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Meta-organismal tryptophan metabolism: an appealing therapeutic target in CKD-MBD

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Despite important advances over the past few decades, chronic kidney disease-mineral and bone disorder remains a major clinical therapeutic challenge. Traditional interventions targeting hyperphosphatemia, impaired vitamin D metabolism, and secondary hyperparathyroidism overall failed to meet expectations. This calls for a paradigm shift. The 2023 Madrid Chronic Kidney Disease-Mineral and Bone Disorder Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference advocated a holistic approach to replace the current parathyroid hormone-calcium phosphate–centric approach. In this context, the fibroblast growth factor 23–α-Klotho axis has emerged as a key regulator of mineral metabolism and a potential novel therapeutic target. In parallel, meta-organismal tryptophan dysmetabolism recently gained interest as a novel pathogenic driver of both chronic kidney disease–associated osteoporosis and cardiovascular disease. Chronic kidney disease not only profoundly disturbs microbial and endogenous tryptophan metabolism, but also causes accumulation of tryptophan metabolites, some of which are increasingly recognized as uremic toxins, including indoxyl sulfate, kynurenine, and kynurenic acid. They may confer cardiovascular and skeletal toxicity either by inducing direct cellular toxicity or by activating the aryl hydrocarbon receptor. While adding another level of complexity to the pathogenesis of chronic kidney disease-mineral and bone disorder, these insights also create novel therapeutic opportunities.

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Chronic kidney disease (CKD) is a global health issue, affecting 10%–15% of the general population. It is especially prevalent in the older patients and is predicted to become the fifth worldwide cause of mortality by 2040.[1,2] Patients with CKD experience multiple complications, some of which occurring already early in the course of the disease. These include anemia, acidosis, hyperkaliemia, and disturbances of mineral metabolism. In 2006, Kidney Disease: Improving Global Outcomes (KDIGO) coined the term CKD-mineral and bone disorder (CKD-MBD) as a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following: abnormalities of calcium, phosphorus, parathyroid hormone, or vitamin D metabolism, abnormalities in bone (i.e., turnover, mineralization, volume, linear growth, or strength), and vascular or other soft-tissue calcification.[3] CKD-MBD contributes to the excessive burden of cardiovascular disease and fractures in patients with CKD, and as such represents an important therapeutic target. Therapy so far focused on hyperphosphatemia, vitamin D deficiency, and—most of all—hyperparathyroidism, but overall failed to meet expectations.[4–6] This sobering observation calls for a paradigm shift. A 2023 KDIGO controversies meeting suggested a holistic approach to replace the current parathyroid hormone–centric approach and to that end also introduced the terms CKD-associated cardiovascular disease and osteoporosis. It was emphasized that CKD-MBD results from the individual and combined effects of traditional and CKD-specific risk factors, the latter including the interplay of disturbances to mineral metabolism, uremic toxins, and the immune, endocrine, neurohormonal, and gut systems.[7] This line of reasoning aligns with the increased awareness of interorgan crosstalk as having an important role in health and disease.[8]

Tryptophan metabolites may modulate the immune, metabolic, and neuronal responses at both local and distant sites,[9,10] positioning meta-organismal tryptophan metabolism as a promising therapeutic target. Meta-organism is defined as the combination and interactions of the macroscopic host (animals or plants) and all the microbial agents (bacteria, archaea, fungi, etc.). A key concept is that these interactions are bidirectional, with the host shaping its

microbiota and, in turn, being influenced by it.[11] Meta-organismal tryptophan metabolism is disturbed in aging and chronic inflammatory conditions.[12,13] Acknowledging CKD as a state of microinflammation and premature aging,[14] it is likely that tryptophan metabolism is disturbed in CKD as well. Tryptophan metabolites, furthermore, are largely cleared by the kidneys and thus accumulate in the setting of CKD.[15] As such, many of these metabolites are classified as uremic toxins, with harmful effects being reported on the cardiovascular system, skeleton, and the kidney. Further adding to the complexity of the disorder, other gut-derived uremic toxins such as trimethylamine and its oxidized derivative trimethylamine-N-oxide have also emerged as important contributors to CKD-associated cardiovascular and skeletal complications.[16]

In this review, we dissect the accumulating evidence pointing toward tryptophan dysmetabolism and metabolites as drivers of CKD-associated cardiovascular disease and osteoporosis. These insights add another level of complexity to the pathogenesis of CKD-MBD but also create novel therapeutic opportunities.

Meta-organismal tryptophan metabolism in health and CKD

Tryptophan is the largest of the 9 essential amino acids.[17] It is notably found in dairy, soy, bread, and fruits such as bananas. Dietary tryptophan is either used for protein synthesis or metabolized via 4 distinct pathways: the endogenous kynurenine, serotonin, and interleukin-4–induced 1 pathways, and the microbial indole pathway.[9] The kynurenine pathway accounts for 95% of tryptophan utilization and involves the rate-limiting enzymes tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase 1 and 2 (IDO1 and IDO2). IDO1 and IDO2 both catalyze the same reaction but differ in that IDO2 has a much lower affinity for tryptophan than IDO1. Tryptophan 2,3-dioxygenase is located primarily in the liver, is constitutively expressed, and is responsible for the production of most of the kynurenine in the circulation, at least under basal conditions; in contrast, IDO is expressed in multiple cell types including mesenchymal stem cells and macrophages to regulate local tryptophan breakdown. IDO1 and IDO2 are inducible by inflammation, primarily by interferon-γ, and the resulting tryptophan depletion is suggested to attenuate immune responses.[18,19] IDO functions at the interface between inflammation and tolerance, regulating and fine-tuning immune homeostasis while establishing an environment that supports mechanisms of self-tolerance.[20] Kynurenine is the main initial stable metabolic product of the enzymatic breakdown of tryptophan. The kynurenine/tryptophan ratio has been considered a proxy of IDO1 activity, but its validity can be questioned in the setting of CKD.[21,22] Downstream, the kynurenine pathway produces a plethora of metabolites along the nicotinamide adenine dinucleotide, picolinic, and kynurenic acid branches. The second endogenous pathway encompasses the conversion of tryptophan into serotonin (5-hydroxytryptamine) by the enzyme tryptophan hydroxylase 1 in enterochromaffin cells in the gut and beyond. The interleukin-4–induced 1 pathway is mainly operational in cancer cells and produces indo-3 pyruvic acid, which subsequently is converted into indole-3-acetic acid, indole-3-lactic acid, or kynurenic acid.[23,24]

Dietary tryptophan escaping intestinal absorption is metabolized by gut microbiota via the indole pyruvate pathway into a myriad of metabolites, including indole. Indole is absorbed and subsequently metabolized by phase I and II detoxification pathways in the liver, with indoxyl sulfate representing the major end product (Figure 1). The importance of microbial tryptophan metabolism is suggested by the observation of increased levels of circulating tryptophan in germ-free mice.[25] Microbial tryptophan metabolites may affect both the gut ecosystem and distant organs.[9,10,26,27]

Once in the systemic circulation, most tryptophan metabolites (kynurenine, kynurenic acid, indoxyl sulfate, indole-3-acetic acid, melatonin, and quinolinic acid)[15] rely on renal tubular secretion, involving organic anion transporter 1 and 3, for their systemic clearance, because of tight protein-binding. Remote sensing and signaling in kidney proximal tubules stimulate gut microbiome–derived organic anion removal, further strengthening the concept of inter-organ crosstalk.[28]

Both endogenous and microbial tryptophan metabolites may have direct cellular effects but are also ligands of the aryl hydrocarbon receptor (AhR). The AhR, located in the cytoplasm of numerous cell types, is a member of the PER-ARNT-SIM superfamily of transcription factors. In its inactive cytoplasmic state, the AhR is part of a multiprotein complex that includes a 90 kDa dimer of heat shock protein (HSP90), the AIP (or XAP2) protein, the cochaperone p23, and the protein kinase SRC.[29] After ligand binding, the AhR is freed from the protein complex, and it migrates to the nucleus where it binds ARNT and acts as a transcription factor by binding to the xenobiotic response element in the promoter of many genes involved in detoxification (*CYP1A1*, *AHRR*, etc.). The AhR can modulate the activation of various transcription factors such as the nuclear factor κB but can also interact with cytosolic proteins and act as an E3 ubiquitin ligand, regulating the half-life of various proteins, such as tissue factor.[30] Importantly, downstream effects are context dependent, with properties of the ligand, exposure kinetics, species, and type of cell all being relevant.[31]

Mounting evidence indicates that tryptophan metabolites play an important role in maintaining homeostasis in several organ systems. With regard to the immune system, indoleacrylic acid and indole-3-propionic acid directly stimulate the secretion of the anti-inflammatory cytokine interleukin-10 in macrophages, and inhibit the secretion of proinflammatory cytokines interleukin-1β and interleukin-6 in peripheral blood mononuclear cells and tumor necrosis factor-α in innate immune cells.[32] In the gut, several microbial tryptophan metabolites have been shown to synergistically activate the AhR and play a crucial role in maintaining the gut barrier integrity.[27,33,34] In parallel, 5-hydroxytryptophan, a metabolite of the endogenous

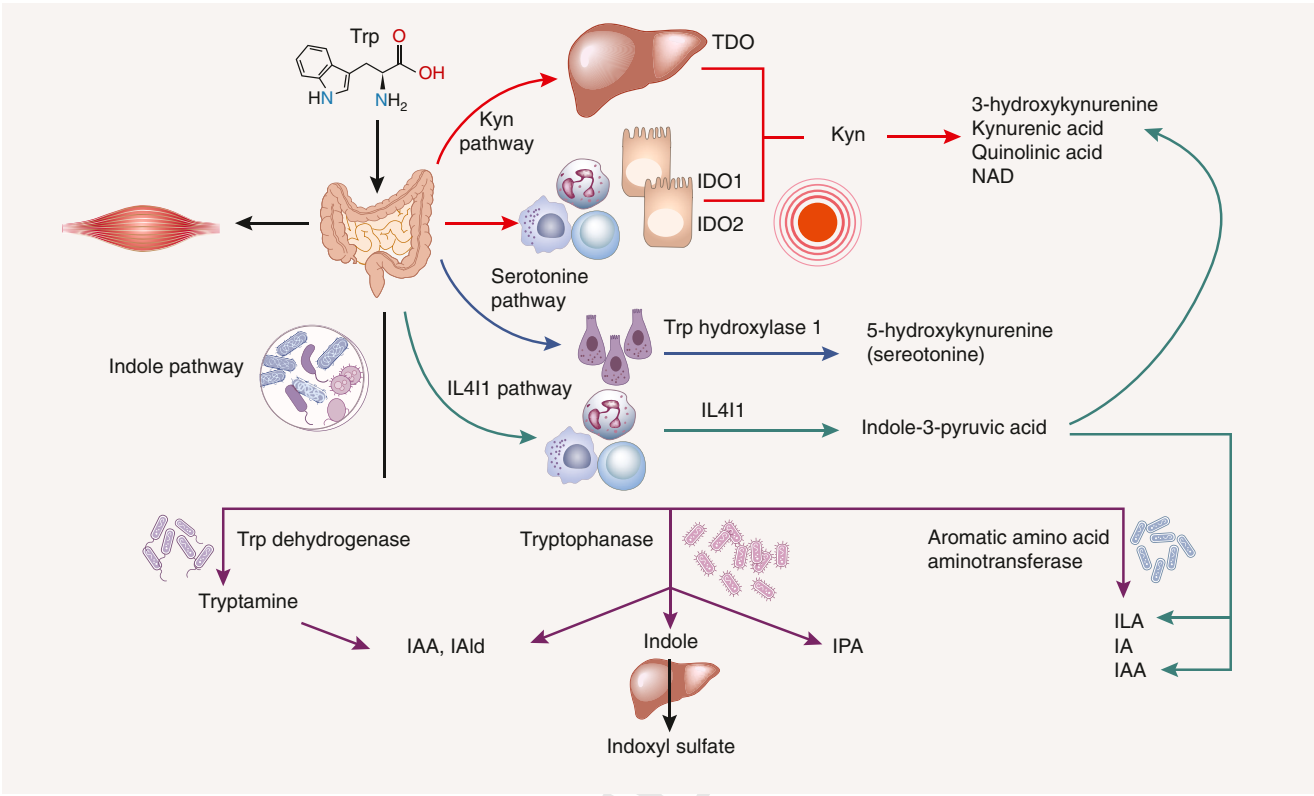

Figure 1 | Tryptophan metabolization pathways. Tryptophan (Trp) can either be used for protein synthesis or metabolized via 4 pathways: the kynurenine pathway involves the tryptophan 2,3-dioxygenase (TDO) in the liver and the indoleamine 2,3-dioxygenase 1 and 2 (IDO1 and IDO2) in mesenchymal cells and macrophages. IDO1 is inducible by inflammation. The serotonin pathway involves the tryptophan hydroxylase 1 in the enterochromaffin cells in the gut. The interleukin-4–induced 1 (IL4I1) pathway produces indole-3-pyruvic acid, which can be further metabolized into kynurenic acid, indole-3-acetic acid (IAA), or indole-3-lactic acid (ILA). The indole pathway involves 3 different enzymes possessed by different bacteria: the tryptophan dehydrogenase converts tryptophan into tryptamine, which is subsequently metabolized into IAA and indole-3-aldehyde (IAld). Tryptophanase can produce 3-indolepropionic acid (IPA) and indole, which will be converted into indoxyl sulfate in the liver after entering circulation. Aromatic amino acid aminotransferase converts tryptophan into ILA, indole-3-acrylic acid (IA), and IAA. NAD, nicotinamide adenine dinucleotide. Q14

serotonin pathway, can communicate signals from the gut to local neurons, and disturbing this signaling causes gut motility alterations.[35] 5-Hydroxytryptophan cannot cross the blood-brain barrier but can be metabolized from tryptophan in the brain where it acts as a key neurotransmitter involved in the regulation of sleep and emotions.[36]

A disturbed tryptophan metabolism has been reported in several diseases,[37,38] but whether it is a cause or consequence of the disease is a matter of debate.[39] Information on the impact of CKD on tryptophan metabolism is scanty. Several lines of evidence indicate that CKD is a state of chronic microinflammation, which activates enzymes such as IDO1. This promotes a metabolic shift of tryptophan catabolism toward the kynurenine pathway, at the expense of the indole and serotonin pathways.[40] Moreover, recent data combining a CKD mouse model and a human CKD cohort suggest a second shift in the kynurenine pathway itself from nicotinamide adenine dinucleotide to kynurenic acid production.[41] These shifts may confer cardiovascular and skeletal risks, but may also provoke constipation, sleep disorders, and neuropsychiatric disorders, all prevalent complications in patients with CKD.

Furthermore, CKD causes the accumulation of tryptophan metabolites, which, independent of alterations of tryptophan metabolism, may confer harm, either through direct toxicity or through activating the AhR.

Role of tryptophan dysmetabolism and tryptophan metabolites in CKD-associated cardiovascular disease

Growing evidence points toward disturbed tryptophan metabolism and accumulation of tryptophan metabolites as drivers of CKD-associated cardiovascular disease. Although an increase in IDO1 expression may be atheroprotective,[39] deviation of downstream kynurenine metabolism toward the quinolinic branch[37] and impaired conversion of quinolinic acid into nicotinamide adenine dinucleotide,[42] conversely, may confer cardiovascular risks. It may be hypothesized that increased IDO1 activity, being protective in the acute phase, may turn maladaptive when chronically activated, for example, by inflammation. Several tryptophan metabolites generate intracellular oxidative stress (independent of AhR activation), and as such may trigger harmful cellular phenotypic changes both in the vasculature and the heart.[43,44]

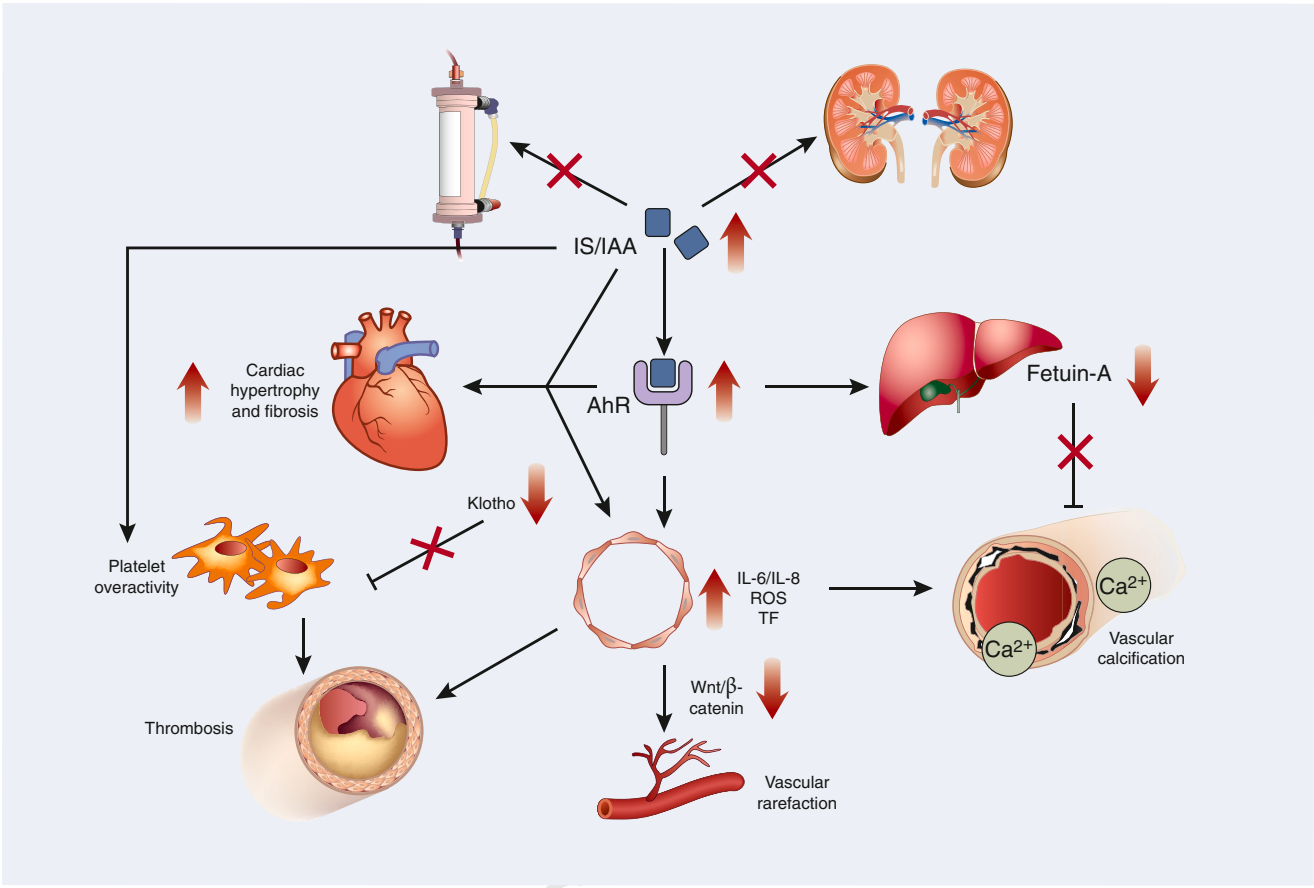

Figure 2 | Tryptophan dysmetabolism and chronic kidney disease (CKD)–associated cardiovascular disease. Indoxyl sulfate (IS) and indole-3-acetic acid (IAA) accumulate in CKD due to reduced renal clearance and poor dialysis removal. This accumulation leads to aryl hydrocarbon receptor (AhR) overactivation, which in turn (i) reduces the liver production of fetuin-A, a key anticalcification protein; (ii) causes cardiac hypertrophy and fibrosis; (iii) increases the production of reactive oxygen species (ROS) and inflammatory cytokines, leading to impaired angiogenesis; and (iv) increases tissue factor (TF) expression and activity, contributing to increased thrombotic risk. IS and IAA can also directly increase platelet activity. The inhibitory effect of klotho on platelet overactivity is decreased because of reduced klotho levels in CKD. IL, interleukin.

Furthermore, the accumulation of tryptophan metabolites in CKD renders CKD a state of "AhR overactivity."[45] An increased AhR activity has also been reported in a CKD mice model in various tissues (e.g., brain, aorta, heart, and kidney).[46] AhR overactivity may confer cardiovascular harm by triggering vascular inflammation, calcification, and rarefaction through various mechanisms,[47–54] and increase thrombogenicity, either by activating platelets or by increasing the expression and activity of tissue factor[55–57] (Figure 2).

Several clinical studies have shown an association of specific tryptophan metabolites,[58] circulating AhR activity,[57] and markers of IDO1 activity[59,60] with cardiovascular morbidity and mortality.[41]

Role of tryptophan dysmetabolism and metabolites in CKD-associated osteoporosis

Tryptophan metabolites may promote a negative bone mineral balance by disturbing osteoblastogenesis[61–64] and/or by promoting osteoclastogenesis,[65,66] at least in part involving altered AhR signaling. AhR signaling is closely connected to key signaling pathways related to bone remodeling, including the nuclear factor κB, Wnt, mitogen-activated protein kinases,[67] and nuclear factor erythroid 2–related factor 2 signaling pathways. AhR$^{-/-}$ mice with systemic or osteoclast-specific deficiencies in AhR expression exhibit increased bone mass with decreased bone resorption, and bone resorption increases in mice overexpressing constitutively activated AhR.[66] Evidence indicates that the AhR is a positive regulator of osteoclastogenesis *in vitro* by mediating various activities of myeloid-lineage cells. Similarly, smoke carcinogens cause bone loss through AhR-dependent osteoclastogenesis.[68] Indeed, the smoke toxin benzo(a)pyrene is an AhR ligand. Genetic and pharmacologic evidence demonstrates that benzo[a]pyrene and AhR agonists act through AhR-regulated detoxifying enzymes CYP1A1, CYP1A2, and CYP1B1 to stimulate osteoclastogenesis. AhR overactivity has been associated with decreased bone mass and strength in a uremic animal model,[69] but confirmatory clinical data are scarce.

Acknowledging the intricate relationship between the skeleton and the immune system,[70] it has been speculated

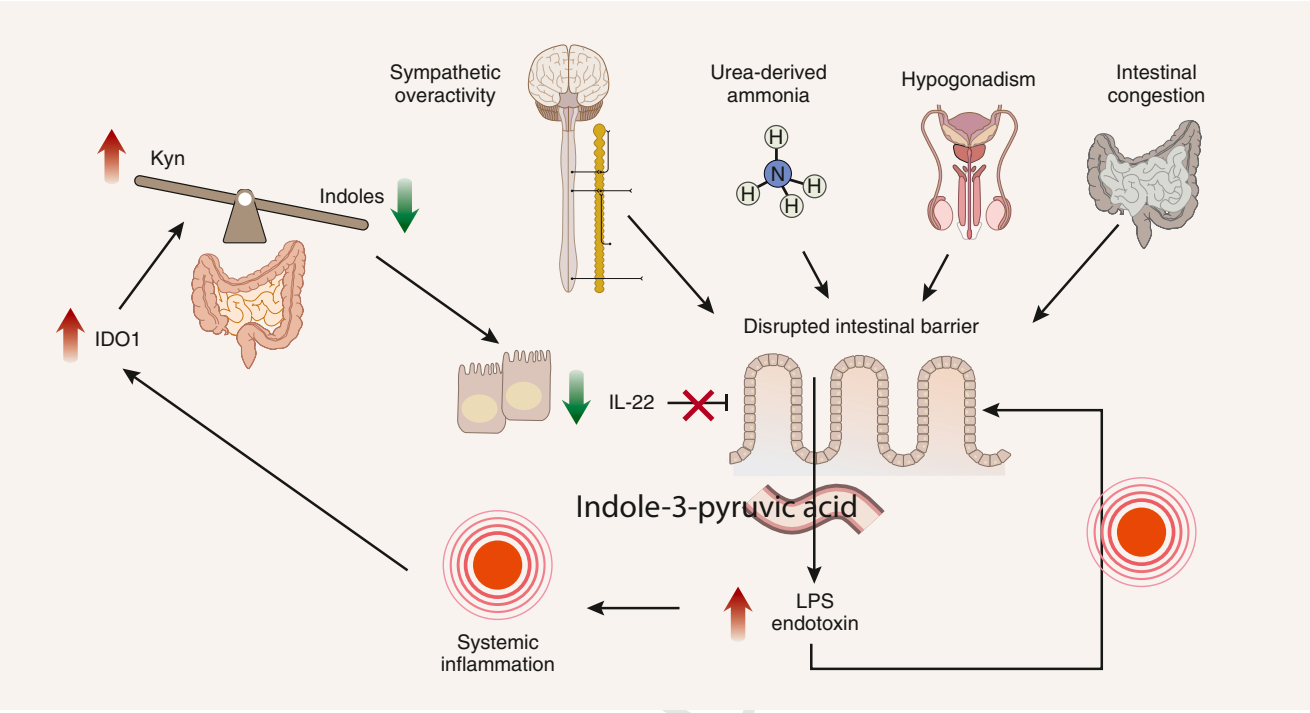

Figure 3 | Tryptophan dysmetabolism and inflammation. Factors associated with a disrupted gut epithelial barrier. Interleukin-22 (IL-22) produced by lymphoid cells acts as a key protector of intestinal barrier integrity through tight junction protein regulation and antimicrobial peptide production. Systemic inflammation associated with chronic kidney disease induces indoleamine 2,3-dioxygenase 1 (IDO1) overactivation, driving tryptophan metabolization through the kynurenine pathway, thereby decreasing indole production and therefore intestinal aryl hydrocarbon receptor activation. The subsequent decrease in interleukin (IL)-22 production contributes to intestinal barrier disruption. This increases the leakage of endotoxins and lipopolysaccharide (LPS), fueling inflammation in a vicious circle.

that tryptophan dysmetabolism may compromise bone health through the immune system.[20,71] AhR signaling may cause the expansion of both Th17 and Treg cells in a ligand-dependent manner.[72] The Treg-Th17 balance is increasingly recognized to be crucial in regulating bone destruction not only in classic chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and periodontitis, but also in the osteoporosis of postmenopausal women. It is therefore a promising pathway to be further explored in CKD-associated osteoporosis.[73–76]

Patients with fragility hip fractures and a low femoral bone mass were characterized by high kynurenine levels in the bone marrow.[77] Interestingly, high kynurenine concentrations were associated with increased TRAP-5b and receptor activator of NF-κB ligand levels. However, in aggregate, experimental and clinical data overall reveal both beneficial and adverse skeletal effects of increased AhR signaling.[29] This heterogeneity may be explained by the specific conditions of experimental settings examining the effect of different ligands (e.g., exposure kinetics, cell type, and culture medium) all playing a decisive role.[78–80] While kynurenic acid showed bone catabolic properties, picolinic and quinolinic acid were found to exhibit anabolic properties.[81] The skeletal effects of indoxyl sulfate and kynurenine are modified by parathyroid hormone and male sex steroids, respectively.[79,82] Bone outcomes may also depend on the production site, with gut-derived serotonin inhibiting bone formation, while brain-derived serotonin promoting bone mass gain.[83,84] Most importantly, studies so far focused on a single AhR ligand, thereby ignoring the complexity of the *in vivo* situation. Indeed, *in vivo*, bone metabolism reflects the impact of a myriad of exogenous and endogenous AhR ligands acting in concert with a multitude of humoral and hormonal effectors.

Role of tryptophan dysmetabolism and tryptophan metabolites in CKD-associated inflammation

Inflammation is increasingly recognized to be involved in the pathogenesis of CKD-associated osteoporosis and cardiovascular disease[85] and as such represents an important therapeutic target. A plethora of endogenous and exogenous mediators are known to induce inflammation in the CKD setting. Tryptophan metabolites can elicit inflammation either directly by activating well-defined cellular inflammatory pathways or indirectly by inducing cellular senescence.[85] In recent years, the disruption of the epithelial barrier has emerged as another important culprit in this context. Its pathogenesis is multifactorial and includes sympathetic overactivity, intestinal congestion, hypogonadism, an increased exposure to urea-derived ammonia and ammonium hydroxide, and depletion of short-chain fatty acids as important drivers. Tryptophan

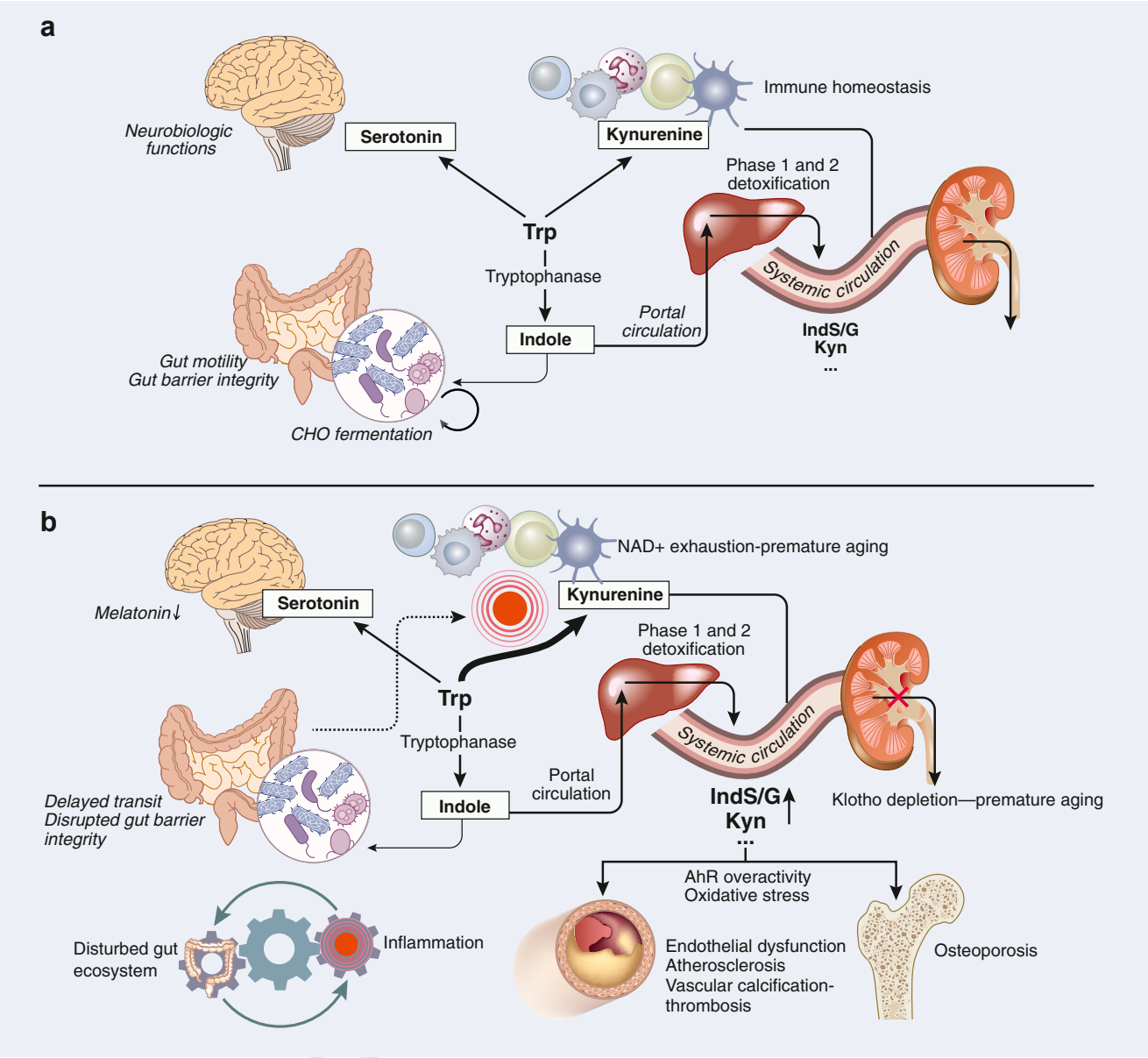

Figure 4 | (a,b) Meta-organismal tryptophan metabolism in health and chronic kidney disease. AhR, aryl hydrocarbon receptor; CHO, Chinese hamster ovary; NAD, nicotinamide adenine dinucleotide; Trp, tryptophan. Q16Q17

dysmetabolism is increasingly recognized as another potential pathogenic factor. Increased intestinal IDO1 activity translates into increased production of kynurenines at the expense of generation of indole derivatives by gut microbiota.[86] Indoles control the regeneration of intestinal epithelial cells, expression of tight junction proteins, and the production of antimicrobial peptides indirectly through AhR activation in lymphoid cells, which in turn produce interleukin-22,[27] a cytokine with well-known effects on intestinal homeostasis.[86,87] The susceptibility of colitis induction in germ-free or AhR knock-out mice illustrates the importance of microbial tryptophan metabolites.[33] However, further validation in the context of CKD is warranted, as transcriptomic data from human CKD cohorts and from animals with experimental CKD do not consistently show elevated IDO1 expression (Björn Meijers *et al.*, unpublished observations). Disruption of the gut epithelial barrier enables entry of lipopolysaccharides and other microbiota-associated molecular patterns into the systemic circulation, which in turn elicit a systemic inflammatory response and contribute to pathologic processes in distant organs (Figure 3). Lipopolysaccharides from Gram-negative bacteria can be recognized by Toll-like receptor-4, leading to the activation of MyD88, nuclear factor κB, and mitogen-activated protein kinase signaling, which promotes inflammation in the intestinal wall and beyond, thereby fueling a vicious feed-forward cycle. A similar pattern has been described in obesity.[86]

Therapeutic perspectives

The generation, elimination, and signaling of tryptophan metabolites may be targeted by dietary, nutraceutical, and pharmacologic means. A 2024 translational study showed that dietary fiber may direct microbial tryptophan metabolism via metabolic interactions in the gut microbiota. Specifically, dietary fiber repressed tryptophanase expression, thereby allowing tryptophan to be metabolized to protective indole-3-propionic acid.[88] These findings are corroborated by clinical studies showing reduced indoxyl sulfate and increased indole-3-propionic acid levels in individuals consuming a high dietary fiber diet.[89,90]

Most tryptophan metabolites are strongly bound to albumin. Consequently, removal by conventional dialysis is poor. The development of new strategies to improve the clearance of protein-bound uremic toxins could improve the prognosis of patients. Assuming that the adverse health effects of tryptophan metabolites are mainly mediated by AhR signaling, AhR blockers or modulators may represent a promising therapeutic option model.[54] Both synthetic chemicals and phytochemicals may serve this goal. Several synthetic small molecules targeting AHR signaling have the potential to be used in cancer immunotherapy approaches[91] and may theoretically also confer skeletal and cardiovascular benefits. Polyphenols are a class of compounds found in many plant foods. They are overall perceived as health-promoting nutraceuticals. Among them, resveratrol, which is found in berries, peanuts, and grapes, has not only anti-inflammatory and antioxidative properties but also the ability to inhibit the AhR.[92] In a series of experimental studies, resveratrol was shown to reduce indoxyl sulfate–induced oxidative stress and to restore osteoblastogenesis.[62,93] Clinical trials with resveratrol are scarce and yielded inconsistent findings. A 2024 randomized controlled trial in 28 CKD patients with diabetes showed improved endothelial function in the resveratrol group.[94] In another trial, a 4-week daily supplementation with 500 mg of resveratrol, however, failed to substantially impact Nrf2 and nuclear factor κB expression in nondialyzed patients with CKD.[95] Both differences in resveratrol dosing and formulation may account, at least partly, for inconsistent results. Urolithins, that is, compounds partly originating from microbial metabolism of the polyphenol ellagic acid, have been historically associated with similar health benefits as resveratrol, namely antioxidant, anticancer, and anti-inflammatory properties.[96] In 2018, Muku *et al.*[97] suggested that these beneficial effects may be mediated through inhibition of AhR as they demonstrated that urolithin A could bind to AhR, antagonize the effect of the AhR ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin, and attenuate the cytokine-induced interleukin-6 production *in vitro*. To date, highly specific AhR antagonists have been scarcely tested in experimental CKD models, and no selective AhR blockers have been administered to human patients with CKD, highlighting the need for further preclinical and clinical studies to evaluate safety and efficacy.

Conclusion

CKD-MBD remains a major therapeutic challenge. Current paradigm promotes a holistic approach to replace the parathyroid hormone-calcium phosphate–centric approach. Meta-organismal tryptophan dysmetabolism and AhR overactivity are common features of CKD and may be involved in the pathogenesis of CKD-associated osteoporosis and cardiovascular disease. While adding another level of complexity to the pathogenesis of CKD-MBD, these insights also create novel therapeutic opportunities. Numerous nutraceuticals have AhR inhibiting properties and as such may prove to be useful adjuncts to conventional therapies, along the "food as medicine"concept.[98]

DISCLOSURE

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