Abstract

Background and aims: The type 2 diabetes mellitus (T2DM) is a common comorbidity of chronic hepatitis C (CHC). This study intended to investigate the impact of direct-acting antiviral agents (DAAs)-induced sustained virological response (SVR) on glycometabolism in CHC patients with T2DM.

Methods: We searched PubMed, Scopus, Web of Science, and Embase up to July 7th, 2021. Studies reporting the association between DAA-induced SVR and glycometabolism in diabetic patients were retained. Changes in glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) levels before DAA treatment and after SVR were conducted meta-analyses with random-effects models.

Results: 1371 potentially relevant articles were screened. Our analysis included 16 studies with data for 5024 patients. A significant improvement was noted in glycemic control in SVR group, with a mean HbA1c reduction of 0.57% (95% CI: 0.46–0.69%; I^2=72.8%) and FPG reduction of 22.28mg/dL (95% CI: 13.35–31.21mg/dL; I^2=96.18%). Conversely, changes of HbA1c in non-SVR group were a mean increase of 0.03% (95% CI: -0.15–0.22%; I^2=68.75%). Subgroup analyses about HbA1c and FPG classified by study type both showed decline of the two indicators after SVR, and especially a reduction of HbA1c, 0.52% (95% CI: 0.39–0.65%; I^2=73.5%) in retrospective study subgroup and 0.70% (95% CI: 0.54–0.87%; I^2=36.15%) in prospective study subgroup, indicating lower heterogeneity in prospective studies. Egger's test suggested publication bias in impact of DAAs on FPG, and no

publication bias in impact on HbA1c. Sensitivity analyses confirmed robustness of the results.

Conclusion: The glyco-metabolic control improved in terms of HbA1c and FPG level after DAA-induced SVR. However, further large and well-designed prospective cohort studies are still warranted and a prolonged follow-up is needed.

Keywords: hepatitis C; diabetes mellitus; glyco-metabolic control; direct-acting antiviral; HbA1c; FPG.

1. What's already known about this topic?

DAAs have replaced IFN-based therapy as the standard anti-HCV therapy. However, the impact of DAA-induced SVR on glyco-metabolic control in HCV diabetic patients is controversial.

2. What does this article add?

We found that after DAA-induced SVR, the glyco-metabolic control in HCV diabetic patients improved in terms of HbA1c and FPG. This will necessitate monitoring of glyco-metabolic parameters in related patients to avoid hypoglycemia, and will reduce the patients' physical and ecnomic burden about T2DM.

1. Introduction

Hepatitis C virus (HCV) infection affects 170 million individuals worldwide, and it represents a major cause of liver cirrhosis and hepatocellular carcinoma (HCC) [1]. Chronic HCV infection not only increases the risk of developing type 2 diabetes mellitus (T2DM) in patients at high risk for metabolic syndrome, but also worsens the glycemic control in patients with established T2DM [2, 3]. On the contrary, the presence of T2DM or hyperglycemia is also significantly associated with an increased risk of HCC. The complex interaction between chronic HCV infection and T2DM, as well as their effects on the prognosis of patients, raises the importance of glycol-metabolic control in diabetic patients with HCV infection.

With a higher sustained virological response (SVR) rate of more than 90% [4], a short-duration and minimal side effects, the new direct-acting antiviral agents (DAAs) have replaced the interferon (IFN)-based therapy as the standard anti-HCV therapy. Previous IFN-based studies suggested that the clearance of HCV leads to an improvement in insulin resistance (IR) and a two-thirds decrease in the risk of T2DM development [5-7]. If DAAs can further improve the glycemic control of diabetic HCV patients, this will reduce the burden of patients, either physical or economic burden, and reduce the complications then prolong their lives. Recently, an increasing number of studies investigated the association between glycemic control and clearance of HCV with DAAs. Several studies [8-22] have shown that eradication of HCV infection with DAAs significantly improves the levels of glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG), while other studies [23-26] failed to find any significant improvement in glyco-metabolic control among patients achieving SVR after treatment with DAAs. Therefore, the link between glycemic control and DAAs therapy is yet to be identified. Herein, we performed a systematic review and

meta-analysis of relevant studies to investigate whether eradication of HCV infection with DAAs could improve the glycemic control in diabetic patients.

2. Methods

A systematic review and meta-analysis of the literature were conducted in accordance with the published protocol (PROSPERO registration no. CRD42021225239). Reporting is in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. We also followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for the meta-analysis of included studies [28]. Two investigators independently screened the abstracts, followed by data extraction and assessment of risk of bias. Any selection discrepancies were resolved by a third investigator.

2.1 Data sources and searches

We conducted a literature search of PubMed, Scopus, Embase and Web of Science up to July 7th, 2021, for relevant publications with no study type restriction. Publications describing whether eradication of HCV infection with DAA treatment is associated with improved glyco-metabolic control in patients with diabetes were retained. Search terms were “HCV” OR “hepatitis C” AND (“direct-acting antiviral” OR “direct antiviral agent” OR “DAA”) AND (“diabetic” OR “diabetes” OR “DM”). The detailed search strategy is illustrated in **Table S1**.

2.2 Study selection

All the abstracts identified in the literature search were scanned, and those of potential

interest were selected for full-text review. We included publications wherein participants were diabetic patients with HCV infection who achieved SVR after receiving DAA-based antiviral therapy. Patients with undetectable HCV RNA at 12 weeks post-treatment were considered to achieve an SVR [4]. We included studies with available data on glyco-metabolic status before and after DAA treatment (at least 12 weeks from the end of therapy). The studies were excluded that involved only non-diabetic individuals and HCV-related liver transplant recipients. Also, studies that only reported outcomes of interest before and during DAA therapy, studies wherein participants received IFN therapy, and case reports were excluded. Finally, 16 studies were included in the meta-analysis (**Fig. 1**).

2.3 Data extraction

Data were extracted by two investigators independently. Data extraction included the name of first author, publication year, country or region, study type, sample size, SVR rate, age, male %, time of follow-up (from the end of therapy), HbA1c and FPG values before DAA therapy and after SVR, control group (patients untreated or without SVR), dosing interruption or lowering of hypoglycemic agents. The data were recorded in Microsoft Word and Excel using pre-specified forms.

2.4 Quality assessment

Quality assessment was based on the Newcastle–Ottawa scale (NOS). The NOS was developed to assess the quality of observational studies based on their design, content and usability. A “star system” has been proposed, wherein a study is assessed in three domains: selection (maximum four stars), comparability (maximum two stars), and

exposure/outcome (maximum three stars). We judged the studies with a score of at least seven stars as high quality, indicating that these studies were at low risk of bias.

2.5 Data synthesis and statistical analysis

The outcome was defined as improved glyco-metabolic control after SVR by DAAs, which was evaluated by changes in HbA1c and FPG. Control group (non-SVR group) was patients untreated or without SVR in the same studies, and changes in HbA1c and FPG levels were also be calculated.

As mentioned above, the SVR is ascertained by an undetectable HCV RNA level at least 12 weeks after completing the antiviral therapy. Studies [29, 30] have shown more than 99% patients who achieve an SVR12 with DAA therapy might achieve SVR24.

The two parameters (HbA1c and/or FPG) pre- and post-SVR in SVR group and the changes of HbA1c/FPG levels in non-SVR group in clinical studies were used to conduct meta-analysis on the effects of DAA therapy. In these studies included in the meta-analysis, HbA1c is expressed in National Glycohemoglobin Standardization Program (NGSP) units (%) or International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (mmol/mol). The HbA1c values expressed in IFCC units were converted to in NGSP units by the formula: *NGSP-HbA1c(%)=0.0915IFCC-HbA1c(mmol/mol) ＋2.152,* with means and standard deviation (SD). Similarly, the FPG data were normalized to mg/dL, and some data expressed in mmol/L was converted by the formula: *mg/dL=mmol/L×18.*

Pre- and post-DAA therapy changes in HbA1c and FPG levels were calculated using a random-effects model where any differences between studies were considered

even if no statistically significant heterogeneity was noted. Changes of HbA1c and FPG in control group were also calculated using the same method. Statistical heterogeneity was assessed using the inconsistency index (I^2), with I^2 values over 50% indicating substantial heterogeneity. Subgroup analyses were performed to explore the potential sources of heterogeneity, and sensitivity analyses were conducted to further confirm the robustness of the results. Publication bias was evaluated with Egger's tests.

All statistical tests were two-sided, and $p<0.05$ was considered significant. Statistical analyses were conducted using the Stata version 16.0 software program (Stata Corp LP in College Station, TX).

3. Results

3.1 Literature search and characteristics of included studies

Fig. 1 showed the results of literature search and study selection. Searches of Pubmed, Scopus, Embase, and Web of Science yielded 1371 citations. After excluding duplicates and examining the abstracts and full texts, we initially identified 16 relevant studies.

This meta-analysis included 16 eligible studies involving 5024 subjects with more than 12-week follow-up after the end of DAA therapy. Among these studies, 1 were conducted in Japan, 4 in Italy, 5 in the USA, and 6 in Egypt; the mean age was 60.01 years (range: 41–91 years, except for 2 studies data unavailable), and the mean proportion of male sex was 80.94% (range: 44.1–97.5%, except for 4 studies data unavailable). The SVR rate in these studies varied, ranging from 86% to 100%. Details of the 16 studies are summarized in **Table 1**.

3.2 Risk of bias assessment

Sixteen studies included in the meta-analysis received seven to nine stars on the NOS, suggesting a low risk of bias. The details of the quality of bias assessment are shown in **Table S2**.

3.3 Association between glyco-metabolic control and DAA-induced SVR.

A total of 16 studies reported data on the association between DAA-induced SVR and HbA1c (n=15) or FPG (n=10), and in non-SVR group HbA1c (n=5) and FPG (n=2) were also analyzed. Meta-analyses were performed using a random-effects model. **Fig. 2** displays the pooled results from 15 studies, suggesting that DAA-induced SVR is significantly associated with a mean HbA1c reduction of 0.57% (95% CI: 0.46–0.69%; I^2=72.8%; p=0.00). **Fig. 3** displays the estimated results from 10 studies, indicating that DAA-induced SVR is significantly associated with a mean FPG reduction of 22.28mg/dL (95% CI: 13.35–31.21mg/dL; I^2=96.18%; p=0.00). Conversely, the pooled results of HbA1c from 5 studies in non-SVR group were increase of 0.03% (95% CI: -0.15–0.22%; I^2=68.75%; p=0.74) (see **Fig. 4**). The FPG levels in non-SVR group [8, 10] did not show significant changes. As the limited data (n=2), we could not conduct a meta-analysis on FPG levels in control group.

3.4 Subgroup/sensitivity analysis

To explore potential sources of heterogeneity across the included studies， we conducted subgroup analyses according to the study type. First, when the comparison

on HbA1c was stratified by different study types of retrospective and prospective studies (**Fig. 5**), 10 retrospective studies and 5 prospective studies were retrieved. Subgroup analysis showed that the reductions of HbA1c were 0.52% (95% CI: 0.39–0.65%; I^2=73.5%; p=0.00) in retrospective study subgroup and 0.70% (95% CI: 0.54–0.87%; I^2=36.15%; p=0.18) in prospective study subgroup. In the subgroup analysis, the heterogeneity was lower in prospective studies (I^2 =36.15%) than that in retrospective studies (I^2 =73.5%), indicating that additional prospective studies are needed for high-quality evidence. Second, regarding another indicator, FPG, we also conducted a subgroup analysis according to the study type (**Fig. 6**). 6 retrospective studies and 4 prospective studies were identified. The two subgroups both observed a decline in FPG [18.07 mg/dL (95% CI: 7.57–28.57 mg/dL; I^2 =93.94%; p=0.00) in retrospective studies and 33.75 mg/dL (95%CI: 8.43–59.06 mg/dL; I^2 =95.78%; p=0.00) in prospective studies]. P=0.00 indicated that the decrease in FPG in both subgroups was statistically significant, while the heterogeneity in both subgroups was high (both I^2 >50%).

To confirm the robustness of the results, we also conducted a sensitivity analysis. The sequential elimination of each of the included studies did not have a significant impact on the association between DAA-induced SVR and the glycemic control, as reflected by the decline in either HbA1c (**Fig. 7**) or FPG (**Fig. 8**), also had no significant impact on the changes of HbA1c in non-SVR group (**Fig. 9**), showing the robustness of the meta-analysis results.

3.5 Publication bias.

Egger's tests suggested publication bias existing in the studies included about FPG

changes (Prob > |z| = 0.0242), but no publication bias about HbA1c reduction in SVR patients (Prob > |z| = 0.9614). We did not conduct Egger's test in non-SVR group due to the insufficient number of studies available (n=5).

4. Discussion

The effect of HCV eradication with DAAs on glycometabolism in diabetic patients is yet unknown. Most of previous studies involved few cases, which was unreliable to draw a definite conclusion. Although a meta-analysis carried out by Carnovale et al. [31] in 2018 suggested glycemic improvement after HCV eradication with DAAs, data were limited in HbA1c (n=5) and FPG (n=3) levels in SVR patients. Recently, an increasing number of related studies were published. To further evaluate the impact of DAA-induced SVR on glyco-metabolic control, we performed this updated meta-analysis including not only SVR patients but also non-SVR patients as control group.

Data on 5024 individuals from 16 cohort studies [8-10, 13, 14, 19-21, 23, 32-38] were available in this meta-analysis. Our meta-analysis provides evidence suggesting the association between the glyco-metabolic control and HCV eradication by DAAs in diabetic patients, and quantified the improvement in HbA1c and FPG levels, a mean reduction in HbA1c (0.57%) and FPG (22.28 mg/dL) levels. Conversely, the pooled results of HbA1c changes in non-SVR group was a mean increase of 0.03%. Typically, a composite endpoint due to a decrease in HbA1c (minimum 0.5%) [39, 40] or FPG (minimum 20 mg/dL) is considered as improvement in glycemic control, as reported previously [9, 41]. Since the changes in both the indicators in DAA-induced SVR group

were above these criteria in our meta-analysis, glycemic control was considered improved. Data of control group further demonstrated the impact of DAAs on glyco-metabolic control. Besides, seven studies [8, 10, 14, 20, 21, 23, 32] showed a decrease in the level of antidiabetic agents, either the dosage or the kind of medicine. These findings provided more positive evidence for our results.

The mechanisms responsible for the improvement in the glyco-metabolic control in HCV diabetic patients has not been completely clarified. A possible explanation could be that HCV can interfere with insulin signaling and promote IR [42, 43], which plays a key role in the development of T2DM. Recent studies [44, 45] reported the role of viral replication in inducing a novel apoptosis-like death of pancreatic beta-cells, and suggested the role of HCV replication in upregulation of several hepatokines known to decrease peripheral insulin sensitivity. Thus, rapid suppression of HCV replication and concomitant systemic inflammation leads to improvement of IR and restores glucose homeostasis.

During explaining the results of our meta-analysis, several possible limitations need to be taken into account in order to reinforce the conclusion. First, significant heterogeneities were noted when analyzing the HbA1c and FPG changes. The subgroup analysis revealed that the heterogeneity about HbA1c change in prospective studies was low, indicating the presence of other confounding factors in retrospective studies. Besides, data of the two indicators were acquired after SVR12, however, the exact time of post-SVR was different. Most studies followed up for 12 weeks after the end of therapy, while other studies followed up for 24 weeks [9] even 120weeks[21]; these different follow-up periods may contribute to the heterogeneity. Sensitivity analyses conducted by sequentially omitting each study did not alter the findings, suggesting

the robustness of the results. It is worth mentioning that most related studies observed the short-dated impact of DAA-induced SVR on glyco-metabolic control, only Cacciola et al. [21] and Ciancio et al.[22] followed the long-term effect. Future over time follow-up studies are needed to confirm our findings, to determine how durable the DAA-induced SVR associated improvement in glyco-metabolic control is, and to assess the long-term effects on the complications of diabetes such as nephropathy, neuropathy, and cardiovascular disease. Second, publication bias existed in the studies included about FPG changes in SVR patients. The results should be treated cautiously because of the false-positivity that publication bias might lead to. Third， the unmeasured confounding factors, such as changes in lifestyle habits, diet, and concomitant medications, may have contributed to a decrease in HbA1c and FPG in the studies. Hence, exact studies excluding the confounding factors are also required.

However, as discussed above, this meta-analysis showed the positive effect of DAAs on the glyco-metabolic control in diabetic HCV patients, which might reduce the complications of diabetes and thus prolong their lives. These endocrine benefits of DAA-induced SVR will urge doctors to focus on the antiviral therapy of HCV diabetic patients by DAAs, and to lay more emphasis on the lessening of hypoglycemic agents to decrease the risk of hypoglycemia.

5. Conclusion

This meta-analysis provides evidence for the positive impact of SVR achieved by DAAs on the glyco-metabolic control in diabetic HCV patients. We found that after DAA-induced SVR, the glyco-metabolic control improved in terms of HbA1c and FPG levels. Further large and well-designed prospective cohort studies are still

warranted and a prolonged follow-up is needed. These findings serve to pay more attention to the DAAs antiviral therapy for diabetic HCV patients, necessitating monitoring of glyco-metabolic parameters in diabetic HCV patients receiving DAA-based therapy to adjust the dosage of hypoglycemic agents in a timely manner.

Acknowledgements

This study was not supported by any grants.

Conflict of interest

The authors have declared no conflict of interest.

Author contributions

Bing Li, Rui Tian, and Shaoyou Qin designed the study. Bing Li wrote the manuscript. Qian Wang and Xiaoli Li searched the databases, and performed the selection of studies. Qinglei Zeng, Hongyi Li and Shengnan Yang conducted data analysis and interpretation. Rui Tian and Shaoyou Qin approved the final version and should be regarded as co-corresponding authors.

References:

1. Wei, L. and A. Lok, Impact of new hepatitis C treatments in different regions of the world. Gastroenterology, 2014. 146(5): 1145-50.e1-4.
2. Naing, C., J. Mak, S. Ahmed, et al., *Relationship between hepatitis C virus infection and type 2 diabetes mellitus: meta-analysis.* World journal of gastroenterology, 2012. 18(14): 1642-51.
3. White, D., V. Ratziu, and H. El-Serag, *Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis.* Journal of hepatology, 2008. 49(5): 831-44.
4. *EASL recommendations on treatment of hepatitis C: Final update of the series(☆).* J Hepatol, 2020. 73(5): 1170-1218.
5. Kim, H.J., J.H. Park, D.I. Park, et al., *Clearance of HCV by Combination Therapy of Pegylated Interferon alpha-2a and Ribavirin Improves Insulin Resistance.* Gut Liver, 2009. 3(2): 108-15.
6. Kawaguchi, T., T. Ide, E. Taniguchi, et al., *Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2.* Am J Gastroenterol, 2007. 102(3): 570-6.
7. Delgado-Borrego, A., S.H. Jordan, B. Negre, et al., *Reduction of insulin resistance with effective clearance of hepatitis C infection: results from the HALT-C trial.* Clin Gastroenterol Hepatol, 2010. 8(5): 458-62.
8. Ciancio, A., R. Bosio, S. Bo, et al., *Significant improvement of glycemic control in diabetic patients with HCV infection responding to direct-acting antiviral agents.* J Med Virol., 2018. 90(2): 320-327.
9. Abdel Alem, S., A. Elsharkawy, R. Fouad, et al., *Improvement of glycemic state among responders to Sofosbuvir-based treatment regimens: Single center experience.* J Med Virol, 2017. 89(12): 2181-2187.
10. Dawood, A.A., M.Z. Nooh, and A.A. Elgamal, *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, 2017. 41(4): 316-321.
11. Pavone, P., T. Tieghi, G. d'Ettorre, et al., *Rapid decline of fasting glucose in HCV diabetic patients treated with direct-acting antiviral agents.* Clin Microbiol Infect, 2016. 22(5): 462.e1-3.
12. Weidner, P., D. Boettche, T. Zimmerer, et al., *Impact of direct acting antiviral (DAA) treatment on glucose metabolism and reduction of pre-diabetes in patients with chronic hepatitis C.* J Gastrointestin Liver Dis, 2018. 27(3): 281-289.
13. Gilad, A., Z.P. Fricker, A. Hsieh, et al., *Sustained Improvement in Type 2 Diabetes Mellitus is Common After Treatment of Hepatitis C Virus With Direct-acting Antiviral Therapy.* J Clin Gastroenterol, 2019. 53(8): 616-620.
14. Hum, J., J.H. Jou, P.K. Green, et al., *Improvement in Glycemic Control of Type 2 Diabetes After Successful Treatment of Hepatitis C Virus.* 2017. 40(9): 1173-1180.
15. Ikeda, A., K. Ikeda, A. Takai, et al., *Hepatitis C Treatment with Sofosbuvir and Ledipasvir Accompanied by Immediate Improvement in Hemoglobin A1c.* Digestion, 2017. 96(4): 228-230.
16. Pashun, R.A., N.T. Shen, and A. Jesudian, *Markedly Improved Glycemic Control in Poorly Controlled Type 2 Diabetes following Direct Acting Antiviral Treatment of Genotype 1 Hepatitis C.* Case Reports Hepatol, 2016. 2016: 7807921.

17. Fabrizio, C., A. Procopio, L. Scudeller, et al., *HCV and diabetes: towards a 'sustained' glycaemic improvement after treatment with DAAs?* Clin Microbiol Infect, 2017. 23(5): 342-343.
18. Drazilova, S. and M. Janicko, *Glucose Metabolism Changes in Patients with Chronic Hepatitis C Treated with Direct Acting Antivirals.* Can J Gastroenterol Hepatol., 2018. 2018: 6095097.
19. Lanini, S., B. Bartolini, C. Taibi, et al., *Early improvement of glycaemic control after virus clearance in patients with chronic hepatitis C and severe liver fibrosis: a cohort study.* New Microbiol, 2019. 42(3): 139-144.
20. Takahashi, H., T. Nakahara, T. Kogiso, et al., *Eradication of hepatitis C virus with direct-acting antivirals improves glycemic control in diabetes: A multicenter study.* JGH Open, 2021. 5(2): 228-234.
21. Cacciola, I., G. Russo, R. Filomia, et al., *Over time evaluation of glycaemic control in direct-acting antiviral-treated hepatitis C virus/diabetic individuals with chronic hepatitis or with cirrhosis.* Liver Int., 2021.
22. Ciancio, A. and D.G. Ribaldone, *Long-term follow-up of diabetic and non-diabetic patients with chronic hepatitis C successfully treated with direct-acting antiviral agents.* 2021. 41(2): 276-287.
23. Stine, J.G., J.A. Wynter, B. Niccum, et al., *Effect of Treatment with Direct Acting Antiviral on Glycemic Control in Patients with Diabetes Mellitus and Chronic Hepatitis C.* Ann Hepatol, 2017. 16(2): 215-220.
24. Teegen, E.M., M. Dürr, M.M. Maurer, et al., *Evaluation of histological dynamics, kidney function and diabetes in liver transplant patients after antiviral treatment with direct-acting antivirals: Therapy of HCV-recurrence.* Transpl Infect Dis, 2019. 21(1): e13020.
25. Chaudhury, C.S., J. Sheehan, C. Chairez, et al., *No Improvement in Hemoglobin A1c Following Hepatitis C Viral Clearance in Patients With and Without HIV.* J Infect Dis, 2017. 217(1): 47-50.
26. Huang, J.F., C.F. Huang, M.L. Yeh, et al., *The outcomes of glucose abnormalities in chronic hepatitis C patients receiving interferon-free direct antiviral agents.* Kaohsiung J Med Sci, 2017. 33(11): 567-571.
27. Liberati, A., D.G. Altman, J. Tetzlaff, et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration.* Bmj, 2009. 339: b2700.
28. Stroup, D.F., J.A. Berlin, S.C. Morton, et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.* Jama, 2000. 283(15): 2008-12.
29. Burgess, S.V., T. Hussaini, and E.M. Yoshida, *Concordance of sustained virologic 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, 2016. 15(2): 154-9.
30. Martinot-Peignoux, M., C. Stern, S. Maylin, et al., *Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin.* Hepatology, 2010. 51(4): 1122-6.
31. Carnovale, C., M. Pozzi, A. Dassano, et al., *The impact of a successful treatment of hepatitis C virus on glyco-metabolic control in diabetic patients: a systematic review and meta-analysis.* Acta diabetologica, 2019. 56(3): 341-354.

32. Boraie, M., Y. Elnaggar, M. Ahmed, et al., *Effect of direct acting antiviral therapy of Chronic Hepatitis C virus on insulin resistance and Type2 DM in Egyptian patients (prospective study).* Diabetes & metabolic syndrome, 2019. 13(4): 2641-2646.
33. Carnovale, C., M. Gentili, C. Magni, et al., *The impact of a successful treatment of HCV on glyco-metabolic control in diabetic patients.* Antivir Ther, 2019. 24(2): 147-149.
34. Abdo, M., A. Rabiee, Z. Abdellatif, et al., *Impact of sustained virological response on metabolic disorders in diabetic chronic hepatitis C virus patients after treatment with generic sofosbuvir and daclatasvir.* Eur J Gastroenterol Hepatol, 2020.
35. Hussein, H.A., A.S. Allam, and A.S.A. Moaty, *Evaluation of Glycated Haemoglobin (HbA1c) Level in Type 2 Diabetic Chronic HCV Non-cirrhotic Treatment-Naïve Egyptian Patients Eradicated with Sofosbuvir Plus Daclatasvir.* Curr Diabetes Rev, 2020. 16(2): 165-170.
36. Mada, P.K., M.E. Malus, A. Parvathaneni, et al., *Impact of Treatment with Direct Acting Antiviral Drugs on Glycemic Control in Patients with Hepatitis C and Diabetes Mellitus.* Int J Hepatol., 2020. 2020: 6438753.
37. Wong, A.H., J. Sie, A. Chen, et al., *Glycemic Control after Initiating Direct-Acting Antiviral Agents in Patients with Hepatitis C Virus and Type 2 Diabetes Mellitus Using the United States Integrated Healthcare System.* J Res Pharm Pract, 2020. 9(1): 16-23.
38. Zied, H., N. Abo Alnasr, A. El-Bendary, et al., *Effect of treatment with direct antiviral agents (DAAs) on glycemic control in patients with type 2 diabetes mellitus & hepatitis C virus genotype 4.* Diabetes & metabolic syndrome, 2020. 14(4): 679-682.
39. Lenters-Westra, E., R.K. Schindhelm, H.J. Bilo, et al., *Differences in interpretation of haemoglobin A1c values among diabetes care professionals.* Neth J Med, 2014. 72(9): 462-6.
40. Little, R.R., C.L. Rohlfing, and D.B. Sacks, *Status of hemoglobin A1c measurement and goals for improvement: from chaos to order for improving diabetes care.* Clin Chem, 2011. 57(2): 205-14.
41. Beig, J., D. Orr, B. Harrison, et al., *Hepatitis C Virus Eradication with New Interferon-Free Treatment Improves Metabolic Profile in Hepatitis C Virus-Related Liver Transplant Recipients.* Liver Transpl, 2018. 24(8): 1031-1039.
42. Persico, M., M. Capasso, E. Persico, et al., *Suppressor of cytokine signaling 3 (SOCS3) expression and hepatitis C virus-related chronic hepatitis: Insulin resistance and response to antiviral therapy.* Hepatology, 2007. 46(4): 1009-15.
43. Vanni, E., M.L. Abate, E. Gentilcore, et al., *Sites and mechanisms of insulin resistance in nonobese, nondiabetic patients with chronic hepatitis C.* Hepatology, 2009. 50(3): 697-706.
44. Wang, Q., J. Chen, Y. Wang, et al., *Hepatitis C virus induced a novel apoptosis-like death of pancreatic beta cells through a caspase 3-dependent pathway.* PLoS One, 2012. 7(6): e38522.
45. Gastaldi, G., D. Gomes, P. Schneiter, et al., *Treatment with direct-acting antivirals improves peripheral insulin sensitivity in non-diabetic, lean chronic hepatitis C patients.* PLoS One, 2019. 14(6): e0217751.