Review Article

Incidence of *Diabetes Mellitus* in Patients Having Chronic Hepatitis B &C

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Abstract

Chronic hepatitis C virus (HCV) and diabetic mellitus (DM) are two public health issues that have a significant financial impact on health-care systems. Hepatitis, cirrhosis, and hepatocellular cancer are all symptoms of HCV infections. They've also been linked to the pathogenesis of extrahepatic symptoms, such as metabolic illnesses like diabetes mellitus. Longitudinal and cross-sectional studies have found that people with chronic HCV infections had a greater incidence and prevalence of diabetes than those of HBV sufferers. Chronic HCV infections are accelerated histologically and clinically and lead to Diabetes mellitus. With the development of novel treatments like as direct-acting antiviral agents that enhance glycemic control in these individuals, therapy has recently progressed.

Keywords: Chronic hepatitis, diabetic mellitus, cancer, cirrhosis.

INTRODUCTION

Hepatitis is an inflammation of liver occurring worldwide and is a major reason of deaths and sickness [1]. Among five types of hepatitis, Hepatitis A,B,C,D,E, Hepatitis B and C are widespread and lead to chronic diseases. It can be acute or chronic. If it ends in six months acute hepatitis results but if it lasts for more than six months and prolongs for years it become chronic. An estimated 354 million people worldwide live with hepatitis B or C.

Hepatitis B is a Liver disease caused by hepatitis B virus. Virus is a blood bornePathogen invades the liver tissues, and start multiplication results in hepatic inflammation which results in liver damage. Hepatitis B undiagnosed for many years can silently damage the liver without showing symptoms [2]. Initialviral entry signs and symptoms including joint pain, abdominal pain, dark urine, fever, yellowing of skin, and fatigue. Low Albumin level, and High AST, ALT levels indicate liver damage [3]. HBV is transmitted by contact with contaminated blood, reuse of contaminated needles, sexual contact, and blood transfusion.

Hepatitis C virus belongs to Flaviviridae family having single stranded RNA (ssRNA) with a positive-sense genetic material of about 10 kb [4]. HCV strains are categorized into a variety of heritably discrete classes, recognized as isolates, subtypes, quasispecies, and genotypes, by their elevated amount of hereditary diversity [5]. Hepatitis C has no symptoms at first, but if gone untouched, it can direct to chronic liver disease [6]. Because of unsafe medical procedures and an inadequate healthcare delivery system in hospital settings, HCV is a major problem in Pakistan, with terrifyingly elevated incidence range of 4.5-10% [7]. According to studies, in Sialkot 15.6 % blood donators are HBV and HCV carriers [8].

About 240 million citizens globally have HBV chronic infection, while 150 million have HCV infection claimed by World Health Organization (WHO, 2014) [9]. Diabetes is a group of metabolic illnesses begin by insulin reaction, insulin secretion, or a combination of two [10]. With a prevalence of 6.9%, Pakistan, a lower-middle-income country, is currently ranked 4th in the world in terms of diabetic cases. A large portion of Pakistan's population remains undiagnosed, of about 7.9 million people [11]. Diabetes mellitus is classified in two types Type-1 and Type-2 diabetes.

Type 1 diabetes is characterized by pancreatic β cells destruction due to an autoimmune mechanism. It leads to complete insulin deficits and accounts for 5-10% of DM cases [12]. Type 2 diabetes affects for 90% to 95% of diabetic people. It is characterized by insulin

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resistance and varying degrees of insulin deficit. It can also direct to increased glucose production in the liver [13].

Mechanism Involvedin HCV induced Diabetogenic action

Hepatitis C virus (HCV) infections and diabetes mellitus (DM) are two of the most serious

public health issues confronting health-care systems across the world [14, 15]. In glucose metabolism, the liver plays a crucial function. Alterations in glucose homeostasis, carbohydrate intolerance, and insulin resistance are common in chronic liver disorders, which can lead to diabetes [16, 17].
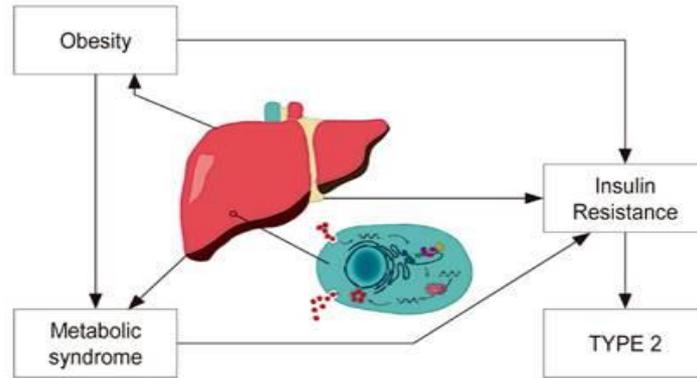

Figure 1: Relationship between HCV and metabolic abnormalities [17]

Apoptosis is not triggered directly by the viruses. Liver cells infection stimulates the innate and adaptive immune systems, triggering an inflammatory response that results in cellular damage and death, including viral-induced apoptosis via the death receptor-mediated signaling pathway. Individuals with a weakened immune system are more likely to acquire chronic infection. Natural killer cells (NK cells) i.e. Type I interferon's are the key drivers of the early innate response and are responsible for creating a cytokine environment. Natural killer cell activity is decreased in chronic Hepatitis B and C [18].

HCV and Type-2 Diabetes mellitus

Higher frequency of Type 2 Diabetes mellitus among HCV patients is the outcome of inflammatory cytokines and HCV viral particles cause change in insulin sensitivity [19]. Insulin résistance was mainly observed in peripheral tissues such as skeletal muscle tissues rather than in liver. HCV induced insulin resistance do overproduction of tumor necrosis factor alpha (TNF-α) which results in increased lipolysis in different adipocyte genes expression by TNFα-induced insulin resistance which results in insulin resistance due to lipid metabolism dysfunction. Along TNF-α, some other cytokines such as IL-6 and numerous adipokines have a role in pathogenesis of HCV-induced IR as well in steatosis of nonalcoholic fatty liver disease [20].
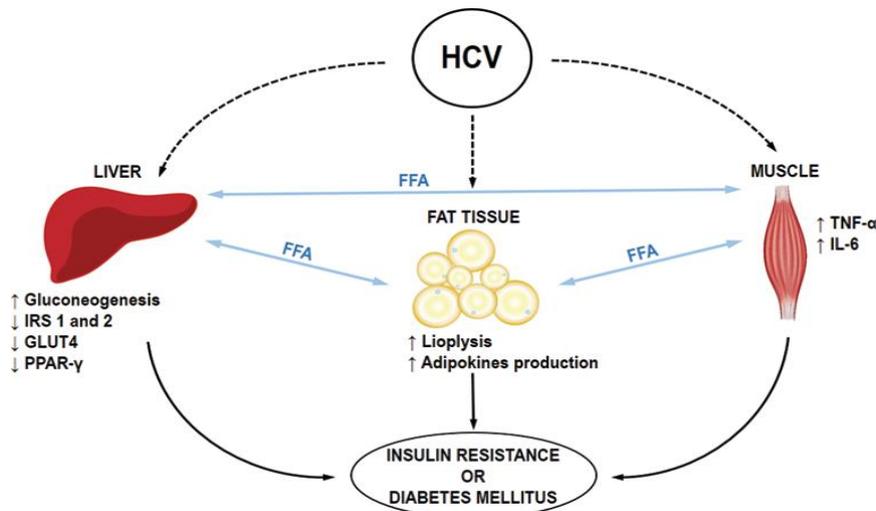
Figure 2: Pathophysiological mechanism of HCV-induced insulin resistance [20]

Diagnostic Tests

For hepatitis diagnosis Liver functioning tests are done with a physical exam and medical history. ALT, AST, ALP, LDH, and GGT these enzymes are found in the liver and are all related. With a positive Hepatitis B/C antigen test and the abnormal liver enzyme tests, it can be concluded that the person is suffering with Hepatitis B/C.

Table 1: Criteria for diagnosis of DM

Criteria	Quantity
Random blood glucose*	≥ 200 mg/dL
Fasting blood glucose*	≥ 126 mg/dL
OGTT*	≥ 200 mg/dL
HBA$_{1C}$	≥ 6.5 %

* HBA$_{1C}$: glycosylated hemoglobin; OGTT: oral glucose tolerance test.

Prevention

The probable link between HCV infections and the development of diabetes necessitates the implementation of preventative measures. These should be focused on lifestyle adjustments that can lower the chance of acquiring DM and HCV infections, as well as routine screening for DM in HCV patients, as well as examination of additional risk factors such obesity, dyslipidemia, and alcohol use that can hasten the advancement of both. People should be given proper awareness to overcome further disease spread [21].

Vaccination against viral hepatitis B is proved to be a unique tool to prevent hepatitis. Earlier studies examined the improvement of insulin resistance after successful treatment with interferon and ribavirin therapies in HCV patients [22]. Glycemic control appears to improve HCV treatment with newer direct-acting antiviral drugs (DAA) in both DM and non-DM patients, according to clinical trials [23, 24]. Additional research is needed to enhance preventive strategies and promote suitable and cost-effective programmes for diabetic individuals with chronic HCV monitoring and treatment. Two illnesses, diabetes mellitus and chronic HCV, should be treated with a multifactorial approach.

Table 2

Age	Location	Screened population	Findings	References
4 to 17 years old	District, Azad Jammu Kashmir and Bagh	300 children (150 men and 150 females)	Blood transmissionfound to be a major and frequent threat element for the HBC and HCV spread and Liver sickness worldwide, with hepatitis C virus most widespread in Pakistan.	[24]
age: 55 ± 14 years	Hospital Jean-Verdier, (Paris)	152 chronic hepatitis C patients and 152 controls (69 males and 83 females)	Diabetes mellitus is more common in chronic hepatitis C patients than in individuals with other liver illnesses, findings imply that hepatitis C virus infection plays a role in the development of diabetes.	[25]
mean age of 53 ± 10	Duhok province, Iraqi Kurdistan	375 patients (125 males and 250 females)	Among the risk factors drunkenness was linked to both HBV and HCV infections in diabetic patients,. Hemodialysis was found to be another risk factor for HCV transmission in diabetic individuals with end-stage renal disease (ESRD), but not for HBV.	[26]
5–65 years	Swat area of northern Pakistan	590 persons (290 males and 300 females)	Hepatitis B and C are the most common blood-borne hepatic illnesses globally. HCV illness discovered to be the most common liver infection in community, leading to the conclusion that viral hepatitis among the seemingly healthy population and pollution-free environment is due to an alarming situation regarding liver infections, particularly HCV.	[27]
age group 24-34 years	Gujarat	250 patients (100 males and 150 females)	Stated that Hepatitis C virus sufferers were found to be more affected by diabetes as well as Diabetes incidence was observed to be more in women (60%) than that of men (40%)	[28]
adult subjects	United States of America	15,316 subjects (7,411 males	There is more threat of suffering with diabetes in patients who are hepatitis c infected individuals.	[29

Age	Location	Screened population	Findings	References
(20 y/o)	(California, Taiwan)	and 7,905 females)	Substantially less is thought about the hepatitis B infection (HBV) disease in diabetes. Serology proof that Effective HBV vaccination was connected with a decrease of diabetes.	
16->50 years	Punjab province Pakistan	58,680 clinically healthy, adult men,	Men from Multan (9.6%) had the highest rate of HCV seropositivity, followed by Lahore (9.4%) while those of the Bahawalpur district had the lowest rate (5.0%). General observation was Men from all districts had a gradual rise in seroprevalence as they grew older.	[30]
<15->60 years age	Malakand Division of Northern Pakistan	950 (750 males and 200 females)	Higher incidence of HBV illness was observed in urban areas of Northern Pakistan because of the government insufficient involvement as well as weak sanitized steps. To prevent the Hepatitis B virus disease outbreak, it's recommended that people be made aware of the potential risk factors and that immunization be extended to rural areas.	[31]
15-25 and 37-45 year age group	Teaching Hospital (Mansehra) and PAF Hospital (Islamabad)	400 reproductive age pregnant females	Hepatitis was found maximum in low-income pregnant women and minimum in high-income pregnant women and found to be most common in the second trimester and least common in the first trimester. Incidence of hepatitis was highest in the 15-25 year age group and lowest in the 37-45 year age group.	**[32]**
males mean age 53.2 ± 1.4 years	Hippokration General Hospital, Athens, Greece	189 outpatients and 189 control subjects (all males) 81 CHB and 108 CHC and	Oral glucose tolerance test (OGTT shows a higher frequency of glucose intolerance among chronic hepatitis B and C sick persons when contrasted by growth, gender, and body mass index. glucose resistance is hugely common among persistent HCV patients than in persistent HB sick persons.	[33]
mean age 45.8 ± 15.11 years,	China	1783 patients 389 CHB patients 1343 no CHB 207 patients with the DM	In CHBSick persons increased viral number, long duration of illness, and the prevalence of hepatic cirrhosis, and alcoholic steatosis had the greatest risk of adult onset diabetes mellitus/ Type-2 diabetes mellitus T2DM development. Diabetes mellitus (DM) is connected with higher threat of hepatic illness and fatality among sick persons through persistent hepatitis B	[34]
young person men with ages range 17–22 years	Punjab and Sindh, North-West Frontier province, Baluchistanand Azad Kashmir	5707 younger man examined, 95 were HCV effected and 167 were found HBV effected	The prevalence of HBsAg in Punjab and Sindh provinces were significantly higher than in North-West Frontier province, Baluchistan and Azad Kashmir However, the prevalence of anti-HCV in Punjab (1.92%) was lower than in Sindh (4.14%). In order to control Hepatitis spread Health education to the general public, including barbers, would be an important tool.	[35]
18-60 years age	Khaniwal, Faisalabad, Gujranwala, Sialkot, Bahawalpur Multan, Lahore district of Punjab Province	5914 blood donors, 5840 (98.74%) were male and 74 (1.25%) were female	Findings indicate that The government drug enforcement agencies should use HCV core antigen detection and combo testing to avoid false positive HCV results as these is much safer screening methods for HCV detection and that using these methods will help to prevent the disease from spreading further.	[36]

Age	Location	Screened population	Findings	References
mean age 46.56 years) less than 60 years-old	China	507 subjects (243 men and 264 women;	Persistent viral contaminations, for example, the hepatitis C infection (HCV) and human immune system can decrease the muscle's reaction to insulin, in this manner causing insulin obstruction. Furthermore, insulin resistance is linked to hepatic steatosis.	[37]
mean age 44.2 ± 12 years	France	Total 123 79 males, 44 females	Viral components are linked to metabolic disorders (DM) among persistent hepatitis C ill persons. Findings suggest that ageing, chubbiness, extreme hepatic fibrosis, METAVIR fibrosis and a family history of diabetes were all found to be predictive of DM with HCV patients.	[38]
52±12 years age	Eastern Europe, North Africa, Middle East and Asia.	45 HCV patients 88HBV patients control group of 90 subjects	When patients with and without diabetes were compared, it was discovered that having a healthy family history of diabetes, having the HCV Ib genotype, and having a more extreme liver histology strongly linked to DM.	[39]
20-60 years age	United States of America	9841 persons	According to research, those over 40 with HCV infections had three times the risk of developing type 2 diabetes is not infected. There was no evidence of a link to TYPE 1. People with type 2 diabetes were more likely to be older, have a high BMI, and have a poor socioeconomic position.	[40]
HCV 47.7-8.9 Control group mean age 48.2 9.4	Johns Hopkins Hospital, Baltimore, Maryland, U.S.	97 cirrhotic patients with HCV (cases) with 194 HCV-negative patients with cirrhosis	Age, obesity, DM in the family,African-American ancestry, and HCV and HIV coinfections are all risk factors for the development of DM.	[41]
Adults between the age of 18-90 years	Five districts of Punjab (RahimYar Khan, Multan, Bahawalnagar, Faislabad and Sialkot) in Pakistan	343 adults (113 males 230 females)	stated that in low-resource countries, like Pakistan,The general public has little understanding of diabetes risk factors, management, and care. To improve understanding of diabetes prevention and treatment, private teaching campaigns must be administratedat national level to progress diabetes stoppage.	[26]

Every research work has its own limitations and research gap. Because of the lack in proper prospective research studies, the clinical impact of successful antiviral medication on the long-term prognosis of T2DM in diabetics with CHC is yet unclear [44]. The findings based on secondary data obtained for the goal of determining the *Diabetes Mellitus* pervasiveness in individuals suffering by persistent hepatitis B and C is one limitation. Results of the study may not be completely generalized and figures may not be accurate, due to restricted number of samples and non-availability of resources. Because in most studies, particularly in Pakistan, the population sample selected is limited to a particular area. Hence, the sample size may not be representative of the whole district population and Studies on understanding the epidemiology of viral hepatitis and related risk factors are limited.

This work should be extended in different areas specifically in backward, rural areas to overcome this issue. Resources should be made available and funding should be provided so that large sample size can be gathered for authentic research study and for public benefit to cope with such diseases [45]. There is an urgent need for the implementation of preventive and control strategies to halt the rapid increase in seroprevalence of HBV and HCV. To curb the fast growth in HBV and HCV seroprevalence, preventative and control techniques must be implemented immediately. Health practitioners must be trained. The long-term and appropriate funding of public-sector hepatitis initiatives is likewise a critical issue that should not be neglected [46].

CONCLUSION

HCV and DM infection are two diseases that have a significant influence on global health and health care. The high frequency of type 2 diabetes in HCV patients with chronic hepatitis corresponds to evidence that the virus is a risk factor for the development of diabetes and other carbohydrate metabolism disorders. Direct viral impacts, insulin resistance, inflammatory cytokines, and other immune driven processes appear to be involved in the association of HCV with DM. Additionally; HCV-infected people have a greater frequency of diabetes than those infected with the hepatitis B virus (HBV).Age, obesity, family histories of diabetes, and HCV-HIV coinfections are all risk factors for the development of diabetes in patients infected with HCV. Glycemic control and insulin resistance are improved with DAA therapy. Additional research are needed to improve prevention policies and promote adequate and cost-effective programs for diagnosis, treatment and monitoring of diabetic patients with chronic HCV.

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