A Review of Non-Alcoholic Fatty Liver Disease: From Obesity to Liver Transplant

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Summary

Non-alcoholic fatty liver disease (NAFLD) is becoming an increasingly common etiology of liver disease in the United States. As the prevalence of diabetes and obesity continues to increase, it will soon surpass hepatitis C as the most common etiology of end stage liver disease in the western world. NAFLD like many liver diseases can progress to cirrhosis, and patients often suffer morbidity secondary to the complications of portal hypertension. The exact percentage of hepatocellular carcinoma (HCC) that occurs in NAFLD patients is unknown, however, unlike many other liver diseases there is small potential for development of HCC independent of cirrhosis. Various conservative and pharmacologic therapies have been studied with varying degrees of efficacy including lifestyle modifications, bile acids, insulin sensitizers, vitamin E, and bariatric surgery. However, the only curative treatment for NAFLD cirrhosis is liver transplant. As the epidemic that is NAFLD continues to grow, more studies will need to be done to develop new therapies and curative treatments.

Résumé

La stéatose hépatique non alcoolique est une hépatopathie de plus en plus courante aux États-Unis. Au vu de la hausse continue de la prévalence du diabète et de l'obésité, elle surpassera bientôt l'hépatite C au rang de principale cause d'hépatopathie terminale dans la population occidentale. La stéatose hépatique non alcoolique, à l'instar de nombreuses affections hépatiques, peut évoluer vers la cirrhose, et les patients présentent souvent des affections concomitantes secondaires aux complications de l'hypertension portale. Le pourcentage exact de carcinome hépatocellulaire apparaissant chez les personnes atteintes de stéatose hépatique non alcoolique est inconnu, mais il faut savoir que, à l'encontre d'autres maladies hépatiques, il y a un faible risque de carcinome indépendant de la cirrhose. Divers traitements conservateurs et pharmacothérapies ont été étudiés, dont la modification des habitudes de vie, les acides biliaires, les insulinosensibilisateurs, la vitamine E et la chirurgie bariatrique; ils sont d'efficacité variable. Le seul traitement curatif de la cirrhose secondaire à la stéatose hépatique non alcoolique demeure la greffe de foie. L'épidémie de stéatose hépatique non alcoolique prenant de l'ampleur, la recherche devra se poursuivre pour aboutir à la mise au point de nouveaux traitements, notamment des traitements curatifs.

Non-alcoholic fatty liver disease (NAFLD) is becoming an increasingly prevalent etiology of liver disease in the United States. Surveys conducted by the National Health and Nutrition Examination Survey (NHANES) show the prevalence of other chronic liver diseases such as hepatitis B virus (HBV) and hepatitis C virus (HCV) has remained stable over the years, while the prevalence of NAFLD has been steadily increasing.¹ NAFLD is present in approximately 30% of adults and is reported as the etiology of asymptomatic liver enzyme elevation in approximately 45–90% of patients.^{2,3} The increasing prevalence of NAFLD mirrors the increase in the percentage of obesity, diabetes, hypertension, and the metabolic syndrome in our population. Today NAFLD is considered the hepatic equivalent of the metabolic syndrome.⁴ NAFLD is rapidly becoming the most common diagnosis prior to liver transplant; thus it is important to recognize the risk factors and natural history of this disease.

NAFLD includes a wide spectrum of liver pathology ranging from steatosis without inflammation to non-alcoholic steatohepatitis (NASH), advanced fibrosis, liver failure, and cirrhosis.⁵ Histologically, NAFLD is difficult to distinguish from alcohol-induced liver injury; thus it is necessary to ensure that individuals diagnosed with NAFLD are consuming less than 30 grams (gm) per day for men and less than 20 gm per day for women.^{6,7}

There is a proposed “two hit” hypothesis for the development of NAFLD. The “first hit” is insulin resistance, which leads to steatosis of the liver. The “second hit” is oxidative stress induced by development of reactive oxygen species from fatty acid oxidation, which, in combination with insulin resistance, leads to NAFLD. The exact mechanism by which oxidative stress and insulin resistance predispose to NAFLD remains uncertain.^{8,9} However, it has been proposed that visceral adiposity and adipokines, as well as cytokines such as IL-6 and TNF- α , may play a role.¹⁰ Genetic susceptibility might also contribute, as shown by the increased prevalence of NAFLD in patients with the PNPLA3 polymorphism.¹¹

Risk Factors for NAFLD

The main risk factors associated with development of NAFLD are diabetes mellitus (DM) type II, obesity, and hyperlipidemia. In a review, Miyake and colleagues noted that high body mass index, elevated alanine aminotransferase (ALT), low total bilirubin, hyperuricemia, elevated hemoglobin A1c, insulin resistance, and elevated ferritin were all associated with increased probability of developing NAFLD.¹² However, others have reported the principal associated risk factors for NAFLD to be obesity and hyperlipidemia.⁶

Approximately 18.5% of obese individuals have been

found to have histologic evidence of steatohepatitis, compared to 2.7% of lean individuals.¹³ Also, DM type II and obesity have been demonstrated to be associated with increasing severity of NAFLD.^{13,14} Other risk factors for progression to fibrosis include advanced age and inflammation on initial biopsy.¹⁵

In addition, it has been shown that patients found to have steatosis on liver biopsy tend to follow a more benign course, whereas patients with advanced fibrosis or steatohepatitis have a much poorer prognosis. The finding of steatohepatitis on histology often predicts development of cirrhosis and its liver-related complications.^{5,15}

NAFLD and Cirrhosis

Approximately 3–15% of patients with NAFLD develop cirrhosis; however, this progression of NAFLD to end-stage liver disease can take decades.^{6,17,18} Several studies have looked at the risk factors for progression to NASH cirrhosis. In a multi-centre cross-sectional study of 1365 patients, Nakahara found poor glucose control and age to be directly associated with advanced stages of fibrosis.¹⁹ Another study cited age over 45 years, diabetes, and obesity as risk factors for progression to advanced fibrosis and cirrhosis, as well.⁵

Patients with NAFLD-related cirrhosis may be asymptomatic until they present with findings of advanced-stage cirrhosis, including hepatic encephalopathy, ascites, and/or variceal bleeding.²⁰ It is often difficult to diagnose NAFLD once it has progressed to NASH cirrhosis, as steatosis frequently disappears with progression of disease. Consequently, in advanced disease, NAFLD-associated cirrhosis may be indistinguishable from other etiologies of cirrhosis.¹⁸ However, once other causes of advanced liver disease have been excluded, it is reasonable to presume that cirrhotic patients with features of the metabolic syndrome including obesity, diabetes, and hyperlipidemia have NAFLD-related cirrhosis.²¹

We now know that a large proportion of chronic liver disease of unknown etiology or “cryptogenic cirrhosis (cc)” is actually NAFLD-related cirrhosis.^{20,21} One study found that patients with cryptogenic cirrhosis have a prevalence of diabetes and obesity that is similar to patients with NASH and higher than that of patients with cirrhosis due to autoimmune or viral liver disease.²⁰ In a study of patients who had undergone liver transplant for cryptogenic cirrhosis, NAFLD was diagnosed as the etiology of liver disease in approximately 66% of cases.²² These studies indicate the estimated percentages of NAFLD-related cirrhosis might be underestimated, since cases of cryptogenic cirrhosis are often not taken into consideration.

Similar to other causes of cirrhosis, NAFLD-related cirrhosis is associated with hepatocellular carcinoma (HCC). Therefore, it is important to perform routine surveillance

imaging to screen these patients for the development of HCC.

NAFLD and HCC

Traditionally, hepatocellular carcinoma (HCC) has been described predominantly in patients with cirrhosis from alcohol-induced liver injury and hepatitis B and C (with and without cirrhosis). The incidence of HCC in the US has increased approximately 80% in recent decades. Half this increase has been attributed to new cases of hepatitis C; however, it is speculated that the remainder may be due to NAFLD.²³ The exact percentage of HCC that occurs in NAFLD cirrhosis is unknown. However, the risk factors for development of HCC in NAFLD have been identified as male sex and age over 50 years.²⁴ There is growing evidence that NAFLD, without cirrhosis, is also a risk factor for HCC.²⁵

Multiple studies have shown that some patients with NAFLD can develop HCC in the absence of cirrhosis. Ertle et al looked at 162 patients with HCC and found that approximately 42% ($p < 0.005$) of patients with NAFLD-associated HCC developed HCC in the absence of cirrhosis. These patients typically had features of the metabolic syndrome, including hyperlipidemia, type 2 DM, and obesity, compared to non-NAFLD patients with HCC. The authors hypothesized that the metabolic syndrome is an independent risk factor for developing HCC in NAFLD patients.²⁶ Although NAFLD might be an independent predictor of HCC, patients with NAFLD-related cirrhosis had a higher incidence of HCC (approximately 10–13%), compared to patients with NAFLD who did not have cirrhosis (0.5%) after a mean follow-up of 7.5 years.^{27,28} Compared to other etiologies of liver disease, the overall risk of HCC in NAFLD is still lower than that of HCC from other causes, specifically hepatitis-c related cirrhosis.²⁷

Treatment

There are no proven therapies for NAFLD at this time; treatment is focused on management of comorbid conditions; lifestyle modifications; pharmacotherapy, including bile acids, insulin sensitizers, and vitamin E; and bariatric surgery.

Lifestyle Modification

As NAFLD is frequently associated with diabetes, obesity, and the metabolic syndrome, it should be no surprise that lifestyle modification, including weight loss, diet, and exercise remain the cornerstone of management. One study randomized obese individuals with biopsy proven NASH to an intensive lifestyle intervention group, versus a control group, and observed them over 48 weeks. The participants who lost more than 7% of their weight were shown to have significant improvements in liver histology, including improvements in steatosis, lobular

inflammation, and ballooning injury. Overall, the study showed that weight reduction significantly impacts liver histology with important implications for progression of disease.²⁹ These findings were further supported by a meta-analysis that demonstrated the effect of weight loss on liver histology in NAFLD.³⁰ In comparison, exercise alone benefits liver steatosis but not transaminases.³¹ The current AASLD guidelines state that 3–5% of weight loss can improve steatosis, but up to 10% may be necessary for improvement in necroinflammation.³²

Pharmacotherapy

Currently no pharmacologic therapy has been approved for use in NAFLD or NASH. Medications for weight loss, agents for hyperlipidemia, glucose-lowering agents, and antioxidants have all been investigated.

Insulin Sensitizers

Insulin sensitizers, such as metformin and the thiazolidinediones, have been proposed for treating NAFLD. Metformin is an oral biguanide used to treat DM type 2. The mechanism of action is to increase insulin sensitivity by decreasing hepatic glucose production, decreasing intestinal absorption of glucose and improving peripheral insulin uptake.³³ An open-label study on metformin use in NASH patients found an initial improvement in transaminases, but only a modest improvement in hepatic steatosis and inflammation at one year (33% and 20%, respectively).³⁴ Similarly, a randomized-controlled trial found no significant difference in liver histology between metformin and placebo in patients with biopsy proven NAFLD. However, the study did find that metformin led to overall improvements in weight, low-density lipoprotein (LDL) cholesterol, blood glucose levels, and hemoglobin A1c.³⁵

Thiazolidinediones, such as pioglitazone and rosiglitazone, are peroxisome proliferator activated-receptor gamma agonists (PPAR-gamma agonists). They activate the PPAR-gamma receptor to alter the transcription of several genes involved in lipid and glucose metabolism.³⁶ Thiazolidinediones decrease insulin resistance by increasing glucose use by tissues and decreasing glucose production.³⁷ A meta-analysis looking at the effects of current treatments in NAFLD found that thiazolidinediones slowed progression of fibrosis and showed improvements in histologic activity and inflammation, though weight gain was a side effect in up to 75% of patients.³⁸ Other studies found improvements in hepatic steatosis with thiazolidinediones, as well, yet they also re-demonstrated the side effect of weight gain similar to the previous study.^{15,20}

A meta-analysis comparing thiazolidinediones and metformin in the treatment of NASH determined that the thiazolidinediones led to significant improvements in hepatic

steatosis, hepatocyte ballooning, and alanine aminotransferase (ALT) levels, but had no significant effect on fibrosis or inflammation in patients with diabetes. However, in patients without diabetes, the thiazolidinediones showed improvement in all categories, including fibrosis. In contrast, metformin did not show any histologic or biochemical benefit.³⁹ Metformin is currently not recommended as a treatment of liver disease in NAFLD. Pioglitazone can be used in biopsy proven NASH; however, most studies of its effectiveness were done solely in non-diabetic patients.³²

Bile Acids

Bile acids have also been used to treat NAFLD. It has been hypothesized that dysregulation of bile acid transport and signalling may play a role in the pathogenesis of NAFLD.⁴⁰ One study showed that ursodeoxycholic acid reduced ALT to normal levels in approximately 24.5% of patients.⁴¹ However, a systematic review from the Cochrane Review determined there is currently not enough evidence to support the use of ursodeoxycholic acid for the treatment of NAFLD; therefore, it is currently not recommended for treatment of NAFLD or NASH.^{32,42}

Vitamin E

Vitamin E has also been studied in the treatment of NAFLD. Vitamin E is a fat-soluble antioxidant that interferes with lipid oxidation and the production of reactive oxygen species.⁴³ Reactive oxygen species play a central role in the “two hit” hypothesis and the development of NASH, as discussed. The PIVENS trial found that vitamin E was associated with a significant improvement in NASH when compared to placebo. Treatment with vitamin E resulted in improvements in aspartate aminotransferase (AST) and ALT levels, hepatic steatosis, and lobular inflammation without change in fibrosis.⁴⁴ At this time, vitamin E has only been found to be effective in patients who do not have diabetes.^{44,45} The American Association for the Study of Liver Diseases (AASLD) guidelines state that vitamin E improves histology in non-diabetic patients with NASH and can be used at a dose of 800 IU/day in this population.³² However, the use of vitamin E remains controversial, as several studies have shown an increased risk of all-cause mortality when vitamin E is used in doses greater than 400 IU/day. Thus it should be used with caution.^{46,47}

Bariatric Surgery

The effects of bariatric surgery in the treatment of NAFLD have also been assessed. Klein et al found that patients who lost approximately 29% of their initial body weight after gastric bypass surgery had a decrease in adipose tissue lipolysis, endogenous glucose production, secretion of very-low density

lipoprotein and steatosis, as well as a decrease in the mediators associated with the development and progression of fibrosis.⁴⁸ Another study evaluated 18 patients two years after undergoing Roux-en-y gastric bypass and discovered resolution of steatosis in 84% and resolution of fibrosis in 75% of those who lost over 60 percent of their weight.⁴⁹ Weight loss after gastric bypass surgery has been associated with improved blood glucose control, steatosis, lobular inflammation, and fibrosis, as well as resolution of liver disease in approximately 89%.⁵⁰ Nevertheless, for patients with NAFLD who have progressed to cirrhosis with decompensation, liver transplant is the treatment of choice.

Liver Transplant in NASH

As the number of patients with NAFLD who progress to cirrhosis rises, liver transplant is becoming an increasingly important intervention.⁵¹ End-stage liver disease from cryptogenic cirrhosis accounts for approximately 7–14% of liver transplants.⁵²

The assessment of patients with NAFLD for liver transplant involves most of the same workup as in other liver diseases. However, some pre-transplantation considerations are specific to NAFLD patients. For instance, as previously described, most NAFLD patients have diabetes and obesity. Diabetes mellitus has been found to be an independent predictor of poor survival after transplant.⁵³ Multiple studies also found patients with pre-transplant diabetes to have higher morbidity and mortality than their non-diabetic counterparts, likely secondary to higher frequency of cardiovascular complications, renal failure, and infections.⁵⁴ One case-control study found an increased incidence of complications involving cardiovascular, ophthalmologic, renal, musculoskeletal, hematologic, respiratory, and neurologic systems in diabetic patients with NAFLD who underwent liver transplant. They also found a higher rate of minor and major infections and malignancies post-transplant in diabetic patients.⁵⁵ Given the risk of significant morbidity and mortality in diabetics, these patients should undergo thorough pre-transplant cardiovascular evaluation and close evaluation of other comorbid conditions.

The amount of steatosis in the donor liver must also be considered prior to transplantation of a patient with NAFLD. Donor livers with severe steatosis (approximately > 60%) have a larger risk of primary non-function in the allograft. Marsman et al performed a prospective study evaluating the outcomes of patients transplanted with livers with up to 30% steatosis. They found a significant decrease in four-month graft survival and two-year patient survival in patients transplanted with the steatotic livers. Limited graft survival in these patients was attributed to primary graft dysfunction or non-function. In the study, fatty infiltration was an independent predictor of poor

outcome after transplantation.⁵⁶ In addition, steatosis of the donor liver has been shown to be associated with development of de novo NAFLD after liver transplant.⁵⁷ Despite these findings, due to the shortage of donor organs, it is often necessary to allow some degree of steatosis in the donor in order to use as many potential donor livers as possible.⁵⁸ Most transplant surgeons perform a biopsy of cadaveric livers prior to transplantation to determine degree of steatosis; however, this practice is controversial in living donors, as there are risks associated with the procedure.⁵⁹ Currently, most transplant centres allow for approximately 10–30% steatosis in the donor liver prior to transplantation.⁶⁰

It is speculated that, with the rising proportion of patients with NAFLD, liver transplants for NASH cirrhosis would surpass that of hepatitis C-cirrhosis related liver transplant. However, it appears patients with NAFLD-induced cirrhosis have lower associated MELD scores, which could therefore affect the number of patients eligible for liver transplantation.⁶¹

Outcomes After Liver Transplant

Overall, mortality after liver transplant for NAFLD patients is comparable to liver transplants due to other indications. The assessment of 54,687 liver transplant recipients from the UNOS registry found that graft survival at 1, 3, 5, and 10 years for NASH patients was comparable to liver transplants for cholestatic liver disease and hepatitis B and better for alcoholic liver disease, hepatitis C, and hepatocellular carcinoma. Moreover, patient survival at 1, 3, 5, and 10 years post-transplant was 89%, 85%, 84%, and 84%, respectively. Survival was similar to that of cholestatic disease and HBV and better than alcoholic liver disease, HCV, and HCC.⁵³ Another study by Afzali et al evaluated 53,738 liver transplant recipients from the UNOS registry and found better survival for liver transplants due to NASH, compared to alcoholic liver disease, HCV, and HCC and poorer survival than transplants due to cholestatic disease, HBV, and autoimmune hepatitis.⁶²

There are varying data on recurrence of NAFLD after liver transplant; nevertheless, most studies agree that NASH patients do not frequently require re-transplantation. Patients who develop recurrence of steatosis and NAFLD typically have a higher average BMI in comparison to those who do not develop recurrence.⁵⁸ One single center study of 88 patients with NAFLD-related liver transplant found recurrence in 34 (39%), isolated steatosis in 9, steatohepatitis in 25, and advanced fibrosis in 3 patients. Factors associated with recurrence included higher pre and post-transplant body mass index (BMI) and elevated post-transplant triglyceride levels. Patients with recurrence in this study were also on higher doses of steroids.⁶³ In addition, patients with the genotype PNPLA3 rs738409-G who have

undergone liver transplant have an increased likelihood of developing graft steatosis and recurrence as well.⁶⁴

De novo NAFLD after liver transplant has been described in up to 31% of patients who have undergone liver transplantation. One multicentre retrospective study found a prevalence of 31.1% of NAFLD and 1.6% of NASH after liver transplantation.⁶⁵ As discussed, pre-transplant steatosis is a risk factor for the development of NAFLD in post-transplant patients. Other risk factors for de novo NAFLD after transplant include use of tacrolimus, hyperlipidemia, post-transplant diabetes, and obesity.⁵⁸ Unfortunately, many immunosuppressants, including corticosteroids and calcineurin inhibitors such as tacrolimus, promote development of the metabolic syndrome, which in turn can lead to the development of NAFLD.

Conclusion

NAFLD is becoming an increasingly common etiology of liver disease in the US. As the prevalence of diabetes, obesity, and metabolic syndrome are increasing in our population, the frequency of NAFLD is steadily increasing as well. In certain patients, NAFLD can progress to NASH cirrhosis and place patients at risk of developing complications of end-stage liver disease. There is currently no approved medical therapy for NAFLD, and liver transplant is the only curative treatment. Therefore, more studies on NAFLD are needed in order to develop novel therapies.

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