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BRIEF REPORT

No Improvement in Hemoglobin A1c Following Hepatitis C Viral Clearance in Patients With and Without HIV

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Hepatitis C clearance with directly acting antivirals (DAAs) may be associated with acute decreases in hemoglobin A1c (HbA1c). We prospectively evaluated 251 chronic hepatitis C virus (HCV)-infected subjects (31% human immunodeficiency virus [HIV] positive) pre- and post-DAA therapy (median follow-up 28 months). Changes in HbA1c and glucose were minimal and did not differ by sustained virologic response (SVR), HIV, diabetes, or fibrosis. Following SVR, mean change in HbA1c was −0.022 ± 0.53%; however, total and low-density lipoprotein cholesterol increased significantly. Subjects with HIV had smaller transaminase reductions after SVR. Sustained benefits in glycemia were not identified following HCV clearance irrespective of HIV, diabetes, or fibrosis stage, whereas lipid alterations may warrant further investigation.

Keywords. hemoglobin A1c; hepatitis C virus; glucose metabolism; human immunodeficiency virus; diabetes.

Multiple studies have shown an increased risk of developing type 2 diabetes in the setting of chronic hepatitis C virus (HCV), due in part to the predicted direct effect of the virus on glucose metabolism and insulin resistance [1]. Successful eradication of HCV with interferon-based treatment regimens has been linked with lower fasting glucose levels, improved insulin resistance, and improvements in diabetes mellitus, suggesting a reduced incidence of metabolic comorbidities in patients who achieve a sustained virologic response (SVR) compared with those who do not [2–5]. Studies are now examining the acute effect of HCV clearance on glucose metabolism and diabetic manifestations during and following treatment with directly acting agents (DAAs) [6]. Decreases in fasting glucose levels and hemoglobin A1c (HbA1c) were identified during HCV treatment with viral clearance [7, 8]. There remains, however, a need for larger prospective studies to address the longer-term impact of SVR achieved with DAAs on glucose homeostasis, diabetes, and other metabolic factors. This study aimed to determine the potential long-term benefits of SVR on HbA1c and metabolic factors in a cohort of subjects with HCV genotype 1 treated with newer DAAs.

METHODS

As part of a prospective, longitudinal cohort study of long-term health outcomes in adults with viral hepatitis (NCT01350648), pre- and post-HCV treatment HbA1c values were determined for 251 subjects with chronic HCV genotype 1 a/b infection. All subjects provided written informed consent and the protocol was approved by the National Institute of Allergy and Infectious Diseases IRB. Data were collected from the period 31 August 2011 to 9 January 2017.

Participants completed annual visits with nonfasting/random laboratory tests, demographic, and clinical data collected each year. For the purpose of the pre- and post-HCV treatment analyses, pretreatment baseline was defined as HbA1c determination between 5 months before HCV treatment and ≤5 days after the start of therapy. Post-treatment was defined as the last available HbA1c obtained after HCV treatment. Pretreatment fibrosis scores were obtained from liver biopsy (n = 233) or Fibrosure test (n = 17) closest to the start of treatment. SVR was defined as absence of HCV RNA ≥12 weeks after termination of treatment, confirmed at each visit. Patients were considered diabetic by an HbA1c value ≥6.5%, established diagnosis of type 2 diabetes from the medical record, or an active prescription for antidiabetic agent(s).

We calculated the change in HbA1c, glucose, lipid, and aminotransferase levels between pre- and post-HCV treatment and evaluated the influence of SVR and various clinical characteristics (eg, human immunodeficiency virus [HIV], diabetes) on the degree of change. Statistical comparisons between groups were completed using Wilcoxon test, or ANOVA for multigroup comparisons. Within-group comparisons of pre- and post-treatment changes were performed using paired *t* test. All analyses were completed using JMP software (Version 13.0, SAS Institute Inc., Cary, NC).

RESULTS

Participants (n = 251) had a mean duration of follow-up of 28 ± 13 months, and 241 of the participants achieved SVR (Table 1). Of the 241 participants with SVR, 28 (12%) had experienced prior HCV treatment failure. A subset of 79 (31%) subjects was coinfected with HIV and 72 (91%) of these had HIV

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Table 1. Pretreatment Demographic Characteristics

Baseline Characteristic	Total (n = 251)
Age, years	56.3 ± 8.01
Male, n (%)	173 (69)
Race	
Black, n (%)	201 (80)
White, n (%)	47 (19)
Mixed, n (%)	3 (1)
HIV+, n (%)	79 (31)
Diabetes, n (%)	42 (17)
BMI, kg/m^2	28.6 ± 6.3
Fibrosis stage	
F0-1, n (%)	151 (60)
F2-3, n (%)	73 (29)
F4, n (%)	26 (10)
Months follow-up	28.2 ± 13
HbA1c, %	5.75 ± 0.82
Glucose, mg/dL	103.2 ± 32.1
Cholesterol, mg/dL	161.1 ± 36.1
HDL, mg/dL	51.9 ± 22.4
LDL, mg/dL	86.6 ± 31.9
Triglycerides, mg/dL	122.2 ± 71.7
ALT, U/L	56.6 ± 37.0
AST, U/L	66.0 ± 48.7

Values are means ± standard deviation, unless noted.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HIV, human immunodeficiency virus.

Table 2. Change in HbA1c, Glucose and Transaminase Levels by SVR, HIV, and Diabetes Status

Characteristic	Delta HbA1c (%)	*P* value	Delta Glucose (mg/dL)	*P* value
SVR (n = 241)	0.0 (−0.2, 0.2)	.26	−1 (−14, 14)	.06
No SVR (n = 10)	−0.1 (−0.4, 0.2)		−18 (−33, 1)	
HIV+ SVR (n = 74)	0.0 (−0.2, 0.2)	.71	1 (−11, 13)	.66
HIV- SVR (n = 167)	0.0 (−0.2, 0.3)		−3 (−16, 15)	
Pre-tx DM SVR (n = 41)	−0.1 (−0.8, 0.3)	.29	−6 (−43, 25)	.21
Pre-tx No DM SVR (n = 199)	0.0 (−0.2, 0.2)		0 (−12, 13)	
Characteristic	**Delta ALT (U/L)**	***P* value**	**Delta AST (U/L)**	***P* value**
SVR (n = 234)	−34 (−56, −15)	.09	−20 (−45, −9)	.07
No SVR (n = 10)	−5 (−77, 3)		−6 (−43, 3)	
HIV+ SVR (n = 71)	−26 (−45, −9)	.0007	−13 (−43, −3)	.007
HIV− SVR (n = 163)	−38 (−61, −20)		−22 (−48, −12)	
Pre-tx DM SVR (n = 39)	−35 (−51, −18)	.89	−21 (−38, −13)	.96
Pre-tx No DM SVR (n = 194)	−32 (−58, −14)		−20 (−46, −9)	

Values are reported as median (interquartile range). *P* values represent between-group comparison in calculated deltas for each variable.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; SVR, sustained virologic response; tx, treatment.

viral RNA below the limit of detection at HCV pretreatment. Forty-two (17%) subjects met criteria for type 2 diabetes at baseline, and 33 (79%) of these subjects were receiving antidiabetic medication(s). HCV treatment regimens varied: 34 (14%) received interferon (IFN), ribavirin (RBV), and directly acting agents (DAAs); 41 (16%) were treated with RBV and DAAs; 175 (70%) were treated with DAAs only; and 1 was treated with IFN and DAAs. The DAA treatment regimens contained a wide spectrum of agents, including asunaprevir, beclabuvir, daclatasvir, ledipasvir, sofosbuvir, and telaprevir.

There was no difference in change in HbA1c from baseline to last follow-up between subjects who achieved SVR compared to those who did not (Table 2). Among the subjects who achieved SVR, change in HbA1c was not significantly different from zero, with a mean change of −0.022 ± 0.53% (P = .52). When change in HbA1c was calculated using a mean of all post-SVR values, the results were similar (−0.019 ± 0.49%, P = .54). Eight subjects (3%) had a decline in HbA1c greater than 1%, while 6 (2%) had an increase greater than 1% following SVR. There was also no significant difference in change in HbA1c values according to HIV status. Pre- versus post-treatment change in random glucose levels also did not differ according to HIV and/or SVR status.

Subjects with HIV had smaller reductions in transaminase values after SVR compared to HIV uninfected participants at follow-up. This difference remained significant independent of SVR status (aspartate aminotransferase P = .001, alanine aminotransferase P = .0002). Among the participants who achieved SVR, there were significant increases in total and low-density lipoprotein (LDL) cholesterol from baseline to follow-up (paired t test pre- vs post-treatment: total cholesterol median increase 9 [IQR −7, 30] mg/dL, P = .0002 and LDL median increase 11 [IQR −8, 29] mg/dL, P = .0003, respectively) and a significant decrease in triglyceride levels (median decrease −6 [IQR −43, 25] mg/dL, P = .008). The changes in lipid values were not correlated with change in HbA1c (all P > .1).

When participants were categorized by fibrosis stage, there was no significant difference in change in HbA1c following SVR based on pretreatment fibrosis score. Furthermore, no significant change in HbA1c was identified when participants who achieved SVR were grouped by F0-1 versus F2-4 (including cirrhotic subjects).

There were 42 subjects with diabetes at the baseline visit; 1 subject with diabetes did not achieve SVR. Of all subjects who did achieve SVR, 5 participants (2%) were newly diagnosed with diabetes during follow-up and 13 (5%) started or increased diabetes medications from baseline to follow-up. Only 7 subjects (3%) decreased their diabetes medications during follow-up. Of the participants who achieved SVR, no significant difference was observed between diabetic (n = 41) and nondiabetic (n = 199) with regard to change in HbA1c or random glucose values during follow-up.

No significant differences were observed for change in HbA1c or random glucose according to sex, race, HCV treatment regimen, HCV retreatment, or months of follow-up.

Notably, there was a statistically significant positive correlation between change in BMI and change in HbA1c (r = 0.17, P = .006). Specifically, an increase in BMI correlated with an increase in HbA1c between baseline and follow-up.

DISCUSSION

The present study represents the largest prospective, DAA-based HCV treatment data set examining the effects of viral clearance on glucose metabolism measured through HbA1c and random glucose values. There were no significant changes in HbA1c following SVR and there was no difference in HbA1c changes between those with SVR and the small subset of subjects without SVR. Additionally, there was no significant difference observed in changes in HbA1c after SVR based on HIV status, fibrosis stage, or diagnosis of diabetes. During the course of follow-up, 7% of participants either intensified their diabetes medication or were newly diagnosed with diabetes, compared to 3% who decreased their diabetes medication. Furthermore, only 3% had a decline in HbA1c greater than 1%, while 2% of participants had an HbA1c increase greater than 1% after SVR. No other factors were observed to affect the change in HbA1c with SVR, including HCV treatment regimen, sex, race, months of follow-up, or history of IFN treatment.

While the clinical course of HCV is changing rapidly in the era of highly effective DAA therapy, cirrhosis and liver disease still contribute to significant morbidity and mortality in the United States [9]. The well-recognized relationship between HCV and insulin resistance is one that may be altered by DAA-based therapy and HCV clearance, and is worthy of further investigation [7, 10, 11].

The current literature supports the incident relationship between HCV and insulin resistance/diabetes, with some studies asserting causation between the virus and development of insulin resistance [2, 5]. Existing clinical studies have retrospectively shown correlations between improved insulin resistance or glucose levels (and subsequent onset of type 2 diabetes mellitus) and successful eradication of HCV with IFN-based therapy [6, 12]. To date, 3 studies have reported evidence of improved glycemia among patients with diabetes achieving SVR with DAA therapy; however, observations were limited to measurements obtained no more than 6 months post-SVR [7, 8, 11]. Recently, Hum et al showed that subjects with type 2 diabetes and HCV who achieved SVR with DAA therapy had slightly greater decreases in HbA1c (−0.37%) than those without SVR (−0.19%, P = .03), but this was not significant after adjusting for demographic characteristics and severity of liver disease. In this retrospective study of 2435 subjects with type 2 diabetes in the Veterans Affairs (VA) system, the significant differences in HbA1c changes by SVR status were limited to those with baseline HbA1c >7.2% and noncirrhotic subjects [10]. Decline in HbA1c among those with higher baseline values may be explained by regression to the mean and, in general, the magnitude of the decline may not represent clinically meaningful changes.

In contrast, we examined a predominantly nondiabetic (83%), black (80%) cohort similarly treated with DAA-based regimens for long-term follow-up (28.2 ± 13 months) and found no effect of SVR on the change in HbA1c and, by extension, glucose metabolism. This observation is in agreement with an Italian study of HCV patients treated with IFN-based regimens, which found no significant difference in diabetes incidence in subjects with or without SVR following a median duration of 8 years of follow-up [13]. While insulin resistance and glucose metabolism may improve acutely with SVR, our study and this long-term follow-up study suggest the effects are likely not durable or clinically significant. Additionally, we observed a positive correlation between body mass index (BMI) and HbA1c during follow-up; increasing BMI may have nullified potential improvements in HbA1c.

HCV has also been shown to disrupt normal lipid metabolism, causing steatosis in the liver and abnormal lipid levels, which may factor into insulin resistance [14]. One study of DAA-based therapy showed increased LDL with declines in VLDL and triglyceride levels during and after successful HCV treatment [15]. Similarly, we observed significant increases in total and LDL cholesterol and significant decreases in triglycerides in subjects who achieved SVR. Despite the observed changes in lipid levels following SVR, there was no relationship between changes in lipid levels and changes in HbA1c.

Unlike HbA1c and glucose levels, liver transaminase levels decreased significantly in response to HCV therapy; however, this reduction was attenuated in the subset of subjects with HIV. Ongoing HIV infection, immune activation, and HIV antiretroviral hepatotoxicity are all potential contributing factors to persistent transaminase elevations in this population post-SVR.

The scope of our study is unique considering the cohort characteristics and, in particular, the prospective follow-up and documented persistent SVR after DAA-based HCV therapy. However, our cohort size is relatively small compared to the published VA cohort studies [10, 12]. Furthermore, the effectiveness of DAA therapy limits our ability to make comparisons to a contemporary cohort failing to achieve SVR; the non-SVR comparator group included only 10 subjects. Fasting glucose was not uniformly available and insulin determinations were not included in this study, limiting our ability to determine insulin resistance. Finally, the number of participants with diabetes was relatively small and may have limited our ability to detect changes following SVR in this subpopulation, on which many contemporary studies have focused [10–12].

Despite evidence that HCV may be related to incidence of type 2 diabetes and worsening glucose metabolism, our study showed that achievement of SVR did not lead to improvements in HbA1c. When accounting for possible confounding characteristics, such as baseline BMI, HIV status, and race, still no significant changes in HbA1c were detected following HCV clearance. While treatment with DAA-based HCV therapy in

patients with diabetes may create short-term improvements in glucose [7, 8] or limited improvements in HbA1c [10, 11], the current study failed to identify sustained benefits in glucose or HbA1c in HCV treated patients with or without diabetes. The findings serve primarily to indicate the necessity for continued monitoring of metabolic parameters in patients with a history of chronic HCV infection, particularly in those with impaired glucose metabolism and/or diabetes. Larger studies of DAA-treated populations with and without diabetes and HIV with longer duration of follow-up are needed to more fully appreciate the long-term implications and health outcomes of HCV clearance.

Notes

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