Incidence of Diabetes Mellitus in Patients with Hepatitis B and C virus Infection

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ABSTRACT

BACKGROUND: Several studies from different parts of the world have found that 13% to 33% of patients with chronic hepatitis have associated diabetes, mostly type II Diabetes Mellitus (DM). Therefore, it is important to identify the magnitude of the problem of diabetes in order to optimize the treatment of chronic hepatitis.

OBJECTIVE: To see the association of diabetes mellitus with hepatitis B or C in patients suffering from HBV or HCV related liver disease.

MATERIAL AND METHODS: The study design was observational that did not involve any ethical issues. The sample size was 150. Hepatitis B and C was confirmed by performing PCR on fully automated Abbott Molecular M2000 real-time system and Diabetes Mellitus was confirmed by performing HbA1c test on fully automated instrument 'Abbott Architect ci8200'

RESULTS: The results indicated that 21.6% of HBV positive cases were found to be Diabetic and 16.2% were found to be at High Risk to Diabetes. While 28.4% of HCV positive cases were found to be Diabeticand19.4% were found to be at High Risk to Diabetes.

CONCLUSION: It is concluded that a strong correlation is present between both Hepatitis B or C and Diabetes Mellitus as the incidence of Diabetes Mellitus is much increased in patients with Hepatitis B or C virus infection.

Key Words: HBV, HCV, Diabetes Mellitus, HbA1c, PCR

INTRODUCTION

HCV has been found to be a major cause of liver disease and liver cirrhosis. According to World Health Organization (WHO) 3% of world's population is currently infected with Hepatitis C virus infection more than 170 million people are chronic carriers of Hepatitis C virus and are at a high risk of developing Hepatocellular Carcinoma (HCC) 3% to 4% of chronically infected individuals develop fatal Hepatocellular Carcinoma. As a non-cytopathic hepatotropic virus, HCV induces acute or chronic liver disease and interacts in a complex way with the immune system. The immune system contributes both to viral infection control and healing as well as in developing chronic infection and liver cirrhosis [(1).] HCV pathogenesis starts after the viral entry into host cells. Interactions between HCV and host immune response (Innate and Adaptive) in the first weeks after entry of virus into host cells may substantially influence the subsequent evolution and the prognosis of infection [(2)].

Viral Entry

HCV is a blood- transmitted virus that reaches the liver via circulation. The CD81 molecule on host cell surfaces acts as a viral receptor, which binds with the viral particle and facilitates its entry in the liver cell [(3)]. The viral envelop protein, E2, binds to the major extra cellular loop of CD8. HCV shows multi-site binding and can also bind to several other molecules. E2 is the most variable viral protein, and therefore, its interactions with CD81 have been reported to be strain-specific [(4)].

Immunopathogenesis

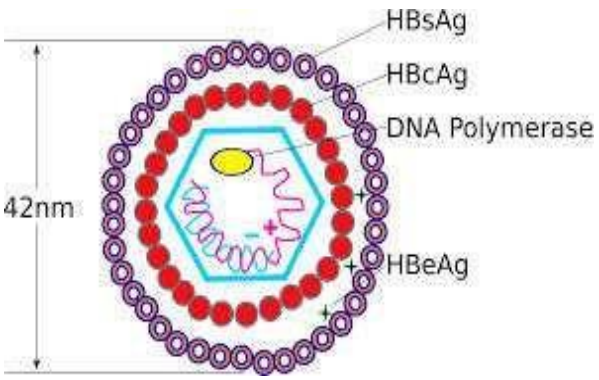
After entry and replication of the virus inside liver cells, the viral molecules are transported to t148he endoplasmic reticulum and associate with major histo compatibility complex (MHC) molecules, which are finally transported to the cell surface. These molecules on the cell surface are recognized by T cells for their immune action. The majorities of Cytotoxic T Lymphocytes (CTLs) are $CD8^+$ and recognize antigens presented on MHC class I molecules. Approximately 10% of CTLs are CD4+ which recognizes antigens presented on MHC II molecules. These CTLs eliminate cells infected with virus, which causes the death of

Hepatocyte sand leads to the Hepatocellular Carcinoma. Thus; CTLs play a major role in immune pathogenesis of HCV infection [(5)].

Diagnosis of HCV

Currently, analysis of hepatitis C infection depends on documentation of Anti-HCV antibodies in serum. A little extent of acute HCV diseases (and chronic infections as well) are serum negative as dictated by Enzyme Linked Immuno Sorbent Assay (ELISA). This can happen in patients with disabled insusceptibility, which can't create a recognizable dimension of hostile to HCV antibodies or in whom immune response generation is postponed. Another circumstance is viral flexibility, which can happen without counter acting agent creation or can be related with a fast loss of them (6).In these cases, intense HCV contamination must be affirmed utilizing RT-PCR.

Hepatitis B



HBV virions are double-shelled particles, 40 to 42 nm in diameter, (Dane, Cameron, & Briggs, 1970) with an outer lipoprotein envelope that contains three related envelope glycoproteins or surface antigens. Within the envelope is the viral nucleo capsid, or core (7). The core contains the viral genome, a relaxed-circular; partially duplex DNA of 3.2 kb, and a polymerase that is responsible for the synthesis of viral DNA in infected cells [8].

Viral Entry and Replication

After tainting a hepatocyte, the HBV genome is conveyed in to the nuclear compartment where cell fix proteins are associated with fixing the viral genome into covalently closed circular DNA (cccDNA). This viral DNA goes about as a transcriptional format (Liang, 2009 for the age of the pre-genomic mRNA (pg mRNA), pre-center mRNA and all other sub viral mRNAs [9]. Therefore, cccDNA is chromatid into viral micro chromosome that at last fills in as an intrahepatic supply of HBV and remains for the duration of the life of the constantly tainted host [4].

Pathogenesis

The HBV replication cycle isn't specifically cytotoxic to cells. This reality agrees well with the perception that numerous HBV transporters are asymptomatic and have negligible liver damage, in spite of broad and continuous intrahepatic replication of the infection [10]. It is presently believed that have invulnerable reactions to viral antigens showed on tainted hepatocytes are the primary determinants of hepatocellular damage.

Genotypes

Generally, HBV was characterized into 4 subtypes or serotypes (adr, adw, ayr, and ayw) in view of antigenic determinants of HBsAg. In the appearance of increasingly sub-atomic methodologies, serotyping of viral strains was supplanted by different genotyping strategies [11].

Diabetes Mellitus

The term diabetes mellitus shows a metabolic issue of various etiology described by interminable hyperglycemia with unsettling influences of starch, fat and protein digestion coming about because of deformities in insulin emission, insulin activity, or both. The impacts of diabetes mellitus incorporate long haul harm, brokenness and disappointment of different organs. Diabetes mellitus may give trademark manifestations, for example, thirst, polyuria, obscuring of vision, and weight reduction. Regularly side effects are not extreme, or might be missing, and thusly hyperglycemia adequate to cause neurotic and useful changes might be available for quite a while before the finding is made. The long-haul impacts of diabetes mellitus incorporate dynamic advancement of the difficulties of retinopathy with potential visual impairment, nephropathy that may prompt renal disappointment, and additionally neuropathy with danger of foot ulcers, Charcot joints, and highlights of autonomic brokenness, including sexual brokenness. Individuals with diabetes are at expanded danger of cardiovascular, fringe vascular and cerebrovascular infection.

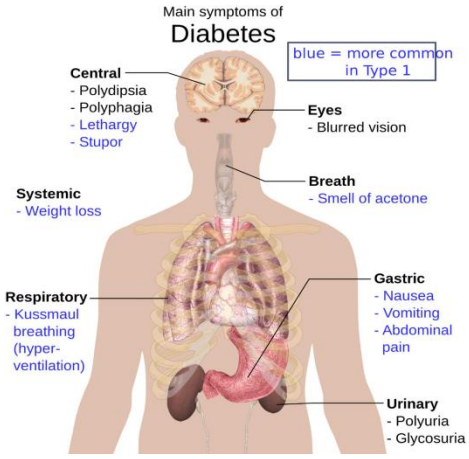


Figure 1.1: Most Common Sign and Symptoms of Diabetes Mellitus

Classification

Grouping of diabetes dependent on etiology information of the physiology of insulin discharge and activity encourages us consider the pathophysiology of diabetes. The new order of diabetes dependent on etiology is appeared as follows:

Type1diabetes: pancreatic beta islet cell destruction leading to absolute insulin deficiency

- autoimmune (most common)
- idiopathic(rare)

Type 1b presents like type 1 (with DKA), then behaves like type2

Type 2 diabetes: varying degrees of insulin resistance and insulin deficiency

Gestational diabetes other specific types [12]

Insulin Regulation

The concentration of plasma glucose level is the most important factor which controls the insulin secretion by β-Islets of Langerhans cells of Pancreas. Pancreatic Insulin secretion is regulated by multiple factors e.g. environmental (nutrition, physical exercise, etc.), amino acids, circulating hormones, neurotransmitters and paracrine factors may also modulate the expression of the diabetic phenotype.

Insulin Deficiency

Insulin deficiency is defined as a pathological condition in which there is an in appropriate decrease in the rate at which the β-cell secretes insulin. Most commonly, normal ranges for the concentration of insulin in plasma are defined as a function of the concentration of glucose in plasma. Nevertheless, because insulin secretion is a dynamic process, the levels of insulin in plasma are not constant, but vary from minute to minute throughout the day. Thus, subtle defects in β-cell function may possibly manifest as abnormalities in the rate at which insulin concentrations change as a function of time.

Insulin Resistance

Insulin resistance is a pathological condition in which there is a shift in the dose-response curve such that the magnitude of the biological response to insulin is decreased. The impaired response to insulin may be noticed either over the entire range of insulin concentrations or only at low concentrations of the hormone in body. Two types of evidence support the conclusion that patients with non-insulin dependent diabetes mellitus

(NIDDM) are resistant to the biological actions of insulin. First, patients with NIDDM have a weakened response to exogenously administered insulin. The second line of evidence is based on the observation that patients with NIDDM are resistant to the action of endogenously secreted insulin [(10)].

Diagnostic Criteria for Diabetes Mellitus

Fasting glucose is the standard measure used for the diagnosis of diabetes in the United States. Historically, Glycated hemoglobin has been recommended only for the determination of glucose control among subjects who have already received the diagnosis of diabetes. New clinical recommendations from the American Diabetes (ADA) Association advocate the use of Glycated hemoglobin in the diagnosis of diabetes, largely on the basis of the established association between Glycated hemoglobin and micro vascular disease [(13)].

Criteria for the diagnosis of diabetes recommended by WHO is:

Blood sugar fasting (BSF) ≥126 mg/dl (7.0mmol/l). Fasting glucose is defined as no food intake for at least 8h.

OR

Indication of hyperglycemia and a random plasma glucose (RPG) ≥200 mg/dl (11.1mmol/l).Random glucose measurement is defined as any time of day without regard to time since last meal. The classical symptoms of hyperglycemia include polyuria, polydipsia and unexplained weight loss.

OR

Two plasma glucose levels should be ≥200mg/dl (11.1mmol/l) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization procedure by using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

OR

An HbA1c of 6.5% is recommended as the cut point for diagnosing of diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.

The OGTT is not recommended for routine clinical use, it may be useful for further evaluation of patients in whom diabetes is still strongly suspected but who have normal fasting plasma glucose.

HbA1c

The use of the HbA1c for the diagnosis of diabetes has previously not been recommended due to lack of global standardization and uncertainty about diagnostic thresholds

HbA1c Interpretation

HbA1c is categorized in three categories that are Non-Diabetic (Normal), High Risk to Diabetes (Pre-Diabetic) and Diabetic. This is based on the different values of HbA1c test.

Methodology:

In this study, 150 Subjects confirmed for viral hepatitis were taken. Diabetes Mellitus was confirmed by Performing HbA1c test on fully automated Abbott Architect ci8200

Collection of blood samples (Venous Blood):

In this study Venous blood samples were collected for 150 confirmed viral Hepatitis positive subjects who are further investigated.

HbA1c

HbA1c test is performed to confirm the Diabetes Mellitus according to the WHO's Diagnostic criteria for Diabetes Mellitus, in those patients that are confirmed of having Hepatitis infection in PCR. Latex enhanced immunoassay method of HbA1c is used. It is based on interaction between antigen molecules of Glycated hemoglobin (HbA1c) and HbA1c specific antibodies coated on latex beads. This cross-link reaction of antibody and antigen results in changes in the solution turbidity which is proportional to the amount of the antigen in the sample.

RESULTS

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Table 1.1: Gender Distribution among subjects

Gender	Frequency	Percentage
Male	70	47%
Female	80	53%

During the study a total of 150 samples of patients were collected. Frequency of gender distribution in total cases was 80 (53%) females and 70 (47%) males (Table 1.1)

Table 1.2: Age variation among subjects

	Minimum Age	Maximum Age	Mean	Standard Deviation
Patient Age	09 Years	81 Years	39.45	14.5

The age range of patients was from 9 to 81 with a mean of 39.45 with the standard deviation of 14.5 i.e. 39.45 ±14.5. (Table 1.2)

Table 1.3: Distribution of Hepatitis B and C virus infected individuals among subjects.

	Detected	Percentage	Not Detected	Percentage
Hepatitis B	37	25%	113	75%
Hepatitis C	113	75%	37	25%

Out of total 150 subjects 37 (25%) were infected with hepatitis B virus and 113 (75%) were infected with hepatitis C virus. (Table 1.3)

Table 1.4: Gender Distribution among Hepatitis B and Hepatitis C positive cases

	Males	Percentage	Females	Percentage
Hepatitis B	26	70%	11	30%
Hepatitis C	44	33%	69	61%

In Hepatitis B positive cases frequency of gender distribution was 26 (70%) males and 11 (30%) females and in Hepatitis C positive cases the frequency of gender distribution were 44

(33%) males and 69 (61%) females. (Table 1.4)

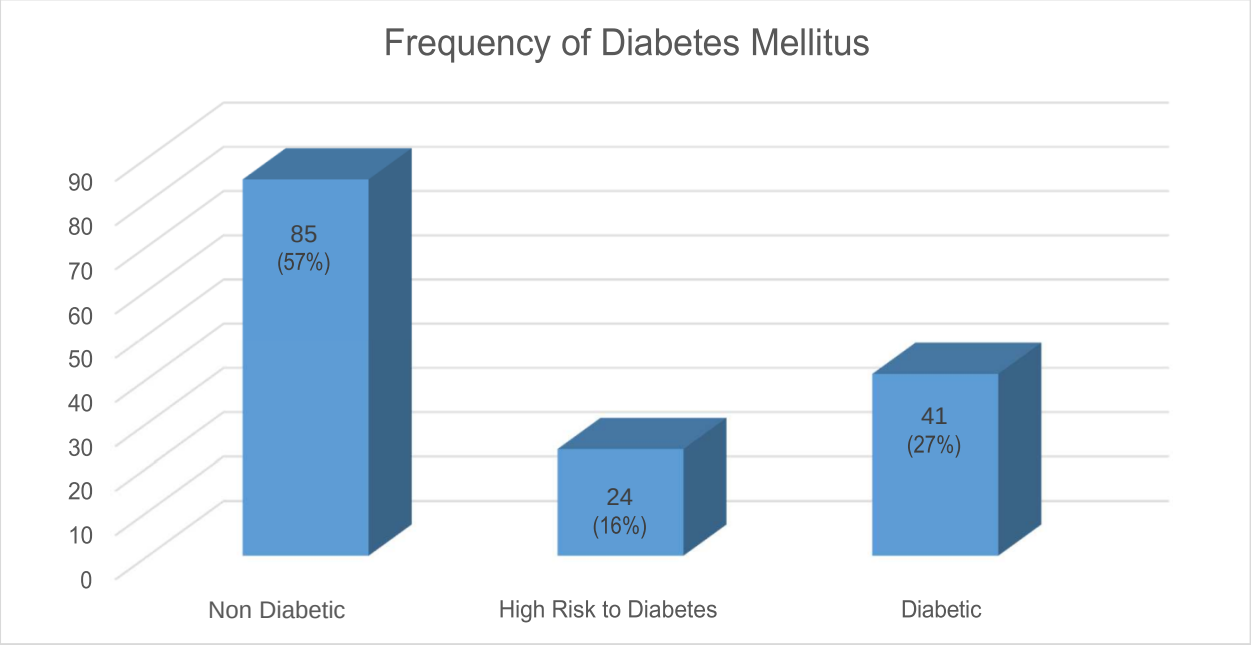
Table 1.5: Frequency of Diabetes Mellitus

HbA1cCategory	Frequency	Percentage
Non-Diabetic	85	57%
High Risk to Diabetes	24	16%
Diabetic	41	27%

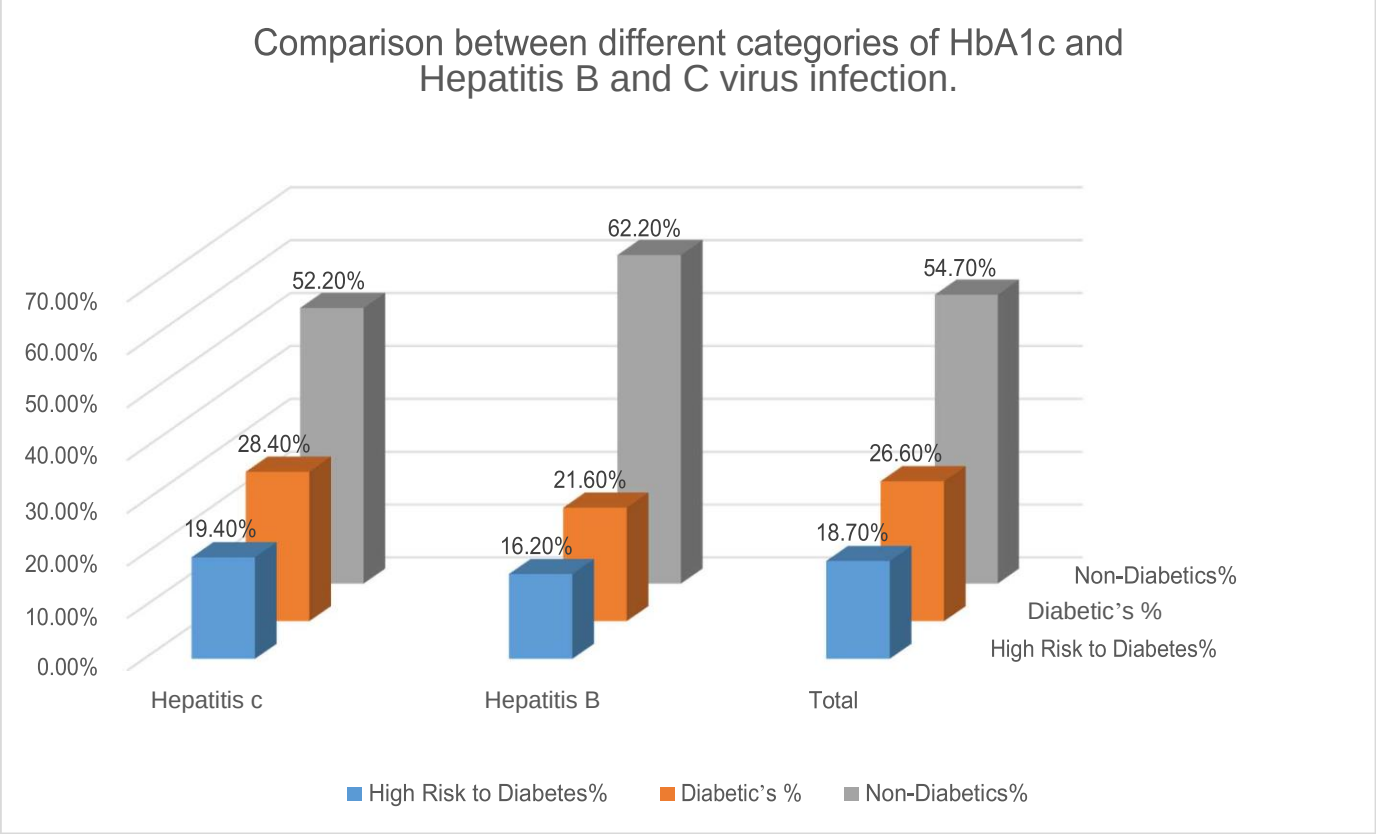
Out of these 150 subjects 85 (57%) were non-diabetic, 24 (16%) were high risk to diabetes and 41(27%) were diabetic. (Table 1.5)

Distribution of different categories of HbA1c among subjects with frequency and percentage frequency is shown in graph 1.1.

Graph 1.1: Frequency of Different categories of HbA1c among subjects



Graph 1.2: Graph showing the presence of diabetes in Hepatitis B and C virus infection



In Hepatitis C positive patients there were 22 (19.4%) were high risk to diabetes, 32 (28.4%) were diabetic and 59 (52.2%) were non-diabetic.

In Hepatitis B positive patients, it was observed that 06 (16.2%) patients were high risk to diabetes, 08 (21.6%) patients were diabetic and 23 (62.2%) were non diabetic

Out of 150 patients a total of 28 (18.7%) patients were high risk to diabetes, 40 (26.6%) were diabetic and 82 (54.7%) were non-diabetic. Which means it is very likely to become diabetic if a person gets infected by hepatitis B or C virus. (Graph 1.2 and Table 1.6)

Table 1.6: Comparison of presence of different groups of diabetes in Hepatitis B and C

	Prevalence	High risk To Diabetes	High risk to diabetes %	Diabetics	Diabetics %	Non-Diabetics	Non-Diabetic %
Hepatitis C	113	22	19.4%	32	28.4%	59	52.2%
Hepatitis B	37	06	16.2%	08	21.6%	23	62.2%
Total	150	28	18.7%	40	26.6%	82	54.7%

Discussion:

Since the discovery of the hepatitis C virus (HCV) in 1989, attention has been paid to the association of chronic HCV infection and the development of diabetes. The risk factors for diabetes include older age, HCV, severe liver fibrosis, family history of diabetes, and liver/kidney transplantation. Emerging evidence in animals and humans has shown that HCV infection induces hepatic steatosis and increases tumor necrosis factor-alpha level, both resulting in the development of insulin resistance and subsequent type 2 diabetes. Interferon is reportedly associated with improved glucose tolerance. However, interferon might enhance underlying autoimmunity against beta cells, leading to overt type 1diabetes that is genetically predisposed or give rise to hyperglycemia, resulting in the development of type 2diabetes. In light of the national epidemic of type 2 diabetes, the link between HCV and diabetes would be a major public health problem. Further clinical researches are awaited in order to effectively detect, prevent, and treat HCV-associated type 2 diabetes, which would also slow the progression of hepatitis C itself.

Conclusion:

The present study represented that it is much likely to get diabetes for those patients suffering with either Hepatitis B or C virus infection. But there are more chances of getting diabetic in patients that are suffering with Hepatitis C as compare to those patients that are suffering with Hepatitis B virus infection. It also showed that the Hepatitis B is more

common in males, but Hepatitis C is more common in females.

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