Managing Diabetes and Liver Disease Association, Guidelines (Consensus) Development

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Abstract

The issue of association between DM and liver disease is growing all over the world. The association between DM and liver disease has relevance to diabetologists, hepatologists, and primary care physicians. Association between these two common diseases (statistical association) is well known, in addition, liver disease associated with DM can be divided into three groups: 1- Liver disease occurring as a consequence of DM: Most important is NAFLD. Vicious circle appears linking fatty liver to DM and DM to progressive liver injury. 2- DM occurring as a complication of liver disease: Hepatogenous diabetes (HD) caused by liver cirrhosis and chronic hepatitis c. 3- Liver disease occurring coincidentally with DM. The Criteria for diagnosis of DM associating liver disease are the same as for the ordinary primary diabetes, taking into consideration the clinical & laboratory differences from the primary T2 DM. In patients with compensated liver disease, HbA1c may be suitable for long term glycemic control. In those with de-compensated condition, an alternative parameter as fructosamine or frequent glucose monitoring is more suitable.

Apart from the increased cardiovascular risk in patients with T2 DM and NFLD, cardiovascular and retinopathic risk is low in HD. An association between chronic HCV infection, atherosclerosis, coronary artery disease and stroke has been reported.

The clinical impact of DM in a hepatic patient is of utmost importance: DM promotes fibrosis progression, affect survival by increasing the risk of hepatocellular failure & variceal bleeding, impairs SVR to antiviral therapy in patient with chronic hepatitis c, and increased incidence of HCC in subjects with HCV.

Basic treatment of diabetes in patients with liver disease includes:
- A sufficient daily energy and protein supply (cirrhotics are malnourished).
- Therapy begin with Oral hypoglycemic with rapid advancement to insulin if blood sugar control is not achieved, transaminasis > 2 folds normal or occurrence of cirrhosis.
- The risk of hypoglycaemia must be considered under pharmacological treatment.
- Suitable oral antidiabetics are insulin sensitizing agents and short-acting insulin secretagogues.

A- Causes of Diabetes association with liver diseases.

B- Criteria for diagnosis and tools to measure long term glycemic control of diabetes associating liver disease.

C- Clinical impact of diabetes associating liver disease.

D- Treatment of diabetes associating liver disease.

E- Management of liver disease associated with diabetes.

F- Other associations between diabetes and liver disease.

A- Causes of Diabetes association with liver diseases

The liver is a central player in buffering plasma glucose contributing either by net hepatic glucose utilization or net hepatic glucose production depending on the plasma glucose level exceeding or falling below the normal level [1].

CLD are common in Egypt as HCV infection alone has a prevalence of 15% [2], also DM has a prevalence of 20% in adult Egyptians [3]. Association between these two common diseases (statistical association) is well known, however, the overall prevalence of association is significantly higher than that expected by a chance association of two very common diseases.

Liver disease associated with DM can be divided into three groups [4]:

1. Liver disease occurring as a consequence of diabetes mellitus
   - Glycogen deposition
   - Steatosis and NASH
   - Fibrosis and cirrhosis
Biliary disease, cholelithiasis and choledochitis
- Complications of therapy of DM (cholestatic and necroinflammatory)

2. DM occurring as a complication of liver disease
- Hepatitis
- Cirrhosis
- HCC
- Fulminant hepatic failure
- Post liver transplantation

3. Liver disease occurring coincidentally with DM
- Hemochromatosis
- Glycogen storage diseases
- Chronic active autoimmune hepatitis
- Autoimmune biliary disease

Nonalcoholic fatty liver disease (NAFLD)

NAFLD is emerging as the most common chronic liver condition in the Western world. It is associated with IR and frequently occurs with features of the MS and strongly associated with T2DM [5]. There is a very high prevalence of NAFLD (>55%) in individuals with T2DM [6]. Also T2 DM is present in 30%-45% of patients with NASH [7].

NAFLD is more frequent among obese (76%), and it is almost universal among diabetic people who are morbidly obese [8]. NASH is present in 50% of severely obese people with diabetes [9].

Clinical evidence that fatty liver plays a role in the development of T2D

NAFLD could be linked to the development of T2DM in predisposed individuals through longstanding hepatic IR and studies have shown an association between fatty liver and altered glucose tolerance/diabetes alone or in the setting of MS, as these conditions have IR as a common pathophysiological mechanism. NAFLD and T2DM association is found in cross-sectional [10,11] and confirmed by prospective studies [12]. NAFLD is associated with IR rather than with impaired β-cell viability, [11] implying that the development of T2D will not occur other than in the presence of a genetic predisposition.

Knowledge of subsets of NAFLD patients particularly prone to develop T2DM is critical in envisaging strategies of prevention. In this regard, it is NASH rather than pure fatty liver that is associated with T2DM [13] and that those with prediabetes, elevated glutamyl transpeptidase and triglycerides and insufficient physical activity are the patients more in need of specific interventions to prevent T2DM [14].

Patients with T2DM and steatosis have substantially more IR than those without steatosis; they also have more dyslipidemia and circulating inflammatory markers [15].

NAFLD in Non-obese

The prevalence of NASH is 3% and 20% in nonobese and obese subjects, respectively. Additionally, the prevalence of NASH associated with both cirrhosis and HCC was reported to be high among patients with T2DM with or without obesity [5].

NAFLD was associated with risk for components of MS and the association was stronger in non-obese than in obese individuals, especially in women [16].

IR and systemic inflammatory response (increase in CRP) are of key importance for inducing NAFLD in apparently healthy non-obese men [17].

NAFLD is very frequent in nonobese diabetics with type 2 but not type 1 disease, and it is associated with hepatomegaly and liver hemodynamic alterations only when it is severe [18].

Hepatogenous diabetes (HD)

HD is diabetes developed as a complication of Cirrhosis [19]. Up to 96% of patients with cirrhosis may be glucose intolerant and 30-60% suffers from HD [20]. Pathophysiology of HD is complex and not precisely known, however IR (hepatic, muscular and adipose tissues), progressive inadequate response of the islet β-cells, as well as hyperinsulinemia, seem to be the pathophysiologic bases for HD [21]. Serum insulin levels are higher in diabetics with CLD than those with lifestyle-related DM [22]. Reduced insulin extraction by the damaged liver and portosystemic shunts result in hyperinsulinemia, which is potentiated by raised levels of contra-insulin hormones [21]. HD can develop whatever the etiology of CLD. Clinical manifestations of HD in the early stages of cirrhosis are virtually absent i.e. subclinical, since FBS levels may be normal and only IR (detected by HOMA/IR) and glucose intolerance (detected by OGTT) may be observed. As liver disease advances, diabetes becomes clinically manifest, therefore HD may be considered as a marker for liver function deterioration [23]. IR is present in 30-70% of individuals with CHC. It can occur early in the course of HCV infection [24]. The prevalence of DM was about 33% in non-cirrhotic patients with CHC, compared with 5.6% in a control group. Egyptian studies showed that DM is more prevalent in patients with HCV and it has been found that the prevalence of DM is 25% among HCV patients of Egypt [25,26]. The mechanisms by which HCV produces IR and DM are not clearly known. HCV induces IR regardless of the BMI and the fibrosis stage. The possible mechanism (Fig 1) is through HCV core protein, TNF-α overproduction, serine phosphorylation of insulin receptors and over expression of SOCs. SOCS-3 inhibits the phosphorylation of Akt and P13K resulting in IR. Genotypes 1 and 4 are significantly associated with IR more frequently than genotypes 2 and 3 [27].

Diabetes alone leads to liver disease

Glycogenic hepatopathy (GH): The key finding in GH, a rare condition in T1DM is glycogen accumulation in the liver causing hepatomegaly and elevated liver enzymes. This is caused by wide fluctuations in both high serum glucose and injected insulin levels [28,29].

In Egypt, GH was diagnosed in 3 cases by liver biopsy in a cohort of 629 children with T1DM [30].

An important differential diagnosis is NAFLD, which can
develop in both type 1 and type 2 DM. Persistent and relatively mild disturbances in liver enzymes favor NAFLD, whereas transaminases flares are more compatible with GH, a final distinction can only be made with a liver biopsy. It is important to distinguish both conditions as NAFLD can progress to cirrhosis whereas in GH liver fibrosis does not develop [31].

On the other hand in a large recent study; higher risk for liver disease has been found among patients with T2DM, known as diabetic hepatopathy. It remains to be determined whether this reflects nonalcoholic fatty liver disease or direct glycemic injury of the liver. Annual screening for liver disease in patients with T2DM might be advised [32].

Evidence based guidelines and recommendations:

1- The association between liver disease and DM is well known, the overall prevalence being significantly higher than that expected by a chance association of two very common diseases. (Level 2)

2- Hepatogenous diabetes (HD) is diabetes developed as a complication of liver cirrhosis what ever its cause. (Level 1)

3- A high incidence of diabetes is present in patients with HCV, even in the absence of cirrhosis. Liver cirrhosis and CHC cause HD. (Level 1)

4- Insulin resistance and hyperinsulinemia are the main pathophysiological bases of hepatogenous diabetes. (Level 2)

5- NAFLD plays a role in the development of type 2 diabetes. Insulin resistance and systemic inflammatory response are of key importance for inducing NAFLD/diabetes; this is even more in apparently healthy non-obese men. (Level 2)

6- Glycogenic hepatopathy (in type1 DM) is a rare condition and coming from a case series only (level 4)

B- Criteria for diagnosis and tools to measure long term glycemic control of diabetes associating liver disease

The Criteria for diagnosis of DM associating liver disease and also prediabetes are the same as for the ordinary primary diabetes [33]. Fasting and 2 hour post 75g glucose blood sugar levels are required for diagnosis, the same as in those without CLD. However, the glycated haemoglobin (HbA1C) is unreliable for diagnosis in patients with cirrhosis [34]. The diabetes associating liver disease in Egypt appears as an optimal condition for screening [35].

Differentiation of HD from primary DM: [36]

HD has particular clinical characteristics:

(1) Unlike the typical T2 DM, it is less frequently associated with risk factors such as age, body mass index, and family history of diabetes.

(2) Lower risk of macro- and micro angiopathic complications

(3) It is more frequently associated with hypoglycemic episodes as a result of impaired liver function.

(4) Moreover, the time at diagnosis of both DM and liver disease is crucial in differentiation.

Clinical manifestations of HD in the early stages of cirrhosis are virtually absent. Studying compensated cirrhotic patients with normal fasting serum glucose and without a family history of type 2 DM have showed that up to 77% had DM or glucose intolerance diagnosed by means of OGTT.

As liver function deteriorates the incidence of DM increases. The ratio of 2hPP / FPG, fasting insulin and HOMA-IR index were significantly higher in HD than the primary T2 DM.

Zhang X, et al [37] found that (Table 1):

1) No diabetic symptoms among any of the post hepatitis or cirrhotic patients with GI or diabetes compared with cases of primary DM with liver dysfunction.

2) The levels of FPG and PPG in chronic hepatitis patients with hepatogenic IGT and DM were lower than those in the patients with primary DM (P<0.05), but the levels of plasma insulin and plasma C peptide were higher (P<0.05).

Tools to measure long term glycemic control

1- HbA1C:

In patients with chronic liver disease HbA1C levels are frequently falsely low, limiting the utility of A1C measurement as a diagnostic test and monitoring tool [39]. It should be avoided if shortened RBCs half life is probable to occur, as hemolysis after ribavirin treatment, which was found to reduce RBCs life span from 120 to 40 days [40]. The same applies if hypersplenism [41] is suspected, or if there is blood loss due to GIT haemorrhage.

2- Fructosamine (FA):

It is measured by spectrophotometric assay which may be affected by hypertriglyceridemia, hyperbilirubinemia, hemolysis, and low serum protein and albumin levels [42]. FA is apparently higher in liver cirrhosis patients with diabetes, due to prolonged half life of serum albumin and reduced rate of synthesis (39). Although correcting FA results for serum albumin was suggested, there is no consensus for this [43].

FA is unaffected by disorders of red blood cells and has the advantage of accurately reflecting shorter-term changes in glycemia that correspond to the half-life of albumin [44]. It estimates the average of blood glucose over the previous 2 weeks.

3- Frequent Self Monitoring of Blood Glucose (SMBG):

Repeated SMBG may reflect short term glycemic control, especially if timed to be pre-prandial and 2h post-prandial. Downloading SMBG readings in the form of glycemic curves on a computer may be of help for following glycemic control. However this method again does not reflect long term glycemic control and requires patient education and empowerment. Repeated SMBG was found to be of limited clinical effectiveness, not cost effective, but may be only of help when a well educated patient is able to...
Table 1: Hepatogenic vs. primary diabetes.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Post hepatic DM</th>
<th>DM with Liver Cirrhosis</th>
<th>Iry DM with liver dysfunction</th>
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<tbody>
<tr>
<td>F&amp;PP Blood Sugar</td>
<td>Lower</td>
<td>Absent</td>
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<tr>
<td>F&amp;PP insulin &amp; c-peptide</td>
<td>↑</td>
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<td>Islet cell antibody Positivity</td>
<td>++</td>
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Evidence based guidelines and recommendations:

1. Until we have more RCT, we can use Fasting and 2 hour post 75 g glucose blood sugar but not Hba1c in diagnosing HD, taking into consideration the clinical & laboratory differences from the primary T2 DM. (Level 3)

2. In patients with compensated liver disease without evidence of shortened RBCs half life, Hba1c may be a suitable tool for blood sugar control. An alternative parameter in decompensated liver condition, as fructosamine or glycated albumin should be advised, provided that serum albumin levels are within normal range. (Level 4)

3. Suggested composite parameter termed liver cirrhosis Hba1c” (47), calculated as [measured Hba1c + glycated Albumin/3] x 1/2.

Evidence based guidelines and recommendations:

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3. Suggested composite parameter termed liver cirrhosis Hba1c”, calculated as [measured Hba1c + glycated Albumin/3] x 1/2 is suggested as a tool for monitoring blood sugar control. (Level 4)

4. Daily SMBG or CGM may be suitable for monitoring advanced liver condition. However this needs proper education of highly empowered patients and represents a financial burden on health care systems. (Level 2)

Recommendations

- Screening for HD especially in chronic HCV patients may be recommended owing to its increased incidence, its negative effect on liver disease progression, feasibility of testing and availability of treatment.

- Owing to the fact that fasting glucose could be normal early in the course of HD, 2h post glucose load is a better screening test.

- Further studies are recommended to test the validity of other tests in HD such as fasting serum insulin, HOMA IR and islet cell antibody test.

C. Clinical impact of diabetes associated liver disease.

Cardiovascular and retinopathic risk is low in hepatogenic diabetes: Hepatogenous diabetes differs from T2DM in that the cardiovascular and retinopathic risk is low [48]. The lower incidence of retinopathy and cerebrovascular disease in diabetes associated with liver cirrhosis may be explained by the protective effects of low serum level of lipids, lower levels of serum Lp(a), decreased coagulation function and thrombocytopenia associated with liver cirrhosis [48,49]. Another possible explanation may be the lower prevalence of hypertension with diabetes in patients with cirrhosis [50].

In patients with T2DM and NAFLD, there is significantly higher prevalence of cardiovascular, cerebrovascular and peripheral vascular diseases than in those without NAFLD [51,52].

Also an association between chronic HCV infection, atherosclerosis, coronary artery disease and stroke has been reported [53], as HCV infection is known to promote immune stimulation, cytokine production, and chronic inflammation [54,55]. Patients with HCV infection were demonstrated to have higher TNF-α levels and a higher risk of cardiac failure and death than patients without HCV infection [56]. Mostafa et al, found a more pronounced intima-media thickness in HCV-positive patients than controls [57]. Cytokine imbalance has also been associated with development of IR in HCV-infected patients. A high TNF-α/adiponectin ratio has been found correlated with IR and atherosclerosis development [58]. Besides the role of HCV in the development of chronic inflammation involving the arteries, HCV RNA sequences and intermediate replicative forms have been detected within carotid plaques, thus suggesting in situ viral replication and consequent local pro-atherogenic action [59,60].

HCV related steatosis can be considered a cardiometabolic risk factor through features of the MS. Indeed, like steatosis, HCV viral load has been found to be independently associated with carotid atherosclerosis. Atherosclerosis was shown to be independently associated with elevated systemic inflammatory markers, such as C-reactive protein and fibrinogen [53].

Cirrhotic Cardiomyopathy

Cirrhotic cardiomyopathy is a clinical syndrome in patients with liver cirrhosis characterized by an abnormal and blunted response to physiologic, pathologic, or pharmacologic stress abnormalities in the absence of other known cardiac disease, but normal response to increased cardiac output and contractility at rest. The development of heart failure and pulmonary...
hypertension occurs after rapid increase in venous return after transjugular intrahepatic portosystemic shunt or liver transplantation, it is distinctively viewed as a high-output heart failure. As many as 50% of cirrhotic patients undergoing liver transplantation show signs of cardiac dysfunction, and 7% to 21% of deaths after orthotopic liver transplantation result from overt heart failure [61-63].

The Clinical Impact of Diabetes Association with liver Disease:

Prognosis is mostly related to Liver disease, affected by comorbidities of associating diabetes (IR & Steatosis):

1- Promotoin of Liver Fibrosis

Diabetes plays a role in the initiation and progression of liver injury. People with T2DM have a higher prevalence of and higher mortality rates from liver-associated disease than the non-diabetic population of equivalent age [64].

In NAFLD, T2DM is an independent predictor of fibrosis, faster fibrosis progression, and increased mortality. Hyperglycemia and hyperinsulinemia may stimulate the proliferation of hepatic stellate cells producing connective tissue growth factor then induces production of collagen. Adipokines, such as leptin and tumor necrosis factor, activate inflammatory pathways that may exacerbate liver injury. Also in HCV, hyperinsulinemia, hyperglycemia, and insulin resistance have all been associated with more severe fibrosis. Patients with hyperglycaemia had higher histological fibrosis stages and progression rates, and had steatosis more frequently than patients with normal serum glucose. Possible mechanisms by which hyperglycemia may contribute to fibrogenesis are:

- Increased formation of advanced glycation end products, that interacts with receptors in hepatic stellate cells with induction of profibrogenic cytokine like connective tissue growth factor.
- Increased OS which, in turn, induce key inflammatory cytokines such as TNF-α and IL-6.

Alternatively, IR rather than hyperglycaemia may be linked to necroinflammatory lesions and hence fibrogenesis. A correlation between IR and fibrosis progression was demonstrated in patients with HCV whether diabetic or not. Also a statistically significant relationship between IR and a higher amount of liver fibrosis and steatosis was shown in another study [65-68].

2- Affect survival by increasing the risk of hepatocellular failure & variceal bleeding.

Two major pathways can contribute for diabetes worsens the clinical course of liver cirrhosis; firstly, DM accelerates liver fibrosis and inflammation as previously mentioned giving rise to more severe liver failure. Secondly, DM may potentiate the incidence of bacterial infections in cirrhotic patients with associated increase in encephalopathy, variceal bleeding, and spontaneous bacterial peritonitis, subsequently increase mortality [69].

The gut microbiota play a key role in chronic inflammatory disease of the liver through a central hypothesis; whereby microbiota products activate the innate immune system to drive pro-inflammatory gene expression thus promoting chronic inflammatory disease of the liver [70].

In NAFLD models, the translocation of bacterial components such as lipopolysaccharide promotes TNF-a release from Kupffer cells and induces hepatic inflammation through TLR4 and TLR9 signaling [71,72].

3- Glucose intolerance impairs sustained response rate to antiviral therapy in patients with chronic hepatitis C.

Hepatic steatosis and insulin resistance are negative predictors (Figure 1,2) for SVR in patients with CH-C treated with peg-IFNα plus ribavirin combination therapy [73].

Manuel Romero-Gomez, et al [74] showed that altered glucose metabolism impairs sustained response to viral treatment while SVR reduces the risk of impaired fasting glucose and/or T2DM development in patients with CHC. HCV core protein (Figure 2) induces expression of TNF-α, which in turn activates SOCS-3, (the cause of IR- Figure 1) which leads to inhibition of Tyr-phosphorylation of signal transducers and activators of transcription 1 (STAT-1) translocation and interferon stimulated genes production, avoiding the antiviral effect of interferon [75].

Indices of insulin resistance including HOMA-IR and whole-body insulin sensitivity index (WBISI) were tested as predictors for SVR. WBISI show higher specificity in prediction of SVR than HOMA-IR [76].

4- Subjects with Hepatitis C virus infection plus diabetes mellitus have an increased risk of hepatocellular carcinoma

A strong association between chronic HCV infection and HCC has been observed [77]. There has been nearly a twofold increase of the proportion of HCC among CLD patients in Egypt in the last few years, with a significant decline of HBV and slight increase of HCV as risk factors [78].

DM is highly suspected to be associated with an increased

Figure 1 The mechanisms by which HCV produces IR and DM, right side: normal insulin signaling, left: effect of HCV.
risk of HCC [79] and multiple systemic reviews and meta-analyses have also found an association. The risk was increased by approximately 2.2-fold [80-83].

The high prevalence of HCV in Egypt and positive association of HCV with DM; makes Egyptian population prone to increasing incidence of HCC which needs urgent attention.

**Pathogenesis of HCV related HCC**

One theory is that there is an imbalance in the microenvironments and cytokines of livers infected with the hepatitis C virus, leading to increased inflammation and cell turnover, which ultimately causes cirrhosis. Poorly differentiated hepatocytes likely proliferate and develop into dysplastic nodules and HCC [84]. In support of this hypothesis is the observation that HCV-induced HCC correlates well with the degree of inflammation and necrosis, and seems to be caused by inflammation rather than specific oncogene activation [85,86]. By contrast, hepatitis B-related HCC does not correlate as well with inflammation, and there appear to be specific oncogenes induced by the virus.

The host immune response may also be an important factor associated with a risk for progression to cirrhosis and cancer [87].

**Role of Diabetes Mellitus in HCC Causation**

It is unclear how glucose intolerance influences hepatocarcinogenesis. Oxidative stress could be an important factor in hepatocarcinogenesis, also hyperinsulinaemia which acts as a growth factor via the activation of 5’adenosine monophosphate-activated protein kinase [MAPK] [88]. More recent studies suggest that the presence of liver inflammation in the context of DM, leads to the exposure of hepatocytes to increased levels of IL-6 and TNF-α, which promote the activation of JAK/STAT-3 and IKKα (a critical kinase for NF-κB activation) /NF-κB signaling pathways respectively, followed by lack of apoptosis, and consequently uncontrolled proliferation of hepatocytes; this results in initiation and promotion of HCC development. TNF-α induced activation of MAPKs are also significant factors for tumour growth. Further pathway is epigenomic reprogramming that drives hepatocellular transformation [89, 90].

**Diabetes and HCV synergism in HCC causation**

In a prospective study, among 165 HCC patients, T2 DM was more prevalent in HCV subjects compared to HBV or non-HBV, non-HCV cases. HOMA-IR was higher in HCC patients with HCV than in those with HBV infection. In 188 patients with chronic hepatitis C, HCC subjects had higher blood sugar, insulin level and HOMA-IR than those with chronic hepatitis and advanced fibrosis. Based on stepwise logistic regression analysis, HOMA-IR was one of the independent factors associated with HCC development [91]. IR is induced by HCV genotype-4 in Egyptian patients irrespective of severity of liver disease. IR starts early in infection and facilitates progression of hepatic fibrosis and HCC development. [92]

**Evidence based guidelines and recommendations:**

1- Cardiovascular and retinopathic risk is low in hepatogenous diabetes. (Level 3).

2- The term cirrhotic cardiomyopathy although present and proved clinically, yet up till now there is no specific diagnostic test, no specific treatment and also prophylactic measures are not recognized. (Level 4)

3- Diabetes plays a role in the initiation and progression of liver injury. (Level 3)

4- In nonalcoholic fatty liver disease, T2 DM is an independent predictor of fibrosis, faster fibrosis progression, and increased mortality. (Level 2)

5- In HCV; hyperinsulinemia, hyperglycemia, and insulin resistance have all been associated with more severe fibrosis. (Level 2)

6- In patients with chronic liver diseases, diabetes mellitus is associated with poor survival as it carries higher risk of hepatic cell failure and hepatic encephalopathy (Level 2). Also, in such patients there is higher prevalence of bleeding esophageal varices (Level 4).

7- The pathogenesis of DM affecting survival may be related to increased susceptibility to infection specially related to gut microbiota (spontaneous bacterial peritonitis). Also related to increased bacterial endotoxins with subsequent stimulation of TLRs. (Level 3)

8- Glucose intolerance impairs sustained response rate to antiviral therapy in patients with chronic hepatitis C, also it is a strong negative predictor for the response to antiviral treatment if it is one of the component of metabolic syndrome before treatment. (Level 2)

9- The presence of diabetes mellitus almost doubles the risk.
of HCC in patients with HCV through multiple mechanisms. (Level 2)

10- The synergism between DM and HCV in causing HCC is unique to HCV as it is not seen with HBV or other causes of cirrhosis (Level 3).

Recommendation

Further studies are needed to investigate whether such patients with HCV cirrhosis with DM will need a more frequent surveillance for HCC for timely detection when cure is possible.

D- Treatment of diabetes associating liver disease

1- Medical Nutrition Therapy and Lifestyle Modifications for Type 2 DM with Liver Disease

A - Medical Nutrition Therapy (MNT) for Type 2 DM:

1. Nutrition therapy can both improve blood glucose levels and slow the progression of diabetic complications. It must consider personal preferences, life style habits and modified to accommodate growth, aging and any complications that develop [93]. Weight loss is recommended for individuals with BMI > 25.0 kg/m2 [94].

2. Carbohydrates: Recommendation is based on the person’s metabolic needs (which are related to the type of diabetes, degree of glucose intolerance and blood lipid levels), the type of insulin and other medications to manage the diabetes and individual preferences [95]. Less than 130 grams of carbohydrates per day is not recommended because the brain and central nervous system have an absolute requirement for glucose as a source for energy [93].

3. Sugars: Recommendations for people with diabetes are similar to those for the general population which suggest minimizing food and beverages that contain added sugars. It must be counted as part of the daily carbohydrate allowance. Use of fructose as an added sweetener is not advised. Artificial sweeteners (such as aspartame, saccharin and sucralose) contain no digestible carbohydrate and can be safely used in place of sugar [93].

4. Fiber: A variety of fiber containing food such as legumes and fiber rich cereals, as well as fruits, vegetables, and whole grain products are recommended as 14 grams of fibers for every 1000 Kcal [96].

5. Protein: Intake should not exceed 20% of energy intake to safeguard against development of nephropathy [93].

6. Dietary fat: Total intake should not exceed 25% to 35% of total Kcal and saturated fat should not exceed 7%. Intake of trans fat should be minimal [94]. Cholesterol intake should be less than 200 milligrams daily. Two or more servings of cold water fish are recommended per week because fish supplies omega 3 fatty acids [93].

7. Vitamin and mineral supplementation is not recommended unless nutrient deficiencies develop [93].

8. Therapeutic lifestyle changes include a reduction in energy intake and an increase in physical activity. At least 150 minutes per week of moderate intensity aerobic physical activity or at least 90 minutes per week of vigorous aerobic exercise. Activity should be done over at least 3 days per week with no more than 2 consecutive days without physical activity. Resistance exercise three times per week may be also recommended [97].

B - MNT for Viral Hepatitis: The primary objective is to spare the liver and provide it with the nutrients needed for regeneration. Frequent small feedings are generally better tolerated, adequate in energy, proteins and micronutrients with a regular meal schedule. Food restrictions other than alcohol are usually not required [98, 99].

2- Oral hypoglycemic drugs and insulin in treatment of diabetes associating liver disease

The liver is a primary site of drug metabolism and the impairment of drug metabolism is proportional to the liver dysfunction. Furthermore, liver disease can sometimes alter kidney function, leading to accumulation of drugs/metabolites even if they are not eliminated by the liver [100,101]. There are hardly any prospective studies on the safety of drugs in cirrhotic patients [102].

Optimisation of diabetic metabolic conditions is not only important to avoid typical diabetic late complications but also cirrhosis-associated complications. Treatment of diabetes associating liver disease appears beneficial as shown in many studies [103-105].

Basic treatment of Diabetes in Patients with Liver Disease

Therapy begins with oral hypoglycemic with rapid advancement to insulin if blood sugar control is not achieved, transaminasins > 2 folds normal or appearance of markers of cirrhosis. The risk of hypoglycaemia must be considered under pharmacological treatment. Patients should first control their diabetes through diet and lifestyle, subsequently, metformin or other insulin sensitizer (in compensated liver cirrhosis) to counteract insulin resistance and consequent hyperinsulinemia [106]. Suitable insulin secretagogue antidiabetics are glinides (decrease in postprandial glucose & risk of hypoglycaemia, its action is at least in part glucose mediated.) and short-acting sulfonylureas [107,108].

Pharmacology of antidiabetics

1- Sulfonylureas (metabolized in the liver): Glyburide has a short plasma half-life (2-10 hrs) but prolonged biological effect due to the formation of active metabolites.Gliclazide has approximately 50% fewer confirmed hypoglycaemic episodes in comparison with glimepiride.

Glipizide is extensively metabolized by the liver (90%). Its shorter half-life makes it less likely than glyburide to produce hypoglycemia. Glimepiride protein binding is greater than 99%. It is extensively metabolized by hepatic cytochrome enzymes. Approximately 60% of the oral dose is eliminated in the urine within 7 days and 40% is excreted in the feces [109,110].

2- Meglitinides: Both repaglinide and nateglinides are rapidly absorbed upon oral administration, producing peak plasma levels within an hour. Repaglinide is rapidly eliminated
from the blood with a half-life of approximately 1 hour. The pharmacokinetics and tolerability of nateglinide in patients with cirrhosis is not significantly different than in control subjects. Moreover, repaglinide and nateglinide have not been associated with hepatotoxicity [111].

3- α-Glucosidase inhibitors: Acarbose is metabolised exclusively within the gastrointestinal tract [112]. It is particularly useful in liver disease, acting directly on the gastrointestinal tract to decrease carbohydrate digestion and thus glucose absorption, thereby decreasing postprandial hyperglycemia. In cirrhotics there was also a reduction in blood ammonia levels, which paralleled an increase in bowel movement frequency. Acarbose is a safe and effective drug in cirrhotic patients with low-grade hepatic encephalopathy and type 2 diabetes mellitus [113,114].

4- Metformin

Metformin does not undergo hepatic metabolism and is excreted unchanged by tubular secretion and glomerular filtration in the urine [115]. Elimination half-life is prolonged in patients with renal impairment and this correlates with creatinine clearance. As metformin is not metabolized via the hepatic CYP450 system, its pharmacokinetic characteristics do not expose patients to drug–drug interactions [112]. Actually, there are no clinically relevant metabolic interactions reported with metformin [116]. There are only a few reported cases of hepatotoxic side effects for metformin [117], but there may be an increased risk of developing lactic acidosis in the setting of impaired liver function.

5- Pharmacology and clinical aspects of Thiazolidinediones (TZD):

TZD are rapidly and extensively absorbed from the GI tract following oral administration. Food may cause a greater delay in peak plasma levels.

Renal elimination of the TZD pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. Most of an oral dose is presumed to be excreted into the bile either unchanged or as metabolites and eliminated in the feces. Although available clinical data show no evidence of TZD-induced hepatotoxicity or ALT elevations, it is recommended to undergo periodic monitoring of liver enzymes and not to initiate in patients exhibiting clinical evidence of active liver disease or increased serum transaminase levels (ALT more than 2.5 times the upper limit of normal) [118]. PPARα discloses anti-inflammatory property and PPAR discloses anti-inflammatory, antifibrogenic and antiproliferative properties in the liver. Treatment with PPARα agonists results in improved insulin sensitivity via diverse mechanisms, both direct and indirect, and both at the level of the liver and at the level of extrahepatic tissues [119].

Hepatic safety of pioglitazone in more than 20,000 patients with type 2 diabetes mellitus in Japan has been proved. Neither temporal nor dose relations were found between pioglitazone and ALT abnormalities [120].

6- Pharmacology and clinical aspects of Insulin: Liver is a major site of metabolism of circulating insulin [121]. Insulin therapy is probably the safest and most effective therapy in patients with liver dysfunction, with the limitation that increased risk of hypoglycemia [122]. In decompensated liver disease patients, insulin requirements may vary. It may be decreased due to reduced capacity for gluconeogenesis and reduced hepatic breakdown of insulin; however it can be increased due to insulin resistance [121].

Without increasing costs, insulin analogs may offer equivalent or improved glycemic control compared to standard insulin while being associated with a lower risk for hypoglycemia, particularly nocturnal and severe hypoglycemia, and while being associated with superior renal and cardiac outcomes compared to human insulin [123].

7- Dipeptidyl Peptidase-4 Inhibitors (DPP-4): As a class, DPP-4 inhibitors are characterised by low risk of hypoglycemia, favorable adverse-effect profile, weight neutral, easy dosing and appear to have the potential, at least experimentally, to decrease β-cell apoptosis and increase β-cell survival. DPP-4 inhibitors are readily absorbed orally. No DPP-4 inhibitor has been shown to inhibit or to induce hepatic CYP-mediated drug metabolism. Accordingly, the number of clinically significant drug-drug interactions is minimal. Systematic reviews of clinical trials suggest that the overall efficacy of all DPP-4 inhibitors is similar [124].

Sitagliptin in Diabetic Patients with Chronic Hepatitis C & in NASH

Higher serum DPP-4 activity was found in CHC patients (in the serum, bile canaliculi, hepatocytes and hepatic stellate cells), a disease known to be associated with diabetes mellitus and insulin resistance.

The sDPP-4 showed correlation with liver tests (ALT, GGT, and ALP) in NAFLD and other CLD, the excess is of hepatic origin. It is hypothesized that in NAFLD the DPP-4 enzymatic activity is increased which might contribute to the development of T2 DM and metabolic deterioration. Based on these results, DPP-4 inhibitors might offer prevention of further metabolic deterioration, especially in NAFLD. The impact of such therapy on the liver fibrosis might also be in the focus (Effect on hepatic stellate cells) [125].

A case–control study, using sitagliptin 50 mg/day for 48 weeks, showed no significant changes of average AST and ALT levels during follow up. Sitagliptin showed effectiveness and safety for the treatment of T2DM complicated with HCV-positive chronic liver disease [126].

Paired liver biopsies from 15 diabetic patients with NASH before and after one year of therapy with sitagliptin 100 mg once daily were studied. Sitagliptin resulted in a significant decrease in ballooning and NASH scores, while the reduction in the steatosis score was of borderline statistical significance. These effects were accompanied by a significant reduction in body mass index, AST, and ALT levels [127].

Sitagliptin is eliminated almost entirely by the kidneys; saxagliptin and vildagliptin are metabolized in the liver [128].

3- Other drugs used in the management of disorders associated with T2 DM.
Statins

Despite a lack of evidence that statins cause liver diseases, many physicians are reluctant to start statins in patients with an out-of-range liver enzyme value [129].

Statins and liver disease [130].

- Chronic liver disease or cirrhosis: If compensated, statins can be used.
- Acute liver disease: Patients with acute liver disease should not take statins until they have recovered.
- Patients with unexplained elevations in serum aminotransferases should not take statins.

Statins and Liver Toxicity

The most common is asymptomatic aminotransferase elevation.

NAFLD is associated with decreased hepatic CYP3A which may carry higher risk of myopathy from statins that are metabolized predominantly by CYP3A (e.g., atorvastatin and simvastatin), especially when used at higher doses. Rosuvastatin has no relation to CYP3A [131,132].

Human studies showed that lipoid-lowering agents are safe and efficacious in patients with NAFLD/NASH and that some of these agents can induce a reduction in the extent of the hepatic steatosis. US FDA currently considers serious statin-related liver injury to be a rare and unpredictable event [133-135]. Statin-fibrate combination therapy should be undertaken cautiously and reserved for patients with severe or refractory hyperlipidemia. In addition, because fibrates may impair liver function, which could lead to higher plasma levels of statins, patients with impaired liver function should not receive this combination [136].

Other hypolipidemic drugs used for combined atherogenic dyslipidemia with IR, diabetes and/or metabolic syndrome [137,138].

- Increasing HDLc with fenofibrates (PPAR-α agonism) in the presence of low LDLc, may be more beneficial than statin therapy alone.
- PPAR-γ agonism (thiazolidinediones), increases triglyceride lipolysis, FFA transport, and conversion of FFAs to triglycerides.
- Niacin, ezetimibe, bile acid sequestrants, and omega-3 fatty acids. Particularly, ezetimibe/statin combinations provide superior lipid-modifying benefits compared with statins monotherapy in atherogenic dyslipidemia.
- “Natural” cholesterol-lowering medications: garlic, oat bran, and vitamin C, having low cost and minimal side effects.

Hypotensive therapy to patients with cirrhosis

Essential hypertension is seldom found in cirrhotics (3-7%) [139].

Chronic treatment with propranolol in advanced cirrhotics controls their hyperdynamic circulation. A possible therapeutic approach for advanced human cirrhosis could be the combination of beta blockade with AT1 receptor antagonism or ACE inhibition [140].

Hydrophilic ACEI (lisinopril) which are not metabolized in the liver are effective and safest (vs. enalapril) [141].

Anti-fibrotic effect of losartan

Experimentally and in patients with NASH, losartan results in the improvement of serum liver enzyme levels and hepatic necroinflammation, with no untoward side effects. Losartan decreases blood markers of hepatic fibrosis, activation of hepatic stellate cells, TGF-β levels, and hepatic fibrosis. These observations suggest that therapeutic use of an angiotensin II receptor antagonist is safe and efficacious for the treatment of NASH [142,143].

In patients with CHC administration of an AT1R antagonist may improve liver scores of fibrosis stage. Studies speculate that the combination treatment of Peg interferons and AT1R blocker may provide a new strategy for anti-liver fibrosis treatment in HCV [144].

4-Insulin sensitizers and prognosis of cirrhosis

Insulin sensitizers

Metformin works by increasing beta oxidation of free fatty acids and reducing the hepatic gluconeogenesis via activation of AMPK pathway; decreasing intestinal glucose absorption; and increasing glucose uptake in skeletal muscle [145]. Furthermore, it is able to modulate the expression of proinflammatory cytokines, such as TNFα and IL-6 [146]. Recent studies indicate that metformin has antioxidant, anti-inflammatory, growth inhibitory and antiangiogenic effects, reducing the risk of some solid tumors, such as prostate, colorectum, breast and pancreas [147]. TZD, especially pioglitazone, is another drug class of insulin sensitizers, acts by activating PPARs [148].

Insulin sensitizers and cirrhosis outcomes

DM and IR could have a special relevance in the pathogenesis of hepatic encephalopathy, through modulating glutaminase activity, releasing proinflammatory cytokines. IR could promote and increase the protein catabolism and ammonia production. Lastly, diabetes is associated frequently with autonomic neuropathy promoting small intestine bacterial overgrowth a well-known trigger of hepatic encephalopathy. Metformin use was shown to be able to reduce the risk of hepatic encephalopathy in diabetic cirrhotic patients, probably by two mechanisms: inhibiting partially glutaminase activity and improving insulin sensitivity [149].

Nkontchou et al, [150] evaluated a group of 100 diabetic patients with biopsy-proven compensated hepatitis C virus cirrhosis who were prospectively followed for 2.3–8.3 yr and evaluated for the development of HCC, liver-related death, or liver transplantation. Within this cohort, the antidiabetes regimen included metformin in 23%, insulin or sulfonylurea in 48%, and diet alone in 29% of subjects. The 5-yr HCC occurrence was significantly lower in the group receiving metformin than in the groups without metformin, and the multivariate analysis revealed that metformin treatment was independently
associated with decreased HCC occurrence and liver-related death or transplantation.

Antidiabetic therapy is being widely evaluated in HCC, showing metformin and TZD as protective agents and sulphonylureas and insulin therapy as negative factors [151,152]. Whether the use of antidiabetic medications alters the risk of HCC has been evaluated in a meta-analysis of 10 studies with 334,307 patients with type 2 diabetes mellitus [153]. The analysis found that there was a reduction in HCC with metformin use. Thiazolidinedione use was not associated with the risk of HCC, whereas sulfonylurea or insulin use was associated with an increased risk of HCC. However, these results should be viewed with caution because there was considerable heterogeneity among the studies included in the analysis. In addition, a post-hoc analysis of randomized trials that was included with the meta-analysis failed to show an association of antidiabetic medication use and the risk of HCC.

Metformin use decreases the risk of hepatocellular carcinoma by several mechanisms including: a) phosphorylated AMPK suppresses the Akt/mTOR signaling pathway, inhibiting cell proliferation [154]; b) modulate the expression of cytokines, such as TNFα and oxidative stress [155]; c) antiproliferative and antineoplastic effects associated with inhibition of mammalian target of rapamycin complex 1. Moreover, metformin is taken up in hepatocytes by the organic cation transporter-1 (OCT-1), which is an essential step for the glucose-lowering effect [156,157]. Interestingly, OCT-1 and OCT-3 expression has been found downregulated in HCC patients and associated with impaired prognosis [158].

Metformin, as quoted from Violeta B. P& Joseph K [159]:

*Is not associated with hepatotoxicity & particularly useful in obese patients.
*Produced 80% reduction of the risk of HCC compared with insulin or sulphonylureas.
*Showed lower recurrence of HCC after radiofrequency ablation.
*Metformin users had a similar survival rate to nondiabetics with HCC

These data provide a foundation for further studies to evaluate metformin in the clinic either as a single agent or in combination with other first-line agents as a treatment option for HCC [160].

**Evidence based guidelines and recommendations:**

1. MNT and lifestyle modifications will avoid an exponential increase in prevalence of DM and uncontrolled diabetics with serious complications and also increase in liver disease morbidities. (Level 1)

2. MNT is a core component of both prevention and management of Type II DM, NASH and hepatitis. (Level 2)

3. Based on pharmacokinetic data and clearance profile, altered drug metabolism is primarily a concern in patients who have advanced liver disease. (Level 2)

4. Treatment of diabetes associating liver disease appears beneficial. (Level 3)

5. Therapy begin with Oral hypoglycemics with immediate use of insulin when blood sugar control is not achieved, transaminasis > 2 folds normal or appearance of markers of cirrhosis. (Level 5)

6. Metformin is an appropriate first-line therapy for most patients except those with advanced liver disease who have an increased risk of lactic acidosis. (Level 3)

7. If hepatic disease is severe, insulin secretagogues should be avoided because of the increased risk of hypoglycemia. (Level 5)

8. The glitazones should be used cautiously in patients with hepatic disease. Pioglitazone may be useful in patients with fatty liver disease. (Level 2)

9. Sitagliptin showed effectiveness and safety for the treatment of T2DM complicated with HCV positive chronic liver disease. (Level 3)

10. DPP-4 Inhibitors in Diabetic Patients with Nonalcoholic Steatohepatitis resulted in a significant decrease in ballooning and NASH scores (Level 4)

11. Insulin must be used with caution, as hypoglycemia may be a problem. Insulin doses need to be frequently adjusted in patients with chronic liver disease. (Level 5)

12. Insulin or insulin secretagogues antidiabetic oral agents are associated with an increased risk for HCC, while in metformin treated patients the risk was reduced. (Level 2)

13. In patients with NAFLD and NASH, statins can be used to treat dyslipidemia, lacking the evidence of increased risk for drug-induced liver injury. (Level 2)

14. Therapeutic use of angiotensin II receptor antagonist for hypertension is safe and beneficial for NASH. (Level 2)

15. Given the clear association between diabetes mellitus and hepatocellular carcinoma, the strict control of glycemia with insulin sensitizers, documented in meta-analysis could be essential in its prevention (Level 1).

16. The early detection and the right management of diabetes mellitus could allow reducing the incidence of hepatocellular carcinoma and cirrhosis outcomes (Level 2).

**Recommendations**

- Acarbose is safe and well tolerated.

- Meglitinides should be used with caution in patients with chronic liver disease (increase dose interval).

**E - Management of liver disease associated with diabetes**

1. **Assessment of Prognosis of Cirrhosis associated with diabetes.**

As mentioned before, patients with liver disease associated with diabetes were at greater risk for the development of adverse outcomes such as cirrhosis, HCC or liver related mortality.

DM has been studied as an independent prognostic factor. In a retrospective and prospective study 354 (98 with diabetes)
of 382 eligible patients were followed for 6 years after inclusion into the study: 110 were alive at the end of follow-up. Prognostic factors identified by Kaplan-Meier analysis, followed by Cox's stepwise regression demonstrated in sequence, albumin, ascites, age, encephalopathy, bilirubin, diabetes, and platelets as prognostic factors of mortality. The larger mortality rate in patients with diabetes was not due to complications of diabetes but to an increased risk of hepatocellular failure [161].

In another study carried out in patients suffering from cirrhosis and refractory ascites, it was observed that the HCC and DM, but not the Child-Pugh score, were independent predictive factors of mortality. [162].

Nishida et al performed the OGTT on a group of 56 patients with cirrhosis and normal fasting blood glucose. A total of 38% of patients were diagnosed with DM, 23% with glucose intolerance, and 39% were normal. After 5 years of follow-up, patients with diabetes and glucose intolerance had significantly higher mortality than normal patients. From a multiple regression analysis only serum albumin and DM were independent negative predictive factors of survival [163].

The Verona Diabetes Study, a population-based study on more than 7000 subjects with T2DM, found an increased risk of death from chronic liver disease and cirrhosis compared with the general population (164).

Perhaps the combination of DM with the currently used scores (Child-Pugh and MELD scores) may enhance the sensitivity and the specificity for prediction of morbidity and mortality rates in cirrhotic patients [165,166].

2- NAFLD, a possible new target for T2 DM prevention and treatment.

The largest multicenter placebo-controlled trial completed to date on the role of pioglitazone in 247 patients with biopsy-proven NASH and without diabetes and cirrhosis, showed that pioglitazone use was associated with a significant amelioration of liver biochemistry, steatosis, liver inflammation, hepatocellular ballooning, as well as insulin resistance, but no improvement in histological findings [167].

Two meta-analyses [168,169] evaluating some high-quality pioglitazone and rosiglitazone trials, concluded that TZDs improve histological steatosis and inflammation, but not fibrosis, compared with controls. In contrast to these results, a recent meta-analysis, evaluating four good quality clinical trials and excluding open label trials in which the control group received active treatment, have shown that TZDs, in particular pioglitazone, significantly improved all hepatic histological features, including fibrosis (170). The discrepancies between these three meta-analyses may be due to the fact that in the latter study the authors conducted a subgroup analysis to assess the efficacy of pioglitazone alone. However, independently of the effect on liver histology, the benefit-safety, long-term profile of TZDs, including pioglitazone, is not yet well established.

In a meta-analysis, treatment of NASH with glitazones, but not metformin, demonstrates a significant histological and biochemical benefit, especially in patients without diabetes. Metformin failed to improve any pooled outcome. Additional studies in nondiabetics are needed to determine if glitazones offer incremental benefit over antioxidants such as vitamin E, which may be equally efficacious or more efficacious, without detrimental side effects such as weight gain [169].

3- Management of HCV associating diabetes with special reference to HOMA IR

Several studies have shown a negative association between increasing levels of IR and reduced rates of initial virological response as well as SVR in chronic hepatitis C patients treated with a combination of pegylated IFN-α and ribavirin. This negative association has also been reported in patients infected with the HCV genotype 2 and 3 [171-173]. In the study by Mogawer et al [174] the relation between IR and Rapid Virological Response in patients with chronic HCV who received Pegylated Interferon and Ribavirin revealed a significant inverse relationship (p value < 0.001). These findings matched with results of Mohamed et al [175] and Khattab et al [176].

It has also been found that curing HCV resulted in amelioration of the HOMA score and in a decreased incidence of T2D after the end of therapy [177]. Similar results have been reported by Chehadeh et al., in a cohort of 181 genotype 4 Egyptian patients [178].

The gold standard for measuring IR is the hyper-insulinemic euglycemic clamp; the technique is mostly used in medical research [179]. Homeostasis model assessment (HOMA), which has improved to HOMA 2 model is easy to use in clinical practice. It can be calculated as follow: HOMA-IR= fasting glucose mg/dl X fasting insulin µU/ml / 405 [180].

Triple therapy of metformin (as insulin sensitizer) with peginterferon and ribavirin improved SVR, but insignificantly except in obese female subjects [181]. Khattab et al. studied 97 Egyptian patients with genotype 4 HCV infection. He showed that the addition of pioglitazone might increase the SVR rate [182].

In the coming years, treatment of chronic HCV will be enforced by a group of medications including polymerase inhibitors, protease inhibitors and others which will definitely improve the outcome of treatment significantly.

Evidence based guidelines and recommendations:

1. The combination of DM with 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 (Level 4).

2. Treatment of NASH with glitazones demonstrates a significant histological and biochemical benefit, especially in patients without diabetes. (Level 1). The benefit-safety, long-term profile of TZDs, including pioglitazone, is not yet well established

3. HOMA-IR index is a major determinant of SVR resulting in 20% lower SVR when it is high. Accordingly it may be recommended to measure and correct IR prior to treatment. (Level 2)

4. Adding metformin to peginterferon and ribavirin was safe and improved insulin sensitivity, yet it failed to show statistically significant difference in SVR apart from significant difference in
response seen in females. Accordingly it may be recommended to add metformin in HCV obese female patients with IR. (Level 2)

F- Other associations between diabetes and liver disease

Post Liver Transplantation Diabetes mellitus: Liver transplantation has generally a 5y survival rate of 70-80%. Given the increasing longevity of those patients, the recognition and prevention of long-term complications after transplantation have become important. New onset diabetes mellitus after transplantation (NODAT), or post transplant diabetes mellitus (PTDM) is common. In liver transplant (LT) recipients followed beyond 1 year, estimates of the prevalence of NODAT vary from 5% to 26% (183).

Risk factors include:

1) Immunosuppressive drugs: Glucocorticoids, calcineurin inhibitors (cyclosporine, and tacrolimus)
2) Weight gain
3) Chronic HCV

The mechanism is mainly through development of an insulin resistant state. As for tacrolimus and cyclosporine; they exert direct cytotoxic effect on pancreatic B islet cells (Tacrolimus more than cyclosporine) [184,185].

The development of diabetes does not adversely affect survival in the first year following transplantation, but it is associated with decreased survival after the first year, mainly due to increased prevalence of infection [186].

NODAT tends to remit over time especially as corticosteroids are withdrawn and the tacrolimus dosage is reduced, and patients may go from insulin therapy to oral hypoglycemic agents to diet control only over the years [185].

Long-Term Management of DM (New-Onset or Preexisting) After LT

The goals of the long-term management of diabetes after LT are not substantially different from the goals for nontransplant patients including standard medical and nutritional therapy. The safety of thiazolidinediones in LT recipients is unproven [187].

Retrospective data sets and a small prospective study suggest that the conversion of immunosuppression from tacrolimus to cyclosporine improves glycemic control in patients with established DM and NODM [183,184]. In addition, modulating immunosuppression, including lowering or stopping glucocorticoids may be of benefit. Because tacrolimus is more diabetogenic than cyclosporine; switching from tacrolimus to cyclosporin in patients with difficult to control diabetes following LT is also an option [188].

HBV and Diabetes

Diabetic patients are at risk of capturing HBV infection:

Acute HBV infection is about twice as high among adults with diabetes aged 23 years and over. HBV core antibody is 60% higher among adults with diabetes than those without diabetes [189,190].

The first reports on the association of HBV and diabetes date back to Mason and co-workers [191]. They reported 21% diabetes in HCV positive vs 12% in HBV positive cirrhotics while in diabetics only 4.2% were HCV and 1.6% HBV infected. Parenteral exposure is still the route diabetic patients’ capture HBV and HCV. Diabetic patients who are on oral treatment are still at risk, as they undergo the frequent self blood glucose monitoring.

The virus has been detected on surfaces such as lancering devices and blood glucose meters, even when no blood is visible. Blood sufficient to transmit the virus has also been found in the reservoirs of insulin pens, resulting in warnings against sharing such devices between patients. This mandates prophylaxis of diabetic patients against HBV through adequate infection control procedures on one side and on the other side by adequate HBV vaccination of diabetic patients (risk patients). All previously unvaccinated adults with diabetes aged 19–60 years be vaccinated against HBV as soon as possible after a diagnosis of diabetes is made, and that vaccination be considered for those aged 60 and over, after assessing risk and likelihood of an adequate immune response [189,192]. The age differentiation in the recommendations is due to economic and cost effectiveness reasons. Also, the immune response to the vaccine declines with age [193].

HBV patients developing diabetes

In HBV infection the disease progression is rather fast, therefore very few patients reach the level of cirrhosis and pancreatic damage influencing lower diabetes incidence in this population [194].

Generally, viral infections and the metabolic syndrome may coexist due to the large prevalence of obesity and T2DM. BMI and HOMA-IR showed independent predictors to metabolic syndrome in patients with CHB. Accordingly, targeted screening and follow-up of HBV-infected patients for abnormalities of glucose metabolism and insulin resistance is highly recommended [195,196]. HBV has extra hepatic sites of viral colonization resulting in extrahepatic manifestations especially the kidneys and pancreas resulting in proteinuria, B cell dysfunction, diabetes and even pancreatic cancer [197,198].

Evidence based guidelines and recommendations:

1- Prevalence of NODAT varies from 5% to 26%. (Level 3)
2- For the treatment of NODM after liver transplantation: The target goal of HbA1c is <7.0% with a combination of lifestyle modifications and pharmacological agents as appropriate. (Level 4)
3- Prognosis of NODAT: The development of diabetes does not adversely affect survival except after the first year following transplantation. NODAT tends to remit over time (Level 5)
4- All diabetic patients should be monitored for an adequate immunity against HBV, immunizing naive cases or boosting previously vaccinated patients. (Level 3)
5- Patients on frequent blood glucose monitoring should undergo strict infection control measures against parenterally transmitted infections especially HBV, special care should be given to those undergoing monitoring of blood glucose in health
care facilities where blood glucose monitoring devices are shared (Level 3).

6-Testing for insulin resistance is a simple and easy to perform test that should be done routinely to all HBV infected patients. Those who test positive should receive frequent monitoring of blood glucose level. (Level 3).

REFERENCES


33. Laurie Barclay. Newly diagnosed diabetes mellitus may increase risk of liver disease. CMAJ. 2010


Zhang L, Shi YL, Hong WX, Jia WD, Li LH. [Diagnostic value of serum islet autoantibody in hepaticogenic diabetes mellitus]. Nan Fang Yi Ke Da Xue Xue Bao. 2006; 26: 1034-1036.


Chiang DJ, Pritchard MT, Nagy LE. Obesity, diabetes mellitus, and liver fibrosis. Am J Physiol Gastrointest Liver Physiol. 2011; 300: G679-G702.


107. Gundling F, Schumm-Draeger PM, Schepp W. [Hepatogenous


118. Drug Class Review: Thiazolidinediones pharmacy. oregonstate.edu/_/dưr_review_2003_11_18_tzd_classreview


123. A Report from the 45th Meeting of EASD 2009 Vienna


125. Ga’bor Finneisz, Ti’meara Varga, Gabriella Lengyel et al. PLOS ONE. 2010; 5.


179. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a


