Journal of Clinical and Nursing Research, 2022, Volume 6, Issue 4
http://ojs.bbwpublisher.com/index.php/JCNR
ISSN Online: 2208-3693
ISSN Print: 2208-3685

Incidence of Diabetes in Hepatitis C Patients in Remote Areas of Pakistan: Effect of Co-Morbidity on HCV Treatment Outcomes at Selected Secondary Care Hospitals

Muhammad Khalid Khan[1]*, Tofeeq ur Rehman[2]

[1]Faculty of Pharmacy, Gomal University, D.I. Khan, 29050, Pakistan

[2]Department of Pharmacy, Quaid I Azam University, Islamabad, Pakistan

***Corresponding author:** Muhammad Khalid Khan, khalid.gomalian@gmail.com

Abstract: The management of Hepatitis C (HCV) varies greatly due to co-morbidities. Association of Type II Diabetes Mellitus (T2DM) and HCV infection is momentous, however, only limited studies available from remote areas of Pakistan. This study aimed to assess the incidence of T2DM in Hepatitis C patients, and to measure the treatment outcomes of anti-HCV therapy in co-morbidity of diabetic patients in remote areas of Khyber Pakhtunkhwa Pakistan**.** A cross-sectional retrospective analysis of HCV patients (n=449) was conducted in the District Hospitals of Bannu and Lakki Marwat, Pakistan. Patients diagnosed of HCV infection and having T2DM as comorbidity were included in the study. The demographic information and laboratory parameters, such as viral load (VL), hemoglobin (Hb), alanine amino transferase (ALT), and platelet count were collected to measure treatment outcomes. T2DM was found in 33.18% of patients and significant association ($p < 0.05$) was found with HCV infection as a co-morbidity. Sofosbuvir (SOF) and Ribavirin (RBV) therapy reduced the mean (SD) VL ($x10^3$) from baseline 357.1±26.23 IU /mL to 14±2.3 IU/mL and 1.3±0.3 IU/mL at 3rd and 6th months of therapy, respectively. Conventional Interferon and Ribavirin (RBV) therapy reduced VL from a baseline 234.57±13.5 IU/mL to 72±7.9 IU/mL and 62 ±3.7 IU/mL at 3rd and 6th months of therapy, respectively. PEG-Interferon+ Ribavirin (RBV) therapy reduced baseline VL from 337±16.27 IU/mL to 18±2.8 and 4±1 at 3rd and 6th month of therapy, respectively. Similarly, Hb, ALT, and platelet count showed variations in all the studied groups. T2DM was highly prevalent and significantly associated with HCV in patients of 40 years or above and SOF+RBV combination therapy showed a better response, both in the diabetic and non-diabetic HCV patients compared to earlier the therapies. To further confirm the finding, a study using a larger population of HCV patients with T2DM should be conducted.

Keywords: Hepatitis C; Type II diabetes mellitus; Co-morbidity

Online publication: July 28, 2022

1. Introduction

Hepatitis C virus (HCV) infection is a major health problem worldwide. Approximately, 170 million people have HCV seroprevalence worldwide, and about 70% - 80 % of HCV cases become chronic leading to liver cirrhosis, end-stage liver disease, and hepatocellular carcinoma [1,2]. In Pakistan, around 10 million people are reported to suffer from HCV infection with varying prevalence in different provinces, such as Punjab (0.4-31.9%), Sindh (4-7%), Khyber Pakhtunkhwa (1.1-9%), and Baluchistan (1.5-3.9%) [3-7].

The presence of co-morbidities in HCV patients are often associated with sub-optimum treatment outcomes [8]. In addition, HCV and Type-II diabetes mellitus (T2DM) both are chronic diseases with a high rate of morbidity and mortality worldwide [9]. Further, the frequency of T2DM was reported to be higher in HCV patients, compared to the normal population, suggesting an epidemiological connection between HCV infection and T2DM [10-12]. The co-morbidity of T2DM with HCV will deteriorate the liver condition, encompassing insulin resistance condition, leading to aggravated liver fibrosis and sub-optimal therapeutic response [13]. Therefore, the treatment choices and management of HCV co-morbidities need substantial expertise in the context of concomitant medications and shift from conventional interferon-based therapies to direct-acting antivirals (DAAs). Although, HCV infected population exhibits higher (13%) prevalence of co-morbidities, compared to the uninfected population (3.7%), however a proper management may improve the treatment outcomes [13,14].

The center for disease control and prevention (CDC) in the 'surveillance of viral hepatitis 2015' reports mentioned that the new DAAs are superior to previous therapies in the characteristic, which it contained a short and simple regimen, with less adverse effects, and better clinical outcomes. In Pakistan, sofosbuvir (a newly registered DAA) was launched in 2015, and very limited literature is available highlighting the outcomes of the new anti-HCV therapy, sofosbuvir (SOF) in the remote areas of Pakistan.

This study was aimed to assess the incidence of T2DM in HCV patients, further measure the treatment outcomes of anti-HCV therapy in co-morbid diabetic in remote areas of Khyber Pakhtunkhwa, Pakistan.

2. Methods

2.1. Study design and participants

A cross-sectional retrospective study was conducted in the following four secondary care hospitals: (1) District Head Quarter (DHQ) Teaching Hospital Bannu; (2) Khalifa Gul Nawaz Hospital Bannu; (3) District Head Quarter Hospital Lakki Marwat; and (4) City Hospital Lakki Marwat, Pakistan. All the HCV patients enrolled in outpatient department between January 2019 to December 2019 were selected for this study. Additionally, patients with aged 18 years and above, PCR positive, and having T2DM as co-morbidity was also included in this study. Patients with incomplete clinical records, above 70 years of age, having comorbidity other than T2DM, and treated earlier than January 2019 were excluded from this study. The information pertaining to demographics and laboratory parameters, such as viral load (VL), hemoglobin (Hb), Alanine aminotransferase (ALT) and platelets (PLT) was collected from Hepatitis Control Program (HCP) corresponding centers. The laboratory parameters were measured at three points; the baseline level, and level at 3rd month (mid) and at 6th month (end) of the therapy, respectively. Treatment outcomes were measured on the basis of laboratory values of sustained virological response 24 weeks post-end of treatment (SVR24) and normal values of Hb, ALT, and PLT. The reference values to measure normal ranges were taken from Merck manual (professional version) and VL was analyzed through HCV Quantitative RNA PCR (Automated Real Time PCR system) test. The positive treatment outcome (end point) was a VL < 15 IU/mL while, the response of therapy was considered negative, when VL was "detected" (VL > 15 IU/mL) at the end of therapy. An elevated ALT, low Hb, and low PLT count at the end of therapy from the normal range were taken as a negative response.

2.2. Ethical Approval

The ethical permission was granted by Bio-Ethics Committee (BEC) of Quaid-i-University Islamabad (BEC-FBS-QAU-69) and from the head of hepatitis control program of each health facility.

2.3. Statistical Analysis

The statistical package for social sciences (SPSS; IBM version 20) was used for data entry and analyses.

Simple descriptive statistics were applied for demographic parameters examination. Inferential statistics, Chi-square, and One Way ANOVA tests were used to determine the association and correlation of categorical variables and continuous variables.

3. Results

Out of 449 patients, 324 (72.16%) were males, and 125 (27.84%) were females. Of those, 300 patients (66.81%) were HCV mono-infected, and 149 patients (33.18%) had T2DM as co-morbidity along with HCV infection. Out of 300 mono-infected HCV patients, 185 patients (61.67%) were from Bannu Hospital (Hospital 1, 2) and 115 (38.33%) were from Lakki Marwat Hospital (Hospital 3, 4). Interestingly, the incidence of T2DM was higher in district Bannu, where out of 149 patients with HCV and T2DM co-morbid, 105 patients (70.47%) are from Bannu Hospital, and 44 patients (29.53%) are from Lakki Marwat Hospitals. The details of diseased, location, and age categories are described in **Table 1.**

Table 1. Prevalence of DM in HCV patients' frequency of different age groups in diabetic and non-diabetic HCV patients

	Total patients (n=449)	**HCV (n=300)**	**HCV/ Diabetic (n=149)**
Study sites			
DHQ hospital Bannu	250 (55.68%)	167 (55.67%)	83 (55.71%)
KGN hospital Bannu	40 (8.91%)	18 (6.0%)	22 (14.76%)
DHQ hospital Lakki	149 (33.18%)	110 (36.67%)	39 (26.17%)
City hospital Lakki	10 (2.23%)	5 (1.66%)	5 (3.36%)
Age range (years)	20-30	75 (25%)	2 (01%)
	31-40	143 (48%)	44 (29%)
	41-50	48 (16%)	59 (39%)
	51-60	30 (10%)	35 (25%)
	61-70	4 (01%)	9 (06%)
Gender	Male	209 (69.7%)	115 (77%)
	Female	91 (30.3%)	34 (23%)

*DHQ= District head quarter hospital, KGNH= Khalifa Gul Nawaz Hospital

Out of 149 HCV/T2DM co-morbidity patients, 94 patients (63.09%) were treated with Interferon+ Ribavirin (IFN+RBV); of those, 35 (37.23%) of them were responders, meanwhile 59 (62.77%) were non-responders. PEG-IFN+RBV combination therapy was administered to 38 patients, of whom 29 (76.32%) were responders, meanwhile 9 (23.68%) were non-responders. SOF+RBV combination therapy was given to 17 patients, 15 (88.24%) of them were responders, while 2 (11.76%) were non-responders. In HCV mono infected (n=300) patients, 220 (73.33%) were given IFN+RBV therapy, 158 (71.82%) are those who responders and 62 (28.18%) were non-responders. Peg-IFN+RBV was given to 66 (22.0%) patients, of whom 53 (80.30%) were responders, and 13 (19.70%) were non-responders. SOF+ RBV therapy was given to 14 (4.67%) patients, and all of those were responders. The results are shown in **Table 2**.

Table 2. Responders and non-responders in diabetic and non-diabetic HCV patients

	Treatments used	No. of patients (n)	Responders*	Non responders	Significance (*p* value)
Diabetic HCV	IFN+RBV	94	35 (37%)	59 (63%)	0.000
	PEG-IFN+RBV	38	29 (76%)	9 (24%)	0.000
	SOF+RBV	17	15 (88%)	2 (12%)	0.000
	Total	149	79 (53%)	70 (47%)	
HCV	IFN+RBV	220	158 (72%)	62 (28%)	0.033
	PEG-IFN+RBV	66	53 (80%)	13 (20%)	0.006
	SOF+RBV	14	14 (100%)	0 (00%)	0.012
	Total	300	225 (75%)	75 (25%)	

*Responders are declared based on VL after the treatment as per sensitivity of PCR equipment; About Real Time PCR (<50 IU/mL = undetectable). Abbreviations; PEG-INF= pegylated interferon; PCR= polymerase chain reaction

3.1. Viral load variations in HCV mono-infected and T2dm co-morbid patients

Measuring the effect of treatments on VL; IFN+RBV combination showed a considerable decrease in the mean (SD), where VL ($x10^3$) level at baseline, at 3rd, and 6th month of therapy were 253(±7.1), 18.3(±0.3), and 8.7(±0.1) IU/ml, respectively. Administration of PEG-IFN+RBV therapy (n=66), reduced VL from baseline 317.22(±9.2) IU/mL, to 8.3(±1.2) IU/mL to 2.3(±0.12) IU/mL at 3rd and 6th month of therapy, respectively. Mean (SD) VL of 14 patients treated with SOF+RBV at baseline was 293.87(±7.32) IU/mL, which dropped to 14.5(±2.3) IU/mL at 3rd month, and became "not detected" at 6th month (end) of therapy as shown in **Table 3**.

Table 3. Effect of treatment combinations on VL, Hb, and ALT in diabetic and non-diabetic HCV patients

Patient group	Treatments used	Effect on viral load (IU/mL) Baseline, 3rd month, 6th month	Effect on Hb (g/dL) Baseline, 3rd month, 6th month	Effect on ALT(U/L) Baseline, 3rd month, 6th month
HCV	IFN+RV	253.00 (7.1), 18.3 (0.3), 8.7 (0.1)	15.23 (0.17), 13.1 (0.14), 12.8 (0.16)	87.45 (5.76), 68 (2.12), 54.3 (2.2)
	PEG-IFN+RV	317.22 (9.2), 8.3 (1.2), 2.3 (0.12)	15.11 (0.19), 13.2 (0.17), 12.7 (0.17)	84.34 (4.45), 58 (2.45), 44.2 (2.11)
	SOF+RV	293.87 (7.32), 14.5 (2.3), <15	14.23 (0.14), 13.3 (0.11), 12.3 (0.13)	97.45 (7.34), 77 (3.37), 39.3 (2.3)
HCV/DM	IFN+RV	234.57 (13.5), 72 (7.9), 62 (3.7)	14.46 (0.14), 12.5 (0.14), 11.1 (0.2)	100.12 (3.7),83 (3.1), 89 (3.6)
	PEG-IFN+RV	337 (16.27), 18 (2.8), 4 (1.0)	14.6 (0.3), 13.5 (0.21), 12.2 (0.31)	110.8 (5.2), 69(3.3), 56.56 (3.8)
	SOF+RV	357.1 (26.23), 14 (2.3), 1.3 (0.3)	14.38 (0.17), 13 (0.31), 12.3 (0.41)	113.1 (9.8), 62 (3.1), 41 (2.3)

*Viral load is measured as per sensitivity of PCR equipment; About Real Time PCR (< 15 IU/mL = undetectable)

3.2. Hemoglobin level variations in HCV mono-infected and T2DM co-morbid patients

Hb levels were checked at baseline (Hb0), at 3rd month (Hb3), and at 6th month (Hb6) of therapy. **Table 3** shows mean bh level of HCV mono-infected patients after treatment with IFN+RBV (n=220), PEG-

IFN+RBV (n=66), and SOF+RBV (n=14). Mean (SD) Hb0 level of patients treated with IFN+RBV was 15.23(±0.17) g/dL, which dropped to 13.1(±0.14) and 12.8(±0.16) g/dL at 3rd and 6th month of the treatment, respectively. The PEG-IFN+RBV therapy showed a mean drop of Hb from 15.11(±0.19) to 13.2 (±0.17) and 12.7 (±0.17) at baseline, 3rd and 6th month, respectively. SOF+RBV therapy reduced the Hb level from baseline 14.23 (±0.14) to 13.3(±0.11) and 12.3 (±0.13) at 3rd and 6th month, respectively. The detail about Hb level in HCV and comorbid T2DM patients, treated with IFN+RBV, PEG-IFN+RBV, and SOF+RBV are given in **Table 3.**

3.3. ALT variations in HCV Mono-Infected and T2DM co-morbid patients

In conventional therapy (IFN+RBV), mean (SD) ALT0 value was greater than normal value, 87.45(5.76) U/L at baseline, which decreased to 68(2.12) U/L at 3rd month and 54.3(2.2) U/L at 6th month of therapy, respectively. Similarly, PEG-IFN+RBV dropped the mean ALT value from baseline 84.34(4.45) U/L to 58(2.45) U/L, and 44.2(2.11) U/L at 3rd and 6th month respectively, which is in the normal range, hence showing positive response. SOF+RBV therapy dropped the mean ALT value from baseline 97.45(7.34) U/L to 77.0(3.37) U/L to normal mean range 39.3(2.3) U/L, at 3rd and 6th month of therapy, respectively. A comparative detail of these three antiviral combinations in HCV and T2DM comorbid patients is given in **Table 3**.

3.4. Platelets count variations in HCV mono-infected and T2DM co-morbid patients

Figure 1a shows mean platelet count variations of HCV mono-infected patients when treated with IFN+RBV, PEG-IFN+RBV, and SOF+RBV combination therapies. PLT0, PLT3, and PLT6 represent the mean count at baseline, 3rd month and at 6th month of therapy, respectively. A decrease in platelet count was observed at the 3rd month of the therapy and no significant decrease was observed at 6th month. In patients on conventional IFN+RBV therapy, platelet count decreased from $244x10^3$ to 232×10^3 at 6th month, which was in normal range. Patients on PEG-IFN+ RBV therapy, a decrease in count from 253×10^3 to 237×10^3 was observed, while patients treated with SOF+RBV faced the platelet count drop from 238×10^3 to 229×10^3.

Similarly, one-way ANOVA analysis showed a drop in PLT count at the 3rd month of the therapy in HCV and T2DM co-morbid patients, however, no significant decrease was observed at 6th month. Patients on IFN+RBV therapy showed a decrease in the PLT count from 224×10^3 to 200×10^3 at 6th month, which is in the normal range. Similarly, patients on PEG-IFN+RBV therapy, PLT count decreased from $239 x10^3$ to 218×10^3, while patients on SOF+RBV showed a drop from 265×10^3 to 250×10^3. **Figure 1b** shows the results of PLT count variation in HCV and T2DM comorbid diseased patients.

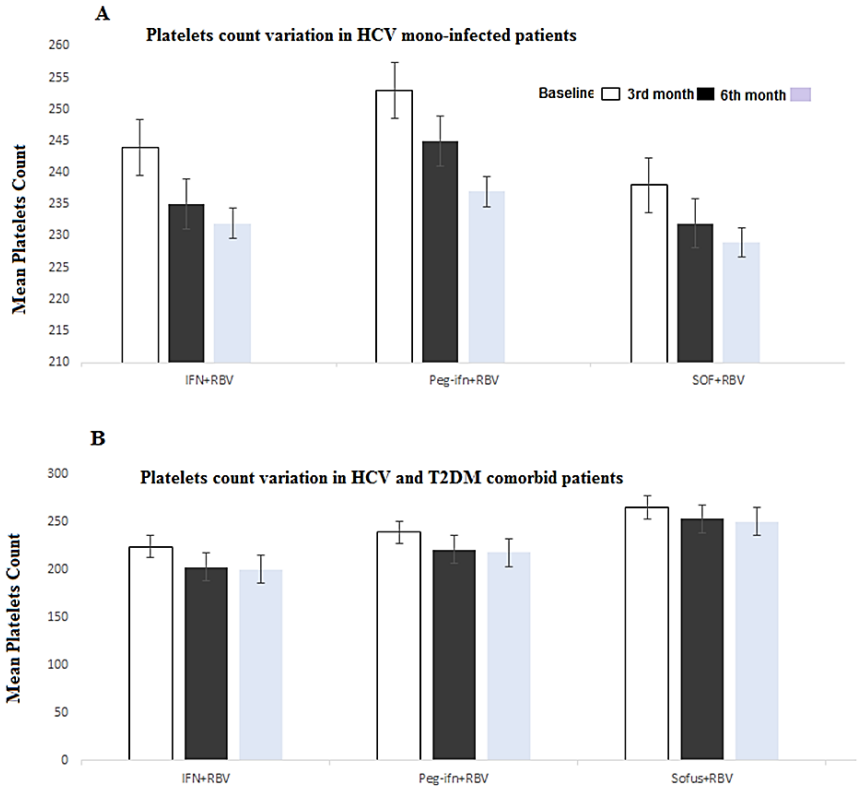

Figure 1. (A) Platelets count variation in HCV mono-infected patients; **(B)** Platelets count variation in HCV and T2DM comorbid patients

4. Discussion

To our knowledge, this is the first study reporting incidence of T2DM in HCV patients and the clinical outcomes of HCV treatment from remote areas of Pakistan. Our study showed that the prevalence of T2DM is 33.18% (n=149) in HCV patients and SOF combined with RBV showed an excellent cure rate (85%) both in diabetic and non-diabetic HCV patients. Comparing the incidence of T2DM in the HCV infected patients and non-infected individuals, we observed a twofold increase of T2DM co-morbidity in HCV infected population, compared to non-infected population. A similar study reported the prevalence of diabetes mellitus (31.5%) in HCV infected population [15]. There was a fair difference in the incidence rate between the two districts. Interestingly, T2DM was more prevalent and significantly associated (p-value < 0.05) with HCV infected patients of 40 years or above. The frequency of T2DM co-morbidity was higher in males than in females, and a similar result was observed in HCV infected population. These findings are conformational to a similar study conducted in the Mexican population [16] in treatment outcomes, the percentage of non-responders (treatment failures) was higher in diabetic-HCV comorbid patients than in non-diabetic HCV patients. Several studies supported our findings, where diabetic HCV patients show poor response to IFN+RBV and PEG-IFN+RBV combination therapies than in non-diabetic HCV patients. The SOF based therapy showed an excellent cure rate both in diabetic and non-diabetic HCV patients, which is confirming the studies conducted of DAAs [17]. A fairly decent normalization of Hb, ALT, and PLT levels were observed after the treatment with SOF while the IFN based therapies were associated with relapses and anemia [18]. It is imperative to scrutinize the prevalence of T2DM as a co-morbidity in a hepatitis C infected population in a prospective study. Moreover, assessment of patient's co-morbidities prior to the start of anti-HCV therapy should be recommended in order to have positive treatment outcomes.

5. Limitation of the Study

This study has certain limitations. Due to nil funding, we were restricted to the remote areas of one province and for the generalization of data, the sample size should be bigger. The patients treated with DAAs were a small portion of the cohort because SOF was newly registered and supplied at the time of the study. No follow-up of non-responders and relapsed cases.

6. Conclusion

This study concludes, that the incidence of T2DM is high in HCV infected patients, while the treatment outcomes with the new SOF therapy is excellent both in diabetic and non-diabetic HCV patients. Future studies on the wider population from remote areas are required to develop guidelines for scaling up the resources in the outreach areas.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Irshad M, Mankotia DS, Irshad K, 2013, An Insight into the Diagnosis and Pathogenesis of Hepatitis C Virus Infection. World J Gastroenterol, 2013(19): 7896–7899.

[2] Li HC, Lo SY, 2015, Hepatitis C Virus: Virology, Diagnosis and Treatment. World J Hepatol, 2015(7): 1377–1379.

[3] Saleha S, Kamal UF, Khan N, et al., 2014, Prevalence of Hepatitis C Virus Genotypes in District Bannu, Khyber Pakhtunkhwa, Pakistan. Hepat Res Treat, 2014(3): 24–28.

[4] Anwar MI, Rahman M, Hassan MU, et al., 2013, Prevalence of Active Hepatitis C Virus Infections among General Public of Lahore, Pakistan. Virol J, 2013(10): 351–54.

[5] Attaullah SK, Ali I, 2011, Hepatitis C Virus Genotypes in Pakistan: A Systemic Review. Virol J, 2011(8): 433–438.

[6] Umer M, Iqbal M, 2016, Hepatitis C Virus Prevalence and Genotype Distribution in Pakistan: Comprehensive Review of Recent Data. World J Gastroenterol, 2016(22): 1684–1687.

[7] Louie KS, Laurent SS, Forssen UM, et al., 2012, The High Comorbidity Burden of the Hepatitis C Virus Infected Population in the United States. BMC Infect Dis, 2012(12): 86–89.

[8] El-Zayadi R, 2009, Hepatitis C Comorbidities Affecting the Course and Response to Therapy. World J Gastroenterol, 2009(15): 4993–4999.

[9] Alaei M, Negro F, 2008, Hepatitis C Virus and Glucose and Lipid Metabolism. Diabetes Metab, 3(4): 692–700.

[10] Aytug S, Reich D, Sapiro LE, et al., 2003, Impaired Irs-1/Pi3-Kinase Signalling in Patients with HCV: A Mechanism for Increased Prevalence of Type 2 Diabetes. Hepatology, 2003(38): 1384–1392.

[11] Allison ME, Wreghitt T, Palmer CR, et al., 1994. Evidence for a Link between Hepatitis C Virus Infection and Diabetes Mellitus in a Cirrhotic Population. J Hepatol, 1994(21): 1135–1139.

[12] Imazeki F, Yokosuka O, Fukai K, et al., 2008, Prevalence of Diabetes Mellitus and Insulin Resistance in Patients with Chronic Hepatitis C: Comparison with Hepatitis B Virus-Infected and Hepatitis C Virus-Cleared Patients. Liver Int, 2008(28): 355–362.

[13] Mehta SH, Brancati FL, Sulkowski MS, et al., 2000, Prevalence of Type 2 Diabetes Mellitus Among

Persons with Hepatitis C Virus Infection in The United States. Annals Internal Med, 2000(133): 592–599.

[14] Allison ME, Wreghitt T, Palmer CR, et al., 1994, Evidence for a Link between Hepatitis C Virus Infection and Diabetes Mellitus in a Cirrhotic Population. J Hepatol, 1994(21): 1135–1139.

[15] Memon MS, Arain ZI, Naz F, et al., 2013, Prevalence of Type 2 Diabetes Mellitus in Hepatitis C Virus Infected Population: A Southeast Asian Study. J Diabetes Res, 2013(4): 36–39.

[16] White DL, Ratziu V, El-Serag HB, 2008, Hepatitis C Infection and Risk of Diabetes: A Systematic Review and Meta-Analysis. J Hepatol, 2008(49): 831–844.

[17] Costantini S, Capone F, Guerriero E, et al., 2012, Cytokine Profile of Patients with Type 2 Diabetes and Chronic Hepatitis C Infection. Plos One, 2012(7): E39486.

[18] Hsu YC, Lin JT, Ho HJ, et al., 2014, Antiviral Treatment for Hepatitis C Virus Infection Is Associated with Improved Renal and Cardiovascular Outcomes in Diabetic Patients. Hepatology, 59: 1293–1302.