# Assessment of erectile function and sexual hormones in chronic hepatitis C-infected patients treated with direct-acting antiviral agents

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**Objective**
To assess the erectile function, serum total testosterone, and serum prolactin levels in naïve chronic hepatitis C virus (HCV)-infected patients before and after administration of direct-acting antiviral agents (sofosbuvir with daclatasvir).

**Design**
A descriptive cross-sectional study was conducted.

**Patients and methods**
A total of 50 married patients less than 60 years old with regular marital life having naïve chronic HCV infection for a minimum of 1 year confirmed by positive serum HCV RNA by PCR who were going to receive 'sofosbuvir and daclatasvir' regimen for 3 months were included in the study.

**Intervention(s)**
Serum total testosterone and serum prolactin levels before and after the treatment course were assessed.

**Main outcome measure(s)**
The abridged form of International Index of Erectile Function questionnaire (IIEF-5) – Arabic version was fulfilled by the patients before starting the treatment course and 6 months afterward.

**Result(s)**
Before starting the treatment course, 28% of the study population complained of erectile dysfunction (IIEF-5 score ≤21). After the treatment course, the total IIEF-5 score was statistically significantly higher and the serum levels of total testosterone and prolactin hormones were statistically significantly lower than their levels before starting the treatment course.

**Conclusion(s)**
Direct-acting antiviral agents (sofosbuvir and daclatasvir) have demonstrated tolerability and safety regarding the erectile function; furthermore, there was significant improvement in the erectile function after the end of the treatment course.

**Keywords:**
direct-acting antiviral agents, hepatitis C virus, prolactin, total testosterone

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## Introduction

Erectile dysfunction is a state of persistent inability to attain and/or maintain an erection sufficient to permit satisfactory intercourse. Psychosocial and physical health may be influenced by ED which may have a major negative effect on the quality of life of the patients and their partners [1].

Sexual dysfunction is one of many of extrahepatic features of hepatitis C virus (HCV) infection. Chronic-infected patients experience erectile dysfunction [2].

Direct-acting antiviral agents (DAAs) disrupt viral replication and thus infection through targeting specific nonstructural HCV-encoded proteins. According to their therapeutic target, DAAs can be classified into NS5B nucleoside polymerase inhibitors, NS5B non-nucleoside polymerase inhibitors, NS5A inhibitors, and NS3/4A protease inhibitors [3,4].

## Patients and methods

### Patients

The present study was carried out on 50 patients less than 60 years old having naïve chronic HCV infection for a minimum of 1 year confirmed by positive serum HCV RNA by PCR. All patients were married with regular active marital life. All patients were also

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evaluated for eligibility for DAA treatment. Exclusion criteria were age above 60 years, other associated liver diseases (e.g., coinfection with hepatitis B viral infection, liver cirrhosis, liver cell failure, and hepatocellular carcinoma), presence of major chronic diseases that may influence erectile function (e.g., diabetes mellitus, hypertension, ischemic heart disease, renal disease, endocrinal disorders, neuropsychiatric illness, autoimmune disease, and cancer), obesity, smoking, drug abuse, use of interferon, use of medications that affect sex hormone and/or vitamin metabolism, intake of erectile dysfunction treatment before or during the study, and failure to achieve a sustained virologic response.

### Assessment of erectile function and sexual hormones

All patients were subjected to the following after giving an informed consent:

(1) History taking.
(2) General and sexual examination.
(3) Evaluation of the erectile function using International Index of Erectile Function questionnaire (IIEF-5): all patients completed the questionnaire form before the initiation of treatment and 6 months afterward.
(4) Measurements of serum total testosterone and serum prolactin level before and after the treatment course were done.

### Direct-acting antiviral agents therapy

All patients received a combination of a single oral daily dose of 400 mg sofosbuvir plus 60 mg daclatasvir for 12 weeks.

### Ethics committee approval

All steps and procedures of this study were ethically approved by the Institutional Review Board of Assiut University. Informed oral consents were taken from all patients before participating in the study, with IRB no: 17100003.

### Statistical analysis

The statistical analysis was performed with the statistical package for the social science (SPSS), version 22.0 software (released 2013; IBM Corp., Armonk, New York, USA).

Quantitative data were expressed as mean ± SD. Qualitative data were expressed as frequency and percentage.

Paired *t* test and Wilcoxon signed ranks tests of significance were used when comparing between two means. For all data, the *P* value was considered significant if less than 0.05.

## Results

The mean age of patients was 41.50 ± 6.79 years. Regarding the occupation, 28% of patients were manual worker, 65% were employee, and 8% were not working. Regarding the residence, 64% of patients were found to live in rural areas (Table 1).

Regarding the IIEF-5 questionnaire, the IIEF-5 score of HCV-infected patients before treatment (21.88 ± 2.84) was significantly lower than that after treatment (23.56 ± 1.39) ($P < 0.001$) (Table 2).

On studying the serum levels of total testosterone and prolactin hormones among HCV-infected patients before starting the treatment course, we found an increase in their levels, with mean and SD of 5.18 ± 2.67 for total testosterone and 9.38 ± 4.26 for prolactin and reported a statistically significant lower levels among the same patients after the end of treatment course, with mean and SD of 3.84 ± 1.91 for total testosterone ($P < 0.001$) and 8.50 ± 3.13 for prolactin ($P = 0.03$) (Table 3).

## Discussion

The present study has been conducted to assess the erectile function, serum total testosterone, and serum prolactin levels in naïve chronic HCV-infected patients before and after the DAA regimen (sofosbuvir with daclatasvir). Sexual functioning represents a crucial aspect of everyday living and exerts a significant effect on people's quality of life [5].

**Table 1 Demographic data of the study population**

| Demographic characteristics | *n*=50 |
|---|---|
| Age (years) (mean±SD) | 41.50±6.79 |
| Occupation [*n* (%)] | |
| Manual worker | 14 (28) |
| Employee | 32 (65) |
| Not working | 4 (8) |
| Residence [*n* (%)] | |
| Rural | 32 (64) |
| Urban | 18 (36) |
| Education [*n* (%)] | |
| Primary education | 8 (16) |
| Secondary education | 12 (24) |
| Higher education | 30 (60) |
| Smoking [*n* (%)] | |
| Nonsmoker | 50 (100) |
| Smoker | 0 |
| BMI (mean±SD) | 24.10±2.06 |

**Table 2 Comparison between International Index of Erectile Function questionnaire score in hepatitis C virus-infected patients before and after treatment**

| Items of IIEF-5 score | HCV-infected patients before treatment (*n*=50) | HCV-infected patients after treatment (*n*=50) | *P* |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| IIEF-1 | 4.56±0.64 | 4.82±0.39 | 0.001 |
| IIEF-2 | 4.48±0.68 | 4.80±0.40 | <0.001 |
| IIEF-3 | 4.60±0.54 | 4.64±0.53 | 0.32 |
| IIEF-4 | 4.32±0.91 | 4.42±0.91 | 0.22 |
| IIEF-5 | 4.04±0.76 | 4.44±0.50 | <0.001 |
| Total IIEF-5 score | 21.88±2.84 | 23.56±1.39 | <0.001 |

HCV, hepatitis C virus; IIEF, International Index of Erectile Function questionnaire. *P* was significant if less than 0.05.

**Table 3 Comparison between the levels of the studied hormones in hepatitis C virus-infected patients before and after treatment**

| Items | HCV patients before treatment (*n*=50) | HCV patients after treatment (*n*=50) | *P* |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Total testosterone (ng/ml) | 5.18±2.67 | 3.84±1.91 | <0.001 |
| Prolactin (ng/ml) | 9.38±4.26 | 8.50±3.13 | 0.03 |

HCV, hepatitis C virus. *P* was significant if less than 0.05.

Sexual problems linked to HCV are more common in males than females and are presented in many cases with erectile dysfunction that affect their quality of life [6].

Our study has demonstrated the negative effect of chronic HCV infection on the erectile function, and also clarified the hormonal abnormalities, which may be related to erectile dysfunction in chronic HCV-infected patients. A clinical and research question has been raised to assess whether HCV could also be related to disturbed sexual functioning in the absence of cirrhosis [7].

In this respect, our study has answered the previously asked question, as erectile dysfunction has been reported before starting the treatment course in 14 of 50 noncirrhotic chronic HCV-infected patients, representing 28% of study population, and on evaluation of the IIEF-5 questionnaire, we reported a statistically significant lower IIEF-5 score than that after the treatment course, with mean and SD of 21.88 ± 2.84 ($P < 0.001$).

Supporting these premises, it was found that 14 (29.8%) noncirrhotic patients reported with diminished erectile functioning [7]. Moreover, a recent study reported disturbed sexual functioning in hepatitis C-infected patients in several domains, including erection, compared with healthy blood donors and linked the level of dysfunction mainly to demographic variables [8].

On studying the serum levels of total testosterone and prolactin hormones before starting the treatment course, we reported statistically significant higher levels than those after the treatment course, with mean and SD of 5.18 ± 2.67 ($P < 0.001$) for total testosterone and 9.38 ± 4.26 ($P = 0.03$) for prolactin.

Our findings coincide with El-Serafi *et al.* [6] who reported that patients' total testosterone level was significantly higher than that of the control group, a finding that was explained by increased levels of sex hormone-binding globulin in HCV-infected patients as a result of increased hepatic production, which eventually ends up in increased total testosterone level. However, the hormone activity is completely separated from its level because the unbound hormone represents the only biologically active fraction [9]. In contrast to those findings, males infected with HCV experienced hypogonadotropic hypogonadism and reported significantly lower levels of total testosterone as a consequence of hypothalamus–pituitary–testis axis dysfunction [10].

In agreement with our results, Hofny *et al.* [11] found increased levels of serum prolactin in HCV-infected patients and correlated the results to semen abnormalities. Moreover, El-Serafi *et al.* [6] reported that prolactin level was significantly higher in patients than the control group.

According to the WHO's 2017 global hepatitis report, the global incidence of HCV infection is 23.7 per 100 000; the estimated number of newly infected persons is 1.75 million; therefore, its eradication remains an enormous challenge [12].

The management of chronic HCV infection has been revolutionized by the advent of DAAs [13]. The cure rates of HCV infection have been significantly improved with the development of DAAs. However, the associated adverse effects represent a potential barrier to their widespread use [12].

Sofosbuvir and daclatasvir provide a higher sustained virologic response rate and shorter treatment duration;

however, limited data are available on the adverse effects resulting from the coadministration of sofosbuvir and daclatasvir [14].

A study reported a case of a 42-year-old man who complained of a sudden sexual dysfunction on starting one of DAA regimen for the treatment of hepatitis C without previous history or risk factors for the event of sexual dysfunction. After a successful 12-week course, his symptoms disappeared upon discontinuation of the treatment [15].

In this respect, our study has not reported any degree of erectile dysfunction as a sexual adverse effect from the coadministration of sofosbuvir and daclatasvir. On the contrary, we have reported an improvement in the erectile function of the patients after the end of the treatment course as noticed from the IIEF-5 score, which was statistically significantly higher than that of before starting the treatment course, with mean and SD of 23.56 ± 1.39 (P < 0.001).

Furthermore, on studying the serum levels of total testosterone and prolactin hormones after the end of the treatment course, we reported a statistically significant lower levels than those before the treatment course, with mean and SD of 3.84 ± 1.91 ($P$ < 0.001) for total testosterone and 8.50 ± 3.13 ($P$ = 0.03) for prolactin.

## Conclusion

Chronic HCV infection was associated with impairment of the erectile function, even in the absence of cirrhosis. This might be attributed to the abnormal hormonal profile in chronic HCV-infected patients.

Chronic HCV infection was also associated with elevated serum levels of total testosterone and prolactin hormones, which became lower after the treatment course.

Interferon-sparing regimen of the DAAs (sofosbuvir and daclatasvir) has demonstrated tolerability and safety regarding the erectile function; furthermore, there was significant improvement in the erectile function after the end of the treatment course.

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**Conflicts of interest**
There are no conflicts of interest.

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