ASSOCIATION OF OBESITY WITH RAPID VIROLOGICAL RESPONSE IN PATIENTS WITH CHRONIC HEPATITIS C

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ABSTRACT

Objective: To determine the association of obesity with rapid virological response in patients with chronic hepatitis C on antiviral therapy.

Methodology: In this prospective cohort study patients suffering from chronic hepatitis C who required treatment were included after getting ethical approval and informed consent. Patient's weight and height was measured and body mass index (BMI) was calculated. Patients were divided into 2 groups; group 1 having BMI <30 and group 2 having BMI >30 in equal numbers. All the patients were put on weekly pegylated interferon plus ribavirin in fixed divided doses. PCR was done at the completion of 4 week to check for rapid virological response (RVR). After completion of study these 2 groups were compared to see whether any significant association exists between BMI and RVR. RVR was also stratified among age, viral load and gender to see their effect as these are potential effect modifiers.

Results: There were 140 (56.3 %) male and 110 (43.7%) female patients with male to female ratio of 1.2:1. Mean age of the patients was 39.78 ±9.85, while mean BMI was 27.40 ±5.86. Overall the RVR was achieved in 53.2% of the patients. Frequency of RVR was 77(61.6 %) in non-obese patients as compared to 56(44.8%) in obese patients with a p value of 0.008.

Conclusion: Obesity is significantly associated with poor RVR in patients with chronic hepatitis C.

Key Words: Hepatitis C, Obesity, Body mass index, Rapid virological response

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INTRODUCTION

Hepatitis C virus (HCV) is a major cause of chronic liver disease (CLD), cirrhosis and hepatocellular carcinoma (HCC) worldwide with a disease burden of about 170 million[1]. It is also one of the major health problem in Pakistan and in certain localities its prevalence is as high as16%[2]. The HCV treatment has changed significantly since the introduction of highly effective directly acting antiviral agents like protease and polymerase inhibitors since 2011 & onwards. A number of new drugs are available or will be available in near future. Thats why there is a rapid change in treatment paradigm and in hepatology association's recommendations. However pegylated-interferon and ribavirin combination therapy continues to be current standard for chronic hepatitis C treatment in Pakistan as most of the drugs are not available in this region[3,4].

Currently sofosbovir based treatment is available but is costly and still not available in government hospitals and through hepatitis control programs. Furthermore the prevalent genotype in our region is Genotype 2 & genotype 3 in which pegylated interferon based therapy is still recommended often with sofosbuvir.

Several host, viral and metabolic factors have been attributed with therapeutic response of CHC patients as well as duration of infection and type of regimen used for treatment. Among host-related factors black race, male gender, old age, obesity, liver fibrosis/cirrhosis, low ALT level and genetic polymorphisms are associated with poor response to antiviral therapy[5,6]. When considering virological factors high viral loads, genotype 1, NS5A and E1-E2 regions genetic polymorphism and mutations in core and interferon sensitivity determining region (ISDR) have been related to poor outcome. Nevertheless, these correlations have not been found in other studies and remain controversial[7-9].

Among several factors, patient's weight is a factor that can affect the outcome of the HCV treatment with combination therapy whether RVR, EVR, ETR or SVR, with high weight associated with poor outcome. The mechanism of this association is not completely understood but It may be due to correlation of BMI with the

degree of steatosis in hepatitis C[10]. Steatosis decreases the contact area between the drugs and the hepatocytes due to increase in lipid deposits within cells thus affecting drug efficacy[11]. Steatosis also seem to correlate with the severity of fibrosis.[10] Clouston et al[12] showed that steatosis was significantly associated with acinar zone 3 steatohepatitis like fibrosis in patients with hepatitis C. Similarly obesity and menopause were linked to HCV relapse after treatment with interferon in another study[13].

Similarly insulin resistance also decreases the chances of SVR and reducing weight leads to an improved in SVR to HCV therapy[14,15]. Increased weight and BMI are also associated with poor RVR and EVR. In a population based study in USA done on 3509 patients in which 1085 patients belong to genotype 2 & 3; RVR in patients with BMI <30 was 68% as compared to 55% in patients with BMI >30 in genotypes 2 and 3[16].

Rationale of this study was that patients who achieve RVR have the highest SVR rate regardless of the genotype which is our ultimate goal of treatment[17]. As obesity is associated with poor virological response in patients with chronic hepatitis C, we want to measure RVR in obese and non-obese patients and its significance. If this association is demonstrated in our population of hepatitis C patients then obese patient can be motivated to reduce weight.

METHODOLOGY

This prospective cohort study was conducted in Hepatitis Clinic and Gastroenterology Unit of Lady Reading Hospital, Peshawar. Sample size was 125 in each group considering percentages of RVR in obese and non obese patients (68% and 55%)[16] with 80% power of test, 95% confidence interval and relative risk of 0.68. Sampling technique was non-probability consecutive sampling.

Both males and females between 18 to 60 years of age were included. Patients suffering from chronic hepatitis C as confirmed by HCV anti bodies by ELISA and positive quantitative PCR in whom we were going to start the combination therapy with pegylated Interferon alpha 2a and ribavirin in fixed dose combination were enrolled.

Patients were having genotype 2 & 3 and normal USG, PT, Hb, TLC and platelets.

Patients suffering from co-infection with hepatitis B or HIV, patients already having cirrhosis and those having other co morbidities were excluded from study.

Above factors are confounders and will make the study results biased if included. Patients with untypeable genotype as well as other than 2 & 3 were excluded because these genotypes are strong independent predictors of RVR and SVR regardless of viral load and obesity when using interferon regimen.

Rapid virological response (RVR) was measured in term of positive (>50 IU/ml) or negative (<50 IU/ml) HCV PCR test which was carried out 4 weeks after starting the therapy. Obesity was measured in term of BMI which is calculated by dividing a person weight in kg by the square of his or her height (in meter) expressed as kg/m^2. BMI of >30 was taken as cutoff for obese patients according to CDC guidelines. Value of 800000 IU/ml was taken as cutoff for low and high viral load according to WHO criteria

After approval from hospital's ethical committee, data was collected from the hepatitis OPD of Gastroenterology Unit, Lady Reading Hospital, Peshawar. Patients fulfilling the inclusion criteria were selected and subsequently put on standard treatment with pegylated interferon alfa 2a plus ribavirin. Patient's weight in kg was measured using a bathroom scale and height was measured using a standard measuring tape (body meter measuring tape with wall mount) and was expressed as meters. After that BMI was calculated and patients were divided into 2 groups; group 1 having BMI<30 and group 2 having BMI >30 in equal number. These patients were monitored at 2 & 4weeks for compliance and side effects like anemia, leucopenia and thrombocytopenia. RVR (rapid virological response) was done at the completion of 4 week and was checked for the presence or absence of HCV-RNA. Those who had undetectable RNA were labeled to have positive RVR while those who had detectable RNA were labeled to have negative RVR. After completion of study these 2 groups were compared to see whether any significant association exists between BMI and RVR. RVR was also stratified among age, viral load and gender to see their effect as these are potential effect modifiers. All information/data was recorded on performa for analysis. Strictly exclusion criteria were followed to control confounders and bias in the study.

Data was analyzed using Statistical Package for Social Sciences (SPSS) software version 17. Frequency and percentages were calculated for categorical variables like gender and RVR. Mean and standard deviation was calculated for the numerical data like age, viral load, weight, height, BMI, Hb, TLC and platelets. RVR was stratified among age, viral load and gender to see the effect modifiers and result were presented in graphs and tables. Chi square test was applied to measure the strength of association between two groups. P value < .05 was considered significant.

RESULTS

The study population consisted of 250 patients. There were 140 (56.3 %) male and 110 (43.7%) female patients with male to female ratio of 1.2:1. Age of the

study population ranged from 19 to 61 years with mean age of 39.78 ±9.85 (Table 1). Among these patients 207 had genotype 3a, 13 had genotype 3b while 3 of the patients had both genotype 3a and 3b. Genotype 2a was positive in 27 patients while none of the patients had 2b genotype.

Mean weight was 71.76 ±14.28 with a range of 40 to 105. Mean height was 162.22 ±9.31 with a range of 5 to 6 while mean BMI was 27.40 ±5.86 (Table 2).

After 4 weeks, PCR was done to see for RVR. Overall the RVR was achieved in 53.2% of the patients. In male the RVR was achieved in 49.3% of the patients while it was achieved in 58.2% of the female patients (Table 3). Frequency of RVR was 77(61.6 %) in non-obese patients as compared to 56(44.8%) in obese patients, p value 0.008 (Table 4).

Association of RVR with gender (p value 0.16), age group (p value 0.41) and viral load (p value 0.89) were

Figure 1: Age distribution of patients

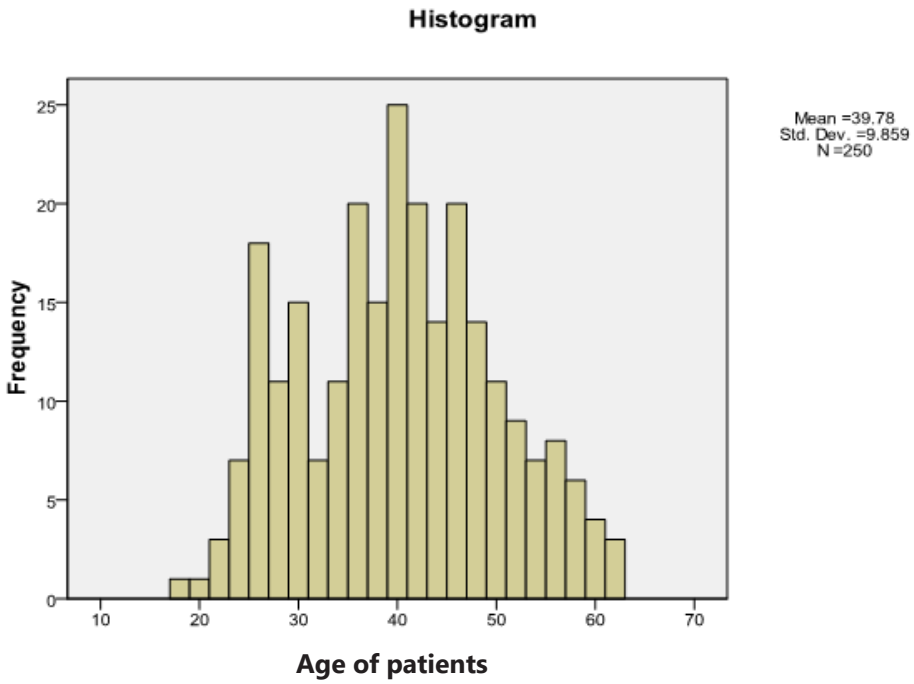

Table 2: Anthropometric distribution of patients

	Min	Max	Mean	SD
Weight (kg)				
Male	49	105	73.06	13.79
Female	31	99	70.01	14.78
Total	31	105	71.76	14.28
Height (in cms)				
Male	154	182	168.66	6.51
Female	142	163	153.13	5.1
Total	142	182	162.77	9.34
BMI				
Male	15.95	39.35	25.7	5.21
Female	15.37	41.74	29.44	6.03
Total	15.37	41.74	27.4	5.86

Table 3: Frequency of RVR (n = 250)

RVR		Frequency	Percent
Male	Yes	69	49.3
	No	71	50.7
	Total	140	100
Female	Yes	64	58.2
	No	46	41.8
	Total	110	100
Total	Yes	133	53.2
	No	117	46.8
	Total	250	100

Table 4: Association of BMI with RVR (n = 250)

RVR		Group		
		Non-Obese	Obese	Total
Yes	Count	77	56	133
	% within RVR	57.9%	42.1%	100.0%
	% within Group	61.6%	44.8%	53.2%
No	Count	48	69	117
	% within RVR	41.0%	59.0%	100.0%
	% within Group	38.4%	55.2%	46.8%
Total	Count	125	125	250
	% within RVR	50.0%	50.0%	100.0%
	% within Group	100.0%	100.0%	100.0%

Chi-square test was applied in which p value was 0.008

Table 5: Association of RVR with gender, age and viral load

RVR		Yes	No	Total	P Value
Sex	Male	69 (51.9%)	71 (60.7%)	140 (56%)	0.16
	Female	64 (48.1%)	46 (39.3%)	110 (44%)	
Age	<40	66 (49.6%)	52 (44.4%)	118 (47.2%)	0.41
	>40	67 (50.4%)	65 (55.6%)	132 (52.8%)	
Viral Load	<800000	91 (68.4%)	81 (69.2%)	172 (68.8%)	0.89
	>800000	42 (31.4%)	36 (30.8%)	78 (31.2%)	
Total		133	117	250	

statistically not significant (Table 5).

DISCUSSION

The response to interferon based HCV therapy is not optimal in certain groups of patients despite increases in RVR and SVR in general. Identifying both favorable and unfavorable factors associated with treatment response in CHC can provide crucial information for better treatment outcome in patients with Hep C. Modification of certain factors like drug dose and weight may increase the odds of successful therapy. Similarly early identification of non-responders may help to limit drug induced side effects as well as healthcare expenses. These patients can be put on direct acting antiviral drugs from the beginning altogether.

Our study demonstrated that obesity when expressed as BMI is significantly associated with poor RVR in HCV patients compared to non-obese. This is in agreement with other studies which measure the outcome of CHC treatment. In a large population study done in USA,

BMI>30 was associated with lesser RVR as compared to BMI <30 in genotype2 (p value 0.008)[16]. In another local study done in genotype 3, SVR in patients weighing less than 65 kg was 70% while SVR in patients weighing >65 kg was 50.46%, (OR=2.277, 95% CI=1.246-4.161, p=0.007)[18]. Reduction in weight improves SVR in HCV therapy. Similarly low weight and BMI are associated with better EVR as well. In a recent study BMI <27 was associated with EVR in 59.3% of patients as opposed to 49.3% in patients with BMI>27 (p value 0.0001)[19]. In the same study weight <75 was associated with EVR in 58.4% of patients as opposed to 51.5% in patients weighing more than 75 kg (p value 0.0095); however this association was not statistically significant.

Similarly in another study BMI >27 was associated with failure to achieve EVR in both univariate and multivariate analyses[20]. In still another study a total of 253 patients were classified into 3 groups i.e. normal, overweight and obese according to BMI and tested for various variable as predictors of response. After adjusting confounding variables and using logistic regression significant differences in treatment response were found according to BMI group, genotype and cirrhosis with a p value <.01 in all. The odds ratio (OR) for successful treatment was 0.23 for obese patients as compared to normal and overweight patients. Obesity, only when defined in terms of BMI is an independent negative predictor of response to hepatitis C treatment[21].

The data about female gender as a predictor of good response to combined interferon therapy is mixed. Female patients had been shown to achieve higher SVR rates compared to males using standard interferon and ribavirin combination in two old studies (p <0.004). However this correlation was not statistically significant in pegylated interferon plus ribavirin registration trials[22]. Similarly in Phase III clinical trials using protease inhibitors boceprevir and telaprevir gender had no impact on SVR rate[23]. In another study logistic regression identified five independent factors significantly associated with good response i.e age <40 years, female gender, viral load <2 million copies/ml, genotype 2 or 3 and minimal fibrosis stage[24,25]. Our data showed a slightly more RVR rate in females than males (58% vs 49%) however this was not statistically significant (p value 0.16).

Most of the randomized control trials using pegylated interferon plus ribavirin combination showed that younger age had increased likelihood of achieving SVR when univariete and multivariate analyses were done. Patients younger than 40-45 years had better SVR rates[26]. In protease inhibitors BOC & SOC phase III trials patients younger than 40 years achieved slightly higher SVR rates in BOC arm[27]. In study done by Rodriguez-Torres et al[19] done in genotype 1 patients to determine factors associated with RVR and SVR to pegINF alfa-2a and ribavirin , there was significant association of age <40 with both RVR and EVR (OR 1.56; p =0.0085). In their study McHutchison et al[28] while comparing pegINF alfa-2a with pegINF alpha-2b with ribavirin in HCV patients reported that age >40 was associated with relapse in final logistic regression after successful achievement of ETR (OR 2.05; p value >0.001). However in our study this association was not found significant (p value =0.41).

Pretreatment viral load affects the treatment outcome in patients with chronic HCV using different cutoffs to define a "low" viral load (<400,000 IU/ml to <800,000 IU/mL)[15]. However this has a lower predictive value for SVR in genotype 2 or 3 compared to genotype 1 which are more IFN-sensitive genotypes. In genotype 3 infected patient SVR was achieved at rates of 81, 70 and 59% at <400,000, 400,000–800,000 and >800,000 IU/ml baseline viral loads respectively. In genotype 2 patients, SVR rates were 82, 79, and 73%, respectively for the same HCV RNA level[24]. In a study conducted by Shiffman et al[29] the SVR rates in patients with a pre-treatment low viral load of 400,000 IU per/ml was 81% which was more as compared to viral load between 400,000IU/ml and 800000IU/ml (74%) and >800,000 IU/ml viral load (67%). Odds ratio for ≤400,000 IU/ ml vs. >800,000 N IU/ml was 3.01(P <0.001) while odds ratio for >400,000 to 800,000 IU/ml vs. >800,000 IU/ml was1.64 (P =0.02). In our study the association was not statistically significant when >800,000 viral load was taken as cut off point. This may be due to different cutoff value for low and high viral load or due to the fact that only genotype 2 & 3 were taken in the study which already have a favorable outcome than other genotypes.

LIMITATIONS OF STUDY

Our study had a few limitations. First ultimate goal of treatment in CHC is to achieve SVR and all conclusions should be drawn based on whether a group of people with certain characteristics achieve SVR or not. Instead we used RVR as a measure of outcome which although is the best predictor of SVR regardless of genotype. We did so because checking for SVR will require a prolonged duration of study (at least 1.5 to 2 years) and there is fear of loss to follow up as patients usually don't show up once the treatment is over. Secondly response to treatment in chronic hepatitis C depends on so many factors including host genetic polymorphism and viral genetic variability and mutation as already mentioned in introduction. Taking into account so many factors was beyond our scope and resources.

CONCLUSION

Obesity was significantly associated with poor RVR in patients with chronic hepatitis C.

RECOMMENDATIONS

Obese patients are likely to have poor SVR as patients who achieve RVR have the highest rate of sustained virological response regardless of the genotype which is our ultimate goal of treatment. So it is advisable to reduce weight in chronic hepatitis C patients before starting them on antiviral therapy.

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CONTRIBUTORS

MUH conceived the idea, planned the study, and drafted the manuscript. MKH and ANB helped acquisition of data and did statistical analysis. AGK supervised the study and critically revised the manuscript. All authors contributed significantly to the submitted manuscript.