Relationship between hepatitis C virus infection and type 2 diabetes mellitus: Meta-analysis

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AIM: To investigate the association between hepatitis C infection and type 2 diabetes mellitus.

METHODS: Observational studies assessing the relationship between hepatitis C infection and type 2 diabetes mellitus were identified via electronic and hand searches. Studies published between 1988 to March 2011 were screened, according to the inclusion criteria set for the present analysis. Authors performed separate analyses for the comparisons between hepatitis C virus (HCV) infected and not infected, and HCV infected and hepatitis B virus infected. The included studies were further subgrouped according to the study design. Heterogeneity was assessed using $I^2$ statistics. The summary odds ratios with their corresponding 95% CIs were calculated based on a random-effects model. The included studies were subgrouped according to the study design. To assess any factor that could potentially affect the outcome, results were further stratified by age group (proportion of $\geq$ 40 years), gender (proportion of male gender), body mass index (BMI) (proportion of BMI $\geq$ 27), and family history of diabetes (i.e., self reported). For stability of results, a sensitivity analysis was conducted including only prospective studies.

RESULTS: Combining the electronic database and hand searches, a total of 35 observational studies (in 31 articles) were identified for the final analysis. Based on random-effects model, 17 studies ($n = 286,084$) compared hepatitis C-infected patients with those who were uninfected [summary odds ratio (OR): 1.68, 95% CI: 1.15-2.45]. Of these 17 studies, 7 were both a cross-sectional design (41.2%) and cohort design (41.2%), while 3 were case-control studies (17.6%). Nineteen studies ($n = 51,156$) compared hepatitis C-infected participants with hepatitis B-infected (summary OR: 1.92, 95% CI: 1.41-2.62). Of these 19 studies, 4 (21.1%), 6 (31.6%) and 9 (47.4%) were cross-sectional, cohort and case-control studies, respectively. A sensitivity analysis with 3 prospective studies indicated that hepatitis C-infected patients had a higher risk of developing type 2 diabetes compared with uninfected controls (summary odds ratio: 1.41, 95% CI: 1.17-1.7; $I^2 = 0\%$). Among hepatitis C-infected patients, male patients (OR: 1.26, 95% CI: 1.03-1.54) with age over 40 years (summary OR: 7.39, 95% CI: 3.82-9.38) had an increased frequency of type 2 diabetes. Some caution must be taken in the interpretation of these results because there may be unmeasured confounding factors which may introduce bias.

CONCLUSION: The findings support the association between hepatitis C infection and type 2 diabetes mellitus. The direction of association remains to be determined, however. Prospective studies with adequate sample sizes are recommended.

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Key words: Hepatitis C; Type 2 diabetes mellitus; Observational studies; Meta-analysis
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INTRODUCTION

Hepatitis C virus (HCV) infections has been identified as one of the leading causes of chronic liver disease with serious sequelae such as end-stage cirrhosis and liver cancer[1]. Moreover, chronic HCV infection has been associated with several extrahepatic complications[2-8]. The suggestion that HCV may be associated with type 2 diabetes mellitus (type 2 DM) was first made by Allison in 1994. Since then, scores of observational studies assessing the association between HCV and type 2 DM have been published. However, these studies have provided inconclusive results, with some studies supporting the excess type 2 DM risk with HCV infection compared to non-HCV infected controls[9,10], and some studies showed differently.[8,11-13]. In 2008, a meta-analysis of observational studies reported an excess type 2 DM risk with HCV infection.[14]. After these reviews were published, new observational studies in which prevalence of type 2 DM in patients with HCV infection was assessed have been carried out in endemic countries. As the epidemiology of HCV is complex and heterogeneous, information from studies across geographic regions is important. Moreover, the current review also assesses the traditional risk factors.

The objectives were (1) to investigate the available evidence on the association between HCV infections and type 2 DM; and (2) to assess the effect of study design and traditional risk factors on the association.

MATERIALS AND METHODS

Data sources and search strategy

Published studies that assess the association between HCV and type 2 DM were searched in MEDLINE, EMBASE and PubMed databases covering the period from 1980 to March 2011. Literature search was carried out using the combination of terms “diabetes”, “diabetes mellitus”, “type II diabetes mellitus”, “type 2 diabetes mellitus”, “type II diabetes”, “T2D”, “T2DM”, “type 2 DM”, “non-insulin dependent diabetes”, or “NIDDM” and “hepatitis”, “hepatitis C”, “hepatitis C virus”, “HCV”, “HVC”, or “chronic hepatitis” and “risk”, “risk factor”, “case-control”, “cohort”, “clinical trial”, “cross-sectional”, “epidemiology”, “observational”, “meta-analysis”, “systematic review”, or “review”. In addition, we searched Cochrane Database of Systematic Reviews, Cochrane Central Database of Controlled Trials, Database of Abstracts of Reviews of Effects, Google Scholar, European Association for the Study of the Liver, Eurosurveillance (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=695), and GlaxoSmithKline (http://www.gsk.com/reportsandpublications.htm). We also searched the reference lists of the retrieved articles and reviews of this field[9,10,13,14]. Our search was limited to human studies and English publications. We also contacted the corresponding authors for any missing data or clarification.

Study selection

Inclusion criteria for studies were: (1) An epidemiologic study design to conduct a primary or secondary data analysis; (2) At least 1 comparison group without HCV; (3) Provision of sufficient data to calculate odds ratio (OR) or relative risk (RR) comparing type 2 DM in HCV infected patients to non-HCV infected patients; (4) Controlled for at least age and gender in the study design or analysis; and (5) Conducted with not less than 20 HCV-infected patients. HCV was confirmed with the detection of anti-HCV (tested with ELIZA) or HCV RNA (detected by reverse transcriptase polymerase chain reaction). Type 2 DM was confirmed with one of the following criteria: (1) Self-reported type 2 DM (i.e., physician diagnosed); (2) Self-reported diabetes with no history of insulin medication; (3) Fasting plasma glucose exceeding 7.0 mmol/L (126 mg/dL) on two separate occasions; or (4) Impaired fasting glycaemia was between 6.1 mmol/L and 7.0 mmol/L with no insulin medication. Where available, hepatitis B virus (HBV) is confirmed with positive hepatitis B surface antigen and/or detectable serum HBV DNA. Definition of covariates such as family history of diabetes was taken directly from included studies. Studies with patients having other causes of chronic liver disease such as cirrhosis, autoimmune hepatitis, steatohepatitis, primary biliary cirrhosis, primary cholangitis, and hepatocellular carcinoma were excluded. One author (Mak JW) first screened titles and abstracts of publications using eligibility criteria.

Two authors (Naing C, Ahmed SI) independently recorded the detailed information from each primary study using piloted forms that include relevant items: author, year of publication, country, confirmation of type 2 DM, confirmation of HCV, confirmation of HBV (if presented), study design, number of controls and of cases, genotype of HCV (if provided), distribution of age and gender, family history of diabetes. Any discrepancy between these two investigators was resolved by discussion, and by consultation with another author (Maung M).

Statistical analysis

The degree of heterogeneity between studies was assessed using chi-square and I² test. An I² value greater than ≥ 50% is considered substantial heterogeneity[15]. We used the assumptions that OR from a case control
study approximates the RR in a cohort study. The summary OR with their corresponding 95% CI was calculated based on a random-effects model. We performed separate analysis for the comparisons between (1) HCV infected and not infected and (2) HCV infected and HBV infected. The included studies were subgrouped by the study design. In order to assess any factor that could potentially affect the outcome, results were stratified by age group (proportion of ≥ 40 years), gender (proportion of male gender), body mass index (BMI) (proportion of BMI ≥ 27), and family history of diabetes (i.e. self reported), where there was enough data. We also examined the funnel plots for potential publication bias among the included studies. A sensitivity analysis was conducted including only prospective studies. Data entry and analysis was performed using RevMan 5.1. The methods and findings of the present review have been reported based on the preferred reporting items for systematic reviews and meta-analysis checklist (PRISMA) (Table 1).

Table 1: Preferred reporting items for systematic reviews and meta-analysis reporting

| Section/topic | No. | Checklist item | Reported on page |
|---------------|-----|----------------|-----------------|
| TITLE         |     | Title: Meta-analysis | Title |
| ABSTRACT      |     | Abstract        |     |
| Structured summary |   | 1 Identify the report as a systematic review, meta-analysis, or both | | |
|               |     | 2 Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number | | |
| INTRODUCTION  |     | Introduction     |     |
| Rationale     |     | Introduction     |     |
| Objectives    |     | Introduction     |     |
| METHODS       |     | Methods: Search strategy and eligibility of relevant studies | | |
| Protocol and registration |   | Methods: Search strategy and eligibility of relevant studies | | |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale | | |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched | | |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated | Search strategy |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis) | Methods: Eligibility of relevant studies, PRISMA flowchart provided |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators | Methods: Data extraction and outcome measures |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made | |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis | |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means) done, including measures of consistency (e.g., I^2) for each meta-analysis | Methods: Statistical analysis |
| Synthesis of results | 14 | |

PICOS: Participants, interventions, comparisons, outcomes and study design; PRISMA: Preferred reporting items for systematic reviews and meta-analysis; NA: Not available.

RESULTS

Study selection

Figure 1 provides a flowchart of the present review. We retrieved 57 full articles. Of these, 26 publications were excluded because: (1) They were reviews; (2) They did not adequately distinguish type 2 DM from diabetes; (3) They were conducted in a special population such as transplant patients; (4) They did not include or provide data on patients without HCV infection; (5) They were conducted in patients with known chronic liver disease; (6) It had less than 20 HCV infected patients; and (7) It had duplicate data. The remaining 31 publications of 35 independent studies were eligible for inclusion in the present meta-analysis. Four publications assessed both HCV positive vs negative and HCV positive vs HBV positive.

Study characteristics

A summary of study characteristics in the present analy-
sis is presented in Table 2. Five studies were carried out in United States\(^{[5,44,48,55,57]}\), and three each in Italy\(^{[41,49,64]}\), Japan\(^{[42,43,59]}\), and Taiwan\(^{[46,49,66]}\), among others. Notably, 4 studies\(^{[51,60,62,67]}\) identified for the present analysis were published between 2010 and March 2011. Of the included studies, 17 studies ($n = 286$ 084) compared HCV-infected participants with those uninfected; 7 were both a cross-sectional design (41.2%) and cohort design (41.2%), while 3 (17.6%) were case-control studies (Figure 2). Nineteen studies ($n = 51$ 156) compared HCV-infected participants with HBV-infected; 4 (21.1%), 6 (31.58%) and 9 (47.4%) were cross-sectional, cohort and case-control, respectively (Figure 3). The sample size of the included studies widely varied from 135\(^{[52]}\) to 126 926 participants\(^{[41]}\).

**Main results**

Of the included studies, 17 studies ($n = 286$ 084) compared HCV-infected participants with those uninfected and the pooled OR was 1.68 (95% CI: 1.15-2.45). There was, however, substantial heterogeneity among studies ($I^2 = 95\%$, heterogeneity $P < 0.001$). Nineteen studies ($n = 51$ 156) compared HCV-infected participants with HBV-infected and the pooled OR was 1.92 (95% CI: 1.41-2.62). There was evidence of considerable heterogeneity among studies ($I^2 = 91\%$, heterogeneity $P < 0.001$). Among HCV-infected patients, based on available data, male patients
Table 3 Stratified analysis of type 2 diabetes mellitus in hepatitis C virus-infected participants

| Description                                      | Cases  | OR    | 95% CI   |
|--------------------------------------------------|--------|-------|----------|
| Age (k = 2; n = 599)                              | 455 vs 144 | 7.39 | 5.82-9.38 |
|   > 40 yr                                        |        |       |          |
|   < 40 yr                                       |        |       |          |
| BMI (k = 5; n = 190)                             | 65 vs 190 | 0.87 | 0.08-9.19 |
|   ≥ 27                                          |        |       |          |
|   < 27                                          |        |       |          |
| Gender (k = 8; n = 757)                          | 401 vs 356 | 1.26 | 1.03-1.54 |
|   Male                                          |        |       |          |
|   Female                                        |        |       |          |
| Family history of diabetes (k = 3; n = 580)      | 420 vs 164 | 4.64 | 0.57-38.04 |
|   Yes                                           |        |       |          |
|   No                                             |        |       |          |

OR: Odds ratio; BMI: Body mass index; k: Number of primary studies; n: Number of participants.

Figure 2 Forest plot of comparison: Hepatitis C virus-infected patients vs hepatitis C virus-noninfected patients, outcome is type 2 diabetes mellitus. HCV: Hepatitis C virus; IV: Inverse variance; T2D: Type 2 diabetes mellitus.

DISCUSSION

This review indicates that patients with HCV infections were at higher risk of developing type 2 DM compared with patients with HBV infection. Findings of this review are comparable with a previous review (summary OR: 1.26, 95% CI: 1.03-1.54) with age over 40 years (summary OR: 7.39, 95% CI: 5.82-9.38) had significantly increased type 2 DM prevalence (Table 3). Funnel plots of the associations between HCV and type 2 DM were investigated, providing little evidence of publication bias (Figure not shown).

For better stability of the results, sensitivity analysis with three prospective studies (n = 6449) provided the pooled OR: 1.41 (95% CI: 1.17-1.7, \( I^2 = 0 \)), supporting the increased frequency of type 2 DM in HCV (Figure 4).
comparison to HBV-infected controls (summary OR: 1.63, 95% CI: 1.11-2.39). The evidence of heterogeneity in these studies could be explained by variation in definition of case and control subjects and in the sample size of the primary studies.

As both these viruses can replicate in extra-hepatic sites they can produce β-cell damage resulting in diabetes[10,61]. The lower risk in HBV infection could be explained by two factors: (1) Hepatitis B has been controlled in most developed countries, with active HBV vaccination programme; the occurrence of chronic HBV and its complications in this countries is very low; and (2) The disease progression is rather fast in HBV infection and therefore very few patients reach the level of cirrhosis and thus diabetes frequency is lower in this population[61].

An excess risk of type 2 DM in HCV infected cases was also observed in comparison to non-HCV infected controls in the present analysis (summary OR: 1.63, 95% CI: 1.11-2.39). The evidence of heterogeneity in these studies could be explained by variation in definition of case and control subjects and in the sample size of the primary studies.

![Figure 3 Forest plot of comparison: Hepatitis C virus-infected patients vs hepatitis B virus-infected patients, outcome is type 2 diabetes mellitus. HCV: Hepatitis C virus; HBV: Hepatitis B virus; IV: Inverse variance; T2D: Type 2 diabetes mellitus.](image-url)
a likelihood of changes in serological status of anti-HCV over the study period. Liver disease and endocrine disorders, both common in the general population, have a bidirectional and complex relationship\(^\text{[49]}\). In addition, it is conceivable that patients with an earlier stage of chronic HCV infection have β-cell dysfunction but that diabetes does not become established until cirrhosis has supervened. Thus, a combination of β-cell dysfunction and insulin resistance is required for overt expression of diabetes mellitus\(^\text{[4,2,10,45]}\). Patients in some of the primary studies were not confirmed for the absence of cirrhosis by liver biopsy which is the best predictor of disease progression\(^\text{[5]}\). As such, we were unable to rigorously exclude cirrhosis individuals from the present analysis, and including these patients in the analysis may have exaggerated the association estimated. Of interest, it has been postulated that HCV has a permissive rather than a direct effect on the development of diabetes and acts in concert with other determinants to lead to diabetes\(^\text{[59]}\). Recent animal model evidence suggests a more direct effect of HCV infection on insulin resistance in the liver\(^\text{[10,49]}\) indicating the role of hepatic tumor necrosis factor-α in affecting insulin signaling in this animal model of HCV infection\(^\text{[7]}\). In the present review, as cross-sectional and longitudinal prospective studies both show the same evidence, an excess type 2 DM risk in HCV-infected persons suggests a direct role of HCV in inducing derangement of glucose metabolism\(^\text{[9,10,45]}\). Further, there may be other factors influencing the development of type 2 DM in HCV infected patients which is not possible to address in the present analysis.

There are limitations to the present study. Most, if not all, observational studies have the potential for ascertainment bias\(^\text{[40,70]}\) particularly for the studies in which diabetes status was defined by self report. Thus, there may be biased estimates of association. Moreover, recall bias is a factor in case-control studies. Although confounding factors were addressed in many of these observational studies, it is likely that there may be unmeasured confounding factors which may introduce bias into our findings. Further, as patient level data were not available for each study, we could not make further adjustments for important factors such as genotype that were not included in most of the primary studies.

### Biological plausibility

Findings of those prospective studies\(^\text{[42,52,60]}\) which have measured HCV prior to diagnosis of type 2 DM support evidence for a temporal relationship between exposure and outcome. In a study\(^\text{[43]}\), a significant link between viral load and diabetes was found and it supported the diabetogenic role of HCV infection. The influence of viral load on the progression rate of type 2 DM was not examined in most of the studies. More research is needed to assess a dose-response association. It is also recommended that surveillance of HCV could indicate whether trends in its incidence continue to reflect changes in the prevalence of type 2 DM in the defined group.

### Public health implications

If the associations do support temporality, the early detection and provision of aggressive antiviral treatment for HCV could prevent the development of type 2 DM, particularly in patients at high risk of HCV.

Nevertheless, the findings of the current analysis, to a certain extent, represent the HCV endemic countries. The present study has significant strengths in two ways: (1) It is comprehensive, including most recent studies; and (2) It addresses traditional risk factors (age, gender, BMI, family history of diabetes) which could potentially affect the outcome. As the prevalence of obese patients obtained in the group of HCV-positive patients with type 2 DM was significantly lower than that in diabetic HCV-negative patients found in an independent study\(^\text{[8]}\) and also in the present meta-analysis, it is suggesting the pathogenesis of diabetes in HCV infection could be different from that in the general population.

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