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Review

The role of eicosanoids in renal diseases – potential therapeutic possibilities

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Eicosanoids are biologically active molecules that are created in the process of oxidation of arachidonic acid (AA) which is a constituent of the cell membrane phospholipids. Throughout the years it was evidenced by experiments that the lipid and lipid-derived metabolites play an important role in physiological and pathological processes in the kidneys. They are being considered as biomarkers in detecting acute kidney injury, nephrotoxicity, glomerulonephritis and early stages of diabetic nephropathy because of their participation in inflammatory processes and in oxidative stress. They might be also considered as potential novel targets of therapy. However, the role of eicosanoids is still not fully clear and needs to be explored in future studies. In this brief review, studies on the role of eicosanoids in physiological and pathological conditions, e.g. acute kidney injury (AKI) and chronic kidney disease (CKD), and in different renal replacement therapies, including kidney transplantation, are being discussed.

Key words: eicosanoids, acute kidney injury, chronic kidney disease, dialysis, renal transplantation

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Abbreviations: AKI, acute kidney injury; AQP2, aquaporin 2; AQP3, aquaporin 3; AA, arachidonic acid; ADPKD, autosomal dominant polycystic kidney disease; CVD, cardiovascular disease; CKD, chronic kidney disease; *c*-AUCB, *cis*-4-[4-(3-adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid; CTGF, connecting tubule- glomerular feedback; COX, cyclooxygenase; cAMP, cyclic adenosine monophosphate; CYP 450, cytochrome P-450; cPLA2, cytosolic phospholipase A2; ESRD, end-stage renal disease; eNaC, epithelial sodium channel; EET, epoxyeicosatrienoic acid; EPO, erythropoietin; eGFR, estimated glomerular filtration rate; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LTA4, leukotriene A4; LTB4, leukotriene B4; LOX, lipoxygenase; NSAID, nonsteroidal anti-inflammatory drug; PD, peritoneal dialysis; PGD2, prostaglandin D2; PGE2, prostaglandin E2; PGF2, prostaglandin F2; PGI2, prostaglandin I2; ROS, reactive oxygen species; TXA2, thromboxane A2; TXB2, thromboxane B2; TGF-beta, transforming growth factor-beta; TNF, tumor necrosis factor; XNDI, X-linked nephrogenic diabetes insipidus

INTRODUCTION

Eicosanoids are biologically active molecules generated in the process of oxidation of arachidonic acid (AA) which is a constituent of cell membrane phospholipids. Similarly to AA, the eicosanoid chain is created from 20 carbon atoms. Phospholipase A2 ($cPLA_2$), a cytosolic enzyme, catalyzes the hydrolysis of ester bonds of phospholipids and releases free AA, which is then converted into eicosanoids (Smith & Murphy, 2002). There are three main metabolic pathways involved in the eicosanoid production and catalyzed by the following enzymes: cyclooxygenase (COX), which converts AA to prostanoids (prostaglandins, prostacyclins and thromboxanes), lipoxygenase (LOX) which first converts AA into the hydroperoxyeicosatetraenoic acid (HPETE), and then gives rise to leukotriens, lipoxines and 5-, 12-, 15-hydroxyeicosatetraenoic acid (HETE). And last but not least, AA is converted into epoxyeicosatrienoic acids (EETs) and 20-HETE *via* the cytochrome P-450 monooxygenase (CYP 450) pathway. AA may also undergo non-enzymatic peroxidation to isoprostanes (Burdan *et al.*, 2006; Câmara *et al.*, 2009; Sałata & Dołęgowska, 2014).

Here, we review the role of eicosanoids in physiology and pathological conditions, e.g. acute kidney injury (AKI) and chronic kidney disease (CKD), and in different renal replacement therapies, including kidney transplantation. Major findings in the experimental and clinical studies on the role of eicosanoids are presented in Table 1. Metabolism of arachidonic acid and potential therapeutic possibilities are shown in Fig. 1.

PHYSIOLOGY OF EICOSANOIDS IN THE KIDNEYS

The COX pathway

Among the prostanoids, the most important biological activity in the kidneys is held by prostaglandin D2 (PGD2), prostaglandin E2 (PGE2) and prostaglandin F2 (PGF2) (Sałata & Dołęgowska, 2014). There are 3 forms of cyclooxygenase described in the literature. COX 1 is a constitutive enzyme that takes part in the maintenance of homeostasis, but it is also expressed in pathological conditions, such as cervical tumors and the Alzheimer's disease (Sales *et al.*, 2002; Sales & Jabbour, 2003; Hoozemans *et al.*, 2008). There is a high concentration of this enzyme in the renal collecting duct epithelial cells and vascular smooth muscles cells. COX 2 is an induced isoform of cyclooxygenase and is mainly associated with inflammation. When it comes to kidneys, it is mainly produced in the glomerulus, cells of renal papilla, and especially in the medullary interstitial cells, macula densa and ascending limb of Henle's loop (Câmpean *et al.*, 2003; Burdan *et al.*, 2006; Sałata & Dołęgowska, 2014; Nørregaard *et al.*, 2015). The third isoform – COX 3 – which is a post-transcriptional modification of COX 1, is selectively inhibited by paracetamol and can act as a regulator in the thermoregulatory center of the brain (Schwab *et al.*, 2003; Câmara *et al.*, 2009). PGE2 is the major prostaglandin expressed in the kidneys. It is produced by 3 isoforms of the prostaglandin E synthase-

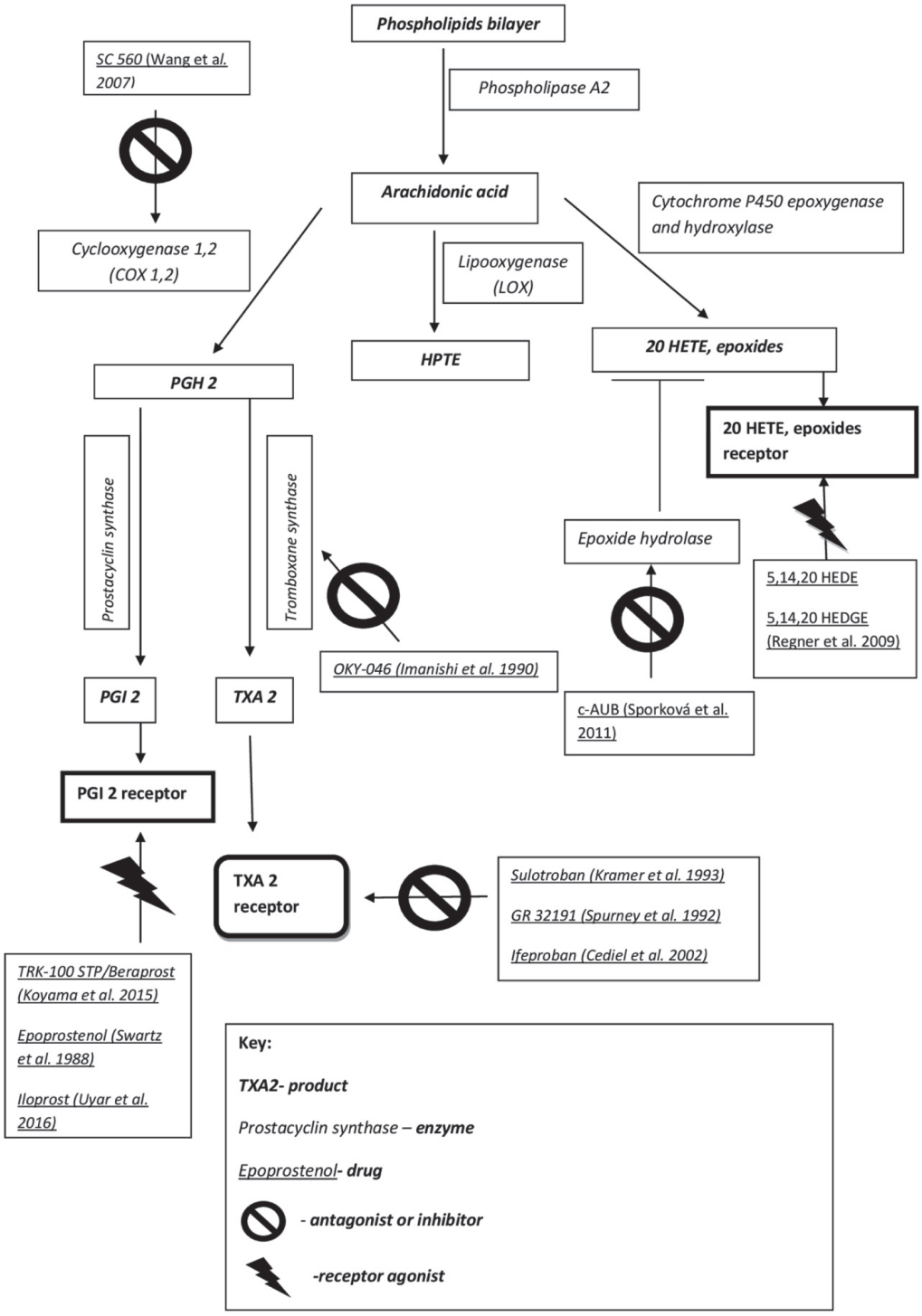

Figure 1. Metabolism of arachidonic acid and potential therapeutic possibilities
Abbreviations: COX, cyclooxygenase; HEDE, 20-hydroxyeicosa-5(Z), 14(Z)-dienoic acid; HEDGE, N-[20-hydroxyeicosa-5(Z),14(Z)-dienoyl] glycine; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LOX, lipoxygenase; PGH2, prostaglandin H2; PGI2, prostaglandin I2; TXA2 thromboxane A2

two microsomal and one cytosolic synthases. PGE 2 regulates the function of kidneys through its four receptors – EP1-4 (Regner, 2012; Nasrallah *et al.*, 2014). They play an important role in inhibiting sodium and water reabsorption, regulation of glomerular hemodynamics and blood pressure (Nørregaard *et al.*, 2015). Stimulation of EP2 and EP 4 receptors can promote urinary concentration. Studies on rats with X-linked nephrogenic diabetes insipidus (XNDI) suggested that EP2 and EP4 agonists increase water channel aquaporin-2 phosphorylation and can partially compensate for a nonfunctional vasopressin type-2 receptor (Olesen *et al.*, 2011). Another study on mice had shown that selective EP4 receptor agonists may reduce all major manifestations of XNDI, includ-

Table 1. Experimental and clinical studies on the roles of eicosanoids in the kidney diseases

First author, year	Model/Population	Main findings
(Badr *et al*., 1986)	Rats	*E. coli* endotoxin may be responsible for decreasing eGFR and filtration fraction by stimulation of the TXA2 biosynthesis and other products of cyclooxygenase metabolism in the kidney.
(Chatziantoniou *et al*., 1990; Badahman & Wilson, 1994; Cediel *et al*., 2002)	Rats	TXA2 may contribute to renal vasoconstriction. Inhibition of TXA2 production results in vasodilatation.
(Chaudhari & Kirschenbaum, 1983)	Rabbits	The concentration of PGE2 in cortical tissue of kidneys is increased in AKI because of its decreased metabolism.
(Jia *et al*., 2012)	Mice	PGE2 increases EPO concentration and decreases anemia after renal mass reduction. It also increases the inflammatory state and provokes renal dysfunction.
(Kramer *et al*., 1993)	Rats	Sulotroban can stop TXA2 dependent vasoconstriction in the early phase of AKI.
(Li *et al*., 2009)	Mice	Selective EP4 receptor agonists may reduce all major manifestations of XNDI, including changes in renal morphology, and may become a new treatment strategy for hereditary nephrogenic diabetes insipidus.
(Makino *et al*., 2002)	Rats	Inhibition of EP1 receptor may prevent the progression of diabetic nephropathy.
(Mangino *et a*l., 1987)	Dogs	12-HETE are biosynthesized in higher amounts by renal cortical tissue which undergoes rejection.
(Mederle *et al*., 2015)	Mice	Decreased activity of COX1 after administration of its inhibitor, called SC-560, leads to lower TXA2 concentration and protects kidneys from AKI.
(Nasrallah *et al*., 2014, 2016; Nasrallah *et al*., 2015; Nasrallah *et al*., 2001; Nasrallah *et al*., 2007)	Mice	Blockade of EP1, EP3 and EP4 PGE2 receptors may be useful in inhibiting renal damage in CKD. COX2-mPGEsynthase 1- PGE2 pathway is related to diabetic nephropathy, hyperfiltration, fibrosis, apoptosis, adiposity, dyslipidemia, and atherogenesis.
(Olesen *et al*., 2011)	Rats	EP2 and EP4 agonists increase water channel aquaporin-2 phosphorylation and can partially compensate for a nonfunctional vasopressin type-2 receptor.
(Park *et al*., 2009)	Rats	20-HETE plays an important role in the development of cysts in ADPKD.
(Regner *et al*., 2009)	Rats	Drugs that affect 20-HETE may be useful in AKI treatment. Administration of 20-HETE analogues (HEDE and HEDGE) results in better urine output and sodium excretion.
(Spurney *et al*., 1992)	Mice	TXA2 is an important agent in decreasing renal function in the model of lupus nephritis.
(Srivastava *et al*., 2014)	Rats	Higher expression of COX 2, EP2 receptor and higher biosynthesis of PGE2 lead to albuminuria due to the change in the structure of podocytes.
(Uriu *et al*., 1994)	Rats	TXA2 plays an important role in the progression of renal injury in diabetes by modulating renin angiotensin system and increasing urinary albumin excretion.
(Vukicevic *et al*., 2006)	Rats	PGE2 decreases tubular necrosis and quantity of apoptotic cells via EP4 receptor. PGE 2 plays an important role in CKD mainly via both, EP 2 and 4 receptors.
(Wang *et al*., 2015)	Mice	Chronic kidney disease predisposes to cardiovascular accidents because of increased concentration of TXA 2.
(Wang *et al*., 2007)	Mice	PGI2 plays an important protective role in AKI caused by endotoxemia, by improving the function of kidneys in PGI2-cAMP-renin pathway.
(Averna *et al*., 2001)	65 patients after renal transplantation	Patients treated with cyclosporine have a higher cardiovascular risk because cyclosporine increases endothelium and platelet activation. Administration of drugs which may decrease or eliminate thromboxane-dependent platelet activation *in vivo* may provide the risk of cardiovascular events reduction in the kidney recipients.
(Courivaud *et al*., 2009)	603 renal transplant recipients	A G>C polymorphism in COX 2 gene promoter leads to decreased COX 2 enzyme production and the concentration of PGE 2 decreases significantly.
(Dreisbach *et al*., 2014)	262 African American patients with CKD	20-HETE plays an important role in the development of cysts in ADPKD.
(Gainza *et al*., 2006)	38 patients on continuous renal replacement therapy	Epoprostenol may be used in renal replacement therapies either alone or with heparin.
(Imanishi *et al*., 1990)	5 patients with chronic vascular rejection after kidney transplantation	Thromboxane A2 synthetase inhibitor, called OKY-046, improved graft function after chronic rejection of kidney.

(Klawitter *et al*., 2014)	110 patients with ADPKD	Blockade of 20-HETE production can be a useful strategy in treatment of ADPKD.
(Koyama *et al*., 2015)	112 CKD patients	Beraprost sodium- PGI2 analogue may improve renal function in patients with CKD suffering from glomerular disease and nephrosclerosis.
(Smith *et al*., 1992)	11 male cyclosporine-treated renal allograft recipients with toxicity symptoms during treatment	Inhibiting the biosynthesis of thromboxane might decrease the nephrotoxicity of cyclosporine.
(Stępniewska *et al*., 2017)	145 patients with CKD: on conservative treatment, on peritoneal dialysis and undergoing chronic haemodialysis	Patients on peritoneal dialysis have higher levels of 12- HETE.
(Swartz *et al*., 1988)	63 ESRD patients with active or recently active bleeding	The efficiency of hemodialysis with epoprostenol was as good as with heparin, in the matter of blood urea nitrogen and creatinine decrease.

Abbreviations: AKI, acute kidney injury; ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; ESRD, end-stage renal disease; EPO, erythropoietin; GFR, glomerular filtration rate; HEDE, 20-hydroxyeicosa-5(Z), 14(Z)-dienoic acid;HEDGE, N-[20-hydroxyeicosa-5(Z),14(Z)-dienoyl]glycine; HETE, hydroxyeicosatetraenoic acid; PGE2, prostaglandin E2; PGI2, prostaglandin I2; TXA2, thromboxane A2

ing changes in renal morphology and may become a new treatment strategy for hereditary nephrogenic diabetes insipidus (Li *et al*., 2009). Another prostaglandin, PGI2, is involved in the maintenance of the GFR level, regulation of renin release and homeostasis of sodium and blood pressure. Last but not least, there is thromboxane A2 which can mediate vasoconstriction induced by angiotensin II and regulates sodium excretion. Results from studies on Wistar-Kyoto and Sprague-Dawley rats had shown that TXA2 might contribute to renal vasoconstriction. Inhibition of TXA2 production, on the other hand, results in vasodilatation (Chatziantoniou *et al*., 1990; Badahman & Wilson, 1994; Cediel *et al*., 2002; Sałata & Dołęgowska, 2014). Moreover, thromboxane B2, which is a metabolite of TXA2, acts as a vasoconstrictor and contributes to angina pectoris and the hepatorenal syndrome *(*Lewy *et al., 1980;* Zipser *et al*., 1983). The natriuretic function of the COX pathway products is regulated via the tumor necrosis factor (TNF) pathway. A furosemide-sensitive Na-K-Cl cotransporter (NKCC2 isoform) in the kidneys accounts for almost all luminal NaCl reabsorption in the thick ascending limb of the Henle's loop. Activity of this transport protein is regulated by humoral factors, but also depends on TN-Falpha which acts in the COX2-PGE2 and COX-independent pathways. Both mechanisms contribute to a decreased expression of NKCC2 and as a result decreased NaCl reabsorption (Ferreri *et al*., 2012). Activity of COX in the kidneys depends on salt loading. COX 2 expression is associated with high-salt loading which has been confirmed in medullary interstitial cells. A high salt concentration does not affect the COX1 expression (Ye *et al*., 2006). Moreover, COX 2 expression is also regulated by PGE 2 action on its EP3 receptor. This mechanism depends on the negative feedback in the Henle's loop (Vio *et al*., 2012).

The LOX pathway

Lipoxygenases are enzymes producing HPETE acids - another type of eicosanoids. HPETE acids are transformed into HETE acids by a glutathione peroxidase. If there is cooperation of two lipoxygenases- 5-LOX and 12- or 15 LOX, lipoxines are being produced. 5-LOX is also a key enzyme in leukotriene A4 (LTA4) production. Next enzyme, leukotriene hydrolase, turns leukotriene A4 into LTB4, which is capable to interact with a LTB4 receptor. Lipoxygenases are located in different parts of kidneys. 5-LOX is commonly expressed in the glomerulus and outer medullary vasa recta. 12-LOX is expressed in the glomerulus. The last one, 15-LOX, is found in the distal part of nephron-collecting ducts. HETE acids take part in blood pressure regulation. LTB4 is known as a chemotactic substance (Dołegowska & Chlubek, 2002). It plays a role in leukocytes' aggregation and adhesion to endothelium and in decreasing the eGFR rate. In contrast, lipoxines are anti-inflammatory molecules. Lipoxines stop the LTB4 dependent adhesion. An increasing concentration of lipoxines plays a key role in limitation of the inflammation process (Reinhold *et al*., 2006; Hao & Breyer, 2007; Sałata & Dołęgowska, 2014).

The Cytochrome P-450 pathway

Cytochrome P-450 hydroxylase and epoxygenase are the final two key enzymes in the eicosanoids' production. Their activity leads to generation of 20-HETE and EETs. These enzymes are located in the renal micro-vessels. 20-HETE and EETs regulate the renal microvascular function. 20-HETE is known as the constrictor of afferent arterioles. EETs work as endothelium dependent hyperpolarizing factors. They activate smooth muscle cells through their impact on large-conductance, calcium-activated K^+ channels in cAMP and protein kinase A dependent mechanisms. In contrast, 20-HETE inhibits the function of these channels. 20-HETE and EETs are also known for their natriuretic function. 20-HETE inhibits activity of the Na^+/K^+-ATPase in the proximal tubule and the Na^+-K^+-$2Cl^-$ co-transporter in the thick ascending limb of Henle's loop. EETs inhibit epithelial sodium channel (ENaC) activity in the collecting duct, lower blood pressure and have renoprotective properties (Hao & Breyer, 2007; Williams *et al*., 2007; Dennis & Norris, 2015; Fan *et al*., 2015; Imig, 2013, 2015). They are degraded by a cytosolic epoxide hydrolase. Use of an inhibitor of this enzyme, called *cis*-4-[4-(3-adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid (*c*-AUCB), in a rat study had shown that such therapy successfully increased the concentration of EETs, improved renal blood flow and increased natriuresis (Sporková *et al*., 2011). Prostaglandins and epoxyeicosatetraenoic acids also mediate the connecting tubule- glomerular feedback (CTGF). CTGF is a mechanism where an increase in sodium concentration in the connecting tubule causes

dilatation of the afferent arteriole. This phenomenon is mediated by prostaglandin E2 which is released from the connecting tubule and binds its EP4 receptor (Ren *et al.*, 2013).

Eicosanoids play an important role in regulating physiological processes, such as the pro-inflammatory response, dilatation of vessels and signal transduction. They influence renal haemodynamics and glomerular filtration rate. Eicosanoids are also involved in the pathogenesis of chronic kidney disease (CKD), acute kidney injury, hypertension, diabetes, metabolic syndrome and cardiovascular disease (CVD), acting as paracrine and inflammatory mediators (Zhao, 2013; Zhao *et al.*, 2015; Chen *et al.*, 2016).

EICOSANOIDS IN THE ACUTE KIDNEY INJURY (AKI)

Hypovolemia

It has been proven that the AKI risk is higher when the nonsteroidal anti-inflammatory drugs (NSAIDs) and COX2 blockers are used. AKI caused by hypovolemia is characterized by higher activity of the renin- angiotensin cascade, which disturbs the balance between vasoconstriction and vasodilatation (Nørregaard *et al.*, 2015). PGE 2 plays an important role in AKI acting via the EP4 receptor and decreasing the quantity of apoptotic cells and tubular necrosis (Vukicevic *et al.*, 2006). Studies in rabbits had shown that the concentration of PGE2 in cortical tissue of kidneys was increased in AKI because of its decreased metabolism. (Chaudhari & Kirschenbaum, 1983). It is considered that thromboxane A2 (TXA2) could be an important agent in AKI caused by hypovolemia. Studies in rats with the use of sulotroban, which is a specific TXA2 receptor antagonist, had shown that sulotroban was able to maintain the eGFR level at physiological ranges even under hypovolemic conditions. According to the presented test, sulotroban could stop TXA2 dependent vasoconstriction in the early phase of AKI (Kramer *et al.*, 1993). Other drugs might be the reason of hypotension-induced AKI. Iloprost is a prostacycline (PGI2) analogue. It is used in the treatment of severe peripheral arterial disease. It is useful and effective because of its vasodilatatory and anti-aggregant functions. However, this drug can be dangerous because of a possibility of causing renal ischemia, which may result in nonoliguric AKI. The risk factors of this condition include smoking and low diastolic blood pressure (Uyar *et al.*, 2016). Still, the same drug can decrease the risk of contrast induced nephropathy by 70% in patients with impaired renal function. Intravenous iloprost administration results in reversing the eGFR rate loss after contrast administration (Spargias *et al.*, 2009). Also, 20-HETE exerts protective effect on the kidney during AKI caused by ischemia. The drugs that affect 20-HETE may be useful in AKI treatment. Administration of 20-HETE analogues to rats results in a better urine output and sodium excretion. In the rat model, 20-HETE analogues act via the blockade of sodium tubular transport (Regner *et al.*, 2009; Roman *et al.*, 2011).

Endotoxemia

Endotoxemia may be another reason for AKI. Studies in adult male Munich-Wistar rats had shown that an E. coli endotoxin can be responsible for decreasing the eGFR and filtration fraction. Stimulation of the TXA2 biosynthesis andother products of cyclooxygenase metabolism in the kidney are the reason for this phenomenon (Badr *et al.*, 1986). On the other hand, it was reported in the mice model that a decreased activity of COX1 after administration of its inhibitor, called SC-560, provides lower TXA2 concentration and as a result protects the kidneys from AKI. It suggests that thromboxane A2 is responsible for the development of AKI during endotoxemia because of COX1 activation (Mederle *et al.*, 2015). In contrast to TXA2, in the mice model, PGI2 plays an important protective role in AKI caused by endotoxemia by improving the function of kidneys in the PGI2-cAMP-renin pathway (Wang *et al.*, 2007).

Obstructive nephropathy

Obstructive nephropathy is a type of AKI caused by the structural or functional hindrance of normal urine flow. During this state, COX2 expression is increased and prostaglandins and thromboxane are being generated. It is considered that PGE2/EP4 receptors might be a possible target in the treatment of obstructive nephropathy. Studies with mice subjected to 24h bilateral ureteral obstruction (BUO) had shown that blockade of COX2 expression results in inhibiting the down-regulation of expression of the water channel proteins aquaporin 2 (AQP2) and aquaporin 3 (AQP3) in the renal cortex of examined animals (Nørregaard *et al.*, 2005; Nilsson *et al.*, 2012; Nørregaard *et al.*, 2015). Another study performed with wild-type mice with unilateral ureteral obstruction (UUO) had shown that the EP4 receptor is a possible target in preventing fibrosis by stopping the inflammatory response (Nakagawa *et al.*, 2012).

EICOSANOIDS IN THE CHRONIC KIDNEY DISEASE (CKD)

PGE 2 plays an important role in CKD mainly *via* both, the EP 2 and 4 receptors. In rat models of CKD, prostaglandins are able to increase GFR and preserve the kidney function. EP2 receptor agonist may possibly increase the survival rate of kidney while the EP4 receptor agonist provided less glomerular sclerosis, better preservation of proximal and distal tubules and blood vessels and less apoptotic cells (Vukicevic *et al.*, 2006). It has been highlighted in mice studies that the chronic kidney disease predisposes to cardiovascular accidents because of increased concentration of TXA 2 which activates its receptors and contributes to the generation of reactive oxygen species (ROS). This results in bigger endothelial activation, leads to microvascular remodeling and might be the reason of cardiovascular accidents (Wang *et al.*, 2015). Another study on mice had shown that TXA2 is an important agent in decreasing the renal function in the model of lupus nephritis. Administration of TXA2 receptor blocker led to higher GFR rate. The use of GR32191-TXA2 receptor specific antagonist reduced the severity of proteinuria and interstitial inflammation. It also decreased the concentration of thromboxane A2 metabolites in urine, similarly to the quantity of IgG glomerular deposits (Spurney *et al.*, 1992).

TXA_2 is mainly synthesized in the blood platelets and leads to their activation, aggregation and vasoconstriction. It is also produced by the kidney mesangial cells and podocytes. In glomerulonephritis, cyclosporine overdosing or kidney graft rejection, it causes a decrease in renal blood flow due to afferent and efferent arterioles constriction, contraction of mesangial cells, injury of the endothelium, deposition of fibrin and extracellular matrix proteins in glomeruli and mesangium, and the progression of kidney failure. Patients with CKD have higher

plasma TXA_2 concentrations than healthy individuals. As a result, patients in advanced stages of CKD are predisposed to thrombotic events and accelerated arteriosclerosis. The concentration of TXA_2 also depends on the type of renal replacement therapy in the end-stage renal disease (ESRD). Haemodialysis treatment causes considerable decrease in the TXA_2 level which appears to be lower than in peritoneal dialysis (PD) and in conservatively treated patients. It is caused by increased oxidative stress during the haemodialysis procedure and platelet impairment in the uremic environment (Zhao & Lint, 2014; Stępniewska *et al.*, 2017).

TRK-100STP, which is a form of drug called Beraprost, a sodium-PGI2 analogue, may improve renal function, especially in patients with CKD suffering from glomerular disease and nephrosclerosis. TRK-100STP is considered to have a potential therapeutic effectiveness (Swartz *et al.*, 1988; Koyama *et al.*, 2015). Another PGI2 analogue – epoprostenol – is regarded as a possible antithrombotic factor. Studies have shown thatefficiency of hemodialysis with epoprostenol was equally good as the one with heparin, in the matter of blood urea nitrogen and creatinine decrease. During hemodialysis with PGI 2, bleeding was reduced up to 50%, especially in th high risk cases. The incidence of hypotension was similar during treatment with PGI2 and heparin. Administration of epoprostenol did not cause significant vasodilatatory episodes. A successful completion of the full, prospectively prescribed hemodialysis with PGI 2 was slightly lower than with heparin (82% versus 93%) (Swartz *et al.*, 1988). It was confirmed that epoprostenol may be used in the renal replacement therapies either alone or with heparin, depending on whether there is a thrombocytopenia and an increased risk of bleeding or a state of hypercoagulability (Gainza *et al.*, 2006). Some studies with mice had shown that blockade of EP1, EP3 and EP4 PGE2 receptors may be useful in inhibiting the renal damage in CKD by slowing the progression of glomerular and tubular injuries (Nasrallah *et al.*, 2001; Nasrallah *et al.*, 2014; Nasrallah *et al.*, 2015).

Diabetes

One of the main causes of CKD is diabetes, which leads to a diabetic nephropathy. PGE2 concentration in diabetes is elevated. COX2-mPGEsynthase 1-PGE2 pathway is connected with diabetic nephropathy, hyperfiltration, fibrosis, apoptosis, adiposity, dyslipidemia, and atherogenesis. Moreover, this pathway plays an important role in the development of a metabolic syndrome in the mice model (Nasrallah *et al.*, 2007; Nasrallah *et al.*, 2016). A study with animal models had shown increased activity of enzymes catalyzing the 20-HETE generation in renal vessels in obesity and diabetes, whichmay be associated with the development of hypertension (Zhao *et al.*, 2015; Chen *et al.*, 2016).

TXA2 plays an important role in the progression of renal injury in diabetes. It modulates the renin angiotensin system and increases urinary albumin excretion. Studies in rats with streptozocin induced diabetes indicated that inhibition of the EP1 receptor may prevent the progression of diabetic nephropathy. Inhibition of this receptor leads to decreased mesangial expansion, decreased transcriptional activation of transforming growth factor-beta (TGF-beta) and fibronectin, and complete suppression of proteinuria. Using EP 1 receptor blocker alone decreases glomerular hypertrophy and proteinuria, while using EP1 blocker and aspirin decreases mesangium expansion as well (Uriu *et al.*, 1994; Makino *et al.*, 2002)

LOX products may also play a role in diabetic nephropathy. A study on mice with streptozocin induced diabetes had shown an increased level of 12/15 LOX and oxidative stress. It was suggested that 12/15LOX inhibition could improve renal function by suppressing inflammation and kidney injury. One of the 12LOX products – 12-HETE is linked to development of hypertension along with diabetic nephropathy (Hao & Breyer, 2007; Klawitter *et al.*, 2014). Patients on peritoneal dialysis, which predisposes them to higher plasma glucose concentration, have also higher levels of 12-HETE. This compound has been proven to have prothrombotic and proinflammatory properties (Zhao *et al.*, 2015; Stępniewska *et al.*, 2017).

ADPKD

Patients with the autosomal dominant polycystic kidney disease (ADPKD) have higher levels of inflammatory activation. It is hypothesized that increased activity of COX, LOX and CYP 450 enzymes, as well as biosynthesis of their products, remains one of the major causes of this condition. In ADPKD the production and concentration of 20-HETE is increased which is related to a lower GRF rate. An increased level of angiotensin II increases the 20-HETE concentration. It is possible that 20-HETE plays an important role in the development of cysts in ADPKD. Because of this, 20-HETE is considered as a possible biomarker of the disease. Moreover, blockade of the 20-HETE production can be a useful strategy in the ADPKD treatment in the rat model (Park *et al.*, 2009; Dreisbach *et al.*, 2014; Klawitter *et al.*, 2014). Even though PGE2 increases erythropoietin (EPO) concentration, and as a result decreases the anemia after renal mass reduction, it also increases the inflammatory state and provokes renal dysfunction. In the cystic kidney rat model, it has been stated that after reduction in renal mass, there was renal blood flow reduction, elevation in blood pressure and proteinuria with no changes in GFR (Kang *et al.*, 2000; Jia *et al.*, 2012). It is regarded that both, the diabetic nephropathy and ADPKD, are syndromes with glomerular hyperfiltration. In these states there is an increased fluid flow shear stress which results in a higher expression of COX 2, EP2 receptor and higher biosynthesis of PGE2. In the rat model, all of these processes lead to albuminuria because of the change in the structure of podocytes (Helal *et al.*, 2012; Srivastava *et al.*, 2014).

EICOSANOIDS IN RENAL TRANSPLANTATION

Presence of urinary PGE2 is considered as a sign of successful renal transplantation. In contrast, a lower PGE 2 production results in a worse graft survival. A G>C polymorphism in the COX 2 gene promoter leads to a decreased expression of the COX 2 gene and thus lower COX2enzyme level results in a significant PGE 2 concentration decrease (el-Sharabasy & el-Naggar, 1991; Courivaud *et al.*, 2009).

Moreover, there is an increased coagulative activation and biosynthesis of thromboxane during kidney transplantation. An increased 20-HETE and TXA_2 synthesis is a sign of ischaemia – reperfusion injury, which is caused by increased oxidative stress during the procedure and results in a delayed graft function after the surgery (Zhao, 2013; Chen *et al.*, 2016). It has been reported that concentration of 11-dehydro-TXB2 – which is an indicator of TXA 2 biosynthesis- is elevated after transplantation. Patients who are treated with cyclosporine have a

higher cardiovascular risk because cyclosporine may increase the activation of endothelium and as the consequence increases the level of TXA 2 and platelet activation. Drugs which decrease the thromboxane dependent activation of platelets might be considered as potentially useful in a group of patients after renal transplantation (Averna *et al*., 2001). Inhibiting the biosynthesis of thromboxane might decrease the nephrotoxicity of cyclosporine (Smith *et al*., 1992). Administration of thromboxane A2 synthetase inhibitor called OKY-046, has improved the graft function in chronic kidney rejection. It also decreased proteinuria (Imanishi *et al*., 1990).

A study in dogs with renal allotransplantation had shown that the LOX products, such as 12-HETE, are biosynthesized in higher amounts by renal cortical tissue which undergoes rejection. This suggests that these products may also take part in the rejection process (Mangino *et al*., 1987).

CONCLUSION

Lipid and lipid- derived metabolites play an important role in the physiology and pathological processes in the kidneys. They are promising biomarkers in detecting acute kidney injury, nephrotoxicity, glomerulonephritis, and early stages of diabetic nephropathy, especially in the context of their participation in the inflammatory processes and oxidative stress. They may be considered as potential novel targets of therapy. However, the role of eicosanoids is still not fully clear and needs to be further explored in the future studies.

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