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Sustained virological response does not improve long-term glycaemic control in patients with type 2 diabetes and chronic hepatitis C

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Abstract

Background: Sustained virological response to treatment for chronic hepatitis C virus may improve short-term glucose control among patients with type 2 diabetes, but the long-term impact remains largely unknown. We used data from the Chronic Hepatitis Cohort Study to investigate the impact of sustained virological response on long-term trends in haemoglobin A1c in patients with type 2 diabetes.

Methods: "Index date" was defined as the date of treatment initiation (treated patients) or hepatitis C virus diagnosis (untreated patients). To address treatment selection bias, we used a propensity score approach. We used a piecewise, linear spline, mixed-effects model to evaluate changes in haemoglobin A1c over a 5-year period.

Results: Our sample included 384 hepatitis C virus patients with type 2 diabetes (192 untreated, 192 treated, with sustained virological response or treatment failure). After adjusting for body mass index, haemoglobin A1c was stable among untreated and treatment failure patients. In sustained virological response patients, Hb1Ac trajectories evolved in three phases: (a) index

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SUPPORTING INFORMATION

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through 6 months post-index, average haemoglobin A1c decreased significantly from 7.7% to 5.4% per 90 days ($P < 0.001$); (b) 6-30 months post-index, haemoglobin A1c rebounded at a rate of 1.5% every 90 days ($P = 0.003$); and (c) from 30 months onward, haemoglobin A1c stabilized at an average level of 7.9 (P-value = 0.34). Results from an analysis restricted to patients receiving direct-acting antivirals were consistent with the main findings.

Conclusion: Successful hepatitis C virus treatment among patients with type 2 diabetes significantly reduces HbA1c shortly after treatment, but these decreases are not sustained long-term. Less than three years after sustained virological response, haemoglobin A1c rebounds to levels similar to untreated/treatment failure patients, and higher than recommended for type 2 diabetic maintenance.

Keywords

CHeCS; direct-acting antiviral DAA; glycaemic control; haemoglobin A1c; interferon

1 | INTRODUCTION

Chronic hepatitis C (HCV) infection directly impairs glucose metabolism and contributes to insulin resistance.[1–4] Among HCV patients with type 2 diabetes (T2D), some studies have shown that sustained virological response (SVR) has been associated with improved glycaemic control and insulin sensitivity; however, these studies have been limited to either small samples or relatively short-term followup (4-15 months after SVR).[5–10] Some studies have reported significant decreases in haemoglobin A1c (HbA1c) immediately after SVR, while a recent report found that HbA1c did not change after a mean duration of 2.5 years.[5] The impact of SVR on long-term glycaemic control in patients remains largely unknown. We used comprehensive longitudinal electronic health record (EHR)-based data from the Chronic Hepatitis Cohort Study (CHeCS)—which includes over 10 000 HCV patients drawn from four large US health systems—to investigate the impact of HCV treatment status and outcome on long-term trends in glucose control in patients with T2D.

2 | METHODS

2.1 | Patient population

Chronic Hepatitis Cohort Study is a retrospective/prospective, observational study that includes patients from four large US health systems. CHeCS follows all guidelines of the US Department of Health and Human Services regarding protection of human subjects; study protocols were approved and are renewed annually by the Institutional Review Boards of Geisinger Clinic (Danville, PA, USA); Henry Ford Health System (Detroit, MI, USA); Kaiser Permanente Hawai'i (Honolulu, HI, USA); and Kaiser Permanente Northwest (Portland, OR, USA). The requirement for written informed consent was waived due to the observational study design and the de-identified nature of the data. The CHeCS study design has been described previously.[5] Briefly, electronic administrative data and EHRs for patients ≥18 years that received health services at any study site from January 1, 2006 to December 31, 2016 were used to identify study candidates; eligibility was confirmed with medical chart abstraction.

For this analysis, the start of the observation period ("index date") was defined as either the date of last treatment initiation (for treated patients) or HCV diagnosis (for untreated patients). We included CHeCS HCV patients with the International Classification of Diseases, 9th edition or 10th edition (ICD9-CM and ICD10-CM) diagnosis codes for type 2 diabetes (250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92 and E11.-) in their EHR. Using prescription claims data, we excluded patients who were not continuously on antidiabetic medications throughout the study period. In addition, patients were excluded if they had hepatitis B virus co-infection.

2.2 | Outcomes of interest

Glycosolated haemoglobin (HbA1c) laboratory result data were summarized using a median smoother for every 90-day interval. Patients with at least one post-index date HbA1c interval were included in the analysis. Due to a lack of normality, data were logtransformed for analysis. Follow-up continued through the earlier date of either patient death or last encounter, for up to 5 years from index. Patients who had prescriptions for antidiabetic medication in the same interval they had an HbA1c measurement were assumed to be continuously on antidiabetic medication and were included in the analysis.

2.3 | HCV treatment status and response

Detailed antiviral medication data (drug name, start/stop dates) were collected via chart abstraction. Data on routine HCV RNA quantification tests were obtained via the EHR. Patients were classified into one of three treatment status groups: (a) treated with SVR (undetectable viral RNA loads ≥12 weeks post-therapy initiation); (b) treatment failure (TF); and (c) untreated.

2.4 | Adjustment for confounding factors

Index date demographic information included patient age, sex and race/ethnicity, and study site. Clinical risk factors included the following: Charlson-Deyo comorbidity indices (calculated from inpatient, outpatient, and claims data for 12 months prior to the index date)[6]; HbA1c laboratory results; body mass index (BMI; kg/m^2); HCV genotype; Fibrosis-4 Index (FIB4; a biomarker for liver fibrosis and cirrhosis); hyperlipidaemia; hypertension; use of statins; and cirrhosis data for up to 2 years prior to index date. Hyperlipidaemia and hypertension within 1 year pre-/post-index date were ascertained using ICD9/10 codes (Table S1). Pharmacy order and fill data were used to define statin use. Due to the observational nature of the study, availability of cirrhosis data varied. Roughly 20% of our sample had liver biopsy/vibration-controlled transient elastography (VCTE) data; 60%-70% had laboratory data for calculation of FIB4. To overcome this variation, we implemented a hierarchical classification algorithm to identify cirrhosis: (a) decompensated cirrhosis identified using our validated Classification and Regression Tree (CART) model[7]; (b) "F4" liver biopsy or VCTE results >12.5; (c) FIB4>5.88 (8); and (d) the presence of ICD9/10 diagnosis codes for cirrhosis in the EHR.

2.5 | Statistical analysis

To account for confounding due to treatment selection bias, we used a propensity score approach based on multiple logistic regression analyses with treatment as the outcome variable, and a large set of index-date demographic variables and clinical risk factors collected as covariates. We used the strategy proposed by Ali et al[9] for selection of possible confounders. Treated patients were then matched 1:1 to untreated patients using propensity scores. Balance of indexdate covariates between treated and untreated patients was compared after matching.

Longitudinal evolution of HbA1c was then estimated using a linear mixed-effects model. Due to non-linear trends in HbA1c observed in the raw data, we used a piecewise linear spline model. The time of change of slope (knot position) was determined using the approach proposed by Fitzmaurice et al.[10] Briefly, we started with high knot density and used a variable selection technique to select the best knot positions, guided by the Akaike information criteria (AIC). The linear mixed-effect model included fixed effects for time and treatment groups, and random components for the intercept and slopes to predict the trajectory of time for each individual patient. In order to compare HbA1c levels pre and post-SVR for treated patients, patients' treatment status was considered to be SVR at the index date if they achieved SVR, otherwise patient's treatment status was considered to be treatment failure (TF) at the index date. We also performed two sensitivity analyses: (a) incorporating postindex time-varying body mass index (BMI) as a covariate; (b) studying HbA1c trajectories among patients who were either untreated or treated with directly acting antivirals (DAAs).

3 | RESULTS

We identified 1288 HCV patients with evidence of T2D; 792 (61%) received antiviral treatment for HCV and 496 (39%) were untreated. Among treated patients, 625 (79%) patients achieved SVR and 167 (21%) had TF as of the date of last follow-up. Among them, 943 patients had at least one post-index date HbA1c result and had antidiabetic medication in the same interval. A total of 422 (45%) were treated with DAAs. With 1:1 matching, 384 patients (192 untreated, 192 treated) were included in our analysis. Median follow-up was 30 months (interquartile range [IQR] 15-51 months). The averge number of HbA1c measurements for patients during follow-up was 3.7. Patient characteristics in the matched cohort are presented in Table 1. Index-date covariates (study site, sex, race, insurance status, BMI, Charlson-Deyo comorbidity score, cirrhotic status, FIB4, hypertension, hyperlipidaemia, statin use, HCV genotype, and HbA1c) were included in the estimation of propensity scores to control for treatment selection bias. Patient characteristics in the treated/untreated cohort were balanced after propensity score matching (Table 1).

Haemoglobin A1c (in natural logarithm scale) was relatively stable across follow-up among untreated and TF patients (Figure 1). In contrast, among the 144 patients with SVR, HbA1c trajectories evolved in three phases: (a) index through 6 months post-index, average HbA1c started off at roughly 7.7 and decreased significantly over time—5.4% per 90 days (Table 2, $P < 0.001$); (b) 6-30 months post-index, HbA1c rebounded at a rate of 1.5% every 90 days ($P = 0.003$); and (c) from 30 months onward (to 60 months), HbA1c stabilized at an average

level of 7.9 (*P*-value for the slope = 0.337). HbA1c was stable among untreated and TF patients. When the sample was restricted to patients with available BMI data (Table 2), HbA1c trajectories were similar to those of the main analysis. In the subgroup analysis of patients treated with DAA-based regimens, follow-up was restricted to 15 months due to more recent treatment receipt. With 1:1 matching, 146 patients (73 untreated, 73 treated) were included in our analysis (Table S2); 66 (90.4%) patient achieved SVR. Among these patients, we observed trends in HbA1c similar to the main analysis (Figure S1): (a) index through 6 months post-index, average HbA1c decreased significantly at a rate of 5.7% (Table S3, $P < 0.001$) every 90 days; (b) 6-15 months post-index (end of follow-up), HbA1c rebounded at a rate of 3.9% ($P = 0.019$) every 90 days. HbA1c was stable among untreated patients; there were too few TF patients to draw valid conclusions regarding trends.

4 | DISCUSSION

In a large, racially diverse cohort of HCV patients with T2D, antiviral treatment status was associated with long-term changes in HbA1c upto 60 months post-index. Among TF and untreated patients, HbA1c remained stable for the duration of follow-up. In contrast, HbA1c decreased significantly ($P < 0.001$) among SVR patients in the first 6 months post-index. This is consistent with observations from studies[11–14] with relatively short followup durations (4-18 months). However, as follow-up progressed, we saw that HbA1c rose 1.5% every 90 days ($P < 0.001$) from 6 to 30 months (2.5 years) post-index, after which it stabilized at levels higher than recommended for type 2 diabetic maintenance.[15]

A number of studies have reported significant decreases in HbA1c immediately after SVR.[6–10] In contrast, a recent report found that reductions in HbA1c immediately following successful treatment were not sustained after a mean duration of 2.5 years.[16] A strength of our longitudinal analysis is that our results allow us to reconcile these apparently conflicting reports. Consistent with studies that had relatively brief follow-up periods, we observed a dramatic and significant decline in HbA1c during the first portion of our follow-up. Given our additional follow-up, we then also observed that HbA1c rebounded to levels as high or higher than at baseline before stabilizing. These results were similar even after adjustment for longitudinal changes in BMI. Likewise, cirrhosis at index date did not impact longitudinal HbA1c. Although the follow-up periods for subgroup of DAA-based regimens were shorter, consistent trends were observed for patients who achieved SVR from DAA and interferon-based regimens.

All patients in this study were prescribed medical treatment for T2D at index date and were on continuous medical therapy for T2D throughout the study period. A limitation of the present study is that we do not have data regarding lifestyle modifications, such as increased physical activity or dietary changes, that may impact glucose control over time, nor were we able to analyse whether T2D treatment type or dose changed during follow-up. This analysis assumed that patients' health-related behaviours and medication patterns did not differ between treatment groups. Given our 1:1 matched design, however, we do not expect there would be significant differences in lifestyle modifications between treatment status groups. Results from the sensitivity analysis that incorporated longitudinal BMI data showed results consistent with the main analysis, further confirming our findings. Likewise, our sensitivity

analysis of patients who achieved SVR after DAA therapy demonstrated HbA1c trajectories consistent with those of the main analysis, suggesting that—regardless of treatment type—improvements in glycaemic control observed during or just after treatment are not maintained long term after SVR.

Another limitation of this study is that a portion of our data are drawn from the interferon era of HCV treatment. We lack sufficient data on the long-term evolution of HbA1c to compare DAA and interferon-based regimens. While it is possible that there may be differences in HbA1c trajectories between patients who achieve SVR with different treatment types, however, patients who received DAA therapy demonstrated HbA1c trajectories consistent with those observed in first 15 month period post-index in the main analysis.

Likewise, there are limitations inherent in the use of observational data drawn from “real world” patients; we used a number of methods to minimize possible confounding. Propensity scores and matching were used to control for treatment selection bias. We also used a piecewise linear spline regression model in our analysis of HbA1c trends, which provides better data fit and interpretation. The robust estimates we observed with this approach suggest its utility as a novel application to the field.

Our analysis shows that SVR to HCV treatment does not improve long-term glycaemic control. Clinicians should be aware that in patients with T2D, HbA1 decreases dramatically shortly after successful treatment, but these decreases are not sustained. Less than three years after SVR, HbA1c rebounds to levels similar to untreated/TF patients, and higher than recommended for type 2 diabetic maintenance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTEREST

Stuart C. Gordon receives grant/research support from AbbVie Inc, Conatus Pharmaceuticals, CymaBay Therapeutics, Gilead Pharmaceuticals, Intercept Pharmaceuticals, and Merck. He serves as an ad hoc consultant/advisor for Abbvie Inc, Dova Pharmaceuticals, Gilead Sciences, Intercept Pharmaceuticals, and Merck & Co. Mei Lu, Jia Li, Lora Rupp, Sheri Trudeau, Talan Zhang, Yueren Zhou, Yihe G. Daida, Mark A. Schmidt, and Joseph A. Boscarino receive grant/research support from Gilead Sciences. Other authors have no conflict of interest to declare.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abbreviations:

BMI	body mass index
CART	Classification and Regression Tree
CHeCS	Chronic Hepatitis Cohort Study
DAA	direct-acting antiviral
EHR	electronic health record
FIB4	Fibrosis 4 Index
HbA1c	haemoglobin A1c
HCV	hepatitis C virus
ICD9/10-CM	International Classification of Disease, Clinical Modification
SVR	sustained virological response
T2D	type 2 diabetes
TF	treatment failure
VCTE	vibration-controlled transient elastography

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Key points

- The impact of sustained virological response (SVR) on long-term glycaemic control in HCV patients with type 2 diabetes remains largely unknown.
- The Chronic Hepatitis Cohort Study (CHeCS) shows that SVR to HCV treatment does not improve long-term glycaemic control.
- Less than three years after SVR, HbA1c rebounds to levels similar to untreated and treatment failure patients.

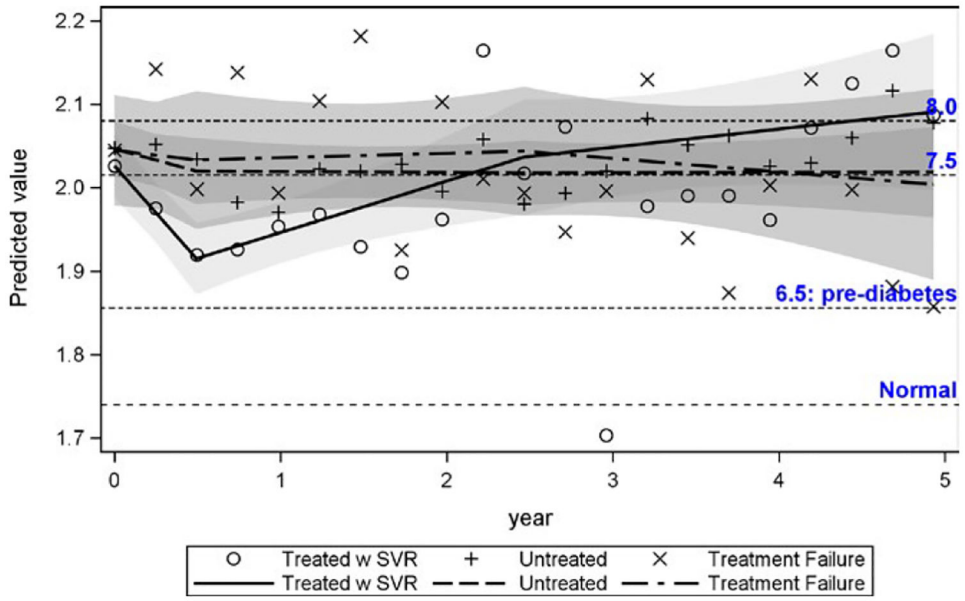

FIGURE 1.

Predicted mean of longitudinal trajectory of glycosolated haemoglobin in log scale ($_{log}$HbA1c) by treatment status and response (Shaded area: 95% confidence band; each interval is 90 d). SVR, sustained virological response

TABLE 1

Differences in exposures and treatment at index date for 1:1 matched cohort using propensity scores

Variable	Response	Untreated (N = 192)	Treated (N = 192)	*P*-value
Age		56.6 ± 10.0	57.6 ± 8.7	0.315
Study site	GHS	39 (20%)	44 (23%)	0.783
	HFHS	86 (45%)	90 (47%)	
	KPHI	16 (8%)	13 (7%)	
	KPNW	51 (27%)	45 (23%)	
Sex	Female	67 (35%)	67 (35%)	1.000
	Male	125 (65%)	125 (65%)	
Race	African American	22 (11%)	20 (10%)	0.654
	White	86 (45%)	79 (41%)	
	Other/Unknown	84 (44%)	93 (48%)	
FIB4	≤1.21	34 (18%)	33 (17%)	0.451
	1.21 ≤ 5.88	101 (53%)	114 (59%)	
	>5.88	18 (9%)	17 (9%)	
	Unknown	39 (20%)	28 (15%)	
Insurance	Medicaid	28 (15%)	29 (15%)	0.083
	Medicare	66 (34%)	46 (24%)	
	Private	95 (49%)	116 (60%)	
	None or unknown	3 (2%)	1 (1%)	
Weighted Charlson-Deyo Comorbidity Score	0	6 (3%)	4 (2%)	0.699
	1	70 (36%)	76 (40%)	
	≥2	116 (60%)	112 (58%)	
Cirrhosis	No	163 (85%)	170 (89%)	0.293
	Yes	29 (15%)	22 (11%)	
HCV genotype	1	128 (67%)	128 (67%)	0.849
	2	20 (10%)	22 (11%)	
	3	8 (4%)	5 (3%)	
	Other/Unknown	36 (19%)	37 (19%)	
Hypertension	Yes	66 (34%)	64 (33%)	0.829
Hyperlipidaemia	Yes	42 (22%)	44 (23%)	0.807
Statin use, ever	Yes	122 (64%)	114 (59%)	0.402
HbA1c[a]		8.0 ± 2.1	7.8 ± 1.8	0.485

FIB4, Fibrosis-4 index; GHS, Geisinger Health System; Hba1c, haemoglobin A1c; HFHS, Henry Ford Health System; KPHI, Kaiser Permanente Hawai'i; Kaiser Permanente Northwest.

[a]Log scale was used for the propensity score calculation. Original scale is presented for ease of interpretation.

[b]Type III analysis using Wald Chi-square test from multiple variable logistic regression.

TABLE 2

Glycosolated haemoglobin (HgA1c): estimated percentage change by treatment status and response

	Phase I: 0–6 mo post-index		Phase II: 6–30 mo post-index		Phase III: >30 mo post-index	
	Change (95% CI)	***P***	**Change (95% CI)**	***P***	**Change (95% CI)**	***P***
Full cohort (n = 384)						
SVR	−5.4% (−7.3%, −3.5%)	<0.001	1.5% (0.5%, 2.6%)	0.003	0.5% (−0.6%, 1.7%)	0.337
TF	−0.6% (−4.4%, 3.4%)	0.773	0.1% (−1.1%, 1.4%)	0.838	−0.4% (−1.7%, 0.9%)	0.538
Untreated	−1.3% (−3.2%, 0.5%)	0.164	−0.0% (−0.6%, 0.6%)	0.927	0.0% (−0.6%, 0.6%)	0.974
Subcohort[a] (n = 306)						
SVR	−4.9% (−6.9%, −2.8%)	<0.001	1.2% (0.1%, 2.4%)	0.034	0.5% (−0.9%, 1.8%)	0.506
TF	−1.2% (−3.4%, 1.0%)	0.290	0.1% (−0.6%, 0.9%)	0.710	−0.3% (−1.1%, 0.4%)	0.374
Untreated	−1.0% (−5.6%, 3.7%)	0.667	0.5% (−1.0%, 2.1%)	0.505	−0.9% (−2.6%, 0.8%)	0.279

CI, confidence interval; SVR, sustained virological response; TF, treatment failure.

[a]Subcohort limited to patients with longitudinal BMI data.