Invited review article

Dietary phosphorus and phosphorus management in patients with chronic kidney disease

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Keywords: chronic kidney disease, phosphorus, phosphorus-to-protein ratio, bioavailability, boil
Accepted: 28 January 2019

Abstract

Among patients with chronic kidney disease (CKD), it is very important to control serum phosphate levels. Elevated serum phosphorus is a major etiologic factor associated with increased cardiovascular morbidity and mortality secondary to osteoporosis or calcification of blood vessels in these patients. To prevent excessive phosphorus intake, it is better to reduce the amount of dietary phosphorus intake; however, foods containing large amounts of phosphorus generally also include large amounts of protein. Therefore, minimizing phosphorus intake should not involve an avoidance of any and all foods containing phosphorus. In recent years, processed foods have become widely available and phosphorus intake from processed foods with phosphorus additives has increased. Since the bioavailabilities of phosphorus in plant-based foods, animal-based foods, and food additives are different, it is necessary to consider the origin of the phosphorus being ingested. However, it seems that clear evidence regarding phosphorus bioavailability has yet to be obtained.

Introduction

In Europe in 1669, Brand, an alchemist, discovered phosphorus as a substance that shone in the urine [1]. Since elemental phosphorus is highly reactive, it is rarely observed to be a free unbound element in nature. Almost all phosphorus molecules exist as part of phosphorus compounds. They are found in large amounts in guanos and bone ash. These have been used as fertilizers for many years and are also widely used in explosives, matches, fireworks, insecticides, and detergents [2, 3]. As can be seen from its initial discovery in human urine, phosphorus is an essential element in the body. It is an indispensable mineral that is highly metabolized and is the fourth most common element among those existing in the body. Phosphorus is essential in all cells to maintain homeostasis [4].

Both organic and inorganic phosphorus forms exist in the human body. Approximately 80% of phosphorus occurs in the bones and teeth as hydroxyapatite bound to calcium as an inorganic phosphorus compound. The remaining phosphorus is present in soft tissues and blood. Phosphorus exists as inorganic phosphate compounds or ions and is responsible for acid / base equilibrium con-

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trol and serum calcium level maintenance.

Some phosphorus exists as organophosphate, for example in phospholipids, phosphoproteins, adenosine triphosphate, creatine phosphate, and nucleic acids. Those forms of phosphorus play important roles in homeostasis and growth in living organisms, specifically in the maintenance of cell membrane structure, lipid forms, carbohydrate and protein metabolism, energy metabolism, regulation of enzyme activity, and nucleic acids [2, 5-7].

Phosphorus absorption in animals occurs via passive transport, by diffusion from the intercellular space of the intestinal tract, and active transport through transporters. The absorbed phosphorus enters the blood and is transported to various tissues including bone [5, 6]. Phosphorus metabolism is controlled by parathyroid hormone (PTH) produced in the parathyroid gland, fibroblast growth factor 23 (FGF23) produced in bone, and activated vitamin D (1,25 (OH) 2D), which is activated in the kidneys. An increase in serum phosphorus increases the secretion of PTH and FGF23 and inhibits phosphorus reabsorption in the kidney. When serum phosphorus levels decrease, phosphorus reabsorption increases, which prevents the loss of phosphorus through urinary excretion [6,8,9]. Consequently, higher dietary phosphorus intake increases phosphorus excretion by the kidneys. In a healthy person, phosphorus transition and release into bones or tissues are in an equilibrium and the phosphorus absorbed from the gastrointestinal tract is almost equal to the amount excreted into the urine [5,6]. Here we introduce various factors related to phosphorus intake of CKD patients with hyperphosphatemia and healthy people, recent research on reducing phosphorus through cooking and diet, and bioavailability of phosphorus.

1. Phosphorus ingestion

The standard intake of phosphorus for adults should be 1000 mg/day for men and 800 mg/day for women according to the Dietary Reference Intakes for Japanese, 2015 [10]. Figure 1 shows the change of the dietary intake of Japanese phosphorus and protein investigated by National Health and Nutrition Survey [11]. Japanese people consumed 1143 mg/day of phosphorus in the year 2000 when they began investigating the dietary phosphorus intake. Dietary intake decreased until 2011, although it continued to exceed the standard reference intake value. After 2011, it increased gradually and in 2016, the intake was 1044 mg/day for men and 916 mg/day for women, both of which exceeded the standard intake values. As will be described, dietary protein also exceeds the recommended amount and both protein and phosphorus intake have shown almost the same fluctuations. However, it should be noted that the National Health and Nutrition Survey has not calculated or reported the exact values of phosphorus in food additives. The composition of each element in the diet investigated has been calculated from the values listed in the Standard Tables of Food Composition in Japan (Table of Food Composition) so that processed foods or cooked dishes not listed in this table are determined by separating them into ingredients in this survey. At that time, phosphorus derived from food additives was not added to the calculation of phosphorus intake because additives in foods could not be accounted for. Therefore, it is highly possibility that phosphorus intake is underestimated [12]. According to the survey of phosphate compound intake by the market basket method in 2013 [13], the intake of phosphorus compounds used in binders was 265.6 mg/person/day for adults. This value is equivalent to 25% to 33% of the standard intake value. Since this survey represents the phosphate compounds derived from only two kinds of binders, it would show higher levels if additional phosphorus intake forms other than solely phosphorus additives were added to the survey.

The phosphorus intake of 32 Japanese young people was examined using a 24-hour urine col-

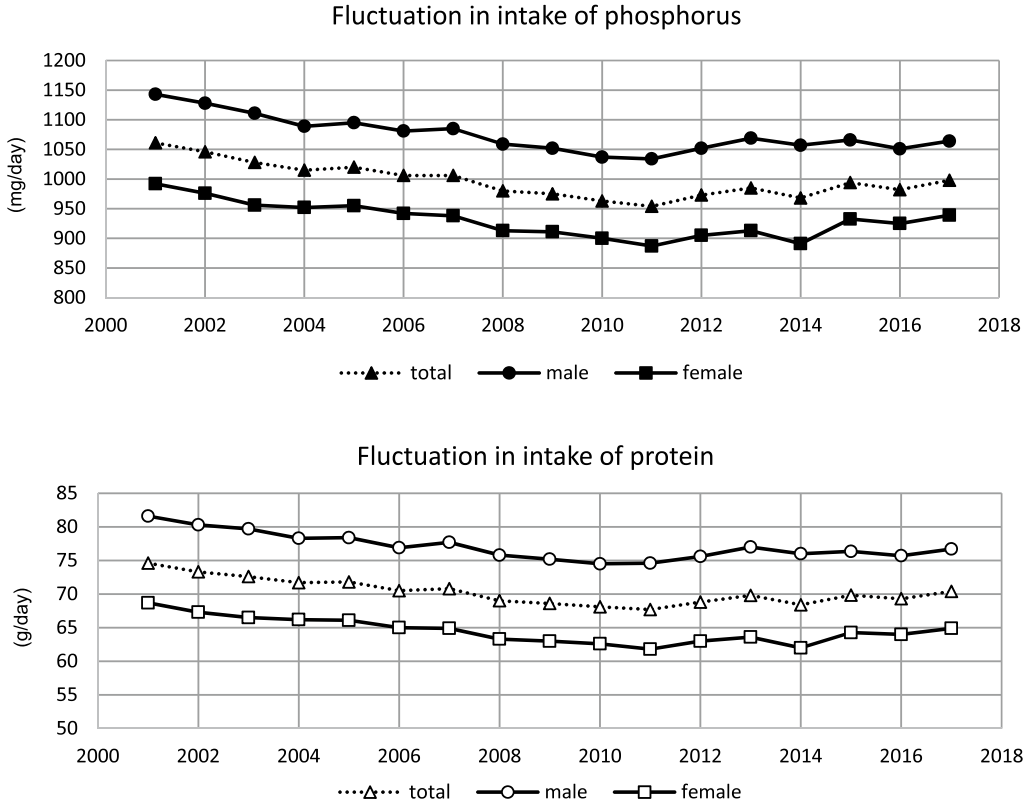

Figure 1. Fluctuation in intake of phosphorus and protein in Japanese over the past 20 years. (Drawn from the data of National Health and Nutrition Survey [11]).

lection method. The average estimated phosphorus intake was 951 mg/day (range, 564 -1445 mg/day) [14]. In addition, the daily intake of 219 Japanese women determined by a weighing of dishes method showed that the intake was, on average, 1223 mg/day [15]. It is the same in Western countries, wherein phosphorus additives could contribute to an increase in phosphorus intake. In Europe, 50% of the total phosphorus intake is reported to be derived from food additives [16]. In the United States, dietary phosphorus intake from phosphorus-containing additives was 320 mg/day on average in 1979 but increased to 470 mg/day in 1990 [17]. In recent years it has been estimated that the intake of phosphorus from food additives exceeds 1000 mg/day depending on the choice of food [18]. Specially, more than 50% of young and middle-aged men take in 1600 mg/day of phosphorus. It is speculated that the increase in fast food consumption has contributed to the increase in phosphorus intake [19].

2. Hyperphosphatemia in patients with CKD

Higher dietary phosphorus intake rarely leads to major changes in serum phosphorus concentrations in people with normal or partly attenuated renal function, as long as the renal fractional excretion of phosphorus can be proportionately increased [20]. However, as CKD progresses, the number of functional glomeruli and tubules decreases, the blood flow rate and filtration flow rate per glomerular body increase, and the intravascular pressure of the capillary blood vessels increases. This causes the glomeruli to harden and their

Table 1. Phosphorus/protein ratio of raw and boiled natural foods estimated from Tables of Food Composition (2015).

Classification	Foods	Protein (g/100g)	Phosphorus (mg/100g)	Phosphorus/ protein ratio	Fluctuation of raw and boiled phosphorus/ protein ratio (%)	Weight change of 100g of dried or raw foods (g)	Protein amount of boiled foods converted to 100g of dried or raw foods (g)	Phosphorus amount of boiled foods converted to 100g of dried or raw foods (mg)
Cereals	Rice (raw)	6.1	95	**15.6**				
	Rice (boied)	2.5	34	**13.6**	87	210	2.9	45
	Udon (dried)	8.5	70	**8.2**				
	Udon (boiled)	3.1	24	**7.7**	94	240	3.5	29
	Spaghetti (dried)	12.2	130	**10.7**				
	Spaghetti (boiled)	5.4	52	**9.6**	90	220	5.5	59
	Soba (dried)	14.0	230	**16.4**				
	Soba (boiled)	4.8	72	**15.0**	91	260	5.4	88
Potatoes	Potato (raw)	1.6	40	**25.0**				
	Potato (boiled)	1.5	25	**16.7**	67	97	1.6	41
	Taro (raw)	1.5	55	**36.7**				
	Taro (boiled)	1.5	47	**31.3**	85	95	1.6	58
Pulses	Kidney bean (raw)	19.9	400	**20.1**				
	Kidney bean (boiled)	8.5	150	**17.6**	88	220	9.0	182
	Pea (raw)	21.7	360	**16.6**				
	Pea (boiled)	9.2	65	**7.1**	43	220	9.9	164
	Soybean (raw)	33.8	490	**14.5**				
	Soybean (boiled)	14.8	190	**12.8**	89	220	15.4	223
Vegetables	Cabbage (raw)	1.3	27	**20.8**				
	Cabbage (boiled)	0.9	20	**22.2**	107	89	1.5	30
	Japanese radish (raw)	0.4	17	**42.5**				
	Japanese radish (boiled)	0.5	14	**28.0**	66	86	0.5	20
	Onion (raw)	1.0	33	**33.0**				
	Onion (boiled)	0.8	25	**31.3**	95	89	1.1	37
	Carrot (raw)	0.8	25	**31.3**				
	Carrot (boiled)	0.7	26	**37.1**	119	87	0.9	29
	Broccoli (raw)	4.3	89	**20.7**				
	Broccoli (boiled)	3.5	66	**18.9**	91	110	3.9	81
	Spinach (raw)	2.2	47	**21.4**				
	Spinach (boiled)	2.6	47	**18.1**	85	70	3.1	67
Fishes and shellfishes	Japanese Jack mackerel	19.7	230	**11.7**				
	Japanese Jack mackerel (boiled)	22.4	250	**11.2**	96	87	22.6	264
	Japanese pilchard (raw)	19.2	230	**12.0**				
	Japanese pilchard (boiled)	22.4	250	**11.2**	93	81	23.7	284
	Chum salmon (raw)	22.3	240	**10.8**				
	Chum salmon (boiled)	25.5	250	**9.8**	91	83	26.9	289
	Mackerel (raw)	20.6	220	**10.7**				
	Mackerel (boiled)	22.6	210	**9.3**	87	84	24.5	262
	Brown sole (raw)	19.6	200	**10.2**				
	Brown sole (boiled)	21.4	200	**9.3**	92	91	21.5	220
	Red sea bream (raw)	20.6	220	**10.7**				
	Red sea bream (boiled)	22.2	260	**11.7**	110	85	24.2	259
	Snow crab (raw)	13.9	170	**12.2**				
	Snow crab (boiled)	15.0	150	**10.0**	82	74	18.8	230
	Common scallop (raw)	13.5	210	**15.6**				
	Common scallop (boiled)	17.6	250	**14.2**	91	82	16.5	256
	Kuruma prawn (raw)	21.6	310	**14.4**				
	Kuruma prawn (boiled)	28.2	390	**13.8**	96	95	22.7	326
	Short-finned squid (raw)	17.9	250	**14.0**				
	Short-finned squid (boiled)	21.9	280	**12.8**	92	76	23.6	329
	Common octopus (raw)	16.4	160	**9.8**				
	Common octopus (boiled)	21.7	120	**5.5**	57	81	20.2	198
Meats	Wagyu beef thigh without subcutaneous fat (raw)	20.2	170	**8.4**				
	Wagyu beef thigh without subcutaneous fat (boiled)	25.7	120	**4.7**	55	65	31.1	262
	Imported beef thigh without subcutaneous fat (raw)	20.0	170	**8.5**				
	Imported beef thigh without subcutaneous fat (boiled)	30.0	130	**4.3**	51	67	29.9	254
	Pork thigh without subcutaneous fat (raw)	21.5	210	**9.8**				
	Pork thigh without subcutaneous fat (boiled)	28.9	190	**6.6**	67	71	30.3	296
	Chicken thigh without skin (raw)	19.0	190	**10.0**				
	Chicken thigh without skin (boiled)	25.1	190	**7.6**	76	70	27.1	271

numbers further decrease [21]. As renal function decreases, phosphorus will be stored in the body, serum phosphorus concentration will rise, and hyperphosphatemia will develop. PTH secretion then increases due to prolonged excessive amounts of phosphorus in serum, which leads to secondary hyperparathyroid hyperplasia. This promotes bone resorption, resulting in decreased bone mass and bone fragility.

Phosphorus and calcium combine in the arteries to cause mineralization (ectopic calcification), which increases the risk of fatal myocardial infarctions and cerebral infarctions. Furthermore, as the serum phosphorus concentration increases, the concentration of FGF23 also increases. It has been shown that an increase in the concentration of FGF23 is also a factor in the development of cardiovascular diseases such as cardiac hypertrophy [5, 22-24]. Ectopic calcification is closely related to prognosis. Follow-up surveillance of patients with CKD has shown that those with vascular calcifications have a poor prognosis and are associated with a high rate of mortality due to cardiovascular disease [25-27]. Additionally, the rate of CKD progression is directly related to the serum phosphorus concentration [28]. From the annual mineral values (phosphorus, calcium, PTH) and mortality in a 3-year cohort of hemodialysis patients, phosphorus would be the strongest predictor for highmortality [29]. Therefore, within the medical guidelines for bone mineral metabolism abnormalities that accompany CKD according to the Japan Society of Dialysis Medicine, serum phosphorus concentration is regarded as the target with the highest management priority in patients with CKD [30].

Elevated serum phosphorus levels may cause cardiovascular disease even in patients without CKD based on the demonstration of a positive correlation between serum phosphorus concentration and cardiovascular mortality [31-33]. Excessive intake of phosphorus increases serum phosphorus levels in patients with CKD as well as healthy people [34]. Therefore, even healthy people should avoid excessive intake of phosphorus.

3. Relationship between phosphorus and protein

Until hemodialysis was introduced, protein was restricted in patients with CKD to delay progression leading to renal insufficiency since excess of protein intake promotes glomerular injury and nitrogen compound accumulation causes uremia [35]. However, when hemodialysis was introduced, it became necessary to ingest appropriate amounts of protein. Controlling serum phosphorus levels in patients with CKD by maintaining adequate dietary phosphorus intake leads to an improved prognosis. However, among patients on dialysis who have insufficient dietary intake, lowering serum phosphorus levels can also risk worsening of the overall prognosis [36]. Based on Shinaberger's report that the hazard ratio for all-cause death was significantly higher when the intake of protein exceeded 1.4 g / kg / day, or was less than 0.8 g / kg / day [37], the Japanese Society of Dialysis Medicine advocated that the lower limit of protein intake should be 0.9 g / kg / day, and the upper limit should be 1.2 g / kg / day. This would avoid excess phosphorus intake as a function of protein intake in patients on chronic dialysis [38]. Protein deficiency invites protein energy wasting and is a major risk for patients with CKD [23].

Therefore, it is strongly recommended that the diet of patients with CKD consist of a necessary amount of protein, but with lower overall phosphorus content [39] and the phosphorus-to-protein ratio should be less than 10 (mg of phosphorus /g of protein) [24]. However, the protein and phosphorus contents in foods are highly correlated. Thus, protein and phosphorus intake are also correlated [40,41] (Figure 2), making it necessary for patients with CKD to closely monitor their intake of protein, as it tends to affect the intake of phosphorus. A 5-year cohort study that used food frequency questionnaires to evaluate 224 patients on hemodialysis showed that higher dietary phospho-

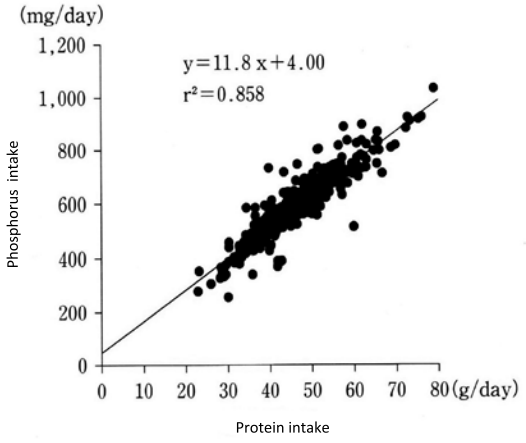

Figure 2. Relationship between protein and phosphorus intake [41].

rus intake and intake of foods with higher phosphorus-to-protein ratios were independently associated with an increased death risk in patients on hemodialysis [42].

Boaz et al. [40] investigated the dietary intake of patients on dialysis and established a formula for dietary phosphorus intake (mg) and protein intake (g): dietary phosphorus (mg) = 128 mg phosphorus + 14 mg phosphorus × protein (g). In the same way, Kalantar-Zadeh et al. [2] created another formula for phosphorus intake: phosphorus (mg) = 78 mg phosphorus + 11.8 mg phosphorus × protein (g), and Cupisti et al. [43] developed the following formula for dietary phosphorus intake: phosphorus (mg) = 102 mg phosphorus + 12.9 mg phosphorus × protein (g).

Applying these formulas to determine the average phosphorus intake from a ~70 g of protein intake in a Japanese adult, the daily phosphorus intake would be 1108, 904, and 1005 mg respectively; the closest value was obtained with the formula established by Cupisti et al. In addition, the average phosphorus-to-protein ratio in a Japanese diet is around 14.2 when calculated using the value for phosphorus and protein intake of the National Health and Nutrition Survey; however, it could actually be even higher, as mentioned previously.

For these reasons, it is necessary for patients with CKD as well as healthy persons to avoid excessive phosphorus intake. This also means that it is necessary to reduce the phosphorus content while maintaining the protein content in food, which can be accomplished by certain cooking methods.

4. Phosphorus in food and reducing phosphorus through cooking

Since natural foods arise from organisms, they always contain phosphorus. However, many processed foods use various inorganic phosphorus compounds as food additives, so the amount of phosphorus in processed foods is often higher than it is in natural foods. In this section, we describe the phosphorus contents in natural and processed foods, and discuss a method of reducing the amount of phosphorus through cooking.

1) Natural foods

Natural foods include animal-based and plant-based foods. Animal-based foods such as meat, milk, and eggs are important protein sources and many of those proteins, carbohydrates, and lipids are esters that are bound to phosphorus. According to the Table of Food Composition (2015) [44], many varieties of meat and fish contain phosphorus at a about 200 mg / 100 g of fresh weight. However, the amount of phosphorus in fish fluctuates greatly compared with other meats because the fat mass varies greatly depending on the fishing season. For example, differences in phosphorus content of 60% among rabbitfish and 23% among white seabream have been documented [45]. There is also a big difference in phosphorus content between egg yolk and egg white. Although egg contains 180 mg of phosphorus / 100 g of fresh weight, the egg yolk (570 mg of phosphorus / 100 g of fresh weight) and the egg white (11 mg of phosphorus / 100 g of fresh weight) [44], with phosphorus-to-protein ratios of 34.5 and 1.0, respectively. The phosphorus-to-protein ratio of

dairy products is relatively high, for example, it is 28.2 for milk.

The chemical form and content of phosphorus in plant-based foods vary depending on the parts or the maturity of the plants. Young leaves as in leafy vegetables have a higher proportion of inorganic phosphoric acid. Foods derived from seeds such as cereals, legumes, and nuts contain phosphorus in storage forms such as phytin or phytic acid [3,46]. Foods originating from seeds are particularly rich in phosphorus, with the amount of phosphorus often being as high as 500 mg / 100 g of fresh weight or more. In contrast, vegetables, fruits, and mushrooms have relatively low phosphorus contents. However, the phosphorus content is high in premature beans such as the young broad bean and Edamame (young soybean). Since the amount of protein is not substantial in plant-based foods, with the exception of some foods such as soybeans, the phosphorus-to-protein ratio is not so important.

Many researchers have described recipes for reducing the phosphorus content in foods. Jones et al. [47] reported that the phosphorus content of some animal- and plant-based foods decreased to 18-84% when they were placed in hot water at 40 °C or 100 °C, stirred vigorously, and then left for 2-8 hours. Vrdoljak et al. [48] studied the changes in protein and phosphorus with various cooking methods and found that when food is cooked by heat, the protein content changes very little; however, the phosphorus content tends to be reduced more with boiling or stewing in a mixture of oil and water, compared to other cooking methods. With these recipes, the phosphorus content decreased to 27-43% for vegetables, 10-49% for meat, 7% for pasta, and 23% for rice. Cupisti et al. [49] found that the phosphorus content was reduced significantly more than protein when minced beef and chicken breasts were boiled for 30 minutes. The rate of decrease in the phosphorus-to-protein ratio was 77-44% after boiling, assuming 100% before boiling. In addition, Ando et al. [50] reported that the reduction of phosphorus and protein was dependent on the shape of the meat mass during boiling. They compared the amount of phosphorus and protein in boiled block beef versus sliced beef. Both the phosphorus and protein contents decreased in the sliced meat more than they did in the block meat and the sliced meat showed a considerable reduction in protein-to-phosphorus ratio. We investigated in detail the changes in the phosphorus and protein content of yellowtail meat by boiling. Both phosphorus and protein decreased in proportion to the surface area of the meat and the reduction of phosphorus was more remarkable (unpublished data). We also examined in detail the reduction of phosphorus in spaghetti by boiling. When boiling noodles for a long time, phosphorus decreased, but when there was not enough boiling water, the phosphorus seeped back into the spaghetti. It was confirmed that a sufficient amount of boiling water is necessary to reduce the amount of phosphorus and that the phosphorus content could be further reduced by washing the boiled spaghetti [51].

These reports showed that phosphorus and the phosphorus-to-protein ratio can be reduced by thinning or cutting the foods prior to boiling them. Moreover, the phosphorus content in foods is reduced with prolonged boiling in a sufficient amount of water. Uehara et al. reported that, regarding rice, the amount of phosphorus can be reduced by washing it sufficiently before cooking [52]. They showed that the amount of phosphorus in rice was reduced by half after washing the rice five times with water.

Table 1 shows the values of phosphorus and protein, the rate of change in the weight of the food caused by boiling, and variations of phosphorus, protein, and phosphorus-to-protein ratio calculated from the value in Table of Food Composition (2015), of representative foods that have both their raw and boiled forms listed. The findings presented cannot be directly compared with the previous report since the heating time is not de-

scribed in the Table of Food Composition (2015), but it can be seen that phosphorus reduced more than protein by boiling for many foods, except some foods such as carrots and sea bream, and that the phosphorus-to-protein ratio in meat decreased compared to that of the other food groups.

2) Food additives

Food additives containing phosphorus are widely used as manufacturing agents for binders, brines, cheese emulsification, nutrition enhancements for iron and calcium, acidulants, and seasonings for flavor enhancement.

Almost all of these food additives consist of inorganic phosphorus, and include compounds such as orthophosphoric acid, pyrophosphoric acid, and condensed phosphate such as polyphosphoric acid or metaphosphoric acid. Among them, polyphosphoric acid and pyrophosphoric acid are most commonly used in processed meat products and are used for reducing processing losses, retarding denaturation by oxidation, maintaining color, preventing bacterial growth, and improving texture [23]. In Japan, there are 30 different phosphate compounds that are currently permitted for use as food additives [53] (Table 2).

Table 2. Food additives including phosphorus permitted in Japan.

Purpose	Substance
Thickening stabilizer, manufacturing agent	Acetylated Distarch Phosphate, Distarch Phosphate, Hydroxypropyl Distarch Phosphate, Monostarch phosphate, Phosphated Distarch Phosphate
Manufacturing agent	Potassium pyrophosphate, Disodium dihydrogen pyrophosphate, Sodium pyrophosphate, Potassium polyphosphate, Sodium polyphosphate, Potassium metaphosphate, Sodium metaphosphate, Diammonium hydrogen phosphate, Ammonium dihydrogen phosphate
Nutritional enhancer, manufacturing agent	Calcium dihydrogen pyrophosphate, Trimagnesium phosphate, Calcium dihydrogen phosphate
Nutritional enhancer	Calcium glycerophosphate, Ferric pyrophosphate
Coloring agent, nutritional enhancer	Riboflavin 5'-phosphate sodium
Acidulant, manufacturing agent	Phosphoric acid
Seasoning, manufacturing agent	Tripotassium phosphate, Dipotassium hydrogen phosphate, Potassium dihydrogen phosphate, Disodium hydrogen phosphate, Sodium dihydrogen phosphate, Trisodium phosphate
Gum base, nutritional enhancer, manufacturing agent	Tricalcium phosphate, Calcium monohydrogen phosphate
Nutritional enhancer, yeast food	Magnesium monohydrogen phosphate

Watanabe et al. [54] studied the protein and phosphorus levels in foods ingested by patients with CKD using a food frequency questionnaire. They found that proteinaceous foods containing phosphate additives contained about twice as much phosphate per gram of protein as fresh foods. León et al. [55] analyzed the amount of phosphorus in some of the top-selling processed foodstuffs and found that an average of 44% of these foods contain phosphorus additives, with more than 67 mg phosphorus / 100 g compared to foods without additives. They also compared the daily phosphorus amount in a meal consisting of processed products containing phosphorus additives and a meal containing no additives. They estimated that the former contained 736 mg more phosphorus than the latter. Sullivan et al. [56] examined 38 kinds of chicken processed products and found that 35 of them used phosphorus additives that included 128-317 mg phosphorus / 100 g. In the equivalent products, the phosphorus content of foods containing additives was significantly higher. In a study by Benini et al. [57], 10 products with and without additives were examined, including ham, roast turkey, and roast chicken breast meat. Foods containing phosphorus additives had about 70% higher phosphorus content on average than foods without additives, but there was no significant difference in the amount of nitrogen. In addition, Cupisti et al. [58] compared the amount of inorganic phosphorus, phosphoprotein, and phospholipid in 20 different ham varieties with and without food additives. The ham with food additives had more than 66% of inorganic phosphorus on average compared with the ham without additives, but there was no significant difference in the phosphorus in proteins and lipids. The phosphorus-to-protein ratio was 16.7 in the foods with additives and 9.8 in the foods without

additives. As described above, the phosphorus content in processed foods containing food additives was higher than that in additive-free processed foods in all the papers reported so far.

Table 3 shows the phosphorus-to-protein ratios of processed livestock and dairy products calculated from the values of the Table of Food Composition. Ham, bacon, and sausage, all processed pork products, had a higher phosphorus-to-protein ratio than natural pork. Dairy products were also originally higher in phosphorus-to-protein ratio than other foods. In particular, the phosphorus-to-protein ratio of processed cheese was higher than that of natural cheese, which is considered to be due to the phosphate additives used as emulsifiers.

We compared the phosphorus content in foods with and without additives among commercially available hams, sausages, bacons, and salmon flakes, and found that there was significantly more phosphorus in the foods with additives, except for the salmon flakes [59]. We also analyzed the phosphorus contents in bread, packed cooked rice, boiled Japanese noodles (udon), and steamed Chinese noodles, based on the presence or absence of yeast food, acidulants, and pH adjusters, which could contain phosphorus. We found that there was no significant difference between the foods with and without food additives [60]. These food additives that are used in these processed foods also include substances other than phosphate compounds. Currently in Japan, food additives are described by their chemical substance names in principle. But, there are food additives that are used for 14 specific purposes (i.e., gum bases, bittering agents, yeast food, etc.), can be listed according to their purpose rather than having to be listed by their specific chemical substance name, and the above food additives are included in this groups. There is also no obligation to indicate the amount of phosphorus in the nutritional display in Japan. Therefore, even for similar foods, it is difficult to determine whether phosphorus additives are present in the food, or to determine the amount of phosphorus from the food material display or package nutrition displays. According to the rules of the European community, manufacturers are obligated to display whether a food contains phosphate or polyphosphates on food labels, but the amount of phosphorus contained in the food is not required to be the displayed [61]. It is our opinion that, in Japan, food labels should at least display the chemical name of all food additives.

The amount of phosphorus in processed foods with phosphorus additives can also be reduced by boiling, as with natural foods. For example, one study reported that when cheddar cheese was immersed in hot water at 100°C, stirred, and then left standing for 1 hour, the amount of phosphorus decreased by 19% [47]. In another report, boiling sausage for 3 minutes resulted in a 7.9% decrease in phosphorus content, and boiling it after cutting it to 1/8th the original size decreased the phosphorus content by 11.8% [62]. However, many pro-

Table 3. Phosphorus/protein ratio of processed meat products and dairy products estimated from Tables of Food Composition (2015).

Foods	Protein (g/100g)	Phosphorus (mg/100g)	Phosphorus / protein ratio
Pork thigh without subcutaneous fat (raw)	21.5	210	**9.8**
Uncured ham (forcing)	24.0	200	**8.3**
Dry sausage	25.4	240	**9.4**
Regular ham	16.7	210	**12.6**
Frankfurt sausage	12.7	170	**13.4**
Vienna sausage	13.2	190	**14.4**
Bologna sausage	12.5	210	**16.8**
Pressed ham	15.4	260	**16.9**
Bacon	12.9	230	**17.8**
Boneless ham	18.7	340	**18.2**
Loin roll ham	16.5	340	**20.6**
Milk	3.3	93	**28.2**
Cottage cheese	13.3	130	**9.8**
Cream cheese	8.2	85	**10.4**
Mozzarella	18.4	260	**14.1**
Camembert	19.1	330	**17.3**
Gouda	25.8	490	**19.0**
Parmesan	44.0	850	**19.3**
Cheddar	25.7	500	**19.5**
Blue cheese	18.8	440	**23.4**
Emmental cheese	27.3	720	**26.4**
Processed cheese	22.7	730	**32.2**
Cheese spread	15.9	620	**39.0**
Cream	2.0	50	**25.0**
Cream made from vegetable fat	6.8	210	**30.9**

cessed foods tend to taste better with the phosphorus additives. The flavor and deliciousness of the foods may be sacrificed because of the boiling process.

5. Phosphorus bioavailability

The actual intake of phosphorus and its bioavailability are greatly related. As mentioned above, phosphorus is absorbed in its inorganic form. The bioavailability of phosphorus from different dietary sources has not been studied in humans, although the bioavailability of phosphorus has been investigated in the livestock industry. As such, all the estimates of bioavailability in past study are based on extrapolations from animal data [63]. By these estimates, the proportion of phosphorus absorbed throughout the gastrointestinal tract is probably 60% of ingested phosphorus on average, but the bioavailability of phosphorus varies with food type. Phosphorus in animal-based foods such as meat or fish exists primarily as intracellular organic compounds and is well-absorbed, as it is easily hydrolyzed and released as inorganic phosphorus in the intestinal tract. Therefore, the bioavailability of phosphorus is relatively high and estimated to be 60-80% [19,61,63,64]. Plant-based foods such as cereals or legumes contain a large amount of phytic acid. Phytase is not expressed in humans, so they are only minimally digested by the intestinal flora or by non-enzymatic hydrolysis reactions. This results in the reduced bioavailability of phosphates from plant-based foods, which is estimated to be 30-40% [61,64,65]. Since most phosphorus additives include inorganic phosphorus, they are considered to be easily digested with bioavailabilities of 90-100% in many reports [2,34,64,66]. Karp et al. [67] conducted experiments on digestive enzymes that were applied to dairy and meat products *in vitro*, to mimic their digestion in the alimentary canal. They dialyzed them and estimated the amount of digestive phosphorus from the amount of phosphorus contained in the dialysate. As a result, the proportion of digestible phosphorus to the total phosphorus was higher in processed foods containing phosphorus compounds as food additives such as processed cheese, ham, and sausage, compared with non-additive products such as milk, unprocessed cheese, and raw meat. They conducted similar experiments with plant-based foods and drinks [68] and showed that the proportion of digestible phosphorus in rye bread, sesames, and legumes was 59%, 6%, and 38%, respectively, of the total phosphorus content. However, that of muffins containing sodium phosphate as a swelling agent was 95% and that of cola and beer was 84-100%. They reported that food containing additives had a high proportion of digestible phosphorus.

On the other hand, St. Jules and colleagues [69] compared four articles [66, 69-71] on the bioavailability of phosphorus, focusing on the ratio of urinary excreted phosphorus content to the type of phosphorus in ingested food. Moe et al. [66] showed that the relative amount of urinary phosphorus was notably higher in an animal-based diet (72%) than in a plant-based diet (52%) even though the amount of phosphorus in both foods was almost the same. This result indicates that foods in the animal-based diet have higher bioavailability than those in plant-based diet. The other three papers examined urine phosphorus levels after ingestion of diet or nutrition supplements containing phosphoric acid with or without additives. The total amount of phosphorus excreted from urine increased as the intake increased in either case, but the ratio of phosphorus excretion in the urine to total phosphorus ingested was not notably different.

Scanni et al. [72] reported that 73% of a sodium phosphate continuously administered by a nasoduodenal feeding tube over a 36-hour period was recovered in the urine, compared to 100% of intravenously infused sodium phosphate. From these facts, it seems that inorganic phosphorus is not completely absorbed from the digestive tract, and the bioavailability of phosphorus additives is not

remarkably high. They presumed that it may have been related to nutrient-nutrient interactions that occurred in the digestive tract. They surmised that those interactions rendered inorganic phosphorus less bioavailable as it bound to minerals, or that the higher phosphorus content of the diets containing phosphorus additives [34,71] resulted in reduced phosphorus absorption, either directly by saturating transporters or indirectly by suppressing calcitriol production [72].

Phosphorus absorption is influenced by the intake of phosphorus and calcium. In rat experiments, the apparent phosphorus absorption was higher with low calcium diets than with normal calcium diets when the amount of ingested phosphorus was kept relatively constant [73]. As Japanese people tend to have a lower calcium intake than people in Western countries, the excessive intake of phosphorus cannot be ignored [74].

Phosphate adsorbents are administered to lower serum phosphorus levels in patients with CKD. Some of these adsorb food-based phosphorus to calcium, lanthanum, or iron, which is subsequently excreted from the body [75]. As is also presumed from this, it seems likely that inorganic phosphorus compounds such as food additives bind with other compounds in foods and change them to hardly digestible compounds. Furthermore, calcitriol increases the absorption of phosphorus [5,76], and the absorption of phosphorus is affected by the content of vitamin D in food and the vitamin D status of the patient. The absorption of phosphorus is also affected by nicotinamide (niacin), which is present in high amounts in fish and meat. Since nicotinamide inhibits the phosphate transporter, serum phosphorus levels decrease when nicotinamide is administered to patients on hemodialysis [77,78].

6. Diets to reduce phosphorus

In patients with CKD, a food containing the necessary amount of protein but less phosphorus is ideal. An example of such a food is the egg white. Taylor et al. [79] reported that patients with CKD who consumes 225 g of pasteurized liquid egg white every day for 6 weeks, showed a decrease in serum phosphorus and an increase in serum albumin.

In a study investigating the effects of animal- and plant-based foods on serum phosphorus levels in 13 patients with CKD, an omnivorous diet containing 70% protein from plants was administered for 4 weeks. They found that the phosphorus in urine decreased significantly [80]. Another study of a crossover tests of vegetarian (containing about 95% of plant-derived protein) and meat (about 20% of them) diets, both containing almost the same nutrients for one week, showed that the concentration of serum phosphorus and FGF23 levels were significantly decreased among those who consumed the vegetarian diet [66]. These reports indicate that diets rich in plant-based foods can reduce serum phosphorus levels. Sanchis et al. [81] investigated the relationship between mineralization of the abdominal aorta and intake frequency of legumes, cereals, and seeds. They reported that calcification was mild in the group that ingested a large amount of these foods. The reason for this is largely due to the phytates and phytic acid in plant-based foods. Furthermore, according to an animal experiment on the effects of phytic acid, mineralization was not observed in the cortical junction of male rats by adding 1% phytic acid to the diet which usually caused mineralization. This suggests that phytic acid may actually have the effect of inhibiting calcification [82]. Moreover, Delgado-Andrade et al. suggested that the digestibility of phosphorus was reduced by a Maillard reaction in products prepared by frying and roasting and that those products suppressed phosphorus absorption based on the amount of phosphorus observed in the feces [83]. Williams et al. [84] argue that limiting dietary grain intake should be reconsidered for patients with CKD in view of the low bioavailability of phytic acid and the benefit of dietary fiber intake.

Sullivan and colleagues compared patients with hyperphosphatemia and CKD who were educated on avoiding foods with phosphorus additives when purchasing their groceries (intervention). They examined the serum phosphorus levels of those who received usual care (control) compared with the intervention group. After 3 months, the serum phosphorus levels in the intervention group became lower than those in the control group [85]. Furthermore, de Fornasari et al. [86] compared an intervention group that received individualized education on replacing processed foods containing phosphorus additives with foods of similar nutritional value without phosphorus additives for 3 months with a control group that received only general nutritional education. Replacing phosphorus-containing foods without additives reduced serum phosphorus levels without interfering with the nutritional status of the patients with CKD. It is obvious that phosphorus levels decrease by avoiding foods containing phosphorus additives.

However, it is problematic that foods without phosphorus additives are generally more expensive. We compared the prices of some processed foods with and without additives and found that, for example, ham and sausage varieties containing no additives were significantly more expensive than those containing additives [59]. Gutiérrez and colleagues [87] investigated the annual income and serum phosphorus levels in the United States and reported that the group with lower annual income tended to have higher serum phosphorus levels compared with a higher annual income group. They presumed that the reason was that the group with the lower annual income was more dependent on processed foods that included more additives such as phosphorus. Leon et al. compared meals containing phosphorus additives and phosphorus additive-free meals in the United States; the phosphorus additive-free meals cost an average of 2 dollars more per day [55]. According to a survey on the actual condition of patients on hemodialysis in Japan [88], households with an annual income of 2 million yen or less account for 22.1% of that population. It is sometimes difficult for low-income patients to purchase foods without phosphorus additives because of the prices. Therefore, low-income patients with CKD may purchase these popular low-cost groceries that include food additives and unknowingly increase their intake of highly bioavailable phosphorus.

As mentioned above, actively choosing and ingesting foods with a low phosphorus-to-protein ratio, boiling foods, substituting plant-based foods for animal-based foods, and avoiding foods that include phosphorus additives as much as possible are effective for improving hyperphosphatemia in patients with CKD. However, boiling food reduces phosphorus content, also decreases mineral micronutrients [89, 90]. Therefore, it is important to pay attention to the potential for mineral micronutrient losses with cooking.

Conclusion

To manage dietary phosphorus in CKD, it is important to focus not only on the phosphorus content of the meal, but also on the chemical structure (inorganic versus organic), type (plant to animal), and phosphorus-to-protein ratio of the foods being ingested. It is known that phosphorus in foods will be reduced by boiling, but it is often unclear how much phosphorus is digested and absorbed after ingesting boiled food. Therefore, further studies will be needed to clarify the changes in chemical structure and bioavailability of phosphorus compounds after food preparation using various cooking methods including boiling, baking, steaming, and frying.

Acknowledgments

We thank Dr. T. Oite for helpful comments on the manuscript. This work was supported by JSPS KAKENHI Grant Number JP 26350132.

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