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Development of Diabetes Mellitus in Chronic Hepatitis B- Decompensated Cirrhotic are at Most Risk

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ABSTRACT

Introduction - Chronic Hepatitis B (HBV) is associated with an increased risk of developing Type 2 diabetes. HBV can impair the liver's ability to process glucose, disrupt metabolic function, and cause systemic inflammation that contributes to insulin resistance. Chronic inflammation from HBV infection can interfere with the metabolic action of insulin, increasing insulin resistance throughout the body. Liver is central to maintaining blood sugar balance. HBV-related liver damage or cirrhosis impairs the liver's ability to store and process glucose, raising diabetes risk. Some studies suggest the Hepatitis B virus can replicate in the pancreas, directly damaging the insulin-producing beta-cells.

Aim of study- To estimate prevalence of development of Diabetes Mellitus in Chronic Hepatitis B patients at tertiary care center of Northern India.

Material and Methods- This study was conducted at Medical Gastroenterology Department at PGIMS, Rohtak**.** It was a prospective study done over five years, from 01.05.2021 to 30.04.2026, during which 300 confirmed hepatitis B patients were investigated for development of diabetes mellitus. For better understanding 100 patients each of inactive carrier, chronic hepatitis on antiviral treatment, cirrhotic patient on antiviral treatment were enrolled. Out of total pool of 300 HBV patients, 186 (62%) were male and 114 (38%) were female. The age group was between 20 yrs- 80 yrs with mean age of 45 years. Patient was labelled diabetic, if blood sugar fasting and post prandial was more than 126mg% and 200 mg% respectively or HbA1C was more than 6.5. Pre-diabetic was defined as blood sugar fasting and post prandial was 100-126mg% and 140-200 mg% respectively or HbA1C was between 5.7- 6.5. All patients who were having HBV infection for at least three years were included in the study. All hepatitis B patients were confirmed on HbsAg on Enzyme linked immunosorbent assay (ELISA) test and HBV DNA Quantitative on Polymerase chain reaction test (PCR). The written informed consent was taken before enrollment in the study.

Observation and Results- Our department is Model treatment Center (MTC) under National Viral Hepatitis Control Program (NVHCP) and is one of the high flow centers in India. On daily basis, 8-10 new and 40 follow up patients of HBV come for consultation and till date 12,000 HBV patients have been enrolled in last twelve years in this program. On prospective analysis of 300 confirmed hepatitis B patients. Out of total pool of 300 HBV patients, 100 patients each of inactive carrier, chronic hepatitis on antiviral treatment, cirrhotic patient on antiviral treatment were enrolled. The new onset diabetes mellitus was seen in 3% of inactive carrier, 10% of chronic hepatitis B on antiviral treatment because of significant fibrosis and 50% of cirrhotic patients. In cirrhotic also, majority were decompensated. On Pre-diabetic analysis, 10% were seen in inactive carrier group, 19% in chronic hepatitis with significant fibrosis and 30% in cirrhotic patients, predominantly in decompensated stage.

Conclusion – There is increased risk of developing diabetes mellitus in HBV patients, especially in cirrhotic stage. The new onset development of diabetes

mellitus is directly proportional to advancement of HBV disease from inactive carrier stage to chronic hepatitis with F2 fibrosis to cirrhotic from compensated to decompensated stage. Hence, all efforts should be done to prevent HBV patient to progress to advanced stage which can be achieved by abstinence from alcohol & smoking, maintaining normal BMI and regular treatment with antiviral wherever indicated.

Keywords*: Hepatitis B, HbsAg, HBV DNA Quantitative, Diabetes Mellitus, Inactive carrier, Chronic hepatitis, Cirrhosis.*

INTRODUCTION

Chronic Hepatitis B (CHB) promotes diabetes (T2DM) by inducing liver damage, which impairs glucose metabolism, and causing systemic inflammation that creates insulin resistance. Additionally, the virus can directly attack pancreas cells. Patients with both conditions face an increased risk of liver fibrosis, cirrhosis, and liver cancer. Research indicates that individuals with Hepatitis B surface antigen (HBsAg-positive) have a significantly higher risk of developing diabetes compared to uninfected individuals. However, antiviral treatments and Hepatitis B vaccinations lower this diabetes risk by suppressing viral replication and preserving metabolic function. Chronic liver inflammation alters normal metabolic pathways and decreases the body's sensitivity to insulin. Hepatitis B virus can replicate in extrahepatic sites, such as the pancreas, directly impairing insulin-producing beta -cells. Liver damage hinders the liver's ability to regulate blood glucose, contributing to erratic blood sugar levels. Medications that inhibit HBV replication can reduce the onset of diabetes and improve metabolic control. Certain diabetes medications like metformin and thiazolidinediones not only manage blood sugar but may also reduce the risk of hepatocellular carcinoma (HCC) in CHB patients.

AIM OF STUDY

To estimate prevalence of development of Diabetes Mellitus in Chronic Hepatitis B patients at tertiary care center of Northern India.

MATERIAL AND METHODS

This study was conducted at Medical Gastroenterology Department at PGIMS, Rohtak**.** It was a prospective study done over five years, from 01.05.2021 to 30.04.2026, during which 300 confirmed hepatitis B patients were investigated for development of diabetes mellitus. For better understanding 100 patients each of inactive carrier, chronic hepatitis on antiviral treatment, cirrhotic patient on antiviral treatment were enrolled. Patient were labelled diabetic, if blood sugar fasting and post prandial was more than 126mg% and 200 mg% respectively or HbA1C was more than 6.5. Pre-diabetic was defined as blood sugar fasting and post prandial was 100-126mg% and 140-200 mg% respectively or HbA1C was between 5.7- 6.5. All patients who were having HBV infection for at least three years were included in the study. All hepatitis B patients were confirmed on HbsAg on Enzyme linked immunosorbent assay (ELISA) test and HBV DNA Quantitative on Polymerase chain reaction test (PCR). The written informed consent was taken before enrollment in the study.

OBSERVATION AND RESULTS

Our department is Model treatment Center (MTC) under National Viral Hepatitis Control Program (NVHCP) and is one of the high flow centers in India. On daily basis, 8-10 new and 40 follow up patients of HBV come for consultation and till date 12,000 HBV patients have been enrolled in last twelve years in this program. On prospective analysis of 300 confirmed hepatitis B patients. Out of total pool of 300 HBV patients, 100 patients each of inactive carrier, chronic hepatitis on antiviral treatment, cirrhotic patient on antiviral treatment were enrolled. Out of total pool of 300 HBV patients, 186 (62%) were male and 114 (38%) were female. Patients predominantly belonged to rural area (195, 65%) in comparison to urban areas (105, 35%). The age group was between 20- 80 yrs with mean age of 45 years. The new onset diabetes mellitus was seen in 3% of inactive carrier, 10% of chronic hepatitis B on antiviral treatment because of significant fibrosis and 50% of cirrhotic patients. In cirrhotic also, majority were decompensated. On Pre-diabetic analysis, 10% were seen in inactive carrier group, 19% in chronic hepatitis with significant fibrosis and 30% in cirrhotic patients, predominantly in decompensated stage. On analysis for development of diabetes mellitus and pre-diabetic stage, there was no statistical difference on gender or residential basis. Majority of patients who developed diabetes and prediabetic state were decompensated cirrhotic and maximum were above 45 years of age.

Table 1- Showing Gender and Residential distribution in total pool of HBV Patients

Total HBV Patients	Males	Females	Rural Background	Urban Background
300	186 (62%)	114 (38%)	195 (65%)	105 (35%)

Table 2- Showing prevalence of Development of Diabetes Mellitus and Pre-Diabetic Stage in various groups of HBV Patients

Total HBV Patients	Chronic Hepatitis-Inactive Carriers- F0-F1 Fibrosis	Chronic Hepatitis B- F2 -F3 Fibrosis- On antiviral treatment	HBV Related Cirrhosis- F4- On antiviral treatment
300	100	100	100
Developed Diabetes Mellitus	3 (3%)	10 (10%)	50 (50%)
Developed Pre-Diabetic Stage	10 (10%)	19 (19%)	30 (30%)

DISCUSSION

Chronic hepatitis B (CHB) is a prevalent infectious disease affecting approximately 4.1% of the global population. **[1]** Hepatitis B virus (HBV) infection has significant deleterious effects on the liver, including decompensation, cirrhosis, and hepatocellular carcinoma (HCC). **[2,3]** Moreover, as the liver plays a crucial role in glucose homeostasis, hepatic injury may lead to disturbances in glycometabolism, thereby elevating the risk of type 2 diabetes mellitus (T2DM). **[4,5]** This metabolic condition is associated with a spectrum of multi-organ comorbidities and increased mortality rates. **[6]** Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder among individuals with chronic hepatitis B (CHB), contributing to additional adverse impacts on both hepatic and extrahepatic systems. Existing evidence suggests a potential positive association between CHB and the development of insulin resistance and T2DM. The presence of T2DM in CHB patients is associated with an increased risk of liver fibrosis, cirrhosis, decompensation, and hepatocellular carcinoma (HCC) occurrence. Moreover, it elevates the risk of non-liver cancers and all-cause mortality in this population. T2DM also serves as the key element in metabolic dysfunction-associated steatotic liver disease, which is prevalent in the CHB population. **[7]** There is controversial correlation between HBV infection and DM. Some studies showed no interaction between the two diseases **[8-11]**; however, a meta-analysis encompassing 15 eligible studies demonstrated that CHB patients exhibited a higher prevalence of DM (8.2%) compared to uninfected controls, particularly prominent in the Asia-Pacific region (OR 1.67). **[12]** A cross-sectional study conducted in China, T2DM patients displayed a higher proportion of HBV infection than non-diabetic controls. **[13]** Beyond prevalence, CHB also influences the incidence of T2DM. A prospective cohort study involving 55,520 Chinese participants reported that individuals with resolved HBV infection or current CHB had a higher risk of developing T2DM than uninfected counterparts during an average follow-up period of 5.6 years. **[4]** Furthermore, a cross-sectional study enrolling 7880 Korean adults receiving health examinations showed that CHB was more associated with insulin resistance determined by the Homeostasis Model Assessment than uninfected individuals. **[14]** Collectively, these findings suggested that the burden of T2DM may be heightened in the CHB population compared to the general population, warranting prompt evaluation and management strategies. The presence of DM will exacerbate liver injury in CHB patients and result in higher risks of hepatic fibrosis and HCC occurrence. **[15]** The process of hepatocarcinogenesis may be mediated by the hyperglycemia- and hyperinsulinemia-induced complicated pathways of lipotoxicity, oxidative stress, and inflammation. **[16]** In our study pool, the characteristic thing noted was that chronic hepatitis B patients in inactive carrier stage, does not lead to development of diabetes mellitus or pre-diabetic stage in significant number of patients. In total 13 % patients developed DM or Pre-Diabetic stage (3% DM & 10% Pre-Diabetic stage). The risk increased to 29% (10% DM & 19% Pre-Diabetic stage) in F2-F3 fibrosis stage. There was huge increase once when patient reached cirrhotic stage, 80 patients (50% DM & 30% Pre-Diabetic stage). Out of these 80 cirrhotic patients, 55 (68.75%) were decompensated. Our study is in alignment with previous studies and supports that HBV patients are at risk of developing type 2 DM but its maximum risk is in decompensated cirrhotic and inactive carriers have no additional risk, whereas HBV patients with F2-F3 fibrosis are midway between the two. As, inactive carriers are also having viral but still not developing DM which hints that its not the prescence of HBV which is responsible for causing type 2 DM but when this virus causes damage on liver, as evidenced by fibrosis or cirrhosis, leads to development of DM. In general, prevalence of developing DM is 30% but in our study group it was 50% which is significantly high. Hence, it thrusts that all maneuvers should be done to prevent advancement of disease in HBV patients. It will lead to decreasing complications, including development of DM and HCC, hence further leading to overall morbidity and mortality associated with HBV.

CONCLUSION

The rising prevalence of T2DM among individuals with CHB, mandates identifying high-risk patients and implementing rigorous monitoring and treatment approaches to enhance prognosis. There is increased risk of developing diabetes mellitus in HBV patients, especially in fibrotic and cirrhotic stage. The new onset development of diabetes mellitus is directly proportional to advancement of HBV disease from inactive carrier stage to chronic hepatitis with F2 fibrosis to cirrhotic from compensated to decompensated stage. Hence, all efforts should be done to prevent HBV patient to progress to advanced stage which can be achieved by abstinence from alcohol & smoking, maintaining normal BMI and regular treatment with antiviral wherever indicated**.**

Conflict of Interest- The authors have no conflicts of interest to declare. No financial support was taken for the same.

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