Significant HbA_{1c} Lowering in Patients Achieving a Hepatitis C Virus Cure

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The immediate clinically significant reduction in hemoglobin A_{1c} following HCV treatment observed in this study contrasts with the expected rise seen with normal disease progression.

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According to estimates, between 2.7 and 3.9 million people are infected with hepatitis C virus (HCV) in the US, with worldwide infection estimated to be about 185 million people.[1-3] The majority of patients infected with HCV develop a chronic infection, which is the leading cause of liver-related complications in the Western world, including cirrhosis, hepatocellular carcinoma, and the need for liver transplantation.[4] In addition to the direct effects HCV has on the liver, extrahepatic complications can occur, often related to the immune-mediated mechanism of cryoglobulinemia, such as vasculitis, renal disease, and palpable purpura. Additionally, > 70 studies globally have associated HCV with insulin resistance and worsening glycemic control.[5,6]

The prevalence of patients infected with HCV that have comorbid type 2 diabetes mellitus (T2DM) is estimated to be about 30%.[7,8] The landmark cross-sectional National Health and Nutrition Examination Survey III study found the prevalence of T2DM among HCV patients in the US aged > 40 years to be about 3-fold higher than those without HCV.[9] These findings were further supported by a Taiwanese prospective community-based cohort study that found a higher incidence of T2DM in HCV-positive patients compared with HCV negative patients (hazard ratio [HR], 1.7; 95% CI, 1.3-2.1).[10] This relationship appears to be separate from the diabetogenic effect of cirrhosis itself as a significantly higher prevalence of DM has been observed in people with HCV when compared with people with cirrhosis due to other etiologies.[11] Although the mechanism for this relationship is not fully understood and is likely multifactorial, it is believed to primarily be an effect of the HCV core protein increasing phosphorylation of insulin receptor substrate-1.[6,12,13] The increased presence of the inflammatory cytokine, tumor necrosis factor-α, is also believed to play a role in the effects on insulin receptor substrate-1 as well as mediating hepatic insulin resistance, stimulating lipolysis, down-regulating peroxisome proliferator-activated receptor-γ, and interfering with β-cell function.[14-17]

The relationship between HCV and T2DM has been further established by measured improvements in insulin resistance among patients undergoing HCV treatment with the pre-2011 standard of care—peginterferon and ribavirin. Kawaguchi and colleagues found sustained treatment responders to have a significant decrease in both the homeostatic model assessment-insulin resistance (HOMA-IR) score, representing insulin resistance, and the HOMA-β score, representing β-cell function.[18] Improvements in the HOMA-IR score were further validated by Kim and colleagues and a nested cohort within the Hepatitis C Long-term Treatment against Cirrhosis (HALT-C) trial.[19,20] Furthermore, Romero-Gómez and colleagues found that patients achieving a cure from HCV treatment defined as a sustained virologic response (SVR) had a nearly 50% reduced risk of impaired fasting glucose or T2DM over a mean posttreatment follow-up of 27 months.[21]

The recent development of direct-acting antivirals (DAAs) has marked significant HCV treatment advances in terms of efficacy and tolerability, leading current guidelines to emphasize that nearly all patients with HCV would benefit from treatment.[22] Despite these guidelines, issues have been documented throughout the US with payors often limiting this costly treatment to only those with advanced fibrotic disease.[23] Although the benefits of HCV treatment on reducing liver-related morbidity and mortality may be most appreciated in individuals with advanced fibrotic liver disease, improvements in insulin

resistance would suggest potential morbidity and mortality benefits beyond the liver in many more at-risk individuals.[24]

Increasingly, cases are being reported of new DAA regimens having a significant impact on reducing insulin resistance as demonstrated by marked decreases in antihyperglycemic requirements, fasting blood glucose, and hemoglobin A_{1c} (HbA_{1c}).[25-30] One striking case describes a patient being able to de-escalate his regimen from 42 daily units of insulin to a single oral dipeptidyl peptidase-4 inhibitor while maintaining goal HbA_{1c} level over a 2-year time period.[31] A database-driven study of veterans found a mean HbA_{1c} drop of 0.37% in its overall included cohort of patients with T2DM who achieved SVR from HCV DAA treatment.[32]

Despite these data, the individual predictability and variable magnitude of improved insulin resistance based on baseline HbA_{1c} remains unknown. The objective of this study was to assess the impact of HCV treatment with short course DAAs on glucose control in veteran patients with T2DM at a single center.

METHODS

This retrospective cohort study was performed at the Department of Veterans Affairs (VA) Northeast Ohio Healthcare System (VANEOHS) in Cleveland. This study received approval from the VANEOHS Institutional Review Board. Retrospective patient data were collected from the Veterans Health Administration (VHA) Computerized Patient Record System (CPRS) electronic health record. Collectively, the VHA has treated > 100,000 patients with DAAs, making it the largest provider of HCV treatment in the US. VANEOHS has treated nearly 2,000 patients with DAAs, rendering it one of the largest single-institution cohorts to be able to examine the effects of HCV treatment on subpopulations, such as patients with T2DM.

Patient Population

Patients were identified using ICD-9/10 codes for T2DM and medication dispense history of hepatitis C DAAs. Patients were included if they had a diagnosis of T2DM, were initiated on a hepatitis C DAA between February 1, 2014 to September 26, 2016. To be eligible, patients were required to have both a baseline HbA_{1c} within 6 months prior to starting HCV treatment as well as a HbA_{1c} within 4 months post-treatment. The HCV treatment included were new short-course DAAs, including sofosbuvir, simeprevir, ombitasvir/paritaprevir/ritonavir ± dasabuvir, ledipasvir/sofosbuvir, elbasvir/grazoprevir, and sofosbuvir/velpatasvir. Patients were excluded if they were not on any antihyperglycemic medications at the start of HCV treatment or did not complete a full HCV treatment course.

Baseline Characteristics

Pertinent demographic data collected at baseline included patient age, gender, HCV genotype, and presence of advanced fibrotic liver disease (defined as a Metavir fibrosis stage 4 on liver biopsy, transient elastography > 12.5 kPa, or radiologic evidence of cirrhosis). HCV treatment initiation and completion dates were collected along with treatment response at 12 weeks posttreatment. Patients were considered to have achieved SVR12 if their hepatitis C viral load remained undetectable at posttreatment day 77 or thereafter. Treatment relapse was defined as a patient who achieved an undetectable HCV RNA by the end of treatment but subsequently had detectable HCV RNA following treatment cessation.

Outcome Measures

Baseline HbA_{1c} was defined as the HbA_{1c} drawn closest to the date of HCV treatment initiation, at least 6 months prior to treatment. Immediate posttreatment HbA_{1c} was defined as HbA_{1c} drawn up to 4 months posttreatment, and sustained HbA_{1c} was captured up to 18 months posttreatment. Antihyperglycemic medication regimens and doses were collected at baseline, the end of treatment, and 3 months posttreatment via medication dispense history as well as provider notes documented in CPRS. Changes in antihyperglycemic medications were defined as net de-escalation, escalation, or no change. De-escalation of antihyperglycemic medication was defined as an overall decrease in dose, decrease in number of medications, or discontinuation of insulin (eg, if same overall number of medications but insulin was changed to an oral antihyperglycemic would have been considered a de-escalation). No change was defined as no overall change in insulin dose, or number of medications (eg, including patients who may have changed from one oral antihyperglycemic

TABLE 1
Baseline Characteristics

Characteristics	N = 157
Age, mean (SD), [range], y	62 (5.1) [45-86]
	No. (%)
Gender	
Male	151 (96)
Female	6 (4)
Race	
African American	88 (56)
White non-Hispanic	55 (35)
Hispanic	2 (1)
Unknown	11 (7)
Other	1 (< 1)
Advanced fibrotic liver disease	66 (42)
Treatment outcome	
SVR12 achieved	147 (94)
Relapse	8 (5)
Lost to follow-up	2 (1)
Genotype	
1a	93 (59)
1b	41 (26)
2	8 (5)
3	5 (3)
4	8 (5)
Indeterminate	2 (1)
Regimens	
Ledipasvir/sofosbuvir +/- ribavirin	122 (78)
Sofosbuvir + ribavirin +/- peginterferon	13 (8)
Ombitasvir/paritaprevir/ritonavir +/- dasabuvir +/- ribavirin	9 (6)
Elbasvir/grazoprevir	6 (4)
Sofosbuvir + simeprevir	5 (3)
Velpatasvir/sofosbuvir + ribavirin	2 (1)
Treatment Duration	
8 wk	40 (25)
12 wk	116 (74)
16 wk	1 (< 1)
No. of antihyperglycemic medications	
1	64 (41)
2	62 (39)
3	27 (17)
4	4 (3)

to another while overall number of medications did not change). Escalation was defined as an increase in dose, increase in number of medications, or initiation of insulin.

The primary endpoint was the change in HbA_{1c} up to 4 months posttreatment in patients achieving SVR12. Secondary endpoints included the sustained change in HbA_{1c} up to 12- and 18-months posttreatment, as well as change in antihyperglycemic medications from baseline to the end of HCV treatment and from baseline to 3 months posttreatment in patients achieving SVR12. Lastly, the changes in HbA_{1c} and net changes in antihyperglycemic medications were compared among patients who achieved SVR12 and those who relapsed.

TABLE 2
Antihyperglycemic Medications at Baseline[a]

Antihyperglycemic Medications	Patients, No. (%)
Metformin	97 (62)
Sulfonylurea	63 (40)
(DPP-4) inhibitor	3 (2)
Thiazolidinedione	1 (< 1)
GLP-1 agonist	1 (< 1)
Insulin	85 (54)
Basal	85 (54)
Bolus	42 (27)
Average total daily dose of insulin (n = 85)	47 units

[a]Patients may be on multiple medications

Statistical Analysis

The anticipated sample size after inclusion and exclusion for this study was 160 patients. As HbA_{1c} is a continuous variable and tested prior to treatment and up to 18-months posttreatment, a paired dependent 2-sided *t* test was used for this study. For a paired dependent *t* test with an α of 0.05 and a power of 80%, a sample size of 160 would be able to detect a moderately small, but clinically relevant effect size of 0.22. Descriptive statistics were used for secondary outcomes. For categorical data, frequencies and percentages are provided.

RESULTS

A total of 437 patients were identified as having a diagnosis of T2DM and being prescribed a HCV DAA, of which 157 patients met inclusion criteria. The 280 excluded patients included 127 who were not on antihyperglycemics at the start of HCV treatment, 147 who did not have HbA_{1c} data within the specified time frame, 4 were excluded due to delayed treatment initiation outside of the study time period, and 2 self-discontinued HCV treatment due to adverse drug reactions.

Baseline Demographics

The majority of patients were male (96%), primarily African American (56%), with a mean age of 62 years (Table 1). Nearly half of the patients were deemed to have advanced fibrotic liver disease, and most had genotype 1 HCV (85%). The

majority of patients were taking ledipasvir/sofosbuvir +/- ribavirin (78%) and achieved SVR12 (94%), while 59% were treated with ribavirin. Of the 10 patients who did not achieve SVR, none were treated with a second HCV regimen during the study period. Most patients were either on a monotherapy (41%) or dual (39%) therapy antihyperglycemic regimen.

Metformin was the most commonly prescribed antihyperglycemic medication (62%), followed by insulin (54%), and sulfonylureas (40%) (Table 2). No patients were on sodium-glucose cotransported-2 (SGLT-2) inhibitors as these were still new to the market during the study's time frame. The mean total daily dose of insulin was 47 units at baseline. Half of all included patients were on basal insulin, and 27% of patients were on a basal/bolus insulin regimen.

Primary and Secondary Endpoints

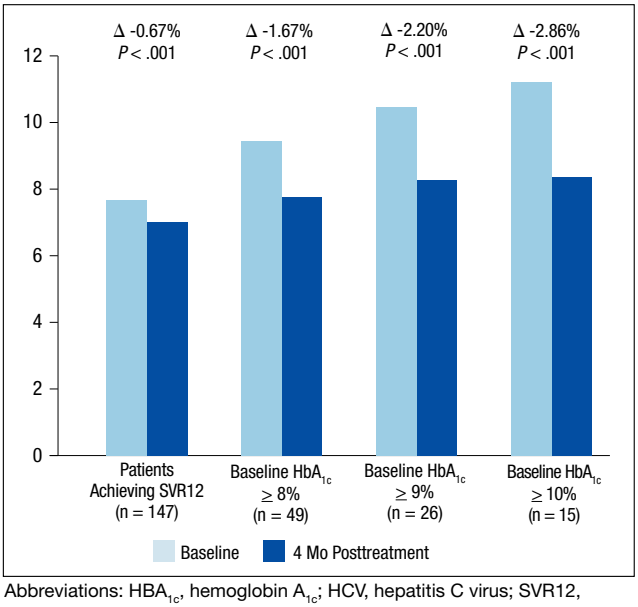
There was a significant immediate HbA_{1c} lowering of 0.67% (from 7.67% to 7.00%; $P < .001$) in patients who achieved SVR12 over a mean of 2-months posttreatment (Figure 1). Patients who achieved SVR12 (121 of 147) had follow-up HbA_{1c} data up to 12 months posttreatment, for which the overall HbA_{1c} lowering was 0.20% ($P = 0.21$) (Figure 2).

In the overall cohort of patients achieving SVR12, the HbA_{1c} lowering was not sustained at 18 months posttreatment. However, a subanalysis demonstrated that patients with baseline $HbA_{1c} \geq 8\%$, $\geq 9\%$, and $\geq 10\%$ had an increasingly larger HbA_{1c} Δ upon HCV treatment completion; the change in HbA_{1c} for these subcohorts did remain significant at sustained time points. Patients with a baseline $HbA_{1c} \geq 8\%$, $\geq 9\%$, and $\geq 10\%$, showed 18-month posttreatment HbA_{1c} decreases of 1.65% ($P < .001$), 2.28% ($P = .004$), and 3.63% ($P = .003$), respectively (Figure 3). By the end of HCV treatment, 20% of the patients who achieved SVR12 had a de-escalation of their antihyperglycemics. This increased to 30% by 3 months posttreatment among those achieving SVR12, in contrast to 13% of patients in the relapse group (Figure 4).

Of the 8 patients who relapsed, there was a significant decrease in HbA_{1c} of 0.90% from 7.54% to 6.64% ($P = .024$) at 4 months posttreatment. Of the relapsers who had HbA_{1c} values up to 12 months and 18-months posttreatment, the observed change in HbA_{1c} was 0.61% and 0.2%, respectively. However, the data are limited by its small numbers. One (13%) of the HCV treatment relapsers had an escalation of their antihyperglycemic regimen, while 1 (13%) had a de-escalation, and the remaining 6 (75%) had no change.

FIGURE 1

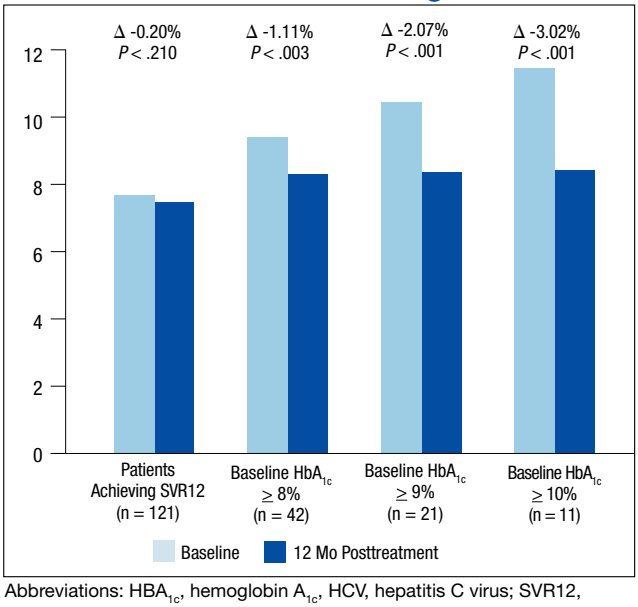
Change in HbA_{1c} at 4 Months Post-HCV Treatment in Patients Achieving SVR12



Abbreviations: HBA_{1c}, hemoglobin A_{1c}; HCV, hepatitis C virus; SVR12, sustained virologic response 12 weeks posttreatment.

FIGURE 2

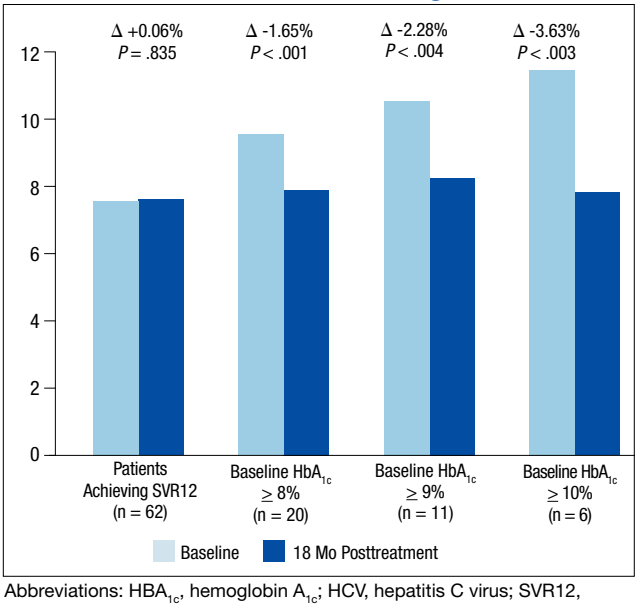
Change in HbA_{1c} at 12 Months Post-HCV Treatment in Patients Achieving SVR12



Abbreviations: HBA_{1c}, hemoglobin A_{1c}, HCV, hepatitis C virus; SVR12, sustained virologic response 12 weeks posttreatment.

FIGURE 3

Change in HbA_{1c} at 18 Months Post-HCV Treatment in Patients Achieving SVR12



Abbreviations: HBA_{1c}, hemoglobin A_{1c}; HCV, hepatitis C virus; SVR12, sustained virologic response 12 weeks posttreatment.

DISCUSSION

The immediate reduction in HbA_{1c} following HCV treatment observed in this study of -0.67% is clinically significant and contrasts with the expected rise in HbA_{1c} seen with normal disease progression. The results from this study are comparable to HbA_{1c} reductions seen with certain oral, antihyperglycemic medications, such as DPP-4 inhibitors, meglitinides, and SGLT-2 inhibitors that have an average HbA_{1c} lowering of 0.5% to 1%. This effect was increasingly magnified in patients with a higher baseline HbA_{1c}.

The sustained effect on HbA_{1c} may have not been seen in the overall cohort achieving SVR12 due to the fairly well-controlled mean baseline HbA_{1c} for this older patient cohort. In addition to improvements in HbA_{1c}, one-third of patients achieving SVR12 required de-escalation of concomitant antihyperglycemic medications. The de-escalation of antihyperglycemics may have made the sustained HbA_{1c} impact underappreciated in the overall cohort. There were also limited sustained HbA_{1c} data to evaluate at the time the review was completed.

Despite the clinically significant magnitude of HbA_{1c} change, this study suggests that this effect is not predictable for all patients with DM achieving SVR12 from HCV treatment. Nineteen percent (28/147) of these patients neither had a decrease in their HbA_{1c} nor a de-escalation of their antihyperglycemic treatment. Patients whose T2DM onset preceded or was independent of the diabetogenic effects of HCV may be more likely to have insulin resistance unaffected by hepatitis C viral clearance. Notably, the small number of treatment relapses in this study limits this group's ability to serve as a comparator. However, one may expect a treatment relapse to have an initial decrease in insulin resistance while the hepatitis C viral load decreases below the level of detectability, yet the effects not be sustained once the HCV relapses.

Of the 35 patients who had their HbA_{1c} decrease to < 6% following HCV treatment, concerningly 29 (83%) had either no change or even had an escalation in their antihyperglycemic regimen. This lack of de-escalation occurred despite 45% (13/29) of these patients continuing insulin posttreatment. These patients may be at a particularly high risk for hypoglycemia. Given the mean age of patients was 62 years, extremely tight glycemic control typically is not the goal for this older patient population with numerous comorbidities and high potential for hypoglycemia unawareness.

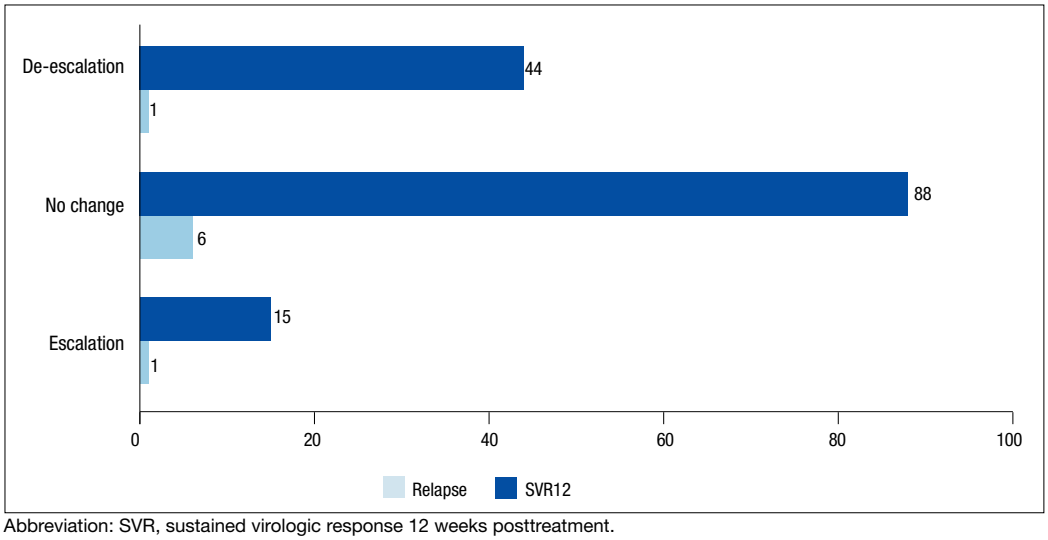
This raises concerns that patients with T2DM undergoing HCV treatment experience a new heightened risk of hypoglycemia, particularly if neither patients or providers managing DM are aware of the high potential for decreased antihyperglycemic needs upon achieving hepatitis C virologic response. It is important that these providers are aware of the mean decreased insulin resistance achieved from hepatitis C viral clearance. Providers managing DM should advise frequent serum blood glucose monitoring with close follow-up to allow for medication adjustments to prevent hypoglycemic episodes occurring during and after HCV treatment.

Limitations

The limitations of this study included small sample sizes in subgroups, and the retrospective design prohibited the ability to quantify and describe hypoglycemic events that may have occurred as a result of HCV treatment. In addition, the documentation of medication changes in CPRS may not have fully accounted for adjustments or self-discontinuations of DM medications. An alternative definition for change in antihyperglycemic medications may have

FIGURE 4

Antihyperglycemic Medication Changes 3 Months Posttreatment



Abbreviation: SVR, sustained virologic response 12 weeks posttreatment.

accounted for the variable HbA_{1c}-lowering between oral antihyperglycemic medications.

Finally, hemoglobin was not collected to account for any impact ribavirin-associated anemia may have had on the immediate posttreatment HbA_{1c} values. Phase 3 DAA trials have demonstrated that between 7% and 9% of patients on ribavirin-containing DAA regimens are expected to have a hemoglobin < 10 g/dL during the HCV treatment course.[33-36] Ribavirin-containing regimens may minimally impact the immediate posttreatment HbA_{1c} result, but not necessarily the 12- or 18-month posttreatment HbA_{1c} levels due to the reversible nature of this adverse effect (AE) following discontinuation of ribavirin.

Future studies may be strengthened by controlling for possible confounders such as concomitant ribavirin, adherence to antihyperglycemic medications, comorbidities, years since initial DM diagnosis, and lifestyle modifications, including a decrease of alcohol consumption. A prospective study also may include data on hypoglycemic events and further determine the sustained response by including an 18- or 24-month posttreatment HbA_{1c} in the protocol.

CONCLUSION

The findings of this study validate the significant HbA_{1c} changes post-HCV treatment described in the recent veteran database study.[32] However, the current study's validated patient chart data provide a better understanding of the changes made to antihyperglycemic regimens. This also is the first study describing this phenomenon of improved insulin resistance to only be observed in approximately 80% of patients infected with HCV and comorbid T2DM. Furthermore, the variable magnitude of HbA_{1c} impact reliant on baseline HbA_{1c} is informative for individual patient management. In addition to the direct benefits for the liver on hepatitis C viral eradication, improvements in HbA_{1c} and the de-escalation of antihyperglycemic regimens may be a benefit of receiving HCV treatment.

The improved DM control achieved with hepatitis C viral eradication may represent an opportunity to prevent progressive DM and cardiovascular AEs. Additionally, HCV treatment may be able to prevent the onset of T2DM in patients at risk. Arguably HCV treatment has significant benefits in terms of health outcomes, quality of life, and long-term cost avoidance to patients beyond the well-described value of decreasing liver-related morbidity and mortality. This may be an incentive for payers to improve access to HCV DAAs by expanding eligibility criteria beyond those with advanced fibrotic liver disease.

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