Non-pharmacological treatment of patients with NAFLD

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Conflicto de interés


- Estudios Clínicos:
  Investigador principal
  - Estudio ARREST (“Aramchol en NASH”, Galmed)
  - Estudio Resolve-it (Elafibranor in NASH, Genfit)
  - Estudio Aurora (Cenicriviroc in NASH, Allergan)
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OUTLINE

✓ Benefits of weight loss & exercise in NAFLD

✓ Achieving weight loss: calories, diet composition and exercise

✓ Practical issues/Innovations

✓ Achieving weight loss 2: Bariatric surgery

✓ Conclusions
CURRENT SCENARIO

- Nash is a global problem that likely will increase as a health burden in the years to come
- NASH can progress to cirrhosis and hepatocellular cancer in 5–15% of patients
- NASH is rapidly becoming the leading cause for end-stage liver disease.
- There are no FDA-approved therapies for NASH
- Patients with NAFLD commonly have the “triple hit behavioral phenotype” (i.e. sedentary behavior, low physical activity and poor diet)

Non-pharmacological treatment: Lifestyle interventions

Lifestyle interventions are the cornerstone of tx *

*AASLD Practice Guidance Hepatology 2017*
A 7%-10% weight loss should be the goal in all overweight/obese NAFLD or NASH patients

Weight loss ≥ 10%
- Fibrosis regression (45% of pts)

Weight loss ≥ 7%
- Ballooning/inflammation (41% to 100% of pts)*
- Steatosis (35% to 100% of pts)*

Weight loss ≥ 3%

*Depending on degree of weight loss

Hannah, 2016 (Analysis of data from 4 randomized studies)
Weight loss via lifestyle intervention in noncirrhotic NAFL patients. Impact in liver histology based on weight loss percentage.

<table>
<thead>
<tr>
<th>Goal – weight loss</th>
<th>5-7%</th>
<th>7-10%</th>
<th>≥10%</th>
</tr>
</thead>
</table>

**Treatment**

Intensive Lifestyle Changes
- Hypocaloric diet (low fat vs. low CH)
- Aerobic exercise (200 min / wks)
- Behavioral therapy

**How long?** – 1 year
**To whom?**

- NASH resolution
- Fibrosis improvement

**Compliance based on weight loss (%)**
- 5-7%: 12%
- 7-10%: 9%
- ≥10%: 10%

Achieving weight loss: Diet

• Limiting total caloric intake is ideal and more important than aiming for a specific nutrient composition

• Limit processed carbohydrates
  White/brown bread, rice
  White/orange potatoes
  Flour/corn
  Pizza/pasta
  Chips
  Fructose-containing sodas and juices

Achieving weight loss: Dietary composition

- **Moderate to high CHO intake**: 45–65% of total daily calories

- **Low to moderate fat intake**: less than 30–35% of total calories with a low saturated and trans fat intake; healthy fat intake (MUFA and omega-3 PUFAs) present in olives, olive oil, seeds, nuts and fatty fish.

- **Protein intake**: The recommended protein intake is 15–20% of total daily calories, limited red and processed meat, and increased consumption of poultry, fish, low- or non-fat dairy products and a blend of vegetable protein sources (beans and legumes).

- **Fiber and antioxidant intake**: Increased consumption of fruits and vegetables, with more focus on prebiotic fiber
Mediterranean diet

Everyday

Once a week

Once a month

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Mediterranean diet (MD) & NAFLD/NASH

✓ The beneficial effect of MD in NAFLD is demonstrated for liver steatosis and metabolic dysfunction, based on few observational studies and small, short-term trials, but with consistent results.

✓ The single components of MD exert health benefits according to firm evidence stemming from animal experiments, epidemiological studies and RCTs.

✓ Plausible molecular mechanisms for the beneficial effect of the MD which have the most significant evidence involve; polyphenols, carotenoids, oleic acid, n-3 polyunsaturated, fatty acids and fibers.

✓ The MD is particularly attractive due to its potential to improve NAFLD even without accompanying weight reduction, which is the main obstacle in lifestyle modification.

Zelber-Sagi et al, Liver International 2016
### Mediterranean diet (MD) & NAFLD/NASH

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study design</th>
<th>Patients</th>
<th>Intervention (duration, type)/ Diet evaluated</th>
<th>Outcomes</th>
<th>Results summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan, 2015 (158)</td>
<td>Cross sectional study</td>
<td>797 apparently healthy Chinese adults (220 NAFLD) pts</td>
<td>Adherence to DQI-I or MD score</td>
<td>NE</td>
<td>$^1$H MRS Adherence to the MD and to the DQI-I was negatively correlated with intrahepatic TG content</td>
</tr>
<tr>
<td>Aller, 2015 (36)</td>
<td>Cross sectional study</td>
<td>82 NAFLD pts</td>
<td>Adherence to MD diet by Mediterranean Diet Assessment Tool</td>
<td>Reported</td>
<td>NE Greater adherence to the MD was associated with lower likelihood of high grade of steatosis and presence of steatohepatitis</td>
</tr>
<tr>
<td>Abenavoli, 2015 (37)</td>
<td>Controlled trial</td>
<td>20 NAFLD pts</td>
<td>6 months, MD vs. no treatment</td>
<td>NE</td>
<td>NE MD led to significant reduction in BMI, serum lipids, HOMA-IR and the FLI. No change in plasma ALT and AST</td>
</tr>
<tr>
<td>Trovato, 2016 (34)</td>
<td>Cross sectional study</td>
<td>532 NAFLD pts and 667 non-NAFLD subjects</td>
<td>Adherence to MD by diet score</td>
<td>NE</td>
<td>Bright Liver Score on US MD score was one of the most powerful independent predictors of fatty liver severity on US, adjusted for BMI and HOMA-IR</td>
</tr>
</tbody>
</table>
Diet composition & NAFLD: Summary

✔ Reduction of Carbs, saturated fats and cholesterol has pathophysiological basis

✔ There are no prospective studies that support an specific diet

✔ Some evidence suggest that Mediterranean diet is a recommended choice for NAFLD/NASH\textsuperscript{1,2}

1.- EASL-EASD-EASO Clinical Guidelines 2016
2.- AASLD Practice Guidance Hepatology 2017
A variety of dietary approaches can produce weight loss in overweight and obese adults if reduction in dietary energy intake is achieved.

- 1,200 -1,500 kcal/d for women, or energy deficit 500 kcal/d
- 1,500 -1,800 kcal/d for men, or energy deficit 750 kcal/d
- 30% energy deficit

*Strength of Evidence: High*
Achieving weight loss: Exercise

Benefits of exercise in NALFD

Changes in the liver
1. Peripheral insulin sensitivity ↑ = de novo lipogenesis ↓
2. Visceral fat ↓ = lipid supply to liver ↓
3. VLDL clearance ↑ = lipid storage ↓

Changes to cardiovascular system
1. Torsion ↓ = myocardial damage ↓
2. EDV ↑ = preload ↑
3. Ca^{2+} handling ↑ = SV ↑ + EF ↑
4. FMD ↑ = O^2 supply ↑

Romero Gómez et al. JHEP 2017
Effect of aerobic exercise dose on IHL and visceral adiposity

Keating et al J Hepatology 2015

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High-Intensity Aerobic Exercise Improves Both Hepatic Fat Content and Stiffness in Sedentary Obese Men with Nonalcoholic Fatty Liver Disease

Sechang Oh, Rina So, Takashi Shida, Tomoaki Matsuo, Bokun Kim,

\[ \Delta \text{Hepatic Stiffness} \]

\[ \Delta \text{NAFLD-FS} \]

12-week program
Physical activity improves metabolism, reduce weight, has protective effects on cardiovascular disease and reduce the risk of cancer.

*Vigorous* rather than *moderate* activity and resistance training should be encouraged.

Moderate exercise might significantly prevent obese and overweight adults from developing liver cirrhosis [Liv Int 2017 (in press)]

The benefits appear to be greater for persons who exceed the minimum recommendations of 150 minutes/week

Pre-Exercise Health Screening and Evaluation
Exercise Prescription for in NAFLD

✓ Limited data (small sample sizes, poor statistical power, and lack of correlation with histopathology)

✓ Exercise associated with a reduction in hepatic fat even in the absence of weight loss

✓ Several studies suggest that resistance training and Aerobic training may be equally effective in reducing hepatic fat and improve other metabolic parameters
Histological analysis: good quality central review in a blinded fashion by two pathologists who were blinded to all study information, intra and interobserver agreements between two readings were goods ($K = 0.73-0.95$).
Components of NAS

- NASH resolution: 25
- NAS: 47
- Steatosis: 48
- Lob. Inflam.: 50
- Ballooning: 39
- Fibrosis regression: 19
- Portal inflam.: 15


Proportion with improvement in histological outcomes
NASH resolution, fibrosis regression (at least one stage) and steatosis improvement in patients after lifestyle intervention according to percentage of weight loss.

<table>
<thead>
<tr>
<th>% Weight loss (WL)</th>
<th>5%</th>
<th>7%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH-resolution</td>
<td>10%</td>
<td>26%</td>
<td>64%</td>
</tr>
<tr>
<td>FIBROSIS-regression</td>
<td>45%</td>
<td>38%</td>
<td>50%</td>
</tr>
<tr>
<td>STEATOSIS improvement</td>
<td>35%</td>
<td>65%</td>
<td>76%</td>
</tr>
<tr>
<td>% Patients achieving WL</td>
<td>70%</td>
<td>12%</td>
<td>9%</td>
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52 weeks of lifestyle intervention

Recommendation for NAFLD

Hypocaloric Mediterranean diet (daily reduction by 500-1000 kcal) + Moderate intensity exercise = Sustained weight loss

- Provide the strongest possible recommendation
- Try to organize a team (Physicians are not the Best Teachers)
- Consider a broad approach (at least patient and family)
- The 5 A’s model (ask, advise, assess, assist, and arrange)

Some practical points (often forgotten)

- Communicate with empathy
- Be sensitive to general stigma against obesity
- Discuss pros and cons of proposed changes to lifestyle
- Explore reasons for perpetual poor dietary and exercise choices
- Encourage self-efficacy
- Offer specific choices of food and exercise
- Design individualized program of eating and physical activity
- Explain treatment and its benefits

Reproduced, with modification, from Bellentani et al., Hepatology 2008;47:746-754.
Innovations: Prescribing apps

- Specific recommendations
- Tracking of advances and compliance
- Requires support and training
In just 12 weeks our users see results like this:

- **7.4kg** reduction in weight
- **995** less calories consumed a day
- **6.8 mmol/mol** mean reduction in HbA1c
- **322 mins** increase in moderate to vigorous activity a week
- **60%** more likely to achieve weight loss with a coach

Outcome data from live evaluation in primary care (North West London), from 2017 BBC1 documentary study *How to Stay Young*, and RCT Trial (Lancet 2015)
✓ Foregut bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH.

✓ It is premature to consider foregut bariatric surgery as an established option to specifically to treat NASH.

✓ Bariatric surgery may be considered on a case by case basis by an experienced bariatric surgery program.

*AASLD Practice Guidance Hepatology 2017*
Bariatric Surgery Improves Fibrosis in Pts With NASH

- Prospective study of bariatric surgery in pts who are morbidly obese with biopsy-validated NASH, ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)

**Distribution of Fibrosis METAVIR Scores**

<table>
<thead>
<tr>
<th>Fibrosis METAVIR Score</th>
<th>Baseline</th>
<th>After 1 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>21.25%</td>
<td>27.5%</td>
</tr>
<tr>
<td>F1</td>
<td>27.5%</td>
<td>40%</td>
</tr>
<tr>
<td>F2</td>
<td>3.75%</td>
<td>13.75%</td>
</tr>
<tr>
<td>F3</td>
<td>7.5%</td>
<td>32.5%</td>
</tr>
<tr>
<td>F4</td>
<td>3.75%</td>
<td>43.75%</td>
</tr>
</tbody>
</table>

Wilcoxon signed-rank paired t test

*P < .003*

[Slide credit: clinicaloptions.com]
CONCLUSIONS

✓ Weight loss have an important impact in NAFL/NASH reducing fibrosis, the main prognostic factor of the disease

✓ Dietary caloric restriction and exercise are currently the cornerstone of therapy for NAFLD but are very difficult to achieve and maintain (i.e. real-life clinical experience is frustrating)

✓ While engaging in physical exercise is beneficial, avoiding sedentarity is equally important

✓ Multidisciplinary and organized teams with structured program increase efficacy/use innovative tools when available

✓ Weight loss is not enough for morbidly obese patients and bariatric surgery should be considered in selected cases
If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.

― Hippocrates