Circadian rhythms of mineral metabolism in chronic kidney disease–mineral bone disorder

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Purpose of review
The circadian rhythms have a systemic impact on all aspects of physiology. Kidney diseases are associated with extremely high-cardiovascular mortality, related to chronic kidney disease–mineral bone disorder (CKD–MBD), involving bone, parathyroids and vascular calcification. Disruption of circadian rhythms may cause serious health problems, contributing to development of cardiovascular diseases, metabolic syndrome, cancer, organ fibrosis, osteopenia and aging. Evidence of disturbed circadian rhythms in CKD–MBD parameters and organs involved is emerging and will be discussed in this review.

Recent findings
Kidney injury induces unstable behavioral circadian rhythm. Potentially, uremic toxins may affect the master-pacemaker of circadian rhythm in hypothalamus. In CKD disturbances in the circadian rhythms of CKD–MBD plasma-parameters, activin A, fibroblast growth factor 23, parathyroid hormone, phosphate have been demonstrated. A molecular circadian clock is also expressed in peripheral tissues, involved in CKD–MBD; vasculature, parathyroids and bone. Expression of the core circadian clock genes in the different tissues is disrupted in CKD–MBD.

Summary
Disturbed circadian rhythms is a novel feature of CKD–MBD. There is a need to establish which specific input determines the phase of the local molecular clock and to characterize its regulation and deregulation in tissues involved in CKD–MBD. Finally, it is important to establish what are the implications for treatment including the potential applications for chronotherapy.

Keywords
activin A, fibroblast growth factor 23, klotho, parathyroid, renal osteodystrophy, vascular calcification

INTRODUCTION

Chronic kidney disease–mineral bone disorder CKD–MBD is a major cause of the excess mortality associated with uremia. CKD–MBD begins early in the course of kidney disease and it is characterized by renal osteodystrophy, increased fracture rates, vascular calcifications and cardiac diseases together with elevations of plasma phosphate, fibroblast growth factor 23 (FGF23), decrease of α-Klotho and an increase in activin A [1–4,5▪]. FGF23 is a hormone secreted by osteocytes which increases renal phosphate excretion [6]. The phosphaturic action of FGF23 requires α-Klotho, an antiaging protein that functions as coreceptor for signal transduction [6]. Activin A is another interesting new factor, a potential biomarker and therapeutic target in CKD–MBD [7,8,9▪]. It is a member of the TGF-β family, essential for kidney development and repair. It is not expressed in the normal kidney but induced in injured kidneys [2,10]. In bone, activin A is secreted by osteoblasts and during bone matrix resorption by osteoclasts. However, its role in bone metabolism is not fully clarified [10,11]. In advanced CKD–MBD secondary hyperparathyroidism (sHPT), calcitriol deficiency and hyperphosphatemia develop.

Proper rhythms in metabolism, hormone secretion, cell cycle and behavior are maintained by a circadian clock, an endogenous, self-sustaining pacemaker that operates with a periodicity of 24 h [12▪,13]. This is to anticipate predictable changes in environment following Earth rotation, day and night and especially changes in light. In mammals the master

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Curr Opin Nephrol Hypertens 2020, 29:367–377
DOI:10.1097/MNH.0000000000000611

KEY POINTS

- The circadian rhythms in metabolism, hormonal secretion, cardiovascular function and bone remodeling are controlled by a molecular circadian clock.
- CKD deregulates the molecular circadian clock in the master circadian pacemaker in hypothalamus and peripheral clocks in tissues involved in CKD–MBD.
- In CKD, disturbances in the circadian rhythm of activin A, as well as fibroblast growth factor 23, parathyroid hormone, phosphate have been demonstrated.
- Chronotherapy might be a relevant and important new approach for future treatments of CKD–MBD that requires further testing.

pacemaker of circadian rhythmicity is in the hypothalamic suprachiasmatic nucleus (SCN). In addition to this central pacemaker a molecular clock has been found in central nervous system (CNS) and peripheral tissues. The SCN is receiving light cues via intrinsically photosensitive retinal ganglion cells and is accordingly coordinating the peripheral and central clocks via neuronal, hormonal and metabolic signaling pathways [14,15]. The circadian rhythms have a systemic impact on all aspects of physiology including metabolism, immunity, cognition, organ function [16]. The hierarchical view on the circadian system level organization has been challenged by the discovery that the hepatic circadian clock was independently entrained by feeding rhythm [17,18]. Kidneys have a robust molecular circadian clock and many genes that determine renal function are expressed in a circadian manner [19,20▪]. Recently, it was shown that in kidney injury induced by adenine diet, CKD mice developed unstable behavioral circadian rhythm and a kidney-to-CNS feedback was proposed [21▪,22▪]. Potentially, uremic toxins can affect SCN [23▪]. Epidemiological studies in humans showed that a disturbed circadian rhythm is associated with an increased risk of osteopenia, metabolic syndrome and cancer. The understanding of the importance of disruption of circadian rhythmicity for the pathophysiology of uremic symptoms is at its beginning [24,25]. Recent results indicate existence of severe disturbances in the circadian rhythm of the CKD–MBD parameters, activin A, FGF23, parathyroid hormone (PTH) and phosphate [12▪]. Here we address the emerging impact of disruption of circadian rhythmicity in mineral homeostasis and organs involved in CKD–MBD.

The molecular circadian clock

The biology of circadian rhythms is complex and understanding the mechanisms in chronobiology is still expanding. In 1971, Konopka and Benzer [26] discovered that the circadian rhythms have a genetic determinant. In 2017, Hall, Rosbash and Young were awarded the Nobel Prize in Physiology and Medicine for their discovery of the molecular clock machinery [27].

Both central and peripheral clocks involve the same set of genes and are regulated by an interplay of positive and negative feedback-loops. In addition, regulation of circadian transcription is also subject to modifications in the epigenetic state that change dynamically over day-night [28].

In the core of the circadian machinery is the complex of Bmal1 (brain-muscle Arnt-like protein 1) and Clock (circadian locomotor output cycles kaput) DNA-binding to E-box and E-box like sequences, which regulate the expression of approximately 10% of the transcripts in the genome in a tissue-specific manner (Fig. 1). Bmal1/Clock – dependent clock-controlled genes peak during the day, whereas the transcription is inhibited by the circadian repressors, Per (Period) and Cry (Cryptochrome) at night. Clock and Bmal1 represent major components of the clock's positive limb. They induce, among others expression of the proteins, Per and Cry, which constitute the major arm of the negative limb. Per accumulates in the cytoplasm, forms a complex with Cry as well as other modulator proteins and acts as repressor of Clock/Bmal1 and subsequently inhibits its own expression, resulting in the oscillation of gene expression in a circadian manner. This main loop is interplaying with other feedback-loops, including those of Rev-erbα or the retinoid acid related orphan receptor mediating opposing actions, repressing or activating *Bmal1* gene expression. The preferential feedback-loop structures vary across tissues and peripheral organs, contributing to tissue-specific circadian rhythms [29].

At the cellular level, regulation of pathways of autophagy, 5' adenosine monophosphate-activated protein kinase, Sirtuin-1, NADP(H) as well as proliferative mechanisms that involve Wnt and mammalian target of rapamycin (mTOR) are connected to the physiological regulation of the body's circadian rhythm [30–34]. For instance, numerous genes, approximately 50, that are involved in Wnt signaling are under circadian regulation and have rhythmic expression profiles [30,31], impacting cell proliferation, renewal and differentiation of stem-cells and tissue patterning. Studies support a cross-talk between the circadian clock and the hypoxia signaling pathway. Cry1 acts as repressor of hypoxia-inducible factors (HIF's) via a specific protein–protein interaction that reduces binding of HIF's to target genes and by altering HIF's half-life [35].

The understanding of the interaction between circadian rhythms and the environment is

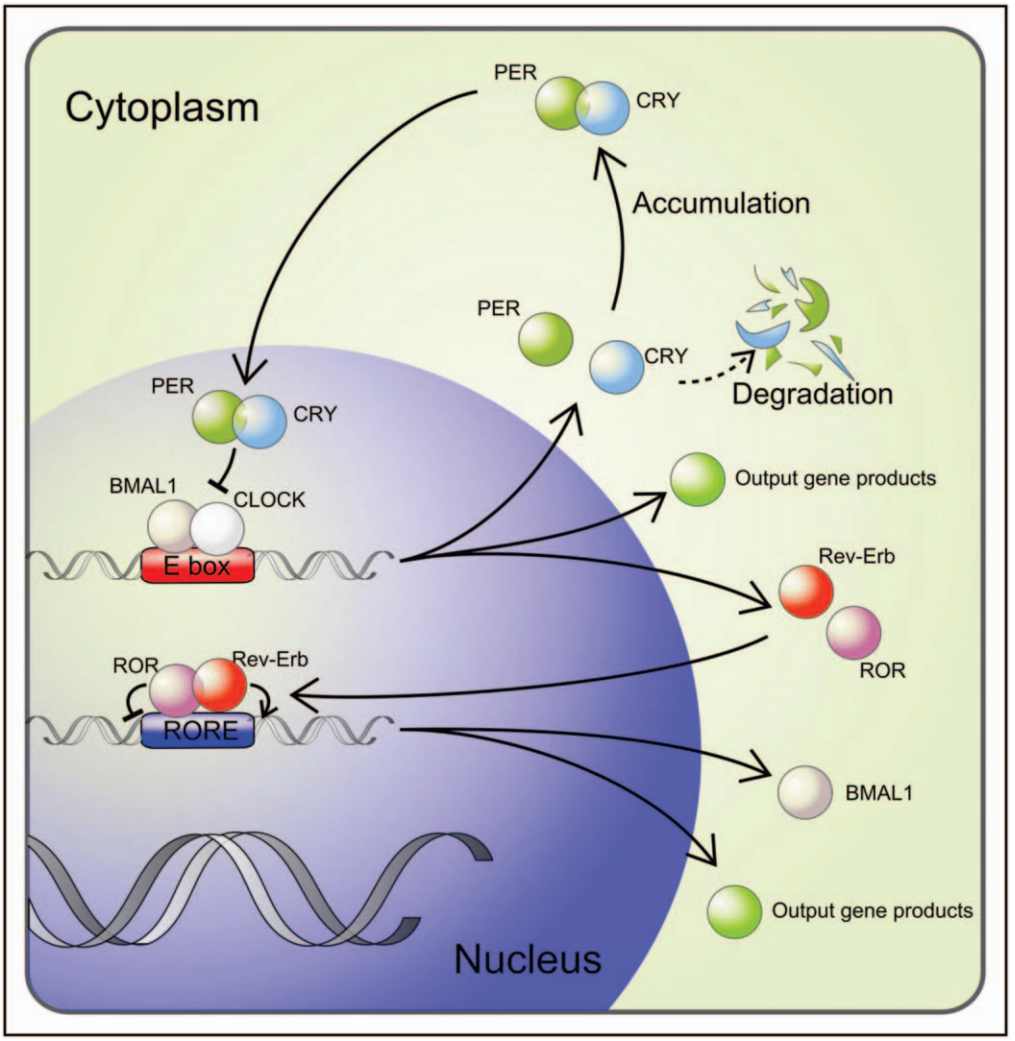

FIGURE 1. The molecular circadian clock. The transcription factors, circadian locomotor output cycles kaput (CLOCK) and brain-muscle Arnt-like protein 1 (BMAL1), are major components of the molecular circadian clock positive limb. CLOCK and BMAL1 heterodimerize, bind to E-box elements in the promoters of period (PER) and cryptochrome (CRY) and drive the negative limb in the feedback loop. PER and CRY proteins translocate back into the nucleus, hindering CLOCK and BMAL1 transcriptional activity, resulting in oscillation of the gene expressions in a circadian manner. This main loop is interplaying with a feedback loop driven by Rev-erb and receptor tyrosine kinase-like orphan receptor (ROR) mediating opposing actions, repressing or activating BMAL1 gene expression. The molecular circadian clock drives the expression of the clock-controlled tissue specific output genes and hereby about 10% of the transcriptome show circadian rhythmicity.

expanding as well. Sunrise and sunset have the primary influence on the circadian rhythms. Interactions with light–dark cycle have now been expanded to include artificial light and blue light from computer screens [36]. Diet, including time restricted feeding and fasting are other key extrinsic cues, interacting with the intrinsic clock [37,38▪]. There are probably other cues such as activity, temperature, oxygen or social cues, all important for CKD patients. As such while operating by the same mechanisms the circadian rhythms may vary between individuals due to environmental differences, age and genetics [39].

Disturbances of the circadian clock

Evidence suggests that disruption of the circadian rhythm may cause serious health problems, contributing to development of cardiovascular diseases, metabolic syndrome, cancer, pulmonary fibrosis, osteopenia and aging [24,40–43,44▪,45]. Epidemiological studies indicate that disturbances of the circadian rhythm are associated with carcinogenesis [46], and shift work is classified as a group 2A carcinogenic factor. Studies have linked molecular clock with cell cycle and proliferation [30,47]. Certain types of cancer have an altered expression of circadian clock genes [47]. Clock components such

as Per1 and Per2, Bmal1 and Cry decrease cell proliferation [48]. Disturbances in circadian rhythms affect the Wnt and HIFs signaling, which is of importance for cancer progression [35,47], and potentially also for the pathogenesis of CKD–MBD, as Wnt and HIFs have fundamental roles in bone metabolism, FGF23 regulation, renal fibrosis and vascular calcification [49,50].

Night shift work alters sleep timing and duration and is associated with low-bone mineral density and an increased risk of fractures [51]. It is however unclear if sleep restriction itself or circadian misalignment cause the changes in bone formation. The perturbation in circadian rhythmicity, but also timing of food intake may alter bone metabolism.

Disturbances of the circadian clock and chronic kidney disease

Daily oscillations in volume of urine production, renal blood flow, glomerular filtration rate (GFR) and electrolyte excretion and their impact on blood pressure (BP) regulation has been known for decades. Disruption in the circadian molecular clock, circadian rhythmicity in organ function and in circulating signals is an emerging concept in the systems biology of CKD. Kidneys have well documented expression of circadian clock genes and many renal transporter genes in the different part of the nephron are clock-controlled [19,20▪]. Recently, it was shown that the intrinsic glomerular circadian clock is regulating GFR [20▪]. In mice lacking Bmal1 in podocytes the circadian rhythm of GFR was lost together with alteration in the diurnal pattern in plasma aldosterone levels. Aldosterone is a major factor in deregulated sodium balance and BP in uremia. Potentially, a disturbance of the circadian molecular clocks in the individual peripheral tissues in CKD might contribute to uremic symptoms. The impact of kidney insufficiency on the CNS might also include disruption of the molecular clock system. Recently, it was shown that in kidney injury induced by adenine diet, CKD mice developed unstable behavioral circadian rhythm with fragmented sleep and lower locomotor activity, associated with lower amplitude in circadian rhythm of *Period 2* expression in the SCN [21▪,22▪]. Uremic toxins can potentially affect the central circadian pacemaker in hypothalamus [23▪]. Misalignment of sleep-wake and fasting-feeding cycles with the endogenous circadian clock as a consequence of night shift work is associated with adverse metabolic effects. Sleep disorders are prevalent in patients with CKD. Melatonin is a hormone primarily released from the pineal gland, involved in sleep-wake timing, BP regulation and in synchronizing circadian rhythms. In CKD the amplitude of the melatonin rhythm decreases as renal function declines and disturbed melatonin rhythm in CKD patients is associated with sleep disorders [52–55]. Furthermore, restless legs syndrome, a sensorimotor disorder with circadian rhythmicity is common in patients with CKD [56]. The prevalence of increased BP during sleep and nondipper pattern is high in CKD population [57▪,58]. CKD patients have higher vagal activity during the day with lower sympathovagal balance at night [59]. Thus, several observations indicate an unbalanced circadian system in uremia, which potentially is representing a previously unrecognized risk factor. In the following the concept of disruption of the circadian clock system in organs involved in CKD–MBD, the parathyroid gland, vasculature and bone is discussed (Fig. 2).

Parathyroid hyperplasia and circadian clock-regulated cell proliferation in secondary hyperparathyroidism

The circadian rhythm of PTH secretion is well described and it is considered truly endogenous [12▪,60]. The parathyroid glands are not controlled by a superior hypothalamic-pituitary axis as many other endocrine glands and are likely to use other hitherto unknown regulatory mechanisms.

In CKD, sHPT is characterized by extensive growth of the glandular size, increasing up to 100-fold and disrupted circadian rhythmicity of PTH secretion [12▪]. Deregulation of the circadian clock might theoretically be of importance for parathyroid hyperplasia in CKD. The cell cycle regulators involved in parathyroid growth are known to be under control of the clock. *c-Myc*, *p20*, *p21* and *cyclin D1* all exhibit circadian pattern of gene expression and TGF-α/epidermal growth factor receptor signaling is known to regulate circadian rhythms within the CNS [61]. In sHPT, *c-Myc* is overexpressed in a substantial fraction of the parathyroid tumors [62]. In uremic rats, dietary phosphate restriction, high dietary calcium or administration of calcitriol prevented parathyroid hyperplasia by inducing the cell cycle inhibitor, *p21*, and decreasing *TGF-α*. An enhanced expression of *TGF-α* is known to promote cell growth and has been found in parathyroid hyperplasia in uremia. In hyperplastic parathyroid glands from uremic patients the expression of the cyclin-dependent kinase inhibitors, *p21* and *p27*, was reduced in a manner, which depended upon the expression of the vitamin D receptor (*VDR*) [63,64]. Transgenic mice overexpressing parathyroid *cyclin D1* developed parathyroid hyperplasia and hyperparathyroidism. Circadian pathways are

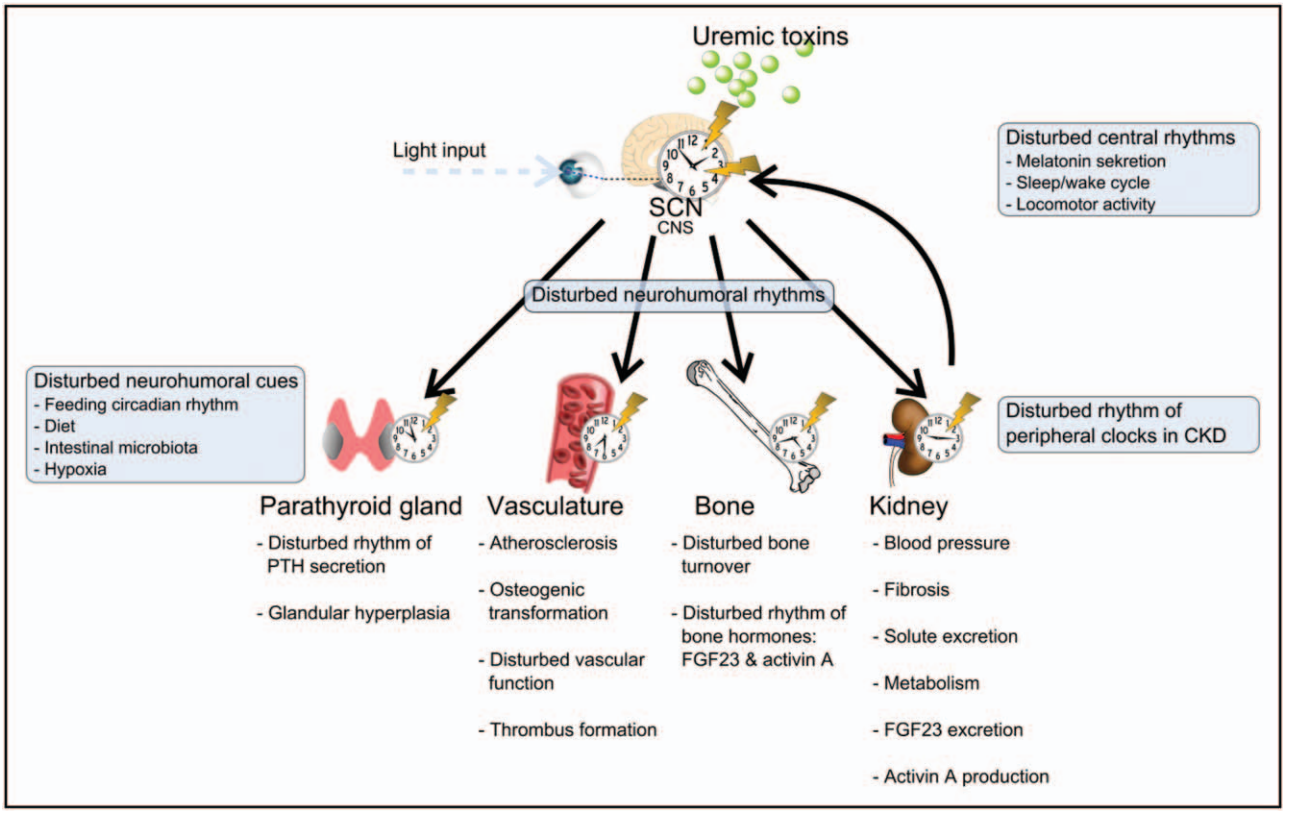

FIGURE 2. A simplified model of disturbed circadian rhythm in chronic kidney disease–mineral bone disorder. The circadian system involves the environmental cues that entrain the central pacemaker, a molecular circadian clock, located in the suprachiasmatic nucleus (SCN) and peripheral molecular circadian clocks, located in the peripheral cells, but being under control of the central pacemaker via neurohumoral signals. The kidney provides feedback input to the central clock as well. In chronic kidney disease the clock in central nervous system is potentially deregulated by uremic toxins, feedback input from the injured kidney as well as by disturbed response to environmental cues. The molecular clocks in organs involved in chronic kidney disease–mineral bone disorder are desynchronized from the central clock. The expressions of the peripheral clock genes in the parathyroid gland, vasculature, bone and kidney are disturbed, contributing to the chronic kidney disease–mineral bone disorder symptoms of secondary hyperparathyroidism, vascular calcifications, renal osteodystrophy, kidney fibrosis and disturbed circadian rhythmicity of the plasma parameters related to chronic kidney disease–mineral bone disorder, activin A, fibroblast growth factor 23, parathyroid hormone and phosphate.

intimately linked to the mTOR pathway [65]. Melatonin, that is controlling circadian rhythm regulates differential processes including cancer growth via mTOR [66], and the mTORC1 pathway is essential for parathyroid cell proliferation in sHPT [67].

In a translational model of CKD–MBD, we examined whether an internal molecular circadian clock was present in the rat parathyroid gland and found a strong expression of core molecular clock genes: *Bmal1*, *Clock*, *Per1–3*, *Cry1–2* and *Rev-Erbα*, all having significant circadian rhythmicity. Furthermore, we found significant rhythmicity of the cell cycle gene *Cyclin D1* in normal rats. In parathyroids from CKD rats *Cyclin D1* expression was deregulated (unpublished data). As such, the demonstrated internal parathyroid circadian clock might be disturbed in uremia and might potentially contribute to the glandular hyperplasia. Parathyroid molecular circadian clock and its regulation by VDR, calcium-sensing receptor (CaR) and phosphate need to be examined in detail.

The vascular circadian clock is disrupted in chronic kidney disease–mineral bone disorder

The cardiovascular system, BP and heart rate and the endothelial function and thrombus formation are regulated by the circadian clock [68,69]. Disruption of 24-h rhythms may lead to cardiovascular disease, including heart failure, fibrosis, myocardial infarction (MI) and arrhythmias [24,25]. In addition, the onset of cardiovascular events such as acute MI, arrhythmias and stroke shows circadian pattern

[40,70,71] and patients with hypertension benefits from antihypertensive chronotherapy [57▪,72].

Arterial calcification can be classified into tunica intima calcification, related to atherosclerosis, and tunica media calcification. Media calcification is predominant in systemic metabolic disorders, such as CKD, diabetes mellitus and aging. Cells with multilineage potential in the arterial wall, pericytes, smooth muscle cells and adventitial myofibroblasts may all contribute to the development of vascular calcifying diseases. In the context of chronic uremia, vascular smooth muscle cell can undergo maladaptive osteochondrocytic differentiation [73]. A functional circadian clock has been demonstrated in the different cell types of the blood vessel layers. The circadian clock components have been found in endothelial cells [74], in vascular smooth muscle cell of lamina media [75] and in cultured fibroblasts from the outer wall of the vessels [40]. An interesting study demonstrated development of atherosclerosis in mice with a disrupted circadian clock (*Bmal1* or *Per2,3* double-KO). Transplantation of blood vessels from these animals into wild-type littermates did not prevent this pathologic development, but still resulted in atherosclerosis [76]. This indicates that the intrinsic vascular tissue clock has an autonomous impact on atherosclerotic disease.

In CKD–MBD patients, a lack of the diurnal variation in arterial stiffness and a loss in nocturnal BP dipping have been demonstrated [58].

Our laboratory examined by RNAseq analysis the transcriptional profile of severely calcified aortas in a CKD–MBD rat model [73]. Several genes related to the circadian clock were expressed in the normal aorta and were significantly deregulated in the calcified uremic aorta. The expression of *Per* genes was significantly downregulated in the calcified aorta, whereas the expression of *Cry* genes was unaffected. The transcriptional activators *Clock* and *Bmal1* were significantly increased in the calcified uremic aorta. Genes reported to be controlled by the clock system were significantly deregulated, as presented in Table 1.

Renal osteodystrophy and circadian clock

Bone remodeling is a complex process by which old bone is removed and replaced by new bone, requiring coordinated interaction between different bone cells. The diurnal variation in bone turnover markers and experimental circadian clock knockout models suggest that circadian rhythmicity is important for bone health [77].

Global deletion of murine Bmal1 led to a low bone mass, associated with increased bone resorption. Osteoclast-specific Bmal1-knockout mice showed a high bone mass phenotype due to reduced osteoclast differentiation [78]. It has been suggested that bone resorption is controlled by osteoclastic Bmal1 through interactions with the steroid receptor coactivator family and upregulation of nuclear factor (NF) of activated T cells, cytoplasmic 1, calcineurin-dependent 1 (Nfatc1) transcription through its binding to an E-box element located on the Nfatc1 promoter [78]. Studies indicate that the clock system is present in osteoblasts as well [79,80]. Coculture experiments revealed that Bmal1-deficient osteoblasts have a higher ability to support osteoclastogenesis, whereas overexpression of Bmal1/Clock inhibited calcitriol-induced receptor activator of NF κB ligand (Rankl) in osteoblasts [81].

Bone turnover has a circadian pattern with bone resorption and to a less extent bone formation increasing at night. A robust diurnal variation of the bone resorption markers N-terminal or C-terminal telopeptide of type I collagen has been shown [82,83]. It was not affected by bedrest, cortisol level, blindness (indicating independence from the light/

Table 1. Disrupted expression of circadian clock genes and clock-controlled genes in the calcified aorta of uremic rats analyzed by RNAseq

Gene	Name	Control (rpkm)	CKD (rpkm)	$\log_2$ (CKD/control)	*P* value
Clock	Circadian locomotor output cycles kaput	2.0	4.5	0.42	<0.0007
Per1	Period circadian clock 1	87	51	−0.11	<0.0007
Per2	Period circadian clock 2	51	32	−0.14	0.003
Icam1	Intercellular adhesion molecule 1	12	28	1.2	<0.0007
Vcam1	Vascular cell adhesion molecule 1	80	293	1.9	<0.0007
Ccl2	Chemokine ligand 2	2.1	26	3.6	<0.0007
Thbd	Thrombomodulin	40	23	−0.8	<0.0007
Ckdn1a	Cyclin-dependent kinase inhibitor 1A	39	79	1.0	<0.0007

CKD, chronic kidney disease; rpkm, read per kilo base per million mapped reads.

dark cycle) or administration of salmon calcitonin. Fasting had a pronounced influence on the circadian variation of bone turnover [84] reducing the amplitude [82]. It is well known that the gut is an important regulator of bone homeostasis with gut-derived factors, including glucose-dependent insulinotropic polypeptide and peptide YY, controlling bone resorption and formation [85]. Recently it has been demonstrated that the intestinal circadian system regulates skeletal homeostasis [86]. The lack of the *Bmal1* gene in the intestine (Bmal1Int−/− mice) caused bone loss, with bone resorption being activated and bone formation suppressed [86]. Mechanistically, Clock protein interaction with VDR accelerates its binding to the VDR response element by enhancing histone acetylation in a circadian-dependent manner, which was lost in Bmal1Int−/− mice. As a result, the rhythmic expression of VDR target genes involved in transcellular Ca absorption was abolished, Ca absorption impaired, and bone resorption activated [86].

The intestinal bacterial composition and function feature daily rhythmicity depending on the cues from the host circadian clock [87]. In a mice model of hyperparathyroidism, impacting the gut microbiome by antibiotics or using germ-free animals PTH-induced bone loss was ameliorated via a T-cell-related mechanism [88▪]. These observations indicate that metabolic bone disorder induced by circadian clock disruption can be affected by aberrations in the intestinal microbiome.

In CKD–MBD, the spectrum of renal osteodystrophy is related to plasma PTH levels and skeletal responsiveness to PTH. It is potentially affected by diurnal variation in circulating PTH and phosphate, and by the internal circadian clock in bone cells as well as the gut–bone crosstalk. Indeed CKD leads to alterations in the intestinal flora [89]. More research is necessary to unravel the relationship between microbiome composition, rhythmicity and renal osteodystrophy, including skeletal response to PTH.

Melatonin suppresses a microgravity stimulated osteoclast activity in the Goldfish Scales Model and is proposed potentially to prevent bone loss during space flight [90]. The circadian rhythm of melatonin is disrupted in CKD. Activin A and FGF23 are primarily bone-derived factors having circadian rhythmicity, and their levels are increased, and rhythmicity abolished in CKD [12▪]. This might potentially indicate a link between circadian clock regulation in bone and development of renal osteodystrophy. The importance of the molecular circadian clock in bone cells for the secretion of activin A and FGF23 in normal and CKD conditions needs however further investigation.

Circadian rhythms in plasma parameters of mineral metabolism in chronic kidney disease–mineral bone disorder

In uremia, disturbances in the circadian rhythms of activin A, FGF23, PTH and phosphate have been demonstrated (Fig. 3). Results from our laboratory showed for the first time existence of a circadian rhythm of plasma activin A, which was disturbed in CKD (Fig. 4) [12▪]. Plasma-phosphate and PTH have circadian rhythms, which should be taken into consideration when interpreting the circulating levels [12▪,91]. Similarly, p-activin A levels need to be related to the time of the day, they are obtained, as four-fold higher values are found at acrophase, compared with nadir (Fig. 4) [12▪].

Recent fascinating studies proposed that the CaR [92], FGFR1 [93,94] and sodium-phosphate cotransporter, PiT2 [95,96] are involved in extracellular sensing of phosphate. Changes in the expression and activity of the phosphate sensing receptors in CKD might contribute to the disturbed circadian rhythm of plasma phosphate and the phosphate regulating hormones, PTH and FGF23 in CKD [97]. Plasma Klotho expresses no circadian variation [12▪]. In addition to, disturbed circadian rhythm in plasma levels in CKD might be due to altered metabolism or the extra-skeletal secretion of FGF23 and activin A. Thus, FGF23 is excreted by the kidney [98] and both induction and secretion of FGF23 from the heart and bone marrow have been observed in CKD [49,99]. In our lab we found significant induction and secretion of activin A from injured kidneys [2] (Fig. 4).

Chronotherapy

Chronotherapy or chronotherapeutic treatment is treatment scheduling according to circadian cycle utilizing time or delivery of medication to affect its efficacy [100,101]. The classical example of benefit from chronotherapy is a more efficient reduction in plasma cholesterol when simvastatin is administrated in the evening. That's because the levels of the 3-hydroxy-3-methylglutaryl CoA reductase, which are reduced by statins, are known to peak in the nighttime hours. Recent evidence has also shown that bedtime administration of antihypertensive medication, compared with the usual intake in the morning may provide a significantly better controlled hypertension and diminished occurrence of major cardiovascular events [57▪]. The mechanism by which this effect takes place is still speculative. Given a potential role of the circadian clock in CKD–MBD, chronotherapy might become an important part of the future treatment of this serious condition [57▪,72,100]. Thus, targeting circadian mechanisms by VDR or CaR activators given as chronotherapy

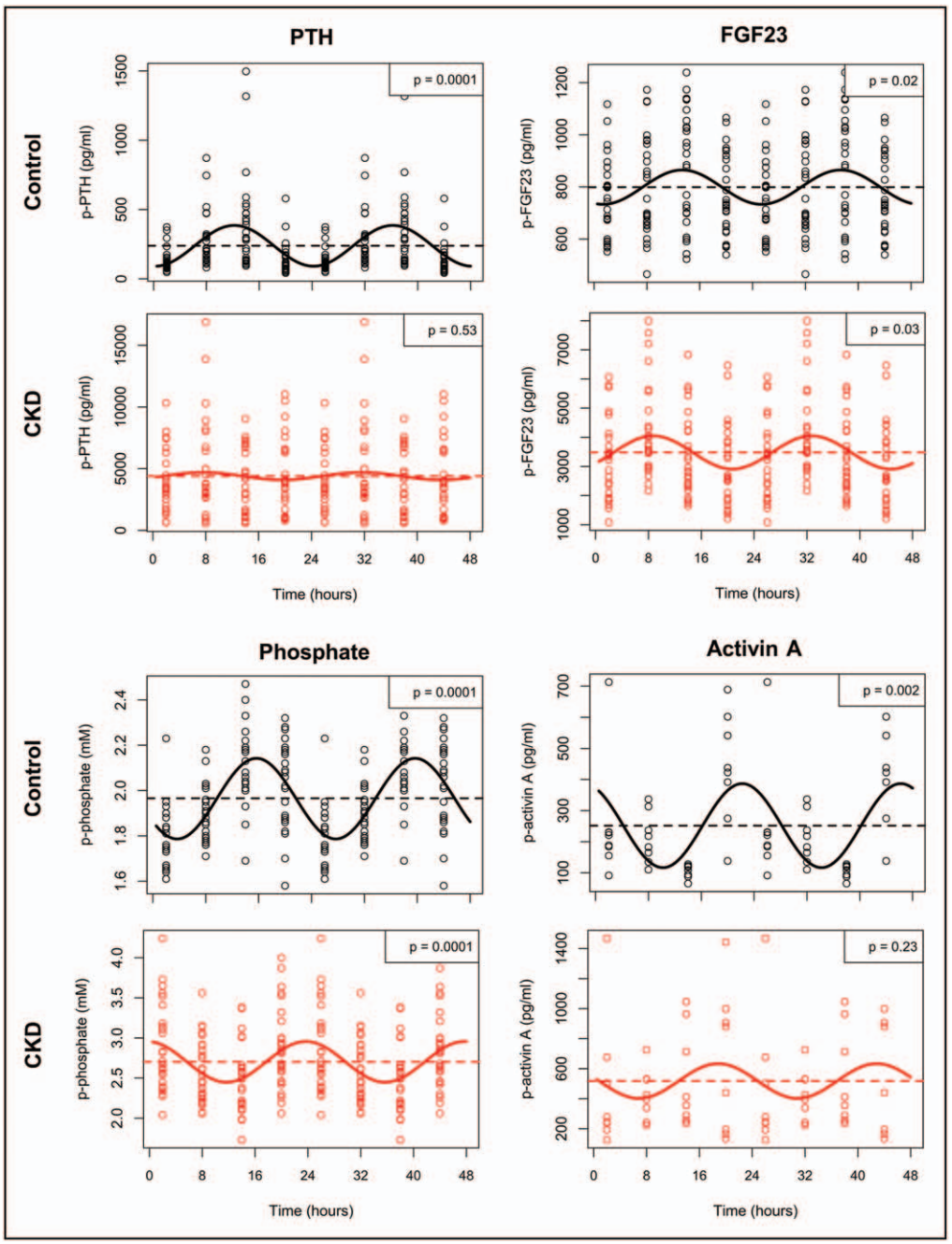

FIGURE 3. Disturbed circadian rhythms of chronic kidney disease–mineral bone disorder parameters in uremia. Circadian rhythms of circulating levels of plasma parathyroid hormone, fibroblast growth factor 23, phosphate, and activin A in chronic kidney disease and age-matched normal control rats are shown. Wistar rats were allocated to control or chronic kidney disease (5/6 nephrectomy and high phosphate diet for 24 weeks). Control rats exhibited circadian rhythm of all parameters. Significant rhythmicity was confirmed by cosinor analysis: parathyroid hormone ($P < 0.0001$), fibroblast growth factor 23 ($P < 0.05$), phosphate ($P < 0.0001$) and activin A ($P < 0.01$). Chronic kidney disease completely obliterated the circadian rhythm of parathyroid hormone and activin A. The circadian rhythms of fibroblast growth factor 23 and phosphate were maintained in chronic kidney disease rats (fibroblast growth factor 23: $P < 0.05$, phosphate: $P < 0.0001$), however, both rhythms were severely disturbed. As such, the acrophase of fibroblast growth factor 23 shifted from 13:00 in control to 09:00 in chronic kidney disease rats, whereas the acrophase of phosphate shifted from 16:00 in controls to 00:00 in chronic kidney disease rats [12▪].

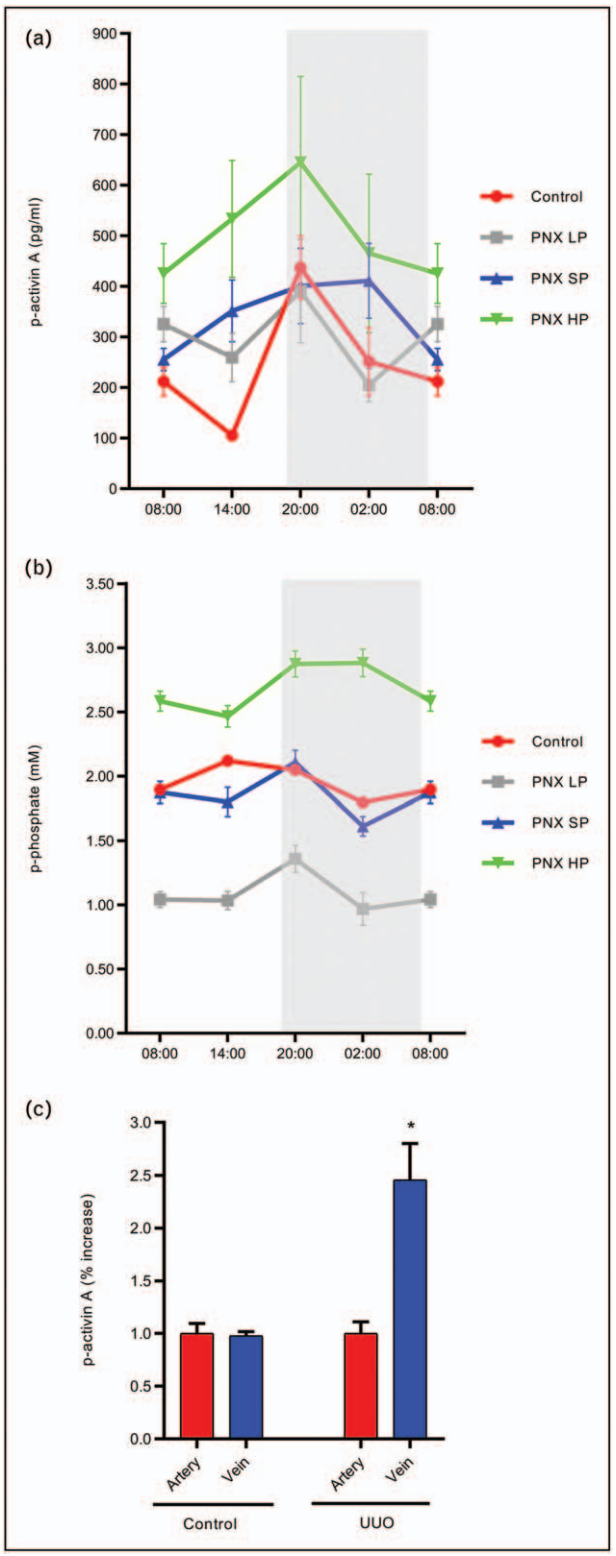

FIGURE 4. Circadian rhythm of plasma activin A and phosphate in normal and uremic rats on different phosphate diets. Induction and secretion of activin A from the injured kidney. Plasma activin A exhibits circadian rhythmicity in control rats, whereas the rhythm is obliterated by chronic kidney disease. An increase in plasma activin A levels was observed in chronic kidney disease rats, but depending upon the time of the day. In chronic kidney disease rats on a low phosphate diet the increase in plasma activin A was inhibited. However, the circadian rhythm was not restored (a). Similarly, circadian rhythmicity of plasma phosphate was disturbed in chronic kidney disease rats. Furthermore, chronic kidney disease rats on a high phosphate diet developed hyperphosphatemia. This was prevented by the low phosphate diet, which however did not restore the circadian rhythmicity of plasma phosphate in chronic kidney disease (b) [12▪]. Kidney injury was induced by unilateral ureter obstruction for 15 days and blood sampling from the isolated renal artery and vein was performed. Activin A was induced and secreted of from the injured kidney (c). partly nephrectomized: 5/6 partial nephrectomy. HP, high-phosphate diet; LP, low-phosphate diet; SP, standard-phosphate diet. Mean ± SEM.

might potentially result in amelioration of the parathyroid hyperplasia in CKD. Melatonin administration can potentially synchronize the internal circadian clocks in organs involved in CKD–MBD and improve bone remodeling. This needs to be examined in translational models. New compounds targeting the circadian clock components of relevance for bone remodeling, inflammation and organ fibrosis are emerging and deserve future investigations [47,80,100]. Finally, physiological and behavioral chrono-enhancement based on enhancement of input to the circadian system such as increasing day-night contrast, regular exercises and regular meal schedule might synchronize the circadian rhythms and have an impact on CKD–MBD.

CONCLUSION

The proper rhythms in metabolism, hormonal secretion, cardiovascular function and bone remodeling are controlled by a molecular circadian clock. Evidence is emerging on the disturbances in the circadian rhythms in CKD–MBD. There is an urgent need to characterize the impact of this malfunction on the parathyroid gland, bone and vascular system in CKD. Thus, what is the specific input that determines the phase of the molecular circadian clock in the peripheral tissues, involved in CKD–MBD, and how is the clock deregulated in CKD. Furthermore, translational studies are warranted to examine the applications for chronotherapy.

Acknowledgements

The authors thank Anders Nordholm, Eva Gravesen and Jakob L. Rukov for conducting many of the experiments referred to in the article.

Financial support and sponsorship

The Kirsten and Freddy Johannsen's Foundation.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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