

■ Items 12–15

A 40-year-old man with type 2 diabetes and a history of an inferior wall myocardial infarction presents with the following physical finding (Figure 1):



**Figure 1.** Eruptive Xanthoma

12. Which *one* of the following lipoprotein disorders could explain this physical finding?
- (A) Apo C-III deficiency.
  - (B) Lipoprotein lipase impairment.
  - (C) Apo B-3500 mutation.
  - (D) Apo E phenotype 3/3.
  - (E) Apo A-II deficiency.

He also complains of mild to moderate abdominal pain radiating into his back. Medications include: glyburide 10 mg qd, enalapril 10 mg qd, simvastatin 40 mg qd, aspirin 325 mg qd, and atenolol 25 mg qd. Fasting lab results are as follows:

Total cholesterol	300 mg/dL
Triglycerides	3000 mg/dL
HDL	30 mg/dL
LDL	N/A
Glucose	150 mg/dL
Amylase	200 mg/dL
Creatinine	2.0 mg/dL

13. Which *one* of the following treatments is NOT indicated in this patient?
- (A) IV hydration.
  - (B) Exchange plasmapheresis.
  - (C) Metformin 1000 mg bid.
  - (D) Insulin.
  - (E) Keep NPO.

After hospitalization, this patient returns to the lipid clinic 2 weeks later. His rash is improved. Although his medications were modified during hospitalization, he decided to resume only the medications he was taking prior to his hospitalization. His labs are as follows:

Total cholesterol	240 mg/dL
Triglycerides	1000 mg/dL
HDL	33 mg/dL
LDL	N/A
Glucose	130 mg/dL
Creatinine	2.1 mg/dL

14. Which *one* of the following therapeutic approaches would be contraindicated?

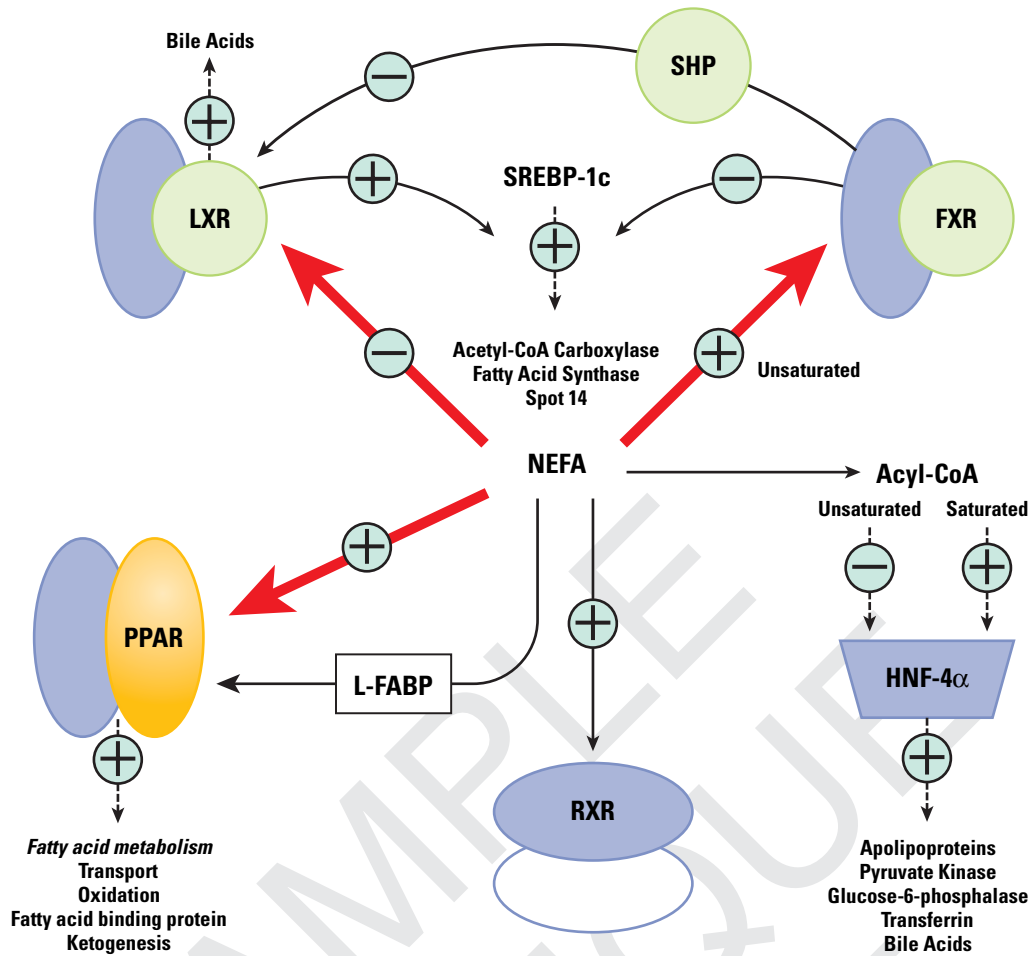
- (A) Gemfibrozil 600 mg bid.
- (B) Fenofibrate 145 mg qd.
- (C) Increase simvastatin to 80 mg qd.
- (D) Colesevelam 6 tablets/day.
- (E) All of the above.

The patient is put on prescription omega-3 fatty acid, 4 capsules per day. His labs were as follows:

Total cholesterol	190 mg/dL
Triglycerides	500 mg/dL
HDL	38 mg/dL
LDL	N/A
Glucose	110 mg/dL
Creatinine	2.0 mg/dL

15. Which *one* of the following mechanisms is NOT associated with the triglyceride-lowering effects of omega-3 fatty acids?

- (A) Omega-3 fatty acids affect gene expression that re-partition metabolic fuels (fatty acids) away from triglyceride storage and towards oxidation.
- (B) Increases lipoprotein lipase activity that improves post-prandial clearance of chylomicrons.
- (C) Stimulates the degradation of Apo B through peroxidation resulting in decreased secretion.
- (D) Inhibits microsomal transfer protein which is necessary for VLDL assembly.
- (E) Inhibits lipogenic genes associated with SREBP-1c.



**Figure 4.** Schematic overview of the regulation of genes by NEFA. NEFA affect at least four metabolic nuclear receptors, PPAR, LXR, FXR, and HNF-4 $\alpha$ . N-3 FA on a carbon-for-carbon basis, are more potent regulators of these genes compared to other PUFA. The net result of the regulation of these genes by n-3 FA is the repartitioning of metabolic fatty acids away from triglyceride storage and towards oxidation.

Adapted from Pegorier JP, et al. *J Nutr* 2004;134(9):2444S-9S.

PUFA, but not monounsaturated or saturated fatty acids, reduce the precursor content of mature SREBP-1c by 60–90%. PUFA may inhibit the SREBP-1c gene expression and/or proteolytic release by inhibiting LXR and stimulating FXR. As mentioned previously, PUFA may competitively inhibit the natural ligand binding of oxysterols to LXR resulting in a reduction in SREBP-1c gene transcription. This suppressive effect can be eliminated by deletion or mutation of LXR responsive elements located in the promoter region of SREBP-1c. However, other evidence suggests that PUFA inhibition of SREBP-1c is independent of LXR. In rats, fish oil feeding suppressed hepatic SREBP-1c-regulated genes, but had no effect on other LXR-regulated genes such as CYP 7A1, ABCG5, or ABCG8. In addition, hepatocytes treated with eicosapentaenoic acid suppressed these lipogenic genes both in the absence and the presence of a synthetic LXR agonist. The inhibition of LXR may be an indirect effect of PUFA stimulation of both FXR and PPAR subtypes. Stimulation of FXR has been shown to enhance the expression of SHP which has a negative feedback effect on LXR activity. Overexpression of both PPAR- $\alpha$  and PPAR- $\gamma$  inhibited SREBP-1c promoter activity induced by LXR in a dose-dependent manner. This effect appears to be due to the reduction of LXR/RXR (retinoid X receptor) which forms the LXR response elements (LXREs). PPAR also utilize RXR, suggesting a competitive inhibition since RXR supplementation attenuated these inhibitions of LXR by PPAR.