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Original Article

Impact of HCV eradication on HBAIC in Genotype 3 Chronic HCV Diabetic Patients

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ABSTRACT

Objective: Hepatitis C Virus (HVC) is a global health concern. WHO estimated that it affects a 170 million people worldwide. In Pakistan, 6.8% of adult population exhibits presence of active disease. With the rise of DAAs especially Sofosbuvir and Velpatasvir, the ETR and SVR is remarkable. Patients who secure seroconversion following DAA treatment experience a drop in their HOMA-IR levels, in contrast to those who don't. It means that these are metabolic benefits of HCV eradication. Based on this hypothesis, we evaluated the benefit on HBAIC in patients achieving ETR.

Methods: the study sample comprised 100 type 2 diabetics who attended gastroenterology clinic at Ghurki Trust Teaching Hospital (GTTH), a tertiary care hospital in Lahore for treatment of HCV infection. All the confirmed type 2 diabetes cases on any therapy were included in the study sample. Data was analysed using SPSS Statistics version 24.

Results: Out of study sample of 100 patients, 100% achieved an end of treatment response (ETR). In our study, mean difference in fasting blood sugar (FBS) from baseline to ETR was found to be a decrease of 48.70 ± 22.20 mg/dL (p Value<0.05). Similarly, the mean difference RBS over the same duration showed a reduction of 98.00 ± 39.70 mg/dL (p value <0.05) Quite interestingly, HbA1c levels also showed a decline of mean difference of 1.10 ± 0.82% from baseline to the 3 months mark (p value<0.05)
Conclusion: Successful eradication of HCV does lead to improvement in Diabetes control in type 2DM.

Key words: Diabetes Mellitus, HCV, ETR, HBAIC, Sofosbuvir, Velpatasvir

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Introduction:

Hepatitis C Virus (HCV) is a global health problem with an estimated 170 million population of world, suffering from this and it leads to fatal complication of cirrhosis and hepatocellular carcinoma[1]. Developing countries, like Pakistan has an estimated prevalence of 6.8% making it more vulnerable to cirrhosis and its complications[2]. Interestingly the most common genotype of HCV is type 3 in Pakistan, which is claimed to be easier to treat as compared to other genotypes[3]. But already alarming figures of prevalence are further intensified when we observe an interplay between HCV and Diabetes Mellitus[4]. Diabetes is already very prevalent in Pakistan with almost every fourth adult is suffering from this disease[5]. The development of Ttype 2 DM is due to two fundamental disturbances: tissues like muscle, liver, and adipose becoming less responsive to insulin, and Pancreatic beta cells gradually losing their ability to produce required insulin in response to needs of body[6]. Genetic predispositions, environmental and lifestyle factors, notably poor diet, lack of physical activity, and resultant obesity, are critical contributors to its development[7]. Various studies believe that almost 70% of individuals with chronic HCV infection are at a risk of developing type 2 DM[8]. This is hypothesized due to alterations in insulin resistance and glucose metabolism mechanisms by the Hepatitis C Virus. Although the exact pathway of this connection is ambiguous but still then there is a possible role of HCV proteins in affecting insulin receptors and increasing the inflammatory cytokine levels[9]. In a local study on the prevalence of T2DM among HCV infected patients showed 26.42% prevalence of T2DM in patients infected with HCV[10]. In another study DM prevalence of 34.80% was seen in HCV infected individuals. Male patients showed a higher prevalence (40.40%) as compared to females (31.20%)[11].

The treatment regimen to treat chronic HCV has witnessed substantial advancements in past decade. Medications known as Direct-acting antivirals (DAAs) has remarkable success rates against all genotypes of HCV with fewer side effects as compared to previously used combination of Interferon and Ribavirin[12].The success of these antiviral agents in terms of better sustained virologic response (SVR) prompted researchers to see its impact on metabolic health of type 2 DM patients[13].

A study done by Eslam et al, to look for positive relationship between HCV eradication and improvement in insulin sensitivity, showed that ppatients who secured an SVR following DAA treatment experienced a significant drop in HOMA-IR levels, as compared to those who didn't achieve SVR[14]. This highlights metabolic benefits of achieving HCV eradication but also provides a food for thought to prioritize HCV eradication as a preventative measure against development of T2DM. In work done globally it is now advocated that HCV infection stimulates the body's immune response, which then leads to secretion of pro-inflammatory cytokines like TNF-a and IL-6. These cytokines have an established role in modulating insulin signalling. When HCV eradication is achieved, levels of these cytokines drop significantly. This decline in pro-inflammatory cytokines then leads to increased insulin sensitivity, thus playing a role in reducing metabolic burden on body and DM[15 16].

We planned this study to investigate the potential of improvement of glycemic indices in Genotype 3 HCV patients who are using Sofosbuvir / Velpatasvir combo of DAA for achieving viral eradication.

Materials and methods

This study was done on 100 participants in Department of Gastroenterology and was a prospective cohort study for six months. Sample size of 100 was calculated by assuming that 85% to 95% of the patients

achieve improved glycaemic control after successful HCV eradication with DAA.

Criteria for Inclusion:

- **i)** Individuals aged 18-60 years.
- **ii)** Both males and females were considered.
- **iii)** Only Individuals with chronic HCV who had achieved an end of treatment response post 12 weeks of DAA administration.
- **iv)** Known type 2 Diabetes Mellitus cases who had pre-treatment HbA1c levels above 7.5 %.

Criteria of Exclusion:

- i) Individuals in the Child Pugh Class B and C.
- ii) Documented dual infection with HIV or hepatitis B virus.
- iii) Established liver cirrhosis or hepatocellular carcinoma.
- iv) Severe accompanying conditions like chronic obstructive pulmonary disease, end-stage renal failure, or congestive heart failure.
- v) Administration of drugs affecting glycemic balance e.g. steroids.
- vi) Documented allergy to DAAs or related medications.
- vii) Expecting mothers or those breastfeeding.
- viii) Those who are not willing or able to adhere to the study's protocols and follow up demands.

Upon acquiring clearance from GTTH ethics committee, a forward-looking cohort analysis was undertaken. Patients fulfilling the inclusion criteria were enrolled in the study after informed written consent.

Initial data of the participants, including age, gender, T2DM's duration, span of HCV infection and genotype were recorded. All HCV patients underwent DAA treatment with oral Sofosbuvir 400mg / velpatasvir 100mg combination daily for a three-month time period. Pre-treatment, blood samples included HbA1c, Fasting Blood Glucose level, random blood glucose, Liver eenzymees measurements including Alanine Aminotransferase, Aspartate Aminotransferase, Serum Bilirubin, Albumin and prothrombin time. The Abbott M-2000 system, was used for real-time PCR HCV RNA plasma levels determination with its sensitivity threshold of 12 IU/mL.

After 12-week duration of therapy, HCV-RNA PCR test was repeated to determine viral load, aiming for ETR readings below 12 IU/L after DAA administration. Metabolic profile including HBAIC, FBS and RBS were also repeated. Data examination was carried out utilizing the Statistical Package for Social Sciences (SPSS), version 24. To evaluate the primary attributes of the study's participants, descriptive statistics were employed. Continuous data points were represented either as mean ± standard deviation (SD) or as median within the interquartile range, contingent upon the situation. Categories of data were denoted through their frequency and proportion. The study's primary focus was on alternations in HbA1c levels from the initial measurement to 12 weeks post-finalization of DAA treatment. Any difference in HbA1c values from the start to 12 weeks post-treatment was evaluated via the paired t-test or the Wilcoxon signed-rank test. Alterations in FPG and RBG readings between the start and the 12-week mark were assessed through the paired t-test or the Wilcoxon signed-rank test. All the statistical evaluations were two-sided, with a p-value less than 0.05 was considered to be of statistical significance.

Results

In this study of 100 patients, 71% (n=71) were female and 29.0% (n=29) were male. Regarding age distribution, 32 of the participants were between 24 and 36 years old, 48 were in the 37-48 years bracket, and 20 were aged between 49 and 60 years.

Mean age of study participants was 46.5 ± 7.34 years.

When examining the duration of diabetes, 28 had been diabetic for 1-3 years, 40 were diabetic for 7 years, and 32 had a diabetes history of 8 years or more. Duration of HCV infection, 34 had been infected for 1-3 years, 46 for 4-7 years, 10 for 8-10 years, and 10 had infection for more than 10 years. The average duration of their diabetes was reported as 8.2 ± 3.20 years, while the HCV infection persisted for an average duration of 6.4 ± 5.40 years. Baseline HbA1c was 9.70 ± 1.60, fasting blood sugar averaged 164.48 ± 36.50 mg/dL, and the mean random blood sugar was 288.30 ± 60.30 mg/dL. When evaluating Liver Function tests mean serum bilirubin was 1.14 ± 0.41 mg/dL and a serum albumin level of 3.50 ± 0.68 g/dL. Amongst Liver enzymes ALT had mean value of 56.69 ± 4.80 IU/L, ALP averaged at 120.44 ± 56.30 IU/L, and the mean PT duration was 11.40 ± 1.28 seconds. (Table 1)

Table 1: Baseline Clinical and Laboratory Parameters

Parameter	Mean	Std.Deviation
Age	46.50	7.34
Duration of Diabetes	8.20	3.20
Duration of HCV infection	6.40	5.40
ALT	56.6	4.80
ALP	120.4	56.30
PT	11.40	1.28
Serum Bilirubin	1.14	0.41
Serum Albumin	3.13	0.78
Basline_HbA1C	8.80	1.60
Baseline Fasting Blood Sugar	164.48	36.50
Baseline Random Blood Sugar	288.30	60.30

In our study, after three months of treatment, the fasting blood sugar in patients averaged at 116.68 ± 26.86 mg/dL. Their random blood sugar post-three months of HCV treatment was 190.70 ± 40.24 mg/dL. Additionally, the HbA1c levels after the same duration were recorded at 7.70 ± 1.58%.

In our study, mean difference in fasting blood sugar (FBS) from baseline to ETR was found to be a decrease of 48.70 ± 22.20 mg/dL (p Value<0.05). Similarly, the mean difference RBS over the same duration showed a reduction of 98.00 ± 39.70 mg/dL (p value <0.05). Quite interestingly, HbA1c levels also showed a decline of mean difference of 1.10 ± 0.82% from baseline to the three months mark (p value<0.05).

Table 2: Difference in Glycemic Parameters from Baseline to ETR

Parameter	Mean	Std. Deviation	P Value
FBS: Mean difference from baseline to 3 months	48.70	22.20	<0.05
RBS: Mean difference from baseline to 3 months	98.00	39.70	<0.05
HBAIC: Mean difference form baseline to 3 months	1.10	0.82	<0.05

In our study cohort, the ETR with SOF VELPA combo showed a remarkable sero-conversion of Hepatitis C infection, with 100% of patient getting negative PCR results at the end of treatment. So, all the study participants were given follow ups and regular monitoring done to sustain the compliance.

Discussion

Hepatitis C Virus infection is a global health concern, that has been silently spreading world-wide. WHO has estimated that it affects 170 million people, or 1-2% of the global population[1]. Developing countries, like Pakistan, is also hit by this infection at an alarming rate, with data suggesting that 6.8% of Pakistan's adult population has HCV infection[2]. Once HCV infection is not properly taken care of, it then leads to a lot of host liver-related complications, ranging from the implication of effects of cirrhosis to the

fatal complications like hepatocellular carcinoma[3]. HCV is further subdivided into six major genotypes and several serotypes. Predominant genotype of HCV in Pakistan is Genotype 3, which is claimed to be easy to treat[4]. But the actual issue is the suggested interplay between HCV and Type 2 Diabetes Mellitus. It has been seen that around 70% of individuals with chronic HCV infection stand have an increased risk of developing type 2 DM[5]. This is because of alterations in insulin resistance and glucose metabolism by various mechanisms attributed to HCV. Although the pathways of this connection are not clear, but what we do recognize that HCV induces proteins which do affect insulin receptors thus raising inflammatory cytokine levels. This leads to increased insulin resistance and ultimately T2DM[17]. The development of T2DM or worsening of already present T2DM can be attributed to fundamental disturbance of insulin resistance, thus tissues such as the muscle, liver and adipose becoming less responsive to insulin[6]. This leads to a pressure on the insulin-producing beta cells of pancreas to produce more and more insulin, thus gradually losing their ability to produce sufficient amounts of insulin, a state called burned out or stressed beta cells. Although, genetic predispositions play a role in its onset, environmental and lifestyle factors, especially poor diet, lack of physical activity, and resultant obesity, have their own role in disease development[7].

In recent years, the number of Pakistani populations with diabetes is also on the rise. In 2016, 11.77% of the population had diabetes. This value increased to 16.98% in 2018 and further escalated to 17.1% in 2019. Now, international diabetes federation has reported that a concerning 26.7% of Pakistani adults had diabetes in 2022, which makes it approximately 33 million people[18]. Of particular concern is the situation in which a patient is having both T2DM and HCV infection. In a study published on the prevalence T2DM among HCV infected patients from Khyber Pakhtunkhwa (KPK), it was found that 26.42% of T2DM in patients are concomitantly infected with HCV[10]. In aanother local investigation, a significant correlation was observed between HCV infection and the incidence of T2DM. It reported a DM prevalence of 34.80% in HCV infected individuals. Interestingly, the male patients exhibited a higher DM prevalence of 40.4% compared to females who showed a prevalence rate of 31.20%[11]. Conditions like metabolic syndrome, dyslipidaemia, central adiposity or hypertension can also increase the risk of T2DM if present alongside. These metabolic derangements might create a synergistic effect, thus markedly elevating diabetes risk[9].

Treatment of chronic HCV has seen substantial advancements in the recent past. From the era of interferon and ribavirin usage to now new medications known as direct-acting antivirals (DAAs). These antiviral agents offer higher cure rates, which in turn leads to better sustained virologic response (SVR) rates and hence, eradication of the virus from the body. They also offer fewer side effects than previous therapeutic regimens[12]. This achievement prompted researchers to probe its impact on metabolic derangement improvement. A study by Eslam et al. in 2011 gave the first indications of a positive relationship between HCV eradication and improvement in insulin sensitivity. In his work, patients who secured an SVR following DAA treatment experienced a drop in their HOMA-IR levels, as compared to those who didn't[14]. This highlighted the metabolic benefits of achieving SVR but also provided an incentive to prioritize HCV eradication in those who need metabolic improvement as well.

On the same lines, we also aimed to investigate the potential of DAA therapy on achieving HBA1C after achieving HCV eradication. The core hypothesis of this study is that achieving eradication of HCV can pave the way for better glycemic control among co-diagnosed patients of

HCV and type 2 DM. HCV infection alters the body's immune response, leading to an increased secretion of pro-inflammatory cytokines, particularly TNF-α and IL-6. These cytokines reduce the insulin signalling thus leading to insulin resistance. Upon HCV eradication, the levels of these cytokines drops leading to an enhanced insulin sensitivity[15 16]. In our study, a total of 100 type 2 DM patients with chronic HCV infection were given Sofosbuvir and Velpatasvir as a dual therapy for three months. They were then evaluated for HBA1C drop pre- and post- treatment. Luckily due to good follow ups and advice, 100% patients achieved SVR. The mean drop of HBAIC observed in our study was 1.10 ($p<0.05$). This result is in complete agreement to work which has been done previously by Yuan et al. They reported a significant glycemic improvement after receiving DAAs therapy; in the form of > 1% reduction in HbA1c level (p value < 0.001). Moreover, their large group of study patients demonstrated reductions in FPG levels, whereas the group that did not achieve SVR showed no significant change in FPG levels. The difference was statistically significant for the SVR group ($p <0.001$). While it was non-significant for the non-SVR group ($p=0.267$)[19]. In another work done by Boraic et al., 240 chronic HCV patients were analyzed for the effects of DAA therapy on glycemic indices. Upon achieving SVR, the diabetic subset showed a decline in HbA1c levels from an initial 7.6 ± 0.69 to 6.7 ± 0.78, while the non-diabetic group showed a reduction from 5.8 ± 0.5 to 5.1 ± 0.3. This study further showed a significant drop in uncontrolled T2 DM cases from 22.4% pre-treatment to 5.2% post-treatment[20]. This is also in close agreement to our study. In an analysis by Zied et al. Comparative assessments of glycemic parameters before and after DAA treatment showed almost similar results to our study. In their study, FBS prior to treatment averaged 219.06 ± 111.36 mg/dl, which decreased post-treatment to 112.37 ± 20.66 mg/dl, ($p=0.009$). RBS initial levels were 309.78 ± 108.7 mg/dl, which subsequently reduced to 191.2 ± 55.15 mg/dl after treatment ($p=0.001$). HbA1c percentages also showed drop of >1 ($p <0.05$)[21]. These results of his work are also in close agreement to results of our study.

A similar work done by Akhtar et al., showed that patients who were having high baseline HbA1c and achieved SVR, had better HbA1c reduction post-treatment compared to non-achievers[8]. Similarly, Hum et al. reported that patients with a higher drop of 0.98 % HbA1c was seen in those who achieved SVR[22]. Our observations closely align with past research, reinforcing the validly and reliability of the results. Although in all these studies different antiviral regimens were used and for different time periods as well still removal of virus from body led to improvement of metabolic profile. However, there were some limitations to our study. The absence of a control group, untreated for Hepatitis C but monitored for glycemic parameters, may have clarified biasness. Also relying on patients to self-report their compliance to therapy usually raises questions of accurate data. Additionally, our study monitored patients for ETR response but longer-term impacts on glycemic parameters must also be seen for sustainability of results. Future studies should look for a more extended period of monitoring, to understand the long-term implications of DAA therapy on glycemic control.

Conclusion

Hepatitis C Virus affects the metabolic profile of patients by increasing the insulin resistance, due to which there is worsening of Glycemic control of T2DM patients. Once eradication of HCV is achieved HBA1C is reduced by almost a value of 1 in T2DM patients co-infected with Genotype 3 HCV infection.

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Author's Contribution:

TT: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
AW, MRJ, UK, UH: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.