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# Non-alcoholic fatty liver disease (NAFLD): a tale of fat and sugar?

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## Abstract

The global diffusion of the so-called Western diet, which is enriched in fat and carbohydrates, such as fructose, has been proposed to be an underlying cause of the increased prevalence of metabolic conditions, including non-alcoholic fatty liver disease (NAFLD). This Smart Card summarizes the main metabolic and hepatic histological features of rodent models fed with diets combining high fat and fructose.

**Keywords:** Fructose, High-fat diet, High-fructose corn syrup, Mice, NAFLD, Non-alcoholic steatohepatitis, Rats, Western diet

## Introduction

Non-alcoholic fatty liver disease (NAFLD), a condition regarded as the hepatic manifestation of the metabolic syndrome, currently represents the most common cause of chronic liver disease [1]. The condition ranges from simple hepatic fat accumulation (steatosis) to non-alcoholic steatohepatitis, where fat is accompanied by hepatocyte injury, and necroinflammation. This condition poses an increased risk of cirrhosis and hepatocellular carcinoma [1]. The dramatic increase in prevalence of obesity, metabolic syndrome, and NAFLD has been linked to the global diffusion of the Western diet, characterized by excess caloric intake due to increased consumption of processed food and beverages, coupled with a more sedentary lifestyle [2,3]. This has led to a significant increase in sucrose and high-fructose corn syrup consumption, both of which contain similar amounts of glucose and fructose [4]. In the USA, for example, fructose consumption has more than doubled in the last three decades [3]. Excessive fructose consumption has been linked to an increased prevalence of meta-

bolic diseases and growing evidence suggests that it may also contribute to the development and severity of NAFLD by exacerbating fat deposition, inflammation, and, possibly fibrosis [5]. Mechanistically, fructose may contribute to NAFLD by promoting *de-novo* lipogenesis, insulin resistance, oxidative stress, bacterial overgrowth, and inflammation [3-7]. The mechanisms responsible for transition to non-alcoholic steatohepatitis are still not completely understood, in part because of the scarcity of animal models that can fully replicate both the histological and metabolic features of human non-alcoholic steatohepatitis [8]. As fructose is likely to act as a dietary 'second hit' [5], effort has recently been put into developing novel experimental models to recapitulate the Western diet by combining high-fat or high-energy diets and fructose. The aim of this Smart Card is to provide a synthetic and exhaustive source for rapid consultation of the currently proposed rodent models of diets combining high fat and fructose, summarizing the metabolic and hepatic consequences of such combinations (Table 1).

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**Table 1 Metabolic and hepatic features of rodent models fed with diets combining high fat and fructose**

Name of model, species, or strain	Diet	Weeks	Metabolic features <sup>a</sup>	NAFLD features <sup>a</sup>	
ALIOS diet (long-chain saturated trans fat)	Standard chow (13.6% kcal from fat (soybean oil (15% saturated fatty acids, 23% monounsaturated fatty acids, 61% polyunsaturated fatty acids)) + gel-water;	16	↑ body weight, ↑ liver weight;	↑ alanine aminotransferase, ↑ aspartate aminotransferase;	[9]
C57BL/6 J mouse	<b>Alios diet: 45% kcal from fat (30% from partially hydrogenated vegetable oil (28% saturated fatty acids, 57% monounsaturated fatty acids, 13% polyunsaturated fatty acids) + high-fructose corn syrup equivalent (55% fructose, 45% glucose by weight) (42 g/l as gel-water)</b>		↑ liver triglycerides; ↑ insulin, ↑ leptin;  = adiponectin; = triglycerides, ↑ cholesterol (plasma)	macrosteatosis (zones 1 and 2), microsteatosis (zone 3);  lobular inflammation; possible ballooning or Mallory-Denk body fibrosis: not observed	
Modified ALIOS (medium chain saturated fatty acids)	Chow diet;	16	↑ body weight, ↑ liver weight;	↑ alanine aminotransferase;	[10]
C57BL/6 J mouse	High-fat diet (58% kcal from fat);  <b>High-fat diet + water with high-fructose corn syrup equivalent (55% fructose and 45% sucrose by weight (42 g/l))</b>		↑ glucose/insulin (fasting);  ↑ HOMA-IR;  ↑ liver triglycerides	steatosis (micro, macro);  lobular inflammation, ↑ apoptosis;  ballooning: not assessed or not reported; ↑ fibrosis	
Fast-food mouse	Standard chow (13% kcal from fat (1% saturated fatty acids) + high-fructose corn syrup in water (42 g/l));	25	↑ body weight, ↑ liver weight;	↑ aspartate	[8]
C57BL/6 J mouse	High-fat diet (60% kcal from fat (1% saturated fatty acids) + high-fructose corn syrup in water (42 g/l));  <b>Fast-food diet (40% kcal from fat (12% saturated fatty acids) +2% cholesterol + high-fructose corn syrup in water (42 g/l))</b>		↑ glucose, insulin (fasting);  ↑ HOMA-IR;  ↓ adiponectin; ↑ cholesterol (plasma)	aminotransferase;  steatosis: panacinar;  (++ macro, + micro); intra-acinar inflammation; ballooning; fibrosis: peri-sinusoidal, -cellular	
High-fat diet + fructose (water)	Control diet (4.8% fat);	8	↑ body weight, = liver weight;	Liver function tests: not assessed or not reported;	[11]
C57BL/6 J mouse	<b>60% fat diet + 30% fructose in water</b>		↑ glucose, ↑insulin (fasting); ↑ HOMA-IR, ↑ GTT-AUC; ↑ leptin;  ↑ triglycerides (plasma), ↑ cholesterol (plasma)	centrilobular fat vacuolation; (↑ Oil Red O); fibrosis: not assessed or not reported	

**Table 1 Metabolic and hepatic features of rodent models fed with diets combining high fat and fructose (Continued)**

High-fat diet + sucrose Wistar rats	Control group (control);  <b>High fat, high sucrose</b>	12	↑ body weight;  =glucose, = insulin; ↑ cholesterol, = triglycerides (plasma); ↑ leptin	Liver function tests: not assessed or not reported; ↑ macrosteatosis	[12]
High-fat diet + fructose (water) C57BL6/J mouse	Control diet;  <b>High-fat diet (72% fat (corn oil/lard); 28% protein, &lt;1% carbohydrates) + 21% fructose in water</b>	8	↑ body weight, ↑ liver weight;  = liver triglycerides, ↑ GTT-AUC;  =glucose, ↑ insulin (fasting)	Liver function tests: not assessed or not reported; ↑ macrosteatosis;  fibrosis: not assessed or not reported	[13]
High-fat diet + fructose (water) Sprague–Dawley rat	Standard chow (5% kcal from fat, 18% proteins, 77% carbohydrates)  Standard chow + fructose in water (30% w/v);  High-fat diet (58% kcal from fat, 18% protein, 24% carbohydrates)  <b>High-fat diet + fructose in water (30% w/v)</b>	12	↑ body weight;  glucose =, ↑ insulin;  ↑ triglycerides, ↑ cholesterol (plasma)	↑ alanine aminotransferase; ballooning + mild steatosis; no inflammation; rare fibrosis	[14]
High-fat diet + fructose (water) Wistar rats	Standard chow (24% protein, 11% fat, 65% carbohydrates (% by weight));  <b>High-fat diet [26% fat, 17% protein, 4% cholesterol, 53% carbohydrates] + 10% (w/v) fructose in water</b>	15	↑ body weight, ↑ liver weight;  ↑ liver triglycerides, ↑ HOMA-IR;  ↑ insulin, = glucose (fasting); ↑ leptin, ↓ adiponectin	↑ alanine aminotransferase, ↑ aspartate aminotransferase; ↑ Oil Red O;  fibrosis: not assessed or not reported	[15]
High-fat diet + fructose (water) Sprague–Dawley rats	Normal chow (4% fat);  <b>High-fat diet (60% kcal from fat) + 10% fructose in water</b>	48	↑ body weight, ↑ liver weight;  = glucose (fasting), ↑ GTT-AUC; ↑ triglycerides, = cholesterol (plasma)	Liver function tests, fibrosis: not assessed or not reported; macroscopic signs of steatosis	[16]
High-fat diet + fructose (water) Sprague–Dawley rats	Low-fat diet: 10% kcal from fat;  <b>Western diet: high-fat diet (45% kcal from fat (soybean oil, lard)) + high-fructose corn syrup-55 (55% fructose, 45% glucose diluted with water to 12.5%)</b>	10	↑ Body weight, ↑ liver weight;  ↑ GTT-AUC/↑ leptin;  = triglycerides (plasma); ↓ cholesterol (plasma)	↑ alkaline phosphatase, = alanine aminotransferase; ↑ liver fat score, ↑ NAFLD activity score;  = lobular inflammation, = ballooning; fibrosis: no	[17]
High-fat diet + fructose (water) Wistar rats	Cornstarch diet;  <b>High-fat, fructose diet (52% carbohydrate, 24% fat, 25% fructose in drinking water)</b>	16	↑ body weight, = liver weight;  ↑ basal glucose;	↑ alanine aminotransferase / ↑ aspartate aminotransferase; ↑ fat vacuoles;	[18]

**Table 1 Metabolic and hepatic features of rodent models fed with diets combining high fat and fructose (Continued)**

			↑ plasma triglycerides (plasma)	↑ portal inflammation; fibrosis: portal	
High-fat diet + fructose (chow)	Standard chow;	16	↑ body weight, ↑ liver weight;	↑ alanine aminotransferase/aspartate aminotransferase;	[19]
C57BL/6 J mice	<b>High-fat, high-fructose diet (in solid diet)</b>		↑ HOMA-IR;	micro/macro-steatosis (pericentral);	
			↑ insulin, glucose (fasting);	fibrosis: not assessed or not reported	
			↑ liver triglycerides		
High-fat diet + fructose (chow)	Control group (cornstarch diet);	5	= body weight;	= alanine aminotransferase;	[20]
Wistar rats	High fructose (70% by weight); High sucrose (70%); High fat (15%); <b>High fat (15%), high fructose (50%)</b>		= plasma triglycerides; = glucose; = liver triglycerides	some macrosteatosis; inflammation: =lobular, = portal; fibrosis: no change	
High-fat diet + fructose (chow)	Low-fat, high-carbohydrate (cornstarch) diet;	32	↑ body weight, ↑ liver weight;	↑ alanine aminotransferase, alkaline phosphatase;	[21]
Wistar rats	<b>High-carbohydrate (fructose/sucrose), high-fat diet</b>		↑ visceral adiposity; ↑ % body fat	= liver triglycerides, lipid deposition; inflammation; fibrosis: not assessed or not reported	
High-fat diet + fructose (chow + water)	Control: cornstarch diet;	16	↑ body weight, ↑ liver weight;	↑ alanine aminotransferase, ↑ aspartate aminotransferase, ↑ alkaline phosphatase;	[22]
Wistar rats	<b>High-carbohydrate, high-fat diet (including condensed milk (39.5%), beef tallow (20%), and fructose (17.5%)) + 25% fructose in water</b>		↑ glucose, = insulin (fasting); ↑ GTT-AUC; ↑ cholesterol, ↑ triglycerides (plasma)	↑ macrosteatosis; ↑ inflammation; mild portal fibrosis	

<sup>a</sup>All indicated changes refer to the experimental group in bold compared with either a control diet or other listed groups.

#### Abbreviations

GTT-AUC: Glucose tolerance test: area under the curve; HOMA-IR: Homeostasis model of assessment - insulin resistance; NAFLD: Non-alcoholic fatty liver disease; w/v: Weight by volume.

#### Competing interests

The author declares that she has no competing interest.

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