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A Correlation between Leptin Hormone and Other Biochemical Parameters in Iraqi Women with Hepatitis C Virus (HCV) in Thi-Qar Governorate in Iraq

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RESEARCH ARTICLE

A Correlation between Leptin Hormone and Other Biochemical Parameters in Iraqi Women with Hepatitis C Virus (HCV) in Thi-Qar Governorate in Iraq

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ABSTRACT

Background: chronic hepatitis C virus (HCV) infection is a major health problem. Females of childbearing age who are infected with hepatitis C are exposed to premature aging of the ovaries, which leads to an imbalance in the levels of sex hormones leptin hormone is associated with all stages of reproductive age. The aim of the present study is to observe levels the liver enzyme, Albumin, total bilirubin, estrogen, progesterone and leptin hormone. Also to evaluate the correlation between (leptin hormone liver enzyme, Albumin, total bilirubin, estrogen and progesterone).**Methods:** Serum liver enzyme, Albumin, total bilirubin, estrogen, progesterone and leptin hormone levels were determined in 33 patients with HCV and 32 healthy subjects. **Results:** When compared to the control group, the levels of liver enzyme, total bilirubin, estrogen, progesterone and leptin hormone were significantly higher in patients with hepatitis C virus ($P \leq 0.05$). On in contrary, levels of Albumin indicated a considerable decrease in patients having hepatitis C virus compared with control subjects ($P \leq 0.05$). The present study has reported a positive correlation between leptin hormone and (liver enzyme, total bilirubin, estrogen and progesterone). Also it has revealed negative correlation between leptin hormone and Albumin.

Keywords: Female sex hormones, Hepatitis C virus, Liver function tests, Leptin hormone, Premenopausal

Introduction

Hepatitis C virus is one of the leading causes of death in people because of terrible consequences on the liver.¹ Recent advancements in antiviral therapy utilising direct-acting antivirals (DAAs) have successfully attained a sustained viral response (SVR) in more than 95% (about 98%–99%) of patients infected with HCV.^{2–4} Several consequences have been documented following the achievement of SVR, which is associated with a remarkably high rate of hepatitis C virus (HCV) elimination. It is well-established that HCV elimination impacts not only liver function but also associated metabolism.^{5,6}

The origin of gender differences in HCV prevalence is not well understood, and several researches have proven that gender plays a significant role in placing women at a higher risk of HCV infection. However, some studies suggest HCV infection is more common and advances faster in males than females. Compared to men, women are more at risk of contracting the HCV through injections, blood, and blood products, especially during pregnancy, labour, and ear piercing. Biological sex and female dominance have also been associated with differences in rates of spontaneous HCV clearance, with a possible role for sex hormones in determining host susceptibility to viral infection.⁷ On the other hand, male dominance can be explained

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by differences in daily environmental life conditions, social, cultural and professional aspects that men deal with more frequently than women, incredibly informal areas such as intravenous drug use, circumcision, sharing use of toothbrushes or razors, tattooing, and wet cupping. (Hiama), or illicit sexual intercourse, in addition to emergency blood transfusions.⁸ Moreover, discrepancies in HCV infection rates between genders may indicate variations in the prevalence of gender-specific high-risk behaviours.^{9,10} Laboratory liver tests are widely regarded as tests that aid in the evaluation of hepatic dysfunction patients undergoing treatment. Some enzymes and metabolic pathway end products that are sensitive to the abnormality that occurs may be used as biochemical markers of liver dysfunction from them (AST, ALT, ALP, TB, Alb, estrogen E2, progesterone and leptin).

In the current research, serum alanine aminotransferase ALT, aspartate amino transferase AST, alkaline phosphates ALP, total bilirubin, and albumin were considered as essential biochemical parameters in patients with hepatitis C virus. Aside from some hormones (estrogen E2, progesterone and leptin). When elevated, alanine aminotransferase (ALT) is a liver enzyme that is a moderately sensitive predictor of liver injury; as a result, the American Association for the Study of Liver Disease and the American Association for the Prevention of Liver Disease also suggest HCV testing for people with elevated ALT levels.¹¹ According to research, manufacturers are more likely to screen patients for HCV if their ALT levels are elevated than if their exposure risk factors are measured.^{12,13} The increased AST level was previously due to mitochondrial injury caused by HCV infection and liver fibrosis progression.¹⁴ Upon the occurrence of hepatocyte apoptosis and damage, there was a considerable increase in blood ALT levels.^{11,15} The aim of this study was to investigate the correlation between (leptin hormone, female sex hormones, AST, ALT, ALP, TB and Alb). The levels of these hormones must be determined and the relationship between them found in order to reduce the problems that occur after complete treatment, as women of childbearing age who are infected with hepatitis C are exposed to premature aging of the ovaries, which leads to an imbalance in the levels of these hormones and thus fewer live births and higher rates of miscarriage and gestational diabetes.

Materials and methods

The present investigation is a prospective study. The samples were collected from patients who have

participated in specialised clinics at AL-Hussein Teaching Hospital and public health in Thi-Qar. Thirty three samples of blood were obtained from women suffered from hepatitis C virus (HCV), and thirty two samples of blood were obtained from healthy women as a control group, the age of subjects ranged between 25–45 years, for the period between 5/10/2021 to 10/7/2022.

Approximately five milliliters of blood were collected and allowed to clot at room temperature for ten minutes in hollow disposable centrifuge tubes for subsequent separation in a centrifuge at a force of 3000 ×g, the acceleration due to gravity (3000 xg). The serum samples were maintained and separated at –20 degrees Celsius before further analysis of biochemical characteristics unless used immediately. The serum was used for the estimation of AST, ALT and ALP, the reagents were supplied by (Linear, Spain). (TB) was measured by reagents were supplied by (Biolabo, France). (Alb) was measured by reagents were supplied by (Biolabo, France). Hormones (estrogen E2, progesterone and leptin) were measured by minividus (biomerieux kit).

Statistical analysis

The results of the experiment were presented as mean ± standard deviations, or mean ± SD. The one-way ANOVA test was employed to compare parameters among the several groups under analysis. $P < 0.05$ indicated statistical significance for the P values. The correlation between the various parameters in each patient group was tested using the person correlation coefficient (r).

Results and discussion

Table 1 indicates that the levels of AST, ALT, and ALP in the patients group are substantially higher than in the control group ($P \leq 0.05$). Also, as in this table, there is a large decrease in Albumin levels in the patients group as compared to the control group ($P \leq 0.05$). The same Table 1 indicates a large rise in total bilirubin (TB) levels in the patients group as compared to the control group ($P \leq 0.05$).

Table 1. Essential laboratory findings for routine investigations.

Parameters	Patients	Control	p.value
ALT (IU/L)	46.08 ± 2.38	32.76 ± 2.67	0.007
AST (IU/L)	44.50 ± 3.09	22.76 ± 2.21	0.002
ALP (IU/L)	73.12 ± 8.07	41.70 ± 3.09	0.003
Albumin (mg/dl)	3.94 ± 0.42	4.83 ± 0.60	0.004
Total bilirubin (mg/dl)	3.46 ± 0.25	0.47 ± 0.13	0.001

Table 2. Levels of serum hormones in patients compared with control groups.

Hormones	Patients	Control	p.value
E2 pg/ml	34.38 ± 4.65	26.37 ± 3.55	0.002
Progesterone ng/ml	0.92 ± 0.09	0.36 ± 0.08	0.002
Leptin ng/ml	13.05 ± 2.27	4.28 ± 0.77	0.003

Table 3. Correlation between leptin hormone and other biochemical parameters for this study.

Leptin with	r	Results
ALT	0.09	positive correlation
AST	0.05	positive correlation
ALP	0.07	positive correlation
Albumin	-0.15	negative correlation
Total bilirubin	0.08	positive correlation
E2	0.17	positive correlation
Progesterone	0.11	positive correlation

Table 2 shows that the levels of E2 and progesterone hormones in the patients community were significantly higher than in the control group ($P \leq 0.05$). In addition, this table indicates a large rise in leptin hormone levels in the patients group as compared to the control group ($P \leq 0.05$).

Table 3 explains the correlation between leptin hormone and other biochemical parameters for this study. A positive correlation was found between Leptin hormone and (AST, ALT, ALP, total bilirubin E2 and progesterone). Also a negative correlation was found between leptin hormone and (Albumin).

The HCV is one of the most dangerous types of viruses. It can cause acute and chronic hepatitis and can lead to cirrhosis and the onset of malignant tumors.¹⁶ Although most patients infected with HCV who get direct-acting antivirals (DAAs) can successfully achieve a cure for the virus, the emergence of HCV resistance to DAAs continues to be a challenging challenge.¹⁷ This study sheds a light on level of leptin hormone in female with Hepatitis C virus infection. It was noticed that after infection with hepatitis c virus, leptin levels increased significantly. Leptin has been proposed to regulate autophagy.¹⁸ Autophagy is an internal process of recycling that plays a crucial role in maintaining cellular balance and controlling the cellular stress response.¹⁹ Autophagy has been linked to the control of liver cells that are already present, such as hepatocytes, hepatic stellate cells (HSCs), and macrophages.^{20,21} There have been reports of the accumulation of autophagosomes in hepatocytes infected with HCV. Furthermore, it has been documented that HCV infection triggers a process known as complete autophagy, which actively facilitates the replication of HCV.¹⁸ Even though leptin is not a classical cytokine, while leptin does not fit the definition

of a conventional cytokine, it can affect several types of immune cells, including polymorphonuclear leukocytes, lymphocytes, monocytes, and macrophages. These cells have receptors for leptin and can be controlled by it. Leptin shares a similar structure with cytokines that are part of the long-chain helical family. Leptin stimulates phagocytosis in monocytes and macrophages via attaching to the Ob-Rb receptor and regulating oxidative stress.²² Furthermore, it stimulates Kupffer cells and macrophages present in the liver, leading to inflammatory responses and the advancement of steatohepatitis. Moreover, leptin controls the process of fat degradation in liver cells, resulting in the buildup of fat in the liver, which is referred to as hepatic steatosis. Extensive research has been conducted on leptin, revealing its role in inducing many aberrant liver illnesses through its impact on distinct signalling pathways in other liver cells. However, it is still unclear if leptin directly causes cell death in liver cells, and the underlying mechanisms have not been fully understood.²³ Leptin is linked to all phases of reproductive age in women. Leptin signalling operates within a specific range under normal bodily settings, and very high or low levels of leptin might negatively affect fertility and the functioning of the ovaries.²⁴ On the other hand, the current study showed the levels of female sex hormones and their relationship to the leptin hormone. it was found that the levels of E2 and progesterone hormones in the patients community are substantially higher than in the control group. Also it was found a positive correlation between Leptin hormone and (E2 and progesterone). The liver is a crucial target tissue for oestrogen signalling.²⁵ Oestrogen exerts a diverse array of protective actions on hepatocytes. Estradiol enhances cellular mitochondrial function in a substrate-specific manner,²⁶ hence reducing the vulnerability of the liver to steatosis. Oestrogen has been discovered to hinder liver inflammation for several reasons:

1. Postmenopausal women often experience increased lipid peroxidation and inflammation in the liver.²⁷
2. Oestrogen signalling reduces the release of pro-inflammatory cytokines and the production of ROS in liver cells.^{28,29}
3. Oestrogen supplementation improves the diminished ability of Kupffer cells to engulf foreign particles by activating Akt.

Elevated progesterone levels are linked to the onset of systemic insulin resistance. Furthermore, this hormone can predict insulin resistance in adolescent girls,²⁹ regardless of other factors. Progesterone

administration in patients with nonalcoholic steatohepatitis (NASH) will cause noticeable inflammation in the liver lobes, whereas oestrogen administration does not have the same effect.

The processes underlying progesterone-induced metabolic liver damage remain uncharacterized. A recent study has found that a lack of progesterone receptor membrane component 1 leads to fatty liver disease by producing new fats in the liver,³⁰ a process known as *de novo* lipogenesis. Another study on metabolism indicates that progesterone enhances the generation of glucose in the liver by influencing the process of gluconeogenesis through the progesterone receptor membrane component 1 (PGRMC1). This effect may worsen high blood sugar levels in those with diabetes who have restricted insulin function.²⁷ Progesterone has been found to induce the creation of ROS through progesterone receptors in end-stage liver disorders. This leads to the expression of transforming growth factor (TGF)- β 1, activation of hepatic stellate cells (HSCs), and the development of extracellular collagen.³⁰ This event enhances the likelihood that progesterone can create a beneficial milieu for tumours, contributing to liver cancer progression. PGRMC1 is regarded as a biomarker for the rapid growth of tumour cells and is highly expressed in various types of cancer. Hepatic PGRMC1 and progesterone receptors remain consistently active when there are high amounts of progesterone in the bloodstream, potentially contributing to the resistance of HCC to chemotherapy.²⁹ Leptin not only influences the generation of gonadotropin-releasing hormone, but it also has a significant impact on the functioning of the ovary and endometrial, as well as participating in embryo development. Due to its influence on the generation of estradiol (E2) by human granulosa cells in response to LH, it has a significant impact. The presence of a connection between E2 and leptin has been proven in the follicular phase of both natural and artificially induced menstrual cycles.³¹

Conclusion

According to the results, the authors concluded that women with hepatitis C have a high levels of AST, ALT, ALP, total bilirubin, E2, progesterone and leptin hormone. A positive correlation was shown between leptin hormone and female sex hormones. So levels of these hormones must be determined and treated, as women of childbearing age who are infected with hepatitis C are exposed to premature aging of the ovaries, which leads to an imbalance in the levels of these hormones and thus fewer live births and higher rates of miscarriage and gestational diabetes.

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Author's declaration

- Conflicts of Interest: None.
- We hereby confirm that all tables are ours.
- No animal studies are present in the manuscript.
- Authors signed on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at University of Thi-Qar.

Authors' contribution statement

A. M. authored and edited the text, incorporated in revisions. S. A. S. performed the analysis of data with revisions. H.R.F. diagnoses, collecting the samples, and performing the tests. All authors cooperated in the tasks of editing, inquiry, and proofreading.

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ارتباط هرمون اللبتين والمعايير البيوكيميائية الاخرى في النساء المصابات بالتهاب الكبد الفيروسي النوع سي في محافظة ذي قار/العراق

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الخلاصة

تعتبر عدوى التهاب الكبد الفيروسي المزمن مشكلة صحية كبيرة. تتعرض النساء المصابات بالتهاب الكبد الفيروسي في سن الانجاب إلى شيخوخة المبيضين المبكرة مما يؤدي إلى خلل في مستويات الهرمونات الجنسية الانثوية. يرتبط هرمون اللبتين بجميع مراحل سن الانجاب. لذا هدفت الدراسة الحالية إلى رصد مستويات انزيمات الكبد، الالبومين، البيلروبين الكلي، الاستروجين، البروجسترون وهرمون اللبتين. أيضا لتقييم العلاقة بين (هرمون اللبتين، انزيمات الكبد، الالبومين، البيلروبين الكلي و الاستروجين والبروجسترون). طرق العمل: تم تحديد مستويات انزيمات الكبد، الالبومين، البيلروبين الكلي، الهرمونات الجنسية الانثوية وهرمون اللبتين في 33 مريضا مع عدوى التهاب الكبد الفيروسي المزمن و 32 من الأصحاء. النتائج: عند المقارنة بمجموعة السيطرة، كانت مستويات انزيمات الكبد والبيلروبين الكلي، الاستروجين، البروجسترون وهرمون اللبتين أعلى بشكل ملحوظ في مرضى التهاب الكبد الفيروسي النوع C ($P \leq 0.05$). على العكس ذلك، أشارت مستويات الألبومين إلى انخفاض كبير في المرضى المصابين بالتهاب الكبد الفيروسي النوع C عند المقارنة مع الأصحاء ($P \leq 0.05$). وجدنا علاقة ارتباط موجبة بين هرمون اللبتين و(انزيمات الكبد، البيلروبين الكلي، الاستروجين والبروجسترون) كما وجدنا علاقة سلبية بين هرمون اللبتين و الألبومين).

الكلمات المفتاحية: الهرمونات الجنسية الأنثوية، التهاب الكبد الفيروسي النوع C، اختبارات وظائف الكبد، هرمون اللبتين، مرحلة ما قبل انقطاع الطمث.