

# Safety and Efficacy of a Very Low Calorie Diet (VLCD) in Fatty Liver

Peter H. Jones MD  
Medical Director

Houston Methodist Weight Management Center



Weill Cornell Medical College

# Objectives

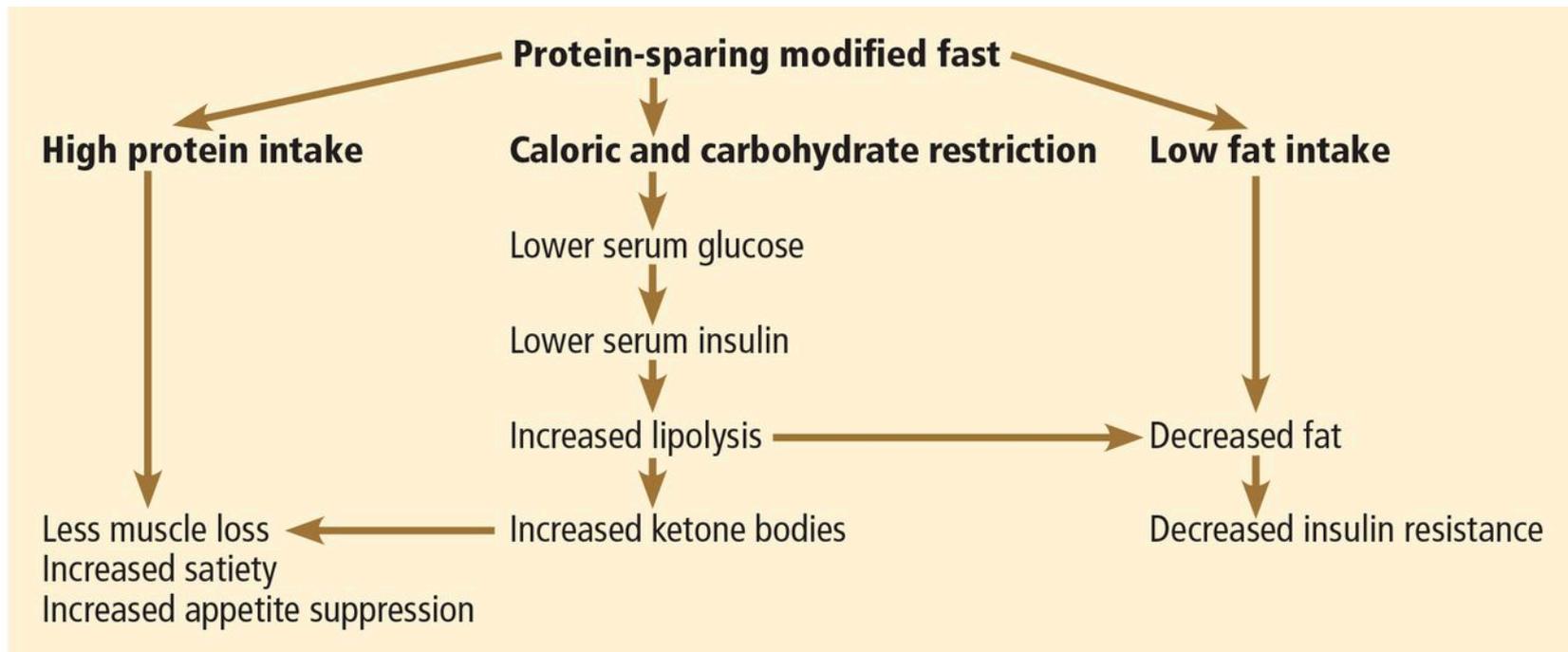
- Explain the clinical presentation and diagnosis of NAFLD (nonalcoholic fatty liver disease) and NASH (nonalcoholic steatohepatitis)
- Understand the common association of NAFLD with metabolic syndrome, insulin resistance and cardiac dysfunction
- Discuss the metabolic, hepatic and body weight effects, as well as safety, of a VLCD in patients with NAFLD and NASH

# Teamwork as a Priority

- The Weight Management Center at Methodist places a high priority on teamwork to help our patients achieve success
- Nurses, dietitians, counselors and exercise physiologists are trusted to help with decisions that insure safety and efficacy of a VLCD in a broad range of patient situations
- We now have a PA-C on our medical staff who works independently at our sites to assess and follow patient compliance and medical safety
- Each team member has the authority to make therapy decisions that affects patient safety and mental well-being. We all trust each other to do the right thing!

# Protein-Sparing Modified Fast

- As a result of carbohydrate restriction, high protein intake, and ketosis, the protein-sparing modified fast leads to lower blood glucose levels (and insulin levels) as well as rapid weight loss, mostly in fat mass, while lean body (fat free) mass is preserved.



# Who Can Medically Benefit from a VLCD?

- T2DM (and selected T1DM on insulin pump)
- Prediabetes/metabolic syndrome/dyslipidemia
- Hypertension
- NAFLD/NASH
- Sleep apnea
- Chronic kidney disease (eGFR 20 – 60 ml/min)
- Osteoarthritis/ need for joint replacement
- Pre-bariatric surgery
- Solid organ transplant candidates:
  - Heart failure, Respiratory failure

# Weight Loss with VLCD Should Improve Most CVD Risk Factors

- Decrease TGRL and non-HDL-C in dyslipidemic patients
- Reduce systolic and diastolic BP
- Increase insulin sensitivity in pre-diabetes
- Improve A1C in T2DM
- Reduce atrial fibrillation symptoms and frequency
- Improve LV function

# NAFLD and Metabolic Syndrome: Targets for Weight Loss

- Nonalcoholic fatty liver disease (NAFLD):
  - Most common cause of chronically elevated ALT/AST (ALT > AST).
  - Most common liver disorder in the US.
  - Spectrum of presentation:
    - 50% steatosis
    - 30% NASH (fibrosis by biopsy)
    - 15% cirrhosis (cryptogenic form)
    - 5% end stage hepatic failure/cancer
- Imaging techniques are suggestive of diagnosis but only biopsy can be used for prognosis.
- Frequently seen in patients with MeS criteria (prediabetes, T2DM, PCOS). Must rule out hepatitis B and C. GWAS have identified PNPLA3 (regulates TG mobilization from lipid droplets) with susceptibility to, and progression of, NAFLD.

# NAFLD, Metabolic Syndrome and CVD: Targets for Weight Loss

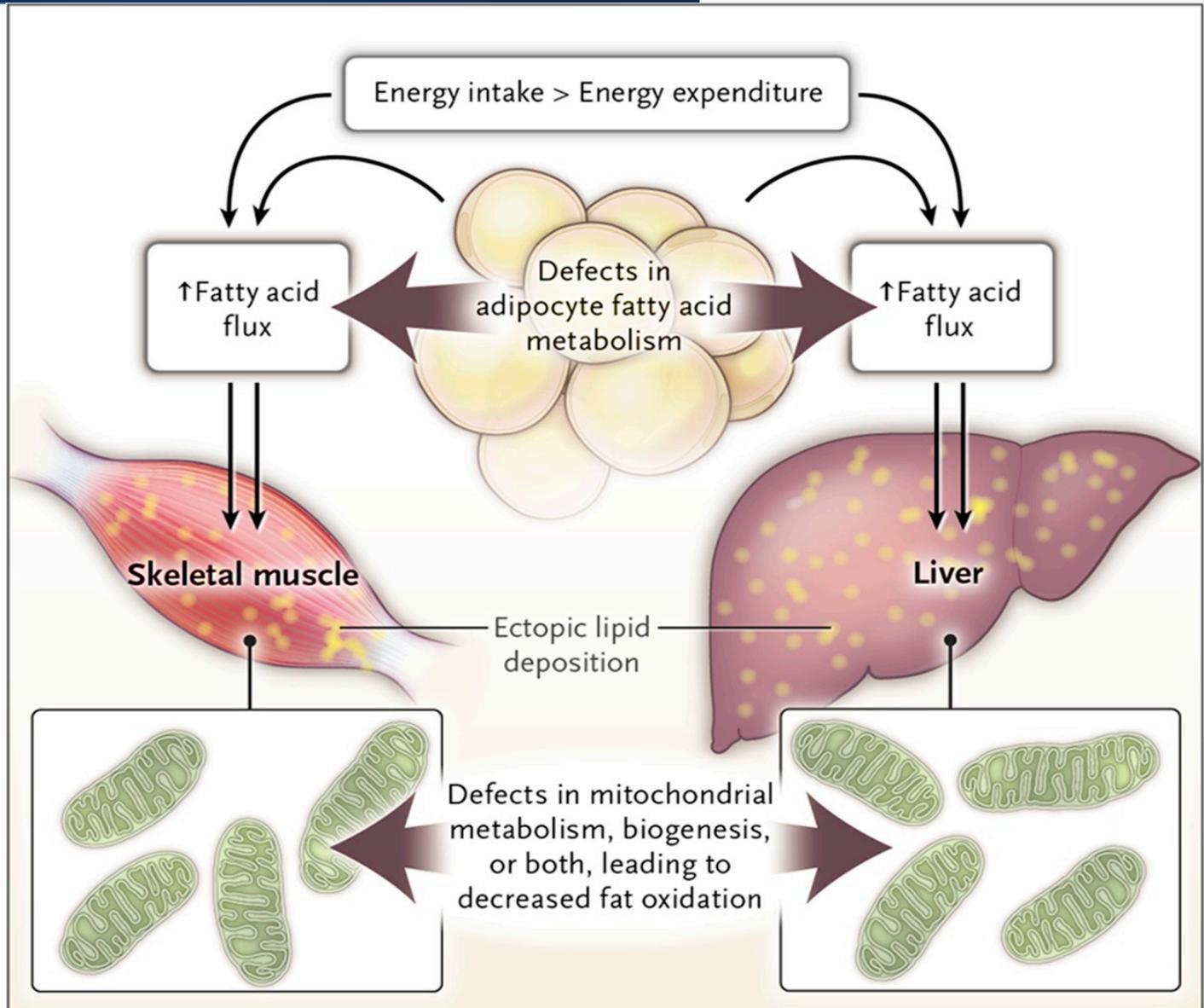
- Most common features associated with NAFLD:
  - visceral adiposity
  - insulin resistance
  - ↑ triglycerides
  - ↑ blood pressure
- Four fold increased risk for metabolic syndrome patients to develop NAFLD over the subsequent year.
- Strong association of NAFLD with cardiomyopathy, atrial fibrillation/flutter and CVD events

Atherosclerosis 2015;239: 192-202

Lancet Diabetes Endocrinol 2019; 7: 313-324

JACC 2019;73: 948-963

# Ectopic Fat in Insulin Resistance

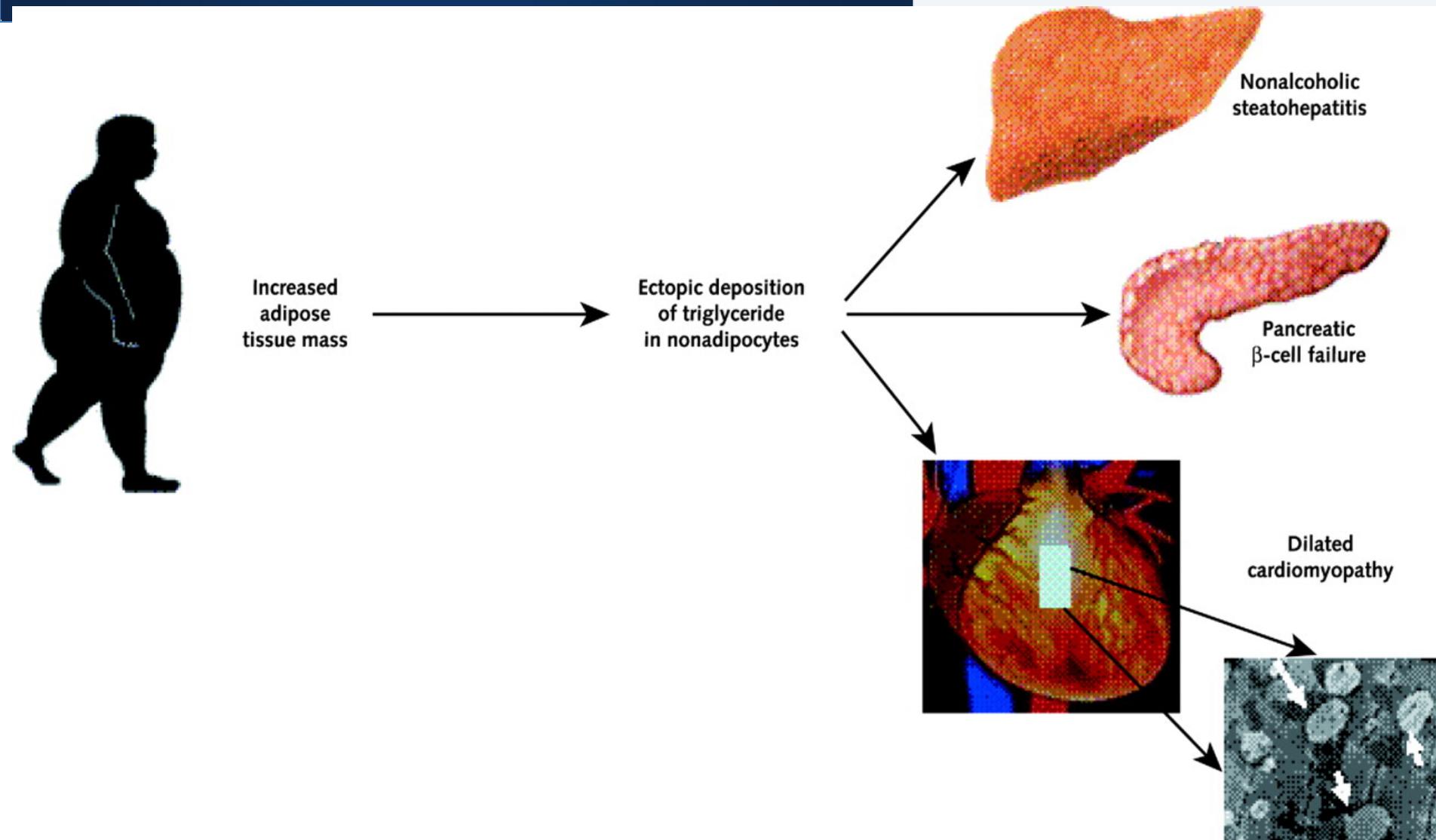


# NAFLD and Cardiovascular Disease

## CENTRAL ILLUSTRATION: Nonalcoholic Fatty Liver Disease Increasing Risk of Cardiovascular Disease: Pathophysiological Mechanisms



# Concept of lipotoxicity



# Adiposity of the Heart

- Excessive fat accumulation in myocardium is cardiotoxic. This can lead to LV remodeling and dilated cardiomyopathies.
- Animal models have shown this “lipotoxicity” in pancreas and liver, as well as the heart. Leptin can reverse this lipid accumulation, as can thiazolidinediones (TZDs).
- Specialized MRI may be able to detect myocardial lipid accumulation, and may be useful in evaluating treatments that can reduce it, such as weight loss.

# Assessing Fatty Liver for Fibrosis

- Liver biopsy is the gold standard for diagnosis
- FIB-4 index uses 4 factors: age, platelet count, ALT, AST  
([www.gihep.com/calculators/hepatology/fibrosis-4-score](http://www.gihep.com/calculators/hepatology/fibrosis-4-score))
- NAFLD fibrosis score (NFS) uses age, BMI, diabetes or prediabetes, albumin, platelet count, ALT, AST  
([www.gihep.com/calculators/hepatology/nafl-d-fibrosis-score](http://www.gihep.com/calculators/hepatology/nafl-d-fibrosis-score))
- FibroSure (LabCorp) uses age gender, GGT, total bilirubin, haptoglobin, apo A, alpha-2 macroglobulin
- Imaging options:
  1. Transient elastography – ultrasound with special transducer. Less accurate with severe obesity
  2. Acoustic radiation force ultrasound
  3. Magnetic resonance elastography – best diagnostic test

# Assessing Fatty Liver for Fibrosis

- Clinical suggestion for evaluation of patient with fatty liver:
  1. Calculate the NAFLD fibrosis score (NFS) and/or use transient elastography
  2. If no fibrosis, or if advanced fibrosis, there is no need to consider biopsy
  3. If there is an intermediate NAFLD fibrosis score or elastography score, then refer for biopsy.

# Treatment Options for NAFLD

- Weight loss: Few well-performed studies to determine the benefit of any method (LCD, VLCD, surgery, anorexigen medications) and none in comparison.
- Insulin sensitizing treatments:
  - Metformin (mixed results, mostly no effect, in few trials)
  - Pioglitazone: several reports of benefit by liver biopsy in nondiabetics
- Antioxidants: positive data to support vitamin E but not for vitamin C, or other vitamins/supplements
- Obeticholic acid (FXR agonist) in phase 2/3 trials has shown reduction in NASH fibrosis score

# Weight Loss Effect on Liver Biopsies in NAFLD

- 261 patients with liver biopsy confirmed NAFLD given a LCD for weight loss over 52 weeks, and had repeat biopsies
- For the group of patients who lost  $\geq 10\%$  of baseline weight:
  - 100% had reduction in disease severity score
  - 90% had resolution of NAFLD
  - 45% had regression of fibrosis

# Very Low Carbohydrate, Isocaloric Diet Effect on Fatty Liver and Metabolism

- 10 patients had liver biopsies and MR spectroscopy to quantify hepatic fat before and after intervention. Measurement of hepatic de novo lipogenesis determined by stable isotope at baseline and study end. 14 day prepared diet, with < 30 gm/day carbohydrate.
- Results:
  - All patients had hepatic fat reduced (mean 44%)
  - Hepatic lipogenesis reduced 80%
  - Inflammatory markers (IL-6, TNF alpha) reduced
  - Hepatic gene expression showed significant increase in PPAR alpha activity, which reflects increased hepatic fatty acid oxidation.

# Hepatic Effects of a VLCD

- Several reports of improved ALT with a VLCD, including transient increases that return to normal [Eur J Nutr 2011;50:235 and Am J Clin Nutr 1992;56 (Suppl);S275]
- Two reports of VLCD effects in patients with established NAFLD over 12 weeks of intervention; One with 41 NAFLD patients (mean BMI 34.5) on 450 kcal/day showing 42% improvement and 5/41 having complete resolution. Another with 42 patients (mean BMI 34) on 800 kcal/day showing 50% improvement and 10/42 having complete resolution. (Nutrition 2009;25: 1129 and Am J Clin Nutr 2006;84: 304)

# Normalizing Beta cell Function in T2DM with a VLCD

- N = 11 T2DM patients on 600 cal/day VLCD (Optifast) for 8 weeks
- Assessed by euglycemic clamp and MRI for hepatic fat
- Results:
  - Weight loss of 15 kg (15% baseline loss)
  - Hepatic glucose production decreased by 1<sup>st</sup> week
  - First phase insulin response increased
  - Hepatic fat reduced 70% by week 8
  - No change in peripheral insulin sensitivity
- Conclusion: Both insulin secretion and hepatic insulin resistance improved within the first few weeks of a VLCD, consistent with loss of hepatic fat.

# Bariatric Surgery Effects on Fatty Liver

- Study of 100 patients with sleeve gastrectomy or RNY followed for one year. Pre-op transient elastography (TE) and NAFLD fibrosis score done at baseline and end of study.
- Significant improvement in TE score in all patients
- Significant improvement in NAFLD fibrosis score
- RNY was better than sleeve gastrectomy in both parameters but not correlated with % weight loss
- Observed a significant increase in ALT and AST in first 1-2 months that returned to normal in many (but not all) patients.

# Bariatric Surgery Effects on Fatty Liver

- Retrospective study of 192 patients with sleeve gastrectomy or RNY who were evaluated at one year. Mean BMI of 42 decreased to 33.
- NAFLD fibrosis score improved in all patients, and the % weight loss did correlate with the score improvement.

# 5 Weeks of Intervention with RNY and VLCD on Insulin Sensitivity in T2DM

	<b>RNY</b>	<b>VLCD (500 cal/d)</b>
Number	11	14
BMI	43.2	39.2
T2DM duration (yr)	5.9	5.5
A1C (%)	8.2	8.5
Wt. loss (% of baseline)	8.1	7.2
Glucose	179 to 125	184 to 110
Insulin	23 to 12.7	13.8 to 6.8
Cholesterol	164 to 126	181 to 154
LDL-C	99 to 77	108 to 99
HDL-C	40 to 30	41 to 35

# Case: NAFLD

- 29 y.o. female with history of PCOS, on oral contraceptives. No other medical problems.  
BMI 37 Wt 219 lb BP 140/80
- Lab at baseline: FPG 105 mg/dL, A1C 5.9%, TG 190 mg/dL, HDL-C 42 mg/dL, ALT/AST 30/22
- After 6 weeks on our VLCD and 21 lb wt loss, lab showed ALT/AST 112/57.
- After 12 weeks of VLCD and 40 lb loss, ALT 39.

# Case: NASH

- 55 y.o. female with biopsy-proven NASH for 1 yr. She is hep C and B negative, and negative for PNPLA3. She has chronic elevations in alk phos, GGT, ALT and AST, with normal bilirubin, albumin and INR. Her history shows obesity, IFG and high TG. Meds are: vit E 1600 U/day, pioglitazone 30 mg/day and lisinopril 20 mg/day.
- BMI 39, weight 228#, WC 51", BP 130/82
- Lab: FPG 92, A1C 5.9%, TG 210, albumin 3.9, alk phos 168 (ULN 115), ALT 92
- After 12 weeks on our VLCD and a 38 lb loss, ALT down to 48, alk phos 140 and TG 125. Pioglitazone was stopped and her hepatologist wants her to lose 80# total before repeating biopsy

# Conclusions

- NAFLD is the most common cause for elevated liver function tests.
- NAFLD is frequently found in patients with obesity and underlying insulin resistance. Therefore, it is associated with hypertension, dyslipidemia and type 2 DM.
- Diagnosis of hepatic fat/fibrosis can be made with fibrosis scores and/or noninvasive tests (transient elastography, MR spectroscopy). Liver biopsy is indicated if an intermediate fibrosis score detected.
- Treatment of NAFLD/NASH includes pioglitazone, vitamin E and weight loss.
- Evidence shows that a VLCD approach for weight reduction can be safe and very effective in patients with NAFLD/NASH, and is comparable to bariatric surgery.