Eastern Journal of Agricultural and Biological Sciences (EJABS)
ISSN: 2753-3247
Website: https://qabasjournals.com/index.php/ejabs

Estimation of some non- routine biomarkers in serum of patients in the final stage of chronic kidney disease in Basrah Province

[1]Muntadher Ali Hassan, [2]Assist prof. Abdulkareem M. Jewad & [3]Mohammed Mahdi Salih

[1]Basrah health department, the center of the step Imam Ali
[2]Southern Technical University, Collage of Health and Medical Technology
[3]Internist.nephrologist, CABM(med.).CABM(nephro.), Basra Teaching Hospital

Corresponding Author: Muntadher Ali Hassan; E-mail: Muntadheralsaadie@gmail.com

ARTICLE INFO

Received: March 10, 2023
Accepted: April 16, 2023
Volume: 3
Issue: 1

KEYWORDS

Chronic kidney disease, end stage renal disease, oxidative stres

ABSTRACT

Chronic kidney disease (CKD) is a reduction in renal function manifested by a GFR of less than 60 mL/min per 1.73 m2 or kidney damage marker, or maybe both, last about 3 months, regardless of actual cause. Based on Available global health estimates, this disorder was responsible for 864 226 mortalities. A case control study included 30 CKD patients and 30 healthy subjects as a control group who visited Al-Basrah Teaching Hospital in AL -Basrah province between October 2021 and February 2022. The Age average for study population was (25-60) years. Serum levels Human AVP, ADMA, KIM-1, HCY, UMOD, SDMA was measured by A Sandwich-ELISA technique. The results demonstrated a significant increase in homocysteine, SDMA, ADMA, AVP and KIM-1 ($P < 0.05$), and significant decrease in the levels of UMOD of patients with CKD compared to the control ($P < 0.05$). According to results, we conclude hyperhomocysteinemia occurs in chronic- and end-stage kidney disease. Uromodulin serves as a robust biomarker for kidney function and allows the identification of early stages of CKD. As a marker of tubular secretion, it might represent remaining nephron mass and therefore intrinsic "kidney function" rather than just glomerular filtration. ADMA and SDMA play a critical role in the process of endothelial dysfunction, and are considered markers of oxidative stress. Increasing of arginein vasopressin and kidney injury molecule-1 suggesting their role in the pathogenesis of deterioration of renal function.

1. Introduction

Chronic kidney disease (CKD) is a reduction in renal function manifested by a GFR of less than 60 mL/min per 1.73 m2 or kidney damage marker , or maybe both, last about 3 months, regardless of actual cause (Levey *et al*., 2015).

Based on Available global health estimates, this disorder was responsible for 864 226 mortalities (or 1.5 percent of all mortality globally) in 2012. Chronic kidney disease was the 14th common cause of death, accounting for 12.2 deaths per one hundred thousand people (dos Santos & da Silva, 2019).

In medical studies for human, Arginine a new screening tool for the timely identification of kidney failure is routinely used. Symmetric Dimethylarginine (SDMA) is an intrinsic methylated style of arginine that's also transported in the blood during usual protein breakdown (Paltrinieri *et al*., 2018).

Asymmetrical dimethylarginine (ADMA) is nitric oxide synthase endogenous inhibitors. ADMA considered as serious risk factor, CVD, atherosclerosis, pulmonary hypertension, atrial fibrillation, stroke, peripheral vascular diseases, diabetes (Ali *et al*., 2014; Liu *et al*., 2016 and Anderssohn *et al*., 2018).

Homocysteine (HCY) is a α-amino acid (non-proteinogenic). Hyper-homocysteinemia is classed as an indicator of CVD, most probably via atherogenesis, that can result in ischaemia.

Uromodulin (UMOD) a 3 urinary glycoprotein known to affect the forming of kidney's calcium calculus (Lau *et al.,* 2008). A type I membrane protein, Kidney Injury molecules-1 (KIM-1) that was explored in 1998 play also a role in CKD diagnosis.

2. Methodology

Participants in this study were 30 CKD patients and 30 healthy subjects as a control group who visited Al-Basrah Teaching Hospital in AL -Basrah province between October 2021 and February 2022. The Age average for study population was (25-60)

years. All patients in this study were examined by hospital specialists. The practical study portion was completed at Southern Technical University/Basrah's Department of Medical Laboratory Technology.

The blood samples were drawn from both (patients and controls), emptied into sterilized test tubes, then left to coagµlate at RT for (30) min. By centrifugation at 3000 rpm for 15 min the blood sample was separated, and the serum stored at -20 (0C) until using.

Too many individuals were excluded because they did not meet the inclusion criteria, such as patients with acute and chronic diseases or diseases other than kidney disease, such as hypertension, and all patients with hormonal imbalance.

GFR Calculation

GFR was calculated by the Modification of Diet in Renal Disease Study (MDRD) equation (Chen et al., 2016)

GFR (mL/min/1.73 m2) = 186 × Serum Cr-1.154 × age-0.203 × 1.212 (if patient is black) × 0.742 (if female).

Serum levels Human AVP, ADMA, KIM-1, HCY, UMOD, SDMA was measured by A Sandwich-ELISA technique

Statistical Analysis

Statistical analyses were done in a statistical package for social sciences (SPSS) version 22. Means and SD were used for data representation. ANOVA was used for assessing a significance difference in the mean of normality distributed variables and Kruskal Wallis test for non-normaly distributed. P-values ($P \leq 0.05$) are significant.

3. Results and Discussion

Table (1) show the results of Homocysteine, SDMA, ADMA, UMOD, AVP and KIM-1 of CKD patient and the control subject, there is significant increase in Homocysteine, SDMA, ADMA,AVP and KIM-1 ($P < 0.05$) , and significant decrease in the levels of UMOD of patients with CKD compared to the control ($P < 0.05$).

Our study agree with (Guo *et al*., 2009 ; Long & Nie 2016) that in individuals with ESRD, the homocysteine level is 3-5 times greater than normal.

Plasma HCY levels are regularly and inversely correlated with creatinine clearance. Significant indirect finding demonstrates that renal function and excessive homocysteine rates in renal disease are associated by this connection (Long & Nie 2016).

In addition to the direct impact of homocysteine on cellular damage or the promotion of sclerotic changes, emerging research has concentrated on a number of major molecular and physiological processes, including oxidative stress, inflammation, endoplasmic reticulum (ER) stress, and hypomethylation. We think that comprehending these pathways might help us better comprehend the pathogenesis of ESRD (Long & Nie 2016).

In a meta-analysis of retrospective studies, Heinz et al. did find that Hcy titer is a potential risk for both CVD and mortality among patients of ESRD who do not receive extra FA supplements or live in areas with mandatory FA fortress. This effect was stronger in prospective studies compared to retrospective ones. The prospective studies that were part of the meta-analysis demonstrated that in Patients who are not receiving supplements, a rise in total homocysteine concentration of 5 mmol/L is linked to a 7% rise in the risk of mortality rates and a 9% rise in the risk of coronary heart disease events (Heinz *et al*., 2009) .

In people with CKD, plasma homocysteine levels are greater. This could put these people at a higher risk of getting atherosclerosis and coronary artery disease (Cohen *et al*., 2019).

This study demonstrates that CKD patients who received hemodialysis frequently have hyperhomocysteinemia. Patients with CKD who have hyperhomocysteinemia are at risk for developing CVD complications, and this condition is frequently linked to vitamin B deficiency. In CKD patients, vitamin B supplementation is strongly advised (Pinzon *et al*., 2020).

A significant increase in ADMA results with CKD patients, in consistency with current study, revealed by researchers as following (Schepers *et al*., 2014; Wang *et al*., 2018 and Oliva-Damaso *et al*., 2019) .

It is widely established that ADMA levels are much higher in ESRD, hypertensive, negative cardiovascular events, renal failure progression, renal fibrosis, and death. ESRD patients receiving hemodialysis exhibited greater ADMA levels than healthy individuals. ADMA appears to be a predictor of cardiovascular outcomes and mortality in ESRD patients receiving dialysis (Oliva-Damaso *et al*., 2019).

Although it has been shown that circulating ADMA levels have increased in CKD patients, there have not been enough studies to determine whether plasma ADMA can be utilized to predict CVD in these people. A meta-analysis revealed link between circulating concentrations of ADMA and Carotid Intimal Media Thickness (CIMT) in CKD patients (Wang *et al*., 2018).

Since ADMA and urea both have low molecular weights, dialysis appears to be the most effective method for getting rid of ADMA in CKD patients. However, research that looked at just how hemodialysis (HD) affected plasma ADMA levels demonstrate that this perspective is oversimplified because a drop in ADMA does not always mean an increase in clinical importance (Schepers *et al*., 2014).

The findings of this study are consistent with those of earlier research, as seen in the following (Yilmaz *et al*., 2006; Carello *et al*., 2006 and Emrich *et al*., 2006) were significant increase in SDMA results with CKD patients.

Our findings highlight a possible pathophysiological involvement for SDMA in the development of CKD and atherosclerotic heart disease in CKD patients not receiving dialysis. Compared to other methylarginines, SDMA more involves predicting the progression of CKD and upcoming atherosclerotic cardiac events. Therefore, SDMA instead of ADMA ought to be the main focus of any subsequent clinical and experimental trials (Emrich *et al*., 2006).

On the other hand, facts support excessively high SDMA and its associated ratios. Similar conclusions have also been noted by earlier studies, who have linked this to diminishing GFR. The minor correlation among SDMA and BP load we found in the research may be explained by the fact that BP loads are also known to rise with declining GFR. We found significant links between eGFR and BP load and SDMA, correspondingly, indicating that BP load and SDMA relationship are most likely effects of decreased GFR (Yilmaz *et al*., 2006).

It isn't recognized if SDMA satisfies all requirements for a perfect GFR indicator, including steady production rate unaffected by other diseases, free glomerular filtration, and absence of tubular reabsorption, despite the fact that there is an strong relation between SDMA and founded assumptions of GFR. However, our examination of the data indicates that SDMA has potential as such a biomarker. A meta-analysis included 2136 participants overall, demonstrated a significant association between SDMA and kidneys function. (Tarnow *et al*., 2004).

Because estimations of GFR from blood creatinine are sensitive even to mild changes in GFR and are compounded by associated with replacing variability due to muscle, protein, aging, and sexuality, the high connection between SDMA and kidneys function is of medical significance (Yilmaz *et al*., 2006).

Our research supports Lv et al 2018 work, which described the connection amongst serum uromodulin, ESKD, and the all fatality in the context of CKD. In spite of the known risk factors for getting CKD, we found that lower levels of serum uromodulin levels were associated with a higher likelihood of incidence ESKD. The bulk of the uromodulin protein that has been broken down by proteolysis is eliminated in the urine; a smaller but still significant proportion is released into the tubulointerstitium (Lv *et al*., 2018).

To our information, this is the only prospective study to examine the connection among serum uromodulin and the progress of renal disease in a CKD patient. Our results were in line with several earlier study' conclusions (Steubl *et al.,* 2016).

In addition, Leiherer et al. (2018) observed that in people with coronary artery disease who had reduced serum uromodulin levels, there was an obvious relationship between kidney function decline and the frequency of CKD. Nevertheless, the majority of individuals in their study had typical or mildly decreased renal function, and throughout follow-up they did not achieve the target of ESKD.

A decrease in uromodulin amount in CKD patients suggests that a decrease in urine uromodulin elimination from apex secretion may be linked to a decrease in basolateral secretion (Fedak *et al.,* 2016). Reduced erythropoietin generation, acid-base balance abnormality and mineral metabolism disorders are all linked to decreased uromodulin amounts, which suggest anomalies in kidney tubulointerstitial functioning. This links the quick improvement in renal dysfunction (Lv *et al*., 2018).

Serum uromodulin acts in the opposite way as the other traditional renal retention measures, with lower amounts associated with worse kidney function. As uromodulin is produced by the units of the thick ascending limb of the loop of Henle, decreased uromodulin may indicate a decrease in the number or functionality of cells in chronic kidney pathology (Risch *et al*., 2014) .

All of (Torres, 2009; Meijer *et al*., 2011; Bankir & Ritz 2013; Zittema *et al*., 2014; Tasevska *et al*., 2016 ; Qiu *et al*., 2021 and Sholokh& Klussmann 2021) revealed significant increase in result of AVP with CKD patients in consistency with current study.

Our study agree with [26] study that noticed vasopressin regulates free water clearance and so plays an important function in water homeostasis. Despite its importance in normal physiology, an emerging body of data shows that vasopressin contributes to the course of CKD. In CKD animal studies and also in diabetic and non-diabetic nephropathies, blood vasopressin is elevated. Vasopressin activity is reduced in CKD models, which promotes tubulointerstitial fibrosis and glomerulosclerosis.

It is now understood that vasopressin, acting through its 3 receptors, has impacts beyond just controlling water flow in the renal collecting duct and contracting of smooth muscle cells. Since hydrated and urine osmolality are commonly disregarded in clinical studies and trials, some of the consequences of this incredibly old hormone secretion, which are obviously beneficial in terms of immediate safety, may have long-term harmful implications if they are not properly recognized.

Vasopressin's effect on the renal in ADPKD is obvious and largely reliant on V2 receptors. Vasopressin plays a much more nuanced involvement in various types of CKD and hypertensive. Vasopressin, via V2 receptors, strongly suggests a role in the evolution of many kinds of CKD and in sodium hypertension, according to animal studies and a few recent investigations. Recent discoveries in rodents and people suggest that vasopressin may contribute to albuminuria and diabetic nephropathy through V2-receptor-mediated effects. These findings point to a potential (Bankir & Ritz 2013).

In some studies, continuous infusion of DDAVP (Desmopressin) made albuminuria and CKD worse. The results were the opposite when V2 receptors were directly blocked. Additionally, lower GFR and albuminuria are associated with greater copeptin levels, a substitute marker for AVP, in individuals who have undergone kidney transplantation (Bankir & Ritz 2013). By activating the renin-angiotensin system, arginine vasopressin may also contribute to the progression of CKD (Torres, 2009).

Based on the research and conclusions, one might hypothesize that AVP elevation has a role in CKD achievement, most likely via an influence on the V2R. Thus, increasing water consumption or pharmaceutical vasopressin blockage are promising possibilities for avoiding eGFR reduction and the development of CKD (Tasevska *et al*., 2016).

The findings of this study are consistent with other research findings, as shown by the considerable improvement in KIM-1 results with CKD patients in the following studies (Zhang *et al*., 2008 ; Chaturvedi & Kapke, 2009 and Prozialeck *et al*., 2009) .

KIM-1 can be utilized as a screening tool for renal disease, including AKI and chronic kidney injury, according to a growing body studies. Our findings concur with those of the studies conducted by (Chaturvedi & Kapke, 2009). Due to its various traits, KIM-1 is a promising biomarker for kidney damage. For instance, KIM-1 is not found in healthy kidney cells and is only expressed in proximal tubular cells that have been injured. The injured cells may continue to express themselves until they have totally recovered. Due to the quick and flawless cleavage of its ectodomain into the lumens of kidney tubules, it can also be discovered in urine (Chaturvedi & Kapke, 2009).

Since urinary KIM-1 levels are closely related to tissue KIM-1 levels and correlate with the degree of renal impairment, measuring urinary KIM-1 is anticipated to be a safe and sensitive method for evaluating kidney damage and possibly for evaluating the treatment potential of kidney failure (Bonventre, 2009). Urinary KIM-1 levels have increased significantly more quickly than BUN and S.Cr. in a nephrotoxicity investigation (Prozialeck *et al*., 2009).

Similar results were seen in the ischemia-reperfusion damage paradigm, where a 10-minute injury increased urine KIM-1 without affecting Cr, creatinine clearance, or proteinuria. Since KIM-1 expression in transplant specimens has been shown to be able to diagnose early tubular necrosis that is not visible by histopathologic inspection and that KIM-1 also aids in differentiating acute tubular necrosis from other allograft failings, KIM-1 be used to direct and personalize renoprotective interference (Zhang *et al*., 2008).

Despite KIM-1's alleged capacity to prevent AKI, a substantial body of data suggests the protein may contribute to the chronic damage of CKD. Patients with CKD and AKI have dedifferentiated tubular epithelium, which suggests that KIM-1 contributes to tubular fibrosis in a variety of chronic renal disorders. The tubulointerstitial damage indicators osteopontin and smooth muscle actin colocalized with KIM-1 expression in tubular epithelial cells in the tissue (De Borst *et al*., 2007 ; Kramer *et al*., 2009).

They hypothesized that KIM-1 expression in tubules was closely related to the dedifferentiation of epithelial cells and might contribute to the onset of interstitial fibrosis.

4. Conclusion

According to results we conclude hyperhomocysteinemia occurs in chronic- and end-stage kidney disease. Uromodulin serves as a robust biomarker for kidney function and allows the identification of early stages of CKD. As a marker of tubular secretion it might represent remaining nephron mass and therefore intrinsic "kidney function" rather than just glomerular filtration. ADMA and SDMA play a critical role in the process of endothelial dysfunction, and are considered markers of oxidative stress. Increasing of arginein vasopressin and kidney injury molecule-1 suggesting their role in the pathogenesis of deterioration of renal function.

References

[1] Levey, A. S., Becker, C., & Inker, L. A. (2015). Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. *Jama*, *313*(8), 837–846.

[2] dos Santos Tirapani, L., & da Silva Fernandes, N. M. (2019). A narrative review of the impacts of income, education, and ethnicity on arterial hypertension, diabetes mellitus, and chronic kidney disease in the world. *Saudi Journal of Kidney Diseases and Transplantation*, *30*(5), 1084.

[3] Paltrinieri, S., Giraldi, M., Prolo, A., Scarpa, P., Piseddu, E., Beccati, M., Graziani, B., & Bo, S. (2018). Serum symmetric dimethylarginine and creatinine in Birman cats compared with cats of other breeds. *Journal of Feline Medicine and Surgery*, *20*(10), 905–912.

[4] Ali, O. A., Chapman, M., Nguyen, T. H., Chirkov, Y. Y., Heresztyn, T., Mundisugih, J., & Horowitz, J. D. (2014). Interactions between inflammatory activation and endothelial dysfunction selectively modulate valve disease progression in patients with bicuspid aortic valve. *Heart*, *100*(10), 800–805.

[5] Anderssohn, M., Rosenberg, M., Schwedhelm, E., Zugck, C., Lutz, M., Lüneburg, N., Frey, N., & Böger, R. H. (2012). The L-arginine–asymmetric dimethylarginine ratio is an independent predictor of mortality in dilated cardiomyopathy. *Journal of*

Cardiac Failure, *18*(12), 904–911.

[6] Liu, X., Hou, L., Xu, D., Chen, A., Yang, L., Zhuang, Y., Xu, Y., Fassett, J. T., & Chen, Y. (2016). Effect of asymmetric dimethylarginine (ADMA) on heart failure development. *Nitric Oxide*, *54*, 73–81.

[7] Lau, W.-H., Leong, W.-S., Ismail, Z., & Gam, L.-H. (2008). Qualification and application of an ELISA for the determination of Tamm Horsfall protein (THP) in human urine and its use for screening of kidney stone disease. *International Journal of Biological Sciences*, *4*(4), 215.

[8] Guo, H., Chi, J., Xing, Y., & Wang, P. (2009). Influence of folic acid on plasma homocysteine levels & arterial endothelial function in patients with unstable angina. *Indian Journal of Medical Research*, *129*(3), 279–285.

[9] Long, Y., & Nie, J. (2016). Homocysteine in renal injury. *Kidney Diseases*, *2*(2), 80–87.

[10] Heinz, J., Kropf, S., Luley, C., & Dierkes, J. (2009). Homocysteine as a risk factor for cardiovascular disease in patients treated by dialysis: a meta–analysis. *American Journal of Kidney Diseases*, *54*(3), 478–489.

[11] Cohen, E., Margalit, I., Shochat, T., Goldberg, E., & Krause, I. (2019). The relationship between the concentration of plasma homocysteine and chronic kidney disease: a cross sectional study of a large cohort. *Journal of Nephrology*, *32*(5), 783–789.

[12] Pinzon, R. T., Sanyasi, R. D. L. R., & Pramudita, E. A. (2020). The proportion hyperhomocysteinemia in chronic kidney disease patients. *Asian Journal of Medical Sciences*, *11*(2), 14–17.

[13] Schepers, E., Speer, T., Bode-Böger, S. M., Fliser, D., & Kielstein, J. T. (2014). Dimethylarginines ADMA and SDMA: the real water-soluble small toxins? *Seminars in Nephrology*, *34*(2), 97–105.

[14] Wang, F., Xiong, R., Feng, S., Lu, X., Li, H., & Wang, S. (2018). Association of circulating levels of ADMA with carotid intima-media thickness in patients with CKD: a systematic review and meta-analysis. *Kidney and Blood Pressure Research*, *43*(1), 25–33.

[15] Oliva-Damaso, E., Oliva-Damaso, N., Rodriguez-Esparragon, F., Payan, J., Baamonde-Laborda, E., Gonzalez-Cabrera, F., Santana-Estupiñan, R., & Rodriguez-Perez, J. C. (2019). Asymmetric (ADMA) and symmetric (SDMA) dimethylarginines in chronic kidney disease: a clinical approach. *International Journal of Molecular Sciences*, *20*(15), 3668.

[16] Yilmaz, M. I., Saglam, M., Caglar, K., Cakir, E., Sonmez, A., Ozgurtas, T., Aydin, A., Eyileten, T., Ozcan, O., & Acikel, C. (2006). The determinants of endothelial dysfunction in CKD: oxidative stress and asymmetric dimethylarginine. *American Journal of Kidney Diseases*, *47*(1), 42–50.

[17] Carello, K. A., Whitesall, S. E., Lloyd, M. C., Billecke, S. S., & D'Alecy, L. G. (2006). Asymmetrical dimethylarginine plasma clearance persists after acute total nephrectomy in rats. *American Journal of Physiology-Heart and Circulatory Physiology*, *290*(1), H209–H216.

[18] Emrich, I. E., Zawada, A. M., Martens-Lobenhoffer, J., Fliser, D., Wagenpfeil, S., Heine, G. H., & Bode-Böger, S. M. (2018). Symmetric dimethylarginine (SDMA) outperforms asymmetric dimethylarginine (ADMA) and other methylarginines as predictor of renal and cardiovascular outcome in non-dialysis chronic kidney disease. *Clinical Research in Cardiology*, *107*(3), 201–213.

[19] Tarnow, L., Hovind, P., Teerlink, T., Stehouwer, C. D. A., & Parving, H.-H. (2004). Elevated plasma asymmetric dimethylarginine as a marker of cardiovascular morbidity in early diabetic nephropathy in type 1 diabetes. *Diabetes Care*, *27*(3), 765–769.

[20] Lv, L., Wang, J., Gao, B., Wu, L., Wang, F., Cui, Z., He, K., Zhang, L., Chen, M., & Zhao, M.-H. (2018). Serum uromodulin and progression of kidney disease in patients with chronic kidney disease. *Journal of Translational Medicine*, *16*(1), 1–9.

[21] Steubl, D., Block, M., Herbst, V., Nockher, W. A., Schlumberger, W., Satanovskij, R., Angermann, S., Hasenau, A.-L., Stecher,

L., & Heemann, U. (2016). Plasma uromodulin correlates with kidney function and identifies early stages in chronic kidney disease patients. *Medicine*, *95*(10).

[22] Leiherer, A., Muendlein, A., Saely, C. H., Brandtner, E. M., Geiger, K., Fraunberger, P., & Drexel, H. (2018). The value of uromodulin as a new serum marker to predict decline in renal function. *Journal of Hypertension*, *36*(1), 110–118.

[23] Fedak, D., Kuźniewski, M., Fugiel, A., Wieczorek-Surdacka, E., Przepiórkowska-Hoyer, B., Jasik, P., Miarka, P., Dumnicka, P., Kapusta, M., & Solnica, B. (2016). Serum uromodulin concentrations correlate with glomerular filtration rate in patients with chronic kidney disease. *Polskie Archiwum Medycyny Wewnętrznej= Polish Archives of Internal Medicine*, *126*(12).

[24] Risch, L., Lhotta, K., Meier, D., Medina-Escobar, P., Nydegger, U. E., & Risch, M. (2014). The serum uromodulin level is associated with kidney function. *Clinical Chemistry and Laboratory Medicine (CCLM)*, *52*(12), 1755–1761.

[25] Torres, V. E. (2009). Vasopressin in chronic kidney disease: an elephant in the room? *Kidney International*, *76*(9), 925–928.

[26] Meijer, E., Boertien, W. E., Zietse, R., & Gansevoort, R. T. (2011). Potential deleterious effects of vasopressin in chronic kidney disease and particularly autosomal dominant polycystic kidney disease. *Kidney and Blood Pressure Research*, *34*(4), 235–244.

[27] Bankir, L., Bouby, N., & Ritz, E. (2013). Vasopressin: a novel target for the prevention and retardation of kidney disease? *Nature Reviews Nephrology*, *9*(4), 223.

[28] Zittema, D., van den Berg, E., Meijer, E., Boertien, W. E., Kobold, A. C. M., Franssen, C. F. M., de Jong, P. E., Bakker, S. J. L., Navis, G., & Gansevoort, R. T. (2014). Kidney function and plasma copeptin levels in healthy kidney donors and autosomal dominant polycystic kidney disease patients. *Clinical Journal of the American Society of Nephrology*, *9*(9), 1553–1562.

[29] Tasevska, I., Enhörning, S., Christensson, A., Persson, M., Nilsson, P. M., & Melander, O. (2016). Increased levels of copeptin, a surrogate marker of arginine vasopressin, are associated with an increased risk of chronic kidney disease in a general population. *American Journal of Nephrology*, *44*(1), 22–28.

[30] Qiu, J., Sato, Y., Xu, L., Miura, T., Kohzuki, M., & Ito, O. (2021). Chronic exercise protects against the progression of renal cyst growth and dysfunction in rats with polycystic kidney disease. *Medicine and Science in Sports and Exercise*, *53*(12), 2485.

[31] Sholokh, A., & Klussmann, E. (2021). Local cyclic adenosine monophosphate signalling cascades—Roles and targets in chronic kidney disease. *Acta Physiologica*, *232*(1), e13641.

[32] Zhang, P. L., Rothblum, L. I., Han, W. K., Blasick, T. M., Potdar, S., & Bonventre, J. V. (2008). Kidney injury molecule-1 expression in transplant biopsies is a sensitive measure of cell injury. *Kidney International*, *73*(5), 608–614.

[33] Chaturvedi, S., Farmer, T., & Kapke, G. F. (2009). Assay validation for KIM-1: human urinary renal dysfunction biomarker. *International Journal of Biological Sciences*, *5*(2), 128.

[34] Prozialeck, W. C., Edwards, J. R., Lamar, P. C., Liu, J., Vaidya, V. S., & Bonventre, J. V. (2009). Expression of kidney injury molecule-1 (Kim-1) in relation to necrosis and apoptosis during the early stages of Cd-induced proximal tubule injury. *Toxicology and Applied Pharmacology*, *238*(3), 306–314.

[35] Bonventre, J. V. (2009). Kidney injury molecule-1 (KIM-1): a urinary biomarker and much more. In *Nephrology Dialysis Transplantation* (Vol. 24, Issue 11, pp. 3265–3268). Oxford University Press.

[36] Kramer, A. B., van Timmeren, M. M., Schuurs, T. A., Vaidya, V. S., Bonventre, J. V, van Goor, H., & Navis, G. (2009). Reduction of proteinuria in adriamycin-induced nephropathy is associated with reduction of renal kidney injury molecule (Kim-1) over time. *American Journal of Physiology-Renal Physiology*, *296*(5), F1136–F1145.

[37] De Borst, M. H., van Timmeren, M. M., Vaidya, V. S., de Boer, R. A., van Dalen, M. B., Kramer, A. B., ... & van Goor, H. (2007). Induction of kidney injury molecule-1 in homozygous Ren2 rats is attenuated by blockade of the renin-angiotensin system or

p38 MAP kinase. *American Journal of Physiology-Renal Physiology*, *292*(1), F313-F320.