

Association of Diabetes Mellitus and Chronic Hepatitis C Infection

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The association between diabetes mellitus and cirrhosis has been speculated since decades. The hypotheses that have been put forward for this association are summarized by Hadziyiannis¹ as follows:

- a.) Diabetes could be the cause of associated liver disease because the nuclear and cytoplasmic glycogen deposit, fat deposit in the hepatocytes and perisinusoidal fibrosis seen in diabetes are also seen in liver cirrhosis. It has been proven that cirrhosis is a rare consequence 'of diabetes², but recently diabetes was implicated in the pathogenesis of cirrhosis through lesions of non-alcoholic steato-hepatitis (NASH). About 25-75% patients with NASH have diabetes and similarly 90% of NASH patients have been found to be obese. In many diabetics progression of NASH to cirrhosis has been documented^{3,4}. The known causes of chronic liver disease like HCV infection may also coexist in diabetics and thus result in cirrhosis.
- b.) The other possibility is implication of chronic liver disease in the etiology of diabetes. Liver plays a pivotal role in the carbohydrate metabolism. This metabolism is deranged in terms of impaired glucose tolerance in about 70% of the cases suffering from liver cirrhosis while frank diabetes occurs in few^{5,7}. Hyperinsulinemia, insulin resistance and hyperglucagonemia characterize this abnormal glucose metabolism. These patients with chronic liver disease develop hyperglycemia with therapeutic doses of steroids or interferon^{8,9}.
- c.) Thirdly the association of chronic liver disease with diabetes may be due to common causes like alcohol, hemochromatosis and autoimmune conditions. Hepatitis B and C are common liver diseases and they tend to occur more in diabetics than in general population. Frequent parenteral exposures in diabetics may be the cause of this high association of HBV and HCV infections. Extra hepatic sites of viral replication i.e. kidneys, pancreas, spleen etc. may also produce many comorbid conditions especially in relation to organ of extra hepatic manifestation^{7,10,11}.

There are several studies pointing to possible link between HCV infection and Type 2 Diabetes Mellitus¹². In one of the retrospective studies on 100 orthotopic liver transplantations for end stage liver disease, Type 2 Diabetes Mellitus was found in 50% of the cases with HCV related liver cirrhosis vs 9% in patients having liver disease unrelated to HCV⁷. In another study there was an increased incidence of HCV infection in 200 Type 2 Diabetes Mellitus patients recruited from UK for a prospective study¹³. Reports from Europe, Middle East and North America also show an increased prevalence of diabetes in patients having chronic liver disease when compared with other chronic liver diseases like primary biliary cirrhosis, primary sclerosing cholangitis, alcoholic liver disease or for that matter chronic HBV related disease¹⁴⁻²⁰.

Mason et al reported a case controlled study on the association of chronic hepatitis C with diabetes mellitus²⁰. Though many studies have been done in the past to see this association but the study by Mason et al deals systematically with all known causal possibilities in relation to diabetes and chronic liver disease. In this study all possible factors related to abnormal glucose handling were excluded. The prevalence of diabetes was found to be higher in HCV related chronic liver disease (21%) than in chronic HBV (12%). Moreover prevalence of chronic HCV infection was much higher in diabetics (4.2%) than in controls (1.6%). Similar association was reported in advanced liver disease cases when

transplant was not available.

The food for thought is - should diabetes be included in the list of extrahepatic manifestations of HCV infection? The reasons for debating this association is the chances of introduction of HCV infection in diabetics as a result of frequent admissions and venepunctures that occur in these patients. Moreover, chronic HCV infection in adults has a very high transition rate to convert to chronicity when compared to HBV, therefore if exposure to the two viruses is similar the prevalence of chronic HCV infection is expected to be much higher than that for chronic HBV.

The mechanism involved in this extrahepatic disease is not yet clear but (a) cytopathic damage due to the viral replication at these extrahepatic sites (b) immunological tissue damage (c) virus associated autoimmunity are the possibilities²¹. In this context, the HCV infection may either trigger latent autoimmunity or induce de novo an autoimmune disease through molecular mimicry and immunological dysregulation. The reasons to support the latter are thyroiditis, thrombocytopenia and lichen planus and aggravation of these disorders by interferon therapy⁸⁻¹⁰. Studies have shown some association of HCV genotype 2a with extrahepatic disease especially diabetes^{22,23}.

In Pakistan the HBsAg carrier rate varies between 4-10%^{24,25}. The Meta analysis of various HBV studies gives a figure of 4% HBV carrier rate (unpublished data). The anti HBs figures in various population groups are around 32% indicating a natural seroconversion, as these figures are of pre vaccination era²⁴. The HCV positivity rate in blood donors and healthy population varies from 1.4-4.4%²⁶⁻²⁸. Keeping these figures in mind it appears that the two viruses are hitting the Pakistani population at almost the same rate of 4%. Qureshi et al²⁹ in this issue of the journal report a rather unusual finding of equal occurrence of diabetes in both HBV and HCV. Their plea is that as two viruses have the same exposure rate therefore their extrahepatic involvement is also similar. The National Health survey of Pakistan reports a 5% prevalence of diabetes mellitus³⁰, which again appears to confirm the above hypothesis. Most of the above figures for HBV are of pre or early HBV vaccination era. It would be interesting to study these figures 2-3 decades after the HBV vaccination when the HBV figures are likely to fall, and see if this equal predisposition of diabetes mellitus persists in chronic HCV and HBV cases.

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