Correlations between serum inflammatory markers and comorbidities in patients with end-stage renal disease

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Abstract

Objectives: Chronic inflammatory processes are common in patients with renal disease, especially those with end-stage renal disease (ESRD), in whom inflammatory markers have been shown to increase with renal function deterioration. ESRD is usually accompanied by other chronic diseases such as hypertension and diabetes. The relationships between ESRD comorbidities and serum levels of inflammatory markers have not yet been fully understood. The aim of this study was to assess serum levels of inflammatory markers in different ESRD cohorts and to investigate the correlations between these inflammatory markers and disease comorbidities.

Methods: A total of 147 patients were grouped according to their comorbid conditions: diabetic only, hypertensive only, diabetic and hypertensive, and neither diabetic nor hypertensive. Serum levels of C-reactive protein (CRP), tumour necrosis factor-alpha (TNF-\textalpha), and interleukin-1-beta (IL-1\textbeta) were investigated in different ESRD cohorts by enzyme-linked immunosorbent assay.

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Results: Serum CRP and TNF-α levels were high in diabetic patients (ρ = 0.0001), hypertensive patients (ρ = 0.0001), and those who had both diseases (ρ = 0.0001), when compared to ESRD patients without these comorbidities. There was no significant change in serum IL-1β levels between patients with diabetes mellitus and/or hypertension compared to patients who did not have these diseases.

Conclusions: Our results showed that, in ESRD patients, CRP and TNF-α seem to be largely affected by patients’ comorbidities, unlike IL-1β, which might be affected more by the dialysis process even in the absence of comorbidities.

Keywords: Cytokines; Diabetes; End stage kidney disease; Hypertension

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Introduction

End-stage renal disease (ESRD), involving severe and irreversible damage to the kidneys, can be fatal in the absence of transplantation or dialysis. ESRD is classified as Stage 5 of chronic kidney disease (CKD), where the glomerular filtration rate (GFR) is less than 15 mL per minute per 1.73 m² body surface area, or where patients are on dialysis irrespective of their GFR.1 Risk factors of ESRD include old age (>60 years), obesity, family history of renal disease, and tobacco and drug usage.2 However, even when they are not the primary cause of kidney disease, diabetes and hypertension are often found as comorbidities in ESRD patients and contribute to the complications of the disease.4 Complications of ESRD are mostly related to inflammation and cardiovascular diseases (CVD) such as atherosclerosis and endothelial dysfunction.1 The exact causes of inflammation in ESRD patients are poorly understood, but have been attributed to decreased cytokine elimination, frequent infections, metabolic acidosis, and diabetes.5 Persistent inflammation and oxidative stress start early in the process of failing kidney function, even among patients with only moderate renal impairment,5 leading to an increase in inflammatory markers such as C-reactive protein (CRP) and cytokines.7

Elevated CRP is associated with endothelial injury and impaired vasodilation, both of which may lead to glomerular damage and progressive loss of kidney function. Tumour necrosis factor-alpha (TNF-α) is a key mediator for pro-inflammatory agonists and is generated in a wide variety of innate and adaptive immune responses, including some forms of chronic kidney disease. It binds to cell surface receptors on target cells and induces expression of adhesion molecules, chemokines for leukocytes, and apoptosis in susceptible cells. Elevated CRP and TNF-α levels have been found to be associated with mortality and cardiovascular complications in ESRD patients.9 At the same time, the pro-inflammatory cytokine interleukin-1-beta (IL-1β) plays a major role in fibrosis and inflammation, and has been linked to kidney disease.10

Although the expression of inflammatory markers (CRP, TNF-α, and others) has been shown to be increased in the serum of ESRD patients,11,12 no studies to date have focused on comparing inflammatory markers in ESRD patients with comorbidities and those without them. Therefore, in this study, we measured serum levels of the inflammatory markers CRP, TNF-α, and IL-1β in ESRD patients who were classified according to the presence of diabetes and hypertension as comorbidities of renal disease, to investigate the relationships between inflammatory markers and disease comorbidities. Understanding these relationships will further elucidate the pathogenesis of inflammation in ESRD.

Materials and Methods

Patient selection

Patients were selected from a chronic renal population on haemodialysis (HD) at a government hospital (Orange Nassau) in Tripoli, North Lebanon. Patients with infectious diseases or malignancies; autoimmune diseases; active liver disease; and those who had recently experienced cardiovascular events (up to 3 months before the study began) were excluded from the study.

After applying the exclusion criteria, 147 patients were selected to participate in the study. All patients were on chronic HD and underwent 3-4 sessions per week that lasted between 3 and 4 h per session using a polysulphone membrane with a final sodium bicarbonate concentration of 32 mEq/L and 3.5 mEq/L of calcium. These patients were then divided into the following cohorts: patients with diabetes only (n = 36),2 patients with hypertension only (n = 40),3 those with both diabetes and hypertension (n = 34), and those with neither (n = 37). Age-matched healthy individuals with normal renal function volunteered to participate as controls (n = 25).

The protocol was approved by the Human Research Ethics Committees at Beirut Arab University and the Lebanese University. Informed consent was obtained from all participants.

Demographic, clinical, and biochemical data collection

Clinical and demographic data were collected from each participant through direct interviews with participants and physicians, as well as analysis of their medical records. The following data were included: age, gender, dialysis-related events (duration and frequency), clinical data (comorbidities, family history of kidney disease, smoking status), and aetiology of renal failure.

Blood samples (10 ml) were collected before initiation of the first dialysis session of the week. At the same time, blood was collected from the healthy donors.

Serum levels of creatinine, urea, haemoglobin, leukocytes, serum glutamate-pyruvate transaminase (SGPT), and electrolytes (sodium, potassium, calcium, and alkaline...
phosphatase) were measured using clinical biochemistry analysers (Medica EasyLyte Plus, USA; UniCel DxC 600, USA).

Serum levels of systemic inflammatory markers

Levels of CRP, IL-1β, and TNF-α were measured in the serum of HD patients by sandwich enzyme-linked immuno-sorbent assay (ELISA) using commercially available kits (Sigma–Aldrich, USA) according to the manufacturer’s protocol. Absorbance values were detected in a microplate reader (BioTek ELx800 Absorbance Microplate Reader, UK) at 570 nm.

Statistical analysis

Statistical analysis was performed using GraphPad Prism software version 6.04 (USA). Data are presented as the mean ± standard deviation (SD) for each parameter. Results were analysed using the t-test or one-way analysis of variance for parametric data and the Mann–Whitney U test for nonparametric data. Correlation analysis was performed using Spearman’s test (ρ), and p ≤ 0.05 was considered significant.

Results

Demographic, clinical, and biochemical characteristics of the 147 ESRD patients enrolled in this study are summarised in Tables 1–3, respectively.

The average age of the patients was 53 ± 14 years, and 55% were male. A family history of kidney disease (parent and/or sibling) was present in 16% of patients, and 37% were smokers or had smoked at some time in their life. In regard to comorbidities, 24% of patients were diabetic only, 27% were hypertensive only, 23% were both diabetic and hypertensive, and 25% were neither diabetic nor hypertensive.

Glomerulonephritis and diabetes were the leading causes of kidney disease (32% and 29%, respectively), while hypertension accounted for 22% of cases, and 16% had unknown causes (Table 1).

Frequency of dialysis was three times per week for 83% of patients, and four times per week for the others (17%). Dialysis session duration ranged from 2 to 4 h. Mean adequacy of dialysis (Kt/V) was found to be 1.2, indicating adequate dialysis (Table 2).

Average levels of electrolytes, SGPT, haemoglobin, creatinine, and leukocytes were within reference ranges for dialysis patients. Urea levels were found to be higher than the normal range, which is as predicted for dialysis patients (Table 3).

Markers of inflammation in different cohorts of ESRD patients

Mean serum concentrations of inflammatory markers in different cohorts of ESRD patients are shown in Figure 1. CRP serum concentrations were significantly higher in hypertensive patients (10.2 ± 6.6 mg/L, p = 0.0001), diabetic patients (12.8 ± 6.9 mg/L, p = 0.0001), and patients with both comorbidities (14.5 ± 9.4 mg/L, p = 0.0001), compared with patients who had neither diabetes nor hypertension (5.2 ± 0.1 mg/L). No statistically significant difference was observed between patients who had neither diabetes nor hypertension and healthy controls (5.2 ± 0.1 mg/L vs. 5.0 ± 0.5 mg/L, p = 0.0978) (Figure 1a).

TNF-α serum concentrations were also significantly higher in hypertensive patients (58.2 ± 28.2 pg/mL, p = 0.0001), diabetic patients (71.4 ± 25.5 pg/mL, p = 0.0001), and patients with both comorbidities (92.54 ± 24.59 pg/mL, p = 0.0002), compared with patients who had neither diabetes nor hypertension (39.75 ± 5.29 pg/mL). No statistically significant difference was observed between patients who had neither diabetes nor hypertension and healthy controls (39.75 ± 5.29 pg/mL vs. 30.17 ± 1.58 pg/mL, p = 0.0996) (Figure 1b).

Unlike CRP and TNF-α, IL-1β serum concentrations showed no statistically significant differences between hypertensive patients (0.64 ± 0.17 pg/mL, p = 0.0970), diabetic patients (0.73 ± 0.15 pg/mL, p = 0.3205), or patients with both comorbidities (0.77 ± 0.15 pg/mL, p = 0.3818), compared to patients who had neither diabetes nor hypertension (0.80 ± 0.22 pg/mL). However, IL-1β serum concentrations of patients without hypertension or diabetes were

| Parameters                        | Characteristics of Patients (n = 147) |
|-----------------------------------|-------------------------------------|
| **Age (years)**                   | 53 ± 14                             |
| **Gender (male)**                 | 55%                                 |
| **Family history of kidney disease** | 16%                                 |
| **Smokers**                       | 37%                                 |
| **Comorbidities**                 |                                     |
| Diabetic only                     | 24%                                 |
| Hypertensive only                 | 27%                                 |
| Diabetic and hypertensive         | 23%                                 |
| Neither diabetic nor hypertensive | 25%                                 |
| **Primary Cause of Kidney Disease** |                                     |
| Diabetes                          | 29%                                 |
| Hypertension                      | 22%                                 |
| Chronic glomerulopathy            | 32%                                 |
| Other                             | 16%                                 |
| Values are expressed as mean ± SD or as percentages (%). |
Table 3: Biochemical Characteristics of Healthy Controls and Haemodialysis Patients, Subdivided by Comorbidities.

| Parameters                          | Healthy (n = 25) | Neither (n = 37) | Diabetic (n = 36) | Hypertensive (n = 40) | Both (n = 34) |
|-------------------------------------|------------------|-----------------|-------------------|-----------------------|--------------|
| Urea (before dialysis) (mg/dL)      | 7–20             | 149 ± 36.2      | 124.6 ± 37        | 134 ± 36.5            | 129.5 ± 33.8 |
| Urea reduction rate (URR)           | N/A              | 68% ± 7%        | 65% ± 6%          | 70% ± 9%              | 65% ± 10%    |
| Creatinine (mmol/L)                 | 60–110           | 109 ± 45        | 90 ± 28           | 110 ± 18              | 97 ± 27      |
| Haemoglobin (g/L)                   | 12–17            | 11.8 ± 1.6      | 10.4 ± 1.6        | 11.2 ± 1.5            | 10.6 ± 1.2   |
| Leukocytes                          | 4.5–11           | 7.2 ± 1.4       | 8.1 ± 1.4         | 7.2 ± 1.9             | 10.7 ± 5.9   |
| Sodium (before dialysis) (mM)       | 135–145          | 139 ± 1.7       | 139 ± 2.7         | 140 ± 1.9             | 137 ± 6.9    |
| Potassium (before dialysis) (mM)    | 3.5–5            | 5.6 ± 0.9       | 5 ± 0.9           | 5.5 ± 0.6             | 5.6 ± 0.8    |
| Calcium (mg/dL)                     | 85–102           | 89.2 ± 11.7     | 90 ± 8.7          | 94.5 ± 9.7            | 88.8 ± 7.4   |
| Alkaline phosphatase (IU/L)         | 44–147           | 95.4 ± 36.6     | 129 ± 57.5        | 155 ± 152.2           | 132.5 ± 59.7 |
| SGPT (IU/L)                         | 7–56             | 26.6 ± 4.4      | 23 ± 9            | 18 ± 5                | 20 ± 9       |

Values are expressed as mean ± SD or as ranges. SGPT: Alanine aminotransferase. N/A: Not applicable.

Figure 1: Serum concentrations of inflammatory markers in healthy controls and different end-stage renal disease patient cohorts. a: CRP serum concentrations; b: TNF-α serum concentrations; c: IL-1β serum concentrations. *p < 0.05; **p < 0.01 compared to the group with neither comorbidity. CRP: C-reactive protein; TNF-α: tumour necrosis factor-alpha; IL-1β: interleukin-1-beta.

Figure 2: a: Correlation between CRP and TNF-α serum concentrations in haemodialysis patients. CRP: C-reactive protein; b: Correlation between CRP and IL-1β serum concentrations in haemodialysis patients. TNF-α: tumour necrosis factor-alpha; IL-1β: interleukin-1-beta.
significantly higher than those of healthy controls (0.80 ± 0.22 pg/mL vs. 0.30 ± 0.02 pg/mL, \( p = 0.0001 \)) (Figure 1c).

There was a significant correlation between CRP and TNF-\( \alpha \) serum concentrations (\( p = 0.0001 \)) (Figure 2a). However, no significant correlation was observed between CRP and IL-1\( \beta \) (\( p = 0.2797 \)) (Figure 2b).

**Discussion**

Over the years, several studies have focused on inflammation in ESRD patients and its role in cardiovascular diseases in these patients.\(^{10,14} \) The aetiology of inflammation has been mainly attributed to dialysis-related or unrelated factors,\(^{15} \) without looking into the association between inflammation and comorbidities found in ESRD patients, such as diabetes and hypertension. In addition to being major risk factors of ESRD, diabetes and hypertension often exist in these patients, either alone or together, even if they were not the primary cause of renal dysfunction.\(^{16} \)

We wanted to investigate whether there was a link between these comorbidities and inflammation in ESRD patients.

In our study, we found an increase in serum inflammatory markers, which is consistent with previous studies.\(^{9} \) However, this increase varied depending on the presence or absence of diabetes and hypertension in ESRD patients. When compared with normal healthy volunteers, serum CRP and TNF-\( \alpha \) levels were normal in ESRD patients who had no diabetes or hypertension but were elevated in patients with either or both comorbidities. Since all the patients’ blood was dialysed in identical processes and conditions, the high CRP and TNF-\( \alpha \) serum levels observed in the diabetic and/or hypertensive ESRD patients are unlikely to be related to the dialysis process itself and its complications.

In hypertensive patients, significant associations have been found between hypertension and chronic inflammatory markers such as CRP, TNF-\( \alpha \), and IL-6.\(^{17-19} \) It has also been shown that an inflammatory response can develop in the arteries of hypertensive mice, characterised by the expression of inflammatory cytokines, chemokines, and adhesion molecules,\(^{20} \) and that inhibition or genetic deletion of these cytokines in animals results in blunted hypertension and reduced end-organ damage.\(^{21} \) As well as this, inflammatory markers are also associated with both types of diabetes, where circulating cytokines (TNF-\( \alpha \), IL-1\( \beta \), INF-\( \gamma \) (Interferon gamma)) can affect beta cell function directly and indirectly by increasing adipocyte inflammation and affecting insulin release.\(^{22} \) This leads to an increase in inflammation, and thus a vicious cycle. Hyperglycaemia, along with other factors such as obesity, activates nuclear factor \( \kappa B \) (NF-\( \kappa B \)) through protein kinase C (PKC) and reactive oxygen species (ROS), to stimulate the expression of cytokines and adhesion molecules leading to diabetic nephropathy, a leading cause of CKD.\(^{23,24} \) These studies show that high serum levels of these inflammatory markers are observed in hypertensive and diabetic patients even in the absence of ESRD, and that diabetes and hypertension are major contributors to inflammation in these patients. It could also explain why levels of inflammatory markers were higher in patients who have both comorbidities, whereas they were similar to those of healthy controls in ESRD patients with neither comorbidity. Thus, reducing hypertension and diabetes-induced inflammation, and further investigating the link between inflammation and these diseases, is a critical step in decreasing cardiovascular risk in dialysis patients.

Of the inflammatory markers that we investigated, we found that only IL-1\( \beta \) levels were high in all ESRD patients with and without diabetes and/or hypertension, unlike CRP and TNF-\( \alpha \), and that levels of this cytokine were similar in all patients. Interleukin serum levels have been shown to be non-existent in ESRD patients before going on dialysis, remain undetectable after the first dialysis session, increase greatly after that,\(^{25-27} \) and are proportional to dialytic age.\(^{28} \) It has also been found that interleukin levels are highly dependent on the bio-membranes used in the dialysis process, and that contact with dialysis membrane causes IL-1 secretion by immune cells \( \textit{in vitro}. \)\(^{30-31} \) This suggests that repeated dialysis sessions and/or the accumulation of dialysis-related factors such as the type of membrane and dialysate contaminants are necessary to induce and amplify the secretion of IL-1. All patient cohorts in this study had been on dialysis for at least a year, indicating that high serum levels of IL-1\( \beta \) could indeed be explained by repeated dialysis processes and their complications over the years.

A limitation of this study could be the small number of participating patients. Further investigation of different cohorts of HD patients with larger numbers would be a good step towards gaining insight into the inflammatory process in ESRD patients, to enhance treatment for these patients and decrease mortality and CVD risks.

**Conclusion**

This study supports the hypothesis that the inflammation observed in ESRD patients on dialysis, assessed by an increase in serum cytokine levels, is related to metabolic, dialytic, and other factors. Unlike CRP and TNF-\( \alpha \), uraemia and its comorbidities do not seem to influence IL-1\( \beta \) secretion, which is more affected by the dialysis process and the biocompatibility of the devices used in the process.

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**Conflict of interest**

The authors have no conflict of interest to declare.

**Ethical approval**

Ethical approval was obtained from the Human Research Ethics committee at Beirut Arab University.

**Consent**

Informed consent was obtained from all participants in the study.
Authors contributions

AKE conceived and designed the study, conducted research, collected and organised data, analysed and interpreted data, and wrote the initial and final draft of the article. DA conceived and designed the study, analysed and interpreted data, provided logistical support, and participated in article preparation. BAO and RYA provided logistical support and participated in article preparation. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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