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Effects of HCV Viral Load on Male Hormones

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ABSTRACT

The hepatitis C virus (HCV) is an infectious agent that causes human hepatitis C disease and serious life-threatening liver damage. The main objective of this research was to establish the association between the levels of plasma sex hormones and hepatitis C infection in Iraqi males. Thirty hepatitis C infected patients were included in the study sample. In addition, a control group of ten healthy peoples was created. HCV infection had been investigated and approved with TaqMan real time PCR technique. The level of hormones in the plasma of progesterone, estradiol, and testosterone had been measured via electrochemiluminescence immunoassay method usingcobas e 411 analyzers. In contrast with the controls, the findings revealed shifts in two of the three analyzed hormones within the patients. In male patients with HCV infection, the mean level of plasma testosterone and estradiol was significantly increased relative to healthy controls($P \leq 0.05$ and $P \leq 0.01$, respectively), although there is no considerable variation between patients and controls in the mean level of plasma progesterone.The age groups have a significant effect in means of PCR viral load and progesterone hormone, while it has no significant impact in mean concentrations of hormones of testosterone and estradiol ($P \leq 0.05$). The statistical analysis for results demonstrated there is non-significant relation among HCV PCR load mean with the levels of testosterone and estradiol, though a significant correlation coefficient with progesterone level ($P<0.05$), the age has non-significant correlated with HCV PCR load.It was deduced that HCV disease patients have a degree of hormonal imbalance that will be explored in current study.

Keywords: Liver disease;Anabolic steroids;Estrogenic hormones; Progesterone; Sex steroids.

INTRODUCTION

The HCV infection is a major public health issue worldwide. Many cases of HCV develop into chronic hepatitis C (CHC), that may also progress to cirrhosis, hepatocellular carcinoma (HCC), and liver fibrosis.The worldwide prevalence of HCV infection is reported at over 170 million individuals, and some studies predicts that HCV infection-related mortality will continue to rise during the next two decades [1,2].The hepatitis C virus develops both chronic and acute infections. New infections with HCV are generally asymptomatic. Some peoples have acute hepatitis that does not contribute to a life-threatening illness. Approximately 30 percent of infected people spontaneously clearance the virus without treatment within six months of infection.Chronic HCV infection will evolve for the remaining 70 percent of individuals. HCV is an enveloped positive strand RNA virus that replicates readily in the liver which is included in the *Flaviviridae* family with in genus *Hepacivirus*. The genome of the HCV RNA is around 9600 long nucleotides and codes for one long polyprotein[3].TheEuropean Region and the Eastern Mediterranean Region are the most affected areas.HCV infection is also common in the general population in countries where infection management procedures are inadequate.Hepatitis C virus infection may be localized in particular populations, depending on the region. The HCV virus has several genotypes (or strains) and their spread differs by country. Nevertheless, strain distribution remains uncertain in many regions[4].Since recent HCV diseases are frequently having no symptoms of illness, less cases are detected when the infection is new. HCV infection is identified with a serological screening for anti-HCV antibodies that recognizes individuals who have been affected with the virus.A nucleic acid analysis for ribonucleic acid of HCV is required to verifyviral infection because around 30% of HCV patientsare spontaneously resolve the infection without the need for medication via a powerful immune response. They will indeed positive for immunological test even though they are no longer infected [5].Men are at dramatically greater prevalence of chronic liver disease through various etiologies of disease, particularly HCV; so, promoting the possible roles of gender-related disparitiesin risk factor exposures as well as gender-based biological differences in progression of disease [6].One of the crucial variables in the development of hepatic fibrosis due to chronic HCV infection is the male sex; therefore, woman hormones can play an important role in slowing hepatic fibrosis progression.It has also been documented that female are more likely than male to overcome

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HCV in the acute phase of disease. These observations suggest the possibility that woman hormones reduce the infection with HCV, either at the stages of manufacturing of infectious virus particles,virus protein synthesis,virus RNA replication, or virus attachment/entry [7]. Antiviral drugs used to fight hepatitis C can cause sexual dysfunction (SD) and reduced libido.SD is the most common side effect of several antidepressant drugs used to curing the depression andanxietyrelated with HCV mixture treatment. SDhas been recorded to be more prevalent in patients with chronic hepatitis C than in peoples with nodefined liver disease[8].Viral etiologies of liver infections have been givenless consideration in the production of gonadal hormone malfunctions. Several investigations have reported sex hormone disorders as the cause of symptoms of liver disease.Malehypogonadism is correlated with liver disease and is characterized by low testosterone.Past research had beenconductedchanges in levels of testosterone and sex hormone-binding globulin (SHBG) in contrast with healthy controls are extrahepatic manifestations of chronic HVC[9].To date, few findings were noted regarding theimpact of HCV infection on the plasma hormone levels. Studies to investigate the impact of HCV on hormone levels are now required. Therefore, the current research was designed to establish the association between the levels of plasma sex hormones (testosterone, estradiol, and progesterone) and hepatitis C infection in some male Iraqi patients.

MATERIALS AND METHODS

A total of one hundred sixty-eight blood samples had been collected from men suspectedof hepatitis C virus infection which attending the special nursing hospital in medical city of Baghdad, for four months, starting from the first of September to the end of December 2018,ten samples were also taken from healthy individuals as control.Peoples with previously confirmed or documented infection with the HCV were the preferred chosen.Gently mix the blood after collection, by inverting the tube 8 times. By centrifugation at 1400 x g for 15 mins during four hours of blood collection, whole blood stored in EDTA tubes must be split into cellular components and plasma.The separated plasma should be transferred into a sterile polypropylene tube. Plasma had been stored at -20°C until use.

RNA extraction was carried out for all collected samples in compliance with the manufacturing instructions of the Ribo-Sorb nucleic acid extraction kit (Sacace, Italy), and stored for use at -20°C.

All RNA specimens werediagnosed byTaqMan real-time PCR (Cepheid SmartCycler, USA) assays and HCV viral load had been identified using HCV Genotype Plus Real-TM kit (Sacace, Italy) according to the protocol supplied by the kit. The findings of the PCR were analyzed with SmartCyclerDx Version 3.0b program.

Testosterone (TES), estradiol (E2), and progesterone (PROGES) plasma levels were quantitatively measured *in vitro* for patients and control using cobas e 411 analyzers (Roche, Germany) by electrochemiluminescence immunoassay "ECLIA".

To detect the effect of difference factors on study parameters, the statistical analysis system-SAS [10] program was used. In this study, the T-test was used to significantly compare means to estimate the correlation coefficient between variables.

RESULTS AND DISCUSSION

Extracted one hundred seventy-eight RNA specimens from bloodsamples of suspected cases and healthy persons were subjected to moleculardiagnosis by real time PCR to determine HCV-RNA. This assay was successful in the quantitative detection of HCV. Only 30 from 168 suspected cases were HCV-positive by real-time PCR, they were therefore regarded as presence of HCV in the specimen and male hormones investigation were performed for those 30 samples. All control samples had been given a negative result when examined by PCR.The range of ages in the studied patient range was (21-63) years with a mean age of 39.23 years, and from 20 years to 58 years as the mean age was 44.5 years for healthy control, with non-significant difference between the groups of age (Table 1).The mean results of HCV PCR load for patients were 13352976.13 ± 4950929.53 IU/ml and 0.00 ± 0.00 IU/ml for healthy control, with a highly significant difference between patient and control ($P \leq 0.01$) (Table 2).The data set in Table (3) exhibited the plasma testosterone mean level in patient males with HCV infection (7.74 ± 0.69 ng/ml) was

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significantly higher than healthy control (5.59 ± 0.43 ng/ml) (P≤0.05) (Figure 1). This result was in accordance with El-Serafi*et al*. [11] who recorded that testosterone had been significantly increased in the patients with HCV infection compared to healthy control.

Overall serum testosterone in infected males with HCV is correlated with a significantly elevated risk of both severe liver inflammatory response and chronic liver fibrosis. Testosterone could be very remarkable in the pathogenesis of chronic hepatic disease linked to HCV in men [6]. Increased concentrations of testosterone compared to individuals who achieved viral clearance of HCV were identified as active HCV infections, the association among testosterone, impaired liver function, and chronic viral infection are complicated. Effective HCV infection and associated damaged liver function are known as both risk factors for hypogonadism and changed semen development. Hypogonadism is also a reported consequence of end phase liver illness [9]. Testosterone is mostly metabolised in the liver, and the testosterone metabolic clearance is reduced in severe liver disease [12]. An investigational research found that the HCV contributes to androgen receptor (AR) signaling rises [13]. AR is a nuclear hormone receptor expressed in the liver, the primary ligand of which is testosterone [14]. Besides controlling genes that are concerned in sexual dimorphism, AR regulates/co-regulates many other genes engaged in multiple related cellular operations for hepatic disease, which include cellular proliferation, apoptosis, differentiation, and inflammatory response [15]. Nguyen *et al*. [16] suggested that hepatic disease in hepatitis C infection modifies androgen status indirectly through elevated sex hormone binding globulin, checking for androgen deficiency must selectively target males with more acute liver disease or reported higher-grade fibrosis. The plasma estradiol mean level in patients with HCV (55.78 ± 3.07 Pg/ml) was significantly higher than healthy control (32.99 ± 2.05 Pg/ml) (P≤0.01) (Table 3 and Figure 2). This result was agreed with Wang *et al.* [17] who indicated that there were significantly higher levels of E2 in male infected with HCV than healthy males.

Farinati*et al*. [18] studied type of estrogen receptor, expression of estrogen receptor, and oxidative damage to DNA in patients with chronic liver disease due to HCV, it indicated that liver positivity for an estrogen receptor variant could result in high genomic deterioration and increased rates of carcinogenesis and cytoproliferation. It was found that because of strong aromatase activity, peripheral transformation of androgens to estrogen enhanced and estrogen levels raised [19]. Conversion of adrenal androstenedione to estrone was also recorded in cirrhotic patients [20]. Iyer*et al*. [21] concluded sex-based variations in basal expression of estrogen receptor α (ERα) in the liver was higher in men than in women, furthermore, the increased subcellular expression of subtypes of ER present in diseased livers associates with inflammatory markers and the expression of proliferative, modulations in ER subtype expression monitored in diseased livers can affect gender-related inequality in HCV-linked pathogenesis. In the liver, estrogen and estradiol receptors defend hepatocytes from cell death, oxidative stress, and inflammatory injury, which all lead to fibrosis. Due to the overall slower development of liver disease and enhanced viral clearance in females, the risk of HCV infection is found mainly in males [22]. By restricting the aggregation of macrophages, monocytes, and suppressing the production of inflammatory cytokinesis, estradiol can serve a convenient role in chronic liver disease [23].

The mean level of plasma progesterone in male infected with HCV (0.655 ± 0.04 ng/ml) revealed non-significantly difference with healthy control (0.693 ± 0.05 ng/ml) (Table 3). This result was conflicted with the study done by Serin [24] who demonstrated that serum progesterone levels were increased in HCV liver disease patients compared to the control group. Yuan *et al.* [23] was observed that progesterone may reduce the E2 impacts by increasing the aggregation of inflammatory cells and the release of their cytokines by the progesterone receptor.

Table (4) showed the comparative relationship of hormonal levels and viral load in age groups. The effect of age variant was statistically non-significant in means concentrations of testosterone and estradiol, and significant effect to mean of PCR viral load and progesterone hormone (P≤0.05).The study by Okafor*et al.* [25] indicated that age was not correlated with the prevalence of HCV among the inspected population. Conversely, increasing age is correlated with HCV prevalence, possibly due to extended HCV infection exposure [26]. Older patients at the time of infection and with compromised immune system are at high risk of developing chronic HCV infection [27].

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The statistical analysis of the findings exhibited there is non-significant negative relation among HCV PCR load mean with the levels of testosterone and estradiol, while there is a significant correlation coefficient with progesterone level ($P<0.05$). The age has non-significant positive correlated with HCV PCR load.

Wang *et al.* [17] recorded that male with increased serum testosterone levels showed inflammatory cytokines and the lowest levels of antibody after viral infection, testosterone reduces immune systems to infection with HCV. Each 1 ng/ml rise in overall serum testosterone had been linked with a 27% expanded danger of cirrhosis and a 16% elevated risk of advanced inflammatory activity among males infected with HCV [6]. One potential reason for these 'proviral' testosterone effects is that it changes the production of lipoprotein in a way that facilitates replication of HCV [28].

Table 1. Patients and control comparison in age.

Group	Mean ± SE of age (year)
Patients	39.23 ±2.41
Control	40.50 ±3.98
T-test	9.658 NS
P-value	0.792
NS: Non-Significant	

Table 2. Patients and control contrast in HCV-PCR.

Group	No.	Mean ± SE of HCV PCR Load IU/ml
Patients	30	13352976.13 ±4950929.53
Control	10	0.00 ± 0.00
T-test	-	327814.39 **
P-value	-	0.0001
** (P≤0.01), SE: Standard Error		

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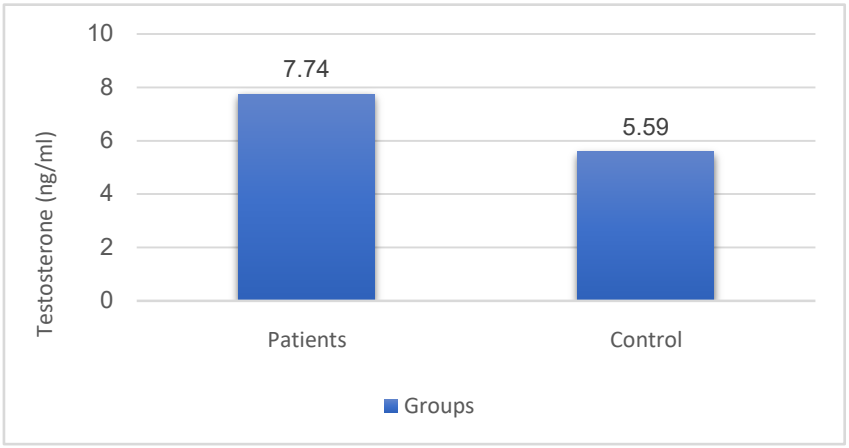

Figure 1. Compare between patients and control in mean of testosterone level.

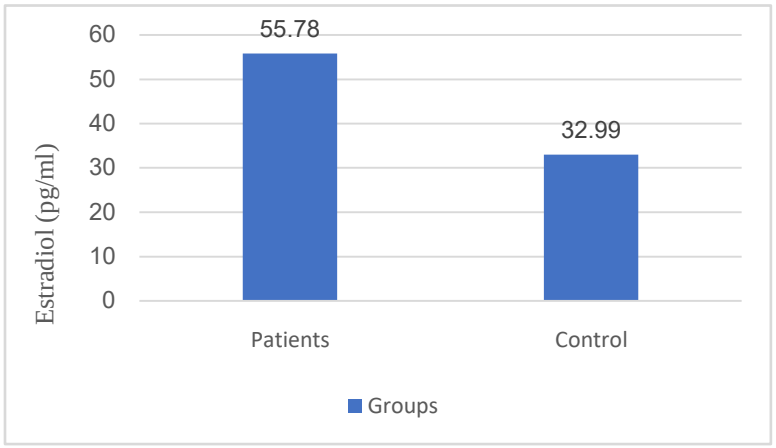

Figure 2. Compare between patients and control in mean of estradiol level.

Table 3. The mean level of hormones in the plasma of the researched groups.

Group	**Mean ± SE**		
	Testosterone (ng/ml)	**Estradiol (pg/ml)**	**Progesterone (ng/ml)**
Patients	7.74 ± 0.69	55.78 ± 3.07	0.655 ± 0.04
Control	5.59 ± 0.43	32.99 ± 2.05	0.693 ± 0.05
T-test	1.419 *	11.115 **	0.181 NS
P-value	0.0449	0.0002	0.671
* (P≤0.05), ** (P≤0.01)			

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Table 4. Effect of age groups in parameters study of patients.

Age group (year)	Mean ± SE			
	HCV PCR Load IU/ml	Testosterone (ng/ml)	Estradiol (pg/ml)	Progesterone (ng/ml)
Least than 30	15871192.33 ±10804297.14	7.008 ± 0.88	44.81 ± 3.64	0.531 ± 0.05
30-40	4632082.18 ±4134045.95	8.23 ±1.34	51.52 ± 5.38	0.667 ± 0.09
More than 40	9363651.29 ±4128580.94	6.67 ± 0.75	52.87 ± 5.09	0.756 ± 0.04
LSD value	873261.07 *	2.802 NS	14.382 NS	0.182 *
* (P≤0.05), NS: Non-Significant				

CONCLUSION

The current work evaluated the potentialcorrelation between male sex hormones and HCV infected Iraqi males. It was concluded that patients with liver disease related with HCV had a degree of hormonal imbalance.The plasma testosterone andestradiol mean level was elevated significantly in meninfected by HCV in compared with healthycontrol, however, there is non-significant difference betweenpatients and control in mean level of progesterone.There is no significant correlation between mean of HCV viralload results and the means levels of testosteroneand estradiol, while there is significant correlation withprogesterone mean levels.The age has non-significant correlated with HCV PCR load.

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CONFLICT OF INTEREST

The author declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES

1. Thong, V.D., Akkarathamrongsin, S., Poovorawan, K., Tangkijvanich, P., and Poovorawan, Y. (2014). Hepatitis C virus genotype 6: Virology, epidemiology, genetic variation, and clinical implication.World journal of gastroenterology, 20(11), 2927-2940.
2. Shin, E., Han, J.W., Kang, W., Kato, T., Kim, S., Zhong, J., Kim, S., Park, S., Sung, P.S., Watashi, K., Park, J.Y., Windisch, M.P., Oh, J., Wakita, T., Han, K., and Jang, S.K. (2020). The beginning of ending hepatitis C virus: A summary of the 26th international symposium on hepatitis C virus and related viruses. Viruses,12(3),302.https://doi.org/10.3390/v12030302.

3. Niepmann, M., and Gerresheim, G.K. (2020). Hepatitis C virus translation regulation. International journal of molecular sciences, 21(7), 2328. https://doi.org/10.3390/ijms21072328.
4. Kyuregyan, K.K., Malinnikova, E.Y., Soboleva, N.V.,Isaeva, O.V.,Karlsen, A.A., Kichatova, V.S., Potemkin, I.A., Schibrik, E.V.,Gadjieva, O.A.,Bashiryan, B.A., Lebedeva, N.N., Serkov, I.L., Yankina, A., Galli, C.,and Mikhailov, M.I. (2019). Community screening for hepatitis C virus infection in a low-prevalence population. BMC public health, 19,1038. https://doi.org/10.1186/s12889-019-7388-7.
5. Liu, L., Zhang, M., Hang, L., Kong, F., Yan, H., Zhang, Y., Feng, X., Gao, Y., Wang, C., Ma, H., Liu, X., Zhan, M., Pan, Y., Xu, X., and Niu, J. (2020). Evaluation of a new point-of-care oral anti-HCV test for screening of hepatitis C virus infection. Virology journal, 17,14. https://doi.org/10.1186/s12985-020-1293-7.
6. White, D.L., Tavakoli-Tabasi, S., Kuzniarek, J., Pascua, R., Ramsey, D.J., and El-Serag, H.B. (2012). Higher serum testosterone is associated with increased risk of advanced hepatitis C-related liver disease in males. Hepatology, 55(3), 759–768. https://doi.org/10.1002/hep.24618.
7. Hayashida, K., Shoji, I., Deng, L., Jiang, D., Ide, Y., and Hotta, H. (2010). 17 β-estradiol inhibits the production of infectious particlesof hepatitis C virus. Microbiology and immunology, 54(11),684–690.https://doi.org/10.1111/j.1348-0421.2010.00268.x.
8. Fawzy, N., Atia, H.A., Galal, S.M., and Shawky, J.A. (2015). Prevalence and risk factors of erectile dysfunction among chronic hepatitis C male patients treated with pegylated interferon-α and ribavirin. Egyptian journal of psychiatry, 36(1), 40-44. DOI: 10.4103/1110-1105.153776.
9. Chaudhury, C.S.,Mee, T., Chairez, C., McLaughlin, M., Silk, R., Gross, C., Kattakuzhy, S., Rosenthal, E., Kottilil, S., Stanley, T.L., and Hadigan, C. (2019). Testosterone in men with chronic hepatitis C infection and after hepatitis C viral clearance. Clinical infectious diseases, 69(4):571-576. doi: 10.1093/cid/ciy965.
10. SAS. 2012. Statistical Analysis System, User's Guide. Statistical. Version 9.1th ed. SAS. Inst. Inc. Cary. N.C. USA.
11. El-Serafi, A.T., Osama, S., El-Zalat, H., and El-Deen, I.M. (2016). Dysregulation of male sex hormones in chronic hepatitis C patients. Andrologia, 48(1), 82-86.https://doi.org/10.1111/and.12425.
12.Henze, L., Schwinge, D., and Schramm, C. (2020). The effects of androgens on T cells: clues to female predominance in autoimmune liver diseases? Frontiers in immunology, 11, 1567. doi: 10.3389/fimmu.2020.01567. eCollection 2020.
13.Kanda, T., Yokosuka, O., and Omata, M. (2013). Androgen receptor and hepatocellular carcinoma. Journal of gastrointestinal & digestive system, S12, 012. DOI: 10.4172/2161-069X.S12-012.
14.Davey, R.A., and Grossmann, M. (2016). Androgen Receptor Structure, Function and Biology: From Bench to Bedside. The clinical biochemist reviews, 37(1), 3–15.
15. Kur, P., Kolasa-Wołosiuk, A., Misiakiewicz-Has, K., and Wiszniewska, B. (2020). Sex hormone-dependent physiology and diseases of liver. International journal of environmental research and public health, 17(8), 2620, https://doi.org/10.3390/ijerph17082620.
16. Nguyen, H.V., Mollison, L.C., Taylor, T.W., Chubb, S.A.P., and Yeap, B.B. (2006). Chronic hepatitis C infection and sex hormone levels: effect of disease severity and recombinant interferon-α therapy. Internalmedicinejournal. 36(6), 362-366.https://doi.org/10.1111/j.1445-5994.2006.01093.x.
17. Wang, F.P., Zhang, P.A., and Yang, X.Y. (2017). Relationship between sex hormones and RIG‑I signaling in peripheral blood mononuclear cells of patients infected with hepatitis C virus. Experimental and therapeutic medicine, 14(3), 2728-2732.
18. Farinati, F., Cardin, R., Bortolami, M., Grottola, A., Manno. M., Colantoni, A., and Villa, E. (2002). Estrogens receptors and oxidative damage in the liver. Molecular andcellularendocrinology, 193(1-2), 85-88. DOI: 10.1016/s0303-7207(02)00100-4.
19. Chen, T., Wu, F., Wang, X., Ma, G., Xuan, X., Tang, R., Ding, S., and Lu, J. (2020). Different levels of estradiol are correlated with sexual dysfunction in adult men. Scientific reports, 10, 12660. https://doi.org/10.1038/s41598-020-69712-6.
20. Serin, A., Akarsu, M.,Akpinar, H., and Simsek, I. (2013). Changes of some hormones levels in patients with hepatitis B virus-related chronic liver disease. Gastroenterology research, 6(4):134-138. doi: 10.4021/gr532w.
21. Iyer, J.K., Kalra, M., Kaul, A., Payton, M.E., Kaul, R. (2017). Estrogen receptor expression in chronic hepatitis C andhepatocellular carcinoma pathogenesis. World journal of gastroenterology, 23(37), 6802-6816.doi: 10.3748/wjg.v23.i37.6802.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 11415 - 11422
Received 05 March 2021; Accepted 01 April 2021.

22. Baden, R., Rockstroh, J.K., and Buti, M. (2014). Natural history and management of hepatitis C: does sex play a role? The journal of infectious diseases, 15,209 Suppl 3, S81-5. doi: 10.1093/infdis/jiu057.
23. Yuan, Y., Shimizu, I., Shen, M., Aoyagi, E., Takenaka, H., Itagaki, T., Urata, M., Sannomiya, K., Kohno, N., Tamaki, K., Shono, M., and Takayama, T. (2008). Effects of estradiol and progesterone on the proinflammatorycytokine production by mononuclear cells from patients withchronic hepatitis C. World journal of gastroenterology, 14(14), 2200–2207. doi: 10.3748/wjg.14.2200.
24. Serin, A. (2019). Hormonal disturbances in patients with chornic hepatitis C. EC Gastroenterology and Digestive System, 6,9, 783-789.
25. Okafor, I.M., Ugwu, S.O., and Okoroiwu, H.U. (2020). Hepatitis C virus infection and its associatedfactors among prisoners in a Nigerian prison. BMC Gastroenterology, 20, 360. https://doi.org/10.1186/s12876-020-01504-8.
26. Puga, M.A.M., Bandeira, L.M., Pompilio, M.A., Croda, J., de Rezende, G.R., Dorisbor, L.F.P., Tanaka, T.S.O., Cesar, G.A.,Teles, S.A.,Simionatto, S., Novais, A.R.T., Nepomuceno, B., Castro, L.S., do Lago, B.V., and Motta-Castro, A.R.C. (2017). Prevalence and incidence of HCV infection among prisoners in central Brazil. PLoS ONE, 12(1), e0169195. DOI: 10.1371/journal.pone.0169195.
27. Reid, M., Price, J.C., and Tien, P.C. (2017). Hepatitis C virus infection in the older patient. Infectious disease clinics of North America, 31(4), 827–838. doi: 10.1016/j.idc.2017.07.014.
28. Langer, C., Gansz, B., Goepfert, C., Engel, T., Uehara, Y., von Dehn, G., Jansen, H., Assmann, G., and von Eckardstein, A. (2002). Testosterone up-regulates scavenger receptor BI and stimulates cholesterol efflux from macrophages. Biochemical and biophysical research communications, 296(5), 1051-1057, 2002.doi: 10.1016/s0006-291x(02)02038-7.