Original Article

Glycemic Control after Initiating Direct-Acting Antiviral Agents in Patients with Hepatitis C Virus and Type 2 Diabetes Mellitus Using the United States Integrated Healthcare System

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ABSTRACT

Objective: Hepatitis C virus (HCV) has an increased risk of Type 2 diabetes mellitus (T2DM). Prior studies found that the eradication of HCV with direct-acting antiviral (DAA) agents led to improved glycemic control in patients with T2DM. We aimed to identify the association between HCV eradication and glycemic control in patients diagnosed with HCV and T2DM. **Methods:** A retrospective observational study was conducted to identify adult patients diagnosed with HCV from January 1, 2014, to August 31, 2017. Patients were included if they were initiated on one of the following DAA agents within the study period: Sofosbuvir/velpatasvir, sofosbuvir/ledispavir, elbasvir/grazopevir. Patients were also required to have the diagnosis of T2DM. The primary outcome of this study was the average change in glycosylated hemoglobin (HbA1c) pre- versus post-DAA agents. **Findings:** Our final cohort consisted of 996 patients diagnosed with HCV and T2DM: Patients who achieved sustained virologic response (SVR) (n = 937, 94%) and those who did not achieve SVR (n = 59, 6%). In the SVR group, there was a 0.3950% reduction in HbA1c ($P < 0.0001$) and in those who did not achieve SVR group, there was 0.3532% reduction in HbA1c ($P = 0.0051$). In the overall study population, SVR group had 0.04% more reduction in HbA1c but was not statistically significant ($P = 0.7441$). **Conclusion:** Both groups had statistically significant reductions in HbA1c when comparing the mean change in average HbA1c pre- versus post-DAA agent. Patients who achieved SVR had a greater absolute reduction in HbA1c by 0.04%; however, this was not statistically significant.

Keywords: *Hepatitis C virus, sustained virologic response, type 2 diabetes mellitus*

Introduction

Chronic hepatitis C virus (HCV) infection is associated with a higher prevalence of Type 2 diabetes mellitus (T2DM).[1,2] The presence of chronic HCV infection increases the risk of developing T2DM for patients with metabolic syndrome by 11-fold and is estimated that up to 33% of chronic hepatitis C patients have T2DM.[1,3] T2DM is one of the most common extrahepatic manifestations of chronic HCV infection and is associated with increased risk for liver, renal, and cardiovascular complications.[4] Specific complications of HCV include cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Decompensated liver cirrhosis together with HCC is the common cause of death associated with chronic HCV infection worldwide.[5,6] In addition, complications of T2DM include retinopathy, kidney failure, diabetic neuropathy, and cardiovascular diseases, including stroke.[7]

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The mechanism for the observed association between HCV and DM2 is unclear, but some evidence suggests that it may be related to increased insulin resistance or expression of pro-inflammatory cytokines. Prior studies, such as Calzadilla-Bertot *et al*. showed patients with compensated HCV cirrhosis having higher rates of decompensation when they had diabetes and insulin resistance. The study also found that insulin resistance was a predictor of overall mortality.[8] Other studies have speculated that HCV proteins increase inflammatory cytokines such as interleukin-2 and tumor necrosis factor-α, which results in an upregulation of gluconeogenesis, enhances lipid accumulation in the liver, and causes insulin resistance.[1,9]

Early identification and treatment of patients with HCV and T2DM may reduce and/or prevent future diabetic complications through improved glycemic control.[4] Several studies have shown the effects of HCV on glycemic control, such as an interferon-based study by Delgado-Borreg *et al*. The study suggested that successful clearance of the HCV could lead to improvement in insulin resistance.[10] In addition, the veterans affairs (VA) healthcare system conducted a study to include national data from 167 medical centers, 875 ambulatory care, and community-based outpatient clinics of the VA system throughout the United States. Hum *et al*. found that the eradication of HCV with direct-acting antiviral (DAA) agents lead to improved glycemic control in patients with T2DM. Patients with more inadequate glycemic control at baseline had even more significant improvement, nearly a 1% drop in glycosylated hemoglobin (HbA1c) associated with sustained virologic response (SVR).[3,11]

While the present study certainly offers a more diverse population of patients and takes place in the US, another trial published in *Journal of Medical Virology* in 2017 addressed this question previously and also found a glycemic benefit in patients with DM when treated with DAAs for HCV in a 100% Caucasian population in Italy.[11] Although evidence suggests that eradication of HCV may be associated with improved glycemic control in patients with T2DM, prior studies are limited. The objective of this study was to investigate whether eradication of HCV infection, with the newest DAA therapies, is associated with improved glycemic control in patients with T2DM using an integrated managed care healthcare system population in the US population.

Methods

This retrospective, observational study was conducted to identify patients from the Kaiser Permanente Southern California (KPSC) health plan aged >18 years old and with the diagnosis of HCV genotypes 1 through 6 from January 1, 2014, to August 31, 2017. The study design was pre- and post-study design with a period of 12 months before index date labeled as preindex and the period of 12 months postindex labeled as postindex. KPSC is an integrated healthcare delivery system with approximately 4.5 million members located in Southern California. Data were derived from the KPSC regional database from 14 medical centers and contain information on patient demographics, diagnoses, prescriptions, laboratory results, medical, and hospital encounters. The KPSC database has an electronic health medical record system that allows for more detailed information to be accessed and included in studies. The KPSC membership currently represents 15% of the underlying population in the Southern California region and this membership closely mirrors the Southern California population; it is racially diverse and includes the entire socioeconomic spectrum.[12] The Institutional Review Board for KPSC approved this study.

Patients were required to be newly initiated on a DAA agent during this period, and this was labeled as index date; the DAA list included: Ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, and elbasvir/grazoprevir. The study end date was August 31, 2017, and hence that all patients had 12 months postindex to evaluate the primary outcome. Patients with any history of interferon and ribavirin-containing regimens, or first-generation DAA agents, or antiviral medications were excluded from the study. Patients were required to have a diagnosis of T2DM or have had a prescription of an antidiabetic medication during the preindex period and up to primary outcome so that patients were on antidiabetic medication when evaluating HbA1c levels. The baseline period was identified as during the preindex period and covariates consisted with gender, race, HCV genotypes, comorbidities (anemia, liver cirrhosis, alcohol use disorder, and chronic kidney disease), and laboratory measurements (international normalized ratio [INR], platelets, bilirubin, and albumin). Patients with HbA1c levels were identified during pre- and post-index periods after the SVR laboratory measurement; multiple HbA1c levels were averaged during their respective periods. Any patients without HbA1c during the pre- or post-index period were excluded. The SVR was defined as undetectable hepatitis C viral load 12 weeks after the end of hepatitis C treatment. Undetectable hepatitis C viral load during that timeframe indicates the cure of HCV. Finally, any patient who did not have an SVR level was excluded.

The primary outcome of the study was to compare HbA1c levels during the pre- versus post-index period among those who achieved SVR. A secondary aim

was to determine if there was a statistically significant difference in the HbA1c levels for patients who achieved SVR versus those who did not achieve SVR. We also sought to identify factors associated with changes in pre- and post-HbA1c levels. Potential confounders and biases may include possibility that patients taking new effective therapy for HCV might be more likely to engage in other healthy behaviors. Additional analysis including multivariable regression analysis was conducted to address potential sources of bias. Multivariable regression analysis was conducted to determine whether independent variables such as genotype, body mass index (BMI), and gender affected the changes in HbA1c. In all categories, there was no statistical difference between gender, BMI, and hepatitis C genotypes (data not shown).

Unadjusted descriptive statistics were conducted to summarize patient characteristics of the two study cohorts (achieved SVR vs. did not achieve SVR). Differences between these patient groups were tested using two-sample *t*-test or Wilcoxon test for continuous variables and the Chi-squared statistic for categorical variables. The mean change in HbA1c from before versus after DAA treatment was calculated. In addition, categories of HbA1c (>7%, >8%, and >9%) were evaluated descriptively to calculate mean differences pre- and post-DAA treatment. Finally, mean change in HbA1c levels for patients with cirrhosis compared to patients with no cirrhosis were descriptively evaluated. A sample size calculation was conducted and it was found that a study population of 71 patients was required to detect a difference of 0.5% of HbA1c with 90% power. Multivariable linear regression was conducted to identify the relationship associated with HbA1c change while controlling for age, sex, race, baseline laboratories, and comorbidities. Additional multivariate linear regression was performed to determine whether independent variables such as genotype, body mass index, and gender impacted the changes in HbA1c. All data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Values of $P < 0.05$ were considered statistically significant.

Results

A total of 29,096 adult patients were diagnosed with HCV in the KPSC region between January 1, 2014, and August 31, 2017. Among 29,096 HCV patients, 25% (n = 7176) were treated with the selected DAAs [Figure 1]. Among those patients, 22% (n = 1559) were diagnosed with T2DM or were on antidiabetic medication for 12 months before index date (DAA agent start date). The final study cohort consisted of 996 patients after applying the inclusion and exclusion criteria, and two

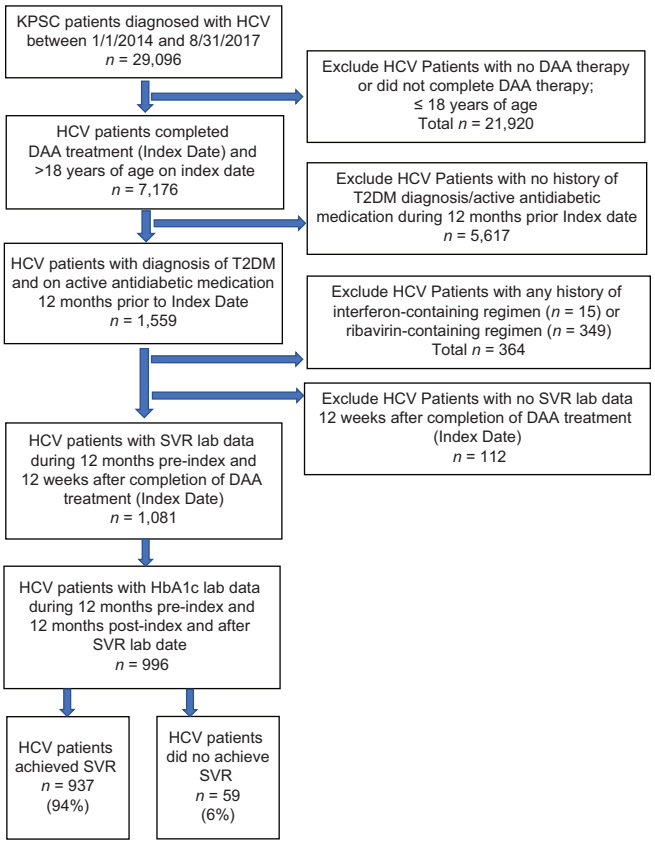

Figure 1: Study cohort selection flow chart

study cohorts were created [Figure 1]: Patients who achieved SVR (n = 937, 94%) and those who did not achieve SVR (n = 59, 6%).

Table 1 provides baseline characteristics for our study cohort. Within the total study cohort (n = 996), the majority of the patients were male (67.3%) and the average age was 61 years (standard deviation [SD] 8.1). The race was relatively similar in representation: Caucasian (n = 307, 30.8%), African American (n = 293, 29.4%), and Hispanics (n = 310, 31.1%). Majority of the patients identified had hepatitis C genotype 1 (n = 868, 87.1%) and were treated with ledispavir/sofosbuvir (n = 892, 89.6%). The baseline antidiabetic medications for patients diagnosed with T2DM before initiating DAA medications were identified and are shown in Table 1. The majority of the patients who were on antidiabetic medications were on metformin (43.4%), sulfonylureas (19.7%), and insulins (14.8%). Statistical findings included gender, where males were shown not to achieve SVR (~80%) compared with achieved SVR (66.5%), P = 0.0365; laboratory measurement for platelets were higher in mean levels for the patients who achieved SVR (186.7) compared to patients who did not achieve SVR (155.1) (P = 0.0011); finally, bilirubin levels were also found to be statistically different (P = 0.0030).

Table 1: Baseline patient characteristics

Characteristics	Total (*n*=996)	Achieved SVR (*n*=937)	Did not achieve SVR (*n*=59)	*P**
Gender, *n* (%)				
Male	670 (67.3)	623 (66.5)	47 (79.7)	0.0365[a]
Age (years±SD)	61.3±8.13	61.3±8.24	62.3±6.21	0.2266[b]
Race, *n* (%)				
White	307 (30.8)	290 (30.9)	17 (28.8)	0.6580[a]
Black	293 (29.4)	271 (28.9)	22 (37.3)	
Hispanic	310 (31.1)	293 (31.3)	17 (28.8)	
Asian	57 (5.7)	55 (5.9)	2 (3.4)	
Other	29 (2.9)	28 (3.0)	1 (1.7)	
Genotype, *n* (%)				
1	868 (87.1)	817 (87.2)	51 (86.4)	0.8105[a]
2	38 (3.8)	36 (3.8)	2 (3.4)	
3	34 (3.4)	33 (3.5)	1 (1.7)	
4	42 (4.2)	38 (4.1)	4 (6.8)	
6	14 (1.4)	13 (1.4)	1 (1.7)	
DAA Treatment*, *n* (%)				
LDV/SOF	892 (89.6)	835 (89.1)	57 (96.6)	0.1682[a]
SOL/VEL	78 (7.8)	76 (8.1)	2 (3.4)	
EBR/GZR	26 (2.6)	26 (2.8)	0 (0)	
Comorbidities, *n* (%)				
Anemia	135 (13.6)	130 (13.9)	5 (8.5)	0.2399[a]
Alcohol use disorder	184 (18.5)	169 (18.0)	15 (25.4)	0.1561[a]
Chronic kidney disease	108 (10.8)	102 (10.9)	6 (10.2)	0.8637[a]
Liver cirrhosis	600 (60.2)	567 (60.5)	33 (55.9)	0.4857[a]
Clinical measurements (mean±SD)				
Albumin (mg/dL)	3.7±0.49	3.7±0.49	3.6±0.57	0.0625[b]
Bilirubin (µmol/L)	0.8±0.46	0.8±0.46	0.9±0.38	0.0030[b]
Body mass index (kg/m^2)	30.3±5.83	30.3±5.85	30.4±5.54	0.9223[b]
INR	1.1±0.24	1.1±0.23	1.1±0.33	0.0547[b]
Platelets (10^9/L)	184.8±71.23	186.7±70.85	155.1±71.21	0.0110[b]
Medications for Diagnosed T2DM				
Alpha-glucosidase inhibitors	1 (0.1)	1 (0.1)	0 (0.0)	
Biguanide (metformin)	432 (43.4)	408 (43.5)	24 (41.0)	
Biguanide/sulfonylurea	42 (4.2)	36 (3.8)	6 (10.0)	
DPP-4 inhibitors	8 (0.9)	8 (0.9)	0 (0.0)	
GLP-1 agonists	4 (0.4)	4 (0.4)	0 (0.0)	
Insulins	147 (14.8)	141 (15.1)	6 (10.0)	
Meglitinide	1 (0.1)	1 (0.1)	0 (0.0)	
SGLT2 inhibitors	1 (0.1)	1 (0.1)	0 (0.0)	
Sulfonylurea	196 (19.7)	182 (19.4)	14 (24.0)	
Thiazolidinediones	11 (1.2)	11 (1.2)	0 (0.0)	

**P*<0.05 was defined as a statistically significant difference between the two groups. The following statistical test was used to calculate the *P* value: [a]Chi-square test was used for categorical variables, [b]Wilcoxon test was used for continuous variables. DAA=Direct-acting antiviral, LDV/SOF=Ledipasvir/sofosbuvir, SOL/VEL=Sofosbuvir/ledipasvir, EBR/GZR=Elbasvir/grazoprevir, INR=International normalized ratio, T2DM=Type 2 Diabetes, DPP-4=Dipeptidyl peptidase-4, GLP=Glucagon-like peptide, SGLT2=Sodium glucose co-transporter 2, SVR=Sustained virologic response

As shown in Table 2, the mean HbA1c pre- versus post-DAA treatment for patients who achieved SVR (n = 937) was 7.5% and 7.1%, with a mean change of 0.3950 (P < 0.0001). The mean HbA1c for patients pre- versus post-DAA agent who did not achieve SVR (n = 59), was 7.4% and 7.1%; the mean change in HbA1c was 0.3532 (P = 0.0051). The difference in HbA1c between patients who achieved SVR and those who did not was 0.0418 (P = 0.7441), which was not statistically significant.

Further analysis was conducted and adjusted based on the HbA1c baseline. There were no significant changes between patients who achieved SVR compared to patients who did not achieve SVR with baseline

HbA1c levels >7%, >8% and >9% [Table 3]. In addition, other potential confounders such as baseline cirrhosis, were also analyzed. Patients with cirrhosis and without cirrhosis also showed no significant difference in mean HbA1c between the two study groups [Table 4]. Results from the multivariable regression analysis showed substantial predictors to be age and INR that are associated with changes in HbA1c from pre- to post-DAA treatment. As patients increase in age, they have a 0.01 decrease in their HbA1c turn (P = 0.0058). Patients with increase in INR levels have 0.33 smaller decreases for HbA1c pre-post difference (P = 0.0453). Patients who did not achieve SVR were to have 0.04 slighter decrease for HbA1c pre-post difference. Table 5 displays the factors associated with the changes in HbA1c levels pre- and post-difference.

Discussion

In the US, an estimated 29.1 million people are diagnosed with T2DM, and 1.4% of the population have chronic HCV.[3] Patients with chronic HCV infection is

Table 2: Hemoglobin A1c information for hepatitis C virus patients who achieved sustained virologic response and did not achieve sustained virologic response

HbA1c information	Achieved SVR (n=937)			P*
	Pre-index	Post-index	Mean change±SD	
Mean±SD	7.5±1.45	7.1±1.25	0.3950±0.93	<0.0001[b]
Range (%minimum–%maximum)	4.6–14.3	4.5–14.6		
HbA1c information	**Did not achieve SVR (n=59)**			P*
	Pre-index	Post-index	Mean change±SD	
Mean±SD	7.4±1.45	7.1±1.10	0.3532±1.18	0.0051[b]
Range (%minimum–%maximum)	5.1–10.9	5.1–9.8		
Total mean change between groups			0.0418	0.7441[b]

*P<0.05 was defined as a statistically significant difference between the two groups. The following statistical test was used to calculate the P value: [b]Wilcoxon test was used for continuous variables. DAA=Direct acting antiviral, HbA1c=Hemoglobin A1c, HCV=Hepatitis C virus, SVR=Sustained virologic response, SD=Standard deviation

Table 3: Different hemoglobin A1c levels (>7%, >8% and>9%) pre- and post-direct acting antiviral treatment*

HbA1c levels	Study groups	Mean HbA1c (%)±SD		Mean change in HbA1c±SD	Mean difference between groups	P*
		Pre-index Prior DAA treatment	Post-index After DAA treatment			
>7% (n=570)	Achieved SVR (n=540)	8.4±1.25	7.7±1.28	0.76±1.35	−0.0654	0.7944[b]
	Did not achieve SVR (n=30)	8.5±1.23	7.7±1.05	0.83±1.05		
>8% (n=309)	Achieved SVR (n=291)	9.3±1.17	8.0±1.50	1.23±1.52	−0.0442	0.9034[b]
	Did not achieve SVR (n=18)	9.3±1.02	8.2+1.14	1.28±1.06		
>9% (n=140)	Achieved SVR (n=130)	10.2±1.17	8.4±1.81	1.83±1.78	0.4291	0.4562[b]
	Did Not Achieve SVR (n=10)	10.1±0.69	8.7±1.29	1.40±1.29		

*P<0.05 was defined as a statistically significant difference between the two groups. The following statistical test was used to calculate the P value: [b]Wilcoxon test was used for continuous variables. Patients are not mutually exclusive since some patients could be in multiple categories. DAA=Direct-acting antiviral, HbA1c=Hemoglobin A1c, HCV=Hepatitis C virus, SVR=Sustained virologic response, SD=Standard deviation

Table 4: Hemoglobin A1c levels within cirrhosis hepatitis C virus patients pre- and Post-direct-acting antiviral treatment

Number of cirrhosis patients	Study groups	Mean HbA1c (%)±SD		Mean change in HbA1c±SD	Mean difference between groups	P*
		Pre-index Prior DAA treatment	Post-index After DAA treatment			
Cirrhosis (n=600)	Achieved SVR (n=567)	7.5±1.46	7.2±1.31	0.37±1.20	−0.0424	0.7808[b]
	Did not achieve SVR (n=33)	7.2±1.43	6.8±1.04	0.42±1.082		
Without cirrhosis (n=396)	Achieved SVR (n=370)	7.5±1.42	7.1±1.14	0.37±1.20	0.1540	0.5079[b]
	Did not achieve SVR (n=26)	7.7±1.60	7.4±1.09	0.27±1.07		

*P<0.05 was defined as a statistically significant difference between the two groups. The following statistical test was used to calculate the P value: [b]Wilcoxon test was used for continuous variables. DAA=Direct-acting antiviral, HbA1c=Hemoglobin A1c, HCV=Hepatitis C virus, SVR=Sustained virologic response, SD=Standard deviation

Table 5: Multivariable linear regression to identify the relationship of factors associated with changes in hemoglobin A1c levels (pre- and post- direct-acting antiviral treatment)

Patient Variables	Estimate	*P**
No SVR versus SVR	−0.04	0.8195[a]
Age (years)	−0.01	0.0058[b]
Female versus male	−0.09	0.2750[a]
Race		
Asian	−0.08	0.6700[a]
Black	−0.03	0.7596[a]
Hispanic	−0.05	0.6175[a]
Other	0.29	0.2213[a]
White (reference)	1.00	
BMI (kg/m^2)		
Underweight (reference)	1.00	
Normal	0.06	0.9275[b]
Obese	0.06	0.9315[b]
Overweight	0.14	0.8331[b]
Laboratory levels		
Albumin (mg/dL)	−0.11	0.2168[b]
Bilirubin	0.06	0.5253[b]
CBC	0.0004	0.5609[b]
INR	−0.33	0.0453[b]
Comorbidities		
No anemia versus anemia	−0.04	0.7692[a]
No CKD versus CKD	0.19	0.1373[a]
No alcohol use versus alcohol use	0.11	0.2627[a]
No liver cirrhosis versus liver cirrhosis	0.002	0.9856[a]

*P<0.05 was defined as a statistically significant difference between the two groups. The following statistical test were used to calculate the P value: [a]Chi-square test was used for categorical variables, [b]Wilcoxon test was used for continuous variables. DAA=Direct acting antiviral, HbA1c=Hemoglobin A1c, CKD=Chronic kidney disease, SVR=Sustained virologic response, CBC=Complete blood count, INR=International normalized ratio, BMI=Body mass index, BMI normal=18.5–24.9, BMI overweight=25.0–29.9, BMI obese=≥30.0, BMI underweight=<18.5, SVR=Sustained virologic response

four times more likely to develop T2DM than in patients without HCV.[3] Researchers have suggested that there is a two-way association between HCV and T2DM. HCV is associated with accelerated steatosis that is mediated through increased production of the lipogenic substrate, upregulation of lipogenesis, and disruptions of fatty acid metabolism.[1] Other mechanisms have suggested that proinflammatory cytokines secreted by HCV may also affect beta-cell function by disrupting insulin signaling.[13] The eradication of HCV has been shown to reduce the risk of HCC, to improve liver fibrosis, and to decrease the risk of other complications of chronic liver disease in the interferon era of HCV treatment.[4] Several studies have inferred successful clearance of HCV can lead to improvements in insulin resistance and reduction in HbA1c.[3,4,8,11] The benefits of glycemic control in patients with comorbidities of HCV and T2DM have been speculated, but not extensively investigated with the new DAA agents.

A *post hoc* analysis of six studies followed patients with chronic hepatitis C genotype 1, treated with paritaprevir/ritonavir/ombitasvir/dasabuvir, revealed a significant drop in fasting glucose (-8.87 mg/dl by week 12; $P < 0.0001$) in the treatment group compared to the placebo group.[14] The VA Health System also conducted a study including, 2435 patients who were treated with either ledipasvir/sofosbuvir, paritaprevir/ritonavir/ombitasvir/dasabuvir, or simeprevir/sofosbuvir combination therapies which demonstrated a significantly higher reduction in the mean HbA1c level in the SVR group (0.98% ± 1.4%) compared to the no-SVR group (0.65% ± 1.5%) ($P = 0.02$).[3] The reduction in HbA1c level associated with SVR was restricted to patients with a high baseline HbA1c level but showed no significant difference among patients with HbA1c ≤7.2% at baseline and with or without cirrhosis.[3] Although the VA did conduct a recent study with DAA agents, the patient demographics were limited to the veteran population. The aim of our study was to validate the findings conducted by the VA Health System but within an integrated health system representing a diverse patient demographic and socioeconomic population.

Within the total study cohort ($n = 996$), the majority of the patients were male (67.3%) and the average age was 61 years (SD 8.1). The race was relatively similar in representation: Whites ($n = 307$, 30.8%), Blacks ($n = 293$, 29.4%), and Hispanics ($n = 310$, 31.1%). Majority of the patients identified had hepatitis C genotype 1 ($n = 868$, 87.1%) and were treated with ledispavir/sofosbuvir ($n = 892$, 89.6%) [Table 1]. Our results were similar to the findings conducted by the VA system and demonstrated that eradication of HCV with DAA agents improved glycemic control in patients with T2DM. The VA study showed a nearly 1% reduction in HbA1c exclusively in the SVR group; however, our results show an approximate 0.4% reduction in HbA1c not only in the SVR group but also in those who did not achieve SVR. Regardless of HCV treatment success or failure, the reduction in HbA1c in the respective study groups was statistically significant ($P < 0.001$ in SVR group and $P = 0.0051$ in No SVR group) [Table 2]. Contrary to the VA study, the reduction in HbA1c did not differ in patients who achieved SVR from those patients who failed to achieve SVR ($P = 0.7741$) [Table 2]. In support of our findings, a prospective study followed 251 patients with chronic HCV genotype 1 and HIV co-infection. The patient population included 31% HIV positive patients and 17% of patients were diagnosed with T2DM. The DAA

treatment regimens contained a wide spectrum of agents, including asunaprevir, beclabuvir, daclatasvir, ledipasvir, sofosbuvir, and telaprevir. They found that HbA1c reduction in patients with SVR was 0.022% ± 0.53% and that the drop in HbA1c levels after the completion of therapy was unchanged in the group of HCV/HIV co-infected patients with SVR when compared to the group of HCV/HIV co-infected patients without SVR.[15]

We also wanted to identify whether baseline HbA1c levels affected the primary outcome of the study [Table 3]. While the VA study showed, the reduction in HbA1c level associated with SVR was restricted to patients with a high baseline HbA1c level; our research showed no difference in outcomes. Our research shows that there were more considerable mean changes in HbA1c when baseline HbA1c were higher; however, there were no significant changes between patients who achieved SVR compared to patients who did not achieve SVR with baseline HbA1c levels >7%, >8% and >9% [Table 3]. Similarly, we wanted to identify if levels of cirrhosis in patients with hepatitis C affected the changes in HbA1c pre- versus post-DAA treatment. We found that baseline HbA1c, patients with cirrhosis and no cirrhosis had no statistically significant effect in HbA1c reduction [Table 4]. An *ad hoc* analysis was conducted to determine whether antidiabetic medications contributed to the decrease in HbA1c in both groups. At baseline, 43.4% of patients were on metformin, 14.8% were on insulin, and 19.7% were on sulfonylurea [Table 5]. Additional covariate analysis was conducted to determine if gender, baseline BMI, and HCV genotypes contributed to changes in HbA1c. In all categories, there was no statistical and clinical significance.

Although several studies show that decreases in fasting glucose and HbA1c were identified after HCV viral clearance, our findings demonstrate a reduction in HbA1c following treatment of DAA agents is associated with HCV suppression, regardless of successful viral clearance. DAA agent's inhibition of HCV replication may have an immediate effect in slowing hepatic steatosis, reducing the secretion of proinflammatory cytokines, and improving insulin resistance. It is essential to consider that the lowering of HbA1c level represents only one mechanism by which HCV eradication could potentially influence cardiovascular risk. Treatment of HCV has the potential to impact a large proportion of patients with respect to liver disease and diabetes control. However, there is a need for more extensive prospective studies to address the longer term impact of SVR achieved with DAAs on T2DM.

Limitations of the study include study design with the inability to correct for unmeasured confounders and bias including possibility that patients taking new effective therapy for HCV might be more likely to engage in other healthy behaviors. Another limitation of the study is the small sample size for nonresponders. Finally, there is limited clinical significance since all patients with HCV are offered treatment regardless of the presence of DM2.

The strengths of this study include the sample size. This study is the first of its kind to evaluate the utilization of the newer DAA agents and effect on HCV eradication and glycemic control in T2DM in a real-world population within an integrated system. As with many database studies, there are some limitations to address. In this study, we did not calculate the adherence of HCV medications since this may impact patients not achieve SVR. There are also unmeasured confounding factors such as changes in lifestyle habits, diet, and concomitant medications that may have contributed to reduction in HbA1c. Finally, this study was not powered to detect a 0.5% reduction in HbA1c between achieved SVR and did not reach SVR groups.

In this analysis, consistent with clinical trials and prior studies, patients on DAA therapies achieved SVR >90%, and furthermore, results suggest that the change in HbA1c after successful eradication of HCV with DAA treatment had no different than with those who had failed treatment. Patients with more inadequate glycemic control at baseline did not have statistically significant changes between achieving SVR and not achieving SVR. This suggests that treatment with DAA agents regardless of complete eradication of HCV infection may potentially have an immediate beneficial effect on hepatic inflammation and glycemic control. This study highlights the need for the long-term evaluation of HCV eradication on glycemic control in patients with T2DM. Long-term studies should incorporate the benefits of HCV eradication after 2–3 years of DAA completion and achieving SVR.

Authors' Contribution

Alicia Wong was the lead researcher and was involved in all aspects of the research. John Sie and Angela Chen contributed to the concept, design, data analysis, and manuscrupt editing and review. Dr. Basuki Gunawan contributed as the content expert. Joanie Chung had a role in data and statistical analysis portion of the research. Lastly, Nazia Rashid contributed to the literature search, data and statistical analysis, and manuscript preparations, editing and review.

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Conflicts of interest

All authors do not have any financial benefits or potential conflicts of interest with regard to the work. Alicia Wong was a postgraduate pharmacy resident at the time of this research study; John Sie, Angela Chen, Dr. Basuki Gunawan, Joanie Chung, and Nazia Rashid were employees of KPSC when the study was conducted.

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