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Practice guidelines

Managing diabetes and liver disease association: Practice guidelines from the Egyptian Association for the Study of Liver and Gastrointestinal Disease (EASLGD)

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Preamble

In September 2013 a working group of outstanding experts in the field of hepatology, diabetes, nutrition, pharmacology, and specialist in EBM has participated in the development of evidence-based guidelines for management of diabetes and liver disease association. A preliminary report has been published before. The working group and the Egyptian Association for the Study of Liver and Gastrointestinal Disease (EASLGD) joined in revising and updating the work. Updates, revisions, and criticism were received in 2016–2017 and a final practice guidelines were presented during 2017 board meeting.

A narrative review had been prepared before and this related consensus-based practice guidance are based on a formal review and analysis of the recently published world literature on the topic (Medline search up to September 2017) and the experience of the authors and independent jury, reviewers and advisory board.

One of the main aims of this work is to highlight the unique issue of "diabetes associating liver disease" and to start considering it as a separate type of diabetes like gestational diabetes.

Common abbreviations: DM: Diabetes mellitus, CLD: Chronic liver disease, HOMA/IR: Homeostasis Model Assessment of Insulin Resistance, IR: Insulin resistance, NAFLD: Non alcoholic fatty liver disease, NASH: Non alcoholic steatohepatitis, T1 DM: Type 1 DM, T2 DM: Type 2 DM, HD: Hepatogenous diabetes, HCC: Hepatocellular cancer, SVR: Sustained virologic response, DAAs: Direct- acting antiviral agents, HCV: Hepatitis C virus infection.

Subtopics

1- Causes of Diabetes associating liver diseases.
2- Criteria for diagnosis and tools to measure long-term glycaemic control of diabetes associating liver disease.
3- The clinical impact of diabetes associating liver disease.
4- Treatment of diabetes associating liver disease.
5- Management of liver disease associated with diabetes.
6- Other associations between diabetes and liver disease.

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Causes of diabetes associating liver diseases

1- There is a strong association between liver diseases and diabetes that is higher than expected by a chance of association of two very common diseases.
2- Patients with T2DM should be screened for NAFLD, as it is accompanied by higher insulin resistance and worse metabolic profile.
3- Screening for HD especially in chronic HCV patients is recommended owing to its increased incidence and its negative effect on liver disease progression.
4- In spite of their rarity, glycogenic hepatopathy should be considered in the differential diagnosis of hepatomegaly with elevated liver enzymes in T1DM patients. Diabetic hepatosclerosis should be taken into account in the differential diagnosis of cholestasis in DM.

Criteria for the diagnosis of diabetes associating liver disease

5- Two-hour blood sugar level post glucose load is a better screening test for HD owing to the fact that fasting glucose could be normal early in the disease.
6- In patients with compensated liver disease, HbA1c may be suitable for blood sugar control. In decompensated liver condition, fructosamine may be more suitable. Frequent self-monitoring of blood glucose or continuous glucose monitoring may be suitable for the advanced liver condition.

The clinical impact of diabetes associating liver disease

7- The risk of cardiovascular and retinopathic complications is low in HD in comparison to DM types 1 and 2.
8- The term cirrhotic cardiomyopathy although present and proved clinically especially after liver transplantation and transjugular intrahepatic portosystemic shunt (TIPS), yet there is no specific diagnostic test or line for treatment.
9- Patients with T2DM should be assessed for NAFLD and vice versa to ensure early diagnosis and medical care to prevent and minimize the occurrence of NASH, DM, macro and microangiopathies.
10- Aggressive treatment of classical cardiovascular risk factors is advisable in T2 DM patients with NAFLD.
11- Studies are needed to show an independent hepatic contribution to the increased CVD risk in NAFLD and whether treatment of NAFLD will ultimately prevent or slow the development and progression of CVD.
12- Patients infected with HCV should be screened for metabolic disorders. When confounding risk factors are present (IR, DM, hypertension, >55 years old, severe liver fibrosis or steatosis), monitoring for increased risk of CAD, atherosclerosis or stroke is mandatory.
13- Awareness about the fact that T2DM is a significant risk factor for liver injury may improve diagnosis and interventions to minimize the progression of chronic liver disease.
14- DM is associated with poor patient survival in those with chronic liver diseases, either through acceleration of liver fibrosis with subsequent progression to cirrhosis and HCC or through increased risk of infections with its sequel in cirrhotic patients.
15- Glycaemic control was a predictor of SVR in the interferon-based therapy of HCV but not with DAAs. SVR is associated with improvement of diabetic control.
16- Insulin resistance has a strong impact on the development of HCC and HOMA-IR is an important biomarker for its prediction particularly in non-cirrhotic HCV patients.

Treatment of diabetes associating liver disease

17- Treatment of DM associating liver disease appears to have significant clinical impact. We have to define the target HbA1c and assess the degree of decompensation of the liver together with the associated comorbidities.
18- Medical nutrition therapy (MNT) and lifestyle modifications will avoid an exponential increase in the prevalence of DM and uncontrolled diabetics with serious complications and prevent increase in liver disease morbidities.
19- Assessment of nutritional status in cirrhotic patients by Subjective Global Assessment (SGA) and anthropometric measurements is necessary. Patients should be educated regarding nutrition (frequent small feedings and carbohydrate-rich bedtime snacks). Prolonged fasting periods should be avoided.
20- The recommended diet plan for liver cirrhosis patients includes 25–40 Kcal/kg body weight/day, and proteins in amount of1.2–1.5 g/kg/day (for medically refractory hepatic encephalopathy: 0.6–0.8 g/kg/day).
21- Regarding micronutrients fat-soluble vitamins are recommended for all patients with compensated liver disease, folic acid and thiamine for patients with a history of alcohol abuse and sodium restriction for patients with ascites and oedema.
22- Metformin, if tolerated and not contraindicated, is recommended as first-line therapy for patients with diabetes and CLD.
23- If hepatic disease is severe, insulin secretagogues should be avoided because of the increased risk of hypoglycaemia.
24- Dipeptidyl peptidase-4 inhibitors (DPP-4 Is) showed effectiveness and safety in the treatment of T2DM complicated with HCV with chronic liver disease in patients with up to Child B stage.
25- Newer pharmacologic treatments for T2DM, Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT-2 Is), have not been widely used in patients with CLD. They are worthwhile, exhibit positive effects on weight, and are associated with minimal risk of hypoglycaemia.
26- Insulin must be used with caution, as hypoglycaemia may be a problem. Insulin analogues are preferred in the context of hypoglyacemia. Insulin doses need to be frequently adjusted in patients with CLD.
27- Insulin or insulin secretagogues antidiabetic oral agents are associated with an increased risk of HCC, while in metformin and thiazolidinediones treated patients the risk is reduced.
28- Metformin, thiazolidinediones, and statins can inhibit the development of hepatic fibrosis, improve liver biochemistry and histology, and protect against steatohepatitis and hepatic fibrosis in patients with T2DM. It is suggested to have a protective role against HCC in such patients.
29- In patients with NAFLD and NASH statins can be used to treat dyslipidaemia, lacking the evidence of increased risk for drug-induced liver injury.
30- Ezetimibe could be used in patients affected by both NAFLD and dyslipidaemia, having a clinical benefit and adequate safety profile.
31- In patients with NAFLD and NASH, the use of angiotensin II receptor antagonist for hypertension is safe and beneficial.
32- Early erectile dysfunction screening for diabetic men associated with liver disorders is recommended, and should be associated with screening of neuropathy, retinopathy, and nephropathy. HBA1c control is important as well as change lifestyle, cessation of smoking, and avoidance alcohol and anabolic steroids.

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Management of liver disease associated with diabetes

33- The inclusion of DM in the currently used liver cirrhosis scores (Child-Pugh and MELD scores) may enhance the sensitivity and the specificity for prediction of morbidity and mortality rates in cirrhotic patients.
34- A clear differentiation between pre-existing diabetes and HD should be made when assessing the added risk of diabetes on cirrhosis mortality and morbidity.
35- Pioglitazone appears to have beneficial effects on NASH histology. Metformin is safe and has been shown to improve the metabolic derangements associated with NAFLD with no significant improvement in liver histology. GLP-1 analogs are increasingly showing promising results.
36- It is recommended to follow up lipid profile (rebound increase in the lipid profile after clearing HCV by DAAs) and blood sugar levels following SVR in order to adjust doses of medications used in diabetic and dyslipidaemic patients.
37- Direct antiviral agents should be prescribed only after revising all types of medications used by the patient. Checking for drug interactions prior to treatment is mandatory.

Other associations between diabetes and liver disease

New onset diabetes mellitus after liver transplantation (NODAT)

38- Two subtypes of newly diagnosed diabetes after transplantation could be studied separately; temporary (1–6 months) and persistent (>6 months) types.
39- A formal diagnosis of newly diagnosed diabetes after transplantation is best made when patients are stable on their maintenance immunosuppression, with stable graft function and in the absence of acute infections (After 3 months by most authors).
40- Protocoled follow up and surveillance for metabolic syndrome and its components should be strictly followed to avoid morbidity due to cardiovascular events and mortality due to graft loss and serious infections in such immunosuppressed patients.

HBV and diabetes mellitus

41- All diabetic patients should be vaccinated against HBV.
42- No matter whether HBV is related to a higher incidence of diabetes and/or NAFLD; those patients need higher medical attention. Improve diabetic control should be part of the surveillance protocols of HBV patients.
43- In adults with HBV infection, DM is associated with the progression to more severe liver outcomes, including cirrhosis, HCC and death.

Further reading

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