Phosphate Metabolism

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For a long time, phosphate, the anion that incorporates the element phosphorus, has been considered of minor relevance compared to its most studied parent calcium. However, the interest in phosphate metabolism has been remarkably increased in the last two decades. This has been mainly driven, among others, by two factors. The first one relates to the appreciation that hypophosphatemia (as well as hyperphosphatemia), has deleterious effects not only on bone but also on other organs and systems such as skeletal muscle, myocardium, the haematopoietic, respiratory and central nervous systems, in addition to sensory organs [1]. Further impetus has been fuelled by finding molecular mechanisms underlying congenital diseases characterized by hypo and hyperphosphatemia and discovery of drugs reversing the culprit mechanism. It is therefore consequential devoting a special issue of *Calcified Tissue International* to phosphate metabolism.

Dr Munro Peacock elegantly reviewed phosphate metabolism emphasizing differences occurring in different periods of life, addressing old and new systemic actors involved in its homeostasis [2]. There has been a long-standing debate on the putative mechanisms underlying the sensing of changes in phosphorus concentrations in humans. Kritmetapak and Kumar [3], shed lights on this important aspect. Multicellular organisms have developed complex systems of phosphorus sensing. Indeed, there is a strong evidence that type III sodium phosphate cotransporter acts as a cell-surface phosphorus sensor to changes of extracellular concentrations. There is no doubt that inorganic phosphate is fundamental in the process of biomineralization, a complex and lifelong process needed to maintain the structural integrity of the

three specialized mineralized tissues, i.e. bone, teeth and ossicles. However, Bhadada and Rao highlight that the exact mechanisms underlying this process are not fully understood [4].

It is a common finding that deviations from normal values of serum phosphate often go unnoticed by general practitioners, but also by doctors working in hospitals of National Health Systems and in Academic centres. However, both reduced and increased values of serum phosphate represent important biochemical clues of silent diseases. Roux's group [5] offers a detailed overview of diseases and drugs that cause hypo and hyperphosphatemia. Step by step approaches to investigate these biochemical abnormalities, reported in Figs. 1 and 2, are particularly illustrative. The most striking scientific advances concerning pathogenetic mechanism, have been made in understanding congenital diseases causing hypophosphatemia in children [6]. Some of these conditions may go unrecognized and are diagnosed later in life; this situation may pose difficulties concerning type and duration of treatment as outlined by Marcucci and Brandi [7]. Congenital diseases causing hyperphosphatemia, are described by Ito and Fukumoto [8]. Scientific advances in understanding mechanisms underlying these conditions have been made; however, developments in therapy lag behind those reached in hypophosphatemic conditions. Bacchetta and co-workers [9] give a detailed description of deleterious effects of hyperphosphatemia in patients with kidney failure suggesting optimal treatment in the context of complex mineral and bone disorders associated with chronic kidney disease.

Tumour induced osteomalacia represents a difficult clinical condition to diagnose and treat [10, 11]. Recently there has been a surge of case descriptions in the literature, hopefully implying a raising awareness of the disease. Collins's group [12] report the latest advances in the field and propose a new nomenclature under the “umbrella term” of oncogenic osteomalacia, to include all cases of benign or malignant neoplasms associated with FGF23 excess.

Until recently, therapy of hypophosphatemic conditions related to fibroblast growth factor 23 excess was

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limited to oral phosphate and vitamin D metabolites. The commercialization of burosumab, a monoclonal blocking antibody to FGF23, for treatment of X-linked hypophosphatemia, opened new possibilities of cure [13], as outlined by Athonvarangkul and Insogna KL. Following treatment with burosumab biochemical abnormalities were reversed; these changes were accompanied by significant reductions in stiffness, with a trend toward increased physical function and reduced pain with concomitant improvement in quality of life of these patients [14].

In conclusion, this issue devoted to physiology and pathology of phosphate metabolism represents an important and timely up to date. We hope that in the next future translational researches from bench to bedside keep up with the development of the last decades giving more hope to patients with diseases whose therapy was deemed to be only symptomatic.

Compliance with Ethical Standards

Conflict of interest Prof. S. Minisola served as speaker for Abiogen, Amgen, Bruno Farmaceutici, Diasorin, Eli Lilly, Shire, Sandoz, and Takeda. He also served in advisory board of Abiogen, Kyowa Kirin, Pfizer, and UCB. MLB has received honoraria from Amgen, Bruno Farmaceutici, Calcilytix, and Kyowa Kirin; academic grants from and/or was speaker for Abiogen, Alexion, Amgen, Bruno Farmaceutici, Eli Lilly, Kyowa Kirin, MSD, NPS, Servier, Shire, and SPA; and has been consultant for Alexion, Bruno Farmaceutici, Kyowa Kirin, Servier, and Shire.

References

1. Florenzano P, Cipriani C, Roszko KL, Fukumoto S, Collins MT, Minisola S, Pepe J (2020) Approach to patients with hypophosphatemia. *Lancet Diabetes Endocrinol* 8:163–174
2. Peacock M (2020) Phosphate metabolism in health and disease. *Calcif Tissue Int.* <https://doi.org/10.1007/s00223-020-00686-3>
3. Kritmetapak K, Kumar R (2020) Phosphate as a signaling molecule. *Calcif Tissue Int.* <https://doi.org/10.1007/s00223-019-00636-8>
4. Bhadada SK, Rao SD (2020) Role of phosphate in biomineralization. *Calcif Tissue Int.* <https://doi.org/10.1007/s00223-020-00729-9>
5. Koumakis E, Cormier C, Roux C, Briot K (2020) The causes of hypo- and hyperphosphatemia in humans. *Calcif Tissue Int.* <https://doi.org/10.1007/s00223-020-00664-9>
6. Imel EA (2020) Congenital conditions of hypophosphatemia in children. *Calcif Tissue Int.* <https://doi.org/10.1007/s00223-020-00692-5>
7. Marcucci G, Brandi ML (2020) Congenital conditions of hypophosphatemia expressed in adults. *Calcif Tissue Int.* <https://doi.org/10.1007/s00223-020-00695-2>
8. Ito N, Fukumoto S (2020) Congenital hyperphosphatemic conditions caused by the deficient activity of FGF23. *Calcif Tissue Int.* <https://doi.org/10.1007/s00223-020-00659-6>
9. Bacchetta J, Bernardor J, Garnier C, Naud C, Ranchin B (2020) Hyperphosphatemia and chronic kidney disease: a major daily concern both in adults and in children. *Calcif Tissue Int.* <https://doi.org/10.1007/s00223-020-00665-8>
10. Minisola S, Peacock M, Fukumoto S, Cipriani C, Pepe J, Tella SH, Collins MT (2017) Tumour-induced osteomalacia. *Nat Rev Dis Primers* 3:17044
11. Marcucci G, Masi L, Ferrari S, Haffner D, Javaid MK, Kamenický P, Reginster JY, Rizzoli R, Brandi ML (2018) Phosphate wasting disorders in adults. *Osteoporos Int* 29:2369–2387
12. Florenzano P, Hartley IR, Jimenez M, Roszko K, Gafni RI, Collins MT (2020) Tumor-induced osteomalacia. *Calcif Tissue Int.* <https://doi.org/10.1007/s00223-020-00691-6>
13. Athonvarangkul D, Insogna KL (2020) New therapies for hypophosphatemia-related to FGF23 excess. *Calcif Tissue Int.* <https://doi.org/10.1007/s00223-020-00705-3>
14. Insogna KL, Briot K, Imel EA, Kamenický P, Ruppe MD, Portale AA, Weber T, Pitukcheewanont P, Cheong HI, Jan de Beur S, Imanishi Y, Ito N, Lachmann RH, Tanaka H, Perwad F, Zhang L, Chen CY, Theodore-Oklota C, Mealiffe M, San Martin J, Carpenter TO (2018) A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: week 24 primary analysis. *J Bone Miner Res* 33:1383–1393

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