脂肪肝的西醫藥治療
Western medicine treatment on fatty liver

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Disclosures

- Advisory board member: AbbVie, Gilead, Janssen, Otsuka, Roche
- Consultancy: Merck, Novomedica
- Speaker: Abbott, AbbVie, Echosens, Gilead, Novartis
Fatty liver

Less common causes:

Drugs (e.g. methotrexate, steroids)

Rapid weight loss

Acute fatty liver of pregnancy
Non-alcoholic fatty liver disease (NAFLD) 
The spectrum of disease

Non-alcoholic fatty liver (NAFL)  Non-alcoholic steatohepatitis (NASH)  Progressive liver fibrosis  Cirrhosis

Courtesy of Dr Anthony Chan, PWH
Hong Kong, n=1013
NAFLD 27%, ALD 0.4%

Shanghai, n=3175
NAFLD 15%, ALD 1%

Guangzhou, n=3543
NAFLD 15%, ALD 2%

Chengdu, n=9094
NAFLD 6%, ALD 3%

Jilin, n=6043
NAFLD 16%, ALD 4%

Fan JG. J Gastroenterol Hepatol 2013;28(Suppl 1):11
Wong VW et al. Gut 2012;61:409
The HK-MRS Study

N = 922

- No fatty liver
- Fatty liver by $^1$H-MRS: 28%
- No or minimal fibrosis
- Advanced fibrosis or cirrhosis by Fibroscan: 4%

Wong VW et al. Gut 2012;61:409
Public health implications

>1,000,000 adult NAFLD patients in HK

40,000 have advanced fibrosis or cirrhosis

20-30% will develop liver cancer and cirrhotic complications
## Fibrosis progression in NAFLD

<table>
<thead>
<tr>
<th>Year 3</th>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0</td>
<td>17</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>F1</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>F2</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>F3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>F4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>15</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>52</td>
</tr>
</tbody>
</table>

1/4 patients had increased liver fibrosis

Wong VW et al. Gut 2010;59:969-74
Histological progression of NAFLD

First Liver Biopsy

Second Liver Biopsy
Fatty liver has become the 2\textsuperscript{nd} leading indication for liver transplantation in USA

Wong RJ et al. Gastroenterology 2015;148:547
## Mortality of NAFLD patients

<table>
<thead>
<tr>
<th>Causes of death (rank)</th>
<th>Normal population</th>
<th>NAFLD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CVS disease</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Liver disease</td>
<td>13</td>
<td>3</td>
</tr>
</tbody>
</table>

**Adams LA et al. Gastroenterology 2005;129:113**
Metabolic syndrome and fatty liver

Metabolic syndrome criteria:
1. High BP
2. Hyperglycemia
3. Hypertriglyceridemia
4. Low HDL-C
5. Central obesity

Wong VW et al. Gut 2012;61:409
Investigations for suspected NAFLD

• Confirm the diagnosis

• Assess disease severity

• Associated cardiometabolic diseases
Diagnosis

- Bright liver under ultrasound
- Liver enzymes can be normal in >half of cases
- Exclude other liver diseases (e.g. viral hepatitis)
Diagnostic workup

- Minimal workup: HBsAg, anti-HCV
- Alcohol and drug history
- Less common liver diseases according to clinical presentation and local epidemiology

Problems of liver biopsy for the evaluation of NAFLD

• Contraindications
  – Bleeding tendency
  – Ascites

• Complications
  – Pain
  – Bleeding

• Sampling error

N=41, biopsies of both lobes of liver

Merriman et al. Hepatology 2006;44:874
NAFLD fibrosis score

- Derivation and validation in 733 NAFLD patients
- 6 parameters: age, hyperglycemia, BMI, platelet, albumin, AST/ALT ratio

AUROC for F3 disease:
- 0.88 in estimation group
- 0.82 in validation group

Angulo et al. Hepatology 2007;45:846
Transient elastography (FibroScan®)
Liver stiffness measurement (LSM)
Controlled attenuation parameter (CAP) and liver fat

<table>
<thead>
<tr>
<th>Steatosis</th>
<th>≥10%</th>
<th>≥33%</th>
<th>≥66%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUROC</td>
<td>0.80</td>
<td>0.86</td>
<td>0.88</td>
</tr>
<tr>
<td>Cutoff</td>
<td>222</td>
<td>233</td>
<td>290</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>76%</td>
<td>87%</td>
<td>78%</td>
</tr>
<tr>
<td>Specificity</td>
<td>71%</td>
<td>74%</td>
<td>93%</td>
</tr>
</tbody>
</table>

Sasso et al. J Viral Hepat 2012;19:244
Treatment of NAFLD

- Lifestyle modification, weight reduction
- Treat associated metabolic disorders (statin is safe)
- Pharmacological treatment for NASH
- Bariatric surgery if morbidly obese
NAFLD-Diet Study

People who underwent population screening (n = 1069)

Excluded (n = 915):  
- Contraindications to magnetic resonance imaging (n = 52)  
- Failed magnetic resonance spectroscopy (n = 1)  
- No fatty liver (n = 658)  
- Hepatitis B infection (n = 91)  
- Hepatitis C infection (n = 3)  
- Significant alcohol consumption (n = 13)  
- Normal alanine aminotransferase (n = 83)  
- Refusal to consent (n = 14)

NAFLD patients randomised (n = 154)

Allocated to intervention group (n = 77)  
- Lost to follow-up and discontinued intervention due to tight schedule (n = 2)  
- and poor mobility (n = 1)

Allocated to control group (n = 77)  
- Lost to follow-up and discontinued intervention due to tight schedule (n = 6)

Analysed (n = 77)  

Wong VW et al. J Hepatol 2013;59:536
Proportion of patients with resolved NAFLD

Wong VW et al. J Hepatol 2013;59:536
Degree of weight loss and remission of NAFLD

<table>
<thead>
<tr>
<th>Percentage of weight loss from baseline to month 12</th>
<th>Number of patients with resolution of NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.0%</td>
<td>13</td>
</tr>
<tr>
<td>3.0-4.9%</td>
<td>41</td>
</tr>
<tr>
<td>5.0-6.9%</td>
<td>50</td>
</tr>
<tr>
<td>7.0-9.9%</td>
<td>60</td>
</tr>
<tr>
<td>≥10.0%</td>
<td>97</td>
</tr>
</tbody>
</table>

n = 72
Fructose and NAFLD

First pass effect
Not controlled by insulin

Not a substrate for glycogen synthesis

Substrate for lipogenesis

Vos and Lavine. Hepatology 2013;57:2525
# Pharmacological treatment of NASH

**Vitamin E**
- Anti-oxidant
- Reduces liver fat and inflammation
- Neutral effects on insulin resistance
- Uncertain effects on the cardiovascular system and malignancy

**Pioglitazone**
- Insulin sensitizer
- Reduces liver fat and inflammation
- Causes weight gain ± fluid retention
- May increase the risk of bladder cancer
Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D., David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D., and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

NEJM 2010;362:1675
PIVENS Study

247 patients with biopsy-proven NASH

- Pioglitazone, N=80
- Vitamin E, N=84
- Placebo, N=83

Baseline to Week 96

Sanyal et al. NEJM 2010;362:1675
# Histological changes at 96 weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Vitamin E</th>
<th>Pioglitazone</th>
<th>P (Vitamin E vs placebo)</th>
<th>P (Pioglitazone vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome*</td>
<td>19%</td>
<td>43%</td>
<td>34%</td>
<td>0.001</td>
<td>0.04</td>
</tr>
<tr>
<td>Improvement in steatosis</td>
<td>31%</td>
<td>54%</td>
<td>69%</td>
<td>0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Improvement in lobular inflammation</td>
<td>35%</td>
<td>54%</td>
<td>60%</td>
<td>0.02</td>
<td>0.004</td>
</tr>
<tr>
<td>Improvement in ballooning</td>
<td>29%</td>
<td>50%</td>
<td>44%</td>
<td>0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Improvement in fibrosis</td>
<td>31%</td>
<td>41%</td>
<td>44%</td>
<td>0.24</td>
<td>0.12</td>
</tr>
<tr>
<td>Resolution of NASH</td>
<td>21%</td>
<td>36%</td>
<td>47%</td>
<td>0.05</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Improvement of ballooning by ≥1 point; no increase in fibrosis; NAFLD activity score declines by ≥2 points or to ≤3 points

Sanyal et al. NEJM 2010;362:1675
Biochemical and weight changes

Sanyal et al. NEJM 2010;362:1675
Farnesoid X receptor (FXR)
FXR agonist in NAFLD and T2DM

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=23)</th>
<th>25 mg OCA (n=20)</th>
<th>50 mg OCA (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>D43</td>
<td>Baseline</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>37</td>
<td>48</td>
<td>41</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>166</td>
<td>174</td>
<td>163</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>98</td>
<td>107</td>
<td>98</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>40</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>178</td>
<td>178</td>
<td>193</td>
</tr>
<tr>
<td>ELF</td>
<td>8.2</td>
<td>8.5</td>
<td>8.4</td>
</tr>
</tbody>
</table>

Mudaliar et al. Gastroenterology 2013;145:574
FLINT Study: Obeticholic acid for NASH

- Resolution of NASH: 13% OCA (n=102), 22% Placebo (n=98)
- Improved fibrosis: 19% OCA, 35% Placebo
- Improved ballooning: 31% OCA, 46% Placebo
- Improved steatosis: 38% OCA, 61% Placebo
- Improved lobular inflammation: 35% OCA, 53% Placebo
- Improved portal inflammation: 12% OCA, 13% Placebo

Neuschwander-Tetri et al. Lancet 2015;385:956
Take home messages

- NAFLD is the most common chronic liver disease worldwide and is emerging to be an important cause of cirrhosis and liver cancer.
- NAFLD is strongly associated with metabolic syndrome, cardiovascular disease and malignancy.
- Apart from diagnosis and risk stratification, it is important to detect and manage the associated metabolic disorders.
- Vitamin E and pioglitazone may be considered in selected NASH patients.
Thank you!

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