International Journal of Medical Toxicology & Legal Medicine **Volume 27, No. 5, 2024**
e-ISSN: 0974-4614
p-ISSN: 0972-0448
https://doi.org/10.47059/ijmtlm/V27I5/057

Assessing IL-35 and IL-36 concentrations in Hemodialysis Patients with and without HCV

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Received: 18.09.2024 Revised: 10.10.2024 Accepted: 16.11.2024

ABSTRACT
Background: IL-35 and IL-36 are cytokines involved in immune modulation and inflammatory processes. Despite their established roles in various inflammatory and immune-mediated conditions, their specific contributions to end-stage renal disease (ESRD) and hepatitis C virus (HCV) infection in hemodialysis patients are not well understood.
Objective: This study aimed to investigate the serum levels of IL-35 and IL-36 in ESRD patients undergoing hemodialysis, with and without HCV infection.
Methods: A cross-sectional study was conducted, including 92 ESRD patients (47 HCV-positive and 45 HCV-negative) and 45 healthy controls. Serum levels of IL-35 and IL-36 were measured using enzyme-linked immunosorbent assay (ELISA).
Results:IL-35 levels were comparable between controls (5.23 ± 4.24 ng/dL) and HCV-negative hemodialysis patients (4.83 ± 4.54 ng/dL; $p = 0.665$). However, HCV-positive patients exhibited significantly higher IL-35 levels (11.48 ± 4.13 ng/dL) compared to both controls and HCV-negative patients ($p < 0.001$). IL-36 levels were significantly elevated in both HCV-negative and HCV-positive hemodialysis patients (54.1 ± 21.7 ng/dL and 68.6 ± 52.4 ng/dL, respectively) compared to controls (26.3 ± 33.5 ng/dL; $p < 0.001$).
Conclusion:L-35 is significantly upregulated in HCV-positive hemodialysis patients, indicating its potential role in immune regulation in the context of HCV infection. Elevated IL-36 in all hemodialysis patients reflects its involvement in the systemic inflammatory state associated with renal failure. These findings provide quantitative insights into the roles of IL-35 and IL-36 in hemodialysis and HCV, underscoring their potential as biomarkers or therapeutic targets.

Keywords: interleukin-35, interleukin-36, Hepatitis C virus, hemodialysis, renal failure.

1. INTRODUCTION

End-stage renal disease (ESRD) is a severe condition characterized by the near-complete loss of kidney function, necessitating renal replacement therapy, such as hemodialysis, to sustain life [1]. Hemodialysis is a widely used therapeutic intervention that eliminates toxins, excess fluids, and electrolytes from the blood [2]. Despite its life-saving benefits, hemodialysis patients are subjected to chronic inflammation, oxidative stress, and immune dysregulation, which significantly contribute to complications such as cardiovascular disease, infections, and poor quality of life [3].

Hepatitis C virus (HCV) infection is a significant global health burden, particularly prevalent among patients ESRD undergoing hemodialysis [4]. HCV is a hepatotropic virus that primarily targets the liver, causing chronic inflammation, fibrosis, and potentially progressing to cirrhosis and hepatocellular carcinoma [5]. However, its impact is not confined to the liver. In hemodialysis patients, HCV infection is associated with systemic inflammation, immune dysregulation, and a higher risk of morbidity and mortality. Hemodialysis patients are at

an increased risk of HCV transmission due to the nature of the treatment, which involves repeated vascular access and exposure to shared medical equipment [6]. Despite advancements in infection control measures, HCV prevalence remains significantly higher in hemodialysis populations compared to the general population [4]. Moreover, the interaction between HCV infection and the hemodialysis-associated immune disturbances can amplify the pro-inflammation, leading to worsened clinical outcomes.

Interleukin-35 (IL-35) is a relatively novel anti-inflammatory cytokine that belongs to the IL-12 family [7]. It is composed of two subunits: EBI3 (Epstein-Barr virus-induced gene 3) and IL-12p35 α, which are expressed by various immune cells, including regulatory T cells (Tregs), B cells, and some antigen-presenting cells [8]. Unlike other cytokines, IL-35 exhibits a primarily immunosuppressive role by promoting regulatory T and B cell function while inhibiting pro-inflammatory responses mediated by effector T cells, such as Th1 and Th17 [9].

Severalinvestigationsaimed to find the role of IL-35 in maintaining immune homeostasis and its involvement in a variety of diseases. IL-35 may help modulate cytokine levels and protect against the onset of autoimmune diabetes [10]. It has also shown that IL-35 levels are elevated in allergic rhinitis [11]. In autoimmune conditions such as rheumatoid arthritis [12] and multiple sclerosis [13], IL-35 levels are often dysregulated, suggesting its potential as a therapeutic target. Additionally, IL-35 has been implicated in cancer progression, where it may suppress anti-tumor immunity, and in infectious diseases, where it can modulate host-pathogen interactions [14,15]. Its role in chronic inflammatory states, such as those experienced by ESRD patients undergoing hemodialysis, is still under investigation, with evidence pointing toward its potential involvement in modulating systemic inflammation and organ-specific immune responses.

Interleukin-36 (IL-36) is a pro-inflammatory cytokine belonging to the IL-1 cytokine family, which includes three agonists (IL-36α, IL-36β, and IL-36γ) and one antagonist (IL-36Ra) [16]. IL-36 plays animportant role in mediating immune responses by binding to its receptor, IL-36R, which is expressed on various immune and structural cells, including keratinocytes, macrophages, dendritic cells, and epithelial cells [17]. Activation of IL-36 signaling triggers downstream pathways, such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), leading to the production of additional pro-inflammatory cytokines and chemokines that amplify immune responses [18].

IL-36 has been extensively studied in the context of inflammatory and autoimmune diseases, particularly in psoriasis, where it is thought to contribute to the recruitment and activation of inflammatory cells in the skin [19]. Beyond dermatological disorders, IL-36 is implicated in systemic inflammatory conditions, including rheumatoid arthritis [20], inflammatory bowel disease [21], and infections [22]. Elevated IL-36 levels have been associated with excessive inflammation, suggesting its role in the pathogenesis of diseases characterized by immune dysregulation.

In the context of ESRD and hemodialysis, IL-36 may contribute to the chronic inflammatory state observed in these patients [23,24]. Its potential involvement in kidney-related inflammation and its interaction with other cytokines, such as IL-35, remain areas of active investigation. Exploring IL-36 levels in hemodialysis patients with and without HCV infection may provide valuable insights into its role in the interplay between inflammation, immune regulation, and kidney disease.

This study aims to explore the levels of IL-35 and IL-36 in hemodialysis patients, with and without hepatitis C virus (HCV) infection, to better understand its contribution to the immune dysregulation seen in this population.

2. MATERIALS AND METHODS

Study Design and Population

This cross-sectional study included 92 patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis and 45 healthy individuals serving as a control group. The hemodialysis patients were divided into two subgroups based on the presence or absence of hepatitis C virus (HCV) infection, resulting in HCV-positive and HCV-negative groups. Patients with coexisting autoimmune diseases, acute infections, or malignancies and those with active systemic inflammatory conditions unrelated to HCV or ESRD were excluded.

Sample Collection

About six milliliters of peripheral blood samples were collected from all participants under aseptic conditions. For hemodialysis patients, blood was drawn immediately before the start of their routine dialysis session to avoid any confounding effects from the procedure. The blood sample were separated into two parts. In part one, 5ml of blood was placed in a gel tube and left for about 15min at 37°C for coagulation and then centrifuged for10-15min at 2000 xg. Serum then stored at -20°C until analysis. Blood for hemoglobin analysis was collected in EDTA-treated tubes for hemoglobin measurement. Hemoglobin levels were measured promptly to avoid any degradation of the sample.

Measurement of Cytokine Levels

Biochemical parameters, including urea, creatinine, albumin, calcium, phosphate, and hemoglobin levels, were analyzed using standard methods on a Beckman Coulter AU680 Chemistry Analyzer (Beckman Coulter Inc., Brea, CA, USA). The analyzer was calibrated according to the manufacturer's instructions, and quality control procedures were performed daily to ensure accuracy and precision. Serum levels of IL-35 and IL-36 were quantified using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions (Bioassay, Human Interleukin-35 and Human Interleukin-36 ELISA Kits, China). The absorbance was measured at 450 nm using a microplate reader, and cytokine concentrations were calculated from the standard curve generated for each assay.

Statistical Analysis

Data were analyzed using SPSS statistical software version 26. Descriptive statistics were calculated for demographic and biochemical parameters, and results were expressed as mean ± standard deviation (SD). Pearson correlation analysis was used as appropriate. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

A group of 92 ESRD patients on hemodialysis were involved in this study, alongside 45 healthy participants as a control group. The hemodialysis patients were further categorized into two subgroups: those with HCV and those without HCV.

Age and sex distributions were matched across all groups to eliminate potential confounding effects. Concentrations of IL-35 were comparable between controls (5.23 ± 4.24 ng/dL) and HCV-negative hemodialysis patients (4.83 ± 4.54 ng/dL; $p = 0.665$). However, HCV-positive patients had significantly elevated IL-35 levels (11.48 ± 4.13 ng/dL) compared to both controls and HCV-negative hemodialysis patients ($p < 0.001$), suggesting that HCV infection could upregulate IL-35 in the inflammatory milieu of hemodialysis. IL-36 was significantly higher in both hemodialysis sub-groups (54.1 ± 21.7 ng/dL and 68.6 ± 52.4 ng/dL) compared to controls (26.3 ± 33.5 ng/dL; $p < 0.001$). While the difference between HCV-positive and HCV-negative subgroups did not reach statistical significance ($p = 0.087$), the trend toward higher IL-36 levels in the HCV-positive group warrants further investigation. Table1 shows these results.

Table 1: Demographic, biochemical, and interleukin concentration of hemodialysis patients with and without HCV compared to healthy controls

Variable	Control Group (n= 45)	Hemodialysis sub-groups			
		without HCV (n=46)	p-value [a]	with HCV (n=46)	p-value
Age (years) (±SD)	38.3 (±11.1)	38.9 (±14.3)	0.824	41.1 (±13.9)	0.289[a]
					0.453[b]
Male sex	23 (51.1%)	23 (50%)	0.917	20 (43.5%)	0.471[a]
Female sex	22 (48.9%)	23 (50%)		26 (56.5%)	0.536[b]
Urea mg/dL (±SD)	25.1 (±7.1)	173.24 (±50.57)	<0.001	192.89 (±48.82)	<0.001[a]
					0.061[b]
Creatinine mg/dL (±SD)	0.7 (±0.1)	9.2 (±2.4)	<0.001	10.4 (±2.5)	<0.001[a]
					0.022[b]
Albumin g/dL (±SD)	4.2 (±0.3)	3.4 (±0.8)	<0.001	3.5 (±0.7)	<0.001[a]
					0.422[b]
Ca++ mg/dL (±SD)	9.2 (±0.5)	7.6 (±1.5)	<0.001	7.3 (±2)	<0.001[a]
					0.428[b]
Phosphate mg/dL (±SD)	3.2 (±0.5)	5.9 (±1.8)	<0.001	7 (±2.2)	<0.001[a]
					0.013[b]
Hemoglobin mg/dL (± SD)	13.2 (±1.5)	8.8 (±2.2)	<0.001	9.1 (±2)	<0.001[a]
					0.500[b]
IL-35 ng/dL (±SD)	5.23 (±4.24)	4.83 (±4.54)	0.665	11.48 (±4.13)	<0.001[a]
					<0.001[b]
IL-36 ng/dL (±SD)	26.3 (±33.5)	54.1 (±21.7)	<0.001	68.6 (±52.4)	<0.001[a]
					0.087[b]

[a] P value was calculated in reference to the control group. [b] P value was calculated between the hemodialysis groups, with and without HCV.

In addition, the analysis revealed a strong positive correlation between IL-35 and IL-36 levels in both hemodialysis groups. In the hemodialysis group without HCV infection, the correlation coefficient was r = 0.779, with a p-value < 0.0001, indicating a highly significant relationship. Similarly, in the hemodialysis group with HCV, the correlation coefficient was r = 0.688, also with a p-value < 0.0001, suggesting a strong association despite the presence of HCV infection.

4. DISCUSSION

The immune system plays a fundamental role in the progression of chronic conditions such as end-stage renal disease (ESRD) and hepatitis C virus (HCV) infection, both of which are associated with systemic inflammation and immune dysregulation. Cytokines like IL-35 and IL-36 have emerged as key regulators in inflammatory and immune responses, with IL-35 predominantly exhibiting immunosuppressive effects and IL-36 promoting inflammation [8,16]. ESRD patients, particularly those on hemodialysis, face additional complications such as anemia and altered biochemical markers, while HCV infection further exacerbates inflammatory and immune responses. This study builds on these foundations to explore how these cytokines behave in such complex pathological conditions.

This study demonstrated distinct alterations in serum levels of IL-35 and IL-36 among hemodialysis patients. IL-35 levels were significantly elevated in patients compared to controls, particularly in the HCV-positive group. Conversely, IL-36 levels showed an increase in both hemodialysis groups, with the significant elevated concentrations observed in HCV-negative patients. Additionally, a strong positive correlation between IL-35 and IL-36 was observed in both patient subgroups.

Interleukin 35

The elevated levels of IL-35 observed in hemodialysis patients, particularly those with HCV infection, reflect its known anti-inflammatory and immunosuppressive properties. IL-35, produced by regulatory T and B cells, suppresses pro-inflammatory responses by inhibiting Th1 and Th17 proliferation and inducing regulatory T cells [25]. These findings suggest IL-35 acts as a compensatory mechanism to counteract the immanent chronic inflammation in hemodialysis and the immune dysregulation caused by HCV infection. Similar increases in IL-35 have been reported in other conditions of chronic inflammation and immune activation, such as multiple sclerosis and rheumatoid arthritis, where IL-35 levels are inversely associated with disease severity [12,13]. Diabetic rats with renal dysfunction showed reduced levels of IL-35, suggesting impaired Treg activity in the inflammatory environment of diabetic nephropathy [26].Studies examining IL-35 levels in lupus nephritis (LN) have yielded differing findings: one study observed elevated serum and urine IL-35 levels in LN patients compared to those without nephritis, correlating strongly with disease activity and renal involvement [27]. Conversely, another study reported significantly reduced serum IL-35 levels in LN patients compared to SLE patients without nephritis, with lower levels associated with increased disease activity and reduced renal function (eGFR) [28]. These contrasting results may reflect differences in study populations, disease activity, or underlying mechanisms influencing IL-35 regulation in LN.However, the comparable IL-35 levels between the control and HCV-negative groups in our study suggest that hemodialysis alone does not significantly affect IL-35 production and future studies should further explore the mechanistic pathways of IL-35 in this population.

In chronic hepatitis B virus (HBV) infection, elevated IL-35 levels were observed in patients compared to healthy controls, correlating positively with viral load and Treg frequency while showing an inverse correlation with CD8+ cytotoxic T lymphocyte activity [29]. This suggests IL-35 contributes to immune modulation by enhancing Treg activity and suppressing HBV-specific CD8+ T cell responses, potentially aiding viral persistence.

In the context of chronic HCV infection, IL-35 has been shown to play a dual role, as described by a study measuring IL-35 levels in patients with hepatitis C. Serum IL-35 was significantly elevated in these patients and correlated with viral RNA levels, suggesting a role in sustaining viral persistence through the suppression of antiviral immune responses. Furthermore, IL-35 enhanced the activity of regulatory T cells (Tregs), increasing the production of immunosuppressive cytokines like IL-10 and IL-35[30]. This underscores the immunosuppressive nature of IL-35, which may contribute to both the persistence of HCV and protection against liver injury, providing insight into its complex immunoregulatory role in chronic HCV infection. These findings align with the elevated IL-35 levels observed in HCV-positive hemodialysis patients in our study, which may serve as an adaptive response to reduce inflammation but could also impair immune surveillance and increase susceptibility to infections.

Interleukin 36

The present study demonstrates a significant elevation of IL-36 levels in both HCV-negative and HCV-positive hemodialysis patients compared to healthy controls. These findings align with existing literature on the pro-inflammatory role of IL-36 in chronic inflammatory states, including kidney dysfunction and viral infections, suggesting that IL-36 may serve as a key mediator of systemic inflammation in this population.

Hemodialysis patients are known to experience chronic low-grade inflammation due to the uremic milieu, incompatibility of dialysis membranes, and recurrent exposure to oxidative stress [31]. IL-36, a member of the IL-1 cytokine family, has been implicated in amplifying inflammatory responses by activating downstream NF-κB and MAPK pathways, which stimulate the production of other pro-inflammatory mediators such as IL-6, TNF-α, and IL-8 [16]. Additionally, the frequent blood draws and vascular access procedures associated with hemodialysis can trigger local inflammatory responses, further contributing to elevated IL-36 levels. Thus, the elevated IL-36 levels observed in our hemodialysis patients, irrespective of HCV status, likely reflect its role in the inflammatory cascade associated with ESRD.

The higher IL-36 levels in HCV-positive patients compared to their HCV-negative counterparts in our study may be attributed to the additional inflammatory burden imposed by HCV infection. Previous studies have shown that HCV infection triggers robust immune activation, with IL-36 being upregulated as part of the antiviral response. IL-36 is known to enhance the activation and proliferation of T cells and dendritic cells [32], potentially serving as a mechanism to counteract viral replication. However, this immune response may also exacerbate chronic inflammation, contributing to tissue damage and fibrosis. This dual role of IL-36 in both immune defense and inflammation may explain its elevated concentrations in HCV-positive patients.

Experimental evidence further supports the role of IL-36 in kidney pathology. Studies in renal ischemia-reperfusion [23] and unilateral ureteral obstruction (UUO) mouse models have demonstrated increased IL-36 expression in renal tissues, correlating with markers of inflammation and fibrosis. In these models, IL-36 signaling was shown to amplify renal damage through NLRP3 inflammasome activation and recruitment of immune cells, including macrophages and T cells [24]. Similarly, IL-36α has been identified as a key driver of tubulointerstitial inflammation and fibrosis, both of which are hallmarks of CKD [33]. The elevated IL-36 levels in our hemodialysis study may, therefore, reflect its involvement in the systemic and renal inflammatory responses characteristic of advanced kidney disease. Interestingly, IL-36 signaling also plays a role in viral and non-viral fibrotic diseases, including renal fibrosis. In human and murine studies, IL-36α was shown to enhance the production of profibrotic mediators such as IL-17, IL-23, and TGF-β, promoting ECM deposition and fibrosis [34].

Furthermore, given the elevated IL-36 levels in HCV-positive hemodialysis patients, it is plausible that IL-36 contributes to the fibrotic processes observed in HCV-associated renal damage.While both HCV-negative and HCV-positive hemodialysis patients exhibited elevated IL-36 levels, the slightly higher levels observed in the HCV-positive group may suggest an additive effect of HCV infection on the inflammatory burden. HCV infection is known to induce chronic liver inflammation, which can further exacerbate the systemic inflammatory response and contribute to increased IL-36 production [35]. However, the relatively small difference in IL-36 levels between the two groups suggests that the impact of HCV infection on IL-36 levels in this context may be modest.

The observed positive correlation between IL-35 and IL-36 in both hemodialysis groups may indicate a shared role in the immune dysregulation seen in end-stage renal disease. IL-35, known for its anti-inflammatory properties, may influence IL-36 levels indirectly, given that IL-36 is typically pro-inflammatory and involved in tissue inflammation. This interplay could reflect compensatory immune mechanisms attempting to balance inflammation and immunosuppression in hemodialysis patients. Such correlations could also be influenced by shared regulatory pathways or overlapping cellular sources, such as T cells or dendritic cells, which are activated differently in the context of hemodialysis and comorbid conditions like HCV. Further studies would be required to clarify the mechanistic relationship between these interleukins.

5. CONCLUSION

In conclusion, the elevated IL-35 levels, particularly in HCV-positive patients, suggest a compensatory anti-inflammatory response, while increased IL-36 levels in both HCV-negative and HCV-positive patients highlight its pro-inflammatory role in systemic inflammation and potential tissue damage. Moreover, the positive correlation between these cytokines underscores their involvement in immune regulation in ESRD. These findings suggest that IL-35 and IL-36 could serve as valuable biomarkers and therapeutic targets, emphasizing the need for further research into their roles and clinical implications.

Declarations

Funding: No funding was received for conducting this study.

Conflicts of interest: The authors have no financial or proprietary interest in any material discussed in this article.

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