Austin Journal of Clinical Medicine

Austin Publishing Group

Open Access Full Text Article

Review Article

Of Mice and Men: A Review of Dietary Murine Models of Nonalcoholic Fatty Liver Disease (NAFLD) and How It Correlates to Human Disease

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Received: February 28, 2014; Accepted: April 06, 2014; Published: April 08, 2014

Abstract

Nonalcoholic fatty liver disease (NAFLD), is a problem of increasing significance worldwide and is comprised of a spectrum of disease from hepatic statuses to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis and even hepatocellular carcinoma (HCC). NAFLD has become one of the most common causes of liver disease and is related to the increasing prevalence of obesity, diabetes, hyperlipidemia and sedentary lifestyle. As there are no approved medical treatments for NAFLD at this time and the information is limited regarding the molecular mechanisms driving disease progression there has been extensive research using murine models of NAFLD to mimic the human disease. Furthermore, there is a paucity of molecular markers that can reliable predict NAFLD and the progression within this spectrum of disease to end-stage liver disease. This article will review the different dietary murine models of NAFLD and how they relate to human NAFLD and longitudinal means of measuring disease prediction and progression.

Keywords: Nonalcoholic; Liver Disease; Human Disease

Abbreviations

NAFLD: Nonalcoholic Fatty Liver Disease; NASH: Nonalcoholic Steatohepatitis; NAFL: Nonalcoholic Fatty Liver; HCC: Hepatocellular Carcinoma; MCD: Methionine and Choline Deficient; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; HFD: High-Fat Diet; T2D: Type 2 Diabetes; ROC: Receiver Operator Characteristic; CK-18: Cytokeratin-18; Adipo-IR: Adipose Tissue Insulin Resistance

Introduction

The expanding epidemic of worldwide obesity is paralleled by the increasing incidence of Nonalcoholic fatty liver disease (NAFLD), resulting in NAFLD becoming the most frequent disease of the liver. NAFLD is defined as evidence of hepatic steatosis (via imaging or histology) with no secondary causes of hepatic fat accumulation as seen in alcohol consumption, medications, or hereditary disorders [1]. In the majority of NAFLD patients, there is an association with metabolic risk factors such as obesity, diabetes mellitus, insulin resistance, sedentary lifestyle and hyperlipidemia. NAFLD is a spectrum of disease from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis and even hepatocellular carcinoma (HCC). NASH implies that there is hepatocyte injury (ballooning) in the presence of steatosis with lobular inflammation with or without fibrosis [2]. Not all patients progress from simple steatosis to NASH and the cause of this progression is not well understood. NAFLD is associated with a 15-20% risk of progression to cirrhosis, and cirrhosis inherently carries the risk of hepatocellular carcinoma [3].

There are multiple causes of hepatic fat accumulation, but the main contributing factor seems to be the over intake of nutrition, especially fat, fructose and sucrose acting as a catalyst for hepatic lipogenesis. This so called "Western-diet" has been increasing worldwide and as a consequence so has the incidence of NAFLD. Hepatic fat accumulation has been linked to type 2 Diabetes Mellitus (T2D) and hepatic insulin resistance [4,5]. The estimates of worldwide prevalence of NAFLD ranges from 6-33% with a median of 20% in the general population with estimated prevalence of 3-5% for NASH [6].

There are currently no approved medical therapies for the treatment of NASH with the mainstay of treatment being weight reduction and exercise. To develop future therapies for NAFLD/NASH animal models are currently being implemented to further characterize the disease. While there are many different animal models, murine models constitute the bulk of research used to elucidate the mechanisms behind NAFLD/NASH. The range of models consists of diet induced, genetically altered mice or genetically altered mice receiving specialty diets. Furthermore, liver biopsy remains the gold standard for the diagnosis of NASH although this procedure carries increased morbidity and mortality compared to other, less reliable means such as imaging studies. This review will focus on different dietary murine models of NAFLD, longitudinal evaluations of NASH and potential predictors of NASH and how they relate to human disease. Genetic models of NAFLD have produced a wealth of knowledge regarding this disease process, but are beyond the scope of this paper.

Analysis and Interpretation

Dietary Murine Models of NAFLD

Methionine and Choline Deficient (MCD) Diet

In contrast to the over-nutrition that is seen in NAFLD patients a common mouse model of NAFLD, the MCD diet, is a nutrient deficient

Citation: Asgharpour A, Vincent R, Min HK. Of Mice and Men: A Review of Dietary Murine Models of Nonalcoholic Fatty Liver Disease (NAFLD) and How It Correlates to Human Disease. Austin J Clin Med. 2014;1(2): 1010.

dietary model of NAFLD. This diet generally consists of sucrose, low amounts of fat content, and deficiencies in methionine and chorine. This model has been shown to develop histopathological features such as lobular inflammation, macrovesicular steatosis, varying degrees of fibrosis, and necrosis associated with NASH [7,8]. Hepatic steatosis occurs in 1-2 weeks in the MCD diet secondary to enhanced uptake of fatty acids and decreased hepatic secretion of very-low-density lipoproteins [9,10]. However, the histological distribution of hepatic steatosis is periportal in MCD mice and not perivenous as seen in humans [11]. Mice later show lobular inflammation and both perisinusoidal and pericentral fibrosis. There are marked elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) as soon as 2 weeks after starting the MCD diet and at levels that are generally higher than in humans [9]. The MCD diet causes oxidative stress via impaired β-oxidation, as well as changes in pro-inflammatory cytokine and adipokine expression related to liver injury. It was recently shown that mice fed an MCD diet share the most similarity to drug transporter expression in human NASH [8]. and this may be an important consideration for future drug development. Despite the many advantages of the MCD diet, these mice lack a similarity of metabolic features seen in human NASH patients. In the MCD diet mice lose weight from baseline compared to control mice, in contrast to the obesity related to human disease. The common hyperglycemia and insulin resistance seen in human NASH is also absent in MCD fed mice. There also exists variability within and between mouse strains that should be considered when utilizing this model. It was discovered that the gut microbiota may be playing a role in human NASH that actually produces a choline deficiency. The gut microbiota that results from a high fat diet can lead to the formation of intestinal microbiota that convert choline to methylamines, reducing plasma phosphatidylcholine [12,13].

High-Fat Diet (HFD)

In line with the over nutrition seen in humans, mice fed a HFD show similar metabolic features seen in human NASH with obesity, impaired glucose tolerance, insulin resistance, dyslipidemia and increased expression of regulators of lipogenesis and proinflammatory cytokines [14]. There have been numerous mouse models using a HFD with varying compositions of fat (% of saturated fat) at different content levels (30-70% of total calories), and varying mouse strain resulting in variability of steatosis, inflammation, fibrosis and tumorgenesis [15,16]. Epidemiological studies have linked Type 2 diabetes (T2D) with numerous cancer types and the strongest relationship has been with hepatocellular carcinoma [17]. The HFD model mice exhibit characteristics of T2D so it is not surprising to see tumor formation in this model. The level of fibrosis seen in these mice is in general less than that seen in the MCD diet and takes a longer duration of feeding to produce. C57BL/6 mice are a very common mouse strain used due to their similar susceptibility to the metabolic syndrome seen in human NASH and the development of the full spectrum of histologic changes. A C57BL/6 HFD fed mouse can be pushed towards developing significant sinusoidal and pericellular fibrosis at nine weeks with forced, gastric cannula feeds [18]. HFD fed mice develop the full spectrum of disease seen in humans from simple steatosis to tumorgenesis, however, fully developed cirrhosis is not often seen. Cirrhosis may not be necessary for the progression of tumors in these mice as is the case in human NASH patients. While the drug transporter profile in HFD fed mice is similar to that seen in human NASH, there are more similarities to mice fed an MCD diet [8]. The inflammation induced by HFD in mice can also be seen in the intestine, depending on the gut microbiata, leading to bacterial translocation or absorbed bacterial metabolites contributing to NAFLD/NASH [12]. A recent study showed that the microbiota of C57BL/6 mice fed a HFD differs depending on the extent of metabolic disease (hyperglycemia vs euglycemia) and when these microbiata were transferred to germ-free mice there was a similar level of disease seen in recipient mice compared to donor mouse with the germ-free mouse receiving microbiota from the mouse susceptible to metabolic disease developing steatohepatitis and the absence of steatohepatitis in the germ-free mouse receiving the microbiota of the mouse without signs of metabolic disease [19].

High-Fructose and Western Diets

Other murine models of NAFLD have incorporated high-frucotse in both solid and liquid diet formats with both HFD and with standard diets. Regardless of format, a high-fructose diet produced insulin resistance and NAFLD with some weight gain but not as much as that seen with a HFD [20,21]. The high-fructose diet also causes elevation in inflammatory markers, possibly due to increased intestinal translocation of endotoxin [20].

Western diets are considered high in both fat content and fructose and provide the most congruent comparison to the spectrum of metabolic diseases, including NAFLD, seen in humans. Mice fed a Western diet exhibit obesity, insulin resistance, dyslipidemia, hyperglycemia and NAFLD. In particular a Western diet has demonstrated an increased patterns of inflammation, fibrosis, endoplasmic reticulum stress and lipoapoptosis in mice [22]. The same study also demonstrated increased steatohepatitis and fibrosis in Western diet compared to HFD and the Western diet demonstrated steatohepatitis with ballooning on histology [22]. Interestingly, a study using ezetimibe, an inhibitor of intestinal cholesterol absorption, was able to reduce hepatic steatosis, serum cholesterol and insulin resistance in mice fed a HFD, but not in a high-fructose diet [21], this study may lead to further insights in the mechanisms leading to more sever metabolic disease and more aggressive forms of NAFLD.

Longitudinal Evaluation of NASH and potential predictors

Liver Biopsy

While Liver biopsy is the gold standard for diagnosis of NAFLD/NASH there has been limited experience with survival liver biopsy mouse models. Clapper [23] has demonstrated that C57BL/6 mice fed a HFD with high fructose content exhibit varying degrees of NAFLD including hepatic steatosis, hepatic steatosis with fibrosis, and cirrhosis at ~20 weeks. The investigators in this study were also able to perform survival surgery liver biopsies in mice, with a >99% survival rate, and were able to run gene and protein analyses on the biopsy samples [23]. Survival liver biopsies in mouse models of NAFLD may provide a means of correctly stratifying treatment response to the heterogeneity of disease seen at the same time point in isogenic mice. The same limitations seen in human liver biopsy of not obtaining a representative samples, cost, morbidity, and rare mortality also exist for mouse liver biopsies.

Imaging

While hepatic steatosis is often an incidental finding on CT scans and MRI done for other purposes, and can reliable be seen with ultrasound, steatohepatitis and fibrosis are more elusive to detect on imaging. In fact, ultrasound has proven to be an effective non-invasive means of detecting liver lesions in humans and is the standard to monitor cirrhotic patients for progression of disease to HCC [24]. High-frequency ultrasound has also been used in models of NAFLD to specifically look for more advanced lesions such as metastatic changes or HCC, but more recent studies have shown that high-frequency ultrasound can detect earlier lesions that lead to HCC and may be able to play a more prognostic role before the development of full blown HCC [25] in models that lack the level of fibrosis and cirrhosis seen in humans. Other studies have used potential biomarkers for NAFLD associated with mitochondrial dysfunction with PET imaging to stage liver disease in a MCD model of NAFLD with promising results linking the expression of the marker of mitochondrial dysfunction to the progression of disease within the spectrum of NAFLD to fibrosis [26]. While there are insights to imaging mouse models of NAFLD, there still exists a gap in understanding the progression of disease beyond the establishment of simple hepatic steatosis.

Biochemical Predictors of NASH

Common Laboratory Findings

For most patients the signs of liver disease are noticed with routine laboratory testing with a primary physician. Commonly elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels may reflect the presence of hepatic inflammation, steatosis and eventual fibrosis although they are uncommonly greater than four times the upper limit of normal. Separation of other liver diseases has been attempted. Although levels of ALT tend to be higher in patients with NAFLD compared to those without, population cohort studies have demonstrated that ALT levels are within normal limits in nearly 80% of patients with fatty liver [27]. Furthermore, aminotransferase levels tend to fall over time as hepatic steatosis and inflammation improves as fibrosis progresses [28]. When fibrosis becomes advanced, the ALT : AST ratio may become reversed, or the levels of both may become normal [29]. Several studies of hepatology clinic patients undergoing liver biopsy and morbidly obese individuals undergoing bariatric surgery have found ALT levels to be higher in the presence of NASH than in those with simple steatosis, although this has not been universally observed [30-33]. To further complicate matters, several series have reported a similar range of histological changes among patients with raised and normal ALT levels [34,35]. For example receiver operator characteristic (ROC) curve analysis, the accuracy of ALT for determining NASH in 139 patients with NAFLD was only 0.58 (95% *CI* 0.49–0.68) [36]. Poor diagnostic accuracy was also found in 54 NAFLD patients in a Turkish study where ALT and AST both provided area under the curve (AUC) values of 0.61 for distinguishing NASH from simple steatosis [37]. In a study of 233 women undergoing bariatric surgery, the adjustment of different ALT cut-offs for diagnosing NASH improved sensitivity for the diagnosis of NASH (42% to 72%); however, this was at the expense of specificity, which fell from 80 to 42% [38].

In summery patients with NAFLD who have high levels of ALT are therefore more likely to have NASH; however, NASH and advanced fibrosis cannot be excluded on the basis of a normal ALT level. Also ALT levels cannot distinguish NAFLD or NASH from other liver diseases.

Markers of cell death as a Marker of NASH

The single most promising plasma biomarker for the diagnosis and grading of NASH is the caspase-generated CK-18 fragment (CK-18) concentration. In past studies apoptosis has been noted as being one of the key pathways of liver injury and cell death in patients with NASH [39]. CK-18 is a major intra-hepatic intermediate filament protein that is cleaved by caspase enzymes during apoptosis and was thought to be a possible marker. Cytokeratin-18(CK-18) has been found to be increased in NASH compared with simple steatosis and can be assessed in the plasma [32,36]. It has also been noted that CK-18 fragment levels are higher in NASH patients compared to those with simple steatosis and fall with weight loss induced by bariatric surgery [32,36]. However, further studies on the value of CK-18 in NASH have met mixed results.

The Pioneering work mentioned above by Feldstein [36] showed promising results for CK-18 in predominantly Caucasian populations with a relatively small number of patients [32,36]. More recent data have somewhat less convincing, with a sensitivity and specificity for NASH and fibrosis in the 0.65 to 0.75 and 0.75 to 0.85 range, respectively [40-43]. Larger studies have been consistent with the current findings about the modest correlation of CK-18 with NASH and fibrosis [41-44]. Of note, CK-18 alone was not able to clearly discriminate between mild to moderate/severe grades of fibrosis and its predictive value was not significantly superior to that of ALT [45]. Despite these shortcomings it is possible that the future of CK-18, and of non-invasive testing for NASH, may be in targeting high-risk patients (i.e., with the metabolic syndrome and/or T2DM) with a combination of simple relevant metabolic measurements such as adipose tissue insulin resistance (Adipo-IR index = fasting FFA x insulin) [46,47]. plasma adiponectin [48] and/or with additional specific circulating markers of apoptosis (i.e., soluble Fas and soluble Fas ligand) as suggested in pilot studies [40,43,49]. In addition, recent studies have demonstrated that circulating oxidized fatty acids are novel biomarkers for the non-invasive diagnosis of NASH. Because these biomarkers can reflect the levels of cell death and oxidative stress, two key pathological mechanisms of liver injury in NASH, future studies to assess the potential synergistic effects of measuring both types of biomarkers simultaneously are warranted [50,51]. Currently that is the focus of future studies, investigating the best combination of factors to provide the best diagnostic value while also gauging the severity of NASH.

Conclusion

As discussed in this review, there are many different dietary mouse models of NAFLD/NASH being implemented to elucidate the true molecular and metabolic nature of NAFLD onset and it's progression through the spectrum of disease from simple steatosis to more advanced disease with fibrosis, cirrhosis and HCC. While there exists varying degrees of metabolic disease and liver damage between the different dietary models, each has provided insight into different aspects of NAFLD and will play a role in future discovery

depending on the hypothesis being questioned. Regardless of the dietary model used, there is heterogeneity of disease progression within these models, despite the mice being isogenic, that needs to be sorted via liver biopsy, imaging system or new biochemical markers so that future therapeutic studies can make more meaningful comparisons. The fact that the isogenic mice have such varying levels of disease from steatosis to tumor formation at the same time point only further demonstrates that there are epigenetic factors at play and as mentioned earlier the gut microbiota may play a pivotal role. With more clinically meaningful and accurate models a clearer understanding behind the interplay between NAFLD, obesity, and insulin resistance can be unraveled and medical therapies can be developed to treat this ever growing epidemic.

Acknowledgement

The authors wish to acknowledge support from the Basic Research Program (project no. PJ90693833) of the National Institute of Horticultural and Herbal Science (NIHHS), RDA, Republic of Korea, which provided funds for this review.

References

1. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Gastroenterology. 2012; 142: 1592–1609.
2. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005; 41: 1313-1321.
3. Sanyal AJ. NASH: A global health problem. Hepatol Res. 2011; 41: 670-674.
4. Jornayvaz FR, Shulman GI . Diacylglycerol activation of protein kinase CÎµ and hepatic insulin resistance. Cell Metab. 2012; 15: 574-584.
5. Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. Gastroenterology. 2012; 142: 711-725.
6. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011; 34: 274-285.
7. Leclercq IA, Farrell GC, Field J, Bell DR, Gonzalez FJ. CYP2E1 and CYP4A as microsomal catalysts of lipid peroxides in murine nonalcoholic steatohepatitis. J Clin Invest. 2000; 105: 1067-1075.
8. Canet MJ, Harwick RN, Lake AD, et al. Modeling Human Nonalcoholic Steatohepatitis-Associated Changes in Drug Transporter Expression Using Experimental Rodent Models. Drug Metab. Dispos. In press. 2014.
9. Anstee QM, Goldin RD. Mouse models in non-alcoholic fatty liver disease and steatohepatitis research. Int J Exp Pathol. 2006; 87: 1-16.
10. Zeisel SH, Blusztajn JK. Choline and human nutrition. Annu Rev Nutr. 1994; 14: 269-296.
11. Koteish A, Diehl AM. Animal models of steatosis. Semin Liver Dis. 2001; 21: 89-104.
12. Schnabl B, Brenner DA . Interactions Between the Intestinal Microbiome and Liver Diseases. Gastroenterology. 2014; .
13. Dumas ME, Barton RH, Toye A, Cloarec O, Blancher C. Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice. Proc Natl Acad Sci U S A. 2006; 103: 12511-12516.
14. Kanuri G, Bergheim I. In Vitro and in Vivo Models of Non-Alcoholic Fatty Liver Disease (NAFLD). Int J Mol Sci. 2013; 14: 11963-11980.
15. Nishikawa S, Yasoshima A, Doi K, Nakayama H, Uetsuka K . Involvement of sex, strain and age factors in high fat diet-induced obesity in C57BL/6J and BALB/cA mice. Exp Anim. 2007; 56: 263-272.
16. Nakamura A, Terauchi Y. Lessons from mouse models of high-fat diet-induced NAFLD. Int J Mol Sci. 2013; 14: 21240-21257.
17. Johnson JA, Carstensen B, Witte D, Bowker SL, Lipscombe L. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia. 2012; 55: 1607-1618.
18. Deng QG, She H, Cheng JH, French SW, Koop DR. Steatohepatitis induced by intragastric overfeeding in mice. Hepatology. 2005; 42: 905-914.
19. Le Roy T, Llopis M, Lepage P, Bruneau A, Rabot S. Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice. Gut. 2013; 62: 1787-1794.
20. Bergheim I, Weber S, Vos M, Krämer S, Volynets V. Antibiotics protect against fructose-induced hepatic lipid accumulation in mice: role of endotoxin. J Hepatol. 2008; 48: 983-992.
21. Ushio M, Nishio Y, Sekine O, Nagai Y, Maeno Y. Ezetimibe prevents hepatic steatosis induced by a high-fat but not a high-fructose diet. Am J Physiol Endocrinol Metab. 2013; 305: E293-304.
22. Charlton M, Krishnan A, Viker K, Sanderson S, Cazanave S, McConico A, et al. Fast food diet mouse: Novel small animal model of NASH with ballooning, progressive fibrosis, and high physiological fidelity to the human condition. Am. J. Physiol. Gastrointest. Liver Physiol. 2011; 301: 825–834.
23. Clapper JR, Hendricks MD, Gu G, Wittmer C, Dolman CS, Herich J, et al. Diet-induced mouse model of fatty liver disease and nonalcoholic steatohepatitis reflecting clinical disease progression and methods of assessment. Am. J. Physiol. Gatro. Liver Phys. 2013; 305: 483-495.
24. Maruyama H, Ebara M. Recent applications of ultrasound: diagnosis and treatment of hepatocellular carcinoma. Int J Clin Oncol. 2006; 11: 258-267.
25. Fernández-Domínguez I, Echevarria-Uraga JJ, Gómez N, Luka Z, Wagner C. High-frequency ultrasound imaging for longitudinal evaluation of non-alcoholic fatty liver disease progression in mice. Ultrasound Med Biol. 2011; 37: 1161-1169.
26. Xie L, Yui J, Hatori A, Yamasaki T, Kumata K. Translocator protein (18 kDa), a potential molecular imaging biomarker for non-invasively distinguishing non-alcoholic fatty liver disease. J Hepatol. 2012; 57: 1076-1082.
27. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004; 40: 1387-1395.
28. Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. J Hepatol. 2005; 42: 132-138.
29. Guha IN, Parkes J, Roderick PR, Harris S, Rosenberg WM. Non-invasive markers associated with liver fibrosis in non-alcoholic fatty liver disease. Gut. 2006; 55: 1650-1660.
30. Fracanzani AL, Valenti L, Bugianesi E, Andreoletti M, Colli A. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. Hepatology. 2008; 48: 792-798.
31. Milner KL, van der Poorten D, Xu A, Bugianesi E, Kench JG. Adipocyte fatty acid binding protein levels relate to inflammation and fibrosis in nonalcoholic fatty liver disease. Hepatology. 2009; 49: 1926-1934.
32. Diab DL, Yerian L, Schauer P, Kashyap SR, Lopez R. Cytokeratin 18 fragment levels as a noninvasive biomarker for nonalcoholic steatohepatitis in bariatric surgery patients. Clin Gastroenterol Hepatol. 2008; 6: 1249-1254.
33. Harrison SA, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut. 2008; 57: 1441-1447.
34. Sorrentino P, Tarantino G, Conca P, Perrella A, Terracciano ML. Silent non-alcoholic fatty liver disease-a clinical-histological study. J Hepatol. 2004; 41: 751-757.

35. Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology. 2003; 37: 1286-1292.

36. Feldstein AE, Wieckowska A, Lopez AR, Liu YC, Zein NN. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis: a multicenter validation study. Hepatology. 2009; 50: 1072-1078.

37. Kayadibi H, Gültepe M, Yasar B, Ince AT, Ozcan O, Ipcioglu OM, et al. Diagnostic value of serum prolidase enzyme activity to predict the liver histological lesions in non-alcoholic fatty liver disease: a surrogate marker to distinguish steatohepatitis from simple steatosis. Dig Dis Sci. 2009; 54: 1764–1771.

38. Kunde SS, Lazenby AJ, Clements RH, Abrams GA. Spectrum of NAFLD and diagnostic implications of the proposed new normal range for serum ALT in obese women. Hepatology. 2005; 42: 650-656.

39. Feldstein AE, Canbay A, Angulo P, Taniai M, Burgart LJ. Hepatocyte apoptosis and fas expression are prominent features of human nonalcoholic steatohepatitis. Gastroenterology. 2003; 125: 437-443.

40. Younossi ZM, Jarrar M, Nugent C, Randhawa M, Afendy M. A novel diagnostic biomarker panel for obesity-related nonalcoholic steatohepatitis (NASH). Obes Surg. 2008; 18: 1430-1437.

41. Francque SM, Verrijken A, Mertens I, Hubens G, Van Marck E. Noninvasive assessment of nonalcoholic fatty liver disease in obese or overweight patients. Clin Gastroenterol Hepatol. 2012; 10: 1162-1168.

42. Joka D, Wahl K, Moeller S, Schlue J, Vaske B. Prospective biopsy-controlled evaluation of cell death biomarkers for prediction of liver fibrosis and nonalcoholic steatohepatitis. Hepatology. 2012; 55: 455-464.

43. Koehler E, Swain J, Sanderson S, Krishnan A, Watt K, Charlton M. Growth hormone, dehydroepiandrosterone and adiponectin levels in non-alcoholic steatohepatitis: an endocrine signature for advanced fibrosis in obese patients. Liver Int. 2012; 32: 279–286.

44. Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011; 140: 124–131.

45. Cusi K, Chang Z, Harrison S, Lomonaco R, Bril F. Limited value of plasma cytokeratin-18 as a biomarker for NASH and fibrosis in patients with non-alcoholic fatty liver disease. J Hepatol. 2014; 60: 167-174.

46. Lomonaco R, Ortiz-Lopez C, Orsak B, Webb A, Hardies J, Darland C, et al. Effect of adipose tissue insulin resistance on metabolic parameters and liver histology in obese patients with non-alcoholic fatty liver disease. Hepatology. 2012; 55:1389–1397.

47. Gastaldelli A, Cusi K, Pettiti M, Hardies J, Miyazaki Y. Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. Gastroenterology. 2007; 133: 496-506.

48. Gastaldelli A, Harrison S, Belfort-Aguiar R, Hardies J, Balas B. Pioglitazone in the treatment of NASH: the role of adiponectin. Aliment Pharmacol Ther. 2010; 32: 769-775.

49. Tamimi TI, Elgouhari HM, Alkhouri N, Yerian LM, Berk MP. An apoptosis panel for nonalcoholic steatohepatitis diagnosis. J Hepatol. 2011; 54: 1224-1229.

50. Zein CO, Lopez R, Fu X, Kirwan JP, Yerian LM, McCullough AJ, et al. Pentoxifylline decreases oxidized lipid products in non-alcoholic steatohepatitis: new evidence on the potential therapeutic mechanism. Hepatology. 2012; 56: 1291–1299.

51. Feldstein AE, Lopez R, Tamimi TA, Yerian L, Chung YM. Mass spectrometric profiling of oxidized lipid products in human nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. J Lipid Res. 2010; 51: 3046-3054.

Austin J Clin Med - Volume 1 Issue 2 - 2014
ISSN : 2381-9146 | www.austinpublishinggroup.com

Citation: Asgharpour A, Vincent R, Min HK. Of Mice and Men: A Review of Dietary Murine Models of Nonalcoholic Fatty Liver Disease (NAFLD) and How It Correlates to Human Disease. Austin J Clin Med. 2014;1(2): 1010.