

ACE and ACE2 in kidney disease

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Key words: Angiotensin-converting enzyme; Angiotensin-converting enzyme 2; Diabetic nephropathy; Kidney disease; Renin angiotensin system

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Core tip: In the kidneys, angiotensin-converting enzyme 2 (ACE2) is expressed in the proximal tubules and less strongly in the glomeruli. The synthesis of inactive Ang 1-9 from angiotensin I (Ang I) and the catabolism of Ang II to produce Ang 1-7 represent the main functions of ACE2. Ang 1-7 reduces vasoconstriction, water retention, salt intake, cell proliferation, and reactive oxygen stress, and also has a renoprotective effect. Thus, in the non-classical renin angiotensin system the ACE2-Ang 1-7-Mas axis counteracts the ACE-Ang II-AT1 axis. This review examines recent human and animal studies about ACE and ACE2 expression in various renal diseases.

Abstract

Renin angiotensin system (RAS) activation has a significant influence on renal disease progression. The classical angiotensin-converting enzyme (ACE)-angiotensin II (Ang II)-Ang II type 1 (AT1) axis is considered to control the effects of RAS activation on renal disease. However, since its discovery in 2000 ACE2 has also been demonstrated to have a significant impact on the RAS. The synthesis and catabolism of Ang II are regulated *via* a complex series of interactions, which involve ACE and ACE2. In the kidneys, ACE2 is expressed in the proximal tubules and less strongly in the glomeruli. The synthesis

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INTRODUCTION

The renin-angiotensin system (RAS) has a significant influence on renal disease progression. Angiotensinogen

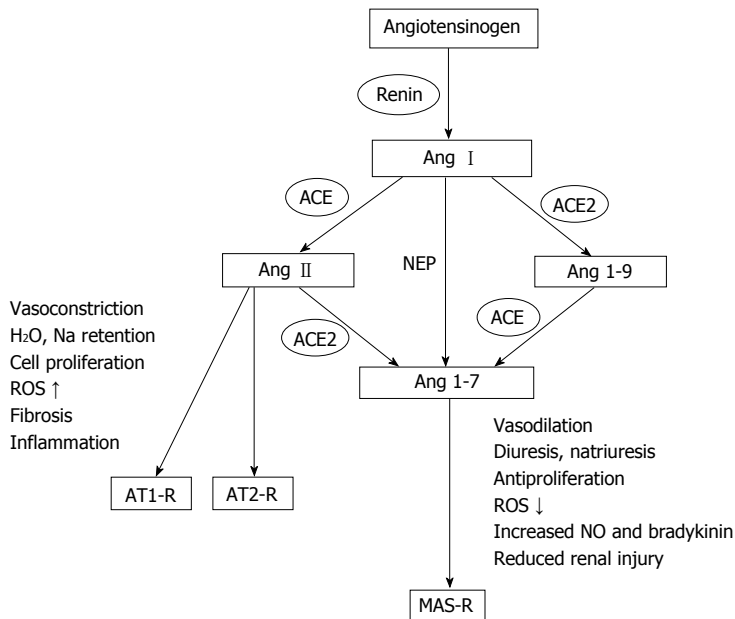


Figure 1 Roles of angiotensin-converting enzyme and angiotensin-converting enzyme 2 in the renin angiotensin system. Angiotensinogen is cleaved by renin to form angiotensin I (Ang I), which is converted to Ang II by ACE. The main function of ACE2 is to synthesize inactive Ang 1-9 from Ang I and to produce the vasodilatory and antiproliferative molecule Ang 1-7 from Ang II. Ang I acts a substrate for neprilysin, which cleaves it to form Ang 1-7. Ang II binds to the Ang II type 1 receptor (AT1-R) and AT2-R. The Mas receptor (MAS-R) is a specific receptor for Ang 1-7. The ACE2-Ang 1-7-MAS axis counteracts the effects of the ACE-Ang II-AT1 axis. ACE: Angiotensin-converting enzyme; NO: Nitric oxide; NEP: Neprilysin; ROS: Reactive oxygen species.

is broken down by renin to give angiotensin I (Ang I), and angiotensin-converting enzyme (ACE) subsequently converts Ang I to angiotensin II (Ang II). In the kidneys, the ACE-Ang II type 1 (AT1) axis (the classical RAS) promotes sodium and water retention, oxidative stress, vasoconstriction, cell proliferation, inflammation, and fibrosis (Figure 1). In 2000, ACE2^[1,2] was discovered, which indicated that the RAS is more complex than was previously imagined. The synthesis of inactive Ang 1-9 from Ang I and the catabolism of Ang II to form Ang 1-7, which binds to the Mas receptor (its specific membrane receptor) and counteracts the effects of Ang II, are the main functions of ACE2^[3,4]. Ang I is also a substrate for neprilysin, which cleave it to produce Ang 1-7^[4]. In the non-classical RAS, the ACE2-Ang 1-7-Mas axis counteracts the effects of the ACE-Ang II-AT1 axis. Specifically, it induces natriuresis, reduced oxidative stress, vasodilation, antiproliferative activity, and diuresis by upregulating the concentrations of nitric oxide and prostaglandins. These processes contribute to protecting the kidneys from damage (Figure 1)^[4-7]. Ang 1-7 is also metabolized by ACE^[4]. Furthermore, accumulating evidence indicates that the ACE/ACE2 ratio regulates the production and accumulation of Ang II and that ACE2 deficiency leads to higher Ang II concentrations^[8-13].

This review examines recent studies about the roles of renal ACE and ACE2 in various conditions (Table 1) and potential treatments for renal disease that target these molecules.

RENAL DISTRIBUTION OF ACE AND ACE2

In mouse kidneys, the apical brush borders of the proximal tubules exhibit colocalization of ACE and ACE2, but this is not the case in the glomeruli^[14]. Whilst ACE2 is expressed in podocytes and less strongly glomerular mesangial cells, only endothelial cells have been found to express ACE^[14].

In agreement with the findings of animal studies, the apical brush borders of the proximal tubules in human kidneys exhibit marked ACE and ACE2 colocalization, and both ACE and ACE2 were also detected in the glomeruli although at lower concentrations^[15,16]. Furthermore, in immunoelectron microscopy studies of human kidneys, it was confirmed that ACE is expressed at the proximal tubule brush borders and in glomerular endothelial cells^[17]. ACE has also been detected within renal vascular endothelial cells^[18]. On the other hand, no previous studies have used immunoelectron microscopy to examine the distribution of ACE2 in human kidneys.

Glomerular ACE2 expression was found to be markedly weaker than that observed in the proximal tubules in both diabetic and normal control kidneys in all of the species examined in the above-mentioned studies.

RENAL ACE/ACE2 RATIO

ACE2 counteracts the effects of ACE by catabolizing

Table 1 Renal angiotensin-converting enzyme and angiotensin-converting enzyme 2 protein expression in various diseases

Diseases	Species	Glomerular ACE	Tubular ACE	Glomerular ACE2	Tubular ACE2	Ref.	Year
Type 1 DM	Rats	↑	↓	↑	↓	Tikellis <i>et al</i> ^[30]	2003
Type 2 DM	Mice	ND	↓	ND	↑	¹ Ye <i>et al</i> ^[9]	2004
Type 2 DN	Mice	↑	↓	↓	↑	Ye <i>et al</i> ^[14]	2006
Type 1 DM	Rats	↑	↑	↓	↑	Moon <i>et al</i> ^[31]	2008
Type 2 DN	Mice	ND	ND	↓	↑	Chodavarapu <i>et al</i> ^[32]	2013
Type 2 DN	Humans	ND	ND	↑	↑	Lely <i>et al</i> ^[34]	2004
Type 2 DN	Humans	↑	↑	↓	↓	Mizuiiri <i>et al</i> ^[15]	2007
Type 2 DN	Humans	↑	↑	↓	↓	Reich <i>et al</i> ^[16]	2007
Primary glomerulopathy	Humans	ND	ND	↑	-	Lely <i>et al</i> ^[34]	2004
IgA nephropathy	Humans	↑	↑	↓	↓	Mizuiiri <i>et al</i> ^[36]	2011
Hypertension	Rats	ND	ND		↓ ¹	Prieto <i>et al</i> ^[41]	2011
Hypertension	Humans		↑ ¹		↓ ¹	Koka <i>et al</i> ^[45]	2008
Nephrosclerosis	Humans	-	↓	-	↓	Wang <i>et al</i> ^[22]	2011
Subtotal nephrectomy	Rats		ND		↓ ¹	Velkoska <i>et al</i> ^[46]	2009
Subtotal nephrectomy	Rats		↑ ¹		↓ ¹	Eräranta <i>et al</i> ^[47]	2012

¹No description about expression pattern of glomerular and tubular ACE and ACE2. DM: Diabetes mellitus; DN: Diabetic nephropathy; ND: Not done; ACE: Angiotensin-converting enzyme; -: No changes.

Ang II to produce Ang 1-7. The balance between the effects of these two molecules affects the renal RAS, and hence, the ACE/ACE2 ratio might represent the key parameter that is driving the regulation of the renal RAS^[8-13]. In healthy conditions, ACE2 activity rises along with ACE activity, but imbalances can develop under disease conditions^[12]. It is suggested that the main priority of the RAS is to achieve an appropriate balance between ACE and ACE2 activity. The ACE-Ang II-AT1 axis has been suggested to have detrimental effects on the RAS, whereas the ACE2-Ang 1-7-Mas axis counteracts the ACE-Ang II-AT1 axis and seems to play a renoprotective role^[19].

Various studies have used kidney injury models to investigate the ACE/ACE2 ratio. For example, Ye *et al*^[9] demonstrated that higher ACE2 concentrations and lower ACE protein concentrations in the renal tubules had renoprotective effects in the early stages of the condition experienced by *db/db* mice (rodent model of type 2 diabetes) without nephropathy. In a recent study, significantly increased concentrations of ACE2 mRNA, ACE mRNA, and Ang II were detected in the plasma and renal cortical tissue of streptozotocin (STZ)-treated rats (rodent model of type 1 diabetes) compared with the control rats^[20]. In addition, the STZ-treated rats exhibited the greater increase in ACE mRNA as opposed to ACE2 mRNA compared with the normal controls^[20]. In rats, the consumption of a high salt diet led to a higher glomerular ACE/ACE2 ratio, resulting in kidney damage and oxidative stress^[8]. Hamming *et al*^[21] reported low sodium intake or ACE inhibition does not affect renal ACE2 despite large changes in renal ACE in healthy rats and they suggested that renal ACE inhibition and dietary sodium restriction affect renal ACE and ACE2 *via* different mechanism.

In humans, kidney biopsies have indicated that hypertensive patients have higher ACE/ACE2 mRNA

ratios^[10]. In addition, we detected high ACE/ACE2 ratios in patients with type 2 diabetes and overt nephropathy; thus, such changes might play a role in renal damage^[15]. In a study of patients with hypertensive nephrosclerosis, Wang *et al*^[22] detected a correlation between the glomerular ACE/ACE2 protein ratio and the extent of glomerulosclerosis and an inverse correlation between the glomerular ACE/ACE2 protein ratio and the estimated glomerular filtration rate (eGFR)^[22]. Conversely, no associations were detected between the tubulointerstitial ACE/ACE2 ratio and histological or clinical parameters^[22].

Battle *et al*^[12] suggested that as ACE and ACE2 are regulated *via* different mechanisms and the ACE/ACE2 ratio could be misleading^[12]. Pohl *et al*^[23] demonstrated that whilst the ACE2 is expressed along the entire renal tubular segment ACE is only expressed in the brush-border membrane of the late proximal tubules and they suggested that surface expression of ACE and ACE2 differed as a function of endocytosis^[23].

Together, the findings of these studies indicate that increases in the ACE/ACE2 ratio induced *via* the ACE-Ang II-AT1 axis have a significant influence on the development of severe kidney damage. On the other hand, renal ACE/ACE2 ratio data should be interpreted carefully, as ACE and ACE2 are regulated *via* independent mechanisms.

CHRONIC KIDNEY DISEASE

In dogs, Mitani *et al*^[24] found that chronic kidney disease (CKD) kidneys exhibited weaker ACE immunoreactivity than normal kidneys and detected a negative association between ACE expression and renal tissue damage. However, both upregulated and downregulated ACE2 expression were detected in dogs with CKD, and ACE/ACE2 immunoreactivity did not exhibit a close relationship with renal tissue damage^[24]. Burrell *et al*^[25] suggested

that renal ACE2 deficiency and a lack of cardiac ACE2 activation might influence the progression of cardiac and renal tissue damage in rats with CKD. Furthermore, the detrimental cardio-renal effects of CKD were only partially abrogated by long-term ACE inhibition^[25]. However, the CKD rats used in their study might not have been a suitable CKD model, as they were killed 28 days after subnephrectomy. Dilauro *et al.*^[26] found that renal ACE2 expression was reduced in a mouse model of early CKD, and this led to increased albuminuria *via* an AT1 receptor-dependent blood pressure-independent mechanism.

In a recent study, Roberts *et al.*^[27] found that hemodialysis CKD patients exhibited lower plasma ACE2 activity than pre-dialysis CKD patients, and female hemodialysis patients displayed lower plasma ACE2 activity than male hemodialysis patients. The lower plasma ACE2 activity exhibited by dialysis patients might slow the catabolism of Ang II, which may be responsible for the high prevalence of cardiovascular disease among these patients^[27]. Human plasma is known to contain an endogenous ACE2 inhibitor^[28]. However, Wysocki *et al.*^[29] reported that this cannot explain the lower plasma ACE2 activity seen in dialysis patients as the removal of the inhibitor by dialysis resulted in higher plasma ACE2 concentrations. Recently, it has been indicated that plasma ACE2 has renoprotective effects in CKD, but more studies of the plasma ACE2 concentrations of pre-dialysis and dialysis CKD patients and healthy subjects are necessary to confirm this.

Diabetic nephropathy

Diabetic nephropathy is a representative disease of CKD and is linked to activation of the renal RAS, resulting in Ang II-induced tubular and glomerular damage. In a study involving diabetic rats, Tikellis *et al.*^[30] observed reduced renal expression levels of ACE and ACE2 mRNA, higher glomerular ACE and ACE2 protein expression levels, and lower tubular ACE and ACE2 protein expression levels at 24 wk after the administration of STZ. Furthermore, the rats' ACE2 protein expression levels rose after treatment with an ACE inhibitor^[30]. In a study examining *db/db* mice without nephropathy, Ye *et al.*^[9] detected higher ACE2 protein expression and lower ACE protein expression in the animal's renal tubules, which resulted in renoprotective effects. However, as the study had involved young *db/db* mice with early stage diabetes, they could not rule out the possibility that the ACE2 expression levels of the mice might subsequently fall as nephropathy developed^[9]. Moreover, they speculated that reduced ACE2 expression and upregulated ACE expression gradually induce kidney damage in diabetes^[9]. Ye *et al.*^[14] also examined the glomeruli of *db/db* mice with established diabetic nephropathy and observed upregulated ACE protein expression and downregulated ACE2 protein expression. In the glomeruli of rats with STZ-induced diabetes, Moon *et*

al.^[31] noted stronger and weaker ACE and ACE2 staining in the glomeruli, respectively, at 8 wk after the administration of STZ, but observed increase in both ACE and ACE2 staining in the tubules compared with the control rats. In a study of *db/db* mice, Chodavarapu *et al.*^[32] detected reduced glomerular ACE2, increased tubular ACE2 and ADAM17, and suspected ectodomain shedding of active renal ACE2 in the urine.

In humans, we observed downregulated ACE2 expression and upregulated ACE expression in both the glomeruli and tubulointerstitium of diabetic patients with overt nephropathy, which led to the diabetic patients having significantly higher ACE/ACE2 ratios than the controls ($P < 0.001$) (Figure 2)^[15,33]. We also detected a positive correlation between the ACE/ACE2 ratio and the serum creatinine, fasting blood glucose, proteinuria, hemoglobin A1c, and blood pressure values and an inverse correlation between and the eGFR ($P < 0.001$)^[15]. In addition, Reichi *et al.*^[16] observed decreased ACE2 expression and increased ACE expression in the glomeruli and tubules in biopsy samples collected from patients with type 2 diabetes-induced kidney disease. Conversely, Lely *et al.*^[34] detected upregulated ACE2 expression in the glomerular and peritubular capillary endothelia in all types of primary and secondary renal disease as well as renal transplant patients; however, they only examined 8 diabetic patients and did not concentrate on the variation in ACE2 expression between biopsy samples from diabetic nephropathy patients and normal renal tissue from patients underwent surgery for renal tumors. In a real time PCR study in which 8 diabetic patients with overt proteinuria were compared with 66 non-diabetic patients with renal disease, ACE mRNA expression was significantly increased, but ACE2 mRNA expression was not significantly changed in the diabetic patients^[35]. The differences between the results obtained in human studies of type 2 diabetic nephropathy and those obtained using *db/db* models of diabetes without nephropathy^[9] might have been due to the different stages of diabetes, as no human studies of early stage diabetes have been conducted.

Taken together, human biopsy studies have suggested that upregulated ACE expression and downregulated ACE2 expression are seen at both the glomerular and tubular levels in established diabetic nephropathy. Whilst most animal studies detected associations between diabetes and increased ACE expression and decreased ACE2 expression in the glomeruli, tubular ACE and ACE2 expression were demonstrated to be significantly decreased and increased, respectively.

Primary glomerular disease

In the study by Lely *et al.*^[34], increased ACE2 expression was detected in the glomerular and peritubular capillary endothelia in all primary renal diseases (including 8 cases of IgA nephropathy, 5 cases of focal glomerulosclerosis, and 18 cases of membranous glomerulopathy), but no

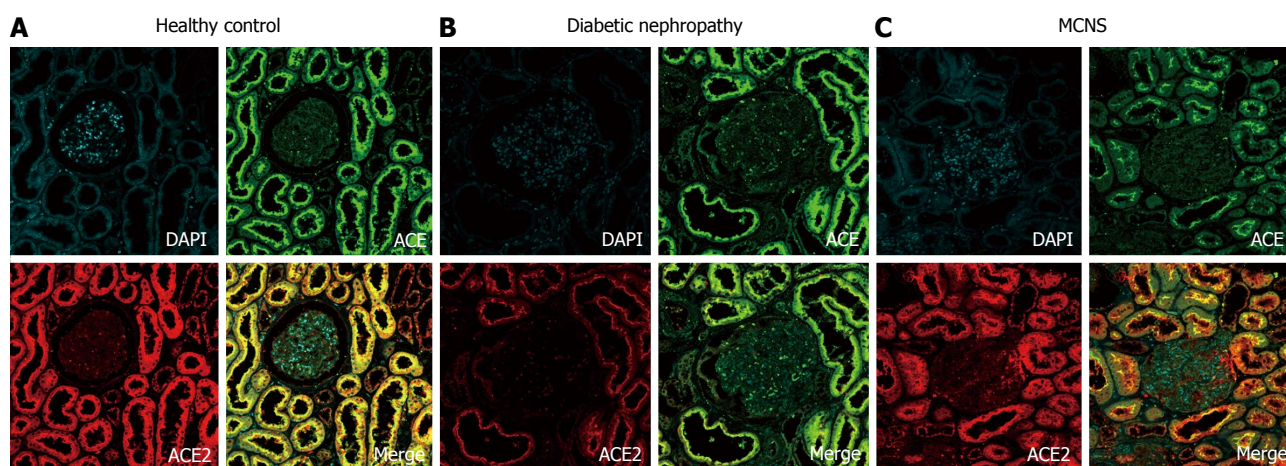


Figure 2 Images obtained with confocal microscopy of triple immunofluorescence staining of angiotensin-converting enzyme (green), angiotensin-converting enzyme 2 (red), and nuclei (DAPI; blue) in kidney specimens. In healthy subjects, marked co-localization of ACE and ACE2 (yellow) was observed in the apical brush borders of the proximal tubules (A). Both ACE and ACE2 were also present in the glomeruli, but the glomeruli exhibited weaker staining than the proximal tubules (A). In diabetic kidneys, stronger ACE expression and weaker ACE2 expression were detected in the proximal tubules, and no marked colocalization of ACE and ACE2 was observed (B); however, similar ACE and ACE2 staining patterns were seen in patients with minimal change nephrotic syndrome (MCNS) and healthy controls (C). Adapted with permission from Mizuri *et al.*^[33]. ACE: Angiotensin-converting enzyme.

variations in ACE2 expression were detected between the different renal diseases. In a previous study, we detected lower ACE2 and higher ACE expression in the glomeruli and tubules of 30 patients with IgA nephropathy than in those of 20 healthy controls^[36]. In addition, patients with membranous nephropathy, but not those with minimal change nephrotic syndrome, also displayed downregulated tubular ACE2 expression^[36]. We excluded patients that were taking ACE inhibitors or AT1-receptor blockers, which might partly explain the differences between our findings and those of Lely *et al.*^[34]. In a study examining kidney biopsies from patients with focal segmental glomerulosclerosis and patients with chronic allograft nephropathy Reich *et al.*^[16] demonstrated that the ACE2 and ACE mRNA levels of these samples did not differ from those of the control samples.

We suggest that upregulated ACE expression and downregulated ACE2 expression represent a generalized response to kidney damage^[36], but further studies of ACE and ACE2 expression in the kidneys based on human renal biopsy samples are necessary to confirm this.

HYPERTENSION

The renal RAS acts independently of the systemic RAS and is suggested to aid blood pressure control^[37]. Imbalances between Ang 1-7/ACE2 and Ang II/ACE expression downregulate Ang 1-7 synthesis and promote renal Ang II expression and hypertension. Crackower *et al.*^[38] found that all hypertensive rat strains exhibited significantly downregulated ACE2 mRNA and protein expression. Tikellis *et al.*^[39] found that the kidneys of spontaneously hypertensive rats demonstrated

significantly upregulated ACE2 expression and activity at birth and that at the onset of hypertension tubular ACE2 expression decreased, but glomerular expression paradoxically rose. Furthermore, in ACE2-deficient mice, a link was detected between severe hypertension and the excessive renal accumulation of Ang II^[40]. In the kidneys of Goldblatt hypertensive rats, upregulated renin expression in the collecting duct was found to be associated with upregulated ANG II and ACE expression and downregulated ANG 1-7 and ACE2 expression^[41]. Samuel *et al.*^[37] found that in obese Zucker rats, renal Ang II expression was upregulated and ACE2-AT(2)R-MasR axis expression was downregulated by high Na consumption. ACE2 increases the synthesis of Ang 1-7 from Ang II, which helps to avoid the excessive accumulation of Ang II^[42]. Furthermore, strategies such as increasing ACE2 activity and promoting Ang II catabolism have been found to be useful for ameliorating hypertension^[43]. In addition, recombinant ACE2 has been demonstrated to increase plasma ACE2 after Ang II infusion, which results in blood pressure and plasma Ang II normalization^[44].

In a study of human renal biopsy samples in which total RNA was examined, the ACE to ACE2 ratio was found to be significantly higher in hypertensive subjects than in the controls^[10]. In a study involving real-time PCR and immunohistochemistry, Koka *et al.*^[45] found that hypertensive nephropathy and hypertensive cardiopathy displayed significantly increased ACE expression and decreased ACE2 expression. Furthermore, Wang *et al.*^[22] reported that hypertensive patients exhibited significantly reduced protein expression levels of ACE and ACE2 in the tubulointerstitium compared with the controls, whereas there was little difference between the glomerular ACE and ACE2 protein expression levels

of the two groups.

The above studies indicate that ACE and ACE2 are important for keeping the RAS in balance, and variations in ACE and ACE2 expression might be associated with hypertension.

SUBTOTAL NEPHRECTOMY

In rats, Velkoska *et al.*^[46] found that subtotal nephrectomy resulted in the lowering of ACE2 activity; however, these changes were reversed by ACE inhibition. In 5/6 nephrectomized rats, Eräranta *et al.*^[47] found that dietary phosphate loading led to greater tissue damage and upregulated renal ACE expression. It can be said that renal ACE2 expression is downregulated after subtotal nephrectomy, which might increase the deleterious effects of Ang II on the kidneys.

CLINICAL IMPLICATIONS OF CIRCULATING ACE2 AND URINARY ACE2

Only a small number of studies have examined the activity of circulating ACE2 in humans. Soro-Paavonen *et al.*^[48] demonstrated that type 1 diabetes patients with micro- or macrovascular disease display higher circulating ACE2 activity, suggesting that ACE2 might act to counteract the effects of such conditions. Soler *et al.*^[49] found that plasma ACE2 activity can be assessed in kidney transplant recipients and is positively correlated with age and the serum levels of urea, γ -glutamyl transferase, glycosylated hemoglobin, creatinine, aspartate transaminase, and alanine transaminase. It is also reported that soluble ACE2 activity correlates with hypertension and soluble ACE concentration decreases, while soluble ACE2 concentration increases in systolic heart failure^[50]. The above studies indicate that plasma ACE and ACE2 levels might be useful biomarkers of the RAS in renal and coronary diseases.

In order to identify biomarkers of kidney disease progression, urine is readily collected and available. Soluble ACE2 has been detected in human urine^[51], which might have been due to the excretion of the protein from renal cells or from plasma *via* glomerular filtration. Using Western blotting and an enzyme-linked immunosorbent assay, we found that patients with diabetic nephropathy had higher urinary ACE2 protein levels than the healthy controls^[52]. In addition, Park *et al.*^[53] demonstrated that the urinary ACE2 concentration is strongly correlated with type 2 diabetes mellitus and is an independent predictor of microalbuminuria. Renal transplant patients with diabetes have also been found to have increased urinary ACE2 levels^[54]. The conversion of membranous ACE2 into its soluble form is partially dependent on tumor necrosis factor- α convertase (ADAM17), which is responsible

for increased ectodomain shedding of ACE2 at least *in vitro*^[52,55]. Patients with renal disease exhibit increased expression levels of ADAM17^[56]. We propose that ACE2 ectodomain shedding is associated with reduced renal ACE2 expression in patients with diabetic nephropathy^[52]. A recent study demonstrated that insulin treatment reduced ADAM17 and ACE2 shedding in the kidneys of diabetic Akita mice^[57]. The above findings suggest that the urinary ACE2 protein level and ACE2 activity are useful as biomarkers of diabetic nephropathy.

ACE2 AS A THERAPEUTIC TARGET IN KIDNEY DISEASE

ACE1 temporarily downregulates Ang II expression, and Ang II receptor blockers increase Ang II levels. Both types of molecule suppress Ang II activity incompletely; therefore, combining RAS inhibitors with ACE2 activators might lead to more complete downregulation of the RAS^[12]. Qudit *et al.*^[58] found that human recombinant ACE2 (hrACE2) slowed the progression of diabetic nephropathy and lowered NADPH oxidase activity and blood pressure. In addition, their *in vitro* study indicated that the protective effect of hrACE2 is derived from upregulated Ang 1-7 expression and downregulated Ang II expression^[58]. Another study demonstrated that whilst hrACE2 treatment was effective at increasing plasma ACE2, it did not affect renal or cardiac ACE2 activity^[44].

Xanthenone (XNT)^[59] and diminazene (DIZE)^[60] are ACE2 inhibitors. Hernández Prada *et al.*^[59] found that the acute *in vivo* administration of XNT to spontaneously hypertensive rats led to improvements in their cardiac function and reduced their blood pressure. Jarajapu *et al.*^[60] proposed that the short-term administration of XNT or DIZE to diabetic patients with complications is not effective at treating diabetic endothelial progenitor cell dysfunction. Moreover, recently Haber *et al.*^[61] confirmed a lack of enhancement of ACE2 enzymatic activity by XNT and DIZE *in vitro* and *ex vivo* experiments in both mice and rat kidney. Therefore, the suggestion that ACE2 activators have supra therapeutic effects on kidney disease than classical RAS inhibitors is speculative at present, although enhancing ACE2 activity might represent a new therapeutic strategy for Ang II overactivity.

CONCLUSION

ACE and ACE2 play significant roles in the RAS, and both enzymes are strongly expressed in the kidneys, where their actions aim to achieve a balance between the ACE-Ang II-AT1 axis and ACE2-Ang 1-7-Mas axis. In addition, the renal ACE/ACE2 ratio seems to have a significant impact on a variety of diseases including diabetes, hypertension, IgA nephropathy, and subtotal nephrectomy.

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