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Bi-Directional Effect Of Diabetes Mellitus And Chronic Liver Disease.

Odoh G[1], Uwakwe J.N[2] Puepeth FH[1].
1.Department of Internal medicine, Jos University Teaching Hospital, Jos, Nigeria.
2.Department of Internal medicine, DalhatuAraf Specialist Hospital, Lafia

ABSTRACT
The liver plays a very important role in maintenance of glucose homeostasis in the body, hence disorders of the liver are usually associated with varying degrees of glucose abnormalities, these ranges from glucose intolerance to overt diabetes mellitus (DM) . Overt Diabetes Mellitus has been reported in about 30% of patients with cirrhosis of the liver and glucose intolerance in about 96% of the patients.
Some of the aetiopathogenic factors involved include; hyperinsulinaemia with insulin resistance from decrease hepatic clearance, impair insulin secretion from pancreatic β cells, hepatitis C viral infection, hepatic inflammation, hypoxia/hypoxia inducible factors, reduce incretin effect and effect of medications used in treatment of viral induced liver disease. Conversely, there is a strong relationship between the insulin resistance syndrome, characterize by glucose intolerance and or type 2 DM with different stages of chronic liver disease. Several studies have reported a 2-2.5 fold increase in the risk developing cirrhosis and associated death from chronic liver disease. Some of the aetiopathogenic factors involved include; activation of hepatic stellate cells by hyperinsulinaemia and rising plasma glucose, inflammation, aptotosis, angiogenesis and effect of anti-diabetic medications.
This review aim to explain the aetiopathogenic factors in liver disease and diabetes mellitus that are involved in the predisposition to the development of diabetes and chronic liver disease and to raise awareness on the subject.

Key Words: *Diabetes mellitus, Liver disease,aetiopathogenic, bidirectional effect.*

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I. INTRODUCTION.

The liver plays a very important role in maintenance of glucose homeostasis in the body[1].Abnormalities of glucose metabolism including; glucose intolerance and diabetes mellitus (DM) are common findings in patients with chronic liver disease. Overt Diabetes Mellitus has been reported in about 30% of patients with cirrhosis of the liver and glucose intolerance in about 96% of the patients[2]."

Hepatogenous diabetes" ,a term first used in 1906 to describe the high incidence of diabetes in cirrhotics[3] has increasingly become relevant over the years .Hepatogenous diabetes was further described in the 1960s by Megyesi et al[4] and Muting et al[5] to relate association of insulin resistance and impaired glucose intolerance in patients with chronic liver disease. Conversely, there is a strong relationship between the insulin resistance syndrome, characterized by glucose intolerance and or type 2 DM with different stages of chronic liver disease[6,7]. Several studies have reported a 2-2.5 fold increase in the risk developing cirrhosis and associated death from chronic liver disease[8-10].The association/predisposition of the two diseases to each other may be related partly to the shared aetiology /mechanism leading to the two disease conditions. Some of which include Nonalcoholic fatty liver Disease(NAFLD), Hemochromatosis, autoimmne liver disease and Hepatitis C Virus (HCV)Infection[11,12]. Some of the pathophysiologic mechanisms /aetiologic factors, however, are related to just one of the disease condition.

II. Mechanism Of Chronic Liver Disease Predisposing To Glucose Intolerance/Type 2diabetes Mellitus

DECREASE INSULIN CLEARANCE BY THE LIVER.

About 60% of secreted insulin is metabolised by the Liver. In cirrhosis of the liver, most of the functional liver cells are replaced by extensive fibrosis and formation of regenerative nodules. This reduction in the functional liver cell mass, is associated with formation of portosystemic collaterals resulting in decrease hepatic first pass extraction. This will result in decrease insulin metabolism/ extraction by the liver leading to systemic hyperinsulinaemia[13,14.]Additionally, the late stage of liver cirrhosis has been reported to be associated

with pancreatic islet cell hypertrophy[15], which will further worsen the hyperinsulinaemia. The resulting hyperinsulinaemia from above leads to down regulation of insulin receptors from persistent stimulation.This will result in reduction in insulin receptor affinity, number of receptors exposed to the surface of target cell and diminution of their effectiveness as a transmitters of stimulatory signals for glucose uptake[16]. These changes lead to insulin resistance and subsequently glucose intolerance which may range from impair glucose intolerance, impair fasting glycaemia or overt DM.

Beside a decrease in hepatic cell mass in patients with cirrhosis, decrease in skeletal muscle mass, a feature seen in chronic liver disease, is also thought to be a contributory factor to glucose intolerance. Studies have reported impairment in insulin stimulated glucose uptake into skeletal muscle in cirrhotic patients[17,18]. Mechanism for the impair insulin action is not clear, but this is thought to be related to decrease in number of functional insulin receptors on skeletal muscles as a result of the decrease in skeletal muscle mass in patients with cirrhosis of the liver.

ROLE OF ADVANCE GLYCATION END PRODUCTS.

Although hyperglcaemia leads to formation of advance glycation end products(AGEs), however, the liver is also the catabolic site for AGEs hence, AGEs is expected to rise in chronic liver disease.AGEs have been reported to induce insulin resistance and β-cell injury prior to onset of diabetes in patients with chronic liver disease[19].Levels of AGEs in patients with cirrhosis of the liver correlates with severity of the disease[19,20] and a significant decline in the Level of AGEs is seen after liver transplantation[21]. This further suggest that chronic liver disease is responsible for rise in AGEs.

HYPOXIA AND HYPOXIA IDUCIBLE FACTOR(HIF)

Hypoxia is commonly reported in patients with advance cirrhosis[22], the extent of hypoxia is related to the severity of liver cirrhosis[22]. Hypoxia inducible factors(HIF), a family of transcriptional regulators usually mediates tissue response to hypoxia. They have been implicated in the development of liver fibrosis invitro in murine models[23,24]. The HIF have also been implicated in the development of β-cell dysfunction and diabetes mellitus[25]. The precise mechanism for induction of diabetes is complex and related to the type of HIF involved. While a mild increase in HIF 1-α is good for β-cell function and glucose tolerance, a high level HIF-1 observed in severe hypoxia are deleterious to β-cell function[26]. And will predispose to development of hepatogenous diabetes.

REDUCED INCRETIN EFFECT.

The Naturally occurring incretin hormones, Glucose-dependent Insulinotropic Polypeptide(GIP) and Glucagon-Like Peptide 1(GLP-1) play very important roles in maintaining glycaemic control[27]. GLP-1 is a gut-derived incretin hormone that stimulate insulin secretion, suppress glucagon secretion and induce satiety in a glucose dependent fashion. The activities of these hormones is rapidly terminated by hydrolysis via the effect of Dipeptidyl Peptidase-4(DPP-4) hormone. The activities of this hormone have been reported to be up-regulated in patients with cirrhosis of the liver, this will reduce the incretin effect via their rapid metabolism of the incretin hormones, which will predispose to impair glucose tolerance and diabetes mellitus[28,29].

CHRONIC HEPATITIS C VIRAL INFECTION.

Hepatitis C virus infection can alter glucose metabolism via either a direct effect of the virus core protein[30]or indirectly via cytokine stimulation. In transgenic mice, the core encoding region of HCV was reported to induce insulin resistance and use of anti-TNF antibodies was reported to reverse this effect[31].The direct effect of HCV on inducing insulin resistance was also demonstrated by Kawaguchi et al[32] when he demonstrated inhibition of insulin signaling by HCV proteins. Additionally, studies on chronically infected patients suggested that increase oxidative stress and intrahepatic inflammation with increase inflammatory makers like TNF-α are also contributing factors to insulin resistance and glucose intolerance[33,34] in HCV infection with chronic liver disease. Other contributing factors include

HEPATIC INFLAMATION.

Type 2 DM and cardiovascular diseases are associated with subclinical inflammation. Chronic hepatic inflammation and inflammation related to visceral adiposity are related to chronic systemic inflammation in the prediabetic state. Cai et al.,35 and Arkan et al36 demonstrated relationship between chronic low hepatic inflammation and systemic insulin resistance which is mediated by elevated circulating IL-6 levels.

HEPATOKINES.

Some studies have demonstrated that mechanisms of induction of metabolic diseases by fatty liver may differ from that of expanded adipose tissue mass. Some of the factors released from the fatty liver, protein feutin

A, a sex-hormone binding globulin and selenoprotein P called the hepatokines, have been demonstrated to be involved in the pathogenesis of insulin resistance and associated with sub-clinical inflammation[37,38].

EFFECT OF THE PANCREAS IN THE SETTING OF CHRONIC LIVER DISEASE.

The liver and pancreas anatomically, are closely related; blood vessels and ducts in these organs are anatomically related to each other. Hence, disease processes affecting the liver can easily affect the pancreas. Many studies in humans and animals have reported acute or chronic pancreatic disease in subjects with chronic liver disease irrespective of the aetiology,[39-42]. An inflamed liver induced by mild endotoxemias associated with impairment of pancreatic insulin secretion[43]. Studies by Petrides et al[44] and Picardi et al[45] suggest altered secretion of insulin by the β-cell of the pancreas may contribute to development of overt diabetes.

EFFECTS OF MEDICATIONS USE IN TREATING LIVER DISEASE

Interferon therapy used to treat hepatitis B and C has been reported to induce hyperglycemia, resulting in the development of type 2 diabetes, and necessitating increased insulin requirements in patients with type 1 diabetes.[46-48]This is thought to be due to the development of insulin autoantibodies from the use of interferon.[49]

III. Mechanisms Of Chronic Liver Disease Resulting From Type 2 Diabetes Mellitus

ACTIVATION OF HEPATIC STELLATE CELLS

The hepatic stellate cells, which are liver specific pericytes are located in the space of Disse. The stellate cells when activated promote fibrosis through extracellular matrix production and reduce extracellular matrix degradation[50].This process usually occur when the liver is chronically injured. Glucose and insulin have been reported to have profibrogenetic properties on hepatic stellate cells.This was demonstrated by Friedman et al[51]when they noticed over expression of a key profibrogenic gene; Connective Tissue Growth Factor (CTGF), on incubation of stellates cells with high glucose or insulin.Advance Glycosylation End Products(AGES) are usually produced due to hyperglycemia and oxidative stress.Receptors for AGES have been found to be over express in activated hepatic stellate cells[52,53]. This up regulation of receptors for AGES might imply that they are involve in activation of stellate cells. From the above findings, Type 2DM,characterise by hyperinsulinaemia and hyperglycaemia can be seen to be an important factor in the development of and /or progression of chronic liver disease.

INFLAMMATION

Inflammation has been described as a key factor in the formation of hepatic fibrosis[54]. Diabetes has been described as an autoinflammatory disease[55]. The systemic inflammation induce by type 2 DM, stimulate release of Leptin, adiponectin, TNF-α, Interleukin-6 from chronically inflamed adipose tissue[56,57]. Transformation Growth Factor-β1 and leptin activate stellate cells , which produces collagen resulting in fibrosis and subsequently cirrhosis of the liver[58-61].Leptin and TNF-α have also been reported to activate inflammatory pathways that worsen liver damage62. Adiponectin a regulator of insulin sensitivity and tissue inflammation[63], is reduced in insulin resistance state, hypoadiponectinaemia has also been reported to play a role in liver disease progression[64,]

APOPTOSIS.

Dysregulation of insulin receptor pathway associated with insulin resistance in patients with type 2 diabetes has been reported to promote liver apoptosis[65] Patients with Non Alcoholic Steato-Hepatitis(NASH) have also been reported to have increase levels of cytokeratin 18, a biomarker of liver apoptosis, associated with liver fibrosis[66,67].

Apoptosis, a type of cell death characterize by fragmentation of dying cells into membrane bound vesicles, called apoptotic bodies, is a key player in progression of liver fibrosis[68]. Engulfment of apoptotic bodies by hepatic stellates cells stimulate their fibrogenic properties, hence promoting hepatic fibrosis, which might lead to cirrhosis[69].

ANGIOGENESIS.

Which involves formation of new blood vessels from existing blood vessels, has been described to play a vital role in the development of diabetic complications like; nephropathy, retinopathy as well as macrovascular complications[70] These complications are thought to result from activation of Connective

Tissue Derived Growth Factors (CTGF) by angiogenesis[72,73].Leptin ,an adipokine formed as a result of inflammation in adipose tissue induce by type 2 DM, has been described to mediate formation of neo-vascularisation via activation of Vascular endothelial growth factor(VEGF). And the neovascularisation has been reported to play an important role in the development of liver fibrosis in rat models[74].Relating Neovascularisation and fibrosis of the liver was further supported by a study which showed positive correlation

between neovasculrisation, insulin resistance as well as liver fibrosis[75]. This suggests that insulin resistance a core feature of type 2 DM by mediating neovascularisation promote liver fibrosis.

HEPATIC SINUSOIDAL CAPILLARISATION

This refers to loss of endothelial cell fenestrations due to deposition of collagen and extracellular matrix protein in the space of disse. It has been implicated in the progression of liver fibrosis[76].Although the role of insulin signaling and hyperglycaemia on endothelial fenesteration and development of liver fibrosis has not been studied[77], the increase in extra-cellular matrix deposition in the space of disse observed in liver biopsies from patients with DM suggest that hepatic sinusoidal capillarisation may promote liver fibrosis in patients with diabetes[78-79].

EFFECTS OF ANTIDIABETIC MEDICATIONS

Some antidiabetic medications have been associated with varying degrees of liver injury. The sulphonylureas have been reported to cause hepatitis, with associated necroinflammatory and granulomatous changes[80]. The older sulphonyureas, though not currently in use, have been associated with hepatic injury; chlopropamide is associated with cholestatic hepatitis in 0.5% of patients while Acetahexamide can cause hepatocellular necrosis[81].

IV. CONCLUSION

Diabetes Mellitus, a major public health problem predispose to development of liver disease via varying mechanisms. Conversely, chronic liver disease, also a major cause of morbidity and mortality also predispose to development of glucose intolerance and overt diabetes via various mechanisms. We advocate for early screening for either of the two diseases in the presence of Diabetes mellitus or Chronic liver Disease. This will help in early identification, initiation of appropriate treatment modality which will slow progression or prevent above described pathogenetic mechanisms and therefore reduction and or prevention of significant attendant morbidity and mortality.

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