بسم الله الرحمن الرحيم

Liver transplantation in MAFLD

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Definition

- Metabolic (dysfunction)-associated fatty liver disease (MAFLD) formerly known as non-alcoholic fatty liver disease (NAFLD)

- It is a heterogeneous condition of fatty liver disease which might be influenced by multiple factors including age, gender, hormonal status, ethnicity, diet, alcohol intake, smoking, genetic predisposition, the microbiota and metabolic status (*Estes C et al., 2018*)

NAFLD/MAFLD debate

- The current nomenclature NAFLD defining a disease by what it is NOT (e.g. non-alcoholic) is inappropriate and we should aim for positive diagnostic criteria.

- There is a growing evidence of the superior utility of the term metabolic (dysfunction) associated fatty liver disease (MAFLD) definition for clinical and academic practice (*Fouad Y etal., 2021*)

Definitions and subgroups (*Haung Q et al 2021*)

- **NAFLD**:

was diagnosed if an adult with **steatosis confirmed by ultrasound** *without*

(1) high alcoholic consumption (over one drink daily among women or over two drinks daily among men)

(2) presence of hepatitis BsAg or HCV- Ab

(3) iron overload (transferrin saturation ≥ 50% along with serum ferritin ≥ 400 µg/L in women and ≥500 µg/L in men)

Definitions and subgroups (*Haung Q et al 2021*)

- **MAFLD**

  was defined by the international expert consensus statement in 2020 (*Eslam M etal., 2020*), including **ultrasound confirmed hepatic steatosis** plus one of the three criteria:

1) Overweight or obesity defined as BMI ≥ 25 kg/m^2
2) Presence of type 2 diabetes mellitus, and
3) Metabolic disorders

Metabolic disorders

- Are described by *any two indicators*:

(1) Waist circumference (WC) ≥ 102 cm in men or ≥88 cm in women

(2) Blood pressure ≥140/90 mmHg or taking anti-hypertension drugs

(3) Raised triglycerides (plasma triglycerides ≥ 1.70 mmol/L or taking specific anti-lipid agents)

(4) Reduced HDL cholesterol (plasma HDL <1.0 mmol/L for men and <1.3 mmol/L for women or taking specific agents)

Metabolic disorders

- (5) prediabetes status (FPG 5.6–6.9 mmol/L, or 2-h post-load glucose levels 7.8–11.0 mmol or HbA1c 5.7–6.4%)
- (6) HOMA-IR ≥ 2.5
- (7) plasma high-sensitivity C-reactive protein (CRP) level > 2 mg/L.

MAFLD and Liver transplantation

- Non-alcoholic fatty liver disease (NAFLD) is a pathological condition, which ranges from simple steatosis (NAFL) to non-alcoholic steatohepatitis (NASH) and cirrhosis.
- The liver is primarily involved – however, systemic metabolic complications are often present in patients with NAFLD.
- Recently the term metabolic dysfunctionassociated fatty liver disease (MAFLD) has been proposed to better describe liver disease associated with metabolic dysfunction leading to discussions within the scientific community regarding potential consequent changes in diagnosis, clinical management and drug development.

- NASH requires identification of *3 pathognomonic features on liver biopsy*: ballooning, lobular inflammation and steatosis. (*Bedosa et al 2017*)

- Differentiating NASH from NAFLD is paramount for determining the prognosis of liver disease.

- Patients affected by NASH are at risk of worsening outcomes, such as end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC).

- It is estimated that 20% of patients with NASH develop cirrhosis, whereas the risk of HCC in patients with NASH increased 7.7-fold between 2002–2016, from 2.1% to 16.2% (*Younossi etal.,2019*)

- Prevalence rates of NAFLD in patients with diabetes mellitus (DM) and morbid obesity are nearly 58% and 30% (*Younossi etal.,2019*)

- Controversial data still exist regarding strategies for optimal candidate evaluation before LT and optimal management of metabolic complications after LT

NAFLD/NASH

Before Liver Transplantaion

- According to data from the European Liver Transplant Registry (ELTR) and the United Network for Organ Sharing (UNOS) databases, NAFLD/NASH has been the fastest growing indication for LT in the last 20 years
- It is the second leading indication for LT among adults in the United States
- Increase has been seen in Europe and USA with NAFLD-related cirrhosis accounting for 1.2% of LTs in 2002 compared to 8.4% in 2016 and 21.5% in 2018 (*Cotter TG etal.,2020*)

NAFLD/NASH

- Similarly, NAFLD/NASH is considered the fastest growing cause of HCC in both Europe and the United States

- In a recent modelling study, France is predicted to have the largest increase in incident HCC cases (117%), and the UK the smallest (88%). Similarly, in the United States the incidence of NAFLD/NASHrelated HCC has been estimated to increase by 137% between 2015 and 2030. (*Estes etal., 2018*)

NAFLD/NASH

- Several factors favour the development of HCC in the context of NAFLD/NASH, including *genetic polymorphisms* (i.e. PNPLA3 and TM6SF2) and *environmental modifiers* such as sedentary lifestyle and high-caloric intake, which lead to obesity and insulin resistance
- Usually patients with NASH and HCC are older, have large tumours, and are sometimes difficult to screen with ultrasound because of obesity.
- Moreover, non-cirrhotic patients with NAFLD/NASH are usually not included in screening programe

NAFLD/NASH

- It is estimated that only 15% of patients with HCC and NAFLD/NASH are diagnosed at Barcelona Clinic for Liver Cancer (BCLC) stages 0 or A, which would enable a curative approach to the neoplastic disease (*Anstee Q 2019*)
- Indeed, while the proportions of HCC related to HCV or alcohol-related liver disease remained stable, the proportion of HCC related to NAFLD/ NASH increased 7.7 fold
- It has been considered as rapidly growing indication of LT in Europe and USA

NAFLD/NASH

After liver transplantation:

- After LT, patients with NAFLD are more prone to develop peri-surgical complications such as infections, whereas in the long-term, they have a higher incidence of malignancies (33%) and cardiovascular events (24%) compared to patients transplanted for other reasons (*Van den Berg EH etal.,2018*)

- It has same incidence of complications as in other indications of LT as regard graft and overall survival.

NAFLD/NASH

- In a meta-analysis, the mean 1-, 3-, and 5-year rates of recurrent and de novo NAFLD were 59%, 57%, 82% and 67%, 40%, 78%, respectively.
- The incidence of post-transplant NASH was significantly higher when considering recurrent NASH (53%, 57.4%, and 38% at 1, 3, 5 years after LT, respectively) compared with de novo NASH (13%, 16%, and 17%, respectively) (*Saed N etal.,2019*)
- Post-transplant high BMI, post-transplant hyperlipidaemia, and a history of alcohol abuse are considered predictors of postLT graft steatosis

MAFLD

Metabolic –Associated Fatty Liver Disaease is associted with common metabolic disaeses like:

- DM
- Morbid Obesity
- Dyslipidemia

MAFLD

Diabetes Mellitus:

Before Liver transplantation:

- Pre-LT DM is often associated with liver diseases, such as HCV or NAFLD, with a prevalence of 33%–66% amongst patients with NAFLD (*Leite NC etal., 2009*)
- Two distinct mechanisms seem to be responsible for the development of DM in patients with chronic liver disease:

  1-Impairment of insulin secretion or sensitivity due to a specific aetiological agent, such as HCV, alcohol or NAFLD

  2-Hepatogenous DM, is strictly related to pancreatic beta-cell dysfunction, which is proportional to liver disease severity and loss of liver function (reversible)

Diabetes Mellitus

Before transplantaion:

- It is important to assess glycaemia in all potential LT candidates and to optimise the management of patients who show unsatisfactory glycaemic control.
- Several issues need to be taken into account when considering pharmacological treatment of pre-LT DM, such as the development of side effects, the risk of hypoglycaemia, and potential limitations due to the presence of acute kidney injury.
- In patients with Child-Pugh class C, the use of non-insulin agents should be avoided and insulin remains the only safe treatment option

Diabetes Mellitus

After Liver transplantation:

- The prevalence of new-onset DM ranges between 13% and 28% in the first 3 years after surgery.
- DM severely affects the prognosis of LT recipients, with higher 10-year mortality, infection rates and cardiovascular events.(*Bhat V etal., 2018*)
- Male gender, ethnicity, family history and hepatitis C are well-identified risk factors for the development of posttransplant DM. (*Delgado –Borrego A 2004*)
- Oral hypoglycemic drugs are first tried and when therapeutic goals are not achieved or symptomatic metabolic decompensation is present, insulin remains the therapy of choice

Obesity

Before Transplantation:

- Nearly 95% of patients with morbid obesity (BMI >40 kg/m2) present with MAFLD, (*Sasaki A etal., 2014*)
- Obese patients with MAFLD are often affected by sarcopenia and myosteatosis, which can negatively affect waiting list mortality and post-LT outcomes. (*Czigany Z etal., 2020*)
- In patients with ESLD, a linear association has been described between high BMI and high rates of clinical decompensation, independently of the aetiology of liver disease

Obesity

Before Transplantation:

- Obesity represents a relevant challenge in the LT setting, as it can make the procedure technically difficult, with potentially high rates of complications.
- These considerations led to several transplant centres applying specific BMI thresholds and weight loss requirements for LT candidates
- Weight reduction before LT is mandatory through behavioural therapy ,diet regimen drugs and exercise.

Obesity

After Liver transplantation:

- Weight gain tends to increase progressively over time, with reported obesity rates of 33.7% and 40.3% at 1- and 5-years post-transplant, respectively. (*Richard J etal.,2005*)
- Identified risk factors for post-LT obesity include age >50 years, pre-LT obesity and NASH as the indication for LT
- Post-transplant obesity can lead to complications, such as the development of DM, graft steatosis, and de novo malignancies

Obesity

After Liver transplantation:

- Lifestyle modifications and a low calorie diet represent the cornerstone of weight gain prevention after LT.
- Moreover, supervised physical activity is considered safe after LT in stable patients and effective for glucose homeostasis, which could be particularly beneficial in patients transplanted for MAFLD/NASH-related liver disease
- When indicated, bariatric surgery can be a therapeutic option; In the setting of LT, sleeve gastrectomy is always preferable to Roux-en-Y gastric bypass, not only because of potential malabsorption of immunosuppressive drugs, but also the inaccessibility of the gastric remnant in case of gastric bleeding or if endoscopic access to the biliary tree is required (*Diwan TS etal., 2018*)

Obesity

After Liver transplantation:

- More recently *endoscopic bariatric therapy* has emerged as a potential approach for obese patients with MAFLD. This includes such as intragastric balloons, endoscopic sleeve gastroplasty, endoscopic small bowel by-pass and duodenal mucosal resurfacing
- Available data suggest that intragastric balloons induce rapid short-term weight loss,, whereas endoscopic sleeve gastroplasty leads to stable long-term excess body weight loss (*Salomone F etal.,2020*)

Dyslipidaemia

- Dyslipidaemia is common in the post-LT setting, with a prevalence rate ranging between 45% and 71%
- Hypertriglyceridaemia is more frequent in the early period, whereas hypercholesterolemia seems to increase later, with 30% of patients presenting with elevated cholesterol levels 1 year after LT (*Fussner LA etal 2015)*
- Immunosuppressive therapy ,DM, obesity and genetic predispositions, represent the principal determinants of post-LT dyslipidaemia
- Compared to the pre-transplant setting, dyslipidaemia developing after LT is usually refractory to dietary interventions, so a pharmacological approach is used

Other Medical complications

Cardiovascular:

- Patients with MAFLD are at higher risk of cardiovascular events compared to those without MAFLD.
- In patients with ESLD, severe peripheral vasodilatation can mask myocardial dysfunction, so-called cirrhotic cardiomyopathy, rendering pre-LT cardiovascular risk stratification difficult
- Increase in cardiovascular-related 1-year mortality after LT in patients with MAFLD vs. patients transplanted for alcohol-related liver disease (26% vs. 8%) *Rachwan etal.,2020*

Kidney Dysfunction

- Recent studies have estimated that pre-LT CKD is significantly and independently associated with post-LT mortality
- Moreover, it has been demonstrated that NASH is an independent predictor of CKD *(Fussner etal.,2015)*
- A recent study based on the UNOS database showed that NAFLD/NASH-cirrhosis is the most rapidly growing indication for simultaneous liver-kidney transplant in the United States, whereas kidney graft outcome was 1.5-fold inferior to other indications (*Singal etal 2016*)
- Specific strategies in post-LT management should be reserved for patients with NASH who present with CKD at LT. (immunosupression strategy)

MAFLD as indications for LT

- The prevalence of MAFLD as an indication for LT for both ESLD and HCC has significantly increased both in Europe and in the United States.
- MAFLD is now the second most common etiology of chronic liver disease among individuals listed for LT in the United States
- Remarkably, during the past 10 years, the prevalence of NAFLD as an indication for LT has increased by 170%. During the same period, hepatitis C virus (HCV) and alcoholic cirrhosis as an indication for LT only increased by 14% and 45% respectively (*Wong etal)*

- In the years to come, MAFLD will probably become the **leading indication for LT** because of:

(1) the worldwide increasing prevalence of MAFLD paralleling the increasing prevalence of MS, diabetes and obesity;

(2) the absence of a valid noninvasive diagnostic tool to allow the early diagnosis of the disease leading to the under recognition of MAFLD before the cirrhotic stage;

(3) the absence of therapies that can effectively prevent disease progression;

(4) the new direct-acting antiviral era and the possibility to cure HCV resulting in a stabilization or in a decreasing of the number of cases of HCV-related ESLD.

Outcome of MAFLD on patients on waiting list for LT

- Globally, patients with MAFLD on the waiting list for LT are older, have higher body mass index (BMI), higher prevalence of type 2 diabetes, metabolic comorbidities and lower glomerular filtration rate.
- While on the waiting list, If patients with morbid obesity have a higher model for end-stage liver disease (MELD) score, they are less likely to be transplanted because usually they need treatment of comorbidities
- Second, if listed with a MELD score of less than 15, MAFLD patients seem to have a longer waiting list period because of a slower disease progression rate.

Impact of MAFLD on potential Donor pool

- Recent data based on expected demographic trends in the United States and past donor utilization indicate a further exacerbation of the donor shortage for LT.
- Assuming the actual trends in the prevalence of diabetes and obesity, it has been estimated that the overall liver graft utilization in 2030 will fall from 78% to 44% (*Orman etal 2013*)
- The prevalence of biopsy-proven MAFLD among potential living donors ranged from 15% to 53% in different studies and disqualified 3%–21% of potential liver grafts (*Menirvini etal 2009*) although it needs more assessment

- Several strategies have been developed to optimize results when using fatty liver grafts: shortened ischemia time, ischemic and pharmacological preconditioning of liver grafts to improve microcirculation and mitochondrial function.

Lastly but not last

- The current results of LT in general are excellent, with 1-, 3-, and 6-month survival of 94%, 91%, and 88% respectively.
- The critical period after LT is the first 6 months with 49% of deaths and 65% of retransplantations occurring during this time interval *(Charlton etal 2011)*
- Obesity, type 2 diabetes and CV morbidities are frequently associated with MAFLD and may also have a negative impact on short and long-term outcomes after LT.

THANK YOU

Mansoura liver transplantaion team

940 cases LDLTx (2004-2022)