ORIGINAL ARTICLE

To Determine Improvement of Sustained Virological Response by Adding Metformin with Interferon & Ribavarin as Compared to Interferon & Ribavirin Alone in Chronic Hepatitis C patients with Insulin Resistance

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ABSTRACT

Aim: To determine the improvement of Sustained Virological Response by adding Metformin in regular therapy, interferon and Ribavarin as compared to combination therapy alone in chronic hepatitis C patients with Insulin resistance (IR)

Methods: Total 148 cases of PCR carried out for diagnosis of hepatitis "C" infection and HOMA-IR with a cut of point >2.5 were enrolled in the study from out-patient department of Mayo hospital, Lahore, Pakistan. Patients with HOMA-IR >2.5 were given metformin 850mg twice daily for one week. If HOMA-IR did not decrease by 50% then metformin 1000mg twice daily would be given for another one week to see the response. Patients with 50% decrease in HOMA-IR, with Metformin therapy were included in the study and respective dose of metformin was continued for the period of study. Patients were then divided in two groups, group "A" and group "B" by simple random sampling method; **Group A** patients were treated with standard therapy and **Group B**: were treated with metformin and standard therapy. All patients with detectable HCV-RNA genotype 3 by PCR, insulin resistance (>2.5) determined by HOMA-IR and fasting blood sugar < 100mg/dl were included in study. Patient diagnosed with malignancy, renal dysfunction, under treatment with immunosuppressive therapy, any stigmata of de-compensated liver disease, diabetes mellitus type II or taking any anti diabetic therapy and pregnancy or breast feeding mothers were excluded from study. Sustained virological response was defined as undetectable serum HCV-RNA level (<50IU/ml) after 24 weeks of treatment by qualitative polymerase chain reaction method.

Results: This study included 148 patients. The range of patients age was 25 to 70 years old with average age of 48.51 11.25 years, Out of 148 patients, 83(56.08%) were males while 65 (43.92%) were female, thus both treatment groups had more male cases than female also showed insignificant difference between treatment groups and age distribution as well as clinical characteristics of patient as p-value > 0.05. HOMA-IR score showed statistically insignificant difference among both treatment group at baseline (P-value > 0.05). The mean value of the SVR was significantly improved in metformin added standard therapy group at 24th and 48th week as compared to standard therapy group. In terms of difference, two treatment groups in polymerase chain reaction were statistically significant as (P-value <0.05) at 12th and 48th while at 24th week. **Conclusion:** The standard combination therapy in patients of chronic hepatitis C with insulin resistance due to inclusion of Metformin results in improvement in SVR as compared to standard therapy alone

Keywords: HCV hepatitis C virus (HCV), Insulin resistance (IR), polymerase chain reaction (PCR), homeostasis model assessment (HOMA-IR) score, sustained virological response (SVR)

INTRODUCTION

About 150 million peoples are chronically infected with HCV worldwide according to latest WHO estimate. The highest estimated prevalence for the chronic infection is 4.8% in Pakistan[1]. Chronic hepatitis C might lead to fibrosis evolution; among patients emerging chronic hepatitis C around 20-30% will have cirrhosis of liver within nearly between 20 to 40 years and develops in up to 85% of patients with virus of hepatitis C[2]. In these patients, there is around three time more risk of impairment of glucose metabolism and insulin resistance (IR)[3]. The bidirectional and complex association of HCV and IR is considered, the precise pathogenesis is still unidentified. According to some clinical remarks the expansion of IR in HCV patients is due to A 'fat independent' mechanism[4]. IR and Obesity is linked with Non Alcoholic Fatty Liver Disease (NAFLD) and fatty infiltration to the liver. In epidemiological research, IR is determined by Homeostasis Model Assessment Score (HOMA-IR), a simple clinical tool that might be easily utilized. Insulin sensitivity can be calculated by HOMA-IR, using insulin concentration and fasting blood glucose[5].

By using current therapies, sustained response has been achieved of Hepatitis C infected patients with ribavirin and interferon in more than half of patients. Advanced fibrosis, insulin resistance and high viral load are amongst the aspects which declines response to therapy[5]. Sustained virological response is decreased by impaired insulin sensitivit[5,6]. There is an independent relationship between lower sustained virological response and impaired fasting glucose[7]. Hepatitis C virus increases insulin resistance and insulin resistance recovers with lessening in the threat of diabetes and glucose abnormalities after the clearance of HCV[5,7,8]. A widely prescribed oral biguanide is metformin that decreases the insulin secretion and glucose level and expands glucose profile by reducing output of hepatic glucose and in skeletal muscle, by growing glucose uptake. As biguanide might be dealt by insulin resistance, "for patients of insulin resistance and chronic hepatitis C, SVR can be improved by adding metformin" as suggested

by Xie *et al*[9]. Manuel Romero-Gomez *et al* conducted a research on Hepatitis C genotype1 and observed SVR was 53% in those treated by metformin and in patients dealt by standard therapy and in placebo were 42%[10]. Role of adding metformin in treatment of chronic hepatitis C with insulin resistance in genotype 3, were mostly unidentified[11]. I have conducted a study by adding metformin to standard interferon therapy to define improvement in SVR in patients of insulin resistance and genotype 3.

The present research aims at effectiveness of treatment of hepatitis C with insulin resistance as an additional drug by means of metformin in addition to standard therapy of ribavirin & interferon.

Chronic hepatitis C: The persistence of HCV RNA in serum for 6 months or longer was defined as **C**hronic Hepatitis C by quantitative polymerase chain reaction method. **INSULIN RESISTANCE (IR):** A state having depressed level of response to insulin within person's body tissues. It will be diagnosed in patients having a HOMA-IR score of 2.5 or more[12].

Sustained virological response: An untraceable serum HCV-RNA level (<50IU/ml) after 24 weeks of treatment by qualitative polymerase chain reaction method is defined as SVR.

HOMA-IR Score: The score used to discriminate population with IR to normal individual is known as "HOMA SCORE or Homeostasis model assessment score". It was determined as follows: Fasting insulin (mu/l) x fasting blood glucose (mmol/l) /22.5[13].

MATERIALS AND METHODS

It will be Quasi Experimental Interventional Study performed in East Medical Ward, Mayo Hospital, Lahore. for 2 years from the approval of synopsis from 28th February 2014 to 27th February 2016. Sample size of 148 (74 in each groups) patients was calculated by using 80% Power of Test, 5% level of significance and by taking expected percentage of SVR as 59.2%[11] with standard therapy+Metformin and 38.8%[11] with standard therapy alone. The data here included were taken from research done in genotype 1 as no research for genotype 3 was available. In our working setup most of the patients present with genotype 3 and its sub-types[14].

$$n = \frac{\left(z_{1-\alpha}\sqrt{2\bar{P}(1-\bar{P})} + z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right)^2}{\left(P_1 - P_2\right)^2}$$

Group A: Treatment of patients with standard therapy.
Group B: Treatment of patients with standard therapy along with metformin.

Sampling technique: For inclusion of patients' purposive sampling was employed and while for grouping of patients, A and B simple random sampling was used. HCV-RNA genotype 3 patients, detectable by polymerase chain reaction having insulin resistance greater than (2.5) by homeostasis model assessment (HOMA-IR) method, who were willing to participate and those consisting of fasting blood sugar level less than 100mg/dl will be ***included*** while those with known pregnancy or breast feeding, with any malignancy, renal dysfunction, under treatment with immunosuppressive therapy, with any stigmata of de-compensated liver disease like ascites, oesophageal varices palmer erythema, gynaecomastia, caput medusa, taking any anti diabetic therapy or with diabetes mellitus type II were excluded.

Data collection procedure: After getting approved by the Ethical Committee of Hospital, patients satisfying inclusion and exclusion criteria were taken for research. The respondents in the study belonged to the Out-Patient Department of Mayo Hospital.. The whole basic demographic information was also recorded along with attainment of Informed consent. Patients were expected from out-patient department, for conformation of hepatitis "C" infection real time PCR was carried out. HOMA-IR score was calculated. Patients with HOMA-IR >2.5 were given Metformin 850mg twice daily for one week. If HOMA-IR does not decrease by 50% then Metformin 1000mg twice daily was given for another one week. Those with 50% decrease in HOMA-IR, with Metformin therapy, were involved in the study and respective dose of Metformin was continued for the period of study. Simple random sampling was applied to divide patients in two groups, group "A" and group "B". Patients were informed about study and written consent taken. Patient's clinical history were taken and investigations (white blood cells, Haemoglobin, Platelets, prothrombin time, Liver function test, International Normalization Ratio, activated partial thromboplastin time, renal function test, fasting blood sugar level, fasting insulin, polymerase chain reaction, Genotyping, thyroid stimulating hormone test) were carried out. Patients in group A had received standard therapy (interferon 3 million units, s/c, three times per week and Ribavirin 15mg/kg three times per day) and patients in group B had received standard therapy (interferon 3 million units, s/c, three times per week and Ribavirin 15mg/kg three times per day) with Metformin. This therapy was extended for 24 weeks for both groups. PCR for HCV RNA was performed at the end of therapy to assess end treatment response and patients then were followed up after 24 weeks of treatment and PCR for HCV RNA was repeated to assess SVR. Study variables to be considered were; gender, age, virological response on the basis of PCR. Through pre-designed proforma , all data was recorded.

Data analysis procedure: By Using SPSS 23, data was entered and analyzed with help of mean ± SD, Quantitative data (age, BMI, PCR) was presented. While for Qualitative data frequency table, percentages and appropriate charts were used. Comparison between both groups of SVR were made by using chi-square test. P-value<0.05 was declared as significant.

RESULTS

Table 1: Descriptive and inferential statistics of the Demographical characteristics

	Treatment		Total
	Group A (standard therapy) (n=74)	Group B Metformin and standard therapy (n=74)	
Male	42(56.76%)	41(55.40%)	0.92
Female	32(43.24%)	33(44.59%)	

Out of 148 patients; in group A (standard therapy), 42(56.76%) patients were males and 31(41.89%) patients were females while in the group B (Metformin and standard therapy) 41(55.40%) patients were males and 33(44.59%) were female patients, thus a both the treatment groups had more male cases than female, (P-value > 0.05) (table1).

Table-2: Age distribution with respect to treatment groups

	Treatment		Total
	Group A (standard therapy) (n=74)	Group B Metformin and standard therapy (n=74)	
Age	44.21±5.752	42.84±6.929	0.1927

The mean age presentation in group A (standard therapy) was 44.21±5.752 years, in group B (Metformin and standard therapy) was 42.84±6.929, showed insignificant difference between treatment groups and age distribution as p-value > 0.05

Table-3: Descriptive and inferential statistics of the patient clinical characteristics with respect to the treatment groups.

	Treatment		P value*
	Group A (standard therapy) (n=74)	Group B Metformin and standard therapy (n=74)	
WBC	4.421±5.752	4.284±6.929	0.1927
Hb (g/dl)	14.3±4.34	14.9±5.55	0.465
Pit	218.66±49.52	212.98±48.92	0.489
ALT	89.71±58.75	95.69±69.29	0.573
AST	56.71±48.75	65.69±57.29	0.306
Bilirubin mg/dL	0.75 ± 0.48	0.69 ± 0.52	0.467
ALP (IU/L)	81.3± 40.2	86.5± 47.6	0.473
Albumin (g/dL)	2.6±0.4	2.7±0.6	0.234
PT (seconds)	16.7±2.49	17.0±2.55	0.47
APTT (seconds)	46.7±6.4	45.6±6.8	0.312
INR	1.4±0.90	1.2±0.70	0.1335
Creatinine (mg/dL)	0.73±1.14	1.03±1.17	0.599
BUN (mg/dL)	55.7± 15.8	58.9±18.9	0.265
Fasting BSL	103.6±17.2	104.3±24.2	0.236
Fasting insulin (U/l)	12.6± 3.4	13.7±3.8	0.065
Insulin resistance HOMA-IR score	3.70 ± 0.72	3.80± 0.65	0.376

**P value- for independent sample t test among groups (no significant difference among any lab parameters among groups)*

Table-4: Compare Polymerase Chain Reaction with respect to treatment groups (standard therapy Vs Metformin and standard therapy) at 24th and 48th week

Sustained virological response	Baseline at Receiving (n=74)	24th week (n=74)	48th week (n=74)
Group A (standard therapy)	74(100%)	34(41.89%)	40(52.50%)
Group B (Metformin and standard therapy)	74(100%)	44(59.45%)	53(71.62%)
P-value	1.00	0.048	0.041

The mean WBC, Hb (g/dl), ALT, AST, Bilirubin (mg/dl), ALP (IU/L), Albumin (g/dl), PT (seconds), APTT (seconds),INR, Creatinine (mg/dl), BUN (mg/dl), Fasting BSL, Fasting insulin (U/l) and HOMA-IR score showed statistically insignificant difference among the both treatment group (P-value > 0.05).

Among 148 patients who were randomly divided into two groups by using computer generating method (each group included 74 patients). Group A received standard therapy treatment and Group B received Metformin and standard therapy at 1st and 48th week. The differences between two groups in SVR were statistically significant as P-value <0.05) at 24th and 48th (P <0.05. SVR improved in both groups whereas it was comparatively higher in Group B (P-value< 0.05).

DISCUSSION

Our results showed that male group chronic HCV patients reported higher benefit for treatment (standard vs. metformin added standard therapy) than female patient indicating that men are at increased benefit of standard treatment (56.08%) vs. 55.40%). ROMERO-GO´ MEZ et al established that diabetes is more prevalent in females compared to non-diabetics (56% vs. 56.29%)[10]. Another study by Jian-Wu Yu et al established that treatment therapy is more prevalent in males as (61.22% vs. 63.2%)[15]. Present results showed that mean age in group A and group B respectively were (44.21±5.752 vs. 42.84±6.929) years. In a study by Sharifi HA et al (2014) age of group A and B group were (41.5±11.2 vs. 41.9±11.0 years) similar to our study[16]. Further study by Romero-Go´ MEZ et al., found mean age was 47.1±8.5 vs. 47.7 ±8.9 years. J.-W. Yuet al, examined that in both A and B treatment group mean age was (42 ±6 vs. 40 ±7) years respectively. Present study reported mean HOMA index scale in group A than group B at baseline was as (3.70 ± 0.72 vs. 3.80± 0.65) respectively. In contrast to this study J.W. Yu et al observed a mean HOMA index scale in group A than group B at baseline was (3.80 ±0.71 vs. 3.91 ±0.78). Present study established that metformin was more effective, successfully to demonstrate advantage in patients with initially high HOMA-IR after treatment. ROMERO-GO´ MEZ et al showed that mean HOMA index in both treatment group was high at baseline as 4.31 ±2.24 vs. 4.42 ±2.62[10]. Sharifi et al found less mean HOMA index scale in group B as compared to group A was less at baseline (1.88±1.50 vs. 2.14±1.81), due to small sample size Sharifi et al study showed dissimilar results.(17) Our results showed that metformin + standard therapy is more effective in terms of achieving SVR at 24thand 48th week followup as (59.45% vs. 41.89%) and (71.62% vs. 52.50%). Rouabhia S et al, 2015 reported achieving SVR in patients receiving standard therapy + metformin was significantly higher than in patients receiving standard therapy at 48th week follow –up as (75% vs. 60%)[16].

Further study by ROMERO-GO´ MEZ et al analyzed that there were no differences between arms at baseline, also showed significant achievement of SVR in the metformin+standard therapy group as compared to standard therapy group (54% vs 48%) at 48th week (71% vs. 63%)[10]. According to Jian-Wu Yu et al reported

significant advantage for metformin group although p-value was borderline at 0.043, results initiated that SVR improved in both groups after treatment, although achievement of SVR in those receiving standard therapy + metformin was significantly higher than in those receiving standard therapy at 24th week as (77.4% vs. 35.8%)[15].

However, mechanism of action of metformin, in patients with chronic hepatitis C with insulin resistance, appears to be increasing peripheral insulin sensitivity, because of this, standard therapy alone may be less effective in this study. Further study by Sharifi et al., reported that SVR was 79% in controls (intention to-treat) versus metformin group 75% which wasn't significantly changed. Sharifi et al., studied and could not found a significant benefit for metformin in our study we did not observe an insignificant difference in SVR[17]. Metformin could be favored due to reasons that it works directly on liver, though PPAR γ agonist effect on peripheral metabolism, using unlike insulin sensitizers in a huge cohort of patients with hepatitis C with distinct genotypes[10]. The present research represents the result slightly dissimilar with previous literatures at 24th week due to that reasons.

CONCLUSION

We evidence benefit in adding metformin to the treatment of CHC in terms of improving SVR. Metformin is harmless and relatively well stood in patents of hepatitis C, the addition of metformin with standard treatment may improve global SVR in patients of chronic HCV. Moreover, to confirm the findings of study, larger randomized controlled trial need to be carried out.

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