

Comorbid hepatitis C does not modulate prevalence or severity of diabetic retinopathy

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Purpose: There are limited and conflicting data regarding the impact of comorbid hepatitis C virus (HCV) infection on diabetic retinopathy (DR). This study sought to compare the prevalence and severity of DR among patients with diabetes mellitus (DM) with and without HCV.

Patients and methods: This was a retrospective, case-control study of patients with DM comparing 120 patients with comorbid HCV and 120 age-matched controls. DR prevalence and several measures of severity were compared between groups. Subgroup analyses were performed among HCV patients with cirrhosis, comorbid HIV, or history of treatment with interferon. Statistical analysis for between-group comparisons utilized both univariate and multivariate analyses.

Results: Cases and controls exhibited similar baseline characteristics: average hemoglobin A1c, DM duration, and age ($p>0.05$). Among cases and controls, there was no difference in DR prevalence (35.8% versus 42.5%, respectively, $p=0.29$) or severity ($p>0.05$). Within the HCV subgroup, DR severity was reduced in patients with HIV or cirrhosis. However, multivariate analysis identified reduced DM duration in these subgroups as the primary contributor to lesser DR severity, rather than HIV or cirrhosis.

Conclusion: In this study, comorbid HCV did not modulate the prevalence or severity of DR among patients with DM. These findings may inform clinical monitoring among HCV-positive diabetics undergoing ophthalmic evaluation.

Keywords: cirrhosis, diabetes mellitus, retinopathy, hepatitis

Introduction

Diabetes mellitus (DM) is among the most significant drivers of morbidity in the United States, diagnosed in 23 million patients and precipitating more than \$245 billion of direct and indirect healthcare expenditure.^{1,2} Among the risk factors for developing DM, studies suggest, is hepatitis C virus (HCV) infection, potentially due to the virus's disruption of hepatic glucose metabolism.^{3,4} In fact, the Third National Health and Nutrition Examination Survey revealed an over 3-fold increase in the prevalence of type 2 diabetes mellitus (DM2) among HCV-positive patients ≥ 40 years old, as compared to those without HCV.⁵ In support of this link between liver disease and glucose metabolism, liver transplantation has been found to reverse glucose intolerance and insulin resistance.⁵ Further, a pharmacologic "cure" of HCV (ie, a sustained viral response following antiviral therapy) is associated with 50–67% reduction in DM incidence.⁶

While the contribution of HCV to glycemic control and to DM has been the subject of much prior work, few studies have evaluated the potential role, if any, of HCV in microangiopathic complications of DM, such as diabetic retinopathy (DR).

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Of patients with DM over 40 years old, 28–40% suffer from DR, making it a leading cause of blindness in the United States.^{7,8} Potential mechanisms by which HCV may influence DR incidence or severity include glucose dysregulation and insulin resistance, due to either viral- or immune-related effects on the liver. In addition, the virus may infect lymphatic cells or induce chronic low-grade inflammation that secondarily influences DR, the pathogenesis of which is known to include a prominent inflammatory component. The potential contribution of HCV to inflammatory ocular disease is highlighted by a recent study suggesting higher rates of uveitis among patients with HCV infection.⁹

In light of recent advances in the treatment of HCV that now allow for a high cure rate for the virus, any association of HCV with DR may be an indication for HCV screening and treatment among DM patients undergoing ophthalmic evaluation.¹⁰ However, to date, there are limited studies evaluating the impact of HCV on DR. Existing studies present conflicting findings, variably suggesting increased, equivalent, or reduced DR risk or severity among DM patients with HCV.^{3,11–15}

To reconcile these contradictory findings, this study sought to determine whether HCV influences the prevalence or severity of retinopathy among diabetics through a retrospective chart review of patients with DM and HCV, compared to age-matched controls with DM without HCV. This work presents the rate of DR among patients with HCV versus without, shedding light on the relationship between HCV and microangiopathic complications of diabetes.

Patients and methods

This was a retrospective, observational, case–control study of patients with DM and HCV (“cases”) evaluated at the Weill Cornell Medicine Department of Ophthalmology between January 1, 2007, and December 31, 2012, and age-matched patients with DM without HCV (“controls”). The study was approved by the Weill Cornell Medical College (WCMC) Institutional Review Board and was performed in a fashion compliant with the Health Insurance Portability and Accountability Act and the tenets put forth in the Declaration of Helsinki.

Inclusion criteria for cases were as follows: (1) diagnosis of DM (International Classification of Diseases, Ninth Revision 250.XX), (2) diagnosis of HCV (presence of detectable HCV viral RNA by quantitative polymerase chain reaction from the serum), and (3) ophthalmology

clinic evaluation with dilated fundus exam (DFE). Cases were identified through the Informatics for Integrating Biology and the Bedside (i2b2) software, which queried data from the electronic medical record (EMR) of WCMC to identify patients meeting the aforementioned criteria (using diagnosis codes and lab values). Subsequently, inclusion criteria were verified by manual EMR review. Inclusion criteria for controls were as follows: (1) diagnosis of DM, (2) no history of diagnosis of HCV by history or laboratory testing, and (3) ophthalmology clinic evaluation with DFE. Exclusion criteria for both groups were as follows: gestational DM, pre-DM, impaired glucose tolerance, and receipt of liver transplant at any point during the study period. For the case group, achievement of HCV cure (defined as sustained virologic response or undetectable HCV viral load 12 weeks after completion of treatment) was an additional exclusion criterion. Controls, matched to the case group by age (half-decade) and DM type (type 1 or type 2) in 1:1 fashion, were selected randomly from the pool of subjects meeting inclusion/exclusion criteria.

The EMR was reviewed to collect the following data: age, gender, type of DM, duration of DM, average hemoglobin A1c (HbA1c) over all visits, presence or absence of hypertension (HTN), presence or absence of dyslipidemia (DLD), specifically hyperlipidemia or hypertriglyceridemia, HIV co-infection, and hepatitis B co-infection. For the HCV group, history of treatment with interferon (IFN), current or prior, and presence or absence of cirrhosis (with confirmation on imaging or biopsy) were determined.

Ophthalmology clinic notes were reviewed to determine, for each eye, the most severe stage of DR, characterized as no retinopathy, nonproliferative diabetic retinopathy (NPDR), or proliferative diabetic retinopathy (PDR). The determination of the presence of DR and, if applicable, its severity, was determined by the attending ophthalmologist caring for the patient, based on review of diagnostic tests (eg, color fundus photography, optical coherence tomography) and findings from the DFE (eg, presence of microaneurysms, dot/blot hemorrhages, neovascularization, etc.). Several additional measures of DR severity were recorded: prior treatment for diabetic macular edema (DME), including laser, intravitreal anti-vascular endothelial growth factor (anti-VEGF), or intravitreal steroids; prior surgery for PDR (eg, for vitreous hemorrhage or retinal detachment); and best-corrected visual acuity (BCVA) at final study visit. BCVA was assessed using a Snellen visual acuity chart, with manifest refraction as

available. For each patient, the eye with more severe DR was included in the study.

The difference of covariates (age, duration of DM, average HbA1c, presence of HTN, presence of DLD, presence of hepatitis B infection and/or HIV coinfection) and endpoints (DR prevalence and severity) between cases and controls was determined by 2-Proportion z-Test, Fisher's Exact Test, and 2-Sample *t*-Test. The Python 3.6 statistical software (Python Software Foundation) was used for these analyses. Within cases, subgroup analyses were performed to understand any additional risk of DR occurrence or severity associated with several variables, including current or prior treatment with IFN, HIV co-infection, and presence of cirrhosis. Similar statistical analyses as detailed above were used to compare differences in endpoints between sub-groups. Multivariate regression was then used to investigate the impact of covariates (age, duration of DM, average HbA1c, HTN, HIV, and cirrhosis) on the association between HCV and DR. The R version 3.4.3 statistical software (R Foundation for Statistical Computing, 2017) was used for this analysis. Comparisons were considered significant at $p \leq 0.05$.

Results

Of the 259 potential cases identified by i2b2, 120 met inclusion criteria for the "DM with HCV" cohort ("cases") and were included in the study. Thus, 120 patients, matched by age and type of DM to patients in the case group, were included as "controls." Cases and controls exhibited similar baseline characteristics with respect to age (65.4 versus 64.9 years, $p=0.60$), DM duration (8.8 versus 9.6 years, $p=0.45$), comorbid HTN (85.0% versus 77.5%, $p=0.14$), and average HbA1c (7.9 versus 8.1, $p=0.34$) (Table 1). The populations differed in several expected ways: HCV patients were more likely to be male (62.5% vs 33.3%, $p<0.001$) and to have HIV (26.7% versus 4.2%, $p<0.001$) and were less likely to have DLD (32.5% versus 54.2%, $p=0.05$). Among the HCV group, none were found to be coinfecting with active hepatitis B (Table 1).

There was no significant difference in the prevalence of DR between patients with and without HCV (35.8% versus 42.5%, $p=0.29$) (Table 2). Specifically, NPDR was observed in 29.2% and 30.8% of patients with and without HCV, respectively, and PDR was observed in 6.7% and 11.7%, respectively ($p=0.35$). Further, there was no significant difference in the severity of DR, as measured by several additional outcomes (treatment for DME, surgery for PDR, and final BCVA). Treatment for DME (including laser therapy and intravitreal anti-VEGF and steroids) was

Table 1 Baseline characteristics of patients with diabetes mellitus with or without hepatitis C

Characteristic		Hepatitis C (n=120)	Control (n=120)	p-Value
Age (years)		65.4	64.9	0.60
Gender	Women, n (%)	45 (37.5)	80 (66.7)	<0.001
	Men, n (%)	75 (62.5)	40 (33.3)	
Average HbA1c (%)		7.9	8.1	0.34
Duration of DM (years)		8.8	9.6	0.45
Hypertension, n (%)		102 (85.0)	93 (77.5)	0.14
Dyslipidemia, n (%)		39 (32.5)	65 (54.2)	0.05
HIV, n (%)		32 (26.7)	5 (4.2)	<0.001
Hepatitis B, n (%)		0 (0)	N/A	N/A

Abbreviations: HbA1c, hemoglobin A1c; DM, diabetes mellitus.

recorded in 5.8% of patients with HCV and 13.3% of controls ($p=0.08$). Surgery for PDR (specifically for vitreous hemorrhage or retinal detachment) was observed in 4.2% of both cases and controls ($p=1.0$). Moreover, final BCVA was not significantly different between patients with and without HCV (logMAR 0.20 versus 0.25 [Snellen 20/32 versus 20/36], respectively, $p=0.42$). When examining only the subset of patients with any DR, final BCVA also did not differ significantly between those with and without HCV (logMAR 0.33 versus 0.42 [Snellen 20/43 versus 20/53], respectively, $p=0.48$).

Several covariates specific to the HCV cohort were also investigated. Among HCV patients, 38% ($n=45$) had ever been treated with IFN, 27% ($n=32$) had HIV, and 41% ($n=47$) exhibited documented evidence of cirrhosis on imaging or biopsy (Figure 1). Within the HCV cohort, subgroup analyses were performed to investigate the impact of these covariates on the occurrence and/or severity of DR (Figure 1). The prevalence of DR was not significantly different in any of the sub-groups explored: 31.1% versus 37.8% in those treated with IFN versus not, respectively ($p=0.46$); 31.3% versus 37.5% in HIV-positive versus HIV-negative, respectively ($p=0.52$); and 31.9% versus 38.2% in those with cirrhosis versus without, respectively ($p=0.49$). DR severity was similar in patients with and without a history of IFN therapy ($p=0.43$), while patients with HCV with comorbid HIV ($p=0.02$) and cirrhosis ($p=0.03$) exhibited less severe DR (Figure 1). However, in multivariate analysis, neither HIV (OR=1.29, $p=0.66$) nor cirrhosis

Table 2 Prevalence and severity of diabetic retinopathy among patients with diabetes mellitus with or without comorbid hepatitis C

Outcome	Hepatitis C (n=120)	Control (n=120)	p-Value
DR prevalence, n (%)	43 (35.8)	51 (42.5)	0.29
DR severity	No DR, n (%)	77 (64.2)	0.35
	NPDR, n (%)	35 (29.2)	
	PDR, n (%)	8 (6.7)	
Treatment for DME prevalence, n (%)	7 (5.8)	16 (13.3)	0.08
Surgery for PDR prevalence, n (%)	5 (4.2)	5 (4.2)	1.0
BCVA, logMAR (Snellen)	0.20 (20/32)	0.25 (20/36)	0.42
BCVA among patients with DR, logMAR (Snellen)	0.33 (20/43)	0.42 (20/53)	0.48

Abbreviations: DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; DME, diabetic macular edema; BCVA, best-corrected visual acuity.

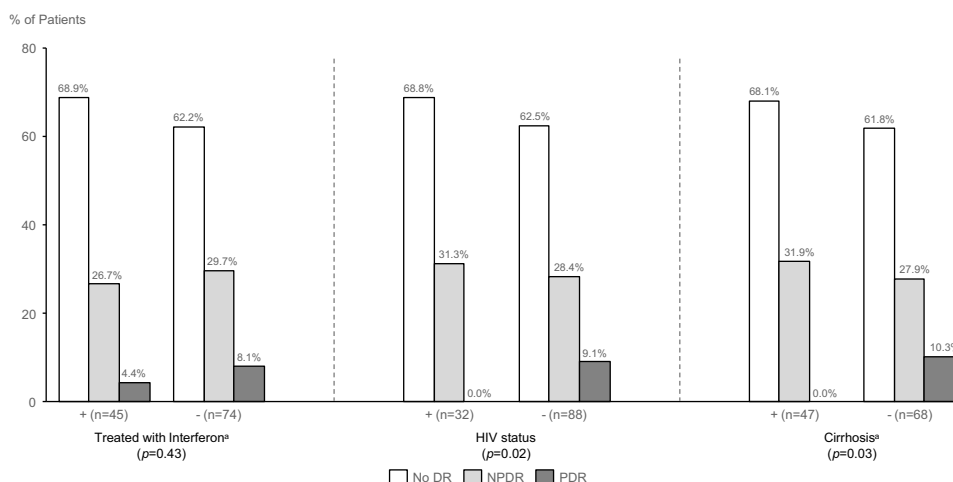


Figure 1 Severity of diabetic retinopathy in subgroups of patients with diabetes mellitus and hepatitis C.

Note: ^aData were not available for all subjects.

Abbreviations: DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

(OR=0.69, $p=0.45$) were significant contributors to DR (Table 3). In fact, DM duration was the only significant contributor to DR severity (OR=1.14, $p<0.001$) in a

multivariate model including HTN, HIV, age, HbA1c, DM duration, and cirrhosis.

Discussion

DR is a leading cause of blindness among working-age adults in the United States.^{7,8} Several risk factors for the development of microvascular complications of DM, such as DR, have been consistently identified, namely, cumulative glycemic exposure and DM duration.^{16–18} Existing research regarding the role of HCV has primarily focused on its contribution to the development of DM. Prior studies have identified an up to 3-fold increase in the development of DM among patients with HCV.⁵ However, there are few studies investigating the role of HCV in the development of microangiopathic complications

Table 3 Logistic regression model of covariates, reference is no retinopathy

Variable	Odds ratio	p-Value
HTN	1.32	0.73
HIV	1.29	0.66
Age	0.99	0.73
HbA1c	1.06	0.71
DM duration	1.14	0.0005
Cirrhosis	0.69	0.45

Abbreviations: HTN, hypertension; HbA1c, hemoglobin A1c; DM, diabetes mellitus.

of DM such as DR. Moreover, the few studies reported to date present conflicting results: studies have reported increased, equivalent, or decreased prevalence and/or severity of DR among DM patients with HCV.^{3,11–15}

To reconcile the conflicting studies, we conducted a retrospective, observational, case-control study to compare the prevalence and severity of DR among 120 patients with DM and HCV and 120 age-matched control patients with DM without HCV. Key findings in this study were as follows: (1) HCV infection was not associated with a difference in prevalence or severity of DR among patients with DM and (2) among patients with DM and HCV, the presence of cirrhosis or HIV infection did not modulate the risk or severity of DR.

In this study, HCV infection was not associated with a difference in prevalence or severity of DR among patients with DM. These findings are consistent with several prior studies.^{3,11,12} However, these findings contrast with a 1995 study in Japan, which found significantly higher rates of DR in patients with DM and HCV.¹³ Specifically, Setoguchi et al reported a higher rate of DR in patients with HCV, as compared to control patients (without HCV) with and without normal liver function.¹³ However, in their study, the HCV group exhibited a longer duration of DM than the control group with liver dysfunction. The longer duration of DM, based on the well-established impact of DM duration on DR, may account for the increased rates of DR in the HCV group. Though, such a difference in baseline characteristics was not observed in comparing the HCV group with the control group with normal liver function. Additional differences in methodology compared to the present study exist: Setoguchi et al determined HCV status by the presence of seroconversion of HCV antibodies, while the current study did so through measurement of serum HCV viral load.¹³

Of the studies that have suggested reduced DR prevalence or severity in HCV patients, most have looked at subpopulations within the HCV population, such as patients with chronic liver disease or cirrhosis. For example, Kuriyama et al reported significantly lower prevalence of DR among DM patients with comorbid liver disease (primarily but not exclusively due to HCV) compared to those with DM only.¹⁴ In this study, we performed subgroup analyses to explore covariates more prevalent within or specific to the HCV population. Patients with HCV complicated by cirrhosis as well as patients with HIV co-infection were found to have significantly less severe DR compared to patients with HCV alone. However, in multivariate regression, neither cirrhosis nor HIV were significant contributors to DR. In fact, DM

duration was found to be the only significant contributor to DR in multivariate regression. Lower rates of DR among patients with DM and HCV with concurrent cirrhosis or HIV related to the shorter duration of DM in these groups, perhaps due to increased mortality related to cirrhosis or HIV itself. This finding supports the potential for survival bias to yield fewer DM-related complications among HCV patients with cirrhosis or HIV. Relatedly, Marchesini et al noted reduced rates of retinopathy among DM patients with cirrhosis than in DM controls without cirrhosis, although the etiology of cirrhosis (hepatitis or non-hepatitis) was not specified.¹⁵ Similarly, Burgess et al reported a negative association between HIV and DR (OR=0.16, $p=0.02$).¹⁹ In further support of a potential role for survival bias, Greca et al reported significantly lower rates of DR among the subset of HCV patients on dialysis compared to patients without HCV.¹²

This study has several limitations, including the inherent limitations of a retrospective observational study. In addition, the relatively small sample size ($n=240$) and population from a single, tertiary academic center may limit generalizability. Some metrics studied, such as duration of DM, are difficult to accurately determine in a retrospective study. However, we expect both the case and control groups to be equally affected. Finally, a significant share (up to 50%) of HCV patients in the United States are undiagnosed.^{20,21} As a result, patients with undiagnosed HCV may have been included in the control group.

Today, there are approximately 3.5 million Americans infected with HCV, many of whom are undiagnosed and untreated despite the availability of direct-acting antiviral (DAA) therapy.^{22,23} Given the size of this population, potential complications of HCV (eg, due to metabolic dysregulation) could represent significant public health issues in the future. The availability of DAA (which have demonstrated sustained viral response in >90%) makes an investigation into this disease state and its complications particularly relevant.¹⁰ For example, if HCV contributed to increased risk or severity of DR among patients with DM, clinicians may consider screening patients for risk factors for HCV, especially given the emergence of DAA therapies. What is more, the size of the HCV-positive population has increased significantly in recent years in the setting of the opioid epidemic in America (with patients suffering from substance abuse transitioning from oral opioids to intravenous opioids). The incidence of HCV has more than tripled from 2010 to 2016.²² However, this study did not identify a

significant difference in the prevalence or severity of DR between diabetic patients with and without HCV. Prospective studies are needed to augment our understanding of the contribution of HCV to diabetic microangiopathies, as such knowledge has the potential to inform future management and screening efforts of diabetics undergoing ophthalmic evaluation.

Conclusions

Though the relationship between DM and HCV has been the subject of numerous studies, there are limited and conflicting data on the impact of HCV on microangiopathic complications of DM such as DR. This retrospective, observational, case-control study attempted to reconcile these conflicting data. The findings demonstrated no significant increase in the prevalence or severity of DR among DM patients with HCV, as compared to those without HCV.

Ethics approval and informed consent

The study was approved by the Weill Cornell Medical College (WCMC) Institutional Review Board (IRB) and was performed in a fashion compliant with the Health Insurance Portability and Accountability Act and the tenets put forth in the Declaration of Helsinki. The WCMC IRB granted a waiver of informed consent based on the following: the research involves no more than minimal risk to subjects, the waiver does not adversely affect the rights and welfare of subjects, the research could not be carried out without the waiver, and a significant portion of patients included in this retrospective study have been lost to follow-up.

Data sharing statement

The data were derived from patients evaluated at the Weill Cornell Department of Ophthalmology between January 1, 2007, and December 31, 2012. The software Informatics for Integrating Biology & the Bedside (i2b2) was used to identify relevant patients. Data are available upon request.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Dr Robison Vernon Paul Chan reports personal fees from Alcon, personal fees from Allergan, personal fees from Beyeonics, personal fees from Visunex Medical Systems, personal fees from Genentech, outside the submitted work. Dr Szilard Kiss reports personal fees and non-financial support from Adverum, personal fees from Allergan, personal fees from BioMarin, personal fees from Regeneron, personal fees and non-financial support from RegenXBio, personal fees and non-financial support from Genentech/Roche, personal fees and non-financial support from Optos, during the conduct of the study. Dr Donald JD'Amico report grants from Research to Prevent Blindness, Inc., during the conduct of the study. Dr Sonal Kumar reports research support, speakers bureau, and advisory board support from Gilead and Abbvie, outside the submitted work. The authors report no other conflicts of interest in this work.

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