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Review

The bone and the kidney

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ABSTRACT

Renal tubular diseases may present with osteopenia, osteoporosis or osteomalacia, as a result of significant derangements in body electrolytes. In case of insufficient synthesis of calcitriol, as in renal failure, the more complex picture of renal osteodystrophy may develop. Hypothetically, also disturbed renal production of BMP-7 and Klotho could cause bone disease. However, the acknowledgment that osteocytes are capable of producing FGF23, a phosphaturic hormone at the same time modulating renal synthesis of calcitriol, indicates that it is also bone that can influence renal function. Importantly, a feed-back mechanism exists between FGF23 and calcitriol synthesis, while Klotho, produced by the kidney, determines activity and selectivity of FGF23. Identification of human diseases linked to disturbed production of FGF23 and Klotho underlines the importance of this new bone–kidney axis. Kidney and bone communicate reciprocally to regulate the sophisticated machinery responsible for divalent ions homeostasis and for osseous or extraosseous mineralisation processes.

It has been known for many years that renal patients are affected with bone disease as a result of significant derangements in divalent ions [1–3]. In recent years, it has become evident that it is not only kidney patients who are affected with bone disease but also bone patients who may present with kidney disorders. There is, in fact, evidence that bone cells are capable of synthesising substances necessary for some kidney functions (Fig. 1). In this review, we will recapitulate the links between these two "distant" organs, trying to guess the new clinical scenarios.

Primary kidney diseases with secondary bone involvement

Secondary involvement of bone in patients with either acute or chronic renal disease is a frequent clinical finding. Because both organs are involved in the homeostasis of body electrolytes, this is considered the common basis for the reciprocal influence. Electrolyte disturbances may occur secondary to either a specific defect of some renal tubular-cell activity (generally associated with normal glomerular filtration rate) or a generalised involvement of the organ affecting both glomerular and tubular structures (mostly resulting in variable degrees of renal failure). Also, we must consider the possibility of kidney-produced substances affecting bone-cell activity. Calcitriol (or 1,25-dihydroxyvitamin D), the active metabolite of vitamin D, is the most renowned of these substances, but new actors could also be at play, as illustrated schematically in Fig. 1. Accordingly, in clinical practice, we can try to distinguish specific tubular defects of single ion transportation from generalised renal diseases involving many or most of the electrolytes. Alternatively, a deregulated synthesis of kidney-produced substances may affect bone-cell activity and be responsible for contemporary renal and bone disorders (Table 1).

Tubular diseases

Renal tubular acidosis (RTA). Impairment of bicarbonate reabsorption or reduced net acid excretion are respectively, responsible for proximal or distal RTA. Inherited causes are mostly observed as isolated defects of specific transport proteins [4], while acquired disorders are possibly associated with complex defects in tubular transportation [5]. In clinical practice, chronic renal failure represents the most common cause of chronic metabolis acidosis. However, produced, acidosis will predictably affect bone mineral composition. In fact, acute acidosis, through the induction of an ion exchange between H^+ and Ca^{2+} [6], elicits the buffer function of bone by directly dissolving its mineral component. In chronic acidosis, bone-cell activity is also affected through the induction of PGE2 [7] and RANKL production [8], which result in disturbed bone collagen synthesis by osteoblasts and increased osteoclast differentiation [9]. Acidosis also inhibits the expression of selective calcium transportation channels in renal tubular cells, thus inducing increased urinary calcium excretion and negative calcium balance [10]. Typically, the clinical hallmark of bone involvement in acidosis is osteomalacia, as a result of defective mineralisation and low bone formation; while in case of increased osteoclastic activity and

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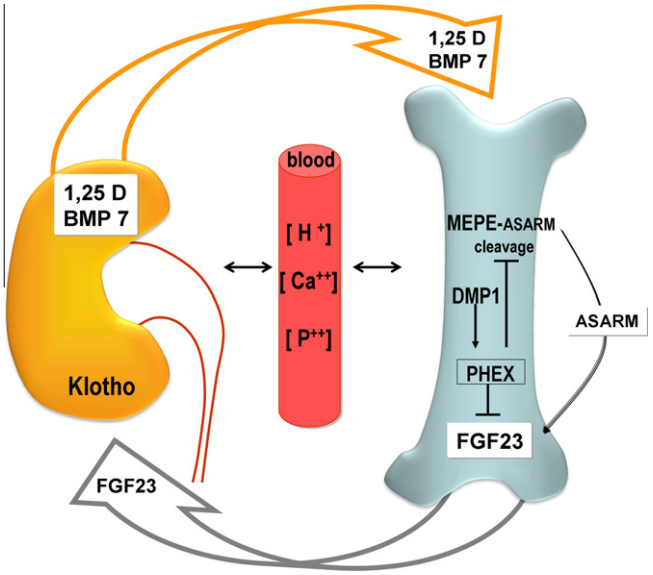

Fig. 1. Simplified scheme of the bone–kidney axis. Besides calcitriol, also kidney-derived BMP-7 can influence bone cells activity. On the other hand, FGF23, produced by bone cells, affects renal calcitriol synthesis and phosphate excretion. At the same time FGF23 activity is influenced directly or indirectly by bone derived proteins. In particular, ASARM, resulting from cleavage of MEPE, exerts a phosphaturic effect; DMP1, by stimulating PHEX, indirectly reduces FGF23 activity. The hormonal dialogue between bone and kidney is responsible for blood electrolyte homeostasis. 1,25D: Calcitriol; BMP-7: Bone morphogenetic protein 7; DMP1: Dentin matrix protein 1; MEPE: Matrix extracellular phosphoglycoprotein; ASARM: Acidic Serine–Aspartate-rich Motif; PHEX: Phosphate-regulating gene with homologies to endopeptidase on the X chromosome; FGF23: Fibroblast growth factor 23.

urinary calcium leak, is osteopenia or osteoporosis. *Disorders of renal Ca transport*. Tubular defects of calcium handling can be responsible for renal calcium leak, negative calcium balance and then osteoporosis [11]. In idiopathic hypercalciuria, disturbed calcium handling is not limited to the kidney, but involves intestine and bone as a result of multiple genetic and dietary factors [12]. The clinical picture of hypercalciuria may be complex even in monogenic disorders. As an example of complexity, mutation of the voltage-dependent chloride transporter, CLC-5, has been associated with four different phenotypes: Dent's disease, X-linked recessive hypophosphataemic rickets (XLRH)[1], X-linked recessive nephrolithiasis (XRN), and Japanese idiopathic low molecular weight proteinuria (JILMWP). It must be noted that the first two of these syndromes, besides hypercalciuria, nephrocalcinosis, phosphaturia and proteinuria, are also characterised by rickets [13]. The different phenotype would be the result of variable tubular disfunctions resulting from functional loss of ClC-5, which is responsible for several defects in tubular endocytosis and/or protein trafficking. In particular, also PTH and vitamin D tubular metabolism can be affected, thus contributing to the variable phenotypes [14,15]. *Disorders of renal P transport*. SLC34A1 transgenic mice present with the absence of the sodium/phosphate co-transporter 2a (Na/Pi 2a), which participates in the active, transcellular resorption of phosphate in the kidney. Biochemical abnormalities include hypophosphataemia, hypercalciuria and increased levels of calcitriol, thus resembling the human syndrome of hereditary hypophosphataemic rickets with hypercalciuria (HHRH) [16]. The difference is, however, that in the human syndrome, the involved gene affects expression not of the Na/Pi 2a but of the Na/Pi 2c co-transporter [17]. *Complex tubular defects*. Multiple defects in tubular transportation are generally referred to as Fanconi syndrome, presenting with hypophosphataemia, hypercalciuria, aminoaciduria, glycosuria, acidosis, vitamin D deficit and then osteomalacia or rickets [18].

Glomerulo-tubular diseases with renal failure

The typical electrolyte disturbances of chronic renal failure are hyperphosphataemia and hypocalcaemia, which are both responsible for increased parathyroid gland secretion [19,20]. However, abnormal levels of these ions are detectable only late in the course of renal failure, while it is now evident that the earliest biochemical change is a reduction of circulating levels of calcitriol [21]. And it is known that calcitriol, by activating its receptor, VDR, directly affects bone-cell activity by modulating the RANKL–OPG system [22]. Besides calcium, phosphate and parathyroid hormone, also metabolic acidosis is detectable in more advanced stages of renal failure As a whole, these biochemical alterations combine to produce the clinical picture of secondary hyperparathyroidism of uraemia, including the complex and specific bone disease known as renal osteodystrophy (ROD). Bone histology changes widely in renal failure, from high-turnover bone lesions (with increased bone resorption, hyperosteoidosis, and marrow fibrosis) to low-turnover bone lesions with or without defective mineralisation. The association of low turnover and defective mineralisation is responsible for the most severe forms of osteomalacia, while the condition of low turnover with a normal mineralisation rate is typical of so-called adynamic bone. Besides turnover and mineralisation, the amount of trabecular bone volume is also affected. According to the prevailing metabolic imbalance, a mixed form can also be observed, while the early phases are mostly referred to as "mild lesions" [23,24]. It is worthy mentioning that inadequate treatment stategies with phosphate binders and/or vitamin D may contribute to bone lesions. Very recently, for the purpose of homogeneity, a simplified classification of ROD has been proposed in the nephrologic community, which specifically takes into account bone turnover (high, normal or low), mineralisation (normal or low) and volume (high, normal or low), named the "MTV classification" [25]. A comparison between the two classification is proposed in Table 2. From a pathophysiological point of view, it must be underlined that these disturbances of bone-cell activity and bone structure composition significantly affect bone quality and its mechanical competence. In fact, the occurrence of any type of fracture in renal patients is higher than normal and associated with increased morbidity and mortality [26]. It is also important to underline that bone mineral density (BMD), the most widely employed method to assess the risk of fracture, is devoid of diagnostic value in renal patients [27]. In fact, BMD value does not allow to recognize the type of bone lesion, and as a result of disturbed mineralisation and turnover, the content of calcium per unit of bone volume becomes different from normal. For this reason bone biopsy is the only method to correctly diagnose ROD and should be employed more widely employed in renal patients. The importance of a correct bone diagnosis comes from the modification that has very recently occurred in the clinical consideration of secondary hyperparathyroidism and renal osteodystrophy. In fact, vascular calcification (a frequent finding in uraemia, responsible for increased mortality) is now regarded as a complex transdifferentiation process of vascular smooth muscle cells, which turn into osteoblast-like cells, as a result of excessive levels of circulating calcium and phosphate. As such, vascular calcification represents a true ossification phenomenon [28–31], pathogemetically linked with this metabolic disease. Accordingly, we now hypothesise that

[1] *Abbreviations used:* RTA, renal tubular acidosis; XLRH, X-linked recessive hypophosphataemic rickets; XRN, X-linked recessive nephrolithiasis; JILMWP, Japanese idiopathic low molecular weight proteinuria; ROD, renal osteodystrophy; BMD, bone mineral density; CKD-MBD, chronic kidney disease-mineral bone disorder; BMPs, bone morphogenetic proteins; FGF23, fibroblast growth factor 23; ADHR, autosomal dominant hypophosphataemic rickets; ARHR, autosomal recessive hypophosphataemic rickets; DMP1, dentin matrix protein 1; XLH, X-linked hypophosphataemic rickets.