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ORIGINAL ARTICLE

Impact of Successful HCV Eradication on Glycemic Control in Chronic HCV Patients with Type II Diabetes Mellitus

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ABSTRACT

Introduction: Chronic HCV infection has been implicated as a risk factor for new onset diabetes mellitus type II and worsening of glycemic control in patients with already established Diabetes due to defined molecular mechanisms. The impact of successful HCV eradication with direct-acting antiviral agents (DAAs) on glycemic control in HCV patients with concomitant Diabetes mellitus is being assessed by several studies but still unclear due to scarce data in literature, which specifically address this aspect of DAAs.

Objective: To study the impact of successful HCV eradication with DAAs based regimes on glycemic control in a cohort of Chronic HCV patients with concomitant Type II Diabetes Mellitus.

Materials and Methods

Study design: Descriptive Case series

Study place: Department of Gastroenterology, Lahore General Hospital, Lahore.

Duration: Six months i.e. 15-2-2021 to 15-8-2021

Data collection procedure: 110 patients, who fulfill the inclusion, were enrolled in the study.All patients of Hepatitis C received DAAs in the form of Oral Sofosbuvir 400 mg and Oral Daclatasvir 60 mg daily for 12 weeks without Ribavirin. Only Child Pugh class A and class B patients were included. Before starting treatment glycosylated haemoglobin (HbA1c) and Viral load by HCV RNA polymerase chain reaction was also checked. All the patients were followed at the end of treatment i.e. at 12 weeks(from the baseline) and then three months after treatment (at 24 weeks), for viral load testing by HCV RNA polymerase chain reaction and HbA1c levels.

Results: In this study 91% patients achieved sustained virological response and 83% of the patients achieved improved glycemic control after successful HCV eradication. Age (23-33: 16.5%, 34-44: 40.7%, 44-54: 29.7% p-value=0.728) and gender (Male: 39.6% & Female: 60.4%, p-value=0.142) have no significant association with glycemic control of patients.

Conclusion: Based on the findings of this study, it can be concluded that oral DAAs can help improving the glucose levels and glycemic control significantly in HCV patients with concomitant Type II diabetes mellitus and successful HCV eradication can prevent the long term complications of diabetes and may need dose reduction for insulin therapy in these patients

Keywords: Glycemic control, dual-acting antiviral agents, chronic hepatitis C virus infection, Diabetes Mellitus

INTRODUCTION

Hepatitis C is devastating viral infection which is the main cause of chronic liver disease all over the world as about 71 million people worldwide have become victim of this menace[1]. In Pakistan, it is estimated that 17 million people have been suffering from this silent killer[2]. HCV genotype are generally spread according to the specific geographic area. For instance, 1a and 1b are common in Europe, USA and Japan whereas 3a is responsible for liver damage in Pakistan[3]. Its genetic material has been isolated and characterized as single stranded RNA virus belonging to the member of Flaviviridae[4]. This infection is becoming a major health problem regarding liver cirrhosis of developing countries like Pakistan that has the second highest prevalence rate of hepatitis C after Egypt who falls at top of the Hepatitis C sufferers in the world[1].

In Pakistan, blood donors, health professionals, drug abusers and chronic liver disease patients are particularly vulnerable and contribute in the approximately 40% prevalence of hepatitis C in the country[5]. Another grave situation prevails where blood collected from donors at various spots are transfused to needy patients by using low quality kits for screening of Hepatitis C and B virus which gives false results and cause viral infection to innocent patients[6]. Chronic HCV infection may cause other problems such as immune system disorders and diabetes[7]. Type-2 Diabetes mellitus has been found a common co morbid condition in approximately one-thirds of HCV-infected patients. It is not clear that HCV directly or indirectly affect the insulin sensitivity in these patients[8].

At least in one study it has been found that proteins of the virus impair downstream signaling and appropriate regulation of glucose metabolism[9]. It is also suggested that an indirect effect of HCV on insulin may be due to increased production of pro inflammatory cytokines from sinusoidal liver cells that interferes with insulin-signaling pathways leading to insulin resistance in HCV infected patients[10].

Diabetes is linked to worsening cases of HCV. In addition, autoimmune problems associated with HCV may

enhance the risk for developing type 1 diabetes[11]. The preexisting diabetes put the patient at risk for a more aggressive course of HCV[12]. It can be accompanied increased scarring and cirrhosis, poorer response to medication, and increased chances for developing liver cancer in the sufferers of this disease[13].

Directly acting antiviral agents (DAAs) régimes are associated with high SVR i.e. >90% and have exceptional acceptability in both type of patients i.e. treatment-naive patients and treatment-experienced patients whether cirrhosis is present or not[14]. The underlying mechanism about the relationship between HCV and diabetes is not fully understood, but it has been linked with development of insulin resistance. The rationale of the study is to assess the impact of successful treatment of HCV with DAA on glycemic control in patients with type II diabetes mellitus in Pakistan.

MATERIAL AND METHODS

Study Design: Descriptive Case Series
Setting Gastroenterology Department, Lahore General Hospital, Lahore.
Duration: 6 months i.e. 15-2-2021 to 15-8-2021
Sample Size: Sample size of 110 cases is calculated by taking confidence interval equal to 95%, margin of error equal to 8% and the prevalence of glycemic control on the basis of glycosylated hemoglobin in previously uncontrolled diabetes (HbA1c level > 7.5) 3 months after the end of therapy as 76% in previous studies.15
Sampling Technique: Non-probability consecutive sampling
Inclusion Criteria

- Patients of age 18-60 years
- Both male and female gender were included
- Patient with Chronic HCV achieving Sustained virological response after 12 weeks of DAA treatment
- Poorly Controlled Type II diabetes mellitus with pretreatment HbA1c ≥7.5%
- Child Pugh class A and B

Exclusion Criteria

- Co infections with HBV, HIV or already taken treatment for HCV (medical record)
- Pregnant women
- Anemic Patients Hemoglobin< 10 mg/dl

Data Collection Procedure: After approval from hospital ethical committee, 110 patients who fulfill the inclusion were enrolled. All basic demographic information of each variable (name, age, address and contact) was also noted. Detailed history was obtained. All patients of Hepatitis C received DAAs in the form of oral Sofosbuvir 400 mg once daily and oral Daclatasvir 60 mg once daily. Before starting treatment with DAAs therapy basic laboratory tests were carried out which included, ALT,AST, serum bilirubin & albumin levels, complete blood count, prothrombin time, Ultrasonography ,glycosylated hemoglobin (Baseline HbA1c) and detailed clinical examination to label Child Pugh class as per operational definition. Only class A & B patients were included. . All these patients were treated as above and were followed after three months (at 12 weeks), where they were assessed again for viral load by HCV RNA polymerase chain reaction to look for SVR i.e. undetected HCV viral load on polymerase chain reaction at 12weeksi.e<15 I U /l at the end of treatment. Patients who achieved Sustained virological response after 12 weeks of DAA regimes were also checked for HbA1c level for glycemic control at 12 weeks after the completion of therapy. All the data was recorded in data collection performas.

Data Analysis: The collected data was organized & statistically analyzed using SPSS V 22. Only Quantitative data was presented as Mean and SD (i.e. age, HBAIC values, Viral load on polymerase chain reaction in IU/ml, BMI and duration of type II diabetes) while qualitative data as frequency and percentages like gender, child Pugh class and outcome variable i.e. glycemic control.

RESULTS

Mean age of patients was 42.50±9.67 years. In study population 47(42.7%) were male and 63(57.3%) were female. The mean viral load at baseline was 1419923.97±3916312.12mIU/L which was reduced to zero (0) after 12 weeks of treatment in all patients. At baseline mean HbA1c level was 10.18±1.99 and after 24 weeks it was 9.65±2.05 respectively. Table-1

Sustained virological response was achieved in 91% of the patients.

As per operational definition glycemic control that is 0.5 % reduction in HBA1c levels at 12 weeks after successful eradication of HCV was seen in 83% of the patients. Fig-1

Table 1: Demographics

n	110
Age (years)	42.50 ± 9.67
Male	47 (42.7%)
Female	63 (57.3%)
Viral Load at Baseline	1419923.97 ± 3916312.12
Viral load at 12th week	0.0 ± 0.0
HbA1c at baseline	10.18 ± 1.99
HbA1c at 24th week	9.65 ± 2.05

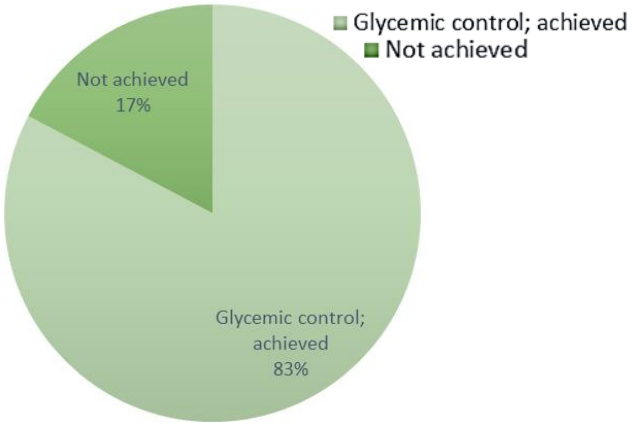

Figure-1: Glycemic control In HCV treated patients

DISCUSSION

Patients diagnosed with chronic HCV have significantly higher rate of type II diabetes, irrespective of stage of chronic liver disease stage than patients without liver cirrhosis or patient of hepatitis B virus infection. Type II diabetes mellitus is the common comorbid disease in about 1/3rd patients of chronic HCV[16]. But, the phenomena by

which the high hazard of type II diabetes occurs is still unclear. HCV infection can activate the autoimmune reactions against the pancreatic beta cells in hereditarily susceptible patients that lead to the direct destruction of the beta cells; thus, resulting the type I diabetes; or phenomena that is associated with raised insulin resistance[17,18].

Genotype 3 is the 2nd most prevalent in numbers globally after genotype 1 and more prevalent in Pakistan.1 The treatment of genotype 3 with interferons have proved to be troublesome, tedious, sometimes ineffective with no response or relapse.19 In case diabetes is co morbid condition with Hepatitis C, treatment can be more challenging. The body's cells can become more insulin resistant with HCV. Therefore, more smart and effective treatment is needed. The goal of HCV therapy is Sustained Virological response (SVR), which is defined as the absence of detectable HCV RNA at 12 and 24 weeks after completion of therapy respectively[19].

In this study 91% patients achieved. 83% of the patients achieved glycemic control. Age (23-33: 16.5%, 34-44: 40.7%, 44-54: 29.7% p-value=0.728) and gender (Male: 39.6% & Female: 60.4%, p-value=0.142) have no significant association with glycemic control of patients.

Recent studies have demonstrated that end of treatment Virological response in Chronic HCV patients treated with DAA after 3 months was obtained in 94.6% patients. They further subdivided their cases into three subgroups, I with HbA1c level < 6.5, group II with 6.5 to 7.5 and group III with level more than 7.5. Glycemic control in group III (HbA1c level >7.5) was seen in 19 (76%) of cases in their respective group while 6 (24%) had not[15].

Another study showed patients in whom SVR was achieved had more decrease in the mean HbA1c level i.e. 7.2% to 6.8% than patients in whom SVR was not achieved i.e. from 7.3% to 7.1%. The reduction in the HbA1c level was more in patients in whom SVR was achieved (0.98%) than in patients in whom SVR was not achieved (0.65%) [20].

Ciancia et al., done a study in 2018, found that the diabetic responders had significantly more reduction in blood glucose level and HbA1c (p-value < 0.001). With insignificant difference in the fasting blood glucose (p-value = 0.707) and HbA1c (p-value = 0.780) as compared to non-responders[21]. Another study done recently by Boraie reported that after SVR; HbA1c was reduced from 7.6±0.69% to 6.7±0.78% among diabetics than from 5.8±0.5% to 5.1±0.3% in non-diabetics, with reduction in the frequency of uncontrolled diabetes from 22.4% to 5.2% patients after treatment[22].

The data regarding the impact of DAAs therapy on the HCV patients with type II diabetes is still conflicting. In contrary, few trials i.e. done by Stine et al.[23], Chaudhury et al.[24], and Giordano et al.[25], proved that there was insignificant difference observed between HbA1c before and after treatment in responders (p-value = 0.268). But in those trials, may be effects was lower due to several factors like type of antiviral used, old age group and more advanced liver disease, obesity, and liver steatosis. The cause may in part be due to diabetes and hyperglycemia clinical management with pharmacological treatment instead of to the main viral clearance mechanism itself as close to one-third of our cohort have increased antihyperglycemic dosages.

HCV impairs the glucose metabolism by directly altering pro-inflammatory cytokine levels through viral proteins and indirectly. The immediate effect of the insulin receptor substratum-1 interaction is due to the increased insulin receptor substratum-1 degradation due to up-regulation of serine/threonine phosphorylation or increased activation of the cytokine signaling suppressor 3 [26]. These overt activities on the insulin signal pathway interfere with downstream signalling and proper glucose metabolism regulation[27].

An indirect effect of HCV was also indicated for insulin sensitivity due to increased development of proinflammatory cytokines from sinusoidal hepatic cells, which interferes with the mechanisms of insulin signaling and contributes to the insulin resistance[10,28]. The possible prospect of switching to interferon-free therapy prevents interferon's hyperglycemic, autoimmune-mediated effects. In addition, such therapies include a fast oral, well-tolerated treatment scheme that helps achieve greater SVR after 12 weeks and reduces progression of the insulin resistance[29].

CONCLUSION

Based on the findings of this study it can be concluded that oral DAAs can help in controlling and improving the glycemic level significantly in HCV patients with diabetes mellitus with successful HCV eradication thus prevent the long term complications of Diabetes and reduction in insulin therapy in such patients.

Limitaions: Single center study Lack of long term data of diabetes control and complications in HCV patients.

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