WEIGHT GAIN AND OBESITY AFTER LIVER TRANSPLANTATION

Obesity in post liver transplant patients is an increasing problem which is under recognised with no definite guidelines for surveillance or treatment.

Susie Hamlin
Senior Specialist Hepatology, Liver Transplant/ ICU Dietitian, Leeds Teaching Hospitals NHS Trust

Julie Leaper
Senior Specialist Hepatology, Liver Transplant/ ICU Dietitian, Leeds Teaching Hospitals NHS Trust

Susie and Julie work in hepatology and liver transplantation, providing nutritional advice to patients with complex nutritional issues. They are joint clinical liver leads for the gastroenterology specialist group of the British Dietetic Association.

Sixty-seven percent of men and 57 percent of women in the UK are overweight or obese from data that uses a Body Mass Index (BMI) of over 25kg/m2 to define overweight and a BMI over 30kg/m2 or more to define obese (1). The incidence of post liver transplant (LTX) obesity is suspected to be higher than the UK population figure. As the incidence of overweight and obesity rises in the general population, more people than before become ill with liver diseases with a BMI higher than seen in previous decades (2).Obesity also accelerates the progression of liver cirrhosis in patients with Hepatitis C and alcohol related liver disease (ARLD) (3).

Most significantly, there is a rising epidemic of patients presenting for LTX assessments with non-alcoholic fatty liver disease (NAFLD), which is considered the hepatic manifestation of metabolic syndrome and directly linked to obesity and being overweight (4). NAFLD is defined as the presence of >five percent deposition of triglycerides in the liver in the absence of significant alcohol consumption. This results in a liver injury similar to the hepatic injury seen in ARLD. The stages of disease progression are the same as ARLD in that they range from simple steatosis, fibrosis to non-alcoholic steatohepatitis (NASH) and finally cirrhosis (5, 6). As NAFLD is directly linked to Metabolic Syndrome (MS), being overweight and obesity, more patients with NAFLD present for LTX assessment with additional risk factors for cardiovascular disease.

A recent analysis of the Scientific Registry of Transplant Recipients in the USA confirmed that NASH, as an indication for LTX, increased over sevenfold from 2001 to 2009, while no other indication for liver transplantation increased over the same time period (7). In the UK and western societies, with rising rates of obesity, a similar clinical picture is predicted in the coming years. NAFLD is now the third most common indication for LTX and is predicted to surpass Hepatitis C and alcohol as the leading indication for LTX in the near future due to the increase in features of metabolic syndrome (8). This is important as obesity affects outcome both at the time of transplant and in the longer term (9). The United States United Network for Organ Sharing (UNOS) database examined the outcomes of 29,000 LTX patients which showed higher early and late mortality, mostly as a result of adverse cardiovascular events in overweight and obese patients (10).

Some weight gain after LTX is inevitable, as most cirrhotic patients on a waiting list for LTX display characteristics of protein energy malnutrition, regardless of their underlying disease or diagnosis of NASH, cirrhosis and presence of obesity. Muscle wasting is apparent, despite dry BMI being >25kg/m2 due the severe metabolic changes that occur in cirrhosis (11). These patients recover their nutritional status, but seem to achieve a higher weight than pre-transplant, which increases the prevalence of overweight and obesity after LTX (12, 13).

The reasons for weight gain are multifactorial. Having undergone a transplant, patients feel better, appetite improves, taste changes resolve, abdominal distension and early satiety from ascites resolve, metabolism returns to a non-catabolic

state, patients can relax pre-transplant dietary restriction and functional ability is improved. Dietetic therapy in the first three months post-transplant aims to recover nutritional status and, during the initial three months post-transplant, this is the time corticosteroids are often prescribed which aids appetite and can promote weight gain.

Rezende et al (14) examined weight changes and incidence of excessive weight up to three years post LTX. The incidence of excessive weight (BMI ≥25kg/m2) and obesity (BMI ≥30kg/m2) was measured before LTX and at year one, two and three post LTX. The results demonstrated a significant number of patients who were overweight or obese one, two and three years after LTX and who were also overweight before having liver disease ($p < 0.01$), but the percentage of patients with excessive weight (BMI >25kg/m2) was higher within two (51.3%) and three years (56.3%) after surgery than before liver disease (49.4%). These studies support the need for weight loss strategies in patients post LTX which should be considered during the three to six months post-operative period following initial rehabilitation.

As life expectancy of post LTX patients increases, the problems associated with excessive weight gain rise too, including greater incidence of post transplant metabolic syndrome (PTMS) and cardiovascular events post LTX (8). NAFLD and NASH can reoccur in patients post LTX and the risks of it developing are directly linked to post-transplant overweight and obesity, female sex, Type 2 diabetes or family history of Type 2 diabetes and development of PTMS (15). PTMS has an estimated prevalence of 44 to 58 percent in LTX recipients and is associated with increased cardiovascular mortality (16). Weight loss in overweight obese patients post LTX with concurrent medical treatment of each element of PTMS has benefits both in term of cardiovascular and liver outcomes (17). Evaluation of the weight gain after LTX is necessary to identify overweight and obesity and propose strategies to prevent and treat as the extent and consequences of this condition are becoming increasingly well recognised.

Three key interventions that have been shown to be effective in weight loss management are:

1 weight loss via dietary means
2 bariatric surgery
3 Orlistat use

DIETARY INTERVENTION

Guidelines produced by the American Gastroenterological Association (2002) following a systematic review of the evidence at that time stated that:

- those who are overweight (body mass index >25kg/m2) and have NAFLD should be considered for a weight loss program;
- a target of 10 percent of baseline initial weight should be the goal of weight loss;
- weight loss should proceed at a rate of one to two lb/wk;
- exercise 30 to 60 minutes daily is recommended (daily exercise can help achieve weight loss and improve insulin sensitivity);
- those with a body mass index of >35kg/m2 and NAFLD can be considered for more aggressive weight management, including a gastric bypass.

A more recent review by NICE in 2011 (18) concluded that: 'Weight reduction with different measures for treating NAFLD is recommended.'

Other cohort studies looking at NAFLD have observed a beneficial effect in ALT and cardiovascular outcomes with five to 10 percent weight loss initially, then aiming for 0.5-1.0Kg/week (19). Studies have also reported beneficial results with weight loss on NASH by lowering body weight and increasing physical activity (20). Another study showed weight loss of at least three to five percent appeared to be necessary to improve steatosis, but greater loss of up to 10 percent may be needed to improve necroinflammation (19).

A randomised control trial by Promrat et al (21) examined the effects of lifestyle intervention (LI) using diet, exercise and behaviour modification, with a goal of seven percent to 10 percent weight reduction on the clinical parameters of NASH. Patients were randomised to a lifestyle intervention and received an intensive weight loss program based on the Diabetes Prevention Program 'Look AHEAD', used in the USA for Type 2 diabetes with successful outcomes, or structured education provided by a health professional in large groups every 12 weeks (control) (22). After 48 weeks of intervention patients in the LI group lost an average of 9.3% of their weight versus 0.2% in the control group ($p=0.003$).

Patients who achieved a weight loss goal (>7.0%) compared with those who lost less than

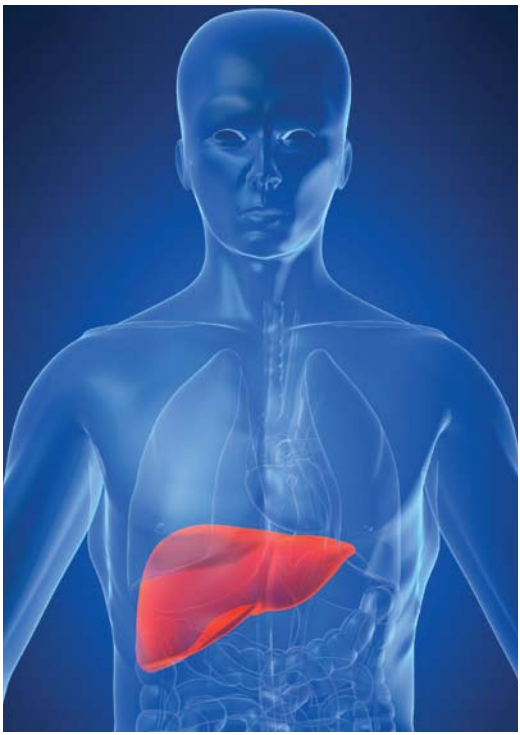
7.0% had significant improvements in steatosis (-1.36 versus -0.41 p<0.001) and Nash Activity Score (-3.45 versus -1.18 p <0.001). This study adds strong evidence that weight loss and exercise improve histological liver features in patients with NASH and, therefore, could be an appropriate treatment in NAFLD/NASH recurrence in LTX patients.

There appears to be a clear benefit in five to 10 percent weight loss in NAFLD and seven percent weight loss in NASH. Achieving this weight loss is a challenge in clinical practice. The level of intensity of treatment to reduce weight by five to 10 percent would require access to weight management services in local areas. NICE Guidance 53 (23) gives a framework for the provision of obesity services and there has recently been a change in commissioning for Tier 2 obesity services to local authorities. There is likely to be large discrepancies in the availability of Tier 2 and 3 services in different areas.

BARIATRIC SURGERY POST LTX

Bariatric surgery is known to improve metabolic profiles in non-transplant patients and this may be beneficial in preventing recurrence or development of NAFLD post LTX (24). There is a small number of case reports published that describe bariatric surgery post LTX. As yet, it is not clear how and when to consider bariatric surgery and the type of bariatric operation to do in this group. Procedures that induce malabsorption, such as Roux En Y bypass and duodenal switch, are likely to result in difficulties with the management of immunosuppression levels. This problem could be avoided with bariatric surgeries that restrict volume consumed, such as gastric band and sleeve gastrectomy, as this would have very little influence on the absorption of immunosuppression medications. Lin et al (25) and Butte et al (26) both described case reports with sleeve gastrectomy post LTX. Another case report by Campsen et al (27) describes a gastric band placement at the time of LTX which reported good outcomes and weight reduction from BMI 42 kg/m2 to 34kg/m2 within six months of surgery.

There is evidence that outcomes at BMI +40kg/m2 at time of transplant are poor and some LTX centres use BMI greater than 40kg/m2 as an excluding factor from liver transplantation (28).



However, it is highly likely that, as the number of patients with overweight and obesity having liver transplants for NAFLD and other conditions increases and the predicted post transplant weight gain occurs (29), there will be more patients presenting with BMI +35kg/m2 with co-morbidities or BMI =40kg/m2 post LTX who will be eligible to access Tier 4 bariatric services.

THE ROLE OF ORLISTAT

Historically, Orlistat was not considered suitable for LTX recipients because it was thought to interfere with the absorption and resulting suboptimal serum levels of immunosuppression drugs Tacrolimus and Cyclosporine. With the rising incidence of obesity post LTX, the use of Orlistat is being reconsidered.

In a meta analysis of 16 clinical trials by Rucker et al (30), Orlistat reduced weight by 2.9kg (95 percent confidence interval 2.5kg to 3.2kg). Another small cohort study (N=15) by Cassiman et al (31) described the safe short-term use of Orlistat in a post-transplant group of patients on tacrolimus. The patients were advised to take tacrolimus separately from meals, one hour before the meal,

or more than two hours after. Orlistat was taken half an hour before meals and target tacrolimus levels were achieved throughout the study.

This study was the first to show that immunosuppression could remain within therapeutic levels whilst taking Orlistat. This area needs further research and development of clear guidelines on proposed Orlistat use in post LTX patients. It would be imperative that patients could access their local Tier 3 obesity services if they met the referral criteria of BMI +35kg/m2 with significant co morbidities or BMI +40kg/m2 in line with NHS England. Guidance on timing of immunosuppression medication and frequent blood tests would be required during the treatment period.

CONCLUSION

The barriers to providing obesity-centred initiatives in post liver transplant patients lie in the lack of recognition of prevalence and clear treatment pathways for this group of patients. There are no local, regional or national initiatives specifically for this group of patients despite the long-term increased cardiovascular risk and clear benefit of weight loss programs which can achieve five to 10 percent weight loss. The development of treatment pathways to identify obese and overweight patients and develop referral criteria within the first six months post operatively to signpost patients to appropriate Tier 1-4 obesity services in their local areas, is underway .Leeds Teaching Hospitals NHS Trust liver unit covers a population of approximately seven million which crosses several local authorities providing Tier 1 and 2 services and clinical commissioning groups that provide Tier 3 and 4 services. The inequality will lie in what services are offered in different areas as weight loss programs cannot be supported by regional liver units.

For article references please email info@networkhealthgroup.co.uk