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ORIGINAL ARTICLE

Reversal of insulin resistance by HCV clearance through direct-acting antiviral treatments in chronic hepatitis C patients.

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ABSTRACT… Objective: To assess the effect of direct active antiviral treatment on insulin resistance reversal in hepatitis C genotype 3 patients achieving sustained virologic response. **Study Design:** Case-control study. **Setting:** Department of Medicine, Nishtar Medical Hospital, Multan. **Period:** May 2024 to October 2024. **Methods:** A total of 100 hepatitis C genotype 3 patients with advanced liver fibrosis being considered for treatment with DAAs were selected for study. Patients were divided into cases i.e. 50 patients treated with DAAs and the control group i.e. 50 patients left untreated. Blood plasma and serum samples were collected prior to treatment initiation, after treatment completion, and at 3-month follow-up to check insulin and glucose levels in cases. In the control group, patients were assessed at the start of the study (Time 0) and at the 3-month follow-up. **Results:** HCV clearance was achieved in all patients and 47 patients (94%) achieved SVR. Hepatic stiffness in cases was 20.07 ± 10.21 kPa before the start of treatment and 19.78 ± 8.5 after treatment and significantly lower at follow-up (13.34 ± 7.9) ($p<0.001$). A significant association between HOMA-IR and HCV-RNA levels was noted at baseline and a trend was found for hepatic stiffness ($p=0.069$) and BMI ($p=0.060$). **Conclusion:** HCV clearance through direct-acting anti-viral treatment improves or reverses insulin resistance in Hepatitis C genotype III patients reducing the risk of diabetes mellitus, advanced liver fibrosis metabolic syndrome, and cardiovascular events.

Key words: HCV, Hepatic, Hepatitis C, Insulin Resistance.

INTRODUCTION

Hepatitis C virus is a viral hepatic infection leading to inflammation along with a high risk of extrahepatic conditions including diabetes and insulin resistance.[1] Globally, HCV infection is a leading cause of morbidity and mortality due to its hepatic and extrahepatic manifestations and widespread epidemiology.

Literature published by clinical trials and experimental studies has reported that HCV acts as a precursor of insulin resistance.[2,3] Irrespective of the degree of hepatic infection and HCV genotype, 30 to 70% of HCV patients are diagnosed with IR.[4] However, the highest rate of insulin resistance is noted in patients with HCV genotypes 1 and 3 and genotype 2 patients are least susceptible to IR. A strong association between insulin resistance and viral burden is reported in HCV genotype 3 infection patients which implies that these two conditions are directly linked.[5]

Insulin resistance is a risk factor for pre-diabetes and diabetes type II if left untreated, fatty liver disease, and liver fibrosis.[6,7] Direct antivirals have emerged as a new gold standard for the management and treatment of viral hepatitis C patients. A high efficacy and safety profile of DAA has been reported by several trials with 90-98% of the patients achieving SVR.[8]

Considering the fact that HCV is directly related to insulin resistance, we formed a hypothesis that treatment of viral hepatitis DAAs can cause improvement or reversal of insulin resistance. This study was conducted to assess the effect of direct active antiviral treatment on insulin resistance reversal in hepatitis C genotype 3 patients achieving sustained virologic response.

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METHODS

A case-control study was conducted in the Medicine Department of Nishtar Medical Hospital, Multan from May 2024 to October 2024. A total of 100 hepatitis C genotype 3 patients with advanced liver fibrosis being considered for treatment with DAAs were selected for study by consecutive sampling. The sample size was calculated by Epi Info software by setting a 95% confidence interval, 70% population proportion, and 5% margin of error. Patients with HBV or HIV co-infection, diabetics, and patients on biguanides and thiazolidinediones were excluded. All patients provided their informed consent to become a part of the study. The ethical board of the hospital approved the study after approval from ethical committee (12527/NMU/07-08-24).

Patients were divided into cases i.e. 50 patients treated with DAAs and the control group i.e. 50 patients left untreated. Patient history including anthropometric measurements (BMI and waist circumference), clinical data (liver function tests, fasting blood glucose levels, serum cholesterol and triglycerides, and blood count), and radiological data (liver ultrasound) was noted. Liver fibrosis was evaluated by performing transient elastography. Real-time PCR was obtained for assessing RNA levels and Innolipa assay determined genotype.

Blood plasma and serum samples were collected prior to treatment initiation, after treatment completion, and at 3-month follow-up to check insulin and glucose levels in cases. In the control group, patients were assessed at the start of the study (Time 0) and at the 3-month follow-up. Immunoassay was used to assess insulin levels and HOMA was used to assess insulin resistance and beta-cell function by formulas used in Adinolfi et al.[9] The HOMA-IR cut-off was 1.82 as calculated by Hydrie et al.[10]

All data was analyzed by SPSS version 24. Mean ± SD was used to present data. Paired t-test was performed to assess differences in quantitative values before and after treatment. The association between HOMA and associated factors was assessed by Spearman correlation. The association between HOMA-IR and independent variables was assessed by linear regression analysis. A p-value less than 0.05 was taken as significant.

RESULTS

A total of 50 HCV genotype III patients were administered direct-acting antivirals and 50 patients were included in the untreated control group. Patients' data, treatment outcomes, and follow-up data are shown in Tables-I, II, and III.

Insulin resistance at t0 was 54% vs 56%. The treatment regimen in cases was Simeprevir + sofosbuvir (±ribavirin) in 44% of patients, Ombitasvir/paritaprevir/ritonavir + dasabuvir (±ribavirin) in 46% of patients, and 10% of patients were treated with Ledipasvir/sofosbuvir (±ribavirin). HCV clearance was achieved in all patients and 47 patients (94%) achieved SVR. Hepatic stiffness in cases was 20.07 ± 10.21 kPa before the start of treatment and 19.78 ± 8.5 after treatment and significantly lower at follow-up (13.34 ± 7.9) ($p<0.001$). Liver stiffness and steatosis did not change significantly in the control group during the study period.

Fasting glucose and insulin levels and HOMA-IR levels were significantly reduced despite no change in lifestyle, diet, or medication of patients who achieved SVR ($p<0.001$). Fasting glucose was 96.63 ± 11.04 mg/dl at baseline which showed significant improvements at follow-up (84.21 ± 15.28). The control group showed no significant variations in glucose, insulin, or IR.

36 patients (76.6%) out of 47 patients who achieved SVR showed significantly improved HOMA levels. Among 27 patients (54%) who had insulin resistance before treatment, 11 (40.8%) had normal IR after SVR and 26% showed no change. After viral clearance, 76% of cases showed improved IR. Viral clearance led to a significant reduction in beta-cell distress (120.3 ± 45.8) and an increase in HOMA-S (105 ± 69.7). A significant association between HOMA-IR and HCV-RNA levels was noted at baseline and a trend was found for hepatic stiffness ($p=0.069$) and BMI ($p=0.060$).

An independent correlation between HOMA-IR and HCV-RNA was also revealed by regression analysis (B= 0.710, 95% CI: 0.1-1.309, p=0.026). At follow-up, persistent insulin resistance was related to high fibrosis score (p<0.035) with an overage IR value of 16.86 ± 10.17 kPa and non-IR value of 11.92 ± 8.44 kPa (p=0.039, 95% CI: 0.241-8.78).

	Cases (n=50)	Controls (n=50)
Age	65 (40-77)	64 (43-75)
Male gender	25 (50%)	24 (48%)
BMI	26.2 ± 3.54	26.4 ± 3.77
ALT	106 ± 70	103 ± 73
Serum cholesterol	149 ± 30	155 ± 29
Triglycerides	97 ± 30	95 ± 31
Arterial hypertension	20 (40%)	21 (42%)
HOMA-IR	5.03 ± 3.57	4.76 ± 4.58
HOMA-S	80.4 ± 63	82.5 ± 65.1
HOMA-B	137.2 ± 65.1	141.5 ± 75.4
Fasting insulin	17.18 ± 12.09	16.90 ± 13.07
Fasting glucose	96.63 ± 11.04	97.76 ± 11.22
Insulin resistance	27 (54%)	28 (56%)
Hepatic stiffness	20.07 ± 10.21	19.88 ± 9.33

Table-I. Patients' data before the start of treatment

	Cases (n=50)
BMI	26.3 ± 3.71
ALT	23 ± 13
Serum cholesterol	153 ± 19
Triglycerides	99 ± 23
Arterial hypertension	20 (40%)
HOMA-IR	2.43 ± 1.75
HOMA-S	105 ± 69.7
HOMA-B	120.3 ± 45.8
Fasting insulin	11.52 ± 3.16
Fasting glucose	85.66 ± 21.23
Insulin resistance	14 (28%)
Hepatic stiffness	19.78 ± 8.5

Table-II. Data of patients at the end of treatment

	Cases (n=47)	Controls (n=50)
BMI	26.3 ± 3.71	26.2 ± 3.38
ALT	25 ± 11	109 ± 85
Serum cholesterol	155 ± 17	149 ± 31
Triglycerides	103 ± 21	93 ± 36
Arterial hypertension	20 (40%)	21 (42%)
HOMA-IR	2.31 ± 1.76	4.85 ± 5.10
HOMA-S	109 ± 65.4	83.7 ± 68.4
HOMA-B	118.5 ± 41.6	143 ± 70.4
Fasting insulin	10.47 ± 4.16	17.3 ± 11.18
Fasting glucose	84.21 ± 15.28	97.76 ± 11.22
Insulin resistance	15 (30%)	29 (58%)
Hepatic stiffness	13.34 ± 7.9	20.34 ± 10.17

Table-III. Patient data at 3-month follow-up

DISCUSSION

This study was conducted to assess the effect of direct active antiviral treatment on insulin resistance reversal in hepatitis C genotype 3 patients achieving sustained virologic response. The results showed that viral clearance improves glucose metabolism and insulin sensitivity reduces insulin resistance irrespective of BMI or fibrosis degree. Insulin resistance persisted in patients with high fibrosis scores implying that they retain some degree of HCV pathology. These findings comply with previous literature.[11,12,13]

76.6% of HCV patients treated with direct-acting antivirals achieved SVR and showed significant improvement or complete absence of insulin resistance due to increased insulin sensitivity and reduced beta-cell distress which were independently related to viral RNA and its clearance. Glucose and insulin levels also significantly reduced after treatment confirming HCV as a pathogenic risk factor for insulin resistance. Previous studies conducted in HCV patients treated with interferon therapy achieved SVR and showed improvement in glucose levels and IR similar to our study.[14,15] But weight loss was a confounding factor in interferon-treated patients in these studies which contributed to a reduction in insulin sensitivity.

The current study results showed that non-interferon treatment also shows improved IR even without weight loss as an adverse effect indicating that BMI was not related to this improvement. This finding can form the basis of the hypothesis that DAA treatment reduces the risk of diabetes mellitus and metabolic syndrome in Hepatitis C patients. Prior studies that treated HCV patients with DAAs and achieved SVR reported that the frequency of DM was 2-3 times lower than patients who did not achieve SVR.[16,17]

Another hypothesis can be drawn from the finding that viral clearance improved glycemic levels, it can be possible that diabetic HCV patients can show improved glucose homeostasis after treatment.[18] A recent study backed this hypothesis despite the fact that patients gained significant weight.[19]

CONCLUSION

HCV clearance through direct-acting anti-viral treatment improves or reverses insulin resistance in Hepatitis C genotype III patients reducing the risk of diabetes mellitus, advanced liver fibrosis metabolic syndrome, and cardiovascular events.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Arif Rahim Khan:** Proof reading.
2	**Shahnawaz Hassan Gardezi:** Data collection and Analysis.
3	**Ali Raza:** Writing and Interpretation.