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Diabetes and Liver an Association: Hepatogenous Diabetes Mechanism and Some Evidences

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Abstract

A literature search was conducted in different databases to study the topic of liver problems and diabetes. The aim of the study was to explore more about an association of diabetes mellitus with the liver. The study shows that diabetes does indeed have an effect on liver. Similarly, liver problems like chronic liver disease lead to diabetes which is known as hepatogenous diabetes. Common liver problems seen in diabetes patients include but not limited to fatty liver, decreased glycogen levels, risk of liver cancer etc. Like any medical problem, any knowledge about any subject is never enough, therefore we recommend more studies in the near future to broaden our understanding about the association of the liver with diabetes.

Keywords: Diabetes; Diabetes complications; Diabetes and liver; Diabetes and fatty liver; Diabetes and hepatitis; Diabetes and cirrhosis

Introduction

"*Doctor! I do have diabetes and I have been compliant with my medication, but now I have this epigastric pain….my primary doctor thinks it's my liver.*" If you are a gastroenterologist, and a patient comes to you with such complain, what will you do? It can make the management of such patient difficult if the clinician is not aware that there is an association of diabetes with liver. This short review is our attempt to highlight the possible association between the diabetes type-1, type-2 and liver.

Diabetes mellitus is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or due to insulin resistance when cells do not respond to the insulin that is produced [1]. The resultant high blood sugar produces the classical symptoms of polyuria, polydipsia and polyphagia. Diabetes mellitus can be Type 1 DM, which results from autoimmune destruction of insulin-producing beta cells of the pancreas or of Type 2 DM, which begins with insulin resistance and relative insulin deficiency [2,3]. There are various complications due to Diabetes which can be divided into two types. Microvascular complications include Diabetic retinopathy, Diabetic nephropathy and Diabetic neuropathy. Similarly, macrovascular complications include atherosclerosis, coronary heart disease, stroke cerebrovascular disease etc. [4].

In this mini review, we will highlight the topic about the association of liver diseases with diabetes mellitus. The published data is sufficient to show that there is a possible association between the two. Sometimes liver problems lead to diabetes mellitus, while sometimes diabetes affects liver. We hope that this article will be helpful for young scientist and physicians interested in this aspect of endocrinology and gastroenterology.

The article will be comprised of a method section, followed by the discussion. In the discussion, we will highlight the possible liver problems with diabetes (type 1 and 2). The review will be concluded with the findings that there is indeed an association between liver problems and pancreatic problems like diabetes. However, the association of liver cancer with diabetes remain dubious due to mix findings and conflicting results of some studies. Therefore, we will recommend future studies on the subject to bring more details for the interested readers.

Methodology

The research methodology involves gathering relevant abstract, papers and reviews from different publications and journals in PubMed, Wiley, Elsevier, Google Scholar, and others without any date restriction. The literatures gathered were pertinent to types, complications and liver based effects of Diabetes. Keywords for the review included: Diabetes, Diabetes complications, Diabetes and liver, Diabetes and fatty liver, Diabetes and hepatitis, Diabetes and cirrhosis. Each abstract was evaluated through determination of the relevance on the research review. After reviewing over two hundred and fifty abstracts and articles, the relevant ones were chosen for inclusion on the final paper. The focus was made on the subject of Diabetes and its effects on liver. The data was obtained from different research projects, experiments, journals, systematic reviews, mini reviews, and case series.

PRSIMA checklist was followed to complete the review. Therefore, the following inclusion and exclusion criteria were selected. The inclusion criteria included, the articles published about the subject of the association of liver and diabetes mellitus were selected. The articles published after the year 1955 after selected to keep the literature updated with a combination of old and new literature. The articles strictly about human studies and clinical trials were included. While the exclusion criteria included, the articles with vague or no clear findings were excluded.

Discussion

Diabetes and liver: An association

According to Consoli et al. increased glucose output is the result of fasting hyperglycemia of non-insulin dependent diabetes mellitus

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(NIDDM). There was also a correlation with fasting blood glucose. In the same study, a new isotopic approach was applied for determination of contributions by gluconeogenesis and glycogenolysis through infusions of [6-3H] glucose and [2-14C] acetate. The approach was applied in 14 post-absorptive NIDDM patients and in nine healthy subjects (same age and weight) to trace overall hepatic glucose output and phosphenol pyruvate gluconeogenesis. The finding of this study was that the overall liver output was increased by 2 times in NIDDM patients while there was three-fold raise in phosphenol pyruvate glucogenesis. [5].

Glycogen related liver changes in diabetes

In the patients suffering with acute diabetes, Glycogen synthesis is affected. The liver glycogen during post prandial and post 24-hour fast state was calculated in streptozotocin (STZ)-diabetic rats by Ferranini et al. The short term diabetic animals were observed to have reduced liver glycogen levels in post prandial state. However, this was not true for long term diabetic rats. There was a reduction in hepatic glycogen in acute diabetes during fasting but increased in chronic diabetes. The liver glycogen synthase percentage in active form (synthase a) was seen less than normal in short term diabetic and old nondiabetic rats. However, there was a remarkable increase in long term diabetic animals [6]. Manderson et al. quantitative and qualitative analysis of liver glycogen and related enzymes in patients with severe unstable Diabetes mellitus with hypoglycemic episodes revealed that the liver glycogen content was high with normal molecular structure and normal enzyme activity. Hence, some patients with brittle diabetes mellitus experience increased liver glycogen levels due to wide variations in blood sugar and frequent doses of soluble insulin but not due to enzyme deficiency [7].

Fatty liver and perisinusoidal fibrosis

The association of diabetes with fatty liver is well documented [8]. A particularly interesting suggestion was made by Bogoch et al. They suggested that humans possess same dynamic change in hepatic lipids as experimental animals. The neutral fats are most involved during the accumulation of lipids in the diabetic liver. The degree of fatty metamorphosis of liver was not observed to be directly correlated with any other histochemical or laboratory observations. A suggestive correlation between marked increases of lipids and hepatomegaly was seen among the diabetes patients [9]. A study in diabetic hepatitis by Nagore et al. suggested that the lesion in some diabetic patients was periportal rather than perivenular in location and there was presence of nuclear vacuolation of hepatocyte nuclei [10]. There are other studies performed to observe the relation of fatty liver with diabetes [11,12].

Perisinusoidal fibrosis is also common in the liver of type I diabetic patients. A study by Bernau et al. in genetically susceptible BB rats suggested that liver perisinusoidal fibrosis in type I diabetic patients might have link to a genetic abnormality rather than to hyperglycemia [12]. Falchuk et al. observed the intermediate lesion between fatty steatosis and cirrhosis in diabetes. A study was performed in maturity onset diabetic patients with hepatomegaly, which showed collagen surrounded swollen hepatocytes containing intracellular hyaline without presence of polymorphonuclear neutrophils and regenerating nodules [13].

Hepatogenous diabetes: Insulin resistance and liver

We have discussed some liver alterations caused by diabetes, or some liver problems prevalent in diabetic patients. However, when a chronic liver disease leads to diabetes, this condition is known as hepatogenous diabetes (HD). Not much has been written about it. Yet some studies exist that describe the exact pathophysiological mechanism of this disease. Insulin resistance is thought to be the culprit leading to hepatogenous diabetes. In order to compensate the insulin resistance, the pancreatic β-cell insulin secretion increases dramatically. Eventually leading to B-cell exhaustion. Hence, developing diabetes [14,15]. The mechanism how insulin resistance ensues, involves portosystemic shunts and decreased overall liver mass. As a result, insulin clearance is impaired, hence leading to peripheral insulin resistance though down-regulation of insulin receptors. Augmented levels of advanced-glycation-end products and hypoxia-inducible-factors are also involved in the pathophysiology of hepatogenous diabetes [16]. Reduced insulin expression and augmented pancreatic transcription factor PDX-1 in islets in liver cirrhosis patient's pancreas has also been described as a pathophysiological mechanism involved in this disease [17]. In addition, TCF7L2 polymorphisms (also considered to be possible cancer risk) are also found associated with HD [18].

In a study by Kawaguchi et al. the features of insulin resistance in relationship to chronic liver disease was reviewed. The study suggested that hepatogenous diabetes is caused due to increased insulin resistance which is often associated with chronic liver disease. The factors responsible for development of hepatogenous diabetes are hepatic parenchymal cell damage, portal systemic shunting and Hepatitis C virus infection. Liver failure, hepatocellular carcinoma and gastrointestinal hemorrhage are the major causes of death in cirrhotic patients with diabetes. The exogenous insulin or sulfonylureas may promote hepatocarcinogenesis in the patient with hepatogenous diabetes. The hepatogenous diabetes differ from lifestyle-related type 2

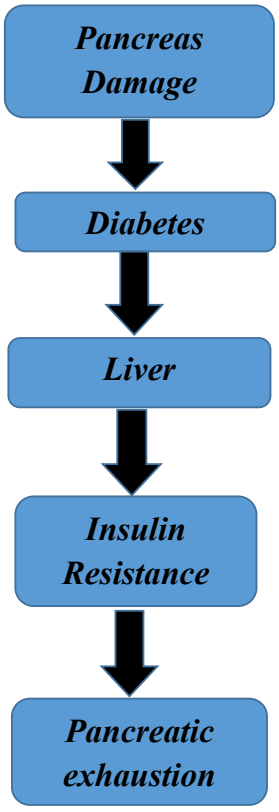

Figure 1: The Flow chart showing the cyclical nature of the association of diabetes with liver. The pancreatic damage leads to diabetes and that eventually leads to liver problems like fatty liver (eventually leading to cirrhosis). However, in hepatogenous diabetes, the chronic liver disease (cirrhosis) leads to pancreatic damage because of insulin resistance compensation.

Author and Year	Country	Study Design	Population	Findings
Consoli et al. [5]	USA	Clinical Trial	4 post-absorptive NIDDM subjects and in 9 nondiabetic volunteers of similar age and weight	Raised gluconeogenesis is the mechanism behind raised liver glucose output in NIDDM
Ferrannini et al. [6]	Italy	Animal Study	Diabetic Rats	In the fed state, hepatic glycogen levels were tremendously reduced in short-term diabetic animals but not in long-term diabetic rats as compared with age-matched nondiabetic animals, despite comparable hyperglycemia (portal plasma glucose levels of 424 mg/100 ± 21 mg/100 and 449 mg/100 ± 24 mg/100 mL, short- and long-term diabetics, respectively). While in the fasted state, hepatic glycogen was depleted in acute diabetes but remarkably augmented in chronic diabetes
Ludwig et al. [8]	USA	Review Article	NA	Nonalcoholic steatohepatitis (NASH) is associated with Diabetes
Sakata et al. [17]	Japan	Cross-Sectional Study	35 human autopsy pancreatic tissue samples	Islet hypertrophy and a marked increase in PCNA-positive cells in islets are found in cirrhotic liver tissue.
Kawaguchi et al. [20]	Japan	Review Article	NA	Liver parenchymal cell destruction, portal-systemic shunt and Hep C lead to hepatogenous insulin resistance/diabetes
García-Compean et al. [21]	Mexico	Review Article	NA	Insulin resistance in muscular, liver, adipose tissues, and hyperinsulinemia could be involved in the pathophysiology of hepatogenous diabetes.
Fan et al. [26]	China	Case-control study	48 cases of Hepatocellular Carcinoma (HCC) line after TACE with HD, 48 controls of Hepatocellular Carcinoma (HCC) line after TACE without HD	Family history of diabetes, HBV DNA, liver function Child-Pugh C, major larger tumors >10 cm, the initial embolism area >70% were independent risk factors of HD in patients with hepatocellular carcinoma (HCC) after transcatheter arterial chemoembolization (TACE)
Kuroda et al. [27]	Japan	Prospective and a retrospective Study	(Study 1). 41 patients (20 cirrhotic, 21 non-cirrhotic; age, 67.9 ± 13.3; female., Study 2). A retrospective chart review with human autopsy specimens was conducted, and vessels and islets of the pancreas were analyzed in 43 patients (20 cirrhotic, 23 controls; age, 71.5 ± 11.6; female, 15)	Pancreatic congestion in found in the patients with cirrhosis. Pancreatic congestion and insulin secretion are correlated.
Jeon [28]	Republic of Korea	Trial	195 cirrhotic, Patients	Hepatogenous Diabetes and insulin resistance have relationships with portal hypertension and variceal hemorrhage
Holstein et al. [35]	Germany	Prospective cohort study	52 patients with cirrhosis	Hepatogenous diabetes differs from type 2 diabetes in that there is less chances family history and that the Heart problems and retinopathic risk is low

Table 1: Some studies showing the association of diabetes with liver.

diabetes in its pathogenesis, cause of death, assessment, and therapeutic strategy [18]. The hepatogenous diabetes is developed by about 30% chronic liver disease patients. There are other studies conducted about Hepatogenous diabetes [19-37].

Another subject of investigation has been on solving the dilemma on prior occurrence of liver disease or diabetes. Studies from Hickman et al suggest that development of chronic liver disease and cirrhosis occurs after diabetes and diabetes is the factor to initiate and develop the liver injury [38]. The American Diabetes Association do not yet recognize Hepatogneous Diabetes [39], and no treatment has been proposed officially for the problem. However, liver transplant has been described as a successful mode of treatment in one study [40,41]. Therefore, it is premature to suggest or comment on a possible best treatment for HD (Figure 1 and Table 1).

Hepatitis C, kidney and diabetes

Simó et al. suggested association between diabetes mellitus and Hepatitis C virus induced chronic viral liver disease. Both hepatitis patients and those with cirrhosis were found to acquire glomerulonephritis. Hepatitis C virus was more correlated with Glomerular injury compared with Hepatitis B virus. Simo et al. observed high prevalence of Hepatitis C Virus infection in diabetic patients. There was a presence of abnormal LFTs in most of anti -HCV positive patients. The study suggested that Hepatitis C virus may have direct role in development of diabetes [42].

Cancer, hemochromatosis and diabetes

According to Iovanescu et al. there was no correlation between diabetes mellitus and hepatocellular carcinoma. [43]. On the other hand, an association of hemochromatosis with diabetes is also studied by Adams et al. [44], and hemochromatosis is well known to cause liver cancers. Therefore, this suggests an indirect association of diabetes with liver problems.

Some surprising findings were shown by La Vechia et al. They studied the relationship between diabetes mellitus and primary liver cancer in a certain population. The finding in the whole population was that a history of diabetes mellitus could explain only about 8% of liver cancer cases [45]. Contrary to this, a study by Adami et al. however, suggested that diabetic patients are at increased risk of developing primary liver cancer and cancers of the biliary tract [46]. This suggests, additional studies are needed in determination of whether patients with insulin-dependent DM and those with non-insulin-dependent DM differ in the risk for primary liver cancer. These mix results could be confusing and it could therefore be premature to say anything with confidence about this association.

Some Recent Research Evidence

Some recent literature point toward interesting findings and provide a new insight into the association of liver with diabetes. A recent study by Hodson et al. in 2016 focused on liver triacylglycerol accumulation in females with gestational diabetes mellitus. The authors point towards

a finding that the non-pregnant women who have a history of GDM, have increased hepatic triacylglycerol, while triacylglycerol in women currently suffering from GDM was not raised [47]. Moreover, the women with a history of GDM have a higher risk for non-alcoholic fatty lover disease (NAFLD). Another study demonstrated that insulin resistance and a large waist circumference are independently linked with the presence of NAFLD. While glucose intolerance is not associated with it [48]. Diabetes and liver have also been studied in relation to Gallic acid (a potent antioxidant). De Oliveira et al. studied the effects of Gallic acid on the biochemical, histological and oxidative stress in the diabetic rats' liver and kidney. The findings showed that Gallic acid indeed have a protective effect against the evaluated parameters. Moreover, Gallic acid can also reduce the catalase and glutathione S-transferase, and vitamin C levels activity in the liver of diabetic rats. Gallic acid also decreased the nuclei numbers and augmented the core area in liver tissue. Furthermore, glomerular area augmentation was also observed in kidney tissue. Thus, the study concluded that Gallic acid has a protective effect against oxidative stress-induced damage in the diabetic state [49].

Conclusion

We attempted to write this review about the association of diabetes mellitus with one of the largest organs of body, liver. Enough data exists to justify a concrete relationship, between diabetes and the liver. The changes seen in a Diabetic patient's liver include fatty liver, reduction in glycogen, reduction in gluconeogenesis, increased risk of liver and biliary tract cancers. There could be many other liver problems associated with diabetes mellitus. However, the length of this article does not permit us to mention the details of each liver problem associated with diabetes. Yet this paper can serve as a good modality to learn about the fact that diabetes and liver have a pathological relationship. It is quite evident from the discussion above, that either liver problems lead to diabetes or vice-versa. Hence, there is a great chance, that the future studies will broaden our knowledge about more question marks linked with this association.

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