

Effect of HCV Treatment on Circulating Pituitary Hormones

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ABSTRACT

AIM: To analyse the relationship between pegylated interferon therapy and levels of pituitary hormones.

METHODS: 49 chronic HCV patients were recruited at specialized hepatology clinic in National Hepatology and Tropical Medicine Research Institute (NHTMRI), Cairo; they were treated with pegylated interferon and ribavirin according to the standard treatment criteria and regimen. Pituitary hormones levels were assessed at week 0, 24 of treatment.

RESULTS: Significant changes in the pituitary hormones levels were noticed with perceived rise in Thyroid-stimulating hormone (TSH), Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Human growth hormone (HGH), Dehydroepiandrosterone (DHEAS), Prolactin and Cortisol, while significant reduction in the levels of Testosterone, free Testosterone and sex hormone were observed.

CONCLUSION: Treatment of HCV with Peg-IFN/RBV may be associated with pituitary hormonal dysfunction which may lead to many neglected side effects like libido, erectile dysfunction and galactorrhea.

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Key words: HCV; Pegylated Interferon; Pituitary hormones

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INTRODUCTION

HCV is a major cause of liver-related morbidity and mortalities; it represents a major public health problem in Egypt and worldwide^[1]. There is a large underlying reservoir of HCV related liver diseases^[2]. HCV infection affects more than 170 million persons worldwide, with 20-30% of infected patients eventually developing cirrhosis and its complications. In low- prevalence areas, such as Europe and North America, the incidence rate of anti-HCV ranges from 0.5% to 1.1%, where as it reaches more than 20% in high-prevalence areas such as Egypt^[3].

An established relationship between endocrine system and the liver where the hormone inactivation and synthesis of protein binding hormones takes place. Impairment of hepatocytes function may lead to disturbed homeostasis of the endocrine system^[4].

Several important therapeutic advances have occurred in management of chronic HCV, particularly with the combination therapy of interferon (INF) and ribavirin (RBV) which improves the overall sustained virological response rates to about half of the patients^[5,6].

In vitro and *in vivo* data indicates multiple, but contradictory effects of IFN on pituitary hormone secretion, there is evidence that when interferon alpha used therapeutically in chronic hepatitis B and C and in certain malignancies, it can precipitate or exacerbate autoimmune endocrine diseases, especially of the thyroid gland^[7]. GH insufficiency is common in patients with HCV infection, it may improve during long-term therapy with pegylated IFN-alpha, this improvement in GH secretion during treatment may be due to a direct drug effect or related to suppress of the viral load^[8].

MATERIALS AND METHODS

The study was revised and approved ethically by the institutional review board (IRB). Forty nine patients aged 44.59±7.42 years (mean ±SD) with chronic HCV were enrolled.

Both HCV antibodies and RNA were detected in the serum of all studied patients. Anti-HCV antibody was measured by the third generation Abbott HCV EIA 3.0 (Abbott Laboratories, Ludwigshafen, Germany). HCV RNA was detected by RT-PCR

QIAmp Viral RNA Kit (QLAGEN, Santa Clarita, USA). Base line growth hormone, Cortisol, FSH, LH, Prolactin, TSH, DHEAs, total and free testosterone tests were done by using ELISA technique. Baseline GH, FSH, LH, Prolactin, TSH, Cortisol and DHEA were measured by using solid phase enzyme – linked immuno sorbent assay. The assay system uses an anti-hormone antibody for solid phase immobilization and a mouse monoclonal anti- hormone antibody is labelled with conjugate solution. The intensity of the color formed is directly proportional to the concentration of the hormone in the test sample^[9]. Total and free testosterone were measured by using enzyme immunoassay test follows the typical competitive binding scenario. Competition occurs between a unlabeled antigen (present in standards, controls and patient samples) and an enzyme-labelled antigen conjugate for a limited number of antibody binding sites on the micro well plate. The intensity of the color formed is inversely proportional to the concentration of the hormone in the sample^[10]. A dose response curve of absorbance unit vs. concentration is generated using results obtained from the calibrator. Concentrations present in the controls and patients samples are determined directly from this curve.

Chronic hepatitis was confirmed by histological observation of specimens obtained by true-cut needle biopsy (HS 16 G. Italy). Histological grades of chronic hepatitis was determined according to Metavir score where necroinflammation is classified into (A0=no inflammation; A1=mild inflammation; A2=moderate inflammation; A3=severe inflammation) and fibrosis is classified into (F0=No fibrosis; F1=Portal tract expansion by fibrosis; F2= less than 50% bridging fibrosis; F3=more than 50% bridging fibrosis including incomplete cirrhosis; F4= Established cirrhosis)^[11].

None of the studied patient had decompensated cirrhosis, auto-immune disorders, DM, renal dysfunction, concomitant HBV infection, cardiac insults or any malignancy.

All patients received pegylated interferon α -2A (Pegasys180 mcg)[®] in a once weekly basis and Ribavirin 1000 or 1200 mg/day according to body weight(≤ 75 kg, >75 kg).The treatment was initiated for 24 weeks for all patients and those who achieved negative HCV RNA continued the treatment till 48 weeks. Pituitary hormones were analyzed at base line and at 24 weeks of treatment.

Statistical analysis

Description of variables was presented as follows:

Description of quantitative variables was in the form of mean, standard deviation (SD).

Description of qualitative variables was in the form of numbers (No.) and percent (%).

Percent change in pituitary hormones levels before and after IFN therapy was calculated as follows:

$$\frac{\text{Level (after)} - \text{Level (before)}}{\text{Level (before)}} \times 100$$

Data were explored for normality using Kolmogorov-Smirnov test of normality. The results of Kolmogorov-Smirnov test indicated that most of data were normally distributed (parametric data) so parametric tests were used for the comparisons.

Comparison between quantitative variables was carried out by student *t*-test of two independent samples and by paired samples *t* test for repeatedly measured variables. Repeated measures Analysis of Variance (ANOVA) test was used instead of *t*-test when comparing between more than two groups of independent variables. Results were expressed in the form of *P*-values.

Comparison between qualitative variables was carried out by Chi-Square test (χ^2). Fisher exact test was used instead of Chi-square test when one expected cell or more were ≤ 5 .

Correlation between quantitative variables was carried out by Pearson correlation test. Results were expressed in the form of correlation coefficient (R) and *P*-values.

The significance of the results was assessed in the form of *P*-value that was differentiated into:

Non-significant when *P*-value > 0.05

Significant when *P*-value ≤ 0.05

Highly significant when *P*-value ≤ 0.01

RESULTS

27 patients out of 49 showed negative viremia after 24 weeks of treatment (55.1%), while 22 patients failed to show virological response to treatment (44.9%). Table 1 showed the baseline characteristics for the studied groups, the mean age was (44.59 \pm 7.42); 35 patients were males (71%) while 14 patients were females (29 %); the mean body weight was (80.69 \pm 13.23); the mean baseline viral load was (998121 \pm 2456236); the mean ALT level was (65.37 \pm 41.76), AST (63.26 \pm 40.21); as regarding fibrosis score: 34 patients were F1 (69%), 9 patients were F2 (18%), 6 patients were F3 (13%), no F4 patients were found in the studied group; the necro-inflammatory score of the studied liver biopsies was either A1 in 30 patients (61 %) or A2 in 19 patients (39%) with no A3 score was found in the studied group.

Table 1 Baseline characteristics of the studied group.

	Patients with chronic hepatitis C
Age (year)	44.59 \pm 7.42
Sex (M/F)	35/14
Weight	80.69 \pm 13.23
PCR (Baseline) IU/mL	998121 \pm 2456236
ALT /IU/mL	65.37 \pm 41.76
AST / IU/mL	63.26 \pm 40.21
Fibrosis score (F1/F2/F3)	34/9/6
Necro-inflammatory score (A1/A2)	30/19

High significant differences were noted between the pre and after treatment levels of DHEAS (1.01 \pm 0.39) (1.63 \pm 0.42) respectively with ($p < 0.001$). HGH (1.39 \pm 1.46) (3.83 \pm 3.24) respectively with ($p < 0.001$). Cortisol (81.73 \pm 26.85) (109.02 \pm 28.66) respectively with ($p < 0.001$). Testosterone (6.24 \pm 2.19) (3.93 \pm 1.10) respectively with ($p < 0.001$). Free testosterone (16.37 \pm 6.42) (9.88 \pm 5.84) respectively with ($p < 0.001$). Sex hormone (44.58 \pm 19.65) (32.36 \pm 17.59) respectively with ($p < 0.001$). Prolactin (200.89 \pm 94.72) (281.11 \pm 145.49) respectively with ($p < 0.001$) and TSH (1.55 \pm 0.76) (2.11 \pm 1.08) respectively with ($p < 0.001$).

Also significant differences were noted between pre and post-treatment levels of LH (2.87 \pm 1.29) (3.56 \pm 2.16) respectively with ($p = 0.050$) and FSH (4.84 \pm 2.10) (5.90 \pm 2.50) respectively with ($p = 0.030$).

The serum levels were significantly increased post treatment in DHEAS, HGH, Cortisol, Prolactin, LH, FSH and TSH. On the other hand significant declining was achieved post treatment in the levels of Testosterone, Free Testosterone & sex hormone (Table 2). The mean percent change in the levels of the studied hormones was shown in table 3. Either positively changed to higher levels as in DHEAS (83.85 \pm 82.17), HGH (491.39 \pm 889.32), cortisol (49.6 \pm 64.69), Prolactin (66.95 \pm 112.48), LH (43.32 \pm 96.86), FSH (46.06 \pm 88.4) and TSH (61.56 \pm 106.93) or negatively changed to lower levels as in Testosterone (-32.03 \pm 20.6), free Testosterone (-37.54 \pm 25.65) and sex hormones (-26.1 \pm 23.97).

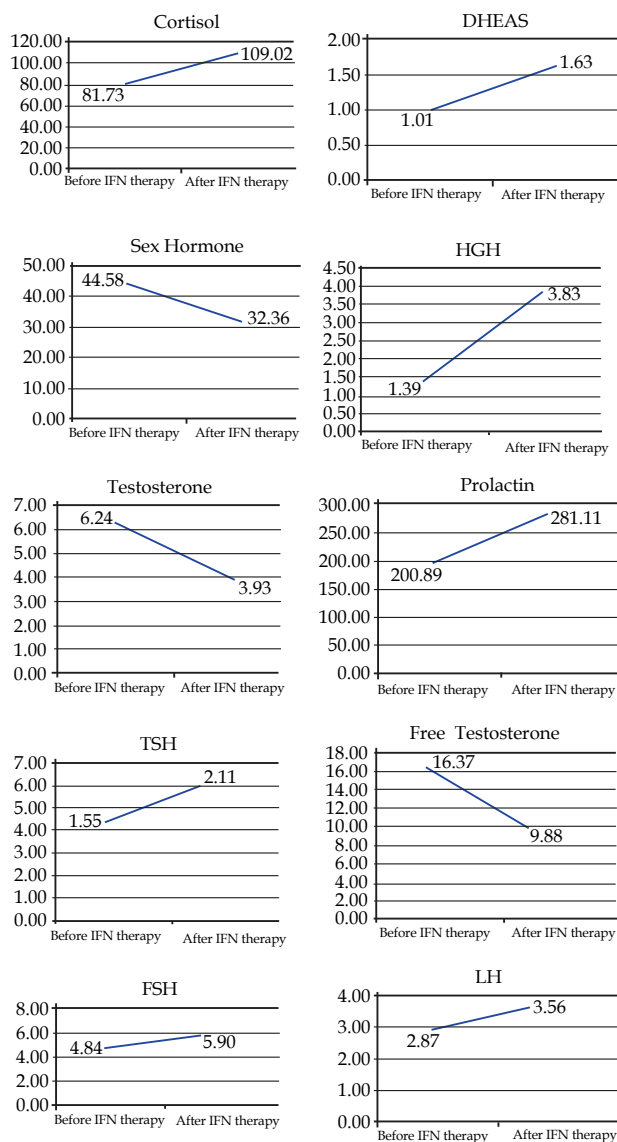


Figure 1 Pituitary hormones levels before and after interferon therapy.

Table 2 Pituitary hormones before and after IFN therapy.

	Before IFN therapy		After IFN therapy		P value
	Mean	SD	Mean	SD	
DHEAS	1.01	0.39	1.63	0.42	<.001
HGH	1.39	1.46	3.83	3.24	<.001
Cortisol	81.73	26.85	109.02	28.66	<.001
Testosterone	6.24	2.19	3.93	1.10	<.001
Free Testosterone	16.37	6.42	9.88	5.84	<.001
Sex hormone	44.58	19.65	32.36	17.59	<.001
Prolactin	200.89	94.72	281.11	145.49	0.001
LH	2.87	1.29	3.56	2.16	0.050
FSH	4.84	2.10	5.90	2.50	0.030
TSH	1.55	0.76	2.11	1.08	0.001

Table 3 Percent change in Pituitary hormones after IFN therapy.

	Mean	SD
	Percent change	Percent change
DHEAS	83.85	82.17
HGH	491.39	889.32
Cortisol	49.60	64.69
Testosterone	-32.03	20.60
Free Testosterone	-37.54	25.65
Sex hormone	-26.10	23.97
Prolactin	66.95	112.48
LH	43.32	96.86
FSH	46.06	88.40
TSH	61.56	106.93

DISCUSSION

Egypt is the country with the largest pool of HCV in the world^[12]. In 2008, a Demographic Health Survey (DHS) was carried out in Egypt revealing HCV antibody prevalence nationwide of 14.7% (95% CI 13.9-15.5%) in age group (15-59)^[13]. Combined treatment with (Peg-IFN) α -2a or α -2b plus ribavirin is considered now as the standard therapy for chronic HCV infection^[14]. Unfortunately, various side effects of IFNs have been reported. Because cytokines, which include IFNs, can affect endocrine functions. Endocrinological abnormalities are sometimes observed in patients with chronic HCV treated with IFNs^[15].

Our study was conducted over 49 patients with chronic HCV, treated with (Peg-IFN) α 2a and ribavirin. They underwent assessment for circulating levels of pituitary hormones prior to initiating interferon therapy and after 24 weeks of treatment. Evident affection was noticed on various levels either increasing or decreasing post-therapy. In our study, a significant rise in TSH level was noticed post-treatment (2.11 \pm 1.08) in comparison to the base-line level (1.55 \pm 0.76). In accordance to Ward & Bing-You, IFN- α induces thyroid dysfunction in 3 to 14% of all treated patients with chronic hepatitis C, leading to hypothyroidism, hyperthyroidism, or thyroiditis. In a few patients, thyroid disease will develop in the absence of anti-thyroid antibodies, a scenario that suggests a non-immune mediated mechanism. More often, patients develop anti-thyroid antibodies, which may progress to overt thyroid dysfunction. Through its immunomodulatory properties, IFN- α seems to act through major histocompatibility complex class I antigens to produce anti-thyroid antibodies and thyroid disease^[16].

A significant decline in sex hormones were encountered in the levels of Testosterone, free Testosterone and sex hormone (6.24 \pm 2.19) (3.93 \pm 1.10), (16.37 \pm 6.42) (9.88 \pm 5.84), (44.58 \pm 19.65) (32.36 \pm 17.59) pre-treatment and post-treatment respectively. On the other hand a remarkable rise was noticed in the levels of FSH, LH, Prolactin, HGH and DHEAS being (4.84 \pm 2.10) (5.90 \pm 2.50), (2.87 \pm 1.29) (3.56 \pm 2.16), (200.89 \pm 94.72) (281.11 \pm 145.49), (1.39 \pm 1.46) (3.83 \pm 3.24), (1.01 \pm 0.39) (1.63 \pm 0.42) pre-treatment and post-treatment respectively, alterations of the pituitary–testicular axis and adrenal gland function may occur during interferon treatment of patients with chronic hepatitis C. The assessment of interferon-induced changes in sex hormone serum levels has been so far limited to small studies^[17,18]. Testicular functions is known to be controlled by gonadotropins (LH, FSH) and is affected by prolactin levels; Kraus *et al* observed a significant decline of free and total testosterone serum concentrations in 34 male patients treated with interferon alfa-2b (5 MIU three times weekly) ($n=19$)+ribavirin ($n=15$) for 6-12 months; they evaluated the time course and concentrations of gonadotropins and prolactin; LH levels (as well as FSH serum concentrations) were not much affected during interferon treatment^[17]. In our study, we assume that the observed testosterone decrease is associated with simultaneous rise in FSH, LH levels raising the possibility for the direct interferon effect on alteration of the pituitary–testicular axis. This, however, cannot be entirely proven as gonadotropin secretion pulsatility was not analyzed. Kraus *et al* demonstrated that the mean serum prolactin levels were much increased during interferon therapy, parallel to our work we supposed that interferon therapy either directly affected lactotrope cells in the pituitary, or hypothalamic factors which control prolactin secretion, or both; elevated levels of prolactin are usually associated with sexual dysfunction, such as reduced libido, erectile dysfunction, diminished ejaculate volume and oligospermia^[19].

In conclusion, (Peg-IFN) expected side effects revision should

extend to the usually under estimated symptoms like (galactorrhea . Libido, erectile dysfunction...) as treatment may be associated with pituitary hormonal dysfunction which may lead to these undesirable symptoms that can affect the treatment adherence and compliance.

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