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EDITORIAL

Nonalcoholic Steatohepatitis: The Second Leading Indication for Liver Transplantation in the USA

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Nonalcoholic steatohepatitis (NASH) is a severe form of nonalcoholic fatty liver disease (NAFLD), characterized by the histologic presence of hepatic steatosis, ballooning degeneration, and lobular inflammation, with or without peri-sinusoidal fibrosis [1]. In NASH, steatosis is associated with chronic inflammation that may progress to cirrhosis and hepatocellular carcinoma (HCC). Progression to cirrhosis is variable, being influenced by genetic and environmental factors; approximately 11% of patients with NASH progress to cirrhosis within 15 years [2]. HCC may develop in up to 13% in patients with NASH and cirrhosis [2].

NASH is strongly related to obesity and metabolic syndrome (MS), conditions with a high prevalence in the USA and in several countries worldwide. As of 2014, 20% of American teenagers and 36% of adults are obese (BMI $\geq$ 30 kg/m^2) [3].

Since NASH was first assigned as a diagnostic category by United Network for Organ Sharing (UNOS) in 2001 [3], the prevalence of NASH as an indication for liver transplantation (LT) was unknown prior to 2001. Most cases that were formerly classified as cryptogenic cirrhosis (CC) were most likely cases of NASH-induced end-stage liver disease (ESLD).

In this issue of *Digestive Diseases and Sciences*, Cholankeril et al. [3] report on the temporal trends and outcomes of LT for NASH in the USA based on a review of the United Network for Organ Sharing and Organ Procurement and Transplantation (UNOS/OPTN) 2003–2014 database. The authors reported that infection with the hepatitis C virus (HCV) was the leading indication for LT, encompassing nearly 33% of all LTs. Overall, the second leading indication for LT was alcoholic liver disease (ALD) with 15% of all cases. NASH was the third most common indication for LT overall, being accountable for 13% of all LTs. Yet, NASH-related LTs experienced a 162% increase in prevalence from 2003 to 2014. Indeed, NASH became the second leading indication for LT after 2008, accounting for 17.4% of all LTs performed in the USA in 2014 [3].

Cholankeril et al. have reclassified from CC to NASH the cases of all obese patients (BMI $\geq$ 30 kg/m^2) that underwent LT for CC [3]. This measure was clearly justified, as it is now accepted that the majority of CC patients actually have undiagnosed NASH [4]. Nevertheless, there are enough reasons to believe that the prevalence of NASH-related LT in the USA might have been even higher than reported by the authors. It is not uncommon to diagnose NAFLD in patients with a BMI $<$ 30 [1]. Thus, patients with CC that were previously obese and lost weight before being listed for LT could have had NASH as the cause of their ESLD. Reclassifying CC patients with BMI $<$ 30 kg/m^2 that were previously obese into NASH cirrhosis would further increase the prevalence of NASH as an indication for LT in the USA. Unfortunately, information on prior obesity and weight loss is not usually available on transplant registries worldwide.

Obesity and MS may also contribute to chronic liver damage due to other etiologies. In other words, obese individuals suffering from ESLD attributed to diseases other than NASH (e.g., HCV, ALD) do have some "NASH component" contributing to the etiology of ESLD. This potential influence of obesity and MS on ESLD secondary to HCV and ALD was not evaluated in the study.

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Post-LT outcomes are primarily influenced by factors specific to the indication for LT. For example, LT for ALD is influenced by recidivism, HCV by viral recurrence, and NASH by recurrent NASH and the morbidities associated with the MS. The outcomes of LT for NASH were similar to those of LT performed for ALD. Patients with NASH who underwent LT experienced superior outcomes compared to those reported for LT of HCV recipients in the USA [3]. There are reasons to believe that future studies may yield results different than those reported for LTs performed from 2003 to 2014. HCV recurrence traditionally has been one of the main causes of death and graft failure in LT recipients with hepatitis C [5]. With the availability of newer antiviral agents, eradication of the virus is possible in nearly 95% of all LT recipients [6]. Thus, there is a strong hope that recurrence of HCV in the liver graft may not be as problematic in the near future. Therefore, outcomes of LT for HCV should likely improve in the near future, becoming superior to those of LT performed for NASH.

A recent survey has compared the prevalence of chronic liver disease (CLD) in American adolescents and young adults in two different periods (1988–1994 and 1999–2004) [7]. The authors detected a sharp increase in the prevalence of CLD from 12.9% in 1988–1994 to 28.5% in 1999–2004. Moreover, NAFLD was the most common etiology of CLD in American teenagers and young adults, accounting for 22% of all cases of CLD in this patient population [7]. The prevalence of CLD in teenagers and young adults has remained stable after 2004 (27.7%) [7]. Thus, maintenance in the current prevalence of NASH-related LTs should be expected in the forthcoming years.

Metabolic risk factors potentially worsen in the setting of post-transplant immunosuppression. All LT recipients are at risk of hyperlipidemia, diabetes mellitus, hypertension, and cardiovascular disease. Weight gain is common after LT, contributing to an elevated prevalence of MS in LT recipients. Post-transplant NAFLD occurs in 40–70% of all LT recipients. Moreover, NASH may recur in up to 25% of all LT recipients [2]. A substantial proportion of LT recipients with recurrent NASH will experience graft loss. Nearly 5% of all LTs will fail secondary to recurrent NASH [8].

Besides recurrence of NASH cirrhosis, cardiovascular mortality is a major concern in LT recipients with MS. Hyperlipidemia and MS are present in nearly 50% of all LT recipients [2]. Hyperlipidemia is an independent risk factor for cardiovascular disease. Our group has developed a tailored approach for the management of dyslipidemia in LT recipients. In consultation with a specialized dietitian who prescribed an individualized diet plan based on estimated basal metabolism and consisting of a maximum of 25% of the total energy value derived from fat and <200 mg/day of cholesterol, we were able to control dyslipidemia in >80% of all LT recipients enrolled [9]. Others have performed sleeve gastrectomy concomitant to LT with satisfactory weight control [10].

In summary, NASH-related cirrhosis has assumed prominence as being currently the second leading indication for LT in the USA. Although genetic factors contribute toward the development of NASH, obesity and MS remain the leading causes. Primary prevention of obesity through behavioral changes that include adoption of a healthy diet and regular exercise is highly recommended in addition to pharmacological treatment of diabetes, obesity, and dyslipidemia in order to prevent progression to NASH and its feared complications. Surgical treatment of refractory obesity should be employed as needed. Similar medical interventions should be considered for LT recipients presenting with MS, obesity, and dyslipidemia.

Compliance with ethical standards

Conflict of interest The author has no conflicts of interest related to this publication.

References

1. Loomba R, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol*. 2013;10:686–690.
2. Kappus M, Abdelmalek M. De novo and recurrence of nonalcoholic steatohepatitis after liver transplantation. *Clin Liver Dis*. 2017;21:321–335.
3. Cholankeril G, Wong RJ, Hu M, et al. Liver transplantation for nonalcoholic steatohepatitis in the US: Temporal trends and outcomes. *Dig Dis Sci*. (Epub ahead of print). doi: 10.1007/s10620-017-4684-x.
4. 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.
5. Chedid MF, Rosen CB, Nyberg SL, Heimbach JK. Excellent long-term patient and graft survival are possible with appropriate use of livers from deceased septuagenarian and octogenarian donors. *HPB (Oxford)*. 2014;16:852–858.
6. Saxena V, Khungar V, Verna EC, et al. Safety and efficacy of current DAA regimens in kidney and liver transplant recipients with hepatitis C: Results from the HCV-TARGET study. *Hepatology*. 2017. doi:10.1002/hep.29258.
7. Doycheva I, Watt KD, Rifai G, et al. Increasing burden of chronic liver disease among adolescents and young adults in the USA: A silent epidemic. *Dig Dis Sci*. 2017;62:1373–1380.
8. Rowe IA, Webb K, Gunson BK, et al. The impact of disease recurrence on graft survival following liver transplantation: A single centre experience. *Transpl Int*. 2008;21:459.
9. Pinto AS, Chedid MF, Guerra LT, Cabeleira DD, Kruel CD. Dietary management for dyslipidemia in liver transplant recipients. *Arq Bras Cir Dig*. 2016;29:246–251.
10. Heimbach JK, Watt KD, Poterucha JJ, et al. Combined liver transplantation and gastric sleeve resection for patients with medically complicated obesity and end-stage liver disease. *Am J Transpl*. 2013;13:363–368.