Review Article

Aldosterone: Implications in Diabetic Nephropathy

Fasiha Abdul Rehman*[,1,4], Zaid Abdul Razzak[2], Syed Saad Hussain[3]

[1]Department of Pharmacy, University of Karachi, Pakistan.

[2] Department of Neuropharmacology, International Center for Chemical and Biological Sciences, University of Karachi, Pakistan.

[3] Department of Pharmacy, IQRA University, Karachi, Pakistan.

[4] Clinertia Research Services, Karachi, Pakistan.

Abstract: Objective: The focus of this review is to summarize the recent advancement to understand the molecular pathogenesis of diabetic nephropathy (DN). Also, to highlight the role of abnormal aldosterone secretion on the development and progression of diabetic nephropathy.

Background: Diabetic Nephropathy (DN) is a progressive disease of nephron due to slow progressive failure of kidney tubule to perform its filtration process. It is often associated with proteinuria and glomerular stiffening which eventually leads to low glomerular filtration rate, finally succumbs the patient toward the end stage of kidney disease. The abnormal level of aldosterone in diabetes mellitus is a fatal combination to combat because of progressive development of diabetic nephropathy.

Methods: We reviewed the literatures for implications of aldosterone in diabetic nephropathy. The literatures that were related to different aspects of diabetic nephropathy in relation to aldosterone were analyzed and summarized in this review article.

Result & Conclusion: Aldosterone, a mineralocorticoid of corticosteroid hormones releases under the influence of adrenocorticotrophic hormone (ACTH) from zona glomerulosa of adrenal gland of kidney. In normal physiological condition it regulates the renin-angiotensin system of kidney, which regulates the resorption and conservation of sodium (Na^+), potassium (K^+) ions and water (H_2O) from distal tubule. Aldosterone secretion, despite an important regulator to maintain the equilibrium of water and ions in the body, its non-regulated higher secretion gives rise to various pathological conditions. Additionally, we also discuss the risk factors associated with the use of mineralocorticoid receptor antagonist and renin-angiotensin-aldosterone therapy, and suggesting the need of robust and controlled methods to administer these drugs.

Keywords: Aldosterone, Diabetic nephropathy (DN), Diabetes mellitus, Mmineralocorticoid receptor antagonists, Renin angiotensin system.

ALDOSTERONE - THE BASIC CONCEPTS

The aldosterone hormone is a type of the mineralocorticoid group of corticosteroids and it is secreted from the outermost zone of adrenal gland called as Zona Glomerulosa [1, 2]. The aldosterone secretion is regulated by adrenocorticotropic hormone (ACTH) to a very lower extent; rather its principal physiological regulators are atrial natriuretic peptide (ANP), plasma potassium level (K^+), and renin-angiotensin system [1, 2].

There are two distinct physiological states for aldosterone secretion. a) Hyperkalemia b) Hypovolemia. In the former one, increased level of potassium ion depolarizes the voltage gated calcium (Ca^{2+}) channels of the cells, thus stimulating the aldosterone secretion [3, 4]. In the hypovolemic condition, type 1 receptor signaling of angiotensin II (AngII) induced by the rennin-angiotensin system in glomerular cells, activates the aldosterone secretion via Ca^{2+} biosynthesis pathway [3, 4]. Regardless of activating pathway in the distal tubule, aldosterone hormone increases the transcriptional activity of mineralocorticoid receptor (MR) and also modulates the level of electrolyte mediators in order to maximize the resorption of either Na^+ or K^+ in the distal nephron [5].

Obliging the current belief, the secretion of aldosterone shows bi-phasic response at cellular level. In the first phase, membrane transport proteins are stimulated due to deceleration of normal vital cellular process, as a result Na^+ ion reuptake occurs at aldosterone sensitive distal tubule of nephron. In second phase which lasts about for few hours, Na^+ ion re-absorption occurs via three primary Na+ transporters: Epithelial sodium channel (ENaC) α subunit transporter of collecting tubule, sodium – chloride (Na^+- Cl^-) symporter of distal tubule, and sodium – potassium adenosine triphosphatase (Na^+- K^+ ATPase) α subunit proximal tubule [5].

There are three types of cells in kidney tubules: principal cells, intercalated cells and distal convoluted tubule cells. The overall response of upraised level of aldosterone accompanied with the re-absorption of ions is to be regulated by the coordinated action of these tubular cells [1, 5]. The re-absorption of Na^+ ion accomplished by four different mechanisms as described below, are the cause for transportation of Na^+ through the cell membrane into the blood stream and hence indirectly enhancing the retention of water molecules in the

*Address correspondence to this author at the Department of Pharmacy, University of Karachi, Karachi, Pakistan
Email: fasiha.ark@gmail.com

collecting duct [1, 2].

Enhancing the number of Na^+-K^+ ATPase in the basolateral membrane which develops an electrochemical gradient for sodium by moving Na^+ into interstitial and intercellular spaces while moving K^+ into the cell [6].

Principal cells of tubule express a heterotrimeric protein which only allows Na^+, called epithelial sodium ion channel (ENaC) [7]. Aldosterone directly enhances the epithelial sodium channel's expression by activating it through the binding with mineralocorticoid receptor (MR), which drives K^+ secretion through apical K^+ channel [8].

MR controls ENaC function at multiple levels mainly by regulating the Serine/Threonine (Ser/Thr) kinase, serum and glucocorticoid-inducible protein kinase-1(SGK1) and the ubiquitin ligase Nedd4-2 [7] preventing ubiquitination, internalization and degradation, resulting in increased plasma membrane levels of ENaC.

Regulation of serine protease increases the opening probability of ENaC under the influence of aldosterone. ENaC consist of three subunits among them α and γ subunits are duly activated by inhibitory domain cleavage, mediated by serine proteases of any origin such as prostasin, plasmin and kallikrein [9-11].

PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY (DN)

End-stage kidney disease consists of two leading causes: diabetic nephropathy and diabetic kidney disease. The incidence of diabetes in the end stage kidney disease accounts for 30% to 50% of total incidence. Whereas, only 30% to 40% of population with diabetes develop diabetic nephropathy [12]. Diabetic neuropathy (DN) has been defined as progressive albuminuria associated with low glomerular filtration rate (GFR), hypertension and retinopathy in diabetic patient [13]. Proteinuria which can be either microalbuminuria with an albumin to creatinine ratio (ACR) of 30-300 mg/g or macroalbuminuria with an ACR > 300mg/g, is considered as marker to predict the point of onset of renal disease while being the factor to contribute to renal damage [14].

Pathophysiology of DN is not completely clear, but there are many risk factors associated with the pathology of DN. It includes insufficient glycemic control, hypertension, glomerular hyper-filtration and tobacco smoking. Others factors contributing to its development are proteinuria, obesity, and dyslipidemia. Genetic predisposition also plays an important role in the development of DN, because recent studies show that an individual with a family history can be more prone to develop DN [14, 15].

Furthermore, there are three more factors like oxidative stress, inflammation and endothelial dysfunction, considered to be the potential risk factor for the development of diabetic nephropathy [16]. Oxidative injury caused due to oxidative stress speeds up the process of inflammation by increasing the level of secretory cytokines. Consequently, it aggravates the vessel rigidity and inhibits the flow mediated dilation (FMD) of blood vessels [16, 17].

Insufficient glycemic control raises the glomerular mesangial pressure of nephron and simultaneously promotes the transforming growth factor-β (TGF-β) and platelet derived growth factor (PDGF) induced synthesis of matrix protein while down-regulating its degradation. As a result, thickening of glomerular basement membrane and fibrosis of tubules occurs. Additionally, it allows the higher extent of advanced glycation end products (AGE's) which concomitantly also increases the fibrosis of tubule [2].

There are five stages of kidney deterioration attributed to DN; initial three stages appear asymptomatic. Usually moderate-to-severe symptoms appeared from stage four which include, hands, ankles and legs swelling due to retention of water, hematuria and hypoxemia induced fatigue. If stage four symptoms are left untreated, they can lead to stage five end-stage renal disease (ESRD) where the kidneys fail to meet the daily requirements of clearance and filtration. The only possible treatments then left for ESRD are dialysis or kidney transplant [18].

ALDOSTERONE IN DIABETIC NEPHROPATHY – FROM INNOCENT PASSOVER TO SILENT CULPRIT

The renin-angiotensin system with aldosterone forms renin-angiotensin-aldosterone system (RAAS) is responsible to regulate the renal hemodynamic system. One of the hallmarks of its dysfunction is diabetic neuropathy [19]. Genome-wide studies suggested that Alu repeat sequence is located in the Angiotensin Converting Enzyme (ACE) gene [20]. The dysfunctionality ACE gene due to insertion-deletion (in-del), linearly increases the aldosterone level, consequently causes aldosterone toxicity and blood vessels fibrosis [21]. Increased level of aldosterone also triggers up-regulated TGF β1 expression [22].

The ultimate fate of increased level of aldosterone is, it further activates the extracellular signal-regulated kinases 1/2 (ERK1/2) dependent pathway in a dose-dependent manner to activate collagen types I, III and IV, which leads to severe tubule-interstitial fibrosis and collagen deposition [23]. In addition to these mechanisms, the phosphorylation of SGK1 and SGK1-dependent NF-κB (nuclear factor kappa light chain enhancer of activated B cells) activity is also enhanced by aldosterone. Briefly, all interconnected mechanisms which lead to the loss of function of nephron are directly or indirectly affected by abnormal up-regulation of aldosterone [24].

Previous studies reported that aldosterone can also alter the

glomeruli structurally and functionally, this damage induces the considerable rise in the glomerular permeability to albumin, leading to albuminuria [25]. Hence, albuminuria can be linearly correlated with the change in glomerular permeability. Additionally, deficiency of this enzyme may also mediate pro-inflammatory, pro-fibrotic, and pro-oxidative effects of aldosterone causing glomerular damage. Since, angiotensin converting enzyme II is also responsible for producing the renal protective atrial natriuretic peptide (ANP), it has been observed that aldosterone also decreases the glomerular expression of ANP [26].

Clinical studies have shown a strong correlation between insulin resistance and aldosterone. Aldosterone induces direct inhibition of insulin signaling via a series of complex events, encompassing actions on insulin receptor substrate 1 (IRS-1) and substrate 2 (IRS-2), affecting insulin receptor expression. Hence, aldosterone induced insulin resistance may be directly accountable for the development and progression of comorbid condition of cardiovascular disease and diabetes induced nephropathy [27, 28].

Contrary to the direct effects that aldosterone may have on insulin resistance, many of the effects of aldosterone in epithelial as well as non-epithelial tissues have been found to be increased in the state of hyperglycemia. In diabetics, activity of renal Type 2 11β-hydroxysteroid dehydrogenase (11 β-HSD2), enzyme which converts cortisol to cortisone preventing circulating cortisol from activating mineralocorticoid receptors (MR) [29], is considerably reduced due to increase aldosterone secretion.

The possible actions of aldosterone that may collectively lead to dysfunction of glucose metabolism can be summarized as below [27].

- Decrease in functioning of pancreatic β cells.
- Down-regulation of insulin receptors.
- Indirect reduction of insulin secretion via loss of potassium.
- Increase in insulin resistance by promoting renin-angiotensin system (RAS) activation in response to potassium loss [30].

MINERALOCORTICOID BLOCKADE - A PROMISING FUTURE

Diabetic nephropathy management is divided into 4 major areas: renin-angiotensin system (RAS) inhibition, hypo and hyper-glycemic control, cardiovascular risk alleviation, and controlled hypertension. Recommended therapy for targets include: a hemoglobin A1c (concentration < 7%) and blood pressure (< 140/90 mm Hg) linked with concomitant use of a RAS-blocking agent [12]. In severe cases, dialysis is also anchored with the ongoing therapy, that's why diabetic nephropathy still persists with high risk of morbidity and mortality rate [27, 31].

The management of diabetic nephropathy revolves not only around adequate glycemic control but also necessitates addressing the evaluation and intervention of hypertension and dyslipidemia [27]. Comprehensive treatment is required in all these aspects to minimize the early onset and progression of nephropathy.

Current guidelines recommend renin-angiotensin system (RAS) inhibitors including, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) as the preferred key treatment options. However, new therapeutic interventions are required for more efficient and effective control of the disease and to limit its progression. In this regard, blockade of aldosterone by mineralocorticoid receptor (MR) antagonist, also called as aldosterone antagonist including spironolactone, eplerenone and finerenone [31] have appeared as a potential future therapy. They may fill the gaps currently being faced with ACEIs and ARBs therapy and will provide desired renal protection, anti-albuminuria and decrease in cardiovascular events [27, 32].

One of the particular characteristics of diabetic nephropathy is proteinuria, particularly albuminuria; and RAS inhibitors in addition to hypotensive effect have anti-proteinuria effect as well. Conversely, their ability to reduce proteinuria declines over the period of time due to the so-called "phenomenon of proteinuria" or "albuminuria breakthrough". In this case, the initial reduction achieved in albuminuria through RAS inhibitors doesn't last longer despite the compliance to therapy and it again rises in the same fashion as seen with aldosterone levels [33, 34].

In many randomized clinical trials, inclusion of an MR antagonist in angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) therapy regimen has shown marked decrease in both systolic and diastolic values of blood pressure relative to the decrease seen with monotherapy of RAS inhibitors. The adequate hypertension control so achieved causes an apparent decrease in raised glomerular pressure, consequently providing better renal protection, even in terms of improved effects on proteinuria and GFR [31].

Recent studies show that diabetes patient who takes aldosterone blockers also have minimized level of the pro-fibrosis and pro-inflammatory mediators with better renal protection [35]. This is consistent with the finding that administration of MR antagonist like eplerenone, also showed a significant reduction in the above side effects of abnormal aldosterone secretion, demonstrating the potential of the drug for a better renal outcome [36].

Recent studies also show that the combination therapy did not show any improvement in GFR value compared with that of the monotherapy. However, it did help in maintaining a comparatively more stable GFR following the co-administration of a RAS inhibitor and an MR antagonist. Hence, it's

suggested that adequate suppression of aldosterone is needed to attain the desired level of GFR value and this may necessitate the use of MR antagonists along with the currently recommended treatment options [18]. Previous studies have also suggested that antagonizing MRs may prevent progression of renal damage via decreasing oxidative stress, blocking up-regulation of renal MRs, reducing growth factors such as TGF-B1 and limiting the renal fibrosis [37].

As discussed previously, aldosterone may have a direct deleterious effect on insulin's sensitivity which may become another factor requiring aldosterone's blockade in diabetics, preferably even before the onset of nephropathy. Unfortunately, there is no recent clinical data available to support this possible outcome but it may be the focus of future investigations [38].

RISK FACTORS- THE REASON OF AVOIDANCE

On the basis of available data and clinical experiences, the benefits conferred by MR antagonists are beyond the doubt. Nevertheless, apart from the beneficial effects being promised by the incorporation of MR antagonists there also exists a serious concern of hyperkalemia [39].

Aldosterone primarily modulates the rate of renal K^+ secretion, permitting the balance between urinary K^+ output and its dietary intake [40]. It promotes potassium excretion by enhancing the up-regulation of K^+ channels, consequently enhances the apical membrane's permeability for potassium. Secondly, increase in Na^+- K^+ ATPase expression also contributes to increase intracellular K^+ across basolateral membrane, promoting its further secretion into tubular fluid. Additionally, transport of Na^+ via sodium channels depolarizes the apical membrane which serves as a driving force to supplement renal potassium secretion. Finally, the cumulative effect of all these actions severely enhances the potassium transport across baso-lateral membrane, causing increased excretion of renal potassium.

The risk of hyperkalemia with the use of MR antagonist is the major concern that may limit its use especially in patients with pre-existing risk or a history of hyperkalemic events. Moreover, RAAS inhibitors also possess the potential for hyperkalemia and combining them with MR antagonist besides providing greater renal protection, will aggravate the hyperkalemic risk for patient. It may call for appropriate measures to be taken when incorporating RAAS inhibitors in the therapy, such as, patient monitoring via laboratory surveillance [41].

CONCLUSION

In conclusion, it's quite evident that aldosterone has a key role not only in the development but also in the progression of diabetic nephropathy and both the classical and non-classical actions of this hormone are held accountable for this contribution. Suppression of aldosterone can be achieved by RAS inhibitors (ACEIs or ARBs) to some extent, but more effective and adequate inhibition can be accomplished by directly targeting aldosterone via MR antagonist.

The addition of MR antagonists in the therapeutic regimens of diabetic nephropathy that are being employed and recommended as per the present day guidelines, will provide a more effective approach pertaining to renal protection, as evident in various experimental and clinical studies. However, the combination treatment has shown a much higher incidence of hyperkalemia raising a major concern to be considered before initiating the treatment. This implies that more clarification and information is required regarding different aspects of aldosterone and MR antagonists. Large scale, prospective clinical studies are essential to further investigate the potential effects of these drugs, since the data available to date is limited but it does hold a promise about the much greater affectivity that these can confer in terms of renal protection among diabetics. However, for an appropriate use of MR antagonists that can confer higher affectivity with much lesser adverse effects and inclusion of these drugs in the treatment guidelines of diabetic nephropathy, further research and analysis is necessary.

AUTHORS' CONTRIBUTION

All authors have contributed equally.

CONFLICT OF INTEREST

Declared none.

ACKNOWLEDGEMENTS

We would like to acknowledge Clinertia Research Services in assisting in the formatting of the manuscript for this review article.

REFERENCES

[1] Koeppen BM, Stanton BA. Berne & levy physiology. Philadelphia, PA: Mosby Elsevier 2009.

[2] Hilal-Dandan R, Brunton LL, Goodman LS, Gilman A. Goodman and Gilmans manual of pharmacology and therapeutics. New York: McGraw Hill Education Medical 2013.

[3] Spät A, Hunyady L. Control of aldosterone secretion: A model for convergence in cellular signaling pathways. Physiol Rev 2004; 84(2): 489-539. DOI: 10.1152/physrev.00030.2003

[4] Boulkroun S, Fernandes-Rosa F, Zennaro M. Molecular and cellular mechanisms of aldosterone producing adenoma development. Front Endocrinol 2015; 6. DOI: 10.3389/fendo.2015.00095

[5] Shibata S. 30 years of the mineralocorticoid receptor: Mineralocorticoid receptor and NaCl transport mechanisms in the renal distal nephron. J Endocrinol 2017; 234(1): T35-T47. DOI: 10.1530/JOE-16-0669

[6] Lifton R, Gharavi A, Geller D. Molecular mechanisms of human hypertension. Cell 2001; 104(4): 545-56. DOI: 10.1016/S0092-8674(01)00241-0

[7] Pearce D, Soundararajan R, Trimpert C, Kashlan O, Deen P, Kohan D. Collecting duct principal cell transport processes and their regulation. Clin J Am Soc Nephrol 2015; 10(1):

135-46. DOI: 10.2215/CJN.05760513

[8] Xu N, Hirohama D, Ishizawa K, *et al.* Hypokalemia and pendrin induction by aldosterone. Hypertension 2017; 69(5): 855-62. DOI: 10.1161/HYPERTENSIONAHA.116.08519

[9] Vallet G, Ahmaidi S, Serres I, *et al*. Comparison of two training programmes in chronic airway limitation patients: Standardized versus individualized protocols. Eur Respir J 1997; 10(1): 114-22. DOI: 10.1183/09031936.97.10010114

[10] Narikiyo T, Kitamura K, Adachi M, *et al*. Regulation of prostasin by aldosterone in the kidney. J Clin Investig 2002; 109(3): 401-8. DOI: 10.1172/JCI0213229

[11] Svenningsen H, Egerod I, Dreyer P. Strange and scary memories of the intensive care unit: A qualitative, longitudinal study inspired by Ricoeur's interpretation theory. J Clin Nurs 2016; 25(19-20): 2807-15. DOI: 10.1111/jocn.13318

[12] Umanath K, Lewis J. Update on diabetic nephropathy: Core curriculum 2018. Am J Kidney Dis 2018; 71(6): 884-95. DOI: 10.1053/j.ajkd.2017.10.026

[13] Lim A. Diabetic nephropathy - complications and treatment. Int J Nephrol Renovasc Dis 2014; 7: 361-81. DOI: 10.2147/IJNRD.S40172

[14] Fleisher LA. Anesthesia and uncommon diseases. Philadelphia: Elsevier Saunders 2012.

[15] Ahmed M, Kishore G, Khader H, Kasturirangan M. Risk factors and management of diabetic nephropathy. Saudi J Kidney Dis Transplant 2013; 24(6): 1242. DOI: 10.4103/1319-2442.121310

[16] Cheng H, Harris R. Renal endothelial dysfunction in diabetic nephropathy. Cardiovasc Hematol Disord-Drug Targets 2014; 14(1): 22-33. DOI: 10.2174/1871529X14666140401110841

[17] Niedowicz DM, Daleke DL. The role of oxidative stress in diabetic complications. Cell Biochem Biophys 2005; 43(2): 289-330. DOI: 10.1385/CBB:43:2:289

[18] Rao V, Rao LV, Tan SH, Candasamy M, Bhattamisra SK. Diabetic nephropathy: An update on pathogenesis and drug development. Diabetes Metab Syndr 2019; 13(1): 754-62. DOI: 10.1016/j.dsx.2018.11.054

[19] Jain AK, Cuerden MS, Mcleod I, *et al*. Reporting of the estimated glomerular filtration rate was associated with increased use of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers in CKD. Kidney Int 2012; 81(12): 1248-53. DOI: 10.1038/ki.2012.18

[20] Afghahi H, Miftaraj M, Svensson A, *et al*. Ongoing treatment with renin-angiotensin-aldosterone-blocking agents does not predict normoal buminuric renal impairment in a general type 2 diabetes population. J Diabetes Complications 2013; 27(3): 229-34. DOI: 10.1016/j.jdiacomp.2012.10.010

[21] Murakami T, Iwamoto T, Yasuda G, *et al*. Role of renin-angiotensin system inhibitors in retardation of progression of end-stage renal failure: A retrospective study. Clin Exp Nephrol 2016; 20(4): 603-10. DOI: 10.1007/s10157-015-1191-2

[22] Tylicki L, Jakubowska A, Lizakowski S, Świetlik D, Rutkowski B. Management of renin-angiotensin system blockade in patients with chronic kidney disease under specialist care. Retrospective cross-sectional study. J Renin Angiotensin Aldosterone Syst 2015; 16(1): 145-52. DOI: 10.1177/1470320314550018

[23] Zeeuw DD, Ramjit D, Zhang Z, *et al*. Renal risk and renoprotection among ethnic groups with type 2 diabetic nephropathy: A post HOC analysis of RENAAL. Kidney Int 2006; 69(9): 1675-82. DOI: 10.1038/sj.ki.5000326

[24] Giacchetti G, Sechi LA, Rilli S, Carey RM. The renin-angiotensin-aldosterone system, glucose metabolism and diabetes. Trends Endocrinol Metab 2005; 16(3): 120-6. DOI: 10.1016/j.tem.2005.02.003

[25] Bernardi S, Michelli A, Zuolo G, Candido R, Fabris B. Update on RAAS modulation for the treatment of diabetic cardiovascular disease. J Diabetes Res 2016; 2016: 1-17. DOI: 10.1155/2016/8917578

[26] Azadbakht MK, Nematbakhsh M. Angiotensin 1-7 administration alters baroreflex sensitivity and renal function in sympathectomized rats. J Nephropathol 2017; 7(2): 79-82. DOI: 10.15171/jnp.2018.19

[27] Sato A. The necessity and effectiveness of mineralocorticoid receptor antagonist in the treatment of diabetic nephropathy. Hypertens Rese 2015; 38(6): 367-74. DOI: 10.1038/hr.2015.19

[28] Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med 2017; 23(7): 804-14. DOI: 10.1038/nm.4350

[29] Dammann C, Stapelfeld C, Maser E. Expression and activity of the cortisol-activating enzyme 11β-hydroxysteroid dehydrogenase type 1 is tissue and species-specific. Chem Biol Interact 2019; 303: 57-61. DOI: 10.1016/j.cbi.2019.02.018

[30] Tal B, Sack J, Yaron M, *et al*. Increment in dietary potassium predicts weight loss in the treatment of the metabolic syndrome. Nutrients 2019; 11(6): 1256. DOI: 10.3390/nu11061256

[31] Sun L-J, Sun Y-N, Shan J-P, Jiang G-R. Effects of mineralocorticoid receptor antagonists on the progression of diabetic nephropathy. J Diabetes Investig 2017; 8(4): 609-18. DOI: 10.1111/jdi.12629

[32] Lozano-Maneiro L, Puente-García A. Renin-angiotensin-aldosterone system blockade in diabetic nephropathy. Present evidences. J Clin Med 2015; 4(11): 1908-37. DOI: 10.3390/jcm4111908

[33] Perkins BA, Bebu I, de Boer IH, *et al*. Risk factors for kidney disease in type 1 diabetes. Diabetes Care 2019; 42(5): 883-90. DOI: 10.2337/dc18-2062

[34] Ma T, Xu L, Lu L, *et al*. Ursolic acid treatment alleviates diabetic kidney injury by regulating the ARAP1/AT1R signal-

ing pathway. Diabetes Metab Syndr Obes 2019; 12: 2597-608. DOI: 10.2147/DMSO.S222323

[35] Koszegi S, Molnar A, Lenart L, *et al*. RAAS inhibitors directly reduce diabetes induced renal fibrosis via growth factor inhibition. J Physiol 2019; 597(1): 193-209. DOI: 10.1113/JP277002

[36] Rakugi H, Ito S, Itoh H, Okuda Y, Yamakawa S. Long-term phase 3 study of esaxerenone as mono or combination therapy with other antihypertensive drugs in patients with essential hypertension. Hypertens Res 2019; 42(12): 1932-41. DOI: 10.1038/s41440-019-0314-7

[37] Vallon V, Thomson SC. The tubular hypothesis of nephron filtration and diabetic kidney disease. Nat Rev Nephrol 2020; 16(6): 317-36. DOI: 10.1038/s41581-020-0256-y

[38] Zullig LL, Jazowski SA, Davenport CA, *et al*. Primary care providers' acceptance of pharmacists' recommendations to support optimal medication management for patients with diabetic kidney disease. J Gen Intern Med 2020; 35(1): 63-9. DOI: 10.1007/s11606-019-05403-x

[39] Miller AJ, Arnold AC. The renin-angiotensin system in cardiovascular autonomic control: Recent developments and clinical implications. Clin Auton Res 2019; 29(2): 231-43. DOI: 10.1007/s10286-018-0572-5

[40] Falk RS, Heir T, Robsahm TE, *et al*. Fasting serum levels of potassium and sodium in relation to long-term risk of cancer in healthy men. Clin Epidemiol 2020; 12: 1-8. DOI: 10.2147/CLEP.S216438

[41] Hunter RW, Bailey MA. Hyperkalemia: Pathophysiology, risk factors and consequences. Nephrol Dial Transplant 2019; 34(Suppl_3): iii2- iii11. DOI: 10.1093/ndt/gfz206

Received: June 23, 2020 Revised: December 27, 2020 Accepted: December 28, 2020