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Research Article

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Impact of Liver Cirrhosis on the Occurrence of Diabetes Mellitus and Glucose Intolerance among Liver Cirrhosis Patients in European Gaza Hospital: A Retroactive Study

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Abstract

Background: *Third of liver cirrhosis patients have diabetes mellitus. In addition, most of patients with cirrhosis may be glucose intolerant. This study aimed to shed light on the impact of liver cirrhosis on the occurrence of diabetes mellitus among liver cirrhosis patients.*

Materials and Methods: *This study is a retrospective analytical study design. The study was a descriptive study. The study was conducted at the gastroenterology outpatient clinic in European Gaza Hospital. Data were collected retrospectively from patients records and from patients themselves when attending at the clinic. The study was conducted during the period from September 2022 to February 2023. The study tool is a self-designed questionnaire based on most recent published literature. The questionnaire included basic information about the patients, data related to liver cirrhosis and some laboratory work done for the patients.*

Results: *A total of 70 patients were included in the study, with more than half being male (60%). The mean age of participants was 61.97 ± 11.54 years. The most frequent cause of liver cirrhosis among participants was cryptogenic (54.3%), and two-thirds of the participants had comorbid conditions besides liver cirrhosis, with diabetes mellitus being the most frequent (54.3%). The majority of participants were overweight or obese, with a mean body mass index of 31.15 kg/m2. Ultrasound imaging showed that most participants had severe steatosis (88.6%) and a shrunken liver (72.9%). The laboratory findings showed raised mean alanine transaminase (ALT) and aspartate aminotransferase (AST) levels, with high levels of triglycerides and cholesterol.*

Conclusion: *Most participants were overweight or obese. More than half of the participants had comorbidities, including diabetes mellitus, and cryptogenic liver cirrhosis was the most prevalent etiology. Most liver ultrasounds indicated significant steatosis. Participants had increased alanine transaminase, aspartate aminotransferase, triglycerides, and total bilirubin.*

1. Introduction

Up to 96% of people with cirrhosis may be glucose intolerant and 30% may be clinically diabetic [1]. Presently, it is a topic for controversy whether type 2 diabetes mellitus (DM), in the absence of additional risk factors leading to metabolic syndrome (obesity and hypertriglyceridemia), might be a risk factor for the development and progression of liver disease [2-4]. On the other hand, the diabetes which develops as a consequence of cirrhosis is known as “hepatogenous diabetes” and is not recognized by the American Diabetes Association and the World Health Organization as a separate autonomous entity [5].

The liver plays a significant function in carbohydrate metabolism as it is responsible for the balancing of blood glucose levels by means of glycogenogenesis and glycogenolysis [5-11]. In the presence of hepatic illness, the metabolic balance of glucose is

disrupted as a consequence of diseases such as insulin resistance, glucose intolerance and diabetes [6,8,11,12]. Insulin resistance occurs not only in muscle tissue, but also in adipose tissue, and this paired with hyperinsulinemia appear to be key pathophysiologic bases of diabetes in liver disease [1,3,5,6,13-17]. Moreover, the etiology of liver disease is crucial in the occurrence of DM, as non-alcoholic fatty liver disease (NAFLD), alcohol, hepatitis C virus (HCV) and hemochromatosis are commonly related with DM [1-3,7,18].

DM in individuals with compensated liver cirrhosis may be subclinical, as fasting serum glucose levels may be acceptable. In these circumstances, it is required to do an oral glucose tolerance test (OGTT) to identify an impairment of glucose metabolism [19]. The natural history of hepatogenous diabetes is distinct from that of hereditary type 2 DM, as it is less usually linked with microangiopathy. In contrast, the patient with cirrhosis and diabetes suffers more often from consequences of cirrhosis, which might cause death [2,4,19].

Management of diabetes in the cirrhotic patient is challenging because of the existence of liver impairment and the hepatotoxicity of oral hypoglycemic medications. Hence, pharmaceutical treatment must be constantly monitored for the risk of hypoglycemia [3,5,19].

1.1. Justification

Liver cirrhosis and diabetes mellitus are both significant health issues that affect millions of people worldwide. While both conditions can occur independently, they often coexist, and the relationship between them remains poorly understood. There is growing evidence to suggest that the presence of liver cirrhosis can increase the risk of developing diabetes mellitus, but the exact mechanisms underlying this association are not fully understood.

Understanding the relationship between liver cirrhosis and diabetes mellitus is crucial for several reasons. Liver cirrhosis is a common condition that is associated with significant morbidity and mortality. Diabetes mellitus, on the other hand, is a major risk factor for cardiovascular disease and other complications. Therefore, identifying and managing diabetes mellitus in liver cirrhosis patients could help reduce the burden of morbidity and mortality associated with both conditions.

Liver cirrhosis is often caused by chronic alcohol consumption, viral hepatitis, or non-alcoholic fatty liver disease (NAFLD), all of which are associated with an increased risk of developing diabetes mellitus. Therefore, understanding the relationship between these conditions could help identify individuals who are at a higher risk of developing diabetes mellitus and may benefit from targeted interventions.

The relationship between liver cirrhosis and diabetes mellitus is complex and multifactorial, involving factors such as insulin resistance, inflammation, and oxidative stress. Therefore, studying this relationship could provide valuable insights into the underlying mechanisms and help identify potential targets for future therapies.

1.2. Research Problem

Liver cirrhosis is a chronic liver disease that affects millions of people worldwide and is associated with various complications, including the development of diabetes mellitus. However, the impact of liver cirrhosis on the occurrence and progression of diabetes mellitus remains poorly understood. Therefore, the research problem is to investigate the relationship between liver cirrhosis and diabetes mellitus, including the prevalence, risk factors, and underlying mechanisms of diabetes mellitus in liver cirrhosis patients. This study aims to provide insights into the prevention, diagnosis, and management of diabetes mellitus in patients with liver cirrhosis, ultimately improving their clinical outcomes and quality of life.

1.3. Significance

The impact of liver cirrhosis on the occurrence of diabetes mellitus among liver cirrhosis patients is a significant topic of research for several reasons:

Prevalence and risk factors: Determining the prevalence and risk factors of diabetes mellitus in liver cirrhosis patients is essential for identifying patients at higher risk for developing this condition and implementing early interventions.

Clinical outcomes: Understanding the relationship between liver cirrhosis and diabetes mellitus is important for predicting and improving clinical outcomes in patients with these conditions. Diabetes mellitus can exacerbate the complications of liver cirrhosis, and vice versa, leading to increased morbidity and mortality.

Management strategies: Developing effective management strategies for diabetes mellitus in liver cirrhosis patients is critical for improving patient outcomes and quality of life. These strategies may include lifestyle modifications, pharmacotherapy, and liver transplantation, among others.

Public health: Addressing the impact of liver cirrhosis on the occurrence of diabetes mellitus has significant public health implications, as both of these conditions are major health concerns globally and contribute to a significant burden of disease and healthcare costs.

Advancing scientific knowledge: Investigating the mechanisms underlying the association between liver cirrhosis and diabetes mellitus can help advance our understanding of the pathophysiology of these conditions and may lead to the development of new therapeutic targets and approaches.

2. Objectives

1. To determine the prevalence of diabetes mellitus among liver cirrhosis patients.
2. To identify the risk factors associated with the development of diabetes mellitus in liver cirrhosis patients, such as age, gender, BMI, etiology of liver cirrhosis, etc.
3. To examine the relationship between the severity of liver cirrhosis and the onset and progression of diabetes mellitus.
4. To provide recommendations for the management of diabetes mellitus in liver cirrhosis patients based on the study findings.
5. To contribute to the existing literature on the relationship between liver cirrhosis and diabetes mellitus and to identify future research directions in this area.

2.1. Research Questions

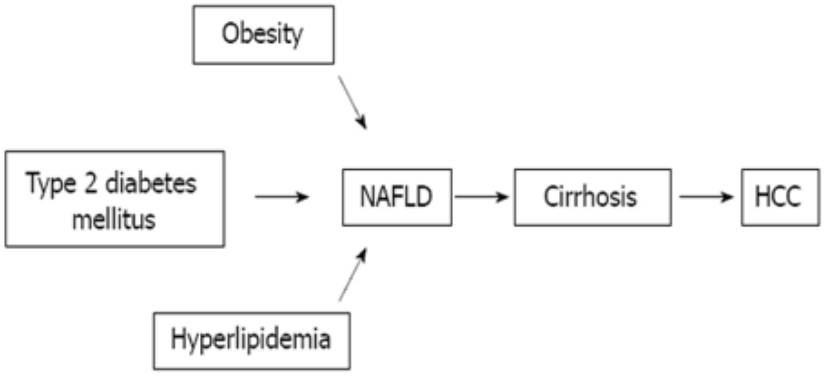
1. What is the prevalence of diabetes mellitus among liver cirrhosis patients, and how does it vary by patient characteristics such as age, gender, and etiology of liver cirrhosis?
2. What are the risk factors associated with the development of diabetes mellitus in liver cirrhosis patients, and how do they interact with each other?
3. What is the relationship between the severity of liver cirrhosis, as measured by the Child-Pugh score or MELD score, and the onset and progression of diabetes mellitus?
4. What are the optimal management strategies for diabetes mellitus in liver cirrhosis patients, including lifestyle modifications, pharmacotherapy, and liver transplantation, based on the study findings?
5. What are the existing gaps and controversies in the literature on the relationship between liver cirrhosis and diabetes mellitus, and what are the potential future research directions in this area?

2.2. Literature Review

TYPE 2 DM AS A RISK FACTOR FOR NAFLD AND HCC

Epidemiology

Several studies suggest that type 2 DM may have an etiological role in chronic liver disease and HCC regardless of alcohol and viruses (Figure 1) [4].



Throughout the course of 10 years, researchers monitored 173643 people with type 2 DM and 650620 participants without type 2 DM, both of whom had chronic liver disease excluded at enrolment and one year afterwards. Diabetic individuals had an increased risk of developing non-alcoholic chronic liver disease and HCC compared to the general population. The risk was increased by a factor of 2 and was not affected by characteristics such as alcoholism, viral hepatitis, or socioeconomic status [4]. This study's large sample size is a strength, but it has been criticized for several reasons. First, the participants were all men (98%), and second, the diagnoses of type 2 diabetes, chronic liver disease, and hepatocellular carcinoma were obtained from a database rather than being confirmed biochemically and histopathologically. There was also a failure to account for other components of the metabolic syndrome (such as obesity and dyslipidemia, all of which are known to have a role in the development of NAFLD) [20].

Standardized incidence of HCC was greater in males with type 2 DM (4.0, 95% CI: 3.5-4.6) and women with type 2 DM (2.1, 95% CI: 1.6-2.7) compared with the general population in a large-scale Danish study [21]. Similar findings have been seen in other investigations involving a smaller sample of patients [22,23].

Diabetes mellitus (DM) was more prevalent in patients with HCC than in controls in a recent case-control study involving 465 patients (31.2% vs 12.7%, OR 3.12 95% CI: 2.22-4.43). In 84% of cases, DM had been diagnosed before the occurrence of HCC, and its average duration was 181.4 months, indicating that it was type 2 DM in most cases [24]. The above information raises the possibility that type 2 DM is itself a risk factor for the development of HCC. Researchers found an increased threat when HCV, liver fibrosis, and alcohol were all present. In a recent study, individuals with chronic hepatitis C (CHC), diabetes mellitus (DM), and severe fibrosis were shown to have a 3-fold higher chance of developing hepatocellular carcinoma (HCC) during 5 years of follow-up (13% vs. 5%) [25].

2.3. Non-Alcoholic Fatty Liver Disease (NAFLD)

Simple steatosis, steatohepatitis, fibrosis, and cirrhosis are all parts of non-alcoholic fatty liver disease (NAFLD). Fatty liver, the mildest form of NAFLD, affects an estimated one-third of American adults [26]. The buildup of fat, mostly triglycerides, in liver cells in the context of insulin resistance leads to primary fatty liver, which usually develops as part of the metabolic syndrome, which consists of obesity, type 2 DM, and dyslipidemia [27]. NASH is a severe form of NAFLD that results in not only steatosis but also inflammation, cell destruction, and fibrosis of the liver. In spite of this, a frequency of 2%-3% has been ascribed to NASH. As NASH is recognized as a disease entity and may lead to cirrhosis and liver failure, it is believed to be the leading cause of cryptogenic cirrhosis [28,29].

2.4. Pathophysiology

The numerous pathways through which type 2 DM could develop NAFLD have mostly been examined in isolation and have been shown to be variable. The fatty liver, obesity, and insulin resistance have all been linked to liver damage [1,3,4]. Increased intake of free fatty acids and de novo liponeogenesis in the he-

patocytes lead to intracellular buildup of triglycerides, which manifests as fatty liver. Simultaneously, the liver secretes less extremely lowdensity lipoproteins. Increased mitochondrial oxidative stress on triglycerides leads to an increase in free radical and peroxisome production, causing liver damage in the form of cellular necrosis and inflammation [30,31]. Adipokines (cytokines generated by the adipocytes), such as leptin and tumor necrosis factor-alpha (TNF-alpha), are produced in excess and contribute to the mitochondrial oxidative stress [32]. Reducing the regulating adipokine adiponectin increases the production and activity of inflammatory adipokines [33]. Inflammatory and necrotic cell mediators, as well as adipokines, stimulate liver stellate cells into producing more collagen, connective tissue growth factor, and extracellular matrix, all of which promote fibrosis [34]. (Figure 2).

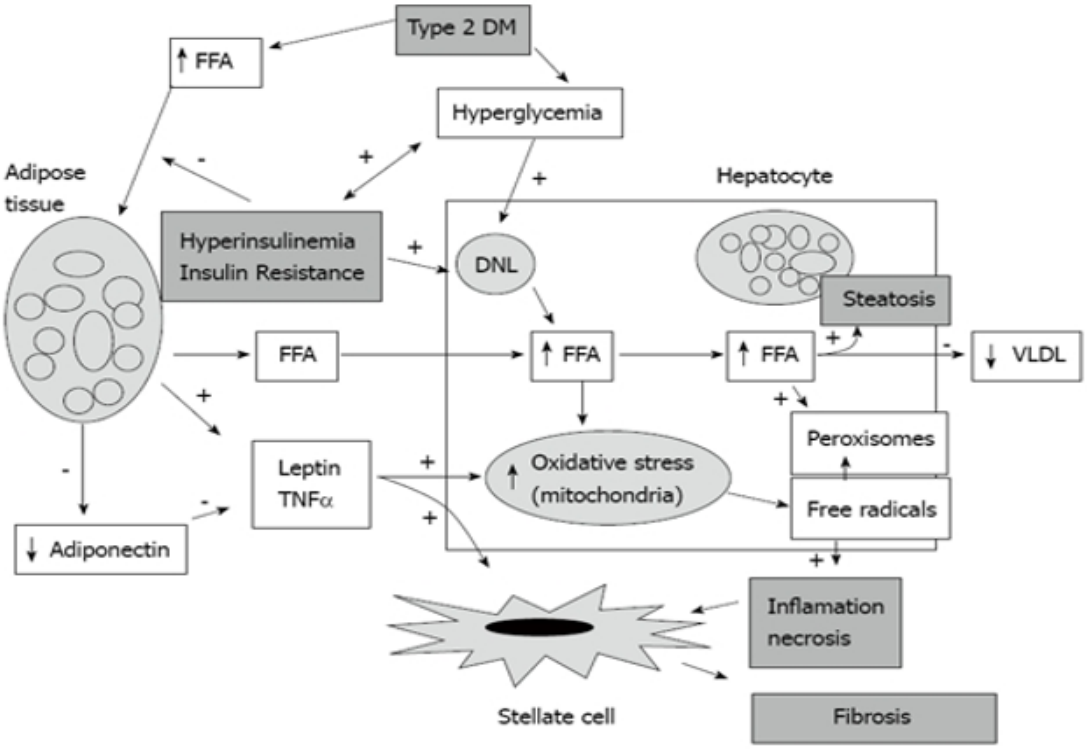


Figure 2: Liver damage caused by type 2 DM. Insulin resistance promotes release of free fatty acids (FFA) from adipose tissue. The FFAs are accumulated in the liver cells, and de novo liponeogenesis (DNL) contributes also. The reduced secretion of very lowdensity lipoprotein (VLDL) by hepatic cells saturates hepatocytes producing steatosis. Mitochondrial oxidative stress is increased as a result of excess intracellular FFAs and the influence of adipokines (leptin and tumor necrosis factor alpha (TNF-α). Excess of oxidative stress produces free radicals which in turn induces inflammation and cellular necrosis. Tissue inflammation stimulates the stellate cells to produce collagen

2.5. DM As A Complication of Cirrhosis-Hepatogenous Diabetes

2.5.1. Epidemiology

The reported incidence of glucose intolerance ranges from 60–80%, while the incidence of diabetes ranges from 20–60%, depending on the etiology, the severity of liver damage, and the diagnostic criteria [3,5,16,19]. Most individuals with chronic liver disease will have insulin resistance and glucose intolerance from the earliest stages of the illness [35,36]. Hepatogenous diabetes may be seen as a sign of severe liver disease [37] since the diabetes becomes clinically apparent as liver function declines.

Hepatogenous diabetes has several potential causes, including alcoholism, hepatitis C virus infection, hemochromatosis, and nonalcoholic steatohepatitis (Figure 3).

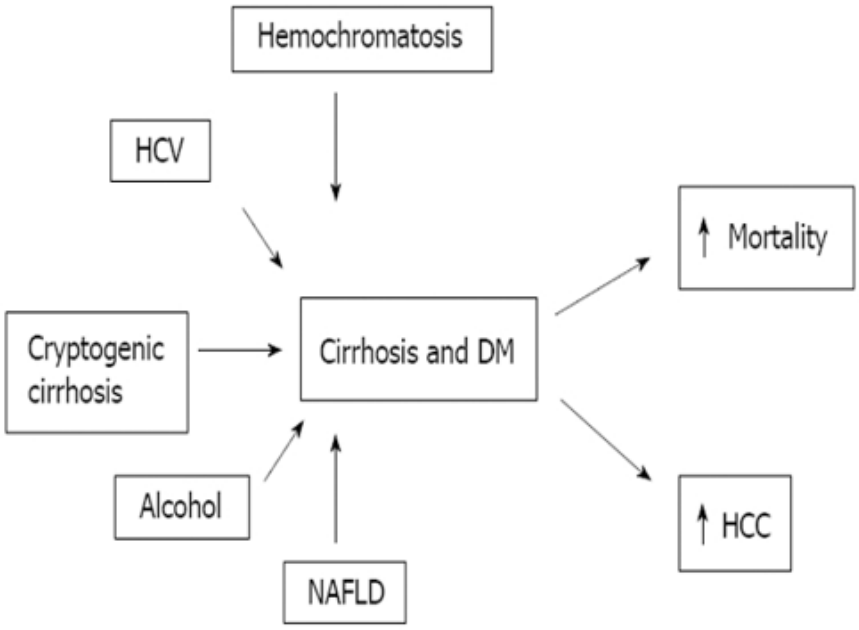


Figure 3: Etiology of Liver Cirrhosis most Frequently Associated with Diabetes Mellitus

NASH: NASH is a severe manifestation of NAFLD. NASH is associated with visceral obesity, hypertriglyceri-demia, and virtually all patients have insulin resistance. Therefore, it is not surprising that type 2 DM is present in 30%-45% of patients with NASH [38].

In contrast, it has been shown that obesity itself is a significant risk factor for serious liver disease [39,40]. The increased release of adipokines is a hallmark of obesity, which is characterized by enlarged adipose tissue that is in a state of chronic inflammation. These adipose tissue cytokines have a systemic impact, with a focus on the liver; they cause insulin resistance, hyperglycemia, and hyperinsulinemia; these abnormalities impair hepatic lipid metabolism. Direct stimulation of liver stellate cells by cytokines, of which TNF- is the best researched component, induces hepatic fibrosis [41]. By reducing body fat, metabolic syndrome symptoms including hyperlipidemia and fatty liver may be alleviated [42].

The National Health and Nutrition Examination Survey found that those over the age of 40 with CHC had a threefold greater risk of developing diabetes compared to people with non-C chronic hepatitis [43]. Among patients with CHC who did not develop cirrhosis, Knobler et al. found that the prevalence of DM was 33%, compared with 5.6% in a control group [44]. Fatty liver was seen in 30%-70% of individuals with chronic HCV infection [45].

More than 40% of CHC patients are known to have glucose intolerance, and more than 17% are diagnosed with diabetes. The insulin resistance these individuals exhibit is also an independent risk factor for steatosis in relation to fibrosis severity [7,46-48].

It is unclear how HCV causes insulin resistance and diabetes. There is no correlation between BMI or fibrosis stage and the fact that HCV produces insulin resistance. The HCV core protein induced insulin resistance, steatosis, and DM in a transgenic mouse model. It appears that an increase in TNF- production was the main cause of this. The insulin receptors (IRS-1 and IRS-2) have their serine residues phosphorylated by this cytokine, and the overproduction of suppressor of cytokines is also stimulated (SOC-3). Both Akt and phosphatidylinositol 3-kinase phosphorylation are suppressed by SOC-3. Glucose absorption into cells may be prevented if any of these diseases affecting insulin's intracellular signaling also prevented GLUT-4 transactivation. Anti-TNF- medications, such as infliximab, may prevent the development of insulin resistance in transgenic mice by blocking TNF-. Therefore, HCV causes insulin resistance through TNF- generation, IRS serine phosphorylation, and SOCs overexpression. Overproduction of TNF- in individuals with CHC is also associated with increased fibrosis progression and decreased interferon response [40].

Genotypes 1 and 4 of HCV are strongly related with insulin resistance more commonly than genotypes 2 and 3 (37% vs 17%), suggesting that HCV genotype may be important in the incidence of glucose metabolic diseases [47]. Genotypes 1 and 4 have been shown to have a less persistent viral response to antiviral treatment compared to genotypes 2 and 3. Patients with this condition often show little improvement after receiving antiviral therapy, and insulin resistance may play a role in this. Consistent with this, patients with HCV genotype 1 and HOMA > 2 (insulin resistance) exhibited a 2-fold worse sustained response to therapy than patients with HOMA 2 (32.8% vs 60.5%, respectively) in a recent study [49]. Experiments using Huh-7 cells infected with HCV RNA show that the addition of interferon prevents viral replication, lending credence to this theory. Adding insulin at a dosage of 128 mcU/mL (equivalent to that found in hyperinsulinemic conditions) to interferon completely eliminated its capacity to prevent viral replication [50]. Lastly, peginterferon with ribavirin therapy has shown poorer long-term success in patients with CHC and insulin resistance than in individuals without insulin resistance [40,49].

Once the mechanisms in CHC that cause insulin resistance and diabetes mellitus have been activated, it seems that their progression is unaffected by viral activity. In fact, a recent research found that in individuals with chronic hepatitis and normal fasting blood glucose, HCV clearance by pegylated interferon and ribavirin therapy did not diminish the incidence of DM during a period of 8 years of follow-up following treatment. The prevalence of DM was comparable across patients who showed a sustained response and those who did not (14.8% vs 18.5%, respectively) [51].

There is a strong association between alcohol use and the development of diabetes in those with alcoholic liver disease [52]. Among individuals consuming more than 270 g of alcohol per week, the risk is increased by a factor of 2 compared to those consuming less than 120 g/wk [53]. Insulin-mediated glucose absorption is significantly decreased after an acute alcohol administration. Diabetes mellitus (DM) is a common complication in individuals with a history of chronic drinking due to the high prevalence of chronic pancreatic damage and destruction of pancreatic islet -cells [1].

Genetic hemochromatosis is a condition of iron metabolism that causes the buildup of iron in many organs, most notably the liver. A change in the HFE gene causes this condition. Iron may also enter the pancreas and the heart muscle. The acinus of exocrine secretion in the pancreas has the highest proportion of iron. Yet, the insulin-producing -cells in the Langerhans are also damaged by invasion. This explains why between 50% and 85% of those with severe hereditary hemochromatosis also have diabetes [54]. The increased incidence of DM is likely also attributable to glucose metabolic problems brought on by liver damage [1,5].

2.5.2. Pathophysiology of Hepatogenous Diabetes

Hepatogenous diabetes' pathogenesis is convoluted and incompletely understood. The disruption in glucose metabolism is driven in large part by insulin resistance in peripheral tissues (adipose and muscle tissue) [1,2,9,11,14-17]. Increased levels of contra-insulin hormones (glucagon, growth hormone, insulin-like growth factor, free fatty acids, and cytokines) have been hypothesized to amplify the effects of hyperinsulinemia caused by impaired insulin extraction due to liver injury and portosystemic shunts [2,11,15,17]. Although hepatic insulin extraction disruption does not seem to play a major role, a new research reveals that in individuals with Child B grade liver cirrhosis, hyperinsulinism may be generated by an increase in the pancreatic -cell sensitivity to glucose [55]. Several etiologic agents in liver illness, including hepatitis C virus, alcohol, and iron infiltration, have been hypothesized to reduce the insulin secretion activity of pancreatic -cells [9]. In conclusion, it seems that insulin resistance in muscle and an insufficient response from the -cells to release insulin to address the deficit in insulin action may both play a role in the development of glucose intolerance. Fasting hyperglycemia and a diabetes glucose tolerance profile originate from a gradual reduction in insulin production and the development of hepatic insulin resistance (Figure 4) [14,15].

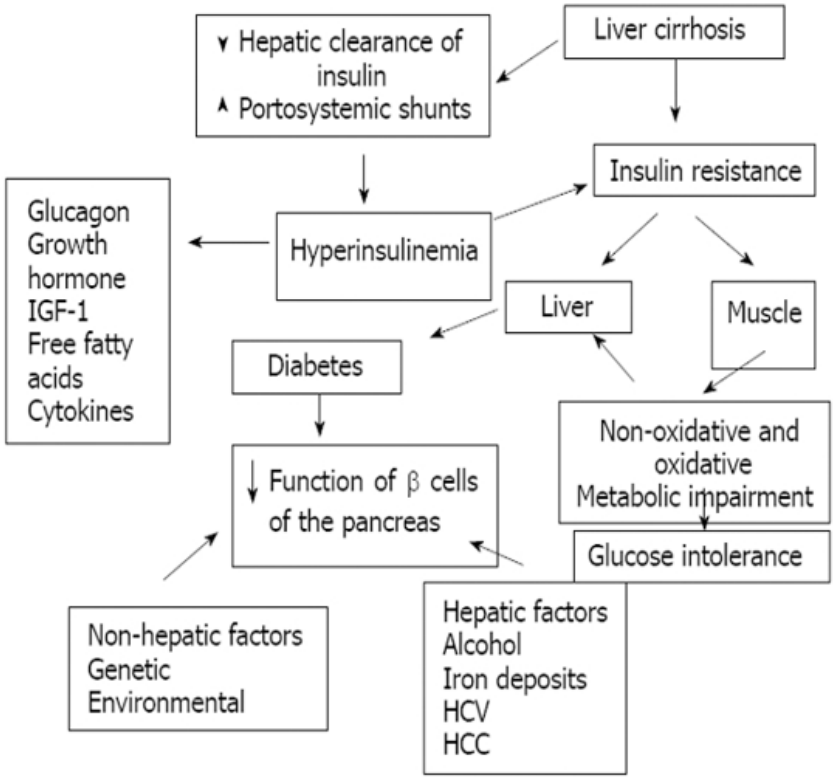


Figure 4: Pathophysiology of hepatogenous diabetes. One of the main abnormalities is insulin resistance in muscular cells and the hepatic tissue. Insulin resistance in muscle impairs non-oxidative and oxidative glucose metabolism. The reduction of insulin clearance by the damaged liver and the presence of portosystemic shunts in one hand and the desensitization of the beta cells of the pancreas produced by diverse factors on the other hand may produce hyperinsulinemia. With progression of the diabetes there is a reduction in sensitivity of β-cells for production of insulin.

Differentiation between hepatogenous diabetes and type 2 DM may be challenging. Postprandial plasma glucose to fasting plasma glucose ratios (2.27 vs 1.69), fasting insulin concentrations (23.2 vs 11.6 microIU/mL), and the HOMA-Insulin Resistance index (8.38 vs 3.52) were all found to be significantly higher in patients with hepatogenous diabetes than in patients with type 2 DM in a recent study. This means that the insulin resistance in liver cirrhosis is greater than in type 2 DM, and that the impaired hepatic insulin breakdown may be a crucial cause of hyperinsulinemia in liver cirrhosis [56].

2.6. TYPE 2 DM and Hepatogenous Diabetes Aggravate Liver Cirrhosis and HCC

2.6.1. DM Increases Morbidity and Mortality of Liver Cirrhosis Patients

Very few researches have looked at how type 2 DM and hepatogenous DM affect the clinical outcome of cirrhosis and HCC. A higher risk of complications has been seen in patients with cirrhosis of any origin who had diabetes, as shown in cross-sectional retrospective studies [5,38,57,58]. Based on data from more than 7,000 people with type 2 DM, the Verona research found that those with the condition had a 2.52-fold (CI 1.96-3.2) higher risk of mortality at 5 years compared to the general population [59]. Liver disease and more severe fibrosis are linked to DM, obesity, and steatosis, according to other studies [60,61].

Notably, despite their widespread use as short- and long-term prognostic tools for cirrhotic patients, neither the Child-Pugh nor the Model for End-Stage Liver Disease (MELD) Scores contain DM or glucose intolerance in their parameters [62,63]. Interesting findings, however, have been shown in prospective longitudinal investigations of cirrhotic patients in which DM has been examined as a standalone prognostic factor. Three hundred and fifty-four (98 with diabetes) of 382 eligible patients were tracked for six years following enrollment in the trial; 110 were still alive at the end of follow-up. Kaplan-Meier analysis and Cox's stepwise regression revealed the following factors to be significant predictors of mortality: albumin, ascites, age, encephalopathy, bilirubin, diabetes, and platelets. The higher mortality rate in patients with diabetes was not attributable to diabetes-related complications but rather to an increased risk of hepatocellular failure [58]. With the inclusion of varices, diabetes lost its significance as a covariate in a subset of 271 patients, but regained its importance when patients who died of gastrointestinal bleeding were removed.

Another research found that HCC and DM, but not the Child-Pugh score, were independent prognostic variables of death in patients with cirrhosis and refractory ascites on the waiting list for liver transplantation. Patients with refractory ascites and diabetes had a 32% and 18% chance of survival after 1 and 2 years, respectively. However, patients with refractory ascites who did not have DM had a 62% and 58% chance of survival, respectively [64].

Nishida et al. carried out the OGTT on 56 cirrhotic individuals with normal fasting blood glucose. Diabetic retinopathy was seen in 38% of patients, glucose intolerance in 23%, and normal levels in 39%. Diabetes and glucose intolerance were associated with a considerably increased risk of death after 5 years of follow-up (44% and 32% versus 5%, respectively). According to a multivariate analysis, serum albumin and diabetes were the only two covariates independently associated with a decreased likelihood of survival [19].

Retinopathy, cardiovascular, and renal problems occur less commonly in people with hepatogenous diabetes than in those with genetic type 2 DM [5,58]. There is a strong correlation between diabetes and cirrhosis, and liver failure is a leading cause of mortality in cirrhotic patients [4,19,58].

2.6.2. DM Increases the Severity and Mortality of HCC

At the current time, type 2 DM is recognized as a risk factor for the development of HCC. There is a tenfold increase in the risk of HCC when hepatogenous diabetes is present in addition to hepatitis B and C virus infection and alcoholic liver cirrhosis [1,2].

Diabetes mellitus increases the mortality risk for individuals with HCC compared to people with HCC who do not have DM. Patients with HCC with diabetes mellitus had a greater 1-year death rate than those without DM, according to a separate research of 160 patients. However, the sickness was more widespread in these people [65].

2.7. Pathophysiologic Mechanisms

It is unclear how or why diabetes exacerbates liver cirrhosis's clinical progression. To begin, diabetes mellitus has been shown to hasten fibrosis and inflammation in the liver, leading to more severe liver failure. Second, there is evidence that diabetes might amplify the occurrence of bacterial infections in cirrhotic patients, which are linked to higher mortality [66,67].

The first explanation is that insulin resistance causes an increase in adipokine (adipose tissue-secreted cytokine) production, including leptin and TNF-, which in turn activates the inflammatory pathways that worsen liver damage [68]. Adiponectin, on the other hand, is a cytokine secreted by adipose tissue that controls insulin sensitivity and inflammation [69]. Decreased adiponectin levels are indicative of insulin resistance in the liver and the periphery [70]. Progression of liver disease has been linked to hypoadiponectinemia [70,71].

As for the second, cirrhotic people with diabetes may be more prone to developing life-threatening infections, which is a direct result of the immunosuppression that diabetes may cause. Patients with cirrhosis who develop spontaneous bacterial peritonitis have a significant risk of dying in the hospital from complications such sepsis, liver failure, and hepatorenal syndrome. In contrast, individuals with esophageal variceal hemorrhage have a high prevalence of infection, which increases their risk of dying while in the hospital [72]. Nevertheless, whether DM also affects mortality in individuals with additional cirrhosis sequelae has to be determined. Future research should focus on elucidating the specific mechanisms via which DM may affect liver function, since modulation of these may be effective for reducing consequences.

2.8. Clinical Implications of DM in the Course of Liver Cirrhosis and Treatment of Diabetes

2.8.1. Clinical Manifestations

Early stages of cirrhosis seldom display any clinical signs of diabetes mellitus. Recently published research found that up to 77% of compensated cirrhotic individuals with normal fasting blood glucose and no family history of type 2 DM developed DM or glucose intolerance identified by OGTT. Subclinical DM was found in 38% of cases [19]. Clinical diabetes may be interpreted as an indicator of liver failure since its prevalence rises as liver function declines.

Hepatogenous diabetes differs clinically from hereditary type 2 DM in several ways: (1) it is less often associated with risk factors like age, body mass index, and a family history of diabetes; (2) it is less often associated with retinopathy, cardiovascular complications, and renal complications; and (3) it is more often associated with hypoglycemic episodes due to impaired liver function [2,19].

The relevance of DM as a prognostic factor of morbidity and mortality in cirrhotic patients has been little researched, despite the global pandemic of obesity, DM, and metabolic syndrome. It is also unclear how early detection and treatment of diabetes could affect the clinical progression of cirrhosis.

2.9. Treatment

Treatment of diabetes mellitus (DM) may affect the clinical course of liver disease, but few researches have investigated which therapies are most effective for DM in cirrhotic individuals.

Differentiating the management of type 2 diabetes in people without liver disease from that of those with cirrhosis, the following factors should be considered: Most oral hypoglycemic medications are processed in the liver; (4) patients often have bouts of hypoglycemia; and (1) almost half of patients suffer malnutrition.

As insulin resistance is the primary driver at this stage, a change in lifestyle may be the first line of therapy for individuals with mild to moderate hyperglycemia and compensated liver disease. Yet, excessively restricted diets may undermine these therapeutic approaches by worsening malnutrition in certain individuals. Nevertheless, people with active liver disease may not benefit from exercise that reduces insulin resistance [15].

Oral hypoglycemic medications may be necessary when type 2 diabetes develops in the late stages of liver disease. Nevertheless, as the liver is responsible for metabolizing the vast majority of these medicines, careful attention to blood glucose levels during therapy is necessary to prevent hypoglycemia [73]. The insulin resistance-lowering biguanides might be helpful here. Because of the potential for lactic acidosis, the biguanide metformin is largely contraindicated in patients with severe liver failure and in those who continue to consume alcohol [74,75].

Patients with alcoholic cirrhosis often exhibit pancreatic islet -cell destruction; nonetheless, insulin secretagogues, although being safe medications in this population, are likely to be ineffective since they do not improve insulin resistance. Patients with this condition have compensatory hyperinsulinemia on a chronic basis until the islet -cells are depleted.

Patients with liver cirrhosis may benefit from using alpha-glucosidase inhibitors because of the danger of postprandial hyperglycemia that is often seen in this patient population. Control of postprandial and fasting blood glucose levels were considerably improved with the administration of acarbose, an alpha-glucosidase, in a randomized, double-blind research including 100 patients with compensated liver cirrhosis and insulin-treated DM [76]. Acarbose significantly reduced postprandial blood glucose level in a crossover, placebo-controlled investigation of individuals with hepatic encephalopathy. Also, the patients' plasma ammonia levels dropped and their bowel motions were more regular [77]. Ammonia levels dropped because bowel movements inhibit the growth of proteolytic bacteria in the gut, most likely [77].

Cirrhotic individuals with diabetes mellitus may benefit greatly from thiazolidines due to their ability to improve insulin sensitivity. Nevertheless, due to concerns over its hepatotoxic effects, troglitazone has been taken off the market. It is suggested that rosiglitazone and pioglitazone not be started in patients with signs of active liver disease or alanine transaminase values that are more than 2.5 times the upper limit of normal [78]. While these medications are being used, strict supervision is required.

Patients with cirrhosis and diabetes may have different insulin needs. As insulin resistance is more common in people with compensated cirrhosis, while hepatic metabolism of insulin is considerably reduced in patients with decompensated cirrhosis, the former may have higher needs. Treatment with insulin should ideally be administered in a hospital setting, where patients may be closely monitored for signs of hypoglycemia [79].

Lastly, insulin sensitivity and glucose tolerance both return quickly to normal after a liver transplant. An increase in hepatic clearance and peripheral glucose elimination may be responsible for this impact. This latter impact may follow after persistent hyperinsulinemia has been treated [16,80]. Reducing insulin resistance, liver transplantation has been shown to reverse hepatogenous diabetes in 67% of cirrhotic-diabetic individuals. Persistently low -cell function, as assessed by an oral glucose tolerance test (OGTT), was the reason why 33% of patients did not achieve full remission from diabetes. Because to this anomaly, individuals may one day be candidates for a combined islet transplant [81].

3. Methodology

3.1. Study Design

This study is a retrospective analytical study design. The study was a descriptive study. Since the aim of the study is to determine the impact of liver cirrhosis on the occurrence of diabetes mellitus among patients with liver cirrhosis at gastroenterology unit in European Gaza Hospital, this is the most appropriate design for the study objectives.

3.2. Study Setting

The study was conducted at the gastroenterology outpatient clinic in European Gaza Hospital. Data were collected retrospectively from patients records and from patients themselves when attending at the clinic. The study was conducted during the period from September 2022 to February 2023.

Participants and sampling. The study included all liver cirrhosis patients at European Gaza Hospital. The study data were collected from medical records and from patients.

3.3. Data Collection

Data were collected from medical records retrospectively using a self-designed questionnaire based on most recent published literature. In addition, some data was obtained from patients at their appointment in the clinic.

3.4. Instruments

The study tool is a self-designed questionnaire based on most recent published literature. The questionnaire included basic information about the patients, data related to liver cirrhosis and some laboratory work done for the patients.

3.5. Statistical Analysis

Data obtained from questionnaire were entered and analyzed using SPSS program version 23 computer software. Sociodemographic data were presented using descriptive statistics as means, median, percentages and standard deviation. Independent T test and one-way Anova are used to show statistical significance among patients' characteristics and tool scores. Chi square test is used to show relationship between categorical variables.

3.6. Permission and Ethical Considerations

An approved permission was gained from the Ministry of Health in Gaza Strip to collect data from patients' medical records. Moreover, oral consent was gained from patients to participate in the study.

4. Results

The study included 70 patients in which more than half of them were males (n= 42, 60%) and the rest were females (n= 28, 40%). The mean age among study participants was 61.97 + 11.54 years. The median age was 62.5 years and age ranged from 20 to 83 years. Age groups distribution is presented in Figure 5. As shown, the peak age group is at older population.

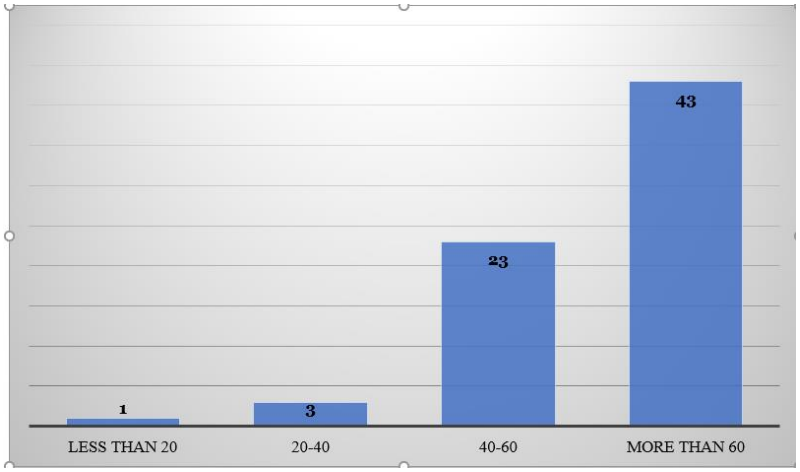


Figure 5: Age Groups Distribution Among Study Participants

Most of participants were from southern region of Gaza Strip as shown in Figure 6. The vast majority of study participants were married (n= 68, 97.1%) while 2 participants were single (2.9%). Among study participants, the mean weight was 90.5 kg and the mean height was 1.72 m. The mean body mass index among study participants was 31.15 kg/m2. This reflects overweight and obese participants.

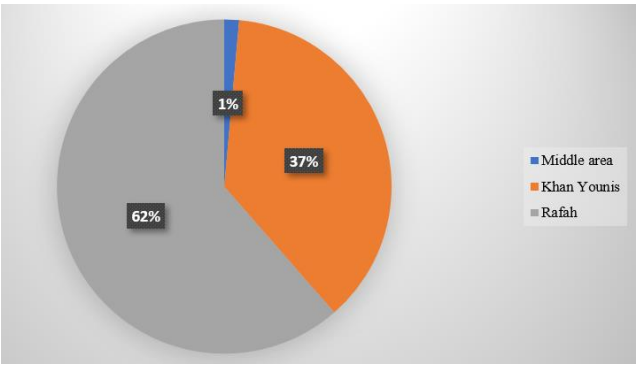


Figure 6: Distribution of Study Participants According to their Residency Place

The duration of liver cirrhosis among study participants varied. It ranged from less than a year to 11 years. The median duration among study participants was 4 years. The most frequent cause of liver cirrhosis among study participants was cryptogenic (n= 38, 54.3%) (Figure 7).

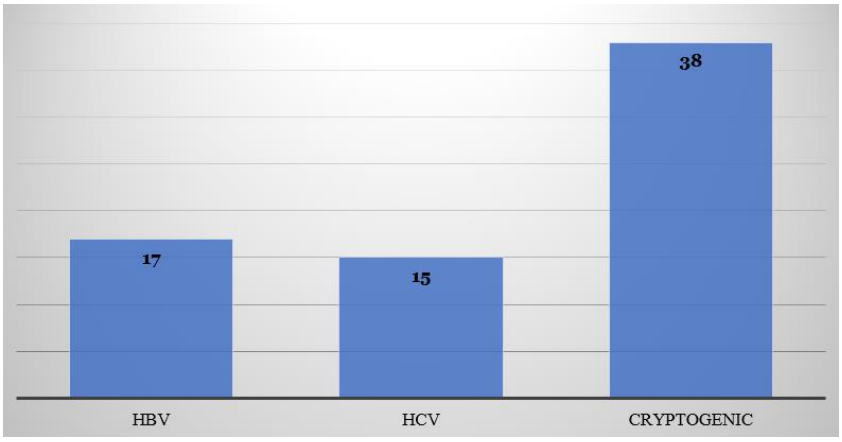


Figure 7: Causes if Liver Cirrhosis among Study Participants

There were two thirds of study participants having comorbid conditions besides liver cirrhosis. The most frequent comorbid condition was diabetes mellitus (n= 38, 54.3%). Table 1 shows the frequency of comorbid conditions among study participants.

Comorbid condition	Frequency	Percent
Hypertension	24	34.3
Diabetes Mellitus	38	54.3
Cardiovascular Diseases	18	25.7
Chronic Kidney Disease	3	4.3
Hepatocellular Carcinoma	11	15.7

Table 1: Comorbid Conditions Among Study Participants

There is only one patient who had diabetes mellitus after the diagnosis of liver cirrhosis. Furthermore, five patients underwent liver transplantation (7.1%). The median level of HbA1c is 8 among diabetic participants and it ranged from 6.5 to 9. Participants were on different management strategies for liver cirrhosis and diabetes as presented in Figure 8 (OHA: Oral Hypoglycemic Agents).

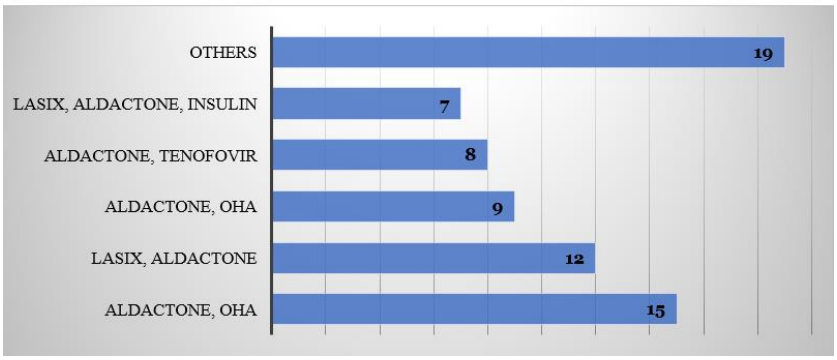


Figure 8: Medical Management of Patients' Condition

The duration of diabetes mellitus among patients ranged from one to 20 years with median duration of 8 years. Participants were evaluated for possible complications of DM along with liver cirrhosis. There were 38 patients with family history of DM (54.3%).

	Frequency	Percent
Smoking (Median of 14 pack year)	9	12.9
History of stroke	3	4.3
History of myocardial infarction	15	21.4

Table 2: Smoking and Complications History of Study Participants

The ultrasound features of the liver were assessed among study participants. Liver was shrunk in the ultrasound imaging among 51 participants (72.9%) (Figure 9). Most of patients had severe steatosis (n= 62, 88.6%) while 8 participants had moderate steatosis (11.4%).

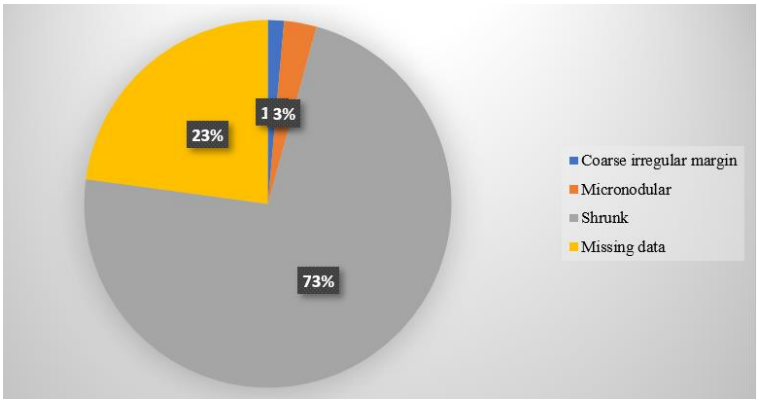


Figure 9: Ultrasound Features of Liver Among Study Participants

The laboratory findings of study participants are summarized in Table 3.

Laboratory test	Mean + SD (min-max)
Alanine transaminase (ALT)	36.45 + 15.65 (13-85)
Aspartate aminotransferase (AST)	36.22 + 17.76 (12-128)
Triglycerides	188.22 + 69.11 (68-264)
Cholesterol	149.71 + 50.83 (85-225)
Total Bilirubin	1.63 + 1.16 (0.7-6)
Direct Bilirubin	0.53 + 0.54 (0.2-3.1)

Table 3: Laboratory Tests of Study Participants

5. Discussion

There are a number of anatomical changes that may occur in people with cirrhosis that reduce insulin extraction by the liver, ultimately leading to elevated systemic insulin levels. Since insulin is mostly metabolized and degraded by parenchymal liver cells, a decrease in liver cell mass results in lower insulin clearance, and an increase in insulin levels is caused by (b) portosystemic venous collaterals as a consequence of decreased hepatic first-pass extraction [81,82]. Insulin levels in the hepatic veins are much higher in cirrhotic individuals who have had surgical portocaval shunts compared to cirrhotic patients who have not undergone such procedures. C-peptide levels, on the other hand, are similar in cirrhotic patients and healthy controls [83]. The fact that glucose management in diabetic individuals deteriorates and circulating insulin levels rise following transjugular intrahepatic portosystemic shunt implantation further lends credence to this theory.

Thus, hyperinsulinaemia may cause insulin resistance by down-regulation of insulin receptors. In fact, hyperinsulinaemia causes a decrease in insulin receptor affinity, a decrease in the number of exposed receptors on the surface of the target cell, and a decrease in the efficiency with which insulin transmits stimulatory impulses into the cell [84].

AGEs are promoted by hyperglycemia, but they may also cause insulin resistance and beta-cell damage in pre-diabetic individuals. The elimination of advanced glycation end products (AGEs) appears to include more than only the kidney [85]. Plasma AGE levels are significantly increased in individuals with cirrhosis who do not have diabetes [86,87]. The levels of AGEs decrease considerably after a liver transplant. Considering these results, it's reasonable to assume that the buildup of AGEs, due to a decreased clearance of AGEs, may increase diabetes in individuals with cirrhosis [88].

Advanced cirrhosis patients often have systemic hypoxia, which correlates with the severity of their liver disease [89]. Family of transcriptional regulators called hypoxia-inducible factors (HIFs) triggers homeostatic response to hypoxia in almost all cells and tissues. In both in vitro and mouse models of hepatic fibrosis, HIFs have been shown to have a role [90,91]. HIFs are also crucial in glucose metabolism and have been linked to the development of diabetes mellitus [92]. HIF, namely HIF-1, is also critical for the reserve of pancreatic -cells. The mechanics, however, are intricate. In fact, the function of pancreatic -cells is compromised in HIF-1 knock-out mice [93]. A little boost in HIF-1 levels improves -cell function and glucose tolerance. Nonetheless, it is known that very high levels of HIF-1, such as those seen in severe hypoxia, are harmful to -cell function 48. Hence, it is possible to hypothesize that hypoxia caused by cirrhosis contributes to the development of hepatogenous diabetes mellitus [94].

Peripheral insulin resistance and hyperinsulinaemia cause glucose intolerance in cirrhosis. Beta-cell secretion, in response to

hyperglycaemia, is significantly reduced in patients with cirrhosis and overt diabetes, compared to patients with cirrhosis and normal glucose tolerance as well as those with glucose intolerance, suggesting that an altered secretion of insulin by beta cells may contribute to the development of overt diabetes [82,85]. Betatrophin is a hormone that is largely produced in hepatocytes and has recently been shown to increase -cell proliferation and enhance glucose tolerance in a mouse model [95]. Recent evidence, however, suggests that betatrophin levels are linked to insulin resistance rather than -cell proliferation. Patients with type 2 diabetes were shown to have higher betatrophin levels than non-diabetic controls [96-98]. Betatrophin levels also correlated strongly with HOMA-IR in a recent research of over a thousand people who are not diabetic. Patients with cirrhosis had considerably higher plasma betatrophin levels than healthy controls. Liver disease severity was also shown to be related to serum betatrophin levels. In addition, individuals with insulin resistance had considerably greater betatrophin levels than those without [99]. These results lend credence to the hypothesis that betatrophin has a functional role in type 2 diabetes, maybe helping to offset the higher insulin demand in those with liver insufficiency [100].

Sugar metabolism abnormalities in cirrhotic individuals vary from simple intolerance to full-blown diabetes. Around 30% have normal glucose tolerance, 30% have impaired glucose tolerance, and up to 30% have overt diabetes 56-59. As a comparison, the whole population has a prevalence of glucose intolerance of around 15% and diabetes of about 8% [101-102].

Patients with cirrhosis may have a more complicated time receiving a diabetes diagnosis. First, in 23% of patients with overt diabetes, fasting serum glucose levels are normal in the early period [103]. In fact, their blood sugar levels are normal when fasting, but they are elevated after eating (>200 mg/L) [104]. Thus, a test for glucose tolerance after eating is required to identify glucose metabolism impairment.

Additionally, distinguishing type 2 diabetes from hepatogenous diabetes is sometimes impossible. Yet, hepatogenous diabetes may display a unique set of symptoms compared to type 2 diabetes. A study of 50 individuals with hepatogenous diabetes found that only 16 percent had a history of diabetes in their own families. Retinopathy affected just 8% of the sample. No cardiovascular fatalities were documented after a mean of 5 years of follow-up, however percent of patients had passed away, mostly from cirrhosis-related causes. This might be because hepatogenous diabetes is often associated with a shorter duration of diabetes than type 2 diabetes, or it could be because cirrhosis-related complications account for a disproportionate share of deaths in these individuals (as shown by the high mortality rate in this group) [105-107].

Liver transplantation alone may improve glucose tolerance and insulin sensitivity in individuals with isolated hepatogenous diabetes, providing further evidence that diabetes is linked to cirrhosis. It is estimated that roughly 30% of liver transplant patients had diabetes, but post-transplantation diabetes remains a relatively frequent illness. Pretransplantation diabetes, old age, a family history of diabetes, and a maximum body mass index above 25 kg/m2 (risk factors for type 2 diabetes) are related with the development of post-transplantation diabetes in individuals who receive a liver graft [108-110]. These findings point to preexisting metabolic problems as a possible cause of diabetes mellitus present at the time of liver transplantation, in addition to severe liver disease. Patients with cirrhosis seem to have an increased chance of developing diabetes due to the reasons of their liver disease. Patients with hepatitis C- or alcohol-related cirrhosis are more likely to develop diabetes than those with biliary cirrhosis [111,112]. Cirrhosis is still linked to cirrhosis on its own. Cirrhotic individuals with hepatitis C infection are more likely to develop diabetes (24% vs. 6%) [113].

In individuals with cirrhosis, glycated haemoglobin (HbA1c) measurements may not reliably represent glycemic status. HbA1c is used routinely for evaluating and managing individuals with diabetes in those without liver problems. The level of hemoglobin A1c (HbA1c) is a good predictor of the onset of diabetes-related problems since it represents glycaemic state during the preceding 2-3 months. HbA1c testing is not reliable in patients with cirrhosis, according to studies of limited patient series. In fact, forty percent of cirrhotic patients who did not have diabetes had HbA1c levels below the normal limit in a non-diabetic reference sample [114,115]. In addition, HbA1c readings for individuals with cirrhosis and concomitant diabetes were within the non-diabetic reference range (between 4 and 6%). High HbA1c was seen in a minority of cirrhotic and diabetic individuals. Although though fasting plasma glucose was greater in individuals with cirrhosis, HbA1c levels were comparable between cirrhotic and controls [116]. It is not known why HbA1c testing fails to reliably represent the degree to which people with cirrhosis have their blood sugar under control. One possible non-glycemic factor is the shortened erythrocyte life span seen in cirrhotic individuals, which is linked to low HbA1c readings. The glycemic state during a 2-to 4-week period may be inferred from fructosamine levels. Patients with cirrhosis may benefit more from monitoring their fructosamine levels than their hemoglobin A1c levels, according to [117-120].

6. Conclusion and Recommendations

In conclusion, the study provides important insights into the characteristics of patients with liver cirrhosis and diabetes mellitus in the Gaza Strip. The study included 70 participants, with a majority being male and from the southern region of the Gaza Strip. The peak age group was the elderly population, and most participants were overweight or obese. The most frequent cause of liver cirrhosis was cryptogenic, and more than half of the participants had comorbid conditions, with diabetes mellitus being the most common. The ultrasound features of the liver showed severe steatosis in most patients. The laboratory findings indicated elevated levels of alanine transaminase, aspartate aminotransferase, triglycerides, and total bilirubin among the study participants.

Based on the results, the following recommendations can be made:

• Public health campaigns should be initiated to raise awareness about the risk factors of liver cirrhosis and diabetes mellitus,

with particular emphasis on lifestyle changes to prevent and manage these conditions.

• Regular monitoring of liver function tests, blood glucose levels, and lipid profiles should be done among patients with liver cirrhosis and diabetes mellitus to identify any potential complications and take appropriate measures to prevent them.

• Healthcare providers should consider implementing tailored management strategies for patients with both liver cirrhosis and diabetes mellitus to improve patient outcomes and quality of life. This may involve a multidisciplinary approach with a team of healthcare professionals working together to manage these complex conditions.

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