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Renal Osteodystrophy: Something Old, Something New, Something Needed

Valentin David[1], **Isidro B. Salusky**[2], **Hartmut Malluche**[3], **Thomas L. Nickolas**[4,*]

[1]Division of Nephrology and Hypertension, Department of Medicine, and Center for Translational Metabolism and Health, Institute for Public Health and Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

[2]Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

[3]Division of Nephrology, Bone & Mineral Metabolism, Department of Internal Medicine University of Kentucky Lexington, KY, USA

[4]Department of Medicine, Columbia Irving University Medical Center, New York, NY, USA

Abstract

Purpose of review—Renal osteodystrophy (ROD) is a complex disorder of bone metabolism that affects virtually all adults and children with chronic kidney disease (CKD). ROD is associated with adverse clinical outcomes including bone loss, mineralization and turnover abnormalities, skeletal deformities, fractures, cardiovascular events, and death. Despite current therapies, fracture incidence is 2- to 100-fold higher in adults and 2- to 3-fold higher in children with compared to without CKD. Limited knowledge of ROD pathogenesis, due to the lack of patient-derived large-scale multi-modal datasets, impedes development of therapeutics aimed at reducing morbidity and mortality of CKD patients. The purpose of the review is to define the much needed infrastructure for the advancement of RDO treatment.

Recent findings—Recently, we created a large-scale data and tissue biorepository integrating clinical, bone quality, transcriptomic and epigenomic data along with stored urine, blood and bone samples. This database will provide the underpinnings for future research endeavors leading to the elucidation and characterization of the pathogenesis of ROD in CKD patients with and without dialysis.

Summary—The availability of an open-access NIH-funded resource that shares bone-tissue based information obtained from patients with ROD with the broad scientific community represents a critical step in the process of discovering new information regarding unrecognized bone changes that have severe clinical complications. This will facilitate future high-impact hypothesis-driven research to redefine our understanding of ROD pathogenesis and pathophysiology and inform the development of disease modifying and prevention strategies

[*]**Corresponding author:** Thomas L. Nickolas. tln2001@cumc.columbia.edu.

Conflict of interest

VD received research funding from Akebia and from Vifor Pharma and consulting honoraria from Keryx Biopharmaceuticals, Vifor Pharma, Luitpold and Amgen outside of submitted work. IBS has received honoraria from Akebia, Inozyme, Ultragenyx, Amgen, Abbvie outside of submitted work. TLN reports consultancy agreements with Pharmacosmos; receiving research funding from Amgen; and consulting honoraria from Amgen and Pharmacosmos outside of submitted work.

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Keywords

chronic kidney disease; biorepository; bone disease; histomorphometry; bone transcriptomics

Introduction

More than one in ten Americans have chronic kidney disease (CKD)[1]. Renal osteodystrophy (ROD), a complex disorder of bone metabolism, affects virtually all adult and pediatric patients with CKD during their lifetimes[2–6]. ROD is associated with adverse clinical outcomes including bone loss [7], mineralization and turnover abnormalities[5], skeletal deformities, fractures[8–13], cardiovascular events[14–16] and death[17]. Despite current therapies, in adults with CKD fracture incidence of the appendicular skeleton more than doubled from 1992 to 2009[18] and is 2- to 100-fold higher compared to age-, sex-matched adults without CKD. Similarly, despite treatment of CKD-MBD, > 50% of adults who developed CKD in childhood reported skeletal symptoms, with 20% reporting handicaps from their bone disease[19] and fracture rates are 2- to 3-fold higher in children with compared to without CKD[20]. Dearth of knowledge regarding ROD pathogenesis impedes development of novel therapeutics aimed at reducing morbidity and mortality of CKD patients. This knowledge gap is primarily due to the lack of patient-derived large-scale multi-modal datasets that permit elucidation of ROD pathogenesis.

We have recently proposed to close this knowledge gap by creating the fundamental infrastructure to facilitate high-impact novel hypothesis-driven clinical and translational research in ROD. Indeed, a large-scale data and tissue biorepository integrating clinical, bone histomorphometric and quality, and transcriptomic data along with stored urine and blood will be created by a multi-disciplinary team of investigators with the use of state-of-the art methods in biomarkers, bone tissue-level materials science, cell biology, transcriptomics and systems biology. The resource creates capacity for research with different hypotheses and methodologies to work from a common empirical base; thus, mitigating key roadblocks that hinder major scientific discovery in ROD (e.g., cohort differences due to small sample sizes). We assume that establishment of this comprehensive resource will provide the underpinnings for high-impact future research endeavors leading to the elucidation and characterization of the pathogenesis of ROD in patients across the spectrum of kidney disease and the development of new therapies. Establishment of the proposed repository and analytical infrastructure will lay the foundation for ground-breaking discovery and the development of novel precision medicine approaches for treating ROD. The availability of an NIH-funded resource that freely shares bone-tissue based information obtained from patients with ROD with the broad scientific community represents a critical step in the process of discovering new information regarding unrecognized bone changes that have severe clinical complications.

ROD: something old

Chronic kidney disease (CKD) affects over 37 million individuals in the United States (US), and 752 million individuals worldwide (CDC.gov/kidneydisease)[21]. CKD grade 5 requiring

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dialysis or transplantation affects over 700,000 Americans. ROD, a systemic disorder of bone structure, metabolism, and cellular function leading to compromised bone strength is present in all these patients as well as in a sizeable fraction of the 37 million in the US with CKD grades 1–4. ROD severity worsens with declining kidney function and it persists even after correction of kidney function with transplantation in adults and children.

The accurate diagnosis of ROD type (low or high turnover, and mineralization characteristics) requires bone biopsy. In the absence of bone biopsy, circulating biomarkers of bone turnover can be used to diagnose ROD type with reasonable accuracy[22, 23]. Skeletal imaging with dual energy X-ray absorptiometry (DXA) or high resolution peripheral quantitative computed tomography (HR-pQCT) do not inform the diagnosis of the ROD type[22]; however, they provide valuable insight into abnormalities of bone quality and strength that may be impaired by ROD. Clinical management of ROD involves treating the biochemical abnormalities of CKD-MBD, including calcium, phosphorus, vitamin D and parathyroid hormone (PTH). In extreme cases, parathyroidectomy may be necessary.

Our current understanding of ROD pathogenesis, which can manifest as a range of disorders, including bone loss, hyperparathyroid bone disease, abnormal bone mineralization, and adynamic bone disease, has not changed in over 50 years[24] and is based on the perception that elevations in PTH that occur with declining kidney function and active vitamin D deficiency results in ROD. The Turnover, Mineralization, Volume (TMV) classification system used to define ROD-type[25] and to "*…. greatly enhance communication, facilitate clinical decision-making, and promote the evolution of evidence-based clinical practice guidelines worldwide*" reflects that notion[26]. However, our rudimentary understanding of ROD pathobiology does not reflect either state-of-the art science in skeletal biology or our current understanding of bone-cell signaling[27–30]. Lack of progress in improving ROD clinical outcomes despite strategies that consider the TMV classification[18] support the need for treatments that are based on state-of-the art science in ROD pathobiology.

Fractures are the ultimate outcome of ROD progression. Fractures are a debilitating injury with prolonged rehabilitation, long-term pain, and increased costs. Only 50% of patients with a hip fracture regain their mobility and remain at their pre-fracture level of independence[31]. As the population ages, predictions about increasing numbers of fractures are staggering: from 1.7 million fractures to 6.3 million fractures between 1990 and 2050[32]. Studies in adults and pediatric patients with CKD grades 3–4[8, 11, 20, 33, 34], on dialysis[35, 36] and after transplantation[10, 37] all demonstrate that patients with CKD have a 2- to 100-fold increase in fracture risk compared to age- and sex-matched individuals without CKD. A 40-year-old woman on dialysis has a 100-fold increased risk of having a hip fracture compared to a 40 year-old in the general population. Even at age 80, the risk in both men and women on dialysis is more than 2-fold greater in patients with, compared to age and sex-matched individuals without CKD[10]. Moreover, despite current CKD-MBD treatment guidelines, fracture incidence of the appendicular skeleton more than doubled from 1992 to 2009 in patients with CKD grade 5 requiring dialysis [18]. Similar findings have been shown in adults with onset of CKD in childhood[19]. Indeed, although early treatment of vitamin D deficiency was estimated to result in >$19 million and 191 quality-adjusted life year (QALY)'s saved, there was minimal fracture incidence reduction, suggesting that

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better strategies are needed for their prevention[38]. The scope of the problem is staggering considering that mortality risk increases 100% in patients on dialysis who sustain a major fracture requiring hospitalization[39, 40] and healthcare associated costs after fracture in patients with CKD exceeded $600 million in 2010[17].

ROD: something missing

Research in ROD is hindered by five key barriers: (1) The complex and heterogenous phenotypes that characterize ROD (i.e., bone loss associated with low, normal, high turnover coexisting with vascular calcifications); (2) The effects of co-morbidities that are concurrent with CKD and that also affect the skeleton (e.g, diabetes, inflammatory and genetic diseases); (3) The clinical and logistical difficulties associated with the bone biopsy process; (4) The skillset and competencies to perform the histologic, histomorphometric, bone quality and transcriptome analyses of the obtained samples; and (5) The lack of free-access to large-scale clinical datasets that span the CKD continuum and that are dedicated to CKD-relevant abnormalities in bone.

ROD: something new

The underlying causes of ROD are complex, and both genetic and environmental factors contribute to its development. The genetic determinants of ROD are complex and involve multiple genes and genetic polymorphisms. Several genes have been identified that are associated with ROD, including those involved in vitamin D metabolism, calcium sensing, and bone remodeling. Indeed, mutations in the VDR gene often lead to impaired bone mineralization. Mutations in the PTH1R gene can lead to abnormal responses to PTH, resulting in changes in bone mineral metabolism and the development of ROD.[41] Several genetic polymorphisms have been identified that are associated with an increased risk of developing ROD.[42, 43]

In addition to the genetic factors, the other molecular mechanisms driving bone disorders in CKD are complex and not yet fully understood. However, Next-Generation Sequencing (NGS) tools have allowed researchers to identify key genes and pathways involved in bone metabolism and mineralization in CKD patients with ROD.[44, 45]

“Bulk” RNA sequencing, also known as RNA-seq, is a valuable technique in studying bone disorders as it offers a comprehensive understanding of biological constituents, helps to identify novel genes, and unravels the interconnected signaling pathways involved in disease mechanisms. However, despite its advantages, the major limitation of “bulk” RNA-seq is the lack of definition of the specific cellular subsets and determination of gene expression differences at the individual cell level, thereby constraining our comprehension of the biological and pathological processes of these diseases.

Recent advances in transcriptomics now permit single cell and single nuclei analyzes of bone cells [46–48]. State-of-the art methods in single cell (sc) and single nuclei (sn) RNA sequencing of bone will lead to major advances in our understanding of ROD pathogenesis and inform the development of targeted disease modifying and curative strategies. In parallel, the identification of open chromatin regions and the profiling

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of chromatin accessibility in individual cells using sc assay for transposase-accessible chromatin sequencing (scATAC) seq allows the study of the epigenetic changes occurring in bone cells in animal and patients with ROD. These new tools can uncover cellular heterogeneity and specific subclusters, can infer the trajectories of various cell states, transitions, and differentiation, might aid in the creation of heterogeneous cellular signaling models through enrichment analyses and might uncover regulatory networks among clusters. Only by identifying the genes and pathways involved in ROD, can we develop targeted therapies that address the underlying causes of the disease, rather than just treating the symptoms or the end-organ effects of disease, such as hyperparathyroidism induced high turnover or increased cortical porosity.[49] These novel methods are only now being applied to bone[50] and more recently to ROD[45], and only a few studies have investigated transcriptomic and epigenetic changes in ROD. Not only do we need further research using RNA-seq in large patient cohorts to fully understand the complex molecular mechanisms underlying ROD and to develop effective treatments but the fundamental infrastructure to develop patient-centered clinically relevant research is lacking, impeding the development of strategies that will improve the lives of patients living with CKD.

ROD: something needed

The establishment of the necessary infrastructure for conducting innovative research on the mechanisms of ROD. To address this gap, we proposed the creation of a large-scale data and tissue biorepository that will integrate clinical, bone histomorphometric and bone quality, transcriptomic and epigenetic data, along with stored urine and blood. This resource, the ROD-Precision Medicine Project (ROD-PMP), will enable high-impact hypothesis-driven clinical and translational research in ROD and lay the foundation for ground-breaking discoveries and the development of novel precision medicine approaches for treating ROD (Figure 1). The establishment of this comprehensive resource is poised to provide a common empirical base for research with different hypotheses and methodologies, thereby mitigating the key roadblocks that have hindered major scientific discovery in ROD. The repository and analytical infrastructure will facilitate the elucidation and characterization of the pathogenesis of ROD in CKD patients with and without dialysis and will represent a critical step in the process of discovering new information about bone changes that have severe clinical complications. The availability of this NIH-funded resource, which freely shares bone-tissue and bone-tissue-based information obtained from patients with ROD with the broader scientific community, has the potential to drive significant advances in the understanding and treatment of ROD in CKD patients.

Aimed at advancing the understanding of ROD pathogenesis and developing targeted disease-modifying and curative strategies, the ROD-PMP aims to address the key barriers in ROD research and develop a bone-based infrastructure for clinical and translational research. The infrastructure includes a data and tissue biorepository, analytical infrastructure, and open-access data sharing. Designed to apply state-of-the-art methods in single-cell and single-nuclei RNA/ATAC sequencing of bone to ROD and link transcriptomic and epigenetic data to detailed clinical and bone histomorphometric and quality phenotypes, the proposed infrastructure will be available to the scientific community to conduct high-impact hypothesis-driven research on ROD.

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Conclusion

The absence of large-scale datasets linking genomic architecture of bone cells to bone-tissue phenotypes, which correlate with bone strength, hinders the development of targeted strategies for preventing ROD-related morbidity and mortality. The proposed repository is not designed to test specific hypotheses but to create an evidence-base that future researchers can draw from and contribute to. Thus, the ROD-PMP offers promise to refine pathogenesis models, identify novel therapeutic targets and translate molecular findings into clinical applications for ROD. The establishment of this unique and critical resource will create new opportunities for scientific discoveries, and innovative and collaborative projects. We expect this resource will permit investigators to unlock knowledge gaps in the molecular pathogenesis of ROD, including circulating and local biomarkers of ROD stage, severity and subtype. These findings will ultimately translate into to the discovery of novel tailored bone targets for ROD diagnosis, monitoring, treatment and prevention.

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KEY POINTS (3–5) (1 point is no more than 1 sentence)

1. A large comprehensive biorepository of urine, blood and bone tissue for phenotyping ROD from adults and children across the CKD continuum is lacking.
2. There is a lack of concomitant bone quality assessments of iliac crest bone biopsy samples by 2D and 3D histomorphometry, bone biomechanics by nanoindentation, bone protein assessment by immunohistochemistry, intrinsic bone material properties by reference point indentation and Fourier Transform Infrared Spectroscopy.
3. There is a need to determine the changes in osseous transcriptome of patients with ROD at tissue and cellular levels, and integrate these data into a framework that will facilitate future high-impact hypothesis-driven research to redefine our understanding of ROD pathogenesis and pathophysiology.

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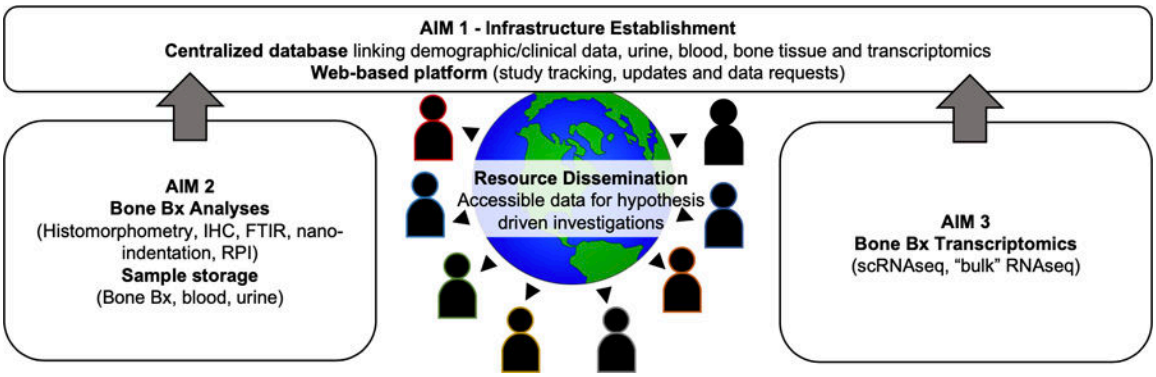

Figure 1: Conceptualization of ROD Precision Medicine Program.

The proposal plans to create the fundamental infrastructure and build a centralized database integrating demographic and clinical bone histomorphometric and quality data, together with transcriptomic and stored urine and blood to facilitate high-impact novel hypothesis-driven clinical and translational research in ROD.