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Depression is not associated with peripheral insulin resistance in patients with chronic hepatitis C infection

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SUMMARY

Depression is common in individuals infected with hepatitis C virus (HCV), and both depression and HCV infection are independently associated with insulin resistance (IR). To evaluate the relationship between depression and IR, among other factors, in an HCV-infected cohort. In this cross-sectional analysis, seventy-four non-type 2 diabetic, noncirrhotic, HCV-infected patients underwent comprehensive clinical, histologic and metabolic evaluation. IR was assessed directly with an insulin suppression test by measuring steady-state plasma glucose (SSPG) levels during continuous infusions of octreotide, glucose and insulin. Logistic regression modelling was used to evaluate predictors associated with depression. Thirty-nine (53%) patients were depressed, and 21 (54%) depressed patients were on at least one antidepressant. A higher estimated proportion of depressed patients were Caucasian (51% *vs* 20%, $P = 0.005$), unemployed (69% *vs* 49%, $P = 0.07$), heavier smokers (18 pack-years *vs* 13 pack-years, $P = 0.07$), on substance abuse therapy (16% *vs* 3%, $P = 0.06$) and had lower HDL levels (1.2 mmol/L *vs* 1.4 mmol/L, $P = 0.01$). The mean SSPG levels in depressed and nondepressed patients were 7.3 and 8.3 mmol/L ($P = 0.45$), respectively. In multipredictor adjusted analysis, only Caucasian race (OR 4.19, 95% CI 1.42–12.35, $P = 0.009$) and lower HDL (OR 0.95, 95% CI 0.89–0.99, $P = 0.046$) were associated with depression. In conclusion, although prevalent, depression was not associated with peripheral IR in this HCV-infected cohort. Attention to other modifiable factors associated with depression in the HCV-infected population is warranted.

Keywords

clamp studies; hepatitis C; impaired fasting glucose; impaired glucose tolerance; insulin resistance; neuropsychiatric

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CONFLICT OF INTERESTS

There are no conflict of interests to disclose.

INTRODUCTION

Approximately 180 million people worldwide and 3.9 million people in the United States (US) are chronically infected with hepatitis C virus (HCV) [1]. While the prevalence of depression in the general US population is estimated to be at least 10% [2], its prevalence in HCV-infected individuals is estimated to be 20–30% and is likely higher given the rate of undiagnosed depression [3,4]. Depression is not only associated with significant economic and healthcare cost, but it is also a leading cause of disability among adults and a known risk factor for poor outcome in several chronic diseases [5]. Furthermore, depression within the context of HCV infection carries its own unique and important considerations. Specifically, severe or poorly controlled depression may preclude HCV treatment eligibility given that interferon alpha may not only worsen pre-existing depression but may cause incident depression [6–8]; coexisting depression may also compromise individuals' ability to complete the full HCV treatment course [8,9]. Moreover, depression in the setting of HCV negatively impacts quality of life and is associated with several other adverse outcomes [10]. Given these significant implications, a more thorough understanding of the factors associated with depression in this population is warranted.

Interplay of multiple factors likely underlies the high prevalence of depression in HCV. Limited data suggest a direct viropathic effect of HCV on neuropsychiatric disease [11–13] and/or an indirect effect via the physiologic response to chronic infection [14–17]. While knowledge of the HCV diagnosis alone has also been associated with depression, additional host and environmental factors that occur with higher frequency in the HCV-infected population, including drug abuse, alcohol abuse and low socioeconomic status, have been implicated as potential factors contributing to their higher prevalence of depression [18,19].

Recent data in the HCV-uninfected population also suggest a role for metabolic factors in depression [20,21]; in a recent meta-analysis of 18 studies, a small but significant association was observed between insulin resistance (IR) and depression [20]. Most studies, however, including those in the meta-analysis, use surrogate measures of IR, such as the homeostatic model assessment (HOMA) and the quantitative insulin sensitivity check index (QUICKI). Although convenient, surrogate measures have a high rate of misclassification with limited reliability in certain populations, as well as limited intraperson reliability [22,23]. Nevertheless, it is plausible that IR may indeed play a role in the observed increased prevalence of depression in the setting of HCV. In fact, HCV is independently associated with IR and those with HCV have significantly higher rates of IR compared to those without HCV [24]. However, there are no published data to date assessing the relationship between depression and IR in HCV-infected individuals.

The aim of this study was to evaluate factors associated with depression in a cohort of non-type 2 diabetic, noncirrhotic, treatment-naïve HCV-infected patients with comprehensive metabolic assessments including direct evaluation of insulin-mediated glucose uptake (primarily in muscle) via the insulin suppression test, which represents an accurate measure of peripheral IR [22,23].

MATERIALS AND METHODS

Patient selection

This is a cross-sectional substudy of a prospective cohort of 100 non-type 2 diabetic, noncirrhotic, viremic HCV-infected patients (detectable HCV antibody and HCV RNA level). Patients were recruited from the San Francisco General Hospital (SFGH) and affiliated clinics at the University of California, San Francisco (UCSF) from 2002 to 2009 and had completed detailed clinical, histologic and metabolic evaluation. Patients with history of prior HCV treatment; presence of clinical, histologic, or known diagnosis of cirrhosis or evidence of decompensated liver disease; and/or clinical diabetes as defined by a fasting serum glucose ≥7.0 mmol/L [25], documented history of diabetes, and/or the use of antidiabetes medications, were excluded. Patients with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) coinfection, non-HCV causes of liver disease, steroid and/or anabolic drug use, pregnancy and/ or any medical condition compromising their ability to participate in the study were also excluded. Patients who had incomplete metabolic evaluation or those with self-reported depression or depressive symptoms but without formal psychiatric evaluation and diagnosis were excluded from the data analysis. This study was approved by the UCSF Committee on Human Research.

Study procedures

All participants were admitted to the UCSF Clinical and Translational Science Institute-Clinical Research Center (CRC) to carry out study tests. Participants underwent medical interview, physical examination, fasting laboratory evaluation and a liver biopsy at enrolment. The Ludwig- Batts scoring system was used for histologic evaluation of liver biopsy.

Population characterization

Data including demographics (age, sex, race), employment status, education level, place of birth, behavioural factors (smoking status, alcohol intake), anthropomorphic measurements, family history of diabetes, HCV mode of transmission and duration of infection, and substance abuse maintenance therapy with methadone were extracted from the initial intake questionnaires.

Metabolic testing

Study participants underwent a 2-day inpatient hospital admission to the CRC for metabolic testing. Protocols for the oral glucose tolerance test (OGTT) and insulin suppression test (IST), which is used to directly measure insulin-mediated glucose uptake [i.e. steady-state plasma glucose (SSPG) level], were previously described [26]. Patients who met criteria for diabetes based on a 2-h plasma glucose level ≥11.1 mmol/L during OGTT were excluded from the analysis. Higher SSPG levels represent higher degrees of IR.

Laboratory evaluation

Serum measurements of liver transaminases, fasting lipid panel, HCV genotype and HCV RNA level (viral load) were evaluated. Insulin and glucose were measured as previously described [26].

Depression assessment

Depression was defined as electronic medical record documentation of a formal psychiatric evaluation during which the patient met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for major depressive disorder. Patients with self-reported depression or depressive symptoms but without formal psychiatric evaluation and diagnosis were excluded from the study. Patients with psychiatric diagnoses other than depression or alternate psychiatric diagnoses combined with depression were also excluded. Additionally, the use and type of psychiatric medication were captured.

Statistical analysis

Descriptive statistics of the patient populations were generated as mean ± standard deviation (SD) and median (range) where appropriate for continuous variables and frequency (%) for discrete variables. Viral, host and metabolic factors were compared between patients with and without depression using the Mann–Whitney *U*-test for continuous variables and the chi-squared test for categorical variables. Logistic regression modelling was used to evaluate the predictors associated with depression from an *a priori* compiled list of candidate predictors. Both single predictor models (unadjusted) and multipredictor models (additionally adjusted for age, sex, race and SSPG) were generated for each predictor. Because of variable data in the literature regarding antidepressant medications (specifically selective serotonin reuptake inhibitors, SSRIs) and IR, we attempted to fit logistic regression models with an additional interaction of SSPG and antidepressant use (along with marginal terms for each variable) to determine whether antidepressant use modified the effect of SSPG on depression. However, because all patients on antidepressants were depressed, the interaction term proved to be inestimable. We therefore proceeded to examine whether SSPG levels differed in depressed patients only with respect to whether or not subjects were on antidepressants using linear models; again, both unadjusted and adjusted models were fitted. Statistical significance was assessed as $P < 0.05$ (2-sided) in all models. All analyses were performed using SAS versions 9.1/9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

Of the 100 patient cohort, 74 patients met eligibility criteria for inclusion in this study, of which 39 (53%) had a diagnosis of depression. Of the patients with depression, 21 (54%) were on one or more antidepressant medication, almost all of which (90%) were SSRIs. Overall, patients had a mean age of 48; 31% were female, 37% self-identified as Caucasian, 26% as African American and 30% as Hispanic/Latino (Table 1). There was no significant difference between the proportion of females and males within each racial group ($P = 0.74$).

When stratified according to the diagnosis of depression, a higher proportion of depressed patients were Caucasian (51% *vs* 20%, *P* = 0.005) and had lower HDL levels (1.2 mmol/L *vs* 1.4 mmol/L, *P* = 0.01) (Table 1). In addition, a higher proportion of depressed patients were unemployed (69% *vs* 49%, *P* = 0.07), smoked a greater amount of cigarettes (18 pack-years *vs* 13 pack-years, *P* = 0.07) and received substance abuse therapy with methadone (16% *vs* 3%, *P* = 0.06). Notably, there was no difference between the proportion of unemployed Caucasians and non-Caucasians (57% *vs* 63%, *P* = 0.64). The estimated duration of alcohol use (29 years *vs* 26 years, *P* = 0.41) and the rate of heavy alcohol use (54% *vs* 40%, *P* = 0.23) were not statistically significantly different between depressed and nondepressed patients, respectively. There were also no statistically significant differences between depressed and nondepressed patients in HCV viral-related parameters, including ALT level, HCV viral load, HCV genotype, duration of HCV infection and injection drug use (IVDU) as mode of HCV transmission; furthermore, the estimated group differences in these variables were too small to be considered clinically important.

With respect to metabolic parameters, the estimated level of IR as reflected by SSPG was 7.3 mmol/L in depressed patients and 8.3 mmol/L in nondepressed patients (*P* = 0.45). In depressed *vs* nondepressed patients, the proportion with impaired fasting glucose (IFG) was 8% *vs* 21% (*P* = 0.11); impaired glucose tolerance (IGT) was 13% *vs* 31% (*P* = 0.37); and metabolic syndrome was 13% *vs* 20% (*P* = 0.40).

Factors associated with depression in HCV infection

In (unadjusted) single predictor analysis (Table 2), only Caucasian race (OR 4.21, 95% CI 1.49–11.91, *P* = 0.007) and lower HDL levels (OR 0.96, 95% CI 0.92–0.99, *P* = 0.04) were statistically significantly associated with depression. Unemployment status (OR 2.38, 95% CI 0.92– 6.16, *P* = 0.07) and substance abuse therapy (OR 6.37, 95% CI 0.73–55.86, *P* = 0.09) were also suggestive of increased risk of depression in the *a priori* expected directions, but these did not reach statistical significance. HCV viral-related factors as well as level of liver injury were not statistically significantly associated with depression. The associated confidence intervals were too wide to rule out clinically important effects, however. With respect to metabolic parameters, IFG, IGT and SSPG were estimated to be negatively associated with depression, but these were not statistically significant. The estimated odds ratio of the association between SSPG and depression was 0.97 (95% CI 0.92–1.03, *P* = 0.31). Further accounting for the use of antidepressants as a covariate did not substantially modify the relationship between SSPG and depression as reflected by its estimated odds ratio of 0.99 (95% CI 0.93–1.06, *P* = 0.83).

In the multipredictor adjusted models that included age, sex, race and SSPG as covariates, Caucasian race (OR 4.19, 95% CI 1.42–12.35, *P* = 0.009) was positively associated with depression (Table 3). The odds ratio with respect to the association between SSPG and depression was very close to 1.0 with a narrow confidence interval (OR 0.99, 95% CI 0.99–1.01), reflecting an absence of any meaningful association. When adding HDL level as a covariate to the model, HDL level was negatively associated with depression (OR 0.95, 95% CI 0.89–0.99, *P* = 0.046). While the odds ratio for Caucasian race decreased with the

addition of HDL level to the model, the estimated odds ratio associated with SSPG (OR 0.99, 95% CI 0.99–1.00) remained essentially unchanged (Table 3).

DISCUSSION

To our knowledge, this is the first study evaluating the relationship between depression and directly measured insulin resistance (IR) in a multiethnic, non-type 2 diabetic, noncirrhotic, treatment-naïve, HCV-infected cohort with detailed metabolic evaluation. We show that depression is not associated with IR in this study population. Although multiple viral- and/or host-related factors may contribute to the high prevalence of depression in the HCV-infected population, we only found Caucasian race and lower HDL levels to be clearly associated with depression in this cohort.

Depression and IR are both associated with HCV infection. Notably, those with HCV have significantly higher rates of IR compared to those without HCV [24]. Consistent with prior reports emphasizing depression as a major comorbidity in the setting of HCV, a high proportion of HCV-infected patients had a formal diagnosis of depression in this study. In fact, the prevalence of depression was approximately 50%, which is higher than the 20–30% prevalence reported in the literature [3,4]; this may highlight the under-recognition of this condition in the HCV-infected population. Identification of and judicious attention to both depression and IR within the context of HCV are important given their negative impact on HCV disease course [27,28], quality of life and overall disease outcomes [10]. Furthermore, comorbid depression may influence HCV treatment candidacy with interferon (IFN)- based antiviral therapy and/or ability to complete the treatment course [8,9], while comorbid IR decreases rates of sustained virologic response to traditional anti-HCV treatment with pegylated IFN and ribavirin [27,28]. Although the newly introduced, direct-acting anti-HCV therapies show promise for reducing the burden of HCV, depression is clearly a multifactorial state. Investigation into the relationship between depression and IR, among other potentially modifiable risk factors, in this particularly at-risk population is therefore warranted.

Depression and IR share several pathophysiologic mechanisms, including activation of the hypothalamo-pituitary-adrenal (HPA) axis, activation of the sympathomedullary system, dysregulation of the central serotonin pathway, notably the tryptophan (TRP)-kynurenine (KYN) metabolic pathway, as well as possible genetic predispositions [29,30]. Additionally, activation of the immune system stimulates a low-level chronic inflammatory state and cytokine release [29,31]. HCV infection itself influences several of these pathways, most notably with respect to chronic inflammation and cytokine dysregulation, but also the TRP-KYN pathway [30,32–34]. There is also evidence to support direct neuroinvasion by HCV [11–13], as well as HCV-mediated compromise of the blood–brain barrier allowing cytokines to directly influence both the HPA axis and alter monoamine (i.e. serotonin, norepinephrine and dopamine) metabolism [14–17].

While there are no studies of depression and IR in the HCV-infected population, studies in the general population have shown an association between depression and disorders of metabolism, including metabolic syndrome and diabetes, with IR implicated as the primary

mechanism underlying this relationship [21,29]. A recent meta-analysis of studies utilizing surrogate measures of IR such as HOMA and QUICKI showed a small but statistically significant association between depression and IR [20]. Although surrogate measures of IR, as opposed to directly measured indices, are convenient in large-scale epidemiologic studies, they have significant limitations that affect their reliability [22]. Similar to that observed in the general population, we have previously shown that surrogate measures of IR in the HCV-infected population can be impacted by degrees of obesity and ethnicity when correlated to the direct measure of insulin-mediated glucose uptake (SSPG levels) via the insulin suppression test [22,23]. Both the insulin suppression test and the euglycemic clamp test measure glucose disposal rates during steady-state physiologic hyperinsulinaemia and are highly correlated ($r > 0.9$) [35]. Our use of a direct, more accurate measurement of peripheral IR via SSPG levels may underlie our finding no significant association between depression and IR. Additionally, we did not find a statistically significant association between depression and severity of liver disease or HCV viral-related factors (such as genotype, duration of disease, IVDU as mode of transmission and HCV viral load). Although some report an impact of HCV viral load on neuropsychiatric testing [36], similar to our study, others have not seen a correlation between peripheral HCV viral load and neuropsychiatric manifestations of HCV [14,15].

When investigating additional predictors, Caucasian race and lower HDL levels were significantly associated with depression in our cohort. A population-based study from the National Health and Nutrition Examination Survey III that included over 8000 participants similarly showed a higher prevalence of depression in Caucasians compared to Mexican Americans and African Americans [37]. The association between race and depression is complex and likely represents an interplay of not only genetic and environmental factors, but also cultural differences influencing the perception and experience of depression, access to and utilization of mental health resources and treatment, as well as patient–provider communication, among other disparities [38–40]. While the incidence of depression-related events during interferon-based HCV antiviral therapy appears higher among Caucasians [8], information on the actual prevalence of depression in HCV across racial and ethnic groups is limited, especially in those who are HCV treatment naïve. With respect to lipid profile and consistent with our findings, a recent meta-analysis evaluating components of metabolic syndrome and their association with depression showed that HDL level was negatively associated with depression [21]. Lower serum HDL has been explored as a marker of major depression, longer duration of depressive symptoms and increased risk for suicidality [41,42]. The pathophysiologic mechanisms underlying the association between HDL and depression are not entirely clear [41], but some have hypothesized that lower lipid levels may lead to lower brain serotonin levels [43,44]. While HCV's neurotrophism and effect on lipid metabolism is described, studies specifically elucidating the relationship between lipid levels and depression in HCV are lacking. A recent study, however, did find that depression in chronic HCV infection was associated with lower plasma levels of apolipoprotein E (apoE) [45], which is required for HCV replication [46]. The authors suggest that low apoE levels compromise the lipophilic blood–brain barrier and may facilitate HCV infection of the CNS, a mechanism implicated in neuropsychiatric pathology in HCV [45].

Our study is subject to limitations inherent to any cross-sectional cohort design in that a cause and effect relationship could not be assessed. Although a larger sample size is desirable, performing direct measurements of IR are logistically challenging and impractical in larger patient cohorts. As opposed to surrogate measures of IR, which require large sample sizes for adequate estimates of IR, direct physiologic measures of IR as utilized in this study allow for accurate measurements of IR with small sample sizes. Indeed, this is the largest cohort of HCV-infected patients to date in which depression was evaluated within the context of directly measured IR.

In conclusion, depression was not associated with IR in our HCV-infected cohort. With the introduction of highly effective direct-acting anti-HCV treatments, the burden of HCV is anticipated to decrease significantly. However, considering the multifactorial nature of depression, interventions directed at other modifiable risk factors in at-risk individuals in this population are warranted.

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Abbreviations

ALT	alanine aminotransferase
BMI	body mass index
CRC	Clinical Research Center
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HOMA	homeostatic model assessment
HPA	hypothalamo-pituitary-adrenal
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IR	insulin resistance
IST	insulin suppression test
IU	international units
IVDU	injection drug use

KYN	kynurenine
LDL	low-density lipoprotein
NIH	National Institutes of Health
OGTT	oral glucose tolerance test
QUICKI	quantitative insulin sensitivity check index
SD	standard deviation
SFGH	San Francisco General Hospital
SSPG	steady-state plasma glucose
SSRI	selective serotonin reuptake inhibitor
TRP	tryptophan
UCSF	University of California, San Francisco
US	United States

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Table 1

Cohort characteristics and stratification according to depression status

Variable	All patients (*n* = 74)	With depression (*n* = 39)	Without depression (*n* = 35)	*P*-value*
Age (mean ± SD), years	48 ± 7	48 ± 7	48 ± 7	0.74
Female sex, *N* (%)	23 (31%)	11 (28%)	12 (34%)	0.57
Race/Ethnicity, *N* (%)				
Caucasian	27 (37%)	20 (51%)	7 (20%)	0.06
African American	19 (26%)	9 (23%)	10 (29%)	
Hispanic/Latino	22 (30%)	7 (18%)	15 (43%)	
Other	6 (8%)	3 (8%)	3 (9%)	
Caucasian, *N* (%)	27 (37%)	20 (51%)	7 (20%)	**0.005**
College education or above, *N* (%)	40 (54%)	22 (56%)	18 (51%)	0.67
US born, *N* (%)	59 (80%)	32 (82%)	27 (77%)	0.60
Unemployment, *N* (%)	44 (60%)	27 (69%)	17 (49%)	0.07
Waist circumference (mean ± SD), cm	94 ± 11	95 ± 11	94 ± 12	0.57
Body mass index, BMI (mean ± SD), kg/m^2	27 ± 4	26 ± 4	28 ± 5	0.20
Current smoker, *N* (%)	41 (55%)	25 (64%)	16 (46%)	0.11
Smoking amount, pack-years				
mean ± SD	16 ± 15	18 ± 16	13 ± 13	0.07
median (min–max)	12 (0–74)	16 (0–74)	12 (0–48)	
Current alcohol consumption, *N* (%)	21 (28%)	9 (23%)	12 (34%)	0.29
Duration of alcohol consumption (mean ± SD), years	28 ± 11	29 ± 10	26 ± 12	0.41
Average alcohol consumption				
<20 g/day	19 (26%)	8 (21%)	11 (31%)	0.19
20–50 g/day	20 (27%)	10 (26%)	10 (29%)	
50–80 g/day	19 (26%)	14 (36%)	5 (14%)	
>80 g/day	16 (22%)	7 (18%)	9 (26%)	
Substance abuse therapy with methadone, *N* (%)	7 (10%)	6 (16%)	1 (3%)	0.06
IVDU as HCV mode of transmission, *N* (%)	55 (74%)	29 (74%)	26 (74%)	0.99
Log_{10} HCV viral load (mean ± SD), IU/mL	5.8 ± 0.7	5.7 ± 0.9	5.9 ± 0.5	0.44
Duration of HCV infection (mean ± SD), years	26 ± 10	26 ± 9	26 ± 11	0.88
HCV genotype, *N* (%)				
Genotype 1	49 (66%)	25 (68%)	24 (69%)	0.82
Genotype 2	12 (16%)	7 (19%)	5 (14%)	
Genotype 3	11 (15%)	5 (14%)	6 (17%)	
Liver histology on biopsy				
Presence of steatosis, *N* (%)	20 (27%)	10 (29%)	10 (36%)	0.60
Fibrosis stage ≥2, *N* (%)	26 (35%)	15 (44%)	11 (39%)	0.70
Inflammation grade ≥2, *N* (%)	38 (51%)	20 (59%)	18 (64%)	0.66
ALT (mean ± SD), units/L	87 ± 78	102 ± 101	71 ± 31	0.85
Total cholesterol (mean ± SD), mmol/L	4.5 ± 1.0	4.5 ± 1.0	4.6 ± 1.1	0.43

Variable	All patients (*n* = 74)	With depression (*n* = 39)	Without depression (*n* = 35)	*P*-value*
LDL cholesterol (mean ± SD), mmol/L	2.7 ± 0.8	2.7 ± 0.8	2.7 ± 0.9	0.96
HDL cholesterol (mean ± SD), mmol/L	1.3 ± 0.3	1.2 ± 0.3	1.4 ± 0.3	**0.01**
Triglycerides (mean ± SD), mmol/L	1.1 ± 0.6	1.1 ± 0.7	1.2 ± 0.6	0.64
Metabolic syndrome†, *N* (%)	12 (16%)	5 (13%)	7 (20%)	0.40
Family history of diabetes, *N* (%)	37 (50%)	17 (44%)	20 (57%)	0.24
Impaired fasting glucose‡, *N* (%)	10 (14%)	3 (8%)	7 (21%)	0.11
Impaired glucose tolerance§, *N* (%)	12 (16%)	5 (13%)	7 (21%)	0.37
Steady-state plasma glucose (SSPG), mmol/L (mean ± SD)	7.8 ± 4.5	7.3 ± 3.9	8.3 ± 5.1	0.45
median (min–max)	6.1 (2.2–18.2)	5.8 (2.2–15.8)	6.4 (2.2–18.2)	

*The Mann–Whitney *U*-test was used for continuous variables and the chi-squared test for categorical variables; statistical significance is at *P*-value of <0.05 (2-sided) and bolded.

†Metabolic syndrome was defined as the presence of three or more criteria, including increased waist circumference, elevated triglycerides, reduced HDL cholesterol, elevated blood pressure and/or elevated fasting glucose [25].

‡IFG was defined as fasting plasma glucose of 5.6–6.9 mmol/L [25].

§IGT was defined as 2-h glucose level of 7.8–11.0 mmol/L during the oral glucose tolerance test [25].

Table 2

Variables associated with depression in HCV (unadjusted single predictor model)

Variable	Odds ratio	95% Confidence interval (CI)	*P*-value*
Age (per 10 years)	0.99	0.50–1.98	0.99
Female sex	0.75	0.28–2.02	0.57
Caucasian race (*vs* non-Caucasian race)	4.21	1.49–11.91	**0.007**
College education or above	1.22	0.49–3.06	0.67
US born	1.35	0.44–4.22	0.60
Unemployment	2.38	0.92–6.16	0.07
Waist circumference (per 10 cm)	1.08	0.72–1.62	0.72
Body mass index, BMI (per 5 kg/m^2)	0.64	0.36–1.13	0.13
Current smoker	2.12	0.83–5.39	0.11
Smoking amount (per pack year)	1.03	0.99–1.07	0.12
Current alcohol consumption	0.58	0.21–1.60	0.29
Duration of alcohol consumption (per year)	1.02	0.98–1.07	0.27
Heavy alcohol consumption (≥50 g/day)	1.75	0.70–4.41	0.24
Substance abuse therapy with methadone	6.37	0.72–55.86	0.09
IVDU as HCV mode of transmission	1.00	0.35–2.85	0.99
Log_{10} HCV viral load (IU/mL)	0.62	0.31–1.27	0.19
Duration of HCV infection (per 10 years)	1.02	0.64–1.64	0.92
HCV genotype 1 (*vs* nongenotype 1)	1.05	0.39–2.82	0.93
Liver histology on biopsy			
Presence of steatosis	0.75	0.26–2.18	0.60
Fibrosis stage ≥2	1.22	0.44–3.37	0.70
Inflammation grade ≥2	0.79	0.28–2.23	0.66
ALT (per 10 units/L)	1.07	0.98–1.17	0.12
Total cholesterol (per mmol/L)	1.00	0.99–1.01	0.52
LDL cholesterol (per mmol/L)	1.00	0.99–1.01	0.95
HDL cholesterol (per mmol/L)	0.96	0.92–1.00	**0.04**
Triglycerides (per mmol/L)	1.00	0.99–1.01	0.79
Metabolic syndrome	0.59	0.17–2.06	0.41
Family history of diabetes mellitus	0.58	0.23–1.46	0.25
Impaired fasting glucose	0.32	0.08–1.36	0.12
Impaired glucose tolerance	0.57	0.16–1.99	0.38
SSPG (per 0.56 mmol/L)	0.97	0.92–1.03	0.31

*Statistical significance is at *P*-value of <0.05 (2-sided) and bolded.

Table 3

Variables associated with depression in HCV (multipredictor models)

	Model 1*			Model 2†		
Variable	**Odds ratio**	**95% CI**	***P*-value**	**Odds ratio**	**95% CI**	***P*-value**
Age (per 10 years)	1.00	0.48–2.10	1.00	1.25	0.56–2.76	0.58
Female sex	0.70	0.24–2.06	0.52	1.19	0.36–3.96	0.78
Caucasian race (*vs* non-Caucasian race)	4.19	1.42–12.35	**0.009**	3.13	0.99–9.88	0.05
SSPG (per 0.56 mmol/L)	0.99	0.99–1.01	0.84	0.99	0.99–1.00	0.33
HDL (per mmol/L)				0.95	0.89–0.99	**0.046**

*Model includes addition of age, sex, race and SSPG.

†Model includes addition of age, sex, race, SSPG and HDL. Statistically significant *P*–value is bolded.