



## Review article

## Managing diabetes and liver disease association

Abd Elkhalek Hamed <sup>a,b,\*</sup>, Medhat Elsahar <sup>a,i</sup>, Nadia M. Elwan <sup>f</sup>, Sarah El-Nakeep <sup>d</sup>, Mervat Naguib <sup>c</sup>, Hanan Hamed Soliman <sup>f</sup>, Ashraf Ahmed Aboubakr <sup>b</sup>, Amany AbdelMaqsood <sup>c</sup>, Heba Sedrak <sup>c</sup>, Samir N. Assaad <sup>e</sup>, Reda Elwakil <sup>a,d</sup>, Gamal Esmat <sup>a,c</sup>, Samira Salh <sup>h</sup>, Taymour Mostafa <sup>c</sup>, Sherif Mogawer <sup>c</sup>, Sameh Emil Sadek <sup>b</sup>, Maha M. Saber <sup>j</sup>, Hanan Ezelarab <sup>j</sup>, Asem Ashraf Mahmoud <sup>b</sup>, Souad Sultan <sup>c</sup>, Mohamed El Kassas <sup>g</sup>, Ehab Kamal <sup>k</sup>, Naglaa M. ElSayed <sup>c</sup>, Shorouk moussa <sup>c</sup>

<sup>a</sup> The Egyptian Association for the Study of Liver and Gastrointestinal Disease (EASLGD), Egypt

<sup>b</sup> Department of Internal Medicine, Hepatology, and Diabetes, Egyptian Military Medical Academy, Egypt

<sup>c</sup> Kasr Al Aini, Egypt

<sup>d</sup> Ain Shams University, Egypt

<sup>e</sup> Alexandria University, Egypt

<sup>f</sup> Tanta University, Egypt

<sup>g</sup> Helwan University, Egypt

<sup>h</sup> Department of Pharmacy, Cairo University, Egypt

<sup>i</sup> Police Medical Academy, Egypt

<sup>j</sup> Department of Clinical Nutrition National Research Centre, Egypt

<sup>k</sup> Medical Department, National Research Centre, Egypt

## ARTICLE INFO

## Article history:

Received 9 August 2018

Accepted 26 August 2018

## Keywords:

Diabetes mellitus

NAFLD

NASH

Liver disease

Management

## ABSTRACT

There is strong association between liver diseases and diabetes (DM) which is higher than expected by a chance association of two very common disorders. It can be classified into three categories: Liver disease related to diabetes, hepatogenous diabetes (HD), and liver disease occurring coincidentally with DM. The criteria for the diagnosis of diabetes associating liver disease are the same for primary diabetes. Two hours post glucose load is a better screening test for HD. HbA1c may not be suitable for diagnosis or monitoring of diabetes associating advanced liver disease. Apart from the increased cardiovascular risk in patients with type 2 DM (T2 DM) and NAFLD, the cardiovascular and retinopathy risk is low in HD. Patients with metabolic derangement should be screened for NAFLD which in turn may predict T2 DM development. Similarly, patients with established T2 DM should also be screened for NAFLD which further contributes to diabetes worsening.

Diabetes is a significant risk factor for progression of the chronic liver disease. It is associated with poor patient survival.

Treatment of diabetes associating liver disease appears beneficial. Metformin, if tolerated and not contraindicated, is recommended as a first-line therapy for patients with diabetes and chronic liver disease (CLD). If the hepatic disease is severe, insulin secretagogues should be avoided because of the increased risk of hypoglycaemia. Pioglitazone may be useful in patients with fatty liver disease. DPP-4 inhibitors showed effectiveness and safety for the treatment of T2 DM in CLD patients up to those with child B stage. GLP-1 receptor agonists and SGLT-2 inhibitors exhibit positive effects on weight and are associated with minimal risk of hypoglycaemia. Insulin must be used with caution, as hypoglycaemia may be a problem. Insulin analogues are preferred in the context of hypoglycaemia.

Statins can be used to treat dyslipidaemia in NAFLD, also the use of angiotensin II receptor antagonist for hypertension is safe and beneficial.

Given the clear association between diabetes mellitus and hepatocellular carcinoma, the strict control of glycaemia with insulin sensitizers can be essential in its prevention.

**Common abbreviations:** ADA, American Diabetes Association; AGEs, Advanced glycation end products; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, Diabetes mellitus; GI, Glucose intolerance; HOMA/IR, Homeostasis Model Assessment of Insulin Resistance; IR, Insulin resistance; NAFLD, Non alcoholic fatty liver disease; NASH, non alcoholic steatohepatitis; PAI-1, Plasminogen activator inhibitor-1; PLDT, Post-transplant diabetes mellitus; PPARs, Peroxisome proliferator-activated receptors; T1 DM, Type 1 DM; T2 DM, Type 2 DM; TGF- $\beta$ , Transforming growth factor beta; TNF- $\alpha$ , Tumour necrosis factor  $\alpha$ .

\* Corresponding author at: Egyptian Military Medical Academy, Department of Internal Medicine Hepatology and Diabetes, Egypt.

E-mail address: [akhalek\\_hamed@hotmail.com](mailto:akhalek_hamed@hotmail.com) (A.E. Hamed).

<https://doi.org/10.1016/j.ajg.2018.08.003>

1687-1979/© 2018 Pan-Arab Association of Gastroenterology. Published by Elsevier B.V. All rights reserved.

The addition of DM to 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.

In the new era of directly acting antiviral agents (DAAs) for HCV treatment, it is recommended to follow up lipid profile and blood sugar levels following SVR in order to adjust doses of medications used in diabetic (SVR is associated with reduction in insulin requirements) and dyslipidaemic patients (rebound increase in the lipid profile after clearing the virus may increase risk of cardiovascular disease (CVD)). The issues of post liver transplant diabetes and relation between DM and chronic HBV are highlighted.

This narrative review and Consensus-based practice guidance (under revision and criticism) 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 reviewers.

© 2018 Pan-Arab Association of Gastroenterology. Published by Elsevier B.V. All rights reserved.

## Causes of diabetes association with liver diseases

The association between liver disease and diabetes mellitus (DM) is well known, the overall prevalence is significantly higher than that expected by a chance association of two very common diseases. This relationship between DM and CLD can be classified into the following categories:

- Liver disease related to diabetes [1]: Either aggravated by diabetes (NAFLD/NASH) or caused by diabetes (glycogenic hepatopathy and diabetic hepatosclerosis).
- Diabetes as a result of liver disease: Hepatogenous diabetes [2].
- Liver disease occurring coincidentally with DM: Chronic active autoimmune hepatitis and autoimmune biliary disease [3].

### Nonalcoholic fatty liver disease (NAFLD)

NAFLD is a wide spectrum disease ranging from simple steatosis, NASH to liver cirrhosis [4] and is the most common type of CLD in the Western world [5].

### The epidemiological evidence of the association between NAFLD and T2DM

The prevalence of NAFLD among diabetics varies from 50 to 90% [6,7]. More than half of diabetic patients have bright liver on ultrasound and 87% of those had biopsy-proven NAFLD [7]. On the other hand, many studies showed increased incidence of T2 DM in patients with NAFLD independently of ordinary risk factors [8–10]. The risk of T2 DM ranged from 33% to 55% in patients with NAFLD [11,12]. A meta-analysis of 20 observational studies, involving more than 115 000 individuals, demonstrated that NAFLD was associated with an almost two-fold increased risk of T2 DM over a median period of 5 years [13]. An independent retrospective study of 38 291 individuals showed higher risk of diabetes in patients with NAFLD with high fibrosis score than those with low fibrosis score [6].

The incidence rates of T2 DM were 3.2% in the non-overweight without NAFLD group, 14.4% in the non-overweight with NAFLD group, 8.0% in the overweight without NAFLD group and 26.4% in the overweight with NAFLD group [8]. However, there are racial and ethnic differences among different studies for example, most of the Asian studies showed that the increased risk of NAFLD and increased level of insulin resistance was independent of obesity [14].

### The pathological link between NAFLD and T2 DM

Accumulation of lipid intermediates e.g. diacylglycerol and ceramides in the liver lead to hepatic insulin resistance, increased hepatic gluconeogenesis, and exhaustion of pancreatic  $\beta$  cells [15]. Moreover, oxidative stress provoked by hepatocyte fat deposit stimulates the release of inflammatory mediators such as, IL-6, TNF- $\alpha$ , and Fetuin-A which play role in the development of T2 DM [16].

Diabetes can hasten the progression of NAFLD to NASH, severe fibrosis, cirrhosis and hepatocellular carcinoma [17,18]. On the other hand, the occurrence of NAFLD in T2DM patients is accompanied by higher insulin resistance and poorer metabolic profile [19]. In contrast, improvement of NAFLD is associated with 70% risk reduction of developing T2DM, independently of common risk factors [20].

### Glycogenic hepatopathy (GH)

GH is a rare under-recognized disease characterized by the combination of poorly controlled diabetes, acute liver injury with marked elevation in serum aminotransferases and characteristic histological features on liver biopsy that include marked glycogen accumulation, no or mild fatty changes, no or minimal inflammation and intact architecture with no significant fibrosis [21]. The essential component in the pathophysiology of GH is the wide fluctuation in glucose and insulin levels [22]. GH typically presents in children and adolescents with T1 DM [23], but it can also be observed in adult T1 DM [24] and recently reported in T2 DM [25]. GH may be mistaken for NAFLD [26]. Glycaemic control is the only therapy needed for GH [27].

### Diabetic hepatosclerosis (DHS)

DHS is a noncirrhotic form of perisinusoidal fibrosis with basement membrane formation without steatosis observed in liver biopsies of people with diabetes [28].

DHS occurs in subjects with long-lasting T1 DM and T2 DM and microvascular disease in other organs, especially the kidney and has been proposed to represent the hepatic manifestation of diabetic microangiopathy. It is often associated with hyaline arteriosclerosis, while, by definition, typical features of NASH or alcoholic hepatopathy are absent [29].

DHS is a marker of severe DM. Its pathogenesis is suggested to be of metabolic origin due to prolonged hyperglycaemia and increased AGEs, leading to enhanced lipid peroxidation, with their byproducts inducing vasoconstriction and increasing platelet adhesion and aggregation, which results in basement membrane and small artery thickening [30].

Clinically, the majority is silent but the condition may present with full-blown cholestasis, may be secondary to mechanical compression or ischaemia of the biliary ducts caused by perisinusoidal fibrosis. Elevation of alkaline phosphatase is frequent [31,32]. Treatment options are likely to be similar to other diabetic microvascular complications.

### Hepatogenous diabetes (HD)

HD is a term used for DM developing as a complication of cirrhosis. 96% of cirrhotic patients may have GI and 30–60% suffer

from HD. The possible pathophysiology involves peripheral IR, in addition to hyperinsulinaemia due to reduced insulin clearance caused by the diseased liver.  $\beta$ -cell dysfunction caused by increased AGEs and hypoxia-inducible factor and decreased beta-trophin by the diseased liver will lead to progressive impairment in insulin secretion and frank diabetes [31].

NASH, alcoholic cirrhosis, chronic hepatitis C and haemochromatosis are more frequently associated with hepatogenous diabetes. Genetic factors rather than liver or pancreatic damage were found to be involved in the susceptibility to develop HD [32,33].

Patients with alcoholic liver disease are at high risk for diabetes, directly related to the amount of alcohol consumption. They have chronic damage in pancreatic islet  $\beta$ -cells resulting in DM [34].

A 3-folds higher risk for DM in HCV patients was identified in individuals over 40 years. Egyptian studies showed that DM is more prevalent in HCV positive patients and report a prevalence of 25% [35].

DM can be observed in about 50–85% with hereditary haemochromatosis. Deposition of iron in the pancreas affects exocrine secretion and may infiltrate islets of Langerhans with damage to  $\beta$ -cells [36]. As in T2 DM, both  $\beta$ -cell dysfunction and impaired insulin sensitivity are responsible for hepatogenous diabetes. Yet, the pathophysiology of HD is still partly different from that of T2 DM [37].

Liver transplantation was found to improve glucose tolerance and insulin sensitivity in 67% of cirrhotic-diabetic patients (those with preserved  $\beta$ -cell function), in the remaining 33%, glucose tolerance was not improved due to impaired  $\beta$ -cell function [38].

### Criteria for the diagnosis of diabetes associating liver disease

#### Criteria for the diagnosis of diabetes associating liver disease

The criteria for the diagnosis of DM associating liver disease and also prediabetes are the same as for the ordinary primary diabetes according to ADA.

In the early stage of cirrhosis, fasting serum glucose levels is normal in 23% of patients, whereas post-prandial blood glucose may be  $<200$  mg/L, thus an oral glucose tolerance test is needed. Fasting and 2 h post 75 g glucose blood sugar levels are required for diagnosis, the same as in those without CLD. However, the glycated haemoglobin (HbA1C) is unreliable for diagnosis or the monitoring of glycaemic control in patients with cirrhosis [2,31].

#### Differentiation of hepatogenous DM from primary DM

HD has particular clinical characteristics: It is more frequently associated with hypoglycaemic episodes as a result of impaired liver function, it is less frequently associated with risk factors such as age, body mass index and family history of diabetes. This is because diabetic state in CLD could be acquired secondary to liver disease per se, not due to genetic background [39]. Moreover, the time at diagnosis of both DM and liver disease is crucial in differentiation [40].

Zhang X, et al found no diabetic symptoms among any of the posthepatic or cirrhotic patients with glucose intolerance or dia-

betes compared with cases of primary DM with liver dysfunction. Also, the levels of FPG and PPG in the posthepatic patients were lower than in those in patients with primary DM, but the levels of plasma insulin and plasma C peptide were higher [41]. Zhang L found another interesting difference, which is the higher prevalence of islet cell antibody positivity in HD. This may serve as a laboratory test for distinguishing HD from primary T2 DM [42]. (Table 1).

#### Tools to measure long-term glycaemic control in patients with diabetes and liver diseases

**HbA1c** is more likely to be falsely low in patients with chronic liver disease. It should not be relied upon if shortened red blood cells' half-life is probable. The same applies if hypersplenism is suspected, or if there is blood loss due to gastrointestinal haemorrhage [43].

**Fructosamine (FA)** is measured by a spectrophotometric assay which may be affected by hypertriglyceridaemia, hyperbilirubinaemia, haemolysis, and low serum protein and albumin levels. FA is apparently higher in liver cirrhosis patients with diabetes, due to the prolonged half-life of serum albumin and reduced rate of synthesis [44]. FA is unaffected by disorders of red blood cells and has the advantage of accurately reflecting shorter-term changes in glycaemia (previous 2 weeks) that correspond to the half-life of albumin [45].

**Frequent Self-Monitoring of Blood Glucose [SMBG]** may reflect short-term glycaemic control, especially if timed to be pre-prandial and 2 h post-prandially. Downloading SMBG readings in the form of glycaemic curves on a computer may be of help for following glycaemic excursions [46].

#### Continuous glucose monitoring [CGM]

There are two types of CGM: Retrospective and real-time monitoring with the former found to be as effective as HbA1c in glycaemic control, while the later found to be more effective than HbA1c. This was a general statement conclusion in a systematic review for diabetes mellitus patients in general, not specified for diabetic patients with liver disease [47].

### The clinical impact of diabetes associating liver disease

#### Cardiovascular impact

#### Cardiovascular and retinopathy risk in cirrhotic patients with hepatogenous diabetes

HD has morbidity and mortality outcomes different from T1 DM and T2 DM, Cardiovascular and retinopathy risks are lower in HD. Mortality is likely due to liver-related causes rather than diabetic complications [48]. This lower risk could be explained by multiple factors: Better lipid profile and lipoprotein A [49], impaired bleeding profile and thrombocytopenia associated with liver cirrhosis [50] and the tendency towards low or normal blood pressure in cirrhotic patients [51]. In addition, HD is not burdened by the genetic susceptibility, high BMI and hyperlipidaemia that are associated with T2 DM [48].

**Table 1**  
Hepatogenic vs. primary diabetes.

	Post hepatic DM	DM with liver cirrhosis	1ry DM with liver dysfunction
Symptoms		absent	++
F and pp blood sugar	lower		equally high
F and pp insulin & C-peptide	increased	decreased	more decrease
Islet cell antibody positivity	++	+	

**Cirrhotic cardiomyopathy (CCM).** It is defined as cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities (prolonged QT interval) in the absence of other known cardiac disease [52]. The prevalence of CCM is reported to be between 40 and 50% in cirrhotic patients independent of liver disease aetiology [53].

Patients affected show high morbidity and mortality, where liver failure severity is correlated with heart failure severity mainly left diastolic dysfunction [54]. Cardiac function is nearly normal at rest.

Aldosterone antagonists may have beneficial effects in terms of a reduction in left ventricular dilatation and wall thickness and improvement of diastolic function [55]. Nonselective  $\beta$ -blockers have been shown to improve the prolonged QT interval and might reduce the hyperdynamic load [56]. An improvement after liver transplantation is expected and validates the concept that cardiomyopathy is truly cirrhotic in origin [57].

#### *Cardiovascular impact in patients with T2 DM and NAFLD*

There is now growing evidence that NAFLD, especially in T2 DM, may be linked to an increased risk of developing cardiovascular disease (CVD) independently of other known risk factors (abdominal obesity, ectopic fat accumulation, dysglycaemia, IR, atherogenic dyslipidaemia, and hypertension) or racial background [57–60]. In a study including 2839 patients with T2 DM, NAFLD patients had remarkably higher age and sex-adjusted prevalence of coronary, cerebrovascular, and peripheral vascular disease than their counterparts without NAFLD [61].

The mechanism is not completely understood. Deregulated hepatic microRNAs appear to be associated with NAFLD severity, and may promote coronary artery disease (CAD) through lipid metabolism alteration and/or promotion of systemic inflammation [62].

Endothelial dysfunction, oxidative stress, changes in gut microbiota and altered hormonal and inflammatory cytokine profiles can collectively result in the development of a pro-inflammatory, pro-atherogenic, and pro-thrombotic milieu [63,64]. In NASH, the expression of adiponectin by liver parenchymal cells was downregulated and inversely correlated with steatohepatitis grade [65,66]. Adipocyte fatty acid-binding protein, an adipokine involved in the pathogenesis of atherosclerosis, was strongly associated with NAFLD in T2 DM patients [65]. Many gene polymorphisms have been reported to be related to NAFLD and CAD [67,68].

**NAFLD related macroangiopathy.** A subclinical cardiovascular disease has been shown to be more prevalent in the presence of NAFLD. More prevalent carotid plaques with thickening of intima-media thickness (IMT) associated with higher levels of triglycerides, cholesterol, and PAI-1 was demonstrated [69]. This is also shown in a systematic literature review [70]. Several cross-sectional studies have shown that NAFLD is associated with an increased coronary artery calcium (CAC) score, which is a marker of early atherosclerosis and a powerful predictor of CVD [58]. A meta-analysis of 27 cross-sectional studies has reported a strong association of NAFLD not only with CAC score but also with other markers of subclinical atherosclerosis, such as increased carotid IMT, reduced flow-mediated vasodilation, and increased arterial stiffness [71]. A similar relation was observed in children, adolescents, and elderly patients [72–74]. Evidence has supported a strong, graded relationship between NAFLD and the angiographic severity of CHD. NAFLD has been independently associated with presence of high risk coronary atherosclerotic plaques, impaired myocardial perfusion and adverse outcomes following primary percutaneous coronary interventions, which can be attributed to an increased risk of in-stent restenosis after bare-metal stenting in native coronary arteries [58]. Also, the severity of NAFLD histol-

ogy is associated with higher all-cause death and predicts the risk of future CVD events [75]. The presence and severity of NAFLD on ultrasound are strongly associated with increased QTc interval in patients with T2 DM [76]. Cardiovascular autonomic dysfunction has been correlated with the presence of autonomic dysfunction in T2 DM patients [77].

On the other hand, in the Diabetes Heart Study [78], 623 randomly selected participants were evaluated for hepatic steatosis (diagnosed by CT). There were no significant associations between the liver-spleen attenuation ratio (a marker of hepatic steatosis) and coronary, aortic, or carotid calcium, or carotid intimal thickness.

To date, a large body of evidence has suggested that NAFLD is not simply a marker of CHD but also may play part in the development and progression of these cardiac complications. The clinical implication of these findings is that patients with NAFLD may benefit from more intensive surveillance and early treatment interventions aimed at decreasing the risk of CHD [58]. The identification of NAFLD in patients with T2 DM may predict CVD risk, with important management implications [79]. T2 DM patients with NAFLD should be considered as a high-risk group for developing macroangiopathy, even if the latter is not clinically detected [74]. Therefore, further prospective studies are needed to detect whether NAFLD poses an independent risk for CVD above and beyond known metabolic risk factors. Currently, it is not known whether improving NAFLD will ultimately prevent the development of CVD.

**NAFLD related microangiopathy.** NAFLD is less prevalent in T2 DM patients suffering from microangiopathies [80]. On the other hand, it was reported that NAFLD is associated with an increased prevalence of chronic kidney disease (CKD) and proliferative/laser-treated retinopathy in T2 DM independently of numerous baseline confounding factors. A link between NAFLD, retinopathy, and CKD may be due to the increased release of some pathogenic molecular mediators from the liver: AGEs, reactive oxygen species, C-reactive protein (CRP), PAI-1, IL-6, TNF- $\alpha$ , TGF- $\beta$  and other pro-inflammatory cytokines [79].

#### *Association of Chronic HCV Infection, atherosclerosis, CAD, and Stroke*

HCV related metabolic disorders include steatosis, NAFLD, IR, T2 DM, impaired GT and disturbances in lipid homeostasis [81]. Surprisingly, the effect of these metabolic disturbances on cardiovascular events is not always similar to that of non-HCV individuals, even sometimes contradictory, which raises the question of the associated protective or exaggerating factors changing the outcome in those patients.

**Pathophysiology.** Viral RNA presence in the intimal plaques was observed, suggesting a local inflammatory trigger [82,83]. Also, the presence of inflammatory markers in sera was independently associated with atheromatous plaques causing endothelial injury and atheromatous instability [84,85]. In addition, HCV increases cholesteryl ester transfer protein, promoting the cholesterol esters transfer from HDL to VLDL and LDL.

**HCV in relation to atherosclerosis.** Due to the chronic inflammatory state, the risk of atherosclerosis increases in HCV infected patients despite the low lipid profile [84,86]. A meta-analysis [87] and an Egyptian study [88] found an association between HCV infection and carotid atherosclerosis risk independent of the established and known risk factors.

Lipid profile shows variability according to the liver function status: Those who cleared the virus show rebound increase in the lipid levels in blood with its sequel, while patients with decompensated liver disease demonstrate a decrease in lipid profile with increase in coagulation profile, decrease in platelet count and



decrease in the blood pressure, which was translated into decrease in the cardiovascular risk [81].

**HCV in relation to CAD and CAD mortality.** The risk of major cardiovascular events are higher in patients with HCV infection compared to controls, independent of the severity of the liver disease or common cardiovascular risk factors [85]. In addition to increased risk of atherosclerosis in HCV patients, another explanation for CAD risk is limitation of administration of protective treatment (antiplatelets and anticoagulants) in HCV patients with known metabolic risks, for fear of bleeding from the gastrointestinal tract or concerns about drugs which might cause further liver decompensation [89].

A meta-analysis concluded that there was a higher risk of CAD in HCV patients with already existing risk factors (like DM, hypertension, smoking) [90].

Although the effect of DAAs on HCV associated atherosclerosis is still unclear, it is suggested that virologic cure can decrease insulin resistance and endothelial cells and monocytes infection. On the other hand, the autoimmune effect of HCV will not be affected along with the risk of a rebound increase in the serum cholesterol and LDL-C. In a study conducted on HCV genotype-1 infected patients receiving sofosbuvir plus ribavirin, there was an apparent increase in LDL particle size and serum concentration early on treatment, while the VLDL concentration and triglycerides particle size decreased. The treatment outcome did not depend on these variables but it was noticed that before therapy and in relapsed patients the LDL concentration was lower [91]. So a hypothesis was proposed that cure could induce the “perfect storm” for atherosclerosis mandating close monitoring and even consideration of statin therapy but this was not addressed in a clinical trial [92]. Serum cholesterol and triglycerides increase with interferon therapy and return to baseline after treatment [93].

**HCV in relation to the risk of cerebrovascular stroke (CVS).** A meta-analysis showed that the risk of CVS is increased with HCV infection [94]. CVS risk was decreased in HCV treated patients, in a group with interferon-based therapy by 60% [95]. The same was shown with a decrease in risk of haemorrhagic stroke, particularly in cirrhotic patients. This could be explained by the prevention of deterioration of the coagulation profile in those patients [96].

#### *Impact of diabetes associating liver diseases on the liver*

##### *Promotion of liver fibrosis*

Obesity and increased fasting glucose levels were associated with increased severity of hepatic fibrosis in alcoholic liver disease, independently of daily alcohol intake and duration of alcohol abuse [97].

IR is increasingly recognized to be associated with severe fibrosis in chronic HCV patients [98,99]. The presence of diabetes in HCV patients was associated with more severe hepatic fibrosis independent of iron loading, male gender and alcohol consumption, possibly due to the oxidative injury of hyperglycaemia [100].

Excessive hepatic stellate cell activation is one proposed mechanism by which IR can induce fibrosis. IR activates the lipid biosynthetic pathway in the liver resulting in dyslipidaemia and increased steatosis, which can accelerate liver fibrosis [101]. IR plays an important role in NAFLD progression [102]. Statin use is negatively associated, while insulin and sulfonylureas are positively associated with NASH histology [103–106].

##### *Diabetes affects survival by increasing the risk of hepatocellular failure and variceal bleeding*

T2 DM was associated with increased risk of hospital admission and mortality for all common CLDs [107]. DM was an independent

predictor of poor survival in alcoholic hepatitis and cirrhosis regardless of alcohol amount and cirrhosis aetiology [108]. DM is independently associated with hepatic encephalopathy in patients with cirrhosis [109].

The mechanisms by which diabetes worsens the clinical course of liver cirrhosis have not been clearly established. Two major pathways can contribute to this: DM accelerates liver fibrosis and inflammation giving rise to more severe liver failure [110]. Furthermore, DM may potentiate the incidence of bacterial infections in cirrhotic patients with an associated increase in encephalopathy, variceal bleeding, and spontaneous bacterial peritonitis and subsequently increase mortality [111,112]. DM is independently associated with variceal bleeding in cirrhotic patients, especially in those with Child-Pugh Class A and the risk of bleeding increases with poor glycaemic control [113].

Gut microbiota products activate the innate immune system to drive pro-inflammatory gene expression, thus, promoting chronic inflammatory disease of the liver [114]. In NAFLD models, the translocation of bacterial components promotes TNF- $\alpha$  release from Kupffer cells and induces hepatic inflammation through TLR4 and TLR9 signaling [115,116]. NAFLD severity was found to be associated with gut dysbiosis and a shift in the metabolic function of the gut microbiota [117].

##### *Relation between glucose intolerance and antiviral therapy in patients with chronic hepatitis C*

Altered glucose metabolism impairs sustained virological response (SVR) to interferon viral treatment, while SVR reduces the risk of IFG and/or T2 DM development in patients with chronic hepatitis C [118]. The presence of T2 DM or haemodialysis did not affect SVR in DAAs treatment [119]. Also, markedly improved glycaemic control in poorly controlled T2 DM following DAAs treatment of genotype 1 hepatitis C was reported [120].

##### *DM association with CLD as a risk for HCC*

HCC had the highest incidence rate among primary cancer in a national and regional study performed in Egypt in 2014 [121].

A retrospective analysis of the US Veteran Registry found that diabetes increased the risk of primary liver cancer only in the presence of other risk factors such as hepatitis C or B or alcoholic cirrhosis [122]. Another study found an increased HCC risk in diabetic patients independently from alcoholic liver disease and viral hepatitis [123]. HCV and HBV infections, diabetes and smoking are the main determinants of HCC development in Egypt [124].

Diabetes has been proposed as a risk factor for HCC in HCV patients with or without cirrhosis, even after eradication of HCV [125]. This risk diminishes significantly 2 years after SVR [126].

**Mechanism and pathogenesis of increased HCC in diabetic HCV patients.** One mechanism by which HCV can cause HCC is its core protein which can cause the downregulation of insulin receptor substrate-1 signaling [127]. Concurrent DM may be a surrogate of a more systemic metabolic syndrome or concurrent NAFLD or NASH and when coincident with HCV leads to increased risk of fibrosis and HCC [128]. Hyperinsulinaemia may play a crucial role as an important factor in the onset or progression of HCC through up-regulation of insulin signal cascades; this could promote fibrogenesis [129].

It is possible that HCV eradication reduces HCC risk not only via reversal of fibrosis and prevention of further histologic injury, but also via improvements in insulin resistance and metabolic health [128].

HOMA/IR ( $\geq 2.5$ ) independently correlated with the development of HCC. HOMA/IR is a simple and practical biomarker for predicting the development of HCC, particularly for non-cirrhotic patients, irrespective of treatment outcome, serum ALT or AFP level [130].

## Treatment of diabetes associating liver disease

### *Lifestyle changes: nutrition and physical activity*

#### *Spots on nutrition of diabetic and hepatic patients*

The prevalence of clinically significant malnutrition varies from 65% to 100% among patients with chronic liver disease [131].

European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines recommend applying the Subjective Global Assessment (SGA) and anthropomorphic measures (i.e. triceps skin-fold thickness and midarm circumference) to identify patients at risk for malnutrition and to quantify malnutrition with bioelectrical impedance analysis [132].

Malnutrition in patients with chronic liver disease results from a variable combination of inadequate intake, poor quality diet, maldigestion, malabsorption, altered macronutrient metabolism and hypermetabolic state. Sarcopenia or loss of skeletal muscle mass is the major component of malnutrition and is a frequent complication of cirrhosis that adversely affects clinical outcomes. It contributes to the aggravation of other complications of cirrhosis including encephalopathy, ascites, and portal hypertension [133]. Protein malnutrition represents an independent prognostic factor for survival in patients with liver cirrhosis [134,135].

Liver cirrhosis is associated with energy malnutrition, with numerous metabolic disorders, such as hypoalbuminaemia, with an imbalance between branched-chain amino acids and aromatic amino acids and with reduced zinc serum concentrations [136].

T1 DM and T2 DM treatment plans should include medical nutrition therapy (MNT) [137]. Diabetes MNT includes assessment of an individual's metabolic and lifestyle parameters, identification of nutrition goals, the intervention designed to achieve these goals, and evaluation of clinical outcomes [138]. In addition to weight loss, other goals including the prevention or delay of diabetes onset and reduced cardiovascular events are targeted as well [139]. A variety of eating patterns have been shown modestly effective in managing diabetes including Mediterranean diet was the most effective dietary option [140–142].

#### *Diet planning for patients with chronic liver disease: [143,144].*

- \* Optimal energy intake: 25–40 kcal/kg/day
- Carbohydrate: 50–70% of daily calories with decreased simple sugars specially fructose
- Lipids: 10–20% of daily calories with increased MUFAs and PUFAs
- \* Protein intake

Daily protein intake: 1.2–1.5 g/kg, 0.6–0.8 g/kg. With acute encephalopathy vegetarian protein is preferred over animal protein.

- \* Small meals evenly distributed through the day and a bedtime snack of complex carbohydrates minimizes muscle loss and reduces the risk of hypoglycaemia in diabetic cirrhotic.
- \* Branched-chain amino acid supplementation may help achieve daily protein goals in patients who are protein intolerant, this can improve clinical outcome in advanced cirrhosis.
- \* Moderate sodium restriction (80–120 mmol/day or 4.6–6.9 g salt/day) is a mainstay of therapy in ascites.
- \* Fluid restriction is not recommended until serum sodium decreases to <120–125 mmol/L.
- \* Correction of folate, vitamin B 12, vitamin D, and vitamin A deficiencies.

#### *Physical activity*

Physical activity enables reduction of expression of lipogenic genes, fat accumulation, or insulin resistance and improves car-

diorespiratory fitness. Benefits have been found following both aerobic exercise and resistance training (not in cirrhotics), and remain even after exercise cessation [145].

### *Pharmacotherapy of diabetes associating liver disease*

Pharmacologic options are, for the most part, similar to patients without liver disease. Only patients with severely impaired liver function have altered drug metabolism. While patients with liver disease are not predisposed to hepatotoxicity, the underlying liver disease may increase the severity of drug-induced liver injury [146].

#### *Oral antidiabetic drugs and insulin in the treatment of diabetes associating liver disease*

##### *Pharmacology and clinical aspects of antidiabetics.*

**Sulfonylureas (metabolized in the liver).** Glyburide has a short plasma half-life (2–10 h) but prolonged biological effect. Glipizide has approximately 50% fewer confirmed hypoglycaemic episodes in comparison with glimepiride. Glipizide has a shorter half-life that makes it less likely than glyburide to produce hypoglycaemia. Glimepiride protein binding is greater than 99%. It is extensively metabolized by hepatic cytochrome enzymes [147,148]. Sulphonylureas may be injurious in NAFLD due to weight gain with prolonged duration of action in patients with CLD.

**Meglitinides.** Both repaglinide and nateglinide are rapidly absorbed upon oral administration. Repaglinide and nateglinide have not been associated with hepatotoxicity [149].

**$\alpha$ -Glucosidase inhibitors.** Acarbose is particularly useful in liver disease, acting directly on the gastrointestinal tract to decrease carbohydrate absorption. In cirrhotics, there was also a reduction in blood ammonia levels, so it is an effective drug in cirrhotic patients with low-grade hepatic encephalopathy and T2 DM [150].

**Metformin.** It has been shown to lower body fat and improve hepatic insulin sensitivity [151]. Continuation of metformin after cirrhosis diagnosis reduced the risk of death by 57%.

**Thiazolidinediones (TZDs).** TZDs are effective in sensitizing the adipose tissue to insulin hence promoting fatty acid uptake and storage. TZDs act as agonists of the PPAR $\gamma$  which are highly expressed in adipocytes. Its main function is to promote and maintain the whole body insulin sensitivity [152].

**Incretins dipeptidyl peptidase-4 inhibitors (DPP-4 I).** DPP-4 has a major role in fibroblast activation in the liver by activating hepatic stellate cells (HSCs). DPP4-I markedly inhibits liver fibrosis development in rats via suppression of HSCs proliferation and collagen synthesis. Since DPP4-I is widely used in clinical practice, this drug may represent a potential new therapeutic strategy against liver fibrosis [153].

Higher serum DPP-4 activity was found in CHC patients [154]. Sitagliptin is effective and safe for the treatment of T2 DM associated with HCV [155]. It is suggested that sitagliptin can be administered effectively and safely to patients with diabetes mellitus complicated by CLD, including liver cirrhosis [156].

**Glucagon-like peptide-1 receptor agonist (GLP-1RA).** In addition, to be effective glucose-lowering agents, GLP-1 analogues promote weight loss [157]. Preclinical studies have found that incretins can improve hepatic steatosis. Effects could be due to, an overall improvement in metabolic parameters as well as a direct effect on the hepatocyte GLP-1 receptor, suppressing hepatic lipogenesis. Improvement mostly occurs independently from weight loss [158,159].

**Sodium-glucose cotransporter-2 inhibitors [SGLT-2 Is].** No dosage adjustment for SGLT2Is is necessary for patients with mild or moderate hepatic impairment [160]. In the EMPA-REG OUTCOME study, empagliflozin significantly reduced the risk of the composite

primary endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke [161].

**Insulin.** Short-acting insulins are preferred because the duration of action may vary in CLD [162]. Insulin analogs may offer equivalent or improved glycaemic control compared to standard insulin and with a lower risk for hypoglycaemia. 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 [163].

The impact of early diagnosis and treatment of diabetes on the clinical course of patients with cirrhosis and diabetes is unknown. However, it is tempting to speculate that it could be beneficial. There is no clinical trial that specifically targeted treatment of patients with coexistent diabetes and cirrhosis [31] (Table 2).

#### Other drugs used in the management of disorders associated with T2 DM

##### Lipid disorders.

**Statins.** Due to its antioxidant and anti-inflammatory properties, the increased cardiovascular risk among NAFLD patients and the frequent NAFLD dyslipidaemia, statins are an appealing tool in NAFLD. In a large cohort of patients with NAFLD, statins use was accompanied by lower hepatic fibrosis. These data reiterate both the safety and benefit of statins in NAFLD [103]. However, until randomized clinical trials with histologic endpoints prove their efficacy, statins should not be used to specifically treat NASH.

**Fibrates.** Fibrates activate transcription factors belonging to the PPAR- $\alpha$  family, which regulates lipid and glucose metabolism as well as inflammation. Statins-fibrate combination therapy should be undertaken cautiously and reserved for patients with severe or refractory hyperlipidaemia. 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 [165].

**Omega-3 fatty acids.** They have a crucial role in the alteration of the hepatic gene expression, thus, switching lipogenesis to fatty acid oxidation and catabolism; moreover, they improve insulin sensitivity and reduce TNF $\alpha$  levels [166].

**Ezetimibe.** Has been suggested to reduce inflammatory processes during its metabolism in the liver and improving liver sensitivity to insulin [167,168]. Due to its antioxidant capacity and safety profile, ezetimibe is a good option for NAFLD patients with high cardiovascular risk factors [169]. Cholesterol-lowering by both statin and ezetimibe combinations has also been shown to

improve necroinflammation and reverse hepatic fibrosis in diabetic mice models [170].

**Antihypertensive drugs in cirrhotic patients.** Experimentally and in patients with NASH, losartan results in the improvement of serum liver enzyme levels and hepatic necroinflammation. Losartan decreases blood markers of hepatic fibrosis, activation of hepatic stellate cells, TGF- $\beta$  levels, and, thus hepatic fibrosis. [171]. In patients with CHC administration of an AT1R antagonist may improve liver scores of fibrosis stage [172].

#### Insulin-sensitizing agents and prognosis of cirrhosis and HCC

##### Insulin-sensitizing agents and prognosis of cirrhosis

Metformin has been shown to reduce the risk of hepatic encephalopathy in diabetic cirrhotic patients, probably by 2 mechanisms: Inhibiting partially glutaminase activity and improving insulin sensitivity [173].

Diabetic patients with compensated HCV cirrhosis were treated by different antidiabetic drugs and evaluated for the development of HCC, liver-related death or liver transplantation. The 5-yr HCC occurrence was significantly lower in the group receiving metformin than other groups. Moreover, metformin treatment was independently associated with decreased liver-related death or transplantation [174].

##### Insulin-sensitizing agents and hepatocellular carcinoma

Some studies found that thiazolidinedione treatment is significantly associated with a reduced incidence of HCC [175], while others reported that TZDs did not modify the risk of HCC [176]. A meta-analysis that involved one randomized controlled trial and 12 observational studies showed that metformin is chemoprotective with low incidence of HCC while insulin was associated with increased risk so the choices for antidiabetic treatment in diabetic cirrhotic patients is metformin first, second TZDs, followed by sulphonylurea while insulin was ranked as lowest in prevention of HCC [175], these results should be interpreted with caution due to considerable heterogeneity among studies included in such analysis.

#### Andrological aspects of diabetes associating liver disease

The most important sexual health indicator is erectile dysfunction (ED). The risk factors are age, duration of diabetes, peripheral neuropathy, body mass index, cigarette smoking, hypertension,

**Table 2**  
Therapeutic options for treatment of DM in patients with cirrhosis and their potential benefit (modified from [31,164]).

Therapy	Mechanism of action	Useful in T2 DM	Useful in patients with cirrhosis and DM	Side-effects/risks
<i>Lifestyle interventions: Low fat diet-Physical exercise</i>	Decrease liver and adipose fat-Increase insulin sensitivity	Very useful	Potentially useful	Malnutrition frequent-Physical exercise may not be feasible in patients with advanced cirrhosis
<i>Metformin: First line therapy</i>	Increase insulin sensitivity	Very useful	Very useful, decreased risk of HCC and HE, longer survival	Contraindicated in patients with renal dysfunction. Theoretical risk of lactic acidosis
<i>Thiazolidinediones</i>	Increase insulin sensitivity	Useful	No available data	Contraindicated in patients with advanced cirrhosis because of the risk of hypoglycaemia
<i>Secretagogues: Sulphonyureas-Glinides</i>	Increase endogenous production of insulin	Useful	Not useful	
<i>Incretins: GLP-1 receptor analogues-DPP-4 inhibitors</i>	Increase insulin sensitivity	Very useful-Obese patients (weight loss)	Decrease liver fibrosis and inflammation	Benign digestive side-effects
<i>Alpha-glucosidase inhibitors</i>	Decrease carbohydrate absorption in the bowel	Useful	May be useful in patients with HE	
<i>Insulin</i>	Substitutive treatment	Often necessary	Often necessary	Risk of hypoglycaemia
<i>SGLT2 Is</i>		Ameliorated diabetes	??	

dyslipidaemia, alcohol consumption and lack of exercise [177–179].

In NAFLD testosterone deficiency is associated with increased visceral adipose tissue and IR in males. Alcoholic liver disease causes gonadal dysfunction from toxic effects of alcohol. Alcoholics have phenotypic changes due to hormone imbalance, with earlier decreased serum testosterone due to alcohol itself whereas the E2 increase is evident after long periods of intake, and thus hypogonadism precedes liver feminization [180].

Cirrhotic men have signs of hypogonadism due to reduced production of albumin affecting the ratio of free testosterone to albumin-bound testosterone and total testosterone levels, physical disturbance by protein malnutrition and hypothalamic–pituitary–gonadal axis by reduced pulsatile secretion of LH and response to gonadotropin-releasing hormone [181,182].

Poor glycaemic control is associated with ED in T2 DM, specially among young age group while age is the only significant independent risk factor among older age group [183,184]. There is a significant positive correlation between ED in patients on insulin and either macrovascular disease or neuropathy [185].

The management includes oral phosphodiesterase type 5 inhibitors, use of intracorporeal injection of prostaglandin E1 or the use of penile prosthesis as the last resort [178].

## Management of liver disease associated with diabetes

### *Prognosis of cirrhosis associated with diabetes*

The impact of diabetes on lowering cirrhotic patients' survival has been demonstrated. The risk of acquiring HE and its severity, the increased risk of ascites, and bacterial infections in chronic liver disease patients with diabetes is higher than those without diabetes [186,187].

Assessment of cirrhosis in diabetics may be better distinguished from the prognostic markers of cirrhosis in nondiabetics, as studies showed that it is not correlating with the current Child-Pugh and MELD scoring systems [188]. Perhaps the addition of DM to the currently used scores may enhance sensitivity and specificity for prediction of morbidity and mortality rates in cirrhotic patients [32,189]. Post liver transplantation-free survival was shorter in diabetics, independent of MELD score. Diabetes had an effect on prognosis in those with baseline MELD score <10, while those with MELD >10 were not affected by it. This could be explained by separating HD which occurs in late cirrhosis and has no effect on the survival, and the effect of pre-existing diabetes which by itself deteriorates the liver functions and the general condition of the patient undetected by the conventional scoring systems available [187].

### *NAFLD: A possible new target for T2 DM prevention and treatment*

Diabetes and NAFLD are reciprocal risk factors and when they occur together, an increasing body of data (previously discussed) demonstrates that diabetes is more difficult to manage and that NAFLD is more likely to progress. NAFLD is not only one of the more prominent chronic liver diseases, but also a new predictive marker of T2 DM, with potential therapeutic implications [190]. The ideal drug will need to address not only the liver complications but prevent cardiovascular death, the main cause of mortality in this patient population [191].

As NAFLD and T2 DM share some common pathophysiologic mechanisms, they may also share the same treatment with restoring insulin action as the main target of treatment [192].

### *Metformin*

Kita, Y et al., found improvement in liver transaminases and metabolic syndrome features on metformin therapy. However, to date, only a few data are available regarding histological changes after metformin therapy [193].

### *Thiazolidinediones*

A double-blind randomized placebo controlled study found that pioglitazone (45 mg daily for 18 months) ameliorated the primary endpoint, NAFLD activity score in patients with NASH and prediabetes or T2 DM [194]. The response to pioglitazone in NASH can be predicted by the increase in plasma adiponectin levels within the first 1–3 months after treatment initiation [195]. Recently, its long-term safety (with some precautions) and efficacy was confirmed in patients with NASH and either impaired fasting glucose and/or impaired glucose tolerance or T2 DM [192].

### *Incretins*

Liraglutide significantly improved serum markers of adipose inflammation (leptin and adiponectin), improved liver histology and led to weight loss [191]. In the most comprehensive study to date, the LEAN (Liraglutide Efficacy and Action in Non-alcoholic steatohepatitis) trial showed benefit for biopsy-proven NASH who were treated for 48 weeks with liraglutide at a dose of 1.8 mg per day [192]. Meta-analysis of clinical trials of liraglutide in T2 DM, [196] have suggested that GLP-1RAs could improve NASH and it has been shown to be an effective treatment for those with and without diabetes [197]. Studies with DPP-4 inhibitors have reported mixed results regarding liver fat reduction [198–200].

### *Sodium-glucose cotransporter 2 (SGLT2) inhibitors*

In patients with diabetes, levels of plasma aminotransferases decrease during treatment with SGLT2 [201]. Pooled data from four 26 week placebo-controlled studies of canagliflozin (n = 2313) and two 52 week active-controlled studies of canagliflozin vs sitagliptin (n = 1488) found significant reductions in plasma ALT with canagliflozin 300 mg compared with placebo or sitagliptin [202]. Changes in aspartate aminotransferase were fully explained by the reduction in HbA1c and body weight.

### *Metabolic effects of HCV in the era of recently developed DAAs*

In the era of new DAAs, there will be a rapid change in peripheral and intra-hepatic metabolic pathways, implicating a direct effect of HCV replication on lipid homeostasis. Several studies have indicated that virus-induced lipogenic genes over-expression exerts a strong influence on inflammation and fibrosis progression, rather than causing the lipid accumulation observed in patients with steatosis [203].

Sofosbuvir treatment has been associated with an increased concentration and size of the LDL particles following viral clearance [91]. In a retrospective study using direct antiviral agents, HCV eradication was associated with an increase in total cholesterol and LDL. Also, a significant decrease in HbA1c was observed, which may be through repairing defects in phosphatidylinositol 3 kinase (PI3K) and tyrosine kinase activator (AKT) phosphorylation pathways as well as improvement in insulin resistance. Such findings should draw attention to the great need to follow patients after viral eradication to spot changes in blood sugar levels and lipid pattern [204].

### *Drug-drug interactions of DAAs*

Most of the metabolism-related DDAs involve the cytochrome P450 (CYP) enzyme superfamily [205].



## Other associations between diabetes and liver disease

### *New onset diabetes mellitus after liver transplantation (NODAT)*

Survival rates of transplanted patients have improved significantly. Accordingly, long-term metabolic complications like DM have gained increasing interest. [206,207]. NODAT is new onset DM after transplantation (PLDT: Post-transplant DM). Mostly, the term PLTD rather than NODAT is reverted to in an acknowledgment that diabetes diagnosed after transplantation might be pre-existing but undiagnosed.

In a retrospective study involving Egyptian liver transplant recipients including 40 patients, the incidence of NODAT was 25% [208]. In a meta-analysis [209]; all studies found were retrospective, the overall incidence of NODAT was 30.2%. The prevalence and incidence vary with the time from transplantation with the highest being during the first 6 months and declining after the first year.

It is important to note that even temporary NODAT occurring from 1 to 6 months post-transplantation, could be responsible for a decreased recipient and graft survival [210].

### *Impact on transplant outcome*

Mortality and morbidity are mainly related to graft survival, infections, cardiovascular complications and chronic renal insufficiency [211–213].

In the study by Lv *et al.*, patients had no pre-transplant diabetes mellitus, however; NODAT was associated with reduced survival, increased incidence of sepsis and chronic renal insufficiency [214]. In another study, cryptogenic cirrhosis, hypertension, and CAD were 2–3 times more common in recipients with NODAT than those without [215]. On the contrary, a retrospective analysis (13,736 transplant recipients), showed that NODAT alone was not associated with an increased risk of graft failure, mortality or cardiovascular mortality, but pretransplant DM was the only factor associated with cardiovascular mortality 1 year post-transplant [216].

In one meta-analysis, the collective prevalence of metabolic syndrome post-transplant was 39%, with new-onset metabolic syndrome prevalence of 35%, causing an increase in the cardiovascular events but not mortality [217].

### *Pathogenesis and risk factors*

In addition to the risk factors of DM in the general non-transplant population, certain factors are unique in organ transplant recipient, particularly liver transplant recipient. Chronic HCV (synergistically or independently) is one of the major risk factors for developing NODAT [218]. Other risk factors include older age, male gender, high BMI, donor graft steatosis, impaired fasting blood sugar, and more importantly the immunosuppressive drugs [209,219,220].

Regarding immunosuppressives, steroids are the cornerstone in the first 3–6 months after transplantation (highest incidence of NODAT during the first 6 months). Calcineurin inhibitors, CNI (tacrolimus, cyclosporine) exert an apoptotic effect on pancreatic  $\beta$  cells [221]. Other immunosuppressives as IL-2 receptor antagonists are on the contrary protective against NODAT, mainly due to avoidance of beta cell destruction [222].

Gut microbiota disturbance can occur with liver transplantation due to various causes like antibiotic regimens, operative and post-operative stress. This could lead to blooming of certain species as proteobacteria. In mice it has been demonstrated that tacrolimus could cause an imbalance between bacteroides and firmicutes. Both could lead to a state of insulin resistance and NODAT [223].

### *Diagnosis and management*

The diagnosis, goals of long-term management and treatment of PLTD are not substantially different from the general population [224,225]. The main concern should be for the allograft and patient survival. In the peri- and early postoperative period, insulin is generally required. When insulin requirements are low, oral agents may be substituted if graft function is normal. In addition, modulating immunosuppression may be of benefit [226]. NODAT tends to remit over time especially as corticosteroids are withdrawn and CNI dosage is reduced, and patients may shift from insulin therapy to oral hypoglycaemic agents to diet control only over the years [227].

### *HBV and diabetes mellitus*

It is known that diabetic patients are at increased risk of contracting HBV because of their regular blood glucose monitoring and unavoids contamination of these devices. The Centers for Disease Control and Prevention recommended HBV vaccination for all diabetic patients [228].

The question remained, whether HBV per se (without cirrhosis) causes DM or not and the risk factors involved in this causal relation. The other aspect of the issue is the synergistic effect of DM and chronic HBV on liver fibrosis and development of HCC [229,230].

### *HBV as a risk factor for diabetes mellitus*

Studies (mostly on Asian populations) demonstrated a higher prevalence of diabetes mellitus in HBV patients (up to 14%) compared to age and gender-matched general population (9%) [231–233]. But, they all fail to define if HBV is a risk factor for the development of diabetes mellitus. Limitations were many in these studies [234–236]. In another study on patients with DM versus non-diabetic control, it was found that the prevalence of HBV infection was higher in patients with T2 DM versus non-diabetics (13.5 vs 10.0%,  $p = 0.004$ ), but there was no increase with adult-onset autoimmune DM [237].

On the other hand, some studies showed no relation between HBV and development of diabetes mellitus [238,239] (HBV itself is not pro-diabetic).

### *HBV and steatosis*

The more important question is if HBV can cause steatosis/IR as in the case of HCV.

In a meta-analysis including 17 studies [240] HBV infection may have a paradoxical protective effect on liver steatosis. In addition, hepatic steatosis in HBV-infected patients was similar to the general population and was mainly associated with; DM, male gender, alcohol consumption, and hyperlipidaemia, with a negative association with the HBV viral load, while genotype and HBeAg status had no influence.

On the other hand, in a meta-analysis including four studies [241], assessing the prevalence of the metabolic syndrome in relation to chronic HBV, lower tendency of metabolic syndrome with HBV infection was found, but this was not statistically significant.

Chao *et al.*, studied a cohort of 2903 government employee with chronic HBV for serum level of insulin and incidence of HCC in 17 years follow up period. They found that elevated insulin levels are an independent risk factor for HCC among HBV carriers even after correction of other metabolic factors [242].

It goes without saying that the presence of steatosis per se in HBV patient will increase stress on hepatocytes and promotes further progression and fibrosis. No matter whether HBV-IR related to a higher incidence of diabetes and/or NAFLD; those patients need higher medical attention.

### Synergistic effect of HBV and DM on fibrosis progression and incidence of HCC

DM was found to be an independent factor associated with cirrhosis and its decompensation and a significant synergistic factor in the development of HCC in patients with chronic HBV infection [243,244]. Whether these results reflect the synergistic effect of DM and the inflammatory state or if these are specific to HBV (as in the case with HCV) remains to be elucidated.

The debate is not closed as a recent retrospective case-control study [245], found that there was no increased risk of HCC with DM in infected HBV patients. In another meta-analysis, a strong evidence-based association between HBV, DM and progression of liver disease in the form of cirrhosis progression, decompensation, HCC, the need for liver transplantation and/or mortality [246].

These data compelled physicians to insist on improved diabetic control, which should be part of the surveillance protocols of HBV patients.

### References

- [1] Upadhyay R. Diabetic hepatopathy. In: Munjal YP, editor. In API Textbook of Medicine 2017. p. 314–8.
- [2] Orsi E, Grancini V, Menini S, Aghemo A, Pugliese G. Hepatogenous diabetes: is it time to separate it from type 2 diabetes? *Liver Int* 2017;37(7):950–62.
- [3] Levinthal GN, Tavill AS. Liver disease and diabetes mellitus. *Clin Diab* 1999;17(2).
- [4] Petaja EM, Yki-Jarvinen H. Definitions of normal liver fat and the association of insulin sensitivity with acquired and genetic NAFLD—a systematic review. *Int J Mol Sci* 2016;17(5).
- [5] Ahmed M. Non-alcoholic fatty liver disease in 2015. *World J Hepatol* 2015;7(11):1450–9.
- [6] Chan WK, Tan AT, Vethakkan SR, Tah PC, Vijayanathan A, Goh KL. Non-alcoholic fatty liver disease in diabetics—prevalence and predictive factors in a multi-racial hospital clinic population in Malaysia. *J Gastroenterol Hepatol* 2013;28(8):1375–83.
- [7] Prashanth M, Ganesh HK, Vima MV, John M, Bandgar T, Joshi SR, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus. *J Assoc Phys India* 2009;57:205–10.
- [8] Fukuda T, Hamaguchi M, Kojima T, Hashimoto Y, Ohbora A, Kato T, et al. The impact of non-alcoholic fatty liver disease on incident type 2 diabetes mellitus in non-overweight individuals. *Liver Int: Off J Int Assoc Study Liver* 2016;36(2):275–83.
- [9] Ming J, Xu S, Gao B, Liu G, Ji Y, Yang F, et al. Non-alcoholic fatty liver disease predicts type 2 diabetes mellitus, but not prediabetes, in Xi'an, China: a five-year cohort study. *Liver Int* 2015;35(11):2401–7.
- [10] Li WD, Fu KF, Li GM, Lian YS, Ren AM, Chen YJ, et al. Comparison of effects of obesity and non-alcoholic fatty liver disease on incidence of type 2 diabetes mellitus. *World J Gastroenterol* 2015;21(32):9607–13.
- [11] Bae JC, Rhee EJ, Lee WY, Park SE, Park CY, Oh KW, et al. Combined effect of nonalcoholic fatty liver disease and impaired fasting glucose on the development of type 2 diabetes: a 4-year retrospective longitudinal study. *Diabetes Care* 2011;34(3):727–9.
- [12] Shibata M, Kihara Y, Taguchi M, Tashiro M, Otsuki M. Nonalcoholic fatty liver disease is a risk factor for type 2 diabetes in middle-aged Japanese men. *Diabetes Care* 2007;30(11):2940–4. Epub 007 Jul 31.
- [13] Ballestri S, Zona S, Targher G, Romagnoli D, Baldelli E, Nascimbeni F, et al. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome: evidence from a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2016;31(5):936–44.
- [14] Bae JC, Cho YK, Lee WY, Seo HI, Rhee EJ, Park SE, et al. Impact of nonalcoholic fatty liver disease on insulin resistance in relation to HbA1c levels in nondiabetic subjects. *Am J Gastroenterol* 2010;105(11):2389–95.
- [15] Valenti L, Bugianesi E, Pajvani U, Targher G. Nonalcoholic fatty liver disease: cause or consequence of type 2 diabetes? *Liver Int: Off J Int Assoc Study Liver* 2016;36(11):1563–79.
- [16] Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010;363(14):1341–50.
- [17] Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol* 2005;42(1):132–8.
- [18] McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol* 2015;62(5):1148–55.
- [19] Lomonaco R, Bril F, Portillo-Sanchez P, Ortiz-Lopez C, Orsak B, Biernacki D, et al. Metabolic impact of nonalcoholic steatohepatitis in obese patients with T2DM. *Diabetes Care* 2016;39(4):632–8.
- [20] Yamazaki H, Tsuboya T, Tsuji K, Dohke M, Maguchi H. Independent association between improvement of nonalcoholic fatty liver disease and reduced incidence of type 2 diabetes. *Diabetes Care* 2015;38(9):1673–9.
- [21] Silva M, Marques M, Cardoso H, Rodrigues S, Andrade P, Peixoto A, et al. Glycogenic hepatopathy in young adults: a case series. *Rev Esp Enferm Dig* 2016;108(10):673–6.
- [22] van den Brand M, Elving LD, Drenth JP, van Krieken JH. Glycogenic hepatopathy: a rare cause of elevated serum transaminases in diabetes mellitus. *Neth J Med* 2009;67(11):394–6.
- [23] Rubio-Rivas M, Montero-Alia P, Ordi-Ros J, Labrador M. Hepatic glycogenosis and diabetes mellitus. *Med Clin (Barc)* 2005;125(7):279.
- [24] Imtiaz KE, Healy C, Sharif S, Drake I, Awan F, Riley J, et al. Glycogenic hepatopathy in type 1 diabetes: an underrecognized condition. *Diabetes Care* 2013;36(1):e6–7.
- [25] Umpaichitra V. Unusual glycogenic hepatopathy causing abnormal liver enzymes in a morbidly obese adolescent with well-controlled type 2 diabetes: resolved after A1c was normalized by metformin. *Clin Obes* 2016;6(4):281–4.
- [26] Parmar N, Atiq M, Austin L, Miller RA, Smyrk T, Ahmed K. Glycogenic hepatopathy: thinking outside the box. *Case Rep Gastroenterol* 2015;9(2):221–6.
- [27] Al-Hussaini AA, Sulaiman NM, AlZahrani MD, Alenizi AS, Khan M. Prevalence of hepatopathy in type 1 diabetic children. *BMC Pediatr* 2012;12:160.
- [28] King RJ, Harrison L, Gilbey SG, Santhakumar A, Wyatt J, Jones R, et al. Diabetic hepatosclerosis: another diabetes microvascular complication? *Diabetic Med: A J Br Diabetic Assoc* 2016;33(2):e5–7.
- [29] Nazzari E, Grillo F, Celiento T, Picciotto A, Ferone D, Murialdo G, et al. Diabetic hepatosclerosis presenting with severe cholestasis. *Diabetes Care* 2013;36(12):e206.
- [30] de Oliveira Andrade LJ, Raymundo Paraná R, Bittencourt AMV, Santana de Melo PRS, Nunes VLC. Diabetic hepatopathy. *Braz J Med Human Health* 2015;3(2):61–6.
- [31] Elkrief L, Rautou P-E, Sarin S, Valla D, Paradis V, Moreau R. Diabetes mellitus in patients with cirrhosis: clinical implications and management. *Liver Int* 2016;36(7):936–48.
- [32] Garcia-Compean D, Jaquez-Quintana JO, Gonzalez-Gonzalez JA, Maldonado-Garza H. Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. *World J Gastroenterol* 2009;15(3):280–8.
- [33] García-Compeán D, González-González JA, Lavallo-González FJ, González-Moreno EI, Villarreal-Pérez JZ, Maldonado-Garza HJ. Hepatogenous diabetes: is it a neglected condition in chronic liver disease? *World J Gastroenterol* 2016;22(10):2869–74.
- [34] Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J Hepatol* 2000;32(2):209–17.
- [35] Hamed AE, Abbas B, Shaltout I, Esmt G, Gomez R, Kumar A, et al. Managing diabetes and liver disease association, guidelines (consensus) development. *J Endocrinol Diabetes Obes* 2015;3(3):1073.
- [36] Adams PC, Kertesz AE, Valberg LS. Clinical presentation of hemochromatosis: a changing scene. *Am J Med* 1991;90(4):445–9.
- [37] Kawaguchi T, Taniguchi E, Itou M, Sakata M, Sumie S, Sata M. Insulin resistance and chronic liver disease. *World J Hepatol* 2011;3(5):99–107.
- [38] Pallayova M, Wilson V, John R, Taheri S. Liver transplantation: a potential cure for hepatogenous diabetes? *Diabetes Care* 2013;36(7):e97.
- [39] Nishida T, Tsuji S, Tsujii M, Arimitsu S, Haruna Y, Imano E, et al. Oral glucose tolerance test predicts prognosis of patients with liver cirrhosis. *Am J Gastroenterol* 2006;101(1):70–5.
- [40] Kim MG, Choi WC. Differential diagnosis of diabetes mellitus caused by liver cirrhosis and other type 2 diabetes mellitus. *Korean J Hepatol* 2006;12(4):524–9.
- [41] Zhang X, Shen W, Shen D-M. [A clinical analysis of liver disease patients with abnormal glucose metabolism] 2006; p. 289–92.
- [42] Zhang L, Shi YL, Hong WX, Jia WD, Li LH. Diagnostic value of serum islet autoantibody in hepatogenic diabetes mellitus. *Nan Fang Yi Ke Da Xue Xue Bao* 2006;26(7):1034–6.
- [43] Krishnan SM, Dixit NM. Estimation of red blood cell lifespan from alveolar carbon monoxide measurements. *Transl Res* 2009;154(1):15–7.
- [44] Trenti T, Cristani A, Cioni G, Pentore R, Mussini C, Ventura E. Fructosamine and glycated hemoglobin as indices of glycaemic control in patients with liver cirrhosis. *Ric Clin Lab* 1990;20(4):261–7.
- [45] Youssef D, El Abbassi A, Jordan RM, Peiris AN. Fructosamine—an underutilized tool in diabetes management: case report and literature review. *Tenn Med* 2008;101(11):31–3.
- [46] Clar C, Barnard K, Cummins E, Royle P, Waugh N. Self-monitoring of blood glucose in type 2 diabetes: systematic review. *Health Technol Assess* 2010;14(12):1–140.
- [47] Poolsup N, Suksomboon N, Kyaw AM. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. *Diabetol Metab Syndrome* 2013;5:39–40.
- [48] Garcia-Compean D, Jaquez-Quintana JO, Lavallo-Gonzalez FJ, Reyes-Cabello E, Gonzalez-Gonzalez JA, Munoz-Espinosa LE, et al. The prevalence and clinical characteristics of glucose metabolism disorders in patients with liver cirrhosis, prospective study. *Ann Hepatol* 2012;11(2):240–8.
- [49] Fujiwara F, Ishii M, Taneichi H, Miura M, Toshihiro M, Takebe N, et al. Low incidence of vascular complications in patients with diabetes mellitus

- associated with liver cirrhosis as compared with type 2 diabetes mellitus. *Tohoku J Exp Med* 2005;205(4):327–34.
- [50] Abe T, Nakajima A, Satoh N, Koizumi T, Sakuragi S, Ono T, et al. Clinical characteristics of hepatitis C virus-associated retinopathy. *Jpn J Ophthalmol* 1995;39(4):411–9.
  - [51] Llach J, Gines P, Arroyo V, Rimola A, Tito L, Badalamenti S, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. *Gastroenterology* 1988;94(2):482–7.
  - [52] Moller S, Henriksen JH. Cirrhotic cardiomyopathy. *J Hepatol* 2010;53(1):179–90.
  - [53] Nazar A, Guevara M, Sitges M, Terra C, Sola E, Guigou C, et al. LEFT ventricular function assessed by echocardiography in cirrhosis: relationship to systemic hemodynamics and renal dysfunction. *J Hepatol* 2013;58(1):51–7.
  - [54] Fouad TR, Abdel-Razek WM, Burak KW, Bain VG, Lee SS. Prediction of cardiac complications after liver transplantation. *Transplantation* 2009;87(5):763–70.
  - [55] Wong F. Cirrhotic cardiomyopathy. *Hep Intl* 2009;3(1):294–304.
  - [56] Wiese S, Hove JD, Bendtsen F, Moller S. Cirrhotic cardiomyopathy: pathogenesis and clinical relevance. *Nat Rev Gastroenterol Hepatol* 2014;11(3):177–86.
  - [57] Targher G, Bertolini L, Rodella S, Tessari R, Zenari L, Lippi G, et al. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. *Diabetes Care* 2007;30(8):2119–21.
  - [58] Mantovani A, Ballestri S, Lonardo A, Targher G. Cardiovascular disease and myocardial abnormalities in nonalcoholic fatty liver disease. *Dig Dis Sci* 2016;61(5):1246–67.
  - [59] Targher G, Lonardo A, Byrne CD. Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus. *Nat Rev Endocrinol* 2017;14:99.
  - [60] Sirbu O, Floria M, Dascalita P, Sorodoc V, Sorodoc L. Non-alcoholic fatty liver disease-From the cardiologist perspective. *Anatolian J Cardiol* 2016;16(7):534–41.
  - [61] Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* 2007;30(5):1212–8. Epub 2007 Feb 2.
  - [62] Braza-Boils A, Mari-Alexandre J, Molina P, Arnau MA, Barcelo-Molina M, Domingo D, et al. Deregulated hepatic microRNAs underlie the association between non-alcoholic fatty liver disease and coronary artery disease. *Liver Intl* 2016;36(8):1221–9.
  - [63] Yang W, Xu H, Yu X, Wang Y. Association between retinal artery lesions and nonalcoholic fatty liver disease. *Hepatol Intl* 2015;9(2):278–82.
  - [64] Federico A, Dallio M, Masarone M, Persico M, Loguercio C. The epidemiology of non-alcoholic fatty liver disease and its connection with cardiovascular disease: role of endothelial dysfunction. *Eur Rev Med Pharmacol Sci* 2016;20(22):4731–41.
  - [65] Koh JH, Shin YG, Nam SM, Lee MY, Chung CH, Shin JY. Serum adipocyte fatty acid-binding protein levels are associated with nonalcoholic fatty liver disease in type 2 diabetic patients. *Diabetes Care* 2009;32(1):147–52.
  - [66] Nobili V, Carpino G, Alisi A, Franchitto A, Alpini G, De Vito R, et al. Hepatic progenitor cells activation, fibrosis, and adipokines production in pediatric nonalcoholic fatty liver disease. *Hepatology* 2012;56(6):2142–53.
  - [67] Li XL, Sui JQ, Lu LL, Zhang NN, Xu X, Dong QY, et al. Gene polymorphisms associated with non-alcoholic fatty liver disease and coronary artery disease: a concise review. *Lipids Health Dis* 2016;15:53.
  - [68] Karajamaki AJ, Bloigu R, Kauma H, Kesaniemi YA, Koivurova OP, Perkiomaki J, et al. Non-alcoholic fatty liver disease with and without metabolic syndrome: different long-term outcomes. *Metabolism* 2017;66:55–63.
  - [69] Choi SY, Kim D, Kang JH, Park MJ, Kim YS, Lim SH, et al. Nonalcoholic fatty liver disease as a risk factor of cardiovascular disease: relation of non-alcoholic fatty liver disease to carotid atherosclerosis. *Korean J Hepatol* 2008;14(1):77–88.
  - [70] Sookoian S, Pirola CJ. Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. *J Hepatol* 2008;49(4):600–7.
  - [71] Oni ET, Agatston AS, Blaha MJ, Fialkow J, Cury R, Sposito A, et al. A systematic review: burden and severity of subclinical cardiovascular disease among those with nonalcoholic fatty liver; should we care? *Atherosclerosis* 2013;230(2):258–67.
  - [72] Pacifico L, Chiesa C, Anania C, De Merulis A, Osborn JF, Romaggioli S, et al. Nonalcoholic fatty liver disease and the heart in children and adolescents. *World J Gastroenterol*: WJG 2014;20(27):9055–71.
  - [73] El-Koofy NM, Anwar GM, El-Raziky MS, El-Hennawy AM, El-Mougy FM, El-Karakasy HM, et al. The association of metabolic syndrome, insulin resistance and non-alcoholic fatty liver disease in overweight/obese children. *Saudi J Gastroenterol* 2012;18(1):44–9.
  - [74] Takeuchi Y, Ito H, Komatsu Y, Oshikiri K, Antoku S, Abe M, et al. Non-alcoholic fatty liver disease is an independent predictor for macroangiopathy in Japanese type 2 diabetic patients: a cross-sectional study. *Intern Med* 2012;51(13):1667–75. Epub 2012 Jul 1.
  - [75] Ekstedt M, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006;44(4):865–73.
  - [76] Targher G, Valbusa F, Bonapace S, Bertolini L, Zenari L, Pichiri I, et al. Association of nonalcoholic fatty liver disease with QTc interval in patients with type 2 diabetes. *Nutr Metab Cardiovasc Dis* 2014;24(6):663–9.
  - [77] Kumar MS, Singh A, Jaryal AK, Ranjan P, Deepak KK, Sharma S, et al. Cardiovascular autonomic dysfunction in patients of nonalcoholic fatty liver disease. *Int J Hepatol* 2016;2016:5160754.
  - [78] McKimmie RL, Daniel KR, Carr JJ, Bowden DW, Freedman BI, Register TC, et al. Hepatic steatosis and subclinical cardiovascular disease in a cohort enriched for type 2 diabetes: the diabetes heart study. *Am J Gastroenterol* 2008;103(12):3029–35.
  - [79] Targher G, Bertolini L, Rodella S, Zoppini G, Lippi G, Day C, et al. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and proliferative/laser-treated retinopathy in type 2 diabetic patients. *Diabetologia* 2008;51(3):444–50. Epub 2007 Dec 6.
  - [80] Lv WS, Sun RX, Gao YY, Wen JP, Pan RF, Li L, et al. Nonalcoholic fatty liver disease and microvascular complications in type 2 diabetes. *World J Gastroenterol* 2013;19(20):3134–42.
  - [81] Vespasiani-Gentilucci U, Gallo P, De Vincentis A, Galati G, Picardi A. Hepatitis C virus and metabolic disorder interactions towards liver damage and atherosclerosis. *World J Gastroenterol* 2014;20(11):2825–38.
  - [82] Boddi M, Abbate R, Chellini B, Giusti B, Giannini C, Pratesi G, et al. Hepatitis C virus RNA localization in human carotid plaques. *J Clin Virol: Off Publ Pan Am Soc Clin Virol* 2010;47(1):72–5.
  - [83] Petta S, Torres D, Fazio G, Camma C, Cabibi D, Di Marco V, et al. Carotid atherosclerosis and chronic hepatitis C: a prospective study of risk associations. *Hepatology* 2012;55(5):1317–23.
  - [84] Adinolfi LE, Restivo L, Zampino R, Guerrero B, Lonardo A, Ruggiero L, et al. Chronic HCV infection is a risk of atherosclerosis: role of HCV and HCV-related steatosis. *Atherosclerosis*. 2012;221(2):496–502.
  - [85] Domont F, Cacoub P. Chronic hepatitis C virus infection, a new cardiovascular risk factor? *Liver Intl: Off J Int Assoc Study Liver* 2016;36(5):621–7.
  - [86] Ishizaka N, Ishizaka Y, Takahashi E, Tooda E, Hashimoto H, Nagai R, et al. Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening. *Lancet* 2002;359(9301):133–5.
  - [87] Huang H, Kang R, Zhao Z. Is hepatitis C associated with atherosclerotic burden? a systematic review and meta-analysis. *PLoS One* 2014;9(9):e106376.
  - [88] Mostafa A, Mohamed MK, Saeed M, Hasan A, Fontanet A, Godslan I, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. *Gut* 2010;59(8):1135–40.
  - [89] Voulgaris T, Sevastianos VA. Atherosclerosis as Extrahepatic manifestation of chronic infection with hepatitis c virus. *Hepatitis Res Treat* 2016;2016:7629318.
  - [90] Petta S, Maida M, Macaluso FS, Barbara M, Licata A, Craxi A, et al. Hepatitis C virus infection is associated with increased cardiovascular mortality: a meta-analysis of observational studies. *Gastroenterology* 2016;150(1):145–55. e4.
  - [91] Meissner EG, Lee YJ, Osinusi A, Sims Z, Qin J, Sturdevant D, et al. Effect of sofosbuvir and ribavirin treatment on peripheral and hepatic lipid metabolism in chronic hepatitis C virus, genotype 1-infected patients. *Hepatology* 2015;61(3):790–801.
  - [92] Bassendine MF, Nielsen SU, Bridge SH, Felmlee DJ, Sheridan DA, Packard CJ, et al. Hepatitis C virus and atherosclerosis: a legacy after virologic cure? *Clin Res Hepat Gastroenterol* 2016.
  - [93] Hamamoto S, Uchida Y, Wada T, Moritani M, Sato S, Hamamoto N, et al. Changes in serum lipid concentrations in patients with chronic hepatitis C virus positive hepatitis responsive or non-responsive to interferon therapy. *J Gastroenterol Hepatol* 2005;20(2):204–8.
  - [94] He H, Kang R, Zhao Z. Hepatitis C virus infection and risk of stroke: a systematic review and meta-analysis. *PLoS One* 2013;8(11):e81305.
  - [95] Hsu CS, Kao JH, Chao YC, Lin HH, Fan YC, Huang CJ, et al. Interferon-based therapy reduces risk of stroke in chronic hepatitis C patients: a population-based cohort study in Taiwan. *Aliment Pharmacol Ther* 2013;38(4):415–23.
  - [96] Arase Y, Kobayashi M, Kawamura Y, Suzuki F, Suzuki Y, Akuta N, et al. Impact of virus clearance for the development of hemorrhagic stroke in chronic hepatitis C. *J Med Virol* 2014;86(1):169–75.
  - [97] Raynard B, Balian A, Fallik D, Capron F, Bedossa P, Chaput JC, et al. Risk factors of fibrosis in alcohol-induced liver disease. *Hepatology* 2002;35(3):635–8.
  - [98] Ziada DH, El Saadany S, Enaba M, Ghazy M, Hasan A. The interaction among insulin resistance, liver fibrosis and early virological response in Egyptian patients with chronic hepatitis C. *Can J Gastroenterol* 2012;26(6):325–9.
  - [99] Dokmeci A, Ustundag Y, Hulagu S, Tuncer I, Akdogan M, Demiroş H, et al. The association between insulin resistance and hepatic fibrosis in patients with chronic hepatitis C: an observational, multicenter study in Turkey. *Turk J Gastroenterol* 2014;25(5):546–52.
  - [100] Wood MJ, Powell LW, Dixon JL, Ramm GA. Clinical cofactors and hepatic fibrosis in hereditary hemochromatosis: the role of diabetes mellitus. *Hepatology* 2012;56(3):904–11.
  - [101] Goto K, Lin W, Zhang L, Jilg N, Shao RX, Schaefer EA, et al. The AMPK-related kinase SNARK regulates hepatitis C virus replication and pathogenesis through enhancement of TGF-beta signaling. *J Hepatol* 2013;59(5):942–8.
  - [102] Dowman JK, Tomlinson JW, Newsome PN. Pathogenesis of non-alcoholic fatty liver disease. *QJM: Int J Med* 2010;103(2):71–83.
  - [103] Goh GBB, Pagadala MR, Dasarthy J, Unalp-Arida A, Sargent R, Hawkins C, et al. Diabetes mellitus, insulin, sulfonylurea and advanced fibrosis in non-alcoholic fatty liver disease. *J Diabetes Metab* 2014;5:410.



- [104] Dongiovanni P, Petta S, Mannisto V, Mancina RM, Pipitone R, Karja V, et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. *J Hepatol* 2015;63(3):705–12.
- [105] Pastori D, Polimeni L, Baratta F, Pani A, Del Ben M, Angelico F. The efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease. *Dig Liver Dis: Off J Ital Soc Gastroenterol Ital Assoc Study Liver* 2015;47(1):4–11.
- [106] Nascimbeni F, Aron-Wisniewsky J, Pais R, Tordjman J, Poitou C, Charlotte F, et al. Statins, antidiabetic medications and liver histology in patients with diabetes with non-alcoholic fatty liver disease. *BMJ Open Gastroenterol* 2016;3(1):e000075.
- [107] Wild SH, Morling JR, McAllister DA, Kerssens J, Fischbacher C, Parkes J, et al. Type 2 diabetes and risk of hospital admission or death for chronic liver diseases. *J Hepatol* 2016;64(6):1358–64.
- [108] Raff EJ, Kakati D, Bloomer JR, Shoreibah M, Rasheed K, Singal AK. Diabetes mellitus predicts occurrence of cirrhosis and hepatocellular cancer in alcoholic liver and non-alcoholic fatty liver diseases. *J Clin Transl Hepatol* 2015;3(1):9–16.
- [109] Butt Z, Jadoon NA, Salaria ON, Mushtaq K, Riaz IB, Shahzad A, et al. Diabetes mellitus and decompensated cirrhosis: risk of hepatic encephalopathy in different age groups. *J Diabetes* 2013;5(4):449–55.
- [110] Senanayake SM, Niriella MA, Weerasinghe SK, Kasturiratne A, de Alwis JP, de Silva AP, et al. Survival of patients with alcoholic and cryptogenic cirrhosis without liver transplantation: a single center retrospective study. *BMC Res Notes* 2012;5:663.
- [111] Garcia-Tsao G. Bacterial infections in cirrhosis: treatment and prophylaxis. *J Hepatol* 2005;42(Suppl(1)):S85–92.
- [112] Cheruvattath R, Balan V. Infections in patients with end-stage liver disease. *J Clin Gastroenterol* 2007;41(4):403–11.
- [113] Yang CH, Chiu YC, Chen CH, Chen CH, Tsai MC, Chuah SK, et al. Diabetes mellitus is associated with gastroesophageal variceal bleeding in cirrhotic patients. *Kaohsiung J Med Sci* 2014;30(10):15–20.
- [114] Chassaing B, Etienne-Mesmin L, Gwartz AT. Microbiota-liver axis in hepatic disease. *Hepatology* 2014;59(1):328–39.
- [115] Ferreira DF, Fiamoncini J, Prist IH, Ariga SK, de Souza HP, de Lima TM. Novel role of TLR4 in NAFLD development: Modulation of metabolic enzymes expression. *BBA* 2015;1851(10):1353–9.
- [116] Mridha AR, Haczeyni F, Yeh MM, Haigh WG, Ioannou GN, Barn V, et al. TLR9 is up-regulated in human and murine NASH: pivotal role in inflammatory recruitment and cell survival. *Clin Sci (Lond)* 2017;131(16):2145–59.
- [117] Boursier J, Mueller O, Barret M, Machado M, Fizanet L, Araujo-Perez F, et al. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. *Hepatology* 2016;63(3):764–75.
- [118] Romero-Gomez M, Fernandez-Rodriguez CM, Andrade RJ, Diago M, Alonso S, Planas R, et al. Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. *J Hepatol* 2008;48(5):721–7.
- [119] Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour Jr H, et al. Grazoprevir plus elbasvir in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet* 2015;386(10003):1537–45.
- [120] Pashun RA, Shen NT, Jesudian A. Markedly improved glycaemic control in poorly controlled type 2 diabetes following direct acting antiviral treatment of genotype 1 hepatitis C. *Case Rep Hepatol* 2016;2016:7807921.
- [121] Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in Egypt: results of the national population-based cancer registry program. *J Cancer Epidemiol* 2014;2014:437971.
- [122] Koh WP, Wang R, Jin A, Yu MC, Yuan JM. Diabetes mellitus and risk of hepatocellular carcinoma: findings from the Singapore Chinese Health Study. *Br J Cancer* 2013;108(5):1182–8.
- [123] Si WK, Chung JW, Cho J, Baeg JY, Jang ES, Yoon H, et al. Predictors of increased risk of hepatocellular carcinoma in patients with type 2 diabetes. *PLoS One* 2016;11(6):e0158066.
- [124] Atti EA. HCC burden in Egypt. *Gastroenterol Hepatol: Open Access*. 2015;2(3):00045.
- [125] Hung CH, Lee CM, Wang JH, Hu TH, Chen CH, Lin CY, et al. Impact of diabetes mellitus on incidence of hepatocellular carcinoma in chronic hepatitis C patients treated with interferon-based antiviral therapy. *Int J Cancer* 2011;128(10):2344–52.
- [126] Hedenstierna M, Nangarhari A, Weiland O, Aleman S. Diabetes and cirrhosis are risk factors for hepatocellular carcinoma after successful treatment of chronic hepatitis C. *Clin Infect Dis* 2016;63(6):723–9.
- [127] Paziienza V, Clement S, Pugnale P, Conzelman S, Foti M, Mangia A, et al. The hepatitis C virus core protein of genotypes 3a and 1b downregulates insulin receptor substrate 1 through genotype-specific mechanisms. *Hepatology* 2007;45(5):1164–71.
- [128] Dyal HK, Aguilar M, Bartos G, Holt EW, Bhuket T, Liu B, et al. Diabetes mellitus increases risk of hepatocellular carcinoma in chronic hepatitis C virus patients: a systematic review. *Dig Dis Sci* 2016;61(2):636–45.
- [129] Kawaguchi T, Izumi N, Charlton MR, Sata M. Branched-chain amino acids as pharmacological nutrients in chronic liver disease. *Hepatology* 2011;54(3):1063–70.
- [130] Hayashi T, Ogawa E, Furusyo N, Murata M, Hayashi J. Influence of insulin resistance on the development of hepatocellular carcinoma after antiviral treatment for non-cirrhotic patients with chronic hepatitis C. *Infect Agents Cancer* 2016;11:9.
- [131] Gokturk HS, Selcuk H. Importance of malnutrition in patients with cirrhosis. *Turk J Gastroenterol* 2015;26(4):291–6.
- [132] Plauth M, Cabre E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, et al. ESPEN guidelines on enteral nutrition: liver disease. *Clin Nutr* 2006;25(2):285–94.
- [133] Dasarthy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol* 2016;65(6):1232–44.
- [134] Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, et al. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatology: Off Clin Pract J Am Gastroenterol Assoc* 2012;10(2):166–73.
- [135] Merli M, Giusto M, Lucidi C, Giannelli V, Pentassuglio I, Di Gregorio V, et al. Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. *Metab Brain Dis* 2013;28(2):281–4.
- [136] Grungreiff K, Reinhold D, Wedemeyer H. The role of zinc in liver cirrhosis. *Ann Hepatol* 2016;15(1):7–16.
- [137] Chamberlain JJ, Rhinehart AS, Shaefer Jr CF, Neuman A. Diagnosis and management of diabetes: synopsis of the 2016 american diabetes association standards of medical care in diabetes. *Ann Int Med* 2016;164(8):542–52.
- [138] Tinker LF, Heins JM, Holler HJ. Commentary and translation: 1994 nutrition recommendations for diabetes, diabetes care and education, a practice group of the American dietetic association. *J Am Diet Assoc* 1994;94(5):507–11.
- [139] Nguyen V, George J. Nonalcoholic fatty liver disease management: dietary and lifestyle modifications. *Semin Liver Dis* 2015;35(3):318–37.
- [140] Abenavoli L, Renzo LD, Lorenzo AD. The efficacy of Mediterranean diet in non-alcoholic fatty liver disease. *Bratisl Lek Listy* 2016;117(8):486.
- [141] Abenavoli L, Milic N, Larussa T, Suraci E, Imeneo M, Medic M, et al. P.01.3 efficacy of mediterranean diet and antioxidants in overweight patients with non-alcoholic fatty liver disease. *Dig Liver Dis* 2016;48:e130–1.
- [142] Papamiliadous ES, Roberts SK, Nicoll AJ, Ryan MC, Tsiopoulos C, Salim A, et al. A randomised controlled trial of a mediterranean dietary intervention for adults with non alcoholic fatty liver disease (MEDINA): study protocol. *BMC Gastroenterol* 2016;16:14.
- [143] Miguel AL, Saloum Y. Nutrition, fluid, and electrolytes in chronic liver disease. *Clin Liver Dis* 2016;7(1):18–20.
- [144] DiNicolantonio JJ, O'Keefe JH, Lucan SC. Added fructose: a principal driver of type 2 diabetes mellitus and its consequences. *Mayo Clin Proc* 2015;90(3):372–81.
- [145] Ordonez R, Carbajo-Pescador S, Mauriz JL, Gonzalez-Gallego J. Understanding nutritional interventions and physical exercise in non-alcoholic fatty liver disease. *Curr Mol Med* 2015;15(1):3–26.
- [146] Schenker S, Martin RR, Hoyumpa AM. Antecedent liver disease and drug toxicity. *J Hepatol* 1999;31(6):1088–97.
- [147] Rydberg T, Jonsson A, Roder M, Melander A. Hypoglycaemic activity of glyburide (glibenclamide) metabolites in humans. *Diabetes Care* 1994;17(9):1026–30.
- [148] Scherthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, Kvapil M, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. *Eur J Clin Invest* 2004;34(8):535–42.
- [149] Choudhury S, Hirschberg Y, Filipek R, Lasseter K, McLeod JF. Single-dose pharmacokinetics of nateglinide in subjects with hepatic cirrhosis. *J Clin Pharmacol* 2000;40(6):634–40.
- [150] Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diabetes Care* 2007;30(3):734–43.
- [151] Tiikkainen M, Hakkinen AM, Korshenninnikova E, Nyman T, Makimattila S, Yki-Jarvinen H. Effects of rosiglitazone and metformin on liver fat content, hepatic insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type 2 diabetes. *Diabetes* 2004;53(8):2169–76.
- [152] Kintscher U, Law RE. PPARgamma-mediated insulin sensitization: the importance of fat versus muscle. *Am J Physiol Endocrinol Metab* 2005;288(2):E287–91.
- [153] Kaji K, Yoshiji H, Ikenaka Y, Noguchi R, Aihara Y, Douhara A, et al. Dipeptidyl peptidase-4 inhibitor attenuates hepatic fibrosis via suppression of activated hepatic stellate cell in rats. *J Gastroenterol* 2014;49(3):481–91.
- [154] Firneisz G, Varga T, Lengyel G, Feher J, Ghyicz D, Wichmann B. Serum dipeptidyl peptidase-4 activity in insulin resistant patients with non-alcoholic fatty liver disease: a novel liver disease biomarker. *PLoS One* 2010;5.
- [155] Arase Y, Suzuki F, Kobayashi M, Suzuki Y, Kawamura Y, Matsumoto N. Efficacy and safety in sitagliptin therapy for diabetes complicated by chronic liver disease caused by hepatitis C virus. *Hepatol Res* 2011;41.
- [156] Asakawa M, Mitsui H, Akihisa M, Sekine T, Niitsu Y, Kobayashi A, et al. Efficacy and safety of sitagliptin for the treatment of diabetes mellitus complicated by chronic liver injury. *SpringerPlus* 2015;4(1):346.
- [157] Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006;368.
- [158] Ding X, Saxena NK, Lin S, Gupta NA, Anania FA. Exendin-4, a glucagon-like protein-1 (GLP-1) receptor agonist, reverses hepatic steatosis in ob/ob mice. *Hepatology* 2006;43(1):173–81.
- [159] Ben-Shlomo S, Zvibel I, Shnell M, Shloma E, Chepurko E, Halpern Z, et al. Glucagon-like peptide-1 reduces hepatic lipogenesis via activation of AMP-activated protein kinase. *J Hepatol* 2011;54(6):1214–23.



- [160] Mosley JF, Smith L, Everton E, and Fellner C. Sodium-Glucose linked transporter 2 (SGLT2) inhibitors in the management of type-2 diabetes: a drug class overview. *P&T*. 2015;40(7).
- [161] Dailey GE. Empagliflozin: a new treatment option for patients with type 2 diabetes mellitus. *Drugs Today (Barc)* 2015;51(9):519–35.
- [162] Mukhopadhyay J. Use of insulin in chronic liver disorders. *Med Update* 2005;203–5.
- [163] Henriksen JH, Tronier B, Bulow JB. Kinetics of circulating endogenous insulin, C-peptide, and proinsulin in fasting nondiabetic man. *Metabolism* 1987;36(5):463–8.
- [164] Zhao Y, Xing H. A different perspective for management of diabetes mellitus: controlling viral liver diseases. *J Diabetes Res* 2017;2017:5625371.
- [165] Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. *Circulation* 2004;109(23 Suppl 1):III50–7.
- [166] Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. *Gastroenterology* 2014;147(2):377–84. e1.
- [167] Hughes EA, Tracey I, Singhal S, Patel J. Unexpected beneficial effect in the use of ezetimibe in non-alcoholic fatty liver disease. *Med Hypotheses* 2006;67(6):1463–4.
- [168] Yamagishi S, Nakamura K, Matsui T, Sato T, Takeuchi M. Inhibition of intestinal cholesterol absorption by ezetimibe is a novel therapeutic target for fatty liver. *Med Hypotheses* 2006;66(4):844–6.
- [169] Yoneda M, Fujita K, Imajo K, Mawatari H, Kirikoshi H, Saito S, et al. Induction of microsomal triglyceride transfer protein expression is a candidate mechanism by which ezetimibe therapy might exert beneficial effects in patients with nonalcoholic steatohepatitis. *J Gastroenterol* 2011;6(3):415–6. author reply 7.
- [170] Van Rooyen DM, Gan LT, Yeh MM, Haigh WG, Larter CZ, Ioannou G, et al. Pharmacological cholesterol lowering reverses fibrotic NASH in obese, diabetic mice with metabolic syndrome. *J Hepatol* 2013;59(1):144–52.
- [171] Hirose A, Ono M, Saibara T, Nozaki Y, Masuda K, Yoshioka A, et al. Angiotensin II type 1 receptor blocker inhibits fibrosis in rat nonalcoholic steatohepatitis. *Hepatology* 2007;45(6):1375–81.
- [172] Sookoian S, Fernandez MA, Castano G. Effects of six months losartan administration on liver fibrosis in chronic hepatitis C patients: a pilot study. *World J Gastroenterol* 2005;11(48):7560–3.
- [173] Ampuero J, Ranchal I, Nunez D, Diaz-Herrero Mdel M, Maraver M, del Campo JA, et al. Metformin inhibits glutaminase activity and protects against hepatic encephalopathy. *PLoS One* 2012;7(11):e49279.
- [174] Nkontchou G, Cosson E, Aout M, Mahmoudi A, Bourcier V, Charif I, et al. Impact of metformin on the prognosis of cirrhosis induced by viral hepatitis C in diabetic patients. *J Clin Endocrinol Metab* 2011;96(8):2601–8.
- [175] Lai SW, Chen PC, Liao KF, Muo CH, Lin CC, Sung FC. Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. *Am J Gastroenterol* 2012;107(1):46–52.
- [176] Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *Am J Gastroenterol* 2013;108(6):881–91. quiz 92.
- [177] Gline S, Sharlip ID, Hellstrom WJ. Modifying risk factors to prevent and treat erectile dysfunction. *J Sex Med* 2013;10(1):115–9.
- [178] DeLay KJ, Haney N, Hellstrom WJG. Modifying risk factors in the management of erectile dysfunction: a review. *World J Men's Health* 2016;34(2):89–100.
- [179] Rew KT, Heidelberg JJ. Erectile dysfunction. *Am Fam Physician* 2016;94(10):820–7.
- [180] Mody A, White D, Kanwal F, Garcia JM. Relevance of low testosterone to non-alcoholic fatty liver disease. *Cardiovasc Endocrinol* 2015;4(3):83–9.
- [181] Foresta C, Schipilliti M, Ciarleglio FA, Lenzi A, D'Amico D. Male hypogonadism in cirrhosis and after liver transplantation. *J Endocrinol Invest* 2008;31(5):470–8.
- [182] Sinclair M, Grossmann M, Gow PJ, Angus PW. Testosterone in men with advanced liver disease: abnormalities and implications. *J Gastroenterol Hepatol* 2015;30(2):244–51.
- [183] Binmoammar TA, Hassounah S, Alsaad S, Rawaf S, Majeed A. The impact of poor glycaemic control on the prevalence of erectile dysfunction in men with type 2 diabetes mellitus: a systematic review. *JRSM Open* 2016;7(3). 2054270415622602.
- [184] Lu CC, Jiann BP, Sun CC, Lam HC, Chu CH, Lee JK. Association of glycaemic control with risk of erectile dysfunction in men with type 2 diabetes. *J Sex Med* 2009;6(6):1719–28.
- [185] Cho NH, Ahn CW, Park JY, Ahn TY, Lee HW, Park TS, et al. Prevalence of erectile dysfunction in Korean men with Type 2 diabetes mellitus. *Diabet Med* 2006;23(2):198–203.
- [186] Jepsen P, Watson H, Andersen PK, Vilstrup H. Diabetes as a risk factor for hepatic encephalopathy in cirrhotic patients. *J Hepatol* 2015;63(5):1133–8.
- [187] Elkrief L, Chouinard P, Bendersky N, Hajage D, Larroque B, Babany G, et al. Diabetes mellitus is an independent prognostic factor for major liver-related outcomes in patients with cirrhosis and chronic hepatitis C. *Hepatology* 2014;60(3):823–31.
- [188] Chen YW, Chen HH, Wang TE, Chang CW, Chang CW, Chen WC, et al. The dissociation between the diabetes and both Child-Pugh score and in-hospital mortality in cirrhotic patients due to hepatitis B, hepatitis C, or alcoholic. *Hep Intl* 2011;5(4):955–64.
- [189] Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. *J Hepatol* 2005;42(Suppl 1):S100–7. Epub 2004 Dec 24.
- [190] Fruci B, Giuliano S, Mazza A, Malaguarnera R, Belfiore A. Nonalcoholic fatty liver: a possible new target for type 2 diabetes prevention and treatment. *Int J Mol Sci* 2013;14(11):22933–66.
- [191] Filozof C, Goldstein BJ, Williams RN, Sanyal A. Non-alcoholic steatohepatitis: limited available treatment options but promising drugs in development and recent progress towards a regulatory approval pathway. *Drugs* 2015;75(12):1373–92.
- [192] Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med* 2016;165(5):305–15.
- [193] Kita Y, Takamura T, Misu H, Ota T, Kurita S, Takeshita Y, et al. Metformin prevents and reverses inflammation in a non-diabetic mouse model of nonalcoholic steatohepatitis. *PLoS One* 2012;7(9):e43056.
- [194] Koehler EM, Plompen EP, Schouten JN, Hansen BE, Darwish Murad S, Taimr P, et al. Presence of diabetes mellitus and steatosis is associated with liver stiffness in a general population: the Rotterdam study. *Hepatology* 2016;63(1):138–47.
- [195] Bril F, Portillo Sanchez P, Maximos M, et al. Metabolic predictors of response to pioglitazone treatment in patients with prediabetes or type 2 diabetes mellitus and nonalcoholic steatohepatitis. *Diabetes* 2015;64:A337.
- [196] Armstrong MJ, Houlihan DD, Rowe IA, Clausen WHO, Elbrønd B, Gough SCL, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes with elevated liver enzymes: individual patient data meta-analysis of the LEAD programme. *Lancet* 2013;381:S20.
- [197] Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016;387(10019):679–90.
- [198] Fukuhara T, Hyogo H, Ochi H, Fujino H, Kan H, Naeshiro N, et al. Efficacy and safety of sitagliptin for the treatment of nonalcoholic fatty liver disease with type 2 diabetes mellitus. *Hepatogastroenterology* 2014;61(130):323–8.
- [199] Macauley M, Hollingsworth KG, Smith FE, Thelwall PE, Al-Mrabeh A, Schweizer A, et al. Effect of vildagliptin on hepatic steatosis. *J Clin Endocrinol Metab* 2015;100(4):1578–85.
- [200] Cui J, Philo L, Nguyen P, Hofflich H, Hernandez C, Bettencourt R, et al. Sitagliptin vs. placebo for non-alcoholic fatty liver disease: a randomized controlled trial. *J Hepatol* 2016;65(2):369–76.
- [201] Hayashizaki-Someya Y, Kurosaki E, Takasu T, Mitori H, Yamazaki S, Koide K, et al. Ipragliflozin, an SGLT2 inhibitor, exhibits a prophylactic effect on hepatic steatosis and fibrosis induced by choline-deficient L-amino acid-defined diet in rats. *Eur J Pharmacol* 2015;754:19–24.
- [202] Leiter LA, Forst T, Polidori D, Balis DA, Xie J, Sha S. Effect of canagliflozin on liver function tests in patients with type 2 diabetes. *Diabetes Metab* 2016;42(1):25–32.
- [203] McPherson S, Jonsson JR, Barrie HD, O'Rourke P, Clouston AD, Powell EE. Investigation of the role of SREBP-1c in the pathogenesis of HCV-related steatosis. *J Hepatol* 2008;49(6):1046–54.
- [204] Morales AL, Junga Z, Singla MB, Sjogren M, Torres D. Hepatitis C eradication with sofosbuvir leads to significant metabolic changes. *World J Hepatol* 2016;8(35):1557–63.
- [205] Wolf KK, Gifford BT, Brantley SJ, Watkins PB, Paine MF. Drug metabolism, transport, and pharmacogenomics. In: Yamada's Textbook of Gastroenterology. John Wiley & Sons, Ltd; 2015. p. 626–38.
- [206] Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. a report from the European Liver Transplant Registry (ELTR). *J Hepatol* 2012;57(3):675–88.
- [207] EASL. EASL recommendations on treatment of hepatitis C. *J Hepatol* 2015;63(1):199–236.
- [208] Algareem N, Sholkamy A, Alshazly M, Daoud A. New-onset diabetes and hypertension as complications of liver transplantation. *Transplant Proc* 2014;46(3):870–2.
- [209] Li DW, Lu TF, Hua XW, Dai HJ, Cui XL, Zhang JJ, et al. Risk factors for new onset diabetes mellitus after liver transplantation: a meta-analysis. *World J Gastroenterol* 2015;21(20):6329–40.
- [210] Davis BC, Shadab Siddiqui M. Liver transplantation: the role of metabolic syndrome. *Curr Treat Options Gastroenterol* 2017;15(2):316–31.
- [211] Moon JI, Barbeito R, Faradji RN, Gaynor JJ, Tzakis AG. Negative impact of new-onset diabetes mellitus on patient and graft survival after liver transplantation: long-term follow up. *Transplantation* 2006;82(12):1625–8.
- [212] CDC. Diabetes and hepatitis b vaccination. information for diabetes educators. Centers Dis Control Prev 2012. Publication No. 220421.
- [213] Algareem N, Elshazly M, Sholkamy A, Daoud A. Diabetes and hypertension in liver transplant recipients: prevalence and predictors. *Transplant Int* 2013;26(Suppl. 2):185–339.
- [214] Lv C, Zhang Y, Chen X, Huang X, Xue M, Sun Q, et al. New-onset diabetes after liver transplantation and its impact on complications and patient survival. *J Diabetes* 2015;7(6):881–90.
- [215] Yoo HY, Thuluvath PJ. The effect of insulin-dependent diabetes mellitus on outcome of liver transplantation. *Transplantation* 2002;74(7):1007–12.
- [216] Kuo HT, Lum E, Martin P, Bunnarapadist S. Effect of diabetes and acute rejection on liver transplant outcomes: An analysis of the organ procurement and transplantation network/united network for organ sharing database.

- Liver Transplant : Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc 2016;22(6):796–804.
- [217] Thoenner LB, Rostved AA, Pommergaard HC, Rasmussen A. Risk factors for metabolic syndrome after liver transplantation: a systematic review and meta-analysis. *Transplant Rev* 2017.
- [218] Younossi Z, Stepanova M, Saab S, Trimble G, Mishra A, Henry L. The association of hepatitis C virus infection and post-liver transplant diabetes: data from 17 000 HCV-infected transplant recipients. *Aliment Pharmacol Ther* 2015;41(2):209–17.
- [219] Lane JT, Dagogo-Jack S. Approach to the patient with new-onset diabetes after transplant (NODAT). *J Clin Endocrinol Metab* 2011;96(11):3289–97.
- [220] Anastacio LR, Ribeiro Hde S, Ferreira LG, Lima AS, Vilela EG, Toulson Davisson Correia ML. Incidence and risk factors for diabetes, hypertension and obesity after liver transplantation. *Nutr Hosp* 2013;28(3):643–8.
- [221] Hjelmestaeth J, Asberg A, Muller F, Hartmann A, Jenssen T. New-onset posttransplantation diabetes mellitus: insulin resistance or insulinopenia? impact of immunosuppressive drugs, cytomegalovirus and hepatitis C virus infection. *Curr Diabetes Rev* 2005;1(1):1–10.
- [222] Xue M, Lv C, Chen X, Huang X, Sun Q, Wang T, et al. Effect of interleukin-2 receptor antagonists on new-onset diabetes after liver transplantation: a retrospective cohort study. *J Diabetes* 2016;8(4):579–87.
- [223] Ling Q, Xu X, Wang B, Li L, Zheng S. The origin of new-onset diabetes after liver transplantation: liver, islets, or gut? *Transplantation* 2016;100(4):808–13.
- [224] Lucey MR, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the study of liver diseases and the American society of transplantation. *Liver Transplant* 2013;19(1):3–26.
- [225] Wilkinson A, Davidson J, Dotta F, Home PD, Keown P, Kiberd B, et al. Guidelines for the treatment and management of new-onset diabetes after transplantation. *Clin Transplant* 2005;19(3):291–8.
- [226] Dumortier J, Bernard S, Bouffard Y, Boillot O. Conversion from tacrolimus to cyclosporine in liver transplanted patients with diabetes mellitus. *Liver Transplant: Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2006;12(4):659–64.
- [227] Bigam DL, Pennington JJ, Carpentier A, Wanless IR, Hemming AW, Croxford R, et al. Hepatitis C-related cirrhosis: a predictor of diabetes after liver transplantation. *Hepatology* 2000;32(1):87–90.
- [228] CDC. Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep Centers Dis Control Prev* 2011;60:1709–11.
- [229] Yoon H, Lee JG, Yoo JH, Son MS, Kim DY, Hwang SG, et al. Effects of metabolic syndrome on fibrosis in chronic viral hepatitis. *Gut Liver* 2013;7(4):469–74.
- [230] Fu SC, Huang YW, Wang TC, Hu JT, Chen DS, Yang SS. Increased risk of hepatocellular carcinoma in chronic hepatitis B patients with new onset diabetes: a nationwide cohort study. *Aliment Pharmacol Ther* 2015;41(11):1200–9.
- [231] Imazeki F, Yokosuka O, Fukai K, Kanda T, Kojima H, Saisho H. Prevalence of diabetes mellitus and insulin resistance in patients with chronic hepatitis C: comparison with hepatitis B virus-infected and hepatitis C virus-cleared patients. *Liver Int: Off J Int Assoc Study Liver* 2008;28(3):355–62.
- [232] Cotler SJ, Dhamija MK, Luc BJ, Siqueira F, Bartram AH, Layden TJ, et al. The prevalence and clinical correlates of elevated ALT levels in an urban Chinatown community. *J Viral Hepatitis* 2010;17(2):148–52.
- [233] Khalili M, Sanyal A, Cloonan Y, Ghany M, Kim W, Chung R, et al. Factors associated with diabetes and prediabetes in HBV-infected patients residing in North America: results from the hepatitis B research network (HBRN). *Hepatology* 2013;58:513A.
- [234] Huang J, Ou HY, Lin J, Karnchanasorn R, Feng W, Samoa R, et al. The impact of hepatitis b vaccination status on the risk of diabetes, implicating diabetes risk reduction by successful vaccination. *PLoS One* 2015;10(10):e0139730.
- [235] Khalili M, Lombardero M, Chung RT, Terrault NA, Ghany MG, Kim WR, et al. Diabetes and prediabetes in patients with hepatitis B residing in North America. *Hepatology* 2015;62(5):1364–74.
- [236] Li M, Zhou H, Guan Y, Peng H, Wang S, Zhang P, et al. Positive hepatitis B surface antibody is associated with reduced risk of diabetes mellitus in retired female Chinese workers. *J Diabetes* 2016;8(1):158–61.
- [237] Lu J, Hou X, Tu H, Tang Z, Xiang Y, Bao Y, et al. Chronic hepatitis B virus infection status is more prevalent in patients with type 2 diabetes. *J Diabetes Invest* 2017;8(4):619–25.
- [238] Spradling PR, Simons B, Narayanan M, Xing J, Homan C, Bulkow L, et al. Incidence of diabetes mellitus in a population-based cohort of persons with chronic hepatitis B virus infection. *J Viral Hepat* 2013;20(7):510–3.
- [239] Huang Z-S, Huang T-S, Wu T-H, Chen M-F, Hsu C-S, Kao J-H. Asymptomatic chronic hepatitis B virus infection does not increase the risk of diabetes mellitus: a ten-year observation. *J Gastroenterol Hepatol* 2010;25:1420–5.
- [240] Machado MV, Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. *J Gastroenterol Hepatol* 2011;26(9):1361–7.
- [241] Wang CC, Tseng TC, Kao JH. Hepatitis B virus infection and metabolic syndrome: fact or fiction? *J Gastroenterol Hepatol* 2015;30(1):14–20.
- [242] Chao LT, Wu CF, Sung FY, Lin CL, Liu CJ, Huang CJ, et al. Insulin, glucose and hepatocellular carcinoma risk in male hepatitis B carriers: results from 17-year follow-up of a population-based cohort. *Carcinogenesis* 2011;32(6):876–81.
- [243] Huang YW, Wang TC, Lin SC, Chang HY, Chen DS, Hu JT, et al. Increased risk of cirrhosis and its decompensation in chronic hepatitis B patients with newly diagnosed diabetes: a nationwide cohort study. *Clin Infect Dis* December 2013;V57(12):1695–702.
- [244] Zheng Z, Zhang C, Yan J, Ruan Y, Zhao X, San X, et al. Diabetes mellitus is associated with hepatocellular carcinoma: a retrospective case-control study in hepatitis endemic area. *PLoS One* 2013;8(12):e84776.
- [245] Han H, Deng H, Han T, Zhao H, Hou F, Qi X. Association between hepatocellular carcinoma and type 2 diabetes mellitus in Chinese hepatitis B virus cirrhosis patients: a case-control study. *Med Sci Monit: Int Med J Exp Clin Res* 2017;23:3324–34.
- [246] Younossi Z, Kochems K, de Ridder M, Curran D, Bunge EM, de Moerloose L. Should adults with diabetes mellitus be vaccinated against hepatitis B virus? a systematic review of diabetes mellitus and the progression of hepatitis B disease. *Hum Vaccin Immunother* 2017;13(11):2695–706.