Evaluation of CD10 and E-cadherin as Biomarkers in Chronic Kidney Disease Progression at Al-Najaf Province/Iraq

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KEYWORDS
Chronic Kidney Disease (CKD), E-cadherin, CD10, diagnostic criteria, Renal Failure

ABSTRACT
Chronic Kidney Disease (CKD) is when kidney function deteriorates over three months, resulting in a build-up of waste in the blood and tissues. Common causes of CKD include diabetes and hypertension. The study aims to investigate the association of (E-cadherin, CD10) and other biomarkers in patients suffering from CKD and the possibility of using them as diagnostic criteria. The cohort of 96 patients with CKD and the control group of 88 healthy individuals comprised the current stud. The levels of CD10, E-cadherin, and other biochemicals were measured in the serum of the experimental group and the patients. The findings demonstrated that in contrast to healthy individuals, patients with CKD had significantly lower serum concentrations of E-cadherin ($p<0.05$), while there was no significant difference in CD10 levels between the patient and control groups ($p>0.05$). These results corroborate data indicating an essential role the E-cadherin marker may play in the development of chronic kidney disease.

1. Introduction

Renal function gradually declining over time is the hallmark of chronic kidney disease (CKD), a prominent and rapidly expanding global health concern. It is linked to several problems, as well as elevated chances of death, end-stage kidney disease (ESKD), and cardiovascular disease. CKD patients have a higher incidence of cancer, potentially due to factors like chronic Inflammation, oxidative stress, and changes in intestinal microbiota[1]. Excess cortisol in CKD may contribute to higher mortality and morbidity, with dysregulation including blunted diurnal decline and impaired negative feedback [2]. The prevalence of CKD is highest in older adults, with ageing being a significant risk factor for both CKD and its associated cardiovascular mortality [3]. Early detection of CKD is crucial, yet current biomarkers like serum creatinine and cystatin C are limited, with research focusing on novel markers such as KIM-1, NGAL, and L-FABP [4]. Cardiovascular disease (CVD) is a leading cause of death in CKD, with both traditional and non-traditional risk factors contributing to adverse cardiovascular events [5,6]. Lifestyle modifications, nutritional interventions, and medications such as RAAS blockade and SGLT2 inhibitors can delay CKD progression [7]. Diabetes, hypertension, and older age are primary risk factors for CKD, with management of these conditions being critical in CKD care[8]. CKD of unknown etiology (CKDu) is emerging in certain regions, with potential causes including heat stress and agrochemical exposure, necessitating global research efforts[9]. The WHO projects CKD to become the 5th most common chronic disease by 2040, highlighting the need for early intervention and new treatments in general practice [10]. E-cadherin is a protein that plays a critical role in cell adhesion and is implicated in various kidney diseases. Its expression and interaction with other proteins can be a biomarker of kidney injury and disease progression. E-cadherin serves as a potential biomarker for early detection of diabetic nephropathy, with its urinary levels increasing significantly before the onset of Microalbuminuria and correlating with the glomerular filtration rate[11]. Pathogenic Leptospira species express proteins that bind to E-cadherin, which may induce acute kidney injury by altering E-cadherin interactions and increasing NGAL expression in kidney cells[12]. In a neonatal rat model of hydronephrosis, the expression level of E-cadherin decreases with the severity of kidney injury, suggesting its role in assessing kidney damage and recovery[13]. Aberrant expression of E-cadherin in clear cell renal cell carcinoma is associated with aggressive tumor characteristics and poor prognosis, indicating its potential as a prognostic marker and therapeutic target[14]. CD10 expression is increased in several cancers, including renal cancer, and has been associated with the aggressiveness and progression of tumors. Anti-CD10

monoclonal antibodies have shown antitumor activity in renal cancer models, suggesting a potential therapeutic role [15]. The expression of CD10 in urothelial carcinoma correlates with the histological grade and pathological stage of the tumor, indicating its involvement in tumor differentiation and progression[16]. CD10 is also implicated in the regulation of angiogenesis in renal cell carcinoma (RCC), as evidenced by its association with microvessel density and tumor progression[17] This study aims to assess the effects of chronic renal disease on variations in the serum concentration of CD10, E-cadherin, and other biochemical substances. Additionally, this study aims to evaluate the possible prognostic importance of these biomarkers in the early detection of chronic kidney disease.

2. Methodology

Subject population:

From August to December 2023, the Kidney Disease Center at the Al-Sader Teaching Hospital in Najaf, Iraq, will be the site of the study. Sixty-eight patients (48 males and 48 girls) were involved in this study. Thirty to seventy was their age range. Nephrology specialists made diagnoses based on the radiological study, individual symptoms, and family history—analyses in the lab for confirmed creatinine, urea, and albumin. Every patient admitted to the hospital with clinical or biochemical evidence of chronic renal disease was included in this research. On the initial visit, baseline information was gathered for each patient, including age, sex, medical history, duration of illness, and family history. All patients give their verbal consent prior to taking the sampling.

Control:

The patients and controls (N:176) were matched for age and sex and comprised eighty healthy individuals as the control group. This control group was studied using ELISA. Each control group member was asked to complete a questionnaire and had no family history of the illness**.**

Statistical analysis:

The study used the statistical package for social sciences (SPSS, version 23) for statistical analysis. The independent t-test, standard deviation, and Nominal regression were applied for group comparisons. All statistical tests were deemed significant at a significance level of less than <0.05.

3. Results and Discussion

3.1. Demographic and clinical characteristics of chronic kidney disease (CKD) patients and the control groups

Based on Table (3.1),. The study evaluated the clinical and demographic characteristics of individuals with chronic kidney disease (CKD) with control patients to assess any possible variations in biomarker levels between the two groups—table 4.1. The mean age of the patients (48.69±11.51 years) and controls (46.36±12.11 years) did not differ statistically significantly; however, the study did find significant differences in several biomarkers that indicate renal function. Compared to controls, CKD patients had noticeably higher levels of glucose, urea, creatinine, and vimentin, which suggested compromised renal function and perhaps increased systemic Inflammation and fibrosis.

Table 3.1: Comparison of Demographic and clinical characteristics of chronic kidney disease(CKD) patients and the control groups.

Variables	Mean	SD	Median	IQR	p-value

Age (year)	**Patients**	48.69	11.51	46.50	39.00-58.75	0.194# Ns
	Control	46.36	12.11	45.00	36.00-54.75	
Glucose (mg/dl)	**Patients**	193.75	74.82	190.05	124.13-271.25	0.0001*
	Control	98.13	14.59	93.40	87.00-112.98	
Urea (mg/dl)	**Patients**	163.22	28.80	162.58	140.01-180.03	0.0001*
	Control	21.21	5.68	20.57	16.34-26.86	
Creatinine (mg/dl)	**Patients**	9.26	3.74	8.43	6.16-11.87	0.0001*
	Control	0.66	0.22	0.65	0.47-0.82	
Albumin(g/dl)	**Patients**	3.43	0.40	3.40	3.18-3.82	0.0001*
	Control	4.35	0.73	4.35	3.87-4.83	
eGFR (mlmin1.73m2)	**Patients**	33.80	25.70	20.15	11.88-64.85	0.0001*
	Control	129.16	53.98	113.60	97.55-162.38	
CD10(ng/ml)	**Patients**	2.36	0.98	2.35	1.62-2.99	0.223# Ns
	Control	2.19	0.88	1.91	1.53-2.81	
E-cadherin(ng/ml)	**Patients**	26.33	10.14	24.79	18.50-33.24	0.0001*
	Control	53.80	14.42	52.00	42.26-63.00	

**Significant differences at p-value <0.05. SD: Standard Deviation. IQR: inter quartile range. NS: non-significant. #: Independent T-test for normal distribution.GFR:glomerular filtration rate. CD10:cluster of differenation 10. Patients n=96 / Control n=80.*

Significant differences in the number of biomarkers related to renal function were found in the investigation. Compared to controls, CKD patients had noticeably higher levels of glucose, urea, and creatinine, which suggested compromised renal function and perhaps increased systemic Inflammation and fibrosis further highlighting the association between elevated glucose levels and renal dysfunction, suggesting a link between glucose tolerance status and CKD risk [18]. Additionally, the adverse clinical outcomes associated with an elevated urea-to-creatinine ratio in CKD patients were emphasized by 9, which supports our results. The association between hyperuricemia and CKD emphasizes its role in Inflammation and fibrosis, which aligns with our findings of elevated urea and creatinine levels indicative of impaired renal function [19] studied the clinical significance of saliva urea and creatinine levels in CKD patients, proposing a noninvasive method for diagnosing kidney disease [20]. Investigated serum biochemical derangements and associated risk factors in 612 confirmed chronic kidney disease (CKD) patients in Pakistan. Elevated creatinine and urea levels were found in all patients, with hyperuricemia present in 63.4% [21], proposed urinary vimentin mRNA as a potential biomarker for renal fibrosis, which resonates with our observation of elevated vimentin levels in CKD patients, indicating potential fibrotic processes [22]. Conversely, CKD patients demonstrated lower levels of albumin, eGFR, and E-cadherin, further corroborating compromised renal function and impaired glomerular filtration rate in this population. [23] demonstrated in elders

that lower serum albumin levels were strongly associated with kidney function decline, independent of urine albumin and inflammatory markers.

Interestingly, while the mean CD10 levels were slightly higher in CKD patients than controls, this difference did not reach statistical significance. However, this observation may still have clinical relevance, suggesting a potential role for CD10 as a biomarker warranting further investigation in the context of CKD diagnosis and prognosis[24]

3.2. Biomarkers as independent predictors of severity albuminuria in CKD patients

The results of the nominal regression analysis shown in Table (3.2) revealed insightful findings regarding the relationship between biomarkers and the severity of albuminuria in CKD patients. Specifically, our analysis identified E-cadherin as the sole biomarker, demonstrating a statistically significant association with macroalbuminuria in CKD patients (OR = 0.701, p = 0.004). This signifies that for every one-unit increase in E-cadherin levels, there is a corresponding 0.701 decrease in the odds of experiencing macroalbuminuria. Hence, it can be inferred that higher levels of E-cadherin may exert a protective effect against the development of macroalbuminuria in CKD patients.

Table 3.2: Nominal regression for identifying the independent biomarkers in Macroalbuminuria of CKD patients

Macroalbuminuria	B	p-value	OR	95% CI	
Intercept	5.317	0.124			
CD10(ng/ml)	0.379	0.273	1.460	0.742	2.875
E-cadherin(ng/ml)	-0.355	0.004 *	0.701	0.551	0.891

**The reference category is Microalbuminuria. B: effect size. OR: odds ratio. CI: confidence interval*

Conversely, our study did not observe statistically significant associations between macroalbuminuria and the biomarkers CD10 ($p \geq 0.05$). Despite their inclusion in the analysis, this biomarker did not demonstrate an independent predictive value for the severity of albuminuria in CKD patients, suggesting their utility in this context may be limited. One potential mechanism by which E-cadherin may influence albuminuria is by preserving the structural integrity of the renal tubules. Higher levels of E-cadherin may help maintain the tight junctions between renal tubular cells, preventing albumin leakage across the tubular epithelium. This can contribute to a decrease in the severity of albuminuria in CKD patients.

3.3. Demographic and clinical characteristics of CKD patients with diabetes and those without diabetes.

The comparison between chronic kidney disease (CKD) patients with diabetes (Np-DM group) and those without diabetes (Np group) revealed significant differences in demographic and clinical characteristics. The Np-DM group was notably older, with a mean age of 51.39 years compared to 43.28 years for the Np group (p = 0.001). Additionally, patients with diabetes exhibited significantly higher mean levels of glucose, urea, creatinine, and E-cadherin. Their levels of albumin and estimated glomerular filtration rate (eGFR) were lower than the Np group (p = 0.0001). Notably, the two groups had no substantial difference in mean CD10 levels (p = 0.614). CKD patients with diabetes tend to be older and exhibit higher levels of glucose, urea, creatinine, and E-cadherin while having lower levels of albumin and eGFR compared to those without diabetes—Table (3.3)

Table 3.3: Demographic and clinical characteristics of CKD patients with diabetes and those without diabetes

Variables		Mean	SD	Median	IQR	p-value
Age (year)	**Np**	43.28	8.43	43.50		0.001# *
	Np-DM	51.39	11.94	51.50		
Glucose (mg/dl)	**Np**	109.88	19.58	108.80	96.63-124.38	0.0001*
	Np-DM	235.69	53.79	237.30	189.88-285.40	
Urea (mg/dl)	**Np**	141.18	18.94	138.08	130.04-155.25	0.0001*
	Np-DM	174.24	26.54	174.55	156.01-185.79	
Creatinine (mg/dl)	**Np**	5.44	1.13	5.73	4.75-6.19	0.0001*
	Np-DM	11.16	3.06	10.73	8.40-13.00	
Albumin(g/dl)	**Np**	3.91	0.13	3.91		0.0001*
	Np-DM	3.20	0.25	3.24		
eGFR (mlmin1.73m2)	**Np**	68.01	7.48	70.25	64.55-73.78	0.0001*
	Np-DM	16.70	8.76	13.85	10.38-20.18	
CD10(ng/ml)	**Np**	2.44	1.00	2.41	1.62-3.07	0.614# Ns
	Np-DM	2.33	0.97	2.28	1.53-2.99	
E-cadherin(ng/ml)	**Np**	37.50	7.38	35.87	32.36-43.91	0.0001*
	Np-DM	43.28	8.43	43.50	16.36-24.80	

**Significant differences at p-value <0.05. SD: Standard Deviation. IQR: inter quartile range. NS: non-significant. #: Independent T-test for normal distribution*

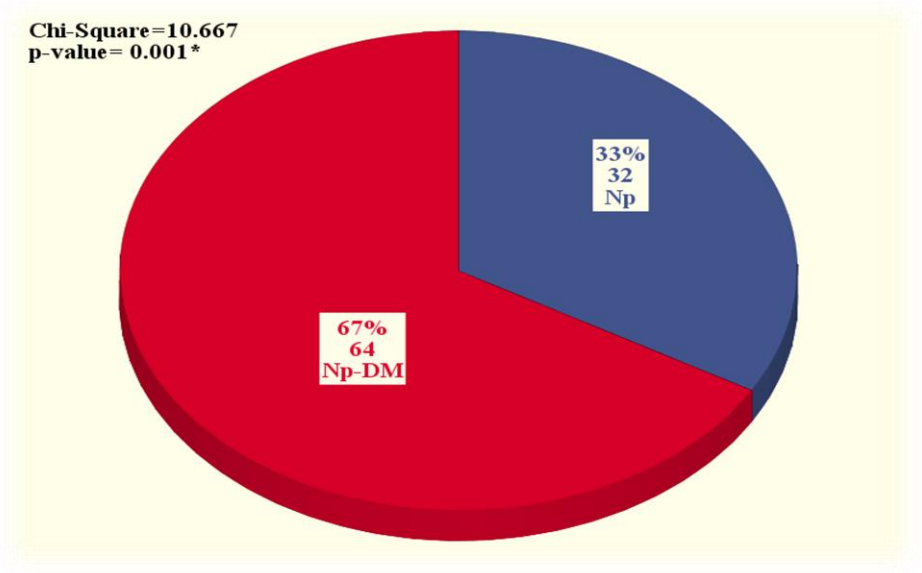

Figure 3.1: Distribution of Np and Np-DM patients. Values are expressed as percentage and number of patients, 33% Np and 67% Np-DM.

Some researchers observed distinct metabolic changes in CKD patients with diabetes compared to those without diabetes, with diabetes impacting metabolic signatures more significantly in early-stage CKD[25]. This supports our findings of higher levels of glucose, urea, and creatinine in CKD patients with diabetes. Additionally, other researchers found significant associations between blood urea and creatinine levels with hyperglycemia in diabetic patients, further corroborating our results regarding elevated urea and creatinine levels in CKD patients with diabetes [26,27]. These consistent findings across studies emphasize the importance of considering diabetes status when assessing biomarkers and clinical characteristics in CKD patients.

3.4. Biomarkers as independent predictors of chronic kidney disease.

In the study of diagnostic criteria for chronic renal biomarkers, our analysis revealed intriguing findings regarding the role of biomarkers as independent predictors of chronic kidney disease (CKD), particularly in diabetic nephropathy (Np-DM). Nominal regression analysis unveiled E-cadherin as the sole statistically significant biomarker (OR = 0.609, p = 0.0001) associated with Np-DM in CKD patients. Notably, a one-unit increase in E-cadherin correlated with a 0.609 decrease in the odds of developing Np-DM, suggesting a potential protective effect against diabetic nephropathy within the CKD population. However, our analysis did not identify statistically significant associations between CD10 and Np-DM ($p \geq 0.05$). These results underscore the potential utility of E-cadherin as a biomarker for risk stratification and management of diabetic nephropathy in CKD patients. More research is needed to understand this phenomenon's fundamental mechanisms and processes. Additional research is needed to clarify the underlying mechanisms and clinical implications of these findings Table (3.4).

Table 3.4**:** Nominal regression for identifying the independent biomarkers in diabetic nephropathic CKD patients

Np-DM	**B**	**Sig.**	**OR**	**95% CI**	
Intercept	11.273	0.006			
CD10(ng/ml)	0.218	0.665	1.243	0.463	3.336
E-cadherin(ng/ml)	-0.496	0.0001*	0.609	0.478	0.775

**The reference category is Np. B: effect size. OR: odds ratio. CI: confidence interval*

Furthermore, E-cadherin can influence cell survival, proliferation, and apoptosis signaling pathways. It can modulate the activation of key signaling molecules such as β-catenin, which is involved in cell proliferation and survival. Disruption of these pathways can lead to the onset of diabetic nephropathy. Higher levels of E-cadherin may help maintain the normal balance of these signaling pathways and prevent pathological changes in the kidneys[28]. This finding aligns with other researchers, who identified urinary E-cadherin as a novel biomarker for diabetic nephropathy, demonstrating its upregulation in DN groups compared to controls [29]. Additionally, some researchers corroborated the role of E-cadherin in DN progression, highlighting its decreased levels in DN patients compared to healthy controls, supporting the notion of its involvement in epithelial-to-mesenchymal transition (EMT)[30].

4. Conclusion

Our results demonstrate the complex pathophysiology of chronic kidney disease (CKD), underscoring the need to consider a range of biomarkers to evaluate renal function fully and the course of the disease. Interestingly, E-cadherin strongly correlated with macroalbuminuria in patients with chronic kidney disease (CKD), making it a viable biomarker. Higher levels of E-cadherin have been shown to protect against macroalbuminuria, highlighting the protein's potential as a prognostic marker and calling for more research into its clinical implications for managing chronic kidney disease. On the other hand, our study did not find any statistically significant relationships between vimentin and CD10 and macroalbuminuria, indicating that these markers may not be reliable indicators of the severity of albuminuria in individuals with chronic kidney disease. Additionally, comorbidity-related differences in biomarker levels were seen in our research of CKD patients, underscoring the significance of customized approaches to diagnosis and treatment.

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