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Emerging Role of Microtubule-Associated Protein 2 as a Prognostic Factor for Renal Dysfunction

Fatima Ghazi Talab[1,2] and Hind Shakir Ahmed[2*]
[1]College of Medicine, Al Nahrain University, Baghdad, Iraq.
[2]Department of Chemistry, College of Education for Pure Science (Ibn Al-Haitham), University of Baghdad, Baghdad, Iraq.
[*]Corresponding Author.

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Abstract

Chronic kidney disease (CKD) is a severe medical disorder manifested by a decline in kidney function over an extended period. This leads to the accumulation of toxins and the gradual inability to remove excess waste and fluids from the body. Microtubule-associated protein 2 (MAP2) is part of a protein family that regulates microtubule structure and cellular metabolism. This study aims to analyze the effectiveness of these parameters in evaluating CKD and its associated mechanisms in Iraqi patients. The study was conducted from December 2023 to May 2024. Ninety subjects enrolled in this study: 60 patients with CKD who attended the Baghdad Teaching Hospital/Medical City/ Dialysis Unit in Baghdad, Iraq. Additionally, 30 healthy subjects were designated as the control group. Their ages ranged from 48 to 65 years. The present results indicated significantly higher serum MAP2 levels in CKD patients undergoing dialysis as compared to the control (616.10±12.25 vs. 125.48±10.14) ρg/mL. In addition, the present results revealed a significant positive correlation between serum MAP2 and levels of various parameters, including fasting glucose, lipid profile, and renal function tests. A significant negative correlation exists between serum MAP2 levels and serum total protein, albumin, and estimated glomerular filtration rate. It was found that higher levels of serum MAP2 in hemodialysis patients reveal their critical role in renal dysfunction. Therefore, this factor may serve as a biomarker of kidney injury progression among patients with CKD.

Keywords: Chronic kidney disease, Glomerular filtration rate, Lipid profilr, Microtubule associated protein 2, Renal function test.

1. Introduction

Chronic kidney disease (CKD) is characterized by a progressive decline in renal function over time, typically resulting from a reduction in blood supply to the kidneys. This disorder results in cellular structural anomalies, including those inside neural cells (1).

Waste and toxins build up in the blood of patients with CKD, which negatively impacts general health and raises the risk of cardiovascular diseases (CVD). Because the kidneys play

a serious role in maintaining fluid and electrolyte balance and ultimately preventing the development of end-stage renal disease (ESRD), primary diagnosis and adequate management are imperative. Thus, sustaining a high quality of life requires prevention and knowledge of this disease (2,3).

Essential kidney functions, including blood urea and creatinine levels, are greatly impacted by CKD (4). Increased blood urea levels resulting from compromised renal function may worsen overall health and contribute to the development of hypertension (HTN) (5). Due to its role in muscle metabolism, creatinine is a sensitive marker of renal function; higher blood levels indicate worse kidney clearance (6,7). Additionally, evaluating the glomerular filtration rate (GFR) reveals the kidneys' role in filtering waste products and toxins from the blood. A reduced GFR is indicative of deteriorating CKD and additional deterioration in kidney function, which worsens the disease's symptoms and complications (8). It was first discovered that microtubules (MTs) were bound and stabilized by microtubule-associated proteins (MAPs).

Nevertheless, research is being conducted on their intricate roles as MT cytoskeleton regulators and their participation in various cellular processes, such as spindle assembly and neuronal development (9). In diabetic nephropathy (DN), disruption of these proteins triggers a pathogenic reaction that reorganizes the cytoskeleton of leg cells, breaks down connections, and acquires mesenchymal characteristics (10). Structural proteins called MAPs bind to tubulins, facilitating assembly. Tau, MAP2, and MAP4 belong to the classical family of MAPs. Large and small proteins are essential for the architecture of the cytoskeletal network in eukaryotic cells through their interactions with MAPs. Cellular functions, such as motility, trafficking, and division, depend on MTs, which are organized into discrete arrays with unique dynamics. They need MAPs, which fall into one of five categories (11). MAP2 is required to maintain the structural stability of neural fibers and MT dynamics within nerve cells. Although MAP2 is predominantly detected in the brain and central nervous system, it can also be identified in other cells, such as kidney cells (12). The effects of oxidative stress and kidney inflammation on renal cells linked to CKD are the main mechanisms underlying the relationship between MAP2 and CKD (13). For instance, damage from kidney inflammation can lead to changes in MAP2 expression, potentially contributing to cellular dysfunction and structural impairment in kidney tissues (14). Hence, this study aims to evaluate the role of MAP2 in evaluating CKD and its associated biochemical factors among Iraqi patients.

2. Materials and Methods

2.1 Study design

Ninety individuals, aged 48–65 years, were enrolled in this study from December 2023 to May 2024 at Baghdad Teaching Hospital/ Medical City/ Dialysis Unit in Baghdad, Iraq, and participated in this study; 60 patients with CKD and 30 healthy subjects as a control group. A questionnaire containing age, height, weight, and other diseases was recorded; CKD diagnosis was confirmed based on eGFR calculated via the CKD-EPI 2021 equation, with values $\leq$ 60 mL/min/1.73 m² for at least 3 months or evidence of renal impairment, such as urinary albumin $\geq$ 30 mg/g creatinine (15).

2.2 Inclusion and exclusion criteria

Inclusion criteria were an age range of 48 to 65 with ESRD, who were on a hemodialysis program for at least 6 months before recruitment. Exclusion criteria were AKI, pregnancy, type 1 diabetes, liver disease, thyroid dysfunction, and malignancy.

2.3 Biochemical analysis

Each participant's sex, age, weight, height, body mass index (BMI), and systolic and diastolic blood pressure (SBP and DBP, respectively) were measured, along with other anthropometric and clinical data. A biochemical automated analyzer (Cobas e411) was used to test the FSG and renal function test levels, including serum urea, creatinine, total protein, and albumin levels. Glycated hemoglobin (HbA1c) was measured by the Bio-Rad VARIANT hemoglobin A1C. The eGFR was calculated using the CKD-EPI formula (16).

$$eGFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age} \quad (1)$$

[For women and serum creatinine > 0.7 mg/dL]

$$eGFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age} \quad (2)$$

[For men and serum creatinine > 0.9 mg/dL].

Additionally, serum MAP2 level was measured using a sandwich enzyme immunoassay kit from Elabscience, USA (Cat No: E-EL-H2539); the sensitivity was 18.75 ρg/mL, with a detection range of 31.25-2000 pg/mL.

2.4 Statistical analysis

The Statistical Package for the Social Sciences (SPSS)-IBM 29, Chicago, USA was used to analyze the data. All results were shown as means ± standard deviation (SD). The chi-square test was used to compare percentage values. The independent samples t-test was used to compare numerical variables between two groups. Also, the correlation coefficient (r) between MAP2 and other study parameters in the CKD group was determined. A *p*-value < 0.05 was considered significant (17).

3. Results

Body mass index, SBP, and DBP were significantly ($p < 0.05$) elevated in CKD patients compared to controls, as shown in **Table (1**).

Table 1. Demographic, anthropometric, and clinical manifestations of the studied groups

Parameters	Mean ± SD		*p*-value
	CKD	Control	
Number	60	30	-
Male/ Femal no. (%)	38(63%)/22(37%)	15(50%)/15(50%)	0.001
Age (Years)	55.60 ± 10.22	53.43 ± 5.46	0.06
BMI (kg/m^2)	30.52 ± 2.14	24.85 ± 1.12	0.001
SBP (mmHg)	152.30 ± 2.41	120.60 ± 0.21	0.001
DBP (mmHg)	90.21± 1.87	82.15 ± 1.02	0.030
Causes or other disease:			
- DN	35(58%)		
- Primary nephritis	14(23%)	-	-
- HTN	40(66%)		

$p < 0.05$: Significant.

Patients' FSG, urea, and creatinine showed significant increases ($p= 0.001$) compared to the controls. Serum total protein, albumin levels, and eGFR decreased considerably ($p= 0.001$) in the CKD group compared to the controls, as shown in **Table (2**). Moreover, **Table (3**) reveals significantly higher ($p= 0.0001$) levels of MAP-2 in CKD patients compared to the controls.

Additionally, current outcomes reveal a significant ($p< 0.05$) positive correlation between MAP2 and various parameter levels, including FSG, urea, and creatinine. Also, the current results indicate a significant ($p< 0.05$) negative correlation between MAP2 levels and serum

total protein, albumin, and eGFR. Additionally, no considerable correlation was detected between the serum MAP2 levels and HbA1c, as presented in **Table (4)**.

Table 2. Glycemic profiles and renal function tests of the studied groups

Parameters	Mean ± SD		*p*- value
	CKD (n= 60)	Control (n= 30)	
FSG (mg/dL)	158.44 ± 17.26	98.20 ± 5.31	0.001
HbA1c (%)	8.25 ± 1.12	5.67 ± 0.08	0.06
Urea (mg/dL)	135.40 ± 8.45	20.05 ± 1.12	0.001
Creatinine (mg/dL)	10.13 ± 0.82	0.62 ± 0.01	0.001
Total protein (g/dL)	3.77 ± 1.40	6.80 ± 1.25	0.001
Albumin (g/dL)	2.78 ± 1.24	4.50 ± 1.12	0.001
eGFR (mL/min/1.73m^2)	23.72 ± 7.70	105.80 ± 5.06	0.001

p < 0.05: Significant.

Table 3. Serum MAP2 of the studied groups

Parameters	Mean ± SD		*p*- value
	CKD (n= 60)	Control (n= 30)	
MAP2 (ρg/mL)	616.10 ± 12.25	125.48 ± 10.14	0.0001

p < 0.05: Significant.

Table 4. Correlation coefficient between MAP2 and other study parameters in the CKD group

Parameters	MAP2 (ρg/mL)	
	r	*p*
FSG (mg/dL)	0.540	0.001
HbA1c (%)	0.145	0.08
Urea (mg/dL)	0.358	0.005
Creatinine (mg/dL)	0.650	0.001
Total protein (g/dL)	-0.432	0.001
Albumin (g/dL)	-0.348	0.030
eGFR (mL/min/1.73m^2)	-0.520	0.001

p < 0.05: Significant.

4. Discussion

A primary global public health concern that affects millions of individuals is CKD. It is linked to higher death rates and concomitant diseases, such as CVD (18). The current data analysis of the biological and behavioral components revealed that the risk of developing CKD was significantly associated with patients aged 40 to 65 years. This suggests that kidney function typically diminishes with age. After age 30, the GFR, a crucial measure of renal function, progressively declines (19,20). This decrease intensifies by the age of forty. As people age, this progressive loss of kidney function is a significant risk for developing CKD (21). Several biological factors make individuals aged 40 to 65 more susceptible to CKD, such as HTN and diabetes, which increase with age (22). Diabetes and HTN are major contributors to CKD, which is likely found in patients aged 40 to 65 years, as people between these ages are more likely to develop these illnesses or have persistent instances that lead to an increased risk of CKD (23). These disorders are substantial risk factors for developing CKD. People between the ages of 40 and 65 are more likely to develop these illnesses or have persistent instances, which raises their risk of CKD. The aging process leads to cellular changes that damage the kidneys, including decreased cellular efficiency and increased renal fibrosis. These alterations diminish the kidneys' resistance to illness and damage (24).

Reduced physical activity also harms CV health and could induce additional load on the kidneys (25).

Kidney function is impacted by CVD, which is elevated by smoking as well as long-term alcohol use/ alcohol disorders that can directly affect the kidneys. A lengthy history of these detrimental practices may increase the risk of CKD in people between the ages of 40 and 65 (26). It's essential to track biomarkers, such as urea, while evaluating kidney function and the course of CKD. A critical sign of renal failure in CKD is elevated urea levels. For the disease to be effectively managed, it is essential to understand the mechanisms causing urea accumulation and their associated clinical implications (27). Urea is the waste product produced by the liver's degradation of proteins. Urine is the product of filtration and excretion after being carried by the blood to the kidneys, and it is effectively eliminated from the blood in healthy kidneys, thereby keeping serum levels low (28).

Uremia, a condition where urea builds up in the blood, is caused by the kidneys' diminished capacity to filter urea in patients with CKD. The kidneys excrete urea and other waste products less efficiently as CKD worsens due to decreased GFR (29). A defining feature of CKD is a decline in GFR correlated with elevated serum urea levels. In addition, patients with CKD may experience worsening urea buildup due to various factors, such as increased protein catabolism, dehydration, and certain medications (30). Elevated urea levels have essential clinical ramifications for CKD patients; CKD patients who have elevated urea concentrations are at markedly increased risk of CV disease (31). Uremia contributes to endothelial dysfunction, inflammation, and arterial stiffness, all of which increase the risk of CV events, i.e., heart attack and stroke (32). Uremic toxins interfere with protein metabolism and appetite regulation, leading to reduced muscle mass and strength, which negatively impacts quality of life and, consequently, survival (33). Creatinine, a metabolic waste product, is a key biomarker for kidney health. The kidneys remove it from the blood and excrete it as urine (34). Serum creatinine concentrations are a dependable predictor of the GFR. Baseline creatinine levels can be influenced by several factors, including age, sex, muscle mass, and dietary intake; however, a persistent increase in creatinine levels typically indicates impaired kidney function. Serum creatinine levels rise as CKD worsens because the GFR keeps declining, as GFR is a vital metric for evaluating renal function and CKD stage (35). A healthy kidney's GFR is typically 90-120 mL/min/1.73 m^2; therefore, a drop in GFR level suggests a decline in renal efficiency and function. Reduced GFR in CKD is caused by mechanisms that increase injury to the kidney's filtering units, or nephrons. Multiple mechanisms, including vascular alterations, tubulointerstitial injury, and glomerular damage, cause the decrease in GFR. Anemia, hypervolemia, and HTN, in addition to low levels of serum total protein and albumin, are common comorbidities in patients with ESRD (36).

Primarily known for its role in stabilizing MTs in neurons is MAP2, which has also been implicated in renal pathology. In CKD, MAP2 may help preserve the shape of renal cells, especially podocytes, which are crucial for kidney function (37). Also, MAPs are necessary, under normal conditions, for preserving MT structure and function. They have the power to control the interaction between MTs and other cellular constituents and strengthen microtubule stability and assembly. Furthermore, MAPs are made up of two functional regions: an acidic salient binding domain that projects outward and forms a horizontal bridge connecting the MAP to other cell components, cytoskeleton components, membranes, and other structures, and an alkaline binding domain that attaches to the side of the MT. MAPs can regulate the phosphorylation and dephosphorylation of specific amino acids due to their their ability to bind to MTs (38).

This MAP2 is involved in signaling pathways affecting cell survival and stress response, potentially influencing kidney damage. It may contribute to inflammation and fibrosis in CKD, ultimately worsening kidney function over time. Understanding MAP2's involvement in CKD could lead to the development of new diagnostic markers and therapeutic strategies to preserve kidney function and improve patient outcomes (39).

Some studies indicate that podocytes play a crucial role in the GF barrier dysfunction caused by the hyperphosphorylation of MAP2 and MAP4. It is widely acknowledged that the pathogenesis of proteinuria and glomerulosclerosis is significantly influenced by podocyte loss and dysfunction (40). Podocytes are terminally differentiated cells that line the glomerular basement membrane (GBM) of glomerular capillaries. Podocytes, which utilize the GBM to resist outward expansion and maintain glomerular structural integrity, primarily function through their foot processes (41). Podocytes subjected to pathological stressors undergo a range of alterations, including dissociation, apoptosis, hypertrophy, and EMT, depending on the extent of the injury (42). Due to their limited developmental capability, podocyte detachment from the GBM and apoptosis will inevitably lead to cell loss or dropout. This will decrease podocyte density, ultimately compromising GF and leading to proteinuria. Investigational evidence indicates that in the late phase of CKD, when proteinuria is already evident, podocyte defeat occurs. Thus, rather than podocyte loss, it is more likely that irregular changes in podocyte function or differentiation are widespread, and proteinuria tends to present with a wide range of clinical conditions. Podocytes lose common mesenchymal markers such as collagen I and fibronectin. They also acquire epithelial markers, such as P-cadherin and Nephrin, de novo as they undergo the epithelial-mesenchymal transition (EMT) (43).

Nephrin is an essential component of the slit diaphragm cell adhesion complexes, and its absence causes the slit diaphragm to become less cohesive, facilitating the separation of podocytes from the GBM (44). It has been associated with hypoxia, reactive oxygen species, growth factors, pro-fibrotic cytokines, advanced glycation end products, and metalloproteinases (45). Podocytes vary from other renal cells in that they undergo severe EMT and die in response to injury or unpleasant stimuli, making them terminally differentiated and incapable of reproducing. This study's intriguing conclusion comes from it. Consequently, endothelial cells undergo an EMT, which leads to an increase in mesenchymal cells. Moreover, proteinuria may be connected to either podocyte EMT or overt death. To accomplish EMT, MAP2 has to rearrange the cytoskeleton, and this is the default result of EMT triggering, also serving as a switch in this study (46).

An evidence study revealed that actin restructuring is closely associated with the elimination of the foot process, which is linked to proteinuria. Further research is necessary to determine the precise mechanism controlling cytoskeletal rearrangement during meniscal cell EMT, as it is currently unknown. Actin-MT interactions are a phenomenon that controls several essential cellular functions, including cell division and motility. It has been demonstrated that MAPs play a crucial role in regulating MT and actin connections during the development of cytoskeletal networks (47). Hyperphosphorylated MAP4 exhibited signs of pathological alterations in DN, including proteinuria, senescence, and significant EMT of meniscal cells (48).

Furthermore, in MAP4 models, hyperglycemia made these degenerative alterations in the kidneys worse. As a result, the cumulative damage caused by either high blood glucose or MAP4 hyperphosphorylation worsens aging and nephropathy over time. Although age is not the primary factor, aged organs and cells cannot compensate for their decline. The p38/

mitogen-activated protein kinases (MAPKs) have been identified as a key modulator of inflammatory responses and mitochondrial dysfunction in diabetes, as well as other aspects related to the pathophysiology of DN (49). Renal proximal tubule epithelial cells have been shown to contain p38/ MAPKs, which have been linked to EMT (50).

5. Conclusion

Patients with CKD had increased serum MAP2 levels, indicating its vital role in renal failure. MAP2 may, therefore, be regarded as a biomarker of the development of renal injury in CKD patients. Hypoxia and oxidative stress may contribute to this, as they can work in tandem with increased albuminuria and decreased GFR to elevate serum MAP2 levels.

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Conflict of Interest

The authors declared that they have no conflicts of interest.

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Ethical Clearance

The Institutional Scientific Committee at the University of Baghdad approved this study in accordance with the Declaration of Helsinki for human studies, which is consistent with the instructions of the Iraqi Ministry of Health and Environment (No. 85954 on 22/11/2023).

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