

**Original Research Article**

**HEPATITIS C TREATMENT BY DIRECTLY ACTING ANTIVIRAL AGENTS AND  
ITS IMPACT ON GLYCEMIC CONTROL**

UNDER PEER REVIEW

**ABSTRACT:**

**OBJECTIVE:** To evaluate Hepatitis C treatment by directly acting antiviral agents and its impact on glycaemic control.

**STUDY DESIGN:** This is an observational study.

**SETTING:** This study was conducted in Medicine department Civil Hospital Karachi from March 2018 to December 2019.

**MATERIAL & METHOD:** Patients visiting the outpatient department of the hospital having documented HCV infection having type 2 diabetes mellitus were included in the study. All participants were given directly acting antiviral treatment for 12 weeks. After treatment they were assessed for achievement of sustained virological response (SVR). Pre-treatment and post treatment fasting blood glucose levels and HbA1c levels were checked. SVR is defined as serum HCV RNA which is undetectable (<50IU/ml) after 12 weeks of antiviral treatment.

**RESULTS:** Around 332 patients matched our inclusion criteria. Amongst these there were 219 males and 113 females. The mean age of patients was  $39.44 \pm 2.19$  years. All the selected participants started therapy on Sofosbuvir-velpatasvir (pangenotypic NS5A-NS5B inhibitor single-pill combination regimen that has potent activity against hepatitis C virus (HCV) genotypes 1, 2, 3, 4, 5, and 6.) plus ribavirin. After treatment with directly acting antiviral therapy 231 (69.57%) patients achieved sustained virological response. Patients who achieved SVR showed improved glycaemic control than those who didn't. Patients with cirrhosis showed decreased chances of attainment of SVR. Fasting blood glucose levels and HbA1c were also decreased, decreasing the amount of insulin required for diabetes control.

**CONCLUSION:** Our study showed that treatment with directly acting antiviral treatment improved glycaemic control in HCV infected patients. Other factors like BMI, presence of cirrhosis, mean serum HCV RNA levels and adherence to treatment were major predictors for achievement of SVR.

**KEY WORDS:** Hepatitis C Treatment, Directly Acting Antiviral Agents, Glycaemic Control.

## **INTRODUCTION:**

Hepatitis C is a leading cause of morbidity and mortality worldwide, having prevalence of 3.9%. In the United States it has an incidence of 0.7 per 100,000 cases (1). HCV infection is linked with higher prevalence of type 2 diabetes mellitus. It increases the risk of development of type 2 diabetes mellitus by 11 fold. Several studies performed have shown that HCV infection increases the risk of type 2 diabetes mellitus in patients with risk factors(2). Various mechanisms contribute to the explanation behind this relationship of HCV infection and risk of diabetes mellitus. HCV proteins augment threonine and serine phosphorylation of insulin receptors, causing insulin resistance. Furthermore proinflammatory cytokines like tumor necrosis factor and interleukin 6 stimulate gluconeogenesis and lipogenesis. These changes in metabolism exacerbates insulin resistance in persons with risk factors for type 2 diabetes mellitus (3). HCV infection has been proven to deteriorate glycaemic control, thus leading to the hypothesis that HCV eradication can lead to improved glycaemic control. Previously there have been a lot of studies conducted upon HCV eradication and its impact on glycaemic control (4). Two of such trials have demonstrated that interferon and ribavirin have led to improvement in insulin resistance just after 20 weeks of treatment (5). Since there are no large-scale studies conducted on changes on glycaemic control, its impact will be observed by interferon-free regimens like Sofosbuvir-velpatasvir. It is still unclear that HCV eradication is the primary reason for improved glycaemic control or directly acting antiviral regimens for HCV treatment(6). Risk factors for metabolic syndrome and family history of type 2 diabetes mellitus are predisposing factors for diabetes. Also it was found that insulin resistance was directly proportional to the degree of liver fibrosis in HCV infected patients (7). Various studies have reported decrease in insulin resistance after attainment of SVR. A study proved that HCV infected patients treated by Sofosbuvir-velpatasvir with and without ribavirin treatment regimens are persistent with improved glycaemic control. The potential biases were prevented by prolonged follow-up and eliminating side effects of treatment (8). Although SVR reduces the incidence of development of type 2 diabetes mellitus, the clinical finding isn't much relatable to the situation. This discrepancy is due to variation in baseline characteristics of patients like weight, genetics, lifestyle, physical activity and cirrhosis (6). It is really important to identify if HCV is the major preceding factor for insulin resistance. Very few studies have eliminated these biases and role of HCV in development of type 2

diabetes mellitus (9). Our study aims to assess the impact of glycaemic control by HCV treatment by directly acting antiviral agents.

## **MATERIAL & METHOD:**

This study was conducted in Medicine department Civil Hospital Karachi from March 2018 to December 2019. Patients visiting the outpatient department of the hospital having documented HCV infection having type 2 diabetes mellitus were included in the study. Eligibility criteria for documented HCV infection was positive anti HCV antibody and serum HCV RNA. Patients with positive hepatitis B serology, immunocompromised states and having previous terminated antiviral treatment were excluded from the study. The confirmation of diabetes was made by fasting blood glucose levels and HbA1c levels. Patients included in the study were decided to be given Sofosbuvir-velpatasvir and ribavirin treatment for HCV infection. Doses for these drugs were adjusted by the patient's body weight. All participants were given directly acting antiviral treatment for 12 weeks. After treatment they were assessed for achievement of sustained virological response (SVR). Pre-treatment and post treatment fasting blood glucose levels and HbA1c levels were checked. SVR is defined as serum HCV RNA which is undetectable (<50IU/ml) after 24 weeks of antiviral treatment.

## **RESULTS:**

Around 332 patients matched our inclusion criteria. Amongst these there were 219 males and 113 females. The mean age of patients was  $39.44 \pm 2.19$  years. All the selected participants started therapy on Sofosbuvir-velpatasvir alpha plus ribavirin. During the treatment 15 patients were excluded from the study due to early discontinuation of therapy. Reasons for early discontinuation of therapy include severe side effects, elevated bilirubin levels, decrease in red blood cell count. After treatment with directly acting antiviral therapy 231 (69.57%) patients achieved sustained virological response. Table-1 shows the response of patients after completion of treatment.

Patients who achieved SVR showed improved glycaemic control than those who didn't. Patients with cirrhosis showed decreased chances of attainment of SVR. Fasting blood glucose levels and HbA1c were also decreased, decreasing the amount of insulin required for diabetes control.

## **DISCUSSION:**

Hepatocytes are necessary for homeostasis of glucose, continuously regulating between glucose production and glycogen breakdown. Several pathways are found to explain HCV mediated insulin resistance, and it has been supported by literature. After treatment with directly acting antiviral agents, fasting blood glucose and HbA1c levels have been declined (10). In patients who had normal glucose metabolism with HCV infection show a decrease in fasting plasma glucose levels after directly acting antiviral treatment. This shows that subclinical insulin resistance is present with HCV infection (11). A research done in 2018 shows that improvement in glucose metabolism was independent of the participant's BMI (12). In the previous studies done there have been various factors responsible for the varying rates of SVR achieved. One such study done in Taiwan similar to our study was conducted in two groups of a population. It suggested that better SVR was achieved in Caucasians with less duration of treatment than African Americans. Also the better response rates are associated with appropriate dose of ribavirin(13).The genotype of HCV infected also had a major impact on treatment response, as patients infected with subtype 1b had more rapid decline in serum RNA(14). The baseline characteristics of patients are directly related to treatment response. Factors associated with good response to treatment with Sofosbuvir-velpatasvir plus ribavirin include female gender, young age at presentation, low serum HCV RNA levels, and low BMI. Poor prognosis is invariably associated with presence of cirrhosis on liver biopsy (15). Previous data suggests that insulin resistance further aggravates hepatic fibrosis. High insulin levels promote secretion of extracellular matrix and this vicious cycle goes on (16).However, coinfection with hepatitis B is not linked with fibrosis and insulin resistance as suggested by researchers till now. Insulin resistance has been found to be a major factor in SVR attainment, recognizing the degree of insulin resistance in every individual will help in managing treatment regimens. Treatment based on the patient's baseline characteristics and insulin resistance have been proven more efficacious(17). Early identification of risk factors and strategies for compliance are needed to improve treatment response. Insulin resistance and serum HCV RNA levels are the most important points associated with SVR and treating insulin resistance before starting treatment increases the response rate. Predicting degree of insulin resistance and other metabolic disturbances can also provide a better approach to patients (18). Previous study done shows that SVR decreases insulin resistance and change in anti-diabetic medication is needed then. Further it states that patients who achieved SVR had significant decrease in levels of anti-diabetic

medications (10). Insulin requirements were decreased by 51% in patients who achieved SVR and metformin use was also decreased(3). Combination regimens are linked to more adverse effects and hence early discontinuation. Other factors associated with treatment response are infection with genotype 2 and 3, viral load < 2 million copies/ml, extremes of age and degree of fibrosis (19). Also it has been shown that combination treatment with Sofosbuvir-velpatasvir and ribavirin for 24 weeks has better response rates than Sofosbuvir-velpatasvir alone. Combination regime has been shown to be more efficacious and has a better safety profile (19).

### **CONCLUSION:**

Our study showed that treatment with directly acting antiviral treatment improved glycaemic control in HCV infected patients. Other factors like BMI, presence of cirrhosis, mean serum HCV RNA levels and adherence to treatment were major predictors for achievement of SVR.

### **REFERENCES:**

1. Mada PK, Malus ME, Chen B, Adley S, Castano G, Moore M, et al., editors. 2222. Impact of Sustained Virologic Response Achieved Through Newer Direct Acting Antivirals in Hepatitis C Infection on Diabetes Mellitus. Open Forum Infectious Diseases; 2018: Oxford University Press.
2. Mehta SH, Brancati FL, Strathdee SA, Pankow JS, Netski D, Coresh J, et al. Hepatitis C virus infection and incident type 2 diabetes. Hepatology. 2003;38(1):50-6.
3. Bastard J-P, Maachi M, van Nhieu JT, Jardel C, Bruckert E, Grimaldi A, et al. Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both in vivo and in vitro. The Journal of Clinical Endocrinology & Metabolism. 2002;87(5):2084-9.
4. Arase Y, Suzuki F, Suzuki Y, Akuta N, Kobayashi M, Kawamura Y, et al. Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C. Hepatology. 2009;49(3):739-44.
5. Delgado-Borrego A, Jordan SH, Negre B, Healey D, Lin W, Kamegaya Y, et al. Reduction of insulin resistance with effective clearance of hepatitis C infection: results from the HALT-C trial. Clinical Gastroenterology and Hepatology. 2010;8(5):458-62.

6. Simó R, Lecube A, Genescà J, Esteban JI, Hernández C. Sustained virological response correlates with reduction in the incidence of glucose abnormalities in patients with chronic hepatitis C virus infection. *Diabetes Care*. 2006;29(11):2462-6.
7. Petit J-M, Bour J-B, Galland-Jos C, Minello A, Verges B, Guiguet M, et al. Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. *Journal of hepatology*. 2001;35(2):279-83.
8. Mada PK, Malus ME, Parvathaneni A, Chen B, Castano G, Adley S, Moore M, Hieda M, Alam MJ, Feldman M, King JW. Impact of treatment with direct acting antiviral drugs on glycemic control in patients with hepatitis C and diabetes mellitus. *International journal of hepatology*. 2020 Jan 13;2020.
9. Kawaguchi T, Ide T, Taniguchi E, Hirano E, Itou M, Sumie S, et al. Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. *The American journal of gastroenterology*. 2007;102(3):570.
10. Hum J, Jou JH, Green PK, Berry K, Lundblad J, Hettinger BD, et al. Improvement in glycemic control of type 2 diabetes after successful treatment of hepatitis C virus. *Diabetes Care*. 2017;dc170485.
11. Salomone F, Catania M, Montineri A, Bertino G, Godos J, Rizzo L, et al. Hepatitis C virus eradication by direct antiviral agents improves glucose tolerance and reduces post-load insulin resistance in nondiabetic patients with genotype 1. *Liver International*. 2018;38(7):1206-11.
12. Kasai D, Adachi T, Deng L, Nagano-Fujii M, Sada K, Ikeda M, et al. HCV replication suppresses cellular glucose uptake through down-regulation of cell surface expression of glucose transporters. *Journal of hepatology*. 2009;50(5):883-94.
13. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *The Lancet*. 2001;358(9286):958-65.
14. Jensen DM, Morgan TR, Marcellin P, Pockros PJ, Reddy KR, Hadziyannis SJ, et al. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon  $\alpha$ -2a (40 kd)/ribavirin therapy. *Hepatology*. 2006;43(5):954-60.
15. Cammà C, Bruno S, Di Marco V, Di Bona D, Rumi M, Vinci M, et al. Insulin resistance is associated with steatosis in nondiabetic patients with genotype 1 chronic hepatitis C. *Hepatology*. 2006;43(1):64-71.

16. Paradis V, Dargere D, Vidaud M, de Gouville AC, Huet S, Martinez V, et al. Expression of connective tissue growth factor in experimental rat and human liver fibrosis. *Hepatology*. 1999;30(4):968-76.
17. Cacoub P, Carrat F, Bédossa P, Lambert J, Pénaranda G, Perronne C, et al. Insulin Resistance Impairs Sustained Response Rate to Peginterferon Plus Ribavirin in Hiv-hcv Co-infected Patients: Homavic-anrs Hc-02 Study: Hiv, Therapy. *Hiv Clinical Trials*. 2008;9:8.
18. CHU CJ, LEE SD, HUNG TH, LIN HC, HWANG SJ, LEE FY, et al. Insulin resistance is a major determinant of sustained virological response in genotype 1 chronic hepatitis C patients receiving peginterferon  $\alpha$ -2b plus ribavirin. *Alimentary pharmacology & therapeutics*. 2009;29(1):46-54.
19. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, et al. Randomised trial of interferon  $\alpha$ 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon  $\alpha$ 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *The Lancet*. 1998;352(9138):1426-32.



Table-1: comparison of characteristics between two groups

Characteristics	With SVR	Without SVR
BMI	22.1 ± 3.4	25.3 ± 1.9
Total bilirubin (mg/dl)	0.83 ± 0.03	0.91 ± 0.07
Fasting blood glucose (mg/dl)	101 ± 3.4	112 ± 5.3
HbA1c	7.9 ± 1.9	9.3 ± 1.2
Mean HCV RNA (million IU/ml)	5.8	6.3
With cirrhosis	12.3%	28.4%