

NON-PHARMACOLOGICAL TREATMENT OF NASH: DIET, EXERCISE, ROLE OF SURGERY

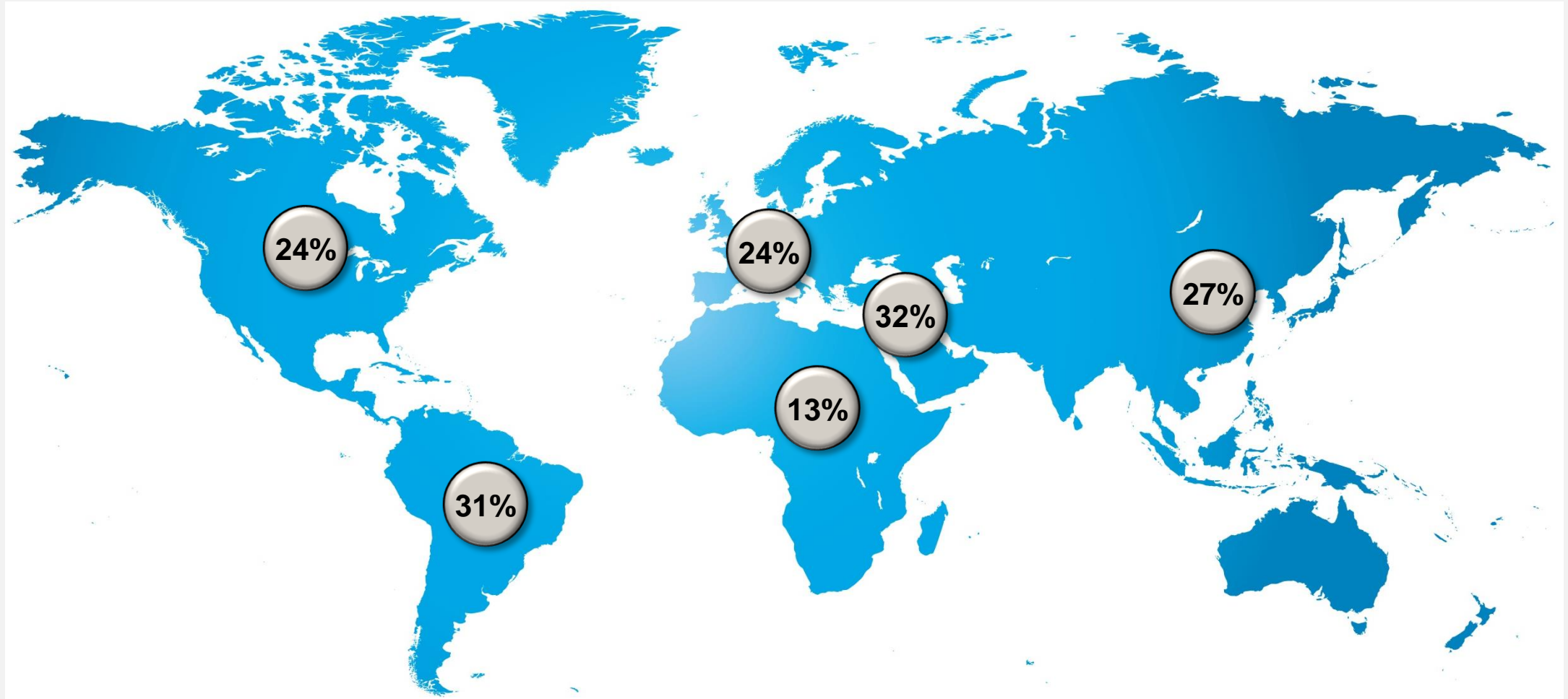
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ESTIMATED GLOBAL PREVALENCE OF NAFLD: 25%



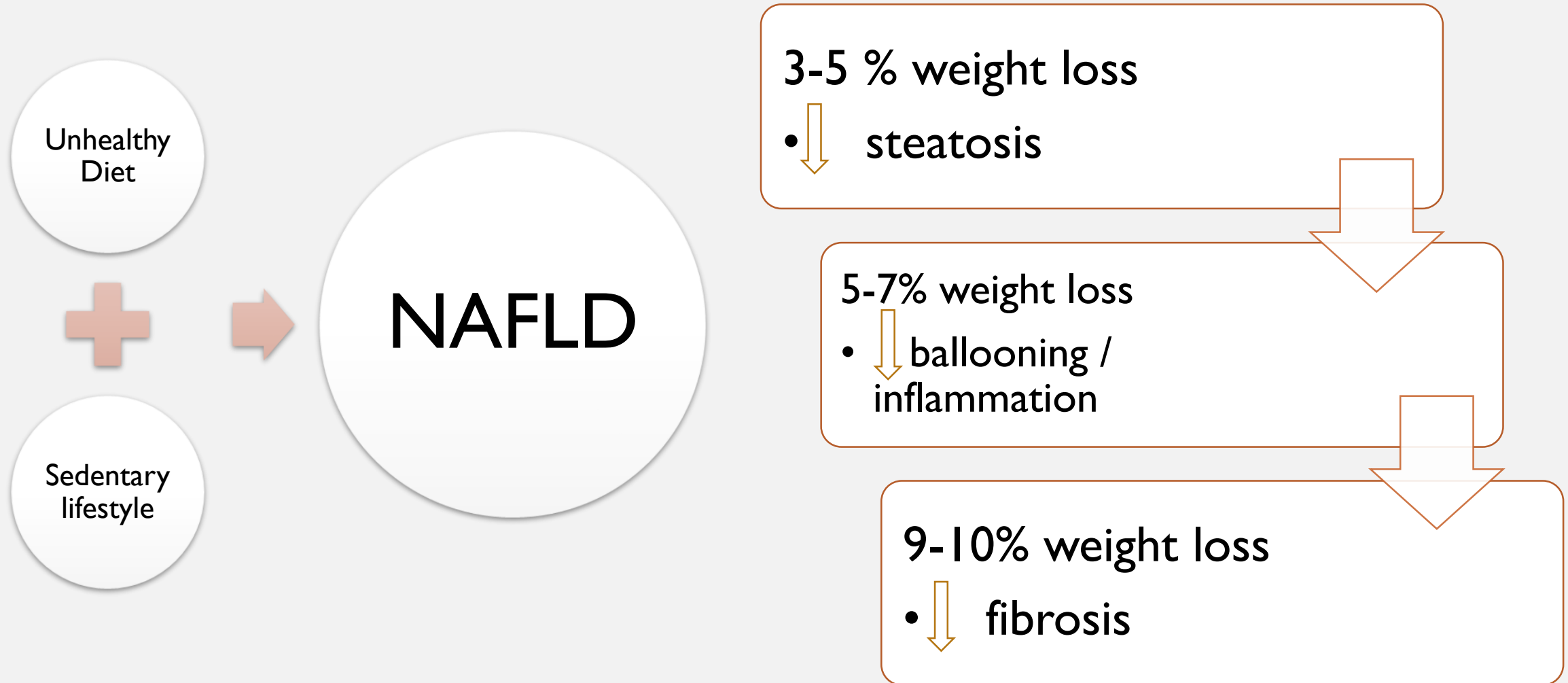
Meta-analysis: NAFLD diagnosed by imaging (US, CT, MRI/SPECT; n=45 studies).

Younossi. Hepatology. 2016;64:73.



Slide credit: clinicaloptions.com

POWERFUL RELATIONSHIP



COMPONENTS OF A LIFESTYLE APPROACH TO NAFLD

Energy restriction

- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Fructose intake

- Avoid fructose-containing food and drink



Coffee consumption

- No liver-related limitations

Comprehensive lifestyle approach

Daily alcohol intake

- Strictly below 30 g men and 20 g women



Macronutrient composition

- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Physical activity

- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors



FACTORS AFFECTING WEIGHT

Biological

- Pregnancy, Menopause
- Thyroid, PCOS, Medications

Social

- Holidays
- Income
- Marriage

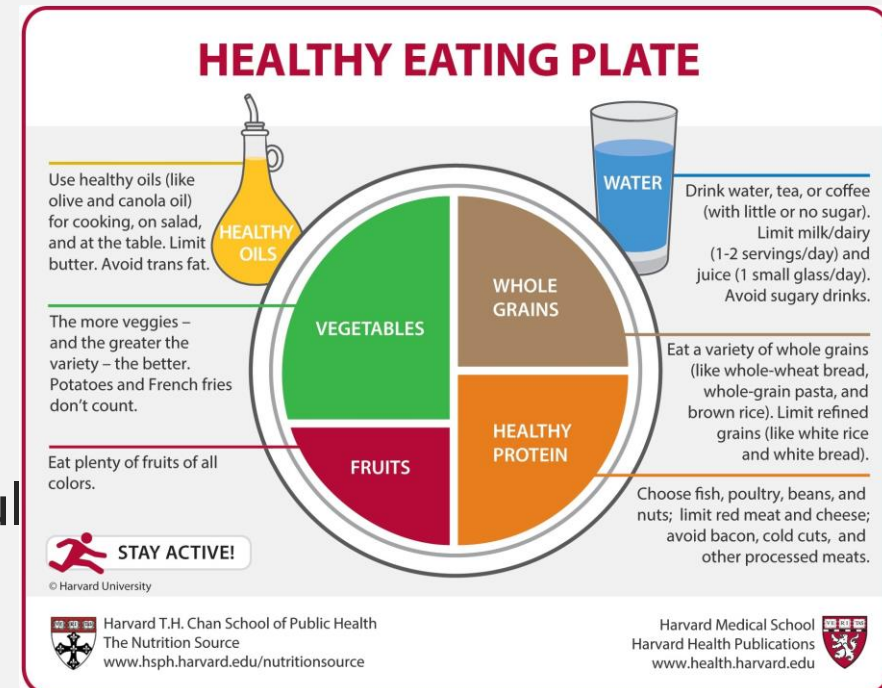
Psychological

- Stress/anxiety/depression
- Eating disorders
- Sleep deprivation

- insulin, thiazolidinediones, and sulfonylureas
- haloperidol, clozapine, risperidone, olanzapine, and lithium
- amitriptyline, imipramine, paroxetine, and sertraline
- valproate, carbamazepine, and gabapentin
- steroids and birth control pills
- beta-blockers such as propranolol and metoprolol

AVOID STIGMATIZING

- Attention to language – avoid terms like “fat”, “morbidly obese”, “obese”
- Emphasize goals
- Discuss healthy eating habits instead of what patients cannot eat
- Food choices, low glycemic index foods
- Portion sizes
- “Healthy eating plate”
- Discuss amount of sugar in common foods
- No evidence that SMALL amounts of alcohol are harmful
- COFFEE IS GOOD



SOFT DRINK CONSUMPTION IN NAFLD

Table 1

Soft drink consumption linked with nonalcoholic fatty liver disease (mean \pm

| Dietary constituent | NAFLD (n = 31) | Controls (n = 30) | P value |
|---|-------------------|----------------------|---------|
| Total energy intake (kcal) | 2300 \pm 500 | 2200 \pm 600 | 0.3 |
| Added sugar (g/d) | 75.6 \pm 8.4 | 33.6 \pm 12.6 | 0.001 |
| Percent of added sugar from soft drinks | 43% | 8% | 0.001 |

NAFLD: Nonalcoholic fatty liver disease.



TYPES OF DIET

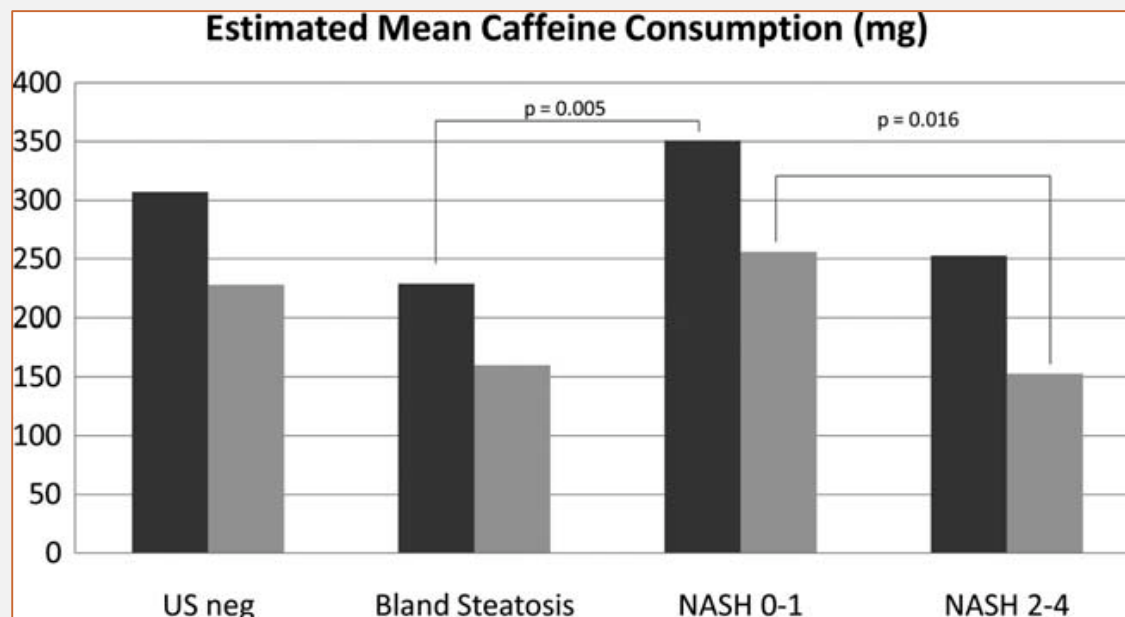
- Low carb vs. Low calorie
 - Both result in similar weight loss – Browning et al Am J Clin Nut 2011
 - Greater liver fat loss with low carb (by MR spectroscopy)
- Low fat vs. Low carb
 - Not enough head-to-head studies – Rodriguez-Hernandez et al. Ann Hepatol 2011, Haufe et al. Hepatol 2011
 - Unclear if there is a difference in % weight loss and % fat loss
- High protein diet, low glycemic index
 - Associated with improved weight maintenance – Larsen et al. NEJM 2010
 - Decrease in wt, liver fat, CAP/LS per fibroscan

MEDITERRANEAN DIET

- Most studies are cross-sectional or of short duration/follow-up
- In limited studies:
 - Patients with NAFLD following Mediterranean diet are less likely to progress to NASH
 - Improved insulin sensitivity
 - Reduces steatosis



COFFEE CONSUMPTION ASSOCIATED WITH REDUCED FIBROSIS IN NAFLD



| Stage of Fibrosis | Coffee Caffeine Per Day (mg) |
|-------------------|--------------------------------|
| 1 | 255.89 (coffee cup equiv=1.87) |
| 2 | 170.30 (coffee cup equiv=1.24) |
| 3 | 122.00 (coffee cup equiv=0.89) |

ROLE OF PHYSICAL ACTIVITY

Aerobic exercise



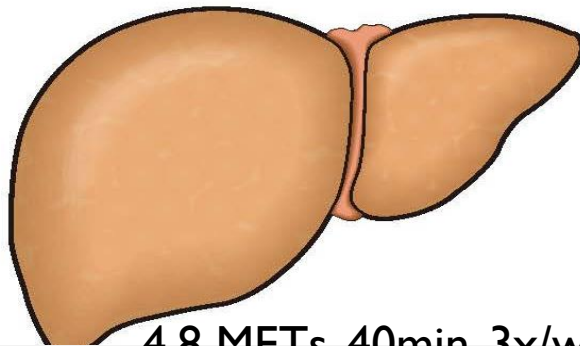
1. Activation of lipolysis
2. Up-regulation of UCP-1 and PPAR γ
3. Alteration in adipocytokine

Resistance exercise



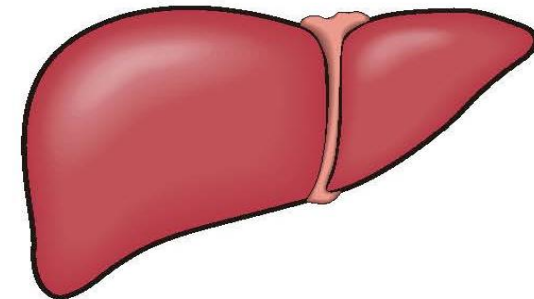
1. Hypertrophy of type II muscle fibers
2. Activation of GLUT4, AMPK, and caveolins
3. Alteration in myokines

[NAFLD]



4.8 METs, 40min, 3x/wk x 12 wk

[Normal Liver]



3.5 METs, 45 min, 3/wk x 12 wk

Improvement

Similar metabolic changes, similar reduction steatosis (12-17%),
less energy expended in resistance group.

AHA RECOMMENDATIONS

- 2 hours and 30 minutes (150 minutes) of moderate-intensity aerobic activity (i.e., brisk walking) every week **and**
- muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders, and arms).

OR

- 1 hour and 15 minutes (75 minutes) of vigorous-intensity aerobic activity (i.e., jogging or running) every week **and**
- muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders, and arms).

OR

- An equivalent mix of moderate- and vigorous-intensity aerobic activity **and** muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders, and arms).

EXERCISE

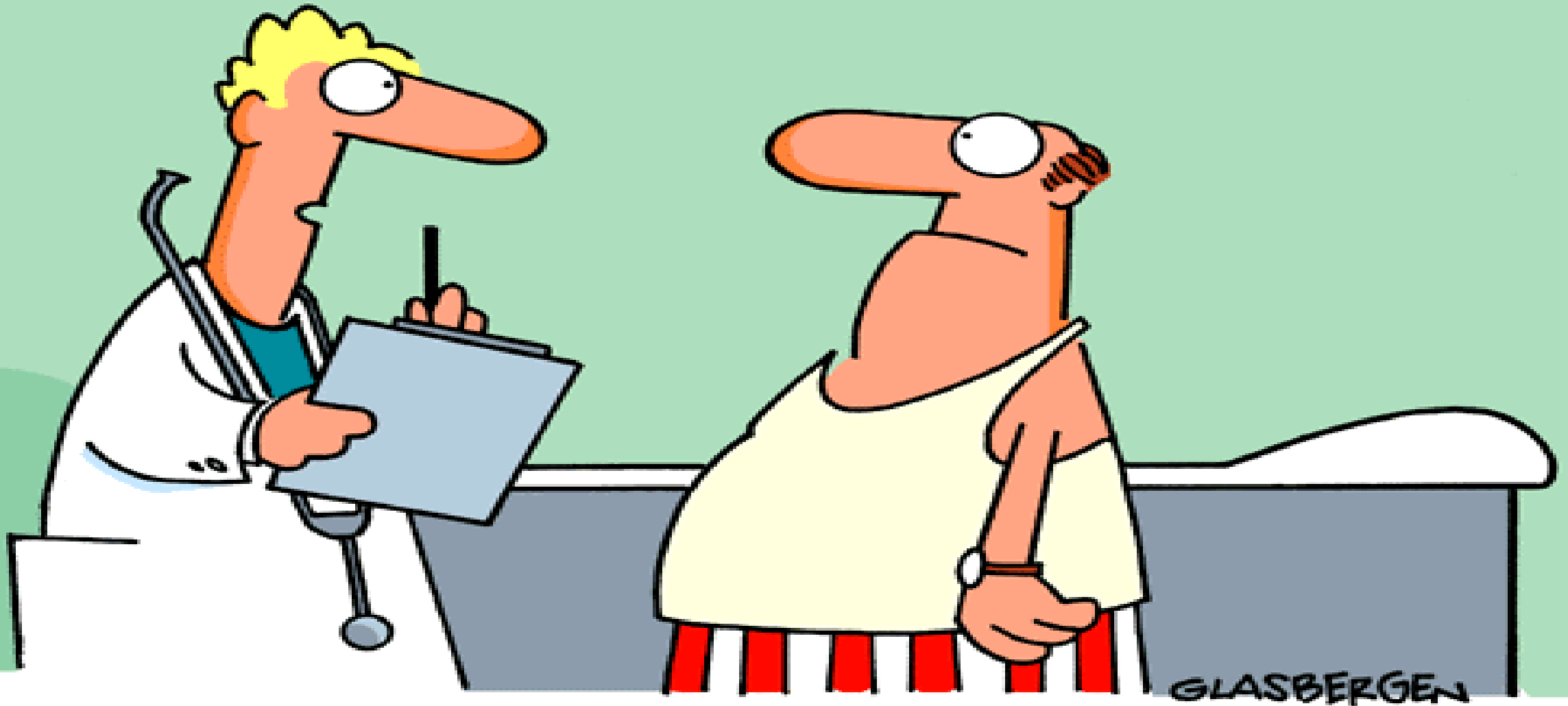
- A large, cross-sectional study assessed the relationship between meeting/exceeding US national guidelines for physical activity and NAFLD severity
 - Self-reported
 - 813 patients NAFLD patients from the NASH CRN
 - Divided into 3 exercise categories based on time spent in activity and metabolic equivalents (METS):
 - Inactive (54%)
 - Moderate (20%): >150 min/week; Activities with MET values 3-5.9
 - Vigorous (26%): >75 min/week: Activities with MET values >6

EXERCISE

- Vigorous exercise associated with decreased adjusted odds of having NASH
 - OR: 0.65 (0.43-0.98)
- Doubling recommended time spent in vigorous exercise (>150 min/week), associated with decreased adjusted odds of advanced fibrosis
 - OR: 0.53 (0.29-0.97)



Younger age, higher education, higher income, lower BMI and no diabetes



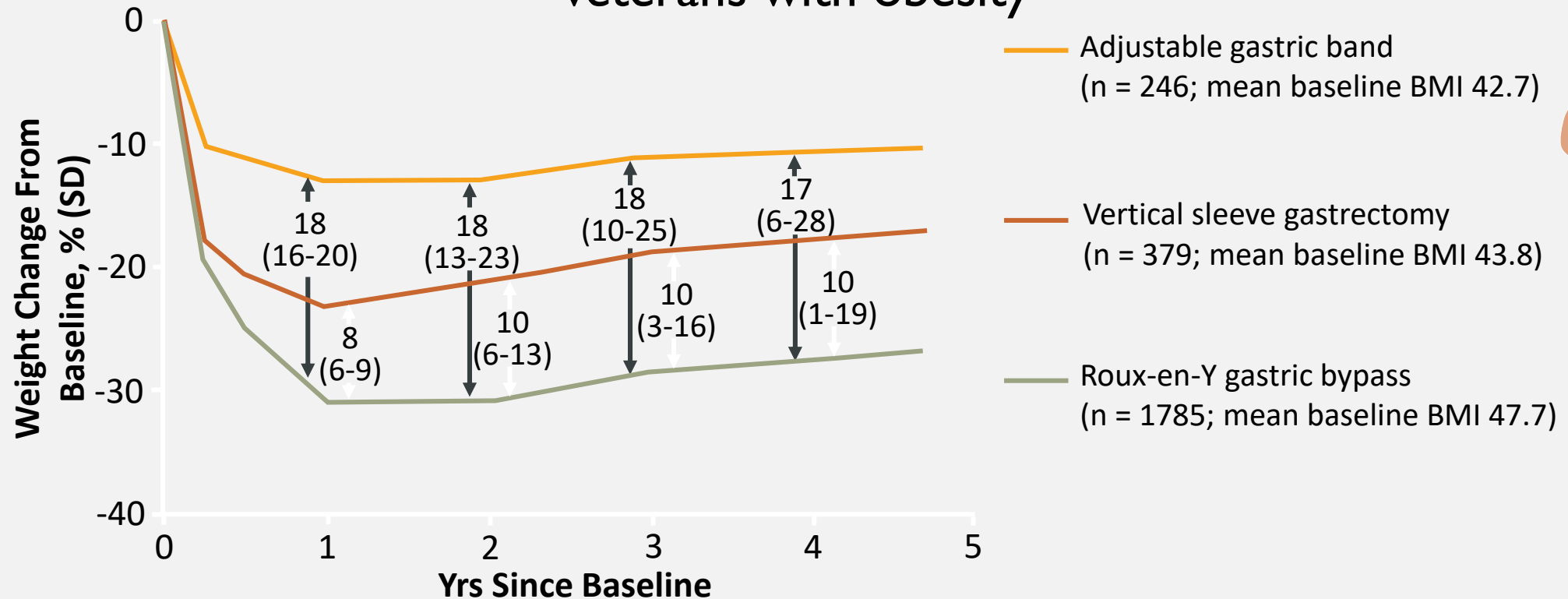
“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”

TREATMENT: SURGERY

- Bariatric surgery is an option in patients unresponsive to lifestyle changes and pharmacotherapy
 - Reduces weight and metabolic complications
 - Stable results in the long term

WEIGHT LOSS: LONG-TERM RESULTS WITH BARIATRIC SURGERY PROCEDURES

Multicenter, retrospective cohort study of N = 2410 veterans with obesity



BARIATRIC SURGERY IMPROVES LIVER HISTOLOGY IN OBESE PATIENTS

- Prospective study in morbidly obese patients with **biopsy-validated NASH**, \geq 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)^[1]
- Meta-analysis of 32 cohort studies of bariatric surgery in obese patients (n = 3093 biopsies)^[2]

| Outcome | Baseline | After 1 Yr |
|-------------------------------------|----------------|----------------|
| Mean BMI \pm SD | 49.3 \pm 8.2 | 37.4 \pm 7.0 |
| Patients with NASH resolution, % | NA | 85.0 |
| Patients with fibrosis reduction, % | NA | 33.8 |

| Characteristic | Outcome |
|---|---------|
| Mean reduction in NAS, points | 2.39 |
| Patients with resolution of NAFLD components, % | |
| ▪ Steatosis | 66 |
| ▪ Inflammation | 50 |
| ▪ Ballooning | 76 |
| ▪ Fibrosis | 40 |
| Patients with new or worsening histologic NAFLD components, % | 12 |

ENDOSCOPIC WEIGHT LOSS DEVICES AND PROCEDURES

- Several varieties approved or in development
 - Gastric balloon systems
 - Gastric emptying systems
 - Endoscopic sleeve gastropasty
 - Duodenal-jejunal bypass sleeves
- Current guidelines do not address these methods
- Not widely available
- Some small studies specifically address NAFLD
 - Improved biochemical or histologic measures consistent with weight loss
- Could consider in patients who refuse pharmacologic or surgical approaches

WEIGHT LOSS: WEIGHT MANAGEMENT MEDICATIONS

| Drug | Daily Dose for Weight Loss | MoA | Mean Weight Loss, % Total Body Weight | Improves NAFLD? |
|---|---------------------------------|---|---------------------------------------|---|
| Orlistat ^[1,2] | 360 mg PO | Lipase inhibitor | 8.78 (8.30 in NASH ^[2]) | In small studies but not RCT ^[3] |
| Lorcaserin ^[1] | 20 mg PO | 5-HT _{2c} serotonin receptor agonist | 7.9 | Not studied |
| Phentermine/t opiramate ^[1] | 7.5/46 mg or 15/92 mg PO | Multiple | 9.6-12.4 | Not studied |
| Naltrexone/ bupropion ^[1] | 32/360 mg PO titrated to max | Multiple | 8.1 | Not studied |
| Liraglutide ^[1] | 3 mg SC titrated to max | GLP-1 agonist | 9.2 (5.5 in NASH* ^[4]) | LEAN study* ^[4] |

*Studied in NASH at 1.8-mg dose approved for diabetes, not 3-mg dose approved for weight loss.

Mean efficacy criterion: significant difference in mean proportion achieving weight loss $\geq 5\%$ drug vs placebo

Categorical efficacy criterion: weight loss $\geq 5\%$ in $\geq 35\%$ of participants, with a significant and ≥ 2 -fold difference in proportion achieving this in drug vs placebo groups

1. Garvey. Endocr Pract. 2016;(suppl 3):1. 2. Harrison. Hepatology. 2009;49:80
3. Wang. Biomed Rep. 2018;9:90. 4. Armstrong. Lancet. 2015;387:679.

SUMMARY OF WEIGHT LOSS IN NAFLD

- Counsel all patients on healthy lifestyle with **diet, exercise, lifestyle**
- To achieve and maintain weight loss, consider:
 - adjunctive **pharmacologic approaches in overweight individuals (BMI > 27)**
 - **surgical approaches** in otherwise eligible obese individuals

| Diet, Exercise, Lifestyle | Pharmacologic Approaches | Bariatric Surgery |
|---------------------------------------|--|---|
| ~ 5% to 8% weight loss ^[1] | ~ 8% to 10% weight loss ^[1] | ~ 10% to 30% weight loss ^[2] |

CONCLUSIONS

- Weight loss of 3-5% improves fatty liver
- Weight loss of 9-10% or more improves histologic findings of NASH
- Moderate intensity exercise, performing both aerobic and anaerobic (resistance) events, 3-5 times per week is recommended
- Exercise coupled with a moderate caloric restricted diet, utilizing low glycemic index foods is optimal
- Eliminate fructose containing beverages
- Sleep 7-9 hours per night
- Regular coffee consumption may be helpful for NAFLD fibrosis