

## Putting NAFLD in Perspective: An Overview of the Pathophysiology

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Director, Division of Gastroenterology and Hepatology  
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### Disclosures

- Advisory board/Consultant
  - Nimbus Therapeutics
  - Bristol Myers Squibb
  - Boehringer-Ingelheim
  - Janssen
  - Conatus

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### Pathophysiology of NASH and targets of therapy

- What happened to the “Two-hit hypothesis”?
  - (Hit 1: steatosis, Hit 2: oxidant stress, lipid peroxidation, injury)
  - Degree of steatosis does not correlate with NASH severity
  - Oxidant stress occurs but not yet shown to be necessary
- Alternative paradigm: “Lipotoxic liver injury”
  - Free fatty acids promote the generation of toxic lipids
  - Neuschwander-Tetri, B. A. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: the central role of nontriglyceride fatty acid metabolites. *Hepatology* (2010) 52:774-788.

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## Free fatty acids

Composition of Ivory Soap

Fatty acid sodium salt	% w/w	# Carbon atoms	# Double bonds
Lauric	12.8	12	0
Myristic	7.5	14	0
Myristoleic	0.6	14	1
Palmitic	21.8	16	0
Palmitoleic	3.7	16	1
Stearic	13.6	18	0
Oleic	31.6	18	1
Linoleic	3.1	18	2
Other (includes C6-C10)	5.2	--	--

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## Lipotoxic Liver Injury (NASH)

Liver  
free fatty  
acids

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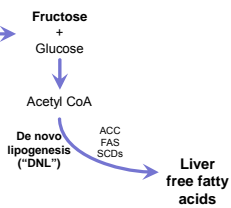
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## Lipotoxic Liver Injury (NASH)



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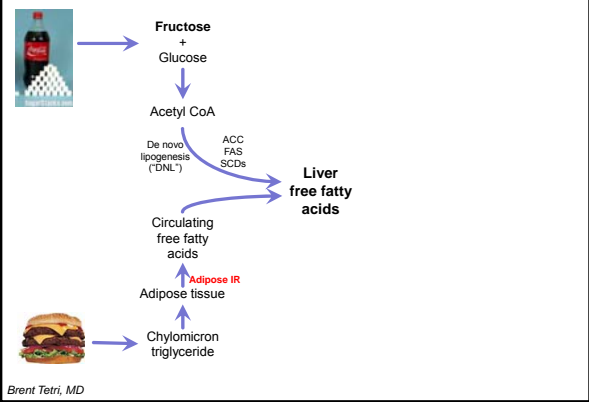
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**Lipotoxic Liver Injury (NASH)**




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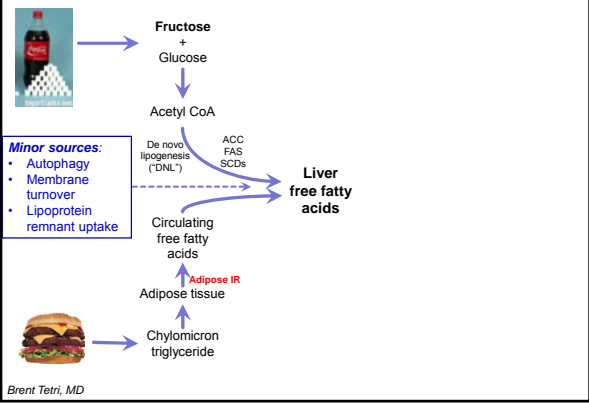
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**Lipotoxic Liver Injury (NASH)**




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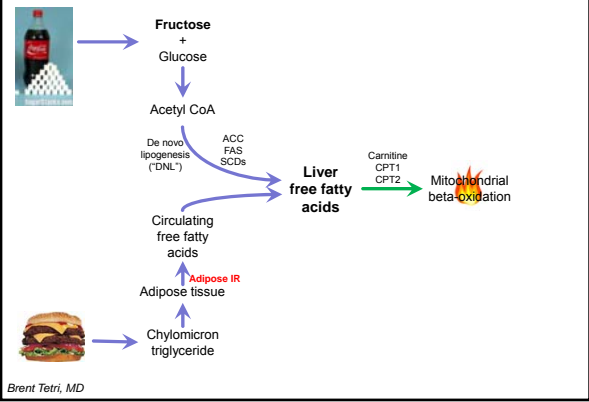
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**Lipotoxic Liver Injury (NASH)**




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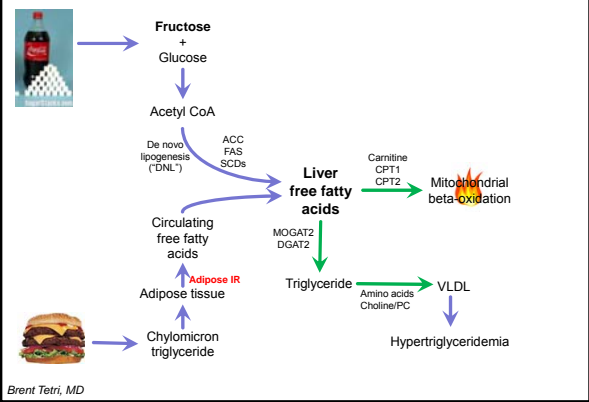
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### Lipotoxic Liver Injury (NASH)



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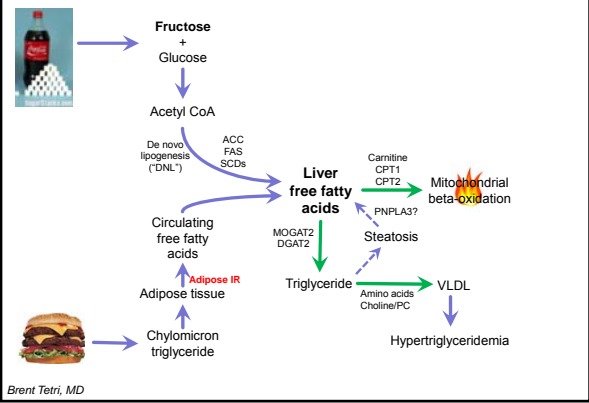
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### Lipotoxic Liver Injury (NASH)



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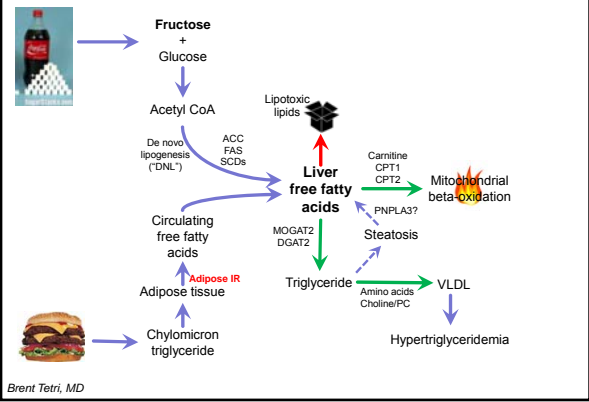
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### Lipotoxic Liver Injury (NASH)



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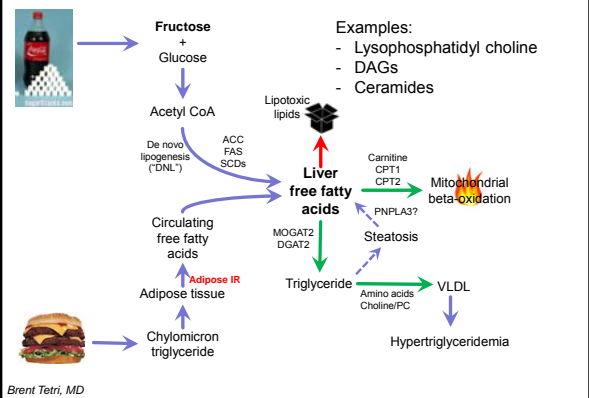
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### Lipotoxic Liver Injury (NASH)




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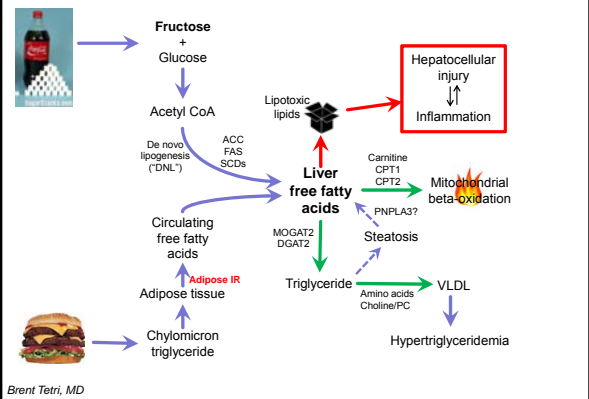
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### Lipotoxic Liver Injury (NASH)




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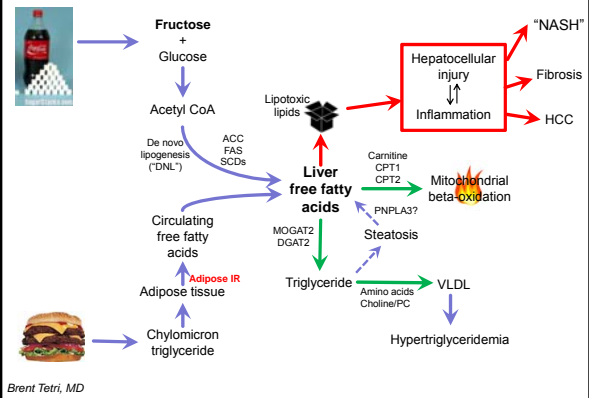
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### Lipotoxic Liver Injury (NASH)




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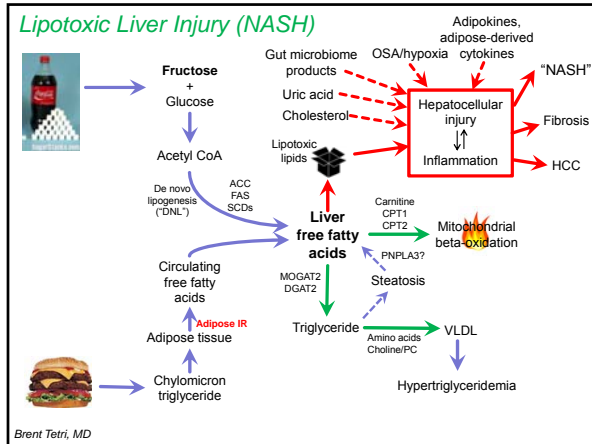
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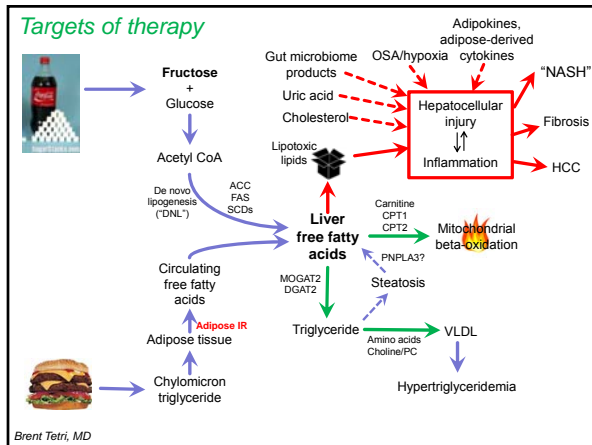
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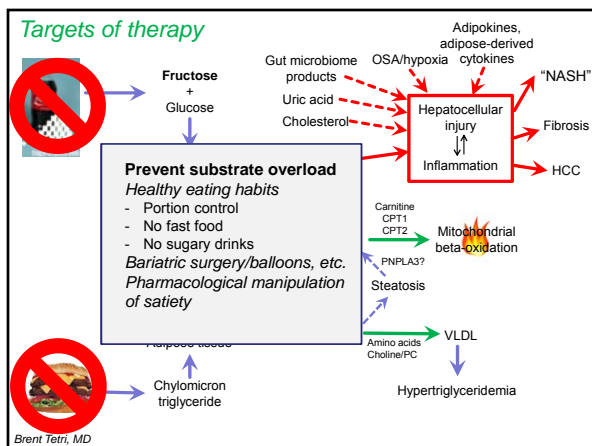
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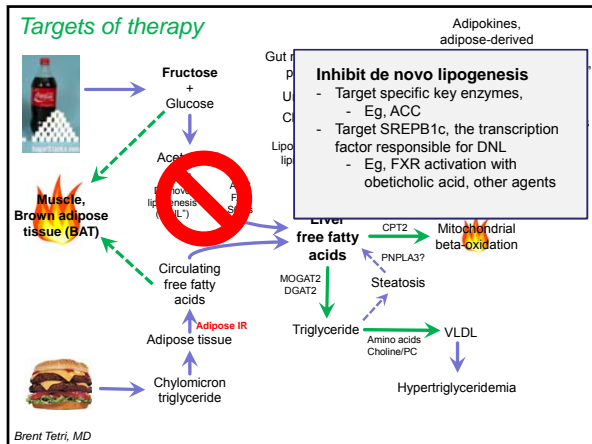
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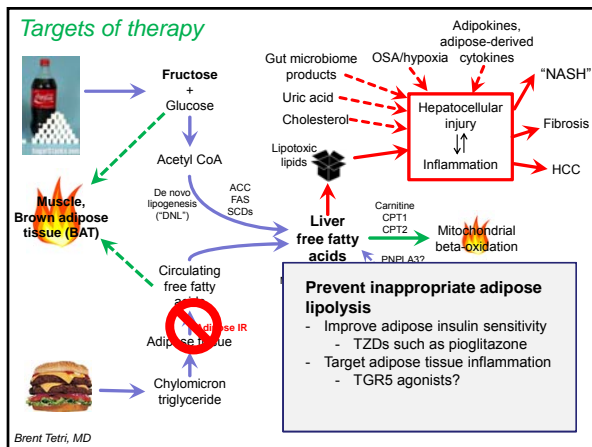
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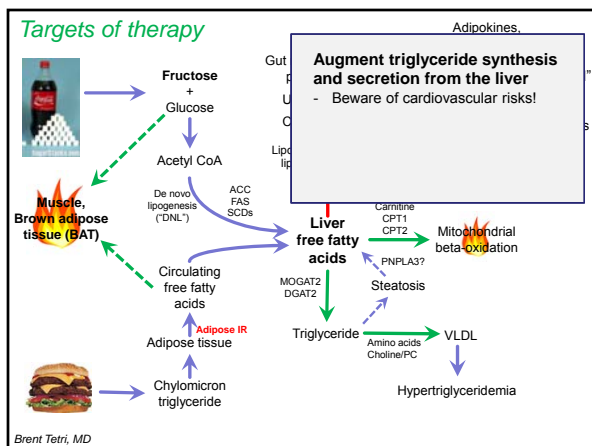
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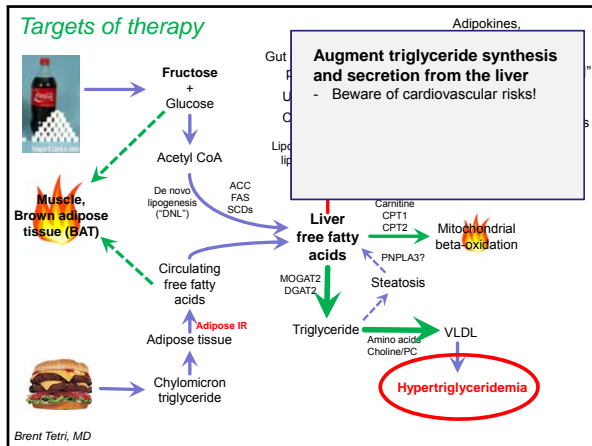
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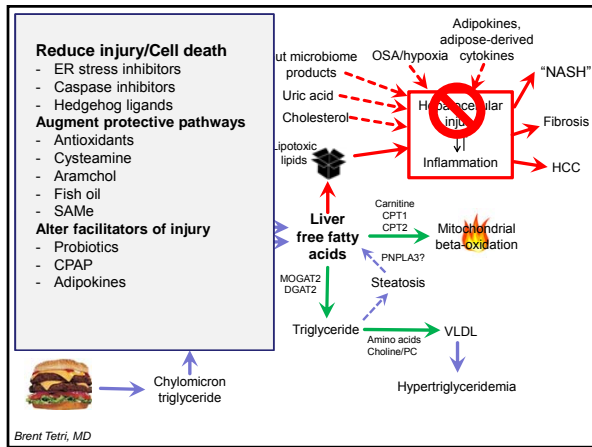
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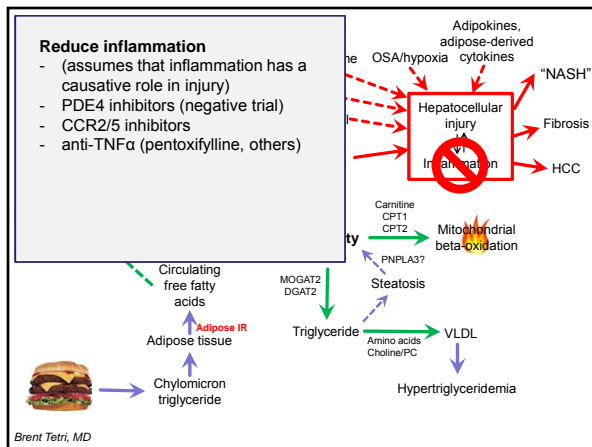
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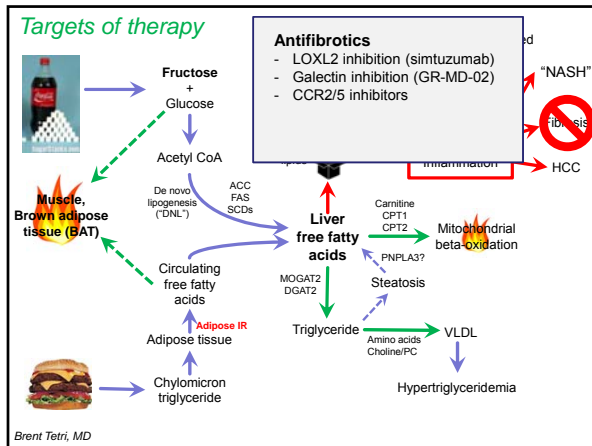
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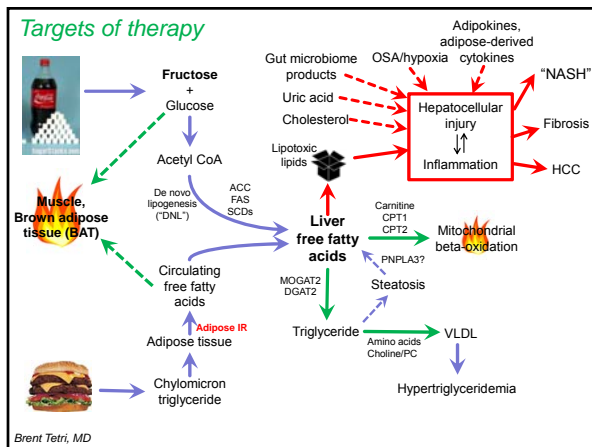
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**Summary**

- The lipotoxicity paradigm predicts therapeutic targets
- The optimal therapeutics may be ones that target:
  - Substrate availability
  - Energy efficiency
- NASH treatment needs to be personalized, will likely include several approaches for each patient

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