Improvement in Glycemic Control of Type 2 Diabetes After Successful Treatment of Hepatitis C Virus

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OBJECTIVE

Hepatitis C virus (HCV) infection is associated with diabetes and may worsen glycemic control in patients with diabetes. We aimed to investigate whether eradication of HCV infection with direct-acting antiviral (DAAs) agents is associated with improved glycemic control in patients with diabetes.

RESEARCH DESIGN AND METHODS

We identified 2,435 patients with diabetes who underwent interferon-free and ribavirin-free DAA-based antiviral treatment for HCV in the national Veterans Affairs health care system. Changes in average hemoglobin A1c (HbA_{1c}) level and use of antidiabetic medications 1 year before and after antiviral treatment were compared between patients who achieved sustained virologic response (SVR) and those who did not.

RESULTS

Among patients with elevated baseline HbA_{1c}, the drop in HbA_{1c} associated with antiviral treatment was greater in those who achieved SVR (0.98%) than in those who sustained treatment failure (0.65%) (adjusted mean difference 0.34, $P = 0.02$). Use of antidiabetic medications decreased more in patients who achieved SVR than in those who sustained treatment failure, especially for the use of insulin, which dropped significantly from 41.3% to 38% in patients achieving SVR compared with a slight increase from 49.8% to 51% in those who sustained treatment failure.

CONCLUSIONS

DAA-based eradication of HCV is associated with improved glycemic control in patients with diabetes as evidenced by decreased mean HbA_{1c} and decreased insulin use. These endocrine benefits of SVR provide additional justification for considering antiviral treatment in all patients with diabetes.

Epidemiological studies have shown that hepatitis C virus (HCV) infection is associated with a higher prevalence of type 2 diabetes mellitus (T2DM) (1–6). Additionally, in patients with risk factors for the metabolic syndrome, the presence of chronic HCV infection increases the risk of the development of T2DM by 11-fold (7). Molecular mechanisms provide explanations by which HCV infection might increase the risk of the development of T2DM or worsen glycemic control in patients with established T2DM. For example, HCV proteins increase serine and threonine phosphorylation of insulin receptor substrate-1, which contributes to insulin resistance (IR) (8–11). In addition, HCV proteins increase the release of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, which then upregulate gluconeogenesis and enhance lipid accumulation in the liver (12–14).

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If HCV infection indeed worsens glycemic control, then HCV eradication (known as sustained virologic response [SVR]) may improve glycemic control in patients with diabetes. In support of this hypothesis, previous interferon-based studies suggested that successful clearance of HCV could lead to improvement in IR (15–19). Patients without diabetes demonstrated improvement in an oral glucose tolerance test before and after treatment of HCV (16). Two other studies in patients without diabetes showed improvement in HOMA-IR, a measure of IR, from baseline to 20 weeks after successful treatment with interferon and ribavirin therapies in 96 patients from the HALT-C (Hepatitis C Antiviral Long-term Treatment against Cirrhosis) trial (18) (including 21 who achieved SVR) and 89 patients from Japan (19) (including 29 who achieved SVR). To our knowledge, there have been no large studies looking at glycemic control in patients with diabetes after the eradication of HCV.

Additionally, clearing the virus may prevent the development of IR in the future, as shown in a study (15) where achieving SVR caused a two-thirds reduction in the risk of T2DM development in HCV-positive patients treated with interferon. However, these studies were confounded by treatment-induced weight loss, a common side effect of interferon, which was a component of all HCV antiviral regimens prior to 2014.

It is unclear whether HCV eradication achieved by interferon-free, direct-acting antiviral (DAA) regimens results in improvement in glycemic control of patients with T2DM. The aim of this study is to compare patients with diabetes who achieve SVR with those who do not with respect to glycemic control as assessed by changes in hemoglobin A_{1c} (HbA_{1c}) levels and use of medications for treatment of diabetes before and after antiviral treatment with DAA agents.

RESEARCH DESIGN AND METHODS

This study underwent the appropriate institutional review board approval at Puget Sound Veterans Affairs (VA) Medical Center in the state of Washington and Portland VA Medical Center in the state of Oregon.

Data Source

Patient data were derived from the VA Corporate Data Warehouse, a national electronic repository of data from all 167 medical centers and 875 ambulatory care and community-based outpatient clinics of the VA system throughout the U.S. (20). The VA health care system is the largest provider of integrated HCV care in the U.S.

Study Population

There were 24,089 HCV antiviral regimens initiated in the VA nationally from 1 January 2014 (the month after sofosbuvir [SOF] was approved by the Food and Drug Administration) to 30 June 2015 and completed before 1 October 15. We excluded any regimen that included interferon or ribavirin (n = 12,069), leaving 12,020 regimens of ledipasvir (LDV)/SOF monotherapy, paritaprevir/ritonavir/ombitasvir and dasabuvir monotherapy, or SOF plus simeprevir (SMV) combination therapy. Interferon-containing regimens were excluded because of their confounding effect on weight loss and anemia and because they are currently obsolete. Ribavirin-containing regimens were excluded because ribavirin-induced hemolytic anemia, which can artificially decrease HbA_{1c} levels because of the decreased life span of red blood cells (21–23). Patients without a diagnosis of T2DM prior to undergoing antiviral treatment (n = 8,295) as well as those who received prior antiviral treatment (n = 736), which may have had cumulative effects on glycemic control, were excluded from the study. Finally, 237 patients without SVR data and 349 patients without HbA_{1c} data both before and after treatment were excluded, leaving 2,435 patients in the current analysis, including 2,180 patients who achieved SVR and 255 who did not.

Definition of Diabetes

The presence of diabetes was defined by ICD-9 codes for T2DM (ICD-9 codes 250.00–250.92) recorded at least twice together with either a measurement of HbA_{1c} $>$6.5% or an active prescription of for antidiabetic medication over the 12 months prior to treatment (Supplementary Table 1) (24).

Baseline Characteristics

We ascertained age, sex, race/ethnicity, and HCV viral genotype. The diagnoses of alcohol use disorders, cirrhosis, and decompensated cirrhosis were based on the ICD-9 codes listed in Supplementary Table 2, which have been widely used and validated in VA medical records (25–29). All comorbid diagnosis variables were ascertained using ICD-9 codes recorded at least twice, on separate days, before the initiation of antiviral treatment. We extracted the laboratory tests shown in Table 1 and recorded the value of each test closest to the treatment start date within the preceding 6 months. We calculated the Fibrosis-4 (FIB-4) score (FIB-4 = [age $\times$ AST]/[platelets $\times$ $ALT^{1/2}$], where AST is aspartate aminotransferase and ALT is alanine aminotransferase), which is associated with advanced fibrosis and cirrhosis (30).

SVR

SVR was defined as a viral load below the lower limit of quantification $\geq$12 weeks after the end of treatment (31). When the SVR at $\geq$12 weeks was not available, SVR was defined by viral load testing between 4 and 12 weeks after treatment completion, which accounted for 149 of 2,435 SVR determinations or 6.1%. SVR at 4 weeks is known to have 98% concordance with SVR at 12 weeks (positive predictive value 98%; negative predictive value 100%) in SOF-treated patients (32).

Change in HbA_{1c} Before and After Treatment

HbA_{1c} is widely accepted as a diagnostic and monitoring test for diabetes because it measures the integrated index of glycemia over the life span of a red blood cell (33). Primary care providers in the VA health care system receive electronic clinical reminders yearly to screen for diabetes with the HbA_{1c} level, and patients with diabetes are monitored as frequently as every 3 months for glycemic control using HbA_{1c} level. The mean of the HbA_{1c} measurements of patients was calculated for the 12-month period prior to treatment ("pretreatment") and the 12-month period from 3 to 15 months after treatment ("post-treatment"). The 3 months after treatment were excluded to avoid any direct effect of antiviral treatment itself on HbA_{1c} level since it reflects glycemic control over the preceding 3 months.

Change in Antidiabetic Medications Before and After Treatment

We identified all antidiabetic medications taken either immediately prior to HCV treatment (pretreatment) or 15 months after the end of treatment (post-treatment), categorized into the following nine classes:

Table 1—Baseline characteristics of patients who received DAA-only therapies according to whether they achieved SVR or not

	All patients (*N* = 2,435)	No SVR (*n* = 255)	SVR (*n* = 2,180)
Male (%)	97.5	99.2	97.3
Age, years (mean ± SD)	62.2 ± 5.2	61.7 ± 5.7	62.2 ± 5.1
BMI, kg/m^2 (mean ± SD)	30.2 ± 5.7	30.7 ± 5.7	30.1 ± 5.7
Race/ethnicity (%)			
White, non-Hispanic	38.3	35.3	38.6
Black, non-Hispanic	43.6	42.8	43.7
Hispanic	5.4	6.3	5.3
Other	1.6	2.4	1.5
Declined to answer, missing	11.1	13.3	10.9
Genotype (%)			
1	99.3	99.8	99.4
4	0.7	1.2	0.6
DAA HCV treatment regimen (%)			
LDV/SOF	56.2	43.9	57.7
PrOD	5.5	2.0	5.9
SMV plus SOF	38.3	54.1	36.5
HCV RNA viral load >6 million IU/mL (%)	49.5	62.8	48.0
Cirrhosis (%)	37.3	54.5	35.3
Decompensated cirrhosis (%)	10.4	20.0	9.3
Alcohol use disorder (%)	41.4	45.1	40.9
Laboratory results (%)			
Anemia*	27.2	34.3	26.3
Creatinine >1.1 mg/dL	30.9	27.1	31.4
Platelet Count<100 k/μL	18.9	33.7	17.2
Bilirubin > 1.1 g/dL	14.1	24.6	12.9
Albumin < 3.6 g/dL	31.4	47.8	29.5
INR > 1.1	25.4	35.2	24.2
FIB-4† score >3.25	41.6	54.3	40.0
Glycemic control			
HbA_{1c} (mean ± SD)	7.20 ± 1.5%	7.27 ± 1.6%	7.20 ± 1.5%
Diabetes medications			
Any diabetes medication (%)	75.2	78.0	74.8
Insulin (%)	42.2	49.8	41.3
Classes of diabetes medications (mean ± SD)	1.16 ± 0.9	1.15 ± 0.9	1.16 ± 0.9

PrOD, paritaprevir/ritonavir/ombitasvir and dasabuvir. *Anemia is defined as a hemoglobin concentration of <13 g/dL in men or <12 g/dL in women. †FIB-4 score = [age × AST]/[platelets × $ALT^{1/2}$].

insulins, metformin, sulfonylureas, thiazolidinediones, sodium–glucose cotransporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors, meglitinides, α-glucosidase inhibitors, and glucagon-like peptide 1 agonists (Supplementary Table 1).

We derived the following three measures of antidiabetic medication use, comparing the post-treatment to the pretreatment period:

1) Number of unique antidiabetic medication classes (34). For example, a patient prescribed metformin and insulin, is assigned a number 2 for two distinct medication classes. For combination medications, such as Glyxambi (metformin and empagliflozin), it was considered to be two distinct medication classes.
2) Percentage of patients taking any antidiabetic medications.
3) Percentage taking insulin.

Statistical Analysis

We compared patients who achieved SVR with those who did not, with respect to the change in mean HbA_{1c} level 12 months before and 3–15 months after treatment (post-treatment minus pretreatment) with or without adjusting for potential confounders using multivariate linear regression. Potential confounders included age, sex, race/ethnicity, cirrhosis, platelet count, hemoglobin level, creatinine, bilirubin, albumin, international normalized ratio (INR), BMI, and FIB-4 score. Subgroup analyses included patients with low (≤7.2%) or high (>7.2%) baseline HbA_{1c} level (7.2% [55 mmol/mol] was the mean level in our study population) and patients with or without cirrhosis.

We also compared patients with and without SVR with respect to the change (post-treatment minus pretreatment) in the three measures of use of antidiabetic medications defined above.

Changes in mean body weight, hemoglobin concentration, or creatinine level before and after treatment may occur and may, in turn, affect HbA_{1c} levels (35). We, therefore, calculated the mean levels of these three characteristics before treatment (12 months prior to treatment) and after treatment (12-month period from 3 to 15 months after treatment), calculated the change (post-treatment minus pretreatment), and adjusted for this change when determining the association between SVR and HbA_{1c} level or antidiabetic medication use.

RESULTS

Baseline Characteristics

Among 2,435 patients with diabetes who were infected with HCV and were treated with interferon-free and ribavirin-free regimens, the average age was 62.2 years; the average BMI was 30.2 kg/m^2; and the vast majority were male (97.5%), had genotype 1 HCV (99.3%), and were treated with LDV/SOF (56.2%) or SMV plus SOF (38.3%) (Table 1). The most common racial/ethnic group was non-Hispanic black (43.6%) followed by non-Hispanic white (38.3%) and Hispanic (5.4%). Cirrhosis (37.3%) and even decompensated cirrhosis (10.4%) were common, with 75.2% of patients receiving at least one antidiabetic medication and 42.2% of patients receiving insulin.

Compared with patients for whom treatment failed, those who achieved SVR were less likely to have cirrhosis (35.3% vs. 54.5%) and decompensated cirrhosis (9.3% vs. 20%) and were less likely to be receiving antidiabetic medications (74.8% vs. 78.0%) or insulin (41.3% vs. 49.8%). There were notable differences in albumin levels, INR, bilirubin, platelet count, and FIB-4 scores between the two groups (Table 1), with the treatment failure group displaying markers of more severe liver disease. Patients who achieved SVR were more likely to be

treated with LDV/SOF and less likely to be treated with SMV plus SOF than patients for whom treatment failed.

Change in HbA_{1c} Associated With SVR

Pretreatment HbA_{1c} level was similar in patients who achieved SVR (7.20% [55 mmol/mol]) and those who did not (7.27% [56 mmol/mol]). The drop in average HbA_{1c} level after treatment was greater in those achieving SVR, (from 7.2% [55 mmol/mol] to 6.82% [51 mmol/mol], a mean drop of 0.37 ± 1.2%) than in those for whom treatment failed (from 7.27% [56 mmol/mol] to 7.08% [54 mmol/mol], a mean drop of 0.19 ± 1.3%), yielding a mean difference (0.37% minus 0.19%) of −0.18% (P = 0.03). After adjusting for all the baseline characteristics listed in Table 2, the adjusted mean difference (AMD) in the HbA_{1c} drop between the SVR and treatment failure groups was 0.13 (P = 0.1).

The drop in HbA_{1c} level associated with SVR was restricted to patients with a high baseline HbA_{1c} level. Among patients with a pretreatment mean HbA_{1c} of >7.2% (55 mmol/mol; the mean pretreatment HbA_{1c} level in our study population), the decrease in mean HbA_{1c} level was significantly greater in the SVR group (0.98 ± 1.4%) compared with the no-SVR group (0.65 ± 1.5%), with an AMD of 0.34 (P = 0.02) (Table 2). Among patients with HbA_{1c} ≤7.2% (55 mmol/mol), there was no significant difference between patients with and without SVR in the change in HbA_{1c} level. Also the significant drop in HbA_{1c} level associated with SVR was restricted to patients without cirrhosis and not to patients with cirrhosis (Table 2).

Change in Antidiabetic Medication Use Associated With SVR

The baseline number of classes of antidiabetic medications pretreatment was similar in the group that achieved SVR (1.15 ± 0.9) and the group that did not (1.16 ± 0.9). The number of classes of antidiabetic medications decreased slightly after antiviral treatment, more so in the patients who achieved SVR than in those who did not, but this difference was not statistically significant (Table 3). Also, the proportion of patients who were receiving treatment with antidiabetic drugs decreased slightly more in patients who achieved SVR than in those who did not, but this difference was not statistically significant.

Table 2—Impact of HCV eradication (SVR) on HbA_{1c}

	Pretreatment, HbA_{1c}, mean (SD)	Post-treatment HbA_{1c}, mean (SD)	Absolute change in HbA_{1c} (post-treatment from pretreatment)	Mean difference in HbA_{1c} drop in SVR vs. no SVR groups	P value	Adjusted* mean difference in HbA_{1c} drop in SVR vs. no SVR	P value
All patients							
No SVR	7.27 (1.6)	7.08 (1.5)	−0.19 (1.3)	−0.18	0.03	−0.13	0.1
SVR	7.20 (1.5)	6.82 (1.3)	−0.37 (1.2)				
Patients with pretreatment HbA_{1c} >7.2							
No SVR	8.54 (1.2)	7.89 (1.6)	−0.65 (1.5)	−0.33	0.02	−0.34	0.02
SVR	8.54 (1.2)	7.56 (1.3)	−0.98 (1.4)				
Patients with pretreatment HbA_{1c} ≤7.2							
No SVR	6.1 (0.7)	6.4 (1.06)	0.22 (0.9)	−0.15	0.04	−0.05	0.5
SVR	6.2 (0.6)	6.3 (0.9)	0.07 (0.8)				
Patients with cirrhosis							
No SVR	7.2 (1.5)	6.9 (1.4)	−0.27 (1.35)	−0.02	0.8	0.05	0.7
SVR	7.1 (1.5)	6.8 (1.3)	−0.30 (1.29)				
Patients without cirrhosis							
No SVR	7.4 (1.6)	7.3 (1.6)	−0.09 (1.3)	−0.33	0.005	−0.31	0.01
SVR	7.2 (1.4)	6.8 (1.2)	−0.42 (1.2)				

*Adjusted by multiple linear regression for age, sex, race/ethnicity, cirrhosis, platelet count, hemoglobin level, creatinine, bilirubin, albumin, INR, BMI, and FIB-4 score.

Table 3—Impact of HCV eradication (SVR) on use of antidiabetic medications

	Pretreatment	Post-treatment	Difference (post-treatment from pretreatment)	Mean difference in SVR vs. no-SVR groups	*P* value	Adjusted* mean difference in SVR vs. no-SVR groups	*P* value
Number of classes of antidiabetic medications							
All patients							
No SVR	1.15 (0.9)	1.14 (0.8)	−0.003 (0.7)	−0.06	0.2	−0.06	0.2
SVR	1.16 (0.9)	1.10 (0.9)	−0.07 (0.7)				
Patients with pretreatment HbA_{1c} >7.2							
No SVR	1.53 (0.8)	1.44 (0.9)	−0.09 (0.8)	−0.03	0.7	−0.04	0.6
SVR	1.62 (0.8)	1.50 (0.9)	−0.12 (0.9)				
Patients with pretreatment HbA_{1c} ≤7.2							
No SVR	0.80 (0.8)	0.87 (0.8)	0.07 (0.6)	−0.1	0.08	−0.09	0.1
SVR	0.83 (0.8)	0.81 (0.8)	−0.03 (0.6)				
Percentage of patients receiving antidiabetic medications							
All patients							
No SVR	78.0	74.9	−3.1	−0.8	0.7	−1.0	0.7
SVR	74.8	70.9	−3.9				
Patients with pretreatment HbA_{1c} >7.2							
No SVR	95	88.3	−6.7	1.7	0.6	−0.2	1
SVR	92.8	87.8	−5.0				
Patients with pretreatment HbA_{1c} ≤7.2							
No SVR	63.0	63.0	0	−3.2	0.4	−1.9	0.6
SVR	61.8	58.7	−3.2				
Percentage of patients receiving insulin							
All patients							
No SVR	49.8	51.0	1.2	−4.5	0.04	−4.2	0.04
SVR	41.3	38.0	−3.3				
Patients with pretreatment HbA_{1c} >7.2							
No SVR	72.5	68.3	−4.2	−1.3	0.7	−1.7	0.7
SVR	64.6	59.1	−5.5				
Patients with pretreatment HbA_{1c} ≤7.2							
No SVR	29.6	35.6	5.9	−7.8	0.003	−6.1	0.03
SVR	24.4	22.7	−1.7				

*Adjusted by multiple linear regression for age, sex, race/ethnicity, cirrhosis, platelet count, hemoglobin level, creatinine, bilirubin, albumin, INR, BMI, and FIB-4 score.

The proportion of patients receiving treatment with insulin decreased more significantly in patients who achieved SVR (from 41.3% to 38%) than in patients who did not (who actually had a slight increase in the proportion of patients receiving treatment with insulin from 49.8% to 51.0%; AMD −4.2%; $P = 0.04$) (Table 3). This reduction in insulin use in patients achieving SVR compared with patients in whom treatment failed was more profound among patients with a low pretreatment HbA_{1c} level of ≤7.2% (55 mmol/mol). Also the reduction in insulin use in patients achieving SVR was not associated with a concomitant increase in the use of metformin (i.e., it was not caused by the substitution of metformin for insulin in patients with improved liver function after SVR, who prior to treatment were felt to be ineligible for treatment with metformin). In fact, use of metformin also decreased from before to after antiviral treatment by 2.2% in patients achieving SVR and by 1.9% in patients for whom treatment failed.

Impact of Changes in Body Weight, Hemoglobin Concentration, and Serum Creatinine Level on the Drop in HbA_{1c} Associated With SVR

Comparing the post-treatment to pretreatment periods, weight increased slightly more in patients with SVR than in those for whom treatment failed (Table 4). Hemoglobin concentration decreased significantly more in patients for whom treatment failed than in patients who achieved SVR. Serum creatinine level increased slightly and equally in patients who did and did not achieve SVR. When additionally adjusting for changes in weight, hemoglobin concentration, and serum creatinine level, the associations between SVR and HbA_{1c} drop or antidiabetic medication use were essentially unchanged.

CONCLUSIONS

Our results suggest that the eradication of HCV with DAA therapy leads to improved glycemic control in patients with T2DM. HbA_{1c} values decreased and the proportion of patients receiving insulin decreased in patients who achieved SVR compared with those for whom treatment failed. Patients with poorer glycemic control at baseline who had a higher pretreatment HbA_{1c} level had an even greater improvement, nearly a 1% drop in the HbA_{1c}, associated with SVR.

In the U.S., an estimated 9.8% of the population, or 29.1 million people, have diabetes, and 1.4% of the population, or 3.5 million people, have HCV (36,37). T2DM is nearly four times more likely to develop in patients with HCV than in patients without HCV (38). Thus, the treatment of HCV has the potential to impact a remarkable proportion of the population not only with respect to liver disease but also diabetes control.

Eradication of HCV has been shown to reduce the risk of hepatocellular carcinoma, to improve liver fibrosis, and to decrease the risk of other complications of chronic liver disease (39). However, the effects of HCV eradication on the extrahepatic manifestations of HCV have not been well studied in the new era of DAAs. Our study supports the idea that HCV eradication leads to a reduction in HbA_{1c} in patients with diabetes. It is well established that the microvascular complications of diabetes, including nephropathy, neuropathy, and retinopathy, improve with lowered HbA_{1c} level (40,41). Therefore, early treatment of HCV could potentially slow the onset and progression of microvascular diabetes complications. Given the study period, we were unable to evaluate whether improved glycemic control was durable beyond the 15-month period after antiviral treatment and whether the effects subsequently lead to reductions in the long-term risk of diabetic complications since interferon-free DAA regimens have only been available since 2014.

It is important to note that the lowering of HbA_{1c} levels represents only one mechanism by which HCV eradication could potentially influence cardiovascular risk. HCV infection also causes the development of circulating low-density immune complexes that induce an inflammatory response (42), which could improve after HCV eradication. On the other hand, a virologic cure has been shown to result in increases in serum cholesterol and LDL cholesterol levels (43,44), which may aggravate early atherosclerotic lesions and increase cardiovascular risk. Thus, the net effect of HCV eradication on long-term cardiovascular risk remains to be determined.

Prior studies (45) have demonstrated an association between central adiposity related to T2DM and hepatic steatosis. The decrease in HbA_{1c} level achieved by medications such as thiazolidinediones or glucagon-like peptide 1 receptor agonists in patients with diabetes has been shown to improve hepatic fat content (46). As our study has shown an improvement in HbA_{1c} levels with the successful eradication of HCV, treatment may also improve hepatic steatosis, which frequently accompanies HCV-related liver disease.

Table 4—Impact of HCV eradication (SVR) on body weight, hemoglobin concentration and serum creatinine level

	Pretreatment	Post-treatment	Mean change (post-pre)	Mean difference in change in SVR vs. no SVR	*P* value	Adjusted* mean difference in change in SVR vs. no SVR	*P* value
Weight (kg)							
No SVR	97.9 (18.6)	98.1 (19.0)	0.15 (6.1)	0.58	0.1	0.63	0.1
SVR	94.8 (18.6)	95.5 (18.8)	0.73 (5.6)				
Hemoglobin (g/dL)							
No SVR	13.6 (1.7)	13.1 (1.8)	−0.54 (1.5)	0.25	0.005	0.30	0.001
SVR	13.9 (1.7)	13.6 (1.8)	−0.29 (1.3)				
Creatinine (mg/dL)							
No SVR	1.01 (0.3)	1.13 (0.55)	0.11 (0.35)	0.008	0.8	0.02	0.5
SVR	1.08 (0.51)	1.21 (0.70)	0.12 (0.43)				

Values are reported as the mean (SD). *Adjusted by multiple linear regression for age, sex, race/ethnicity, cirrhosis, platelet count, hemoglobin level, creatinine, bilirubin, albumin, INR, BMI, and FIB-4 score.

Recent studies (47) have even shown that patients with compensated HCV cirrhosis have higher rates of decompensation when they have diabetes and IR and that IR was a predictor of overall mortality. Thus, it is tempting to speculate that HCV eradication might prevent the development of decompensated cirrhosis not only by the elimination of the fibrotic and hepatotoxic effects of HCV, but also by reducing HbA_{1c} levels and improving IR in patients with T2DM, but future long-term studies are necessary to demonstrate this.

We reported that DAA-induced SVR was associated with a nonsignificant decrease in the proportion of patients with diabetes who were receiving antidiabetic medications and in the number of classes of antidiabetic medications and a significant decrease in the proportion of patients receiving insulin. The elimination of insulin after SVR was achieved was more common in patients who had relatively well-controlled diabetes at baseline ($HbA_{1c} \leq 7.2\%$) than in those with a baseline HbA_{1c} level of $>7.2\%$. This de-escalation of insulin is clinically relevant as it can be a cumbersome medication for patients to administer, can lead to hypoglycemic episodes if administered incorrectly, and is a frequent reason for medication noncompliance. Providers should be aware that glycemic control could improve after DAA-induced SVR and should be closely monitored for the need to remove insulin from therapy.

Antidiabetic medications, in particular insulin and sulfonylureas, have been implicated in increasing the risk of hepatocellular carcinoma, because the medications effectively increase the serum levels of insulin, a growth-promoting hormone (48–50). Therefore, it is possible that the decrease in insulin use after successful treatment with DAAs may also have antihepatocarcinogenic effects.

One limitation of our study is that we are unable to assess whether patients received additional medications outside the VA system. Previous studies (51) showed that patients who are enrolled and actively engaged in the VA health care system receive almost all their medications from the VA system. Although we adjusted for a large number of potential confounders, it is impossible to exclude the possibility that the drop in HbA_{1c} level that we observed in association with SVR was related to unmeasured confounding. For example, lifestyle changes such as better eating habits and exercise can also change the HbA_{1c} level and may also be associated with SVR, but these were not measured in this study.

In summary, glycemic control improves in patients with diabetes after DAA-induced SVR. Patients not only have an improvement in HbA_{1c} level after achieving SVR, they are also less likely to require insulin. These endocrine benefits of SVR provide additional justification for considering antiviral treatment in all patients with diabetes. Future studies are needed to confirm our findings, to determine how durable the SVR-induced improvement in glycemic control is over time, and to assess the long-term effect on complications of diabetes such as nephropathy, neuropathy, and cardiovascular disease.

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