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Review Article

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An update on the Association between Liver and Diabetes mellitus

Arun Kumar D[1] and Swaminathan S*[2]

[1]Lab Technologist, Department of Biochemistry, Central Lab

[2]Chief of Biochemistry , Department of Biochemistry, Central Lab, SRM Medical College Hospital and Research Centre, Kattankulathur.Kancheepuram District 603 203, South India

*Corresponding Author E-mail: glorynathan@gmail.com

ABSTRACT

Liver is the most important organ involved in the entire metabolism of ingested food, synthesis of bioenzymes and removal of toxic substances. Its role in glucose metabolism has extensively been studied, and any liver dysfunction will affect many metabolic regulatory path ways. Alteration in liver function is said to affect Diabetes Mellitus status, its regulation and complications. A host of diseases of the liver such as cirrhosis, liver carcinoma, infections are said to have an impact on diabetes mellitus. This review paper highlights the recent findings on the role of liver in Diabetes mellitus, its future directions and the current concept on newer testing strategies and its clinical usefulness.

Keywords: *DM, HCC, NIDDM, NAFLD, HCV.*

INTRODUCTION

There is a strong correlation between diabetes mellitus (DM) and the liver: diabetic patients have typical histological lesions and alterations in glucose metabolism are commonly found in subjects with chronic liver disease. The pathogenesis of impaired glucose metabolism during chronic liver disease has not yet been fully understood: further clinical and experimental studies should clarify this issue[1]. There is a mutual relationship between DM and liver disorders. Diabetic patients suffer from liver disorders more frequently and liver dysfunction patients are at a higher risk of developing diabetes. Diabetes is probably the most common cause of chronic liver disorders in developed countries[2]. Preliminary data suggest that in the postprandial state, increased gluconeogenesis represents the primary mechanism responsible for impaired suppression of hepatic glucose production. Given the primary role of increased hepatic gluconeogenesis in the pathogenesis of hyperglycemia in Non Insulin Dependent Diabetes Mellitus (NIDDM), development of new drugs aimed at correcting the factors that might cause increased gluconeogenesis (e.g., increased free fatty acid oxidation and hyperglucagonemia) might open the way for new form of treatment of this disorder[3]. The increased phosphoenolpyruvate gluconeogenesis accounted for 89 ± 6% of the increase in overall hepatic glucose output in the NIDDM subjects and was significantly correlated with the fasting plasma glucose concentrations. Increased gluconeogenesis is the predominant mechanism responsible for increased hepatic glucose output in NIDDM[4].

LIVER CIRRHOSIS

Overt and sub clinical DM is associated with liver complications and death in cirrhotic patients. Treating diabetes is difficult in cirrhotic patients because of the metabolic impairments due to liver disease and because the most appropriate pharmacologic treatment has not been defined. It is also unknown if glycemic control with hypoglycemic agents has any impact on the course of the liver disease[5]. Cirrhosis secondary to hepatitis was associated with a lesser presence of DM only in patients with Hepatocellular Carcinoma (HCC). Liver cirrhosis was strongly associated with DM, with around 40 % of diabetic

patients. In the group of patients with Liver cirrhosis without HCC, diabetes was not associated with the etiology of cirrhosis[6]. DM increases the mortality of cirrhotic patients. Treatment of the diabetes is complex due to liver damage and hepatotoxicity of oral hypoglycemic drugs. occurrence and exacerbation of HCC[7]. Diabetes are at an increased risk of liver cirrhosis and its decompensation over time[8].

The presence of DM at baseline in patients with cirrhosis was associated with an increased risk of spontaneous bacterial peritonitis, which may represent an increased susceptibility to infections. However DM was not clearly associated with increased mortality in these patients[9]. DM may worsen immunodepression in cirrhotic patients thus increasing the incidence of severe infections which may further have a deleterious effect on hemodynamics and capillary permeability. A diabetic patient with advanced cirrhosis and sepsis usually has markedly increased capillary permeability, high hydrostatic pressure due to hyperdynamic circulation, and compromised lymphatic drainage capacity[10]. The presence of liver disease makes the treatment of diabetes complex, and additional research is needed to determine the best treatment strategies in these patients[11]. After adjustment for a number of factors (age, impaired fasting glucose, body mass index (BMI), waist hip ratio (WHR), elevated alanine aminotransferase (ALT), family history of diabetes and presence of hypertension and hyperlipidemia. Nonalcoholic fatty liver disease (NAFLD) was the only predictor of incident diabetes in those with and without impaired fasting glucose at baseline. A growing evidence connecting NAFLD to NIDDM highlights the importance of its recognition in an effort to target those at the highest risk of diabetes for lifestyle and pharmacologic intervention[12].

The Diacylglycerol-Protein kinase hypothesis can explain the occurrence of hepatic insulin resistance observed in most cases of NAFLD associated with obesity, lipodystrophy and NIDDM[13]. No antidiabetic agent has hitherto been shown to exert a beneficial effect on hepatic fibrosis. However, pharmacological treatment could be considered in patients with non-alcoholic steatohepatitis (NASH) not responding to lifestyle intervention. and long-term studies are needed to shed more light on the effect of antidiabetic treatment on NAFLD[14]. The identification of NAFLD should be sought as part of the routine assessment of NIDDM, as sought the microvascular complications and cardiovascular disease, because it is essential for the early diagnosis and proper intervention. Diet, exercise training, and weight loss provide significant clinical benefits and must be considered as the first line for treating NAFLD[15]. NAFLD patients had a markedly greater carotid intima-media thickness (IMT) among diet-controlled NIDDM individuals the significant increase of carotid IMT in the presence of NAFLD is largely explained by homeostatis model assessment (HOMA)-estimated insulin resistance[16].

The current body of evidence strongly suggests that NAFLD is likely to be associated with increased cardiovascular disease (CVD) risk, and raises the possibility that NAFLD may be not only a marker but also an early mediator of atherosclerosis[17]. Recent prospective studies have reported that NAFLD is associated with an increased incidence of metabolic syndrome (MetS) and NIDDM, independent of obesity and other components of MetS. Thus, NAFLD may not only be a liver disease but also an early mediator of NIDDM and MetS. Future studies might address the question whether earlier adjustment to a more efficient lifestyle or a pharmacological treatment that mobilizes fat out of the liver could reduce these risks[18]. Therapeutic goals for NAFLD should address nutrition, physical activity, and avoidance of smoking to prevent not only end-stage liver disease but also CVD[19]. Treatment is aimed at correcting the risk factors for NAFLD and using potentially hepatoprotective agents. Ursodeoxycholic acid and betaine appear particularly promising in early trials[20].

Livers of diabetics had significantly more severe steatosis and rich perisinusoidal collagen IV, laminin and smooth muscle actin accumulation without histologically detectable NASH and irrespective of the degree of steatosis. Obese patients with NIDDM and insulin resistance develop more severe NAFLD and early sinusoidal fibrosclerosis[21]. NAFLD is now recognised as the hepatic component of MetS, and is an example of ectopic fat accumulation in a visceral organ that causes organ-specific disease, and affects risk of other related diseases such as NIDDM and CVD. NAFLD is a spectrum of fat-associated liver conditions that can culminate in end stage liver disease, HCC leading to the need for liver

transplantation[22]. The presence of NAFLD in NIDDM is also associated with increased overall mortality[23].

HEPATOCELLULAR CARCINOMA

Several cohort studies have suggested a metabolic pathway from nonalcoholic fatty liver, nonalcoholic steatohepatitis, cryptogenic cirrhosis, and eventually hepatocellular carcinoma. Although cardiovascular risk remains the major cause for excess mortality in NIDDM, the risk of progressive liver disease should no longer be underscored[24]. The significant synergy between heavy alcohol consumption, hepatitis virus infection, and DM may suggest a common pathway for hepatocarcinogenesis. Exploring the underlying mechanisms for such synergisms may indicate new HCC prevention strategies in high-risk individuals[25]. Also thiazolidinediones seem to prevent tumor formation in the liver via the inhibition of peroxisome proliferator-activated receptor gamma-independent regulation of nucleophosmin. More debated is the role of sulfonylureas in decreasing HCC incidence in diabetic patients. Further investigations are needed to define reliable indications to therapy and surveillance in patients with diabetes or insulin resistance[26].

Also meta-analysis of 7 cohort studies found a statistically significant increased risk of HCC mortality for individuals with and without diabetes. This meta-analysis shows that diabetes is associated with moderately increased risk of HCC prevalence, as well as HCC mortality. Considering the rapidly increasing prevalence of DM, there is need for cancer prevention in diabetic individuals. Further investigation is needed to focus on the potential mechanism for the pathogenesis of HCC and the link between HCC and different types, severity, treatment and duration of diabetes[27]. Metformin is a promising therapeutic agent for the elimination of tumor-initiating HCC cells and suggest as-yet-unknown functions other than its inhibitory effect on the activated protein kinase / mammalian target of rapamycin pathway[28]. NASH-based fibrosis is an essential histological process for diabetic populations to accelerate the development of HCC[29]. Hyperglycemia and co-presence of low LDL-C plus low triglyceride (TG) might enhance, while insulin or statin usage might attenuate the promoting effect of chronic hepatitis B virus (HBV) infection on HCC in NIDDM[30].

GLYCOGEN STORAGE DISEASE

Glycogenic hepatopathy (GH) is a rare cause of serum transaminase elevations in type 1 diabetes mellitus. Clinician's awareness of GH should prevent diagnostic delay and will provide better insight into the prevalence of GH[31]. As in children, liver enzyme abnormalities are unreliable in predicting the presence or the extent of glycogenosis. Hepatic glycogenosis can occur at any age, and therefore should be included in the differential diagnosis of hepatomegaly in all insulin-requiring diabetics[32]. Glycogen storage hepatomegaly in diabetics may not be only due to an acute restoration from diabetic ketoacidosis, but may also be due to an over insulinization in an attempt to maintain a euglycemic condition in spite of excess food intake[33].

INFECTIONS

When diabetics present with soft tissue infection, physicians should consider the possibility of underlying necrotizing infection and pursue surgical evaluation if there are signs of systemic illness, characteristic skin findings, failure to respond to antibiotics, or characteristic radiographic findings[34]. Diabetic complications are more common if longer the duration of the disease that has been present. A significant percentage of these complications come in the form of infections. Because these complications are generally related to disease duration, clinical problems are very frequently seen in the elderly population. Moreover, infectious complications in older diabetics have poorer outcomes[35].

Among those at high risk for diabetes, persons with HCV infection were more than 11 times as likely as those without HCV infection to develop diabetes. Among those at low risk, no increased incidence of diabetes was detected among HCV-infected persons. Pre-existing HCV infection may increase the risk for NIDDM in persons with recognized diabetes risk factors. Additional larger prospective evaluations are needed to confirm these preliminary findings[36]. The temporal relation of HCV infection to the development of NIDDM remains unknown. HCV infection is an independent predictor of diabetes, especially for anti-HCV and persons who are younger or have a higher body mass index[37].

LIVER ABSCESS

An emphysematous liver abscess is a fatal condition that often occurs in patients with uncontrolled diabetes mellitus[38]. In the DM and non-DM groups, the cure rates for percutaneous drainage with antibiotics were 90.3% and 92.0%, respectively, and the cure rates for surgery with antibiotics were 93.9% and 95.2%, respectively[39]. The association between K pneumoniae liver abscess and diabetes is so close that a search for underlying diabetes mellitus is warranted in all patients with K pneumoniae liver abscess. Fortunately, earlier diagnoses and better treatment modalities have improved the outcome for these patients[40].

ALCOHOL ABUSE

Chronic use of alcohol is considered to be a potential risk factor for the incidence of NIDDM, which causes insulin resistance and pancreatic β-cell dysfunction that is a prerequisite for the development of diabetes[41]. Diabetes patients who are at-risk drinkers are likely to have poor diabetes treatment adherence, leading to increased morbidity and mortality. Alcohol consumption by diabetes patients is often inadequately assessed and addressed in their medical care[42]. Chronic heavy alcohol ingestion may aggravate NIDDM and may possibly lower brain-derived neurotrophic factor level[43].

VLDL

Hepatic SH2B1 gene is not required for the maintenance of normal insulin sensitivity and glucose metabolism; however, it regulates liver triacylglycerol synthesis, lipolysis, and VLDL secretion[44]. Hepatic VLDL-apoB100 overproduction may be stimulated by ceramides and sphingosine and inhibition of sphingolipid synthesis can reduce circulating VLDL in hamsters and improve circulating lipids--an effect that is possibly due to improved insulin signaling and reduced lipogenesis but is independent of changes in inflammation[45]. TNF-alpha induces whole-body insulin resistance and impairs hepatic insulin signaling accompanied by overproduction of apoB100-containing VLDL particles, an effect likely mediated via TNF receptor 2[46]. As insulin resistance progresses, a number of pathways are altered that further augment VLDL hypersecretion, including hepatic inflammatory pathways. Insulin plays a complex role in regulating glucose metabolism, and it is not surprising that the role of insulin in VLDL and lipid metabolism will prove equally complex[47].

TRIGLYCERIDE

Adipose triglyceride lipase in mice are protected from high-fat diet induced insulin resistance and reveal a tissue specific disparity between lipid accumulation and insulin sensitivity[48]. The therapeutic advantage of secondary hyperlipidemia in children with diabetic ketoacidosis is the use of Bifiform Baby for in the elimination of main infringement of a metabolism of lipids in the given disease--hypertriglyceridemia[49]. leading to high prevalence of hyperlipidemia and need of monitoring serum lipid concentration in IDDM patients[50]. Fibrate therapy is the first choice in the isolated hypertriglyceridaemia as well as in type V. hyperlipoproteinaemia. On the basis of the guidelines far more patients with diabetes should be treated with lipid lowering therapy than before[51].

The insulin-resistant diabetes course affects virtually all lipids and lipoproteins. Chylomicron and VLDL remnants accumulate, and triglycerides enrich HDL& LDL leading to higher levels of potentially atherogenic particles and low levels of HDL cholesterol. Hyperglycemia eventually impairs removal of triglyceride-rich lipoproteins, the accumulation of which accentuates most patients with NIDDM who have risk factors for coronary artery disease and qualify for aggressive LDL cholesterol-lowering therapy. At the same time, it is presently unknown whether improved glycemic control decreases coronary artery disease risk in such patients[52].

LIVER ENZYMES

The prevalence of elevated serum ALT > 740 U/L was 33.4% in boys, and 19.6% in girls respectively. In boys, ALT correlates with BMI, WHR, total cholesterol, triglyceride, HDL-cholesterol, systolic and diastolic blood pressure, HOMA-IR, fasting serum insulin, and in girls ALT was found to correlate with BMI, WHR, total cholesterol, triglyceride, glucose, systolic and diastolic blood pressure, among obese Korean children, insulin resistance and ALT, lipid profile, BMI, WC, blood pressure showed significant

correlation. Especially, in boys, higher ALT is founded to be independently associated with insulin resistance[53].

Higher ALT concentrations were cross-sectionally associated with obesity and whole-body and hepatic insulin resistance and prospectively associated with a decline in hepatic insulin sensitivity and the development of NIDDM. The above findings indicate that high ALT is a marker of risk for NIDDM and suggest a potential role of the liver in the pathogenesis of NIDDM[54].

There were no association found between sex, ethnicity, obesity, impaired glucose tolerance, with AST or ALT in the prediction of NIDDM. When entered into the same model with adjustment for demographic variables, both C-reactive protein and ALT independently predicted NIDDM. In addition, AST and ALT were positively associated after excluding moderate to heavy drinkers. Baseline elevations of these markers may reflect NAFLD or related pathophysiology[55]. Available data indicate moderate associations of ALT with the risk of NIDDM events, which may be attributable to publication bias. There was no evidence for an increased risk of NIDDM with AST. Large prospective studies may still be needed to establish the magnitude and nature[56]. Elevated levels of serum gamma-glutamyltransferase (GGT) levels have been found to predict the development of NIDDM in adults. The role of GGT in insulin resistance among children is largely unknown. Measures acquired included weight, height, percent body fat,waist circumference, blood pressure, blood glucose and insulin, C-reactive protein, total cholesterol, triglycerides, HDL-Cholesterol, GGT, AST and ALT[57].

Elevated liver enzymes were associated with family history of diabetes mellitus In particular, elevated GGT was related independent of the other variables[58]. As determination of GGT activity is a low-cost, highly sensitive, accurate and frequently used laboratory test and there is association of this enzyme with the most important risk factors of NIDDM and CVD, its serum levels should be considered as a marker of insulin-resistance when NAFLD is supposed to be present or there is obesity[59]. The association of serum GGT with NIDDM reflects exposure to persistent organic pollutants, as these substances, which have a very long half-life, may influence diabetes risk by residing in adipose tissue as endocrine disruptors; and that similar substances may interact with obesity to cause NIDDM[60].

As a marker of the amount of conjugated xenobiotics, recent epidemiological findings about serum GGT imply the possibility of harmful effects of various environmental pollutants at background levels currently regarded as safe[61]. Possible interactions between serum GGT and BMI and their effects on the risk of prevalent NIDDM and homeostasis model assessment insulin resistance[62]. People with high serum GGT have higher mortality, partly because of the association between GGT and other risk factors and partly because GGT is an independent predictor of risk[63].

INSULIN RESISTANCE

Genetic variants associated with genes in the glycine biosynthesis pathways do not provide consistent evidence for a role of glycine in diabetes-related traits[64]. Clinical criteria assess the risk for NIDDM with greater sensitivity and specificity than the combination of all known genetic variants[65]. Low IGF-I levels might have a role in insulin resistance among HCV viremic patients[66] Activation of the TNF-alpha system has a pivotal role in the inflammatory process of chronic hepatitis C, and TNF-alpha levels correlate with the degree of inflammation. TNF-alpha is known to cause insulin resistance, with similar defects in the insulin signalling pathway to those described in HCV infection. A model of mice transgenic for the HCV core protein demonstrated insulin resistance, glucose intolerance, and elevated intrahepatic TNF-alpha mRNA; all of which were ameliorated by anti-TNF-alpha antibodies. In addition, diabetic HCV patients have significantly higher levels of soluble TNF-alpha receptors, compared to non-diabetic HCV patients and controls. TNF-alpha may be the link between HCV infection and diabetes, suggesting an additional mechanism of diabetes with important implications for prognosis and therapy[67].

CONCULSION

The role of liver in diabetes mellitus has been reviewed in this article bringing into focus the recent advances in the etiology of the role of liver and various diseases associated with Diabetes Mellitus. This article also highlights the potential factors responsible in liver dysfunction and suggests ways to alleviate

such factors. Liver enzymes and alterations in lipid profiles have been thought to play a part in Diabetes. More laboratory based tests such as C-RP. ALT, GGT, TNF, HCV and IGF-1 must be developed as an aid in the diagnosis of not only liver diseases, but also Diabetes Mellitus.

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