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ORIGINAL ARTICLE

The impact of a successful treatment of hepatitis C virus on glyco-metabolic control in diabetic patients: a systematic review and meta-analysis

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Abstract

Aims The effect of HCV eradication following the use of direct-acting antiviral drugs (DAAs) on the glyco-metabolic control is unknown. Through a meta-analysis of available clinical studies, we investigated whether eradication of HCV infection with interferon-free DAAs is associated with improved glyco-metabolic control in diabetic patients.

Methods We searched the PubMed, MEDLINE and Embase, up to 08th June 2018, for all studies evaluating whether eradication of HCV infection with DAAs is associated with changes in glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG) levels from baseline in human subjects, without restrictions for study type and language. Data were independently extracted by two researchers using pre-specified forms. Random effects meta-analyses were conducted on HbA1c and FPG levels before/after HCV eradication.

Results We found a significant mean reduction in HbA1c levels of −0.45% (95% CI −0.60 to −0.30%; $P<0.001$) and in FPG levels of −22.03 mg/dL (95% CI −41.61 to −2.44 mg/dL; $P=0.03$), with high heterogeneity between studies ($\chi^2=20.4$, $P<0.001$, $I^2=80\%$ and $\chi^2=35.8$, $P=0.001$, $I^2=94\%$, respectively). The number of available manuscripts did not allow conducting a meta-regression to elucidate the role of sustained virological response and other confounders in determining the effect of direct-acting antiviral agents on HbA1c reduction.

Conclusions We found a significant improvement in glyco-metabolic control after HCV eradication (in terms of glycated haemoglobin and fasting plasma glucose levels reduction) following direct-acting antiviral treatment in patients with established diabetes, including a consequent positive impact on anti-diabetic therapies.

Keywords Glyco-metabolic control · HbA1c · FPG · Direct-acting antiviral agents · Hepatitis C

Abbreviations

HCV	Hepatitis C virus
SVR	Sustained virological response
HbA1c	Haemoglobin A1c, A1C, glycosylated haemoglobin, glycated haemoglobin, glycol-haemoglobin
DAA	Direct-acting antiviral
IFN	Interferon
NOS	Newcastle–Ottawa Scale
CT	Clinical trial
FPG	Fasting plasma glucose
CI	Confidence interval

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Introduction

Hepatitis C virus (HCV) is a major cause of chronic liver disease, including cirrhosis and cancer. The World Health Organization reported that 170 million people are chronically infected with HCV globally [1]. Epidemiological studies have shown that HCV infection is associated with a higher prevalence of type 2 diabetes, affecting one-third of individuals with chronic HCV infections [2–5]. In turn, type 2 diabetes seems to increase the risk of hepatocellular

carcinoma [6, 7]. Reducing the incidence of diabetes and improving the glyco-metabolic control of diabetic patients with HCV infection are of paramount importance.

The new direct-acting antiviral (DAA)-based eradication of HCV, producing a sustained virological response (SVR) in nearly all cases, is expected to improve liver function and, consequently, normalise an altered glucose profile. Furthermore, it is not possible to exclude a direct or indirect influence of HCV clearance on glucose metabolism, since several studies have shown that HCV impairs glucose metabolism directly via viral proteins and indirectly by altering pro-inflammatory cytokine levels [8–13].

With interferon (IFN)-based therapy, the successful treatment of HCV was low, endocrine benefits were difficult to test also for a negative impact of anti-HCV therapies on metabolism [14, 15], yet clinical trials suggested that successful clearance of HCV could improve insulin resistance and type 2 diabetes [16, 17]. With the DAA-based eradication of HCV and high SVR rates, recent studies suggested that successful clearance of HCV could effectively improve glyco-metabolic control in patients with diabetes, as evidenced by decreased mean haemoglobin A1c (HbA1c) levels [18, 19]. A clinically meaningful tapering of hypoglycaemic therapy in diabetic patients was observed post-SVR [18, 19]. Some studies, however, failed to identify maintained benefits in patients with or without diabetes [20, 21]. The correlation between HCV infection eradication with DAA agents and improved glyco-metabolic control in patients with or without diabetes thus remains unclear. We conducted a systematic review and meta-analysis of relevant studies to assess whether eradication of HCV infection with DAA agents is associated with improved glyco-metabolic control in patients with diabetes.

Methods

In accordance with a published protocol (PROSPERO registration no. CRD42018099700), we performed a systematic review and meta-analysis [22]. Reporting is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines (Supplementary Tables 1 and 2, respectively) [23, 24]. A multidisciplinary panel of experts was formed to determine the review protocol and carry out all aspects of the review.

Data sources and searches

All studies evaluating whether eradication of HCV infection with DAA-based antiviral treatment is associated with improved glyco-metabolic control in patients with diabetes mellitus were searched in the PubMed, MEDLINE, Embase databases with no language and study type restriction, up to 08th June 2018. The search strategy is available in Supplementary Fig. 1.

A hand search of articles from relevant reviews was conducted to identify studies for potential inclusion. Other studies from cross-references were included (see the PRISMA diagram in Fig. 1).

Study selection

All titles and abstracts were assessed independently in duplicate to identify potentially relevant articles. Studies fulfilling the following criteria were included: peer-reviewed studies reporting sufficient data to enable assessment of glyco-metabolic response in HCV patients following HCV eradication with DAA-based antiviral treatment, without study type restriction. We placed no language restrictions, we obtained all articles potentially eligible for inclusion in English. As individuals with undetectable HCV RNA 12-week post-treatment are considered to have a SVR and virological response, we only included studies with data on glyco-metabolic response available at least 12-week post SVR. We excluded studies that included IFN/ribavirin therapy, because of IFN metabolic effects and low SVR rates [14, 25], moreover, ribavirin affects HbA1c [26]. We excluded studies that reported outcomes of interest before and during DAA therapy only and studies that involved patients without diabetes. We excluded conference abstracts. Selected full-texts were reviewed in duplicate independently. Reasons for exclusion of full texts were recorded. Disagreements between reviewers were resolved by consensus and consultation with the expert group.

Data extraction and quality assessment

Data were independently extracted by two researchers (CC and MP) using pre-specified forms. Discrepancies were resolved by consultation. Extracted data included bibliographic reference; year of publication; study type (clinical trial, observational study, case study); study design (randomised double-blind; open-label; cross-sectional; prospective; retrospective); HbA1c and fasting glucose levels before and after DAA-based antiviral treatment; length of post-SVR follow-up; age, as mean and span; male %; HCV genotype; DAA-based antiviral treatment and hypoglycaemic agents; concomitant drugs; concomitant medical conditions; control group (patients untreated or without SVR); number of patients reducing hypoglycaemic drugs. Record management was performed using Microsoft Excel.

Two researchers assessed methodological quality and bias with the Newcastle–Ottawa Scale (NOS) [27]. NOS is a checklist with eight items that outline three quality components: selection, comparability, outcome (Supplementary

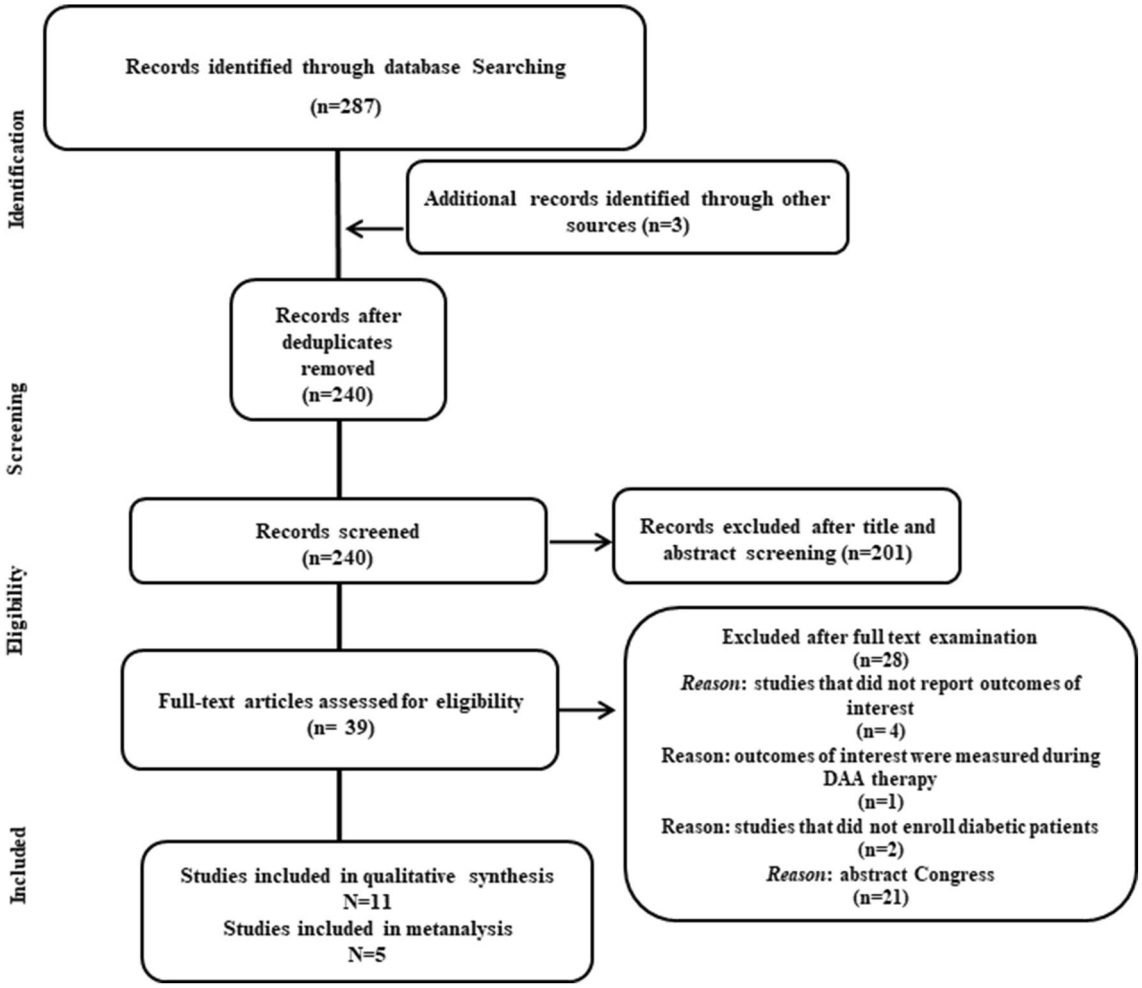

Fig. 1 PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram of process of study selection

Table 3). Each item is scored one or two and summed for a total indicating high (0–4), moderate (5–6), and low (7–9) risk of bias. Any discrepancy was resolved by consultation. Supplementary Table 3 reports the NOS used for this study. For CTs, we used the Downs And Black Checklist [28]. It consists of 27 questions on reporting quality (10 questions), external validity [3], internal validity (bias and confounding, [13], and statistical power [1]. Most scores range from 0 to 1, except one item on the reporting confounders subscale ranging from 0 to 2. The scale has a maximum score of 28; each paper was graded "excellent" (26–28 points), "good" (20–25 points), "fair" (15–19 points) or "poor" (< 14 points).

Data synthesis and analysis

The primary outcome was the glyco-metabolic control after treatment of HCV. Improvement in glyco-metabolic control was assessed by evaluating changes in glycated haemoglobin (also called A1C, haemoglobin A1C, glycol-haemoglobin, or HbA1c) and glucose level after HCV eradication with DAA-based antiviral treatment (post-SVR). The effect on glyco-metabolic control was established by analysing fasting plasma glucose (FPG) level.

The gold standard for determining HCV eradication is to demonstrate persistently undetectable HCV RNA levels after treatment. The SVR is ascertained by an undetectable HCV RNA level using a sensitive assay (typically with a lower limit of 25 IU/mL) at least 12 weeks after completing HCV therapy [29]; individuals with an undetectable HCV RNA level at 12-week post-treatment are considered to have achieved an SVR12 and virological response [29]. Among persons who achieve an SVR12 with DAA therapy, more than 99% achieve an SVR24 [30, 31]. The endpoint of DAAs therapy is to achieve permanent undetectable HCV RNA levels in blood and a complete virological response [32].

Clinical studies on glyco-metabolic control pre- and post-treatment (HbA1c and/or FPG) were used to conduct a meta-analysis on the effects of DAAs therapy. Retrieved HbA1c data were normalized to percentage, with their means and standard deviations; FPG data were already expressed

consistently as mg/dL. We collected for each study: the number of patients with glyco-metabolic data; the percentage of patients with SVR; mean patient age; male patients percentage. Manuscripts reporting incomplete data were excluded from meta-analyses. We calculated changes before–after therapy, in HbA1c and FPG levels, considering the mean differences, reporting 95% confidence intervals (CIs), using the inverse variance method in random effects models. This choice was made to compensate for the high heterogeneity in patient characteristics and study design that we observed. A negative result indicates a decrease of either HbA1c or FPG in its unit of measure; a positive result indicates an increase. Heterogeneity between studies was measured using the I^2 statistic: $P < 0.10$ is considered indicative of statistically significant heterogeneity and an I^2 value of 40% or more is considered indicative of sizeable heterogeneity. Sensitivity analyses were performed: Begg's funnel plots were drawn to show potential risks of publication bias. Egger's tests were used to statistically assess the asymmetry of funnel plots when the number of studies exceeded 3; statistically significant asymmetry was claimed when the intercept reached significance levels ($P < 0.05$) within the regression model SND = intercept + b*precision. Review Manager 5.3 (Copenhagen, the Nordic Cochrane Centre, the Cochrane Collaboration) was used to conduct this meta-analysis.

To elucidate the role of possible confounding variables on meta-analysis results, we attempted to carry out random effects meta-regressions of mean differences (as ln of absolute values of mean differences) against sample size (as inverse variance of mean differences) and one variable in turn among: percentage of patients with SVR, average patient age, average male percentage. Analyses were conducted by SPSS v.22 (IBM, Chicago, USA) with the addition of the MetaReg package.

Results

We screened 287 records for inclusion, 39 articles were reviewed in full (Fig. 1). From 11 full-texts that met inclusion criteria, data were extracted [18–20, 33–40]. Data for meta-analysis were available from five studies with a total of 2750 diabetic HCV patients [18, 19, 33, 36, 39].

Study characteristics

Two studies were open-label trials [36, 40], three prospective observational studies [19, 20, 34], five retrospective observational studies [18, 33, 35, 37, 39] and one case study [38]. Four studies had a control group (untreated or without SVR patients) [18–20, 36]. As reported in Table 1, all studies we included in our analysis were performed recently, between 2016 and 2018. When excluding the only case study we included in our qualitative analysis [38], sample size of patients treated with DAA-based antiviral treatment ranged from 13 to 2435 (in total 3214 HCV patients with diabetes were included in our analysis); the percentage of patients who achieved SVR ranged from 89.5 to 100%. In 72.7% of studies included, SVR was achieved in ≥ 94.5% of enrolled patients. The mean age ranged from 52 to 71 years; patients were mostly male (% sex male range 29.2–97.5), infected with HCV of genotype 1 (a/b) and exposed to SOF-based regimens.

Eleven studies enrolled patients with HCV and diabetes [18–20, 33–40]; in seven studies (63.6%), patients had an established diagnosis of type 2 diabetes [18–20, 33, 36–38]. Two studies included HIV/HCV co-infected patients [20, 37]. Beig included adults transplanted for HCV-related cirrhosis or hepatocellular carcinoma [35], these patients were on 'stable immunosuppression' prior to the new treatment (subjects with steroid cessation for more than three months and no anti-rejection medication dose change for more than three months). The study results are detailed in Table 2. Outcomes included FPG and/or HbA1c, before and after eradication of HCV infection with DAA-based antiviral treatment. In nine studies, FPG and/or HbA1c values referred to subjects with diabetes [18–20, 33, 35–39], while glyco-metabolic changes were available for the total mixed cohort (diabetic and non-diabetic patients) in two studies [34, 40]. All studies included in our analysis reported changes in glyco-metabolic response, i.e., pre-SVR vs. post-SVR values; four studies also reported changes in glyco-metabolic response both in the SVR group and in the non-SVR group in cohorts of type 2 diabetes patients [18–20, 36]. In eight studies, data on the anti-diabetic treatment changes (dosing interruption or lowering, no patients) were available (Table 2). The follow-up period (post-SVR) ranged from 12 weeks to 28.2 months from the end of treatment. In eight studies (72.7%), DAA-based antiviral treatment was associated with an improvement in glyco-metabolic control after successful HCV treatment [18, 19, 33–38].

Improved glyco-metabolic control after successful treatment of HCV

In the study performed by Ciancio [19], baseline FPG and HbA1c levels and anti-diabetic medications were comparable between who achieved SVR (Group 1) and not (Group 2). Diabetic patients with SVR showed a significant decrease of FPG (152.4 ± 56.4 mg/dL vs. 134.3 ± 41.3 mg/dL, $P = 0.002$) and HbA1c (6.9% vs. 6.4%, $P < 0.001$) levels 12-week post-SVR; in the diabetic untreated group, no significant FPG (145.3 ± 30.2 vs. 140.0 ± 47.9 mg/dL, $P = 0.710$) and HbA1c (7.0% vs. 7.2%, $P = 0.780$) variation was evident. Hypoglycaemic agents tapering because of improved glycaemic control was observed exclusively in

Table 1 Description of studies included in the qualitative analysis

Author, year (ref.)	Meta-analysed	Type	Design	Control (patients without SVR)	Subjects	Total no. of patients with diabetes	% of patients with SVR	FPG and/or HbA1c values refer to patients with diabetes	Mean age years; (range)	% Sex: males
Alem 2017 [33]	Yes	OBS	RET	No	HCV; T2DM	65/65 (100%)	100	Yes	56.7	69.2
Beig 2018 [35]	No	OBS	RET	No	HCV; liver transplant patients; DM	38/91 (41.7%)	96	Yes	58; (52–62)	81
Chaudhury 2017 [20]	No	OBS	PRO	Yes	HCV; HIV; T2DM	42/251 (17%)	97.6	Yes	56.3	69
Ciancio 2018 [19]	Yes	OBS	PRO	Yes	HCV; T2DM	122/122 (100%)	91.8	Yes	61.39	70.3
Dawood 2017 [36]	Yes	CT	OL	Yes	CHC; T2DM	400/400 (100%)	94.5	Yes	52.8	46.8
Fabrizio 2017 [37]	No	OBS	RET	No	HIV; HCV; T2DM	59/59 (100%)	NA	Yes	68	67.8
Huang 2017 [40]	No	CT	OL	No	CHC; DM	13/65 (20%) 10/65 pre-DM (15.3%) 1/65 subclinical DM (1.5%)	98.5	No	59.8	29.2
Hum 2017 [18]	Yes	OBS	RET	Yes	HCV; T2DM	2435/2435 (100%)	89.5	Yes	62.2	97.5
Ikeda 2017 [34]	No	OBS	PRO	No	HCV; DM	13/36 (36%)	100	No	71	53
Pashun 2016 [38]	No	CR	–	No	HCV; T2DM	1	100	Yes	52	0
Stine 2017 [39]	Yes	OBS	RET	No	HCV; DM	26/26 (100%)	96.8	Yes	56	76.9

CHC chronic hepatitis C, *CR* case report, *CT* clinical trial, *HCV* hepatitis C virus, *NA* not available, *OBS* observational study, *OL* open-label, *PRO* prospective, *RET* retrospective, *SVR* sustained virological response, *T2DM* type 2 diabetes mellitus

Table 2 Summary of study findings

Author, year (ref.)	Cohort (No of patients treated with DAAs; % SVR)	Follow-up (from EOT)	Group 1 Hb1Ac [B] % (mmol/mol)	Group 1 Hb1Ac [A] % (mmol/mol); *P* value	Group 1 FPG [B] (mg/dL); Mean ± SD	Group 1 FPG [A] (mg/dL) Mean ± SD; *P* value	Group 2Hb1Ac [B] % (mmol/mol)	Group 2 Hb1Ac [A] % (mmol/mol); *P* value	Group 2 FPG [B] (mg/dL) or Mean ± SD	Group 2 FPG [A] (mg/dL) or Mean ± SD; *P* value	Hypoglycaemic agents dosing interruption or lowering (no of patients; %)
Alem 2017 [33]	65; (100)	24 weeks	md. (I.R.): 6.9 (52)	md. (I.R.): 6.4 (46); $P = < 0.001$	md. (I.R.): 113.0	md. (I.R.): 103.0; $P = 0.005$	NA	NA	NA	NA	NA
Ciancio 2017 [19]	G_1:101; (100) G_2:21 without SVR (untreated or relapser)	12 weeks	6.95 (Mean ± SD 52.2 ± 15.4)	6.4 (Mean ± SD 46.5 ± 16.2); $P = < 0.001$	152.4 ± 56.4	134.3 ± 41.3; $P = 0.002$	7 (Mean ± SD 53.4 ± 9.5)	7.2 (Mean ± SD 55.3 ± 20.6); $P = 0.78$	145.3 ± 30.2	140.0 ± 47.9; $P = 0.71$	G_1 = 8 of 19 (42.1%) patients treated by OHA reduced or suspended their therapy and 13 of 46 (28.2%) patients on insulin therapy decreased the dosage or withdrew the treatment
Ikeda 2017 [34]	36; (100)	12 weeks	5.85 (40)	5.65 (38); $P = < 0.01$	NA	NA	NA	NA	NA	NA	3 (25%) patients were able to reduce the dose of diabetes medication
Chaudhury 2017 [20]	G_1:41 with DM; (100) G_2: 199 without DM (100)	28.2 ± 13 months	md.(I.R.) = -0.1 (− 0.8, 0.3)[a]		md.(I.R.) = − 6 (− 43, 25)[a]		md.(I.R.) = 0.0 (− 0.2, 0.2)[a] $P = 0.29$[d]		md.(I.R.) = 0 (− 12, 13)[a] $P = 0.21$[d]		G_1: 7 (3%) patients decreased their diabetes medications
	G_1:241; (100) G_2: 10 without SVR		md.(I.R.) = 0.0 (− 0.2, 0.2)[a]		md.(I.R.) = − 1 (− 14, 14)[a]		md.(I.R.) = − 0.1 (-0.4, 0.2)[a] $P = 0.26$[d]		md.(I.R.) = − 18 (− 33, 1)[a] $P = 0.06$[d]		

Table 2 (continued)

Author, year (ref.)	Cohort (No of patients treated with DAAs; % SVR)	Follow-up (from EOT)	Group 1 Hb1Ac [B] % (mmol/mol)	Group 1 Hb1Ac [A] % (mmol/mol); *P* value	Group 1 FPG [B] (mg/dL); Mean ± SD	Group 1 FPG [A] (mg/dL) Mean ± SD; *P* value	Group 2Hb1Ac [B] % (mmol/mol)	Group 2 Hb1Ac [A] % (mmol/mol); *P* value	Group 2 FPG [B] (mg/dL) or Mean ± SD	Group 2 FPG [A] (mg/dL) or Mean ± SD; *P* value	Hypoglycaemic agents dosing interruption or lowering (no of patients; %)
Dawood 2017 [36]	G_1: 400; (94.5) G_2: 60 untreated	3 months	Mean ± SD 8.1 ± 0.4[c](65)	Mean ± SD 7.3 ± 0.3[c] (56)	184.5 ± 27.9[c]	136.5 ± 22.5[c]	Mean ± SD 8.2 ± 0.4(66)	Mean ± SD 8.3 ± 0.4(67)	178.1 ± 24.3	180.1 ± 26.2	G_1: 78 pts (26.7%) needed to decrease the dose of anti-diabetic treatment; 61 patients needed to decrease the insulin dose and 17 patients needed to decrease the gliclazide dose
Huang 2017 [40]	65; (98.5)	12 weeks	Mean ± SD 5.6 ± 0.6 (38)	Mean ± SD 5.5 ± 0.6 (37); *P* = 0.17	99.1 ± 17	NA	NA	NA	NA	NA	NA
Hum 2017 [18]	G_1: 2,180; (100) G_2: 255 without SVR	from 3 to 15 months	Mean ± SD 7.20 ± 1.5 (55)	Mean ± SD 6.82 ± 1.3 (51); *P* = 0.03	NA	NA	Mean ± SD 7.27 ± 1.6 (56)	Mean ± SD 7.08 ± 1.5 (54)	NA	NA	The proportion of patients receiving treatment with insulin decreased more significantly in patients who achieved SVR (from 41.3 to 38%) than in patients who did not (*P* = 0.04)

Table 2 (continued)

Author, year (ref.)	Cohort (No of patients treated with DAAs; % SVR)	Follow-up (from EOT)	Group 1 Hb1Ac [B] % (mmol/mol)	Group 1 Hb1Ac [A] % (mmol/mol); *P* value	Group 1 FPG [B] (mg/dL); Mean ± SD	Group 1 FPG [A] (mg/dL) Mean ± SD; *P* value	Group 2Hb1Ac [B] % (mmol/mol)	Group 2 Hb1Ac [A] % (mmol/mol); *P* value	Group 2 FPG [B] (mg/dL) or Mean ± SD	Group 2 FPG [A] (mg/dL) or Mean ± SD; *P* value	Hypoglycaemic agents dosing interruption or lowering (no of patients; %)
Beig 2018 [35]	38; (100)	24 and 48 weeks	5.4 (Mean ± SD 35.5 ± 4.3)	5.2 (Mean ± SD 33.3 ± 3.6); *P* = 0.03	122 ± 31	103 ± 20 *P* = 0.01	NA	NA	NA	NA	Of 26 treated with diabetic treatment (24 on insulin alone, 2 on insulin plus OHA), 10 did not maintain on any hypoglycaemic treatment following successful antiviral therapy (38.4% from the baseline)
Fabrizio 2017 [37]	59; (NA)	12 and 24 weeks	NA	NA	154 ± 52	*P* < 0.001[b]	NA	NA	NA	NA	1 patient required an insulin reduction due to hypoglycaemia (1.7%)
Pashun 2016 [38]	1; (100)	15 months	11.9 (107)	5.5 (37)	NA	NA	NA	NA	NA	NA	Her insulin regimen was reduced with continued improvement in HgA1c
Stine 2017 [39]	26; (96.8)	12 weeks	7.36 (57)	7.11 (54); *P* = 0.268	NA	NA	NA	NA	NA	NA	None

[B] before DAA, *[A]* after DAA, *DM* diabetes mellitus, *EOT* end of treatment, *OHA* oral Hypoglycemic agents, *SVR* sustained virological response, *NA* not available, *NS* not significant, *md. (I.R.)* values reported as median (interquartile range)

[a]Delta

[b]The only available data

[c]Improved glycemic control group

[d]*P* values represent between-group comparison in calculated deltas for each variable

patients with SVR. Nine (8.9%) patients had to taper their anti-hyperglycaemic medications compared to 1 (4.8%) of Group 2 ($P=0.34$). Alem also found a significant decline in FPG and HbA1c (from 113.0 mg/dL to 103.0 mg/dL, $P=0.005$ and from 6.9 to 6.4%, $P<0.001$, respectively) at SVR24, in 65 diabetic patients with chronic HCV treated with SOF-based treatment [33]. Subgroup analysis for the changes in FPG and HbA1c values in relation to the type of antihyperglycemic medications showed a significant decline of FPG in patients receiving oral hypoglycaemic agents (116.5 mg/dL vs. 100.0 mg/dL, $P=0.008$) and significant decrease in HbA1c among patients receiving both insulin and oral hypoglycaemic agents (6.7% vs. 6.2%, $P=0.007$ and 7.0% vs. 6.5%, $P=0.001$, respectively).

Dawood, to evaluate the factors associated with improved glyco-metabolic control after DAAs, divided diabetic patients with SVR3 (378 patients, 94.5%) into two groups according to improved (292 patients, 77.2%), and or not (86 patients, 22.8%) glyco-metabolic control [36]. In the improved group, 78 patients (26.7%) tapered antihyperglycemic medications (61 insulin, 17 gliclazide). None of the glyco-metabolically improved patients needed to taper metformin or dipeptidyl peptidase-4 inhibitor. After three months of DAA therapy, the mean FPG reduction in the IGC group was 49.1 mg/dL (from 184.5 ± 27.9 mg/dL to 136.5 ± 22.5 mg/dL); the mean reduction of HbA1c was 0.8% (from 8.1 ± 0.4% to 7.3 ± 0.3%) with a maximum reduction of 1.1% (from 8.7 to 7.6%) observed in one patient. Multivariate logistic regression analysis showed that the family history and duration of type 2 diabetes had a significant influence on improved glycaemic control.

Hum found drops in HbA1c associated with SVR restricted to diabetic patients with a high baseline HbA1c [18]. Among diabetic patients with pre-treatment (12-month) mean HbA1c > 7.2%, the decrease was significantly greater than in the SVR group (8.5 ± 1.2% vs. 7.5 ± 1.3%) as compared with the non-SVR group (8.5 ± 1.2% vs. 7.9 ± 1.6%). Among diabetic patients with pre-treatment HbA1c ≤ 7.2% there was no significant difference based on SVR. The variety and extent of antihyperglycemic medications decreased after DAA treatment, more so in patients who achieved SVR.

Beig assessed the impact of post-transplant DAA therapy, as the proportion of recipients who tapered or withdrew hypoglycaemic treatment at SVR 24/48 [35]. Before antiviral therapy, 26 (41%) patients were on diabetic treatment, of whom 10 (38.4% of antiviral-treated) could withdraw hypoglycaemic treatment. 38 liver transplant recipients were not taking antihyperglycemic medications at the time of antiviral therapy; the mean plasma glucose level in these patients decreased by 20 mg/dL at 24 weeks post-DAA treatment (122 ± 31 mg/dL vs. 103 ± 20 mg/dL, $P=0.01$). Nineteen diabetic patients had paired HbA1c data available before and after DAA treatment; plasma HbA1c levels declined from mean 5.4% at baseline to 5.2% at 44 weeks post SVR ($P=0.03$). Improvements in metabolic control were greater in patients infected with HCV genotype 1 than in those infected with other genotypes [35].

Fabrizio assessed if a significant FPG and HbA1c reduction occurred in their population (59 HCV patients with type 2 diabetes) and was maintained after DAA treatment end [37]. Anti-diabetic treatment was insulin in 16 patients and oral hypoglycaemic agents in 31 patients; two subjects used both, ten were not treated. The reduction was significant at week 4 ($P=0.023$), 8 ($P=0.017$), and at SVR 24 ($P<0.001$). One patient required insulin reduction due to hypoglycaemia. Conversely, four patients experienced a worsened glyco-metabolic control (three during, one after treatment). In patients with no SVR12, FPG levels were unchanged. Pashun observed a significant improvement in diabetic control after successful HCV treatment with DAA therapy in a diabetic 52-year-old morbidly obese woman [38].

A significant improvement in glyco-metabolic control after HCV eradication was also reported by Ikeda [34] in a mixed cohort of patients with and without diabetes. In 36 patients with HCV eradication (13 had a diabetes diagnosis; 36.1%), HbA1c levels (HbA1c values referred to the total cohort) decreased significantly at SVR12 (from 5.8 to 5.5%, $P<0.01$). Among patients with diabetes, six were treated with insulin, six with oral hypoglycaemic agents. One of six patients treated with insulin and two of six patients with oral hypoglycaemic agents taper medications during or after DAA treatment.

Unchanged glyco-metabolic control after successful treatment of HCV

Three studies found no significant improvement in glyco-metabolic control after successful HCV treatment [20, 39, 40]. Of these, two studies enrolled a mixed cohort of diabetic and non-diabetic patients [20, 40]; in one case, FPG and HbA1c values referred to the total mixed cohort [40]. No change in HbA1c was found 12-week post SVR, by Stine among 26 HCV patients with type 2 diabetes, treated with DAAs (from 7.3 to 7.1%, $P=0.268$). In addition, 31% patients required dose escalation or the initiation of insulin therapy [39].

Chaudhury et al. found no significant difference in changes in HbA1c and glucose from baseline to last follow-up between subjects who achieved SVR compared to those who did not (median follow-up 28 months) in a mixed cohort of patients (17% were diabetic) [20]. Of the participants who achieved SVR, no significant difference was observed between diabetic ($n=41$) and non-diabetic ($n=199$) patients with regard to change in HbA1c or random glucose values during follow-up. Of 42 subjects with diabetes, only seven

subjects (3%) decreased their diabetes medications during follow-up.

A mixed cohort of chronic HCV patients with and without diabetes was enrolled in the study performed by Huang et al. [40]. Thirteen (21.7%) patients had DM before recruitment, whilst the diagnosis of subclinical DM, prediabetes, and normoglycemia were 1 (1.7%), 10 (16.7%), and 36 (60%) patients, respectively. HbA1c level (values referred to the total cohort) 12 weeks after the end of treatment was 5.5 ± 0.6%, not significantly different from baseline (5.6 ± 0.6%, $P = 0.17$).

Quality assessment

According to the NOS scale, observational studies included in our analysis were rated at a low risk of bias (scores range 7–9) (Supplementary Table 4). According to the Downs & Black Scale, the quality grade we assigned to open-label trials were: "poor" (≤ 14 points) for Huang [40] (total score: 12) and "fair" (19–15 points) for Dawood [36] (total score: 18). Detailed checklists are in Supplementary Tables 5 and 6.

Meta-analysis

Five studies were suitable for a meta-analysis of the effect of DAA treatment on the glyco-metabolic control indicator HbA1c [18, 19, 33, 36, 39]; we could meta-analyse three studies on the variations of FPG levels attributed to DAA therapy in patients with type 2 diabetes [19, 33, 36]. Selected studies were one open-label trial [36], one prospective observational study [19] and three retrospective observational studies [18, 33, 39]. SVR was reached by all treated patients in only one study [33], while others reported SVR occurring in 89.5 up to 98.5% treated patients. In view of these critical heterogeneities, meta-analyses were conducted with a random effects model.

HbA1c

Regarding variations of HbA1c levels attributed to DAA therapy, we could meta-analyse five studies [18, 19, 33, 36, 39]. Meta-analysis (Fig. 2) showed a mean HbA1c reduction of − 0.45% (95% CI − 0.60 to − 0.30%), $Z = 5.88$, $P < 0.001$; heterogeneity between studies was high, with $\chi^2 = 20.4$, $P < 0.001$, $I^2 = 80\%$. For sensitivity analyses, Begg's funnel plot was drawn (Supplementary Fig. 2), showing no qualitative evidence of asymmetry. Asymmetry was formally assessed by Egger's test, which did not support the presence of a significant asymmetry: the regression model containing precision and intercept did not fit (overall model $P = 0.095$, $R^2 = 0.55$), at variance with the regression model containing only precision (overall model $P = 0.018$, $R^2 = 0.74$), thereby excluding a significant role of the intercept, i.e., asymmetry. To elucidate further the role of SVR and other possible confounders in determining the effect of DAAs on HbA1c reduction, we carried out random effects meta-regressions of mean HbA1c differences against sample size and one possible confounding variable in turn, from: percentage of patients with SVR, average patient age, average male percentage. None of the meta-regressions produced significant models, an event that was expected in view of the limited number of studies available for inclusion.

FPG

Four studies reported on variations of FPG levels attributed to DAA therapy [19, 33, 36] and their meta-analysis (Fig. 3) showed a significant mean reduction in FPG levels of − 22.03 mg/dL (95% CI − 41.61 to − 2.44 mg/dL), $Z = 2.20$, $P = 0.03$, with extreme heterogeneity between studies, $\chi^2 = 35.82$, $P < 0.001$, $I^2 = 94\%$. For sensitivity analyses, Begg's funnel plot was drawn (Supplementary Fig. 3), showing no qualitative evidence of asymmetry. Asymmetry was not formally assessed by Egger's test, due to the insufficient number of studies available.

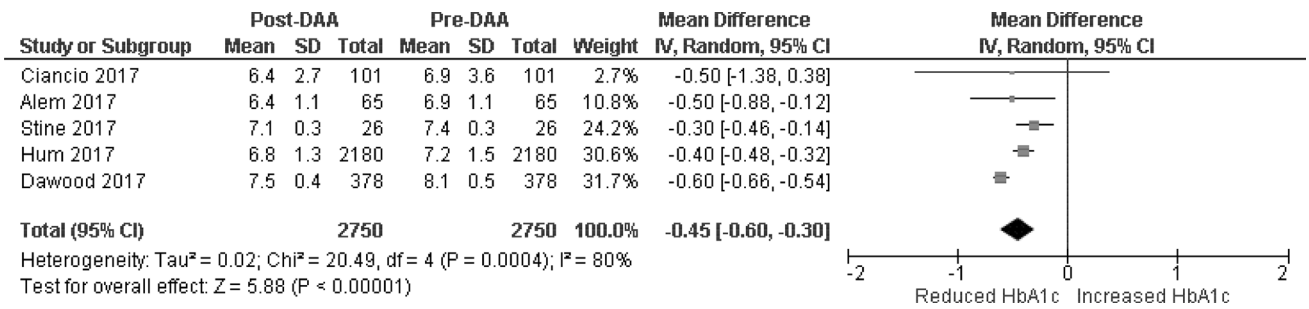

Fig. 2 Forest plot of pre- and post-SVR HbA1c values in diabetic patients

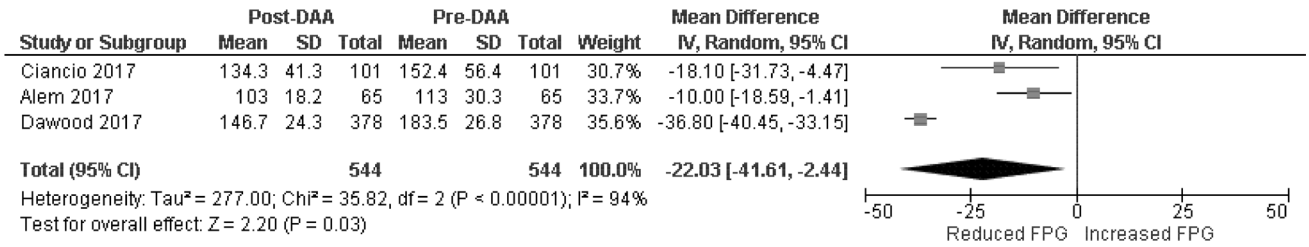

Fig. 3 Forest plot of pre- and post-SVR FPG values in diabetic patients

Discussion

It is unclear whether HCV eradication achieved by interferon-free, DAA regimens results in improvement in glyco-metabolic control of patients with diabetes. This is the first systematic review and meta-analysis quantifying this improvement.

Despite considerable heterogeneity, in 72.7% of studies that met our eligibility criteria, the glyco-metabolic control improved after HCV eradication, in terms of HbA1c and/or FPG levels reduction [18, 19, 33–38]. Five studies used a composite endpoint given by the reduction of FPG and HbA1c, to better evaluate the glyco-metabolic response [19, 20, 33, 35, 36]. In two of these, a significant reduction was detected in HCV patients with type 2 diabetes at 24 weeks [33] and 3 months post-SVR [36]; the long-term follow-up they considered, assured a complete virological response in HCV patients [30–32], suggesting that HCV eradication may have improved glyco-metabolic control.

Three studies reported significant differences between SVR and non-SVR groups (untreated patients or patients who did not achieve SVR) in cohorts of type 2 diabetes patients [18, 19, 36], further supporting the direct role of the HCV eradication for improving glyco-metabolic control. However, as part of a retrospective study, we cannot exclude the possibility that differences between SVR and non-SVR groups in the study performed by Hum et al., might be induced by differences in adherence to antiviral as well as anti-diabetic treatment [18]. Participants without antiviral therapy might have less contact with medical caregivers and therefore might be less motivated to care about their glucose control. While in the remaining studies mentioned above [19, 36], FPG and HbA1c were prospectively assessed both at baseline and > after 12 weeks from the end of therapy in each patient of the two groups, i.e., SVR and untreated patients, thus confirming the reliability of findings [19, 36]. Importantly, SVR induced a clinically significant amelioration of glyco-metabolic control in diabetic HCV patients, also impacting on anti-diabetic therapy (including both insulin and oral hypoglycaemic agents) in seven studies [18, 19, 34–38]. In contrast, no change both in FPG and in HbA1c was found from baseline to at least 12-week post SVR in three studies [20, 39, 40]. These conflicting results may be explained by the study design they used to assess glyco-metabolic response in HCV patients. Stine was able to assess pre- and post-treatment HbA1c values in 26 patients only [39], and in the study performed by Huang (categorised as poor quality study according to the Downs & Black Scale) thirteen (21.7% of the total cohort) patients had diabetes before recruitment, whilst the diagnosis of subclinical diabetes, prediabetes, and normoglycemia were 1 (1.7%), 10 (16.7%), and 36 (60%) patients, respectively, making it difficult to draw reliable conclusions from these studies. In addition, in the study performed by Chaudury, FPG was not uniformly available and the number of participants with diabetes was relatively small [20], which may have limited their ability to detect changes following SVR in this subpopulation, on which other studies have focused [18, 19, 33]. Interestingly, Chaudury failed to identify maintained benefits in glucose or HbA1c in HCV patients post-SVR, however, a medication reduction was detected only among diabetic patients who achieved SVR [20].

The correlation between HCV eradication following DAA-based therapy and improvement in glyco-metabolic control we suggest, is strongly supported by findings previously discussed; the clinical significance of this hypothesis for patients with established diabetes remains unclear, due to the high variety in sample size and type of studies that addressed this issue.

We scrutinized this issue conducting a meta-analysis of the effect of DAA treatment on the glycaemic control indicators HbA1c and FPG in 2750 patients with established diabetes (99% with type 2 diabetes) [18, 19, 33, 36, 39]. We found a significant mean reduction in HbA1c levels of -0.45% and in FPG levels of − 22.03 mg/dL, confirming that a significant improvement in glyco-metabolic control (regardless of the type of DAA used), occurs in patients with established diabetes after HCV eradication. Whether this reduction is of clinical importance is an important issue, since improved glyco-metabolic control may have clinical relevance also in terms of anti-diabetic therapy changes. Although we were unable to conduct a meta-regression on possible confounders, we cannot exclude the possibility that the absolute reductions in HbA1c we detected (0.45%)

might be clinically significant because a clinically meaningful tapering of hypoglycaemic therapy in diabetic patients was observed following the glyco-metabolic improvement post-SVR in most of the studies included in our analysis [18, 19, 34–38]. Effectively, a change of 0.5% (a little higher than we found) in HbA1c is considered a clinically meaningful cutoff point eliciting the advice to change treatment among diabetes care professionals [41]; in line with this, a decrease of HbA1c of at least 0.5% when compared to baseline values was considered a significant improvement on the glycemic state in some studies we included in our analysis [33, 36].

Although additional prospective studies are needed to confirm the association our data suggest that HCV eradication by interferon-free DAA regimens improves the glyco-metabolic control in patients with diabetes, with a consequent positive impact on anti-diabetic therapy.

Limits and strengths

This is the first systematic review examining the impact of HCV eradication following DAAs on glyco-metabolic outcomes assessing the change in post SVR HbA1c and FPG levels from baseline in patients with HCV and diabetes. This is important since improved glyco-metabolic control may have clinical relevance also in terms of anti-diabetic therapy. The small number of studies and the heterogeneity between studies are two important limitations, affecting the consistency of meta-analytical results, which were however significant. It should also be noted that only in six studies a composite end point given by the reduction of FPG and HbA1c was used, while other reports were incomplete. In addition, due to the limited number of studies available for inclusion in meta-analysis, we were unable to conduct meta-regressions to evaluate the possible role of confounding variables.

Conclusion

Despite the heterogeneity across studies, we demonstrated a significant improvement in glyco-metabolic control after HCV eradication, in terms of HbA1c and FPG levels reduction, following DAA treatment in patients with established diabetes and with a positive impact on diabetic therapy. Although larger prospective studies, with a more complete baseline assessment and a prolonged follow-up, are needed to appreciate fully the long-term implications and health outcomes of the endocrine benefits of SVR. These findings serve also to indicate the necessity for a close monitoring of metabolic parameters in diabetic patients receiving DAAs,to guide the tapering of anti-diabetic drugs to avoid hypoglycaemic events.

Author contributions CC and MP conceptualized and designed the study, carried out the data extraction and statistical analyses, drafted the manuscript and the summary tables, revised and approved the final manuscript as submitted. AD and FD contributed to literature extraction and manuscript revision and approved the final manuscript as submitted. MG and CM participated in the conceptualization and design of the study, participated in the analysis of the data, revised the article, and approved the final article as submitted. EC and SR participated in the conceptualization and design of the study, participated in the analysis and interpretation of the data, revised the article, and approved the final article as submitted. PF contributed to concept and design of the study, participated in the analysis and interpretation of the data, coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted. PF is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent For this type of study formal consent is not required.

References

1. World Health Organization. Hepatitis C. Available from: http://www.who.int/mediacentre/factsheets/fs164/en/. Accessed 2 Jun 2018
2. Lecube A, Hernández C, Genescà J, Simó R (2006) Glucose abnormalities in patients with hepatitis C virus infection: epidemiology and pathogenesis. Diabetes Care 29:1140–1149
3. Mason AL, Lau JY, Hoang N, Qian K, Alexander GJ, Xu L et al (1999) Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology 29:328–333
4. Antonelli A, Ferrari SM, Giuggioli D, Di Domenicantonio A, Ruffilli I, Corrado A et al (2014) Hepatitis C virus infection and type 1 and type 2 diabetes mellitus. World J Diabetes 5:586–600
5. Naing C, Mak JW, Ahmed SI, Maung M (2012) Relationship between hepatitis C virus infection and type 2 diabetes mellitus: meta-analysis. World J Gastroenterol 18:1642–1651
6. Lai MS, Hsieh MS, Chiu YH, Chen TH (2006) Type 2 diabetes and hepatocellular carcinoma: a cohort study in high prevalence area of hepatitis virus infection. Hepatology 43:1295–1302
7. Veldt BJ, Chen W, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP et al (2008) Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. Hepatology 47:1856–1862

8. Kawaguchi T, Yoshida T, Harada M, Hisamoto T, Nagao Y, Ide T et al (2004) Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. Am J Pathol 165:1499–1508
9. Parvaiz F, Manzoor S, Iqbal J, Sarkar-Dutta M, Imran M, Waris G (2015) Hepatitis C virus NS5A promotes insulin resistance through IRS-1 serine phosphorylation and increased gluconeogenesis. World J Gastroenterol 21:12361–12369
10. Shi H, Tzameli I, Bjørbaek C, Flier JS (2004) Suppressor of cytokine signaling 3 is a physiological regulator of adipocyte insulin signaling. J Biol Chem 279:34733–34740
11. Basaranoglu M, Basaranoglu G (2011) Pathophysiology of insulin resistance and steatosis in patients with chronic viral hepatitis. World J Gastroenterol 17:4055–4062
12. Parvaiz F, Manzoor S, Tariq H, Javed F, Fatima K, Qadri I (2011) Hepatitis C virus infection: molecular pathways to insulin resistance. Virol J 18:474
13. Lecube A, Hernández C, Genescà J, Simó R (2006) Proinflammatory cytokines, insulin resistance, and insulin secretion in chronic hepatitis C patients: a case-control study. Diabetes Care 29:1096–1101
14. Romero-Gómez M, Del Mar Viloria M, Andrade RJ, Salmerón J, Diago M, Fernández-Rodríguez CM et al (2005) Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. Gastroenterology 128:636–641
15. Poustchi H, Negro F, Hui J, Cua IH, Brandt LR, Kench JG et al (2008) Insulin resistance and response to therapy in patients infected with chronic hepatitis C virus genotypes 2 and 3. J Hepatol 48:28–34
16. Simó R, Lecube A, Genescà J, Esteban JI, Hernández C (2006) Sustained virological response correlates with reduction in the incidence of glucose abnormalities in patients with chronic hepatitis C virus infection. Diabetes Care 29:2462–2466
17. Delgado-Borrego A, Jordan SH, Negre B, Healey D, Lin W, Kamegaya Y (2010) Reduction of insulin resistance with effective clearance of hepatitis C infection: results from the HALT-C trial. Clin Gastroenterol Hepatol 8:458–462
18. Hum J, Jou JH, Green PK, Berry K, Lundblad J, Hettinger BD (2017) Improvement in glycemic control of type 2 diabetes after successful treatmen of hepatitis C virus. Diabetes Care 40:1173–1180
19. Ciancio A, Bosio R, Bo S, Pellegrini M, Sacco M, Vogliotti E et al (2018) Significant improvement of glycemic control in diabetic patients with HCV infection responding to direct-acting antiviral agents. J Med Virol 90:320–327
20. Chaudhury CS, Sheehan J, Chairez C, Akoth E, Gross C, Silk R et al (2017) No improvement in hemoglobin A1c following hepatitis C viral clearance in patients with and without HIV. J Infect Dis 217:47–50
21. Carvalho JR, Velosa J, Serejo F (2018) Lipids, glucose and iron metabolic alterations in chronic hepatitis C after viral eradication-comparison of the new direct-acting antiviral agents with the old regimens. Scand J Gastroenterol 20:1–7
22. Prospero international prospective register of systematic reviews. Available from: https://www.crd.york.ac.uk/PROSPERO/. Accessed 2 Jun 2018
23. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151:264–269
24. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283:2008–2012
25. Greenberg PD, Rosman AS, Eldeiry LS, Naqvi Z, Bräu N (2006) Decline in haemoglobin A1c values in diabetic patients receiving interferon-alpha and ribavirin for chronic hepatitis C. J Viral Hepat 13:613–617
26. Unnikrishnan R, Anjana RM, Mohan V (2012) Drugs affecting HbA1c levels. Indian J Endocrinol Metab 16:528–531
27. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 2 Jun 2018
28. Downs SH, Black N (1998) The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 52:377–384
29. AASLD-IDSA Recommendations for testing, management, and treating hepatitis C. Monitoring patients who are starting hepatitis C treatment, are on treatment, or have completed therapy. Available from https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCVGuidance_May_24_2018a.pdf. Accessed 2 Jun 2018
30. Burgess SV, Hussaini T, Yoshida EM (2016) Concordance of sustained virological response at weeks 4, 12 and 24 post-treatment of hepatitis c in the era of new oral direct-acting antivirals: A concise review. Ann Hepatol 15:154–159
31. Martinot-Peignoux M, Stern C, Maylin S, Ripault MP, Boyer N, Leclere L et al (2010) Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virological response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. Hepatology 51:1122–1126
32. European Association for the Study of the Liver (2017) EASL recommendations on treatment of hepatitis C 2016. J Hepatol 66:153–194
33. Abdel Alem S, Elsharkawy A, Fouad R, Adel E, Abdellatif Z, Musa S et al (2017) Improvement of glycemic state among responders to sofosbuvir-based treatment regimens: single center experience. J Med Virol 89:2181–2187
34. Ikeda A, Ikeda K, Takai A, Takahashi K, Ueda Y, Marusawa H et al (2017) Hepatitis C treatment with sofosbuvir and ledipasvir accompanied by immediate improvement in hemoglobin A1c. Digestion 96:228–230
35. Beig J, Orr D, Harrison B, Gane E (2018) HCV eradication with new IFN free treatment improves metabolic profile in HCV-related liver transplant recipients. Liver Transpl. https://doi.org/10.1002/lt.25060
36. Dawood AA, Nooh MZ, Elgamal AA (2017) Factors associated with improved glycemic control by direct-acting antiviral agent treatment in Egyptian type 2 diabetes mellitus patients with chronic hepatitis C genotype 4. Diabetes Metab J 41:316–321
37. Fabrizio C, Procopio A, Scudeller L, Dell'Acqua R, Bruno G, Milano E (2017) HCV and diabetes: towards a 'sustained' glycaemic improvement after treatment with DAAs? Clin Microbiol Infect 23:342–343
38. Pashun RA, Shen NT, Jesudian A (2016) Markedly improved glycemic control in poorly controlled type 2 diabetes following direct acting antiviral treatment of genotype 1 hepatitis C. Case Rep Hepatol. 2016:7807921
39. Stine JG. Wynter JA, Niccum B, Kelly V, Caldwell SH, Shah NL (2017) Effect of treatment with direct acting antiviral on glycemic control in patients with diabetes mellitus and chronic hepatitis C. Ann Hepatol 16:215–220
40. Huang JF, Huang CF, Yeh ML, Dai CY, Hsieh MH, Yang JF et al (2017) The outcomes of glucose abnormalities in chronic hepatitis C patients receiving interferon-free direct antiviral agents. J Med Sci 33:567–571
41. Lenters-Westra E, Schindhelm RK, Bilo HJ, Groenier KH, Slingerland RJ (2014) Differences in interpretation of haemoglobin A1c values among diabetes care professionals. Neth J Med 72:462–466

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