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Original Research Article

Impact of Direct-Acting Antiviral Treatments on Insulin Resistance Reversal in Chronic Hepatitis C Patients

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Abstract: *Hepatitis C virus (HCV) infection is linked to metabolic complications, including insulin resistance (IR), which can increase the risk of type 2 diabetes mellitus (T2DM), liver fibrosis progression, and cardiovascular diseases. Direct-acting antiviral (DAA) therapy has revolutionized HCV treatment, leading to sustained virologic response (SVR), but its impact on insulin resistance remains under investigation, particularly in HCV genotype three patients.* ***Objective:*** *To assess the effect of direct active antiviral treatment on insulin resistance reversal in hepatitis C genotype three patients achieving sustained virologic response.* ***Methodology:*** *A case-control study was conducted in the Medicine Department of Mayo Hospital from Aug 2024 to November 2024. A total of 100 hepatitis C genotype three 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 before 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 the 3-month follow-up.* ***Results:*** *Insulin resistance at t0 was 56% vs 58%. HCV clearance was achieved in all patients, and 48 (96%) achieved SVR. Hepatic stiffness in cases was 19.12 ± 9.1 kPa before the start of treatment and 18.84 ± 7.3 after treatment and significantly lower at follow-up (12.45 ± 8.0) ($p<0.001$). Liver stiffness and steatosis did not change significantly in the control group during the study period. Fasting glucose was 95.59 ± 10.10 mg/dl at baseline, showing significant improvements at follow-up (83.17 ± 12.36). The control group showed no considerable glucose, insulin, or IR variations. 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.*

Keywords: HCV, Hepatic, Hepatitis C, Insulin Resistance

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Introduction

Hepatitis C virus (HCV) is a viral hepatic infection that leads to inflammation and a high risk of extrahepatic conditions, including diabetes and insulin resistance (1). Due to its hepatic and extrahepatic manifestations and widespread epidemiology, HCV infection is a leading cause of morbidity and mortality globally.

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 two patients are least susceptible to IR. A strong association between insulin resistance and viral burden is reported in HCV genotype three infection patients, implying 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. Several trials have reported a high efficacy and safety profile of DAA, with 90-98% of the patients achieving SVR (8).

Considering that HCV is directly related to insulin resistance, we formed a hypothesis that treatment of viral hepatitis with DAAs can improve or reverse it. This study assessed the effect of direct active antiviral therapy on insulin resistance reversal in three patients with hepatitis C genotype who achieved sustained virologic response.

Methodology

A case-control study was conducted in the Medicine Department of Mayo Hospital from Aug 2024 to November 2024. A total of 100 hepatitis C genotype three 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, people with diabetes, 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.

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 to assess RNA levels, and the Innolipa assay determined the genotype.

Blood plasma and serum samples were collected before 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 the 3-month follow-up. Immunoassay was used to determine insulin levels, and HOMA was used to evaluate insulin resistance and beta-cell function using formulas used in Adinolfi et al.[9]The HOMA-IR cut-off was 1.82 as calculated by Hydrie et al. (10).

All data were analyzed using 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 evaluated using the 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

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 56% vs 58%. The treatment regimen in cases was Simeprevir + sofosbuvir (±ribavirin) in 46% of patients, Ombitasvir/paritaprevir/ritonavir + dasabuvir (±ribavirin) in 48% of patients, and 12% of patients were treated with Ledipasvir/sofosbuvir (±ribavirin). HCV clearance was achieved in all patients, and 48 (96%) achieved SVR. Hepatic stiffness in cases was 19.12 ± 9.1 kPa before the start of treatment and 18.84 ± 7.3 after treatment and significantly lower at follow-up (12.45 ± 8.0) (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 95.59 ± 10.10 mg/dl at baseline, which showed significant improvements at follow-up (83.17 ± 12.36). The control group showed no considerable glucose, insulin, or IR variations.

Thirty-five patients (74.4%) out of 47 who achieved SVR showed significantly improved HOMA levels. Among 28 patients (56%) who had insulin resistance before treatment, 12 (42.8%) had regular IR after SVR and 26% showed no change? After viral clearance, 78% of cases showed improved IR. Viral clearance led to a significant reduction in beta-cell distress (119.5± 43.9) and an increase in HOMA-S (104±70.2). 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 average 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).

Table 1: Patients' data before the start of treatment

	Cases (n=50)	Controls (n=50)
Age	64 (39-75)	63 (42-72)
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	95.59 ± 10.10	96.82 ± 10.10
Insulin resistance	28 (56%)	29 (58%)
Hepatic stiffness	19.12 ± 9.18	18.93 ± 8.28

Table 2: Data of patients at the end 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	104±70.2
HOMA-B	119.5 ± 43.9
Fasting insulin	11.52 ± 3.16
Fasting glucose	85.66 ±21.23
Insulin resistance	14 (28%)
Hepatic stiffness	18.84±7.3

Table 3: Patient data at 3-month follow-up

	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	83.17 ± 12.36	96.81 ± 10.16
Insulin resistance	15 (30%)	29 (58%)
Hepatic stiffness	12.45 ± 8.0	19.41 ± 9.13

Discussion

This study assessed the effect of direct active antiviral treatment on insulin resistance reversal in three patients with hepatitis C genotype who achieved sustained virologic response. The results showed that viral clearance improves glucose metabolism and insulin sensitivity and 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 (11-13).

74.4% 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 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 in HCV patients treated with interferon therapy achieved SVR and showed improvement in glucose levels and IR similar to our study (14, 15). However, weight loss was a confounding factor in interferon-treated patients in these studies, contributing to reduced insulin sensitivity.

The current study showed that non-interferon treatment also shows improved IR even without weight loss as an adverse effect, indicating that BMI was unrelated 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 is possible that diabetic HCV patients can show improved glucose homeostasis after treatment (18). A recent study backed this hypothesis even though 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.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRBEC-MM-044-24)

Consent for publication

Approved

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Conflict of interest

The authors declared the absence of a conflict of interest.

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Review of Literature, Data entry, Data analysis, and drafting article.
HK (Assistant Professor)
Conception of Study, Development of Research Methodology Design,
KR (CMO)
Study Design, manuscript review, critical input.
MAR (Resident)
Review of Literature, Data entry, Data analysis, and drafting articles.
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Conception of Study, Development of Research Methodology Design,

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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