Prevalence of Type 2 Diabetes Mellitus among Hepatitis C Virus-Infected Patients: A Systematic Review and Meta-Analysis

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Keywords

Diabetes mellitus · Hepatitis C virus · Meta-analysis · Prevalence

Abstract

Background: The ever-increasing global prevalence of hepatitis C infection is fueling the burden of diabetes mellitus, which exacerbates various complications and may be a cause of death of millions of people. Several studies have reported that hepatitis C virus infection is an important risk factor for the development of diabetes mellitus. However, fragmented studies have reported variable and inconsistent findings regarding the prevalence of type 2 diabetes mellitus among hepatitis C virus-infected patients. Therefore, this meta-analysis aimed to estimate the overall prevalence of type 2 diabetes mellitus among patients infected with hepatitis C virus. **Methods:** This systematic review and meta-analysis includes original articles reporting on cohort and cross-sectional studies. A systematic search was performed in

PubMed, ScienceDirect, and Google Scholar. A random-effects meta-analysis model was used to estimate the global pooled prevalence of type 2 diabetes mellitus among hepatitis C-infected patients. A sensitivity analysis was conducted to check the stability of the summary estimate. Heterogeneity was assessed using the I^2 statistic. A subgroup analysis was also conducted based on geographical region. Funnel plots were used to spot publication bias. **Results:** A total of 40 eligible articles reporting data on 14,765 study participants were included in this meta-analysis. The pooled prevalence of type 2 diabetes mellitus among hepatitis C virus-infected patients was 19.67% (95% CI: 17.25, 22.09). The subgroup analysis showed a pooled prevalence of 27.72% (95% CI: 20.79, 34.65) in Africa, 20.73% (95% CI: 17.57, 23.90) in Asia, 16.64% (95% CI: 6.79, 26.49) in North America, and 15.02% (95% CI: 10.66, 19.38) in Europe. **Conclusions:** The

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overall prevalence of type 2 diabetes mellitus among hepatitis C virus-infected patients was considerably higher than in the general population in a global perspective. The highest prevalence was noted in Africa and Asia, followed by North America and Europe. Therefore, early intervention is needed (prevention and early treatment of hepatitis C virus infection) to prevent the development of type 2 diabetes mellitus.

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Introduction

Diabetes mellitus (DM) constitutes one of the leading causes of death across the globe, accounting for 8.4% of global all-cause mortality [1]. DM is known for its complications such as cardiovascular disease, stroke, nephropathy, leg amputation, retinopathy, impaired immunity, and nerve damage [2]. In pregnancy, poorly controlled DM increases the risk of fetal death and other long-term consequences that impact significantly on the quality of life [3].

On the other hand, hepatitis C virus (HCV) infection is a growing global health threat; approximately 150–200 million people have been infected with it [4, 5]. Each year, 1.75 million people newly acquire an HCV infection. The most affected regions are Eastern Mediterranean and European regions, with prevalence rates of 2.3 and 1.5%, respectively [6]. According to some reports, 350,000 people per year die due to HCV-related diseases [7, 8].

Though HCV remains a serious public health issue, no vaccination and no post-exposure prophylaxis are available yet [9]. It causes chronic, life-long infections, resulting in progressive liver damage that leads to cirrhosis and hepatocellular carcinoma [5]. HCV also has extrahepatic effects such as cryoglobulinemia, sporadic porphyria cutanea tarda, glomerulonephritis, and thyroid disorders, perhaps due to the impact of the virus on the host immune system [10]. Evidence suggests that slow progression of HCV infection is the major cause of DM; notably, the virus appears to affect glucose metabolism through alteration of the host innate immune response [11]. The prevalence of DM is on the rise; it is predicted that its prevalence among adults will rise to 10.4% by 2040 [12].

Not only in high-income countries but also in low- and middle-income countries, the prevalence of DM has risen faster over the past decade [13]. The International Diabetes Federation estimates that 1 in 11 adults has DM, with a global estimate of 425 million. However, DM is unequally distributed across the globe, and some regions are

more affected than others depending on the type and number of its various causes [14].

Several studies have reported that HCV infection is associated with type 2 DM (T2DM). Even though the exact biological mechanisms are not fully understood, some hypotheses suggest that a change in carbohydrate and hepatic lipid metabolism, expression of the HCV core protein, and the activity of hepatic tumor necrosis factor- α induce insulin resistance through alterations to the insulin receptor substrate signaling pathway [15, 16]. Studies reported that the prevalence rates of DM among patients with HCV infection range from 7.4 to 43.2% [17, 18].

However, so far there has been no systematic review and meta-analysis that estimated the global burden of T2DM among HCV-infected patients. We conducted a systematic review and meta-analysis to summarize the existing data on the prevalence of T2DM among HCV-infected patients at the global level. This provides the empirical evidence necessary for researchers, policymakers, and public health stakeholders to derive health-promoting policies, allocate resources, and set priorities for monitoring future trends.

Methods

Search Strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard [19]. The study protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42018083409). A comprehensive literature search was conducted to identify studies performed on the prevalence of T2DM among HCV-infected patients and published up to December 2017. Searches were carried out systematically in the following electronic bibliographic databases: PubMed, Google Scholar, and ScienceDirect. The following keywords were used to select relevant studies: (Diabetes Mellitus) OR DM [MeSH Terms] AND (Hepatitis) OR (Hepatitis C virus) [MeSH Terms] OR HCV [MeSH Terms] AND prevalence. The search terms were used separately and in combination using Boolean operators like “OR” or “AND.” Duplicate data were excluded.

Eligibility Criteria

Inclusion Criteria

Studies published in peer-reviewed journals and that reported the prevalence of T2DM among HCV-infected patients were included. All studies were original research articles published in English and contained the minimum information (study participants and number of diabetes events) that helps to calculate a pooled estimate of the global prevalence. Moreover, studies were included in which DM was diagnosed (1) using a fasting plasma glucose level ≥ 126 mg/dL (7.0 mmol/L), (2) using a 2-h plasma glucose level ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test, or (3) using a random plasma glucose level ≥ 200 mg/dL (11.1

Fig. 1. Flow chart depicting the selection of studies for a systematic review and meta-analysis of the prevalence of type 2 diabetes mellitus among patients infected with hepatitis C virus.

mmol/L) in patients with classic symptoms of hyperglycemia or hyperglycemic crisis. The full texts of the studies meeting these criteria were retrieved and screened to determine their eligibility.

Exclusion Criteria

Studies on gestational or type 1 DM, non-original papers (such as reviews, editorials, letters, and commentaries), and studies in which it was unknown/unclear how DM had been diagnosed were excluded. Studies conducted on patients with HCV-HIV or HCV-HBV coinfection or on antiviral drug users were also excluded, as well as those on patients with other causes of liver disease – in particular, those known for the development of DM, such as hemochromatosis. Furthermore, studies on patients who had undergone liver or kidney transplantation were not included in this study.

Study Selection and Quality Assessment

Three reviewers (S.A., M.M., and A.E.) independently screened the titles and abstracts to consider articles for full-text review. The quality of the studies was assessed using the Joanna Briggs Institute (JBI) quality appraisal criteria [20]. The following items were used to appraise cohort and cross-sectional studies: (1) appropriateness of inclusion criteria; (2) description of study subject and setting; (3) valid and reliable measurement of exposure; (4) objective, standard criteria were used; (5) identification of confounders; (6) strategies for handling confounders; (7) outcome measurement; and

(8) appropriateness of statistical analysis. Studies that reached 50% and above on the quality scale were considered at low risk of bias. Any disagreement was solved by consensus.

Data Extraction

A data extraction tool was developed. Information regarding the country, year of publication, type of study, study design, study setting, number of participants, age range of the population, diagnostic criteria for each condition, and number of T2DM cases was retrieved. Data extraction was performed by three reviewers (S.A., M.M., and A.E.) independently, and cross-checked for consistency.

Data Analysis

The extracted data were entered into Microsoft Excel and analyzed using Stata version 11 (StataCorp, 2009; College Station, TX, USA). A weighted inverse-variance random-effects meta-analysis model was used to obtain an overall summary estimate of the prevalence across studies. A sensitivity analysis was conducted to check the stability of the summary estimate. Assessment of publication bias was performed using funnel plots. Heterogeneity across the studies was evaluated by the I^2 statistic. I^2 provides the percentage of variability due to heterogeneity rather than chance differences and/or sampling error, and I^2 values of 25, 50, and 75% were considered as representing low, medium, and high heterogeneity, respectively. We performed a subgroup analysis by continent in cases of substantial heterogeneity.

Table 1. General characteristics and outcomes of the included studies ($n = 40$)

Study [Ref.], year	Study design	Country	Sample size, n	Prevalence, %	Study quality
Ghourri et al. [21], 2014	Cross-sectional	Pakistan	100	28	Good
Lecube et al. [68], 2004	Cross-sectional	Spain	498	23	Good
Akbar et al. [22], 2002	Cross-sectional	Saudi Arabia	165	21.2	Good
Chiquete et al. [50], 2012	Cross-sectional	Mexico	125	17.6	Good
Anthony [54], 2016	Cross-sectional	Rwanda	298	22.48	Good
Caronia et al. [42], 1999	Cross-sectional	UK	1,151	23.6	Good
Bo et al. [23], 2015	Cross-sectional	Asia	1,887	9	Good
Azam et al. [24], 2017	Cross-sectional	Bangladesh	1,950	22.6	Good
Memon et al. [25], 2013	Cross-sectional	Pakistan	361	31.5	Good
Ryu et al. [26], 2001	Cross-sectional	South Korea	95	24	Good
Mason et al. [43], 1999	Cross-sectional	UK	495	21	Good
Rouabhia et al. [55], 2010	Cross-sectional	Algeria	261	39.1	Good
Selm [27], 2012	Cross-sectional	Yemen	71	21	Good
Raouf et al. [56], 2012	Cross-sectional	Egypt	100	24	Good
Hong et al. [28], 2017	Cohort study	South Korea	784	8.7	Good
Wang et al. [29], 2003	Cross-sectional	Taiwan	363	18.18	Good
Imazeki et al. [30], 2008	Cross-sectional	Japan	544	13.6	Good
Antonelli et al. [46], 2005	Cross-sectional	Italy	564	12.6	Good
Qureshi et al. [31], 2002	Cross-sectional	Pakistan	302	24.5	Good
Zein et al. [51], 2005	Cross-sectional	USA	179	14.5	Good
Khan et al. [32], 2013	Cross-sectional	Pakistan	164	16.46	Good
Arao et al. [33], 2003	Cross-sectional	Japan	707	20.94	Good
Petit et al. [45], 2001	Cross-sectional	France	123	13	Good
Chehadeh et al. [34], 2009	Cross-sectional	Kuwait	181	39.8	Good
Lin et al. [35], 2017	Cohort study	Taiwan	930	16.7	Good
Huang et al. [36], 2007	Cross-sectional	Taiwan	642	15	Good
Huang et al. [37], 2008	Cross-sectional	Taiwan	683	37.8	Good
Kanwal et al. [52], 2015	Cross-sectional	USA	528	26.9	Good
Antonelli et al. [44], 2004	Cohort study	Italy	229	14.4	Good
Konishi et al. [38], 2009	Cohort study	Japan	197	12	Good
Kwon et al. [18], 2005	Cross-sectional	Korea	88	43.2	Good
Liu et al. [39], 2012	Cross-sectional	Taiwan	5,754	10.53	Good
Masarone et al. [47], 2007	Cross-sectional	Italy	180	7.8	Good
Montenegro et al. [48], 2013	Cohort study	Italy	616	10.1	Good
El-Zayadi et al. [57], 1998	Cross-sectional	Egypt	591	25.4	Good
İba Yılmaz et al. [49], 2015	Cross-sectional	Turkey	62	8.1	Good
Cheng et al. [40], 2014	Cross-sectional	China	297	28.2	Good
Stepanova et al. [53], 2012	Cohort study	USA	335	7.71	Good
Amarapurkar and Patel [41], 2008	Cross-sectional	India	200	22	Good
Rao et al. [17], 2015	Cross-sectional	China	947	7.4	Good

Results

Characteristics of the Included Studies

A total of 1,156 potential articles were identified through the systematic literature search. After removal of duplicates, 542 articles were screened by title and abstract, and 144 were found to be eligible for full-text assessment. Of these full-text-screened articles, 40 (including 14,765 study participants) were found to be eligible

for meta-analysis. Figure 1 shows the flow chart of study selection and exclusion.

The included studies were conducted all around the world and published up to December 2017. Overall, of the 40 studies included in the meta-analysis that reported the prevalence of T2DM among HCV-infected patients, 23 were from Asia [17, 18, 21–41], 9 were from Europe [42–49, 68], 4 were from North America [50–53], and 4 were from Africa [54–57]. Regarding the study design, 34 were

Table 2. Sensitivity analysis of the included studies to estimate the pooled prevalence of T2DM among HCV-infected patients

Study omitted	Prevalence of T2DM among HCV-infected patients, % (95% CI)	Study omitted	Prevalence of T2DM among HCV-infected patients, % (95% CI)
Ghouri et al. [21], 2014	19.49 (17.05, 21.93)	Khan et al. [32], 2013	19.75 (17.29, 22.21)
Lecube et al. [68], 2004	19.58 (17.13, 22.02)	Arao et al. [33], 2003	19.63 (17.18, 22.09)
Akbar et al. [22], 2002	19.63 (17.18, 22.08)	Petit et al. [45], 2001	19.83 (17.38, 22.29)
Chiquete et al. [50], 2012	19.71 (17.26, 22.17)	Chehadeh et al. [34], 2009	19.19 (16.80, 21.56)
Anthony et al. [54], 2016	19.59 (17.15, 22.04)	Lin et al. [35], 2017	19.76 (17.27, 22.26)
Caronia et al. [42], 1999	19.55 (17.12, 21.98)	Huang et al. [36], 2007	19.80 (17.32, 22.29)
Bo et al. [23], 2015	19.99 (17.46, 22.51)	Huang et al. [37], 2008	19.11 (16.84, 21.39)
Azam et al. [24], 2017	17.15 (22.00, 19.58)	Kanwal et al. [52], 2015	19.46 (17.0, 21.88)
Memon et al. [25], 2013	19.35 (16.94, 21.75)	Antonelli et al. [44], 2004	19.81 (17.34, 22.27)
Ryu et al. [26], 2001	19.58 (17.13, 22.02)	Konishi et al. [38], 2009	19.87 (17.41, 22.33)
Mason et al. [43], 1999	19.63 (17.18, 22.09)	Kwon et al. [18], 2005	19.22 (16.81, 21.63)
Rouabhia et al. [55], 2010	19.17 (16.79, 21.55)	Liu et al. [39], 2012	19.98 (17.33, 22.63)
Selm [27], 2012	19.64 (17.20, 22.08)	Masarone et al. [47], 2007	19.98 (17.53, 22.44)
Raouf et al. [56], 2012	19.57 (17.13, 22.01)	Montenegro et al. [48], 2013	19.94 (17.46, 22.43)
Hong et al. [28], 2017	19.99 (17.50, 22.47)	El-Zayadi et al. [57], 1998	19.50 (17.08, 21.93)
Wang et al. [29], 2003	17.25 (22.17, 22.17)	İba Yilmaz et al. [49], 2015	19.94 (17.49, 22.39)
Imazeki et al. [30], 2008	19.84 (17.36, 22.33)	Cheng et al. [40], 2014	19.44 (17.02, 21.87)
Antonelli et al. [46], 2005	19.87 (17.39, 22.36)	Stepanova et al. [53], 2012	19.99 (17.54, 22.46)
Qureshi et al. [31], 2002	19.54 (17.10, 21.98)	Amarapurkar and Patel [41], 2008	19.61 (17.16, 22.06)
Zein et al. [51], 2005	19.80 (17.34, 22.26)	Rao et al. [17], 2015	20.01 (17.55, 22.49)
Combined	19.67 (17.25, 22.09)		

T2DM, type 2 diabetes mellitus; HCV, hepatitis C virus.

cross-sectional and 6 were cohort studies. The JBI quality appraisal checklists indicated that none of the included studies were of poor quality. After quality assessment, the 40 studies were subjected to meta-analysis. Table 1 presents the characteristics and outcomes of the reviewed studies.

Prevalence of T2DM among HCV-Infected Patients

Forty studies were included in the systematic review and meta-analysis, and all were used for estimation of the prevalence of T2DM among HCV-infected patients. Accordingly, the prevalence of T2DM among HCV-infected patients ranges from 7.4% [17] to 43.2% [18]. In this study, the estimated global pooled prevalence of T2DM among HCV-infected patients was 19.67% (95% CI: 17.25, 22.09; $I^2 = 96.2\%$; $p = 0.000$). The subgroup analysis based on geographical area (continent) showed prevalence rates for T2DM among HCV-infected patients of 27.72% (95% CI: 20.79, 34.65) in Africa, 20.73% (95% CI: 17.57, 23.90) in Asia, 16.64% (95% CI: 6.79, 26.49) in North America, and 15.02% (95% CI: 10.66, 19.38) in Europe (Fig. 2).

Sensitivity Analysis

We made the sensitivity analysis of the prevalence of T2DM among HCV-infected patients by applying a random-effects model (Table 2). The analysis was done to evaluate the effect of each study on the pooled estimated prevalence of T2DM by excluding each study step by step. The result was that the excluded studies did not show much difference in the prevalence of T2DM among HCV-infected patients.

Publication Bias

The included studies were visually assessed for potential publication bias with a funnel plot. The funnel plot symmetrically indicates the absence of publication bias, since more than 95% of the studies fell within the triangular region (Fig. 3).

Discussion

HCV infection and DM are two major public health problems worldwide. In this systematic review and meta-analysis, we identified 40 studies at the global level that

Fig. 2. Forest plot of the global pooled estimates (ES) of the prevalence of type 2 diabetes mellitus among hepatitis C virus-infected patients from a random-effects model. The midpoint and the length of each segment indicates the prevalence and 95% CI, whereas the diamond shape shows the combined prevalence of all studies.

Fig. 3. Funnel plot of the prevalence of type 2 diabetes mellitus among hepatitis C virus-infected patients.

reported the prevalence of T2DM among HCV-infected patients.

According to those, the pooled prevalence of T2DM among HCV-infected patients was 19.67% (95% CI: 17.25, 22.09). This result was much higher than the global prevalence of DM (8.5%) among the general population [1]. The reason behind the high prevalence of T2DM among HCV-infected patients in this study could be that patients with HCV are at risk of developing DM through several pathways. A systematic review and meta-analysis done by Naing et al. [58] showed an excess risk of T2DM in cases with HCV infection compared to non-HCV-infected controls (OR: 1.63; 95% CI: 1.11, 2.39). This could be due to the processes by which HCV causes T2DM, i.e., through direct viral effects, insulin resistance, proinflammatory cytokines, chemokines, and other immune-mediated mechanisms [59]. This was supported by an experimental study that showed that expression of the HCV core protein induces hepatic insulin resistance through alterations of the insulin receptor substrate 1 signaling pathway [60]. Likewise, a study using an animal model has indicated a direct effect of HCV infection on insulin resistance in the liver [61]. In addition to the diabetogenic effects of HCV infection, poor management and treatment of HCV infection, low access to health care, high blood pressure, high cholesterol levels, lack of physical activity, weight gain, and behavioral risk factors might contribute to the increased prevalence of T2DM among HCV-infected patients.

In the subgroup analysis, the pooled prevalence of T2DM among HCV-infected patients was 27.72% (95% CI: 20.79, 34.65) in Africa, which was higher than the pooled prevalence in Asia (20.73%; 95% CI: 17.57, 23.90), in Europe (15.02%; 95% CI: 10.66, 19.38), and in North America (16.64%; 95% CI: 6.79, 26.49). This variability might be due to differences in ethnicity, sample size, and characteristics of the study population. Differences in access to health care services, the variability in early HCV screening and diagnosis from country to country, differences in the management of HCV infection, and the lack of an effective strategy for controlling HCV infections in some countries also might contribute to the differences in the above results between continents. Moreover, differences in lifestyle and behavioral factors might also be underlying factors.

Evidence shows that Africa has the highest WHO-estimated regional HCV infection prevalence rate (5.3%). However, no data were found on the use of medications with HCV infection in Africa, even though treatment, e.g., with peginterferon and ribavirin, is recommended for patients with chronic HCV infection [62]. It is noteworthy that the high prevalence rates of HCV infection in Africa, accompanied by poor management of HCV infection, might fuel HCV-related complications, especially T2DM. This is why in the current study the pooled prevalence of T2DM among HCV-infected patients was higher in Africa than on other continents.

According to the current study, the pooled prevalence of T2DM among HCV-infected patients in Africa (27.72%; 95% CI: 20.79, 34.65) was much higher than the estimated prevalence of DM in Africa (1%; rural areas) and in sub-Saharan Africa (5–7%; urban areas) [63] and than the pooled result of a meta-analysis of DM prevalence (5.7%) in Zimbabwe [64]. Likewise, the pooled prevalence of T2DM among HCV-infected patients in Europe (15.02%; 95% CI: 10.66, 19.38) was much higher than the estimated prevalence of DM (8.5%) among the general population in Europe [65]. Furthermore, the pooled prevalence of T2DM among HCV-infected patients in Asia (20.73%; 95% CI: 17.57, 23.90) was higher than the estimated prevalence of DM (9%) among the adult population of the South-East Asia Region [66]. Moreover, the pooled prevalence of T2DM among HCV-infected patients in North America (16.64%; 95% CI: 6.79, 26.49) was higher than the estimated prevalence of DM (9.4%) among the US population [67]. As mentioned before, it is found to be reasonable that HCV infection might contribute to the rising burden of T2DM.

Conclusions

Despite the great heterogeneity and lack of original studies in some countries, our study observed a high prevalence of T2DM among HCV-infected patients compared to the general population. Moreover, the pooled prevalence in Africa was higher than in Europe and North America. Therefore, early intervention is needed (prevention and early treatment of HCV infection) to prevent the development of T2DM. This helps to reduce the coexistence of HCV infection and T2DM as well as exacerbated complications. Besides, policymakers, researchers, and stakeholders should consider effective strategies and preventive measures regarding HCV infection and T2DM.

Statement of Ethics

The authors have no ethical conflicts to disclose.

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Disclosure Statement

The authors declare that they have no competing interests. The study received no funding.

Data Availability

The data will be available upon request from the corresponding author.

Author Contributions

S.A.: conception of the research protocol, design of the study, review of the literature, data extraction, and statistical analysis. S.A. and A.E.: data analysis and interpretation and drafting of the manuscript. M.M. and S.E.: data interpretation and review of the manuscript. S.A., D.G., and A.E.: data extraction and quality assessment. All authors critically revised the paper and they agree to be accountable for all aspects of the work.

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