Insulin resistance is associated with progression to hepatic fibrosis in a cohort of HIV/hepatitis C virus-coinfected patients

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Objective: Hepatitis C virus (HCV) infection is associated with higher insulin levels and insulin resistance. We evaluated factors associated with insulin resistance in a cohort of HIV/HCV-coinfected patients and determined the effect of insulin resistance on the development of hepatic fibrosis.

Methods: Data were analysed from 158 nondiabetic participants in a prospective Canadian cohort of HIV/HCV-coinfected patients. Patients were defined as having insulin resistance using the homeostasis model for assessment of insulin resistance (HOMA-IR) index. Factors associated with a high index (HOMA-IR $\geq$2) were identified using multivariate logistic regression. Incidence rates of liver fibrosis [aspartate aminotransferase-to-platelet ratio index (APRI) $\geq$1.5] were calculated, and multivariate time-dependent Cox regression models used to assess the effect of baseline insulin resistance on the risk of developing an APRI score of at least 1.5 during follow-up.

Results: Overall, 56% had baseline HOMA-IR of at least 2. In the adjusted multivariate logistic analysis, only baseline BMI of more than 25 kg/m^2 remained associated with insulin resistance [adjusted odds ratio 3.66, 95% confidence interval (CI) 1.70–7.92]. Rates of progression to significant hepatic fibrosis (APRI $\geq$1.5) were higher in those with HOMA-IR of at least 2 (16.32 per 100 person-years, 95% CI 6.68–25.97) compared with those with HOMA-IR less than 2 (7.95 per 100 person-years, 95% CI 0.16–15.75). Baseline HOMA-IR of at least 2 was associated with the development of significant fibrosis (adjusted hazard ratio 7.71, 95% CI 2.55–23.36).

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Conclusion: In this first longitudinal analysis, insulin resistance was very common among coinfected patients and was associated with modifiable risk factors such as elevated BMI. Insulin resistance was found to be strongly associated with progression to hepatic fibrosis over time.

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Introduction

Hepatitis C virus (HCV) infection has been associated with an increased risk for insulin resistance and diabetes [1] with 30–70% exhibiting some degree of insulin resistance [2]. Insulin resistance has been associated with a wide variety of adverse health outcomes such as cardiovascular disease and cancer and with decreased response to HCV therapy among HCV-monoinfected patients [3–6]. The homeostasis model for assessment of insulin resistance (HOMA-IR) index is a well validated noninvasive method to measure insulin sensitivity [7]. HCV-infected individuals have been shown to have higher HOMA-IR scores (compared with uninfected matched controls [1]) which have been associated with fibrosis and steatosis in cross-sectional analyses [8]. In HIV-infected patients, HCV has also been shown to be associated with the presence of insulin resistance [9–11], but its association with progressive fibrosis is less clear [12]. We evaluated factors associated with insulin resistance in a cohort of HIV/HCV-coinfected patients and determined the impact of insulin resistance on the development of liver fibrosis prospectively.

Materials and methods

Study design, setting and population

The Canadian Co-infection Cohort Study [CCC, CIHR Canadian HIV Trials Network (CTN222)] is a prospective multicentre study recruiting HIV/HCV-coinfected patients at 16 centres across Canada since 2003 with approval by participating research ethics boards and has been described in detail elsewhere [13]. As of October 2010, 955 patients were enrolled. To evaluate factors associated with insulin resistance, we included nondiabetic participants (based on recorded medical history and current prescription for insulin or oral hypoglycaemic medication) with at least one study visit between April 2003 and October 2010 and available baseline values of fasting insulin and glucose ($n = 185$). This sample was further restricted to assess the effect of insulin resistance on fibrosis progression. Only participants ($n = 85$) with virologic evidence of active HCV infection (HCV-RNA-positive, COBAS AMPLICOR HCV Test, version 2.0, Roche Diagnostics, Hoffmann-La Roche Ltd, Laval, Canada), an aspartate aminotransferase (AST)-to-platelet ratio index (APRI) less than 1.5 and absence of end-stage liver disease (ESLD) at study entry were studied. Patients were censored on their last clinic visit prior to October 2010, when an outcome occurred, at death or at initiation of HCV treatment.

Measurements

Insulin resistance was determined at baseline for all eligible patients using the HOMA-IR [fasting insulin (mIU/l) × fasting glucose (mmol/l)/22.5] [7]. APRI was used as a noninvasive surrogate marker for liver fibrosis defined as follows: 100 × (AST (U/l)/upper limit of normal)/platelet count (10^9 cells/l) [14]. An APRI of at least 1.5 was considered significant fibrosis (corresponding to a biopsy score ≥F2) [14–16].

Statistical analyses

Multiple logistic regression was used to identify factors independently associated with insulin resistance (HOMA-IR ≥2, a cut-point indicative of insulin resistance in other analyses [5,17,18]). The natural logarithm of the APRI [ln(APRI)], which nearly normalizes the distribution, was used in these analyses [19].

We estimated incidence rates of liver fibrosis (APRI≥1.5) among those without fibrosis at baseline. Poisson count models were used to calculate confidence intervals (CIs) for incidence rates. Multivariate time-dependent Cox regression models were constructed to assess the effect of insulin resistance at baseline on the risk of developing an APRI of at least 1.5 during follow-up and included covariates that had statistically significant hazard ratios in univariate analyses along with those determined a priori to be clinically important. Insulin resistance was modelled either as a categorical variable (HOMA-IR<2 or ≥2) or as a continuous variable, using 2 log-base HOMA-IR to account for the skewed distribution of HOMA-IR values while allowing for straightforward clinical interpretation (e.g. risk for each doubling in HOMA-IR was estimated). Robust variance estimation was used in all Cox regression analyses to account for the correlation of data contributed by the same participant at multiple visits. Statistical analyses were performed using R program for Windows Release 2.11.1 (R cran, Auckland, New Zealand).

Results

Overall, 158 individuals were included in the primary analysis. The major reason participants were excluded from the study was lack of fasting measures of insulin or glucose ($n = 755$). Included patients were similar in all regards to those excluded except there were fewer men (63 vs. 76%) and IDUs (74 vs. 82%) and more combination antiretroviral therapy (cART) users (88 vs. 80%). Notably, there was no difference in BMI, alcohol use, median CD4 cell count or types of ART (protease inhibitor vs. nonnucleoside reverse transcriptase inhibitor) used between those included and excluded. Overall, the median age was 45 years [interquartile range (IQR) 40–50], 63% were male, 23% had history of recent IDU and 89% received cART. At baseline, 70 (44%) had HOMA-IR less than 2; 45 (28%) had an index of 2.0–3.9; 22 (14%), had an index of 4.0–5.9, and 21 (13%) had HOMA-IR at least 6. There was no statistically significant association between baseline insulin resistance and baseline hepatic fibrosis ($n = 32$), although the median HOMA-IR was higher at 2.7 (IQR 1.8–4.5) compared with 0.8 (IQR 0.5–1.4, $P = 0.35$) for those with baseline APRI less than 1.5.

Factors associated with baseline insulin resistance

In adjusted multivariate analysis, only BMI of at least 25 was strongly associated with baseline insulin resistance (see Table 1, HOMA-IR ≥ 2). Although receipt of protease inhibitor-based therapy was associated with insulin resistance in univariate analysis, this association was attenuated in multivariate analysis.

Factors associated with the development of fibrosis

Fifteen individuals (18%) developed significant hepatic fibrosis (APRI ≥ 1.5) with median follow-up of 1.4 (IQR 1.0, 1.7) years. Rates of progression to significant fibrosis were higher in those with HOMA-IR of at least 2 (16.32 per 100 person-years, 95% CI 6.68–25.97, $n = 11$) compared with those with HOMA-IR less than 2 (7.95 per 100 person-years, 95% CI 0.16–15.75, $n = 4$).

In multivariate analyses, baseline HOMA-IR of at least 2 and HOMA-IR modelled as a continuous variable were both strongly associated with progression of hepatic fibrosis (Table 2). Among other covariates, only baseline APRI was also associated with fibrosis progression. Given the small number of events, we did not include more covariates in the final model. In sensitivity analyses, we examined cART use, triglycerides and ethnicity which were not associated with fibrosis nor did their inclusion in the multivariate model alter the main results (data not shown).

Discussion

Insulin resistance was present in a majority of HIV/HCV-coinfected cohort participants with 56% having a baseline HOMA-IR of at least 2 and a significant proportion having very high levels of insulin resistance (27% having HOMA-IR score ≥ 4). As we excluded those receiving oral hypoglycaemics or insulin, this finding suggests that a substantial number of coinfected persons are not recognized as having impaired glucose tolerance and are, thus, at risk for common complications of insulin resistance [3,4,20]. Presence of insulin resistance was associated primarily with classic and potentially modifiable risk factors: elevated BMI and waist circumference. Although fasting glucose was higher among those having HOMA-IR of at least 2, all had values within the normal range; thus, fasting insulin levels are required to identify individuals with insulin resistance.

Table 1. Univariate and multivariate analysis of factors associated with baseline insulin resistance[a].

Variables	Univariate analysis Odds ratio (95% confidence interval)	Multivariate analysis Adjusted odds ratio (95% confidence interval)
Age	1.01 (0.98–1.05)	1.02 (0.98–1.07)
Female sex	0.86 (0.45–1.66)	0.72 (0.33–1.56)
Aboriginal	1.07 (0.42–2.70)	1.25 (0.40–3.94)
Duration of HIV infection	1.00 (0.95–1.06)	–
Duration of HCV infection	0.98 (0.96–1.02)	0.98 (0.95–1.02)
CD4 cell count (per 100 cells/μl)	1.03 (0.90–1.17)	1.05 (0.90–1.23)
HIV viral load < 50 copies/ml	0.91 (0.47–1.76)	0.81 (0.36–1.80)
cART use	1.29 (0.49–3.46)	–
PI	2.02 (1.06–3.87)	1.81 (0.88–3.72)
NNRTI	0.64 (0.32–1.25)	–
HCV-RNA-positive	1.45 (0.60–3.51)	2.06 (0.80–5.27)
Genotype 1	1.44 (0.64–3.26)	–
APRI (ln)	1.34 (0.91–1.95)	1.26 (0.80–1.99)
History of end-stage liver disease	1.02 (0.35–2.89)	–
BMI ≥ 25.0	3.78 (1.88–7.61)	3.66 (1.70–7.92)
Baseline waist circumference	1.03 (1.00–1.05)	–

[a]Insulin resistance defined as homeostasis model for assessment of insulin resistance≥2. APRI, aspartate aminotransferase-to-platelet ratio index; cART, combination antiretroviral therapy; HCV, hepatitis C virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2. Multivariate Cox proportional hazards model of factors associated with development of aspartate aminotransferase-to-platelet ratio index score of at least 1.5 during follow-up.

Variables	Adjusted hazard ratio	95% confidence interval
Insulin resistance modelled as HOMA-IR≥2 vs. <2		
HOMA-IR>2	7.72	2.55–23.36
Age (years)	0.98	0.88–1.09
Female sex	0.85	0.27–2.63
Duration of HCV infection (per year)	1.05	0.99–1.12
BMI ≥ 25	0.73	0.24–2.28
Baseline APRI (ln)	7.92	1.94–32.42
Time updated CD4 cell count (per 100 cells/μl)	0.92	0.81–1.06
Time updated HIV viral load < 50 copies/ml	0.74	0.24–2.29
Insulin resistance modelled with HOMA-IR as a continuous variable		
HOMA-IR (log-base 2)	1.48	1.12–1.86
Age (years)	1.00	0.91–1.09
Female sex	0.82	0.26–2.55
Duration of HCV infection (per year)	1.02	0.97–1.10
BMI ≥ 25	0.83	0.29–2.34
Baseline APRI (ln)	5.20	1.31–20.69
Time updated CD4 cell count (per 100 cells/μl)	0.92	0.79–1.08
Time updated HIV viral load < 50 copies/ml	0.77	0.20–2.99

The population ($n = 85$) is defined as those with no baseline history of fibrosis or end-stage liver disease and confirmed presence of hepatitis C virus (HCV)-RNA. Median follow-up period was 1.4 years (interquartile range 1.0, 1.7 years). APRI, aspartate aminotransferase-to-platelet ratio index; HOMA-IR, homeostasis model for assessment of insulin resistance.

To understand whether insulin resistance contributes to the development of hepatic fibrosis, longitudinal studies in persons not having fibrosis or advanced liver disease are required. Ours is the first such longitudinal study to examine this question in coinfected patients. We found insulin resistance was strongly associated with development of hepatic fibrosis. In adjusted analyses, the risk of developing fibrosis was nearly eight times greater in the presence of insulin resistance and was independent of BMI. Furthermore, for each doubling in HOMA-IR score there was a 48% increase in risk for progression to fibrosis. This finding suggests that efforts to improve insulin sensitivity may potentially reduce rates of fibrosis progression among coinfected persons. Given the rise of ESLD morbidity and mortality among HIV/HCV-coinfected persons, the identification of this potentially modifiable risk factor for liver disease progression is of enormous relevance.

The prevalence of insulin resistance in our Canadian cohort is somewhat greater than that reported in other populations. Among 170 coinfected patients from France, the prevalence of insulin resistance was 37% [17]. In 1041 HIV-infected Spanish patients, the prevalence was 48% among 373 HIV/HCV-coinfected patients compared with 33% in those without HCV infection [11].

We could not demonstrate an association of specific antiretroviral agents with the presence of insulin resistance at baseline. Particularly, certain protease inhibitors and cumulative exposure to nucleoside reverse transcriptase inhibitors, especially stavudine, have been implicated in previous studies [21–24]. In contrast, there has been no clear association of specific drug class or duration of ART exposure and insulin resistance in coinfected populations [9,10]. The lack of association between ART exposure and insulin resistance in our study and others may be due to a lack of power, given the relatively small numbers of individuals analysed to date, or may reflect more complex effects of ART on HCV-related disease [25,26].

Prior cross-sectional studies in coinfected persons have not identified a clear relationship between insulin resistance and presence of hepatic fibrosis [12,17]. In contrast, in a cross-sectional study of 330 coinfected patients undergoing transient elastography, 64% of those with HOMA-IR of at least 4 had measures of at least 9 kPa compared with 39% of those with HOMA-IR less than 4 ($P < 0.0001$), and HOMA-IR of at least 4 was an independent predictor of elevated liver stiffness (adjusted odds ratio 5.33, 95% CI 2.70–10.49) [27]. Insulin resistance has been associated with higher estimated fibrosis progression rates in monoinfected populations [1] but not in a small study of coinfected patients [12]. Finally, in HCV monoinfection, HOMA-IR more than 2 has been associated with decreased sustained virologic responses (SVRs) to HCV therapy. In coinfected patients, however, studies on the impact of insulin resistance on SVR have been contradictory [18,28,29].

Mechanisms by which insulin resistance occur in HCV-infected patients have not been fully elucidated, but include effects of inflammatory cytokines such as tumour necrosis factor alpha [30], other cytokine signalling pathways (e.g. upregulation of suppressor of cytokine signaling-3 protein) [31] and effects on insulin–receptor substrate which interferes with insulin signalling [32]. Whether HIV directly plays a role remains unclear.

Our study has some potential limitations. Overall, a significant proportion lacked fasting glucose and insulin values and, therefore, was excluded from analysis. This limited our power to determine associations between insulin resistance and such factors as specific antiretroviral drug classes or HCV genotype. The large number of excluded patients also potentially could have introduced a selection bias. Use of HOMA-IR in the evaluation of insulin resistance in HCV-infected patients is well established [33], and we used a HOMA-IR score of at least 2 to define significant insulin resistance, as used in other North American and European coinfected populations [5,17,18,34], although other cut-offs have been used [12]. We used the APRI score as a surrogate marker for hepatic fibrosis rather than liver biopsy. APRI has been validated against liver biopsy in our cohort as well as others and is widely accepted as a surrogate marker and is highly specific for fibrosis stages equal to or greater than F2 Metavir score (significant fibrosis, few septa) [14]. A limitation of not using serial biopsies is the potential interplay between insulin resistance and hepatic steatosis, itself a consequence of insulin resistance, which may contribute to fibrosis progression [17].

Conclusion

Given the very high prevalence of insulin resistance, its known association with important health outcomes and its associated high risk for liver disease progression observed in this study, routine screening for insulin resistance among coinfected persons may be warranted. Interventional studies to manage modifiable risk factors for insulin resistance and evaluate the role of pharmacotherapy in modifying the course of liver disease progression and improving HCV treatment outcomes among HIV/HCV-coinfected persons are needed.

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Conflicts of interest

M.H. has acted as a consultant for Merck, Vertex, Pfizer, viiv, Ortho Janssen and has been a speaker for Merck and Ortho Janssen. S.W. has been a consultant/member of advisory board for the following pharmaceutical companies: Abbott, Merck, Tibotec, Gilead, Bristol-Myers Squibb, and viiv. C.C. has acted as a consultant for Merck and a speaker for Merck and Roche. N.P. has been a member of the advisory board of Abbott, Bristol Myers Squibb, Gilead, Merck, and viiv. M.B.K. has been a consultant to Merck, viiv, Gilead, has received research funding from Merck and has received speakers' honoraria from viiv, Gilead and Bristol-Myers Squibb. K.R., E.E.M., J.C., M.P., S.S. have no conflicts of interest to declare.

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