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Association of type 2 diabetes and hepatitis C virus infection in Pakistani population: A meta-analysis

Sher Zaman Safi[1, 2*], Humaira Shah[3], Muhammad Imran[4], Mamoon Noreen[5], Zahira Latif[6],
Fouzia Rehman[2], Abid Ali[7], Naushad Muhammad[8], Yasir Waheed[9], Talha Bin Emran[10, 11],
Shah Alam Khan[12], Vorticella Subramaniyan[1], and Ikram Shah Bin Ismail[1]

[1] *Faculty of Medicine, Bioscience and Nursing, MAHSA University,
Genaro, Selangor, 42610 Malaysia*

[2] *Interdisciplinary Research Centre in Biomedical Materials,
COMSATS University Islamabad, Lahore Campus, Lahore, Punjab, 54000 Pakistan*

[3] *Knowledge and Research Support Services, University of Management and Technology,
Lahore, Punjab, 54770 Pakistan*

[4] *Department of Microbiology, University of Health Sciences, Lahore, Punjab, 54600 Pakistan*

[5] *Women University, Multan, Punjab, 60000 Pakistan*

[6] *Regional Blood Centre Peshawar, Peshawar, Khyber Pakhtunkhwa, Pakistan*

[7]*Department of Zoology, Abdul Wail Khan University, Marden, Khyber Pakhtunkhwa, 23200 Pakista Pakistan*

[8]*Department of Dental Materials, Institute of Basic Medical Sciences,
Khyber Medical University Peshawar, Peshawar, Khyber Pakhtunkhwa 25100, Pakistan*

[9]*Department of Molecular Biology, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, 44000 Pakistan*

[10] *Department of Pharmacy, BGC Trust University Bangladesh, Chittagong, 4381 Bangladesh*

[11] *Department of Pharmacy, Faculty of Allied Health Sciences,
Daffodil International University, Dhaka, 1207 Bangladesh*

[12] *Department of Pharmaceutical Chemistry, College of Pharmacy,
National University of Science and Technology, Arabia, Muscat, Oman*

*Corresponding author
Email address: safi.nust@yahoo.com

Abstract

        In Pakistan and other developing countries, the available data on the association of T2DM and HCV is limited. We therefore made an attempt to report the association of HCV and diabetes in Pakistani population through this meta-analysis. HCV and diabetes related studies were identified using various key words, from a number of databases including CINAHL, PubMed, Web of Science and Embase. Using RevMan5, the main outcome was regarded as type 2 diabetes associations with hepatitis c virus infection in Pakistan. Independent analyses were made for "HCV in diabetic patients" and "diabetes cases in hepatitis C virus patients". Using random effect model, odds ratios were calculated with 95% CIs (dichotomous data). I2 statistics were used to calculate heterogeneity. From a total of 53 studies, we finally selected 6 studies for the meta-analysis. Using random effects model, hepatitis c virus patients in 3 studies (n = 1,902) demonstrated that HCV is a risk factor in developing diabetes, contrary to patients with no HCV infection (OR 0.01, 95% CI: 0.00-0.06, I2 = 0%; RR 0.01, 95% CI: 0.00-0.07, I2 = 0%). The remaining 3 studies (n = 13,710) had reported HCV infections in type 2 diabetic patients and patients with no diabetes. Similarly, our meta-analysis revealed higher prevalence of HCV infections in patients with type 2 diabetes (OR 0.7, 95% CI: 0.17-0.42, I2 = 32%; RR 0.30, 95% CI: 0.20-0.46, I2 = 32%) as compared to patients with no type 2 diabetes mellitus. Our meta-analysis demonstrates a significant link between HCV and T2DM. Further studies are recommended with adequate sample sizes

Keywords: HCV, diabetes, meta-analysis, HCV-diabetes association, liver diseases

1. Introduction

        Both, hepatitis C virus infections (HCV) and type 2 diabetes (T2DM) are worldwide prevalent diseases with heavy morbidities and deaths (Manor *et al.,* 2021; Naris *et al.,* 2021; Safi, Qvist, Kumar, Batumalaie, & Ismail, 2014; Waheed, Shafi, Safi, & Qadri, 2009). It is documented that type 2 diabetes is approximately 8.3% prevalent among the adults and it is presumed it will increase to 9.9% by the year 2030 (Safi, Qvist, Yan, & Ismail, 2014; Whiting, Guariguata, Weil, & Shaw, 2011). Similarly, HCV is also a globally widespread pathogen with a seroprevalence of over 185 million infections worldwide (Mohd Hanafiah, Groeger, Flaxman, & Wiersma, 2013; Safi *et al.,* 2010).

        The association of T2DM and HCV was reported in 1994, which was later, further investigated by other researchers in 1996 (Allison, Wright, Palmer, & Alexander, 1994; Simo, Hernandez, Genesca, Jardi, & Mesa, 1996). Recent evidences, in which HCV infiltrates with glucose metabolism, have placed HCV in the list of diabetogenic agents (Any *et al.,* 2007; Custro *et al.,* 2001). HCV induced autoimmune phenomena such as blockage of insulin receptors cytotoxic effects on pancreatic β cells have also been demonstrated (Antonelli, 2003; Romero-Gómez, 2006). The epidemiological association of HCV and T2DM has been reported from two viewpoints. Some reports have demonstrated high HCV prevalence in patients with T2DM (Balik, Yilmaz, Turkcapar, & Yasa, 1999; Chen, Li, Chen, See, & Lee, 2006; Safi & Shah, 2014), while other researchers have narrated increased risk of T2DM in HCV infected patients (White, Ratziu, & El-Serag, 2008). There are also reports where investigators did not find any association between T2DM and HCV (Balogun, Adeleye, Akinlade, Kuti, & Otegbayo, 2006; Picaro *et al.,* 2002).

        In Pakistan 10 million people are suffering from HCV with a prevalence rate of 6%. Approximately 50% cases of hepatocellular carcinoma (HCC) and 70% cases of chronic liver diseases are because of hepatitis C virus infections. These infections are accompanied with extrahepatic manifestations including insulin resistance which consequently lead to diabetes and obesity (Jadoon *et al.,* 2010; Mansha *et al.,* 2017; Muhammad, Amin, Anjum, & Javed, 2010; Safi *et al.,* 2011; Safi *et al*., 2012; Waheed, Shafi, Safi,

& Qadri, 2011). Diabetes is one of the serious health problems in the country with 7.1 million people being diabetic. It is estimated that there will be 13.8 million people diabetic by 2030 (Shaw, Sicree, & Zimmet, 2010).

        The link between HCV and other diseases including T2DM is an established fact but the mechanisms of these links are not clear. Some studies have reported explanations at molecular level; however many aspects are yet to be explored. Some studies support T2DM as risk factor for acquiring HCV infections and other studies claim that HCV rises the likelihood of T2DM development. In Pakistan, there are studies on this subject but a conclusive meta-analysis, which can document data and can clearly connect the dots between HCV and T2DM is missing. In this meta-analysis, our objective is to determine the exact HCV-T2DM association and to explain the significance of HCV-induced T2DM or T2DM-induced hepatitis C virus infections in HCV and T2DM patients respectively. This will increase the awareness among HCV and T2DM patients, health care workers and general public in Pakistan.

2. Materials and Methods

2.1 Literature search

        Relevant peer reviewed articles, which have assessed the link between HCV and T2DM were identified using MEDLINE, PubMed, EMBASE and CINAHL databases. Articles with titles, abstracts, keywords or text words containing the keywords "diabetes", "hepatitis C virus", "link between diabetes and hepatitis c virus", "HCV", "T2DM", "HCV and T2DM", "diabetes type II and HCV in Pakistan", "hepatitis C virus and type II diabetes mellitus in Pakistan", "prevalence of diabetes in Pakistan", "prevalence of HCV in Pakistan", " Risk factors of hepatitis C in Pakistan", "diabetes and HCV disease burden in Pakistan", "HCV as diabetogenic factor in Pakistan", "diabetes clinical trials in Pakistan", "WHO data on diabetes and HCV in Pakistan" and "case control studies of HCV and diabetes in Pakistan". While searching literature, we also included reference lists of relevant studies, review articles, electronic theses and abstracts published in national and international conferences. We kept our search restricted to studies on

human which were published in English language journals. Studies were excluded at this stage if they did not fulfil our criteria of inclusion.

2.2 Study selection

This study was conducted according to the PRISMA statement for reporting of meta-analysis and systematic reviews (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). We included all studies comparing HCV and T2DM. Articles with epidemiological study design and primary and secondary data were included. All studies were required to provide sufficient data for odds ratio (OR) or relative risk (RR) calculation. Studies were divided into two groups: (A) Studies conducted on determining the prevalence of T2DM in HCV infected patients and (B) studies with HCV prevalence in T2DM patients. All studies were required to have reported their relevant controls. Number of patients in each study with adequate number of controls and origin of the study (Pakistan) were also taken into account. Studies with

only HCV and T2DM (with no control) were excluded. Articles with fewer subjects were also excluded.

2.3 Statistical analysis

For this study, the primary conclusion was correlation of T2DM and HCV infection. Through random effect model, the association of HCV and T2DM was estimated using relative risk (RR) and odds ratio (OR) with 95% confidence intervals (CI) for dichotomous data and inverse variance. Chi-square and I^2 statistics were used to assess the degree of heterogeneity between the studies. An I^2 value more than 50% was reflected significant heterogeneity. Forest plot was used to illustrate the estimates. Publications bias was evaluated using funnel plot. The meta-analyses were conducted using Reman 5.3. The findings and methods in this meta-analysis have been included on the basis of PRISMA checklist of preferred reporting items for meta-analysis and systematic reviews as given in Table 1 (Liberati, 2009).

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

Section	No	Checklist items	Reported on page no
Title			
Title	1	Identification of a report as meta-analysis, systematic review or both.	Meta-analysis
Abstract			
Structured summary	2	Provision of a summary which may include objectives, background, methods, results, conclusion, criteria, interventions and participants.	Abstract
Introduction			
Rationale	3	Description of the prime objective and rationale of why the specific study was conducted, what was known and what was missing.	Introduction
Objectives	4	Provision of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
Methods			
Protocol and registration	5	If a protocol available, then indicate where it could be accessed, or if a registration available, provide the registration details.	Methods
Eligibility criteria	6	Specification of key criteria of the study	Search strategy and eligibility of relevant studies
Information sources	7	Description of all the information about the sources including databases	Literature search
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Literature search
Study selection	9	Describe the process of study selection such as eligibility and screening	study selection
Synthesis of results	10	State the information of handling data including measures of consistency (e.g., I^2) for each meta-analysis.	Results
Results			
Study selection	11	Describe the studies which were included, how they were screened for eligibility with all reasons for those which were excluded.	Study Selection
Study characteristics	12	State the characteristics for which data were extracted from each study, such as PICOS and study size etc.	Study characteristics
Risk of bias within studies	13	Describe data on the basis of risk of bias of each study	Funnel plot
Results of individual studies	14	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Main results
Synthesis of results	15	Describe results of each meta-analysis done.	Main results
Discussion			
Summary of evidence	16	Summarization of the main findings including the strength of evidence for each main outcome.	Discussion
Limitations	17	Describe the limitation of the study.	Discussion last paragraph
Conclusions	18	Present a few lines conclusion as interpretation of the key results with future prospects.	Conclusion

3. Results

3.1 Study selection

Our search strategy resulted in total 53 articles as shown in the flowchart (Figure 1). Of these, 33 articles were excluded, as they did not meet our selection criteria. They were excluded because: (i) They were review papers; (ii) the data was mixed with HIV or HBV; (iii) authors were Pakistani but study was not conducted in Pakistani population; (iv) hepatocellular carcinoma (HCC) was due to other factors; (v) duplication. Off the remaining 20 publications, 14 articles were excluded after thorough reading and understanding. They were excluded because: (i) Not adequate data was provided on patients with T2DM and HCV infections; (ii) there were no control group. The remaining 6 articles qualified for the meta-analysis. Off 6, 3 publications (Hussain *et al.,* 2016; Nadeem *et al.,* 2013; Qureshi *et al.,* 2002) had assessed diabetes mellitus type 2 in patients with HCV and other 3 had evaluated HCV infections in cases with T2DM (Jadoon, Shahzad, Yaqoob, Hussain, & Ali, 2010; Kanwal *et al.,* 2016; Sadiq & Raja, 2015).

3.2 Study characteristics

All of 6 included studies were carried out in Pakistan in Pakistani population. Due to limited studies on this subject in Pakistan, we could not find other studies published in 2017 or before 2002. From the included studies 3 publications had assessed T2DM in HCV infected patients (n = 1,220) and control subjects (n = 682) with a total sample size 1,902 subjects. Other 3 publications had evaluated HCV infections in T2DM patients (n = 3,360) and control subjects (n = 10,350) comprising a sample size of 13,710.

3.3 Main results

A total of 6 observational studies from initial 53 records were subsequently selected for the meta-analysis. Off 6 included studies, 3 articles (n = 1,902) had evaluated T2DM in HCV infected patients with those uninfected. The random effects model shows that in comparison to patients with no HCV, HCV patients revealed a higher risk of developing
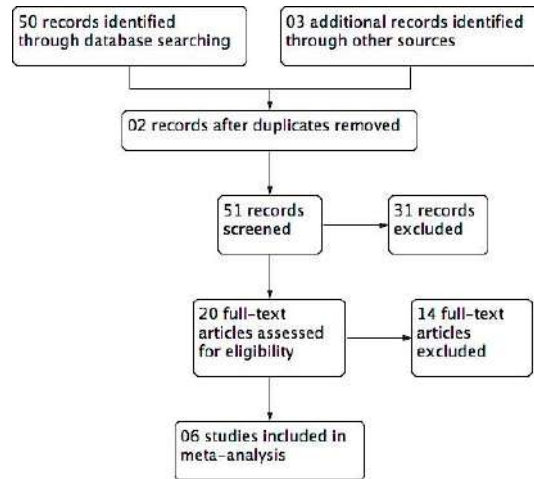

Figure 1. Flowchart of included and excluded studies for this meta-analysis

T2DM (OR 0.01, 95% CI: 0.00-0.06, I2 = 0%; RR 0.01, 95% CI: 0.00-0.07, I2 = 0%). The other 3 studies included (n = 13,710) had evaluated the incidence of HCV infections in patients with T2DM and those with no T2DM (Figure 2 and 3). Similarly, HCV prevalence was high in patients having T2DM (OR 0.7, 95% CI: 0.17-0.42, I2 = 32%; RR 0.30, 95% CI: 0.20-0.46, I2 = 32%) as compare to those with no Type 2 diabetes mellitus. We found 0% heterogeneity in the first case and 32% in the second case. Funnel plots showed minor suggestion of publication bias (Figure 4 and 5).

4. Discussion

This meta-analysis included 6 studies evaluating the association of T2DM and HCV in patients with HCV and T2DM respectively. The remaining article did not clearly meet our inclusion criteria. As all the studies were carried out in Pakistan, a country with less resources and research facilities, therefore the included studies were of moderate quality. However, these data have wide representation and validity of the association of T2DM and HCV in Pakistani population.
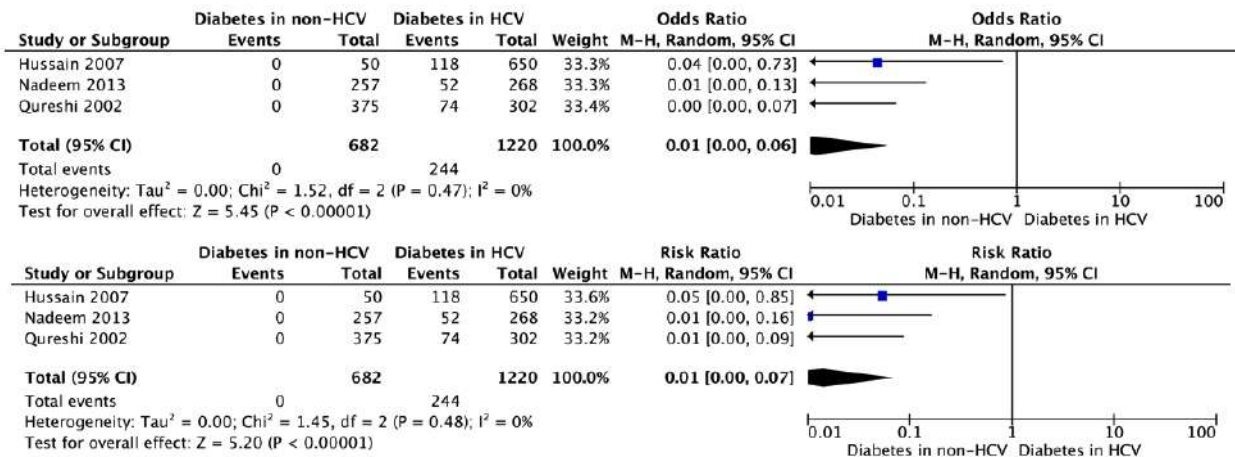

Figure 2. Forest plots comparing diabetes in HCV infected and non-infected subjects using OR (First forest plot) and RR (Second forest plot)
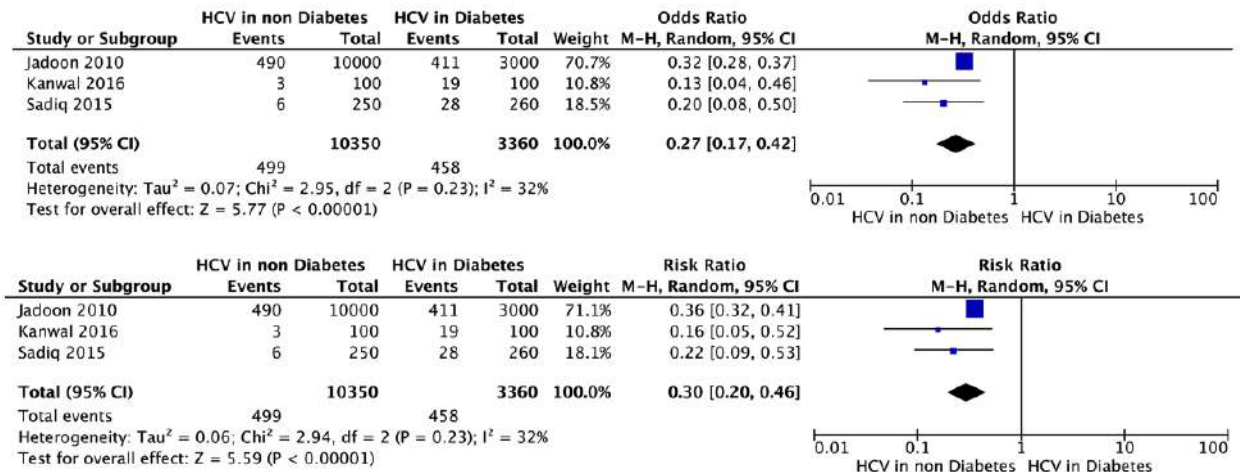
Figure 3.   Forest plots comparing HCV prevalence in diabetic and non-diabetic subjects using OR (First forest plot) and RR (Second forest plot)
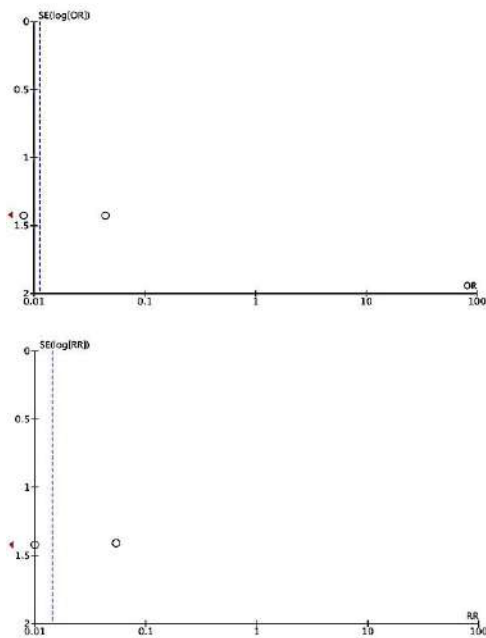

Figure 4.   Funnel plots comparing diabetes in HCV infected and non-infected subjects using OR (First forest plot) and RR (Second forest plot)
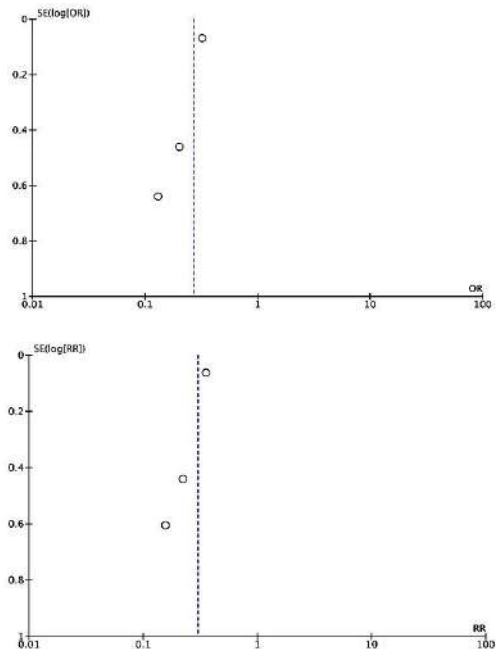

Figure 5.   Funnel plots comparing HCV prevalence in diabetic and non-diabetic subjects using OR (First forest plot) and RR (Second forest plot)

This meta-analysis is the first ever meta-analysis conducted on this subject in Pakistani population. Our data demonstrate that patients with hepatitis C infections are at high threat of developing T2DM (OR 0.01, 95% CI: 0.00-0.06, I2 = 0%; RR 0.01, 95% CI: 0.00-0.07, I2 = 0%). These findings are in accordance with the previously reported studies, carried out in mixed populations of the world. In 2012, Naing carried out a meta-analysis, comprising 31 studies from 16 countries (Naing, 2012). In 17 studies, with a sample size of 286084 individuals, they compared HCV infected patients with those who were uninfected. Their findings revealed HCV infection as a significant risk factor for T2DM (OR: 1.68, 95% CI: 1.15-2.45). In another review, authors have reported significant risk of diabetes in patients

infected with HCV as compared to the controls in potential studies (HR = 1.67, 95% CI: 1.28–2.06) as well as retrospective (OR =1.68, 95% CI: 1.15–2.20) (White *et al.,* 2008). These studies signify that HCV act as an independent risk factor for the onset of T2DM.

HCV and T2DB have a two-way association. There have been reports on the role of insulin resistance and T2DM on the severity of HCV infections. Reduced virological response to anti-viral therapy has also been reported in diabetic patients. Hsu et al. reported a strong relation between severity of fibrosis in HCV infected patients and diabetes (Hsu *et al.,* 2010). Similarly, Hui et al. revealed insulin resistance as a predictor of fibrosis in HCV infected patients (Hui *et al.,* 2002; Hui *et al.,* 2003). A large cohort study,

carried out in Taiwan has also confirmed this association where they observed a 2-3-fold increased risk of cirrhosis in patients who had developed diabetes in HCV infected patients (Huang *et al.,* 2014). According to our results, there is an excess risk of HCV infections in patients with T2DM (OR 0.7, 95% CI*:* 0.17-0.42, I2 = 32%; RR 0.30, 95% CI*:* 0.20-0.46, I2 = 32%). Increased prevalence of HCV in T2DM has been reported by various investigators (Ba-Essa, Mobarak, & Al-Daghri, 2016; Naing, 2012; Ranabir, Laloo, Walke, Bhimo, & Prasad, 2015) which confirm the significance of our results.

Numerous clinical, epidemiological and experimental studies have provided substantial evidences that HCV modulates glucose metabolism, leading to diabetes and insulin resistance. In a study, they obtained liver samples from 42 chronic patients of HCV with 10 samples as control. They found reduced tyrosin phosphorylation and increased expression of IRS-1. Surprisingly, its interaction with downstream effector PI3k, was reduced (Aytug, Reich, Sapiro, Bernstein, & Begum, 2003). Hepatic steatosis is quite prevalent in HCV patients and this may play a part in the progression of diabetes during infection of hepatitis C virus (Mihm, 2010). Various studies have confirmed increased reactive oxygen species (ROS) in mitochondria during hepatitis C infection which may trigger cytokines such as TGF-β, IL-6 and TNFα (Bureau *et al.,* 2001; Gong, Waris, Tanveer, & Siddiqui, 2001; Korenaga *et al.,* 2005). These cytokines, specially TNFα can directly affect the signaling pathway for insulin in patients of hepatitis C (Durante-Mangoni *et al.,* 2006; Elsammak *et al.,* 2005). This has also been reported that HCV stimulates TGF-β which act as a key operator of hepatic fibrogenesis (Goto *et al.,* 2013). All these mechanisms provide key information about the HCV induced T2DM and vice versa.

A study reported an increased prevalence of T2DM in HCV patients, and the achievement of sustained viral response (SVR) led to a decreased incidence of T2DM during the interferon treatment (Drazilova, Gazda, Janicko, & Jarcuska, 2018). Improved insulin resistance has also shown decrease in the development of T2DM (Hum & Jou 2018; Zhang, Cooper, & Doyle, 2020). In this meta-analysis we have evaluated the association between T2DM and HCV, but with some limitations. First, we could not include more than 6 studies in this meta-analysis as very limited literature is available on relevant studies from Pakistan. Secondly, most of the observational studies device the possibility for ascertainment bias. Despite these limitations, our meta-analysis offers several advantages. This is the first meta-analysis performed from Pakistan, a country with over 182 million people. This study provides ample amount of convincing evidence for the two-way association of T2DM and HCV.

5. Summary

In summary, hepatitis C virus infection is a significant risk factor in the progression of type 2 diabetes mellitus in Pakistani population. (OR 0.01, 95% CI*:* 0.00-0.06, I2 = 0%; RR 0.01, 95% CI*:* 0.00-0.07, I2 = 0%)*.* The incidence of HCV is considerably higher in patient with T2DM than in non-diabetic controls. (RR 0.30, 95% CI*:* 0.20-0.46, I2 = 32%; OR 0.7, 95% CI*:* 0.17-0.42, I2 = 32%).

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