Caspian J Intern Med 2020; 11(4):346-354
DOI: 10.22088/cjim.11.4.346

Review Article

Recurrence of fatty liver disease following liver transplantation for NAFLD-related cirrhosis: Current status and challenges

Arash Dooghaie Moghadam (MD) [1]
Pegah Eslami (MD) [2]
Niloofar Razavi-Khorasani (MD)[1]
Bobak Moazzami (MD) [1]
Farbod Zahedi-Tajrishi (MD) [3]
Ermia Farokhi (MD) [1]
Kamyab Makhdoomi Sharabiani (MD) [2]
Alireza Mansour-Ghanaei (MD) [2]
Azim Mehrvar (MD) [4]
Morteza Aghajanpoor Pasha (MD) [5]
Sandra Saeedi (MD) [5]
Shahrokh Iravani (MD) [4*]

1. Liver Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran
2. Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Student Research Committee, Babol University of Medical Sciences, Babol, Iran
4. Research Center for Cancer Screening and Epidemiology, AJA University of Medical Sciences, Tehran, Iran
5. Gastroenterology and Hepatobiliary Research Center, AJA University of Medical Sciences, Tehran, Iran

*** Correspondence:**
Shahrokh Iravani, Research Center for Cancer Screening and Epidemiology, Imam Reza (501) Hospital, AJA University of Medical Sciences, Etemad zadeh Ave, Tehran, Iran

E-mail: ltrc.tehran@gmail.com
Tel: 00989373919897

Received: 29 Oct 2019
Revised: 4 March 2020
Accepted: 11 April 2020

Abstract

Non-alcoholic fatty liver disease (NAFLD) is emerging as a major health problem worldwide. NAFLD is a continuum of disease ranging from mild liver steatosis to severe steatohepatitis, which will ultimately lead to end-stage liver disease with high morbidity and mortality rates. This disorder is considered as a silent liver disease. The metabolic syndrome and its components are accounted as the major risk factors for the progression of NAFLD to NASH and cirrhosis. Liver transplantation is considered as an appropriate treatment for the end-stage disease. For the last two decades, NASH has been the most common reason for liver transplantation, especially in the developed countries; however, the outcome of post-transplantation in these patients is of a great concern. The recurrent NASH and NAFLD seem to be the usual issues in LT. Steatosis appears in more than 80% of LTs; however, re-transplantation caused by steatohepatitis is rare. Recently, several risk factors of the recurrent NAFLD, including age, donor steatosis, metabolic syndrome, and immunosuppressant agents, have been introduced. Among the metabolic syndrome components, obesity seriously has negative effects on the outcomes of post-liver transplantation in patients. Unfortunately, there is no standard medicine to prevent or treat the recurrent NAFLD; however, it seems that weight loss and lifestyle modification play critical roles in controlling or inhibiting the recurrent NAFLD or NASH.

Keywords: Liver transplantation, Non-alcoholic fatty liver disease, Hepatic steatosis; Steatohepatitis, Liver cirrhosis, Metabolic syndrome, Insulin resistance, Obesity.

Citation:
Dooghaie Moghadam A, Eslami P, Razavi-Khorasani N, Moazzami B, Zahedi-Tajrishi F, et al. Recurrence of fatty liver disease following liver transplantation for NAFLD-related cirrhosis: Current status and challenges. Caspian J Intern Med 2020; 11(4): 346-354.

Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease worldwide. This disorder can lead to end-stage liver disease and encompasses a spectrum of liver damages ranging from uncomplicated steatosis to cirrhosis (1). Liver transplantation (LT) has been considered as the treatment of choice for nonalcoholic fatty liver disease (NASH) - related cirrhosis. Moreover, NASH is the most common etiology for LT in industrial countries (2, 3). Although LT is a standard treatment used for the NASH cases, there is limited information on the prevalence of the disorder recurrence in patients undergoing transplantation because of NASH (4). Furthermore, the best prevention or treatment techniques for the recurrent NAFLD are still unknown (5). Accordingly, we evaluated the previous studies on the prevalence ratio of the recurrent NAFLD in the LT patients. Moreover, we spared our efforts to detect the best management methods for decreasing and controlling this disorder that could exacerbate the outcome of liver transplantation.

Pathogenesis: Although multiple mechanisms have been proposed for the pathogenesis of NAFLD, the exact underlying etiology remains yet to be fully elucidated (6). Environmental and genetic factors as well as insulin resistance have been proposed to play a pivotal role in progression to NAFLD (7, 8). The initial accumulation of triglycerides within hepatocytes (i.e., steatosis) triggers the hepatocellular injury (9). This steatosis can be further complicated by death and inflammation of hepatocytes; a condition known as nonalcoholic steatohepatitis (NASH). On the other hand, individuals with genetic variants in the Patatin-like phospholipase domain containing 3 (PNPLA3), responsible for hydrolysis of triacylglycerol molecules in adipocytes, are susceptible to NAFLD development regardless of the existence of metabolic syndrome (10, 11). Moreover, alteration in transmembrane 6 superfamily member 2, encoding E167K (rs58542926 C/T), and lipid transporter located endoplasmic reticulum could lead to the impairment of lipid disposal pathways and resulted in hepatic accumulation of triglycerides (12). Therefore, the three main steps in the progression to NAFLD is steatosis, lipotoxicity and inflammation, collectively known as 'three-hit' process (13).

Previous studies showed a strong association between steatosis development and diets, gut microbiota, genetic background, and regulation of de novo lipogenesis via lipogenic transcription factors including sterol regulatory binding protein-1c (SREBP1c) that were involved in mediating the effect of insulin on hepatic gene expression, and carbohydrate-responsive element-binding protein (chREBP) that were regulated by glucose for gene transcription(14-16). The adipose tissue is the primary site for storage of triacylglycerol (TAG) and during periods of energy deprivation, fatty acids generated from TAG hydrolysis will used as a fuel by various organs. However, an ectopic fat deposition in tissues other than adipose tissue seems to occur among the obese subjects. It has been shown that the upregulation of fatty acid transport proteins (FATPs) and FAT/CD36 (fatty acid translocase) that is commonly elevated in obese cases and NAFLD patients, resulted in the increased uptake of fatty acid by organs such as the skeletal and hepatic tissues (17, 18). Excess fatty acid accumulation in the liver resulted in lipotoxicity via amplification of oxidative stress leading to organelle dysfunction, which mainly derived from mitochondrial dysfunction (19, 20). Therefore, the oxidation of free fatty acids by dysfunctional mitochondria leads to the over production of reactive oxygen species (ROS) that is known as the primary cause of oxidative stress (21). Finally, oxidative stress in NAFLD patients (also characterized by the third insult) will ultimately result in hepatocyte death and demonstrated as histopathological alterations and biochemical features of the liver involvement (22). The genetic and epigenetic factors affecting NAFLD are also of great importance. The PNPLA3 gene encodes an enzyme responsible for intracellular trafficking of lipids, hence variants of this gene could play a crucial role in the progression to steatosis as well as the susceptibility to hepatocellular malignancies (23). The genes TM6SF2 (24) and MBOAT7 (25) are also involved in lipid homeostasis, making them important factors in the development of steatosis as well.

Epidemiology: The global incidence of NAFLD has increased significantly over the past few decades (table 1) (26). A cohort conducted in the United States reported that nearly 33% of Americans were diagnosed with NAFLD, although the reported diagnoses of NAFLD were not validated by histological studies (27, 28). According to the International Liver Transplantation Society (ILTS) consensus conference on NAFLD and liver transplantation, the prevalence rate of NAFLD is about 25% worldwide and it became the most common chronic liver disease. In addition, they reported a significant direct correlation between obesity and the incidence of NAFLD (28). Differences in sex and race/ethnicity can affect the prevalence rate of NAFLD. For instance, NAFLD was shown to be more prevalent in Hispanics when compared to African-Americans in several studies (29, 30). This fact could partly be explained by different lifestyles and body fat distributions among the different ethnic groups. The increased incidence of NAFLD is also frequently found among the potential liver transplant donors. In many occasions, liver studies of a seemingly healthy candidate donor reveal that the donor has already been affected by the terminal stage of the liver disease (31).

Liver transplantation: LT is a surgical treatment technique for all types of end-stage hepatic disease. Although it is frequently used as the treatment of hepatitis C, LT is now being investigated as the treatment of NAFLD (32, 33). Such increasing trend can be explained by global rapid lifestyle changes towards an unhealthy and sedentary one, which promotes obesity, hypertension, diabetes, and hepatitis among many other etiologies. With the recent improvements in non-surgical methods used to treat viral hepatitis, the LT would predominantly be used to treat NAFLD instead of viral

hepatitis in the near future. The 1, 3 and 5 year survival rates of LT patients diagnosed with NASH are 87.6%, 82.2% and 76.7%, respectively (21). Nevertheless, LT alone does not guarantee the beneficial long-term outcome. Post-transplantation treatment techniques are also of great importance as they severely affect the prognosis of surgery. Accordingly, although the new liver may result in the patients' improved overall function, it is at an increased risk of developing recurrent NAFLD or de novo form since the patient's lifestyle is not improved (34).

Table 1. An overview of current studies on NAFLD recurrence following liver transplant.

Author	Year	Title	Aim	Sample	Conclusion
Achuthan Sourianarayanane(4)	2017	Nonalcoholic steatohepatitis recurrence and rate of fibrosis progression following liver transplantation	The comparison of incidences of NASH following LT for NASH with those transplanted for alcoholic liver disease (ALD).	NASH patients = 77 ALD patients= 108	More steatosis and inflammation in NASH arm. progression of fibrosis was more rapid in ALD Arm.
Rohan C. Siriwardana(75)	2015	Recurrence of graft steatosis after liver transplantation for cryptogenic cirrhosis in recently commenced liver transplant program	The short-term follow-up of graft histology in LT patients with previous NAFLD.	Five patients, with cryptogenic cirrhosis underwent liver transplantation from 2012 to 2013	High prevalence of graft steatosis due to recurrent NAFLD was detected.
M_elanie Vallin(41)	2014	Recurrent or de novo Nonalcoholic Fatty Liver Disease After Liver Transplantation: Natural History Based on Liver Biopsy Analysis	Comparison the different aspects of recurrent NAFLD and de novo forms in a cohort study, during 5 years of follow up	De novo arm = 80 Recurrent arm = 11	Recurrent NAFLD was more severe, and irreversible.
El Atrache MM(76)	2012	Recurrence of non-alcoholic steatohepatitis and cryptogenic cirrhosis following orthotopic liver transplantation in the context of the metabolic syndrome	Determination of the prevalence of recurrent NAFLD/NASH in LT patients with previous NASH diagnosis.	83	Metabolic syndrome has an important role in recurrent NASH in post-transplant patients.
Parul Dureja(37)	2011	NAFLD Recurrence in Liver Transplant Recipients	Evaluation of the prevalence of recurrent NAFLD in post-transplant patients in a cohort study between 1993-2007	88	1. Recurrent NAFLD is common in the 5 years. Significant relation between Metabolic syndrome and recurrent NAFLD. 3. No relationship with high mortality.

The definition of post liver transplant-related de novo vs recurrent NAFLD: Post-op NAFLD can be categorized into two distinct subgroups: recurrent and de novo (35). Recurrent NAFLD is defined by the development of fatty liver following LT in the context of a previous NAFLD (35). In other words, such patients undergo LT surgery because of severe

steatohepatitis or cirrhosis. As previously addressed, the underlying etiology of such diseases is a steatotic liver. De novo NAFLD indicates that the steatosis is a new pathology, occurring in a patient with previously diagnosed cirrhosis or hepatitis of different etiologies (e.g alcoholic or viral hepatitis) (36). The subgroups in these two categories are different in etiology, prevalence and to a lesser extent and management.

Prevalence of NAFLD among post-liver transplant patients: There are multiple reports on this matter, mostly assessing the rate of steatosis, NAFLD, steatohepatitis, cirrhosis, and fibrosis during a certain follow-up period of post-transplantation (37). Interestingly, the results of these studies, which are methodologically similar, vary significantly. This may be partly explained by the different follow-up durations between studies. Other explanations may include the difference in the study population, diagnosis criteria, and clinical features (38). Steatosis is common among the patients undergoing liver transplantation. Previous studies showed that steatosis mostly occurs in all the patients after five years of transplantation; however, fibrosis or cirrhosis seems to be rare (18). According to most previous studies, although there is a high incidence of recurrent NAFLD among the LT cases, steatosis mostly does not lead to graft rejection. In general, five year of prognosis among NAFLD patients undergoing LT is excellent (9, 10).

On the other hand, the components of metabolic syndrome seem to be the main causes of recurrent NAFLD among LT patients. These components include obesity, insulin resistance, type 2 diabetes mellitus, arterial hypertension, and dyslipidemia. Andrade et al. (39) in a retrospective study aimed to estimate the prevalence ratio of recurrent and de novo NAFLD in LT cases (39). She found out that 56% of the patients with post- transplantation NAFLD belonged to the recurrent group. Narayaran et al. (40) in a prospective study with 254 LT cases compared the recurrent NAFLD and de novo incidences after two months of transplantation. In contrast to the previous study, they revealed that only 15% of the study population were suffering from recurrent NAFLD. Most of the post- transplantation NAFLD cases belonged to de novo arm.

The other interesting study evaluated these two arms for longer period after transplantation. After a five-year follow-up, the prevalence of steatohepatitis seemed to be more significant in recurrent NAFLD, in comparison to de novo cases. Furthermore, the DM2 incidence was higher in the recurrent arm (41). This study concluded that recurrent NAFLD, in comparison to the de novo cases, is more severe and inevitable (41, 42). On the other hand, the need for a re-transplantation is lower in recurrent NAFLD patients, in comparison to the de novo NAFLD (42).

Pediatric NAFLD following liver transplantation: Pediatric NAFLD following LT has not been extensively studied. This is mostly due to the insufficient number of liver transplant cases. Nevertheless, there are few case reports of such patients, in which the indications of transplantation were some rare cases of NASH due to metabolic syndrome, and slightly more common were instances of progressive intrahepatic familial cholestasis type 1 (PFIC1) (43). The patients in these studies did not meet the criteria for metabolic syndrome.

Risk factors associated with post-transplant NAFLD occurrence: NAFLD affects both children and adults, yet the risk factors are mostly the same with a few differences mostly in the prevalence of etiologies. The following will discuss the risk factors of NAFLD, both in general and post-LT (44). Other risk factors include obesity, age, diabetes and metabolic syndrome in general, all of which traced back to an unhealthy lifestyle (45, 46).

Pre-transplant disease status: The pre-transplant status of the patient is considered as an important risk factor for the occurrence of NAFLD following liver transplant (47). NAFLD is reported to be more common in liver transplant patients because of pre-existing NASH rather than other conditions (48). This is in part due to the lifestyle and other risk factors related to NASH in the first place (e.g. hypercholestrolemia, hypertension and diabetes mellitus). Nearly one-third of cirrhotic patients due to NASH cirrhosis are at increased risk of de novo NAFLD. Studies suggest that the NAFLD recurrence did not affect overall graft and/or patient survival up to 10 years (49). However, the risk of infection and cardiovascular-related morbidity and mortality appears to be more prevalent in these group of patients (49).

The role of PNPLA3 rs738409-G allele as a risk factor for progression to NAFLD has been well-established. Recently, Finkenstedt et al. revealed that the presence of the rs738409-G allele among the recipients is considered to be an independent risk factor for the development of post-transplant steatosis (23). However, similar results were not observed among the liver donors with the same type of PNPLA3 polymorphism. Therefore, these results suggest that PNPLA3 rs738409-G allele is significantly associated with progression

to post-transplant obesity and should be considered as an independent risk factor for de novo NAFLD (50, 51).

Donor steatosis: Donor steatosis is considered as a risk factor for NAFLD development, due to its role in graft survival, injury and rejection. The histological pattern of steatosis is also crucial, as a liver with macrovesicular steatosis is more susceptible to ischemia than a liver with microvesicular steatosis (52). Steatosis in the donor graft is a crucial predictor of transplant success, and several programs attempt to screen for steatotic donor livers accordingly. However, this may not be an accurate measure since a considerable number of mild cases of NAFLD neither display a change in blood aminotrasferase levels, nor present a clinical finding in ultrasonography (53-55). Invasive histological diagnosis is the only accurate and sensitive method for diagnosis of NAFLD. Nevertheless, it is not practically feasible due to the high number of donors. Moreover, it is worth noting that the predictive value of steatosis on graft survival is not supported by sufficient evidence. In fact, there are contradictory results from various studies, and some of them even highlight beneficial effects of steatosis on hepatic regeneration, albeit in animal models (56, 57). Interestingly, there are methods to "precondition" the donor liver to improve the quality and success rate of transplantation. Such methods include a specific diet, or in case of deceased donor organs, other techniques such as ischemic preconditioning (58, 59).

Drugs: In all organ transplant procedures, most patients receive immunosuppressive drugs such as corticosteroids and cyclophosphamides to prevent graft rejection (60). As these drugs can cause metabolic syndrome, they should also be considered as a risk factor for post-transplant NAFLD. Furthermore, these patients receive calcineurin inhibitors post-transplant, which additionally exacerbate hypertension and hypercholesterolemia. Other immunosuppressive drug regimens including tacrolimus and sirolimus are also diabetogenic and can disrupt various metabolism pathways. Moreover, cyclosporine and tacrolimus have significant adverse effects on human bone marrow. Both drugs are also associated with increased incidence of hyperlipidemia (61). The effects of tacrolimus and cyclosporine on graft survival and de novo diabetes have been compared in RCTs, favoring the use of tacrolimus (62).

Corticosteroids are usually a necessary element of the post-surgery drug regimen. They are also a major risk factor for post-surgical side effects. This is the result of corticosteroids' various effects on different parts of the body, which, in general, predispose the body in a metabolic-syndrome-like state. This phenomenon is known as the post-transplant metabolic syndrome, which increases the risk of cardiovascular events (63).

Role of Angiotensin-converting-enzyme (ACE) inhibitors in NAFLD prevention: A study revealed that the use of ACE inhibitors could be associated with decreased induction of de novo NAFLD post LT (odds ratio, 0.09; 95% confidence interval, 0.01-0.92; P<0.042) (36). The mechanism is unclear, but it could be possibly related to the role of ACE-inhibitors in improving insulin sensitivity. On a molecular level, ACE-inhibitors appear to play a part in activation of peroxisome proliferator-activated receptor-γ, which is beneficial in NAFLD patients (64). Furthermore, ACE-inhibitors are antihypertensive, which reduce oxidative stress and hepatic fat accumulation. The latter is demonstrated to be a protective factor in hepatic fibrogenesis (65). Thus, nearly all medications used after liver transplant could disrupt the regular body metabolism. Further, each of these medications uniquely puts the patient at increased risk of post-transplant NAFLD (lipid metabolism disruption, protein disruption, etc.) and other complications such as cardiovascular events (66).

Management: The evidence is lacking with regard to the optimal pharmacological therapy of NAFLD following LT. However, it seems that anti-lipid agents, anti-hypertension drugs, and hypoglycemic therapies could control post-transplant NAFLD by decreasing the prevalence of metabolic syndrome's components (43). Weight reduction combined with dietary modifications has shown to significantly improved post-transplant patient's survival outcome (67, 68). In addition, morbidly obese patients should be candidates for weight reduction surgery as a complimentary treatment to LT (69). Modification of lifestyle or bariatric surgery before the transplant is numbered as the best way to prevent post-transplant recurrence of NASH (70). It is worth mentioning that a subset of patients undergoing LT may end up gaining weight following the surgery, which could lead to a compromised metabolic and results in a new-onset, post-transplant diabetes mellitus type 2 (71). While weight gain occurring during the first months after the transplant is indicative of the liver returning to its normal function, the same cannot be mentioned about weight gain in the long term (34). ILTS consensus conference recommended at least 10% of weight loss as a suitable target. They revealed 5% of weight loss could lead to positive outcome on hepatic histology and more weight reduction could minimize the liver injury and

fibrosis (72). Nutritional status of the patient is also of great importance, since malnutrition is reportedly a common finding in end stage liver disease patients as well as in those with post-transplant setting (73).

Lifestyle modification has different components, including dietary habits, exercise, and limited fatty acid intake. Previous studies suggested that the Mediterranean diet, which contains fruit, vegetables, whole grains, nuts, olive oils, fish, and poultry instead of red meat, could reduce the risk of NASH progression. In addition, this type of diet contributes to decreasing cardiovascular incidents by 30%. This type of diet not only decreases insulin resistance without weight reduction, but also helps to reduce the risks of related malignancies (72). Reducing the fatty acid intake could contribute to the inhabitation of NASH progression (74). According to the ILTS consensus conference on NAFLD and liver transplantation, the limited drink of alcohol helps to control NAFLD. Unfortunately, there is limited data about the role of mild use of alcohol in recurrent NAFLD (72). Although it is the best strategy available so far, many of the risk factors are ultimately inevitable. This makes it absolutely challenging in preventing the condition and causes a high prevalence of NAFLD in LT patients.

In conclusion NAFLD is a common and rapidly growing disease both in the population as a whole and the subset population of liver transplant recipients. There has been multiple risk factors identified to play a crucial role in the development of post-transplant NAFLD. Nonetheless, there is limited data about the long-term outcome of liver transplant in patients with recurrent NAFLD. Further studies should work on this lack. NAFLD could affect the prognosis of the post-transplant patients/graft survival and also affects multiple different organs such as the heart and kidneys. Therefore, efficient management and prevention of NAFLD is strongly encouraged. Although efforts are being made to manage the risk factors in liver transplant patients, improved medication regimen and prevention methods should be taken into account to reduce the morbidity and mortality rates caused by NAFLD.

Acknowledgments

We would like to express our sincere thanks to the director of Liver Transplantation Research Center for their support and guidance.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The authors have no conflict of interest to declare.

Authors' contributions

SS (Critical revision of the manuscript, Study concept), AE (Critical revision of the manuscript), PE, NRK, KMS (drafting of the manuscript), BM, EF, FZT (participated in the literature review), and AM, SI, MA (Study concept and design, critical revision of the manuscript).

References

1. Neuschwander-Tetri BA. Non-alcoholic fatty liver disease. BMC Med 2017; 15: 45.
2. Contos MJ, Cales W, Sterling RK, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. Liver Transpl 2001; 7: 363-73.
3. Shaker M, Tabbaa A, Albeldawi M, Alkhouri N. Liver transplantation for nonalcoholic fatty liver disease: new challenges and new opportunities. World J Gastroenterol 2014; 20: 5320-30.
4. Sourianarayanane A, Arikapudi S, McCullough AJ, Humar A. Nonalcoholic steatohepatitis recurrence and rate of fibrosis progression following liver transplantation. Eur J Gastroenterol Hepatol 2017; 29: 481-7.
5. Said A. Non-alcoholic fatty liver disease and liver transplantation: outcomes and advances. World J Gastroenterol 2013; 19: 9146-55.
6. Petta S, Muratore C, Craxi A. Non-alcoholic fatty liver disease pathogenesis: the present and the future. Dig Liver Dis 2009; 41: 615-25.
7. Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest 2000; 106: 171-6.
8. Tarantino G, Finelli C. What about non-alcoholic fatty liver disease as a new criterion to define metabolic syndrome? World J Gastroenterol 2013; 19: 3375-84.
9. El-Badry AM, Graf R, Clavien PA. Omega 3 - Omega 6: What is right for the liver? J Hepatol 2007; 47: 718-25.
10. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008; 40: 1461-5.

11. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. Hepatology 2011; 53: 1883-94.
12. Dongiovanni P, Petta S, Maglio C, et al. Transmembrane 6 superfamily member 2 gene variant disentangles nonalcoholic steatohepatitis from cardiovascular disease. Hepatology 2015; 61: 506-14.
13. Jou J, Choi SS, Diehl AM. Mechanisms of disease progression in nonalcoholic fatty liver disease. Semin Liver Dis 2008; 28: 370-9.
14. Jiang W, Wu N, Wang X, et al. Dysbiosis gut microbiota associated with inflammation and impaired mucosal immune function in intestine of humans with non-alcoholic fatty liver disease. Sci Rep 2015; 5: 8096.
15. Kirpich IA, Marsano LS, McClain CJ. Gut-liver axis, nutrition, and non-alcoholic fatty liver disease. Clin Biochem 2015; 48: 923-30.
16. Anderson N, Borlak J. Molecular mechanisms and therapeutic targets in steatosis and steatohepatitis. Pharmacol Rev 2008; 60: 311-57.
17. Greco D, Kotronen A, Westerbacka J, et al. Gene expression in human NAFLD. Am J Physiol Gastrointest Liver Physiol 2008; 294: G1281-7.
18. Fabbrini E, Magkos F, Mohammed BS, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proc Natl Acad Sci USA 2009; 106: 15430-5.
19. Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. J Clin Invest 2004; 114: 147-52.
20. Bell M, Wang H, Chen H, et al. Consequences of lipid droplet coat protein downregulation in liver cells: abnormal lipid droplet metabolism and induction of insulin resistance. Diabetes 2008; 57: 2037-45.
21. Sanyal AJ, Campbell-Sargent C, Mirshahi F, et al. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology 2001; 120: 1183-92.
22. Tiniakos DG, Vos MB, Brunt EM. Nonalcoholic fatty liver disease: pathology and pathogenesis. Annu Rev Pathol 2010; 5: 145-71.
23. Finkenstedt A, Auer C, Glodny B, et al. 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: 1667-72.
24. Kozlitina J, Smagris E, Stender S, et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nat genet 2014; 46: 352-6.
25. Mancina RM, Dongiovanni P, Petta S, et al. The MBOAT7-TMC4 variant rs641738 increases risk of nonalcoholic fatty liver disease in individuals of european descent. Gastroenterology 2016; 150: 1219-30.e6.
26. Perumpail BJ, Khan MA, Yoo ER, et al. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World J Gastroenterol 2017; 23: 8263-76.
27. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018; 15: 11-20.
28. Burra P, Berenguer M, Pomfret E. The ILTS Consensus Conference on NAFLD/NASH and Liver Transplantation: Setting the Stage. Transplantation 2019; 103: 19-21.
29. Lopez-Alvarenga JC, Montesinos-Cabrera RA, Velazquez-Alva C, Gonzalez-Barranco J. Short stature is related to high body fat composition despite body mass index in a Mexican population. Arch Med Res 2003; 34: 137-40.
30. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004; 40: 1387-95.
31. Mikolasevic I, Filipec-Kanizaj T, Mijic M, et al. Nonalcoholic fatty liver disease and liver transplantation-Where do we stand? World J Gastroenterol 2018; 24: 1491-506.
32. 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: 1249-53.
33. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015; 148: 547-55.
34. Richards J, Gunson B, Johnson J, Neuberger J. Weight gain and obesity after liver transplantation. Transplant international: official journal of the European Society for Organ Transplantation. Transpl Int 2005; 18: 461-6.
35. Patil DT, Yerian LM. Evolution of nonalcoholic fatty liver disease recurrence after liver transplantation. Liver Transpl 2012; 18: 1147-53.

36. Seo S, Maganti K, Khehra M, et al. De novo nonalcoholic fatty liver disease after liver transplantation. Liver Transpl 2007; 13: 844-7.
37. Dureja P, Mellinger J, Agni R, et al. NAFLD recurrence in liver transplant recipients. Transplantation 2011; 91: 684-9.
38. 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: 431-9.
39. Andrade AR, Bittencourt PL, Codes L, et al. New onset diabetes and non-alcoholic fatty liver disease after liver transplantation. Ann Hepatol 2017; 16: 932-40.
40. Narayanan P, Mara K, Izzy M, et al. Recurrent or de novo allograft steatosis and long-term outcomes after liver transplantation. Transplantation 2019; 103: e14-e21.
41. Vallin M, Guillaud O, Boillot O, et al. Recurrent or de novo nonalcoholic fatty liver disease after liver transplantation: natural history based on liver biopsy analysis. Liver Transpl 2014; 20: 1064-71.
42. Germani G, Laryea M, Rubbia-Brandt L, et al. Management of recurrent and de novo NAFLD/NASH after liver transplantation. Transplantation 2019; 103: 57-67.
43. Gunaydin M, Bozkurter Cil AT. Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment. Hepat Med 2018; 10: 95-104.
44. Dumortier J, Giostra E, Belbouab S, et al. Non-alcoholic fatty liver disease in liver transplant recipients: another story of "seed and soil". Am J Gastroenterol 2010; 105: 613-20.
45. Poonawala A, Nair SP, Thuluvath PJ. Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: a case-control study. Hepatology 2000; 32: 689-92.
46. Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. Hepatology 1999; 29: 664-9.
47. Khullar V, Dolganiuc A, Firpi RJ. Pre-and-post transplant considerations in patients with nonalcoholic fatty liver disease. World J Transplant 2014; 4: 81-92.
48. Younossi ZM, Marchesini G, Pinto-Cortez H, Petta S. Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: implications for liver transplantation. Transplantation 2019; 103: 22-7.
49. Mikolasevic I, Filipec-Kanizaj T, Mijic M, et al. Nonalcoholic fatty liver disease and liver transplantation-Where do we stand? World J Gastroenterol 2018; 24: 1491-506.
50. Rotman Y, Koh C, Zmuda JM, et al. The association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. Hepatology 2010; 52: 894-903.
51. Watt KD, Dierkhising R, Fan C, et al. Investigation of PNPLA3 and IL28B genotypes on diabetes and obesity after liver transplantation: insight into mechanisms of disease. Am J Transplant 2013; 13: 2450-7.
52. Selzner N, Selzner M, Jochum W, et al. Mouse livers with macrosteatosis are more susceptible to normothermic ischemic injury than those with microsteatosis. J Hepatol 2006; 44: 694-701.
53. Wong VW, Wong GL, Tsang SW, et al. Metabolic and histological features of non-alcoholic fatty liver disease patients with different serum alanine aminotransferase levels. Aliment Pharmacol Ther 2009; 29: 387-96.
54. Fracanzani AL, Valenti L, Bugianesi E, et al. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. Hepatology 2008; 48: 792-8.
55. Ahn JS, Sinn DH, Gwak GY, et al. Steatosis among living liver donors without evidence of fatty liver on ultrasonography: potential implications for preoperative liver biopsy. Transplantation 2013; 95: 1404-9.
56. Newberry EP, Kennedy SM, Xie Y, et al. Altered hepatic triglyceride content after partial hepatectomy without impaired liver regeneration in multiple murine genetic models. Hepatology 2008; 48: 1097-105.
57. Vetelainen R, van Vliet A, Gouma DJ, van Gulik TM. Steatosis as a risk factor in liver surgery. Ann Surg 2007; 245: 20-30.
58. Nakamuta M, Morizono S, Soejima Y, et al. Short-term intensive treatment for donors with hepatic steatosis in living-donor liver transplantation. Transplantation 2005; 80: 608-12.
59. Chu MJ, Vather R, Hickey AJ, Phillips AR, Bartlett AS. Impact of ischaemic preconditioning on experimental steatotic livers following hepatic ischaemia-reperfusion injury: a systematic review. HPB (Oxford) 2015; 17: 1-10.

60. Kaufman DB, Shapiro R, Lucey MR, et al. Immunosuppression: practice and trends. Am J Transplant 2004; 4: 38-53.
61. Charco R, Cantarell C, Vargas V, et al. Serum cholesterol changes in long-term survivors of liver transplantation: a comparison between cyclosporine and tacrolimus therapy. Liver Transpl Surg 1999; 5: 204-8.
62. McAlister VC, Haddad E, Renouf E, Malthaner RA, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. Am J Transplant 2006; 6: 1578-85.
63. Iadevaia M, Giusto M, Giannelli V, et al. Metabolic syndrome and cardiovascular risk after liver transplantation: a single-center experience. Transplant Proc 2012; 44: 2005-6.
64. Schupp M, Janke J, Clasen R, Unger T, Kintscher U. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. Circulation 2004; 109: 2054-7.
65. Corey KE, Shah N, Misdraji J, et al. The effect of angiotensin-blocking agents on liver fibrosis in patients with hepatitis C. Liver Int 2009; 29: 748-53.
66. Barnard A, Konyn P, Saab S. Medical Management of Metabolic Complications of Liver Transplant Recipients. Gastroenterol Hepatol (N Y) 2016; 12: 601-8.
67. Giusto M, Lattanzi B, Di Gregorio V, Giannelli V, Lucidi C, Merli M. Changes in nutritional status after liver transplantation. World J Gastroenterol 2014; 20: 10682-90.
68. Newsome PN, Allison ME, Andrews PA, et al. Guidelines for liver transplantation for patients with non-alcoholic steatohepatitis. Gut 2012; 61: 484-500.
69. Tariciotti L, D'Ugo S, Manzia TM, et al. Combined liver transplantation and sleeve gastrectomy for end-stage liver disease in a bariatric patient: First European case-report. Int J Surg Case Rep 2016; 28: 38-41.
70. Bhala N, Aithal G, Ferguson J. How to tackle rising rates of liver disease in the UK. BMJ 2013; 346: f807.
71. Pelaez-Jaramillo MJ, Cardenas-Mojica AA, Gaete PV, Mendivil CO. Post-Liver Transplantation Diabetes Mellitus: A Review of Relevance and Approach to Treatment. Diabetes Ther 2018; 9: 521-43.
72. Ratziu V, Ghabril M, Romero-Gomez M, Svegliati-Baroni G. Recommendations for management and treatment of nonalcoholic steatohepatitis. Transplantation 2019; 103: 28-38.
73. Giusto M, Lattanzi B, Di Gregorio V, Giannelli V, Lucidi C, Merli M. Changes in nutritional status after liver transplantation. World J Gastroenterol 2014; 20: 10682-90.
74. Fan JG, Zhu J, Li XJ, et al. Prevalence of and risk factors for fatty liver in a general population of Shanghai, China. J Hepatol 2005; 43: 508-14.
75. Siriwardana RC, Niriella MA, Dassanayake AS, Liyanage CA, Gunetilleke B, de Silva HJ. Recurrence of graft steatosis after liver transplantation for cryptogenic cirrhosis in recently commenced liver transplant program. Indian J Gastroenterol 2016; 35: 222-4.
76. El Atrache MM, Abouljoud MS, Divine G, et al. Recurrence of non-alcoholic steatohepatitis and cryptogenic cirrhosis following orthotopic liver transplantation in the context of the metabolic syndrome. Clin Transplant 2012; 26: E505-12.