

# Insulin resistance is associated with progression to hepatic fibrosis in a cohort of HIV/HCV co-infected patients

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

**Methods:** Data were analyzed from 158 non-diabetic participants in a prospective Canadian cohort of HIV/HCV co-infected 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 ( $IR \geq 2$ ) were identified using multivariate logistic regression. Incidence rates of liver fibrosis ( $APRI \geq 1.5$ ) 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  $\geq 1.5$  during follow-up.

**Results:** Overall 56% had baseline HOMA-IR  $\geq 2$ . In the adjusted multivariate logistic analysis, only baseline BMI  $> 25$  remained associated with insulin resistance (adjusted OR [aOR] 3.66 (1.70–7.92)). Rates of progression to significant hepatic fibrosis ( $APRI \geq 1.5$ ) were higher in those with HOMA-IR  $\geq 2$  (16.32/100 person-years (PY); 95% CI 6.68–25.97) compared to those with HOMA-IR  $< 2$  (7.95/100PY; 95% CI 0.16–15.75). Baseline HOMA-IR  $\geq 2$  was associated with the development of significant fibrosis (adjusted hazard ratio [aHR] 7.71; 95% CI 2.55–23.36).

**Conclusions:** In this first longitudinal analysis, insulin resistance was very common among co-infected patients and was associated with modifiable risk factors such as

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elevated body mass index. Insulin resistance was found to be strongly associated with progression to hepatic fibrosis over time.

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## Introduction

Hepatitis C infection (HCV) 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 mono-infected patients [3–6]. The homeostasis model for assessment of insulin resistance (HOMA-IR) index is a well validated non-invasive method to measure insulin sensitivity [7]. HCV-infected individuals have been shown to have higher HOMA-IR scores (compared to 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 co-infected patients and determined the impact of insulin resistance on the development of liver fibrosis prospectively.

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) x fasting glucose (mmol/L) /22.5] [7]. APRI was used as a non-invasive surrogate marker for liver fibrosis defined as: [100 x (AST (U/L)/upper limit of normal)]/platelet count ( $10^9/L$ ) [14]. An APRI  $\geq 1.5$  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  $\geq 2$ , 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  $\geq 1.5$ ) among those without fibrosis at baseline. Poisson count models were used to calculate confidence intervals 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  $\geq 1.5$  during follow-up and included covariates that had statistically significant hazard ratios (HRs) 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  $\geq 2$ ) or as a continuous variable, using log-base 2 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).

## Materials and methods

### Study design, setting and population

The Canadian Co-infection Cohort Study (CCC; CTN222) is a prospective multi-centre study recruiting HIV/HCV co-infected 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 non-diabetic 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, Roche Cobas Amplicor assay), an aspartate aminotransferase (AST) to platelet ratio index (APRI)  $< 1.5$  and absence of end-stage liver

## 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 injection drug users (IDU) (74 vs. 82%) and more cART users (88 vs. 80%). Notably, there was no difference in BMI, alcohol use, median CD4 cell count or types of ART (PI vs. NNRTI) used between those included and excluded. Overall, the median age was 45 (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  $< 2$ ; 45 (28%) had an index 2.0–3.9; 22 (14%), 4.0–5.9, and 21 (13%),  $\geq 6$ . 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 to 0.8 (IQR 0.5–1.4;  $p=0.35$ ) for those with baseline APRI  $< 1.5$ .

### Factors associated with baseline insulin resistance (HOMA-IR $\geq 2$ )

In adjusted multivariate analysis only BMI  $\geq 25$  was strongly associated with baseline insulin resistance (see Table 1). 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  $\geq 2$  (16.32

per 100 person-years; 95% CI 6.68–25.97;  $n=11$ ) compared to those with HOMA-IR  $< 2$  (7.95; 95% CI 0.16–15.75;  $n=4$ ).

In multivariate analyses, baseline HOMA-IR  $\geq 2$  and HOMA-IR modeled 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 co-infected cohort participants with 56% having a baseline HOMA-IR  $\geq 2$  and a significant proportion having very high levels of insulin resistance (27% having HOMA-IR score  $\geq 4$ ). As we excluded those receiving oral hypoglycemics or insulin, this finding suggests that a substantial number of co-infected 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. While fasting glucose was higher among those having HOMA-IR  $\geq 2$ , 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 (HOMA-IR  $\geq 2$ ).**

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 Gender	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/ $\mu$ L)	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 (In)	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 $\geq 25.0$	3.78 (1.88–7.61)	3.66 (1.70–7.92)
Baseline waist circumference	1.03 (1.00–1.05)	–

Abbrev. APRI, AST-to-platelet ratio index; BMI, body mass index; cART, combination antiretroviral therapy; HOMA-IR, homeostasis model for assessment of insulin resistance; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

**Table 2.** Multivariate Cox proportional hazards model of factors associated with development of APRI score >1.5 during follow-up (n = 85).

Variables	Adjusted Hazard Ratio	95% Confidence Interval
A. Insulin Resistance modeled as HOMA-IR ≥ 2 vs. HOMA-IR < 2		
HOMA-IR > 2	7.72	2.55–23.36
Age (years)	0.98	0.88–1.09
Female Gender	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
B. Insulin Resistance modeled 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 Gender	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 ESLD and confirmed presence of HCV RNA. Median follow-up period was 1.4 years (IQR: 1.0, 1.7 years). Abbrev. APRI, AST-to-platelet ratio index; BMI, body mass 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 co-infected 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 co-infected persons. Given the rise of ESLD morbidity and mortality among HIV-HCV co-infected 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 co-infected patients from France, the prevalence of insulin resistance was 37% [17]. In 1041 HIV-infected Spanish patients the prevalence was 48% among 373 HCV co-infected 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. In particular certain protease inhibitors and cumulative exposure to NRTIs, 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 co-infected 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 analyzed to date, or may reflect more complex effects of antiretroviral therapy on HCV-related disease [25,26].

Prior cross-sectional studies in co-infected 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 co-infected patients undergoing transient elastography, 64% of those with HOMA-IR ≥ 4 had measures ≥ 9 kPa compared to 39% of those with HOMA-IR < 4 (p < 0.0001) and HOMA-IR ≥ 4 was an independent predictor of elevated liver stiffness (aOR 5.33; 95%CI 2.70–10.49) [27]. Insulin resistance has been associated with higher estimated fibrosis progression rates in mono-infected populations [1] but not in a small study of co-infected patients [12]. Finally, in HCV mono-infection, HOMA-IR > 2 has been associated with decreased sustained virologic responses (SVR) to HCV therapy. In co-infected 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 TNF-alpha [30], other cytokine signaling pathways (e.g. up-regulation of suppressor of cytokine signaling-3 protein) [31] and effects on insulin-receptor substrate which interferes with insulin signaling [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 were excluded from analysis. This

limited our power to determine associations between insulin resistance and such factors as specific antiretroviral drug classes or HCV genotype and 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  $\geq 2$  to define significant insulin resistance, as used in other North American and European co-infected populations [5,17,18,34], although other cutoffs 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  $> F2$  [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].

## Conclusions

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 co-infected 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 co-infected persons are needed.

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## Conflicts of interest

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