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A Review To Explore The Association Between Diabetes Mellitus And Hepatitis

[1.]Sharmistha Chatterjee
AssisstantProfessor,DepartmentofBiochemistry,CollegeofMedicineandSagoreDuttaHospitalKamarhati,Kolkata.

[2.] Biswajit Majumder
AssociateProfessor,Department of Cardiology
ICVS,R.G.KarMedical College

[3.] Debashis Basu
Consultant Diabetoloigist
Apollo Hospital .

Abstract
Both diabetes mellitus and chronic hepatitis due to Hepatitis C infection are epidemiologically extremely important worldwide. But what is more intimidating is the incidence of Diabetes in patients suffering from Hepatitis C. This review aims to look at the epidemiology, etiopathogenesis, clinical features, laboratory findings and clinical management of diabetes occurring in individuals suffering from Hepatitis C. The mechanism of development of insulin resistance in Hepatitis C (HCV) infected individuals have several theories. In this write-up, HCV have been dealt with separately in details. In case of HCV, the mechanism of development of insulin resistance is predominantly immunological. Other mechanisms include increase in oxidative stress, beta cell dysfunction, iron overload and many others. The treatment of diabetics in the setting of HCV and are essentially antiviral regimens alongwith treatment and monitoring of Diabetes mellitus. Considering the colossal statistical figures of prevalence of diabetes and hepatitis, prevention of HCV and transmission is of utmost importance. This comprehensive review aims to look at incidence and pathogenesis of diabetes in HCV infected patients alongwith the effect of the antiviral regime on glucose metabolism.

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A REVIEW TO EXPLORE THE ASSOCIATION BETWEEN DIABETES MELLITUS AND HEPATITIS C

Diabetes Mellitus is a metabolic disorder of immense public health importance. At present, 425 million people are estimated to be suffering from the disease, which is expected to rise to 629 million by 2045.[1] Additionally, an estimated 318 million adults live with impaired glucose tolerance and are likely to develop the disease in future. On the other hand, statistics pertaining to chronic liver diseases consequent to hepatitis C or B infections, are equally intimidating. Worldwide , approximately 325 million people are infected by Hepatitis B and C viruses [2]of which 350,000 patients die of cirrhosis or hepatocellular carcinoma .[3] In India, more than 2 billion people have been affected by HBV infection alone , of which an estimated 350 million are chronically infected.[4,5] The prevalence of diabetic patients has been found to be particularly high in patients of chronic liver disease. [6].Various studies have shown a significant incidence of diabetes in patients of chronic hepatitis C, with or without co-existing cirrhosis.[7].It may also be noted here, that in some studies, diabetes has reported to be more frequently associated with chronic liver disease due to Hepatitis C virus ,rather than Hepatitis B.[8-10] Again,there are studies to demonstrate that prognosis of HCV infection may be worse in diabetic individuals.[11] Apart from the patients in whom diabetes coexists with chronic hepatitis, there also exists another group of patients in whom diabetes arises as a complication of cirrhosis of liver. Traditionally referred to as hepatogenous diabetes, the basic pathophysiology of the disease is insulin resistance in the muscles and adipose tissues and hyperinsulinemia due to an impaired response of the beta cells of the pancreatic islets. Interestingly, there is substantial evidence to show that HCV infection has a definite role in the pathogenesis of the development of diabetes in infected individuals.[12] Further, the pegylated interferon therapy has also been shown to give rise to diabetes (type 1 diabetes along with other autoimmune diseases).Thus there exists a bi-directional association among diabetes and chronic hepatitis which may be synergistic in nature adversely affecting the prognosis of the patient. In the light of the above background it was deemed appropriate to take up a review on a possible association or co-incidence among Diabetes and chronic Hepatitis of viral origin, particularly C.The co-existence of diabetes and hepatitis had been long recognized,way back in 1978 , when the development of diabetes was followed in a cohort of subjects who were affected in an outbreak of epidemic of the infectious hepatitis reported from Nigeria.[12,13] .For the purposes of this review, we searched. Pubmed databases systematically from 1990 to 2018 for publications in English language pertaining to diabetes and chronic liver disease of viral origin. In the following sections, we take a look at the epidemiology, predispositions, pathogenesis, mechanisms of development of the complications and ultimately treatment modalities of

diabetes co-existing with HCV infections.

Hepatitis C

Epidemiology of HCV and diabetes

A possible link in the incidence between HCV and Diabetes was reported by Allison in 1994 [14] where only 9% of HCV negative cirrhotics had diabetes as compared to 50% of HCV positive cirrhotics with diabetes. The data was further reinforced by the Third National Health and Nutrition Examination Survey (NHANES III)[15] and later by Amarapurkar et al [16] and Wang CS et al [17].Studies suggest that male sex.old age ,obesity, liver fibrosis, HIV co-infection as well as family history of DM as strong predictors of development of diabetes in HCV affected individuals.[18,19,20]. While a higher prevalence of HCV antibodies has been consistently reported in T2D patients, the same was not true in T1D. [21,22,23,24]. Lastly, there is enough evidence to suggest that post liver transplant HCV patient may be at an increased risk of development of DM, though how far this may be due to the effects of post transplant drugs like tacrolimus remains debatable.[24,25,26,27].

Pathogenesis: the diabetogenic action of HCV

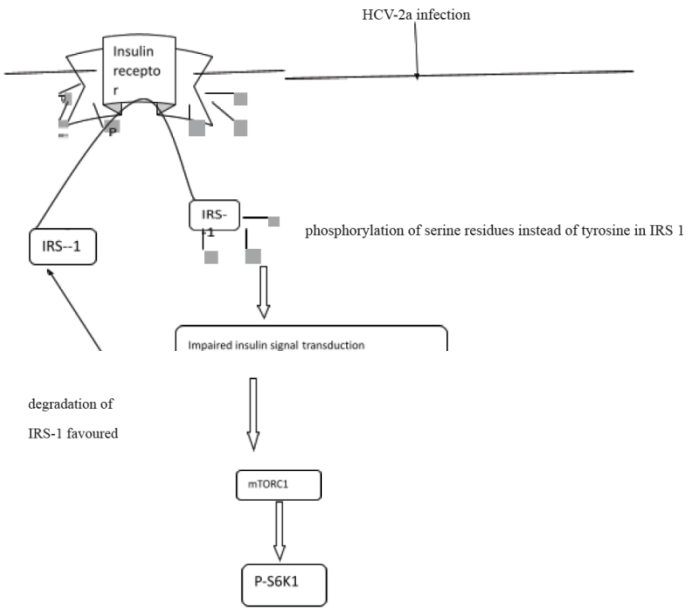
Various mechanisms have been postulated to explain the diabetogenic action of HCV. The following section summarises some of these hypotheses that originated in pursuit of a cause-effect relationship of an endocrine metabolic disease namely diabetes with an infectious agent called HCV.

Insulin resistance

The fundamental mechanisms of development of T2D are defect in secretion of insulin, increased hepatic glucose output and the much talked about insulin resistance.[28] As the liver is the cornerstone of glucose homeostasis and insulin mainly acts by increasing the uptake of glucose at the level of skeletal muscles and adipose tissue, insulin resistance is a fundamental feature of chronic liver disease of various etiologies. Here it may recalled that though HCV is a hepatotrophic virus ,it has cytopathic effects on extrahepatic tissues as well.[29]The precise diabetogenic action of HCV is attributed to the proteosomal degradation of IRS 1 and IRS2 through ubiquitination by HCV core protein via SOCS- 7.[30,31,32,33,34]This leads to paralysis of the downstream AKT/protein kinase B pathway which along with PI3K is crucial to the insulin signaling cascade involved in glucose metabolism.[35,36,37,]

Figure 1: A simple schematic diagram to explain the impairment of the insulin signal transduction in patients infected with Hepatitis C virus.

Key: IRS 1—insulin receptor susbtate 1
HCV-- hepatitis C virus
mTORC 1- mammalian target of rapamycin Complex
PS6K1- S6K1 protein
■ --phosphoryl groups

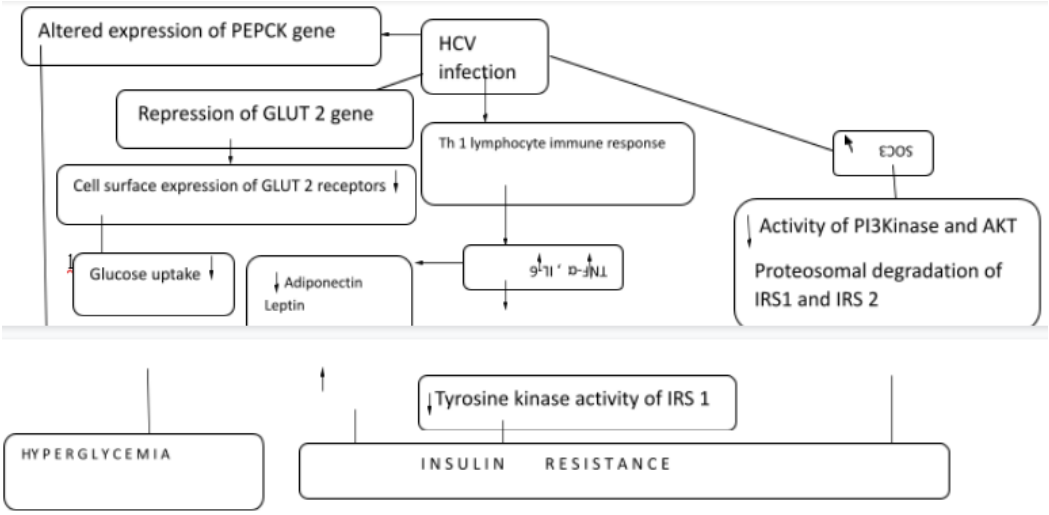


Inflammatory cytokines

Recent evidence shows that HCV plays havoc with the immune signaling mechanism within the liver and in conjunction with the host genetic factors and other environmental determinants can dictate the progression and outcome of the disease.

HCV induces the Th1 lymphocyte immune mediated response which leads to activation of the TNF- α system and elaboration of interleukin -6 levels. These pro-inflammatory cytokines are known to be intensely insulin –resistant in nature.[38,39,40,41,42,43]. Proinflammatory cytokines induce cytokine signalling proteins suppressors and leads to increased gluconeogenesis because of a lack of Akt mediated inhibition of PEPCK gene expression.[44,45].Gluconeogenesis may also be increased by inhibition of tyrosine phosphorylation by leptin in the hepatic cells.[46]TNFα also has a lipolytic effect and increases the serum fatty acids and thus insulin resistance. [47,48]The expression of GLUT-4 mRNA in the muscle and adipose tissue is also reduced byTNFα and may lead to decreased IRS-1 and PPARs..The innate and adaptive response initiated by viral infection leads to elaboration of the pro- inflammatory cytokine cascade and recruitment of a large number of chemokines, like CXCL9,CXCL10 and CXCL 11.HCV escapes this immune response throughTh2/T cytotoxic pathway. This intense inflammatory reaction and dysregulation of the cytokine cascade can also lead to other autoimmune disorders.[49,50,51,52,53]

Figure 2: Diagrammatic representation of TNF –α and IL—6 mediated response in HCV infection leading to development of insulin resistance and hyperglycemia.



Beta cell dysfunction

The exaggerated immune response described above may be responsible for pancreatic beta cell destruction. As GAD 65 shares antigenic regions with HCV polyproteins, molecular mimicry may be one of the mechanisms involved here. The amplified immune response may induce antibodies against GAD and stimulate the production of cytokines like IL-18 which are particularly instrumental in the development of full blown T1D.[54,55,56,57,58,59]When these patients were evaluated for beta cell function and insulin resistance, they showed significant decrease in δ C peptide levels ,HOMA-β, C- peptide and insulin levels, and insulinogenic levels(markers of early phase pancreatic insulin secretion).[60,61,63,64].In chronically infected HCV patients ,proinflammatory cytokines like TNF-α which link obesity to insulin resistance may directly degrade insulin signaling cascade.

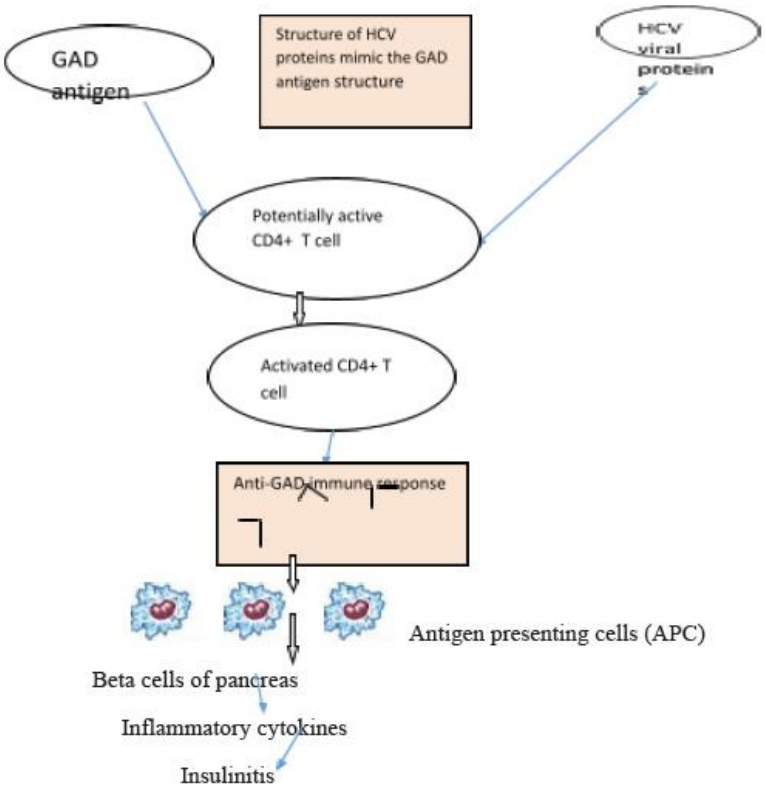


Figure 3: Diagrammatic representation of destruction of beta cells by molecular mimicry: Diagrammatic representation of destruction of beta cells by molecular mimic

Hepatic steatosis

There is sufficient clinical evidence to suggest that hepatic steatosis as a result of HCV infection also plays a significant role in the development of T 1D.[65]Hepatosis is simply the accumulation of fat in the hepatocytes and is found in many other liver diseases including NASH.[66]Experiments suggest that over-expression of two HCV proteins, core and N55A ,localized on the surface of lipid droplets interact with Apolipoproteins A1 and A2 may be directly responsible for accumulation of triglycerides.[67].Inhibition of mitochondrial triglyceridetransfer protein (MTP) ,which is a rate limiting enzyme in the VLDL assembly, may also be directly involved in the process.[68]This steatosis which is by and large independent of immune response , is more frequent in patients infected with HCV genotype 3 (viral steatosis) than HCV genotype 1(metabolic fat) ,those with higher BMI and with greater necrosis and inflammation.[69,70,71,72,73,74,75,76,77,78].The degree of steatosis correlates positively with the titres of intrahepatic negative strand HCV Rna in some studies but not all.[79]Interestingly, a successful antiviral therapy has been associated with decrease in apolipoprotein B and cholesterol levels.

Oxidative stress

An imbalance between the production of the well known pro-oxidant species (like the superoxide anion radical, singlet oxygen, and the highly reactive hydroxyl radical) and the body's ability to detoxify them is referred to as oxidative stress. Viral infection of the liver may be disastrous in this context as the liver plays as important role in the detoxification of harmful substances[80,81,82]Research shows that an increase in ROS production due to HCV infection(2 to 5 times) alongwith a significant decrease in lymphocytes leads to disruption of cell signalling. The HCV increase the oxidative stress. through the Casein kinase 2 and PI-3 kinase The nonstructural protein increase ROS by activating the translocation of NF-κβ and STAT-3 transcription factors. Activation of p38 MAPK (mitogen-activated protein kinase), JNK (c-Jun N-terminalkinase) and AP-1 (activator protein-1) are also involved[83-92].HCV infection shows increased levels of defense enzymes like heme oxygenase (HO-1) [93] and thioredoxin (Trx) [94] and decreased levels of manganese or Cu/Zn superoxide dismutase (SOD), glutathione reductase, and glutathione peroxidase, in the peripheral blood mononuclear cells .The increased oxidative stress induce the over-expression of the 3β-hydroxysterol Δ24-reductase (DHCR24) to which binds the Sp1 transcription factor which in turn decreases apoptosis in hepatocytes disturbing p53 activity. Another TGF β mediated pathway involving NOX4 has also been postulated.[95-100]Since liver is one of the storage sites of iron, increase in levels of iron and serum ferritin maybe involved in the damaging effects of oxidative stress.[101-105].Iron induced oxidative stress may be

involved in hepatic fibrogenessis either as an activator of hepatocyte necrosis or of stellate cells ,Kuffer cells (effector cells) or increased synthesis of collagen in myofibroblasts.[106]. Interferon therapy and Diabetes The standard modality of treatment for HCV infection remains pegylated interferon and ribavirin. Interferons are cytokines produced by all mononuclear cells in response to an immunological insult. Though developed more than 50years ago, interferons have remained the cornerstone of treatment for HCV.The most important adverse effects of interferon therapy is the development of a number of autoimmune conditions like thyroiditis, systemic lupus erythematosus,, rheumatoid arthritis vitiligo, and even some instances of optic neuritis and severe autoimmune hemolytic anaemia. [107-112].But the most important of them all is perhaps , the development of Type 1 Diabetes shortly after initiation of therapy. The development of interferon induced T1DM was first described in 1992 by Fabris and subsequently many other cases came to light in Japan , Italy, Spain and Holland [113-118] In stark contrast to the pathogenesis of Type 2 DM, in chronic HCV infected patients where insulin resistanceplays an important role, autoimmunity is perhaps the most important factor in the causation of T1D in HCV patients on interferon therapy. IFNα binds to its receptors to stimulate the JAK-STAT pathway, which leads to up-regulation of genes responsible for cytokines and adhesion molecules that can trigger autoimmunity in genetically predisposed patients.[119,120,121].. The markers of pancreatic autoimmunity have been shown to increase during treatment with alpha interferon, presumably due to the immunostimulatory effects of IFNα. IFNα therapy induced auto antibody has also been detected against glucagon producing cells(GCA),parietal cells(PCA),glutamic acid decarboxylase (GAD), second islet cell autoantigen (IA2-A), thyroid (thyroid microsomal antibodies or THMA), TSH-receptor (TRAb) , thyroperoxidase and thyroglobulin (TGHA),liver-kidney microsomal (LKMA) ,smooth muscles, nuclei (ANA), mitochondria and even against adrenal cortex and medulla, adrenal 21-hydroxylase and protein tyrosine kinase, [122-126]. The disease has an abrupt onset, with severe hyperglycemia or ketoacidosis as a presenting feature , and almost always requiring insulin therapy. Interestingly, patients seropositive for HCV have a higher cumulative incidence of development of new-onset diabetes after kidney transplantation (NODAT) in Chinese kidney transplant recipients (KTRs) than in those who were not .In fact, the risk increases 3.03 fold (95% confidence interval 1.77-5.18; $P < 0.001$) in patients already infected with HCV.(127)

Clinical Features

In the light of the preceeding discussion, T2DM may be considered to be an extrahepatic manifestation of HCV infection.[127] In fact, patients with HCV infection who have developed T2DM , may have a more severe liver disease and fibrosis compared to non-HCV patients.[128].Most patients of viral hepatitis are likely to be asymptomatic, while others may exhibit the symptoms of chronic hepatic disease like icterus, pruritus, ascitis, palmar erythema, spider naevi, gynaecomastia, features of portal hypertension like splenomegaly, esophageal varices. etc along with hyperglycemia. The age, gender, ethnicity, family history of diabetes, smoking status, use of drugs (statins, fibrates antihypertensives,),time since initiation of IFN therapy---all these factors to be taken into consideration during evaluation of the patient. Patients with T2DM may or may not be obese with a high BMI and those with T1D may present with an acute episode of ketoacidosis or severe hyperglycemia. In either case, patients may exhibit diabetic neuropathy, nephropathy, arthralgia, mixed crypglobulinemia and a host of infections common in diabetes.[129]. Here it may be pertinent to mention that this diabetes developed secondary to liver disease (in this case, HCV infection) differs from the classical diabetes in a few ways. Firstly, there is a smaller association of this diabetes with the traditional risk factors like age, body mass index and family history. Secondly, risk of micro and macroangiopathic complications may be significantly lower.[130] As the liver function is already compromised, the frequency of hypoglycemic episodes is higher in patients who have developed diabetes secondary to HCV infection.[131] For obvious reasons, the incidence of diabetes increases as the hepatic function detetriorates.[132]

Laboratory investigations

A patient suspected of HCV positivity should undergo serologic testing along with genotyping of the virus (genotype 1 notorious for development of diabetes later on), PCR for HCV, and liver function tests , a complete blood count, serum iron, transferrin saturation and an ultrasound upper abdomen and liver biopsy, if indicated. The serum urea and creatinine and urinary albumin excretion, detailed ophthalmological examination, resting electrocardiogram, perfusion studies of the myocardium, Semmes-Weinstein monofilament sensory perception test at the hallux of each foot to be performed for early detection of complications. Serum alanine transaminase, a marker of hepatic steatosis, is perhaps more important of the three liver enzymes. Platelets and leucocyte counts may be lower while serum iron tends to be high. Serum cryoglobulin profile, antinuclear antibodies, rheumatoid factor , autoantibodies against pancreas ,GAD and thyroid should be performed before embarking on IFN therapy. The criteria (as per ADA guidelines), for diagnosis of hepatogenous diabetes and pre-diabetes remains essentially the same as for primary diabetes.[133] In fact, HCV infection is associated with glucose abnormalities in early stages of the disease and most of them could be diagnosed by an OGTT. [134] The levels of PPG and FPG are lower than those in primary diabetic parients but the levels of plasma insulin and

C-peptide were higher in diabetes due to chronic hepatitis. Hba1c values need to be interpreted with caution. A vigilant clinician should keep in mind that the hemolytic anaemia induced by IFNα and ribavirin therapy, hypersplenism and anaemia following massive GI bleed may falsely lower HbA1c values. So, HbA1c values are of limited diagnostic and prognostic significance in hepatogenous diabetes and testing for fructosamine (FA) is indicated in these patients and also for other hemoglobinopathies [135,136,137].The measurement of fructosamie, being a spectrophotometric assay, may be affected by hypertryglyceridemia, hyperbilirubinimia, hemolysis, and low serum albumin and protein values. . A novel non-invasive 13 C breath test was evaluated in Japan and was found to be an useful screening tool for outpatient department for the diagnosis of diabetes secondary to liver pathology and so may be applied to these HCV infected patients,[138] The traditional prognostic instruments like Child-Pugh score as well as the Model for End-Stage Liver Disease do not include diabetes or glucose intolerance in their parameters.[139,140] Retrospective studies have shown that hepatocellular failure and gastrointestinal bleeding accounted for greater mortality than diabetes per se in these patients.

Management

The management of T2DM in the HCV infected patient presents a formidable challenge because of multiple co- morbidities and limited pharmacotherapuetic options. Combined hepatology and diabetology clinics alongwith multidisciplinary team (including a dietitian, diabetes nurse specialist, or podiatrist) is an absolute necessary for efficient screening of diabetic and hepatic complications and also effective individualized counseling regarding the relative pros and cons of the various available treatment modalities.Screening to be performed at the earliest using HBA1c (with 6.5%) as the cut-off in susceptible patients like obese, overweight ,at risk ethnic groups like South Asians, strong family history, previous history of gestational diabetes, etc. [141]There is significant evidence to suggest lifestyle changes (like weight reduction, cessation of smoking and alcohol intake , regular exercise) and improvement of metabolic indices like glycemia and cholesterol and lead to better mortality rates. The treatment of hyperglycemia is tricky in these patients as most of the oral hypoglycemic agents are contraindicated in chronic liver disease. Though metformin is the first choice for diabetics with a BMI >25kg/m 2 , it carries a high risk of lactic acidosis in these patients.[142].It is recommended that patients with chronic liver disease and few other co-morbidities ,should not receive metformin more than 1500mg/day and the drug should be discontinued if thev patient deteriorates. As insulin secretatagogues are metabolized by the liver,they should be avoided in thses patients.[143] Experience with alpha-glucosidase inhibitors are limited and have shown increased risk of hyperammonemia in patients of chronic liver disease.[144,145,146]

Insulin is the safest and antihyperglycemic therapy of choice in these subjects. most significant adverse effect of insulin dosage in these patients is the high possibility of hypoglycemic episodes for which the patients and their care-givers should be adequately counseled. The regimen usually begins with addition of basal insulin to metformin ,if the case permits, as the latter reduces both weight gain and insulin dose.[147]In others ,insulin should be given in either fixed dose regimen or ,basal bolus regimen. Studies with the newer agents like DPP4-inbibitors and GLP 1 analogs are limited. Liver transplantation holds out promise for cure of diabetes in hepatogenous diabetes, but in HCV infected patients, utmost care and discretion should be practised. The aim of the treatment is to reduce the microvascular complications and as such statins are not advocated as they are associated with elevation of liver transaminases.[148,149] Antiviral regimen administered to treat chronic hepatitis C have demonstrated remarkable efficacy to reduce the requirement of insulin in the relevant cases.[150].On the other hand, cases of new onset diabetes due to antiviral agents like ledipasvir and sofosbuvir(approved by the FDA for treatment of chronic Hepatitis C), have also been reported in literature. The mechanism of the hyperglycemia is believed to be due to an increase in insulin resistance.[151

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