

A significant upsurge of body mass index in patients with chronic hepatitis C successfully treated with direct-acting antiviral regimens

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Cite this article as: El Kassas M, Alborai M, Naguib M, et al. A significant upsurge of body mass index in patients with chronic hepatitis C successfully treated with direct-acting antiviral regimens. *Turk J Gastroenterol* 2019; 30(8): 708-13.

ABSTRACT

Background/Aims: There is less data regarding the changes in body mass index (BMI) after treating hepatitis C virus (HCV) patients with new direct-acting antiviral agents (DAAs). This study aimed to assess the changes in BMI in chronic HCV patients treated with DAAs in Egypt and to explore other factors influencing this change.

Materials and Methods: The data of chronic HCV patients who received antiviral therapy with new DAAs in one of Egypt's specialized viral hepatitis treatment centers were retrospectively analyzed. In addition to the routine clinical and laboratory workup, changes in body weight during and after treatment were monitored and BMI was calculated. Viral load was measured at 12 weeks post-treatment to assess a sustained virological response. Patients with documented thyroid abnormalities, bariatric surgery, or ensuing special diets were excluded. BMI of >30 was taken as the cutoff for patients with obesity.

Results: The study included 162 patients with a mean age of 48.56±11.49 years, of whom 61.1% were males, 16% were treatment-experienced, 12% were diabetic, and 29% were obese. Treatment duration was 12 weeks in 84% of patients and 24 weeks in 16% of patients. There was a significant increase in BMI post-treatment as compared to pretreatment measures (28.68±5.35 vs 28.18±4.55) ($p=0.03$). BMI changes were constant regardless of cirrhosis or previous treatment experience.

Conclusion: Treatment of chronic HCV with DAAs was associated with increased body mass index. Further studies are needed to explore if this effect is secondary to treatment with DAAs or is an improvement in the liver function and lifestyle of treated patients.

Keywords: BMI, DAAs, Egypt, HCV, obesity

INTRODUCTION

Chronic hepatitis C infection (CHC) is an important health problem and is a major cause of chronic liver disease, cirrhosis, hepatocellular carcinoma, and death (1). According to the recent models, approximately 71.1 (62.5-79.4) million persons are considered infected with chronic hepatitis C virus (HCV) globally (2). Several metabolic abnormalities have been reported with CHC, including metabolic syndrome, obesity, dyslipidemia, diabetes mellitus, and insulin resistance (3).

The role of obesity in antiviral treatment for CHC has been evaluated previously (4-6). Tarantino and his col-

leagues noted the negative impact of high body mass index (BMI) on the virological response to previously used pegylated interferon (PEG-IFN) and ribavirin (RBV) therapy (7). BMI >30 kg/m² was considered as an independent predictor of non-response to PEG-IFN-based therapy (8). High BMI has been associated with greater degrees of steatosis and fibrosis (9, 10), insulin resistance (11-13), and increased systemic inflammatory responses such as high tumor necrosis factor (TNF) (14), all of which unfavorably affect the treatment outcome. On the other hand, weight loss has been reported during PEG-IFN/RBV therapy in 11%-29% of patients (18-21), which is associated with better treatment response (15-17).

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Received: August 18, 2018 Accepted: December 4, 2018

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DOI: 10.5152/tjg.2019.18514

Until recently, PEG-IFN/RBV had been considered the gold standard of care therapy for CHC patients with sustained virological response (SVR) rates ranging from 54%-56% (18-20). Introduction of well-tolerated, highly effective direct-acting antivirals (DAAs) improved the SVR rates and the patients' quality of life significantly (21,22). Data regarding changes in BMI after treatment with the new DAA are scarce. Previous reports show conflicting results of body weight changes after successful HCV eradication using INF-free regimens or interferon-containing DAA regimens (23,24). In this study, we aimed to assess the changes in BMI of Egyptian CHC patients treated with DAAs along with exploring the other factors influencing such changes.

MATERIALS AND METHODS

Study design and patient recruitment

This was a retrospective cross-sectional study conducted between April 2015 and April 2017 at New Cairo Viral Hepatitis Treatment Center (NCVHTC) (25), a specialized facility affiliated with the Egyptian National Committee for Control of Viral Hepatitis (NCCVH). This center including others were the main pillars of the huge program aimed at controlling the HCV epidemic in Egypt (26,27). In this study, all patients with CHC who were referred to our center to receive DAAs were recruited. We included patients aged 18 years or older, with confirmed CHC that was proved by the positivity of HCV antibodies and HCV-RNA by PCR. The exclusion criteria according to Egyptian HCV treatment protocol were presence of significant liver disease (Child-Turcotte Pugh class C), hepatocellular carcinoma, extra-hepatic malignancies, pregnancy or unwilling to comply with 2 effective contraceptive methods, breastfeeding, or hypersensitivity to any of the study medications, in addition to factors that could impact the patients' weight, such as the presence of thyroid abnormalities, undergoing bariatric surgery, intentional diet control regimen, and the use of weight loss medications.

Procedure

All patients were subjected to full history-taking, including questions on concomitant medications and co-morbidities as well as a clinical examination, including the measurement of baseline weight and height, BMI calculation, and basic pretreatment laboratory investigations, including complete blood counts, liver and kidney functions tests, and hepatitis B surface antigen and alpha-fetoprotein tests. HCV load was measured using Cobas Ampli Prep/Cobas TaqMan HCV-RNA assay (Roche Diagnostics; Pleasanton, CA, USA) at baseline, at the end of treatment, and at 12 weeks post-treatment to assess SVR, which

was defined as negative HCV PCR (<12 IU/mL according to the used test) at 12 weeks after the completion of the treatment course. Relapse is defined as having positive HCV PCR at 12 weeks after completion of the treatment course. The patients' weight in kilograms was measured using a standardized scale and height was measured using a standardized measuring tape (body meter measuring tape with wall mount) in meters. Changes in body weight were regularly monitored during (every 4 weeks) and after treatment (end of treatment and at 4 weeks and 12 weeks post-treatment) and BMI was calculated at every time point by dividing the person's weight in kg by the square of his or her height (in meter) expressed as kg/m². BMI of >30 was taken as the cutoff for patients with obesity according to the Center for Disease Control and Prevention and the International Obesity Task Force criteria for obesity classification (28).

Treatment for chronic HCV

Patients were treated according to the issued protocol by NCCVH with different used regimens including Interferon/Sofosbuvir/Ribavirin (IFN/SOF/RBV), Paritaprevir/Ombitasvir/Ribavirin (PAR/OMP/RBV), Sofosbuvir/Daclatasvir (SOF/DCV), Sofosbuvir/Daclatasvir/Ribavirin (SOF/DCV/RBV), Sofosbuvir/Ledipasvir/Ribavirin (SOF/LED/RBV), Sofosbuvir/Ribavirin (SOF/RBV), and Sofosbuvir/Simeprevir (SOF/SIM). Choice of the used treatment regimen was based on the availability of medications and national HCV treatment recommendations at the time of enrollment.

Statistical analysis

The statistical analysis aimed at identifying the changes in BMI after treatment with DAAs (primary objective) and the effect of other parameters on this change (secondary objective). Categorical data were described using frequencies and percentages and continuous data were described using means, standard deviation (SD), medians, and ranges. Statistical analysis was conducted using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Categorical data were compared using the χ^2 test. BMI before and after treatment was compared using the Wilcoxon test. Percentage change in BMI was calculated by the following equation:

$$(\text{BMI after treatment} - \text{Initial BMI}) / \text{Initial BMI} * 100$$

The percentage change BMI was then compared between categorical variables using the Mann-Whitney U test. Results were considered significant for a p-value < 0.05. All the tests were two-tailed.

Table 1. Baseline characteristics of the study group.

| Baseline characteristic: | All patients (n=162) |
|-----------------------------------|----------------------|
| Treatment received (n, %): | |
| IFN/SOF/RBV | 2 (1.2) |
| PAR/OMP/RBV | 1 (0.6) |
| SOF/DCV | 91 (56.2) |
| SOF/DCV/RBV | 58 (35.8) |
| SOF/LED/RBV | 3 (1.9) |
| SOF/RBV | 6 (3.7) |
| SOF/SIM | 1 (0.6) |
| HCV PCR log ₁₀ (IU/ml) | 5.83±0.83 |
| ALT(IU/L) | 49.31±31.23 |
| AST(IU/L) | 50.35±31.88 |
| Albumin g/dL | 4.02±0.45 |
| Total bilirubin mg/dL | 0.84±0.42 |
| INR | 1.11±0.13 |
| Hemoglobin | 13.50±1.59 |
| WBC×103 mm ³ | 6.18±1.91 |
| platelets×103 mm ³ | 202.51±78.44 |
| FBS mg/dL | 105.67±27.10 |
| HbA1c | 6.24±1.25 |
| AFP (IU/L) Median(IQR) | 5 (3-10) |

Study oversight and ethical considerations

The current study was conducted in accordance with Good Clinical Practice guidelines laid down in the Helsinki Declaration of 1975 and was approved by the ethical committee of the National Hepatology and Tropical Medicine Research Institute in Cairo. Informed consent was obtained from all participants during the enrollment phase before the start of any treatment or data collection.

RESULTS

Our study included 162 patients with a mean age of 48.56 (±11.498) years. The percentage of male patients was higher than female patients (61.1% Vs 38.9%). About 29% of our patients suffered from obesity (BMI >30 kg/m²), 12% were diabetic, 11% were hypertensive, and 16% were treatment-experienced. Ultrasound examination of

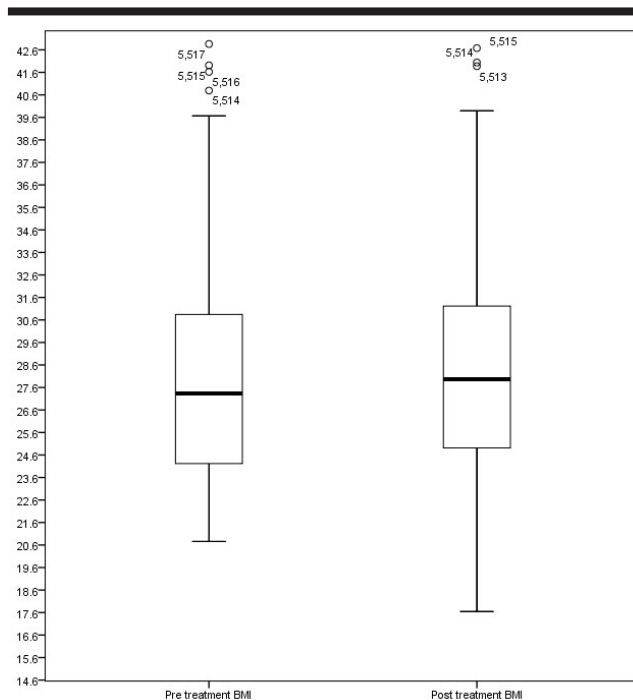


Figure 1. Changes in BMI before and after treatment with DAAs.

the liver confirmed the presence of liver cirrhosis in 13% of the patients while the remaining 87% were non-cirrhotics. The most commonly received DAAs regimen was SOF/DCV±RBV (92% of patients) and the least used regimens were PAR/OMP/RBV and SOF/SIM (0.6% each). The details of the used treatment regimens and baseline laboratory parameters are presented in Table 1.

Treatment duration was 12 weeks in 84% of the patients and 24 weeks in 16% of the patients. There was a statistically significant increase in BMI (28.68±5.35 versus 28.18±4.55) in patients successfully treated with DAAs 12 weeks after completing the course of treatment (p=0.03) (Figure 1). Maximum percentage change of BMI was 36% and the minimum percentage change of BMI was 22.5%, while the mean percentage change (±SD) was 1.63±10.62%. There was no significant difference in BMI percentage change between patients without liver cirrhosis (n=143 patients) and those with liver cirrhosis (n=21 patients). Mean ± SD of BMI percentage change was 2.07±11.43% in patients without liver cirrhosis and 0.18±10.41% in patients with liver cirrhosis (p=0.59). Also, there was no significant difference in BMI percentage change between both treatment-naive and treatment-experienced patients (1.39±11.99% and 4.17±6.11%) respectively with p=0.12 (Table 2).

Table 2. Changes in BMI in both groups.

| | SVR group (162 patients) | | p |
|--------------------------------|-------------------------------|----------------------------|--------|
| | Pretreatment Mean±SD | Post-treatment Mean±SD | |
| BMI (kg/m ²) | 28.18±4.55 | 28.68±5.35 | *0.03 |
| Subgroups of patients with SVR | | | |
| BMI percent change (%) | Non-cirrhotic (n=143) Mean±SD | Cirrhotic (n=21) Mean±SD | |
| | 2.07±11.43 | 0.18±10.41 | **0.59 |
| BMI percent change (%) | Naive (n=138) Mean±SD | Experienced (n=26) Mean±SD | |
| | 1.39±11.99 | 4.17±6.11 | **0.12 |

*Wilcoxon test.

**Mann-Whitney U test.

DISCUSSION

IFN-free DAA regimens for the treatment of CHC have demonstrated more favorable clinical outcomes, a considerable improvement in liver function, an improvement in the quality of life, and an excellent safety profile (29-33). However, the effects of an IFN-free era of HCV treatment on the weight of treated patients have not been investigated in detail. The purpose of this study was to determine the degree of weight change that occurs during the course of DAA treatment in CHC patients and to determine the factors that could affect the patterns of weight change. Most patients in the current study were found not to have obesity at the time of enrollment, but significant weight gain ensued over the course of and after the treatment. Although malnutrition is a well-recognized condition in patients with liver cirrhosis (34), the change in BMI did not differ in treated patients whether they had cirrhosis or not.

Previous studies have shown a reduction in the body weight of patients treated with interferon-based therapy (15,35,36). There are only a few studies that have investigated the effect of DAAs on BMI. The same finding was constant with first-generation proteases that were given in combination with interferon. A study that evaluated the use of PEG-IFN/RBV/telaprevir triple therapy showed that this regimen was associated with more reduction in body weight than PEG-IFN/RBV treatment (24). However, the newer generation DAAs have demonstrated an increase in body weight following treatment of CHC (27).

Our patients who had SVR to DAA treatment showed a 1.93% ($\pm 11.30\%$) increase in their BMI. These results are consistent with a recent study showing that SVR sec-

ondary to DAA treatment was associated with weight gain in a cohort of veterans treated for HCV (37). Another study by Schlevogt and his colleagues demonstrated that 44% of treated subjects had weight gain at long-term follow-up after HCV clearance (29). The authors even demanded identification of the precise subgroup and explanatory mechanisms for this kind of weight gain as they were concerned that such an outcome might erase the beneficial effects of HCV clearance by worsening the hepatic steatosis and aggravating the onset of metabolic syndrome. The reason for such mechanisms leading to an increase in BMI with DAA treatment is unclear. It may be related to the improvement of psychological state, i.e., an increase in appetite or taste sensation with a clearance of HCV (38). Another explanation is that successful treatment is associated with a reduction in inflammatory cytokines and TNF-alpha, both of which act as cofactors in weight loss (39,40).

The limitations of this study are that firstly, it was a cross-sectional retrospective study with small sample size. Due to the unavailability of weight and height for many patients in the database, we did not have enough matching numbers of treatment failure patients with recorded BMI before and after treatment. That is also why we could not include a control group for comparison. Such limitations could be rectified by further prospective studies including all the influential parameters that could be debatable in such a task. Secondly, the patients' diet and psychological condition had not been assessed in detail. Lastly, most of the patients were receiving SOF/DCV (\pm RBV) regimens, which are the main line of therapy in our national program (41). The small number of patients in other treatment regimens made it difficult to compare

the effect of the used regimen, and hence, further studies to compare different regimens are needed. Long-term prospective studies are also needed to assess the permanence of these changes in BMI and their effect on hepatic steatosis and fibrosis and to evaluate the effect of this increase in BMI on the outcomes of HCV treatment.

In conclusion, the current study showed a significant increase in BMI in patients with SVR treated with DAAs for chronic HCV. However, the precise mechanism for this change and its long-term effect needs further evaluation.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of the National Hepatology and Tropical Medicine Research Institute.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.E.K., M.A., M.N., H.O., A.E.T., I.M., M.A., S.E., M.N.W., A.S., M.E., L.A., A.H.E., D.O.; Design – M.E.K., M.A., M.N., H.O., A.E.T., I.M., M.A., S.E., M.N.W., A.S., M.E., L.A., A.H.E., D.O.; Supervision – M.E.K., M.A., M.N., H.O., A.E.T., I.M., M.A., S.E., M.N.W., A.S., M.E., L.A., A.H.E., D.O.; Resources – M.E.K., M.A., M.N., H.O., A.E.T., I.M., M.A., S.E., M.N.W., A.S., M.E., L.A., A.H.E., D.O.; Materials – M.E.K., M.A., M.N., H.O., A.E.T., I.M., M.A., S.E., M.N.W., A.S., M.E., L.A., A.H.E., D.O.; Data Collection and/or Processing – M.E.K., M.A., M.N., H.O., A.E.T., I.M., M.A., S.E., M.N.W., A.S., M.E., L.A., A.H.E., D.O.; Analysis and/or Interpretation – M.E.K., M.A., M.N., H.O., A.E.T., I.M., M.A., S.E., M.N.W., A.S., M.E., L.A., A.H.E., D.O.; Literature Search – M.E.K., M.A., M.N., H.O., A.E.T., I.M., M.A., S.E., M.N.W., A.S., M.E., L.A., A.H.E., D.O.; Writing Manuscript – M.E.K., M.A., M.N., H.O., A.E.T., I.M., M.A., S.E., M.N.W., A.S., M.E., L.A., A.H.E., D.O.; Critical Reviews – M.E.K., M.A., M.N., H.O., A.E.T., I.M., M.A., S.E., M.N.W., A.S., M.E., L.A., A.H.E., D.O.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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