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Diet Corner

Does Fat vs Carbohydrate Overfeeding Matter in the Development of Fatty Liver Disease?

Are saturated fats (SFAs) or polyunsaturated fats (PUFAs) more likely to cause fat deposits in the liver? Fat that accumulates in the liver is known as ectopic fat. And we know that excessive accumulation of both subcutaneous and ectopic or visceral fat distribution causes a chronic state of inflammation and can lead to obesity, which creates a greater risk for type 2 diabetes and cardiovascular disease. Accumulation of visceral and ectopic fat is associated with a higher risk for other diseases than is subcutaneous fat.

1. Individual susceptibility to fatty liver disease depends on genetic as well as environmental factors including macronutrient content of the diet.

2. A 2019 study published in the Journal of Clinical Endocrinology & Metabolism found that participants who were overfed either SFAs or PUFAs gained the same amount of weight. However,

3. Is Sugar or Fat Worse for the Liver? overfeeding of SFAs or sugar (simple carbohydrates)? If you follow the 20% rule indicating natural disease progression in fatty liver disease, approximately 20% of patients with the second state of fatty liver, nonalcoholic steatohepatitis (NASH), will progress to cirrhosis or develop decompensation over 2 years.

4. Therefore, the environmental factors of habitual dietary ingestion and overfeeding are crucial to comorbidities such as fatty liver disease and its progression.

5. When the adipocyte tissue capacity to store excess energy is diminished, as is seen in many obesity phenotypes, hepatocytes store the extra lipids, called intrahepatic triglycerides (IHTGs).

6. Excess free fatty acids (FFAs) resulting from lipolysis and reduced uptake in adipocytes can lead to ectopic fat accumulation in liver, skeletal muscle, and other organs. IHTGs accumulate from fat in the diet (15%) and adipose tissue lipolysis (60%) and also from de novo lipogenesis within the hepatocyte, (25%) usually from excess carbohydrate intake.

7. The high-fat and high-carbohydrate diets seen in obesity predispose to lipotoxicity and glucotoxicity and play a significant role in development of steatosis and progression to NASH.

8. The pathophysiologic mechanisms connecting excess fat and carbohydrates to steatosis and NASH include mitochondrial dysfunction, endoplasmic reticulum stress and oxidative stress.

9. Release of FFAs from insulin-resistant adipocytes activates inflammatory pathways. This reduces hepatocyte capacity to dispose of excess FFAs, which leads to lipoapoptosis, a feature of NASH.

10. Excess Calories Promote Liver Fat Accumulation The degree to which excess calorie intake promote accumulation of fat in the liver is dependent on genetic and environmental factors; however, macronutrient composition of the diet modulates the risk. 11. Fat accumulation from fat ingestion acts through impairments in lipid storage and increased lipolysis in the adipocyte, whereas carbohydrate overconsumption promotes liver fat accumulation via de novo lipogenesis in the liver.

12. The effect is further modulated according to fat and carbohydrate type. Saturated fat and fructose induce the greatest increase in IHTG, insulin resistance, and pathologic ceramides compared with unsaturated fats, which are actually protective.

13. Ceramides are waxy substances containing fatty acids that, along with other metabolites such as branched chain amino acids and diacylglycerols, have been implicated as antagonists of insulin action and are detrimental if circulating levels are excessive.

14. Ceramides can cause insulin resistance and aggregation of low-density lipoprotein (LDL) cholesterol in arterial walls, leading to atherosclerosis. In the mitochondria, ceramides suppress the electron transport chain and induce production of reactive oxygen species.

15. Nutrients including simple sugars, saturated fatty acids, trans fatty acids, and animal protein promote nonalcoholic fatty liver disease (NAFLD) directly by promoting IHTG and inhibiting antioxidant activity and indirectly by affecting insulin sensitivity and triglyceride metabolism.

16. In the regulation of metabolism, these nutrients act on several hepatic nuclear receptors, such as liver X receptor (hepatic fatty acid synthesis), the farsenoid X receptor (VLDL assembly), and peroxisome proliferator–activated receptors (fatty acid oxidation, anti-inflammatory function, hepatic lipogenesis).

17. The gut also modulates fat accumulation through gastric inhibitory polypeptide secretion, which is potently stimulated by saturated fat. The gut also plays a role in NAFLD progression, with gut permeability, the microbiome, and endotoxemia contributing to the risk for NAFLD and NASH.

18. The Effects of Fat vs Carbohydrate Overfeeding In comparing fat or carbohydrate overfeeding on the accumulation of liver fat, studies show a general trend that overfeeding with saturated fat is associated with the greatest risk for hepatic steatosis and increase in aminotransferase levels, independent of changes in body weight.

19. Overfeeding saturated fat increases IHTG more (55%) than does overfeeding unsaturated fat (15%), whereas carbohydrate increased IHTG by 33% in a study by Luukkonen and colleagues.

20. Carbohydrates increased liver fat by stimulating de novo lipogenesis, whereas saturated fat did so by increasing the rate of lipolysis. Saturated fat also induced insulin resistance and endotoxemia and significantly increased plasma ceramides. Ceramides induce skeletal muscle insulin resistance when synthesized as a result of saturated fat activation of TLR4 receptors. Unsaturated fat does not have this effect.

21. Overfeeding different macronutrients increases liver fat by different mechanisms, which may lead to long-term metabolic differences with long-term habitual dietary patterns.

22. Fatty acids are released by intestinal lipolysis and packaged into chylomicrons, which are transported in chyle to the circulation. FFAs are released by chylomicrons and VLDL via intravascular lipolysis and are taken up by adipose tissue or spill over into the circulation.

23. Fatty acids stored in adipose tissue (triglycerides) undergo lipolysis, releasing FFAs especially under fasting conditions. Nonesterified fatty acids are transported to the liver bound to albumin and are the major source of liver triglycerides both after a fast and after a meal.

24. SFA-high diets increase chylomicrons; peripheral lipolysis; and liver SFAs, such as palmitate, which is needed for ceramide synthesis, compared with PUFA-containing diets.

25. SFAs but not PUFAs stimulate ceramide synthesis, and ceramides induce hepatic insulin resistance, inflammation, and mitochondrial dysfunction. Compared with high-carbohydrate diets, SFAs increase serum LDL and high-density lipoprotein (HDL) cholesterol and decrease triglycerides.

26. Sugars such as saccharose (sucrose) and high fructose corn syrup contain glucose and fructose. In excess, these sugars can be converted to SFAs, such as 16:0 palmitate and 18:0 oleate, in the liver via stimulation of de novo lipogenesis. Fructose but not glucose also increases chylomicrons.

27. NAFLD is characterized by increased free sugar intake, chylomicrons, lipolysis, ceramides, insulin resistance of hepatic glucose production, increased VLDL synthesis and serum triglycerides, which lead to lowering of HDL cholesterol.

28. Is There an Antidote? What is the antidote to NAFLD leading to NASH? Weight loss via lifestyle therapy and exercise with or without medication, and bariatric surgery.

29. All types of macronutrient content diets that limit simple sugars and saturated fat and promote healthy fruits and vegetables, lean protein, low-fat dairy, and grains have been shown to reduce liver fat and NAFLD and NASH.

30. Exercise can do so on its own as well. Medications such as glucagon-like peptide 1 agonists and bariatric surgery are also beneficial in terms of reduction in liver fat; the mechanism so far is not.

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