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ORIGINAL RESEARCH PERIOPERATIVE MEDICINE

Detection of the role of biomarkers (IL-18 and ICM-1) in the progression of diabetic nephropathy in type 2 diabetic patients

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ABSTRACT

Background: Diabetic kidney disease (DKD) is one of the most common complications in diabetic patients and is the leading cause of renal disease. It is also a significant risk factor for cardiovascular disease in these patients. The current study was conducted on patients with diabetes-related nephropathy in Saladin's governorate, Iraq. The study aims to assess the association between the levels of interleukin 18 (IL-18) and Intercellular Adhesion Molecule1(ICAM-1) in type 2 diabetic patients and their relation with the development of diabetic nephropathy.

Methods: The recent study focused on patients with diabetes-related nephropathy. We detected IL-18 and ICAM-1 biomarkers in 250 blood samples, distributed as follows: 127 samples from patients with stage II DKD patients, 123 samples from stage IV DKD patients, and 65 blood samples from healthy controls. The samples were grouped based on the estimated glomerular filtration rate (eGFR), calculated using the concentration of creatinine and blood urea nitrogen (BUN) in the blood with the Modification of Diet in Renal Disease (MDRD) eGFR (6 variables).

Results: The present study revealed that the concentration of IL-18 differed significantly ($P \leq 0.01$) between grade IV diabetic kidney patients (3227 ± 205.7 ng/mL) compared to grade II patients (653.4 ± 52.9 ng/mL) and healthy controls (78.278 ± 5.89 ng/mL). Additionally, ICAM-1 levels were significantly higher ($P \leq 0.01$) in stage IV patients (3552 ± 167.2 ng/mL) compared to stage II patients (910 ± 75.6 ng/mL) and healthy individuals (76.12 ± 11.3 ng/mL).

Conclusion: The current study suggests that IL-18 and ICAM-1 biomarkers may contribute to the development of diabetic nephropathy and potentially be used as early indicators of the disease progression.

Abbreviations: DKD: Diabetic kidney disease, DN: Diabetic nephropathy, eGFR: estimated glomerular filtration rate, ICAM-1: Intercellular Adhesion Molecule1, MDRD: Modification of Diet in Renal Disease,

Keywords: Interleukin-18, Intercellular adhesion molecule-1, eGFR, diabetic nephropathy.

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1. INTRODUCTION

Interleukin 18 (IL 18) is a powerful proinflammatory cytokine that possesses multiple properties, it is a member of the IL 1 family of cytokines and was initially described as an interferon (IFN γ) induced factor that is produced in various cell types. It participates in both cellular and humoral responses.[29] It's elevated in the serum and urine of patients with diabetes type 2 (T2DM) and renal disease, it may also serve as a marker of inflammation in the kidney.[1]

Additionally, it increases the number of chemokine receptors in the mesangial cells.[2] Additionally, IL8 increases the expression of the intercellular adhesion molecule 1 (ICAM1) and promotes the apoptosis of endothelial cells.[3] As a result, the assessment of IL-18 in the body can be considered a biomarker for the development of numerous diseases, including nephropathy.[4]

Intercellular adhesion molecule 1 (ICAM-1) is a 90 kD acute-phase protein that is associated with inflammation. It's a cell-surface glycoprotein that is expressed in endothelial cells and leukocytes in the immune system. This protein associated with endothelial cells and leukocytes has been recognized for its significance in maintaining cell-cell interactions and facilitating the migration of leukocytes through the endothelial barrier.[5] The expression of adhesion molecules is greatly enhanced in many tissues during acute and chronic inflammation. Additionally, the increase in soluble adhesion molecules in the circulation during T2DM may be indicative of endothelial damage and the activation of leukocytes in the diabetic environment.[6] Recently, the increasing number of genetic studies on patients with diabetes that include or lack DN, as well as the increasing number of biological studies on animal models of diabetes have led to the suggestion that ICAM1 may be involved in the development of diabetes and DN.[7]

Recently, there has been a lot of research dedicated to the discovery of new biomarkers in the serum or urine that have a variable degree of accuracy in predicting the presence or absence of glomerular or tubular injury.[8] Many of the studies utilized one biomarker or focused on only one stage of diabetic nephropathy when evaluating the diagnostic value of this form of nephropathy to predict the pathological changes that occur as a result of diabetes.[9] As a result, investigations evaluating different biomarkers and their association with different stages of diabetic nephropathy at the molecular level may provide a window into the disease itself, this would allow for the screening and prevention of the common long-term complication of diabetes.[10]

This investigation sought to determine the association between IL-18 and ICAM-1 levels in the serum of diabetic type 2 patients and the development of chronic kidney disease from stage II to stage IV in these patients.

2. METHODOLOGY

This study was conducted at the Tikrit Teaching Hospital in Salah Al-din's governorate, Iraq for a period that extended from December 2022 to July 2023.

The questionnaire used for data collection was designated in Arabic language. Interviewers administer it and it includes mainly closed questions.

This study included 250 participants aged 35-75 years with type 2 diabetic nephropathy stage II and IV, with 65 healthy controls. Their diagnosis was documented by the treating physician. Patients were divided into two groups based on estimated glomerular filtration rate (eGFR) using MDRD eGFR (6 variables) which include (sex, race, age, and the level of creatinine, blood urea nitrogen (BUN), and albumin). Urine and blood samples were obtained from all patients and controls).

We harvested 5 mL of ulnar blood from the participants with a medical syringe, the blood was then placed in a glass gel container and left for 10 min, the container was then placed in a centrifuge at 3500 rpm for 15 min, and the blood serum was obtained. It was attained in 1 mL Eppendorf tubes and the samples were stored at -80°C in a frozen state that was not used for testing.

The concentration of the biomarkers [Interleukin-18 and ICM-1, which is an internal part of the cell] was determined using the well-known immunoassay (enzyme-linked immunoassay) (ELISA)) of the sandwich type, this procedure was carried out using an ELISA reader of Japanese origin and the biomarkers provided by the Chinese company Sunlong Biotech based on the leaflet associated with each indicator at a wavelength of 450nm.

Statistical analysis:

The Statistical Analysis System-SAS (2018) software program was employed to identify and analyze the effects of different factors in the study's parameters. The T-test and Least Significant Difference (LSD) were employed to assess the significance of the differences between the means (ANOVA). The chi-square test was employed to assess the difference and the significance between percentages. $P < 0.05$ was considered significant.

3. RESULTS

The present study showed statistically highly significant differences ($P \leq 0.01$) regarding the concentration of interleukin-18 in grade IV DKD patients (3227.0 ± 205.7 ng/mL) compared to its concentration in grade II DKD (653.4 ± 52.90 ng/mL) and healthy controls (78.278 ± 5.89) (Table 1).

Additionally, there was a significant difference ($P \leq 0.01$) regarding ICAM-1 serum level between the patients with grade IV DKD (3552.0 ± 167.2), and the grade II patients (910 ± 75.6) and the control patients (76.12 ± 11.3), respectively (Table 2).

Table 1: Serum level of IL-18 1 in stage II and stage IV diabetic kidney disease patients

Variables	No.	IL-18 (ng/mL)
Patients/Stage II DKD	127	653.4 ± 52.90 [b]
Patients/Stage IV DKD	123	3227.0 ± 205.7 [a]
Control	65	78.278 ± 5.89 [c]
LSD	----------	749.70 **
P-value		0.01**

*This means having the different letters in the same column differed significantly. ** (P ≤ 0.01); LSD: Least Significant Difference.*

Table 2: Serum levels of ICAM-1 in stage II and stage IV diabetic kidney disease patients

Variables	No.	ICAM-1 (ng/mL)
Patients/Stage II DKD	127	910 ± 75.6 [b]
Patients/Stage IV DKD	123	3552 ± 167.2 [a]
Control	65	76.12 ± 11.3 [c]
LSD	---------	**415.08** **
P-value		0.01**

*[a, b, c]: This means having the different letters in the same column differed significantly. **P ≤ 0.01 considered as significant; LSD: Least Significant Difference.*

4. DISCUSSION

DN involves both alterations to the structural composition of the kidneys and a loss of renal function, the earliest symptoms of DN are structural changes to the kidneys, including increased thickness of the basement membrane and the loss of podocytes, followed by a progression to fibrosis and atrophy.[1] In the final stage, the injured kidney is surrounded by immune cells.[2] Functional, DN patients have increased albumin excretion and have a lower glomerular filtration rate.[3] The present study demonstrated a significant increase in the concentration of interleukin-18 in grade IV diabetic kidney patients compared to the grade II and healthy individuals. This outcome is consonant with,[4] who documented significant differences in the serum levels of IL-18 between patients with T2DM with various levels of nephropathy and controls. Another research by Nakamura et al. (2005), found that the serum and urinary levels of IL-18 were significantly higher in patients with T2DM than in controls.[5]

Clinical studies have demonstrated that elevated levels of IL-18 in the plasma and urine were associated with the development of diabetic nephropathy, additionally, IL-18 was observed to be a predictor of the development of diabetic nephropathy in patients with diabetes and to be associated with the progression of renal failure.[6] IL-18 is involved in the development of nephropathy through its direct effect on the kidneys, as well as its pro-inflammatory effect.[7]

In patients with DN, the expression of IL-18 is high in the serum, urine, and tubular cells of the renal parenchyma.[8] The elevated levels of interleukin-18 in patients with T2DM may be attributed to the increased expression of the gene for interleukin-18 as a result of the increased percentage of sugar in the cells, as well as the increased size of the cells, both of which negatively affect the functionality of the cell and thus lead to an increase in the concentration of interleukin-18 as a result of the effect of the cumulative hyperglycemia on the cells and small and large blood vessels.[9] Polymorphisms in the interleukin-18 gene, decreased insulin sensitivity, and increased probability of infection.

Other investigations have reported that the increase in IL-18 causes an increase in free radical production and damage to the renal tissue, this is likely to have a significant impact on the development of DN, other investigations have demonstrated that increased caspase activity causes the increase in free radical production and the damage to the renal tissue, this is likely to have a significant impact on the development of DN.[10] Also Roland et al. (2010), demonstrated that the concentrations of IL-18 in the blood were positively associated with the degree of oxidative stress, while other studies showed that free radical production was inversely proportional to the level of IL-18 in the blood.[11]

The level of IL-18 was significantly elevated in the melanoma cells, as a result, the induction of IL-18 may be considered to be a new mechanism by which IL-18 contributes to the development of DN.[12] Interleukin-18 is naturally produced in the kidneys as a biologically inactive substance, and is stored in the cytosol of the organ. Once they've matured, they cause a variety of autoimmune diseases, infections, metabolic issues, and small and large vessel diseases, all of which are the cause of diabetic nephropathy. As a result, IL-18 is a marker of disease progression and predictions.[13]

It is typically associated with the development of renal failure, and its increase in serum is a risk factor for patients with diabetes, as it causes damage to the kidneys and is overproduced in those with the disease. Tubular epithelial cells in the renal tissues of patients with diabetes, these cells are said to activate the MAPK

pathways triggered by the transforming growth factor-beta.[14] The results of the statistical analysis in the current study demonstrated a significant increase in the concentrations of ICAM-1 in the fourth grade of diabetes-related kidney disease patients compared to the concentration in the second and healthy individuals as the results of this study concurred with the findings of who reported that the adhesion molecule expressed in endothelial, mesangial and epithelial cells was directly associated with the injury of the kidneys and the development of DN in a rat model.[15] Additionally, Watson et al. (2012), documented that patients with diabetes had a higher concentration of all soluble adhesive molecules in their circulation than controls.[16]

In a study from Malaysia, the authors utilized patients with T2DM. Seman et al. (2015), showed that the plasma levels of the intercellular adhesion molecule-1(ICAM-1) are increased in patients with DN.[17] Luis-Rodriguez et al. (2012), documented that molecules associated with the development of DKD, such as intercellular adhesion molecule-1 (ICAM-1), are elevated in the kidneys of individuals with DKD, they also documented that the levels of these molecules are associated with the development of renal damage. ICAM-1 is common in endothelial cells and leukocytes, and its expression is augmented by cytokine exposure. It is hypothesized that altering the amount of ICAM-1 may serve as a new approach to managing DKD.[18] Intercellular adhesion molecule (ICAM)-1, which is involved in the attachment of leukocytes to endothelial cells, is associated with the increased prevalence of diabetes and the progression of disease in these patients. Intercellular adhesion molecule-1 expression is facilitated by factors like hyperglycemia, advanced glycation end products (AGEs), and other compounds with a high degree of carbonization. And oxidative stress, but it can also be augmented by additional components such as hyperlipidemia, hyperinsulinemia, and increased levels of circulating TNF-α.[17]

Additionally, it is demonstrated that intercellular adhesion molecule-1 is the critical molecule in the mediation of the accumulation of macrophages in the kidneys of individuals with diabetes both in the early and late stages of the disease.[19] ICAM-1 facilitates the activation of T cells and the transmigration of leukocytes to the endothelial layer of the kidneys, its primary receptor being the protein LFA-1. In a diabetes-prone environment and upon cytokine stimulation, the ICAM-1 gene is expressed on the surface of the endothelium. The protein that binds to ICAM-1 is augmented, as a result, the number of lymphocytes in the blood is increased, which causes inflammation.[34] A significant association between the genes and the disease is observed. Several studies have documented an increase in the number of adhesion molecules in patients with diabetes.[20,21]

In 2002, Guler et al. investigated the association between sICAM-1 levels in patients with type 2 diabetic nephropathy. They hypothesized that high sICAM-1 levels may contribute to the development of DN.[22] In addition, experimental studies have shown that in the context of diabetic nephropathy, glomerular ICAM-1 expression is increased and directly correlated with the progression of kidney injury and increased urinary albumin excretion.[23] In patients with chronic kidney disease, plasma ICAM-1 expression is positively correlated with urinary albumin excretion, and this also applies to type 1 diabetes., clinical studies that are both prospective and retrospective have demonstrated that ICAM-1 is crucial to the development and progression of diabetic nephropathy. As opposed to the concerns of type 2 diabetes patients, it is understood that their serum ICAM-1 levels are higher than controls.[24]

Additionally, experimental research has demonstrated that leukocytes are present in all stages of this disease. For the diabetic Nephropathy, it appears that ICAM-1 is crucial to the promotion of macrophage invasion into the renal tissue, which leads to inflammation. Consistent experimental and clinical studies have suggested that ICAM1 is involved in the development of type 2 DKD, ICAM-1-1 can attach to integrins on the surface of leukocytes, which causes them to become attached to the endothelial cells and migrate into the tissue.[25] Additionally, altered hemodynamic conditions caused by the TGF-b-induced accumulation of ECM are also involved in the upregulation of ICAM-1. Additionally, oxidative stress can also increase the expression of ICAM-1.[26]

In the renal mesangial and endothelial cells, advanced glycation end products (AGEs) cause the production of ROS, this activates the NF-kB gene and promotes the release of pro-inflammatory cytokines and adhesion molecules.[27] ICAM-1 is essential for the migration of leukocytes, particularly T cells to the kidneys, deleting ICAM-1 in diabetes-prone mice reduced the symptoms of DN, including increased glomerular thickness, enhanced mesangial matrix expansion, and proteinuria.[28] Adhesion molecules like the intercellular adhesion molecule 1 (ICAM1) have a significant role in the induction of renal inflammation.[29] This molecule has been commonly found in the renal biopsies of patients with DN, and its levels have been associated with the progression of DN.[30]

It's an inducible glycoprotein located on the cell surface.[31] In mice models, the lack of the ICAM1 gene decreases the inflammation of the kidneys, this suggests that ICAM1 is involved in the development of DN.[32] Several lines of evidence suggest that IL-18 has a

significant role in the upregulation of adhesion molecules, reported that IL-18 increased the expression of ICAM-1, and recruited leukocytes, possibly via the activity of NF-KB and the phosphatidylinositol-3 kinase (PI3-Kinase) gene.[31] The release of IL-18 from the endothelium was dependent on the presence of atherosclerosis, this increased the expression of ICAM-1,[34] which subsequently attracted macrophages and triggered additional responses associated with inflammation proposed that IL-18 selectively enhanced the number of intracellular adhesion molecules in human monocytes, which could be inhibited by IL-18bp.[31] Other individuals have reported that IL-18 increases the expression of ICAM-1 in the absence of other inflammatory cytokines like IL-12, TNFα, and/or IFNγ in human monocytes.[35]

5. CONCLUSION

The outcomes of our investigation indicate that proinflammatory cytokines have a significant impact, and contribute to the development of diabetic nephropathy from stage II to stage IV. IL-18 and ICAM-1 levels can serve as indicators for tracking the progression of diabetic nephropathy and as criteria for diagnosing this prevalent and serious disease. It is important to conduct further studies to compare interleukin levels across the five stages of DN and to investigate their role in the disease's development.

6. Data availability

Numerical data generated during this research is available with the authors and can be provided on a reasonable request.

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8. Funding

Self-funded.

9. Conflict of interest

The authors declare no conflict of interest.

10. Ethical and approval consideration

Permission was taken from all patients and health control to fill in the information required and they were assured regarding the confidentiality of their responses. The aim of the study was explained and only those who agreed to participate were included in the study (Ref Letter 3/7/107 in 18/01/2022).

11. Author contribution

WRYA and QMA conceived and planned the experiments. WRYA carried out the experiments. WRYA and QMA planned and carried out the analysis. WRYA and QMA contributed to sample preparation. WRYA and QMA contributed to the interpretation of the results. QMA took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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