Growing challenge of post-liver transplantation non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma worldwide, with an estimated prevalence of 25%. Post-liver transplantation (LT) recurrent or de novo hepatic steatosis is a common complication in recipients, irrespective of transplantation indication. Risk factors for graft steatosis mainly include obesity, immunosuppression, donor steatosis, and genetic factors. Liver transplant recipients are at high risk of developing insulin resistance, new-onset diabetes, and post-transplantation metabolic syndrome that is highly associated with immunosuppressive treatment. Post-LT NAFLD is often underdiagnosed due to the poor sensitivity of most routine imaging methods. The gold standard for the diagnosis of hepatic steatosis is liver biopsy, which is, however, limited to more complex cases due to its invasive nature. There is no approved pharmacotherapy in NAFLD. Lifestyle modification remains the cornerstone in NAFLD treatment. Other treatment strategies in post-LT NAFLD include lifestyle modifications, pharmacotherapy, bariatric surgery, and tailored immunosuppression. However, these approaches originate from recommendations in the general population, as there is scarce data regarding the safety and efficacy of current management strategies for NAFLD in liver transplant patients. Future prospective studies are required to achieve tailored treatment for these patients.

Key Words: Non-alcoholic fatty liver disease; Steatohepatitis; Hepatic steatosis; Liver transplantation; Cirrhosis; Metabolic syndrome

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Core Tip: Non-alcoholic fatty liver disease (NAFLD) is a common complication in liver transplant recipients. Despite the rising prevalence and potentially progressive nature of this entity, there are currently no recommendations regarding NAFLD diagnosis and management in the post-transplant setting. Future studies are urgently needed to fill this knowledge gap and define optimal diagnostic and treatment approaches in this patient population.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by the presence of steatosis in at least 5% of hepatocytes in the absence of any secondary causes, such as excessive alcohol consumption or other chronic liver diseases[1]. NAFLD encompasses a wide spectrum of histological findings, ranging from simple steatosis (non-alcoholic fatty liver, NAFL) to non-alcoholic steatohepatitis (NASH), the latter of which is additionally characterized by lobular inflammation and hepatocyte ballooning[2]. NAFL is generally considered a slowly progressive or non-progressive condition, while NASH is associated with an increased risk of disease progression to cirrhosis and hepatocellular carcinoma[3].

EPIDEMIOLOGY

NAFLD has become the leading cause of chronic liver disease worldwide, with an estimated prevalence of 25%, which is constantly rising in parallel to the worldwide obesity pandemic[4]. NAFLD is often considered the hepatic component of the metabolic syndrome and is associated with other metabolic disorders, such as obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and insulin resistance (IR)[5]. Due to the increasing prevalence and high risk of progression, NASH has become the second most common indication for liver transplantation (LT) in the United States, reporting a 170% increase from 2004 to 2013[6,7]. LT leads to the resolution of NASH-related complications; however, the underlying metabolic risk factors remain, and are even exacerbated following LT, resulting in a high rate of post-LT NAFLD recurrence[8]. In addition, many recipients are prone to develop a post-LT metabolic syndrome (PTMS), mainly due to the reversal of the cirrhosis-related catabolic state and immunosuppression side effects, leading to de novo NAFLD[9].

Recurrent NAFLD

Recurrence of steatosis and steatohepatitis in recipients with a pre-transplant diagnosis of NASH is more common compared to de novo NAFLD, with a prevalence ranging between 8% and 100% in a follow-up period of 1-10 years[10]. Yalamanchili et al[11] studied 257 patients transplanted for NASH or cryptogenic cirrhosis. Post-LT steatosis was reported in 31% of patients; however, bridging fibrosis or cirrhosis was only found in 5% and 10% of recipients after 5 years and 10 years, respectively[11]. In a recent retrospective study of 275 NASH recipients, the prevalence of NAFLD and NASH recurrence was 22% and 11%, respectively[12]. However, it should be underlined that most studies have important heterogeneity regarding NAFLD diagnosis and patient selection. Recipients with cryptogenic cirrhosis as an indication for LT were included in most of these studies, resulting in a possible NAFLD recurrence overdiagnosis[11,13,14].

De novo NAFLD

De novo NAFLD is defined as the presence of steatosis or steatohepatitis in patients who underwent LT for indications other than NASH[15]. Up to one-third of liver transplant recipients develop de novo NAFLD depending on a combination of host and graft factors[16]. Dumortier et al[16] studied 599 non-NASH liver transplant recipients and reported a prevalence of de novo NAFLD of 31%. The authors demonstrated several independent risk factors for the occurrence of post-LT de novo steatosis, such as post-LT obesity, tacrolimus-based immunosuppression therapy, diabetes mellitus, and pre-transplant liver graft steatosis, demonstrating a dose-dependent relationship between the number of these risk factors and the risk of developing de novo NAFLD. In a recent meta-analysis by Losurdo et al [15] the pooled prevalence of de novo NAFLD and NASH was 26% and 2%, respectively, at a follow-up period of 6 mo to 10 years[15]. The highest prevalences were observed in patients transplanted for either alcoholic (37%) or cryptogenic cirrhosis (35%), or those receiving tacrolimus (26%). Data remain,
however, scarce regarding these entities, while the retrospective design and small sample size of most studies represent important limitations.

### RISK FACTORS

Several risk factors have been associated with post-LT NAFLD occurrence (Table 1). As mentioned above, the pre-transplant metabolic risk factors persist following LT, despite the resolution of liver disease. In addition, the commonly used maintenance immunosuppressive regimens, namely corticosteroids, calcineurin inhibitors (CNIs), and mammalian targets of rapamycin (mTOR) inhibitors are directly linked to obesity, hypertension, dyslipidemia, and hyperglycemia, exacerbating the existing metabolic profile of transplanted patients or leading to a new-onset PTMS. Recipients are at high risk of developing PTMS, irrespective of LT indication, with an estimated prevalence ranging from 44%-58% at 6 mo following LT[17]. The presence of PTMS has been associated with both recurrent and de novo NAFLD[16,18,19]. Pre-transplant graft-steatosis, genetics, and other recipient-related risk factors appear to contribute to the development of both recurrent and de novo NAFLD in the transplanted population [20]. In a recent observational study of 108 recipients, it was concluded that recipient-related factors are more important than donor-related factors in the development of NAFLD, following LT[21].

### Genetic factors

Several studies have attempted to reveal the role of genetic predisposition in the development of post-LT NAFLD. Both recipient and donor genetics have been associated with an increased risk of graft steatosis. The role of patatin-like phospholipase domain-containing protein 3 (PNPLA3) in the development of NAFLD is well established. Finkenstedt et al[22] showed that LT recipients who carry rs738409-GG in PNPLA3 are at increased risk of post-LT NAFLD[22]. In another study of 176 liver transplant patients, Trunečka et al[23] demonstrated that the expression of PNPLA3 p.148M variant in donors represents an independent risk factor for graft steatosis[23]. The donor transmembrane 6 superfamily member 2 c.499A allele was also associated with a higher risk of steatosis in recipients[24]. John et al[25] found that recipient, but not donor, adiponectin polymorphisms rs1501299 G/G and rs17300539 G/G were related to a higher prevalence of post-LT graft steatosis[25].

### Immunosuppression

The maintenance immunosuppressive agents used after LT can exacerbate a preexisting metabolic syndrome in recipients, or lead to a new-onset PTMS, thereby contributing to the development of recurrent and de novo NAFLD[26]. Corticosteroids are widely used in the immediate post-operative period against allograft rejection. They increase the hepatic output of glucose and decrease insulin production and peripheral glucose uptake, inducing IR. Corticosteroid use has been associated with an increased risk of T2DM, dyslipidemia, hypertension, and rapid weight gain in recipients following LT [27]. CNI therapy (cyclosporine and tacrolimus) is also recognized as a risk factor for metabolic syndrome and consequent post-LT NAFLD. They are linked to hypertension, dyslipidemia, new-onset T2DM, and chronic renal disease, with tacrolimus having a more prominent diabetogenic effect compared to cyclosporine, which is mainly associated with post-transplant hypertension[26,28,29]. However, studies investigating the direct association between CNI therapy and post-LT NAFLD seem to provide conflicting results[16,30,31]. Another commonly used class of immunosuppressive drugs, mTOR inhibitors, appear to have metabolic adverse effects, being associated with significant dyslipidemia and IR [26]. Sirolimus increases adipose tissue lipase activity and decreases lipoprotein lipase activity, resulting in hypertriglyceridemia, especially with concomitant cyclosporine therapy[32,33]. In a retrospective study of 430 post-LT biopsies, Galvin et al[31] reported that sirolimus use was predictive of de novo NAFLD following LT[31].

### Donor graft steatosis

Donor graft steatosis has also been suggested as a potential risk factor for post-LT de novo and recurrent NAFLD. While microvesicular steatosis does not affect graft function or survival, donor livers with severe macrovesicular steatosis have been associated with an increased risk of primary graft dysfunction, inferior graft survival, and requirement for retransplantation[34]. However, there is not enough evidence to support the predictive role of donor steatosis in the development of post-LT NAFLD. Three studies have indicated an association between pre-existing donor graft steatosis and post-LT NAFLD, whereas findings in a meta-analysis by Saeed et al[35] did not support this association [16,35-37].

### Pre-transplant liver disease

Aside from NASH, specific other LT indications have been associated with an increased risk of de novo NAFLD. Recipients with a pre-transplant diagnosis of alcoholic liver disease (ALD) are at higher risk of developing de novo post-LT steatosis[16,30]. Hepatitis C virus infection was also reported as a risk factor for post-LT NAFLD[31,38]. In a meta-analysis by Losurdo et al[15], the authors reported the highest
prevailance of de novo NAFLD in patients that underwent an LT for ALD and cryptogenic cirrhosis (37% and 35%, respectively)[15].

**PROGNOSIS**

Despite the high prevalence of recurrent and de novo NAFLD following LT, progression to NASH and advanced fibrosis is less frequent in these patients. Dumortier et al. [16] reported recurrent steatosis in 31% of recipients; however, NASH and advanced fibrosis/cirrhosis were only observed in 3.8% and 2.25% of patients[16]. Yalamanchili et al.[11] confirmed these findings, reporting similarly low incidence rates of NASH and cirrhosis in patients with post-LT NAFLD (4% and 10%, respectively)[11]. However, in the meta-analysis by Saeed et al.[35], the authors reported significantly higher rates of recurrent and de novo NASH (38% and 17%, respectively)[35]. Overall survival of patients transplanted for NASH-related cirrhosis is comparable to those with non-NASH indications in most studies[39-41]. In a recent retrospective analysis of 68950 patients that underwent LT for end-stage liver disease of various indications, Haldar et al.[42] confirmed the aforementioned findings and demonstrated a patient survival at 1, 5, and 10 years post-LT of 84.1%, 73.4%, and 61.2%, respectively, for NASH patients that underwent LT[42]. Overall graft survival was also reported similar between NASH recipients vs those with non-NASH LT indications. Mortality in patients transplanted for NASH was mainly attributed to cardio/cerebrovascular disease and infection rather than liver-related complications. However, the true impact of recurrent or de novo NAFLD on overall and graft survival has not been largely investigated. Dureja et al.[43] studied 88 liver transplant recipients and found no difference in post-LT survival between patients with NAFLD recurrence and those without in a follow-up period of 5 years[43]. More relevant studies with longer follow-up time are necessary to clarify whether post-LT NAFLD per se is associated with increased mortality in the post-transplant setting.

**MANAGEMENT**

There are scarce data regarding the treatment of NAFLD in liver transplant patients. Main treatment strategies include lifestyle modifications, pharmacotherapy, bariatric surgery, and alteration in immunosuppression therapy[44]. The first approach in the management of post-LT NAFLD is lifestyle modification including adequate physical activity, weight loss, and calorie restriction. No drugs have been approved for the treatment of NAFLD and none of the proposed pharmacotherapies has been studied in the post-transplant population. In the latest American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines, pioglitazone, and vitamin E, either as monotherapy or as combination therapy, have been proposed as a potential treatment approach in biopsy-proven NASH patients[45]. However, there are concerns about the safety of long-term use of vitamin E, as it has been associated with an increased risk of prostate cancer and hemorrhagic stroke[46,47]. Pioglitazone has been associated with weight gain and should be, therefore, cautiously recommended in transplanted patients, for fear of exacerbating post-LT obesity and PTMS[48]. Bariatric surgery is recommended in cases where obese patients cannot achieve weight reduction following LT; however, there are concerns regarding the potential malabsorption and altered pharma-co kinetics of immunosuppressive drugs[49,50]. Optimization of immunosuppression is of vital importance to reduce drug-induced metabolic risks and subsequent NAFLD in the post-LT period. Early steroid withdrawal, minimization, and alterations of immunosuppressive regimens based on patient’s metabolic complications are common approaches in the management of PTMS. More specifically, in cases where hypertension is the major metabolic complication, conversion from

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**Table 1 Risk factors associated with post-transplantation non-alcoholic fatty liver disease**

| Recipient factors               | Donor factors               |
|--------------------------------|-----------------------------|
| Obesity/post-LT weight gain    | Macroversicular graft steatosis |
| T2DM                           | Genetics                    |
| Dyslipidemia                    |                            |
| Genetics                       |                            |
| Immunosuppression               |                            |
| LT indication: NASH, HCV, ALD   |                            |

ALD: Alcoholic liver disease; HCV: Hepatitis C virus; LT: Liver transplantation; NASH: Non-alcoholic steatohepatitis; T2DM: Type 2 diabetes mellitus.
cyclosporine to tacrolimus has been shown to have a beneficial effect on blood pressure[51]. Similarly, reducing tacrolimus dosage or switching to another immunosuppression regimen has been associated with better glycemic control in recipients with new-onset T2DM[52]. mTOR inhibitors, on the other hand, should be avoided in cases of severe uncontrolled dyslipidemia[32,33].

CONCLUSION

Post-LT NAFLD remains a great challenge for hepatologists and transplant surgeons. Early detection of modifiable risk factors plays a crucial role in preventing disease occurrence. There is an unmet need for specific recommendations regarding both NAFLD screening and management in the post-transplant setting. Post-LT diagnosis tends to be underdiagnosed due to poor sensitivity of routine imaging modalities, whereas liver biopsy is not routinely used for NAFLD diagnosis, due to its invasive nature and possible complications. Regarding disease management, while numerous studies have investigated potential treatment approaches for NAFLD in non-transplant patients, there are scarce data on liver-transplant recipients, with most treatment strategies being extrapolated from recommendations in the general population. However, certain limitations in transplanted patients, such as reduced physical activity, immunosuppressive therapy, and drug-drug interactions with NAFLD treatment regimens, as well as treatment dilemmas regarding minimization or alteration of immunosuppression therapy in the setting of PTMS remain major problems for hepatologists. Prospective, longitudinal studies in liver transplant recipients are necessary to optimize screening, disease monitoring, and treatment in this special patient population.

FOOTNOTES

Author contributions: Kalogirou M wrote the paper; Giouleme O critically revised it for important intellectual content.

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REFERENCES

1 Perumpail BJ, Khan MA, Yoo ER, Cholankeril G, Kim D, Ahmed A. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World J Gastroenterol 2017; 23: 8263-8276 [PMID: 29307986 DOI: 10.3748/wjg.v23.i47.8263]
2 Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012; 55: 2005-2023 [PMID: 22488764 DOI: 10.1002/hep.25762]
3 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]
4 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64: 73-84 [PMID: 26707365 DOI: 10.1002/hep.25831]
5Buzzetti E, Pinzani M, Tsoschatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism 2016; 65: 1038-1048 [PMID: 26823198 DOI: 10.1016/j.metabol.2015.12.012]
6 Mikolasevic I, Filipic-Kanizaj T, Mijic M, Jakopic I, Milic S, Hrstic I, Sobocan N, Simac D, Burra P. Nonalcoholic fatty liver disease and liver transplantation - Where do we stand? World J Gastroenterol 2018; 24: 1491-1506 [PMID: 29662288]
after liver transplantation and patient outcomes. *Liver Transpl* 2016; 22: 644-655 [PMID: 26707008 DOI: 10.1002/lt.24393]

31 Galvin Z, Rajakumar R, Chen E, Adeyi O, Selzner M, Grant D, Sapioschin G, Greig P, Catral M, McGilvray I, Ghanevar A, Selzner N, Lilly L, Patel K, Bhat M. Predictors of De Novo Nonalcoholic Fatty Liver Disease After Liver Transplantation and Associated Fibrosis. *Liver Transpl* 2019; 25: 56-67 [PMID: 30609189 DOI: 10.1002/lt.25338]

32 Morrisset JD, Abdel-Fattah G, Kahan BO. Sirolimus changes lipid concentrations and lipoprotein metabolism in kidney transplant recipients. *Transplant Proc* 2003; 35: 1435-1505 [PMID: 12748247 DOI: 10.1016/s0041-1345(03)00223-1]

33 Trotter JF, Wachs ME, Trouillot TE, Bak T, Kugelmas M, Kam I, Everson G. Dyslipidemia during sirolimus therapy in liver transplant recipients occurs with concomitant cyclosporine but not tacrolimus. *Liver Transpl* 2001; 7: 401-408 [PMID: 11340259 DOI: 10.1053/jlts.2001.23916]

34 de Graaf EL, Kench J, Dilworth P, Shackel NA, Strasser SJ, Joseph D, Pleas H, Crawford M, McCaughan GW, Verran DJ. Grade of deceased donor liver macrovesicular steatosis impacts graft and recipient outcomes more than the Donor Risk Index. *J Gastroenterol Hepatol* 2012; 27: 540-546 [PMID: 21777274 DOI: 10.1111/j.1440-1746.2011.06844.x]

35 Saeed N, Glass L, Sharma P, Shannon C, Sonneniday CJ, Ticnoppa MA. Incidence and Risks for Nonalcoholic Fatty Liver Disease and Steatohepatitis Post-liver Transplant: Systematic Review and Meta-analysis. *Transplantation* 2019; 103: e345-e354 [PMID: 31415032 DOI: 10.1097/TP.0000000000002916]

36 Kim H, Lee K, Lee KW, Yi NJ, Lee HW, Hong G, Choi Y, You T, Suh SW, Jang JJ, Suh KS. Histologically proven non-alcoholic fatty liver disease and clinically related factors in recipients after liver transplantation. *Clin Transplant* 2014; 28: 521-529 [PMID: 24579874 DOI: 10.1111/ctn.12343]

37 Miyakai H, Miura S, Taura N, Shibata H, Sasaki R, Solyama A, Hirakawa M, Takatsuki M, Eguchi S, Nakao K. Risk Factors and Clinical Course for Liver Steatosis or Nonalcoholic Steatohepatitis After Living Donor Liver Transplantation. *Transplantation* 2019; 103: 109-112 [PMID: 29994941 DOI: 10.1097/TP.0000000000002139]

38 Narayanan P, Mara K, Izzy M, Dierkhising R, Heimbach J, Allen AM, Watt KD. Recurrent or De Novo Allograft Steatosis and Long-term Outcomes After Liver Transplantation. *Transplantation* 2019; 103: e14-e21 [PMID: 29994981 DOI: 10.1097/TP.0000000000002317]

39 Bhagat V, Mudrikouglu AL, Nudo CG, Schiff ER, Trakis A, Regev A. Outcomes of liver transplantation in patients with cirrhosis due to nonalcoholic steatohepatitis versus patients with cirrhosis due to alcoholic disease. *Liver Transpl* 2009; 15: 1814-1820 [PMID: 19938128 DOI: 10.1097/0H013e31826bb7c6]

40 Agopian VG, Kaldas FM, Hong JC, Whittaker M, Holt C, Rana A, Zarrinpur 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.0b013e31821e2b7c6]

41 Kennedy C, Redden D, Gray S, Echhoff D, Massoud O, McGuire B, Alkurti B, Bloomer J, DuBay DA. Equivalent follow-up survival in 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]

42 Halder D, Kern B, Hodgson J, Armstrong MJ, Adam R, Berlakovich G, Fritz J, Feurstein B, Popp W, Karam V, Muisesan P, O'Grady J, Jamieson N, Wigmore SJ, Pierreux J, Malek-Hosseini SA, Hidalgo E, Tokat Y, Paul A, Pratschke J, Bartels M, Trunecka P, Settmacher U, Pinzani M, Duvoux C, Newsome PN, Schneeberger S; European Liver and Intestine Transplant Association (ELITA). Outcomes of liver transplantation for non-alcoholic steatohepatitis: A European Liver Transplant Registry study. *J Hepatol* 2019; 71: 313-322 [PMID: 31071367 DOI: 10.1016/j.jhep.2019.04.011]

43 Duréja 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: 21288661 DOI: 10.1097/TP.0b013e31820b6884]

44 Shaker M, Tabbaa A, Albeldawi A, Alkhouri N; Liver transplantation for nonalcoholic fatty liver disease: new challenges and future opportunities. *World J Gastroenterol* 2014; 20: 5320-5330 [PMID: 24833662 DOI: 10.3748/wjg.v20.i18.5320]

45 Leoni S, Tovoli N, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. *World J Gastroenterol* 2018; 24: 3361-3373 [PMID: 30122876 DOI: 10.3748/wjg.v24.i20.3361]

46 Klein EA, Thompson JM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, Minasian LM, Ford LG, Parsons JK, Ford LG, Parson JK, Chil JH, Darke AK, Lippman SM, Goodman GE, Meykens FJ Jr, Baker LH. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2011; 306: 1549-1556 [PMID: 21990295 DOI: 10.1001/jama.2011.1437]

47 Schürks M, Glynn RJ, Rist PM, Tzouri C, Kurth T. Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials. *BMJ* 2010; 341: c5702 [PMID: 21051774 DOI: 10.1136/bmj.c5702]

48 Aghaomamadzadeh N, Niafar M, Dalir Abdolahinia E, Najafi Pour M, Mohamadzadeh Gharebaghi S, Adabi K, Ahadi H. The effect of pioglitazone on weight, lipid profile and liver enzymes in type 2 diabetic patients. *Ther Adv Endocrinol Metab* 2015; 6: 56-60 [PMID: 25941563 DOI: 10.1177/2042018815574229]

49 Lassaily G, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J, Raverdy V, Leteurtre E, Dharancy S, Louvat A, Ronom M, Duhamel A, Pattou F, Mathurin P. Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients. *Gastroenterology* 2015; 149: 379-88; quiz e15 [PMID: 25917783 DOI: 10.1053/j.gastro.2015.04.014]

50 Yemini R, Nesher E, Winker J, Carmeli I, Azran C, Ben David M, Mor E, Keidar A. Bariatric surgery in solid organ transplant patients: Long-term follow-up results of outcome, safety, and effect on immunosuppression. *Am J Transplant* 2018; 18: 2772-2780 [PMID: 29569341 DOI: 10.1111/ajt.14739]

51 Neal DA, Gimson AE, Gibb P, Alexander DJ. Beneficial effects of converting liver transplant recipients from cyclosporine to tacrolimus on blood pressure, serum lipids, and weight. *Liver Transpl* 2001; 7: 533-539 [PMID: 11445383 DOI: 10.1053/lt.2001.24637]

52 Tucee SG. Diabetes mellitus after liver transplant new etiologic clues and cornerstones for understanding. *Transplant Proc* 2003; 35: 1466-1468 [PMID: 12826194 DOI: 10.1016/s0041-1345(03)00528-1]
