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REVIEW

Intestinal alkaline phosphatase modulation by food components: predictive, preventive, and personalized strategies for novel treatment options in chronic kidney disease

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Abstract

Alkaline phosphatase (AP) is a ubiquitous membrane–bound glycoprotein that catalyzes phosphate monoesters' hydrolysis from organic compounds, an essential process in cell signaling. Four AP isozymes have been described in humans, placental AP, germ cell AP, tissue nonspecific AP, and intestinal AP (IAP). IAP plays a crucial role in gut microbial homeostasis, nutrient uptake, and local and systemic inflammation, and its dysfunction is associated with persistent inflammatory disorders. AP is a strong predictor of mortality in the general population and patients with cardiovascular and chronic kidney disease (CKD). However, little is known about IAP modulation and its possible consequences in CKD, a disease characterized by gut microbiota imbalance and persistent low-grade inflammation. Mitigating inflammation and dysbiosis can prevent cardiovascular complications in patients with CKD, and monitoring factors such as IAP can be useful for predicting those complications. Here, we review IAP's role and the results of nutritional interventions targeting IAP in experimental models to prevent alterations in the gut microbiota, which could be a possible target of predictive, preventive, personalized medicine (PPPM) to avoid CKD complications. Microbiota and some nutrients may activate IAP, which seems to have a beneficial impact on health; however, data on CKD remains scarce.

Keywords Intestinal alkaline phosphatase · Chronic kidney disease · Inflammation · Gut microbiota · Predictive diagnosis · Predictive preventive personalized medicine (PPPM/3 PM)

Introduction

Alkaline phosphatases (APs) are ubiquitous membrane-bound glycoproteins that catalyze phosphate monoesters' hydrolysis at an alkaline pH optimum, with the highest activity at pH 9.7. In humans, four different alkaline phosphatase isozymes are known, originating from distinct gene loci. Tissue nonspecific AP (tnAP), also known as TNSAP, TNAP, AP-TNAP, expressed mainly in the liver, bone, and kidney, comprising > 90% of circulating AP. Also, there are the placental-type AP (pAP); germ cell AP, known as placental-like AP; GCAP, plAP-like, or AP-1; and the intestinal AP (IAP) [1].

IAP plays a vital role in the intestinal barrier function, affect bicarbonate secretion, duodenal surface pH, nutrient resorption, local intestinal inflammation, and gut microbiota [2, 3]. Disturbances of IAP functions are associated with persistent inflammatory diseases associated with aging (i.e., inflammageing), inflammatory bowel diseases, type 2 diabetes mellitus, obesity, metabolic syndrome, and chronic kidney disease (CKD) [4, 5].

Chronic kidney disease is a growing public health problem affecting over 850 million people worldwide. Many complications of CKD are associated with high cardiovascular morbidity and mortality risk, such as chronic kidney disease–mineral and bone disorders (CKD-MBD) that involve complex, interrelated changes with alterations in calcium and phosphorus balance and, mineral regulating hormones that affect bone turnover and mineralization and, promote the

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development of vascular calcification [6–8]. Among several markers of MBD, the serum concentration of total AP (tAP) (in the absence of liver disease) is a useful marker of bone turnover, which is widely used together with intact parathyroid hormone (iPTH) to monitor CKD-MBD [8–10]. An elevated AP serum activity is a significant risk factor for all-cause mortality in both the general population and patients with cardiovascular disease (CVD) and CKD [10–12].

Although IAP is not involved directly with MBD, changes on this isoenzyme, such as loss of expression and function, appears to be associated with increased dysbiosis and intestinal and systemic inflammation [13]. Persistent inflammation in the body can be transformed into chronic inflammation. Chronic inflammation is one of the causes of chronic diseases such as diabetes, autoimmune diseases, neurodegenerative disease, CKD, and cancer. Chronic inflammation leads to tissue structure loss, excessive tissue remodeling, and damages of DNA caused by oxidative stress. In this context, many inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α have been used as biomarkers for the prediction of several diseases, including cancer [14].

The gut microbiota is a complex group of microbes located in the distal part of the large intestine that lives in synergy with all body functions. It is known that gut microbiota is relevant in non-communicable diseases' etiology when there is a disbalance of the microbe's colonization, called dysbiosis [15]. Indeed, there is a range of physiological and metabolic changes in CKD, including inflammation, oxidative stress, and accumulation of uremic toxins, which may destabilize these patients' intestinal homeostasis, leading to the development of uremic dysbiosis [16, 17].

Suboptimal health conditions reduce the quality of life, can cause and contribute to several diseases, and inflammatory processes [18–20]. iALP can be extremely useful as an indicator for an in-depth diagnosis of coexisting and health-threatening conditions. Thus, iALP could be used as a predictive diagnosis, targeted prevention, and personalized treatment for CKD individuals. These novel insights have propelled an interest in IAP as a potential target for predicting gut imbalance and preventive, therapeutic interventions. Here, we briefly review aspects of IAP biology and activity and its functions for regulating the intestinal barrier, gut microbiota, transport of nutrients and minerals, and the impact of food components (macronutrients, vitamins, and bioactive compounds) on IAP. With this background, we discuss implications of targeting IAP in CKD, including dietary modulators of IAP gene expression and enzymatic activity that could be of value in CKD as preventive to the development of gut microbiota disorders and inflammation. In this context, predictive, preventive, and personalized medicine (PPPM) can discuss and predict the risk of complications caused by chronic diseases and optimize possible treatments [21]. PPPM is a concept for the implementation of predictive, preventive, and personalized medical interventions. This novel medical approach is more useful to prevent disease development, and it has a more humanized approach to disease control. PPPM prioritizes the attention to all aspects of the tricky parts that define health to change the reactive medical paradigm by all means that can enhance and improve preventive medicine [22].

AP biology and activity

APs belong to a superfamily of metalloenzymes that catalyze the hydrolytic removal of phosphate from various molecules and participate in a wide range of physiological processes [21]. APs are bound to the outer layer of the cell membrane by a glycosylphosphatidylinositol (GPI) anchor. A multigene family and function encode mammalian APs as dimeric molecules. Two Zn2+ ions, one Mg2+, and one Ca2+ ion in the active site's vicinity are fundamental for the enzymatic activity. Moreover, these metal ions contribute substantially to the AP monomer's conformation and indirectly control subunit–subunit interactions [23, 24]. tnAP is almost ubiquitously expressed in all tissues, whereas IAP, pAP, and germ cell AP are tissue-specific isozymes [21] (Table 1). For several of these isozymes, different isoforms have been identified, which share the same protein structure, but differ in glycosylation. Although all APs hydrolyze phosphate esters with a catalytic optimum at an alkaline pH, substrate specificity differs between the different isozymes and isoforms. Whereas not all physiological functions of the APs are known, AP's most well-described functions refer to tnAP and IAP [25]. tnAP plays an important role in bone mineralization, vitamin B6 metabolism, neurogenesis, and influences inflammation through regulation of purinergic signaling [25]. The biological function of pAP, located at the syncytiotrophoblast's microvillus membrane, is still unclear. However, it is known that during pregnancy, circulating pAP activity increases several-fold and has recently been suggested to play a role in maternal to fetal nutrient transport and may be protective against offspring obesity [26]. While germ cell AP's functional role is still unclear, circulating germ cell AP is thought to be an early tumor marker for seminomas, but its use in clinical practice has been flawed by methodological difficulties [13].

The transition of membrane-bound APs to circulating forms involves phospholipase C (enzymes from the membrane that cleave phospholipids), which cleaves the GPI anchor from the AP molecules. Cell apoptosis and cell destruction have been proposed as additional sources for circulating AP activity. Phospholipase D is present in the circulation and is believed to cleave APs bound to remnant membrane fragments. AP levels in the plasma, more specific the tnAP, have been identified as an independent marker for CVD and mortality in healthy populations and CKD, reflecting its role in a

Table 1 Characteristic features of human alkaline phosphatases

Gene	Protein	Tissue distribution	Function
ALPL	Tissue nonspecific (tnAP)	Liver, kidney, bone, nervous system	- Bone mineralization - Vitamin B6 metabolism
ALPI	Intestinal (IAP)	Intestinal epithelial cells	- Detoxification of LPS - Possible modulation of gut microbiota - Regulation of intestinal lipid absorption - Regulation of bicarbonate secretion and duodenal surface pH
ALPP	Placental (pAP)	Syncytiotrophoblast, various tumors	Unknown
ALPPL2	Germ cell (gcAP)	Testis, reproductive tumors	Unknown

wide range of pathophysiological processes involving bone disease, CKD progression, and cognitive dysfunction, an increase of vascular calcification, chronic inflammation, oxidative stress, and fibrosis [27].

IAP is expressed throughout the gastrointestinal tract, specifically on the microvillus brush-border membrane of enterocytes, and its secretion into the gastrointestinal tract, with the most remarkable expression in the duodenum [28, 29]. The serum half-life of IAP is short, and its secretion into serum is preceded by internalization of apical membrane-bound IAP and by increased transcription of IAP and occurs mainly in the form of membrane-containing surfactant-like particles [28, 30].

As demonstrated in mice, there are three genes expressed in the intestine: Akp3, in the duodenum, Akp5 throughout the intestine, and Akp6 with greater expression in the distal intestine [31]. IAP has been considered a main intestinal mucosal defense factor by maintaining the intestinal homeostasis [32, 33], including regulation of bicarbonate secretion and duodenal surface pH, and detoxification by dephosphorylation of lipopolysaccharides (LPS) and, ultimately, control of intestinal and systemic inflammation as described below [33–35].

The monitoring of IAP concentrations by specific kits for determination and quantification in plasma and urine can be an essential biomarker in predicting intestinal disorders. The used method is by separating total AP through electrophoresis, which electrophoretically is isolated and assayed to determine their biochemical properties, reactivity to anti-intestinal or anti-tissue nonspecific AP antibodies, molecular sizes, and sugar chain heterogeneities [36, 37].

The role of IAP as a predictor of altered barrier intestinal and gut microbiota function

IAP is a part of the first line of defense of the intestine and acts in various ways. IAP stimulates gene expression of critical tight junction molecules and their correct cellular localization [38], regulates the concentration of endotoxins [39, 40], inhibits bacterial DNA and flagellin [30], and inhibits luminal ATP through ATP dephosphorylation [41, 42]. IAP exerts an inhibitory effect on the growth and survival of bacteria present in the gut microbiota, with consequent prevention of bacteria translocation from the intestinal lumen to the bloodstream [43]. Specific bacteria and cells treated with calf IAP (cIAP) presented a reduction of IL-8 response, mainly the gram-negative bacteria that may be related to the dephosphorylation of bacterial components such as LPS, CpG DNA, and flagellin.

LPS is a significant component of the gram-negative bacteria cell wall and is composed of polysaccharide chains covalently attached to a single structure, lipid A, a diglucosamine-based acylated phospholipid. The primary toxic moiety of LPS is located within the lipid A, which has two phosphate groups, essential for many biological activities. Contrary to lipid A, monophosphoryl lipid A (MPLA) is non-toxic and can induce tolerance to subsequent LPS exposure [13, 44]. IAP can remove one of the two phosphate groups from the toxic lipid A fraction of LPS, producing monophosphoryl lipid A (MPLA), which promotes the inactivation of LPS [45].

In sepsis, high circulating levels of LPS (endotoxemia) induce a robust inflammatory response. Also, at lower levels, LPS may stimulate low-grade chronic inflammatory responses, such as those observed in obesity, diabetes, CVD, and CKD. Also, the *H. pylori* infection can stimulate the secretion of several inflammatory factors since that the cell wall of *H. pylori* is an LPS by the bond to the transmembrane recognition receptor toll-like receptor 4 (TLR4), which lead to activation of the toll-like receptor signaling pathway [14]. In some intestinal diseases such as colitis and inflammatory bowel disease, IAP mRNA expression is reduced and related to gut inflammation, with a consequent increase of LPS and TLR-4 expression [46, 47]. IAP deficiency also has been associated with ischemic heart disease and type 2 diabetes mellitus [48, 49]. Upon activation by LPS, TLR-4, or MyD88, a standard adaptor downstream of TLRs, mediates the release of proinflammatory cytokines, including IL-6, IL-

1, and TNF through the nuclear-kappa B factor (NF-kB) pathway [50–52]. Counteracting these responses, exogenous IAP can inhibit IκBα phosphorylation and DNA-binding activity of NF-κB in peritoneal macrophages, consequently decreasing the inflammatory cytokines in a TLR4-dependent manner (via the TLR4/NF-κB pathway) [53].

Furthermore, about the establishment of the intestinal flora in early childhood, there is an increase in the IAP activity during this time [54]. It is essential to know that IAP also makes part of the gut microbiota modulation since the born [54]. A study using an IAP knockout model in Sprague-Dawley pups increased dysbiosis with bacterial translocation, and inflammation was reported [55]. Malo et al. [56] demonstrated a profound reduction of aerobic and, to a lesser extent, anaerobic bacteria in mice lacking the duodenal IAP gene Akp3.

Transport of IAP-rich membrane vesicles secreted from the microvillus surfaces of duodenal enterocytes might explain the resistance of duodenal IAP to digestion during the passage to the large intestine. Possible mechanisms of microbiota modulation by IAP include changes in inflammatory regulators, promoting mucosal tolerance to commensal bacteria, and regulating pH in the mucosal microenvironment hydrolyzation of nucleotides. In addition to shaping the intestinal microbiota, IAP also detoxifies microbial components and prevents enteric microbial translocation in the body [57–59].

Supplementation of exogenous IAP by gastrointestinal administration including oral supplementation, can reduce intestinal inflammation (decrease of TNF, IL-6, and IL-1β) [46], increase serum AP activity, promote intestinal tissue regeneration, and decrease the abnormally high permeability of the intestinal tract, thereby preventing LPS-mediated inflammatory response, and (in mice) IAP was found to protect against antibiotic-associated bacterial infections [41, 60, 61]. Additionally, IAP supplementation seems to increase the intestinal epithelial barrier in animals with advanced age by increasing rigid junction proteins' expression. Moreover, IAP supplementation may alleviate the diminished gut integrity associated with aging and extend life-span [62]. Kaliannan et al. [63] reported that both endogenous IAP and oral IAP supplementation could prevent the LPS absorption in rats fed with a high-fat diet and also was able to prevent metabolic syndrome in animals receiving IAP. Economopoulos et al. [64] showed that oral IAP (100 units/ml drinking water) prevented the susceptibility to antibiotic-associated metabolic syndrome in mice treated early in life with azithromycin; IAP decreased total body weight, serum lipids, glucose levels, and liver lipids, and changed the composition of gut microbiota. Oral supplementation of IAP in aging mice regulates the intestinal barrier function, microbial homeostasis, decrease age-related intestinal permeability and systemic inflammation, potentially leading to less fragility and prevention of chronic age-related diseases [65]. Moreover, Singh et al. [57] reported that intestinal IAP treatment (100 U/mL for 14 days) in mice inhibits the LPS-induced IL-1β mRNA expression and activation of NF-κB. They also observed an increase of IAP by inducing autophagy-related genes (Atg5, Atg16, Irgm1, Tlr4, and Lyz) and Atg16 protein expression in the small intestine, and may control intestinal bacterial overgrowth and inflammation.

Regarding sepsis-induced acute kidney injury (AKI), it was observed in the piglet model of AKI that 25 U/kg/h of bovine IAP increased serum and renal tissue AP activity, decreased proximal tubular injury, and prevented AKI [66]. Another study showed preventive and curative effects of treatments with 1 IU/g of calf IAP, which in septic mice decreased the permeability of the small intestine by 50%, and increased mRNA expression levels of claudin-1 and claudin-14, which are main structural tight junction proteins in the intestine [67]. These studies confirmed that IAP influences both inflammatory and intestinal barriers, contributing to intestinal health [66, 67].

Some studies have also used a recombinant human form of AP (IAP and pAP) due to the longest half-life isoenzymes [68], which creates a highly stable, biologically active enzyme compared to isoenzymes separately. Recombinant AP could decrease the inflammatory response by dephosphorylating endotoxin and adenosine triphosphate in human proximal tubular epithelial cells in AKI patients [69]. In another renal ischemia-induced inflammation model in rats, recombinant AP seems to attenuate the renal inflammation and tubular injury provoked by AKI through attenuation of inflammatory and pro-apoptosis markers [70]. In contrast, a randomized, double-blind, placebo-controlled trial using recombinant AP (1.6 mg/kg) for 7 days in AKI patients did not show significant improvement in kidney function [68].

Transport of nutrients and minerals function

IAP has been suggested to be a minute-to-minute regulator of intestinal calcium resorption, as duodenal IAP activity in Sprague-Dawley rats is stimulated by an increased calcium concentration in the duodenal lumen [71]. Increased IAP activity inhibits Ca resorption, hypothetically decreasing luminal pH in the gut, which causes downregulation of TRPV6, a member of the transient receptor potential family of membrane proteins that mediates the uptake of Ca2+ ions [72]. IAP provides a protective mechanism by inhibiting the entry of calcium into enterocytes, thereby preventing calcium overload. A study conducted in mice completely lacking duodenal IAP (Akp3−/−mice) showed mild atrophy of the villi with a lower absorption surface, resulting in higher calcium uptake than in the control mice. During long-term follow-up, mice lacking IAP had better bone properties than controls, providing evidence that IAP regulates calcium absorption [73].

Kuehn et al. [74] investigated the gut-bone axis in mice and observed that IAP-knockout mice presented bone formation changes that were probably associated with dysbiosis and inflammation linked to IAP deficiency. Another study with Akp3−/− mice have shown that the IAP activity in the proximal intestine and 25-hydroxyvitamin D3-24-hydroxylase mRNA levels were decreased, while 1,25 dihydroxy vitamin D3 (1,25(OH)2D3) levels were increased compared with Akp3+/+ mice [75]. Moreover, intestinal inorganic phosphate transport activity was decreased in Akp3−/− mice compared with Akp3+/+ mice. Additionally, Akp3−/−mice with renal failure reduced intestinal inorganic phosphate absorption, leading to an increase in ATP in intestinal epithelial cells. Consequently, there is an increase in entrance calcium into epithelial cells via the P2X7 receptor [75]. Taken together, IAP and Akp3 appear to be essential regulators of intestinal inorganic phosphate [75].

Nutritional strategy as a preventive intervention for IAP modulation

The expression and activity of IAP are directly affected by food intake, i.e., quantity and type of macro- and micronutrients including vitamins and other bioactive nutrients, or by the absence of food, as well as indirectly by the composition of the gut microbiota that in turn is highly dependent on food intake (Table 2). In mice, IAP expression and function are lost with starvation and maintained by enteral feeding [51]. Studies of IAP expression in IAP-knockout vs. wild-type mice and 20 patients post ileostomy in fasted and fed states showed that IAP expression was decreased in patients and mice during fasting with impairment in the barrier function and that IAP supplementation reverted the gut barrier dysfunction [76]. Dietary fat, protein, carbohydrates, vitamins, and minerals are essential dietary modulators that regulate host IAP gene expression and enzymatic activity. This modulation seems to depend on the quantity and type of ingredients in the diet [32, 41].

Rentea et al. [77] have reported that IAP levels of newborn Sprague-Dawley rat pups are influenced by the types of birth (cesarean or vaginal delivery) and feeding (formula or breast). Inhibition of IAP expression and activity was observed in rat pups fed with formula and had a cesarean delivery. Yang et al. [125] have investigated the IAP activity in 122 meconium samples from infants (gestational ages from 24 to 40 weeks). They also analyzed 289 breast milk samples from 78 individual mothers between days 2–49 post-birth to investigate if breast milk serves as a source of exogenous AP to the neonatal intestine. Breast milk of the first-week post-birth had the highest AP activity. These results encourage breast milk feeding and show that preterm birth associates with intestinal disorders, low IAP activity, and decreased detoxification capacity of proinflammatory bacterial products such as LPS [77]. Also, the type of milk formula used for preterm and near-term seems to change the IAP activity. A study showed a beneficial effect of mildly pasteurized whey protein on intestinal integrity and innate defense [78]. The mildly pasteurized whey protein increased IAP activity in the colonic epithelium, improved intestinal maturation, and reduced gut inflammation in preterm and near-term piglets [78]. These studies indicate that the effects on IAP expression and activity differ between food components.

Some studies have currently approached the modulation of gut microbiota and intestinal health as PPPM [79, 80]. Therefore, a personalized and balanced diet contenting macro, micronutrients, and bioactive compounds found in foods can prevent IAP imbalance, improving its activity and expression, including aspects of PPPM, which could, through personalized prevention, avoid complications related to CKD and gut microbiota imbalance.

Fat The fatty acid composition of oil regulates the synthesis and secretion, and the increased appearance of IAP in serum under physiological conditions seems to be mainly associated with lipid resorption [28, 32, 81]. Using a transgenic mouse model, Kaliannan et al. [82] observed that intake of omega-3 fatty acids increases the expression and activity of IAP, reduces the LPS levels, and improves intestinal permeability. Another study investigating the impact of a high-fat diet during pre- and post-weaning periods on the gut microbiota and IAP activity in male rats showed that pups fed with a high-fat diet had enhanced adiposity and increased IAP activity, as well as higher lactobacillus/enterococcus and lower numbers of bacteroides/prevotella in the jejunum and colon than controls [83].

Protein IAP metabolism is affected by protein intake. In preruminant calfs treated with soybean diet, most small intestine enzyme activities, including IAP, were reduced [84]. Replacement of a milk-based diet with wheat or barley diets increased IAP in pigs after only 4 days by increasing mucosal enzyme activity, sodium-dependent intestinal absorption, and response to secretagogues [85]. Fermented milk (yogurt) showed to stimulate IAP in the small intestine of mice. Indeed, milk fermentation leads to protein denaturation, which improves free amino acids bioavailability and can induce brush-border enzyme adaptation.

Moreover, the milk fermentation facilitates access to phosphorylated sites, explaining the increase in IAP activity after consumption of yogurt in the mice [32, 86]. Since studies found that a protein-free diet can lead to low IAP activity [32, 87], the effects of a low-protein diet on IAP in patients with CKD need to be studied, mainly because a low-protein diet is recommended to non-dialysis CKD patients. It is believed that the privation or deficiency in amino acids from protein can decrease IAP concentration, possibly, via reduced intestinal epithelial growth [32].

Table 2 Effects on IAP of interventions using food compounds in animal experimental studies

Reference	Study design/sample	Intervention/follow-up	Results
Johnson et al. (1984) [134]	Experimental/20 male Wistar rats	Group 1: starch or sucrose Group 2: sucrose Group 3: starch, sucrose or guar gum Group 4: starch, sucrose or cellulose for 30 days	Group 3: ↓ IAP activity Group 4: ↑ IAP activity
Montagne et al. (1999) [84]	Experimental/20 Holstein calves	Liquid diet based on skimmed milk powder and soybean protein concentrate for 60 days	↓ IAP and AP total activities
Boudry et al. (2002) [85]	Experimental/45 piglets	Group 1: Diet based on wheat Group 2: Diet based on barley Group 3: Diet based on milk for 35 days	↑ activities of IAP and sucrase in both groups Group 1: ↑ dipeptidyl-peptidase IV activity Group 1 and 2: ↑ sodium-dependent glucose absorption, ↓ diarrhea
Sogabe et al. (2004) [88]	Experimental/16 Sprague-Dawley strain female rats	Glucose diet and lactose diet for 21 days	↑ level of IAP activity in the jejunum from the lactose group rats ↑ IAP mRNA expression
Montoya et al. (2006) [87]	Experimental/10 female Wistar rats	Protein-free diet, as compared to casein, in slightly energy-restricted rats fed for 10 days	Protein-free diet—↓villus width, height to crypt depth ratio in the duodenum and ileum ↓ IAP
Sogabe et al. (2007) [94]	Experimental/26 Sprague-Dawley rats	Group 1: vitamin K1 Group 2: vitamin K2 Both orally administered for 90 days	↑ IAP in both group
Kaur et al. (2007) [135]	Experimental/16 Wistar strain rats	Group 1: coconut oil Group 2: corn oil Group 3: cod liver oil Group 4: Saline Analyses 5 h after oral administration	Groups 1, 2, and 3: ↑ serum AP activity, ↑ Luminal IAP activity
Lynes et al. (2011) [28]	Experimental/adult male C57BL/6 mice	Diet rich in long-chain fatty acids	↑ IAP in the microvillus brush-border membrane of enterocytes ↑ secretion into the gastrointestinal tract
Haraikawa et al. (2011) [95]	Experimental/21 male ICR strain mice	Group 1: vitamin K1 Group 2: vitamin K2 Analysis 4 h after oral administration	Group 1: ↑ IAP activity in the jejunum and IAP mRNA expression Group 2: ↑ IAP mRNA expression
Brun et al. (2012) [71]	Experimental/18 male Sprague-Dawley inbred rats	Group 1: 0.2 g % Ca diet Group 2: 1 g % Ca diet Group 3: 2 g % Ca diet Orally supplemented for 3 days	All groups: ↑ IAP activity in the brush border
Riggle et al. (2013) [60]	Experimental/30 newborn Sprague-Dawley rats—necrotizing enterocolitis	4 or 40 glycine units of bovine IAP intraperitoneally for 3 days	↓TNF-α; IL-6; IL-1β
Ghosh et al. (2014b) [98]	Experimental/ LDLR−/−mice	Western diet for 16 weeks plus 100 mg/kg of curcumin by oral gavage	Western diet: ↑ LPS levels, glucose intolerance and/or heart disease; ↓ intestinal barrier, ↓ IAP activity, expression of tight junction proteins, ZO-1 and Claudin-1 Curcumin: ↓ LPS levels, ↓ lesions in the aortic arch and entire aorta; ↑ intestinal barrier, IAP activity, glucose tolerance, expression of tight junction proteins, ZO-1 and Claudin-1
Okazaki et al. (2017) [89]	Experimental/male Sprague-Dawley rats fed with diet containing 30% lard	4% high or low viscous glucomannan for 2 weeks	↑ colonic AP activity, colonic and gene expression of IAP, fecal levels of IgA, mucins and cecal organic acids ↔ colonic expression of Akp3
Okazaki et al. (2019) [90]	Experimental/42 male Sprague-Dawley rats	Group 1: Control Group 2: Fructooligosaccharides Group 3: Galactooligosaccharides Group 4: Isomaltooligosaccharides	Groups 2, 3, 5, and 6: ↑ IAP activity, fecal AP activity, colonic IAP gene expression, fecal mucins, fecal IgA, *Bifidobacterium* spp. ↓ pH of caecal digesta, *C. coccoides* and *C. leptum* Groups 2, 3, and 4: ↑ ileum AP activity

Table 2 (continued)

Reference	Study design/sample	Intervention/follow-up	Results
		Group 5: Raffinose Group 6: Lactulose	Groups 2 and 5: ↑ colonic expression on Akp3
Rentea et al. (2019) [77]	Experimental/ newborn Sprague-Dawley rat pups	Group 1: Vaginal birth breast fed Group 2: Vaginal birth formula fed Group 3: Preterm cesarean breast fed Group 4: Preterm cesarean formula fed Group 5: Term cesarean breast fed Group 6: Term cesarean formula fed	Group 1: ↑ IAP mRNA expression Formula fed: ↓ IAP mRNA expression Breastfed: ↑ IAP mRNA expression

IAP, intestinal alcaline phosphatase; *TNF-α*, tumoral necrosis fator alpha; *IL*, interleukin; *LPS*, lipopolysaccharide; *ZO-1*, tight junction protein 1; *Akp3*, alkaline phosphatase 3, intestine, not Mn requiring

Carbohydrates Rats fed with a diet containing 10% lactose showed an increase in IAP mRNA expression, suggesting that lactose affects intestinal phosphate metabolism indirectly by regulation of IAP expression [88]. Another study in rats fed a high-fat diet showed that supplementation of glucomannan (a dietary fiber found in the root of the konjac plant) increased the colonic and gene expression of IAP, as well as modulated gut microbiota and increased gut immunoglobulin A, mucins, colonic, and cecal organic acids (n-butyrate, propionate) [89]. A diet with fermentable oligosaccharides increased IAP, IAP gene expression, mucin secretion, and microbial fermentation. There was a significant positive correlation of IAP activity with fecal mucins, caecal lactate, and n-butyrate, as well as *Bifidobacterium* spp. in rats, fed a high-fat diet [90]. Another study showed that Caco-2 cells treated with sialyl lactose and galactooligosaccharides (human milk oligosaccharides) increased IAP expression [91].

Vitamins IAP expression is stimulated by 1,25(OH)2 vitamin D, whereas vitamin D deprivation decreased duodenal IAP activity in rats [92]. Nakaoka et al. [93] have shown that vitamin D restriction and high-fat diet together decreased AP activity in the duodenum in an animal model of menopause. These results indicate that vitamin D restriction in a high-fat diet can suppress IAP mRNA expression in the duodenum. Thus, adequate vitamin D levels could be an essential strategy for regulating IAP expression. Besides, it seems that vitamin K1 and K2 may stimulate the IAP gene expression in mice supplemented with both vitamins; however, the mechanism has not yet been defined [94, 95].

Spices Curcumin increases the catalytic activity and expression of IAP and attenuates the circulating levels of LPS [96, 97]. Indeed, supplementation of 100 mg/kg of curcumin attenuated Western diet damage such as increased LPS production, inflammation, decreased IAP activity and expression, and intestinal barrier alterations. Curcumin increased IAP activity and the expression of tight junction proteins, ZO-1, and Claudin-1 [98]. Ghosh et al. [99] reinforced this idea by showing that intestine-specific expression of human chimeric IAP attenuated Western diet-induced barrier dysfunction and glucose intolerance in transgenic mice.

Dietary intake of other spices such as black pepper, red pepper, ginger, and bioactive compounds (piperine and capsaicin) also increases the IAP levels in rats. Additionally, these spices also induced an increase in the microvilli's length of the rats' jejunum [100].

Additives Dietary additives such as sucrose, titanium dioxide, emulsifier TWEEN 20, and sodium chloride may increase intestinal permeability. A recent study found increased intestinal permeability after treatment with additives, mainly with high sugar, in both Drosophila and a human cell co-culture dramatically reduced the IAP activity in both models [101].

Iron Iron supplementation can decrease the IAP expression, and other brush-border enzymes such as Lys-Ala-dipeptidyl aminopeptidase, mainly because of the possible deposition of iron duodenum [81], also excess of iron can contribute to oxidative stress and intestinal damage [81, 102].

Probiotics The consumption of probiotics has been liked with the development of healthy diets, treatment, and prevention of dysbiosis [103]. Also, probiotics and prebiotics can target tissue such as the kidney, brain, conferring health benefits to extraintestinal sites, and gut microbiota by immune-modulating the metabolic activity in the intestine affecting the intestinal barrier [104]. Moreover, evaluating bacteria

properties and the host's phenotype by a panel of biomarkers is essential for the individualized selection of probiotics used [105, 106]. In this context, probiotics therapy can use as a personalized medicine according to the patients' metabolic patterns in each patient [107]. For example, Borges et al. [108] have observed in a randomized, double-blind, placebo-controlled study with hemodialysis patients that probiotic (*Streptococcus thermophilus*, *Lactobacillus acidophilus*, and *Bifidobacterialongum*, 90 billion colony-forming units per day) increased the serum urea, potassium, and indoxyl sulfate. This demonstrates that the probiotic therapy should be chosen with caution in this kind of patients, and an individual and personalized probiotic therapy is appropriate [106, 107]. Probiotics seem to increase IAP activity [109, 110]. Rats with antibiotic-induced dysbiosis fed with probiotic *Lactobacillus fermentum* Z showed an increase in IAP activity in the jejunum epithelium [109]. Pre-treatment with *Bifidobacterium infantis* in mice with intestinal damage induced by Salmonella prevented the reduction of brush-border enzyme activity, including IAP, also presented a reduction in IL-10 and IL-8 expression [110].

Intestinal AP in CKD

CKD is characterized by the irreversible and progressive loss of renal function and the presence of kidney damage that can be measured by the decline of glomerular filtration rate (GFR) and albuminuria [111]. The kidney loss function brings some complications involved with disease progressions such as CVD, metabolic acidosis, hyperkalemia, hyperphosphatemia, sarcopenia, anemia, dyslipidemia, hyperparathyroidism, and bone diseases [112]. CVD is the leading cause of death in patients with CKD and, in addition to traditional risk factors (obesity, hypertension, diabetes, and dyslipidemia) [113], studies have identified intestinal imbalance of microbiota as a novel factor that may contribute to inflammation and CVD in CKD patients [114, 115]. Kidney injury can also be initially caused by changes in the population of intestinal microorganisms that promote increased levels of inflammation, uremic toxins, and blood pressure [115]. Uremia can modify the biochemical milieu of the intestine due to a high amount of urea in the gastrointestinal tract and secretion of uric acid and oxalate by the colonic epithelium [116–118].

An intact intestinal barrier is essential to prevent the influx of microbes, microbial toxins, bacterial products, antigens, digestive enzymes, degraded food products, and other harmful substances from the gastrointestinal lumen internal [119]. Increased permeability leads to the translocation of products generated by intestinal bacteria, mostly LPS, to the bloodstream [120, 121]. Dysbiosis in patients with CKD is associated with various complications, such as the production of uremic toxins (indoxyl sulfate, p-cresyl sulfate, and indole-3-acetic acid), inflammation, oxidative stress, and insulin resistance, which can promote the progression of kidney failure and the modification of the tight epithelial junctions [119, 122, 123].

In acute cases of inflammation, elevated IAP levels may be beneficial to the patient since it is associated with endotoxin detoxification, inactivation of cytokines, and reduction of oxidative stress that may exert nephroprotective and anti-inflammatory effects [1]. As previously mentioned, the most studied pathway concerning the control of inflammation by IAP is through LPS control. It is believed that IAP prevents the activation of TLR4 via LPS and consequent activation of NF-kB and its subsequent translocation to the nucleus [13, 44]. There is a scarcity of studies on the effects of IAP in CKD. However, it is worth remembering that reduced luminal IAP can lead to an imbalance in intestinal functions and gut dysbiosis, with a consequent increase in the risk of developing intestinal inflammation and gut permeability in CKD [124]. Thus, more studies are warranted on IAP's role in defense of intestinal mucosa and gut microbiota and against local and systemic inflammation in CKD.

In the 1970–1980s, researchers were more interested in IAP; however, recent nephrology studies focus on total AP (Table 3). Some studies showed increased IAP levels in CKD could be due to the liver's inability to remove this circulating enzyme, especially in liver disease [126]. However, the kidneys can also be a potential source of the IAP to the plasma and be responsible for total serum AP elevations in some patients [127]. Zetterberg et al. [37] observed that peritoneal dialysis patients presented higher IAP levels; however, the mechanism by which this increase of IAP occurs is unknown.

Relatively little is known regarding the levels and the role of IAP in CKD. A recent review highlights AP's potential, including IAP, as a novel marker of predictive and treatment targets for CVD in CKD [1]. These observations may open the way for therapeutic strategies involving IAP modulation, aiming to attenuate dysbiosis, improve the gut microbiota, and prevent translocation of LPS and uremic toxins mitigating inflammation [127–131].

It is worth remembering that inflammation in patients with CKD is also linked to increased gut permeability and dysbiosis, which produce high uremic toxin and LPS plasma levels leading to the inflammatory process, making new research on this field essential [16, 17, 132, 133].

Perspectives and preliminary conclusions

Predictive medicine

The measure of IAP concentration in plasma and its gene expression and enzymatic activity can be an essential parameter to predict an imbalance in gut microbiota and intestinal

Table 3 Observational studies on intestinal alkaline phosphatase (IAP) and chronic kidney disease

References	Patients	Results
Walker (1974) [136]	29 HS 44 HD patients 556 other patients (OP)	IAP bands on electrophoresis (%) HS: 48%, HD patients: 50%, OP: 9% Total AP bands on electrophoresis (%) HS: 5 to 16 IU/L, HD patients: 9 to 57 IU/L, OP: 16 to 542 IU/L
De Broe et al. (1974) [137]	111 HD patients	↑ IAP in 29.7% of the patients
Skillen (1977) [138]	100 non-dialyzed patients 114 HD patients	↑ IAP in 15% in HD patients and 10% of non-dialyzed patients. IAP was detected in 36% of those patients with normal serum AP activity
Stěpán et al. (1984) [139]	21 non-dialyzed patients 52 HD patients	Patients without hepatopathy: IAP activity was inversely correlated with Ca serum levels and positively correlated with iPTH levels Patients with hepatopathy: No correlation between iPTH and IAP, IAP in serum was influenced by blood group, liver ALP activity in serum and serum GMT activity.
Alpers et al. (1988) [127]	42 HD patients with ↑ total ALP serum levels	Before HD session: 62% had detectable IAP in plasma (222 IU/L (125–625) IAP measuring by rocket was 17.9 ± 2.3%, and by electrophoresis was 10.2 ± 1.9%. After HD session: IAP of 12.8 ± 3.1% (by rocket), and 9.5 ± 2.1% (by electrophoresis
Tibi et al. (1991) [140]	75 HD patients	↑ total ALP activity in 28 patients; IAP > 23 UI/L in 8 patients (responsible for increase in total AP in only one patient)
Tsumura et al. (2001) [36]	108 CKD non-dialyzed patients 106 healthy subjects	With polyacrylamide gel electrophoresis analysis, authors found atypical AP in serum and urine in patients, which could be an intestinal-type AP
Zetterberg et al. (2005) [37]	2 PD patients	↑ serum total AP and IAP activity

HS, healthy subjects; *HD*, hemodialysis; *CrCl*, creatinine clearance; *PD*, peritoneal dialysis; *iPTH*, intact parathyroid hormone; *AP*, alkaline phosphatase

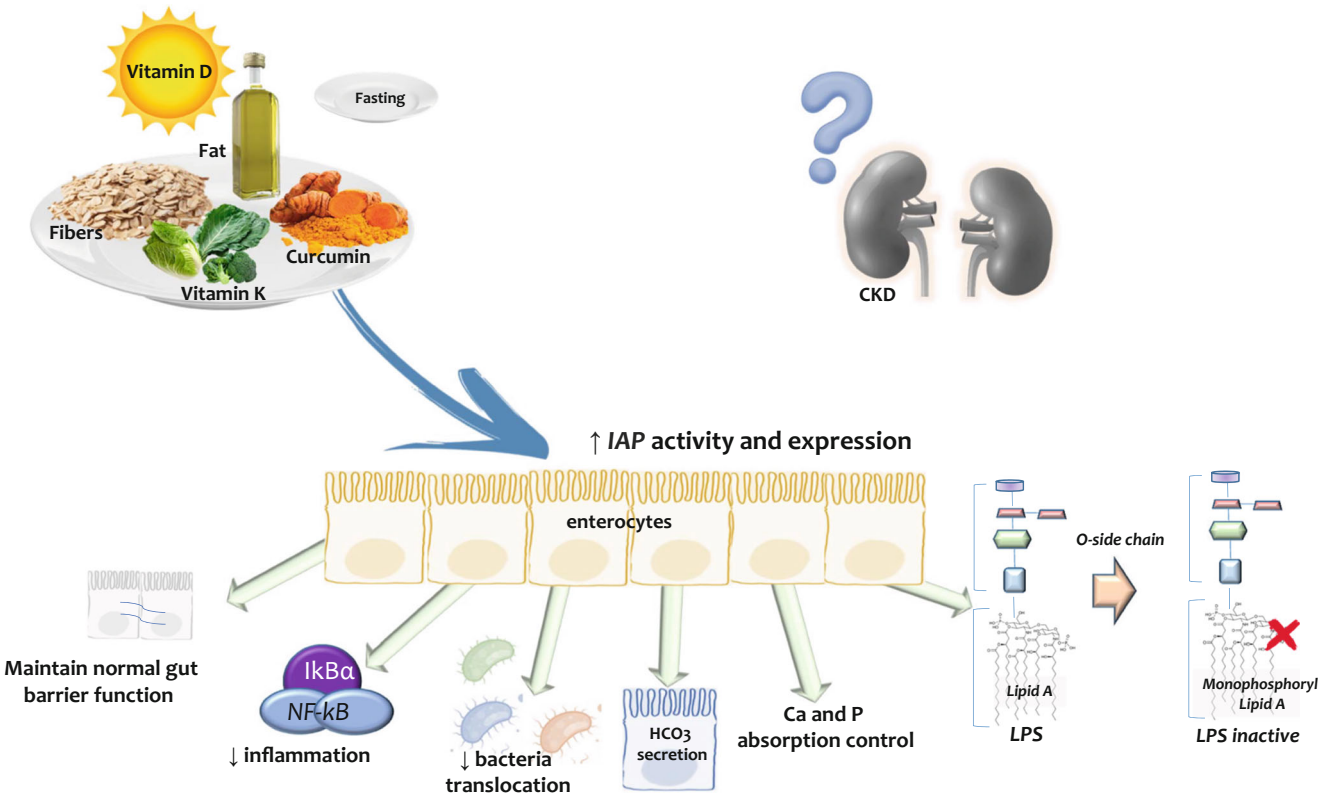

Fig. 1 IAP modulation by food components. Macro- as well as micronutrients and bioactive compounds or fasting influence a range of IAP functions that collectively serve to maintain the homeostasis and structural and functional integrity of the intestine and its transport systems for nutrients, while maintaining the gut barrier function that protects against bacteria translocation. Increased IAP gene expression and activity promoting detoxification of LPS may lead to improvement of both intestinal and systemic inflammation, increase the secretion of bicarbonate, reduce the bacteria translocation and maintain the normal gut barrier function. In patients with CKD, studies are needed to evaluate the possible effects of dietary compounds on IAP activity and expression

function. As well as, IAP could be used as an inflammatory marker together with other markers, such as interleukins to predict inflammation and diseases that are based on the chronic inflammatory process such as intestinal dysbiosis, CVD, obesity, diabetes mellitus in patients with CKD. Currently, it is not common to measure all AP isozymes in patients with CKD. The isoform usually measured is the tAP. However, this review addresses IAP as a potential marker of gut disorders and inflammation in CKD patients and nutritional strategies to IAP modulation, given predictive diagnostics, preventive and personalized medicine by dietary approach. IAP can be determined and quantified in plasma and urine by separating total AP through electrophoresis, as described in the AP biology and activity topic.

Preventive medicine

Through interactions with diet, gut microbiota, and the intestinal mucosal surface from which it is secreted, IAP plays a pivotal role in preserving the intestine and the gut's healthy homeostasis microbiota. This is achieved via regulating the microbial ecosystem, maintaining the integrity of the gut wall, and safeguarding the enterocytes' significant functions, particularly their transport systems for nutrient absorption. At the same time, IAP restricts bacteria's translocation and disarming inflammatory bacterial components by dephosphorylating toxic microbial ligands, such as LPS.

Little is known about the potential consequences of IAP modulation in CKD, but the concept of "food as medicine for CKD" [133] suggests dietary interventions as potentials promoters to target IAP in CKD. The diet's components promoting detoxification of LPS, leading to prevention or amelioration of intestinal and systemic inflammation processes, and normalization of the gut barrier function are described in Fig. 1.

Future of personalized medicine

Personalized nutrition can be used to prevent diseases or complications related to the disease. Concerning CKD, possibly the dietary treatment, according to the characteristics of the disease and the patients, may benefit the patient about quality of life, prognosis, and mortality decrease. The assessment of nutritional status, biochemical tests, including inflammatory markers, oxidative stress, and gut microbiota assessment can lead to secondary benefits to patients since monitoring these conditions even before the installed disease can prevent the onset of previous intervention. In the future, it is believed that the evaluation of the specific genotype of patients will be of a significant increase in personalized nutrition.

Therefore, further experimental studies are needed using models mimicking CKD to evaluate possible effects of dietary compounds on IAP activity and expression and to study whether and how such interventions may promote intestinal health and reduce local and systemic inflammation in CKD. In this context, PPPM can help identify the problem and find a solution to mitigate CKD complications.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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