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Review

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The impact of nephrectomy on bone health

Wpływ nefrektomii na układ kostny

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Summary

Normal kidneys function plays a crucial role in maintaining bone health. This fact is highlighted by the mineral-bone disorder resulting from chronic kidney disease (CKD). CKD impairs the skeletal structure, which in turn leads to a higher prevalence of bone fractures. Because nephrectomy results in a reduced number of nephrons, the question arises if surgically induced nephron loss causes alterations in bone health similar to those observed in CKD.

A large number of studies draw attention to the fact that nephrectomy leads to mineral disturbances. Recent studies are consistent that nephrectomy leads to a decline in phosphate and calcitriol levels and an increase in parathyroid hormone levels. There is no consensus regarding the impact of surgically induced nephron loss on fibroblast growth factor 23 (FGF-23) levels. Whether the observed alterations translate into increased fractures rate is still unclear. Current data is sparse and further studies are required to evaluate the possible adverse impact of nephrectomy on bone health.

This is a review of the literature exploring the impact of nephrectomy on mineral disturbances and bone health.

Keywords: **nephrectomy • bone mineral metabolism • FGF-23 • fracture**

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Abbreviations: **25(OH)D_3** – 25 hydroxyvitamin D_3, 1,**25(OH)$_2$$D_3$** – 1,25-dihydroxyvitamin D_3, **bALP** – bone specific alkaline phosphatase, **CKD** – chronic kidney disease, **CKD-MBD** – chronic kidney disease mineral-bone disorder, **CTX** – C-telopeptide of type 1 collagen, **eGFR** – estimated glomerular filtration rate, **ELISA** – enzyme-linked immunosorbent assay, **FGF-23** – fibroblast growth factor 23, **NTX** – N-terminal cross-linking telopeptide of bone type 1 collagen, **OC** – osteocalcin, **OPG/RANK/RANKL** – osteoprotegerin/receptor activator of nuclear factor kappa beta/receptor activator of nuclear factor kappa beta ligand, **P1NP** –propeptide type 1 N-terminal procollagen, **PTH** – parathyroid hormone, **TRAP 5b** – tartrate-resistant acid phosphatase 5b.

Introduction

It is a well-known fact that kidneys cooperate with bones in the regulation of calcium-phosphate homeostasis, which is essential for bone mineralization and development. Over the last years, our view of the skeleton has evolved and it is widely accepted that bones serve not only as a warehouse for minerals but also as an active endocrine organ. Moreover, evidence is mounting that molecules secreted by osteocytes, such as fibroblast growth factor 23 (FGF-23) and sclerostin, affect not only mineral and skeletal metabolism but also such distinct structures as the cardiovascular system [21,38]. In health the function of kidneys and bone are tightly connected. It is not only the case that substances synthesized by kidneys, such as calcitriol or Klotho, affect bone development, but it is also important to point out that blood concentration of proteins secreted by bones, e.g. sclerostin or FGF-23, are influenced by the degree of renal impairment [45]. Thus, to stress the mutual relationship between these two organs, the concept of the bone-kidney axis has been developed.

The best evidence of kidneys' key role in preserving bone health is chronic kidney disease (CKD). Ongoing pathophysiological process leads to the progressive loss of nephrons and renal function impairment. As kidney function deteriorates, the abnormalities in mineral metabolism begin to develop. This common complication, called CKD-mineral-bone disorder (CKD-MBD) occurs very early in the course of CKD, when glomerular filtration rate is only mildly reduced [35]. It increases fracture risk [23], amplifying morbidity and mortality among CKD patients [41].

Because nephrectomy results in reduced number of nephrons, it is plausible to suspect its impact on bone health. Two large groups of patients that undergo nephrectomy are: living kidney donors and patients with renal tumors. In donors, the estimated glomerular filtration rate (eGFR) decreases after nephrectomy to 60-89 ml/min/1,73m^2 [5,34], which resembles CKD stage 2. Since living kidney donors are healthier than the general population, we may expect that in patients with renal cell carcinoma GFR changes are even more pronounced after surgery. Individuals that undergo nephrectomy due to oncological reasons are older and have comorbidities such as diabetes and hypertension, so their outcome after nephrectomy might be worse[10]. Moreover, even up to 25% of patients with renal cell carcinoma suffer from CKD at the time of surgery[37]. Thus, there is a marked difference in the incidence of CKD after nephrectomy between these two groups. In donor population, CKD after nephrectomy occurs at comparable rates to the general population[16], while in the renal cell carcinoma patients, the risk of CKD development is increased [11]. It is noteworthy that the amount of removed kidney tissue seems to alter the risk of future CKD development. In a prospective, randomized trial, the incidence of CKD in oncological patients was higher following radical rather than partial nephrectomy[39].

Based on the above data, partial nephrectomy is recommended for the management of clinical T1 renal tumors to preserve the maximal amount of healthy renal tissue and reduce the risk of CKD [30]. Indeed, this technique results in better renal function, providing the same oncological outcome as radical nephrectomy [13]. Other clinical benefits of nephron sparing surgery are controversial. Even though studies have reported a reduction in cardiovascular incidents [9], the potentially most important advantage, which is better survival, is still questionable. There are a number of studies showing decreased [42], the same [27] as well as increased [44] mortality after partial nephrectomy due to other causes than cancer.

Data about the impact of nephrectomy on bone health is scarce and unequivocal. On the one hand, studies report altered bone metabolism after kidney donation [25,36,47], but, on the other, the fracture risk was found to be similar among donors and controls [15].

The associations between nephrectomy and disturbances in bone-mineral metabolism are not fully elucidated. Given the fact that in an experimental setting, nephrectomy helps to create a model of CKD to investigate its consequences, the question arises if surgically induced nephron loss in humans causes alterations similar to those observed in CKD. In this article, we will review the literature exploring the impact of nephrectomy on bone health disturbances.

Calcium, phosphorus, calcitriol and parathyroid hormone

Kidneys play an important role in calcium-phosphorus homeostasis. Both ions are involved in bone mineralization [7]. Calcium/phosphate balance is maintained with the assistance of calcitriol, the biologically active form of vitamin D, and parathyroid hormone (PTH). The living kidney donors studies have yielded more information about disturbances in the above mentioned factors after nephrectomy. Shortly after the surgery, hypocalcemia is reported [24,36,46]. A decrease in calcium level stimulates an increase in PTH and, subsequently, the calcium levels return to a normal value and remain unchanged in further observations (180 and 360 days after surgery) [36,46]. It is worth noting that postoperative hypocalcemia with secondary increase in PTH is not limited to nephrectomy but is also described in patients undergoing different abdominal surgeries [28]. All studies are in agreement that kidney removal does not change calcium serum levels in a long-term follow-up. That data is consistently demonstrated in studies with a control group [25,33,47] and comparing calcium levels after nephrectomy to the baseline value [36]. There is still the question about the total calcium balance and how kidney removal impacts urinary calcium excretion. Transient decrease of calcium excretion was reported in a short-term follow-up in kidney donors [36,46]. On the other hand, in the population of nephrectomized patients due to urological indication increase in fractional excretion of

calcium was observed [24]. The observed discrepancies in the evaluated parameters immediately after kidney removal might be related to other factors connected to the surgery, such as hydration, anesthesia or fasting. In a study with a long-term follow-up, Kasiske et al. did not find differences in urinary calcium levels (assessed by fractional tubular resorption) after 6 and 36 months after donation and in comparison to controls [25]. This is contrary to previous findings reporting decreased daily urinary calcium excretion (24 hour calciuria), which can be explained by lower levels of calcitriol and, therefore, decline in intestinal calcium absorption [36,46].

After nephrectomy, calcium levels remain stable, even though there is a decrease in calcitriol level. Kidney removal results in the decline of the active form of vitamin D [6,25,36,47]. Kasiske et al. in their recent prospective study which included 182 kidney donors found that there was inadequate conversion of 25(OH) D_3 to 1,25$(OH)_2D_3$ due to the decreased activity of 1α-hydroxylase (the enzyme responsible for renal conversion of vitamin D) [25]. Reduced 1α-hydroxylase activity after nephrectomy might be the effect of nephron loss as well as enzyme inhibition due to elevated FGF-23 levels.

Another alteration after nephrectomy is the decrease in serum phosphate accompanied by its increased urinary excretion [36,47]. In a long-term follow-up this might be explained by increased serum PTH [25,36,47] and/or FGF-23 [25,47] concentrations, since both of them are known to be phosphaturic. Interestingly, in the days following surgery decrease in serum phosphate and increase in renal excretion of phosphate occurred independently from PTH and/or FGF-23. Ponte et al. reported increased phosphaturia on the third day after surgery when PTH levels normalized and FGF-23 declined [36]. We may speculate that there is another phosphaturic factor responsible for those changes during postoperative days.

A transient rise of PTH due to postoperative hypocalcemia is observed following nephrectomy and then PTH concentration normalizes [36,46]. Later, a progressive increase in PTH has been reported in long-term observation of kidney donors [17,25,33]. It is hypothesized, that reduction in calcitriol synthesis contributes to those changes.

FGF-23 and Klotho

FGF-23 is a hormone produced by osteocytes, which reduces the synthesis of calcitriol and regulates phosphate metabolism by inhibiting proximal tubular phosphate reabsorption. Klotho, a protein mainly expressed in the kidneys, is FGF-23 co-factor and is connected to the FGF-23 biological activity. Since the soluble form of Klotho may act independently from FGF-23, Klotho regulates calcium and phosphorus homeostasis directly. There is strong evidence that Klotho levels decline after nephrectomy [1,36]. It is especially important in the light of recent data related to decreased Klotho with poor outcome of patients with acute kidney injury[40] and CKD[26]. By contrast, FGF-23 behavior after kidney removal is still unclear. Westerberger et al. reported an increase in FGF-23 levels in postoperative days [46]. A subsequent study found a decline in FGF-23 levels during three consecutive days after nephrectomy [36]. The same lack of consistency is present the long-term follow-up studies. Ponte et al. reported the absence of significant changes in FGF-23 on 180 and 360 day after nephrectomy [36]. Although recently published studies suggest FGF-23 elevation in long-term post donation [25,33,47]. The question about FGF-23 behavior is immensely relevant, since FGF-23 levels are linked to adverse outcomes such as cardiovascular events [38], left ventricular hypertrophy [18] and increased risk of death in CKD [21]. It was also reported that elevated FGF-23 increased fracture risk in elderly men [32]; however, results from prospective cohort in over 2,000 patients did not confirm that data [20].

Some discrepancies in results regarding FGF-23 might be explained by diverse GFR level after nephrectomy as well as differences in assays. It is worth remembering that currently two types of ELISA kits are available to determine plasma FGF-23 levels: intact FGF-23, which detect only full length molecule and c-terminal FGF-23, which detect both intact and c-terminal fragments.

Wnt/β-catenin and OPG/RANK/RANKL pathway

One of the most important molecular pathways in bone homeostasis is the Wnt/β-catenin pathway, which is essential for bone mineralization. A major regulator of the Wnt pathway is sclerostin, which is expressed almost exclusively in osteocytes and acts as an inhibitor of bone formation [14]. Interest in sclerostin intensified recently, when studies have shown that circulating sclerostin is probably a new player in CKD-mineral and bone disorder [14]. A number of studies have now reported that higher serum sclerostin levels predict increased fracture risk [2,3]. Recently, it was shown that a high degree of GFR impairment after nephrectomy causes elevated sclerostin blood level [24].

Another system involved in the regulation of bone metabolism and osteoclastogenesis is OPG/RANK/RANKL pathway. Stimulation of receptor activator of nuclear factor kappa beta (RANK) by RANK ligand (RANKL) promotes osteoclast formation. Osteoprotegerin (OPG) protects the skeleton from excessive bone resorption by binding to RANKL and preventing RANK signaling [8]. Even though, based on current literature, proof is scarce, it is probable that OPG/RANK/RANKL pathway might play a role in the pathogenesis of bone disease after nephrectomy. A recent animal experiment demonstrated that bone loss following kidney surgery might be linked to the suppression of OPG/RANK/RANKL system [29].

Table 1. Impact of the nephrectomy on bone turnover markers

Study	Population	Follow-up	bALP	P1NP	OC	CTX	NTX	TRAP 5b
Ponte et al., 2014 [36]	LKD	6 months 1 year	↑ ↔	↔ ↔	- -	↓ ↔	- -	- -
Kasiske et al., 2016 [25]	LKD compared to controls	6 months 3 years	↑ ↑	↑ ↔	↑ ↑	↑ ↑	↑ ↑	↑ ↔

LKD, living kidney donors; bALP, bone specific alkaline phosphatase; P1NP, propeptide type 1 N-terminal procollagen; OC, osteocalcin; CTX, C-telopeptide of type 1 collagen; NTX, N-terminal cross-linking telopeptide of bone type 1 collagen; TRAP 5b, tartrate-resistant acid phosphatase 5b

Table 2. Impact of the nephrectomy on bone and mineral metabolism

Study	Population	N	Follow-up	GFR after surgery	Serum calcium	Urine calcium[a]	Serum phosphate	$TmPO_4$/GFR	25(OH)D	Calcitriol	PTH	FGF-23	Klotho
Short-term follow-up													
Westerberg et al., 2010 [46]	LKD	9	1 day 1 week	76±24 54±13	↓ ↔	↓ -	↔ ↔	↔ ↔	-	↓ ↓	↑ ↔	- ↑	-
Ponte et al., 2014 [36]	LKD	27	1 day 3 days	-	↓ ↓	-	↔ ↓	↓ ↓	-	-	↑ ↔	↓ ↓	↓ ↓
Kakareko et al.,2016 [24]	UP	25	5±2 days	68±26	↓	↑[b]	↓	↓	-	-	↔	-	-
Long-term follow-up													
Gossmann et al., 2005 [17]	LKD	135	11±7 years	99±30	-	-	-	↓[c,d]	-	↓[d]	↑[e]	-	-
Bieniasz et al., 2009 [5]	LKD	40	mean 5.5 years	65	-	-	-	-	-	↓[d]	↑[e]	-	-
Westerberg et al., 2010 [46]	LKD	9	3-6 months	70±14	↔	↓	↔	↔	-	↓	↔	↔	-
Young et al., 2012 [47]	LKD/ controls	198	mean 5.3 years	73±15	↔	-	↓	↑[f]	↔	↓	↑	↑	-
Ponte et al., 2014 [36]	LKD	27	6 months 1 year	63±13	↔ ↔	↓ ↓	↓ ↓	↓ ↓	↔ ↔	↓ ↓	↑ ↑	↔ ↔	↓ ↓
Moody et al., 2016 [33]	LKD/ controls	57	1 year	59±13	↔	-	↔	-	↔	-	↑	↑	-
Kasiske et al., 2016 [25]	LKD/ controls	182	6 months 3 years	68 70	↔ ↔	↔[g] ↔[g]	↓ ↔	↓[c] ↓[c]	↑ ↑	↓ ↓	↑ ↑	↑ ↑	- -

LKD, living kidney donors; UP, urological patients; GFR, glomerular filtration rate; $TmPO_4$/GFR, ratio of tubular maximum reabsorption rate to the glomerular filtration rate; 25(OH)D, 25 hydroxyvitamin D; PTH, parathyroid hormone; FGF-23, fibroblast growth factor 23

a 24 hour calciuria; b urinary fractional excretion of calcium; c tubular reabsorption of phosphate; d below lower limit of normal; e above upper limit of normal; f urinary fractional excretion of phosphate; g tubular reabsorption of calcium

Bone turnover markers

Data regarding the behavior of bone turnover markers after nephrectomy is sparse (Table 1). Ponte et al. evaluated selected markers of bone formation (bone specific alkaline phosphatase, bALP and propeptide type 1 N-terminal procollagen, P1NP) and resorption (C-telopeptide of type 1 collagen, CTX). Six months post donation they found only a significant increase in bALP serum concentration. During the follow-up one year later, bone turnover markers did not change, except for CTX, which significantly increased [36]. Kasiske et al. in their study measured bone formation (bALP, P1NP and osteocalcin, OC) and resorption (CTX, N-terminal cross-linking telopeptide of bone type 1 collagen, NTX and tartrate-resistant acid phosphatase 5b, TRAP 5b) markers before and after kidney donation and additionally compared those findings with matched healthy controls. Interestingly, authors reported increased concentration in all bone formation (bALP, P1NP, OC) and most of the resorption (CTX, NTX) markers evaluated during follow-up. Even though there was no significant change in TRAP 5b after nephrectomy and increased levels of P1NP reached significance only in 6-month follow-up, results generally suggest some changes in bone turnover. This is currently the largest prospective study of kidney donors with control group highlighting that nephrectomy alters markers of bone metabolism. According to the authors, the sequence of events leading to that changes involves: reduction in glomerular filtration rate- decrease in synthesis of calcitriol- secondary hyperparathyroidism [25].

Certainly, bone metabolism markers are very helpful tools in evaluating changes in the formation/resorption balance. Additionally, circulating biomarkers correlate with the risk of fractures and mortality [12]. Although they should be interpreted with caution in patients with altered GFR, some of them, e.g. CTX, have limited use in kidney failure, because they accumulate as renal function declines [31,43]. Thus, it is possible that the changes in some of the bone markers after nephrectomy do not reflect only altered bone metabolism but also decreased elimination. Current studies agree that bALP could be a new standard test to assess bone turnover in CKD, since its serum concentration seems to be independent from kidney function. The same applies to TRAP 5b and to intact form of P1NP, but both need further studies to confirm their applicability in patients with kidney failure. It is also important to emphasize that biomarkers are used to 'monitor' bone health, thus the clinical information should not depend on a single value but on the trend of several values [12]. Even when we take into account these possible limitations of biomarkers, the current data suggests the alterations in bone turnover and possible adverse effect of nephrectomy on the skeletal system.

At present, information about the influence of nephrectomy on bone mineral density is lacking. Since it is an objective, noninvasive, and highly sensitive technique to assess bone condition, it could provide more useful information than bone markers. There is no study conducted after kidney donation and, to our knowledge, only one in patients undergoing nephrectomy for renal tumors [4] measuring bone loss with densitometry. It was shown that radical nephrectomy resulted in a higher degree of the postoperative osteoporosis than partial one (22.6% vs. 12.5%) [4].

Fracture risk

Currently, two large retrospective studies evaluated fracture risk after nephrectomy. Bagrodia et al. evaluated 905 patients after partial or radical nephrectomy due to renal tumors. They reported significantly fewer fractures (4.4% vs. 9.8%) in nephron sparing surgery cohort [4]. The second study in a population over 2,000 living kidney donors did not revealed increased fracture risk in donors compared to controls. Patients were followed-up for a median of 6.6 years, so it is possible that more time is needed to present increased fragility fracture risk in living kidney donors [15]. Given the fact that donors are healthier and younger than general population, fractures may occur many years after kidney removal. The possible link between alterations in bone mineral metabolism and fractures after nephrectomy requires further investigation.

Conclusions

Based on current data, there is no doubt that nephrectomy leads to mineral disturbances (Table 2). Recent studies are consistent about phosphate and calcitriol levels decline, PTH levels increase and no change in calcium concentration after kidney donation [34]. There is no consensus about impact of surgically induced nephron loss on FGF-23 levels. There is a burning question regarding FGF-23 behavior after nephrectomy, since this molecule emerged as one of the most important predictors of adverse outcomes in CKD [19,21,38] and general population [22]. An important point to consider is the possible connection between changes in bone mineral metabolism and fracture risk, which is still unclear. Currently available data about fracture risk is sparse and future studies are warranted. Long follow-up seems to be essential, as it is probable that bone fragility after nephrectomy takes a long time for clinical manifestation. If future studies confirm the negative impact of the nephrectomy on bone health, proper screening and management should be recommended to patients to improve their clinical outcomes.

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