>20</td>
<td>2.0</td>
</tr>
<tr>
<td>Don’t Know</td>
<td>91</td>
<td>9.0</td>
</tr>
</tbody>
</table>
Liver Injury: Hepatitis

Greek ‘itis’ denoting ‘inflammation’

Inflammation of liver

1990

Viruses

Alcohol

Drugs

Obesity

Diabetes

2010

Inflammation of liver

Obesity: Excess Calories

Alcohol

Viruses

Diabetes

Drugs
Is alcohol bad

or

obesity!
Fatty Liver

Alcohol

Fatty liver > 10% liver’s weight

Alcoholic Steatohepatitis (ASH)
Fatty Liver

Alcohol

Fatty liver > 10% liver’s weight

Alcoholic Steatohepatitis (ASH)

Non Alcoholic Steato-Hepatitis, (NASH)

Non-Alcohol
NASH > ASH
N=1000

Obesity, DM, Drugs
Prevalence: 25%

Fatty liver: 80%
Prevalence: 19%

NASH: 20%
Prevalence: 4%

Cirrhosis: 10%
Prevalence: 0.3%

Daily alcohol consumption > 30gm
Prevalence: 10-20%

Fatty liver: 45%
Prevalence: 4-10%

ASH: 85%
Prevalence: 4-8%

Cirrhosis: 3-5%
Prevalence: 0.2-0.3%

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


No Data <10% 10%-14% 15-19% ≥20%

Prevalence of Obesity and Fatty Liver in India

- No Good Data
- 20% overweight, Obese
- 20% Fatty Liver
- 5% Fatty Liver Disease
### Obesity in Indian Children

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Prevalence (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overweight</td>
<td>Obese</td>
<td></td>
</tr>
<tr>
<td><strong>Chennai 1981 (N- 707)</strong></td>
<td>10-15 yrs</td>
<td>9.6%</td>
<td>9.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Delhi, 2002 (N=1988)</strong></td>
<td>10-16 yrs</td>
<td>23.1%</td>
<td>8.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>24.7%</td>
<td>7.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chennai, 2002 (N=3233)</strong></td>
<td>13-18 yrs</td>
<td>17.8%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>15.8%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Obesity and Liver

From Yamai-Zoshi, painted in Japan 800 years ago
Obese People have Fatty Liver

Normal

Fatty Liver
Ultrasound of Fatty Liver

- Fat Layer
- Liver
- Kidney
# Fat in Liver

<table>
<thead>
<tr>
<th></th>
<th>Ultrasound</th>
<th>CT scan</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
</tbody>
</table>

None differentiates steatosis from steatohepatitis.
Normal vs. Fatty Liver
FIBROSIS
Liver Biopsy features of Steatohepatitis

- Steatosis, cytologic ballooning
- Mallory hyaline and inflammation
- Pericellular fibrosis

Room with Cotton!
Non-alcoholic Fatty Liver Disease Spectrum

NAFL → Non-alcoholic Steatohepatitis (NASH) → Cirrhosis

Stage I
- Fat
- Inflammation

Stage II
- Fat + Inflammation
- Ballooning Degeneration

Stage III
- Fat
- Inflammation
- Ballooning Degeneration
- Fibrosis +/− Mallory Bodies

Stage IV
- Fat
- Ballooning Degeneration
- Fibrosis
- Cirrhosis

Brunt et al, 1999
Who wants a Liver Biopsy!

ALTERNATIVE
Fibroscan: Liver stiffness & Liver Fat

A-mode USG. Analysis of the shear wave reflected from the liver. Measures liver stiffness.
Fibroscan: predictive liver stiffness
Fibroscan: Liver stiffness & Liver Fat
Fibroscan: Liver stiffness & Liver Fat

CAP (dB/m)

- IQR: 29 dB/m
- Median: 306 dB/m

E (kPa)

- IQR: 1.0 kPa
- Median: 8.5 kPa

IQR/med.: 12%
Abstract

Background: Hepatic steatosis is an important parameter to assess in chronic liver disease patients. The controlled attenuation parameter (CAP) assesses liver steatosis using transient elastography.

Conclusions: CAP is a novel, non-invasive tool that can detect and quantify steatosis accurately among CHBV, CHCV, and NAFLD patients, the accuracy being similar for all the three groups of patients.
Liver Stiffness Measurements in Patients with Different Stages of Nonalcoholic Fatty Liver Disease: Diagnostic Performance and Clinicopathological Correlation

Ramesh Kumar · Archana Rastogi · Manoj Kumar Sharma · Vikram Bhatia · Pankaj Tyagi · Praveen Sharma · Hitendra Garg · K. N. Chandan Kumar · Chhagan Bihari · Shiv Kumar Sarin

Stiff Liver is bad Liver
How One knows Liver is Unhealthy!

- Nausea, vomit
- Dark Yellow urine, skin, eyes
- Loss of appetite
- Pain in liver area
- Fatigue, weight loss
- Swelling feet
- Generalized Itching
- Darkening of skin
- Blood vomit
Liver cirrhosis

Shrunken, dry hard, nodular liver

Poor Function
Cirrhosis
How One knows Liver is Unhealthy!

• Nausea, vomit
• Dark Yellow urine, skin, eyes
• Loss of appetite
• Pain in liver area
• Fatigue, weight loss
• Swelling feet
• Generalized Itching
• Darkening of skin
• Blood vomit

Don’t Wait Till Symptoms Appear
Outline

- Why the topic
- Liver
- Energy Balance
- Fatty Liver
- Test your Liver
- Excess energy – NAFLD, DM, HT
- Treatment
Tests for liver health

BLOOD

- **Tests of Injury**
  - ALT or SGPT >30 IU/ml
  - Bilirubin >1.5mg/dl
  - Platelets <100,000/ml

- **Synthesis**
  - Albumin <3.5g/dl
  - Blood clotting >3 seconds over control

- **Hepatitis viruses**: B or C

- **Extra Storage**
  - Cholesterol, Triglyceride
  - Sugar

IMAGING

- Ultrasound, CT, MRI

STIFFNESS

- Fibroscan
Liver Injury: Hepatitis

Greek ‘itis’ denoting ‘inflammation’

Inflammation of liver

1990

Viruses
Alcohol
Drugs
Obesity
Diabetes

Inflammation of liver

2010

Obesity: Excess Calories
Alcohol
Viruses
Diabetes
Drugs
Liver Enzyme: ALT

- Normal < 30 IU/ml
- > 40 IU/L Bad
- Correlates with Liver Injury
- Heart Disease
You know your Hemoglobin

15g/dl Good
Hb: 15g/dl

Know Liver Health

ALT (Liver Enzyme)
< 30 IU/ml - Male
<19 – Female
Does ALT Correlate with . . . .

- Fatty Liver disease (NASH)
- Dyslipidemia
- Heart Disease
- Diabetes
Fatty Liver Disease: Diagnosis

ALT >40 IU/ml
Family H/o DM, Dyslipidemia, Obesity

Exclude alcohol use, HBV, HCV

Image liver with US, MRI, or CT
Fatty Liver

Fibroscan

No Fat ++

Stiffness

Yes Liver biopsy
Fibroscan

• 7,000 – 2012-13
• 5 minutes
• Non-invasive
• Can’t differentiate inflammation vs. Fibrosis – Liver Biopsy
Outline

• Why the topic
• Liver
• Energy Balance
• Fatty Liver
• Test your Liver
• Excess energy – NAFLD, DM, HT
• Treatment
“Heart of the Liver”

Energy Balance
• Fatty Liver and Non Alcoholic Fatty Liver Disease (NAFLD)

• Fatty Liver as part of Metabolic Syndrome
Obesity, Fatty Liver and Metabolic Syndrome

Obesity

Non Alcoholic Fatty Liver Disease

Overeating
Inactivity

Adipose tissue hypertrophy and inflammation

↑ TG, FFA
↑ glucose, insulin
↑ E-selectin, CRP
↑ leptin
↓ adiponectin

Endothelial vascular dysfunction

Cardiac lipotoxicity
Energy dysfunction
Fatty Liver and Metabolic Syndrome
Fatty Liver and Metabolic Syndrome

Adipose tissue hypertrophy and inflammation

- High Lipids
  - ↑ TG, FFA
  - ↑ glucose, insulin
  - ↑ E-selectin, CRP
  - ↑ leptin
  - ↓ adiponectin

Endothelial vascular dysfunction

Non Alcoholic Fatty Liver Disease

Obesity

Fatty Liver

Cardiac lipotoxicity Energy dysfunction
Fatty Liver and Metabolic Syndrome

Adipose tissue hypertrophy and inflammation

High Lipids

Diabetes

↑ TG, FFA
↑ glucose, insulin
↑ E-selectin, CRP
↑ leptin
↓ adiponectin

Endothelial vascular dysfunction

Non Alcoholic Fatty Liver Disease

Obesity

Fatty Liver

Cardiac lipotoxicity
Energy dysfunction
Fatty Liver and Metabolic Syndrome

- Adipose tissue hypertrophy and inflammation
- Overeating
- Inactivity
- Obesity
- Diabetes
- Fatty Liver
- High Lipids
- Hypertension
- Endothelial vascular dysfunction
- Non Alcoholic Fatty Liver Disease
- Cardiac lipotoxicity Energy dysfunction
- TG, FFA
- glucose, insulin
- E-selectin, CRP
- leptin
- adiponectin
Fatty Liver and Metabolic Syndrome

Adipose tissue hypertrophy and inflammation

- Hypertension
- High Lipids
- Heart Disease
- Diabetes

Overeating, Inactivity

Obesity

Fatty Liver

Non Alcoholic Fatty Liver Disease

Cardiac lipotoxicity
Energy dysfunction
Liver Fat Precedes Heart Disease

Liver: an alarm for the heart?

Higher Fat around and in Heart Muscles
Fatty Liver, High ALT and Coronary Heart Disease

• High 10 yr. risk of Heart Disease.  
  *(Atherosclerosis 2007)*

• Correlates with endothelial dysfunction – High BP
Fatty Liver, High ALT and Coronary Heart Disease

• High 10 yr. risk of Heart Disease.
  *(Atherosclerosis 2007)*

• Correlates with endothelial dysfunction – High BP
Fatty Liver and Coronary Artery Disease

- Angiography

447 subjects - included

243 Coronary patients (cases)  204 without CAD (controls).

Patients with Coronary Disease had 3 times more fatty liver

Satpathy and Sarin 2004
Results

- Fatty Liver –
  in CAD \( (85/243, 35\%) \)
  without CAD \( (34/204, 16.7\%) \) \( p<0.01 \).

- Metabolic syndrome
  in CAD patients with Fatty Liver \( (67\%) \)
  without NAFLD \( (27\%) \) \( p<0.01 \).

Satpathy and Sarin 2004
ALT and 20-Year Risk of MS, DM and CVD

Framingham Off-Spring Study

Goessling et al
Gastroenterology  2008 Dec
Framingham Off-Spring Study

Goessling et al  Gastroenterology  2008 Dec

Study sample
1848 ,1971
n= 5124

Offspring subjects underwent examinations every 4 yr

Excluded :189 (missing AST,ALT)
27(AST or ALT >3 times)
Other excluded due to excess alcohol intake on follow up

Framingham Offspring Study
(1978-1982)
n= 3863 AST&ALT Level

Present study
N=2812
Combined Effects of Body Weight and ALT Levels

Goessling et al  Gastroenterology  2008 Dec
Combined Effects of Body Weight and ALT Levels

Goessling et al  Gastroenterology  2008 Dec
Risk of Developing Diabetes

Goessling et al  Gastroenterology  2008 Dec

<table>
<thead>
<tr>
<th></th>
<th>Overall Sample</th>
<th></th>
<th>AST or ALT in the Normal Range</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age, sex adjusted</td>
<td>1.41 (1.25–1.60)</td>
<td>&lt;0.0001</td>
<td>1.32 (1.12–1.55)</td>
<td>0.001</td>
</tr>
<tr>
<td>MV adjusted*</td>
<td>1.33 (1.16–1.52)</td>
<td>&lt;0.001</td>
<td>1.24 (1.04–1.48)</td>
<td>0.02</td>
</tr>
<tr>
<td>+adj glucose</td>
<td>1.25 (1.08–1.45)</td>
<td>0.002</td>
<td>1.15 (0.96–1.39)</td>
<td>0.13</td>
</tr>
<tr>
<td>+interim weight change</td>
<td>1.33 (1.17–1.53)</td>
<td>&lt;0.001</td>
<td>1.24 (1.04–1.48)</td>
<td>0.02</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age, sex adjusted</td>
<td>1.72 (1.51–1.94)</td>
<td>&lt;0.0001</td>
<td>1.62 (1.36–1.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>MV adjusted*</td>
<td>1.48 (1.30–1.69)</td>
<td>&lt;0.001</td>
<td>1.34 (1.11–1.61)</td>
<td>0.002</td>
</tr>
<tr>
<td>+ glucose</td>
<td>1.42 (1.23–1.63)</td>
<td>&lt;0.001</td>
<td>1.28 (1.05–1.55)</td>
<td>0.01</td>
</tr>
<tr>
<td>+interim weight change</td>
<td>1.48 (1.30–1.69)</td>
<td>0.01</td>
<td>1.34 (1.11–1.61)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

High ALT : Risk of Developing Diabetes 5-20 times
Combined Effects of Body Weight and ALT Levels

In age-sex adjusted models, there was a significant interaction between the BMI category and ALT levels for the development of DM (Figure 1a; p-value for interaction=0.01), but not for the development of MetS (Figure 1b; p-value for interaction=0.47). Individuals with normal weight and ALT levels in the highest tertile had 5.9-fold increased odds of developing DM after 20 years compared to those normal weight individuals in the lowest third of ALT levels. After 20 years of follow-up, overweight and obese individuals within the lowest tertile of ALT levels had 6.8 and 14.4-fold increased odds for DM, respectively, compared to normal weight individuals in the lowest third of ALT levels (referent). For participants with highest ALT levels, this risk was increased 20 and 30-fold for overweight and obese participants, respectively.
Outline

• Why the topic
• Liver
• Energy Balance
• Fatty Liver
• Test your Liver
• Excess energy – NAFLD, DM, HT, CAD
• Treatment
Relationship of hepatic steatosis and alanine aminotransferase with coronary calcification
# Fatty Liver and ALT on Calcium Risk Score and CAD

Jung et al Clin Chem Lab Med 2010

<table>
<thead>
<tr>
<th>Odd ratio (95% CI)</th>
<th>Study population</th>
<th>Reference group</th>
<th>( \text{ALT}&gt;30 \ U/L )</th>
<th>With both hepatic steatosis and ALT&gt;30 U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.00</td>
<td>Hepatic Steatosis</td>
<td>1.33 (0.78-2.29)</td>
<td>1.91 (0.84-4.30)</td>
</tr>
<tr>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Model 2</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00</td>
<td></td>
<td>1.24 (0.68-2.26)</td>
<td>1.82 (0.78-4.23)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Model 1: adjusted for age, gender, fasting glucose, smoking, and hypertension.

<sup>b</sup> Model 2: adjusted for age, gender, body mass index, waist/hip ratios, uric acid, systolic blood pressure, diastolic blood pressure, GGT, triglyceride, HDL-cholesterol, fasting glucose, smoking, diabetes, hypertension and statin therapy.

<sup>c</sup> p-0.05.
The Association of Liver Transaminase Activity With Presence and Severity of Premature Coronary Artery Disease

Farzad Masoudkabir, MD, MPH¹, Shahrokh Karbalai, MD²,

Abstract
There is growing clinical interest in liver transaminases as novel biomarkers of cardiovascular risk. We investigated the possible association of serum liver transaminase activity with the presence and angiographic severity of premature coronary artery disease (CAD). A cross-sectional study was conducted on 187 younger patients (females <55 years and males <45 years) who underwent coronary angiography and had serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and high-sensitivity C-reactive protein (hsCRP) measured. Evaluation of coronary stenosis was by Gensini score. Both ALT and AST were significantly correlated with the presence of CAD in univariate and multivariate analyses. Both ALT and AST were also significantly correlated with Gensini score even after adjustment for potential confounders. Serum ALT and AST levels are independently positively associated with the risk and severity of premature CAD, suggesting that these enzymes could serve as surrogate markers for cardiovascular risk in this specific group of patients.
Fatty Liver

• Poor Cardio-respiratory Fitness

• Muscle strength
  - 58%, 77% of Normal

  in men and women
Visceral Adipose Tissue (VAT) = Liver Fat

Epicardial Adipose Tissue (EAT)

• Correlate with CV events
  Ectopic fat – Liver and heart
  Sick Fat - Adiposopathy - inflammed secrete proinflammatory adipokines and cytokines

• Fatty Liver – sensitive marker of Adipose tissue inflammation
<table>
<thead>
<tr>
<th>Region</th>
<th>Fat Mass (g)</th>
<th>Lean+ BMC (g)</th>
<th>% Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Arm</td>
<td>2765.4</td>
<td>2188.5</td>
<td>55.8</td>
</tr>
<tr>
<td>R Arm</td>
<td>2766.3</td>
<td>2142.6</td>
<td>56.4</td>
</tr>
<tr>
<td>Trunk</td>
<td>23022.9</td>
<td>23989.7</td>
<td>49.0</td>
</tr>
<tr>
<td>L Leg</td>
<td>7450.0</td>
<td>7793.8</td>
<td>48.0</td>
</tr>
<tr>
<td>R Leg</td>
<td>7441.4</td>
<td>7454.6</td>
<td>50.0</td>
</tr>
<tr>
<td>Sub total</td>
<td>43446.0</td>
<td>43569.3</td>
<td>49.9</td>
</tr>
<tr>
<td>Head</td>
<td>1378.6</td>
<td>4280.7</td>
<td>24.4</td>
</tr>
<tr>
<td>Total</td>
<td>44824.5</td>
<td>47850.0</td>
<td>48.4</td>
</tr>
</tbody>
</table>
BMI has some limitations and an actual diagnosis of overweight or obesity should be made by a health professional. Obesity is associated with heart disease, certain types of cancer, type 2 diabetes, and other health risks. The higher a person’s BMI is above 25, the greater their weight-related risks.
Fatty Liver Disease:
Not a disease of affluence

- Obesity
- Hypertriglyceridemia
- Diabetes
- Hypertension
Progression of Insulin Mediated Diseases

Energy Rich Food/ Inactivity/ Genes

Normal  IR  Obesity

Diabetes  Hypertension  Dyslipidemia  Vascular disease  Liver disease  Cancer

National Screening  Early counseling
High ALT

Common Causes of Death

Diabetes Mellitus

Cardio-vascular

Stroke
Why fat Causes Diabetes, CAD!

Obesity, Genetics, Environment, diet, Activity
(Insulin sensitivity vs. resistance)

\[ \uparrow \text{Free Fatty Acid} \]

\[ \downarrow \text{Metabolic clearance} \]

\[ \uparrow \text{Glucose load} \]

\[ \text{Hyperinsulinemia} \]

\[ \downarrow \text{Hepatic glucose output} \]
Insulin Resistance

3 units Insulin

Liver, Muscle, Heart

Healthy

25 Units Insulin

Liver
Muscle
Heart

Unhealthy
Changing Face of Adipose Tissue

• Not an inactive store of fat, an endocrine organ

• Hormones – adipokines regulate energy intake, expenditure, lipid and carbohydrate metabolism, fertility, circadian rhythm

• Most expansible organ
Liver in Obese

Intestine + Fat

Liver

Adipose Tissue

ADIPOSE TISSUE OVERLOAD!

Accumulation blood vessel macrophages

Foamy Cells

Other organs
How fat Causes Diabetes and BP!

Association of nonalcoholic fatty liver disease with metabolic syndrome in Indian population

Madhusudana Girija Sanal\textsuperscript{a,b,c}, Shiv K. Sarin\textsuperscript{b,a,c,*}
In India: Lean people get Fatty liver disease, DM, HT

- Intestine
- Liver
- Adipose Tissue

Adipose tissue defective!

Accumulation blood vessel macrophages

Foamy Cells

Other organs
Body mass pattern in NAFLD vs. controls. The difference in BMI between the patients and controls is more pronounced at both ends of the distribution. On the lean end of the distribution 50% the controls fall below the BMI of 23 against 21% of the patients while on the obese end of the distribution 10% the patients have a BMI > 30 against 3% of the controls.
### Demographic profile of the study group subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex ((n = 76))</td>
<td>62 (81.6%)</td>
<td>80 (80%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Age (mean ± SD) years</td>
<td>40.05 ± 11.4</td>
<td>44.1 ± 18.7</td>
<td>0.97</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>25.2 ± 3.4</td>
<td>22.7 ± 3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI ≥ 25</td>
<td>31 (51)</td>
<td>23</td>
<td>0.011</td>
</tr>
<tr>
<td>BMI ≥ 23</td>
<td>60 (78.9)</td>
<td>44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>92.9 ± 9.6</td>
<td>80.8 ± 8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Central obesity 90 cm for men and 80 cm for women</td>
<td>54 (70.0)</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Impaired GTT &amp; DM</td>
<td>26 (34.2)</td>
<td>7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (27.6)</td>
<td>13</td>
<td>0.02</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>108 ± 49.2</td>
<td>93.4 ± 36</td>
<td>0.001</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>67 (13–238)</td>
<td>25 (8–46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>48 (21–290)</td>
<td>23 (6–44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL–cholesterol (mg/dl)</td>
<td>39.6 ± 6.1</td>
<td>47 ± 7.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>170 ± 34</td>
<td>165 ±31</td>
<td>0.40</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>169 ± 79</td>
<td>144 ± 32</td>
<td>0.005</td>
</tr>
<tr>
<td>Metabolic syndrome–ATP-III</td>
<td>16 (21.1)</td>
<td>8</td>
<td>0.012</td>
</tr>
<tr>
<td>ATP3 modified</td>
<td>32 (42.1)</td>
<td>12</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean/median (±SD/range) or actual number (%).
Bad fat is inflamed

ATM : Adipose Tissue Macrophage

Over express PPRr in Hepatocyte – Adipocyte function
Gene Expression Profile of Macrophage = Adipocyte
Our Study: Serum Adiponectin is decreased in lean NAFLD

Serum adiponectin is negatively correlated with obesity

In lean Fatty Liver Disease adiponectin is paradoxically reduced

Sick Adipose Tissue
Treatment of Fatty Liver is Prevention of Diabetes and Heart Disease
Health is not Given
it is Earned
Don’t Outsource to a doctor
West is changing for good, India?

Bariatric Surgery – Good But Last Option
# Ideal Weight

<table>
<thead>
<tr>
<th>Height</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>5’</td>
<td>100</td>
<td>90 lbs</td>
</tr>
<tr>
<td>5’1”</td>
<td>106</td>
<td>95</td>
</tr>
<tr>
<td>5’2”</td>
<td>112</td>
<td>100</td>
</tr>
<tr>
<td>5’6”</td>
<td>136</td>
<td>115</td>
</tr>
</tbody>
</table>

Height – 100 = weight
175 cm -100 = 75 kg
Effects of weight reduction

Improves

- Liver Functions
- Diabetes
- Heart
- BP
Body Composition of Asian Indians:

- **Less:**
  - Average BMI
  - Waist and hip circumferences
  - Muscle mass

- **High:**
  - Body fat
  - Waist-to-hip ratio
  - Truncal skinfolds
  - Abdominal sc fat
  - Intra-abdominal fat
Think about your curves more than weight!

Indicates visceral obesity, metabolic syndrome

Waist M < 90 cm
F < 80 cm
IF YOU ARE A MANUFACTURING DEFECT !!

Protect Your Children

Keep Under weight
Peroxisome proliferators-activated receptor γ2 Pro12Ala variant is associated with body mass index in non-alcoholic fatty liver disease patients

A. C. Gupta · A. K. Chaudhory · Sukriti ·
C. Pande · P. Sahuja · Y. Singh · S. F. Basir ·
S. K. Sarin
Why treat patient with NAFLD?

Because they have a **1.7-fold increase** in standardized (age, gender-matched) mortality
Obese and diabetics have 4 times more Cirrhosis and 2.5 times liver cancer

Two together 16 times

Add Alcohol !!
Unconjugated hyperbilirubinemia in patients with non-alcoholic fatty liver disease: A favorable endogenous response

Ramesh Kumar a,*, Archana Rastogi b, J.S. Maras a, Shiv Kumar Sarin a

a Department of Hepatology, Institute of Liver and Biliary Sciences (ILBS), New Delhi-110070, India

The clinical significance of increased frequency of unconjugated hyperbilirubinemia in patients with non-alcoholic fatty liver disease (NAFLD) is unknown. Serum bilirubin is an endogenous anti-oxidant, and oxidative stress plays an important role in the pathogenesis of NAFLD. In this study, we have documented 25.4% prevalence of unconjugated hyperbilirubinemia in 204 consecutive NAFLD patients. These patients had a significantly less severe liver disease on histopathology and/or fibroScan which may be attributed to anti-oxidant effect of bilirubin.
You become what you eat!
Insulin resistance

IKK β

TNF

Bacteria

Intestine

LPS
Dietary interventions in NAFLD

Thoma C, Day C et al. J Hepatol 2011

- 11 studies, 322 participants, few controls
- 4-14% body wt
- High complex carbs, low saturated fat; micronutrients
- Improved insulin sensitivity (proportional to wt loss)
- ALT improvement
- Better results combined with increasing exercise
Physical activity?

- Fatigue is severe  
  *Newton, Day Gut 2009;57:807*

- Lower physical activity (~20% less steps/day)

- Impaired physical fitness ($V_{\text{max}O_2}$) in NASH

- Less severe disease with *vigorous* regular exercise

- *Improving physical activity* most powerful determinant in life-style intervention to correct metabolic indices, ALT
Exercise benefits the person with NAFLD by...

• 150 min fast walking/wk (+ 30% resistive training)
• Stimulates insulin-independent glucose uptake, muscle
• Reduces Diabetes (58% in Finnish, US, Chinese intervention studies), even with minimal weight loss
• Archived effect 10 years later
• More vigorous is better
Drug treatment of NASH

**Experimental**

Pentoxifylline

400 mg three times a day

Anti- Tumor necrosis factor

Turmeric
Drugs to treat hepatic lipid partitioning: insulin sensitizers

- Metformin: evidence does **NOT** support its use
- Thioldazinediones (PPAR-\(\gamma\) agonists, incr. adiponectin)
  - Pioglitazone also has PPAR-\(\alpha\) agonist effects
  - Enhances adipose insulin sensitivity
- PPAR-\(\alpha\) agonists (fenofibrate, bezafibrate)
- Ezetimibe studies show improved insulin sensitivity
Drugs

- Vitamin E 800 U/day – Decreases Oxidative Stress
  
  40% vs 20% Sanyal A, et al. NEJMed 2010

- Fibrates

- Statins: for hypercholesterolemia: safe, use them

- Ezetimibe – Blocks cholesterol uptake pathway
• Look after your liver
• Manufacturing defect
• Know your ALT, Keep <30,
• NO Fatty Liver
• Prevent gall stone
• Prevent Diabetes, Heart Disease, BP
Carry Home Message

• Earn your health
• Weight, waist, Hip,
• Diet – Natural, Complex CHO, Low fat, Salt
  – Turmeric, Citrous fruits, yogurt
• Energy Balance
• Exercise
• Drugs
  – Pentoxy, E,
  – Statins,
• Bariatric Surgery
Institute of Liver and Biliary Sciences
“Heart of The Liver”
Can I give my liver?
But, .....I have only one .....