Use of Insulin in Chronic Liver Disorders

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ABSTRACT

Diabetes mellitus is a common endocrine disorder and its prevalence is increasing worldwide and around 57 million Indians will be diabetic by the year 2025. Chronic liver disorders may arise as a complications of diabetes or as an effect. Chronic hepatitis C is found to be closely interlinked with diabetes. Hyperglycemia plays a key role in increased fibrogenesis, in chronic hepatitis and further progression to cirrhosis of liver. Insulin is the mainstay in controlling hyperglycemia in chronic liver disorder. Human insulin of short acting varieties are preferred choice. Oral hypoglycemic agents are mostly avoided because of its intrinsic hepatotoxicity and bizarre effects. Care must be taken about hypoglycemia during use of human insulin in managing hyperglycemia in chronic liver disorder.

INTRODUCTION

The prevalence of diabetes is increasing worldwide and is expected to affect around 300 million adults all over the world and around 57 million in India by the year 2025. Many liver disorders are indirectly related with diabetes. Chronic Liver disorders may arise in a diabetic as a cause or effect of diabetes. Liver is primarily responsible for regulation of fasting plasma glucose and lipid levels. We do not have many studies from our country showing the association between chronic liver disorder, but studies of Amarpurkar D, Das HS [1] published in Trop. Gastroenterol has confirmed association of chronic liver disease in diabetes mellitus. World literature is also showing several evidences of association of chronic hepatitis & NAFLD with Type 2 DM.[2]

Upto 80% of patients with cirrhosis may be glucose intolerant (Lancet 1967; 2: 1051-1056) and between 10% and 20% may be clinically diabetic (Hepatology 1991; 14: 103-111). Numerous Causes for this association is proposed.

Sulfonylureas, Repaglinide, Metformin and Thiazolidinediones are all extensively metabolized by the liver. So, many clinicians use insulin as a first-line agent in treatment of diabetes in chronic liver disorders. The main risk of insulin treatment is hypoglycemia.[3]

THE ROLE OF THE LIVER IN GLUCOSE HOMEOSTASIS AND INSULIN METABOLISM

The liver uses glucose as a fuel and has the ability to store it as glycogen & synthesize it from non-carbohydrate precursors. Glucose absorbed from the intestinal tract is transported via the portal vein to liver, some authors suggest that most of the absorbed glucose is retained by the liver, so that the rise in peripheral glucose concentration reflects only a minor component of postprandial absorbed glucose. Therefore, it is possible that the liver plays a more significant role than does peripheral tissue in the regulation of systemic blood glucose levels following a meal.[4] Katz et al however, suggested that, most absorbed glucose is not taken up by the liver but is rather metabolized via glycolysis in the peripheral tissue.[5]

Insulin is metabolized by insulinase in the liver, kidney and placenta. About 50% of insulin secreted by the pancreas is removed, by 'first-pass' extraction in the liver. On the other hand exogenous insulin promotes hepatic glycogenesis and inhibits glycogenolysis and promotes protein, cholesterol and triglyceride synthesis gluconeogenesis in the liver and kidney.

The liver, kidney, intestine and platelets contain the enzyme, glucose-6-phosphatase which produces glucose from glucose-6-phasphate and is the final step in the production of glucose via neoglucogenesis. Glucose that is metabolized peripherally may therefore be converted back to glucose or to hepatic glycogen via gluconeogenesis with lactate as the primary substrate.[6] This is known as Cori cycle.

Liver Disease Occuring as a Consequence of Diabetes Mellitus

1. Glycogen deposition
2. Steatosis and nonalcoholic steatohepatitis (NASH)

3. Fibrosis and Cirrhosis
4. Biliary disease, cholelithiasis, cholecystitis
5. Complication of therapy of diabetes (cholestatic and necroinflamatory liver disease)

Diabetes Mellitus and Abnormalities of Glucose Homeostasis Occurring as a Complication of Liver Disease[7]

1. Hepatitis
2. Cirrhosis
3. Hepatocellular carcinoma
4. Fulminant Hepatic Failure

Chronic liver disorders are characterized by different disorders of varying causes and severity in which hepatic inflammation and necrosis continue at least 6 months.[8] The spectrum of chronic liver disease includes

1. Chronic hepatitis
2. Cirrhosis of liver
3. Hepatocellular carcinoma (HCC)
4. Non alcoholic fatty liver disease (NAFLD)
5. Drugs and toxin induced chronic liver injury

Chronic Hepatitis is also a spectrum of disease which includes [8]

a. Chronic hepatitis B
b. Chronic hepatitis C
c. Chronic hepatitis D
d. Autoimmune hepatitis
e. Cryptogenic

DIABETES AND HEPATITIS C INTERACTION IN PRODUCTION OF CHRONIC LIVER DISEASE

There are multiple evidences in literature that Chronic Hepatitis C is having strong association with diabetes. This correlation between HCV infection and DM was investigated at the population level by Mehta et al. who examined 9841 persons older than 21 years and found that persons 40 years of age or older, HCV infection were 3-times more likely than those without HCV infection to have Type 2 DM.[2]

Chronic infection with hepatitis C virus (HCV) results in progressive hepatic fibrosis and cirrhosis in upto 20% cases.[9] Clinical studies have shown that there is a higher prevalence of and more severe steatosis in patients infected with HCV genotype 3 compared with other genotypes.[10]

In patients with non-alcoholic fatty liver disease (NAFLD), insulin resistance appears to be fundamental to the pathogenesis of this disorder irrespective of BMI. Type 2 DM is a risk factor for more severe NAFLD[11] and a study examining risk factors for steatosis and fibrosis in chronic HCV reported a relationship between diabetes and fibrosis level. Recent studies have suggested that increased circulating insulin levels may have a direct role in fibrogenic process. Molecules involved in fibrogenesis such as connective tissue growth factor were increased following culture of hepatic stellate cells with insulin [12] and in patients with chronic HCV, insulin receptors have been demonstrated in hepatic stellate cells.[13] Hyperglycemia results in enhanced formation and deposition of advanced glycation end products. Specific receptors for these advanced glycation end products (RAGE) have been detected in the liver where they are restricted to hepatic stellate cells, the main cellular source of liver collagen. Activation of hepatic stellate cells upregulates the expression of RAGE as does TGF-β, a pivotal pro-fibrogenic cytokine.[14] Hyperglycemia also induces the expression of pro-fibrogenic cytokines, such as connective tissue growth factor, in hepatic stellate cells. It has also been reported that oxidative stress is increased in vivo in the diabetic state through the generation of reactive oxygen species by chronic hyperglycemia and soluble advanced glycated end-products present in blood-stream. These redox changes activate stress-responsive signaling pathways such as nitrogen activated protein kinases which in-turn, induce NF-kB and AP-1-medaited transcripitional activation of key inflammatory genes, such as tumor necrosis factor (TNF) - α and interleukin-6. Alternatively, insulin resistance instead of hyperglycemia per-se may be linked to necro-inflammatory lesion and hence fibrogenesis. In conclusion, high serum glucose is associated with advanced fibrosis and higher fibrosis progression rate in chronic hepatitis C, independent of age at infection and duration of infection. Hence, the measurement of blood sugar and its control in patients with hepatitis C might provide better information about risk of developing fibrosis and then prevention of development of further fibrosis and then cirrhosis.[15]

Hyperinsulinemia and peripheral insulin resistance are frequent and well-documented complications of advanced liver fibrosis & cirrhosis. The etiology of increase in circulating insulin levels is unknown. The increase in circulating C-peptide level seen in patients with chronic HCV probably reflects an increase in insulin secretion by β-cells to compensate for insulin insensitivity.[9] It is also important to note that the prevalence of increased iron deposition and steatosis in the livers of patients with hepatitis C disease have been suggested to confer an insulin resistant syndrome on these patients.[16-17]

APPROACH TO MANGE THE HYPERGLYCEMIA IN DIABETIC WITH CHRONIC LIVER DISEASE

Regardless of whether the diagnosis is that of liver diabetes or type 2 diabetes, decisions about when and how to treat hyperglycemia should take into account co-morbid conditions such as hepatic-dysfunction. HbA_1c level is a poor guide in these cases because hypersplenism reduces erythrocytes life-span and results in spuriously low HbA_1c levels. Therefore, in these patients it is desirable to initiate SMBG to understand hyperglycemia.[18]

Diet & exercise are usually considered a very safe first-line of therapy for patients with mild hyperglycemia. But, dietary restriction in a malnourished cirrhosis may result in a hypoalbuminemia and coagulopathy with lower vitamin K intake.

Every class of oral hypoglycemic medication currently available in our country has been associated with at least a small risk of hepatotoxicity. For patients with marginal hepatic function at baseline, even mild hepatotoxicity can be fatal. Hepatic dysfunction can also cause an exaggerated response to a standard dose of medication and a higher risk of side effects if the drug is metabolized by the liver. Sulfonylureas, repaglinide, metformin

and thiazolidinediones are extensively metabolized by the liver. So, these drugs are preferably avoided in chronic liver disorders specially metformin and thiazolidinediones.

Insulin is the first-line agent to treat diabetes in chronic liver disease like cirrhosis or chronic hepatitis. Short acting insulins are preferred because the duration of action may vary in such situations. Human insulin can only be used because insulin antibody is trapped by Kuffer cells and that can induce further inflammatory reaction. So, short acting human insulins are the only preferred agent in such situations. The role of newer insulin analogues e.g. insulin glargin, in a setting of chronic liver disorder is yet to be clear.

The main risk of insulin is severe hypoglycemia. Patients with cirrhosis have reduced glycogen stores. Glucagon may stimulate less hepatic glycogenolysis in cirrhotic patients than in patients without liver-disease.[19] Also, many patients with severe hepatic dysfunction have hepatic encephalopathy, which may impair their ability to comply with instruction about therapy.

Patients with chronic liver disorder and diabetes have shorter life expectancy than do non-diabetic patients with cirrhosis, but they typically die of complications of liver disease, such as gastrointestinal hemorrhage than for complications of diabetes such as cardiovascular disease.[20] This suggests that in cirrhotic patients, the development of diabetes reflects a greater degree of liver failure.

In this era of liver transplantation, it is seen that the degenerative complications of DM may occur despite apparent remission of the disease after liver transplantation. Pancreatic transplantation has been unable to control degenerative complications of DM. Fioretto et al showed that more than 5 years of normoglycemia after pancreatic transplantation is required to reverse the lesions of diabetic nephropathy.[21]

CONCLUSION

Liver diseases, primary or secondary may lead to or contribute to complications of DM. Hyperglycemia is found to play a key role in development and progression of chronic liver disorders in different situations. So, to control hyperglycemia in a setting of chronic liver disorder, insulin is the first-choice agent to almost all physicians. Care should be taken about hypoglycemia and varieties of insulin to be used to prevent further complications due to therapy.

REFERECES

1. Amarpurkar D, Das HS. Chronic liver disease in diabetes mellitus. Trop. *Gasteroenterol* 2002;2(1): 3-5.
2. Mehta SH, Brancati FL, M Thomas DL, Prevalence of Type 2 Diab. Mellitus in patients with chronic Hepatitis C in US. *Annals of Internal Med* 2000;133:592-599.
3. Petrides AS, Liver Disease and diabetes mellitus. *Diabetes Revs,* 1994;2: 2-18.
4. Bjormstorp P, Sojostorm L Carbohydrate storage in man : Speculation and some quantitative consideration. *Metabolism* 1978;27(suppl 2):1853-65.
5. Katz LD, Gliokman MG, Rapaport S, et al. Splanchnic and peripheral disposal of oral glucose in man. *Diabetes* 1983;32:675-79.
6. Scofield RF, Kosugi K, Kumaran K, Landau BR. Quantitative estimation of the pathways followed in the conversion to glycogen of glucose administered to the fasted rat. *J Biol Chem* 1985; 260: 8777-82.
7. Samar Banerjee, Subhajit Dutta, Diabetes And liver Disease. A.P.I. Medicine Update Vol 14; 2004, 106-113.
8. Harrison's Principles of internal Medicine – 16th ed. P 1844
9. Ingrid J Hickman, Elizabeth E Powell, Johannes B Prins et al. In overwight patients with chronic hepatitis C, circulating insulin is associated with hepatic fibrosis: implications for therapy : *Journal of Hepatology* 2003;39: 1042-1048.
10. Mihm S, Fayazi A, Hartmann H, Ramadori G. Analysis of histopathological manifestations of chronic hepatitis C virus infection with respect to virus genotype. *Hepatology* 1997;25:735-39.
11. Dixon JB, Bhathal PS, O'Brian PE. Non-alcoholic fatty liver disease : predictors of non-alcoholic steatohepatits and liver fibrosis in the severely obese. *Gastroenterology* 2001;121:91-100.
12. Paradis VP, Bonvoust G, et al. High glucose and hyperinsulinemia stimulate connective tissue growth factor expression : a possible mechanism in progression to fibrosis in non-alcoholic steatohepatitis. *Hepatology* 2001;34:738-744.
13. Svegliari – Baroni GR, Di Sairo F, et al. Insulin and insulin-like growth factor-1 stimulation proliferation and type 1 collagen accumulation by human hepatic stellate cell : differential effect on signal transduction pathways. *Hepatology* 1999; 290: 1743-51.
14. Fehorenbach H, Weis Kirchea R, Kasper M, et al. Up-regulated expression of receptors for advanced glycation end products, in cultured rat hepatic stellate cells during transdifferentiation to myofibroblasts. *Hepatology* 2001;34: 943-952.
15. Fibrogenic impact of high serum glucose in chronic hepatic C. Vlat Ratziu, Mona Munteanu et al. *Journal of Hepatology* 2003; 39:1049-55.
16. *Eur J Gastroenterol Hepatoly* 1996; 8: 125-129
17. *American Journal of Gastroenterol* 1997; 92: 1298-1301.
18. Marguerite McNeely. Diabetes in a Patient With Cirrhosis. *Clinical Diabetes*, 2004; 22: 42-43.
19. Petrides AS : Liver disease and diabetes mellitus. *Diabetes Revo* 1994;2: 2-18.
20. Bianchi G, Marchesini G, Zoli M, Bugianesi E, Fabbri A, Pisi E: Prognostic significance of diabetes in patients with cirrhosis. *Hepatology* 1994;20: 119-125.
21. V. Vlaeminck-Guillem, P. Guillem, P. Dequiedt, F R Pruvot, P. Fontaine. Liver Transplantation Eliminates Insulin Needs of A Diabetic Patients. *Diabetes & Metabolism (Paris)* 2000;26:493-496.