



## **Hepatitis C Treatment by Directly Acting Antiviral Agents and Its Impact on Glycemic Control**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Authors DK, AM and HS were involved in conception of idea and study design. Author SMK did the data collection and performed bench work. Author US performed the statistical analysis. Authors ZN and MAI managed the literature searches. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Objective:** To evaluate Hepatitis C treatment by directly acting antiviral agents and its impact on glycemic 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.

**Materials and Methods:** Patients visiting the outpatient department of the hospital having

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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.

*Keywords: Hepatitis C treatment; directly acting antiviral agents; glycemic control.*

## 1. 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.

## 2. MATERIALS AND METHODS

This study was conducted in Medicine department Civil Hospital Karachi from March 2018 to December 2019. We are in the endemic region where patients are exposed to many infected Hepatitis C things such as unsterilized

syringe usage, barber instruments, tattoo Mark's and surgeries etc. Hepatitis C Virus is the cause of cirrhosis in 5 to 20 percent of the chronic hepatitis C patients and its progression slow down by direct acting antiviral treatment. 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. Sustained virologic response (SVR) is internationally defined values of high viral load more than 800,000 IU/ml (international units per millilitre) and low viral load less than 800,000 IU/ml and undetectable below 650 IU/ml at the end of treatment and 6 months later.

### 3. 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. In comparison of pre and post viral treatment the requirement of insulin decreases and patients glucose level controlled effectively.

### 4. 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

**Table 1. Comparison of parameters between pre-treatment, treatment with SVR and without SVR**

Parameters	Pre Treatment	Treatment with SVR	Without SVR
BMI (Mean)	23.2 $\pm$ 1.3	22.1 $\pm$ 3.4	25.3 $\pm$ 1.9
Total bilirubin (mg/dl) (Mean)	1.01 $\pm$ 0.41	0.83 $\pm$ 0.03	1.1 $\pm$ 0.07
Fasting blood glucose (mg/dl) (Mean)	123 $\pm$ 5.4	101 $\pm$ 3.4	121 $\pm$ 5.3
HbA1c (Mean)	9.2 $\pm$ 1.1	7.1 $\pm$ 1.9	9.3 $\pm$ 1.2
AST(IU/L)	48.23 $\pm$ 2.3	21 $\pm$ 3.2	61.25 $\pm$ 1.1
ALT(IU/L)	51.29 $\pm$ 1.3	26 $\pm$ 2.5	57.14 $\pm$ 2.1
INR	1.3 $\pm$ 1.21	1.0 $\pm$ 0.09	1.5 $\pm$ 0.8
With cirrhosis	12.3%	11.3%	28.4%

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].

## 5. 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.

## CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

## ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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