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Effect of Obesity on Disease Progression and Response to Antiviral Treatment in HCV Genotype 4 Patients

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Authors' contributions

This work was carried out in collaboration between all authors. Author LM did the study design and data collection. Author MMN did the statistical analysis and literature searches while writing of the protocol was by author ZZ. All authors read and approved the final manuscript.

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ABSTRACT

Background and Study Aims: Egypt has one of the highest prevalence of hepatitis C virus (HCV) worldwide. Steatosis and high body mass index (BMI) may be associated with disease progression in patients with chronic HCV. The aim of this study was to determine the relationship between obesity defined according to body mass index and response to Pegylated Interferon (IFN) and Ribavirin (RBV) combination therapy in chronic hepatitis C Egyptian patients with genotype 4.
Methods: This retrospective study was conducted on 100 patients with chronic HCV who were candidates for IFN based therapy (PEG-IFN and RBV) from Jan. 2008 to June 2010 at National Hepatology Research Institute, Egypt. All patients were subjected to clinical examination, laboratory investigations, abdominal ultrasonography and liver biopsy. Data analysis was used to reveal whether high BMI was a variable related to treatment non response.

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Results: All patients were classified into two groups according to BMI (non obese, <30 kg/m^2; obese, ≥30 kg/ m^2). It showed no significant difference in response to treatment according to BMI (P= 0.1). BMI at cut off 33.5 kg/m^2 can predict presence of significant fibrosis (› F3) with a sensitivity and specificity of 68.4% and 80.6% respectively with AUC 0.79. Hepatic steatosis was not a risk factor for non response to antiviral treatment.
Conclusions: Our data suggest that obesity, when BMI ≥30 kg/m^2, is not an independent risk factor for impaired response to hepatitis C treatment. While obesity is a predictor of fibrosis progression in patients with chronic hepatitis C.

Keywords: Hepatitis C Virus (HCV); Interferon (IFN); Ribavirin (RBV); Body Mass Index (BMI).

ABBREVIATIONS

HCV: hepatitis C virus; BMI: body mass index; PEG-IFN: pegylated interferon; RBV: ribavirin; AUC: area under Roc curve; SOC: standard of care; ALT: alanine aminotransferase; SVR: sustained virological response; EIISA: enzyme-linked immunosorbent assay; PCR: Polymerase chain reaction; HCC: hepatocellular carcinoma; DM: diabetes mellitus; HTN: hypertension; CBC: complete blood count; LBP: liver biochemical profile; AST: aspartate aminotransferase; ALP: alkaline phosphatase; ANA: antinuclear antibody; HBV: hepatitis B virus; HOMA-IR: the homeostatic model assessment-insulin resistance; ETR: end of treatment response; DAA: direct acting antiviral agents.

1. INTRODUCTION

Egypt has the highest prevalence of hepatitis C virus (HCV) in the world, estimated nationally at 14.7% [1]. Combined treatment of pegylated interferon alfa (PEG-IFNα) and ribavirin (RBV) was the base for HCV treatment, therefore defined as standard of care (SOC) [2]. regrettably, many hepatitis C patients experience considerable side effects and lose SOC treatment response, for that, it is beneficial to identify predictors of response for these patients; clinically and economically [3].

Response to treatment in chronic hepatitis C can be assorted as biochemical as shown by normal alanine aminotransferase (ALT) levels, or virological as shown by the absence of detectable HCV RNA in the serum and histological (<2 point improvement in necro-inflammatory score with no worsening in fibrosis score) [4]. Two of the most important predictors of a sustained virologic response (SVR) are the HCV genotype and to a lesser extent, the baseline viral load. Higher response rates are seen in patients with genotypes 2 or 3 than in those with genotypes 1 and 4 [5,6].

For patients with genotype 4 infection, the sustained virological response rate at 48 weeks of therapy ranges from 50% to 60% [7].

Other predictors of SVR include race [8], IL28B polymorphisms [9], insulin resistance [10], body weight and age [6]. Host genetics have long been under suspicion to play a role in deter mining response to IFN α based treatment in chronic hepatitis C [11].

In chronic HCV patients, the degree of hepatic steatosis and fibrosis may correlate with the body mass index (BMI) [12,13]. Steatosis may be an important risk factor for increased both fibrosis and hepatic necroinflammatory activity, and accordingly associated with reduced rate of sustained virological response to interferon based therapy, Obesity, may be a risk factor for lower response to interferon therapy [14,15].

1.1 Aim of the Work

The aim of this study was to identify whether obesity defined according to BMI was an independent risk factor for impaired response to antiviral therapy in Egyptian patients with chronic hepatitis C genotype 4.

2. PATIENTS AND METHODS

This retrospective study was conducted on 100 naïve patients with chronic HCV. Chronic hepatitis C patients were diagnosed by seropositivity using third generation enzyme-linked immunosorbent assay (ELISA) and HCV RNA by reverse transcription– polymerase chain reaction (RT-PCR).

A detailed history, thorough clinical examination, basic laboratory tests and liver biopsy, were taken prior to treatment. Patients received IFN based therapy (PEG-IFN and RBV), according to the national strategy for the control of viral

hepatitis, in the form of Peg-IFN α 2a (180 µg SC once weekly) and RBV (13-15 mg/kg) for 48 weeks, at National Hepatology and Tropical Medicine Research Institute, Egypt from Jan 2008 to June 2010.

They were 68 males and 32 females. Inclusion criteria for treatment were: adult male or female, positive anti-HCV RNA, thyroid-stimulating factor within normal limits or normal thyroxine levels. Exclusion criteria for treatment were: other causes of liver disease, decompensated liver disease, HCC, patients with (uncontrolled DM, uncontrolled HTN, or with other significant medical illness such as cardiovascular disease or renal failure) and patients with hypersensitivity to IFN or RBV.

Investigations done: (1) Complete blood picture (CBC) (2) Liver biochemical profile (LBP): transaminases; aspartate aminotransferase (AST), and alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum albumin, total bilirubin, INR (3) Kidney function tests (blood urea & serum creatinine). (4) Fasting and 2 hours post prandial blood glucose. (5) Alpha fetoprotein (AFP), antinuclear antibody (ANA), thyroid stimulating hormone (TSH). (6) Hepatitis seromarkers for HCV (anti HCV) and for hepatitis B virus (HBV); (HBsAg, anti HBc and anti HBs) using ELISA technique. (7) HCV RNA tested by PCR nested quantitative by IU/ml. (8) Rectal snip to diagnose active Schistosomiasis. (9) ECG (men over 40, women over 50). Patients were globally evaluated by Child Pugh score [16]. (10) Abdominal ultrasonography (11) Histopathological examination by ultrasound guided liver biopsy (in patients with INR <1.4 and platelet count ≥ 60.000 / mm^3) according to Ishak scoring system [17].

Patients were followed up during anti-viral therapy (for 48 weeks), clinically by regular symptoms checklist, and by laboratory testing including PCR for HCV RNA at start of therapy, 12, 24 & 48 weeks of therapy.

All patients were classified into two BMI groupings (non obese, <30 kg/m^2; obese, ≥30 kg/ m^2). Patients were also divided according to treatment response and patients' weight was used as a variable to assess the use of this parameter to predict treatment response.

The study was approved by the institutional ethical committee, and all patients provided an informed consent.

2.1 Statistical Analysis

Continuous data were presented as mean ± standard deviation while categorical data were presented as number (percent). Correlation between various variables was done using Spearman correlation equation for linear relation. A p value less than 0.05 was considered statistically significant. Receiver operating characteristic curves were constructed to identify the BMI cutoff value that predicts significant fibrosis › F3. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 16 for Microsoft Windows

3. RESULTS

The present study was conducted on one hundred HCV naïve patients. They presented to National Hepatology and Tropical Medicine Research Institute, Egypt, seeking antiviral therapy according to the program supported by the national committee for control of viral Hepatitis C under supervision by Egyptian Ministry of health.

Obese patients (BMI ≥ 30 kg/m^2) had significant fibrosis compared to non obese (BMI < 30 kg/m^2) p value =0.001. AST was significantly higher in obese patients compared to non obese patient (p value =0.01) Table 1.

BMI at cut off 33.5 kg/m^2 can predict presence of significant fibrosis (› F3) with a sensitivity and specificity of 68.4% and 80.6% respectively with AUC 0.79 Fig. 1.

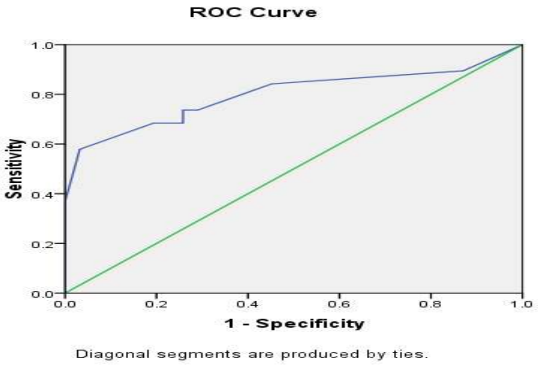

Fig. 1. ROC curve for BMI and stage of fibrosis

There was a positive significant correlation between the BMI and stage of fibrosis (r value 0.6, p value 0.001), also, positive significant correlation between the BMI and AST levels (r value 0.3, p value 0.009) Fig. 2.

End of treatment response was achieved in 60%. There was a statistical significance between treatment response and fibrosis stage (P=0.03), while age, gender, viral load, steatosis did not influence the treatment response Table 2.

Table 1. Demographic features, laboratory data and histopathological features of the studied patients in relation to BMI

Variable	Obese BMI ≥ 30 kg/m^2 (n= 42)	Non obese BMI < 30 kg/m^2 (n=58)	P value
Mean age ± SD	41.6±7.6	39±8.1	0.1
Gender			
Male	30 (71.4%)	38 (65.5%)	0.5
Female	12(28.6%)	20 (34.5%)	
AST (U/L)	69.8±22.4	57.4±24.5	0.01*
ALT (U/L)	56.4±14.9	61.2±22.4	0.2
Pre treatment PCR			
Low (< 800.000 IU/ml)	26 (61.9%)	32 (55.2%)	0.5
High (≥ 800.000 IU/ml)	16 (38.1%)	26 (44.8%)	
Fibrosis			
F1-F3	16 (38.1%)	46 (79.3%)	0.001*
F4-F6	26 (61.9%)	12 (20.7)	
Activity	6(14.3%)	4 (6.9%)	
Minimal	36 (85.7%)	54 (93.1%)	0.2
Mild/moderate			
Response			
Responder	28 (66.7%)	32 (55.2%)	0.2
Non-responder	14 (33.3%)	26 (44.8%)	

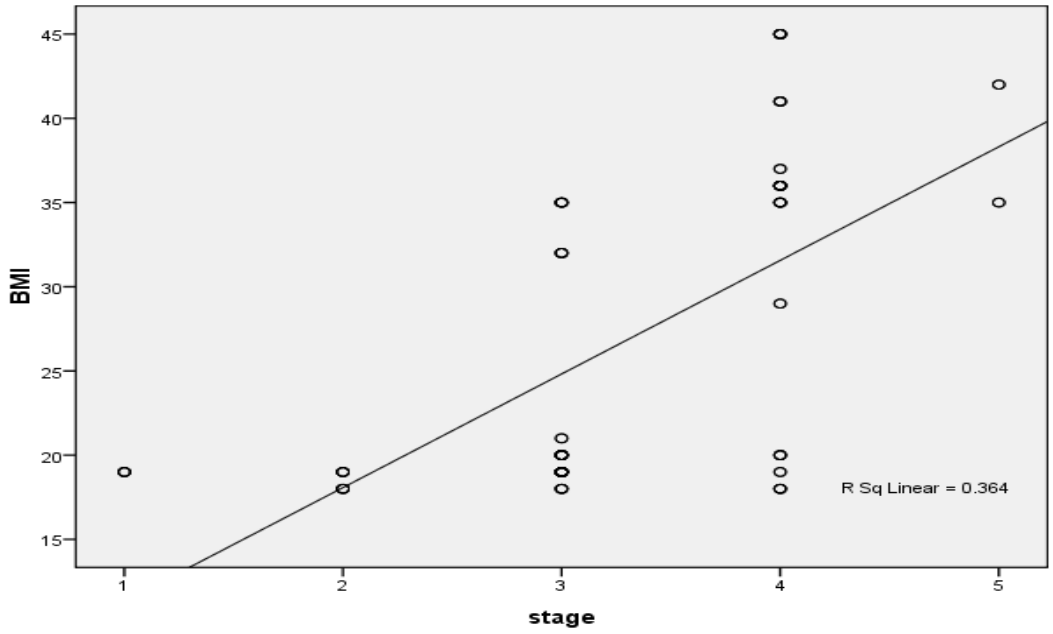

Fig. 2. Correlation between BMI and stage of fibrosis

Table 2. Demographic features, laboratory data and histopathological features of the studied patients in relation to treatment response

Variable	Responder (n= 60)	Non responder (n= 40)	P value
Mean age ± SD	41.3±8.4	38.4±6.9	0.07
Gender			
Male	38 (63.3%)	30 (75%)	0.2
Female	22 (36.7%)	10 (25%)	
BMI (mean± SD)	28.3±9.8	25.1±8.7	0.1
AST (U/L)	65.4±25.9	58.5±21.4	0.1
ALT (U/L)	61.8±22.3	55.2±14.1	0.1
Pre treatment PCR			
Low (< 800.000 IU/ml)	30 (50%)	28 (70%)	0.06
High (≥ 800.000 IU/ml)	30 (50%)	12 (30%)	
Fibrosis			
F1-F3	32 (53.3%)	30 (75%)	0.03*
F4-F6	28 (46.7%)	10 (25%)	

4. DISCUSSION

Previous studies have used weight as a marker of obesity, However BMI, which describes relative weight for height, it correlates with total body fat content, while only weight may not [18].

The mechanism by which obesity may affect the antiviral response to treatment is not completely understood. Several mechanisms have been proposed relating obesity to decreased rates of SVR in response to treatment with peginterferon plus ribavirin in individuals with HCV. First mechanism hypothesizes that obesity is an inflammatory condition, leading to an abnormal immune response to treatment. Second mechanism hypothesizes that obesity gives rise to insulin resistance and hepatic steatosis, which can result in steatohepatitis and hepatic fibrosis, causing interference (direct or indirect) with interferon effect on hepatocytes. Third mechanism hypothesizes that obesity leading to reduced bioavailability of peginterferon alpha [19].

BMI has been shown to correlate with the degree of steatosis seen in hepatitis C, and Bresseler et al. confirmed this association. Furthermore, the degree of steatosis has been shown to correlate with the severity of fibrosis [18].

For increasing the efficacy of combination therapy in obese patients with hepatitis C, we should consider the metabolic effects of obesity. Thus, the most effective approach is to induce weight loss before therapy. As Weight loss is associated with a decrease in steatosis and significant reduction in fibrosis score. Also, weight loss can lead to a reduction in other factors of the metabolic syndrome, as serum triglyceride levels and blood pressure. Moreover; weight loss can control associated morbid conditions as "mean fasting insulin concentration". Treatment of insulin resistance before or in combination with antiviral treatment may also helpful in improvements of chronic hepatitis C patients. Other ways to improve the response to combination therapy include longer duration of treatment and, likely, higher flat doses. Longer treatment, especially in patients with HCV genotype 1 infection, may improve SVR rates. Also, higher doses of peginterferon may improve SVR rates in obese individuals. Not strictly the weight, but higher peginterferon doses should be based on BMI; e.g. 30 kg/m^2 or a starting value for visceral fat or insulin resistance; as measured (HOMA-IR) index [19].

In our study, 42% of studied patients had a high BMI of ≥30 kg/m^2, and it was not a dependent factor associated with failure of treatment response at week 48 (ETR) (p=0.2). This is contrary to Bresseler et al. who found, even though a BMI greater than 30 kg/m^2 predicts the presence of hepatic steatosis, it is only the BMI that remains an independent risk factor for a poor sustained response to antiviral treatment. Furthermore, the presence of hepatic steatosis does not influence the patient's response to antiviral therapy when their BMI is taken into account [18]. Also Poustchi et al. [20] reported that obesity is associated with impaired treatment responses in chronic hepatitis C. A high BMI but not body weight was also inversely correlated with SVR in both IFN and PEG IFN treated individuals [21]. A lower baseline body weight (75–80 kg) was significantly associated with achieving SVR across all genotypes [22].

This difference could be explained by, different study populations regarding risk factors for steatosis as similarly Asselah et al. in his study showed that the degree of steatosis was not associated with fibrosis, while higher BMI was associated with higher degree of fibrosis, suggesting that BMI could be associated with fibrosis through mechanisms other than steatosis [23].

As regard the relation between obesity and disease progression, There is a positive significant correlation between the BMI and stage of fibrosis (r= 0.6, p= 0.001), also there positive significant correlation between the BMI and AST levels (r=0.3, p=0.009). In a prospective trial, a body mass index (BMI) of ≥25 kg/m^2 was significantly associated with fibrosis progression and obesity was a predictor of disease progression in patients with chronic HCV [24]. This agrees with previous studies which found an association between the presence of steatosis and a higher degree of fibrosis, and in several studies which identified among patients with HCV infection, obesity favoured fibrosis [25,26]. Also Asselah et al. in his study reported that, higher body mass index was associated with higher fibrosis degree [23].

A study by Zechini et al. [27] showed a statistically significant positive correlation of baseline aminotransferase values with the hepatitis activity index and fibrosis score. Other studies reported significant positive correlation between AST values and hepatic fibrosis [28,29]. In our study, AST was significantly higher in obese patients compared to non obese patient (p value 0.01), also there was a positive significant correlation between the BMI and AST levels (r value 0.3, p value 0.009).

The scope of hepatitis C treatment attended a great change in 2011 with the approval of the first direct acting antiviral agents (DAA), the (NS3/4A) protease inhibitors boceprevir and telaprevir to treat patients with chronic hepatitis C infection with genotype 1 [30]. They have been replaced by two new medications that were approved by the US Food and Drug Administration (FDA) in 2013 and are now the standard of care for chronic hepatitis C patients. These are the second agents (NS3/4A) protease inhibitor; simeprevir and the first consideration (NS5B) polymerase inhibitor; sofosbuvir [31].

In older treatment regimens as interferon-based treatment which has a varying success rate in virus clearance, depending on viral and host factors. Careful patients selection and monitoring are fundmental in therapy plan, so baseline predictors of response which may be modifiable, including BMI have been studied, by comparison, not as much data are ready for current first line treatment. Many predictors of treatment response may also consider the extent of disease progression. Accordingly the probability of advanced fibrosis increases with a higher number of these predictors [31].

5. CONCLUSION

Our data suggest that obesity, when BMI greater than or equal 30 kg/m2, is not an independent risk factor for impaired response to hepatitis C treatment. While obesity is a predictor of fibrosis progression in patients with chronic HCV.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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