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FREQUENCY OF DIABETES MELLITUS IN PATIENTS WITH CHRONIC LIVER DISEASE

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Abstract

Background & Summary: *The liver is essential and crucial in regulat carbohydrate metabolism and Gluconeogenesis. Its normal function is necessary maintaining glucose levels in the blood and supplying energy to organs. Seve hormones, including insulin, glucagon, growth hormone, cortisol, and catecholami contribute to the regulation of glucose metabolism by the liver. This leading role of liver in glucose homeostasis gives us a clue to the pathogenesis of glucose intolerance Diabetes in liver diseases. There is a strong correlation between diabetes mellitus a liver diseases: several glucose metabolism alterations are commonly found in subj with chronic liver disease. The pathogenesis of impaired glucose metabolism dur chronic liver disease has not yet been fully understood.*

Objective: *The current study's objective was to determine the frequency of Diab mellitus in chronic liver patients.*

Methodology: *It was a descriptive study. A total of 89 samples from patients u chronic liver disease were collected from the tertiary care Hospital of Lahore. 5 (blood samples were drawn from the anti-cubital vein according to proper phlebot protocol and then dispensed in a vial with anticoagulant sodium fluoride for gluc estimation and a vial with anticoagulant EDTA for HbA1c.*

Results: *Out of these 89 samples, 49 (55.1 %) were males & 40 (44.9%) u Females. According to our results, the frequency of present Diabetes in chronic li patients is 61.8%.*

Conclusion: *This study concluded that the frequency of Diabetes in chronic li patients is 61.8%, which is statistically significant. Early analysis of Diabettes, a HbA1c levels, can be utilized as a preventive measure for glycemic control.*

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INTRODUCTION

Diabetes and chronic liver disease are two frequently occurring and linked conditions that seem to worsen each other. The global occurrence of these diseases is increasing, and individuals with Diabetes are at a significantly higher risk for developing liver disease. (1) Many people with liver disease also face the additional health challenge of Diabetes. (2) Some experts believe that this combination may be primarily caused by liver damage, leading to inadequate insulin absorption. (3) Factors such as cancer treatment drugs that raise blood sugar levels, long-term malnutrition, and chronic liver diseases can all play a role in causing insulin resistance and abnormal glucose metabolism. Gluconeogenesis is a process that occurs in the liver that regulates glucose metabolism. (33) Its proper functioning is required to stabilize blood glucose levels and provide energy to organs. Insulin, glucagon, growth hormone, cortisol, and catecholamine are hormones that help the liver regulate glucose metabolism. The liver's central function in glucose homeostasis provides insight into the etiology of glucose intolerance or Diabetes in liver disorders. Diabetes mellitus and liver disease have a close relationship: In those with chronic liver disease, there are several changes in their glucose metabolism. The cause of poor glucose metabolism in chronic liver disease is unknown; more clinical and experimental research is needed to clarify this issue. The average metabolic equilibrium of glucose is disrupted in those with liver disease. Insulin and its counter-regulatory hormones, such as glucagon, have a significant target in the liver, and both hormones are involved in glucose homeostasis in diseases including glucose intolerance, hyperglycemia, and glucose. (34). There is limited information on the frequency of Diabetes in those with chronic liver disease, so the current study aims to investigate this issue further.

1.1. Background and Rationale

Biological and lifestyle factors closely related to liver and Diabetes. The liver is the main target organ affected by diabetes mellitus, inducing regeneration and fibrosis because of peripheral insulin resistance. (4) Unfortunately, diabetes mellitus and chronic liver disease share a set of risk factors that are reflected in their contemporary increasing trend. (5) Diabetes and its complications are the cause of significant costs to societies and health care systems, and by expending health care resources on the management of Diabetes alone, we may fail to save those with other combined chronic debilitating and life-threatening comorbidities such as chronic liver disease. Therefore, the increasing prevalence of Diabetes and chronic liver disease mandates an early, cheap, and cost-effective preventive strategy, interventional, and therapeutic approach. This approach takes the justified initiatives not only to manage the consequences on the liver in patients with Diabetes mellitus resulting in chronic liver disease but also to endeavor the symptomatic improvement of the leading risk factor of Diabetes in patients with chronic liver disease. (6) Epidemiological studies are required to highlight the significance of these interactions and could guide the potential therapeutic strategies and healthcare programs to control the increasing burden of the dual association. (7) In Thailand, early studies have shown the rising trend of association between chronic liver disease and Diabetes. (8) However, the issue is still under-investigated with a meagre rate of various associations and various underlying chronic liver disease etiologies. At the moment, there is a scarcity of comprehensive epidemiological studies that investigated the coexistence of Diabetes in chronic liver disease patients in a large number of study samples with different severities of chronic liver disease etiologies. (9) The Global Burden of Diseases is alarming concerning the twin issue of Diabetes and liver cirrhosis in Thailand. (10) While the mortality rate of liver cirrhosis has been gradually reduced in the past 25 years due to several preventive strategies, the percentage and mortality rate in diabetes-related liver cirrhosis have increased. (11) Nearly 9,000 deaths were reported compared with no deaths 25 years ago. (12) Clearly, the increased twin prevalence of Diabetes and liver cirrhosis-related mortality in Thailand is out of control, and these dual morbidities demand refocused prevention and aggressive intervention. Since this coexistence is linked to etiologies, we may take a policy that the management of these chronic diseases could be significantly improved by multi-disciplinary management of Diabetes, liver cirrhosis, and a combination of abstinence from tobacco, excessive alcohol, and weight loss programs, as well as cancer surveillance and vaccination for infection control.

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Thus, the clinical implications demand that we bridge the gap, defining the extent of dual prevalence and its associated factors to guide proper prevention and treatment programs. (13)

Now that a chronic condition which may promote the association has been detected, therapeutic agents for Diabetes and other conditions that encourage Diabetes might contribute to the setting. Also, the economic burden is minimal, as encouraging people to abstain from tobacco, alcohol, diet, and increased physical activity can prevent these conditions. Moreover, until now, the study's truancy has excluded many patients affected by thalassemia disease and subsequent heart failure before assessing to find out the associations. A time has come in Thailand to identify the actual number, percentage, and factors linked to concomitant Diabetes in patients with chronic liver disease affected by varied etiologies of chronic liver disease to take actions and strategies to prevent and attenuate the initiation and progression of the disorders. The patients that have Refractory ascites & Diabetes show 1- & 2- year percentages & the ratio of survival was 32% % and 18%, respectively. On the other hand, the survival rate of sufferers with refractory ascites was about 62% & 58%, respectively. A study was also conducted with those who were suffering from liver cirrhosis, and HCC & Diabetes were found in those patients. (35) This study was performed on 643 patients, of which 173 were with type 2 diabetes & out of 650 patients, 620 were without any Diabetes. In these patients, the CLD was not found at the time of registration. However, 10 years later, in a cohort study, the HCC & NALD were considerably higher in DM patients correlated with none- diabetic patients. The hazard was two times greater & alcoholic liver disease, viral hepatitis & demographic factors were independent. (36) This study was intense because many people participated in it. Still, it was criticized because it consisted of entire men (98%) by the veteran's affairs department & HCC, Type 2 DM & chronic liver disease were not verified biochemically & histopathological. (37) This study was conducted in Sweden, where approximately 90% of people had type 2 diabetes, according to the national diabetic register. The sufferers of type 2 DM were compared to 5 individuals than the general population, which was related to age, sex & country in a cohort study.

In a study, 406 770 diabetic people & 2 033 850 healthy individuals participated in this research, of which 21 596 934 remained person-years. The occurrence of HCC, DM, liver cirrhosis, liver failure, or death was due to liver disease during this research. (38) This cohort study was conducted on about 240 cirrhotic patients, & Diabetes was found to be hyperglycemia. On the other hand, a group of 411 non-cirrhotic patients of the same age were admitted to the hospital in the same period. Diabetes was found to be more considerable in cirrhotic patients (40 of 240, 16.7%) as compared to none cirrhotic patients. (39) The prevalence of cirrhosis was high in patients before Diabetes. There were 18% of cases in which Diabetes existed first. In the cirrhotic group, Diabetes was maturity-onset with hyperglycemia, low glycosuria & absence of vascular significance (40). According to this study, NFLD occurred in 72.4% of care hospitals in Pakistan & we evaluated these type 2 DM patients. In another type of research, 51% of DM patients had NFLD & was held in urban areas of Pakistan. According to another research conducted in rural areas of Sri Lanka & according to this research NFLD was found to be high & 18% of people survived this. Another study was conducted in urban regions in which high frequency examined about 32.6% investigated. Research shows that the prevalence of NFLD is higher & is a global epidemic in South Asia. (38) This study was conducted in July 2002; the first time HCV was linked to Diabetes in this case-control study. This study shows that HCV-positive cirrhotic patients that had Diabetes were about 21% more than those that were HBV positive 12% cirrhotic patients. (41) But the main thing was that 4.2% of diabetic patients were with HCV & 1.6% were with HBV. HBV conveyance & HCV disclosure rates are critical & meaningful in Pakistan. The HBV carrier rate is 8_10 & HCV carrier rate is 13_16 with a 4% ratio, respectively.

The primary goal of this research was to explain the connection between Diabetes and chronic liver disease with HCV & HBV. (41) According to a current study, HCV infection is linked with type 2 DM & its development & this DM is more familiar in chronic liver patients. Patients who have already suffered from HCV increase the risk of type 2 DM. According to a recent survey in which 1084 people participated, the age

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group was between 44 and 65. Another study was conducted in Taiwan in which 4958 people were under the age of 40 in which DM was not found, but seven years later, in 474 patients, Diabetes was found. The ratio of anti-HCV was about 14.3% & the ratio of HBsAg was about 7.5 & 8.6, where the seronegative individual was type 2 DM in the entire study. (42)

1.2. Scope and Significance

The current study aims to investigate the frequency of diabetes mellitus in patients with chronic liver diseases, focusing on the Indian population. The total number of cases may be included in further research or reviewed for one category separately. Diabetes mellitus is commonly recognized in the elderly; here, we will include patients aged 20 to 90 years for evidence of Diabetes after hepatic abnormalities. As a study population, males predominated over females in the institution. Women who suffer from liver diseases are more conscious about their health and go to the hospital for regular check-ups and appropriate treatment. Diabetes mellitus and chronic liver diseases have a bi-directional relationship. Not only does Diabetes affect the progression of liver diseases, both metabolic and viral-induced, but specific liver diseases also affect insulin sensitivity and carbohydrate metabolism, leading to Diabetes.

There is a definite relationship between liver diseases and diabetes mellitus, which plays a specific role in the progression and treatment of such patients. Although there are corroborative pieces of research stating an association between diabetes and liver diseases, the actual extent of such findings from Indian studies is yet to be researched.

Several articles on liver diseases and Diabetes have been published; however, a scarcity of articles studying such frequencies in the Indian population is noted.

Additionally, studies on hepatitis C virus infection provide a composite picture based on the dual effect of both diseases. This systematic review and meta-analysis, therefore, provide strong evidence for the association of Diabetes with chronic liver disease, cirrhosis of the liver, hepatocellular carcinoma, chronic hepatitis C infection, and primary biliary cirrhosis. This study is significant in providing practical guidance to gastroenterologists and healthcare providers in treating liver disease in patients with Diabetes. It is also valuable for public health, as it will improve the quality of clinical and healthcare practices in managing Diabetes in the elderly. This could be beneficial to developing and low-income countries that do not have a good public health policy. It provides an impetus for healthcare researchers to evaluate and examine the magnitude of liver disease among people with Diabetes in an elderly study population. A tool helps assess hepatic function against a score of Diabetes and liver disease, either independent health score or in combination for a population that usually presents to the public health service with common lifestyle-related diseases.

2. Pathophysiology of Diabetes Mellitus and Chronic Liver Disease

The pathophysiological changes involved in diabetes mellitus and chronic liver diseases are complex. Diabetes mellitus is characterized by insulin resistance, a pathology that is closely linked to the onset and worsening of chronic liver diseases. (14) Both conditions have derangements in systemic glucose and fatty acid metabolism; thus, they may alter each other's course, leading to hepatic dysfunction and extrahepatic disorders. (15) Decreased glucagon synthesis and increased glucose uptake by peripheral tissues are the main targets of Diabetes if liver function tests are standard. In contrast, if liver tests are altered, hypoalbuminemia and disturbances of glycosuria excretion are essential. (16) No less critical are metabolic disturbances of lipids. In both conditions, cholesterol synthesis and transformation blocks occur, forming atherogenic products that significantly increase low-density lipoproteins. (17)

The most common extrahepatic complications that affect chronic liver patients relate to metabolic disturbances, such as fluid and electrolyte retention, as well as glucose and sterol metabolism dysregulation leading to non-cirrhotic hyperglycemic state, nonalcoholic steatohepatitis and atherosclerosis. (18) Insulin resistance is one of the pathogenetic mechanisms in the development of chronic liver diseases, and chronic liver diseases may lead to glucose intolerance and an increased incidence of Diabetes mellitus. (19) It is well known that glucose uptake in hemocytes and adipocytes decreases in the presence of liver toxicity. Lower glycogen synthase activity in the

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liver decreases glycogen storage and triggers insulin resistance. (20)

2.1. Diabetes Mellitus

"Diabetes" usually refers to Diabetes Mellitus (DM), a group of metabolic pathologies characterized by chronic hyperglycemia deriving from defects in insulin secretion and action. (21) DM can be classified into four major categories, namely Type 1 Diabetes, Type 2 Diabetes, other specific types caused by monogenic defects, other specific types caused by diseases of the exocrine pancreas, and gestational Diabetes (GDM), which occurs during pregnancy. Type 1 Diabetes is a chronic immunological disease when the patient's immune system gradually eradicates pancreatic beta-cells. This ultimately leads to total insulin deficiency due to insufficient insulin secretion and plasma insulin. Conversely, the pathogenesis of Type 2 Diabetes (T2D) is characterized by a combination of insulin secretion and insulin resistance impairment, leading to an overall reduction of the efficacy of glucose metabolism. Most cases of Diabetes belong to this type, which is by far the most common one, and develop slowly over years. (22) Eventually, impaired glucose metabolism leads to the development of hyperglycemia-related symptoms, and the patient finally undergoes a formal diagnosis of the disease. Another form of Diabetes may relate to genetic conditions such as maturity-onset Diabetes of the young. (23)

2.2. Chronic Liver Disease

Chronic liver disease has multiple etiologies, the most common of which is viral hepatitis. Given its importance, we will dedicate this discussion to its focus. Hepatitis B and C viruses affect more than 300 million individuals worldwide, leading to cumulative cases of cirrhosis and hepatocellular carcinoma. Hepatitis C is seen in 57.2% of cases, while hepatitis B is responsible for 37.6% of such cases. In about 6-25% of individuals, the infection resolves spontaneously, and these individuals become chronic carriers of the infection. Viral hepatitis can be diagnosed based on serologic testing, virologic testing, or liver biopsy. Other chronic liver diseases include alcoholic liver disease and nonalcoholic fatty liver disease. A bilirubin by-product is transferred via the bloodstream to the liver; however, if the liver does not function properly, bilirubin accumulates in the skin and eyes, resulting in jaundice. Therefore, A poorly functioning liver leads to internal and external bleeding. (24)

3. Epidemiology of Diabetes Mellitus and Chronic Liver Disease

The global prevalence of Diabetes mellitus has been increasing, corresponding to rising trends of obesity and metabolic disease worldwide. Geographically, the highest prevalence of Diabetes is in the WHO Region of the Americas and the lowest in the Eastern Mediterranean Region. Demographically, the global prevalence of Diabetes is higher in urban areas than in rural areas and has been increasing at a higher rate in low- and middle-income countries than in high-income countries while decreasing in some high-income countries. By age group, diabetes prevalence increases with age. By sex, the global prevalence is similar between men and women but varies with age, with a higher prevalence in women than in men in the 55-74 age group. Chronic liver disease (CLD) is defined by evidence of liver inflammation for at least six months, which can lead to fibrosis, cirrhosis, and even hepatocellular carcinoma. CLD can be caused by hepatitis B and C virus infections, heavy alcohol consumption, nonalcoholic fatty liver disease, and other liver toxicants or infections after that, complicating untreated gestational Diabetes. Complications affecting quality of life, such as hepatic encephalopathy, can happen at any level of disease severity. CLD equally affects men and women and is more frequent among individuals of Asian ethnicity. Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis is the most common cause of CLD globally, and many patients with NAFLD/NASH equally have or will develop type 2 diabetes. Persons with Diabetes also have an increased likelihood of liver fibrosis progression and mortality. However, the exact prevalence of NASH among the general population is mainly unknown, pointing to this link as potentially worth further investigation. (25)

3.1. Global Prevalence of Diabetes Mellitus

In 2021, diabetes mellitus was reported in approximately 537 million adults worldwide, and this number is expected to further increase to 643 million by 2030 and 783 million by 2045. (26) It is among the

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top ten leading causes of death. In 2021, it is estimated that 1 in 11 adults worldwide (20–79 years) will live with Diabetes. However, there is a marked variation in the prevalence, ranging from 33.3% in the Republic of Nauru to 4.0% in New Zealand. A country can have a high prevalence of Diabetes either due to a large number of diabetics, as in the case of China, or due to a small population size, as seen in Nauru. Approximately 80% of instances of known Diabetes occur in low- and middle-income countries. The global healthcare expenditure due to Diabetes was estimated to be US $845 billion in 2019. Diabetes leads to significant complications such as coronary heart disease, blindness, end-stage renal disease, and lower-extremity amputations. (27)

3.2. Prevalence of Chronic Liver Disease

Chronic liver diseases are increasing worldwide due to several risk factors and unhealthy lifestyle habits. Heavy alcohol consumption, chronic viral hepatitis, metabolic syndrome, and particularly the so-called nonalcoholic fatty liver disease, tobacco smoking, and genetic and environmental factors are the main factors that could contribute to the determination of chronic liver disease. (28) Significant geographic variations in liver disease prevalence and aetiology exist. Environmental factors and lifestyle are closely related to the cause of chronic liver diseases. Healthcare access also influences the incidence of liver diseases in various geographic regions. Viral hepatitis is frequently contracted during infancy through the consumption of contaminated food and water or blood transfusions, poorly sterilized syringes, lack of hygiene, and being in unhygienic or crowded places. These data support the need to inform the public and implement therapeutic and preventive strategies to improve their access to healthcare, educate people about the dangers of exposure to hepatotropic viruses, regular and moderate alcohol intake, and adopt a healthy lifestyle to avoid developing chronic liver diseases and associated disorders, including diabetes mellitus. Interestingly, some risk factors also contribute to the progression of Diabetes. This mechanism, called multiple metabolic diseases, could undoubtedly lead to an increase in the prevalence of Diabetes, such as chronic liver disease involving tissue fibrosis and cirrhosis. Given the increasing incidence of Diabetes alone and in combination with liver diseases and the burden of these two diseases in healthcare, this is an area for continued research. The global epidemiology of chronic liver disease is presented in a meta-analysis and summarized by each continent and type of liver disease. (29)

3.3. Co-occurrence of Diabetes Mellitus and Chronic Liver Disease

Historical studies of patients with chronic liver disease diagnosis have reported that the mean prevalence of T2DM in these individuals was as high as 31%. Still, other studies have reported changes in plasma glycaemia. The importance of this dual diagnosis is rooted in risk factors common to T2DM and chronic liver disease, such as adiposity, adipose tissue inflammation, and insulin resistance. Insulin resistance leads to hyperinsulinemia, but the liver maintains normoglycemia; thus, blood glucose levels remain standard for some time while hyperinsulinemia continues. During this phase, when the pancreas is slightly overworked, compensating for resistance, fasting glucose levels are not dramatically elevated, and chronic liver injury also has less advanced fibrosis. Fibrosis worsens when the pancreas can no longer produce enough insulin to resist hepatic glucose production; thus, fasting blood glucose levels become elevated. This can easily be managed by diet and lifestyle changes alone. (30)

Regardless of aetiology, the co-occurrence of T2DM and chronic liver disease has a significant impact on the progression and management of both conditions. T2DM is an independent risk factor for the progression of fibrosis. At the same time, NAFLD predicts poor glycemic control, leading to a more rapid requirement for insulin or other glycemic control agents. Perhaps of most significance is that the presence of T2DM in individuals with chronic liver disease often necessitates a lower glycemic target, less use of fructose-rich sweeteners, severe dietary restrictions, and avoidance of large alcoholic beverages than typically recommended, leaving patients intolerant of existing guideline-recommended treatments for their liver disease. This is particularly pertinent for PCOS patients, where avoidance of dietary sugars that can markedly increase hepatic lipogenesis in all chronic liver diseases is recommended. (31)

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4. MATERIAL AND METHODS:

4.1 Study design: Cross-sectional study.

4.2 Duration of study: 3-4 months after the approval of synopsis.

4.3 Study setting: This study was carried out in the pathology department of Azra Naheed Medical College, Lahore.

4.4 Sampling technique: Convenient sampling technique.

4.5 Study population: Patients with chronic liver disease from GIT ward of tertiary care Hospital Lahore.

4.6 Sample size: A total of 89 cases of chronic liver disease were included in this study.

4.7 Inclusion Criteria Gender:

- Male and female.
- **Age** 14-75 years
- Diagnosed cases of chronic liver disease.

4.8 Exclusion Criteria

- Patients with acute-stage liver disease
- Patients having comorbidity (other associated disease) Hemolyzed samples

4.9 DATA COLLECTION PROCEDURE

The questionnaire was designed as a data collection tool to collect information from CLD patients. The questionnaire comprised patients' demographic data, such as name, age, gender, clinical features, detailed history, and other results.

Detailed clinical history and investigations were carried out and recorded.

5 CC blood samples were drawn from the anti-cubital vein according to proper phlebotomy protocol and then dispensed in a vial with anticoagulant sodium fluoride for glucose estimation and a vial with anticoagulant EDTA for HbA1c.

Vials and correctly filled request forms will be labelled. The following tests were done:

- Fasting plasma glucose: by Enzyme colorimetric Glucose oxidase – peroxidase (GOD-PAP) method.
- 2-hour postprandial plasma glucose level: by Enzyme colorimetric GOD-PAP method.
- HbA1C: by fast ion exchange resin separation method.

(It has now been recommended as a diagnostic and screening tool for Diabetes (≥6.5) & and Diabetes (5.7-6.4) by the 2010 American Diabetes Association (ADA).

DIAGNOSTIC CRITERIA FOR DIABETES:

- Fasting glucose level ≥126mg/dl
- 2hour postprandial glucose level ≥ 200mg/dl
- Impaired fasting glucose level 110-126mg/dl
- HbA1C 6.5% or over
- Age, gender, Diabetes mellitus, glucose levels Frequency.

4.10 STATISTICAL DATA ANALYSIS:

Data was entered and analyzed using SPSS software (version 20.2). ± was calculated for quantitative variables such as age—qualitative variables were described using frequencies and analyzed using chi-square.

5. RESULTS:

It was a descriptive study that conducted in a hospital. A total of 89 samples of Diabetes in chronic liver patients were collected. Out of these samples, 49 (55.1 %) were males. Of the 40 (44.9%) samples, 89 were Females. According to our results, the frequency of present Diabetes in chronic liver patients is 61.8%.

Table 1: Gender distribution among patients of CLD

Gender		No. Patients	Valid Percent
Valid	Male	49	55.1%
	Female	40	44.9%
	Total	89	100.0%

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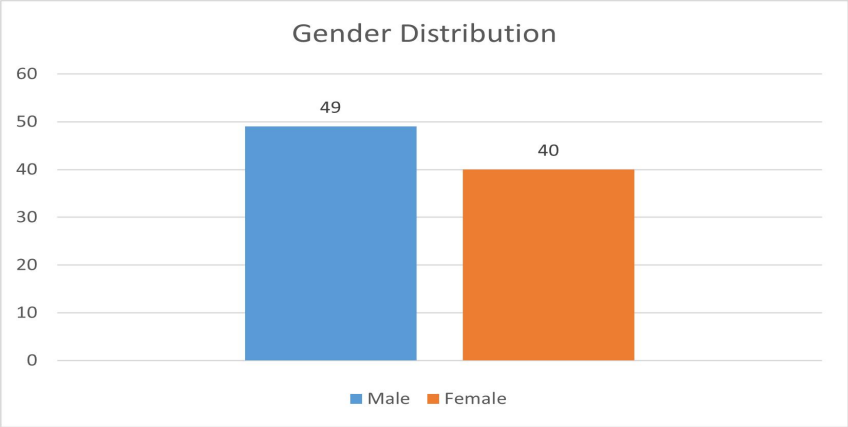

Figure 1: Gender distribution among patients of CLD

This frequency table describes the frequency of males and females with valid and cumulative percentages. In this table total, 89 patients are recorded; males are 49 (61.8%) and females are 40 (44.9%).

Table 2: Distribution of Diabetes among patients of CLD

Diabetes status		Frequency	Percent
Valid	Absent	34	38.2%
	Present	55	61.8%
	Total	89	100.0%

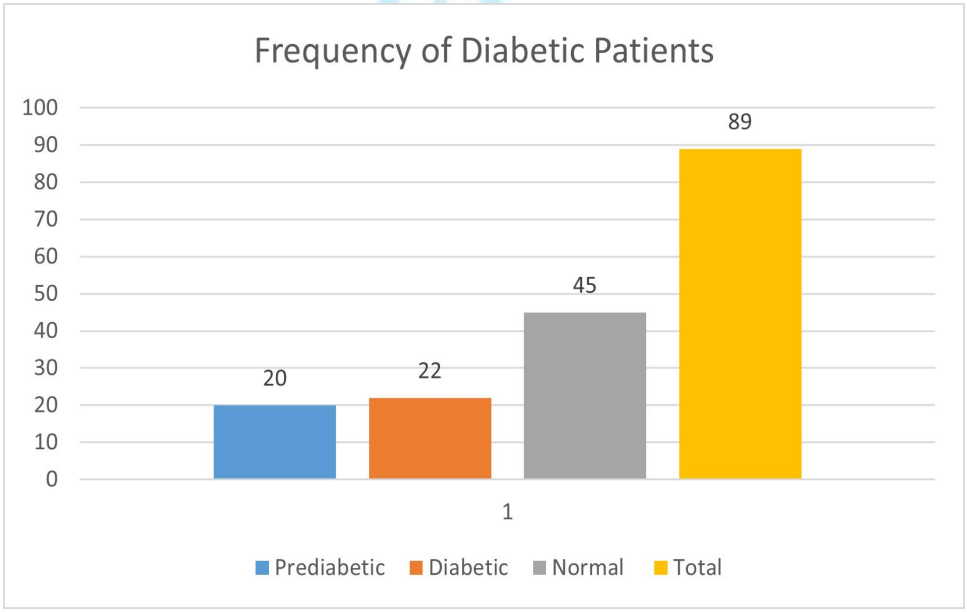

Figure 2: Frequency of Diabetic patients

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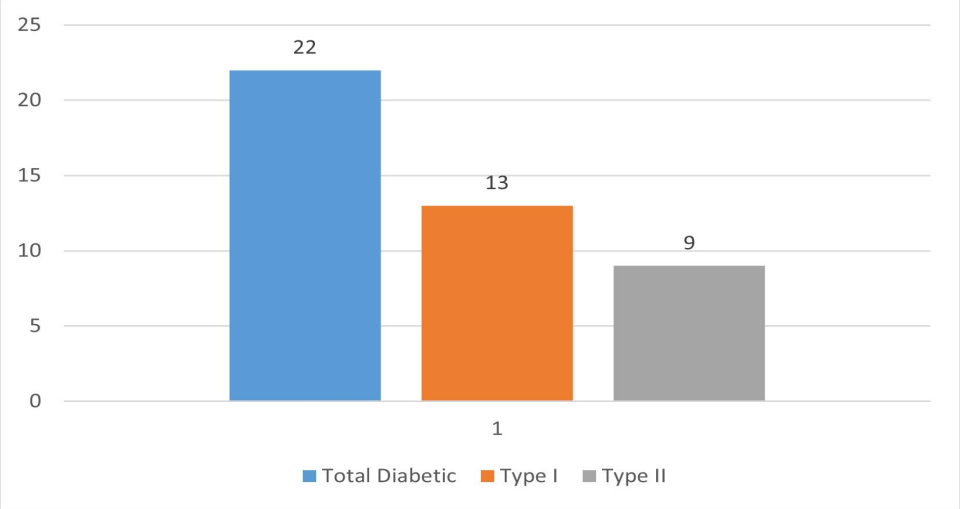

Figure 3: Frequency of Type of Diabetes among Diabetic patients

This table shows the percentage of diabetic and non-diabetic patients out of 49 (55. %1) male patients, 27 had Diabetes, and 22 were non-diabetic. Similarly, in a total of 40 (44.9%) female patients, 28 were diabetic and 12 were non diabetic.

Table 3: Frequency of Diabetes among CLD patients.

		Diabetic		Total
		Absent	Present	
Gender	Male	22	27	49%
	Female	12	28	40%
Total		34	55	89%

6. DISCUSSION:

The study was conducted on about 229 Japanese patients who were infected by hepatitis C infection; 27.7% had liver cirrhosis, and 8.9% had chronic active hepatitis. The 17.5% were Diabetes as correlated to 5.3% in the restraint community. (43) This study agrees that it was conducted on 354 patients, of which 98 are diabetic. Three hundred eighty-two capable patients were followed for 6 years in this study & 110 were living in the last. This study shows a larger mortality ratio of Diabetes that was increased due to HCC over Cancer & liver disease. (44) This study is in agreement with what was conducted in Denmark. This study shows the result that the prevalence of Hepatic cellular carcinoma was high in males & females (4.0, 95% CI: 3.5-4.6) with type 2 Diabetes mellitus DM compared with the general population. (45) The study is in agreement with the recent research held on 465 patients. This study shows that most DM was high in patients with hepatic cellular carcinoma compared to the average ratio (31.2% vs 12.7%, OR 3.12 95% CI: 2.22-4.43). This DM was analyzed before the happening of Hepatic cellular carcinoma in 84% of trials & an average duration of 181.4mo. The above data indicate that DM may be the risk factor in severe cirrhosis, chronic liver & HCC patients. (46) This study is in agreement with the Verona study conducted on more than 7000 individuals who were undergoing type 2 Diabetes Mellitus & the threat of mortality every 5 years were 2.52% higher than (CI 1.96-3.2) in the typical community. (47)

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Many studies indicate that type 2 DM may play a crucial part in the occurrence of liver disease, liver cirrhosis, Hepatic cellular carcinoma & liver cancer. (48,49). The study agrees that it was conducted in Agha Khan Hospital Karachi in 2008_2013. In this study, the individual was diagnosed with type 2 Diabetes Mellitus & NFLD was also found through ultrasound in an adult. This study shows that 146 NFLD patients have been diagnosed with type 2 DM out of 203 patients (71.9 percent). The NFLD was linked with Dyslipidemia (OR 2.38, 95 percent CI 1.06-5.34, p = 0.035), higher LDL (OR 1.02, 95 percent CI 1.01-1.03, p = 0.003), H bA1c (OR1.27, 95 percent CI 0.97-1.68, p = 0.045), and the diastolic blood pressure was about (OR 1.05, 95 percent CI 1.01-1.10). (50)

So, all the above data shows 71.9 percent of Diabetes in NFLD patients. (Multiplicative analysis). (51)

6.1. Clinical Implications and Management Strategies

The presence of Diabetes mellitus in a patient with liver disease, either chronic liver disease or cirrhosis, has relevant clinical and therapeutic implications. (22) On the one hand, diabetes mellitus may contribute to a more severe metabolic or cardiovascular complication of liver disease by acting as a second hepatotoxic hit. On the other hand, the presence of liver disease and hepatic impairment increases the safety profile of the anti-hyperglycemic, glycemia-lowering agents. All of these aspects imply the need for a patient-tailored integrated approach that takes into account the coexistence of two independent and manageable conditions: diabetes mellitus and chronic liver disease/cirrhosis. All these suggestions support the paradigm that "one size does not fit all, not in diabetes, nor in hepatic complications of metabolic or atherogenic liver disease." There are patients with Diabetes and chronic liver disease who are at low or high risk for ultimately developing chronic complications of the former, and early-onset ones at that, for which diabetes mellitus is indeed an established risk factor. (25)

Practical management strategies and clinical implications of the present results reflect an established necessity for interdisciplinary care, focusing in-depth on examining the liver of all type 2 diabetic patients and of complications, including the prevalence of nonalcoholic fatty liver disease and non-invasive evaluation for liver fibrosis. (15) The management of diabetic patients with suspected or confirmed chronic liver disease would indeed benefit from early detection of complications, with a significant reduction in progression and increased patient global prognosis. Challenges still to be tackled from a public health point of view can be derived from these same implications since daily clinical practice is unfortunately remote from these suggestions. Management of concomitant co-occurring conditions such as diabetes mellitus and chronic liver disease should elevate the healthcare providers' responsibility and systematize their recurring investigative actions in exploring both entities.

6.2. Impact of Diabetes Mellitus on Chronic Liver Disease

Diabetes mellitus (DM) and decreased hepatic glucose production resulting from hypo-insulinemia cause chronically abnormal glycogen blood levels of hyperglycemia or hypoglycemia. The liver is a vital target organ in patients with DM for acute and chronic complications. In patients with chronic liver disease (CLD), closely related to liver fibrosis progression, glucose metabolism disorders can also be seen due to deterioration of hepatic glycogen storage. Moreover, it was found that glucose metabolism was more challenging to regulate as the severity of the liver disease increased. Fatty liver, hepatic steatosis-related fibrosis, cirrhotic liver, and hepatocellular carcinoma are closely related to the interaction of DM and CLD. In patients with Diabetes, several adverse health outcomes are possible. DM is associated with a significant increase in overall morbidity and mortality, as well as increased complications during hospitalization in patients with cirrhosis. Additionally, other liver-related morbidity, such as variceal bleeding, acute kidney injury, other transplants, and end-stage liver disease, was reported to increase in patients with chronic liver disease (CLD) and DM. (32)

6.3. Treatment Approaches and Challenges

It should be noted, however, that the possible risks of dual treatment have to be balanced by the magnitude of the expected benefit. Clinical management of Diabetes in a person with NAFLD must be based on the recently released clinical practice guidelines for the

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management of NAFLD/NASH. A multifactorial approach to improve liver and cardiac outcomes is best for treating NAFLD in T2DM or metabolic syndrome. It is well accepted that lifestyle interventions, such as nutritional changes and reduction of body weight, as a consequence, body fat and lean body mass, and increasing physical activity are cornerstones for treating patients with NAFLD/NASH.

Apart from potential issues arising around drug-drug interactions during prolonged polypharmacy, adherence to treatment plans might be an additional obstacle to overcome. Despite the introduction of a plethora of glucose- and lipid-lowering drugs, a high proportion of individuals with NAFLD-related Diabetes still do not receive adequate disease control and have a significant residual risk for developing diabetes complications. To surmount these treatment challenges, pan-disciplinary, patient-centered, and ideally, personalized treatment management by a multi-professional team could provide optimal efficacy. Similarly, lifestyle changes aimed at reducing total and visceral adiposity, improving insulin sensitivity, and normalizing glucose metabolism are of paramount importance. This review will discuss the proposed mechanisms that may help T2DM management with this attitude regarding state of the art for the population. Also, the potential of therapeutic drug targeting to counteract hyperactivity in T2DM with underlying NAFLD will be discussed, involving perspectives from preclinical research and the clinical side.

7. Conclusion and Future Directions

Diabetes mellitus (DM) and chronic liver diseases (CLD) have a bidirectional relationship. The co-occurrence of these two dramatically affects management, treatment outcomes, and survival. There is an urgent need to explore DM in patients with CLD for timely, comprehensive management and treatment. Further research in this area should focus on prospective multinational, multicenter cohort studies from the LC patients in various decompensated stages to evaluate the long-term natural history of type 2 diabetes mellitus (T2DM) in patients with CLD with HBV and HCV infection and to discover if any additional cofactor plays a role in the occurrence of T2DM. There is also a need for research on T2DM in LC patients with cryptogenic CLD.

Practical Recommendations

The objectives were to summarize the interrelation between two critical fatal diseases and their anatomy. We recommend following the guidelines for monitoring and treating patients who are or are going to be diabetic. Additionally, awareness of comorbid diseases and evaluation of the severity of such diseases, especially liver diseases, is essential in making protocols to prevent these risks regularly. It is recommended that physicians, diabetologists, and gastroenterologists should be more involved in integrative care. The impact of this "double burden" of Diabetes and CLD spans from laboratory and radiological evaluation to an integrated multi-platform of etiopathogenesis, addressing access and barriers to care based on a multidirectional model with the patients as the pivot. Future work should aim to personalize patient care and generate robust evidence to enable better clinical management of these individuals. With the call for much-needed policy change, CLD can no longer continue to lurk in diabetes care and make the diabetic landscape more aggressive. This will provide a broader perspective into the dimensions of shared care and an integrated approach. This is a prerequisite to limit the dual burden in the current era. There is a need for expert discussion, including every genetic panorama led by the planner. The findings suggest an unmet need for education and research into the interrelation of liver disease and T2DM. The management of such patients needs to be evidence-based for optimal health outcomes and resource use. Our findings highlight the need for prospectively designed, adequately powered, methodologically rigorous national and multinational research studies to investigate patterns, prevalence, and management of liver disease in patients with T2DM, as well as T2DM in patients with underlying chronic liver disease. Our findings emphasize the need for more research in this area. The implications of this bidirectional relationship between liver diseases and Diabetes can be far-reaching and may significantly impact healthcare resource utilization. A synergy among hepatologists and diabetologists to conduct further research and for the industry to develop evidence-based guidelines in the future is the need of

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the hour. Active research is needed to maintain a global healthcare database on diabetes-liver disease comorbidity, including epidemiology, etiological associations, drug safety and benefit-risk analyses, therapeutic options, optimal targets, and guidelines for best clinical practice. A prophylactic approach and screening for Diabetes among CLD patients has taken a back seat and needs to be revisited. This pattern's clinical and therapeutic implications remain unclear and warrant further investigation.

8. Potential Areas for Further Research

The literature review showed a shortage of contemporary data about Diabetes mellitus in patients with chronic liver disease. The most significant potential area for future research would be to perform multicenter studies combining primary and secondary care patients to accrue representative data on prevalent diabetes mellitus and incident diabetes mellitus. Because diabetes mellitus has been shown to impact the clinical outcome of patients with nonalcoholic fatty liver disease, future studies could concentrate on the long-term consequences of patients with Diabetes mellitus in the presence of other chronic liver diseases. While the shared comorbidity and progression between type 2 diabetes and nonalcoholic fatty liver disease is increasingly recognized, there is currently an unmet need for prospective studies using structured treatment algorithms targeting both metabolic characteristics with Diabetes, the underlying liver disease, and the combined disease simultaneously (or in sequence) to optimize clinical outcomes.

The group suggested that future research focus on evaluating the effect of lifestyle changes and structured patient education to improve treatment outcomes. Additional studies are needed to understand the pathophysiological interactions between the insulin-resistant state in affected patients. Besides the issue of Diabetes and chronic liver disease progression, future studies could also concentrate on the socio-economic implications of living with both diseases, the impact of comorbid chronic liver disease on diabetes-related micro- and macrovascular complications, and liver cancer risk and prognosis in patients with type 1 and type 2 diabetes.

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