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EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

Hormonal Disturbances in Patients with Chornic Hepatitis C

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Received: June 01, 2019; **Published:** August 09, 2019

Abstract

Trials have been performed on changes in hormonal profiles in alcohol-related chronic liver disease. In this article, we will present our findings on hormonal changes in patients with HCV-related chronic liver disease. The study group included 30 patients with chronic liver disease secondary to hepatitis C infection. Additionally, a control group was formed. We investigated serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (T.TES), Free-testosterone (F.TES), Estradiol (E2), Androstenedione (AND), Dehydroepiandrosterone (DHEA), Progesterone (PROGES), Prolactin (PRL), and Sex hormone binding protein (SHGB), which were measured by radioimmunoassay and chemiluminescent immunoassay methods. Serum F.TES levels in patients with HCV-related chronic liver diseases were found to be significantly lower than in control group ($p = 0.002$). Serum free triiodothyronine (fT3) and free thyroxine (fT4) levels in patients with HCV-related cirrhosis was found to be lower than those in control group ($p = 0.04$, $p = 0.02$, respectively). Serum PROGES levels were higher in the both the patients suffering from HCV-related chronic liver disease and those with HCV-related cirrhosis compared to the control group ($p = 0.01$ and $p = 0.04$, respectively). It was concluded that the patients suffering from HCV-related chronic liver disease present a degree of hormonal imbalance that will be discussed in this study.

Keywords: *HCV; Hormone; Chronic Liver Disease*

Abbreviations

TSH: Thyroid Stimulating Hormone; fT3: Free Triiodothyronine; fT4: Free Tetraiodothyronin; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; T. TES: Total Testosterone; F. TES: Free Testosterone; E2:Estradiol; AND: Androstenedione; DHEA: Dihydroepiandrosterone; PROGES: Progesterone; PRL: Prolactin; SHBG: Sex Hormone Binding Protein

Introduction

Many research studies have been done on gonadal and thyroid hormonal profiles in patients with chronic liver disease. The reason for these studies is the exhibition of certain hormonal abnormalities and their clinical presentation in patients with liver disease. Most of these studies have been done on patients with alcoholic liver cirrhosis [1].

Alcohol has an ability to cause impotence and hypogonadism presumably through its effect on hypothalamo-gonadal axis. Autoimmune diseases such as primary biliary cirrhosis have also been observed together with thyroid disorders [2,3]. Chronic systemic diseases such as chronic kidney failure and chronic liver disease have also been observed together with certain endocrinological disturbances [4].

Alongside with diseases mentioned above, genetic diseases that are known to cause liver cirrhosis, such as hemochromatosis, have been shown to be cause abnormalities in the functions of hypophysis and gonadal organs through disturbances in hypothalamo-hypophyseal and hypothalamo-gonadal axes [5].

Endocrinological disturbances seen in patients with chornic viral hepatitis have been linked to treatment of such patients with interferon [6].

Several researches have implicated abnormalities in testosterone, estrogen, and prolactin as the cause for peripheral cirrhosis signs such as spider hemangioma and gynecomastia [7].

As spider hemangioma and gynecomastia are not only observed in patients with alcohol cirrhosis, but also in patients with chronic liver disease due to other etiologies, such as viral hepatitis [8,9].

Chronic hepatitis C virus infection (HCV) is defined as the presence of HCV RNA in serum for longer than 6 months. Serum HCV RNA remains fairly stable during the first month at 4 to 6 log10 iu/ml with serum ALT levels showing fluctuations [10-12]. In many patients, patients with such laboratory results may be diagnosed with chronic hepatitis C due to lack of knowledge about the onset of the disease [13,14]. In general, chronic HCV infection does not produce any clinical signs until the onset of cirrhosis [14].

Research on the correlation between chornic liver disease and gonadal hormone abnormalities have primarily focused on patients with alcoholic liver disease [15]. Viral etiologies of cirrhosis have been given considerably less attention in the development of gonadal hormone dyfunctions. Research into thyroid hormones and hypophyseal hormones such as FSH, LH, and prolactin in viral etiologies of liver cirrhosis has also been limited [16,17].

Decrease in biosynthesis and secretion of testosteron, abnormal changes in morphology of Leydig cells, and loss of germ cells in seminiferous tubules, resulting in testicular atrophy and descreased levels of testosterone have been seen in patients with alcoholic liver disease and liver cirrhosis. Increase in biosynthesis of estrogen has been associated with observable feminization [18]. Alcohol is known to increase the activity of aromatases and secretion of adrogenic substrates including adrenal androstenedione and dehydroepiandrosterone. Ethanol also increases sensitivity to estrogen in sex-hormone-sensitive tissues. Non-receptor cytosolic estrogen-binding-protein levels are also decreased in patients with cirrhosis.

Our aim is to investigate endocrinological abnormalities in patients with chornic liver disease and cirrhosis due to chronic HCV. For this purpose, thyroid stimulating hormone (TSH), triiodothyronine (T3), tetraiodothyronine (T4), free triiodothyronine (fT3), free tetraiodothyronin (fT4), prolactin (PRL), luteinizing hormon (LH), follicle-stimulating hormone (FSH), progesterone (PROGES), adrenocorticotropic hormone (ACTH), dihydroepiandrosterone (DHEAS), androstenodione (AND), sex-hormone-binding hormone (SHBG), estradiol (E2), total testosterone (T.TEST) and free testosterone (F.TEST) will be assessed in order to reveal the presence of hormonal abnormalities in chronic HCV patients.

Materials and Methods

Local ethical board committee approval was first obtained for this study. Patients admitted to Dokuz Eylul University Faculty of Medicine gastroenterology outpatient clinic were assessed. Male patients of 19 to 65 years of age with chronic HCV infections and patients with liver cirrhosis caused by chronic HCV were selected. After signing the consent form, the patients' history and physical examination were obtained. Patients who had no previous hormonal disease and who did not use any hormone replacement drugs were included in the study. All of the data pertaining to the patients' biochemistry, microbiology, radiology, and pathology (liver biopsy) reports were assessed. Patients were grouped into Child-Pugh A, B, and C classes based on the laboratory data and physical examinations. A control

group comprised of healthy volunteer individuals was also formed. Present antiviral and interferon treatments were learned. Radioimmunoassay and chemiluminescent immunoassay were performed for the detection of serum thyroid stimulating hormone (TSH), triiodothyronine (T3), tetraiodothyronine (T4), free triiodothyronine (fT3), free tetraiodothyronin (fT4), prolactin (PRL), luteinizing hormon (LH), follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), dihydroepiandrosterone (DHEAS), androstenodione (AND), sex-hormone-binding hormone (SHBG), estradiol (E2), total testosterone (T.TEST) and free testosterone (F.TEST). Study was designed in a prospective manner.

Inclusion criteria

Patients with chronic HCV infection without liver cirrhosis and those who have liver cirrhosis due to chronic HCV infection have been included in this study.

Exclusion criteria

Patients known or suspected of having an endocrinological disorder other than the primary liver disease and patients unable to participate in the study due to medical, physiological and social reasons were excluded from the study.

Results

30 patients with chronic HCV were included in the study. Sixteen (53%) of themwere patients with chronic HCV without liver cirrhosis and 15 (47%) were patients with liver cirrhosis caused by chronic HCV. Of the patients suffering from liver cirrhosis, 8 were Child-Pugh Class A, 4 were Class B and 3 were Class C. Control group of healthy individuals was comprised of 38 persons. Laboratory findings of chronic HCV patients were compared to those of healthy control group, the results of which are listed in table 1. Based on the comparison results, mean free testosterone was found to be 18,8 ± 9,4 pg/ml in chronic HCV patients and 11,3 ± 5,2 pg/ml in healthy control group (p = 0,002). Mean progesterone levels were found at 0,8 ± 0,3 ng/ml in HCV patients and 0,4 ± 0,3 ng/ml in healthy adults (p = 0,001). Laboratory values of each Child-Pugh group are also shown in table 2. Total testosterone levels of HCV patients had a mean value of 529 ± 228 ng/dl compared to 476,8 ± 151,2 ng/dl in the control group (p = 0,006). LH was found to be 8,3 ± 8,6 mIU/ml in HCV-related cirrhosis patients compared to 1,5 ± 1,6 mIU/ml in healthy adults (p = 0.001). Estrodiol had a mean value of 35,8 ± 17,5 pg/ml in HCV-related cirrhosis vs. 22,8 ± 5,6 pg/ml in healthy adults (p = 0,001); fT3 in HCV cirrhosis 2,9 ± 1,3 vs. 2,9 ± 0,6 pg/ml in healthy control (p = 0,04), fT4 of 1,4 ± 0,6 ng/dl vs. 1,3 ± 0,1 ng/dl (p = 0,02), SHBG of 64,3 ± 45,2 nmol/ml vs. 46,1 ± 23,1 nmol/ml (p = 0,04).

	n
HCV-related chronic liver disease	16
HCV -related cirrhosis	15
Child A	8
Child B	4
Child C	3
Control group	38

Table 1: *Distributions of patients and control group.*

Summary of the comparison of laboratory results between each Child-Pugh Class and healthy control group is depicted in table 3.

	Chronic HCV	Cirrhosis	Control	P1	P2
FSH	6.1 ± 3.5	13.7 ± 13.3	8.1 ± 6.5	≥0.05	≥0.05
LH	3.9 ± 1.4	8.3 ± 8.6	3.5 ± 1.8	≥0.05	≥0.05
E2	23.7 ± 4.4	35.8 ± 17	22.8 ± 5.6	≥0.05	≥0.05
T.TEST	577 ± 228	529.3 ± 228.2	476 ± 151	≥0.05	0.006
F.TEST	18.8 ± 9.4	6.6 ± 4.8	11.3 ± 5.2	0.002	0.003
PRL	13.9 ± .14.8	10.2 ± 4.5	8.8 ± 7.3	≥0.05	≥0.05
AND	2.2 ± 9	2.4 ± 0.7	2.4 ± 1.3	≥0.05	≥0.05
DHAS	159.2 ± 133	71.3 ± 71	177 ± 111	≥0.05	≥0.05
PROGES	0.8 ± 0.3	0.4 ± 0.2	0.4 ± 0.3	0.01	0.04
TSH	1.1 ± 0.5	1.4 ± 0.9	1.2 ± 1	≥0.05	≥0.05
fT3	3.6 ± 0.6	2.9 ± 1.3	2.9 ± 0.6	≥0.05	0.04
fT4	1.1 ± 0.1	1.4 ± 0.6	1.3 ± 0.1	≥0.05	0.02
SHBG	45.1 ± 19.8	64.3 ± 45.2	46.1 ± 23.1	≥0.05	0.05

Table 2: *Distributions of serum hormones levels in patients and control group.*

TSH: Thyroid Stimulating Hormone; fT3: Free Triiodothyronine; fT4: Free Tetraiodothyronin; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; T. TES: Total Testosterone; F. TES: Free Testosterone; E2: Estradiol; AND: Androstenedione; DHEA: Dihydroepiandrosterone; PROGES: Progesterone; PRL: Prolactin; SHBG: Sex Hormone Binding Protein. P1: Serum level of hormones in patients of Chronic HCV compared with Control group P2: serum level of hormones in patients of Cirrhosis compared with Control group: < 0.05 Kruskal-Wallis tests and Mann-Whitney U test.

Testler	Child A	Child B	Child C	Kontrol	P1	P2	P3
FSH	15.8 ± 14.8	11.7 ± 15.0	8.8 ± 5.5	8.1 ± 6.5	0.02	0.02	≥0.05
LH	9.9 ± 11.2	7.3 ± 5.2	5.4 ± 1.2	3.5 ± 1.8	0.001	0.001	≥0.05
E2	28.0 ± 12.8	38.8 ± 26.5	52.4 ± 9	22.8 ± 5.6	0.01	0.01	≥0.05
T.TEST	496.7 ± 203.1	690.0 ± 382.2	632.3 ± 343	476 ± 151	≥0.05	≥0.05	0.001
F.TEST	6.6 ± 4.6	10.9 ± 10.9	8.2 ± 8.1	11.3 ± 5.2	≥0.05	≥0.05	≥0.05
PRL	1.,4 ± 5.3	10.8 ± 4.1	7.9 ± 3.2	8.8 ± 7.3	≥0.05	≥0.05	≥0.05
AND	2.8 ± 0.5	2,.0 ± 0.1	1.4 ± 0.3	2.4 ± 1.3	≥0.05	≥0.05	≥0.05
DHAS	81.9 ± 83.6	143.3 ± 147.8	43.1 ± 36.1	177 ± 111	≥0.05	≥0.05	≥0.05
PROGES	0.4 ± 0.2	0.4 ± 0.3	0.4 ± 0.2	0.4 ± 0.3	≥0.05	≥0.05	0.01
TSH	1.2 ± 1.0	2.2 ± 1.1	1.3 ± 0.9	1.2 ± 1	≥0.05	≥0.05	≥0.05
fT3	2.9 ± 0.6	3,.5 ± 0.4	1.2 ± 0.3	2.9 ± 0.6	0.04	0.04	≥0.05
fT4	1.3 ± 0.1	1.1 ± 0.2	2.1 ± 1.0	1.3 ± 0.1	≥0.05	≥0.05	≥0.05
SHBG	55.9 ± 22.2	85.3 ± 81.9	35.0 ± 0.1	46.1 ± 23.1	≥0.05	≥0.05	0.03

Table 3: *Summary of the comparison of laboratory results between each Child-Pugh Class and healthy control group.*

TSH: Thyroid Stimulating Hormone; fT3: Free Triiodothyronine; fT4: Free Tetraiodothyronin; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; T. TES: Total Testosterone; F. TES: Free Testosterone; E2: Estradiol; AND: Androstenedione; DHEA: Dihydroepiandrosterone; PROGES: Progesterone; PRL: Prolactin; SHBG: Sex Hormone Binding Protein. P < 0.05 Kruskal-Wallis tests and Mann-Whitney U test. P1, P2, P3: Serum level of hormones in patients of Child A, Child B, Child C compared with Control group, respectively.

Discussion

Disorders in thyroid and hypothalamo-hypophyseo-gonadal axis functions have been previously described in patients with chronic liver disease [15-18]. These endocrinological disturbances have been primarily linked to cirrhosis patients. Alongside with these, hypohyseal and gonadal hormone abnormalities have been revealed in patients with liver cirrhosis caused by idiopathic hemochromatosis [19]. Studies focusing on hypothalamo-hypopheo-gonadal axis and thyroid hormones functions in chronic liver disease patients secondary to viral hepatitis have been scarce.

Our study revealed higher levels of FSH and LH in patients with liver cirrhosis caused by HCV. This resembles hormonal changes seen in patients with hypogonadism. This has also been shown in patients with liver cirrhosis caused by chronic alcoholism. These patients show a descrease in testosterone biosynthesis and secretion, morphological abnormalities in Leydig cells, and loss of germ cells in seminiferous tubules. Steenbergen W. has shown the presence of endocrinological functions in gonadal system, especially in male and female alcoholic cirrhosis patients. The primary target of alcohol's effect on primary gonadal failure is due to the toxic effects of ethanol and acetaldehyde [20]. The results of another study reported insufficient response of Leydig cells to gonadotropin stimulation in patients with liver cirrhosis due to causes other than hemochromatosis [21].

In our study, serum estrodiol levels were found to be significantly higher in patients with HCV-related liver cirrhosis patients. Gonadal dysfunction may appear with chronic alcohol use or alcoholic cirrhosis. Peripheral aromatisation of androgens may results in conversion of testosterone to estrodiol [21]. This increase may lead to feminisation. Besides, ethanol increases estrogen sensitivity in tissues responsive to sex hormones. Also, non-receptor cytosolic estrogen-binding protein levels appear to decrease in patients with liver cirrhosis.

Farnetti., *et al.* have researched estrogen receptor expression, estrogen receptor types, and oxidative DNA stress in chronic liver disease caused by HBV and HCV, and put forth that liver estrogen receptor variant positivity leads to increased genomic damage and acceleration of cytoproliferation and carcinogenesis [22]. In alcohol-related chronic liver disease patients specifically, increase in aromatase activity has been shown to lead to increased periferal conversion of angrogens to estrogen leading to increased estrone levels [23,24]. An increase in conversion of adrenal andtroetenedion to estrone has also been reported in cirrhosis patients. These studies and reports are consistent with our findings of elevated estrodiol levels in our study group.

Barreca., *et al.* showed that in seven men with chronic hepatitis C, total testosterone and SHBG levels fell transiently during IFN-α treatment. IFN-α treatment reduced total testosterone but did not affect free testosterone levels [25]. Patients who did not use medication to change hormone levels were included. Severity of liver disease measured by fibrosis score was associated with higher SHBG and lower free testosterone levels. IFN-atreatment reduced total testosterone but did not affect free testosterone levels. In our study SHBG levels in both patient groups higher than control group. Serum F.TES levels in patients with HCV-related chronic liver diseases were found to be significantly lower than in control group. These results are similar to previous studies.

Conclusion

These endocrinological disturbances have been primarily linked to cirrhosis patients. Alongside with these, hypohyseal and gonadal hormone abnormalities have been revealed in patients with liver cirrhosis.

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Volume 6 Issue 9 September 2019