OpenSource DIETS®

Fatty Liver Disease

Report ▶ Repeat ▶ Revise

NAFLD (Non-Alcoholic Fatty Liver Disease)

A Brief Scientific Literature Review- December 2008
by Matthew Ricci, Ph.D., VP, Science Director- Research Diets, Inc.

Non-alcoholic fatty liver disease (NAFLD) is a range of disease states, from steatosis (fatty liver) to non-alcoholic steatohepatitis (also called NASH; steatosis with inflammatory changes) followed by progression to fibrosis, cirrhosis and hepatocellular carcinoma (1). Excess liver fat is believed to be a manifestation of the metabolic syndrome (2) and not surprisingly NASH is associated with obesity, insulin resistance, dyslipidemia and type II diabetes in humans (3). Most obese adults have hepatic steatosis and at least one-third of these individuals will eventually develop worsening NAFLD (4, 5), therefore the prevalence of NAFLD will likely rise with obesity rates.

As with most human diseases driven by diet, fatty liver in rodents is also diet-inducible. Different dietary approaches (likely working by different mechanisms) are available and so researchers should be aware of the advantages and disadvantages of each. Here we briefly summarize three such protocols for inducing fatty liver: feeding a methionine and choline-deficient (MCD) diet, a choline-deficient diet (CD) or a high-fat diet (HFD). Of course, each of these terms does not define a specific diet formula, and the researcher should be aware that there are many variations of each of these diet groups which can have different effects on the phenotype of the animal.

MCD diets

MCD diets have been used for over 40 years to study liver disease. Rodents fed a MCD diet will develop measurable hepatic steatosis by 2-4 weeks which progresses to inflammation and fibrosis shortly thereafter (6, 7). The mechanism for steatosis on a MCD diet appears to be impaired VLDL secretion due to lack of phosphatidyl choline synthesis (8). Importantly, unlike human or other diet-induced rodent models of NAFLD, rodents fed MCD diets lose weight (due to a vastly lower caloric intake) and do not become insulin resistant (9, 10). This is in contrast to the typical human with NASH, who is obese and insulin resistant. The source of dietary fat used in MCD diets can alter the phenotype. By using a polyunsaturated dietary fat source, liver fat oxidation, induction of proinflammatory genes and inflammation can be increased (relative to a more saturated dietary fat) though this does not necessarily result in increased liver damage (11). In a different study, olive oil reduced liver TAG accumulation while fish oil reduced liver cholesterol levels (12).

CD diets

CD diets offer the potential advantage that they also increase liver fat levels, and unlike MCD diets, increase body weight, induce dyslipidemia and cause insulin resistance (13). The mechanisms involved with liver fat accumulation may be different from those at work during MCD diet feeding (14) and liver fat accumulation, liver damage and inflammation is less severe than with MCD diets (13). Interestingly, choline deficiency in the context of a high fat diet can improve glucose tolerance in mice (15) FIG. 1.

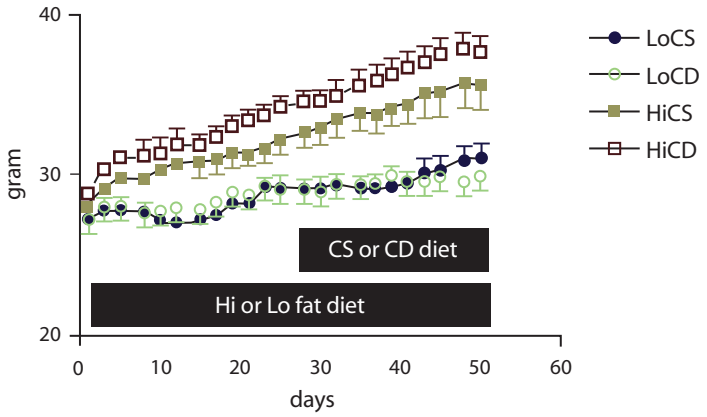

FIGURE 1. Effects of high-fat diet and CDD on body weight. Twelve animals were fed a low-fat diet D12450B(10% calories as fat; Lo), and 12 were fed a high-fat diet D12451(45% calories as fat; Hi) for 8 weeks. During the last 4 weeks, one-half of the animals in each group (n = 6) received a CDD (CD), whereas the other one-half (n = 6) continued on a diet supplemented with choline (CS). Data are expressed as means ± SE. Total weight change was compared by two-way ANOVA with post hoc Tukey's test. Animals on a high-fat diet gained significantly more weight than those on a low-fat diet (HiCS vs. LoCS, P = 0.001). A CDD (CD) had no effect on weight gain. Graphic representation - for details see reference (15).

High-fat diets

High-fat diets (HFD) are well-known to increase body weight, body fat and induce insulin resistance in rodent models. HFD can also increase liver fat levels quite rapidly (within days) and before significant increases in peripheral fat deposition occur (16). Such rapid liver fat accumulation is associated with hepatic insulin resistance (16). Chronically, HFD-induced liver fat accumulation may not follow a linear progression and liver fat levels may actually decrease, then increase again during prolonged HFD feeding (17). When fed for equal lengths of time, HFD feeding results in 10-fold lower liver fat levels compared to what accumulates on an MCD diet (18). In general, HFD feeding does not produce liver fibrosis and only mild steatosis as compared to MCD diets (3).

In a recent issue of Diabetes , Raubenheimer et al., used a combination of a choline-deficient and HFD to examine the effects of excess liver fat on the insulin resistance and glucose tolerance that accompanies diet-induced obesity (15). C57Bl/6 mice were fed either high-fat or low-fat diets with or without choline. Choline deficiency did not affect body weight gain or adipose tissue depot weight but did increase liver triglyceride levels in both low- and high-fat diets. The control HFD increased body weight as well as fasting plasma insulin and glucose levels (versus control low-fat fed animals), suggesting that the mice were becoming insulin resistant. Interestingly, mice fed the choline-deficient HFD had reduced insulin levels compared to those fed the HFD with choline. Furthermore, mice fed the choline-deficient HFD had improved glucose tolerance compared to mice fed the HFD with choline. These researchers also found that choline-deficiency in the context

Resource CENTER

Contact our Resource Center for valuable insight from more than 25 years of product experience in the field of fatty liver disease. Let us formulate the diets to meet your specific study needs.

Custom OpenSource Diets

Research Diets, Inc has pioneered the formulation and production of methionine and choline-deficient (MCD) diets, choline-deficient diets (CD) and high-fat diets (HFD) in laboratory animals. Our scientists specialize in providing custom purified OpenSource diets. By carefully designing the diet formula to fit your protocol, you have complete control over small or large changes in diet composition. Plus you are able to report what your animals were fed, repeat the formula and revise diet composition as necessary.

Incorporate Test Compounds

Research Diets, Inc. will incorporate your test compound into pelleted diets for simple, safe dosing. Feeding test compounds eliminates dosing related stress to the animal, eliminates vehicle effects, and saves time and labor. Consult with one of our scientists on the formula, determine the dosage required and the diet will be produced and shipped in 5 to 7 business days.

Value Added Resource

The value of our products is in the scientific support we provide. Our Resource Center is staffed with Masters and Ph.D. level scientists with access to over 14,000 original formulas and a database of more than 3,800 journal articles. We welcome the opportunity to talk science with researchers throughout the world as we maintain our leadership role as the knowledge base for OpenSource Diet formulation.

BioDAQ Episodic Intake Monitor

BioDAQ E2 Episodic monitoring system measures the ad libitum food and water intake behavior of singly housed lab rats and mice at very high resolution in their home cage. Computer controlled electronics record food and water intake episodically by measuring the moment-to-moment, undisturbed intake behavior of the animals being studied. The animal's behavior defines the variable period for these intake measurements through their native behavior.

RESEARCH DIETS INC.
www.ResearchDiets.com

Where NutriPhenomics® Begins

of a HFD induced the expression of genes for hepatic enzymes involved with FFA esterification to triacylglycerol while gene expression for enzymes involved with fatty acid synthesis and oxidation was unchanged.

The authors concluded that the redirection of fatty acids into hepatic triglyceride storage may be an initial protective mechanism to lower hepatic intracellular fatty acid concentrations. Since elevated intracellular fatty acids are thought to play a causal role in hepatic insulin resistance, their storage as triglyceride would serve to maintain liver insulin sensitivity. Whether or not longer-term feeding of a choline-deficient HFD would eventually lead to impaired insulin sensitivity is unknown.

References

1. Zafrani ES. Non-alcoholic fatty liver disease: an emerging pathological spectrum. Virchows Arch 444: 3-12, 2004.
2. Marchesini G and Babini M. Nonalcoholic fatty liver disease and the metabolic syndrome. Minerva Cardioangiol 54: 229-239, 2006.
3. Anstee QM and Goldin RD. Mouse models in non-alcoholic fatty liver disease and steatohepatitis research. Int J Exp Pathol 87: 1-16, 2006.
4. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A and Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 129: 113-121, 2005.
5. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM and Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 40: 1387-1395, 2004.
6. Sahai A, Malladi P, Melin-Aldana H, Green RM and Whitington PF. Upregulation of osteopontin expression is involved in the development of nonalcoholic steatohepatitis in a dietary murine model. Am J Physiol Gastrointest Liver Physiol 287: G264-G273, 2004.
7. Weltman MD, Farrell GC and Liddle C. Increased hepatocyte CYP2E1 expression in a rat nutritional model of hepatic steatosis with inflammation. Gastroenterology 111: 1645-1653, 1996.
8. Yao ZM and Vance DE. Reduction in VLDL, but not HDL, in plasma of rats deficient in choline. Biochem Cell Biol 68: 552-558, 1990.
9. Kirsch R, Clarkson V, Shephard EG, Marais DA, Jaffer MA, Woodburne VE, Kirsch RE and Hall PL. Rodent nutritional model of non-alcoholic steatohepatitis: species, strain and sex difference studies. J Gastroenterol Hepatol 18: 1272-1282, 2003.
10. Rinella ME and Green RM. The methionine-choline deficient dietary model of steatohepatitis does not exhibit insulin resistance. J Hepatol 40: 47-51, 2004.
11. Lee GS. Yan, JS, Ng RK, Kakar S and Maher JJ. Polyunsaturated fat in the methionine-choline-deficient diet influences hepatic inflammation but not hepatocellular injury. J Lipid Res 48:1885-1896, 2007.
12. Hussein O, Grosovski M, Lasri E, Svlab S, Ravid U and Assy N. Monounsaturated fat decreases hepatic lipid contgent in non-alcoholic fatty liver disease in rats. World J Gastroenterol 13: 361-38, 2007.
13. Vetelainen R, van Vliet A, and vcan Gulik TM. Essential pathogenic and metabolic differences in steatosis induced by choline or methionine-choline deficient diets in a rat model. J Gastroenterol Hepatol 22:1526-1533, 2007.
14. Kulinski A, Vance DE and Vance JE. A choline-deficient diet in mice inhibits neither the CDP-choline pathway for phosphatidylcholine synthesis in hepatocytes nor apolipoprotein B secretion. J Biol Chem 279: 23916-23924, 2004.
15. Raubenheimer PJ, Nyirenda MJ and Walker BR. A choline-deficient diet exacerbates fatty liver but attenuates insulin resistance and glucose intolerance in mice fed a high-fat diet. Diabetes 55: 2015-2020, 2006.
16. Samuel VT, Liu ZX, Qu X, Elder BD, Bilz S, Befroy D, Romanelli AJ and Shulman GI. Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. J Biol Chem 279: 32345-32353, 2004.
17. Gauthier MS, Favier R and Lavoie JM. Time course of the development of non-alcoholic hepatic steatosis in response to high-fat diet-induced obesity in rats. Br J Nutr 95: 273-281, 2006.
18. Romestaing C, Piquet MA, Bedu E, Rouleau V, Dautresme M, Hourmand-Ollivier I, Filippi C, Duchamp C, and Sibille B. Long term highly saturated fat diet does not induce NASH in Wistar rats. Nutr Metab 21:4:4, 2007.

Research Diets, Inc.
20 Jules Lane
New Brunswick, NJ 08901 USA
Tel: 732.247.2390
Fax: 732.247.2340
info@researchdiets.com