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CLINICAL IMPLICATIONS, DIAGNOSIS, AND MANAGEMENT OF DIABETES IN PATIENTS WITH CHRONIC LIVER DISEASES.

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Abstract:

Diabetes mellitus (DM) has a critical role in the development and progression of chronic liver disease (CLD) of different etiologies. Both DM and CLD are strongly connected through worse clinical outcomes which reduced the 40% survival rate in 5 years. The identification of an effective treatment strategy becomes a challenge to manage diabetic patients with liver disease particularly with decompensated cirrhosis. As we have a lack of knowledge of clinical guidelines as well as the medical complexity of this patient folk. We review the epidemiology and pathophysiology of both CLD and DM, insulin resistance impact on the progression of CLD, and practical challenges in diagnosis and monitoring of DM. finally, we discussed the few evidence on pharmacological therapy such as anti-hyperglycemic therapies with liver disease-related clinical outcomes.

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INTRODUCTION:

Liver as a chief organ has an indispensable role to regulate the blood glucose level through different processes such as glycogenesis, lipogenesis, glycogenolysis, and gluconeogenesis during feeding or fasting state.[20] Similarly, the liver is also involved in insulin clearance which is an integral component of insulin metabolism. However, any impairment in liver function may cause severe complications. Diabetes mellitus (DM) is a metabolic disorder that indicates the impaired regulation of blood glucose due to alteration of insulin sensitivity, potently encourage the development of chronic liver disease (CLD). It is noteworthy that insulin resistance in metabolic syndromes considered as an eminent independent pathophysiological consequence to develop non-alcoholic fatty liver disease. [1] A study divulges that fasting insulin level and index of insulin resistance were noted twofold in non-obese patients with non-alcoholic fatty liver disease (NAFLD). [2] Further studies ensuing, 68%-88% of patients with type 2 diabetes mellitus (T2DM) have confirmed NAFLD on histology while DM was also observed in patients with 21-46% of NAFLD. Generally, it is not obscure that the sensitivity of patients with DM has been enhanced up to 2-5 folds to develop non-alcohol fatty liver disease. Ramifications of insulin resistance and diabetes mellitus are true reasons to develop chronic liver disease. [3] DM continuously provide prophecy for more severe disease when CLD progress towards end-stage liver disease. Alternatively, the frequency of DM directly associated with the severity of liver disease based on the score of the model of end-stage liver disease. [4] Nonetheless, various prospective research on patients with compensated or decompensated cirrhosis of multiple causes have frequently illustrated lower survival as 40% survival rate decrease in 5 years especially in diabetic patients as compared to non-diabetic patient. [5] Higher mortality rate in these diabetic patients is because of greater complications with liver failure rather than DM-related macro and microvascular diseases. Clinical information obtained from patients of chronic hepatitis C virus infection shows the baseline data of DM directly involved in the development of ascites, renal dysfunction, and bacterial infection.

Diagnosis:

Traditional Glycemic Markers for Patients with Liver Diseases:

Deleterious effects of DM on the development of chronic liver disease, in addition to the manifestation and management of end-stage liver disease, it is concluded that early diagnosis and better treatment would be more beneficial. In patients with normal fasting plasma glucose and compensated cirrhosis, DM is more challenging to manage. Therefore first the challenge is to find an accurate diagnosis and to evaluate the disorder severity.

Fasting plasma glucose:

Fasting plasma glucose (FPG) is an economical test for the diagnosis of DM. Although its use is limited due to prolong fasting and strict processing requirements while its results are more reliable. Acute illness, alcohol use, and stress may affect FPG.[7] In a study 22% of patients with FPG<110 mg/dL fulfill the diagnostic parameter for DM which depends on oral glucose tolerance test and 107 mg/dL threshold shown by regression analysis. For the diagnosis of DM, 126 mg/dl should be used. [6]

Oral glucose tolerance test:

This gold standard method is preferable for the detection of gestational DM, cystic fibrosis-related with DM. Impaired glucose tolerance formally can be diagnosis which is relevant to cirrhotic patients. Its main drawbacks such as prolonged fasting, length, and complexity during testing may affect the quality of tests in clinical practices. This test cannot be used to determine disease severity and effectiveness due to limited practical establishments. [8]

Hemoglobin A1c:

The main benefit of this test is easy to handle and does not need a fasting condition. Basically, used to determine the treatment effectiveness because it represents the average blood glucose of a month instead of a particular time. Further use as a glycemic marker for patients with mild liver disorder. A study of 16 patients having compensated cirrhosis shown the results lesser than the non-diabetic reference range. [9] Another small study on patients of decompensated cirrhosis with liver transplantation assessment evaluates the same response between A1c measured and average blood glucose. The awful diagnostic response of A1c established a curvilinear correlation between the A1c and erythrocyte, which was found in patients with chronic liver disease as repercussions of hemorrhage concomitant to portal hypertension and coagulopathy. [10]

Non-Traditional Glycemic Markers For Patients With Liver Diseases:

Glycated proteins:

Basically, ketoamine (glycated albumin and fructosamine) are formed by non-enzymatic glycation reaction of glucose to serum proteins and similar way adopted by glycation of hemoglobin. Glycated albumin (GA) has been approved as a potent glycemic marker in patients with chronic kidney

disease as GA level did affect by anemia, erythropoietin therapy, and blood transfusion. There was an inverse relationship was found in a cohort study of cirrhotic. [11]

Serum 1,5-anhydroglucitol:

A dietary monosaccharide that is usually absorbed through the proximal renal tubules but its reabsorption was impeded by glucosuria specifically in patients with hyperglycemia. The most sensitive glycemic marker has evidence of its effects on patients with liver disease. A cohort study elucidated the concern of dietary intake may affect serum 1,5-anhydroglucitol especially in the folk of people suffering from cirrhotic condition because of high prevalent malnutrition. [12]

Management of Diabetes in Patients with Liver Diseases:

The identification of effective treatment strategy for medicine becomes a second challenge to manage Diabetic patients with liver disease particularly with decompensated cirrhosis. There are a few fundamental factors involved in the medical management of both DM and liver disease, such as basic lifestyle interventions including a healthy diet, physical activity, and alcohol or smoking effects. Antihyperglycemic medication often recommended when patients lifestyle intervention failed to control the glycemic condition. Management of these disease needed attention to observe the mechanism of action, side effects and response to liver disease complication with the use of these medication**.**

Metformin	Metformin used as first-line oral therapy in type 2 diabetes without the side effect of cardio protective effects. A randomized clinical trial indicate the improvement in insulin resistance, aminotransferase levels, and liver morphology. [13] Additionally, metformin reduced the 50%-70% risk of hepatocellular carcinoma and 8 folds reduction in incidence of hepatic encephalopathy by inhibiting the glutaminase activity. [14]
Pioglitazone	Pioglitazone significantly improve the aminotransferase level. Help in reduction of hypoglycemia. In experimental models inhibit the development of hepatocellular carcinoma
α-glucosidase inhibitors	α-glucosidase inhibitors reduced the postprandial glycemia and glycemic variation in patients diabetic with compensated cirrhosis and reduced the serum ammonia and ameliorate the intellectual function. [15]
GLP-1 receptor agonists	GLP-1 receptor agonists are a most eminent class of incretin-based therapy for the treatment of type-II diabetes mellitus, help to induce weight loss, and prevent hypoglycemia. It restores the peripheral and hepatic insulin sensitivity and improves the aminotransferases and hepatic steatosis in patients with non-alcohol fatty liver disease. [16]

DISCUSSION:

- The selection of the effective glycemic marker and develop a better anti-hyperglycemic therapy the plan is the third most important challenge in the management of DM and chronic liver disease. A study demonstrated that high mortality in patients with DM and CLD is due to a prominent complication of live failure. [18]
- One more study on 50 patients of NAFLD exhibiting an association between the uses of A1c to improve the liver fibrosis while the impact on CLD etiology was not investigated.it is also unknown that degree of glycemic control is directly related to liver disease severity or incidence. [1]
- Another prospective study shows that 80% of patients with liver cirrhosis may experience glucose metabolic diseases and 30% found with DM. author demonstrated that DM enhances the risk to develop hepatic complications lead to death with liver cirrhosis. It is directly engaged in liver inflammation and fibrosis which induced mitochondrial oxidative stress. Therefore effective control is an immediate need for such disease treatment. [19]
- More research needed to improve the management of CLD for treatment to overcome the securities of patient's life. Although an alternative glycemic marker is required whose diagnostic potential remains unaffected with alteration of erythrocytes.

CONCLUSION:

Eventually, it is concluded that the above-mentioned evidence, makes it clear that DM has a critical role in the development of chronic liver disease. Surprisingly, both DM and CLD have worse clinical outcomes which reduced the survival rate of an individual.

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