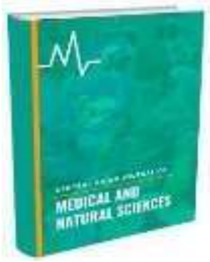

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Article

Impact of IL-37 on Oxidant-Antioxidant Status in Chronic Liver Failure

Maha. DAzez

Department of Pharmaceutical Chemistry, College of Pharmacy, University of Thi-Qar, Thi-Qar, 64001, Iraq

Correspondence author email : maha.D.A@utq.edu.iq

Abstract: Chronic liver failure, characterized by the permanent and gradual loss of liver function over time, is influenced by oxidative stress and inflammation. This study aimed to evaluate the association between interleukin-37 (IL-37) and oxidant-antioxidant status in patients with chronic liver failure, given that IL-37 is activated by reactive oxygen species (ROS). Conducted at Al-AL-Hussein Teaching Hospital in Thi-Qar governorate from August 20, 2023, to February 25, 2024, the study involved 40 patients and 40 controls aged 20 to 60. Blood samples were collected and analyzed using ELISA and other biochemical methods. Results indicated significantly higher levels of IL-37, malondialdehyde (MDA), and ceruloplasmin (Cp) in patients compared to controls ($P < 0.05$), while levels of albumin, glutathione (GSH), and superoxide dismutase (SOD) were significantly lower. A positive correlation was found between IL-37, MDA, and Cp, whereas a negative correlation was observed between IL-37 and albumin, GSH, and SOD. These findings suggest that IL-37 may play a role in the oxidative stress observed in chronic liver failure, highlighting potential targets for therapeutic intervention..

Keywords: Chronic liver failure, IL-37, Oxidant, Antioxidant, Oxidative Stress.

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1. Introduction

Because of its high prevalence as well as unfavorable results of the long-term clinical treatments, liver disease emerged as one of the significant worldwide public health concerns (Wang etal 2014). Yet, most patients receive a diagnosis of cirrhosis or latter stages of liver cancer due to low treatment rates and a lack of knowledge of liver disease risks. Consequently, liver disease causes around 2 million deaths annually (Yang et al 2019). Chronic liver disease, often known as end-stage liver disease, is identified by steady and progressive loss of liver function over a protracted period of time. Chronic hepatitis C or B infections, fatty liver disease, heavy alcohol use, genetic abnormalities, and autoimmune liver illnesses are among the causes that are frequently linked to prolonged liver damage (Nagalli and Sharma, 2024). It is believed that the oxidative stress happens in a few of such conditions (Mitchell et al 2015). According to Sies et al. (2017) and Sayer and Zaidan 2022, oxidative stress (OS) is identified by imbalance between antioxidants and oxidants and an excess of ROS. Because of its metabolic and detoxifying functions, the liver is a significant location for the formation of ROS (Ramachandran and Jaeschke, et al 2011). As a result of the liver cells' powerful anti-oxidant defense systems, which include the non-enzymatic as well as the enzymatic parts, the levels of ROS could be kept in the range of the physiological levels. The start of the necrosis, inflammatory reactions, fibrosis, apoptosis or malignant changes are related to a rise in levels (Allame etal 2023; Haliwell etal., 1999). Damages to the cells of the liver could result in creating pro-inflammatory substances and activate inflammation-causing cells such as the macrophages and the neutrophils that worsen the injury.

Regarding inflammatory cell activation after liver injury due to multiple causes, IL-37 is responsible. It's an anti-inflammatory cytokine located in IL1 family (Jiang et al 2023). IL-37 contributes to blocking diverse types of inflammatory attacks, like proinflammatory cytokines. This makes it different from many other anti-inflammatory cytokines (Yan et al 2019). The objective of the present study has been to make clearer connection between levels of serum IL37 in patients who have liver failure and their oxidant-antioxidant state. Another helpful sign that shows OS and damage from free radicals is malondialdehyde (MDA), mostly taken from peroxidation about polyunsaturated fatty acids in biological samples (Rio et al., 2005; Sayer et al., 2017). The protein that we find in blood plasma the most is albumen (Alb). It's a single chain polypeptide with 585 amino acids and has an approximate weight of 66,500 Da. Roughly 60% of total plasma proteins are made by serum Alb which usually has a half-life around 20 days under usual situations (Taverna et al., 2013; Yang et al., 2014). Alb serves as an independent predictor in relation to hepatic-related mortality, as elucidated by Younossi et al and Rafiq et al (Rafia etal 2009; Younossi et al 2004; Sayer etal 2023). Ceruloplasmin (Cp) is an α-glycoprotein with molecular weight of roughly 132kDa that consists of one chain polypeptide containing around 1046 amino acids (Tipton and Healy, 2007). The main place where Cp is made in our body comes from the liver, mainly as a single chain polypeptide. Through the biosynthetic pathway and its six copper atoms, we get to secrete Cp into plasma as an α2-glycoprotein (Gutteridge, 2005). Enzymatic parts such as GSH and SOD are able to control ROS levels by acting as antioxidants; this helps them keep reactive oxygen species within normal limits for physiological maintenance of body functions (Halliwell, 1999; Allameh etal 2023).

2. Materials and Methods

At the Al-AL-Hussein Teaching Hospital in the Thi-Qar governorate, a group of patients suffering from chronic liver failure participated in the presented work, which took place between August 20, 2023, and February 25, 2024. There are 40 controls and 40 patients with chronic liver failure in this study. Ages of the controls and patients: 20 to 60. For the purpose of separation in a centrifuge operating at 3000 xg, about five milliliters of blood were collected and allowed to clot at the temperature of the room for 10 mins in hollow disposable centrifuge tubes. Unless they were utilized right away, the serum samples have been separated and kept at minus twenty degrees Celsius until biochemical characteristics were measured and analyzed later. ELISA was used to measure IL-37, and ready kits made by Fine, China were used. ELISA was used to measure SOD and GSH with ready kits produced by Elabscience in the US. MDA was calculated using the methodology described in (Muslih et al 2002). Cp was quantified using the methodology described in Menden et al. (1977). Reagents from Biolabo in France have been used to measure allumine. As per the methodology of Webster (1974).

Statistical Analysis

Data analysis was done with SPSS 23.0. The data was presented as mean ± SD. For comparing parameters across all groups under investigation, the independent sample t test has been utilized, and P-values ($P \leq 0.05$) have been taken into account. To evaluate the relationship between the variables, Pearson's correlation was used.

3. Results

The study groups' clinical and demographic characteristics are explained in Table1. There has not been any discernible difference (P > 0.050) in age, BMI, or sex between controls and the patients.

Table 1. Clinical characters in controls and patients

	Patients	Controls	p-value
Age (Years) (Mean ±SD)	46.78±6.87	46.48±7.04	0.249
BMI (Kg/m²) (Mean ±SD)	27.29±5.89	26.23±3.34	0.000
Sex	Male (22) Female(18)	Male (20) Female(20)	
Substance use	5	0	
	0	0	

The levels of IL-37 as well as Oxidant-Antioxidant Status in controls and patients are displayed in Table 2. Compared with the control group, it has been discovered that the patient's group has a significantly higher serum concentration of IL-37, MDA, and CP (P less than 0.05). It was discovered that the patients' group's serum concentrations of SOD, albumin, and GSH were significantly lower than those of the controls group (P= 0.009).

Table2. Levels of IL37 and Oxidant-Antioxidant Status in controls and patients.

Parameters	Patients	Controls	p-value
IL-37 (pg/mL)	74.64 ± 10.31	24.53±5.44	0.003
MDA(μmol/L)	2.87± 0.61	1.32±0.31	0.000
Albumen (g/dL)	3.87 ± 5.62	4.94 ±0.85	0.017
Cp (g/L)	4.86±0.85	2.64± 0.85	0.000
SOD)ng/mL)	3.82±0.96	7.29 ± 1.84	0.016
GSH (Ug/mL)	1.76 ± 0.35	2.75±0.65	0.005

Table 3 demonstrates the positive correlation that exists between MDA, CP, and IL-3. Yet, a negative correlation between albumin, GSH, SOD, and IL-37 was discovered.

Table 3. correlation between IL-37 and other parameters in this work.

IL-37 with	r	p-value	Result
MDA	0.51	0.022	Significant positive correlation
Albumin	- 0.41	0.027	Significant negative correlation
CP	0.44	0.040	Significant positive correlation
SOD	- 0.48	0.043	Significant positive correlation
GSH	- 0.61	0.002	Significant positive correlation

4. Discussion

Under typical circumstances, the liver's highly regulated synthesis of RNS and ROS supports the hepatocytes' normal functioning and development. They are required for microsomal protection, growth, apoptosis, and regeneration. OS, on the other hand, could result from a discrepancy between ROS/RNS generation and intracellular anti-oxidant defense system. A decrease in the cellular antioxidant capacity or an excess of ROS/RNS production may be the cause of this imbalance (Bose et al 2022; Chhikara et al 2021). On liver cells, OS could be detrimental. According to Emanuele et al. (1998), it might result in fibrosis, localized or programmed cell death, or oncogenic consequences (development of cancer). Due to its high metabolic rate, exposure to toxins, and xenobiotic chemicals, the liver is particularly vulnerable to the oxidative stresses (Contreras etal 2022; Shao et al 2022). Elevated OS is often associated with prolonged hepatic illnesses, which include alcoholic liver disease, viral hepatitis, and non-alcoholic fatty liver disease (Baffy et al 2012; Rouf et al 2021; Farzanegi et al 2019). ROS accumulation stimulates IL-37, which in turn suppresses oxidative burst of activated immune cells and reduces ROS production (Fujita and Chen 2015; Xu WD etal 2015; Wu B et al 2014; Sharma et al 2023). The correlation between IL-37 and Oxidant-Antioxidant Statues was therefore examined in this work. It has been discovered that there was imbalance between the patients' endogenous generation of free radicals and their anti-oxidant defense mechanisms, which is what is known as "oxidative stress." This imbalance was detected when comparing the patients group to the controls group. IL-37 and oxidant-antioxidant status were shown to be significantly correlated, according to Pearson's correlation data. This indicates that there could be a production of IL-37 in response to oxidative stress because serum IL-37 was found to be substantially correlated with oxidant-antioxidant characteristics.

5. Conclusion

Study elucidates a significant association between IL-37 levels and the oxidant-antioxidant status in patients with chronic liver failure. The observed elevation of IL-37, malondialdehyde (MDA), and ceruloplasmin (CP) levels, along with the concurrent decrease in albumin, glutathione (GSH), and superoxide dismutase (SOD) levels, underscores the intricate interplay between oxidative stress and the immune response in liver pathology. These findings suggest a potential role for IL-37 as a biomarker for oxidative stress and inflammation in chronic liver failure. Furthermore, the negative correlation between IL-37 and antioxidants highlights the importance of mitigating oxidative stress to alleviate liver dysfunction. Future research should focus on elucidating the mechanistic pathways underlying the regulation of IL-37 in liver disease and exploring therapeutic strategies targeting this cytokine to ameliorate liver injury and improve patient outcomes.

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