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Review

Sex steroids and the kidney: role in renal calcium and phosphate handling

Rougin Khalil [a, *], Na Ri Kim [a], Ferran Jardi [a], Dirk Vanderschueren [a], Frank Claessens [b], Brigitte Decallonne [a]

[a] Clinical and Experimental Endocrinology, KU Leuven, Herestraat 49 Box 902, Belgium
[b] Molecular Endocrinology, KU Leuven, Herestraat 49 Box 901, Belgium

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ABSTRACT

Calcium and phosphate are vital for the organism and constitute essential components of the skeleton. Serum levels are tightly hormonally regulated and maintained by exchange with three major sources: the intestines, the kidney and the bone. The effects of sex steroids on the bone have been extensively studied and it is well known that sex steroid deficiency induces bone loss, indirectly influencing renal calcium and phosphate homeostasis. However, it is unknown whether sex steroids also directly regulate renal calcium and phosphate handling, hereby potentially indirectly impacting on bone. The presence of androgen receptors (AR) and estrogen receptors (ER) in both human and rodent kidney, although their exact localization within the kidney remains debated, supports direct effects. Estrogens stimulate renal calcium reabsorption as well as phosphate excretion, while the effects of androgens are less clear. Many of the studies performed with regard to renal calcium and/or phosphate homeostasis do not correct for the calcium and phosphate fluxes from the bone and intestines, which complicates the differentiation between the direct effects of sex steroids on renal calcium and phosphate handling and the indirect effects via the bone and intestines.

The objective of this study is to review the literature and current insight of the role of sex steroids in calcium and phosphate handling in the kidney.

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* Corresponding author.
E-mail address: rougin.khalil@kuleuven.be (R. Khalil).

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1. Introduction

Calcium is involved in many cellular processes, such as muscle contraction, enzyme activation, cell differentiation, immune response, programmed cell death, and neuronal activity (Pu et al., 2016). Phosphate is essential for several cellular functions as well, including cell signaling, energy exchange, and the formation of lipid bilayers (Tatsumi et al., 2016). In addition, calcium and phosphate are essential components of the skeleton. Together, they form hydroxyapatite, the main component of bone, responsible for its rigidity. Thus, an optimal calcium and phosphate balance is indispensable for bone mass and strength.

In the serum, calcium and phosphate levels are maintained between narrow ranges through several exchange routes: dietary intake via intestinal absorption, renal reabsorption/excretion, and mobilization from bone (Fig. 1). Several 'calciotropic' hormones tightly regulate the in- and effluxes in order to stabilize serum levels of calcium and phosphate: parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), klotho, and 1,25$(OH)_2$-vitamin D. The endocrine actions will be further discussed in the sections below. Chronic imbalances in calcium and phosphate homeostasis can not only lead to bone abnormalities (kidney-bone axis), but also affect other tissues and organs, and lead for example to ectopic calcifications in blood vessels and the kidney, resulting in chronic kidney disease and cardiovascular complications (Pu et al., 2016; Tatsumi et al., 2016).

Besides their well-known effects on the male and female reproductive systems, sex steroid hormones play a role in many other systems and processes, such as the cardiovascular system, the immune system, erythropoiesis, lipid and protein metabolism, and psychosexual and cognitive behavior (De Leon-Nava et al., 2009; Ikeda et al., 2005; Luine, 2008). Furthermore, sex steroids have an impact on the musculoskeletal system (Dubois et al., 2014, 2012; Vanderschueren et al., 2014). It is well established that sex steroid deficiency induces bone loss, leading to osteoporosis, and increased risk for osteoporotic fractures (Almeida et al., 2017; Vanderschueren et al., 2014). Not only female postmenopausal osteoporosis, but also male osteoporosis – for example in men with prostate cancer receiving androgen deprivation therapy - represents a major burden for public health (Vanderschueren et al., 2014).

It was previously demonstrated that the severe osteoporotic phenotype observed in global AR knock out mice could not be fully reproduced in bone cell-specific knock out mice, suggesting that sex steroids regulate processes in other organs which in turn have an impact on bone (Sinnesael et al., 2015, 2012). It can therefore be hypothesized that sex steroids have direct renal effects, hereby influencing the kidney-bone axis. There are several other arguments for the kidney as an important target of sex steroid action. First of all, the kidney expresses both AR and ER, as will be reviewed in the sections below. Furthermore, the kidney mass is sexually dimorphic, and several renal functions display gender differences, including the glomerular filtration rate, inulin clearance, activity of multiple enzymes, pharmacokinetics and pharmacodynamics of various drugs and substances, and the transport of organic compounds and ions (reviewed in (Sabolić et al., 2007)). Several kidney diseases show gender differences in occurrence and/or development as well; sex steroids have been suggested to play a role in the susceptibility to acute kidney injury (Crawford and Moul, 2015; Hodeify et al., 2013; Lapi et al., 2013; Soljancic et al., 2013), the risk and outcome of chronic kidney disease (Khurana et al., 2014; Kummer et al., 2012), the morbidity and mortality of kidney transplant recipients (Antus et al., 2001; Müller et al., 1999), compensatory renal growth after unilateral nephrectomy (Mulroney et al., 1999), kidney stone formation (Lieske et al., 2014; Naghii et al., 2014), as well as effects on the renin-angiotensin

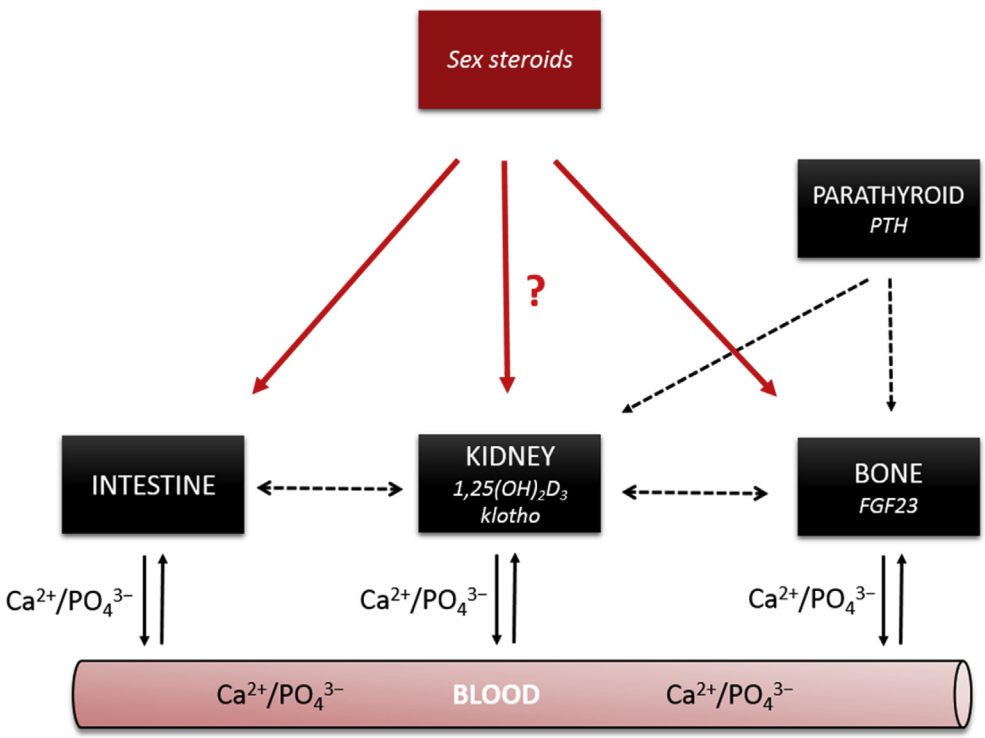

Fig. 1. Regulation of calcium and phosphate homeostasis and the potential contribution of sex steroids. Serum calcium and phosphate levels are kept stable through exchange via the intestines, the kidney and bone. These processes are controlled by calciotropic hormones: 1,25$(OH)_2$-vitamin D and klotho formed by the kidney, PTH secreted by the parathyroid glands, and the bone-derived FGF23.

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