Dietary Phosphorus

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Phosphorus is one of the essential elements of the human body and is required for a diverse range of processes, such as ATP synthesis, signal transduction, and bone mineralization. Inorganic phosphate (Pi) plays a critical function in many tissues of the body: for example, as part of the hydroxyapatite in the skeleton and as a substrate for ATP synthesis. Pi is the main source of dietary phosphorus. Reduced bioavailability of Pi or excessive losses in the urine causes rickets and osteomalacia.

Keywords: Phosphorus ; phosphate ; NPT2a/2b/2c ; PIT1/2 ; Metabolism

1. Importance of Dietary Phosphorus for Bone Health

Pi is required for proper plate growth and bone development, and along with calcium, it comprises the hydroxyapatite that is deposited during mineralization of the vertebrate skeleton. As a result, Pi is critical for the mineralization process (particularly during the growth spurt at puberty [1]), to maintain bone strength after the closure of the epiphyses [2], and during fracture repair and remodeling [3]. The process of matrix mineralization requires the secretion of matrix vesicles (MVs) by osteoblasts and hypertrophic chondrocytes [4][5]. The phosphatase PHOSPHO1 can liberate Pi from phosphocholine and other lipids in the MV membrane [6]. Pi is also thought to be imported into the MVs via PIT1 [6]. MVs induce hydroxyapatite crystal formation [7]. In the presence of sufficient concentrations of extracellular calcium and Pi, these crystals continue to grow after the dissolution of the MV membrane [7]. The ambient extracellular Pi concentration in bone is maintained by tissue non-specific alkaline phosphatase (TNAP), which is abundant in MVs [6]. TNAP cleaves pyrophosphate (PPi) and other organic bisphosphonates, which generates two Pi molecules [6]. A high Pi/PPi ratio is generally thought to favor mineralization [8][9][10]. Clinically relevant, hypophosphatemic individuals exhibit an increased activity of alkaline phosphatase [11]. This allows bone-specific alkaline phosphatase activity to serve as a marker of Pi homeostasis in the bone [[11].

Dietary phosphorus deprivation impairs cell metabolism and causes skeletal demineralization to occur. Moreover, secondary changes due to the adaptive hormonal response (i.e., upregulation of calcitriol, suppression of PTH and FGF23) can be observed. The main process that stimulates bone resorption is calcitriol-mediated activation of osteoclasts through the receptor activator of NF-κB (RANK)–RANK Ligand (RANKL) signaling [12][13]. This process is more important with prolonged dietary phosphorus deficiency and can cause rickets and stunted growth in children and osteomalacia in adults [14][15].

Chondrocytes produce and maintain the extracellular matrix of joint cartilage and permit the longitudinal growth of long bones through endochondral ossification. Pi is essential for normal hypertrophic differentiation and apoptosis, which was shown in several primary [16][17][18] and stable chondrocytic cell lines [19][20]. Hypertrophic differentiation and apoptosis require the activation of ERK1/2 and the mitochondrial–caspase-9 pathway [21]. These processes are blocked by ablation or pharmacological inhibition of the PIT1 transporter or of the mitogen-activated protein kinase kinase 1 [22]. In addition to the ERK pathway, Pi induces nitrate or nitrite, which stimulates nitric oxide synthase (NOS) production and, in turn, stimulates chondrocyte apoptosis [22]. Furthermore, the acute chondrocyte-specific deletion of Pit1 in mice results in pronounced cell death in the first two postnatal days, possibly owing to Pi transport-independent ER stress [23]. Chondrocytes might also regulate systemic Pi homeostasis by secreting FGF23 [21], but it is unknown whether this is under the feedback control of Pi.
In summary, Pi stimulates hypertrophic differentiation and apoptosis in chondrocytes via PIT1, ERK1 and ERK2, and possibly via NOS, which is necessary for normal bone growth and possibly articular cartilage function.

2. Importance of Dietary Phosphorus for Teeth (or Dental Health)

Among the currently known Pi transporters (Slc34a1, Slc34a2, Slc34a3, Slc20a1, Slc20a2, and Xpr1), SLC20A2/PIT2 is the most highly expressed in teeth [24]. However, knockout mouse models showed that no single transporter is essential for initiation of the mineralization process [24]. PIT1 is expressed in ameloblasts and odontoblasts, while PIT2 is expressed in the subodontoblastic cell layer and the stratum intermedium of ameloblasts [25]. PIT2 appears to be involved during the mineralization of dentin, as suggested by the dentin dysplasia described in the global Pit2 knockout [24]. Slc34a1/Npt2a and Slc34a2/Npt2b are expressed in the MRPC-1 rat odontoblast-like mineralizing pulpal cell line [26][27]. Slc34a2/Npt2b is negligibly expressed in ameloblasts during the secretory stage, but it is significantly upregulated in the maturation stage [28].

3. Importance of Dietary Phosphorus for Cardiovascular Health

Hypophosphatemia causes skeletal and cardiac myopathy by reducing intramuscular ATP synthesis and decreasing 2,3-bisphosphoglycerate (2,3-BPG) in erythrocytes (which reduces skeletal muscle oxygenation) [29][30]. Additionally, ventricular arrhythmia can occur in the context of acute myocardial infarction [31]. These hypophosphatemic effects are largely reversible but can lead to rhabdomyolysis, heart failure, and death in some cases [32][33][34][35].

Hyperphosphatemia causes vascular smooth muscle cell (VSMC) apoptosis, osteogenic transdifferentiation, and vascular calcification [36][37][38].High dietary phosphorus finally reduces endothelium-dependent vasodilation in vitro and was shown to reduce flow-mediated vasodilation in healthy men [39]. In a study of normal U.S. adults, Kendrick et al. showed that high-normal levels of serum Pi are associated with a high ankle-brachial pressure index, which is a marker for arterial stiffness [40]. Thereby, high dietary phosphorus may acutely increase the risk of cardiovascular mortality [39].

Pi affects erythrocyte function directly [41][30] and indirectly via FGF23 [42]. Hypophosphatemia reduces the concentration of 2,3-BPG in erythrocytes, since Pi is required for the synthesis of ATP and thus for the glycolytic synthesis of the 2,3-BPG precursor, 1,3-bisphosphoglycerate [43].Blood Pi may indirectly affect hematopoesis by regulating FGF23. FGF23 may stimulate hematopoiesis, as suggested by low erythrocyte counts found in FGF23 null mice [44]. In turn, erythropoietin may stimulate the synthesis and secretion of FGF23 by myeloid lineage LSK cells in the hematopoietic bone marrow [45].

4. Importance of Dietary Phosphorus for Skeletal Muscle Health

Similar to cardiac muscle, Pi is essential in skeletal muscle as a substrate for ATP and CrP synthesis [46][47]. Hypophosphatemia causes a reduction in ATP flux (VATP) in mouse models [48]. Similarly, the ablation of Pit1 and Pit2 in mice is post-natally lethal due to a generalized skeletal muscle myopathy [49]. Likewise, patients with hypophosphatemia develop myopathy in addition to rickets and osteomalacia [47]. Moreover, iatrogenic Pi depletion in patients with chronic renal failure results in proximal myopathy [50], and rhabdomyolysis can occur with severe hypophosphatemia superimposed on simple phosphorus deficiency [51].

On the other hand, hyperphosphatemia may contribute to the development of muscle weakness and frailty, at least in patients with CKD [52][53]. High-medium Pi concentrations cause protein loss in myotubes from rat L6 cells and stimulate autophagy, resulting in myotube atrophy [54].

5. High Dietary Phosphate Reduces Longevity in Higher Species

In higher species such as mice, high dietary phosphorus negatively affects longevity. Pi loading in uremic rats dose-dependently induces inflammation in the aorta, heart, and kidneys [363]. Furthermore, Klotho null mice have severe hyperphosphatemia [55][56]. These mice die prematurely due to vascular and renal calcification, as well as atrophy of the skin, muscle, intestinal, and gonadal tissues[55][56].

The aging-like syndrome of Klotho−/− mice is ameliorated when serum Pi levels are normalized in Npt2a−/− and Klotho−/− double-knockout mice, and it is induced again by placing these double-knockout mice on a high Pi diet [364,365]. This dietary Pi toxicity in Npt2a−/− and Klotho−/− double-knockout mice very much resembles the potential of dietary Pi to modify mortality in CKD patients [57][58][59].

In addition, Pi has recently been implicated in cancer aggressiveness [369]. SLC20A1 may be overexpressed in tongue tumors [370,371], and Npt2b expression is increased in lung cancers [60]. Furthermore, high dietary Pi stimulates the AKT-mammalian target of rapamycin regulatory pathway, leading to higher lung cancer aggressiveness in K-rasLA1 mice [61]. The knockdown of Npt2b with siRNA was shown to decrease the number and size of lung tumors in this mouse model,

suggesting that the regulation of Pi consumption through NPT2b knockdown may be a possible treatment for lung cancer [61][62]. Similarly, a high Pi concentration in the tumor microenvironment has been identified as a marker for tumor progression in mouse mammary gland tumors [63].

Finally, high dietary phosphorus increases fracture risk [64], which has implications for lifespan, since excess mortality for five years following a proximal non-hip or lower leg fragility fracture, and ≥10 years following a hip fracture, have been reported [65]. These results together further support a role for excess phosphorus in reducing longevity, even in humans who have normal kidney function.

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