Biological and Clinical Sciences Research Journal
eISSN: 2708-2261; pISSN: 2958-4728
www.bcsrj.com
DOI: https://doi.org/10.54112/bcsrj.v2024i1.837
*Biol. Clin. Sci. Res. J., Volume, **2024**: 837*
Original research article

CHANGES IN METABOLIC AND RENAL SYSTEM AFTER HCV CLEARANCE IN CHRONIC VIRAL HEPATITIS PATIENTS TREATED WITH DIRECT-ACTING ANTIVIRALS

PASHA H[1*], TARIQ AT[2], BANGASH A[1], SALIM M[1], MOHIUDIN T[1]

[1]Department of Emergency, Shifa International Hospital Islamabad, Pakistan
[2]Department of Internal Medicine, Shifa International Hospital Islamabad, Pakistan
**Correspondence author email address:* hrspsh700@gmail.com

(Received, 27th February 2024, Revised 20th April 2024, Published 21st May 2024)

Abstract: *Chronic hepatitis C infection is associated with metabolic and renal abnormalities, with direct antiviral agents (DAAs) offering a promising treatment approach. However, the influence of hepatitis C virus (HCV) clearance on metabolic and renal parameters in these patients remains underexplored.* ***Objective:*** *This study aimed to assess the impact of HCV clearance on the metabolic and renal system of chronic hepatitis C patients treated with direct antiviral agents.* ***Methods:*** *A prospective study was conducted at the Department of Medicine, Shifa Hospital, Islamabad, from January 2022 to January 2024. A total of 323 patients with chronic hepatitis C treated with DAAs were included. Hepatic and renal function tests were recorded before treatment, post-treatment, and 6-month follow-up. Insulin resistance (IR) and B-cell function were evaluated using the homeostatic model assessment (HOMA). All patients received DAAs treatment, with or without ribavirin. Statistical analysis was performed using appropriate methods.* ***Results:*** *Following HCV clearance, both groups exhibited a significant decrease in fasting glucose and insulin levels and improvements in HOMA-IR values. Additionally, decreased creatinine levels and increased glomerular filtration rate (GFR) indicated enhanced renal function. Sustained virologic response (SVR) emerged as an independent predictor of improvement in GFR and HOMA-IR.* ***Conclusion:*** *HCV clearance in chronic hepatitis C infection, achieved through treatment with direct antiviral agents, leads to notable improvements in renal and metabolic parameters. These findings underscore the importance of achieving SVR in managing chronic hepatitis C.*

Keywords: Direct antivirals, Hepatitis C, Metabolism, Renal

Introduction

One of the significant causes of liver disease is chronic hepatitis C infection, which affects almost over 71 million people globally. (1) The infection damages the liver and manifests the virus in other organ systems. (2) These extrahepatic systematic presentations of HCV are correlated to an increased risk of morbidity and mortality. HCV leads to comorbid diseases like diabetes, kidney disease, cardiovascular disorders, and cerebrovascular disease.

HCV is directly associated with the etiology of glucose metabolism disorders, including insulin resistance and diabetes type II. HCV increases the risk of developing insulin resistance in 80% of the patients and enhances the risk of diabetes up to twofold as compared to non-HCV cases. (3) In addition, a decline in serum LDL, serum total cholesterol, and serum very low-density lipoprotein levels has been reported in HCV patients due to the involvement of lipids in the virus life cycle. (4)

Literature also reports a high incidence of chronic kidney disease in HCV patients, which progresses to end-stage kidney disease rapidly in such cases as opposed to healthy patients. (5) The use of direct-acting antivirals as a treatment for HCV has improved patients' outcomes. Almost 99% of patients achieve a sustained virologic response after treatment with DAAs.(6) Since HCV influences the metabolism and renal system directly or indirectly, we hypothesized that HCV clearance after direct antivirals may change the metabolic and renal variables in infected patients, which is crucial to investigate for better outcomes and follow-up.

This study assessed HCV clearance's influence on the metabolic and renal system of chronic hepatitis C patients treated with direct antiviral agents.

Methodology

A prospective study was conducted in the Department of Medicine, Shifa Hospital, Islamabad, from January 2022 to January 2024. A total of 323 patients with chronic hepatitis C treated with direct antivirals were selected for the study by consecutive selection. Patients who did not respond to antivirals, with HCV relapse, HIV, HBV coinfection, and acute renal failure were excluded. The sample size was calculated by keeping the power of the study at 80%, a 5% error margin, a population size of 2000 participants, and a Confidence Interval of 95% by EpiInfo using the formula mentioned in Bolarinwa et al.(7) All patients provided their informed consent to become a part of the study. The hospital's ethical committee approved the study methodology.

All patients were assessed by recording hepatic and renal function tests, blood counts, triglycerides levels, fasting blood glucose, LDL cholesterol, HDL cholesterol, insulin levels, and serum cholesterol before treatment, after treatment, and at 6-month follow-up. Diabetes type II and impaired fasting glucose were diagnosed by following American Diabetes Association guidelines. (8) Creatinine was evaluated using the HPLC technique (reference value: 0.67-1.17). MDRD six variable equation was used to calculate eGFR. HCV genotyping was done using an

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Innolipa assay, and RNA quantitation was done using a real-time PCR assay.

Insulin resistance and B-cell function were evaluated by HOMA using formulas used in Lewandoski et al.(9) The cut-off value for HOMA-IR was calculated to be 2.50. (8) Patients' BMIs were also recorded before treatment, and abdominal ultrasound and Fibroscan were performed to evaluate the extent of liver fibrosis. All patients received DAA treatment under EASL guidelines. (10)

All data was analyzed using SPSS version 24. Continuous data was presented as means, and IQR and categorical data were shown as percentages. A k-S test was performed to check for data distribution normalcy. Paired t-test was used to assess the normal distribution of continuous data. The rank sum test and Friedman test were performed for non-normal distribution. A mixed model design was used to compare results between patients with different degrees of fibrosis. Predictors of improvement in IR and eGFR were assessed by the Cox regression model after adjustment at baseline. Univariate and multivariate analysis was performed, and data was presented as HR or adjusted HR, respectively, with 95% CI. A probability value of less than 0.05 was significant.

Results

A total of 323 HCV patients treated with direct antivirals were analyzed. Three hundred and twelve patients (96.6%) achieved SVR at 6-month follow-up after treatment. Ninety patients had no moderate degree of fibrosis, and 233 had an advanced degree. The majority of the population had HCV genotype Ia (81.4%). The patients were an average of 67 years old, and 47% were male. F3-F4 patients were more likely to be diabetic (26.6%) than F0-F2 patients (10%). Total cholesterol was significantly higher in F0-F2 patients (172.4 (147.3-191)) than in the advanced fibrosis group (Table I).

A significant decrease in fasting glucose and insulin levels was noted in both groups after HCV clearance and at follow-up (89 (83-100) vs 92 (85-108) and (8.9 (4.6-10) vs 9.7 (6.8-13)). HOMA-IR values also decline with IR improvement (2.10 (1.56-2.5) vs. 2.3 (1.9-2.7)), respectively. Serum triglycerides and LDL levels increased in the F0-F2 group after HCV clearance, and HDL levels significantly decreased. A decrease in creatinine and increased GFR levels in both groups indicated improvement in renal function. Table II shows patients' renal and metabolic profiles before and after treatment and at follow-up.

69% of patients showed improvement in HOMA-IR levels. Those who did not show improvement most likely had advanced fibrosis (17.2 ± 11.3 kPa) as compared to those who showed improvement (9.8 ± 7.0 kPa) ($p<0.001$). HOMA-S increased at follow-up (105 ± 65.6) and after treatment (101 ± 65.8) as compared to baseline values (77.4 ± 53.1) ($p<0.001$). HOMA-B decreased at follow-up (115.3 ± 43.1) and after treatment (120.9 ± 45.6) as compared to baseline (137.5 ± 60) ($p<0.001$). Achievement of SVR was seen as an independent prediction factor of improvement in HOMA-IR (adjusted hazard ratio: 0.271, 95% CI: 0.283-0.697, $p<0.009$) (Table III).

The multivariate analysis presented in Table IV indicates SVR as an independent prediction factor of improvement in GFR (adjusted hazard ratio: 0.063, 95% CI: 0.010-0.541, $p<0.009$), and age proved to be a negative predictor (aHR: 0.961, 95% CI: 0.935-0.981, $p<0.005$).

Diabetic and non-diabetic, hypertensive and not hypertensive, older patients with GFR more than 60 and with normal cholesterol showed improved eGFR, increased cholesterol, and decreased glucose levels after viral clearance. The treatment regimens did not significantly differ in metabolic and renal outcomes. Patients with GFR equal to or less than 60 and hypercholesterolemia showed no notable improvement in renal outcomes, thus being the negative predictive factors (Table V).

Table I: Patients' baseline characteristics

Variables	F0-F2 (n= 90)	F3-F4 (n=233)	P-Value
Male sex	42 (46.7%)	110 (47.2%)	0.990
Age	66 (52-70)	67 (61-72)	0.009
Smoking	36 (40%)	52 (22.3%)	0.010
BMI	24.4 (21.7-26.3)	25.1 (22.8-28.4)	0.036
Diabetes	9 (10%)	62 (26.6%)	0.001
Impaired fasting glucose	23 (25.6%)	47 (20.2%)	0.469
Hypertension	45 (50%)	126 (54.1%)	0.631
Glycemia	96 (85-107)	100 (92-120)	0.538
Cholesterol	172.4 (147.3-191)	152 (124-172)	0.001
Creatinine	0.82 (0.73-0.92)	0.81 (0.5-0.94)	0.065
GFR	78 (66.2-96)	82 (66-98)	0.542
Liver stiffness	5.4 (4.7-6.6)	15.9 (10.7-25.1)	0.001
Genotype			0.282
1a	6 (6.7%)	15 (6.4%)	
1b	3 (3.4%)	6 (2.6%)	
2	7 (7.8%)	12 (5.1%)	
3a	68 (75.5%)	195 (83.7%)	
4	2 (2.3%)	3 (1.3%)	
Mixed	4 (4.5%)	2 (0.8%)	
Child-Pugh score			
A	-	210 (90.1%)	
B	-	23 (9.9%)	
Albumin	4.08 (3.5-4.33)	3.8 (3.4-4.0)	0.008

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Bilirubin	0.55 (0.42-0.81)	0.74 (0.4-0.9)	<0.001
Treatment			<0.001
Ombitasvir/ Paritaprevir/ Ritonavir + Dasabuvir ± Ribavirin	25 (27.8%)	70 (30%)	
Ledipasvir/ Sofosbuvir ± Ribavirin	-	45 (19.7%)	
Sofosbuvir + Daclatasvir ± Ribavirin	4 (4.5%)	39 (16.7%)	
Simeprevir + Sofosbuvir ± Ribavirin	-	34 (14.6%)	
Sofosbuvir/ Velpatasvir ± Ribavirin	24 (26.7%)	21 (9%)	
Elbasvir/ Grazoprevir	8 (8.9%)	14 (6%)	
Glecaprevir/ Pibrentasvir	27 (30%)	10 (4.3%)	
Peg-interferon + Simeprevir ± Ribavirin	2 (2.2%)	-	

Table II: Patients' profile before and after treatment and at follow-up

Variables	F0-F2	P	F3-F4	P	P**
Fasting glucose		<0.030		<0.001	<0.001
Start of treatment	96 (85-105)		100 (91-120)		
End of treatment	92 (85-104)		97 (88-110)		
At follow up	89 (83-100)		92 (85-108)		
Fasting insulin*		<0.001		<0.001	<0.030
Start of treatment	11 (6-14)		15 (9.54-21)		
End of treatment	9 (5.9-12.7)		11.3 (8-16.4)		
At follow up	8.9 (4.6-10)		9.7 (6.8-13)		
HOMA-IR*		<0.001		<0.001	<0.001
Start of treatment	2.77 (2.07-3.10)		4.2 (3.2-4.7)		
End of treatment	2.46 (1.53-3.39)		2.6 (2.0-3.9)		
At follow up	2.10 (1.56-2.5)		2.3 (1.9-2.7)		
Total cholesterol		<0.001		<0.009	<0.462
Start of treatment	169 (150.4-192)		152 (124-171)		
End of treatment	188 (168.1-217.5)		171 (147.3-201.6)		
At follow up	190 (171.6-217)		168 (131-188)		
LDL cholesterol		<0.001		<0.015	<0.010
Start of treatment	100 (82.4-124.1)		90 (66-106)		
End of treatment	120 (102.6-140.5)		98 (76-124)		
At follow up	117 (96-132.4)		102 (86.7-120.1)		
HDL cholesterol		<0.001		<0.483	<0.366
Start of treatment	48 (40-56.2)		48 (38-58.9)		
End of treatment	48 (38-61)		48 (38-58.3)		
At follow up	47 (41-58)		46 (35-55)		
Triglycerides		<0.001		<0.724	<0.001
Start of treatment	92.1 (69.8-114)		91 (75.4-121.3)		
End of treatment	105 (75-137)		90 (69-130)		
At follow up	101 (78-132)		90 (67.5-121.4)		
BMI		<0.003		<0.051	<0.095
Start of treatment	24.4 (21.7-26.8)		25.5 (22.4-28.2)		
End of treatment	25.2 (22.7-27.3)		25.4 (22.3-29.8)		
At follow up	25.8 (22.7-27.3)		26.2 (23.6-29.2)		
Creatinine		<0.001		<0.001	<0.381
Start of treatment	0.77 (0.72-0.90)		0.75 (0.66-0.89)		
End of treatment	0.79 (0.67-0.84)		0.74 (0.71-0.84)		
At follow up	0.72 (0.63-0.92)		0.70 (0.62-0.83)		
GFR		<0.001		<0.001	<0.073
Start of treatment	79 (67.8-97)		83 (67-97)		
End of treatment	81 (69-107)		82 (65-97.3)		
At follow up	89 (75-108)		91 (72.4-107)		

*Diabetics excluded **Mixed model analysis

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Table III: Predictors of HOMA-IR improvement

Variable	Improvement	No improvement	Adjusted univariate analysis			Adjusted multivariate analysis		
			Hazard ratio	**95% Confidence Interval**	**P**	**Adjusted hazard ratio**	**95% Confidence Interval**	**P**
All patients	223 (69%)	100 (31%)						
Age	66 (57-72)	70 (62-75)	0.927	0.900-1.010	<0.030	0.970	0.947-0.995	<0.005
Male gender	101 (45.3%)	51 (51%)	1.310	1.270-2.212	<0.690	1.032	0.585-1.778	<0.940
Hypertension	109 (49.3%)	50 (50%)	1.073	0.787-1.708	<0.448	1.208	0.723-2.071	<0.468
Total cholesterol	160 (132.3-181)	155 (134.7-178)	0.974	0.762-1.063	<0.492	0.100	0.982-1.026	<0.598
Cirrhosis	98 (43.9%)	55 (55%)	0.901	0.920-1.754	<0.242	0.636	0.382-1.110	<0.110
SVR at follow-up	218 (98.2%)	94 (94%)	0.325	0.274-0.996	<0.030	0.271	0.283-0.697	<0.009

Table IV: Predictors of eGFR improvement

Variable	**Improvement**	**No improvement**	**Adjusted univariate analysis**			**Adjusted multivariate analysis**		
			Hazard ratio	**95% Confidence Interval**	**P**	**Adjusted hazard ratio**	**95% Confidence Interval**	**P**
All patients	219 (67.8%)	104 (32.5%)						
Age	66 (57-72)	70 (62-75)	0.963	0.930-0.985	<0.010	0.961	0.935-0.981	<0.005
Male gender	100 (46.1%)	53 (50.1%)	1.325	0.718-2.406	<0.271	1.278	0.710-2.250	<0.422
Hypertension	111 (50.7%)	54 (52%)	1.061	0.592-1.893	<0.864	1.152	0.610-2.180	<0.663
Diabetes	46 (21%)	26 (25%)	0.794	0.394-1.577	<0.488	0.716	0.374-1.428	<0.349
Total cholesterol	160 (132.3-181)	155 (134.2-178)	0.986	0.993-1.023	<0.285	0.998	0.995-1.010	<0.483
Cirrhosis	97 (44.3%)	58 (55.8%)	1.457	0.779-2.658	<0.296	1.367	0.766-2.382	<0.281
SVR at follow-up	215 (98.2%)	98 (94.2%)	0.058	0.010-0.591	<0.020	0.063	0.010-0.541	<0.009

Table V: Outcome of HCV clearance on study variables at follow-up

Patients	**Glycemia**	**P**	**Hypercholesterolemia**	**P**	**GFR**	**P**
Baseline						
Age more or equal to 70	100.2 (91.7-118.6)	<0.020	151.4 (130.5-173.8)		82 (65-95)	
Age less than 70	100 (93-114)	<0.010	162 (136-184)		82.6 (75-110)	
Diabetes	95 (85-104)		167 (147-186)		81 (70-103)	
Non-diabetic	102 (95-130)		153 (125.9-176.3)		80 (68-99)	
Hypercholesterolemia	102 (86-112)		210 (206-230)		83 (70-95)	
No- hypercholesterolemia	101 (92.6-116)		154 (126-170)		80 (67.2-97)	
GFR less or equal to 60	105 (92-132)		132 (103.6-161)		83 (73-101)	
GFR of more than 60	97 (89.2-112)		159 (132.7-181)		83 (72-101)	
Hypertension	100.4 (91-122.6)		154 (129.8-180)		77 (62-94.7)	
No hypertension	100 (88-110)		158 (133-185)		86.8 (77-104.6)	
SOF based treatment	102 (93-125)		153.9 (124-177.8)		91 (71-110)	
Non-SOF based	97 (90-109)		161 (135-180)		81 (70-90)	
After treatment						
Age more or equal to 70	94 (88-105.7)		169 (136-187)	<0.010	90 (69-104)	<0.005
Age less than 70	93 (90-104)		179 (148-205)	<0.001	89 (81-114.7)	<0.003

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Diabetic	123.9 (117-139.5)	<0.001	167 (147-186)	<0.001	81 (71-101)	<0.009
Non-diabetic	89 (84-97)	<0.010	165 (137.8-191.4)	<0.020	90 (70-108)	<0.01
Hypercholesterolemia	100 (84-107)	<0.330	220.3 (210-226.7)	<0.183	86 (74-110)	<0.222
No- hypercholesterolemia	93 (87-105)	<0.02	170 (141-190)	<0.001	91 (75-107)	<0.023
GFR less or equal to 60	99 (89-125)	<0.038	165 (126-182.4)	<0.001	57 (46-65)	<0.379
GFR of more than 60	93 (89-103.5)	<0.094	173 (150-200)	<0.011	91 (77-110.4)	<0.017
Hypertension	92 (87-103)	<0.017	175.3 (145.7-200)	<0.006	83 (69-101)	<0.003
No hypertension	92 (86-103)	<0.026	175.1 (145.2-200)	<0.012	93 (78-111.1)	<0.001
SOF based treatment	95 (90-110.6)	<0.013	171.9 (142.3-199.8)	<0.001	89 (71-109)	<0.008
Non-SOF based	91 (84-103)	<0.023	173 (147.3-200)	<0.006	91 (76-107)	<0.005

Discussion

This study assessed the changes in metabolic and renal systems in HCV patients treated with direct antivirals. The results showed a significant effect of HCV clearance on metabolism and renal profile.

Glucose metabolism improved as the fasting glucose and insulin decreased after viral clearance and insulin resistance improved in all patients regardless of the degree of fibrosis. According to the results, there was an improvement in 90% of patients with IR, among which 58.2% reported average IR values and 31.8% showed improved levels. HOMA-S and HOMA-B values also improved, with the data indicating HCV clearance as an independent predictive factor for improving HOMA-IR.

After SVR, glucose levels reached the normal range in 31.5% of patients with IFR before treatment. Glycemic control improved in 43.3% of diabetics, and they required minimum to no antidiabetic drugs after HCV clearance. No significant difference in non-SVR patients was seen. These results comply with previous data. (11, 12) Adinolfi et al. also reported improved glucose levels, insulin sensitivity, and insulin resistance in advanced fibrosis patients and non-diabetics. (13) In the current study, HCV clearance improved glucose metabolism in patients with all stages of fibrosis, which is independent of the subjects' body mass index (BMI), as an increase in BMI was observed before treatment completion.

Literature also backs these findings of a positive association between HCV clearance and glucose metabolism after treatment with DAAs.(14-16) IR and glucose levels are reduced after the achievement of SVR, improving glycemic control and diminishing the need for drugs. (17, 18) Chaudhury et al.(19) And Carnovale et al. (20) Contradict our study results. We reported advanced fibrosis as a negative predictor of this improvement. Mada et al. (15) And Badry et al. (21) Confirm these findings and also report high BMI, family history of diabetes, and duration of diabetes as a predictor of poor outcomes.

All fibrosis patients in our study showed increased LDL and total cholesterol after clearance, treatment, and follow-up. However, a decrease in HDL and triglyceride increase is not significantly reported in early fibrosis patients. Other studies also report an increase in LDL after clearance, but the results on trends of HDL and triglycerides are inconsistent. (22-24)

In the present study, patients in all fibrosis stages showed improved renal function after clearance as creatinine decreased, and a 10% increase in eGFR was noted. Hence, eGFR is an independent predictive clearance factor, and age influences it negatively. As HCV is related to a high risk of chronic kidney disease, HCV is 10-fold more common in hemodialysis patients and accelerates the progression to end-stage renal disease. However, treating DAAs improves renal function in such patients by decreasing creatinine and proteinuria and increasing eGFR, ultimately reducing the probability of disease progression. (25)

A recent prospective study reported improved eGFR after viral clearance in patients treated with DAAs. (26) People with diabetes and elderly patients did not show significant improvement as compared to younger and non-diabetic patients. Our study results contradict this finding as we noted considerable improvement in diabetics and patients treated with any therapy. Baseline eGFR and advanced age negatively impacted the renal function in our study. This difference in predictive factors in both studies may be due to differences in sample size, demographics, and data analysis techniques. Since neither study recorded the duration of diabetes, a discrepancy in population may have also contributed to this difference.

Conclusion

HCV clearance in chronic hepatitis C infection treated with direct antivirals improves renal and metabolic parameters after achievement of SVR.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate.
Approved by the department concerned. (IRB/SIHI/524 dated 10-10-21)

Consent for publication
Approved

Funding
Not applicable

Conflict of interest

The authors declared an absence of conflict of interest.

Authors Contribution

AHMAD TALHA TARIQ (Resident)
Concept & Design of Study, Final Approval of version
ASFAND BANGASH (HO)

[Citation: Pasha, H., Tariq, A.T., Bangash, A., Salim, M., Mohiudin, T., (2024). Changes in metabolic and renal system after HCV clearance in chronic viral hepatitis patients treated with direct-acting antivirals *Biol. Clin. Sci. Res. J.*, **2024***: 837*. doi: https://doi.org/10.54112/bcsrj.v2024i1.837]

Drafting, data collection
MUHAMMAD SALIM (MO)
Data Analysis
TALHA MOHIUDIN (HO)
Drafting, data collection
HARIS PASHA (HO)
Drafting, data collection

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[Citation: Pasha, H., Tariq, A.T., Bangash, A., Salim, M., Mohiudin, T., (2024). Changes in metabolic and renal system after HCV clearance in chronic viral hepatitis patients treated with direct-acting antivirals *Biol. Clin. Sci. Res. J.*, **2024***: 837*. doi: https://doi.org/10.54112/bcsrj.v2024i1.837]