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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (7): Liver transplant

Non-alcoholic fatty liver disease and liver transplantation: Outcomes and advances

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent causes of chronic liver disease worldwide. In the last decade it has become the third most common indication for liver transplantation in the United States. Increasing prevalence of NAFLD in the general population also poses a risk to organ donation, as allograft steatosis can be associated with non-function of the graft. Post-transplant survival is comparable between NAFLD and non-NAFLD causes of liver disease, although long term outcomes beyond 10 year are lacking. NAFLD can recur in the allograft frequently although thus far post transplant survival has not been impacted. *De novo* NAFLD can also occur in the allograft of patients transplanted for non-NAFLD liver disease. Predictors for NAFLD post-transplant recurrence include obesity, hyperlipidemia and diabetes as well as steroid dose after liver transplantation. A polymorphism in PNPLA3 that mediates triglyceride hydrolysis and is linked to pre-transplant risk of obesity and NAFLD has also been linked to post transplant NAFLD risk. Although immunosuppression side effects potentiate obesity and the metabolic syndrome, studies of immunosuppression modulation and trials of specific immunosuppression regimens post-transplant are lacking in this patient population. Based on pre-transplant data, sustained weight loss through diet and exercise is the most effective therapy for NAFLD. Other agents occasionally utilized in NAFLD prior to transplantation include vitamin E and insulin-sensitizing agents. Studies of these therapies are lacking in the post-transplant population. A multimodality and multidisciplinary approach to treatment should be utilized in management of post-transplant NAFLD.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Liver transplantation; Metabolic syndrome; Outcomes; Management

Core tip: Non-alcoholic fatty liver disease (NAFLD) is a prevalent indication for liver transplantation. It also poses a risk to organ donation, with decreasing rates of suitable allografts. NAFLD frequently recurs in the allograft or develops *de novo*. Post-transplant recurrence is related to obesity and immunosuppression associated metabolic derangements. A polymorphism in PNPLA3 also increases recurrence risk. Pre-transplant data favors sustained weight loss through diet and exercise as the most effective therapy for NAFLD. Vitamin E and insulin-sensitizing agents are occasionally used. Trials on immune-suppression regimens in this population are sorely needed. A multimodality approach to treatment should be utilized in management of post-transplant NAFLD.

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EPIDEMIOLOGY OF NON-ALCOHOLIC FATTY LIVER DISEASE AND ASSOCIATED ADVANCED LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease in the developed world with a prevalence averaging 20% in the ulcerative colitis[1,2]. Its incidence in the developing world is also increasing sharply[3]. Prevalent in adults, it has also become the most common chronic liver disease in children[4]. Mirroring the epidemic of obesity, it is closely related to the metabolic syndrome particularly diabetes and dyslipidemia in association with truncal obesity[5]. Prior to the widespread recognition of NAFLD which was first described as a separate clinic-pathologic entity in 1980[6], many cases of NAFLD were likely classified as cryptogenic liver disease and cryptogenic cirrhosis (CRC). In a study where 39 liver transplant candidates diagnosed with CRC were carefully re-evaluated, 44% had prior biopsy consistent with NAFLD or clinical features of the metabolic syndrome[7].

Although NAFLD has been associated with excess mortality compared to the general population (Hazard ratio 1.34)[8], the natural history of NAFLD is often one of slow progression. In patients with isolated steatosis (fatty liver) the course of liver disease can be frequently benign[9,10]. The progressive form of NAFLD known as Non-alcoholic steatohepatitis (NASH) is associated with hepatocyte damage and consequently can lead to fibrosis as well as cirrhosis and end-stage liver disease[11]. Recently data about the natural history of NAFLD related cirrhosis was reported from four international referral centers. In this study, patients with NAFLD or hepatitis C virus (HCV) associated compensated (Childs A) cirrhosis were enrolled. Over the long term (mean follow up 86 mo for NAFLD and 75 mo for HCV), the incidence of liver related complications and hepatocellular carcinoma (HCC) was lower for NAFLD than for HCV. The probability of remaining free from liver related decompensation was 81.5% in the NAFLD cohort and 76.5% in the HCV cohort at 120 mo of follow up with a higher incidence of complications in HCV when adjusted for age, sex, body mass index and diabetes ($P = 0.03$). The incidence of HCC over follow up was 2.4% in the NAFLD cohort and 6.8% in HCV. Despite these differences, the incidence of cardio-vascular disease and overall mortality were similar between NAFLD and HCV patients (82% survival at 120 mo in both cohorts)[12].

LIVER TRANSPLANTATION INCIDENCE FOR NAFLD

The incidence of liver transplantation related to NAFLD has exploded in the last decade[13]. Although some of the reported increase in incidence of NAFLD related liver transplantation is due to increased recognition of patients previously classified as CRC, the increased incidence of NAFLD related liver transplantation is real. Even if the majority of CRC related liver transplants in prior eras were due to unrecognized NAFLD, the magnitude of increase in transplants for NAFLD far outweighs any classification bias[13]. In an audit of United States national transplant data (SRTR), liver transplants attributed to NAFLD related liver disease increased from 1.2% in 2001 to 9.7% by 2009 and this is now the third most common indication for liver transplantation in the United States[13]. In this study patients with NAFLD receiving a liver transplant were older, more likely to be females, had higher body mass index (BMI) and were less likely to have HCC at transplant compared to all other recipients.

There have been concerns about bias in transplant evaluation and listing of patients with NAFLD related cirrhosis. NAFLD patients are on average older at presentation and have higher rates of obesity and metabolic syndrome raising concerns about worse outcomes of transplant in these patients including increased risks of cardiovascular disease and chronic kidney disease. In a study from a single liver transplant center, the cohort of NAFLD patients with MELD less than 15 at listing were found to progress more slowly compared to patients with HCV and were more likely to die on the waiting list or be taken off the transplant list due to becoming "too sick"[14]. However for patients who were listed with MELD scores over 15 there were no differences in rate of progression of end-stage liver disease, listing rate and receipt of liver transplantation. In another study, patients with NAFLD were equally likely than non-NAFLD patients to undergo liver transplant evaluation, listing and transplantation. In this single center study, NASH patients were older, had similar rates of HCC but increased rates of other prior cancers by history. In addition diabetes and complications of metabolic syndrome were more prevalent in NASH patients. NAFLD patients also had higher creatinine levels at transplant listing than non-NAFLD patients[15]. Routine audits of multicenter and national data will have to be done to see if NAFLD patients are indeed at a disadvantage for evaluation and listing due to these concerns.

OUTCOMES AFTER LIVER TRANSPLANTATION FOR NAFLD

Survival after liver transplantation for NAFLD

Outcomes after liver transplantation in patients with NAFLD have been reported in both large national database audits as well as from single center studies. These studies have been restricted to adult recipients (> 18 years) of liver transplants. In the pediatric population although NAFLD is common, it is a rare indication for liver transplantation[16] (Table 1).

The national databases (UNOS and SRTR) studies have looked at outcomes at 1 year and beyond after liver transplantation (Table 1). Overall 1-year, 3-year and 5-year survival has been comparable between NAFLD and non-NAFLD recipients[13]. In more specific sub-analyses of the same databases post-transplant survival for NAFLD

Table 1 Liver transplantation for non-alcoholic fatty liver disease

Ref.	Patient	Population	Follow up	Graft survival	Patient survival	NAFLD recurrence in graft	Predictors of NAFLD recurrence	Predictors of survival
National registry data								
Charlton *et al*[13]	35781 adults adult liver transplant recipient NASH primary or secondary indication for 1959 recipient	SRTR (US national data) of liver transplant recipients from 2001 to 2009 Included NASH plus 50% of CRC and NASH plus CRC with BMI > 30 kg/m^2)	3 yr post-transplant survival reported	NASH 3-yr survival 76% (similar to other indications)	NASH 1-yr survival 84% and 3-yr 78% CRC 1 -yr survival 86% and 3 -yr 79%Other Diagnoses 1-yr survival 87% and 3-yr 78% (P = 0.67)	Not reported	Not reported	Not reported
Singal *et al*[18]	54687 adult liver transplant recipient NASH 1368 recipients	UNOS adult liver transplant recipients from 1994 to 2009	10-yr survival reported	1-yr, 3-yr, 50-yr and 10-yr survival NASH: 86%, 82%, 80% and 80%NAFLD post-transplant survival similar to cholestatic liver disease, HBV and better than ALD, CRC, HCV and HCC	1-yr, 3-yr, 5-yr and 10-yr survival NASH: 89%, 85%, 84% and 84% NAFLD post-transplant survival similar to cholestatic liver disease, HBV and better than ALD, CRC, HCV and HCC	Not reported	Not reported	For all recipients, age of recipient, male recipient black race, ventilator support pre transplant and MELD score as well as donor risk index associated with worse patient survival
Afzali *et al*[17]	53738 adult liver transplant recipients NASH 1810 recipients	UNOS adult liver transplant recipients from 1997 to 2010	5-yr survival reported	Not reported	1-yr, 3-yr and 5-yr survival NASH: 88%, 82% and 77% Overall adjusted HR for NASH post-transplant mortality compared to other etiologies was 0.75 (95%CI: 0.66-0.85) Adjusted survival was better for NASH than for ALD, HCV, and HCC. NASH survival was worse than cholestatic liver disease, AIH, HBV	Not reported	Not reported	Not specified- although state survival adjusted for several donor, recipient characteristics (individual Hazards ratios not reported)
Single center studies								
Tanaka *et al*[57]	7 patient with NAFLD (425 total LDLT recipients)	Patients with NAFLD that underwent Live donor liver transplant at a single center in Japan between 1996 and 2013	Median follow up 5.3 yr	100% at last follow up	100% at last follow up	1/7 (14%) had recurrent NASH	Not reported	Not reported
El Atrache *et al*[27]	83 recipient, NALFD[46] and CRC[37]	Liver transplant recipients at a single US center between 1996 and 2008	Mean follow up 46 mo	12/83 underwent re-transplantation	12 recipients died. Overall survival not reported	NAFLD recurrence in 20/83 recipients (15 with NASH pre-transplant and 5 with CRC pre-transplant	Predictors of recurrence were metabolic syndrome, hypertension and Insulin use as well as hyperlipidemia after transplant	Five year survival worse for those with metabolic syndrome, hypertension and insulin use No difference in survival between those with NASH recurrence and those without

Dureja *et al*[26]	88 recipients with NAFLD	Liver transplant recipients at a single US center between 1993 and 2007	Mean follow up 82 mo	Not reported	5-yr patient survival similar between those with NAFLD recurrence and those without NAFLD recurrence ($P = 0.78$)	NAFLD Disease Recurrence in 34/88 (39%)	Pre and post-transplant BMI. Triglyceride levels and prednisone dose was higher in those with NAFLD recurrence	Post-transplant survival was worse in NAFLD patients with post-transplant cardiac disease (HR 3.2, 95%CI: 1.3-7.7)
Agopian *et al*[20]	144 recipients with NAFLD (total 1294 transplants)	Liver transplant recipients at a single US center between 1993 and 2011	Mean follow up 2.3 yr	Graft survival similar between NAFLD and non NAFLD (90 d survival 86% for NASH) and lower only than PBC/PSC (90 d graft survival of 94%) 5-yr graft survival for NASH 63% similar to ALD, HBV, CC and PBC/PSC but better than HCV	Patient survival similar between NASH and non-NASH. 90 d survival 90% for NASH 5-yr patient survival for NASH (70%) similar to ALD, HBV, CC and PBC/PSC but better than HCV	NASH recurrence in 23 (16%)	Not reported	Post-transplant BMI > 35 kg/m^2 independent factor for mortality in NAFLD recipients only. Pretransplant dialysis also had worse survival in NASH patients
Kennedy *et al*[21]	129 recipients with NAFLD and 775 with other liver disease	Liver transplant recipients at a single US center between 1999 and 2009	5-yr survival reported	Graft survival not reported	1-yr, 3 -yr, and 5-yr survival NASH: 90%, 88% and 85% Non-NASH: 92%, 86% and 80% (P = NS) Mortality within 4 mo higher in NASH -8.5% *vs* non –NASH 4.2%, $P = 0.04$	Not reported	Not reported	No predictors of survival found
Barritt *et al*[24]	21 recipients with NAFLD and 97 with other liver disease	Liver transplant recipients at a single US center between 2004 and 2007	3-yr survival reported	30-d graft survival worse in NAFLD (81%) *vs* non-NAFLD (95%), $P = 0.02$ 1-yr survival for NAFLD and non-NAFLD patients was 76% *vs* 83%, $P = 0.32$ 3-yr survival was 76% for NAFLD *vs* 73% for non-NAFLD, $P = 0.78$	30-d patient survival worse in NAFLD (81%) *vs* non-NAFLD (97%), (81% *vs* 97%, $P = 0.001$) 1-yr survival for NAFLD and non-NAFLD patients was 76% *vs* 90%, $P = 0.06$ 3-yr survival was 76% for NAFLD *vs* 84% for non-NAFLD, $P = 0.23$	Not reported	Not reported	3-yr survival was significantly worse for diabetic patients compared to non-diabetics (63% *vs* 89%, $P = 0.006$)
Yalamanchili *et al*[22]	40 recipients with NAFLD	Liver transplant recipients at a single German center between 2007 and 2011	1-yr survival reported	Not reported	30 d mortality for NAFLD patients was 25% and 1-yr mortality was 35%	Not reported	Not reported	Patients with BMI > 35 kg/m^2 had worse graft survival (1-yr graft failure 55%) than those with lower BMI

Contos *et al*[32]	30 recipients with CRC and NASH compared to patients with ALD[16] and PBC/PSC[12]	Liver transplant recipients at a single US center between 2004 and 2007	Median follow up 3.5 yr	Graft survival similar between NAFLD and non-NAFLD patients (P = 0.32)	Patient survival similar between NAFLD and non-NAFLD patients (P = 0.32)	100% of the 30 NAFLD patients had steatosis in the graft by 5-yr post-transplant compared to 25% in the ALD and PBC/PSC groups	Steroid dose post-transplant associated with NAFLD recurrence	Not reported
Ong *et al*[31]	51 recipients with CRC	Liver transplant recipients at a single US center between 2004 and 2007	> 6 mo post-transplant, not reported	Not reported	Not reported	Post-transplant NAFLD developed in 25% and NASH in 16%	Predictors of post-transplant NAFLD was pre or post-transplant diabetes and triglyceride levels	Not reported
Bhagat *et al*[19]	71 NAFLD patients compared to 83 ALD patients	Liver transplant recipients at a single US center between 1997 and 2007	Median follow up 1517 d in NAFLD group and 1686 d in ALD group	Graft survival similar between NAFLD (76%) and ALD (82%)	1-yr, 3-yr, 5-yr, and 9-yr survival NASH: 82%, 79%, 75%, and 62% ALD: 92%, 86%, 86%, and 76% (P = 0.17)	NAFLD recurrence was 33% (21/64 NASH patients)	None reported	No predictive factors in NAFLD
Malik *et al*[23]	98 NAFLD recipients compared to 196 with PBC/PSC 196 with ALD 196, with HCV 98, with CR	Liver transplant recipients at a single US center between 2004 and 2007	Mean follow-up was 994 d	Not reported	Survival similar between NAFLD and non-NAFLD recipients 30-d mortality in NAFLD 6.1% 1-yr mortality 21.4% in NAFLD (similar to controls) 3-yr mortality in NAFLD 25% similar to controls, less in PBC (15%) 5-yr mortality (28%) similar in NAFLD patients and controls	Not reported	Not reported	Sepsis accounted for more deaths in NAFLD transplant recipients Liver recipients transplanted for NASH cirrhosis who died within the first post-transplant year were more likely to be older (≥ 60 yr), more obese (BMI ≥ 30 kg/m^2) and have both pretransplant diabetes and Hypertension

NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; ALD: Alcoholic liver disease; PBC: Primary biliary cirrhosis; CRC: Cryptogenic cirrhosis; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; PSC: Primary sclerosing cholangitis; CR: Cryptogenic cirrhosis; LDLT: Living donor liver transplantation.

was better as compared to HCV, alcohol, CRC, and HCC related liver disease[17,18]. When compared to primary biliary cirrhosis (PBC) one study showed similar survival[18] and another study showed worse survival for NAFLD[17].

In single center studies, post transplantation outcomes were also similar between NAFLD and non-NAFLD patients[19-22]. Survival at 1, 3, 5 and 10-year was reported as similar in the studies, although some have demonstrated higher early mortality (30 d) after transplantation in NAFLD than in non-NAFLD patients. Kennedy *at al*[21] reported a twofold higher mortality for NAFLD patients at 4 mo after transplantation than for non-NAFLD patients (8.5% mortality *vs* 4.2% for others). The commonest causes of mortality in NAFLD patients were infectious and cardiac disease. Another study confirmed higher 30-d mortality and 1-year mortality in NAFLD patients, although by 3 years survival were comparable in NAFLD and non-NAFLD patients[23]. In this study infections accounted for the majority of deaths. Factors associated with decreased survival in the cohort of NAFLD patients have included age of recipient post-transplant, diabetes[24], obesity and post-transplant metabolic syndrome[25]; and post-transplant cardiovascular disease[19,23,26]. Close monitoring and critical analysis of early and late outcomes after liver transplantation for NAFLD is thus necessary to further refine criteria and improve outcomes for liver transplantation in NAFLD.

NAFLD recurrence after liver transplantation

Recurrent NAFLD is common[22,26,27]. The recurrence rate depends to some extent on the methodology chosen for detection, (*i.e.*, evaluation of abnormal liver enzymes, liver biopsy, imaging techniques). Use of liver enzymes alone is fairly insensitive as a significant proportion of patients with NAFLD recurrence have normal liver enzymes.

Metabolic syndrome including obesity, diabetes, hyperlipidemia and hypertension are all increased in prevalence after transplantation linked largely to immunesuppression use, particularly steroid use and calcineurin inhibitors. Other factors include post-transplant weight gain due to reduced mobility, at least in the early period and these factors all contribute to recurrence of NAFLD in the allograft[28].

In some studies the risk of allograft steatosis was increased by the presence of the rs738409 single nucleotide polymorphism (SNP) in the *PNPLA3* gene in the recipient[29] as well as post-transplant obesity and diabetes[28]. This polymorphism (rs738409:I148M) in *PNPLA3* has been associated with reduced triglyceride hydrolysis in the adipocyte and increases the risk of developing NAFLD and NASH in the general population[30]. The presence of this SNP in *PNPLA3* in the donor has not been associated with development of allograft steatosis, obesity and diabetes. Thus the role of peripherally mediated triglyceride hydrolysis (in extrahepatic adipose tissue) seems to account for risk of NAFLD recurrence rather than liver related triglyceride hydrolysis, at least in post-transplant NAFLD[28,29].

In a study that systematically re-examined post-transplant biopsies and imaging, recurrent NAFLD was seen in 39% (34/88), with NASH in 25 and isolated steatosis in 9 of these 34 patients within 5 years post-transplant. Severe recurrence (NAS score $\geqslant$ 5) or advanced fibrosis was seen in 6 of the 34 with recurrent NAFLD[26]. NAFLD recurrence was correlated with pre and post-transplant BMI and post-transplant triglyceride levels and prednisone dose at 6 mo post-transplant. In this study post-transplant survival was similar between those with NAFLD recurrence *vs* those without.

Other studies have showed similar rates of NAFLD recurrence with one study showing recurrent NAFLD in 20 of 83 (24%). The metabolic syndrome and insulin use were linked to recurrent NAFLD in this study[27].

Yalamanchili *et al*[22] reported long term outcomes with post-transplant NAFLD recurrence. In this study, recurrent steatosis was reported in 45% of NAFLD transplant recipients and NASH was less common occurring in 4%. Advanced allograft fibrosis or cirrhosis was reported in 5% by 5 years and 10% by 10 years post transplantation and was more common in those with recurrent NASH (31%) *vs* those with steatosis alone (6%) or no steatosis (3%). In this study survival was similar at 1, 5 and 10 years in those with NAFLD and those with other liver diseases at transplant. Death from cardiovascular disease was more common than due to recurrent liver disease attesting to the strong link between the factors that predict development of NAFLD (Metabolic syndrome) and cardiac disease[22].

Other studies have also not shown reduced survival with NAFLD recurrence so far[26], although studies have been limited by a dearth of long term follow up (10 years or more) for large number of patients.

In patients transplanted for CRC, NAFLD has been reported to occur post transplantation and may be due to recurrent disease in a significant number of these patients who likely had undiagnosed NAFLD prior to transplantation. In one study steatosis alone developed in 25% and NASH in 16% of patients transplanted for CRC[31]. Predictors for post-transplant NAFLD in this population included pre or post-transplant diabetes, hypertriglyceridemia and higher BMI. In another study of thirty CRC patients who had the NAFLD phenotype (metabolic syndrome) prior to liver transplantation, recurrent steatosis was seen in 100% by 5 years post-transplant. Steroid dose was correlated with development of post-transplant NAFLD[32].

Very few if any data exist on risk of HCC in NAFLD and outcomes for these patients after transplantation. In a single center study, 17% of NASH cirrhosis patients referred for liver transplantation had HCC (6 noted incidentally on explant) which was higher than the number of patients with PBC/PSC with HCC and similar to ALD and HCV with HCC. Survival in NASH and HCC patients was good after liver transplant with 88% survival at a mean follow-up of 2.5 years[33].

DEVELOPMENT OF *DE NOVO* NAFLD AFTER LIVER TRANSPLANTATION

De novo NAFLD has been reported after liver transplantation in recipients who did not carry the diagnosis of NAFLD prior to liver transplantation. The incidence of *de novo* NAFLD after liver transplantation has ranged from 18% to 33%[34-36] with the progressive form NASH reported in 9% in one report[34]. In a study with liver biopsies done as protocol at 1, 5 and 10 years post-transplantation, as well as for clinical indications, the incidence of *de novo* NAFLD (defined as steatosis greater than 5% after more than 6 mo post liver transplantation) was 31% in 599 recipients with an average follow up of 40 mo. Histological NASH was present in only 3.8%, but perisinusoidal fibrosis was present in 29% and advanced fibrosis/cirrhosis in 2.25%[37]. The increased incidence of perisinusoidal fibrosis without steatohepatitis has not been well described in non-transplant populations and may represent a modified presentation in immunesuppressed individuals who may not present with brisk inflammatory response. In addition 51% of the recipients with *de novo* NAFLD had normal liver enzymes in this study attesting to the importance of liver biopsies and possibly imaging in accurately diagnosing NAFLD.

Factors associated with *de novo* NAFLD include post-transplant obesity, post-transplant diabetes, hyperlipidemia and hypertension[37]. In addition tacrolimus was also associated with recurrent NAFLD and this drug has

been well described as having an increased risk for developing diabetes[38].

In addition in this study a pretransplant diagnosis of alcoholic cirrhosis was associated with an increased risk of *de novo* NAFLD. In this study patients with recurrent alcoholism and recurrent hepatitis C or hepatitis B were excluded from the analysis as these conditions can lead to steatosis. The increased risk of *de novo* NAFLD in patients with prior ALD may reflect an underlying predisposition to NAFLD that could not be diagnosed prior to transplantation due to the concomitant alcoholic steatohepatitis. Donor allograft steatosis was also more prevalent in the group that developed *de novo* NAFLD (30%) as compared to the group that did not develop NAFLD (12.65%). This study did not quantify the degree of hepatic steatosis and nor were any genetic polymorphisms tested for in the donor. Other studies have suggested that donor polymorphisms that regulate cytokine release, inflammation and microsomal triglyceride transfer may be important in risk of developing NAFLD[39]. Protective factors against *de novo* NAFLD may include use of Angiotensin converting enzyme inhibitors[40], although this approach has not been tested in a trial.

The consequences of *de novo* NAFLD are not well known. In the study mentioned above complete regression occurred in 13 % (all with grade 1 steatosis initially), reduction of steatosis was seen in 35%, stability in 22%, and exacerbation in 30%. Higher prevalence of obesity was present in those with progression of histological liver disease[34].

In patients with hepatitis C the risk of developing *de novo* NAFLD is higher and can be linked to recurrence of hepatitis C[35]. Development of *de novo* NAFLD in the allograft can reduce the response rate to current antiviral therapy for hepatitis C and thus impact graft and patient outcomes[35].

MANAGEMENT OF NAFLD AFTER LIVER TRANSPLANTATION

There have been no published trials of pharmacotherapy specifically for post-transplant NAFLD. Analysis of the predictors of post-transplant NAFLD recurrence and data from non-transplant therapeutic studies on NAFLD suggest that sustained weight loss through a combination of dietary changes and exercise are most successful in reversing the histological findings of NAFLD[40], and improving biochemical and metabolic parameters including liver enzymes, insulin resistance, lipid levels and blood pressure in this condition[41].

Studies on pharmacotherapeutic agents in non-transplant patients suggest a role for vitamin E in selected individuals. In non-diabetics a large randomized controlled trial over 48 wk improved the histological features and liver enzymes in NAFLD[42]. Recent concerns about risk of prostate cancer[43] and risk of cardiac disease in susceptible individuals[44], as well as lack of long term data on sustained efficacy and safety may limit its usefulness in the post-transplant population.

The use of PPAR-gamma agonists (*e.g.*, Pioglitazone) improves insulin resistance and has shown some promise in reversing NAFLD in non-transplant patients[45,46]. In a large randomized controlled trial however it was not superior to placebo and inferior to vitamin E in reversing NAFLD[42]. This class of agents is also associated with weight gain and this also limits its utility in treatment of NAFLD[45,46].

Pharmacologic treatment of clinically overt diabetes, dyslipidemia and hypertension should be carried out as per best practice guidelines for managing these conditions[46] and in multidisciplinary teams involving the transplant team, primary care providers[47], diabetes specialists and preventive cardiologists.

Given that to a large extent immune-suppression exacerbates or promotes the development of the metabolic syndrome, immunosuppression modulation should be considered in patients with recurrent NAFLD or at risk of developing recurrent or *de novo* NAFLD. In particular minimization or avoidance of steroids, minimization of calcineurin inhibitor dose and levels and avoiding sirolimus in patients with hyperlipidemia is important in the management of NAFLD, obesity and metabolic syndrome post liver transplantation.

Bariatric surgery for obesity and morbid obesity has shown promising results in non-transplant patients and can reverse some of the metabolic consequences related to obesity such as diabetes[48]. Limited series have reported successful bariatric surgery specifically in patients with NAFLD[49], and in case reports in patients with NAFLD with compensated cirrhosis[50].

For NAFLD patients undergoing liver transplantation there are limited case reports of the utility of bariatric surgery after recurrence of NAFLD post transplantation[51]. There are also risks of exacerbation of NASH after bariatric surgery due to excessive weight loss as well as risks of impaired drug absorption and bacterial overgrowth that can impact post-transplant outcomes. At this point more evidence is needed before advocating bariatric surgery in transplant recipients.

DONORS WITH NAFLD

An adverse consequence of the epidemic of obesity and fatty liver in the population is the impact on suitable donors for liver transplantation. There is an increased risk of primary non-function of the allograft with fatty donors[52]. This data suggest that greater than 30% steatosis in the donor organ increases the risk of primary non-function. As NAFLD in the populations increases, the pool of potentially suitable organs for liver transplantation may diminish as a consequence.

In a Korean paper that evaluated steatosis in potential donors over a year, NAFLD (> 5% steatosis) was present in 51% and greater than 30% steatosis was present in 10.4% with NASH in 2.2%. The prevalence of steatosis was higher in donor over the age of 30, and those donor

with obesity and elevated triglyceride levels. In this study ultrasonography and CT both had limitations in diagnosis of NAFLD (> 30% steatosis in donors) with sensitivity of 92% for ultrasound but positive predictive value of only 34.5% and for CT a sensitivity of 64% and PPV of 45%. More recently the use of MRI Quantification methods for steatosis have been developed and validated independently against liver biopsy showing excellent correlation with histological steatosis grading[53,54]. Although donor biopsies should still be considered before excluding donors as unsuitable due to steatosis, utilization of MRI, particularly for liver donors may in the near future supplant the need for liver biopsies[55].

Although patient and graft survival can be diminished due to use of steatotic grafts, this is possibly not a risk factor for diminished graft survival if it exists in isolation[56]. Selection bias also confounds the picture as grafts that are not utilized due to steatosis may have different outcomes than steatotic grafts that are transplanted[57].

FUTURE DIRECTIONS

With increasing numbers of transplants in patients with NAFLD, current data support a careful audit of both short and long term post-transplant outcomes. Rigorous studies on immune-suppression regimens designed to decrease the incidence of metabolic complications for this population are needed. In addition post-transplant therapy for NAFLD including diet and exercise regimens, pharmacologic agents and bariatric surgery all warrant prospective study. With increasing numbers of donors with fatty livers, outcomes with these grafts should be tracked in prospective databases that include both donor and recipient variables.

REFERENCES

1 **Lazo M**, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, Koteish A, Brancati FL, Clark JM. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988-1994. *Am J Epidemiol* 2013; **178**: 38-45 [PMID: 23703888 DOI: 10.1093/aje/kws448]

2 **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 [PMID: 21623852 DOI: 10.1111/j.1365-2036.2011.04724.x]

3 **Fan JG**. Epidemiology of alcoholic and nonalcoholic fatty liver disease in China. *J Gastroenterol Hepatol* 2013; **28** Suppl 1: 11-17 [PMID: 23855290 DOI: 10.1111/jgh.12036]

4 **Welsh JA**, Karpen S, Vos MB. Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988-1994 to 2007-2010. *J Pediatr* 2013; **162**: 496-500.e1 [PMID: 23084707 DOI: 10.1016/j.jpeds.2012.08.043]

5 **Rahimi RS**, Landaverde C. Nonalcoholic fatty liver disease and the metabolic syndrome: clinical implications and treatment. *Nutr Clin Pract* 2013; **28**: 40-51 [PMID: 23286927 DOI: 10.1177/0884533612470464]

6 **Ludwig J**, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980; **55**: 434-438 [PMID: 7382552]

7 **Marmur J**, Bergquist A, Stål P. Liver transplantation of patients with cryptogenic cirrhosis: clinical characteristics and outcome. *Scand J Gastroenterol* 2010; **45**: 60-69 [PMID: 20030578 DOI: 10.3109/00365520903384742]

8 **Adams LA**, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129**: 113-121 [PMID: 16012941]

9 **Teli MR**, James OF, Burt AD, Bennett MK, Day CP. The natural history of nonalcoholic fatty liver: a follow-up study. *Hepatology* 1995; **22**: 1714-1719 [PMID: 7489979]

10 **Dam-Larsen S**, Franzmann MB, Christoffersen P, Larsen K, Becker U, Bendtsen F. Histological characteristics and prognosis in patients with fatty liver. *Scand J Gastroenterol* 2005; **40**: 460-467 [PMID: 16028442]

11 **Angulo P**. Long-term mortality in nonalcoholic fatty liver disease: is liver histology of any prognostic significance? *Hepatology* 2010; **51**: 373-375 [PMID: 20101746 DOI: 10.1002/hep.23521]

12 **Bhala N**, Angulo P, van der Poorten D, Lee E, Hui JM, Saracco G, Adams LA, Charatcharoenwitthaya P, Topping JH, Bugianesi E, Day CP, George J. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. *Hepatology* 2011; **54**: 1208-1216 [PMID: 21688282 DOI: 10.1002/hep.24491]

13 **Charlton MR**, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 2011; **141**: 1249-1253 [PMID: 21726509 DOI: 10.1053/j.gastro.2011.06.061]

14 **O'Leary JG**, Landaverde C, Jennings L, Goldstein RM, Davis GL. Patients with NASH and cryptogenic cirrhosis are less likely than those with hepatitis C to receive liver transplants. *Clin Gastroenterol Hepatol* 2011; **9**: 700-704.e1 [PMID: 21570483 DOI: 10.1016/j.cgh.2011.04.007]

15 **Park CW**, Tsai NT, Wong LL. Implications of worse renal dysfunction and medical comorbidities in patients with NASH undergoing liver transplant evaluation: impact on MELD and more. *Clin Transplant* 2011; **25**: E606-E611 [PMID: 21958082 DOI: 10.1111/j.1399-0012.2011.01497.x]

16 **Nobili V**, Dhawan A. Are children after liver transplant more prone to non-alcoholic fatty liver disease? *Pediatr Transplant* 2008; **12**: 611-613 [PMID: 18346037 DOI: 10.1111/j.1399-3046.2008.00927.x]

17 **Afzali A**, Berry K, Ioannou GN. Excellent posttransplant survival for patients with nonalcoholic steatohepatitis in the United States. *Liver Transpl* 2012; **18**: 29-37 [PMID: 21932374 DOI: 10.1002/lt.22435]

18 **Singal AK**, Guturu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation* 2013; **95**: 755-760 [PMID: 23370710 DOI: 10.1097/TP.0b013e31827afb3a]

19 **Bhagat V**, Mindikoglu AL, Nudo CG, Schiff ER, Tzakis A, Regev A. Outcomes of liver transplantation in patients with cirrhosis due to nonalcoholic steatohepatitis versus patients with cirrhosis due to alcoholic liver disease. *Liver Transpl* 2009; **15**: 1814-1820 [PMID: 19938128]

20 **Agopian VG**, Kaldas FM, Hong JC, Whittaker M, Holt C, Rana A, Zarrinpar A, Petrowsky H, Farmer D, Yersiz H, Xia V, Hiatt JR, Busuttil RW. Liver transplantation for nonalcoholic steatohepatitis: the new epidemic. *Ann Surg* 2012; **256**: 624-633 [PMID: 22964732 DOI: 10.1097/SLA.0b013e31826b4b7e]

21 **Kennedy C**, Redden D, Gray S, Eckhoff D, Massoud O, McGuire B, Alkurdi B, Bloomer J, DuBay DA. Equivalent survival following liver transplantation in patients with non-alcoholic steatohepatitis compared with patients with other liver diseases. *HPB* (Oxford) 2012; **14**: 625-634 [PMID: 22882200 DOI: 10.1111/j.1477-2574.2012.00497.x]

22 **Yalamanchili K**, Saadeh S, Klintmalm GB, Jennings LW, Davis GL. Nonalcoholic fatty liver disease after liver transplantation for cryptogenic cirrhosis or nonalcoholic fatty liver disease.

Liver Transpl 2010; **16**: 431-439 [PMID: 20373454 DOI: 10.1002/lt.22004]
23 **Malik SM**, deVera ME, Fontes P, Shaikh O, Ahmad J. Outcome after liver transplantation for NASH cirrhosis. *Am J Transplant* 2009; **9**: 782-793 [PMID: 19344467 DOI: 10.1111/j.1600-6143.2009.02590.x]
24 **Barritt AS**, Dellon ES, Kozlowski T, Gerber DA, Hayashi PH. The influence of nonalcoholic fatty liver disease and its associated comorbidities on liver transplant outcomes. *J Clin Gastroenterol* 2011; **45**: 372-378 [PMID: 20733515 DOI: 10.1097/MCG.0b013e3181eeaff0]
25 **Heuer M**, Kaiser GM, Kahraman A, Banysch M, Saner FH, Mathé Z, Gerken G, Paul A, Canbay A, Treckmann JW. Liver transplantation in nonalcoholic steatohepatitis is associated with high mortality and post-transplant complications: a single-center experience. *Digestion* 2012; **86**: 107-113 [PMID: 22846254 DOI: 10.1159/000339344]
26 **Dureja P**, Mellinger J, Agni R, Chang F, Avey G, Lucey M, Said A. NAFLD recurrence in liver transplant recipients. *Transplantation* 2011; **91**: 684-689 [PMID: 21248661 DOI: 10.1097/TP.0b013e31820b6b84]
27 **El Atrache MM**, Abouljoud MS, Divine G, Yoshida A, Kim DY, Kazimi MM, Moonka D, Huang MA, Brown K. Recurrence of non-alcoholic steatohepatitis and cryptogenic cirrhosis following orthotopic liver transplantation in the context of the metabolic syndrome. *Clin Transplant* 2012; **26**: E505-E512 [PMID: 23061759 DOI: 10.1111/ctr.12014]
28 **Watt KD**, Dierkhising R, Fan C, Heimbach JK, Tillman H, Goldstein D, Thompson A, Krishnan A, Charlton MR. Investigation of PNPLA3 and IL28B genotypes on diabetes and obesity after liver transplantation: insight into mechanisms of disease. *Am J Transplant* 2013; **13**: 2450-2457 [PMID: 23859071 DOI: 10.1111/ajt.12355]
29 **Finkenstedt A**, Auer C, Glodny B, Posch U, Steitzer H, Lanzer G, Pratschke J, Biebl M, Steurer M, Graziadei I, Vogel W, Zoller H. Patatin-Like Phospholipase Domain-Containing Protein 3 rs738409-G in Recipients of Liver Transplants Is a Risk Factor for Graft Steatosis. *Clin Gastroenterol Hepatol* 2013; **11**: 1667-1672 [PMID: 23872669 DOI: 10.1016/j.cgh.2013.06.025]
30 **Romeo S**, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2008; **40**: 1461-1465 [PMID: 18820647 DOI: 10.1038/ng.257]
31 **Ong J**, Younossi ZM, Reddy V, Price LL, Gramlich T, Mayes J, Boparai N. Cryptogenic cirrhosis and posttransplantation nonalcoholic fatty liver disease. *Liver Transpl* 2001; **7**: 797-801 [PMID: 11552214 DOI: 10.1053/jlts.2001.24644]
32 **Contos MJ**, Cales W, Sterling RK, Luketic VA, Shiffman ML, Mills AS, Fisher RA, Ham J, Sanyal AJ. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. *Liver Transpl* 2001; **7**: 363-373 [PMID: 11303298 DOI: 10.1053/jlts.2001.23011]
33 **Malik SM**, Gupte PA, de Vera ME, Ahmad J. Liver transplantation in patients with nonalcoholic steatohepatitis-related hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2009; **7**: 800-806 [PMID: 19281869 DOI: 10.1016/j.cgh.2009.02.025]
34 **Seo S**, Maganti K, Khehra M, Ramsamooj R, Tsodikov A, Bowlus C, McVicar J, Zern M, Torok N. De novo nonalcoholic fatty liver disease after liver transplantation. *Liver Transpl* 2007; **13**: 844-847 [PMID: 17029282 DOI: 10.1002/lt.20932]
35 **Testino G**, Sumberaz A, Leone S, Borro P. Recurrent hepatitis C and non-alcoholic fatty liver disease in transplanted patients: a review. *Minerva Med* 2013; **104**: 225-232 [PMID: 23514999]
36 **Sprinzl MF**, Weinmann A, Lohse N, Tönissen H, Koch S, Schattenberg J, Hoppe-Lotichius M, Zimmermann T, Galle PR, Hansen T, Otto G, Schuchmann M. Metabolic syndrome and its association with fatty liver disease after orthotopic liver transplantation. *Transpl Int* 2013; **26**: 67-74 [PMID: 23126674 DOI: 10.1111/j.1432-2277.2012.01576.x]
37 **Dumortier J**, Giostra E, Belbouab S, Morard I, Guillaud O, Spahr L, Boillot O, Rubbia-Brandt L, Scoazec JY, Hadengue A. Non-alcoholic fatty liver disease in liver transplant recipients: another story of "seed and soil". *Am J Gastroenterol* 2010; **105**: 613-620 [PMID: 20040915 DOI: 10.1038/ajg.2009.717]
38 **O'Grady JG**, Burroughs A, Hardy P, Elbourne D, Truesdale A. Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. *Lancet* 2002; **360**: 1119-1125 [PMID: 12387959]
39 **Day CP**. Genes or environment to determine alcoholic liver disease and non-alcoholic fatty liver disease. *Liver Int* 2006; **26**: 1021-1028 [PMID: 17032401 DOI: 10.1111/j.1478-3231.2006.01323.x]
40 **Nobili V**, Manco M, Devito R, Di Ciommo V, Comparcola D, Sartorelli MR, Piemonte F, Marcellini M, Angulo P. Lifestyle intervention and antioxidant therapy in children with nonalcoholic fatty liver disease: a randomized, controlled trial. *Hepatology* 2008; **48**: 119-128 [PMID: 18537181 DOI: 10.1002/hep.22336]
41 **Promrat K**, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, Fava JL, Wing RR. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 121-129 [PMID: 19827166 DOI: 10.1002/hep.23276]
42 **Sanyal AJ**, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; **362**: 1675-1685 [PMID: 20427778 DOI: 10.1056/NEJMoa0907929]
43 **Lippman SM**, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, Parnes HL, Minasian LM, Gaziano JM, Hartline JA, Parsons JK, Bearden JD, Crawford ED, Goodman GE, Claudio J, Winquist E, Cook ED, Karp DD, Walther P, Lieber MM, Kristal AR, Darke AK, Arnold KB, Ganz PA, Santella RM, Albanes D, Taylor PR, Probstfield JL, Jagpal TJ, Crowley JJ, Meyskens FL, Baker LH, Coltman CA. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2009; **301**: 39-51 [PMID: 19066370 DOI: 10.1001/jama.2008.864]
44 **Lonn E**, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, Ross C, Arnold A, Sleight P, Probstfield J, Dagenais GR. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA* 2005; **293**: 1338-1347 [PMID: 15769967 DOI: 10.1001/jama.293.11.1338]
45 **Promrat K**, Lutchman G, Uwaifo GI, Freedman RJ, Soza A, Heller T, Doo E, Ghany M, Premkumar A, Park Y, Liang TJ, Yanovski JA, Kleiner DE, Hoofnagle JH. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. *Hepatology* 2004; **39**: 188-196 [PMID: 14752837 DOI: 10.1053/j.gastro.2008.06.047]
46 **Athyros VG**, Mikhailidis DP, Didangelos TP, Giouleme OI, Liberopoulos EN, Karagiannis A, Kakafika AI, Tziomalos K, Burroughs AK, Elisaf MS. Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study. *Curr Med Res Opin* 2006; **22**: 873-883 [PMID: 16709309 DOI: 10.1002/hep.20012]
47 **Said A**, Gagovic V, Malecki K, Givens ML, Nieto FJ. Primary care practitioners survey of non-alcoholic fatty liver disease. *Ann Hepatol* 2013; **12**: 758-765 [PMID: 24018493]
48 **Hafeez S**, Ahmed MH. Bariatric surgery as potential treatment for nonalcoholic fatty liver disease: a future treatment by choice or by chance? *J Obes* 2013; **2013**: 839275 [PMID: 23431426 DOI: 10.1155/2013/839275]
49 **Klein S**, Mittendorfer B, Eagon JC, Patterson B, Grant L, Feirt N, Seki E, Brenner D, Korenblat K, McCrea J. Gastric bypass surgery improves metabolic and hepatic abnormalities associated with nonalcoholic fatty liver disease. *Gastroenterology* 2006; **130**: 1564-1572 [PMID: 16697719 DOI: 10.1053/j.gastro.2006.01.042]
50 **Takata MC**, Campos GM, Ciovica R, Rabl C, Rogers SJ, Cello JP, Ascher NL, Posselt AM. Laparoscopic bariatric surgery improves candidacy in morbidly obese patients awaiting transplantation. *Surg Obes Relat Dis* 2008; **4**: 159-164; discussion

164-165 [DOI: 10.1016/j.soard.2007.12.009]
51 **Duchini A**, Brunson ME. Roux-en-Y gastric bypass for recurrent nonalcoholic steatohepatitis in liver transplant recipients with morbid obesity. *Transplantation* 2001; **72**: 156-159 [PMID: 11468551]
52 **Marsman WA**, Wiesner RH, Rodriguez L, Batts KP, Porayko MK, Hay JE, Gores GJ, Krom RA. Use of fatty donor liver is associated with diminished early patient and graft survival. *Transplantation* 1996; **62**: 1246-1251 [PMID: 8932265]
53 **Hines CD**, Frydrychowicz A, Hamilton G, Tudorascu DL, Vigen KK, Yu H, McKenzie CA, Sirlin CB, Brittain JH, Reeder SB. T(1) independent, T(2) (55) corrected chemical shift based fat-water separation with multi-peak fat spectral modeling is an accurate and precise measure of hepatic steatosis. *J Magn Reson Imaging* 2011; **33**: 873-881 [DOI: 10.1002/jmri.22514]
54 **Idilman IS**, Aniktar H, Idilman R, Kabacam G, Savas B, Elhan A, Celik A, Bahar K, Karcaaltincaba M. Hepatic steatosis: quantification by proton density fat fraction with MR imaging versus liver biopsy. *Radiology* 2013; **267**: 767-775 [PMID: 23382293 DOI: 10.1148/radiol.13121360]
55 **Lee JY**, Kim KM, Lee SG, Yu E, Lim YS, Lee HC, Chung YH, Lee YS, Suh DJ. Prevalence and risk factors of non-alcoholic fatty liver disease in potential living liver donors in Korea: a review of 589 consecutive liver biopsies in a single center. *J Hepatol* 2007; **47**: 239-244 [PMID: 17400323 DOI: 10.1016/j.jhep.2007.02.007]
56 **Angele MK**, Rentsch M, Hartl WH, Wittmann B, Graeb C, Jauch KW, Loehe F. Effect of graft steatosis on liver function and organ survival after liver transplantation. *Am J Surg* 2008; **195**: 214-220 [PMID: 18154767 DOI: 10.1016/j.amjsurg.2007.02.023]
57 **Tanaka T**, Sugawara Y, Tamura S, Kaneko J, Takazawa Y, Aoki T, Hasegawa K, Sakamoto Y, Yamashiki N, Kokudo N. Living donor liver transplantation for non-alcoholic steatohepatitis: A single center experience. *Hepatol Res* 2013; Epub ahead of print [PMID: 23834427 DOI: 10.1111/hepr.12200]

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