50 Years of Research and Discovery in Chronic Kidney Disease and Mineral & Bone Disorder: The Central Role of Phosphate

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INTRODUCTION
A Phosphate Centric Forum, supported by Genzyme Corporation, was held on 24–25 June, 2010 at the Sheraton West Park Hotel, Munich, Germany, in which 25 medical and scientific experts in the field of chronic kidney disease-related mineral and bone disorder (CKD-MBD) met to present and discuss the central role of phosphate in the development of CKD-MBD, on which research has now celebrated its 50th anniversary.

Phosphate plays a central role in the pathophysiology of CKD-MBD and the progression of CKD and contributes to the disproportionate cardiovascular risk faced by patients with CKD. Adaptation of nephrons attempting to preserve phosphate homeostasis requires endocrine tradeoffs that fuel adverse events of hyperphosphatemia in CKD—secondary hyperparathyroidism, calcium and vitamin
D derangements, vascular calcification, and metabolic bone disorder. Restricting phosphate absorption by use of phosphate binders as glomerular filtration rate declines reduces the need for nephron adaptation and therefore forestalls physiologic derangements downstream of hyperphosphatemia.

A roundtable discussion included the pathophysiology of CKD-MBD, discoveries such as the vitamin D receptor, calcium-sensing receptor, fibroblast growth factor (FGF)-23, and currently available treatment options, as well as future needs regarding research and management of this disorder.

Discussants concluded that placebo-controlled trials are needed in CKD stages 2–4 to investigate the effect of phosphate and phosphate binders on mortality. Various other endpoints were suggested, such as bone disease, progression of CKD, and cardiovascular events. Ongoing studies investigating a broad range of cardiovascular surrogates are due for completion in 2011. Monitoring methods using the less expensive option of phosphate and creatinine are preferred over FGF-23 at the present time, and studies investigating patients over 50–55 years of age with high levels of FGF-23 have been suggested to provide the most valuable data. However, it was generally agreed that FGF-23 may be a uremic toxin, which would support development of anti-FGF-23 strategies in the future.

Development of other therapeutic targets, including biomarkers that assess function of NaPi2a, b, or c (to decrease the reabsorption of phosphate) or Klotho, is considered to be challenging but should remain a long-term goal. The effects of infusion of soluble Klotho, how the bone senses phosphate, and why high levels of FGF-23 are found in non-renal organs are other areas of interest for future research.

This supplement provides a review of five of the topics discussed during the forum: Dr Slatopolsky presents the history of the intact nephron hypothesis and its current implications; Dr Confavreux presents a very new facet of the bone, from a reservoir of minerals to a regulator of energy metabolism; Dr Hruska develops the cardiovascular risk factors in CKD; and Dr Jüppner and Dr Kuro-o revisit the classic physiology in light of the recent discoveries of FGF-23 and Klotho.

DISCLOSURE
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