Kynurenine Pathway in Chronic Kidney Disease: What's Old, What's New, and What's Next?

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ABSTRACT: Impaired kidney function and increased inflammatory process occurring in the course of Chronic Kidney Disease (CKD) contribute to the development of complex amino-acid alterations. The essential amino-acid tryptophan (TRP) undergoes extensive metabolism along several pathways, resulting in the production of many biologically active compounds. The results of many studies have shown that its metabolism via the kynurenine pathway is potently increased in the course of CKD. Metabolites of this pathway exhibit differential, sometimes opposite, roles in several biological processes. Their accumulation in the course of CKD may induce oxidative cell damage which stimulates inflammatory processes. They can also modulate the activity of numerous cellular signaling pathways through activation of the aryl hydrocarbon receptor, leading to the disruption of homeostasis of various organs. As a result, they can contribute to the development of the systemic disorders accompanying the course of chronic renal failure. This review gathers and systematizes reports concerning the knowledge connecting the kynurenine pathway metabolites to systemic disorders accompanying the development of CKD.

KEYWORDS: Tryptophan, kynurenine, chronic kidney disease, thrombosis, neurological disorders, mineral and bone disorders

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Introduction

The essential amino-acid tryptophan (TRP) undergoes extensive metabolism along several pathways, resulting in the production of many biologically active compounds, which exert differential effects on many physiological and pathological processes.[1-3] The vast majority of TRP is metabolized by the kynurenine pathway, leading to the synthesis of the oxidized form of nicotinamide adenine dinucleotide (NAD^+), a coenzyme participating in many cellular processes.[2-4]

In the first step of the kynurenine pathway, TRP is oxidized to N-formylkynurenine using oxidase tryptophan 2,3-dioxygenase (TDO) and two 2,3-indole dioxygenase isoforms (IDO-1 and IDO-2).[5,6] Under physiological conditions, TDO activity is highest in the liver.[7-11] However, the presence of this enzyme has also been confirmed in other organs such as the brain or endometrium. TDO is an enzyme induced by the high substrate availability, as well as glucocorticosteroids, and its activity is allosterically modulated by NADPH in a negative feedback mechanism controlling the kynurenine pathway activity.[7-12] Kynurenic acid (KYNA) activates this enzyme possibly by increasing liver synthesis of another metabolite of this pathway, 3-hydroxyanthranilic acid (3-HAA), which enhances liver TDO.[10,11] IDO-1 occurs in almost all body tissues. Its high activity was detected in small intestine, spleen, lungs, epididymis, kidneys, blood vessel endothelium, and the brain.[10] Under physiological conditions, the IDO-1 expression is low, while interferon-γ (IFN-γ), amyloid peptides, lipopolysaccharide, and other pro-inflammatory factors are potent inductors of its expression and activity.[13,14] IDO-2 has been recently discovered and its physiological significance is still the subject of research. IDO and TDO catalyze the same reaction in parallel in physiological conditions.[10] In the next step, N-formylokinurenine is converted to kynurenine (KYN) by the enzyme formamidase.[6] The presence of KYN has been confirmed in blood, brain, and many peripheral tissues of the body. KYN is metabolized by the 3 pathways, resulting in the formation of KYNA, anthranilic acid (AA), and 3-hydroxykynurenine (3-HKYN).[15-18] The conversion of KYN to 3-HKYN occurs with the participation of kynurenine 3-monooxygenase. The local concentration of 3-HKYN depends on its synthesis and degradation rate as well as transport between different compartments of the body.[19] 3-HKYN is converted to xanthurenic acid (XA) by the kynurenine aminotransferase and to 3-HAA after modification with the kynureninase. The presence of enzymes that catalyze the transformation of both KYN to 3-HKYN and 3-HKYN to XA and 3-HAA was confirmed in almost all tissues of the body.[20,21] 3-HAA is degraded to unstable aminocarboxymuconatesemialdehyde (ACMS), which is enzymatically metabolized by ACMS decarboxylase to aminomuconicsemialdehyde. This compound undergoes non-enzymatic cyclization to picolinic acid, or is transformed non-enzymatically to quinolinic acid (QA).[22] QA is a direct substrate from which NAD^+ is formed.[23-25]

Most of the metabolites of the kynurenine pathway show diverse biological activity and the impact of its biologically active components on body homeostasis cannot be omitted in the course of diseases where significant changes in its activity are observed.[10,26] They play a significant role in the modulation of several physiological, as well as pathological processes, including redox homeostasis, gluconeogenesis, diabetic retinopathy, inflammation, carcinogenesis, and apoptosis.[19,27-36] Numerous KYN derivatives demonstrated toxic effects on the body's cells at higher concentrations. To a large extent, this effect is related to their ability to induce and potentiate

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Table 1. The summary of negative effects of kynurenine pathway metabolites in selected organs and systems associated with disorders accompanying CKD.

ORGAN OR SYSTEM	IMPACT OF KYNURENINE PATHWAY
Kidneys	▪ Elevated KYN level promotes mesangial cells proliferation, while the excess of AA and 3-HKYN significantly suppresses mesangial cells proliferation.[45] ▪ Increased ROS production, induced by 3-HKYN and QA, leads to intensified cell damage and the accelerated rate of apoptosis in renal tissue.[46-49] ▪ QA contributes glomerular fibrosis processes.[45]
Hematopoietic and cardiovascular system	▪ Induction of oxidative stress and AhR activation by KYN and its metabolites increase inflammation and contributes to the development of anemia of inflammation and thrombosis.[50-53] ▪ KYN/TRP ratio is related to carotid intima-media thickness, a presymptomatic predictor of atherosclerosis.[50-52] ▪ In patients with recent ischemic stroke occurs the association between serum KYNA levels and patient mortality.[54,55] ▪ 3-HAA is positively correlated with the concentration of CCL-2 and CCL-4 chemokines. It may be one of the mechanisms involved in the development of atherosclerosis.[56] ▪ KYN increases up-regulates cell tissue factor expression via AhR activation in human arterial smooth muscle cells and regulates thrombosis in an AhR-dependent way.[50,54,57,58] ▪ 3-HKYN levels were independently associated with the presence of cardiovascular disease in uremic patients.[57,58] ▪ Concentration of KYN, 3-HKYN, AA, and QA were positively associated with the level of the crucial factors associated with the development of atherosclerosis, such as like von Willebrand factor, cell tissue factor, thrombomodulin, soluble intercellular adhesion molecule-1, soluble circulating vascular cell adhesion molecule-1, and prothrombin fragments F(1+2). In the end-stage CKD these coagulation factors also showed significant and independent positive associations with increased KYN, 3-HKYN, AA, and QA levels, and AA/KYN and QA/KYN ratios.[40,50,52,53,59-62] ▪ AA also is negatively correlated with the urokinase/urokinase receptor fibrinolytic system in uremic patients.[57,58] ▪ KYN, 3-HKYN, 3-HAA, KYNA, and XA were significantly increased in patients with hypertension, compared to people without this disease.[63] ▪ Elevated KYN concentration is significantly associated with an adverse clinical course in patients with both renovascular hypertension and pulmonary arterial hypertension.[64,65]
Nervous system	▪ QA is the agonist of the N-Methyl-d-aspartic acid receptor and is considered as a brain endogenous excitotoxin. Its neurotoxicity is also connected with pro-oxidant properties, leading to increased lipid peroxidation, and cytoskeletal destabilization, by increasing the phosphorylation of cellular structural proteins in neurons.[66-77] ▪ QA contributes to the increased release of glutamate by neurons, and inhibited its uptake by astrocytes, and block astroglial glutamine synthetase, leading to neurotoxicity associated with excessive glutamate.[78-80] ▪ 3-HKYN contributes to the increase in neuronal cell death rate via apoptosis. The neurotoxicity of 3-HKYN is associated with its pro-oxidative properties.[19,46,81-83] ▪ The excess of 3-HAA is converted to QA, indirectly leading to the intensification of its neurotoxic effects.[84,85]
Pancreas	▪ Accumulation of KYN and its metabolites induced by chronic stress and chronic low-grade inflammation, promotes the development of the type 2 diabetes.[25,86-90] ▪ Formation of the complexes by XA with insulin which reduces insulin activity.[91-97] ▪ 3-HKYN due to its properties can oxidatively damages pancreatic cells.[86,87,90-94] ▪ KYN, KYNA, and other metabolites can also induce pancreatic cells apoptosis probably via AhR activation.[86,91-97]
Skeletal system	▪ KYN and 3-HKYN in bone tissue lead to a decrease in marrow stromal cells cell proliferation and differentiation, though the mechanism directly associated with their pro-oxidative properties, leading to changes in miRNA expression level.[98-102] ▪ Excess of AA and 3-HKYN is associated with reduced viability of BMSC cells *in vitro*.[98] ▪ Peripherally-secreted KYN causes pathological changes in bone structure, probably via the AhR receptor activating the CYP1A1-dependent pathway.[103]

Abbreviations: 3-HAA, 3-hydroxyanthranilic acid; 3-HKYN, 3-hydroxykynurenine; AA, Anthranillic acid; AhR, Aryl hydrocarbon receptor; CKD, Chronic kidney disease; CCL2, Chemokine (C-C motif) ligand 2; CCL4, Chemokine (C-C motif) ligand 4; KYN, Kynurenine; KYNA, Kynurenic acid; QA, Quinolinic acid; ROS, Reactive oxygen species; TRP, Tryptophan; XA, Xanthurenic acid.

oxidative stress, dysregulation of calcium homeostasis and mitochondrial dysfunction in cells, causing severe disorders in cellular metabolism, including disturbances in the functioning of the respiratory chain, leading to cell damage, an increased rate of apoptosis and triggering the inflammatory proces ses.[26-41] This is manifested as a disorder of the homeostasis of various organs and systems.[10,26-41] The authors demonstrated that the toxic effects of KYN and its metabolites are also associated with their ability to activate their physiological receptor, the aryl hydrocarbon receptor (AhR). The AhR belongs to the transcription factors family and has recently been highlighted as playing a key role in regulating the numerous cellular signaling pathways and due to its impact on the maintenance of cellular homeostasis. Therefore, its excessive activation, by the elevated concentration of KYN and its metabolites, may accelerate cell aging processes and their death rate.[26-41]

The effects of the toxic properties of accumulated metabolites of the kynurenine pathway, both through the propagation of oxidative stress by KYN, 3-HKYN, 3-HAA, and QA and overstimulation of the AhR mainly by KYN and KYNA, as well as other mechanisms, such as the formation of complexes with insulin by XA or QA excitotoxic properties, may manifest themselves clinically in the form of systemic disorders, such as anemia, hypercoagulability, atherosclerosis, insulin resistance, kidney tissue damage, neurological disorders, changes in blood pressure, and osteodystrophy (Table 1).[26-36,41-43] Over the years,

Table 2. Changes of kynurenine pathway components in CKD and pathological states accompanying its development with the division into animal models and patients.

COMPOUND	CHANGES IN ANIMAL MODEL	CHANGES IN PATIENTS
Tryptophan	▪ Decrease in plasma, cerebrospinal fluid, kidney, liver, lung, intestine, spleen, brain, and muscle tissue.[44,106,107]	▪ Unchanged or decreased in plasma of CKD patients.[24,50,54,107] ▪ Decreased in plasma of patients with anemia of inflammation and hypertension.[52,63] ▪ Increased or unchanged in plasma of patients with diabetes.[63,86]
Kynurenine	▪ Increase in plasma, cerebrospinal fluid, kidney, liver, lung, intestine, spleen, brain, and muscle tissue.[44,106,107]	▪ Increased in plasma of patients with CKD, anemia of inflammation, diabetes, hypertension, atherosclerosis and increased risk of thrombosis.[50,52,54,56,57,59-61,63,86,111]
3-Hydroksy-kynurenine	▪ Increase in plasma, kidney, liver, lung, intestine, spleen muscle, and brain tissue.[29,44,106]	▪ Increased in plasma of patients with CKD, diabetes, hypertension, atherosclerosis and increased risk of thrombosis.[24,44,50,57,60,61,63]
Kynurenic acid	▪ Increase in plasma, kidney, liver, lung, intestine, spleen, and muscle tissue.[44,106]	▪ Increased in plasma of patients with CKD, diabetes, hypertension, atherosclerosis and increased risk of thrombosis.[50,54,57,59-61,63,86,87]
3-Hydorksy-anthranillic acid	▪ N/A	▪ Increased in plasma of patients with CKD, diabetes, hypertension, atherosclerosis and increased risk of thrombosis.[50,57,60,61,63,87,109,111]
Anthranillic acid	▪ Increase in plasma, kidney, liver, lung, intestine, spleen, and muscle tissue.[44,106]	▪ Increased in plasma of patients with CKD, diabetes, atherosclerosis and increased risk of thrombosis.[50,56,57,59,60,61,63,109]
Xanthurenic acid	▪ Increase in plasma, kidney, liver, lung, intestine, spleen, and muscle tissue.[44,106]	▪ Increased in plasma of patients with CKD, obesity, diabetes, and hypertension.[24,63,86]
Quinolinic acid	▪ Increase in plasma, cerebrospinal fluid, kidney, liver, lung, intestine, brain, and spleen tissue.[44,106,107]	▪ Increased in plasma of patients with CKD, atherosclerosis and increased risk of thrombosis.[24,44,50,54,57,60,61,107,111]

Abbreviations: CKD, Chronic kidney disease; N/A, Data not available.

the excessive supply of these compounds has been observed in patients suffering from a renal failure.[13,14,24,43-44] Therefore, in this review, we present the current state of knowledge linking the kynurenine pathway metabolites to chronic kidney disease (CKD) and main disorders associated with its progression. We focus here on the alterations of the kynurenine pathway activity in the course of CKD and their effect on the severity of inflammatory processes, and functional disorders of organs associated with the development of the systemic disorders accompanying in the course of renal failure.

The alterations of the kynurenine pathway activity in the course of CKD

CKD is a general term relating to heterogeneous disorders in the structure or function of the kidneys affecting about 7% of adults aged 30 and older. The occurrence of at least moderate CKD in the population aged over 65 is estimated to be about 30%.[42,43] Kidney damage leads to a decrease in the excretory, endocrine, and metabolic functions of this organ. Although many indicators of renal damage are nonspecific for the CKD, their early assessment may enable the diagnosis of the disease process before a clinically apparent decrease in renal glomerular filtration.[24,42,43]

In the course of the CKD, the induction of IDO is primarily a consequence of the chronic inflammatory process, especially an increased IFN-γ concentration. An increase in activity of IDO leads to a decrease in tissue and plasma TRP concentration with a simultaneous increase in kynurenine pathway metabolites synthesis.[11,12,39-41] The metabolites of the kynurenine pathway are excreted in the urine.[10,104] They get into the urine during the glomerular filtration process. 3-HKYN, similarly to most of the uremic toxins, is also subject to the tubular secretion process, because its clearance was higher than creatinine, in particular, at low plasma levels, while KYN, due to its low clearance, undergoes resorption in kidney tubules to a significant degree.[24,43,44,104,105] Therefore, the decrease in the glomerular filtration rate (GFR) in the course of the CKD also contributes to their accumulation in the plasma and tissues. The level of KYN, 3-HKYN, XA, KYNA, AA, and QA in the patients' blood and animal tissues (muscles, intestine, lungs, liver, spleen, and brain) positively correlated with the degree of renal insufficiency (Table 2).[24,29,43-44,105-107] In turn, changes in the activity of most of the enzymes of the kynurenine pathway do not correlate with the level of metabolites of this pathway during the progression of CKD.[47] The results of our research confirmed that the activity of kynurenine aminotransferase, kynureninase, 3-hydroxyanthranilate-3,4-dioxygenase, and ACMS decarboxylase is unchanged or even decreased. Only in the case of IDO, TDO, kynurenine 3-monooxygenase, the other authors confirmed a significant increase in their activity in

Table 3. The changes of activity of main kynurenine pathway enzymes in CKD with the division into animal models and patients.

ENZYME	CHANGES IN ACTIVITY IN ANIMAL MODELS OF CKD	CHANGES IN ACTIVITY IN PATIENTS WITH CKD
Tryptophan 2,3-dioxygenase	Increase in liver tissue.[106,107]	N/A
Indoleamine 2,3-dioxygenase	Unchanged in kidney, lung, intestine, spleen, and muscle tissue.[106]	Increase in serum.[54,108]
Kynurenine aminotransferase	Increased in kidney and decreased in liver tissue.[106]	N/A
Kynureninase	Decreased in kidney, and spleen tissue.[106] Increased or decreased in liver tissue.[54,106]	N/A
Kynurenine 3-hydroxylase	Increase in liver and kidney tissue.[106,107]	N/A
3-hydroxyanthranilate-3,4-dioxygenase	Decrease in kidney liver and lung tissue.[106,107]	N/A
Quinolinic acid phosphoribosyltransferase	Decreased in liver tissue.[54]	N/A
Aminocarboxymuconate-semialdehyde decarboxylase	Decreased in liver tissue.[54,107]	N/A

Abbreviations: CKD, Chronic kidney disease; N/A, Data not available.

the course of CKD (Table 3).[54,106-108] It is worth noting that in some cases we discovered some ambiguities. For example, in our studies, unlike the others, we have shown that, in an animal model of CKD, IDO activity in CKD remains unchanged, while kynurenine aminotransferase was increased, but only in the liver tissue.[54,106,108] However, the observed increase level of the above-mentioned TRP metabolites bases on two main causes. Firstly, an enhanced immunological activity leads to an increase in pro-inflammatory factors' levels during the first period of uremia, which causes an increase in the activity of the kynurenine pathway upstream enzymes, and secondly, a decrease in renal excretion of these metabolites due to kidney dysfunction developing during the CKD, leads to their accumulation in peripheral circulation and body tissues of uremic patients.[10,24,29,43,44,56,59,104-110]

Current research indicates that the disturbances in the TRP metabolism and accumulation of its toxic metabolites in the body seem to be one of the most important factors underlying the development of the uremic symptoms, such as neurological disorders, as well as impaired lipid metabolism, and vascular endothelial dysfunction, leading to atherosclerosis, hypercoagulability, bone metabolism disorders, and calcification of the vessels connected with higher prevalence the cardiovascular incidents.[10,26,54,56,59,108-110,112,113]

The role of metabolites of the kynurenine pathway in the development of mitochondrial dysfunction in CKD

In the CKD, increased mitochondrial dysfunction is frequently reported occurrence.[46,47,114-116] Except that, it was proved that the oxidative stress-mediated mitochondrial damage is also an important part of the pathogenesis of diabetic nephropathy.[117] Disruption in mitochondrial function certainly belongs to one of the most important factors responsible for homeostasis disorders at the cellular level responsible for the organs dysfunctions developing in the course of uremia.[46-49,114-121] Disturbances of renal mitochondrial homeostasis could lead to the microvasculature damage, inflammation, fibrosis, and kidney failure. Except that, mitochondrial damage is one of the mechanisms contributing to the development of most of the CKD-associated systemic disorders, because this process is also observed in the cells of all body tissues.[46,47,119-121] Numerous factors are responsible for mitochondrial dysfunction, but at least two are potently related to the kynurenine pathway, overactivated in the CKD course.[46,47] Toxic KYN metabolites may directly interfere with mitochondrial function, for example, by AhR activation. In turn, the excess of 3-HKYN intensifies the reactive oxygen species (ROS) generation, leading to mitochondria function impairment.[19,46] It is associated with a decrease in the activity of peroxisome proliferator-activated receptor-gamma coactivator.[46] It belongs to the family of transcription factors regulating mitochondrial biogenesis and function. Its decrease correlates with the elevated oxidative stress level and may lead to damage to the mitochondrial respiratory chain, alterations in membrane permeability, as well as impairment in Ca^{2+} homeostasis, and mitochondrial antioxidant defense systems.[46,119] Moreover, 3-HKYN disturbs the respiratory chain parameters, decreases the respiratory control index, and lowers the adenosine diphosphate/oxygen and glutamate/malate ratio in mitochondria.[46,47] Research has also shown that an increase in the level of the 3-HAA negatively affects mitochondrial mechanisms, hinders oxygen uptake by mitochondrial respiration with NAD^+-dependent substrates, and uncouples the respiratory chain, and oxidative phosphorylation.[48,49] This is probably due to the increase in ROS concentration associated with its intensified auto-oxidation process accompanying its accumulation in the CKD.

This indicates that the prooxidative properties of KYN and its downstream metabolites in combination with their direct AhR-related toxic effects, result in cellular metabolic disorders and seem to be connected with the induction of increased cell death, via the apoptosis, which leads to the increasing damage

and dysfunction of kidney and other organs, and probably is one of the mechanisms, which contributes, at the cellular level, the development of CKD symptoms and accompanying systemic disorders.[19,49,56,81,109,114-121]

The accumulation of the kynurenine pathway metabolites and functional disorders of renal cells in CKD

Many factors are involved in kidney cell damage in CKD. In turn, most of the metabolites of the kynurenine pathway revealed cellular toxic effects.[11,12] Therefore, their increase observed during renal failure formed the basis for the research on the animal model, which showed that KYN metabolites can regulate mesangial cell proliferation rate and impact gene expression levels in these cells (Table 2).[13] Besides, the increase in level of KYN and its metabolites is associated with the progression of renal failure and glomerular fibrosis. The excess of AA and 3-HKYN suppresses mesangial cells proliferation.[45] In contrast, QA and KYN promoted their proliferation, although this process slows down at their higher concentrations. Besides, QA contributed to the upregulated expression of collagen type-Iα1, type-IVα1, and platelet-derived growth factor-B genes (Table 1).[45] However, the expression level of the hepatocyte growth factor was downregulated, while the insulin-like growth factor-1 was increased with the kynurenine pathway activity. Changes in the level of these factors were accompanied by the increase in the expression of three kynurenine pathway enzyme (kynurenine 3-monooxygenase, kynurenine aminotransferase, phosphoribosyltransferase) in mesangial renal cells.[45] These results suggest that abnormalities in the kynurenine pathway are connected with the dysfunction of mesangial cells and might be associated with the progression of renal failure and glomerular fibrosis. In vitro research also suggests that an accumulation of the above-mentioned KYN metabolites in kidney cells during the CKD progression, through their ability to produce ROS, contributes to increased oxidative stress level severity in renal cells, leading to exacerbated cell damage and the accelerated rate of apoptosis in renal tissue, associated with enhanced inflammatory process within the tissue (Table 1).[45-49]

All this suggests that the accumulation of the metabolites of the kynurenine pathway may contribute to the development of pathological changes in kidney cells, leading to their damage and loss of function, resulting in organ failure. Thus, inhibition of the kynurenine pathway activity in uremic patients could potentially slow or even stop destructive processes in kidney tissue in the course of CKD.

The associations between the overactivity of the kynurenine pathway and inflammatory processes in CKD

Pathological conditions, such as progression of renal failure, the chronic inflammation, and oxidative stress lead to significant changes in the activity of many metabolic pathways, including the kynurenine pathway.[13,14] The accumulation of its metabolites caused by its activation by pro-inflammatory factors contributes to processes leading to the development of many disorders. A loss of kidney function is associated with an increase in the concentration of the inflammation marker, such as neopterin and the activity of the kynurenine pathway.[122,123] Furthermore, research conducted on patients with CKD proved, that IDO activity positively correlated with the severity of CKD (Table 3).[54,56,108] It is also associated with the level of key inflammation biomarkers, such as C reactive protein (CRP) and tumor necrosis factor-α, soluble tumor necrosis factor receptor-1 (sTNFR-1), independently from other parameters, such as age, body weight, and serum creatinine level.[25,54-56,108,109,124] This is another evidence confirming that the activity kynurenine pathway increases with the CKD severity, as a consequence of chronic inflammation. Except IDO, another kynurenine pathway enzyme—kynureninase also plays a pro-inflammatory role in human disease. It has been shown, that its downstream metabolites can induce overexpression of pro-inflammatory factors.[59,109] Kynurenine 3-monooxygenase is known as another crucial regulator of inflammation. Its overactivity leads to the excess of 3-HKYN, contributing to the increase in the apoptosis rate and the enhanced secretion of pro-inflammatory cytokines.[59,109,110] Except that, the concentrations of many kynurenic system components, such as KYN, KYNA, 3-HKYN, AA, and QA, and KYN/TRP ratio, increasing with the severity of CKD, remain independent from serum creatinine level, age, and body weight (Table 2).[24,43,44,59,109,124,125] They are also positively correlated with the levels of before-mentioned inflammatory markers, and other factors, such as cellular adhesion molecules, like soluble intercellular adhesion molecule-1 (sICAM-1) and circulating vascular cell adhesion molecule-1 (sVCAM-1), especially in dialyzed patients.[23,44,56,104-106,109,110] Correlations between them are particularly strong, especially in end-stage renal disease.[23,44,49,54,56,104-106,109,110] Apart from the fact that, the activation of the kynurenine pathway, in the CKD is mainly a consequence of chronic inflammation, some research demonstrated that increase of serum level of kynurenine pathway components, especially KYN, and QA, as well as a QA/KYN ratio, is also associated with oxidative stress markers, such as superoxide dismutase, total peroxide, and malondialdehyde, particularly in patients with end-stage renal disease.[23,26,59,109,110,124,125] Several studies also support the hypothesis that AhR activation by TRP-derived uremic toxins is at least partially involved in worsening inflammation associated with the CKD course. KYN and its metabolites induce T-lymphocytes differentiation, and KYNA activates IL-6 in MCF-7 cells in an AhR-dependent manner.[125]

Interestingly, not all components of the kynurenine pathway present the pro-inflammatory effects. Studies proved, that KYNA, AA, and PA possess anti-inflammatory

properties.[10,126-130] In turn, research on 3-HAA is a source of controversial conclusions. It has been shown that 3-HAA exhibits an anti-inflammatory properties.[49,81,84,126-128] Although Reyes-Ocampo et al. demonstrated that 3-HAA shows a potent pro-inflammatory effect. It is connected with mechanisms that include impairment of cellular energy metabolism, which are not related to early ROS production.[56] However, it may be at least partly related to the fact, that excess of 3-HAA leads to increased QA synthesis, and results in enhanced ROS generation and oxidative cell damage, due to its accumulation.[46,48,49,131] This also may lead to increased secretion of pro-inflammatory factors by damaged cells.

The above reports indicate a significant share of metabolites of the kynurenine pathway in inflammatory processes, including these occurring in the course of CKD. Importantly, among the components of this pathway, some compounds also exhibit anti-inflammatory properties.[84,126-130] Although their degradation products are mostly characterized by pro-inflammatory properties, thus their undue supply leads to an increase in the concentration of their pro-inflammatory metabolites. Therefore, the excessive activation of the kynurenine pathway and increased supply of its metabolites, in general, leads to an exacerbation of the inflammatory process in the body. So, counteracting the accumulation of KYN and its metabolites could potentially be an effective method of controlling inflammation level in uremic patients.

The importance of accumulation of the kynurenine pathway components in the development of anemia atherosclerosis, and thrombosis during CKD progression

As described before, recent studies have proved that the increased activation of the kynurenine pathway, associated with increased oxidative stress, and inflammation levels is related to the risk of the development of anemia, atherosclerosis, and thrombosis in patients with chronic renal dysfunction.[10,25,26,54-56,108,124] The elevated level of 3-HKYN is most frequent in patients with cardiovascular diseases. In the patients with recent ischemic stroke, the authors found that the KYN/TRP ratio inversely correlates with kidney function, and positively with carotid intima-media thickness, a presymptomatic predictor of atherosclerosis. In turn, higher IDO activity is associated with larger carotid plaque, while high KYN and 3-HKYN levels and KYN/TRP ratio are related to oxidative stress markers (Table 1).[54,55]

The disturbances in the peripheral kynurenine pathway activity result in decrease of the TRP plasma level and an increase in the concentration of its toxic metabolites (Table 2).[50-52] The research indicates at least indirect correlations between changes in the level of KYN and its metabolites and the risk of the development of anemia of inflammation in the course of CKD (Table 1).[51,52] Pro-inflammatory cytokines like IFN-γ and tumor necrosis factor-α suppress the growth and differentiation of erythroid progenitor cells, inhibit erythropoietin secretion, and increase hepcidin synthesis.[50-52] Besides, serum concentrations of 3-HKYN, AA, KYNA, XA, and QA are negatively correlated with main hematological parameters in CKD patients.[51,52] Due to the biological properties of KYN metabolites, their long-term accumulation may at least partly worse the parameters of the erythrocytic system in patients. The authors indicated, that in this case, the impact of KYN on hematopoiesis, except induction of oxidative stress mechanisms, may be also connected with AhR-dependent pathway activation.[51-53]

Due to the accumulation of uremic toxins, which show detrimental effects on blood and the vessel wall, the patients with CKD also have an increased risk of thrombosis.[50] This is confirmed by the presence of the positive associations between elevated plasma levels of KYN, 3-HKYN, KYNA, QA, and KYN/TRP ratio, endothelial dysfunction, and the risk of myocardial infarction (Table 2).[60,61] Kynurenine pathway metabolites could be involved in the development of thrombosis by deregulation of plasma coagulation factors, induction of endothelial cell dysfunction, and stimulating cell tissue factor (TF) overexpression, through AhR-pathway (Table 1).[40,50,59,62,132-134] Thus, up-regulation of IDO in coronary atherosclerotic plaques in combination with increasing level of inflammatory factors might contribute to thrombus formation through TF upregulation in activated macrophages (Figure 1).[50,57,59,111]

The research concerning the relationship between the cytokines and kynurenine pathway activity at the background of the CKD-associated complications indicates, that CC-chemokines and KYN metabolites are associated with the accelerated development of atherosclerosis in CKD patients. In these patients there was discovered a significant increase in plasma concentrations of CCL2, CCL4 chemokines, inflammation markers, such as superoxide dismutase, and CRP, as well as several KYN metabolites, like AA, 3-HAA, and KYN/TRP ratio (Table 2).[56] Increase in these compounds, and decrease in the GFR and 3-HAA levels have been recognized as the independent factors significantly associated with increased CCL2 and CCL4 concentrations[56,109] The above-mentioned relationship may represent one of the mechanisms involved in the accelerated atherosclerosis in CKD patients (Table 1).[56] Other studies concerning the effects of changes in the kynurenine pathway activity on endothelial dysfunction and coagulation markers in the CKD patients have shown that an increase in the TRP metabolites level, such as KYN, KYNA, and crucial factors associated with the development of atherosclerosis, like von Willebrand factor (vWF), thrombomodulin (TM), sICAM-1, sVCAM-1 were elevated and positively associated with the stage of CKD and severity of inflammatory processes (Table 2).[59,109] Except that, KYN, 3-HKYN, AA, and QA positively correlated with vWF, and other endothelial dysfunction markers, such as TM, TF, TF-pathway inhibitor system, sICAM-1 and sVCAM-1 level, as well as with prothrombin fragments

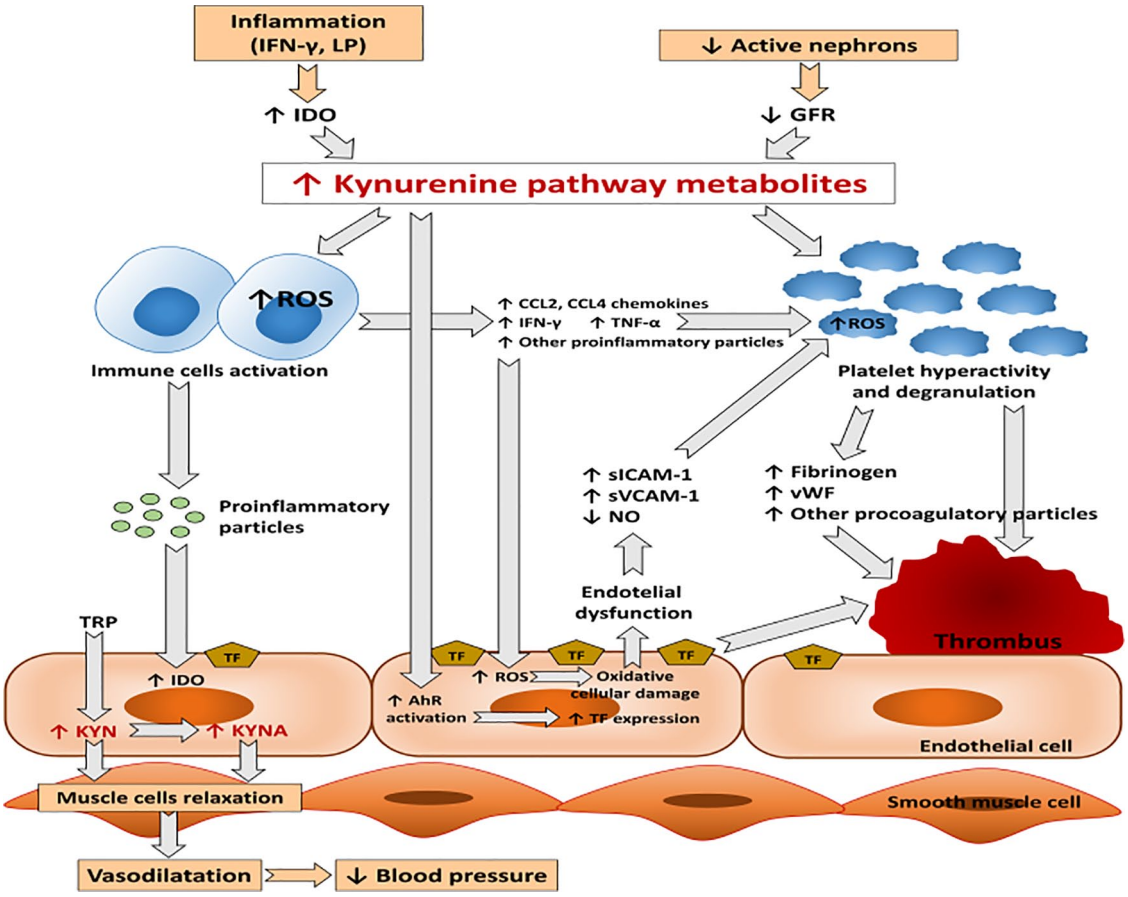

Figure 1. Mechanisms of peripheral kynurenines promoting vasodilatation and thrombosis. Kynurenine pathway metabolites can be involved in the development of thrombosis by deregulation of plasma coagulation factors, induction of endothelial cell dysfunction, and stimulating cell TF overexpression, through AhR-pathway. The up-regulation of IDO in coronary atherosclerotic plaques in combination with the increasing level of inflammatory factors leads to the increased oxidative stress level and the AhR pathway stimulation. It might contribute to thrombus formation through TF upregulation in activated macrophages. Parallel the increase in KYN and KYNA concentration in endothelial cells induce arterial relaxation by activation of the adenylate cyclase and soluble guanylate cyclase pathways. It indicates that the activation of the kynurenine pathway may also represent a local compensatory mechanism counteracting hypertension the increase in blood pressure.
Abbreviations: AhR, Aryl hydrocarbon receptor; CCL2, Chemokine (C-C motif) ligand 2; CCL4, Chemokine (C-C motif) ligand 4; GFR, Glomerular filtration rate; IDO, 2,3-indole dioxygenase; INF-γ, Interferon gamma; KYN, Kynurenine; KYNA, Kynurenic acid; LP, Lipopolysaccharide; NO, nitric oxide; ROS, Reactive oxygen species; sICAM-1, Soluble intercellular adhesion molecule-1; TF, Cell tissue factor; TNF-α, Tumor necrosis factor alpha; TRP, Tryptophan; sVCAM-1, Soluble circulating vascular cell adhesion molecule-1; vWF, von Willebrand factor.

F(1+2) concentration, even in the early stages of the CKD.[40,50,52,53,57-62] Except that, AA was negatively correlated with the urokinase-type plasminogen activator and its receptor levels in uremic patients, also entailing an increase in the prothrombotic potential.[57,58] In the end-stage CKD, the above-mentioned coagulation factors demonstrated additional positive associations with AA/KYN and QA/KYN ratios, not observed in the early stages of CKD.[135-137] This confirms the links between enhanced coagulation in uremic patients and the activation of the kynurenine pathway, especially in the advanced stages of the CKD. KYN and its metabolites are also associated with hyperfibrinolysis, which also is causally related to the development of atherosclerosis and cardiovascular disorders (Table 1).[135-138]

IDO was in turn recognized as a novel marker of immune activation in the early stages of atherosclerosis.[59] Moreover, it is a potential novel contributor to vessel relaxation and metabolism in systemic infections, also activated in acute severe heart attacks.[139-141] Changes in its activity suggest that the kynurenine pathway plays a key role in the increased prevalence of cardiovascular disease due to the presence of a positive relationship between IDO-dependent kynurenine pathway activation, and cardiovascular disease prevalence in end-stage renal disease patients.[57,139-141]

The above-mentioned associations indicate the relationships between kynurenine pathway activity, endothelial dysfunction, hypercoagulability, and the progression of atherosclerosis in CKD.[58] The significant increase in these parameters observed in uremic patients, even at the early stage of the disease, suggests that hypercoagulability and atherosclerosis belong to the early complications of the CKD. It also indicates that 3-HKYN levels were independently associated with the presence of cardiovascular disease in uremic patients (Table 1).[57,58]

Not all metabolites of the kynurenine pathway have a proatherogenic effect. The inverse correlations have been observed between KYNA levels and cardiovascular disease prevalence in dialyzed end-stage renal disease patients. The authors demonstrated that KYN, KYNA, and QA levels are significantly higher in peritoneal dialysis (PD) patients than in healthy ones, whereas TRP was lower in these patients. PD patients with cardiovascular disease have lower KYNA levels compared to patients without heart disease. Therefore, low KYNA levels were independently associated with the presence of cardiovascular disease in PD patients.[142,143] Other important relationships were observed in another study concerning patients undergoing continuous ambulatory PD. In this case, KYNA concentration, and the KYNA/KYN ratio were significantly lower in patients without cardiovascular disease, and they were positively associated with homocysteine levels in all continuous ambulatory PD patients, and with a hyperhomocysteinemia severity in patients with cardiovascular disease.[143-145] These findings are in agreement with previous reports concerning a KYNA protective effect on the vascular wall epithelium against the homocysteine-induced inhibition of endothelial cell proliferation and migration. KYNA mechanism of action appears to be associated with the inhibition of homocysteine-induced cytotoxicity.[143,144] They also indicate, that KYNA may be liberated from epithelial cells in response to a high level of homocysteine or cellular damages caused by the excess of this compound.[143-145] Another anti-atherosclerotic mechanism related to kynurenine pathway activity seems to be related to 3-HAA activity. Its increase in plasma concentration was associated with a decrease in cholesterol and triglyceride levels, inhibition of the uptake of oxidized low-density lipoproteins by macrophages, and the resultant inhibition of atherogenesis in the murine model.[146-148]

The above reports indicate that the above-mentioned TRP metabolites are independently and potently associated with the development of anemia, atherosclerosis, and thrombosis in renal disease patients. They confirm the occurrence of links between disorders in hematopoietic and vascular systems in uremic patients and the activity of the kynurenine pathway. As most of them have a detrimental effect on these systems, they indicate the validity of therapeutic steps aimed at protecting patients against the effects of the accumulation of its metabolites in the course of CKD and research towards more effective methods of reducing the concentration of KYN and its metabolites in patients exposed to their harmful impact.[138-143,149-166]

The importance of the kynurenine pathway metabolites in blood pressure alterations in CKD

Kidney disease is the most common cause of secondary hypertension. Functional or structural renal damage is a much more common cause of hypertension than previously thought. CKD leads to impaired renal sodium and water excretion and excessive secretion of decongestants in the kidneys, with insufficient production of vasodilators.[43,64,65] CKD is the cause of the increased activity of the sympathetic nervous system and hormonal disorders leading to an increase in blood pressure.[43,65] However, the issue of the impact of metabolites of the kynurenine pathway on blood pressure remains a controversial matter. Studies concerning the impact of components of this pathway on blood pressure are still scarce. Only several studies show that the pathobiology and development of renovascular hypertension and pulmonary arterial hypertension are associated with the increase in the kynurenine pathway activity.[64,65] In turn, the Hordaland Health Study proved that hypertensive patients have significantly increased KYN, 3-HKYN, 3-HAA, KYNA, and XA plasma concentrations compared to healthy people (Tables 1 and 2).[63] The alterations of these pathway activity remain in close relationship with blood pressure values, as well as with the activity of pro-inflammatory mechanisms. Also, changes in angiotensin II concentration level and vascular remodeling processes suggest the presence of relationships between them and KYN metabolites levels.[65] Elevated KYN concentration is associated with an adverse clinical course in patients with both renovascular hypertension and pulmonary arterial hypertension (Table 1).[64,65] As the progression of CKD is often accompanied by the development of renovascular hypertension, we could assume that the accumulation of the kynurenine pathway components in the course of renal failure may stimulate the development of this form of hypertension.[64] However, we cannot forget that the impact of KYN and its metabolites on blood pressure remains not fully understood because some studies suggest that certain metabolites of the kynurenic system play a previously unknown contradictory role in the field of vascular tension.[64,65] It has been proved that KYN may also induce arterial relaxation by the activation of the adenylate cyclase and soluble guanylate cyclase pathways. An intravenous administration of KYN transiently and in a dose-dependent way decreases the mean blood pressure in hypertensive rats *in vivo*.[65] In turn, the increase in IDO activity in endothelial cells in response to worsening inflammation during the CKD is recognized as a factor stimulating vasodilation and a contributor to hypotension.[167,168] It suggests that IDO up-regulation may represent a local compensatory mechanism counteracting the increase in blood pressure. The other data from studies both on animals and patients indicate that KYNA and XA may also have vasorelaxation and antihypertension properties (Figure 1). [143,144,169]

These data indicate that the components of the kynurenine pathway can play diverse, sometimes opposite roles in the development of hypertension. Their accumulation in the course of chronic renal failure seems to be at least partly associated with the development of CKD-related hypertension. The amount of research concerning this topic is scarce, while some studies demonstrated that certain kynurenine pathway metabolites may be also components of antihypertensive compensatory mechanisms. Therefore, this issue

requires further research, to better understand the impact of alterations in the kynurenine pathway activity on the development of hypertension.

The impact of the accumulation of the kynurenine pathway metabolites on the development of neurological disorders accompanying the progression of CKD

TRP metabolism via the kynurenine pathway leads to the formation of several neuroactive substances, including KYN, 3-HKYN, KYNA, 3-HAA, AA, and QA. They are involved in the pathogenesis of numerous neurodegenerative diseases.[19,29,30,170] Also, the development of chronic renal insufficiency, accompanied by the accumulation of these compounds, is associated with the worsening of neurological disturbances.[29,30,43] Alterations in the TRP, KYN, 3-HKYN, and QA concentrations were observed within CNS homogenates in uremic rats.[27,29,30,171,172] These substances seem to be responsible for neuronal dysfunction in uremia, especially 3-HKYN, QA, and indirectly AA.[29,30,171] QA is the N-Methyl-d-aspartic acid (NMDA) agonist, while 3-HKYN neurotoxicity is related to its high redox-activity. KYNA, a glutamate antagonist possibly participates in neurodegenerative disorder, as a neuroprotective agent.[171,173] Also AA revealed beneficial effects in neurological disorders related to an enhanced inflammation. However, at the high levels, it becomes a source of increased QA synthesis.[173] Accumulation of the neurotoxic TRP metabolites in the CNS results from the enhanced entry of serum KYN to CNS, resulting from its increase accompanying renal failure, as well as from the elevated activity of IDO, kynurenine 3-monooxygenase, and anthranilate oxidase, and decreased of ACMS decarboxylase in the brain, associated with the increase of systemic inflammation. As a result, the supply of before-mentioned neurotoxic KYN metabolites in the CNS increases, although their brain uptake is very limited.[27,29,30,107,171,173-177]

Within the CNS, QA is produced and released by penetrating macrophages and activated microglial cells. Both types of cells play an important role during neuroinflammatory process development.[27,66,67] Increased release of QA in the course of CKD is related to the above-mentioned changes in the KYN concentration and the activity of the kynurenic system enzymes, observed in the course of CKD.[27,29,30,107,171,174-177] QA belongs to the agonists of the NMDA receptor and is considered as a brain endogenous excitotoxin. The activity and toxicity of QA depends on its levels. In high levels, it launch a chain of detrimental effects, which may induce functional disorders or even apoptotic death of neurons.[66-68] The toxic effect of QA is also connected with its pro-oxidant properties responsible for increased lipid peroxidation, and cytoskeletal destabilization, by increasing the phosphorylation of cellular structural proteins in neurons.[69-77] The gliotoxic effects of QA amplify the inflammatory response. It contributes to the increased release of glutamate by neurons, inhibition of its uptake by astrocytes, and blocks astroglial glutamine synthetase, leading to neurotoxic effect associated with excessive glutamate supply in the brain.[78-80] It affects neurons located mainly in the hippocampus, striatum, and neocortex, due to the selectivity of QA for the specific types of NMDA receptors occurring in those regions.[30,63-80,148-183] Excessive synthesis of QA, along with the exacerbation of the inflammatory process, leads to overexcitation of the NMDA receptor, causing an increased influx of Ca^{2+} into the neuron, which triggers the activation of destructive enzymatic pathways, including protein kinases, phospholipases, nitric oxide synthase, and proteases in neurons (Table 1).[27,131,184] They intensify the decomposition of crucial proteins in the cell and increase nitric oxide levels, leading to an apoptotic response of oligodendrocytes, neurons, and astrocytes connected with intensified NMDA-dependent ROS formation.[185] Finally, the accumulation of QA can trigger neuronal lesions linked to excitotoxicity, including convulsions.[186]

3-HKYN is another metabolite of the kynurenine pathway well-known for its neurotoxic properties, due to its pro-oxidative potential.[19,19,81,82] Its excessive concentration in the CNS leads to increased ROS generation.[19,19,81,82] Similarly to QA, it contributes to the increase in neuronal cell death rate via apoptosis.[19,46,82] The activity of endogenous xanthine oxidase is involved in 3-HKYN-induced H_2O_2 generation, and exacerbates cell damage.[46,81-83] Furthermore, 3-HKYN can reduce copper to generate superoxide and H_2O_2 in a copper-dependent manner.[46] The level of KYN and 3-HKYN were elevated both in the plasma and different brain regions of the uremic animals. KYN concentrations were higher in the cerebellum, midbrain, and cortex compared to the healthy ones, while 3-HKYN in the striatum and medulla than in other structures.[187] This data suggests that the CKD results in deep disturbances on the kynurenine pathway in the CNS, which seem to be at least partly responsible for neurological abnormalities observed in uremia.[30] The direct metabolite of 3-HKYN, 3-HAA also revealed the ability to generate ROS such as hydrogen peroxide and superoxide. However, it is also a highly efficient scavenger of free radicals.[46,48,49] Under physiological conditions, 3-HAA is regularly auto-oxidized to unstable ACMS, which is converted to QA, which, in turn, is transformed to NAD^+, and the concentrations of these compounds remain at the level that does not disturb homeostasis in the CNS.[84,85] In turn, in the course of CKD, their accumulation both directly, and by increased QA synthesis leads exacerbation of neuronal apoptosis rate associated with an increased oxidative stress level and NMDA overexcitation (Table 1).[46,82,85,131,184]

Among the neuroactive KYN metabolites, KYNA is well-recognized as a neuroprotective agent. It abolishes the neurotoxic effects of QA due to its ability to block glutamate receptors, especially the NMDA receptor where it inhibits the actions of the glycine coagonist.[188-190] It also counteracts neurotoxicity through its potent antioxidant activity affecting glutamate signaling through scavenging free radicals. It means that it is also able to counteract the prooxidative effects of 3-HKYN and 3-HAA in physiological states.[74,127,190] Except that, in vitro studies proved that it can block the effects of

exogenously applied acetylcholine or nicotinic receptor-selective agonists, as well as excitatory postsynaptic potentials (EPSPs) mediated by the activation of cholinergic, and nicotinic receptors in hippocampal interneurons.[74,190] KYNA reduced the amplitude of these potentials and was more potent in blocking the nicotinic than the glutamate-mediated EPSPs.[190] During physiological conditions, there is a balance between KYNA and neurotoxic KYN metabolites concentrations. In chronic inflammatory states, such as CKD, the KYNA level is decreased, while 3-HKYN, 3-HAA, and QA are increased. In turn, AA may have beneficial effects in neurological disorders, associated with an inflammatory state. However, its molecular mechanism received relatively little attention so far. Although its excess also leads to an increase in QA synthesis, thus it may indirectly contribute to the exacerbation of neurological symptoms.[173] The chronic imbalance between neurotoxic and neuroprotective kynurenine metabolites may potentiate brain damage.[188]

The presented reports clearly show that the accumulation of KYN and its metabolites, associated with the exacerbation of inflammatory processes and impaired renal excretory capacity, have a significant impact on the neurons damage and development of neurological disorders in the course of CKD. Although some of the intermediate metabolites of the kynurenine pathway has a neuroprotective effect, the excessive activation of this pathway leads to an increase in the imbalance between its neurotoxic and neuroprotective metabolites, resulting in an accumulation of neurotoxic ones. This explains why the inhibitors of the kynurenic system enzymes are considered as potential therapeutics in neurodegenerative disorders.[159-166]

Accumulation of the components of the kynurenine pathway in CKD and the development of diabetes mellitus

CKD can be a consequence or complication of all other civilization diseases, from obesity through diabetes to cardiovascular diseases.[39] It has been also proved that diabetic patients have also increased TRP degradation via the kynurenine pathway, resulting from increased activity of IDO, kynurenine 3-monooxygenase, kynureninase and kynurenine aminotransferase, leading to elevated serum concentration of diabetogenic KYN, 3-HKYN, 3-HAA, KYNA, XA, and AA in comparison with healthy people (Tables 1 and 2).[25,63,86-90] It seems to be related to the increase in the activity of the enzymes of the kynurenine pathway accompanying long-lasting inflammation.[25,86] This relationship prompted researchers to study if the accumulation of uremic toxins, including KYN and its metabolites induced by chronic stress and chronic low-grade inflammation can be one of the mechanisms promoting the development of insulin resistance and type 2 diabetes.[86-89] They proved that KYN and its metabolites may directly contribute to the higher incidence of insulin resistance due to their pro-inflammatory and pro-oxidative properties.[10,19,26] In turn, an increase in 3-HKYN and its metabolite XA concentrations, observed in the course of CKD, is recognized as a factor disturbing insulin secretion and activity, and therefore glucose homeostasis in uremic patients.[86,87,90-93] Therefore, it can be concluded that the changes in the kynurenine pathway activity observed in the course of renal failure may also contribute to the development of diabetes.[86,90-93] Experimental studies suggested diabetogenic effects of numerous kynurenine pathway metabolites, such as XA-induced hyperglycemia, due to the formation of the XA-insulin complex, which reduces insulin activity, and impairment of biosynthesis of insulin by KYN, and KYNA, probably related with the AhR activation, and by 3-HKYN and QA, mainly associated with the induction of oxidative damage of pancreatic cells (Tables 1 and 2).[86,90-97] Therefore, it can be concluded that the changes in the kynurenine pathway activity observed in the course of renal failure may also contribute to the development of diabetes.[86,90-94]

The potent changes in TRP metabolism with the accompanying rise in several bioactive KYN metabolites concentrations also correlates with the severity of kidney function disorders in type 2 diabetic patients with diabetic nephropathy symptoms.[86] It is worth recalling, that the concentration of KYN in the course of CKD was positively associated with circulating pro-inflammatory factors level, such as CRP, tumor necrosis factor-α, independently of changes in glomerular filtration in the kidney.[25,56,55,86,93,124] These data indicate the existence of links between the systemic effect of accumulation of KYN and its metabolites and the inflammatory process in the progression of chronic renal insufficiency accompanying diabetic nephropathy development in type 2 diabetes.[25]

Thus, the chronic stress, as well as chronic inflammation, even low-grade, directly activate enzymes of the upstream steps of the kynurenine pathway and divert downstream steps of this pathway from the biosynthesis of NAD towards the formation and accumulation of diabetogenic downstream metabolites. This combined with the accumulation of uremic toxins, including KYN and its metabolites, due to impaired excretory function of the kidneys seems to be related to an increased risk of type 2 diabetes development.[25,86,91-97]

Associations between the increased activity of the kynurenine pathway and bone metabolism disorders in the course of CKD

Abnormalities in endocrine, mineral, and bone metabolism represent the most complex complications during the CKD progression. Pathological changes in the bone tissue, as the one of the most commonly occurring during the CKD progression, have been classified as the CKD-mineral and bone disorder (CKD-MBD).[42,191,192] Evidence for the accumulation of the metabolites of the kynurenine pathway in the course of chronic renal insufficiency and their impact on bone tissue, prompted some researchers, including our team, to deal with the topic of connections between the CKD, changes in kynurenine system activation and bone metabolism.[31,35,98,187,192-194]

In vitro studies have proven, that the accumulation of KYN and 3-HKYN in bone marrow stromal cells (BMSCs) have been associated with a decrease in cell proliferation and differentiation, though the mechanism which is directly mediated by their pro-oxidative properties. Microarray analysis identified 50 upregulated, and 36 downregulated micro RNAs (miRNAs) in KYN-treated BMSCs. Differentially expressed miRNA includes, among other miR-1281, miR-330-3p, let-7f-5p, and miR-493-5p, important for proper BMSCs proliferation and differentiation.[98-102] Upregulated miRNA fragments are related to glutathione metabolism critical for removing oxidative species (Table 1).[98] It can be assumed that these changes in miRNA expression pattern are the response to KYN-mediated increases in oxidative stress level, disrupting cellular processes important in normal metabolism.[98-102] The high levels of AA and 3-HKYN were also associated with reduced viability of the BMSCs in vitro (Table 1).[98] The increased production of the above-mentioned metabolites may exert cumulative negative effects on BMSCs metabolism and increased their susceptibility to oxidative damage.[99-102] It is known that elevated plasma concentration of KYN, of AA, and 3-HKYN observed in the animal model of CKD, may be associated with an increased risk of femoral and hip fractures and a decrease in bone densitometry parameters.[35,103,193,194] The concentration level of these compounds positively correlates with IDO activity, which in turn is dependent on the severity of inflammation in the body. This allows to conclude that there is a link between inflammation-induced kynurenine pathway overactivity and risk of bone fractures.[35,195]

Research conducted previously by our team established the ability of KYN to modulate metabolic processes in bone tissue. Kalaska et al proved that KYN present in the CNS positively influences on bone formation processes, while peripherally-secreted KYN causes pathological changes in bone structure. Our team observed a positive correlation between KYN in the frontal cortex and TRP in the hypothalamus and striatum and the main parameters of bone biomechanics and geometry, as well as negative between KYN in serum and bone biomechanical and geometric parameters.[103,187] The impact of the KYN in the CNS may be associated with the role of the hypothalamus in the bone regulation and suggests that the frontal cortex and striatum may also take part in the regulation of bone changes in the CKD. However, the exact mechanism associated with the protective effect of KYN in the brain on bone metabolism remains unexplained.[187] The effect of peripheral KYN on bone tissue may be explained by the interaction of KYN with the AhR. Its activation may lead to unfavorable changes in bone metabolism through induction of CYP1A1 transcription and activation of the CYP1A1-dependent pathway (Table 1).[103] Stimulation of the AhR in osteoblasts leads to the inhibition of their proliferation and differentiation in a collagen-induced arthritis mouse model by activation of the signaling pathway dependent on extracellular signal-regulated kinases.[196] In turn, its activation in osteoclasts leads to an increase in their activity and the bone resorption processes.[197] It indicates, that AhR may be crucial in maintaining adequate bone mass and the altered bone properties are highly dependent on the functional AhR. Recent research also indicates the negative effects of exogenous AhR agonists on bone strength in the animal model.[198] We cannot exclude that another pathological mechanism related to the influence of KYN on bone metabolism is responsible for the observed changes. The other authors proved that the elevated level of peripheral KYN in the CKD also led to changes in the activity of other signaling factors, such as the receptor activator of nuclear factor-κB ligand/osteoprotegerin axis, extracellular signal-regulated kinases, and histone deacetylase-3 or runt-related transcription factor 2 expression levels.[103,194,199] We also do not exclude that the observed process was induced by the accumulation of other AhR ligands. Many of them, such as indoxyl sulfate, circulate in the serum of the CKD patients.[200] However, the AhR gene expression in the bone tissue was positively associated with serum KYN concentration, and negatively with the main parameters of bone biomechanics, geometry, and density.[103] It indicates that the above-described mechanism appears to be at least partially complementary to the effect of bone KYN, due to similar correlations between bones and serum KYN levels, and bone densitometry parameters (Figure 2).

It is worth noting that not all metabolites of the kynurenine pathway exert a peripherally unfavorable effect on the bone formation processes. The picolinic acid, one of the end products of the kynurenine pathway shows a strong and dose-dependent osteogenic effect on the hBMSCs in vitro.[181,201] Moreover, TRP degradation by the kynurenine pathway is also increased during osteoblastogenesis.[201] This suggests that its activation plays an important role during the development of the hBMSCs into the osteoblast lineage in vitro and that this process can be even accelerated by exogenous addition of IFN-γ. Besides, the lack of IDO activity in the animal model led to the development of osteopenia. These data, support a newly discovered role for the kynurenine pathway and especially picolinic acid as positive regulators of osteoblastogenesis and bone-formation processes.[181,201]

Results obtained by our team, and other authors indicate that CKD-induced accumulation of peripheral KYN, 3-HKYN, and AA negatively affects the osteoblasts function and bone-forming processes and contributes to the development pathological changes in bone structure. This is associated with the inhibition of catabolic and the acceleration of anabolic processes within bone tissue. Interestingly, not all of the kynurenine system components exert an adverse effect on bone tissue. What is more, the same metabolites, like KYN, may have the opposite influences on bone metabolism, depending on the site of synthesis. So far, the impact of inhibition of the peripheral activity of the kynurenine pathway on bone health has not been recognized. This could be an

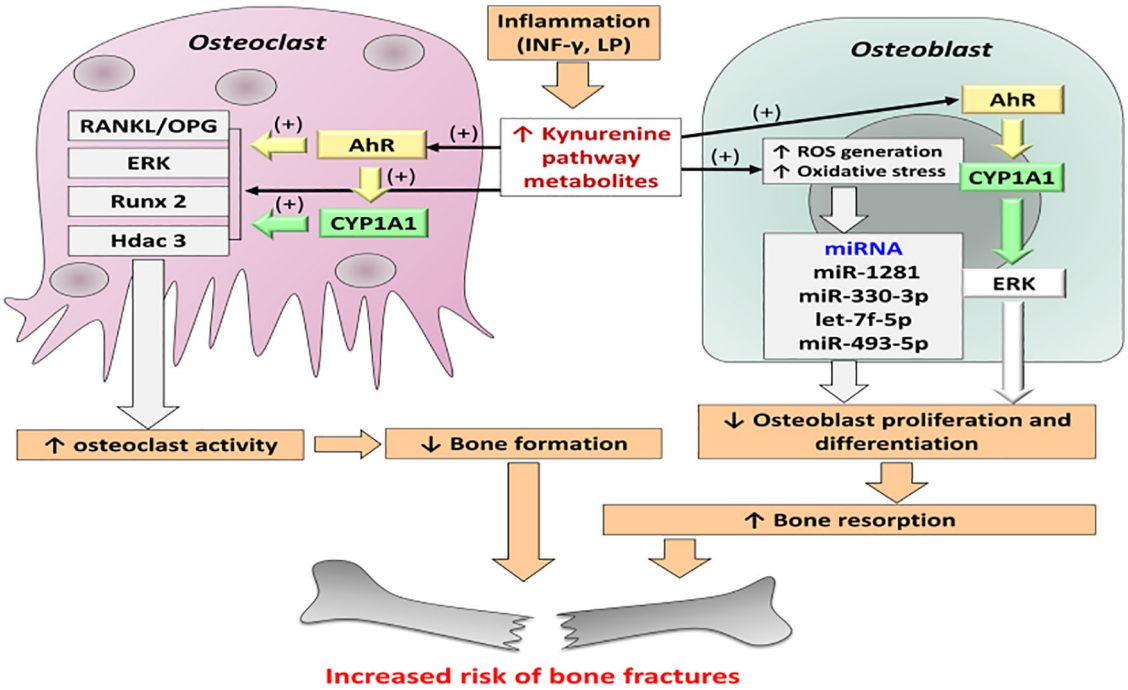

Figure 2. Mechanisms of peripheral kynurenines promoting bone fractures. The effect of circulating kynurenine pathway metabolites on bone tissue may be explained by their interaction with a cytosolic receptor AhR. Its activation may lead to unfavorable changes in bone metabolism through induction of CYP1A1 transcription and activation of the CYP1A1-dependent pathway. In turn, stimulation of the AhR in osteoblasts, through the CYP1A1 pathway stimulation, leads to the inhibition of proliferation and differentiation of osteoblasts in a collagen-induced arthritis mouse model by activating the signalling pathway dependent on extracellular signal-regulated kinases. At the same time, the activation of CYP1A1 in osteoclasts leads to an increase in their activity and exacerbation of the bone resorption process. Elevated level of peripheral kynurenine pathway metabolites in the course of CKD may also induce changes in the activity of other signalling factors, such as the receptor activator of nuclear factor-κB ligand/osteoprotegerin axis, extracellular signal-regulated kinases, and histone deacetylase-3 or runt-related transcription factor 2 expression levels, which also may stimulate osteoclasts and inhibit osteoblast activity.
Abbreviations: 3-HKYN, 3-hydroxykynurenine; AhR, Aryl hydrocarbon receptor; CYP1A1, AhR-dependent cytochrome P450, family 1, subfamily A, polypeptide 1; ERK, Extracellular signal-regulated kinases; Hdac3, Histone deacetylase-3; INF- γ, Interferon-gamma; KYN, Kynurenine; LP, Lipopolysaccharide; miRNA, micro RNA; RANKL/OPG, Receptor activator of NF-kB ligand/osteoprotegerin axis; ROS, Reactive oxygen species; Runx2, Runt-related transcription factor 2.

effective method of counteracting the development of CKD-associated osteodystrophy.

The role of the dialysis therapy in minimizing the harmful effects of accumulation of tryptophan degradation products in the end stages of CKD

IDO and TDO activity and kynurenine pathway's metabolites plasma levels were potently increased in dialyzed patients in the end-stage of chronic renal failure. These increases are positively associated with the level of oxidative stress in the patients' bodies.[19,24,57,98,120,138,142-145] Renal replacement therapy was proposed as the one of the solutions effective in the reduction of the effects of the accumulation of toxic metabolites in patients with advanced CKD stages.[24,138,142,143] Hemodialysis and PD significantly reduce the concentration of all the kynurenine pathway metabolites in the uremic patients plasma.[24,137,138,142,143] More than one research demonstrated strong relationships between kynurenine pathway upregulation and the increase in the oxidative stress level, inflammation and the progression of hemostatic and biochemical disturbances, as well as cardiovascular diseases, in patients with end-stage renal disease.[57,135-143] Therefore, the use of dialysis leads to a reduction in the inflammation, oxidative stress level, and the severity of the hemostatic and biochemical disturbances occurring in the advanced stages of CKD.[24,142,143] It may weaken the uremic symptoms and decrease the prevalence of CKD-associated systemic disorders, resulting from the accumulation of KYN and its metabolites. However, it should not be forgotten, that the efficiency of this solution seems to be limited. Although, the KYN, KYNA, 3-HKYN, AA, XA, and QA plasma concentrations in patients after dialysis were distinctly decreased, they still significantly exceeded a range typical for the healthy people.[24,107,137,138,142,202] It suggests that dialysis does not fully protect patients against the accumulation of these compounds, and the detrimental effects of their chronic influence. What is more, Yilmaz et al showed that the patients undergoing PD therapy have increased the IDO level in comparison with, hemodialysed. Patients on hemodialysis were also less prone to oxidative stress, compared to the PD group. This indicates the greater importance of oxidative stress and IDO activity in patients on PD than in those on hemodialysis.[203]

Another important point is that KYN is not a metabolic end product and is not normally cleared by the kidney. Therefore, in this case, the authors observed a markedly different pattern of accumulation in the CKD than other uremic toxins, normally cleared by renal secretion. The plasma KYN

level is elevated in the course of CKD, but it does not rise proportionally to the decrease in the GFR value.[25,56,105,177,204] This is probably because KYN is rather an intermediary metabolite, mostly reabsorbed by the renal tubules. Consequently, a very small amount of KYN is normally observed in the urine.[105] Most KYN is produced in the liver, and its production depends largely on the dietary intake of TRP. In the advanced stages of CKD, a serum albumin level is strongly decreased. It may lead to the potent increase in the free TRP supply in plasma, which can get into the liver with the bloodstream and become metabolized by TDO, and thus increase KYN and its downstream metabolite synthesis.[205-209] In turn, increased extrahepatic KYN synthesis observed in states with increased inflammation contributes to the increase in plasma KYN level in renal insufficiency.[10] Therefore, although KYN is removed from circulation by dialysis, but it is not clear if the amount of KYN removed from plasma has a notable effect on its average plasma levels in dialyzed patients.[25,142,204] Besides, the authors hypothesized that in serum KYN and other its metabolites such as 3-HKYN or 3-HAA were expected to increase in conditions of renal insufficiency and might transverse the blood-brain barrier and be converted to QA, but they could not prove it.[210] In turn, a considerable rise in the QA plasma concentration is observed in uremic patients and its removal in significant quantities by hemodialysis, discovered in the one our previous studies might be explained by decreased activity of ACMS decarboxylase during the progression of uremia.[25,107,202]

These results indicate that renal replacement therapy, despite its partial effectiveness, is not a fully efficient method of counteracting the accumulation of KYN and its metabolites in the end-stages of CKD. The increased availability of the free TRP supply and the activity of kynurenine pathway enzymes contributes to such a significant increase in the production of KYN and its metabolites, that even dialysis does not fully prevent patients against their accumulation, and thus detrimental effects of their chronic influence. This justifies the search for other ways to protect patients from harmful effects of the accumulation of the kynurenine pathway metabolites. Inhibition of the peripheral activity of the kynurenine pathway could be an effective method of preventing systemic disorders related to the accumulation of its components in patients with advanced CKD.

Summary and future directions

The results of numerous recent research indicate the significant impact of the accumulation of the components of the kynurenine pathway on the general body homeostasis, as well as on the condition of many organs, mainly by their ability to induce oxidative stress, enhance apoptosis rate and exacerbate inflammation. This review indicates that the changes in the activity of the kynurenine pathway accompanying renal insufficiency have a significant effect on most of the important systemic disorders accompanying the CKD progression, such as anemia, hypercoagulability atherosclerosis, neurological disorders, changes in blood pressure, and osteodystrophy.

The discovery of the impact of the TRP active metabolites on numerous metabolic processes in the course of CKD demonstrates a need for the continuation and expansion of studies concerning the role of compounds, such as KYN and its derivatives in the CKD and main systemic disorders associated with its progression. The arguments for this include their occurrence in the brain, blood plasma, and most of the peripheral tissues, extensive metabolic activity, and participation in many physiological and pathological processes in different types of tissue proven by numerous studies. A broader study of this area would open the new possibilities and may give the grounds to the development of new, more effective solutions in the prevention, diagnosis, and treatment of the CKD and systemic disorders related with its progression, which could improve the therapy of this disease and effectively reduce the harmful effects of disorders accompanying its courses, such as atherosclerosis, anemia, thrombosis, neurological disorders, and CKD-MDB.

The main problems associated with disturbances in the kynurenine pathway, observed in patients with the CKD, are connected with the increase in the activity of upstream enzymes responsible for the synthesis of biologically active TRP metabolites, which exert harmful effects on the body and simultaneous inhibition of downstream enzymes responsible for the degradation of these compounds into their low-toxic derivatives. Except that, their accumulation in the body to a certain degree is also independent of enzymatic activity due to impaired renal function. That is why the efforts of experimental pharmacologists should be directed towards new drugs that would allow for efficient and favorable modulation of the kynurenine pathway activity. It can be hypothesized that if KYN and its derivatives are positively correlated with the CKD severity and the occurrence of associated systemic disorders, consequently the efficient modulation of this pathway activity may be an effective method to reduce the severity of some disorders associated with the its progression. In the case of other diseases, certain compounds able to modify the kynurenic system activity have been recently considered as potential drugs.[149-166] Kynurenine aminotransferase inhibitors are considered as the agents for the treatment of neurodegenerative diseases, cognitive disorders, and schizophrenia but their usefulness in the case of CKD-associated neurological disorders seems to be debatable because in the most tissues no increase in this enzyme activity in the CKD was observed.[44,149-153] IDO inhibitors are found as therapeutics useful in cancer therapy.[154-158] As IDO is upregulated both in malignancy and in the course of CKD, the research concerning the use of its inhibitors in the reduction of systemic uremic symptoms appears to be potentially justified.[54,56,154-158] Another enzyme whose activity increases during the CKD progression is kynurenine 3-monooxygenase. Its inhibitors are considered as potential therapeutics in pancreatitis and neurodegenerative diseases.[159-166] This suggests that

they could be potentially useful in the treatment of CKD-associated neurological disorders. The systemic administration of IDO and kynurenine 3-monooxygenase inhibitors seems to be a rational approach to the treatment of the kynurenine pathway abnormalities because it should result in a decrease in the systemic level of cytotoxic kynurenine metabolites, such as KYN, 3-HKYN, and QA. Concerning the metabolites accumulation problem, it should be noted that the dialysis is not a completely effective method of reduction of the kynurenine pathway derivatives concentration in the patients with limited renal excretory capacity. Therefore it seems to be a good direction of studies in the field of experimental pharmacology. If such treatment would prove to be effective it should also at least partly contribute to the reduction of the severity of the CKD-associated disorders. In turn, all actions taken towards minimizing the harmful effects of toxic uremic metabolites, including the components of the kynurenine pathway should result in improved quality of life and reduced mortality in the patients with CKD in the future.

Author contributions

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