INVITED COMMENTARY

The invasion of fatty liver disease in liver transplantation

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Nonalcoholic fatty liver disease (NAFLD) has made its steady, but rapid appearance in the field of liver diseases over the last two to three decades. Other than most liver diseases, NAFLD is seen by a variety of medical specialists, among which hepatologists and gastroenterologists, but also family medicine physicians, radiologists, (bariatric) surgeons, endocrinologists, nutritionists and pathologists, to name a few. NAFLD comprises the full spectrum of simple steatosis (estimated prevalence 6.3–46% [1]) to nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma, all of which arise as a direct consequence of the metabolic syndrome and obesity. As such, it has become a global burden to our health care system. In the USA, where the obesity epidemics has reigned for years, a recent report showed that, at this very moment, NASH is the second most common indication for liver transplantation among adults on the waiting list [2], and is soon expected to beat Hepatitis C.

Unfortunately, obesity affects all ages, and childhood NAFLD has become a serious problem, affecting over 70% of obese children and adolescents [3]. The progression to NASH and/or cirrhosis may have a much higher impact on younger individuals, ultimately necessitating liver transplantation at very young ages. Indeed, NASH cirrhosis has been reported in children as young as 8 years of age [3]. In the current issue of Transplant International, Alkhouri *et al.* [4] have analysed the United Network for Organ Sharing (UNOS) transplant database from 1987 to 2012 to identify all patients under the age of 40, who underwent liver transplantation either for NASH or for cryptogenic cirrhosis in the presence of a BMI $\geq$30 kg/m^2. Using both criteria, they found 330 (N = 111 NASH and N = 219 cryptogenic) patients, representing a mere 1.7% of the total young transplant population. Reassuringly, only 34 patients were under 25 years of age. Nevertheless, 30% of the total population died within a median follow-up of 46 months, with a surprisingly high rate of re-transplantations (11.5%). In contrast to what would be expected, only a minority (8%) of re-transplants were performed for NASH recurrence. Instead, cryptogenic (26%), HCV (13%), auto-immune hepatitis (8%) and other (29%) indications were much more prevalent, which raises the question whether including the cryptogenic category did not, as matter of fact, lead to muddling of the case-mix with the erroneous inclusion of patients with other forms of liver disease. The authors, warning us to be cautious when interpreting the registry data, also make this point. The fact remains that over the last 12 years NASH is steadily increasing as a transplant indication for young patients, albeit to a much lesser degree than adults.

According to a recent report of the World Health Organization [5], 58.6% of European adults are overweight and 23% are obese. Contrary to common belief, these data make painfully clear that Europe is not far behind the United States. Estimates of the number of overweight children in Europe rose steadily and currently one in three 11-year-old children are already overweight or obese. Over 60% of children who are overweight before puberty will be overweight in early adulthood. These data are frightening and without major changes NASH will become the most common liver disease, as well as indication for liver transplantation, in Europe as well.

So what options do we have? Once NAFLD is established at a young age, lifestyle modification, aimed at

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weight reduction, remains the first line intervention, despite the fact that studies to date have failed to show satisfactory long term benefits. This is because weight loss is generally difficult to achieve and is often not durable [6]. In addition, it has never been shown to prevent liver damage or fibrosis. Furthermore, comprehensive evidence-based guidelines are lacking. These are, however, urgently needed to encourage the development of effective and reproducible treatment strategies. Furthermore, a whole array of pharmacological interventions has been tested in young patients with NASH. These include antioxidants such as vitamin E [7], insulin sensitizers such as metformin [7–9], ursodeoxycholic acid [10] and probiotics [11,12]. Unfortunately all major trials have shown no significant biochemical or histological improvement and hence there are no effective medical treatments as of yet. However, many more drugs are currently being tested in animal models and humans and we await the results of these trials eagerly.

Clearly, in the long run, prevention is better than cure. We should give priority to lifestyle changes to prevent obesity. Limiting unhealthy foods and beverages, consuming smaller portions, increasing physical activity and limiting screen time should be part of a healthy family plan. Public awareness should be heightened by using (social) media platforms to re-educate our children (and ourselves) on how to eat properly. In addition, healthy choices should be made easily accessible to all layers of society. Whether this should be done with the same intensity as the global anti-tobacco mass media campaigns by WHO, is food for thought.

The paper by Alkhouri *et al.* [4] makes two things clear. First, current transplant registries do not harbour exact numbers of patients transplanted for NASH. One suggestion is to use pathology reports of liver explants instead of approximating NASH by including cryptogenic cirrhosis and a BMI $\geq$30 kg/m^2. Second, given the high re-transplantation and mortality rate shown by Alkhouri *et al.*, liver transplantation should be the very last resort for NASH. Given, however, that liver transplantation for NASH is bound to increase in the future, attempts to reduce post-transplant morbidity and mortality should be aggressively pursued. One example includes performing bariatric surgery in concert with liver transplantation, which in pilot studies, performed in expert centres, has led to impressive results [13]. Additional examples may include minimizing the use of corticosteroids in the post-transplant setting, as well as optimizing lifestyle and pharmacological control of the metabolic syndrome. It is paramount that our research efforts are directed towards ways to improve and adjust our clinical practice to the new reality.

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REFERENCES

1. 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.
2. 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.
3. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. *Pediatrics* 2006; **118**: 1388.
4. Alkhouri N, Hanouneh IA, Zein NN, *et al.* Liver transplantation for nonalcoholic steatohepatitis (NASH) in young patients. *Transplant Int* 2016; **29**: 418.
5. WHO publications. Available from: http://www.euro.who.int/en/publications.
6. Nobili V, Alisi A, Raponi M. Pediatric non-alcoholic fatty liver disease: preventive and therapeutic value of lifestyle intervention. *World J Gastroenterol* 2009; **15**: 6017.
7. Lavine JE, Schwimmer JB, Van Natta ML, *et al.* Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA* 2011; **305**: 1659.
8. Schwimmer JB, Middleton MS, Deutsch R, Lavine JE. A phase 2 clinical trial of metformin as a treatment for non-diabetic paediatric non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2005; **21**: 871.
9. Nobili V, Manco M, Ciampalini P, *et al.* Metformin use in children with nonalcoholic fatty liver disease: an open-label, 24-month, observational pilot study. *Clin Ther* 2008; **30**: 1168.
10. Vajro P, Franzese A, Valerio G, Iannucci MP, Aragione N. Lack of efficacy of ursodeoxycholic acid for the treatment of liver abnormalities in obese children. *J Pediat* 2000; **136**: 739.
11. Loguercio C, Federico A, Tuccillo C, *et al.* Beneficial effects of a probiotic VSL#3 on parameters of liver dysfunction in chronic liver diseases. *J Clin Gastroenterol* 2005; **39**: 540.
12. Vajro P, Mandato C, Licenziati MR, *et al.* Effects of *Lactobacillus rhamnosus* strain GG in pediatric obesity-related liver disease. *J Pediatr Gastroenterol Nutr* 2011; **52**: 740.
13. 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 Transplant* 2013; **13**: 363.