

ORIGINAL ARTICLE

Eradication of hepatitis C virus with direct-acting antivirals improves glycemic control in diabetes: A multicenter study

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Key words

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Abstract

Background and Aim: Hepatitis C virus (HCV) infection causes insulin resistance and diabetes as extrahepatic manifestations. We aimed to analyze the effect of HCV eradication by direct-acting antiviral (DAA) agents on glucose tolerance.

Methods: The hemoglobin A1c (HbA1c) of 272 patients with HCV infection who achieved a sustained virologic response (SVR) was analyzed at baseline before DAA treatment, at the end of DAA therapy (ETR), and 12 weeks after therapy (Post12W).

Results: There were no significant differences in HbA1c between baseline, ETR, and Post12W in the overall patients. When the data were stratified according to the presence or absence of diabetes, median HbA1c significantly decreased from baseline (7.2%) to ETR (6.8%) and Post12W (6.8%) in the 55 patients with diabetes, whereas there were no significant changes in the patients without diabetes. Basal HbA1c, fasting plasma glucose, and age were independently associated with the changes in HbA1c according to multivariate analysis, and the predictive formula for changes in HbA1c was found to be $\Delta\text{HbA1c} (\%) = 1.449 - 0.4 * \text{HbA1c} (\%) + 0.012 \times \text{Age} (\text{year})$. There were no changes in body mass in diabetic or nondiabetic patients. In diabetic patients taking medication, 63.4% of patients needed less medication.

Conclusions: Eradication of HCV improves glycemic control, indicated by a 0.4% decrease in HbA1c in diabetes.

Introduction

Hepatitis C virus (HCV) infection has several extrahepatic effects.^{1,2} Insulin resistance and diabetes are strongly associated with HCV infection, and HCV infection can contribute to the pathogenesis of metabolic diseases.^{3,4} HCV core protein inhibits the tyrosine phosphorylation of insulin receptor substrate (IRS) 1 by increasing tumor necrosis factor- α expression, which results in insulin resistance.⁵ HCV core protein also upregulates the suppressor of cytokine signaling 3 and causes downregulation of IRS1 and IRS2.⁶ According to an epidemiological study, HCV infection increases the risk of diabetes by 1.63-fold, independent of age and body mass index (BMI).⁷ The presence of

diabetes is also associated with higher liver disease-related mortality, including from liver failure and hepatocarcinogenesis, and the prognosis of patients with HCV infection.^{8–10}

Following these experimental and clinical studies, there has been great interest regarding whether eradication might be associated with amelioration of the insulin resistance and diabetes caused by HCV infection. Several studies have been conducted to test this hypothesis, using interferon-based therapy.¹¹ Although many of these studies have demonstrated an improvement in insulin resistance and/or a reduction in the incidence of diabetes,^{12–18} several other studies have shown only a partial or no effect of HCV eradication.^{19,20} A possible explanation for this

discrepancy is the common adverse effects caused by interferon therapy, including loss of appetite and body mass, which might themselves ameliorate obesity and insulin resistance.

The introduction of direct-acting antiviral (DAA) agents has dramatically changed the treatment of HCV infection, enabling a sustained viral response (SVR) rate in >90% of patients over a short period (8–24 weeks) but without causing severe adverse effects, such as loss of appetite and body mass. Therefore, we conducted a multicenter study to investigate the direct effect of HCV eradication on diabetes in patients receiving DAA therapy.

Methods

Study population. The study population comprised 592 HCV RNA-positive patients who were receiving interferon-free DAA therapy from 2015 to 2016 and did not have HBV surface antigen, had a habitual ethanol intake of <30 g/day for men and <20 g/day for women, and did not have autoimmune hepatitis or other liver diseases. Hemoglobin A1c (HbA1c) was measured in 358 patients, who were originally included in the study, but 80 patients who were being treated with ribavirin were later excluded because ribavirin-induced anemia could decrease HbA1c and might fail to represent the long-term glucose level.²¹ SVR was observed in 272 patients, and data from these individuals were analyzed, including for changes in HbA1c (Supplementary 1). The DAA therapeutic regimens used were oral medication with daclatasvir and asunaprevir (DCV/ASV) for 24 weeks, ledipasvir and sofosbuvir (LDV/SOF) for 12 weeks, or paritaprevir/ritonavir and ombitasvir (PTVr/OBV) for 12 weeks. SVR was defined as a negative test for HCV RNA 12 weeks after (Post12W) treatment was completed (ETR). This study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committees of all the participating institutions.

Clinical and laboratory assessments. Clinical information and data were collected from medical records by the physicians in charge. BMI was calculated in kg/m². There were no patients with decompensated cirrhosis. Diagnoses of compensated cirrhosis and noncirrhosis were based on the information obtained in the medical chart review by individual investigators. All venous blood samples were taken after a 12-h overnight fast. The following laboratory parameters were measured in serum: albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT). Fasting plasma glucose was determined using the glucokinase method. Whole blood was collected in EDTA tubes, and HbA1c was measured using a commercially available procedure in Japan. Serum HCV RNA was identified using the COBAS Taq-Man HCV Monitor Test (both Roche Diagnostics, Tokyo, Japan). HCV genotype was determined by sequencing of the core region. Fibrosis 4 (FIB-4) index was calculated to evaluate advanced liver fibrosis risk as previously reported, and patients were stratified according to the FIB-4 index (<1.45, low risk; 1.45–3.25, intermediate risk; >3.25, high risk).²²

Table 1 Baseline characteristics of the patients achieving sustained virologic response

Characteristics (n = 272)	
Female (%)	142 (52.5%)
Age (year)	69.1 (30–86)
Body mass index (kg/m ²)	23 (16.5–39.4)
Compensate cirrhosis (%)	38 (14.0%)
History of interferon regimen (%)	126 (46.3%)
History of hepatocellular carcinoma (%)	17 (6.3%)
Hemoglobin (g/dL)	13.1 (7.4–19.0)
Hemoglobin A1c (%)	5.8 (4.2–8.7)
Fasting plasma glucose (g/dL)	107 (66–244)
AST (U/L)	43 (2–163)
ALT (U/L)	37 (9–286)
GGT (U/L)	31 (10–293)
FIB-4 index (<1.45, 1.45–3.25, >3.25)	20/101/151
HCV genotype (1a/1b/2a/unknown)	6/250/1/15 (2.2/91.4/0.4/6.1%)
Virus load (Log IU/mL)	6.1 (1.4–7.7)
DAA regimen (%)	
DCV/ASV	143 (52.6%)
LDV/SOF	121 (44.4%)
PTVr/OBV	8 (2.9%)

Data are shown as median (range) or number (%).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCV/ASV, daclatasvir+asunaprevir; FIB-4 index, fibrosis 4 index; GGT, gamma-glutamyl transpeptidase; LDV/SOF, ledipasvir+Sofosbuvir; PTVr/OBV, paritaprevir/ritonavir+ombitasvir.

Statistical analysis. Descriptive statistics (median and range) were determined for all continuous variables. The Wilcoxon signed-rank test was used to compare data acquired at baseline, ETR, and Post12W. Spearman's rank correlation coefficient was used to quantify the associations between changes in HbA1c and other parameters. Stepwise analysis was performed to identify factors that were associated with changes in HbA1c, and a predictive formula for the calculation of changes in HbA1c

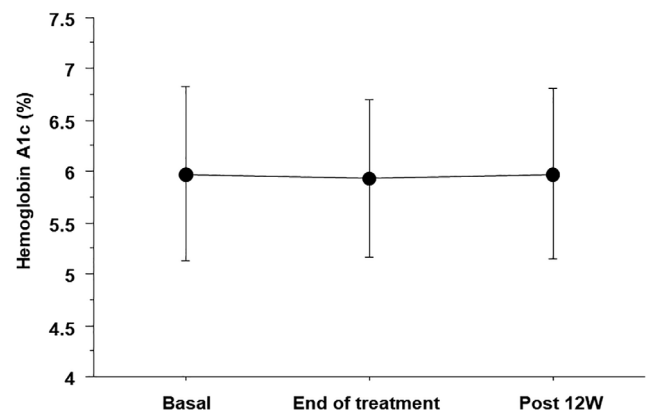


Figure 1 Changes in hemoglobin A1c. Changes in hemoglobin A1c are shown as a polygonal line graph (n = 272). Black dots and error bars indicate mean hemoglobin A1c and standard deviation, respectively.

Table 2 Correlations between the change in hemoglobin A1c between baseline and Post12W and basal parameters

Basal variables	Correlation coefficient	<i>P</i> value
Age	0.123	0.008
BMI	0.004	0.931
Virus load	-0.113	0.063
Hemoglobin	-0.043	0.102
Platelet count	-0.044	0.337
Hemoglobin A1c	-0.319	<0.001
AST	0.061	0.182
ALT	0.015	0.745
GGT	-0.033	0.498
Total bilirubin	-0.006	0.903
Albumin	-0.064	0.167
Fasting plasma glucose	-0.126	0.009
FIB-4 index	0.012	0.848

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4 index, fibrosis 4 index; GGT, gamma-glutamyl transpeptidase.

was generated in this way. $P < 0.05$ was considered to indicate a significant difference. All analyses were performed using IBM SPSS (Version 19.0; SPSS Inc., Tokyo, Japan).

Results

Patient characteristics. The basal characteristics of the patients are summarized in Table 1. An interferon-based regimen had previously been tried in 126 patients. Hepatocellular carcinoma had previously been diagnosed in 17 patients, but all were in remission, and no recurrence was observed during DAA therapy. Compensated liver cirrhosis was diagnosed in 38 patients. There were no patients with decompensated liver cirrhosis. Median FIB-4 index was 3.59 (0.23–27.37), and 151 patients were at high risk of advanced liver fibrosis. Median HbA1c was 5.8% (4.2–8.7), and median fasting plasma glucose was 107 mg/dL. The major genotype was 1b, and the patients were being treated with DCV/ASV, LDV/SOF, or PTVr/OBV. All patients completed the therapeutic regimen, and there was 100% adherence with each therapy.

Changes in HbA1c. HbA1c values at baseline, ETR, and Post12W are shown in Figure 1. Contrary to our hypothesis, there was no significant change in HbA1c during the study.

Analysis of the relationships between changes in HbA1c and other parameters. For a more detailed analysis, we evaluated the relationship between changes in HbA1c

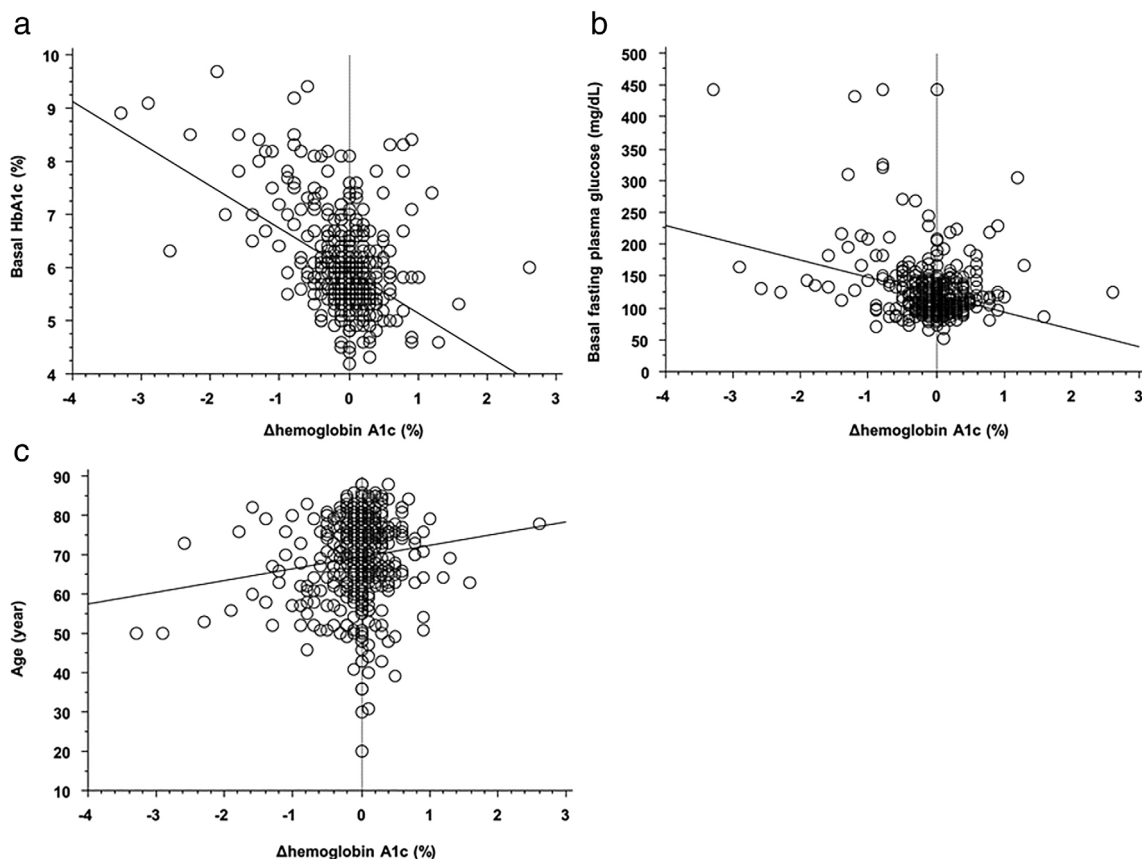


Figure 2 Analysis of the relationships between Δ hemoglobin A1c and other parameters. Correlations between Δ hemoglobin A1c from baseline to Post12W and (a) basal hemoglobin A1c, (b) basal fasting plasma glucose, and (c) age are shown ($n = 272$). Data are presented with open dots (individual patient data) and a line of best fit. Statistics are shown in Table 2.

from baseline to SVR and other parameters at baseline. There was a significant positive correlation with age and negative correlations with basal HbA1c and fasting plasma glucose (Table 2 and Fig. 2). Correlations with other parameters at baseline, including BMI, AST, ALT, hemoglobin, and FIB-4 index, were not significant.

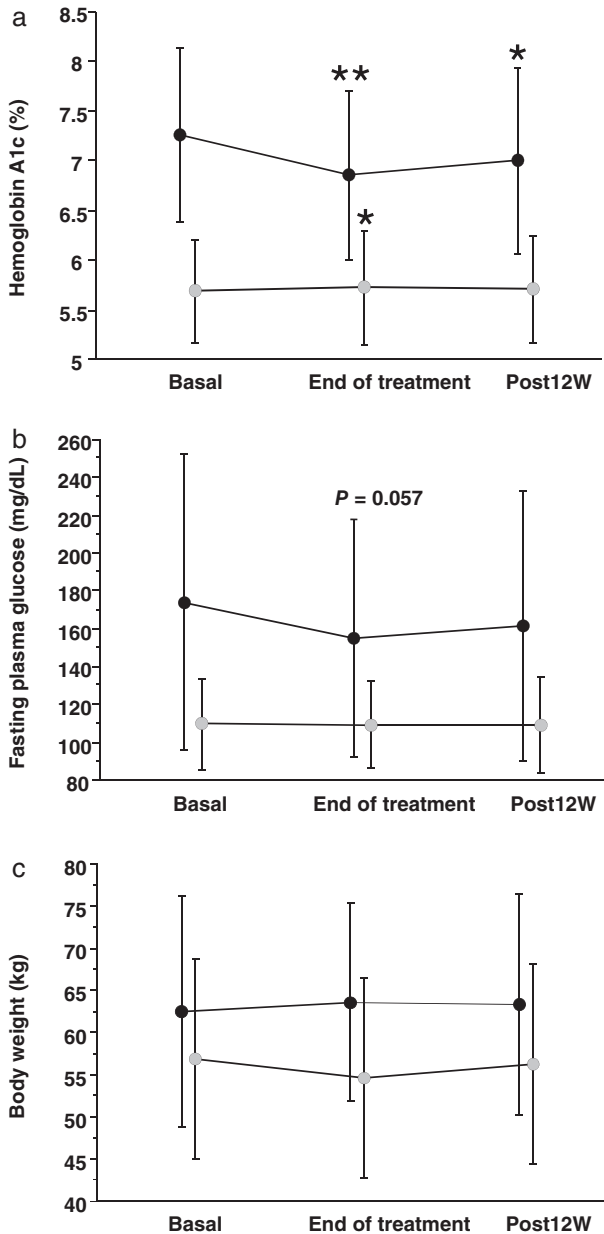


Figure 3 Changes in the glycemic control and body weight in patients with or without diabetes. Changes of (a) hemoglobin A1c, (b) fasting plasma glucose, and (c) body weight are shown as a polygonal line graph. Black dots indicate the mean value of the patients with diabetes ($n = 55$), and the gray dots indicate that of the patients without diabetes ($n = 217$). Error bars represent the standard deviation. $*P < 0.05$, $**P < 0.01$.

Changes in HbA1c in patients with diabetes.

Following the above analysis, we hypothesized that only patients with diabetes might show decreases in HbA1c during DAA therapy. We therefore stratified the 272 patients according to whether (i) they were taking any diabetes medication at the time or (ii) their basal fasting plasma glucose (\leq or >126 mg/dL) and basal HbA1c (\geq or $<6.5\%$). Fifty-five patients met the criteria for diabetes (Fig. 3a). Mean HbA1c significantly decreased between baseline (7.3%) and ETR (6.9%, $P < 0.001$) and Post12W (7.0%, $P < 0.05$) in the diabetic patients but not in the nondiabetic patients. Fasting plasma glucose showed a similar tendency to decrease between baseline and ETR ($P = 0.057$) (Fig. 3b). BMI was also analyzed, but there were no significant changes during the study in either diabetic or nondiabetic patients (Fig. 3c).

Changes in HbA1c and FIB-4 index. Liver fibrosis is associated with the development of diabetes,²³ and insulin resistance, hyperglycemia, and diabetes are associated with the progression of hepatic fibrosis in patients with chronic liver disease.²⁴ We tested whether liver fibrosis predicted using FIB-4 index affected glycemic control in HCV eradication. There was no significant difference in HbA1c and fasting plasma glucose from the baseline in any FIB-4 index categories, and there was no significant difference between the FIB-4 index categories at any timepoint (Supplementary 2).

Medications being taken by patients with diabetes.

Because this was a retrospective study, it might be possible that diabetic patients who had just started a new diabetes therapy or those who had recently changed their medication might have contributed to the measured decrease in HbA1c. Therefore, we surveyed the drugs being taken by the 55 diabetes patients and found that 41 (74.5%) patients were taking medication at baseline, including metformin, oral hypoglycemic drugs, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, and insulin. Of the 41 patients taking medication, none had recently

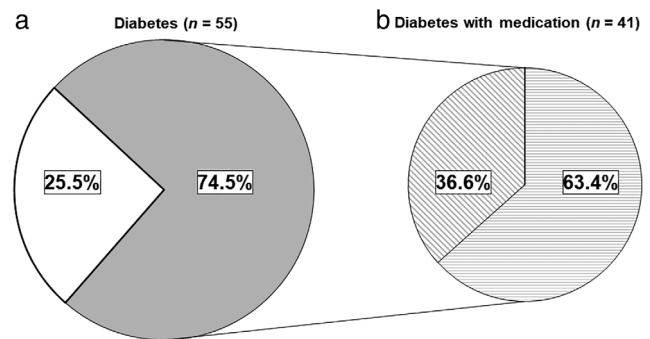


Figure 4 Medication for patients with diabetes. (a) Circle graph of the diabetic patients ($n = 55$) who were taking medication (gray, $n = 41$) and those who were not (white, $n = 14$) at baseline. (b) Circle graph of the diabetic patients on medication ($n = 41$). The area with diagonal lines indicates the patients who were receiving less medication at Post12W than at baseline, and the area with horizontal lines indicates the patients who were receiving the same medication at Post12W. (■), Medication +; (□), medication -; (▨), reduced; (▩), maintained.

Table 3 Stepwise analysis of changes in hemoglobin A1c from basal to Post12W

Model 1			
Basal variables	95% confidence interval (upper, lower)	P value	β value
Age	0.005, 0.019	0.001	0.201
Hemoglobin A1c	-0.497, -0.303	<0.001	-0.477
Model 2			
Variables	95% confidence interval (upper, lower)	P value	β value
Age	0.005, 0.020	0.001	0.209
Fasting plasma glucose	-0.007, -0.003	<0.001	-0.300

increased their medication (in terms of either number of drugs or dose), whereas the amount of medication being taken was reduced during the study in 63.4% of patients (Fig. 4). None of the patients in the nondiabetic group were newly diagnosed with diabetes during the study.

Factors associated with changes in HbA1c and prediction of these changes.

Next, we performed multivariate analysis to identify any parameters showing changes alongside those in HbA1c between baseline and Post12W (Table 3). Of the parameters evaluated at baseline, only basal HbA1c and age showed significant associations with changes in HbA1c. The predictive formula constructed from this information was: $\Delta\text{HbA1c} (\%) = 1.449 - 0.4 \times \text{HbA1c} (\%) + 0.012 \times \text{Age (year)}$ (Model 1). Because there was a strong negative correlation between ΔHbA1c and basal HbA1c, we then excluded basal HbA1c and tested the remaining basal parameters (Model 2). Age and fasting plasma glucose showed associations with ΔHbA1c , and the predictive formula constructed was: $\Delta\text{HbA1c} (\%) = -0.364 - 0.005 \times \text{fasting plasma glucose (mg/dL)} + 0.012 \times \text{Age (year)}$. If basal HbA1c, fasting plasma glucose, and age were all excluded from the analysis, there were no significant parameters to explain ΔHbA1c .

Discussion

Our study of a large population shows that HbA1c significantly decreases by 0.4% when HCV is eradicated with DAA therapy but only in patients with diabetes. The effect is limited for diabetic patients and was not significant in patients without diabetes.

Meissner *et al.* first evaluated HbA1c in DAA therapy and found that it significantly decreased over 24 weeks.²⁵ However, because this study population was treated with SOF + ribavirin, HbA1c could not be used as a marker of glycemic level, as reported by the authors. Another interesting finding of this study was that insulin resistance evaluated by the homeostatic model assessment-insulin resistance (HOMA-IR) did not change between baseline and week 12 of the study. One possible reason for this is that the study population consisted solely of nondiabetic patients. On the other hand, Pavone *et al.* observed a

rapid decline of fasting glucose between baseline and 4 or 8 weeks after the initiation of DAA therapy in a study that included only patients with diabetes.²⁶ Several reports have also shown decreased glucose or HbA1c after the eradication of HCV.^{27–29} Ciancio *et al.* showed improved glycemic control in the diabetic patients with SVR, yet those without SVR showed no significant change.²⁸ Hum *et al.* investigated the changes in average HbA1c 1 year before and after DAA therapy in 2435 patients and demonstrated that decreasing HbA1c (0.98%) was greater in the patients who achieved SVR than those who did not.²⁹ This evidence demonstrates that improvement of glycemic control is independent of virus genotype and therapeutic regimen but is associated with virus eradication. On the other hand, Chaudhury *et al.* reported no decreasing HbA1c after HCV eradication in nondiabetic subjects.³⁰ Another report from Japan has shown the significant but slightly decreasing HbA1c (0.2%) in patients with a nondiabetic range of HbA1c (5.85% in median).³¹ Our data are consistent with these reports and show that the effect of HCV eradication on HbA1c could be limited to diabetic patients.

It might be that the response to HCV infection and HCV eradication among patients depends on their degree of insulin resistance and glucose tolerance. Insulin resistance and glucose intolerance can be caused both by host-related factors, including visceral obesity, and HCV-related factors. In our previous study, visceral obesity strongly correlated with insulin resistance in chronic hepatitis C patients.³² The mean HOMA-IR of the chronic hepatitis C patients without visceral obesity was 1.5 (within the normal range), whereas it was 2.9 in patients with visceral obesity. These findings might imply that visceral obesity is necessary for HCV to induce insulin resistance and, thus, cross-talk between host-related HCV-related mechanisms of insulin resistance. However, when Moucari *et al.* compared HCV patients and HBV patients, the findings suggested that HCV causes insulin resistance independent of metabolic factors and the severity of liver disease.³³ Our present data also suggest that BMI is associated with changes in HbA1c. Although it remains unclear whether the insulin resistance and glucose intolerance caused by HCV infection are independent of or dependent on host-related metabolic factors, our study suggests that the response of glucose tolerance, or at least that of HbA1c, to HCV eradication is different according to whether patients have diabetes or not.

We found that age was also significantly associated with the decreases in HbA1c; older people showed greater decreases in HbA1c during DAA therapy. Aging is known to be a risk factor for insulin resistance and glucose intolerance.^{34,35} Although a mechanism for the effect of aging on HCV-related insulin resistance has not been elucidated, the eradication of HCV might affect the association between age-related and HCV-related insulin resistance and contribute to the improvement of age-related glucose intolerance during HCV infection.

Because our study was retrospective, and detailed lifestyle information was not available, changes in lifestyle during DAA therapy might have affected the observed changes in HbA1c, and this represents a possible limitation of the study, although changes in body weight and medication were recorded. Insulin resistance should be assessed in future research, perhaps by measuring fasting insulin, HOMA-IR, or the effects of glucose

challenge. Changes in the lipid metabolism after HCV eradication, including improvement of fatty liver and increase in cholesterol, were observed in the previous studies,^{22,36} and the association between these changes and glucose metabolism should be tested, which is missing in the current study. However, our study is the first to evaluate changes in HbA1c resulting from the eradication of HCV in a large study population.

It is clear that eradication using DAA treatment should be recommended for patients with chronic hepatitis C. Especially for patients with diabetes, DAA therapy has the advantage of improving glycemia, as well as eradicating HCV, and might contribute to a reduction in the risks of both diabetes and HCV-related mortality.

In conclusion, eradication of HCV using DAA therapy improves glycemic control in patients with diabetes.

Acknowledgments

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Appendix S1. Supporting information.