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ORIGINAL ARTICLE

New onset diabetes mellitus after liver transplantation and hepatitis C virus infection: meta-analysis of clinical studies

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Summary

New onset diabetes mellitus (NODM) postliver transplantation (LT) is very common and may negatively affect patient and graft survival, but its causative mechanism is still unclear. This study was to analyze the connection between Hepatitis C virus (HCV) infection and NODM after LT by systematically reviewing published medical literature. We electronically searched databases of MEDLINE, EMBASE and the Cochrane Library from January 1980 to January 2008. Only retrospective studies could be identified. Seven of them were subjected to the meta-analysis. Analysis was performed by using REVMAN 4.2 software. We found that HCV increased the prevalence of NODM [OR 2.46; 95%CI (1.44, 4.19)]. Then, we further analyzed the association between HCV and persistent-NODM (P-NODM) after LT. The result showed that prevalence of P-NODM was higher in HCV-positive group than in HCV-negative group with marginally statistical significance [OR = 1.39; 95%CI (1.06, 1.83)]. The present meta-analysis based on retrospective studies suggested a significant relationship between HCV and NODM after LT, and it seems that HCV infection might also increase the prevalence of P-NODM. Multicenter, large sized prospective studies are still needed to further confirm these results.

Introduction

Post-transplantation new onset diabetes mellitus (NODM) is a common complication after solid organ transplantation [1]. Published studies have indicated that NODM, especially persistent NODM (P-NODM), may increase the chance of cardiac events, infection, neurological complications and so on, adversely affecting patient and graft survival [2–4]. Thus, it is necessary to elucidate the mechanism underlies. Many risk factors including age, body mass index (BMI), ethnic origin, impaired fasting glucose before transplantation, immunosuppressive agents and hepatitis C virus (HCV) infection, have been supposed to contribute to the high prevalence of NODM [5,6]. HCV infection as one of few modifiable risk factors has been widely investigated in the last decade. A meta-analysis and several recent clinical studies demonstrated a consistent association of HCV infection with NODM after renal transplantation [7–11]. HCV mainly attacks liver cells after invading into human body, and is one of the leading causes for liver transplantation (LT) [12]. However, the relationship between HCV infection and NODM after LT is undetermined. Some but not all studies indicated that HCV infection was an independent risk factor for NODM after LT [3,13–28]. Most of these studies are of small sample size or from a single clinical center. Therefore, the chief aim of the present study was to analyze the available evidence on the relationship between HCV infection and NODM in liver transplant recipients by performing systematic review and meta-analysis of the medical literature.

Patients and methods

Search strategy and data extraction

We searched published studies via MEDLINE (PubMed and OVID Technologies), EMBASE (EMBASE. com), the Cochrane Library (CD-ROM) respectively, and searched meeting abstracts in ISI proceedings (http://apps.isiknowledge.com) and PapersFirst (http://firstsearch.oclc.org). The keywords 'hepatitis c virus', 'diabetes mellitus', 'liver transplantation' and their synonyms or related terms were used. Instead of manual searches, we used the titles of selected specialty Journals, i.e., 'American Journal of Transplantation', 'Liver Transplantation', 'Transplantation', 'Transplantation Proceedings', 'Hepatology' and 'Journal of Hepatology', combining with Mesh term 'liver transplantation' as search strategy to search all related articles electronically published in the six Journals (PubMed). Reference lists from qualitative topic reviews and published clinical trials were also searched. Our search limited to human studies that were published in the English or Chinese literature. Published times were limited from January 1980 to January 2008. Two authors (Tao Chen and Haiyan Jia) independently scanned the titles or abstracts of every record retrieved. Full articles were retrieved for further assessment if the information given suggested that the study was about the relationship between HCV infection and NODM. Data extraction was conducted by two investigators (Tao Chen and Haiyan Jia) and consensus was achieved for all data. Studies were compared to eliminate duplicated reports for the same patients, which included contact with investigator when necessary. Eligibility and exclusion criteria were prespecified.

Criteria for inclusion

The inclusion criteria were as follows: studies about the relationship between HCV infection and NODM; the recipients' age more than 18 years; and loss to follow-up less than 10%. To be included, the patients enrolled in studies should have no history of pre-LT DM. Studies with a few pre-LT DM patients but fulfilled the inclusion and exclusion criteria, would also be included after eliminating pre-LT DM patients.

Criteria for exclusion

The following were considered as exclusion criteria: information about the number of HCV-positive and -negative patients and the prevalence of NODM in HCV-positive and -negative patients was not provided; diagnostic criteria for NODM did not conform to the definition of NODM according to 2003 International Consensus Guidelines [29]; follow-up time was not described or less than 6 months.

Definition

NODM was defined by the ADA/WHO criteria, which was recommended in the 2003 International consensus guidelines to diagnose diabetes after transplantation [29]. Diagnostic criteria include the following: fasting blood glucose levels ≥126 mg/dl (7.0 mmol/l) on two separate occasions, or/and 2-h postprandial blood glucose ≥200 mg/dl (11.1 mmol/l) on two separate occasions. Alternatively, DM was defined as the requirement of glucose lowering medications (insulin or oral hypoglycemic agents). Assessment of HCV seropositive status was made by serological technology (second- or third-generation enzyme-linked immunoadsorbent assay, ELISA) aimed to detect anti-HCV antibody in serum with or without HCV RNA confirmation. No grant or pharmaceutical company supported this meta-analysis.

Statistical methods

REVMAN 4.2 provided by Cochrane Collaboration was employed for meta-analysis. Odds ratios (OR) were calculated for each principal outcome of dichotomous variables. Ninety-five percent confidence intervals (95% CI) were calculated for all parameters. Heterogeneity between trials was tested by both chi-squared test and I-squared test. If there was no heterogeneity, a fixed effects model was used. If heterogeneity was found, sensitivity analysis was conducted. If the reasons that led to the heterogeneity could not be found by sensitivity analysis, a random effects model was used. Publication bias was examined by using a funnel plot if necessary.

Results

Literature review

Our electronic searches identified 87 reports that were selected for full text review (the complete list of these reports is available on request). Sixty-six papers (75.9%) were excluded because they did not meet the inclusion criteria. Of the left 21 studies, six articles (28.6%) without integrity data about the number of NODM in HCV-positive and -negative patients [19,21,24,27,30,31], seven articles (33.3%) with inaccurate diagnostic criteria for diabetes or/and not describing follow-up time or follow-up less than 6 months [6,13,14,17,18,26,32], and one meeting abstracts (4.8%) without integrity data [25] were also excluded. Seven reports (33.3%) providing information on a total of 2104 unique patients were included in the present meta-analysis. Four of these reports did not

mention the methods used to detect HCV [3,16,20,28]. Given the fact that serological technology for anti-HCV antibody and RT-PCR for HCV RNA were the only two methods to confirm HCV infection and both of them could provide confirmative results, we also included them into our meta-analysis. There was a 100% concordance between reviewers with respect to final inclusion and exclusion of studies reviewed on the basis of the predefined inclusion and exclusion criteria.

Patient characteristics

Some salient demographic and clinical characteristics of subjects enrolled in the included clinical trials are shown in Tables 1–4. All these studies were full papers published in English from 2000 to 2007. One of the studies (14.3%) was from Europe, four (57.1%) from north or south America, two (28.6%) from Asia. As shown in Table 1, there were two case–control trials (28.6%) and five retrospective cohort studies (71.4%). The mean age of subject cohort ranged from 47 to 52.6 years and the gender distribution ranged from 53% to 71.1% male (Table 2). The rate of anti-HCV positive LT recipients was between 17.1% and 45%, and the NODM occurrence ranged between 18.3% and 50.4%.

HCV and NODM

Seven studies [3,15,16,20,22,23,28] provided data about NODM and HCV infections of 1899 liver transplant recipients. Total rate of NODM was 53.7% (337/627) in HCV-positive recipients, and 37.5% (477/1272) in HCV-negative patients. Heterogeneity was found among the seven trials ($\chi^2 = 31.74$, $P < 0.0001$, $I^2 = 81.1\%$). It might be caused by confounding factors such as age, immunosuppressive regimens, follow-up time and so on in each included studies (see detail in discussion part). However, the exact reasons could not be found, so a random effects model was performed. The result showed that there was a significantly statistical difference in the prevalence of NODM between two groups, indicating that HCV infection increased the risk of NODM [OR 2.46, 95%CI (1.44,4.19)] (Fig. 1).

Table 2. Baseline characteristics of studies included in the analysis.

Authors	Age (years)	Male (%)	BMI at LT (kg/m^2)	Caucasian (%)
Saliba F	52.6 ± 9.8	71.1	25.3 ± 4.68	98.6
Parolin MB	NR	62.2	>30 13.4%	90.2
Khalili M	49.2 (18.7–71.3)	54.1	>25 46.6%	82.2
Schmilovitz WH	47.3 ± 10.9	56.0	NR	NR
Baid S	50.1 ± 10.1	60.8	NR	86.7
Kishi Y	47 ± 1	53	22.7 ± 0.1	NR
Moon JI	51.5 (18–77)	66.2	NR	75

NR, not reported.

Table 3. Baseline characteristics of studies included in the analysis.

	Subjects without pre-LT DM		NODM	
Authors	HCV-positive, *n* (%)	HCV-negative, *n* (%)	HCV-positive, *n* (%)	HCV-negative, *n* (%)
Saliba F	36 (17.1)	174 (82.9)	15 (41.7)	33 (18.9)
Parolin MB	29 (35.4)	53 (64.6)	10 (34.5)	5 (9.4)
Khalili M	156 (28.1)	399 (71.9)	62 (39.7)	147 (36.8)
Schmilovitz WH	34 (37.4)	57 (62.6)	16 (47.1)	11 (19.3)
Baid S	39 (28.7)	97 (71.3)	25 (64.1)	27 (27.8)
Kishi Y	51 (24.8)	155 (75.2)	29 (56.9)	42 (27.1)
Moon JI	282 (45.6)	337 (54.4)	180 (63.8)	212 (62.9)
Total	627 (33.0)	1272 (67.0)	337 (53.7)	477 (37.5)

HCV, hepatitis C virus; LT, liver transplantation; NODM, new onset diabetes melli.

There were 205 (9.7%) pre-LT DM patients in four studies who were eliminated from this meta-analysis. Among them, seven (two HCV-positive patients, five HCV-negative patients) were from Schmilovitz's study; 22 (eight HCV-positive patients, 14 HCV-negative patients) from Baid's study; 17 (11 HCV-positive patients, six HCV-negative patients) from Kishi's study; 159 (66 HCV-positive patients, 93 HCV-negative patients) from Moon's study.

Table 1. Baseline characteristics of studies included in the analysis.

Authors	Study design	Reference number	Country	Patients, *n*	Year of publication
Saliba F	Co, retrospective	22	France	210	2007
Parolin MB	Co, retrospective	20	Brazil	82	2004
Khalili M	Co, retrospective	15	America	555	2004
Schmilovitz WH	CC, retrospective	23	Israel	98	2003
Baid S	CC, retrospective	28	America	158	2001
Kishi Y	Co, retrospective	16	Japan	223	2006
Moon JI	Co, retrospective	3	America	778	2006

Co, cohort; CC, case–control.

Table 4. Baseline characteristics of studies included in the analysis.

Authors	NODM definition	T-NODM or P-NODM(n/n)	Time after LT
Saliba F	1,2	5/43	6–24 months
Parolin MB	1,2	NR	≥1 year
Khalili M	2	157/52	1.6–6.8 years
Schmilovitz WH	1,2	NR	>6 months
Baid S	2	NR	>6 months
Kishi Y	2	16/55	>6 months
Moon JI	1	108/284	6–122 months

1, Glycemic threshold; 2, use of glucose-lowering medications; NR, not reported.

HCV and P-NODM

According to some studies [3,15,16,32], a great part of NODM was transient-NODM (T-NODM) that could completely relieve and cease medication. T-NODM might also be associated with HCV infection but its effect on transplanted organ and recipients was not as important as persistent-NODM (P-NODM) [3,4]. To analyze the long-term effect of HCV infection on glucose metabolism after LT, we attempted to collect studies containing detailed data on the incidence of P-NODM and T-NODM in both HCV-positive and -negative patients. Only three studies [3,15,16] provided valuable information. Total rate of P-NODM in the three studies was 33.7% in HCV-positive patients and 21% in HCV-negative patients. Heterogeneity was not found among the three trials ($\chi^2 = 2.07$, $P = 0.36$, $I^2 = 3.2\%$), so a fixed effects model was performed. The result indicated that HCV infection might also increase the risk of P-NODM [OR = 1.39, 95%CI (1.06, 1.83)] (Fig. 2).

Discussion

NODM is a common complication after LT, with a current reported prevalence of 18.3–50.4% [3,15,16,20, 22,23,28]. A part of NODM would gradually relieve after LT, but the incidence of the other part – P-NODM was still high, ranging from 7.8% to 45.9% [3,15,16,32]. NODM, especially P-NODM, could increase the chance of infection, graft loss, and subsequently shorten recipients and grafts survival [3,6]. So it is necessary to identify risk factors, especially modifiable risk factors of NODM.

It is well-known that HCV infection is a major cause of chronic liver disease, affecting ~3% of the world's population [33]. It is widely accepted recently that besides the adverse effects on liver, HCV also affects other organs or

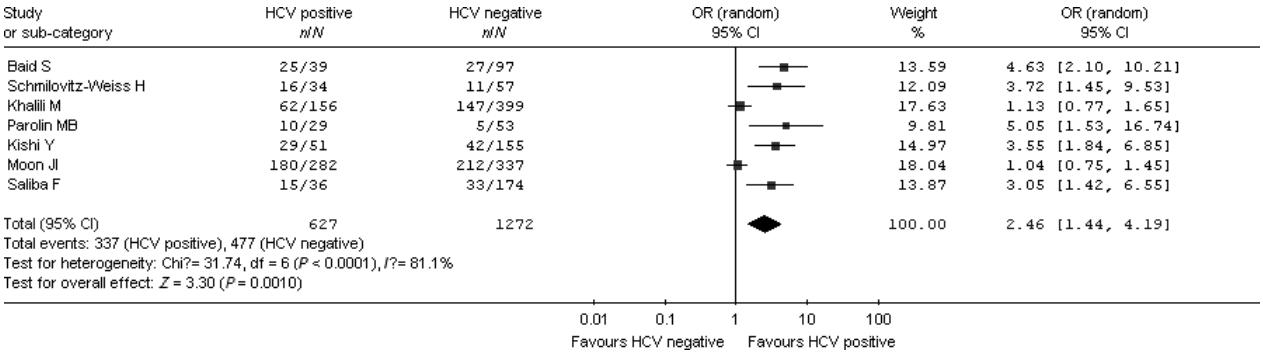

Figure 1 Meta-anlysis result of hepatitis C virus (HCV)'s effect on new onset diabetes mellitus (NODM).

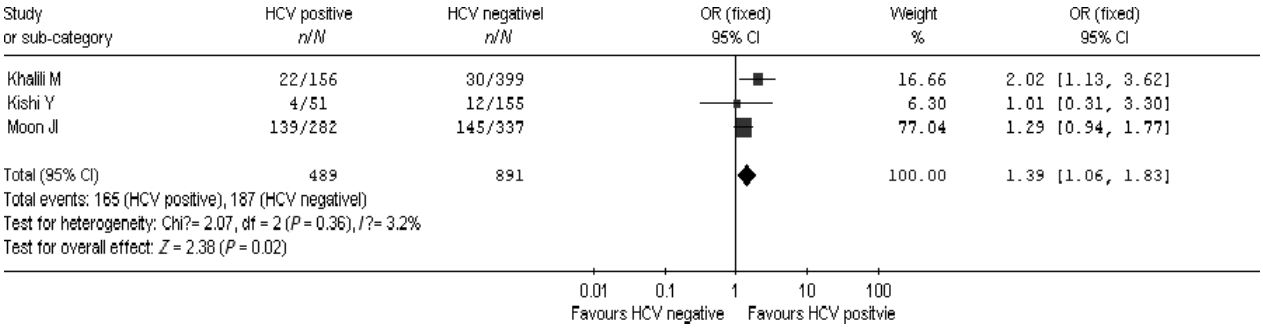

Figure 2 Meta-anlysis result of hepatitis C virus (HCV)'s effect on persistant-new onset diabetes mellitus (P-NODM).

tissues. One of its important extra hepatic manifestations is that it can weaken insulin's ability of lowering hepatic glucose production and of stimulating peripheral tissues' glucose uptake, via iron overload, hepatic steatosis and proinflammatory cytokines, especially TNF-α, eventually leading to glucose metabolism abnormality [34,35,36].

The results of the current study show that HCV infection increased the risk of NODM after LT, and more importantly, could also increase the prevalence of P-NODM. These results are consistent with findings of studies about HCV and other forms of glucose abnormality. For instance, accumulating evidence showed that HCV-infected patients had an increased type-2 diabetes mellitus incidence compared with either subjects with other chronic liver disease or the general population [34]. Similarly, recent studies demonstrated that HCV infection was an important contributor to new onset diabetes after renal transplantation [7]. All of these findings indicated that HCV infection could damage glucose metabolism and trigger diabetes mellitus in different settings. To test this hypothesis, we further searched studies about HCV infection and NODM after other solid organ transplantation, e.g. heart transplantation, and pancreas/kidney transplantation. But no related studies were found. This might result from relatively small number of those kinds of transplantations and relatively low incidence of HCV infection in those kinds of transplants recipients.

Many other factors such as Age, Obesity, African-American origin, use of steroids, and calcineurin inhibitors were also observed to link to NODM, but these observations were not consistent among studies [13–15,19,20,22–28]. One of the possible explanations is that each of these factors might have a minor or modest impact on glucose metabolism after LT, and the risks of NODM could increase when more factors gather in one recipient. Indeed, some of these factors were recognized to be associated with diabetes development among HCV-infected patients. In Thuluvath *et al.*'s study, HCV-infected black people had a higher rate of NODM than white people [26]. Analogous to these findings, two studies showed that in tacrolimus (one kind of commonly used calcineurin inhibitors) treated patients, the incidence of NODM in the HCV-positive patients was higher than in the HCV-negative patients [7,19].

Mortality and morbidity after LT remained high, although newer immunosuppressive regimens have greatly improved patients and grafts survival. Abundant evidence revealed that HCV infection is linked to an increased risk of mortality and morbidity after liver transplantation [37]. What is more, compared with HCV-positive recipients without NODM, there was a significant increase in cumulative mortality in the patients with NODM in HCV-positive patients (14% vs. 56%, $P < 0.01$) [28]. The causes of death were bacterial sepsis, mainly with Gram-negative organisms, and/or opportunistic infections. Antiviral therapy for recurrent hepatitis C in LT is a controversial subject because the currently available therapy, consisting of interferon in combination with ribavirin has serious shortcomings. Up to now, there is lack of evidence to assess the benefit of anti-HCV therapies in LT recipients.

There are some shortcomings in the present meta-analysis. The crucial one is the potential limitation of publication bias. Small sample studies with negative results might not be published. To minimize it, we searched studies as many sources as possible, we firstly searched meeting abstracts about LT through ISI proceedings (http://apps.isiknowledge.com) and PapersFirst (http://firstsearch.oclc.org) from January 1980 to January 2008. One abstract was found and it suggested that HCV had no effects on the incidence of NODM [25]. This abstract involved 549 patients but did not provide detailed information on the number and prevalence of NODM in HCV-positive and -negative patients. Then, we tried to contact the authors of that abstract and other six studies without sufficient information via E-mail. Two of them replied, but the authors failed to supply detailed information. Of the six studies without sufficient information [19,21,24,27,30,31], five (three of them involved the same population) with 921 unique individuals failed to discover a relationship between HCV and NODM [21,24,27,30,31], while another study with 830 subjects showed that HCV infection increased NODM [19]. (More details of these studies are in the appendix.)

Secondly, heterogeneity was found among seven studies when assessing the overall effects of HCV infection on NODM, which might be caused by differences in follow-up time and incidence of T-NODM etc. We firstly performed sensitivity analysis by dividing the seven studies into two subgroups according to follow-up time less or equal and more than a year, but subsequent analysis showed that heterogeneity still existed. Then, we analyzed three of the studies with information on P-NODM, though no statistic significance was found, heterogeneity might still exist for the sake of limited studies number.

Thirdly, the quality of the available trials was not very high. There were no prospective clinical trials. The clinical studies included in this meta-analysis had retrospective and observational design. Most studies were unable to adjust all confounding factors such as age, BMI, race and so on between HCV-positive and -negative groups. Another limitation of these retrospective studies was that the accuracy of the diagnosis of NODM could be influenced by the low reliability of glucose metabolism status pretransplantation, which might not be evaluated as

Appendix. Detailed information of articles about HCV and PT-NODM excluded from the present Meta-analysis.

Author (Published year)	No. of patients (HCV-positive/ negative)	Rate of Pt-NODM (HCV-positive/-negative)	Definition of PT-NODM	Follow-up time
Studies excluded for not providing enough data				
Mirabella S (2005)	830 (328/502)	10.8 (15.5/7.8; $P = 0.001$); HCV increased PT-NODM	2003 international consensus guidelines to diagnose diabetes after transplantation	>10 months
Tueche S.G (2003)	116 (unclear)	26 (unclear) HCV did not affect PT-NODM	ADA	>6 month
Saab S (2006)	253 (113/140)	17.8 (NR/NR, P = 0.19) HCV did not affect PT-NODM	ADA	>6 months
M. Stockman(2002)	552 (NR/NR)	7.2(NR/NR) HCV did not affect PT-NODM	ADA	>12 months
Studies excluded for inaccurate PT-NODM diagnostic criteria OR/AND impropriate follow-up time				
AlDosary A.A (2002)	160 (48/112)	18.8 (37.5/10.7; $P < 0.01$) HCV increase PT-NODM.	Serum random glucose ≥10.0 mmol/l on more than one occasion; requiring specific treatment with either oral hypoglycemic agents or insulin or controlled by diet	>6 month
Soule J.L (2005)	444 (206/238)	32 (40/27; $P < 0.05$) HCV increased PT-NODM	A treated fasting glucose >200 mg/dl; new use of an oral hypoglycemic agent; or new insulin dependence.	>12 months
Knobler H (1997)	47 (13/34)	23 (62/9; $P < 0.001$) HCV increased PT-NODM	FPG 140 mg/dl; random plasma glucose levels were >200 mg/dl or when antidiabetic therapy was required	>12 months
Navasa M (1996)	88 (20/68)	27 (35/25) HCV did not affect PT-NODM	Either requirement of insulin therapy/oral antidiabetic drugs or fasting glucose levels >140 mg/dl on three consecutive occasions	>12 months
Bigam D.L (2000)	233 (99/134)	Not report HCV increase PT-NODM	ADA	3 months
Thuluvath PJ (2003)	247 (78/169)	12.1 (16.7/10.1; P = ns) HCV did not affect PT-NODM	WHO	Not mentioned
C.A. Marroni (1999)	45 (33/12)	22 (24.2/16.7) HCV did not affect PT-NODM	Post-LT DM was defined when two fasting blood glucose values exceeded 140 mg/dl from the seventh day post-LT	>3 months
Meeting abstracts				
A.Tamijmarane1 (2006)	549 (NR/NR)	Not reported HCV did not affect PT-NODM	Not mentioned	Not mentioned

strictly as after transplantation. Fourthly, 'patient-level' data were not available, so it was impossible to perform our own adjustments. Thus, controlled prospective trials are still needed to provide more valuable information.

Conclusion

In summary, this meta-analysis suggest a significant relationship between HCV and DM after LT. HCV infection apparently increases the prevalence of NODM, and could also increase the occurrence of P-NODM. Multicenter large-sized prospective studies are warranted to further evaluate the effects of HCV infection on P-NODM in long-term survivals of LT recipients, and to further investigate the benefits of anti-HCV therapy on incidence of NODM in the HCV-positive recipients.

Authorship

TC: designed research/study, performed research/study, collected data, analyzed data, wrote the paper, reviewed/edited the manuscript. HJ: performed research/study, collected data, analyzed data. JL, XC, HZ: reviewed/edited the manuscript. HT: designed research/study, reviewed/edited the manuscript.

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