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JANA UHLINOVA

Vascular calcification and its associations with obesity and bone mineral density in chronic kidney disease

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Paper III: subject recruitment, examination of patients, data collection, and preparing the publication

2. ABBREVIATIONS

1,25(OH)2D3	1,25-dihydroxyvitamin D
AAC	abdominal aortic calcification
AACS	abdominal aortic calcification score
ABI	ankle-brachial index
ADP	arteria dorsalis pedis
ATP	arteria tibialis posterior
BH	body height
BMI	body mass index
BMD	bone mineral density
BW	body weight
CKD	chronic kidney disease
CKD-MBD	chronic kidney disease-mineral and bone disorder
CV	cardiovascular
CVD	cardiovascular disease
DEXA	dual energy X-ray absorptiometry
ERA	European Renal Association
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
FGF23	fibroblast growth factor
GFR	glomerular filtration rate
KRT	kidney replacement therapy
LVH	left ventricular hypertrophy
PAD	peripheral artery occlusive disease
PD	peritoneal dialysis
PTH	parathyroid hormone
ROD	renal osteodystrophy
S-Alb	serum albumin
S-CRP	serum C-reactive proteiin
S-Crea	serum creatinine
S-i-Ca	serum ionized calcium
S-Ca	serum total calcium
S-Pi	serum phosphate
S-tALP	serum total alkaline phosphatase
S-UA	serum uric acid
S-CHL	serum total cholesterol
S-TG	serum triglyceride
S-Hb	serum haemoglobin
SHPT	secondary hyperparatyreoidism
VC	vascular calcification
VSMC	vascular smooth muscle cells
WHO	World Health Organization

3. INTRODUCTION

Chronic kidney disease (CKD) is a progressive, life-threatening disease which can lead to a broad spectrum of complications and changes in body composition. Cardiovascular diseases (CVD) are the primary cause of mortality in CKD patients. The pathophysiology of CVD in CKD is complex and involves both traditional and uremia-related risk factors (Foley et al., 1998). Obesity is one of the traditional risk factors for atherosclerosis and subsequent cardiovascular (CV) events in the general population, and in CKD patients (Madero et al., 2007; Hsu et al., 2006). The prevalence of obesity is increasing. Furthermore, according to data from some studies, obesity can lead to *de novo* CKD (Stenvinkel et al., 2013; Rhee et al., 2016). However, obesity can be related to better outcomes in advanced CKD (Fleischmann et al., 1999; Kalantar-Zadeh et al., 2003; Rhee et al., 2016). Such "reverse epidemiology" has been described mainly among end-stage kidney disease (ESKD) patients on haemodialysis, but findings about early stages of CKD and patients on peritoneal dialysis are heterogeneous (Ahmadi et al., 2015).

Another alteration in body composition in CKD is kidney disease-mineral and bone disorder (CKD-MBD), a systemic disorder of mineral metabolism resulting from kidney failure (Capusa & Popescu, 2018). CKD-MBD is associated with loss of bone tissue mass, increased risk of fractures, increased vascular calcification (VC), vascular stiffening and vascular senescence (Iseri, Dai et al., 2020). Manifestations of CKD-MBD begin early in CKD, with near-normal kidney function; the severity of CKD-MBD and its clinical outcomes increase with declining renal function (Damasiewicz & Nicolas, 2018). CKD-MBD causes CVD with premature atherosclerosis, arteriosclerosis and accelerated VC, which leads to generalised VC. Moreover, CKD-MBD is characterised by impaired bone health caused by renal osteodystrophy (ROD) and osteoporosis (Iseri, Dai et al., 2020). The pathophysiology of extraosseous calcifications and ROD is closely related, but the bone-vascular axis has not yet been sufficiently studied. Few studies have focused on the relationship between VC and bone mineral density (BMD) in CKD. Some studies have found an inverse association between VC and BMD, while others have found a positive association between VC and loss of BMD. (Schulz et al., 2004; Naves et al., 2008; Toussaint et al., 2011). However, some other studies have not shown any correlations between VC and BMD parameters (Salam et al., 2021). Besides that, associations between obesity and formation of extraosseous calcification in CKD have only been described by a few authors, and the results have been controversial (Yamauchi et al., 2003; Lee et al., 2012; Aoqui et al., 2013; Russo et al., 2014; Chen et al., 2016). Exposing the influence of obesity on VC in CKD patients would be of great benefit in evaluating the effect of obesity in this population at different stages. Therefore, more studies are needed to investigate the impact of obesity on VC. Additionally, it is necessary to clarify the associations between BMD and VC in patients with CKD. These data would be helpful in daily clinical practice to aid early intervention.

4. REVIEW OF LITERATURE

4.1. Chronic kidney disease

4.1.1. Definition and epidemiology

CKD is defined by the presence of kidney damage or decreased kidney function for at least three months, irrespective of the cause. Kidney damage generally refers to pathologic anomalies in the native or transplanted kidney, established via imaging, biopsy, or deduced from clinical markers like increased albuminuria or urinary sediment alterations; decreased kidney function refers to a reduced glomerular filtration rate (GFR), which is usually estimated (eGFR) from the serum concentration of creatinine (Wilson et al., 2021). CKD is classified based on eGFR (G1-G5) and A1-A3 based on the albuminuria, albumin-to-creatinine ratio (ACR) (KDIGO CKD Clinical Practice Guideline, 2024).

According to the epidemiological data 1990–2017 published in 2020, the prevalence of CKD worldwide was 9.1% or 697 million cases in 2017. The all-age global prevalence of CKD increased by 29.3% between 1990 and 2017. In 2017, CKD resulted in 1.2 million deaths and was the 12th leading cause of death worldwide. Together, deaths due to CKD or to CKD-attributable CVD accounted for 4.6% of all-cause mortality (Bikbov et al., 2020). Based on data from Estonian e-health, there were 83,710 patients with diagnosed CKD, or 7.4% of the adult population in 2019 (Rosenberg et al., 2023).

The prevalence of CKD is constantly growing, likely due to the ageing of the world's population. Likewise, the incidence of patients receiving kidney replacement therapy (KRT) has been increasing during the last decades because of the increasing availability of these therapies. According to the European Renal Association (ERA-EDTA) Registry Annual Report 2021, data from 36 countries indicate an incidence of KRT of 145 per million population (pmp), and the prevalence of KRT of 1040 pmp. Compared to the general population, life expectancy was significantly shorter for patients receiving dialysis and after kidney transplantation. Despite the high mortality rate among CKD patients, in recent decades, survival has been improved due to optimal medication and accessibility of replacement therapy (Boerstra et al., 2024). However, there is a risk of progressive complications that need to be studied and treated to improve the quality and duration of life.

4.1.2. Causes and progression of chronic kidney disease

Diabetes and hypertension are the main causes of CKD in all high- and middle-income countries, and also in many low-income countries (Webster et al., 2017; Boima et al., 2025). The other common causes of CKD are CV disorders, obesity, glomerulopathies, polycystic kidney disease, and tubulopathies. Additionally, the function of the kidney is influenced by ageing (Glassock & Rule, 2016).

Regardless of the underlying aetiology, CKD is slowly progressive and leads to irreversible nephron loss, ESKD and/or premature death. The course of early CKD is usually subclinical (Vallianou et al., 2019). Many people with early CKD are asymptomatic and have non-specific symptoms such as lethargy, itch, or loss of appetite (Webster et al., 2017). According to the US Centers for Disease Control and Prevention, 90% of adults with CKD do not know they have CKD, and one in two people with very low kidney function who are not on dialysis are not aware of the fact that they have CKD (Wilson et al., 2021).

CKD is associated with a number of serious complications, including accelerated atherosclerosis, CKD-MBD, VC and anaemia (Reiss et al., 2018). Multiple forms of CV diseases are the leading cause of morbidity and mortality in CKD patients (Drüeke & Massy, 2010). Despite the opinion that the risk of complications rises from stage 3 of CKD, even in early stages, kidney dysfunction is an independent risk factor for CVD and death (Reiss et al., 2018). Screening and detection of early stages of CKD can help establish interventions that may delay the progression of the disease (Levey et al., 2020). Management of the progression and complications of CKD is individual and depends on the underlying aetiology and stage. Management strategies aimed at delaying the progression of CKD include nutritional and lifestyle measures, general medical control to improve CV health, metabolic status and reduce albuminuria. If CKD progresses and complications appear regardless of these interventions, specific drug therapy is indicated (KDIGO CKD Glinical Practice Guideline, 2024).

4.2. Obesity as a risk factor for the development and progression of chronic kidney disease and its impact on outcomes

According to the World Health Organization (WHO), overweight and obesity are defined as conditions where excess or abnormal fat accumulation increases risks to health (WHO, 2010). In the last decades, obesity has reached pandemic proportions, and the number of individuals with obesity has been constantly growing. Obesity, defined as a BMI of 30 kg/m^2 or more, is an established risk factor for poor outcomes. In the general population, obesity shortens life expectancy by more than 9 years (Greenberg, 2013). Overweight and obesity are associated with comorbidities such as atherosclerotic CV disease, type 2 diabetes, hypertension, dyslipidaemia, metabolic syndrome, non-alcoholic fatty liver disease, cancer, osteoarthritis, and sleep apnoea.

Obesity, especially in combination with other risk factors, is associated with a higher risk of *de novo* CKD (Stenvinkel et al., 2013; Rhee et al., 2016). Besides that, some studies have shown the impact of obesity on the decline of kidney function in early CKD and increased albuminuria (Hsu et al. 2006; Garofalo et al., 2017; Pinto-Sietsma et al., 2003). Moreover, it has been shown that obesity is

a strong risk factor for loss of residual kidney function in dialysis patients (Drechsler et al., 2009).

The pathophysiology of obesity is complex, including genetic predisposition, environmental changes, and individual preferences (Stenvinkel et al., 2013). However, about 30% of obese patients seem to be protected against obesity-related metabolic complications. This metabolically benign obesity is characterised by increased gluteo-femoral fat mass, relatively low visceral fat mass, normal adipose tissue function, and normal insulin sensitivity (Blüher, 2012). Moreover, it has been shown that obesity may have a favourable effect on outcome and improve survival in chronic diseases such as ESKD, heart failure, coronary heart disease, acute conditions such as pneumonia, sepsis, acute respiratory distress syndrome and in critically ill patients (Agarwal et al., 2010; Schetz et al., 2019). These correlations were first described in the 1980s, and since then, the phenomenon of "obesity paradox", especially in hemodialysis patients, has been shown by many researchers (Degoulet et al., 1982; Leavey et al., 1998; Fleischmann et al., 1999; Kalantar-Zadeh et al., 2003; Soohoo et al., 2022). The exact mechanisms of the protective effect of obesity are not entirely clear. However, one of the several hypotheses explaining the paradoxical inverse association of BMI and mortality in CKD is protein-energy wasting. Patients with advanced CKD and ESKD have been found to have a significantly high prevalence of cachexia, and its presence is associated with a higher risk of mortality (Obi et al., 2015). Patients with large adipose tissue reserves are believed to have protective mechanisms that prevent lipolysis and fat loss, which may be beneficial in mitigating the consequences of cachexia, such as muscle loss (Naderi et al., 2018). Overweight and obese patients have more stable hemodynamics during the HD procedure compared to malnourished patients. Additionally, research has shown that adipose tissue has a protective effect against chronic inflammation by synthesising and releasing agents which bind factors with proinflammatory activity (Mohamed-Ali et al., 1999). However, other studies have shown that increased adipose tissue mass is related to increased inflammatory activity (Chait, den Harting, 2020). Also, due to short life expectancy in ESKD patients, survival advantages that exist in obese patients may, in the short term, outweigh the harmful effects of it in the long term (Park et al., 2014). A systematic review of the association between BMI and health outcomes in patients with different stages of CKD showed heterogeneous findings, especially among those receiving peritoneal dialysis (PD) and those not on KRT (Ahmadi et al., 2015). The data on the effects of obesity on outcomes in CKD are controversial (Park et al., 2014).

4.3. Chronic kidney disease-mineral and bone disorder

4.3.1. Definition, history and epidemiology

The progression of CKD leads to the systemic mineral and bone disorder that is characterised by one or more of the following: 1) abnormalities of calcium, phosphate, parathyroid hormone (PTH), or vitamin D metabolism; 2) abnormalities of bone turnover, mineralisation, volume or strength, and linear growth; and 3) vascular or soft tissue calcification (KDIGO CKD-MBD Clinical Practice Guideline, 2017). CKD-MBD involves immune dysfunction, inflammation, CVD, including left ventricular hypertrophy (LVH) and hypertension (Mosbah, 2019).

If the disease is limited to the bone, it is referred to as renal osteodystrophy (ROD) (Table 1).

Table 1. Differentiation between chronic kidney disease-mineral and bone disorder and renal osteodystrophy (KDIGO CKD-MBD Clinical Practice Guideline, 2017)

CKD-MBD – systemic disorder of mineral and bone metabolism
Abnormalities of calcium, phosphorus, parathormone and vitamin D
Abnormalities of bone turnover, mineralisation, volume or strength, and linear growth
Vascular or soft tissue calcification
ROD – limited only to CKD bone disease with
Disturbances in bone morphology
Abnormalities in bone biopsy histomorphometry

CKD-MBD, chronic kidney disease-mineral and bone disorder; ROD, renal osteodystrophy

The associations between renal disease and bone abnormalities were first described in 1883 by Lucas with the term „renal rickets“ (Lucas, 1883). In 1930, Bauer et al. established an association between bone lesions and the parathyroid gland (Bauer et al., 1930). In 1942, the term „renal osteodystrophy“ was proposed by Shih-Hao Liu (Liu & Chu, 1942). In the 1960s, with the advent of dialysis, came new bone lesions that were not previously recognised, such as “aluminium bone disease”, “osteosclerosis”, vascular calcification, “tertiary hyperparathyroidism” and “adynamic bone disease”. The decision to use the term “CKD–Mineral and Bone Disorder (CKD–MBD)” to describe the broader clinical syndrome encompassing mineral, bone, and calcific CV abnormalities that develop as a complication of CKD was adopted at a conference organised by Kidney Disease: Improving Global Outcomes in 2005 (Moe et al., 2006). According to research data, 70 to 90% of stage III–IV CKD patients develop alterations in mineral and bone homeostasis (Dousdampanis & Trigka, 2017). Results from the National Health and Nutrition Examination Survey (NHANES) suggested that bone diseases were twice as common in those with an eGFR<60 ml/min/1.73 m^2 compared to those with an eGFR > 60 ml/min/1.73 m^2 (Khairallah & Nickolas, 2018).

4.3.2. Pathophysiology of chronic kidney disease-mineral and bone disorder

Mineral and hormonal disturbances

CKD is characterised by glomerular and tubular sclerosis, leading to reduced glomerular filtration and a reduction in renal parenchymal mass. According to the classic hypothesis of secondary hyperparathyroidism (SHPT), before the discovery of fibroblast growth factor 23 (FGF23) and klotho, phosphate retention due to declined renal function had been considered as the main trigger of SHPT (Waziri et al., 2019). A reduced renal mass leads to reduced activity of 1α-hydroxylase in the renal tubule and thus failure to increase 1,25-dihydroxyvitamin D (1,25(OH)2D3) or calcitriol production when required. In addition, circulating 1,25(OH)2D3 concentrations begin to fall as a direct result of phosphate retention. Lowered 1,25(OH)2D3 leads to reduced calcium absorption from the gut and proximal tubule, thus causing a hypocalcaemia which is counteracted by increased PTH production and secretion. The net effect of SHPT aggravates hyperphosphataemia (via positive feedback). Reduced expression and responsiveness of the vitamin D receptor in the parathyroid gland lead to further enhancement of PTH production, and reduced expression of the calcium-sensing receptor in the parathyroid gland, resulting in parathyroid gland hyperplasia (Waziri et al., 2019). Enhanced parathyroid cell proliferation directly influences hyperphosphataemia (Lewis, 2012) (Figure 1).

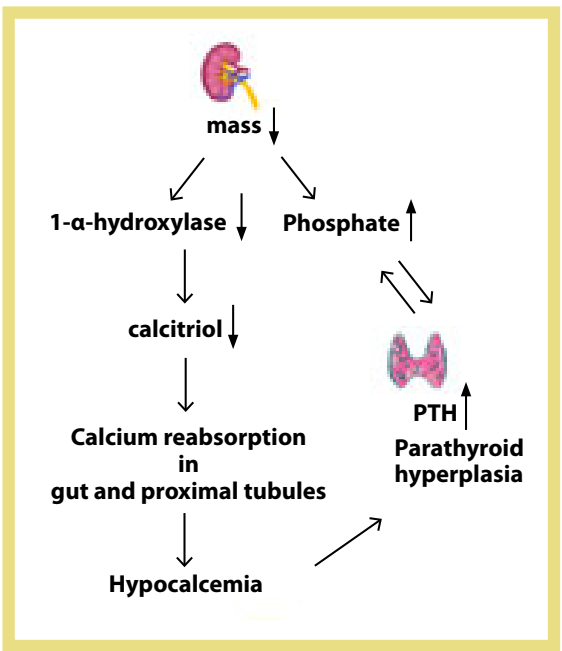

Figure 1. Classic hypothesis of secondary hyperparathyroidism
PTH, parathyroid hormone

The identification of FGF23 and klotho has changed the understanding of the mechanisms underlying the development of SHPT. FGF23 secreted from bone tissue plays a protective role in early CKD as it triggers adaptive changes to restore the normal range of phosphate. FGF23 requires the transmembrane protein, klotho, to bind to the FGF receptor in target organs, such as the kidneys and parathyroid gland (Kuro-o, 2009). Plasma FGF23 levels increase in a compensatory response to progressively worsening renal function, and this is most likely to occur before observed changes in phosphate and PTH levels. In the kidneys, FGF23 reduces phosphate reabsorption and promotes the urinary excretion of phosphate in the proximal tubule; in the distal tubule, FGF23 increases calcium and sodium reabsorption. High levels of FGF23 suppress the synthesis and promote the degradation of 1,25(OH)2D3 by inhibiting the 1-α-hydroxylase and by stimulating the 24-hydroxylase, initiating the development of SHPT. The decrease in serum 1,25(OH)2D3 leads to decreased intestinal calcium absorption. The triad of low calcium levels, 1,25(OH)2D3, and hyperphosphatemia further enhances excessive PTH secretion (Waziri et al., 2019) (Figure 2).

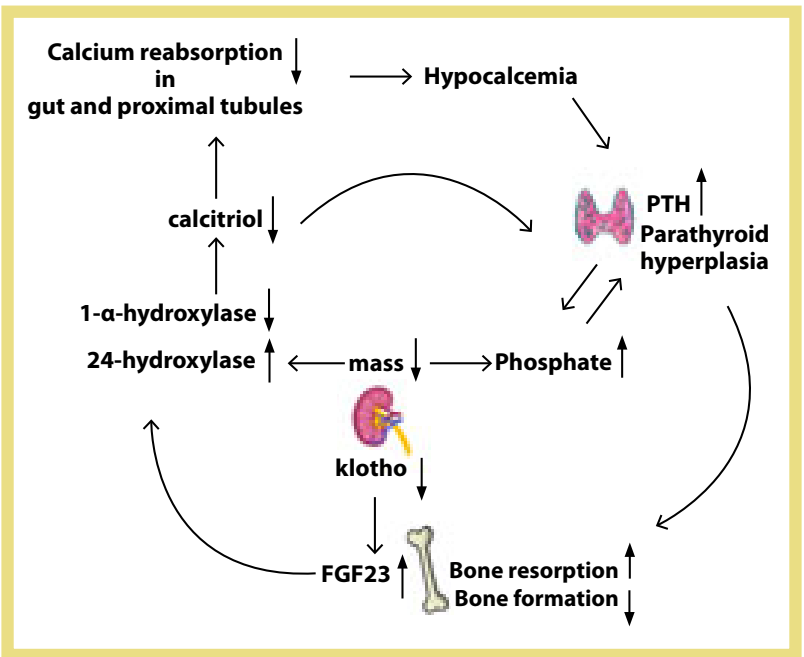

Figure 2. New insights into the pathophysiology of secondary hyperparathyroidism
PTH, parathyriod hormone; FGF23, fibroblast growth factor 23

Vascular calcification

Vascular calcification is a complex biological process initiated and regulated by a variety of molecular signalling pathways and is a life-threatening complication of CKD (Lanzer et al., 2014). Two patterns of VC have been described: calcification of the intimal and medial layers of the vessel wall (KDIGO CKD-MBD Clinical Practice Guideline, 2009; Vervloet & Cozzolino, 2017).

CKD patients most often exhibit calcification of the medial layer of the vessel wall (Reiss et al., 2018). The calcification of the medial layer of the vessel wall occurs in the elastic lamina of large-, medium- and small-size arteries. In individuals with CKD, medial calcification can occur in peripheral arteries and lead to peripheral vascular dysfunction. Moreover, medial calcification was initially known as Mönckeberg's calcification and was described radiographically in upper and lower limbs (Capusa & Popescu, 2018). It develops in early stages of CKD, and the prevalence in patients undergoing haemodialysis (HD) is eight times higher than that in the general population (Vervloet & Cozzolino, 2017; Ureña-Torres et al., 2020). The lack of arterial elasticity may lead to increased pulse pressure, which can contribute to arteriosclerosis with vascular insufficiency and tissue damage (Hutcheson & Goettsch, 2023).

However, individuals with CKD often have concomitant conditions, such as dyslipidaemia, obesity, and hypertension, which predispose to atherosclerosis with further calcification of atherosclerotic plaque (Vervloet & Cozzolino, 2017). Atherosclerotic intimal calcification is characterised by focal lumen-narrowing atheromatous plaques in the intima of large and medium-sized vessels (Reiss et al., 2018). The National Observatory of Atherosclerosis in Nephrology Study (NEFRONA) has demonstrated that CKD, even in early stages, increase the risk of atheromatous plaques (Gracia et al., 2016). Calcification appears to be a natural component of the atherosclerotic plaque's progression, with extensive calcification typically associated with late-stage atherosclerosis (American Heart Association Stage Va and VII) (KDIGO CKD-MBD Clinical Practice Guideline, 2009). The calcification of atherosclerotic plaque can lead to its rupture, resulting in the formation of a thrombus (Vervloet & Cozzolino, 2017; Román-García et al., 2011). Some studies have shown that spotty calcification of lipid plaque can deteriorate its stability, probably due to local mechanical wall shear stress, macrophage and inflammatory cellular infiltration and plaque revascularisation (Vervloet & Cozzolino, 2017).

The mechanisms of VC are complex, it involves the increase in promoters and loss of inhibitors of VC, formation of calcification vesicles, local inflammation, and, as a result, the transformation of vascular smooth muscle cells to osteoblast-like cells, accelerated vascular ageing and ossification of vessels wall (Vervloet & Cozzolino, 2017; Lanzer et al., 2014; Román-García et al., 2011) (Table 2).

The presence and extent of these two calcification types, calcification of the medial layer and calcification of the atherosclerotic plaque within the vessel wall, may differ according to the type and anatomical location of the artery. The clinical consequences of intimal versus medial layer calcification may be

different, with plaque rupture and acute vessel occlusion being the key consequences of intimal disease, and increased arterial stiffness for medial calcification (Vervloet & Cozzolino, 2017). However, some studies of dialysis patients have shown the presence of medial calcification in coronary arteries just beneath the internal elastic lamina (Schwarz et al., 2000; Gross et al., 2007). Therefore, it seems that both forms of VC can coincide and overlap (Lanzer et al., 2014; Nakamura et al., 2009).

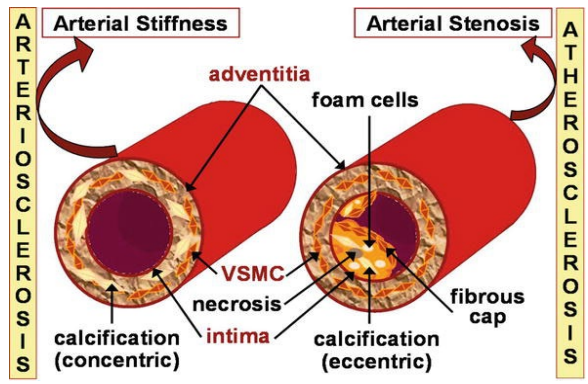

Figure 3. Main types of arterial calcifications and their consequences
VSMCs, vascular smooth muscle cells (Adopted from Capusa and Popescu, 2017)

Table 2. Promoters and inhibitors of vascular calcification

Promoters	Inhibitors
Phosphate overload	Vitamin K
Hypocalcemia/hypercalcemia	Matrix-Gla protein
Parathyroid hormone overload	Klotho
Fibroblast growth factor-23	Fetuin A
Bone morphogenic proteins	Osteoprotegrin
Osteocalcin	Pyrophosphate
Osteopontin	

Valvular calcification is another extraosseous calcification in CKD. The pathophysiology and associated factors of valvular calcification are similar to vascular intima and media calcification. In addition to mineral and hormonal factors, the mechanical stress on valves can be accelerated in CKD due to anaemia, volume overload, high cardiac output, and hypertension. The persistent mechanical stress leads to microfractures of elastic and collagen fibres. Metabolic factors, such as dyslipidaemia, high glucose level, accumulation of uremic toxins and inflammation, lead to valvular lesions (Hénaut et al., 2025; Ureña-Torres et al., 2020; Marwick et al., 2019).

Valvular (aortic valve and mitral annular calcification) were present in 20–25% of 653 patients with CKD stages 3–5 in the Multi-Ethnic Study of Atherosclerosis, whereas the degree of renal dysfunction was only modestly associated with valvular calcification (Ix et al., 2007). The 5-year mortality rate among patients with at least mild aortic stenosis or mitral regurgitation is more than 50% greater than in individuals without CKD (Samad et al., 2017). Declining kidney function accelerates the mineralisation of heart valves, with severe valvular dysfunction occurring in significantly younger patients than in the general population (Urena et al., 1999). In addition to other risk factors, heart valve calcification and fibrosis lead to LVH in CKD patients (Kitamura et al., 2017; Rebić et al., 2015).

In respect of the potential complexity of the pathogenesis of VC and the relatively low ability of radiological techniques to differentiate the location of calcification, the approach to all patients with calcification should be to minimise atherosclerotic risk factors and control biochemical parameters of CKD–MBD (KDIGO CKD-MBD Clinical Practice Guideline, 2017).

Bone mineral density

CKD-MBD is characterised by impaired bone health caused by ROD and osteoporosis. In addition to age- and/or gender-related osteoporosis, ROD and CKD-associated osteoporosis are common disorders of bone quality and strength secondary to effects of metabolic and hormonal disturbances that occur with kidney failure (Iseri, Qureshi et al., 2020; Ketteler et al., 2025). These abnormalities impair bone turnover and mineralisation, collagen structure, and cortical and trabecular microarchitecture. Four pathological diseases of bone in CKD are recognised: high bone turnover disease, adynamic bone disease, slow bone turnover disease, mixed renal osteodystrophy (Mosbah, 2019; Bisson et al., 2018).

Both idiopathic osteoporosis and ROD can lead to increased bone fragility, and may result in bone pain, deformities and fractures (KDIGO CKD-MBD Clinical Practice Guideline, 2017). The risk of fractures is higher in CKD compared to the general population. A lower eGFR is associated with higher fracture risk, being more pronounced in CKD 5D stage (Goto et al., 2019, Pimentel et al., 2017; Damasiewicz & Nickolas, 2018; Jadoul et al., 2006). However, the study of Runesson et al. showed similar results to earlier studies in non-dialysis dependent stage 3–5 CKD. The risk of hip and non-hip fractures increases gradually as kidney function declines. Additionally, this study has shown increased short- and long-term mortality after hip and non-hip fractures in CKD 3–5 non-dialysis patients (Runesson et al., 2020). The pattern of bone disease in CKD has changed over the last 20 years. In the past, high bone turnover was predominant. Nowadays, the gross skeletal abnormalities (renal rickets) are exceptionally rare. Instead, there is also a high prevalence (40–70%) of low bone turnover disease, which weakens the bone and increases fracture risk. Such adynamic bone diseases may be the result of the ageing population and the effects of therapy. Effective treatment of CKD-MBD, therefore, requires attention to both high- and low-turnover bone diseases, aiming to steer a course between the two (Lewis, 2019).

4.3.3. Methods for measurement of bone mineral density and vascular calcification

Measurement of bone mineral density

BMD is a complex parameter that includes alterations of bone microarchitecture and decreased bone quality. In clinical practice, there is a lack of methods to evaluate bone tissue lesions for diagnosing ROD type and predicting outcome. Bone biopsy is the gold standard for evaluating bone tissue quality, which includes bone tissue turnover, mineralisation and volume. Bone biopsy studies have provided important insights into the patterns of ROD, but despite being recommended by KDIGO guidelines for diagnosis of ROD, the utility of this invasive method in routine clinical practice is limited (KDIGO CKD-MBD Clinical Practice Guideline, 2017). There is a great interest in the use of non-invasive approaches to assess bone quality in kidney-related bone disease (Damasiewic & Nickolas, 2018). Among these, alongside conventional Quantitative computed tomography, high-resolution peripheral computed tomography, and micro magnetic resonance imaging, the most popular imaging modality is dual-energy X-ray absorptiometry (DEXA). DEXA is the clinical standard for measuring bone mass and assessing fracture risk in the general population. The measurement of BMD by central DEXA is recommended (Kanis et al., 1994). Central DEXA quantifies the BMD of the central skeleton, including the lumbar spine and hip. In patients with CKD, the measurement of BMD in the lumbar spine may be overestimated due to the presence of the abdominal aorta and vertebral articular calcification. Additionally, in such trabecular bone-rich sites, the changes may not be so rapidly progressive in CKD (Iseri, Dai et al., 2020). Total body DEXA is another method used to assess skeletal mineral status and evaluate body composition. However, BMD data from central and total body DEXA differ, and the recommended method for diagnosing osteoporosis is now central DEXA (Shuhart et al., 2019). Nevertheless, clinical evidence supports the usefulness of total body DEXA in everyday clinical practice, and the optimal choice of DEXA type depends mainly on its purpose. In the context of CKD, compared with central DEXA, BMD measured at peripheral sites may represent a more appropriate method for assessing skeletal mineral status (Nickolas et al., 2013; Iseri, Dai et al., 2020). Many studies have demonstrated the association between low BMD and mortality in patients with CKD, particularly in those with ESKD (Taal et al., 2003; Orlic et al., 2017). The study of Iseri and colleagues has demonstrated a relationship between BMD at specific bone sites measured by total body DEXA and clinical outcomes in ESKD patients (Iseri, Qureshi et al., 2020).

Although DEXA cannot provide details regarding the relative proportion of cortical and trabecular bone or distinguish between different types of ROD, this method is increasingly used to assess BMD and fracture risk, as well as the association between BMD and mortality in CKD patients (Iseri, Dai et al., 2020).

Measurement of vascular calcification

There is a variety of methods available for the assessment of central and peripheral VC, the most common are computed tomography (CT), lateral lumbal radiography of abdominal aorta or plain radiography of pelvis and hands, vascular ultrasound, pulse wave velosity, the ankle-brachial index (ABI).

Computed tomography is considered the gold standard for quantification of VC (KDIGO CKD-MBD Clinical Practice Guideline, 2009). However, its use is limited by radiation exposure, cost, and restricted availability, particulary for peripheral arteries. Plain radiography represents a simple and widely available alternative.

Abdominal aortic calcification (AAC) can be assessed using quantitative scores (Kauppila score) on spine radiographs. Echocardiography offers information on cardiac structure and valvular calcification. Therefore, The Work Group of KDIGO guidelines suggest that plain X-ray and echocardiography are reasonable alternatives to the gold standard of CT-based imaging (KDIGO CKD-MBD Clinical Practice Guideline, 2017).

The ankle-brachial index (ABI) has been reported to be a useful marker for atherosclerosis, and an ABI < 0.9 has been used to diagnose peripheral artery disease (PAD) (Huish et al., 2025). Moreover, for recent two decades an ABI ≥ 1.3 has been used to diagnose medial artery calcification (Chen et al., 2018). Many studies have shown that pathologically high (≥ 1.3) or low (< 0.9) ABI is an independent predictor of cardiovascular and all-cause mortality among CKD patients (Hazique et al, 2025; Parmar et al., 2024; Gu et al., 2019; Qu et al., 2015; Chen et al., 2017). Moreover, it has been shown, that low ABI with symptomatic and asymptomatic PAD is associated with elevated risk of CKD and ESKD (Paskiewics et al, 2024). Therefore, assessment of ABI is a safe, informative, simple, non-invasive method for the detection of both peripheral arterial calcification and PAD.

However, uncertainties in the reliability of different VC testing modalities, and a lack of diagnostic or therapeutic protocols in relation to VC testing in CKD, have led to weak or ungraded recommendations for their use in clinical practice (Smith et al., 2019).

4.3.4. Associations between vascular calcification and bone mineral density

In addition to physical supportive function, bone is an active endocrine organ that interacts with the vasculature by paracrine and endocrine factors. The pathophysiology of ROD is closely related to extraosseous calcification and has common cellular and molecular mechanisms (Toussaint et al., 2008; Damasiewicz & Nickolas, 2018). Low BMD and VC in CKD may represent two sides of the same coin and are commonly referred to as “calcification paradox” or bone-vascular axis (Evenepoel et al., 2017). The synergism of oxidative stress, inflam-

mation, hyperphosphatemia, hypercalcemia, hyperparathyroidism, lack of inhibitors and increase of promoters of VC and medications provides a favourable effect for bone tissue loss and extraosseous calcification. Bone-like cells found in the calcified vascular tissue of some patients, and gene changes identified in mouse models, support the presence of a genetic component in the aetiology of VC (Evenepoel et al., 2019). The mineral redirection hypothesis suggests that progressive bone loss may also contribute to vascular mineral deposition. Excessive bone resorption may cause the release of calcium and phosphate, which, because of excretion failure, are redirected to the arterial wall or heart valves, inducing VC (Farhat & Cauley, 2008).

In clinical practice, alterations in the bone–vascular axis through which impaired bone status is associated with changes in the vascular wall have been previously described in CKD patients. For example, Toussaint et al. showed an inverse association between VC of the superficial femoral arteries as measured by CT and femoral BMD measured by DEXA in predialysis patients (Toussaint et al., 2008). In a study of hemodialysis patients, AAC was inversely associated only with trabecular bone score in the lumbar spine but not with other DEXA-derived BMD parameters (Aleksova et al., 2018). However, some other researchers were unable to find a correlation between VC and BMD parameters (Salam et al., 2021). These conflicting results have likely resulted from the lack of evidence regarding specific methods for detecting, assessing, and investigating the relationship between bone and vasculature. Further studies are needed to gain a better understanding of the similarities and differences in skeletal and vascular mineralisation, which will help determine effective therapeutics.

4.4. Impact of obesity on vascular calcification

Studies in the general population have shown that being overweight or obese is associated with a higher risk of VC (Jensky et al., 2011; Choi et al., 2010; Chen et al., 2022). However, the possible favourable effect of higher body weight or BMI on VC in patients with CV diseases was previously described. These studies were predominantly focused on coronary artery calcification (CAC) in patients with clinically significant coronary lesions (Kovacic et al., 2012; Yokoyama et al., 2019). On the other hand, researchers evaluating the relationship between BMI and PAD have observed that higher BMI is associated with both low and high ABI in patients without CKD (Niu et al., 2012; Doza et al., 2012; Zhang et al., 2013). Only a limited amount of research has focused on the associations between body weight and VC in patients with CKD, and the results have been heterogeneous. A study by Chen et al. demonstrated that the combination of high BMI and left ventricular mass index is associated with abnormally low and high ABI in patients with CKD stages 3–5 (Chen et al., 2016). A study of patients with CKD stage 3–4 showed that visceral adiposity increases the risk of CAC (Aoqui et al., 2013). Similar results regarding correlations between visceral fat and carotid artery thickness, as well as atherosclerotic plaque, have been reported in

other studies of hemodialysis and peritoneal dialysis patients (Yamauchi et al., 2003; Lee et al., 2012). However, a study about the impact of BMI on CV events, renal function and CAC in CKD patients found that high BMI is not associated with the extent and progression of CAC and is not a predictor of CV events (Russo et al., 2014). Therefore, there is still a lack of data about the influence of overweight and obesity on the formation of extraosseous calcifications, the progression of VC, and the prognosis of patients with CKD.

5. STUDY RATIONALE

Despite the fact that obesity is one of the risk factors for CKD and CV diseases, several studies have demonstrated that obesity has a protective effect and is paradoxically linked with a greater survival in patients with advanced CKD, especially dialysis-dependent CKD (Hsu et al., 2006; Stenvinkel, Zoccali, Ikizler, 2013; Fleischmann et al., 1999). The contradictory results indicate the need for more studies that take into consideration different risk factors, as well as kidney function.

CKD-MBD is one of the serious complications of CKD, associated with loss of bone tissue mass, increased risk of fractures and VC (Iseri, Dai et al., 2020). Altogether, these mineral and bone disturbances lead to morbidity and premature mortality in CKD and ESKD. Interactions between bone tissue and vasculature are not yet fully understood, and this may pose difficulties in the timely diagnosis and treatment of patients with low bone mineral density and VC.

The theoretical protective effect of obesity on the formation of VC in CKD has been previously described (Kalantar-Zadeh et al., 2003; Agarwal et al., 2010; Schetz et al., 2019; Soohoo et al., 2022). However, there are gaps in knowledge about the impact of obesity on VC in patients with CKD.

6. AIMS OF THE THESIS

The general aim of this study was to clarify the associations between vascular calcification and body composition in patients with chronic kidney disease.

The specific aims were:

1. To compare vascular calcification in obese and non-obese patients in different CKD stages (Paper I).
2. To determine the impact of obesity on vascular calcification in CKD patients (Paper I).
3. To find out if significant associations exist between vascular calcification and site-specific bone mineral density in patients with CKD (Paper II).
4. To evaluate the prognostic value of abdominal aortic calcification and the prevalence of peripheral arterial disease on all-cause mortality and cardiovascular events in end-stage kidney disease patients on peritoneal dialysis (Paper III).
5. To evaluate the prognostic value of vascular calcification on cardiovascular events and all-cause mortality in obese and non-obese CKD patients (Paper IV).

7. SUBJECTS AND METHODS

7.1. Subjects and design of the study

An overview of subjects and study design is given in Table 3. The main cohort of the study consisted of 168 consecutive patients with CKD of different stages and who were under the supervision of nephrologists (Paper I). Patients were enrolled in the study from 2012 to 2019. All patients with CKD receive treatment for its complications according to the best practice international guidelines (KDIGO CKD Clinical Practice Guideline, 2012).

Ninety patients of the main cohort (168 patients), to whom total body DEXA was performed, were included in the study of associations between VC and BMD, based on the availability of DEXA results (Paper II).

For Paper III, data of PD patients were collected from Sweden, Finland, Denmark and Estonia (total n=249). Twenty patients from our main cohort, who received peritoneal dialysis treatment, were included.

A total of 150 patients from the primary cohort were enrolled on the study aimed to evaluate the prognostic significance of VC on long-term outcome in obese and non-obese CKD patients (Paper IV).

Papers I and II describe the cross-sectional studies, which were conducted at the Department of Internal Medicine, University of Tartu, and Tartu University Hospital between 2012 and 2019. In the first study (Paper I), we compared VC in obese and non-obese CKD patients to define the impact of obesity on the formation of vascular calcifications. The second study (Paper II) was conducted to investigate the associations between VC and BMD at various bone sites in patients with different stages of CKD.

In a prospective observational multicenter study (Paper III) with a follow-up range of 1–61 months (median 46 months), the prognostic role of abdominal aortic calcification (AAC) and the prevalence of peripheral arterial disease on all-cause mortality and CV events in PD patients were evaluated.

In a prospective observational single-centre study (Paper IV), by a 11.2-year follow-up, we evaluated the prognostic value of VC in obese and non-obese patients.

Participating was voluntary, and all subjects signed a written informed consent. The study consisted of a single visit, during which the medical interview and questionnaires were completed. A physical examination and ABI assessment were performed, and blood and urine samples were collected. The X-ray of the abdominal aorta, echocardiography and dual X-ray absorptiometry were planned and done in an outpatient clinic.

Study approval was obtained from the Ethics Committee on Human Research of the University of Tartu, Estonia (**IUT 2–8; approval no. 223/T-17; approval no. 187/T-7**).

7.2. Methods

7.2.1. Medical interview

A face-to-face medical interview was conducted at the time of enrolment. Information about CKD diagnosis (diabetes mellitus, hypertension, glomerulonephritis, interstitial nephritis, polycystic kidney disease, systemic disease, other), its duration, medical family history, harmful habits (smoking, alcohol, drugs) was collected at the interview.

Data on concomitant health conditions (ischemic heart disease, diseases of the heart valves, heart failure, peripheral vascular disease, tumours) were collected and subsequently confirmed using data from electronic health records.

Information about symptoms of PAD (pain, coldness of legs, claudication) was asked for.

Information about the duration of CKD, dialysis modality and duration of KRT, arterial/ischemic ulcers, gangrene, and arteriography procedure findings was confirmed using data from electronic health records.

Data about treatment with antihypertensive medications (ACE inhibitors, ARBs, calcium channel blockers, beta-blockers, diuretics), phosphate binders (calcium-based, non-calcium-based), secondary hyperparathyroidism treatment (active form of vitamin D, calcimimetics), lipid-lowering medications, erythropoiesis-stimulating agents were collected from electronic health records.

7.2.2. Physical examination

A careful physical examination was performed, including measurements of body weight (BW, kg) with an electronic scale in a lightly dressed state and without shoes, and body height (BH, cm) using a stadiometer. BMI was calculated using the standard formula: BMI (kg/m^2) = body weight (kg) / body height (m^2). According to World Health Organization criteria, underweight was defined as BMI < 18.5 kg/m^2, normal weight as BMI < 25 kg/m^2, overweight as BMI 25 – 29.9 kg/m^2 and obesity as BMI ≥ 30 kg/m^2 (WHO, 2010). The blood pressure of both arms was measured mechanically using an aneroid sphygmomanometer after a ten-minute sitting period. Peripheral pulses of arteria dorsalis pedis (ADP) and arteria tibialis posterior (ATP) were assessed within the Microflow S Doppler ultrasound device (Atys Medical, France).

7.2.3. Laboratory data

Blood samples

Laboratory research was carried out at the United Laboratories of Tartu University Hospital. The following biochemical parameters at baseline were assessed: serum albumin (S-Alb, g/L), serum C-reactive protein (S-CRP, mg/L), serum creatinine (S-Crea, μmol/L), serum urea (S-Urea, mmol/L), serum total calcium (S-Ca, mmol/L), serum ionized calcium (S-i-Ca, mmol/L), serum phosphate (S-Pi, mmol/L), serum total alkaline phosphatase (S-tALP, iu/L),

serum uric acid (S-UA, mmol/L), serum vitamin D (S-vit D, nmol/L), serum total cholesterol (S-CHL, mmol/L), serum triglyceride (S-TG, mmol/L). In addition, serum haemoglobin (S-Hb, g/L) was assessed.

Intact parathyroid hormone (iPTH, pmol/L) was assessed by electrochemiluminescence immunoassay.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to assess kidney function. For evaluating fibroblast growth factor 23 (FGF23, U/mL), serum was separated from peripheral venous blood samples, stored at –80 °C, and analysed by the ELISA method (Millipore Corporation, Billerica, MA, USA). The normal range of FGF23 according to the description of the method is <114 U/mL.

Urine samples

To assess albuminuria albumin-to-creatinine ratio (g/mol) was used. Urine samples were collected from first-void urine and analysed by immunoturbidimetric assay.

7.2.4. Methods for assessment of central and peripheral vascular calcification and bone mineral density

Lateral lumbar X-rays and Kauppila scoring system

Lateral lumbar X-rays and the Kauppila scoring system – abdominal aortic calcification score (AACS) were used to assess calcification of the abdominal aorta. The abdominal aorta alongside the first four lumbar vertebrae was divided into four segments using the midpoint of each intervertebral space as a boundary. Anterior and posterior aortic wall segments were evaluated separately. Calcific deposits were graded on a scale of 0–3 at each segment, as follows: 0 – no calcific deposits; 1 – small scattered calcific deposits filling less than one-third of the aortic wall; 2 – one-third to two-thirds of the aortic wall calcified; 3 – at least two-thirds of the aortic wall calcified. The grades of the eight aortic segments were summed up with a Kauppila calcification score, ranging from 0 to 24 points (Kauppila et al., 1997). Two independent radiologists scored all lateral lumbar X-rays. Both observers were kept blind to the clinical and laboratory data.

Ankle-brachial index

The ABI was used for assessing the arteries of the lower limbs. ABI is defined by the ratio of ankle and brachial systolic pressure. Foot systolic pressure was measured with the Atys Microflow Doppler ultrasound device and was assessed on the posterior tibial and dorsalis pedis arteries of both feet. The blood pressure of both arms was measured mechanically. ABI was calculated separately for each leg. The ABI value was determined by taking the higher pressure in the two foot arteries and dividing it by the brachial arterial systolic pressure. In calculating the ABI, the higher of the two brachial pressure measurements was used. The ABI

measurement was done once in each patient after a 15-minute rest period. Patients were classified into ABI < 0.9 in either foot, ≥ 0.9 to < 1.3 in both feet, and ≥ 1.3 in either foot (Winsor, 1950; Gu et al., 2019).

Echocardiography

Echocardiography was performed at Tartu University Hospital by an experienced echocardiographer using a Philips IE33 ultrasound machine (Philips Healthcare, Netherlands). Left ventricular systolic function was assessed via the left ventricular ejection fraction. LVH was defined as suggested by the American Society of Echocardiography/European Society of Echocardiography chamber quantification guideline (Lang et al., 2015), and assessed using septum thickness. The calcification and fibrosis of heart valves were visually evaluated separately for every valve according to standard echocardiography methodology.

Dual X-ray absorptiometry

BMD was assessed by total body DEXA using the Lunar Prodigy Advance device (GE Healthcare, Chicago, IL, USA), which provides results for multiple individual sites. For assessment of BMD, the following anatomical regions were selected: the total body (arms, legs, trunk and spine), total spine, the first to the fourth lumbar vertebrae (L1-L4), femur, femoral neck, ribs and pelvis. BMD for each site was measured quantitatively in grams per square centimetre (g/cm^2). T- and Z-scores for total body, total femur, femoral neck and spine L1-L4 were measured.

7.2.5. Statistical analysis

Means and standard deviations (SD) or medians and ranges were given for continuous variables. All tests were two-sided, and p-values < 0.05 were considered to be statistically significant. Numbers and percentages were given for categorical variables. Continuous variables were compared using the Mann-Whitney U test. Pairwise comparisons were performed with independent samples t-tests for normally distributed variables, and categorical data were analysed using the Pearson chi-square test or Fisher's exact test. Analysis of variance (ANOVA) and Kruskal-Wallis tests were used to evaluate differences between continuous and categorical variables. The Spearman Rank Order Correlation analysis was used to establish the correlation between variables and their significance. General linear models, factorial and quantile regression were performed to determine significant associations between variables. To evaluate the change in AACS of individual segments, the Wilcoxon's test was used. Cox regression models were used to assess time to death (survival) or CV events. Hazard ratios were expressed with their 95% confidence intervals (95% CI). Kaplan-Meier analysis was used to describe the association between AACS categories and all-cause mortality. For **Paper I** and **Paper II,** the data were processed using the Statistica (version 13) software package. For **Paper III,** the SPSS statistical software package (version

20) was used. For **Paper IV,** analyses were performed using the Statistica software (version 14). Survival curves were estimated by the Kaplan–Meier product-limit method and compared by the log-rank test.

Table 3. Overview of the studies` time periods, designs, aims and subjects

Time period	Study design and aim	Subjects	Analysed parameters	Papers I–IV
2012–2019	*Prospective cross-sectional study* Aim: to compare VC in obese and non-obese chronic kidney disease CKD patients, using three methods for measuring VC	168 patients in different stages of CKD (main cohort)	– BMI – Laboratory data – AAC by Kauppila method – ABI – Echocardiography	Paper I
2012–2019	*Prospective cross-sectional study* Aim: to find out associations between central and peripheral calcification and BMD	90 CKD patients of main cohort (N=168), to whom DEXA was done	– Laboratory data – AAC by Kauppila method – ABI – Echocardiography – Total body DEXA	Paper II
2009–2013	*Prospective observational multicenter study* Aim: to evaluate the prognostic role of AAC and the prevalence of PAD on all-cause mortality and CV events in ESKD patients	Peritoneal dialysis patients from 4 countries: Sweden, Finland, Denmark N=229 Estonia N=20 Total N=249	– AACS by Kauppila method – ABI – All–cause mortality – Occurence of any new CV event	Paper III
2012–2024	*Prospective observational single-centre study* Aim: to evaluate the prognostic value of VC on long-term outcome in obese and non-obese CKD patients	150 patients of main cohort (N=168) based on the availability of the required data	– Laboratory data – AACS by Kauppila method – ABI – Echocardiography – CV events – All–cause mortality	Paper IV

AAC, abdominal aortic calcification; AACS, abdominal aortic calcification score; ABI, ankle-brachial index; BMD, bone mineral density; BMI, body mass index; CKD, chronic kidney disease; CV, cardio-vascular; DEXA, dual energy X-ray absorptiometry; PAD, peripheral artery occlusive disease; VC, vascular calcification

8. RESULTS

8.1. Vascular calcification in obese and non-obese patients with different stages of chronic kidney disease to test "obesity paradox" (Paper I)

The study cohort comprised 168 patients (male 45.9%, mean age 59.8 ± 14.8). Diabetes mellitus was present in 41 patients (24.1%), arterial hypertension in 44 (26.2%) patients, and 10 patients (5.9%) were current smokers.

AAC ≥ 1 was observed in 48 patients (28.6%). An elevated ABI (≥ 1.3) was found in 45 patients (26.8%), whereas a reduced ABI (<0.9) was present in 24 patients (14.3%).

Angiotensin-convering enzyme inhibitors or angiotensin receptor blockers were used by 128 patients (76.2%), statins by 78 (46.4%), phosphate binders by 52 (31%), and treatment for SHPT by 35 patients (20.8%).

Detailed characteristics of the baseline clinical and laboratory data for study patients and subgroups are presented in Tables 4, 5 and 6.

Tabel 4. General characteristics of the study group (N=168)

Parameters	
Male, N (%)	77 (45.9)
Age (years)	59.8 ± 14.8
Diabetes, N (%)	41 (24.1)
Hypertension, N (%)	44 (26.2)
BMI (kg/m^2)	28.7 ± 6.8
Smoking, N (%)	10 (5.9)
AAC ≥ 1, N (%)	48 (28.6)
ABI ≥1.3, N (%)	45 (26.8)
ABI<0.9, N (%)	24 (14.3)
ACE/ARB, N (%)	128 (76.2)
Statins, N (%)	78 (46.4)
Phosphate binders, N (%)	52 (31.0)
Treatment of SHPT, N (%)	35 (20.8)
S-Hb (g/L)	125.7 ± 18.4
S-CRP (mg/L)*	2.0 (1 – 107)
S-Albumin (mmol/L)	41.5 ± 5.6
S-Creatinine (μmol/L)	233.2 ± 220.0
S-Urea (mmol/L)	12.6 ± 7.6
eGFR ≥ 45 ml/min/1,73m^2 (N)	68.3 ± 16.9 (68)
eGFR < 45 ml/min/1,73m^2 (N)	22.5 ± 12.3 (100)
S-Calcium (mmol/L)	2.3 ± 0.2
S-Ionised calcium (mmol/L)	1.3 ± 0.1
S-Phosphorus (mmol/L)	1.3 ± 0.5
S-Alkaline phosphatase bone isoenzyme (mmol/L)*	0.0 (0 – 72)
PTH (pmol/L)*	9.5 (0 – 320.4)

Parameters	
Vitamin D (nmol/L)	53.5 ± 25.8
Uric acid (mmol/L)	390.6 ± 106.7
Total cholesterol (mmol/L)	5.5 ± 1.2
HDL-cholesterol (mmol/L)	1.5 ± 1.4
LDL-cholesterol (mmol/L)	3.6 ± 1.1

Data are given as mean values with standard deviations. *Data are given as percentages, median [interquartile range]
BMI, body mass index; AAC, abdominal aortic calcification; ABI, ankle-brachial index; ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; SHPT, secondary hyperparathyreoidism; Hb, haemoglobin; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein

Table 5. Clinical and laboratory data of study patient groups and subgroups

Parameters	Both groups (N=168)	BMI ≥30 kg/m^2 (N=65)	BMI <30 kg/m^2 (N=104)	*p*-value
Male, %	45.9	40.0	50.0	0.2
Age (years)	59.8±14.8	63.3±12.4	57.6±15.7	0.03
Diabetes, N (%)	41 (24.1)	20 (30.8)	21 (20.2)	0.05
Hypertension, N (%)	44 (26.2)	20 (30.8)	24 (23.1)	
BMI (kg/m^2)	28.7±6.8	35.5±5.7	24.5±3.1	0.001
Smoking, %	5.9	4.6	6.7	0.6
Hb (g/L)	125.7±18.4	130.0±17.6	123.0±18.4	0.02
CRP (mg/L)*	2.0 (1–107)	2.0 (1–28)	2.0 (1–107)	0.4
Albumin (mmol/L)	41.5±5.6	42.2±3.4	40.9±6.6	0.6
Creatinine (mcmol/L)	233.2±220.0	185.0±180.0	264.0±237.8	0.007
Urea (mmol/L)	12.6±7.6	11.7±7.1	13.2±7.9	0.1
eGFR ≥ 45 ml/min/1,73m^2 (N)	68.3 ± 16.9 (68)	68.7 ± 16.9 (32)	67.9 ± 17.1 (36)	0.8
eGFR < 45 ml/min/1,73m^2 (N)	22.5±12.3 (100)	24.5±11.0 (33)	21.5±12.8 (67)	0.2
Calcium (mmol/L)	2.3±0.2	2.4±0.2	2.3±0.2	0.5
Ionised calcium (mmol/L)	1.3±0.1	1.3±0.1	1.3±0.2	0.5
Phosphorus (mmol/L)	1.3±0.5	1.26±0.4	1.3±0.5	0.4
Alkaline phosphatase bone isoenzyme (mmol/L)*	0.0 (0–72)	0.0 (0–72)	0.0 (0–1)	0.8
PTH (pmol/L)*	9.5 (0–320.4)	8.6 (2.8–175.9)	9.7 (0–320.4)	0.4
Vitamin D (nmol/L)	53.5±25.8	53.5±21.9	53.6±28.3	0.6
Uric acid (mmol/L)	390.6±106.7	413.0±105.2	376.3±105.7	0.01
Total cholesterol (mmol/L)	5.5±1.2	5.4±1.3	5.5±1.2	0.3
HDL-cholesterol (mmol/L)	1.5±1.4	1.3±0.5	1.7±1.7	0.004
LDL-cholesterol (mmol/L)	3.6±1.1	3.5±1.1	3.6±1.0	0.7

Data are given as mean values with standard deviations. *Data are given as percentages, median [interquartile range]. Statistically significant *p*-value between obese and non-obese groups < 0.05. BMI, body mass index; Hb, haemoglobin; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 6. Clinical and laboratory data of study patient groups and subgroups

Parameters	BMI ≥30 kg/m^2		*p*-value	BMI <30 kg/m^2		*p*-value
	eGFR ≥ 45 (N=32)	eGFR < 45 (N=33)		eGFR ≥ 45 (N=36)	eGFR < 45 (N=67)	
Male, %	34.4	45.5	0.1	52.8	49.2	0.1
Age (years)	60.7±12.4	65.9±12.0	0.1	50.6±15.5	61.4±14.7	0.01
Diabetes, N (%)	8 (25.0)	12 (36.4)	0.1	3 (8.3)	18 (26.9)	0.02
BMI (kg/m^2)	35.6±6.3	35.3±5.0	0.1	24.1±3.2	24.8±3.0	0.1
Smoking, %	3.1	6.1	0.1	2.8	9.0	0.1
Hb (g/L)	136.2±17.2	124.3±16.1	0.01	133.9±16.3	117.5±17.0	0.001
CRP (mg/L)*	2 (1–17)	2 (1–28)	0.1	1 (1–8)	3 (1–107)	0.01
Albumin (mmol/L)	42.5±3.1	42.3±3.7	0.1	43.4±4.5	39.7±7.1	0.04
Calcium (mmol/L)	2.3±0.1	2.3±0.2	0.1	2.3±0.3	2.3±0.2	0.1
Ionised calcium (mmol/L)	1.3±0.1	1.3±0.1	0.1	1.3±0.2	1.3±0.1	0.1
Phosphorus (mmol/L)	1.1±0.2	1.4±0.5	0.01	1.1±0.3	1.5±0.6	0.005
Alkaline phosphatase bone isoenzyme (mmol/L)*	0 (0–1)	0 (0–72)	0.1	0 (0–1)	0 (0–1)	0.1
PTH (pmol/L)*	6.8 (2.8–13.0)	16.2 (36–175.9)	0.01	6.2 (1.4–33.9)	12.9 (0–320.4)	0.001
Vitamin D (nmol/L)	55.9±21.6	51.4±22.2	0.1	61.7±29.3	49.9±27.3	0.1
Uric acid (mmol/L)	374.1±108.9	447.2±90.3	0.02	342.1±92.4	392.3±108.4	0.02
Total cholesterol (mmol/L)	5.5±1.3	5.2±1.4	0.1	5.5±1.0	5.6±1.2	0.1
HDL-cholesterol (mmol/L)	1.4±0.6	1.2±0.3	0.1	1.5±0.5	1.7±2.1	0.1
LDL-cholesterol (mmol/L)	3.7±1.1	3.4±1.1	0.1	3.7±1.0	3.5±1.1	0.1

Data are given as mean values with standard deviations. *Data are given as percentages, medians. Statistically significant *p*-value between obese and non-obese groups < 0.05.
BMI, body mass index; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; CRP, C-reactive protein; PTH, parathyroid hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

There were no differences in the Kauppila score, expressing AAC, between the obese and non-obese patients in the group of 168 CKD patients (male 46%, mean age 59.8±14.8 years) (Table 7). However, the calcification rates depended on the kidney function. In the obese patient group, the Kauppila score was significantly higher in the subgroup with eGFR < 45 ml/min than in patients with better kidney function (eGFR ≥ 45 ml/min) ($p = 0.005$). Among non-obese patients, the same association was observed with lower statistical significance ($p = 0.02$) (Table 8). In comparing obese and non-obese patients with lower kidney function (eGFR <45 ml/min), AAC was a more common finding in obese patients ($p = 0.05$) (Table 9).

High ABI value (≥ 1.3) was presented in obese and non-obese groups without a significant difference ($p = 0.4$) (Table 7). In obese patients ABI ≥ 1.3 was a more common finding in the subgroup with lower kidney function (p = 0.08). No such pattern was found in the non-obese patient group ($p = 0.4$) (Table 8).

The presence of heart valve calcification and fibrosis was high in both the obese and non-obese groups (Table 7). In the group of obese patients, there was no difference between subgroups with higher (eGFR ≥ 45 mL/min) and lower kidney function (eGFR < 45 mL/min) ($p = 0.1$), and the occurrence was high. On the contrary, in the non-obese group, patients with lower kidney function had more heart valve calcification and fibrosis than those with better kidney function ($p = 0.03$) (Table 8).

LVH was a common finding in obese and non-obese patients without a statistically significant difference between groups ($p = 0.05$) (Table 7). The presence of LVH was higher in patients with lower kidney function, independently of BMI (Table 8). Furthermore, in obese patients with eGFR < 45 mL/min, LVH occurred more than in non-obese patients with the same kidney function ($p = 0.01$) (Table 9).

Table 7. Comparison of parameters of vascular calcification in obese and non-obese groups

Parameters	Group 1 Obese patients (BMI ≥30 kg/m^2)	Group 2 Non-obese patients (BMI <30 kg/m^2)	*p*-value
AAC, %	35	24	0.1
ABI ≥1.3, %	14	18	0.4
ABI <0.9, %	17	21	0.4
Heart valve calcification/fibrosis, %	45	33	0.1
LVH, %	51	36	0.05

BMI, body mass index; eGFR, estimated glomerular filtration rate; AAC, abdominal aortic calcification; ABI, ankle-brachial index; LVH, left ventricular hypertrophy

Data are given as a percentage of positive cases: AAC score >1; ABI ≥1.3; ABI<0.9; existence of heart valve calcification/fibrosis; existence of LVH

Statistically significant *p*-value < 0.05

Table 8. Comparison of vascular calcification in obese and non-obese patients divided into subgroups according to kidney function

Parameters	Group 1 Obese patients (BMI ≥30 kg/m^2)		*p*-value	Group 2 Non-obese patients (BMI <30 kg/m^2)		*p*-value
	Subgroup A eGFR≥45	Subgroup B eGFR <45		Subgroup A eGFR≥45	Subgroup B eGFR <45	
AAC, %	19	52	0.005	11	31	0.02
ABI ≥1.3, %	6	21	0.08	14	21	0.4
ABI <0.9, %	16	18	0.7	11	27	0.06
Heart valve calcification, %	34	55	0.1	19	40	0.03
LVH, %	28	73	0.0003	17	46	0.003

BMI, body mass index; eGFR, estimated glomerular filtration rate; AAC, abdominal aortic calcification; ABI, ankle-brachial index; LVH, left ventricular hypertrophy

Data are given as percentage of positive cases: AAC score >1; ABI ≥1.3; ABI<0.9; existence of heart valve calcification/fibrosis; existence of LVH

Statistically significant *p*-value < 0.05

Table 9. Comparison of parameters of vascular calcification according to the kidney function and BMI

Parameters	eGFR ≥ 45		*p*-value	eGFR < 45		*p*-value
	BMI ≥30 kg/m^2	BMI < 30		BMI ≥30 kg/m^2	BMI < 30	
AAC, %	19	11	0.4	51	31	0.05
ABI ≥1.3, %	6	14	0.3	21	21	0.9
ABI <0.9, %	16	11	0.6	18	27	0.3
Heart valve calcification/fibrosis, %	34	19	0.2	54	40	0.2
LVH, %	28	17	0.3	73	46	0.01

BMI, body mass index; eGFR, estimated glomerular filtration rate; AAC, abdominal aortic calcification; ABI, ankle-brachial index; LVH, left ventricular hypertrophy

Data are given as a percentage of positive cases: AAC score >1; ABI ≥1.3; ABI<0.9; existence of heart valve calcification/fibrosis; existence of LVH

Statistically significant p-value < 0.05

In addition, we found a correlation between parameters of peripheral (ABI) and central (Kauppila score, valvular lesions) calcification.

In patients with lower limb calcification (ABI ≥ 1.3) and normal heart valves, Kauppila scores were low. In contrast, patients with a combination of ABI ≥1.3 and heart valve lesions had significantly higher Kauppila scores (as shown in green in Figure 4).

In patients with normal ABI and without heart valve lesions, the Kauppila score was expectedly low. However, in the case of normal ABI but with heart valve lesions, Kauppila scores were high, although not as high as in patients with ABI ≥1.3 (as shown in blue in Figure 4).

In case of atherosclerosis of peripheral arteries (ABI < 0.9), Kauppila scores were relatively high, regardless of the existence of heart valve lesions (as shown in red in Figure 4).

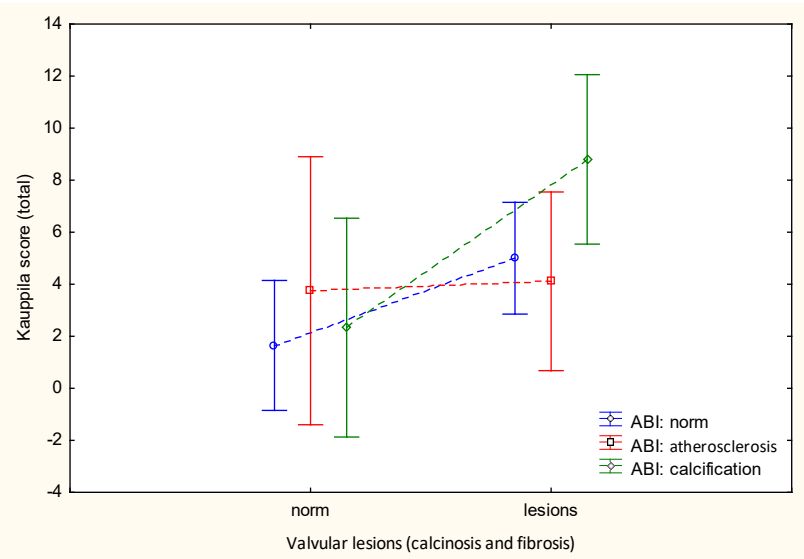

Figure 4. Results of analysis of variance. Abdominal aortic calcification and ABI in CKD patients with heart valve calcification and fibrosis
Mean values, vertical bars denote 0.95 confidence intervals
ABI, ankle-brachial index
ABI norm (blue) ≥0.9–1.3
ABI atherosclerosis (red) <0.9
ABI calcification (green) ≥1.3

Comparing VC in obese and non-obese patients with different CKD stages the results of this study have shown, that obesity did not have protective effect on VC and "obesity paradox" did not apply in CKD.

Moreover, in obese patients with more severe CKD, calcification of the abdominal aorta and peripheral arteries was more pronounced.

8.2. Associations between vascular calcification and bone mineral density in patients with chronic kidney disease (Paper II)

Demographic, clinical and laboratory data of participants are presented in Tables 10 and 11.

Table 10. Clinical characteristics of patients (N=90)

Parameters	Median (range) or frequency (%)
Age (years)	64 (29–87)
Gender (male)	37 (41%)
BMI (kg/m^2)	28 (16–49)
Diabetes, %	28.9
Hypertension, %	27.8
Interstitial nephritis, %	15.5
Glomerulonephritis, %	13.3
Other, %*	14.5
Smoking, %	6.7
Kauppila score ≥1, N (%)	37 (41.1%)
ABI ≥ 1.3, N (%)	21 (23.3%)
ABI <0.9, N (%)	16 (17.8%)
Heart valve calcification/fibrosis, N (%)	42 (46.7%)

*Polycystic kidney disease, systemic vasculitis, amyloidosis
BMI, body mass index; ABI, ankle-brachial index

Table 11. Biochemical characteristics of patients (N=90)

Serum markers	Mean ± SD	Median (range)	Normal range
S-Crea (µmol/L)	261.7 ± 249.4	150.5 (51–1036)	45–104
eGFR (ml/min)	35.2 ± 22.8	33.5 (2–106)	>90
S-Urea (mmol/L)	14.1 ± 7.9	11.9 (3.9–36.0)	< 8.1
S-Hb (g/L)	123.8 ± 18.2	120 (86–164)	121–170
S-CRP (mg/L)	5.0 ± 11.8	2 (1–107)	<5
S-Alb (g/L)	41.7 ± 4.7	42 (27–54)	35–52
S-Ca (mmol/L)	2.33 ± 0.2	2.3 (1.8–2.8)	2.20–2.55
S-Pi (mmol/L)	1.36 ± 0.5	1.2 (0.7–3.4)	0.81–1.45
iPTH (pmol/L)	23.7 ± 43.0	10.5 (1.4–320.4)	1.6–6.9
S-tALP (iu/L)	113.1 ± 162.7	84 (0.9–1390)	35–129
S-CHL (mmol/L)	5.5 ± 1.3	5.3 (3.2–9.8)	<5.5
S-TG (mmol/L)	1.89 ± 1.14	1.7 (0.5–5.1)	<2.0
S-UA (mmol/L)	406.1 ± 92.4	395 (253–718)	143–417
S-vit D (25 OH) (nmol/L)	58.7 ± 27.9	48.5 (14–144)	>50
FGF23 (U/mL)	266.0 ± 602.2	51 (10–2400)	<114

S-Crea, serum creatinine; eGFR, estimated glomerular filtration ratio; S-Urea, serum urea; S-Hb, serum haemoglobin; S-CRP, serum c-reactive protein; S-Alb, serum albumin; S-Ca, serum calcium; S-Pi, serum phosphate; PTH, parathormone; S-tALP, serum total alkaline phosphatase; S-CHL, serum cholesterol; S-TG, serum triglycerides; S-UA, serum uric acid; S-vit. D, serum vitamin D; FGF23, fibroblast growth factor 23

In the group of 90 patients (41% male, mean age 64 years, mean eGFR 35 mL/min) with different stages of CKD, the presence of central and peripheral VC was high: 41% patients with an AAC, expressed by Kauppila score > 1; 47% with heart valve lesions; 23% with an ABI ≥ 1.3.

The existence of abdominal aortic calcification (Kauppila score > 1) was inversely correlated with the mineral density of the femoral neck and total spine BMD. Pathologically high or low ABI (≥ 1.3 or <0.9) was also inversely linked with mineral density of femoral neck, spine L1-L4 and ribs (Table 12).

Mineral density of femur, femoral neck and total body BMD was associated with lesions of the cardiac valves (Table 13).

In a linear multivariate regression analysis, an association was found between heart valve lesions and a high ABI (≥1.3) (p = 0.002).

Table 12. Multivariate regression analysis with variables entering the equation as correlates of BMD measurements, with Kauppila score and ABI as dependent variables (only statistically significant results are marked in the table)

	R^2	Coefficient	95% CI	p-value
Kauppila score	0.53			
BMD femoral neck		-33.5	-49.2 -17.7	0.001
BMD total spine		-25.1	-40.1 -10.0	0.001
ABI	0.39			
BMD femoral neck		-2.21	-3.09 -1.33	0.001
BMD spine L1-L4		-0.77	-1.33 -0.21	0.01
BMD ribs		-1.69	-2.74 -0.65	0.002

BMD, bone mineral density; ABI, ankle-brachial index
Statistically significant p-value <0.05

Table 13. Factorial regression analysis with BMD as an independent variable; heart valve calcification and fibrosis, age, and S-tALP as dependent variables

	R^2	Coefficient	95% CI	*p*-value
BMD femur total	0.43			
Heart valve calcification and fibrosis		-2.48	-4.50 -0.46	0.01
Age		-0.03	-0.06 -0.01	0.02
S-tALP		-0.02	-0.04 -0.01	0.01
BMD femoral neck	0.49			
Heart valve lesions		-2.60	-4.28 -0.92	0.003
Age		-0.03	-0.06 -0.01	0.001
S-tALP		-0.02	-0.03 -0.01	0.001
BMD total	0.41			
Heart valve lesions		-1.88	-3.69 -0.06	0.04
Age		-0.02	-0.04 0.01	0.08
S-tALP		-0.01	-0.03 0.01	0.1

Statistically significant *p*-value <0.05
BMD is the independent variable
BMD, bone mineral density; S-tALP, serum total alkaline phosphatase

An inverse relationship existed between central and peripheral VC and BMD in CKD patients. The mineral density of different skeletal sites was associated with lesions in the heart valves.

8.3. Prognostic role of severity of abdominal aortic calcifications and peripheral arterial disease on outcome of end-stage kidney disease patients (Paper III)

In a study of 249 peritoneal dialysis patients (67% male, mean age 61 years) the etiology of CKD was diabetes in 78 patients (31%), glomerulonephritis in 61 (24%), ischemic nephropathy in 23 (9%), polycystic kidney disease in 15 (6%), interstitial nephritis in 18 (7%), and other in 54 (23%). Twenty-one percent of patients had a history of peripheral arterial disease at baseline, and ADP and ATP were not palpable (either pulse or both pulses) in 25% and 43% of patients, respectively.

Demographic, biochemical and clinical characteristics of patients accoding to AACS and ABI category are shown in Table 14 and 15.

Table 14. Demographic, Biochemical, and Clinical Characteristics in 249 PD Patients According to AACS Category

Variable	Normal AACS 0 N=41 Mean/Number	SD/%	Moderate AACS 1–6 N=38 Mean/Number	SD/%	Severe AACS≥7 N=141 Mean/Number	SD/%	*p*-value
Age (years)	45.3	12.5	57.0	13.7	65.9	10.9	<0.001
Male gender (N, %)	27	66%	25	67%	97	69%	0.903
BMI (kg/m^2)	25.2	3.6	25.3	3.8	26.1	4.3	0.312
Abdominal obesity[b] (N=211)	12	32%	17	45%	77	57%	0.016
Duration of dialysis (months)[a]	8	1–72	11	0–61	15	1–150	0.001
Current smoker (N, %)	4	10%	9	24%	27	19%	0.242
Diabetes (N, %)	10	24%	14	37%	46	33%	0.285
Pulse pressure (mmHg)	50	13	56	16	63	19	<0.001
Comorbidity score[a]	0	0–2	1	0–4	1	0–5	<0.001
Karnofsky scale (%)[a]	90	60–100	80	50–100	80	40–100	<0.001
Serum albumin (g/L)	34	5	34	6	33	6	0.321
Kt/V (urea) per week	2.5	1.0	2.6	1.4	2.2	0.8	0.037
Urinary output (mL/day) [a]	1,200	0–3,200	1,200	0–2,600	900	0–3,600	0.156
History of PAD[c] (N, %)	2	5%	4	11%	41	29%	0.001
All-cause mortality (N, %)	2	5%	7	18%	71	50%	<0.001
New CV event[d] (N, %)	6	15%	15	40%	77	55%	<0.001
Received kidney transplant (N, %)	29	78%	16	53%	28	23%	<0.001
ADP (-/- or -/+) (N=204)	2	5%	4	11%	39	31%	0.001
ATP (-/- or -/+) (N=194)	8	22%	11	32%	59	48%	0.010

PD, peritoneal dialysis; AACS, abdominal aortic calcification score; BMI, body mass index; PAD, peripheral arterial disease; CV, cardiovascular; ADP, arteria dorsalis pedis; ATP, arteria tibialis posterior

[a] Median and ranges.

[b] Abdominal obesity was defined as a waist circumference ≥ 88 cm in women or ≥ 102 cm in men.

[c] Peripheral arterial disease was defined as a history of any of the following: claudication, ischemic ulcers, lower limb amputation, revascularisation, or previous diagnosis of obstruction by angiography.

[d] New CV event was defined as the composite endpoint of myocardial infarction, coronary artery bypass surgery or angioplasty, stroke, hospitalisation due to heart failure, occurrence of a new event related to PAD (ischemic ulcer, gangrene, vascular surgery, amputation), or CV death. The *p*-value shows the difference between the 3 AACS categories.

Table 15. Demographic, Biochemical, and Clinical Characteristics in 249 PD Patients According to ABI Category

Variable	Normal ABI 0.9–1.3 N=120 Mean/Number	SD/%	Moderate ABI <0.9 N=41 Mean/Number	SD/%	Severe ABI >1.3 N=84 Mean/Number	SD/%	*p*-value
Age (years)	58.1	14.4	70.9	9.5	59.4	14.5	<0.001
Male gender (N, %)	78	65%	24	59%	61	73%	0.259
BMI (kg/m^2)	25.6	4.2	25.7	3.6	26.2	4.1	0.486
Abdominal obesity[b] (N=231)	50	44%	29	73%	40	52%	0.008
Duration of dialysis (months)[a]	13	1–150	17	0–78	11	1–102	0.474
Current smoker (N, %)	17	14%	14	34%	12	15%	0.010
Diabetes (N, %)	17	14%	19	46%	40	48%	<0.001
Pulse pressure (mmHg)	56	16	61	22	63	19	0.031
Comorbidity score[a]	1	0–4	2	0–5	1	0–5	<0.001
Serum albumin (g/L)	34	5	33	7	32	5	0.016
Karnofsky scale (%)[a]	90	40–100	70	40–90	80	40–100	<0.001
Kt/V (urea) per week	2.5	1.3	2.2	0.6	2.2	0.5	0.082
Urinary output (mL/day)[a]	1,100	0–3,100	900	0–2,300	900	0–3,600	0.360
AACS[a]	8	0–24	16	0–24	10	0–24	<0.001
History of PAD[b] (N, %)	15	13%	19	46%	17	20%	<0.001
All-cause mortality (N, %)	29	24%	25	61%	36	43%	<0.001
New CV event[b] (N, %)	42	35%	26	63%	37	44%	0.006
Received kidney transplant (N, %)	53	52%	3	9%	25	34%	<0.001
ADP (-/- or -/+) (N=230)	13	12%	20	51%	24	30%	<0.001
ATP (-/- or -/+) (N=220)	34	33%	27	71%	34	44%	<0.001

PD, peritoneal dialysis; ABI, ankle-brachial index; BMI, body mass index; AACS, abdominal aortic calcification score; PAD, peripheral arterial disease; CV, cardiovascular; ADP, arteria dorsalis pedis; ATP, arteria tibialis posterior.

[a] Median and ranges.

[b] Peripheral arterial disease was defined as a history of any of the following: claudication, ischemic ulcers, lower limb amputation, revascularization, or previous diagnosis of obstruction by angiography.

The *p*-value shows the difference between the 3 ABI categories.

Ninety-one patients died during the follow-up (median 46 months, range 1–61 months). A CV death was reported in 51 patients (56% of all deaths). 95 patients experienced a new CV event. An older age, severe calcification (AACS ≥ 7 expressed by Kauppila score), a low or high ABI, diabetes, history of PAD, and low serum albumin level were associated with all-cause mortality. Seventeen out of 30 (57%) patients with a concurrent low ABI and severe calcifications died during the follow-up, compared with 23 out of 60 (38%) patients with a normal ABI together with severe calcifications (p = 0.099). Also, 60% patients with a high ABI and severe calcifications died compared with 38% patients with a normal ABI (p = 0.024).

Severe AAC was a strong predictor of mortality in CKD patients (Figure 5). Neither a low nor a high ABI was independently associated with all-cause mortality or new CV events in the adjusted Cox regression models in which AACS was also included.

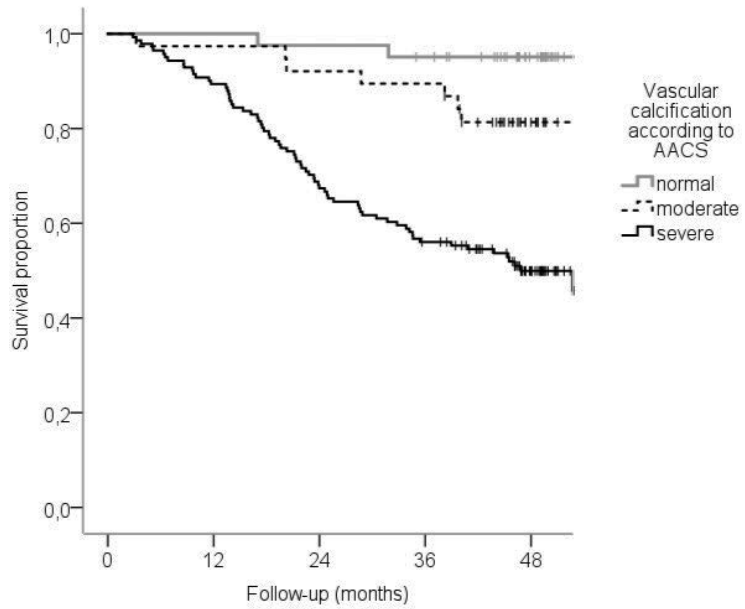

Figure 5. Overall survival by AACS category (normal, moderate, severe) in peritoneal dialysis patients
AACS, abdominal aortic calcification score

8.4. Prognostic value of vascular calcification on long-term outcomes in obese and non-obese patients with chronic kidney disease (Paper IV)

Clinical and biochemical data of studied patients are given in Table 16.

Table 16. Clinical and laboratory characteristics of the whole group and obese (BMI ≥30 kg/m^2) and non-obese (BMI <30 kg/m^2) groups.

	Whole group	BMI <30 kg/m^2	BMI ≥30 kg/m^2	*p*-value
N	150	92	58	
Male, %	46%	52%	36%	0.04
Mean age (years)	60±14	57.8±15.7	64.2±12.4	0.02
S-Hb (g/L)	124.3±18.4	121.7±18.4	128.5±17.7	0.03
S-Creatinine (mcmol/L)	152.0 (51–1036)	181.5 (54–1015)	136.5 (51–1036)	0.002
S-Urea (mmol/L)	13.6±7.6	14.3±7.8	12.5±7.1	0.09
eGFR (ml/min/1,73m^2)	36.4±24.3	32.5±22.9	42.5±25.3	0.02
S-Calcium (mmol/L)	2.3±0.2	2.3±0.2	2.3±0.2	0.6
S-Ionised calcium (mmol/L)	1.3±0.1	1.3±0.2	1.3±0.1	0.4
S-Phosphate (mmol/L)	1.3±0.5	1.4±0.5	1.3±0.5	0.5
S-PTH (pmol/L)	10.0 (0–320.4)	10 (0–320.4)	9.5 (2.9–175.9)	0.8
S-Vitamin D (nmol/L)	52.9±26.3	52.9±29.2	52.9±21.6	0.5
iFGF-23 (U/mL)	43.5 (10–2400)	34 (10–2400)	58.5 (11–2044)	0.02
S-Albumin (mmol/L)	41.3±5.8	40.7±6.8	42.3±3.6	0.5
S-CRP (mg/L)	2.0 (1–107)	2.0 (1–107)	2.0 (1–28)	0.8
S-Uric acid (mmol/L)	396.3±107.4	383.3±106.3	416.5±106.9	0.02
S-Total cholesterol (mmol/L)	5.5±1.3	5.5±1.2	5.3±1.4	0.2
S-HDL-cholesterol (mmol/L)	1.5±1.4	1.7±1.8	1.3±0.5	0.01
S-LDL-cholesterol (mmol/L)	3.5±1.1	3.5±1.1	3.5±1.1	0.8

Statistically significant *p*-value between the obese and non-obese groups < 0.05
BMI, body mass index, Hb, haemoglobin, CRP, C-reactive protein, HDL, high-density lipoprotein; LDL, low-density lipoprotein.

In a study of 150 CKD patients by the 11.2-year follow-up, 70 patients died (47%). Among patients with a BMI ≥ 30 kg/m^2 (N=58), 27 patients died. In the group with a BMI <30 kg/m^2 (N=92), 43 patients died. Twenty-four patients had CV events: stroke, myocardial infarction, decompensated heart failure, amputation due to atherosclerosis or aortic rupture.

In the whole group, AAC score at least 1 ($p = 0.04$) (Figure 6a), pathologically high or low ABI (≥1.3 or <0.9) ($p = 0.02$) (Figure 6b), the presence of LVH ($p = 0.001$), and heart valve lesions ($p = 0.03$) were statistically significant predictors of CV events. Moreover, abnormal ABI ($p = 0.006$) (Figure 7), LVH ($p = 0.009$), and heart valve calcification/fibrosis ($p = 0.02$) were predictors of all-cause mortality.

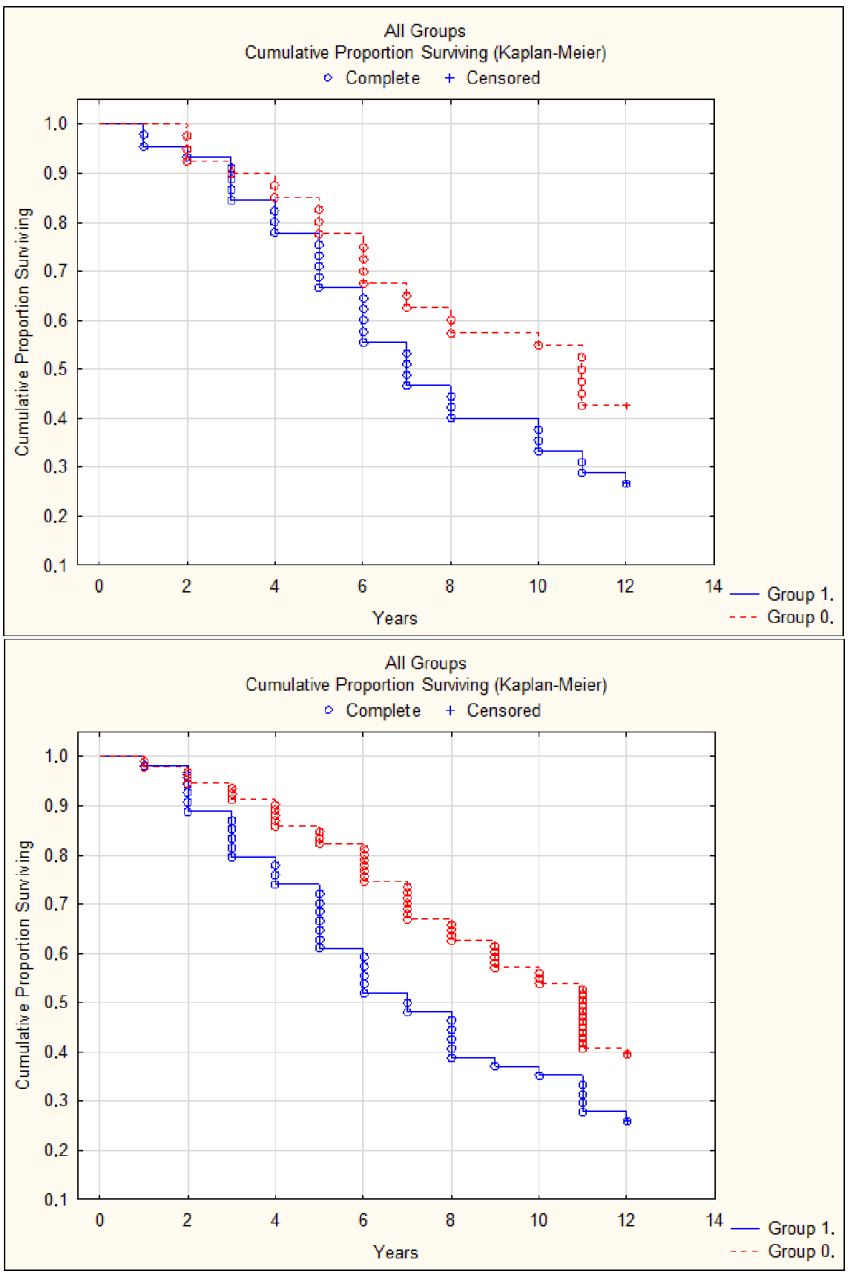

Figure 6. (**a**) CV events (stroke, myocardial infarction, decompensated heart failure, amputation due to atherosclerosis, or aortic rupture) with Kauppila score ≥ 1 (group 1) and Kauppila score 0 (group 0). $p = 0.04$. (**b**) Complications (stroke, myocardial infarction, decompensated heart failure, amputation due to atherosclerosis, or aortic rupture) with ABI ≥1.3 or <0.9 (group 1) and normal ABI (group 0). $p = 0.02$

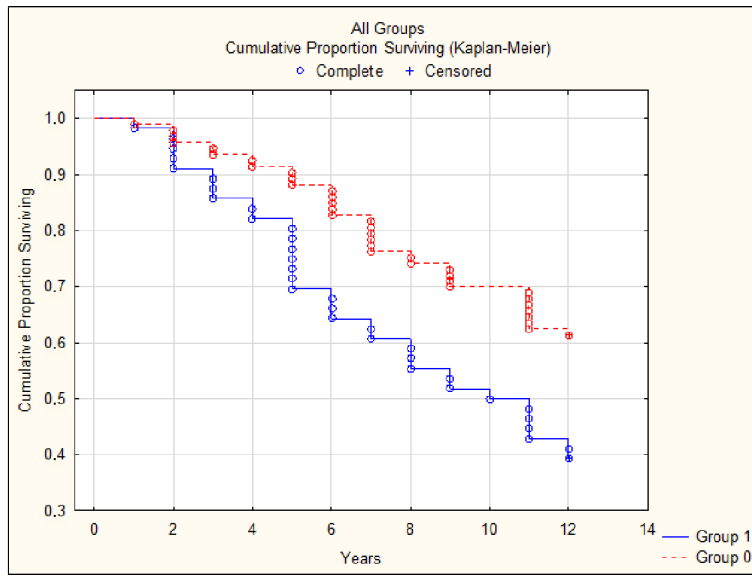

Figure 7. All-cause mortality in the group with ABI ≥1.3 or <0.9 (group 1) and with normal ABI (group 0), $p = 0.006$

Among obese patients (BMI ≥ 30 kg/m^2), only LVH was a significant predictor of CV events (p = 0.01) and all-cause mortality ($p = 0.004$).

In patients with BMI < 30 kg/m^2, ABI was a predictor of CV events ($p = 0.03$) and all-cause mortality ($p = 0.009$), heart valve calcification was a predictor of CV events (p = 0.009) and all-cause mortality ($p = 0.004$), and LVH was a predictor of CV events ($p = 0.02$).

There were no differences in the measured parameters of VC between the obese and non-obese groups. Comparing patients with and without obesity according to the studied parameters, we found no significant differences in complications and mortality (Table 17, Figures 8 and 9).

Table 17. Parameters of vascular calcification, CV complications, and mortality in the obese (BMI ≥ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) groups

	BMI < 30 kg/m^2	BMI ≥ 30 kg/m^2	*p*-value
AACS > 1	27.2%	39.7%	0.1
ABI <0.9 and ≥1.3	53.3%	43.1%	0.2
LVH, (yes)	40.2%	51.7%	0.2
Heart valve calcification/sclerosis (yes)	35.9%	46.6%	0.2
All-cause mortality	47.3%	46.6%	0.9
CV events	65.6%	65.5%	0.9

Statistically significant *p*-value < 0.05

CV cardiovascular, BMI body mass index, AACS abdominal aortic calcification score, ABI ankle-brachial index, LVH left ventricular hypertrophy

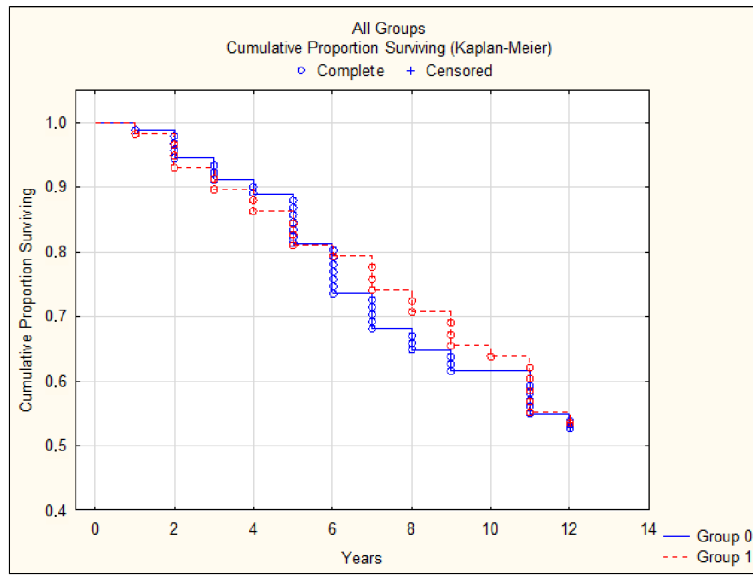

Figure 8. Survival in patients with a BMI < 30 (group 0) and a BMI ≥ 30 (group 1), $p > 0.005$

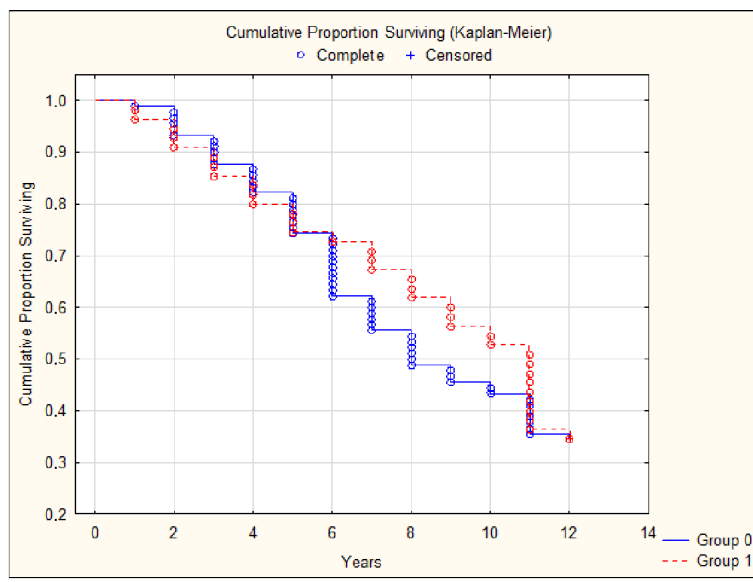

Figure 9. Complications (stroke, myocardial infarction, decompensated heart failure, amputation caused by atherosclerosis, or aortic rupture) in patients with a BMI < 30 (group 0) and a BMI ≥ 30 (group 1), $p > 0.005$

In an unadjusted Cox proportional model, AACS (HR = 1.06) and eGFR (HR = 0.96) were associated with CV complications; age (HR = 0.03) and eGFR (HR = 0.97) were associated with mortality (Table 18(a), (b)).

Table 18. (**a**) Associations between abdominal aortic calcification score, kidney function, and CV complications (stroke, myocardial infarction, decompensated heart failure, amputation caused by atherosclerosis, or aortic rupture) in the whole group (unadjusted Cox regression model). (**b**) Associations between age, kidney function, and mortality in the whole group (unadjusted Cox regression model).

Variable	***p*-value**	**HR (95%CL)**
eGFR	0.0004	0.97 (0.95; 0.98)
AACS	0.01	1.06 (1.01; 1.12)
Variable	***p*-value**	**HR (95%CL)**
Age	0.01	1.03 (1.01; 1.06)
eGFR	0.006	0.97 (0.95; 0.99)

eGFR, estimated glomerular filtration ratio; AACS, abdominal aortic calcification score; HR, hazard ratio.

9. DISCUSSION

9.1. Impact of obesity on vascular calcification in different stages of chronic kidney disease

In this study, VC in obese and non-obese CKD patients was compared, and the impact of obesity on VC in different stages of CKD was investigated. For the detection of VC, we focused on the anatomical allocation of extraosseous lesions using three methods. We used lateral lumbal X-rays and Kauppila scoring system to assess AAC, echocardiography to evaluate valvular calcinosis and fibrosis, and ABI to assess peripheral VC of the lower limbs. According to the results of this study, obesity does not have a protective effect against the formation of VC; the obesity paradox did not apply in our cohort. We showed that among obese patients, AAC was more common, particularly in patients with lower kidney function. Similarly to the results of this study, Inoue et al. found that AAC is more common in subgroups with lower eGFR; however, their study did not account for BMI (Inoue et al., 2018).

High (≥ 1.3) and low (<0.9) ABI were more common findings in subgroups with lower kidney function of both obese and non-obese groups. This finding is clinically important and may help predict poor prognosis. Previous studies have shown that pathologically high or low ABI is an independent predictor of CV and all-cause mortality among CKD patients (Qu et al., 2015; Chen et al., 2017; Gu et al., 2019). The study of Su et al reported higher values of LV mass index and a higher prevalence of LVH in patients with an abnormally low (ABI < 0.9) or high (ABI ≥ 1.3) levels (Su et al., 2012). A study by Chen et al. showed an association between increased body mass and LVH with pathologically high or low ABI in CKD patients (Chen et al., 2016).

Heart valve calcification and fibrosis were the common findings in both obese and non-obese groups. While in the non-obese group, heart valve lesions were more common in patients with lower eGFR; there were no statistically significant differences in kidney function among obese patients, and the incidence of lesions was high. Previous studies showed the high prevalence of valvular calcification in CKD patients, which our study confirmed (Kraus et al., 2015; Ureña-Torres et al., 2020). In our study, we demonstrated an association between heart valve calcification and fibrosis and high ABI (≥ 1.3) in CKD patients, where BMI was not taken into account.

The occurrence of LVH was high in both obese and non-obese groups. The presence of LVH was significantly higher in patients with lower kidney function, similar to the results of other studies (Cioffi et al., 2011; Maqbool et al., 2023).

To our knowledge, there is no previous data comparing obese and non-obese patients at different stages of CKD and the effects of obesity on VC using several diagnostic methods in combination. According to the results of some studies, overweight and obesity have a favourable effect on patients' outcomes (Ahmadi et al., 2015; Rhee et al., 2016). However, the associations between obesity and

mortality, as well as their underlying mechanisms, remain complex and not yet fully understood (Naderi et al., 2018).

The results of our study did not support the "obesity paradox", and we demonstrated that obesity does not have a favourable effect on central and peripheral VC in CKD patients independently of kidney function. Moreover, VC was more pronounced in obese patients with reduced kidney function.

9.2. Associations between vascular calcification and site-specific bone mineral density in different stages of chronic kidney disease

The study highlighted clinically important relationships between VC and site-specific BMD in patients with different stages of CKD. Accordingly, the results of this study indicate that an inverse relationship exists between central and peripheral VC and BMD in CKD patients. Other researchers have also reported similar results (Toussaint et al., 2011). Additionally, our results are supported by previous investigations that have shown not only an inverse correlation between BMD and VC, but also that the progression of VC is accompanied by greater bone loss (Naves et al., 2008; Schulz et al., 2004).

Our approach in this work was to utilise three non-invasive methods for assessing VC (both central and peripheral) and total body DEXA for measuring BMD in different skeletal sites. Although bone biopsy is the gold standard for evaluating bone tissue quality, it is not used routinely in clinical practice due to its invasiveness. Among the numerous non-invasive approaches to assess bone quality in CKD-related bone disease, the most accessible low-dose radiation imaging modality used in routine practice for measuring bone mass and density is DEXA (Evenepoel et al., 2017; Malluche et al., 2014). A recent study by Carvalho et al. has demonstrated a significant association between BMD measured by DEXA and bone histomorphometry data obtained from bone biopsy, supporting the usefulness of DEXA in CKD patients (Carvalho et al., 2017). Based on the results of four prospective cohort studies, the Work Group of KDIGO guidelines concluded that assessment of BMD by DEXA is reasonable if a low or declining BMD will lead to additional interventions to reduce falls or use osteoporosis medications (KDIGO CKD-MBD Clinical Practice Guideline, 2017).

Bone mineral density can be measured by DEXA in different locations. Central DEXA is the clinical standard to measure bone mass, fracture risk and diagnosis of osteoporosis in the general population, but in CKD patients, the BMD of the spine may be overestimated because of aortic calcification (Kanis et al., 2019; Melton et al., 2005). Considering this, total body DEXA is probably a more appropriate method for assessment of skeletal mineral status in CKD (Iseri,

Qureshi et al., 2020; Cohen-Solal, Funck-Brentano, Ureña-Torres, 2020). Nevertheless, the optimal choice of DEXA type to use in clinical practice depends mainly on its purpose and should be selected individually.

In the context of recent research on CKD-MBD, site-specific BMD assessment is very important. The human skeleton is composed of cortical and trabecular bone. Trabecular bone, which makes up two-thirds of total bone surfaces, shows greater metabolic activity than cortical bone (Parfitt, 2002). In contrast to the general population, loss of cortical bone is more severe in CKD patients than loss of trabecular bone. Interestingly, researchers have found that bone mass at cortex-rich sites such as the femoral neck is more affected than trabecular bone, and these appear to be the most useful sites for predicting clinical outcomes in CKD patients (Carvalho et al., 2017; Nickolas et al., 2013). While DEXA cannot provide details regarding the relative proportions of cortical and trabecular bone or distinguish between different types of renal osteodystrophy, it remains a reliable method for evaluating BMD in CKD patients (Iseri, Qureshi et al., 2020). In conclusion, given the high prevalence of vascular calcification in our cohort, we recommend the use of total body DEXA for evaluating BMD in CKD patients.

9.3. Severe abdominal calcification and peripheral arterial disease as predictors of all-cause mortality and cardiovascular events in patients with chronic kidney disease

We evaluated the prognostic value of AAC and the prevalence of PAD on mortality and CV events in end-stage CKD patients. Our study showed that VC, assessed by AACS, was very common in the PD patient population. The result is consistent with other studies (Honkanen et al., 2008; Adragao et al., 2012; Martino et al., 2013; Kraus et al., 2015). Moreover, several studies have assessed the progression of AAC in different stages of CKD and shown rapid progression of VC in earlier stages of CKD, patients on HD, PD, and even kidney transplant patients with functional grafts (Yildiz et al., 2005; Noordzij et al., 2011; Yamamoto et al., 2016; Naganuma et al., 2019; Lankinen et al., 2022). However, 19% of patients in the present study had no visible deposits in any segment. The proportion of dialysis patients without any calcifications is also reported to be approximately the same in other dialysis populations (Honkanen et al., 2008; Adragao et al., 2012; Martino et al., 2013). Perhaps there are some protective mechanisms or genetic factors that influence the formation of VC in uremic patients.

Once it begins, VC progresses gradually with deteriorating kidney function and may rapidly progress on dialysis (Temmar et al., 2010; Goodman et al., 2000). Pre-existing VC might be among the key factors predicting further progression of calcification in CKD patients (Shroff et al., 2013). In the present study, 29% of incident PD patients with a duration of dialysis less than 3 months

had no calcifications. However, severe calcification was found in more than half of the incident patients.

Severe VC, assessed by AACS, was a strong predictor of all-cause mortality and the occurrence of CV events in our cohort. Arterial calcification has previously been shown to be an independent risk factor for mortality in hemodialysis patients (Okuno et al., 2007; Verbeke et al., 2011; London et al., 2003). In recent years, only a few studies have shown that AAC is an independent predictor of CV events, all-cause and CV mortality in PD patients (Martino et al., 2013; Niu et al., 2019).

In advanced CKD, high and low ABI are common findings (O`Hare et al., 2002; Chen et al., 2010). Asymptomatic PAD is prevalent in all CKD stages and was also prevalent in our cohort. The history of PAD was known only in one-fifth of patients at baseline, while more than half of patients had an abnormal ABI. In this study, the presence of PAD was not independently associated with all-cause mortality and CV events.

Nevertheless, both a low and a high ABI were associated with severe calcifications. High AACS was also seen in more than half of patients with a normal ABI. In a subgroup of patients with severe calcifications, the presence of a high ABI was associated with a worse prognosis. There was also a trend towards worse prognosis in patients with a low ABI and severe calcifications compared with those with a normal ABI.

Previously, a low and high ABI have been found to be independently associated with all-cause and cardiovascular mortality in CKD patients (Ono et al., 2003; Adragao et al., 2012; Qu et al., 2015; Bevc et al., 2016; Chen et al., 2017; Gu et al., 2019). A low ABI has also been shown to predict mortality in PD patients (Liu et al., 2009; Tian et al., 2012).

PAD often remains undiagnosed in CKD patients, and the ABI is a simple and noninvasive method that allows the identification of PAD in these heterogeneous patients. The ABI alone, however, is not sufficient for risk stratification, since more than half of the present patients with a normal ABI displayed severe aortic VC. The combined use of several non-invasive methods may likely enable a more accurate estimation of the presence and severity of VC, providing valuable prognostic information. Detection of at least one marker of extraosseous calcification may therefore provide a useful tool in everyday clinical practice.

9.4. Vascular calcification as a predictor of long-term outcomes in obese and non-obese patients with chronic kidney disease

The results of this work showed the associations between markers of VC and long-term outcomes in our CKD cohort. However, obesity did not improve patient outcomes; the results of patients with and without obesity were similar.

The findings of this study confirmed the association between higher AAC and increased risk of CV complications in patients with CKD. However, in this cohort, we did not observe a relationship between AAC and all-cause mortality, despite such associations being reported in our previous study of PD patients and by other authors. The AAC score is independently associated with CV complications and death in the general population and dialysis patients (Peeters et al., 2017; Lewis et al., 2018; Lewis et al., 2019; Niu et al., 2018). In the KNOW-CKD study, AAC was identified as an independent predictor of adverse CV outcomes in pre-dialysis patients (Suh et al., 2022). Moreover, Lankinen et al. described the rapid progression of AAC score in patients with CKD 4–5 on different RRT modalities or conservative treatment (Lankinen et al., 2022).

In the current study, we showed that ABI predicts CV events and all-cause mortality in CKD patients. Both low and high ABI are known to be associated with an elevated risk of mortality in the general population and in patients with CKD (O`Hare et al., 2004; Ix et al., 2007; Adragao et al., 2012; Dorans et al., 2021). Furthermore, previous research has demonstrated that abnormally high or low ABI is an independent indicator of CV and all-cause mortality in CKD patients (Gu et al., 2019; Qu et al., 2015; Chen et al., 2017). Moreover, a retrospective cohort study demonstrated that a high ABI independently predicts major adverse CV events (Nishimura et al., 2016). Additionally, low ABI is a powerful predictor of a decline in kidney function (Chen et al., 2012).

Both valvular calcification and LVH were predictors of CV events and all-cause mortality in our cohort. Notably, LVH was the only significant predictor of outcome among obese patients. Valvular calcification represents a severe form of extraosseous calcification in CKD, leading to LVH and impaired cardiac function (Rebić et al., 2015; Kitamura et al., 2017). Our previous study demonstrated a markedly higher presence of LVH in patients with lower kidney function (Uhlinova et al, 2022), and similar results have been reported by others (Cioffi et al., 2011). In an earlier study within the same cohort, we demonstrated that patients with elevated BMI have an increased risk of VC formation, particularly those with reduced kidney function, with no evidence of the "obesity paradox" in this group (Uhlinova et al, 2022). The present study confirmed that obesity does not have a positive impact on long-term outcomes; the rates of CV complications and mortality were similar in both groups.

Some studies have suggested that being overweight or obese may have a positive impact on patient outcomes (Kalantar-Zadeh et al., 2003; Soohoo et al., 2022; Agarwal et al., 2010; Schetz et al., 2019). However, consistent with our results, other studies have reported no differences in mortality between obese and non-obese CKD patients (Dalrymple et al., 2011).

Furthermore, because of the short life expectancy in ESKD patients, the short-term survival advantage associated with obesity may outweigh the harmful long-term effects of obesity (Park et al., 2014).

10. CONCLUSIONS

1. Vascular calcification was the most pronounced in obese patients with reduced kidney function.
2. Obesity did not have a favourable effect on vascular calcification in CKD patients. The results of this study did not support the “obesity paradox” in the whole group of patients, nor in subgroups with different stages of CKD.
3. An inverse relationship was detected between abdominal aortic calcification, peripheral vascular calcification, and BMD. A significant association was found between peripheral vascular calcification and lesions of the heart valves.
4. BMD at certain bone sites, such as the femur, femoral neck and total BMD, were associated with important valvular lesions. The use of total body DEXA for site-specific assessment of BMD is a more appropriate method in the context of CKD due to abdominal aortic and vertebral articular calcification.
5. Severe abdominal aortic calcification was a strong predictor of all-cause mortality and cardiovascular events in ESKD patients. The presence of peripheral arterial disease was not independently associated with all-cause mortality and new CV events.
6. VC serves as an adverse prognostic marker in CKD, increasing the risk of CV complications and worsening the course of the disease.

11. STRENGTHS AND LIMITATIONS OF THE STUDY

The aim of this study was to clarify the associations between body composition and VC in patients with CKD. To the best of our knowledge, there is no previous data comparing obese and non-obese patients with different stages of CKD. In this study, we used relatively inexpensive and non-invasive methods for detecting calcifications in central and peripheral arteries, which can be used in routine clinical practice. Moreover, the combined use of several non-invasive methods may likely enable a more accurate estimation of the presence and severity of VC, bone disease, and improve understanding of CKD-MBD.

Our study has some limitations also. Although BMI is routinely used for the evaluation and classification of obesity, it is an indirect measure of fat tissue. It does not account for age or gender, and it does not distinguish between subcutaneous and visceral obesity, nor between adipose and muscle mass. We used total body DEXA for assessment of BMD; however, this method does not permit dividing long bones into portions for more accurate measurement of BMD in cortical and trabecular sites. The study cohort was relatively small, and studying a larger sample may be necessary for a more comprehensive understanding of the associations between body composition and VC in CKD patients, thereby improving the efficacy of current therapeutic approaches to improve outcomes in patients with CKD.

12. SUMMARY IN ESTONIAN

Vaskulaarne kaltsifitseerumine ning selle seosed adipoossuse ja luukoe mineraalse tihedusega kroonilise neeruhaiguse korral

Sissejuhatus

Krooniline neeruhaigus (KNH) on progresseeruv, eluiga lühendav haigus, millega kaasneb palju tüsistusi ja muutusi keha koostises. KNH-ga patsientide peamised surmapõhjused on südame-veresoonkonna haigused (SVH), mille patofüsioloogilised mehhanismid on KNH korral keerulised, sest nendes mängivad traditsiooniliste SVH riskitegurite kõrval olulist rolli ka ureemiaga seotud riskitegurid (Foley et al., 1998).

Adipoossus on ateroskleroosi ja sellele kaasnevate SVH-poolsete tüsistuste traditsiooniline riskitegur nii rahvastikus üldiselt kui ka KNH-ga patsientidel (Madero et al., 2007; Hsu et al., 2006). Lisaks võib rasvumine põhjustada ka *de novo* KNH teket (Stenvinkel et al., 2013; Rhee et al., 2016). Samas on aga mitmed uurijad kirjeldanud KNH patsientide hulgas nn adipoossuse paradoksi, kus ülekaal on seotud hoopis parema elulemusega (Fleischmann et al., 1999; Kalantar-Zadeh et al., 2003; Rhee et al., 2016). Sellist paradoksi on kirjeldatud peamiselt KNH lõppstaadiumi patsientide hulgas tehtud uuringutes, kes olid hemodialüüsravil ning tulemused KNH varajastes staadiumides või peritoneaaldialüüsil olevatel patsientidel on seni olnud vasturääkivad (Degoulet et al, 1982; Leavey et al, 1998; Fleischmann et al, 1999; Kalantar-Zadeh et al, 2003; Soohoo et al, 2022).

KNH patsientidel tekkivate erinevate tüsistuste hulgas on mineraalainete tasakaalu häired ja luuhaigus (MLH) väga tõsine tüsistus, mille tagajärjel luukoe mass väheneb. See toob kaasa kõrgenenud luumurdude, veresoonte seinte kaltsifitseerumise, jäigastumise ning veresoonkonna enneaegse vananemise riski (Capusa & Popescu, 2018; Iseri, Dai et al, 2020). Selle tüsistuse kliinilised ilmingud tekivad varakult, peaaegu normaalse neerufunktsiooniga, ja patsientidel ei esine tavaliselt kaebusi. MLH süvenevad neerufunktsiooni langedes (Damasiewicz & Nicolas, 2018), põhjustades SVH koos enneaegse ateroskleroosi ja kiirenenud vaskulaarse kaltsifitseerumisega (VK). See omakorda põhjustab generaliseerunud kaltsifitseerumist. Veelgi enam, MLH-d iseloomustab neerude osteodüstroofia ja osteoporoosist põhjustatud luukoe hõrenemine (Iseri, Dai et al, 2020). Ekstraskeletaalsete kaltsifikaatide ja osteodüstroofia patofüsioloogia on omavahel tihedalt seotud, kuid luu-veresoonkonna telge ei ole piisavalt uuritud. On ainult mõned uuringud, mis keskenduvad VK ja luu mineraalse tiheduse vaheliste seoste uurimisele KNH korral. Mõned neist on leidnud pöördvõrdelise seose VK ja MLH vahel ning luutiheduse vähenemise seoses VK progresseerumisega. (Schulz et al, 2004; Naves et al, 2008; Toussaint et al, 2011). Mõnede teiste autorite uuringutes ei ole siiski leitud korrelatsiooni VK ja MLH parameetrite

vahel (Salam et al, 2021). Lisaks sellele on seoseid adipoossuse ja ekstraskeletaalse kaltsifitseerumise vahel KNH patsientidel kirjeldanud vaid mõned autorid ning nende tulemused on olnud vasturääkivad (Yamauchi et al, 2003; Lee et al, 2012; Aoqui et al, 2013; Russo et al, 2014; Chen et al, 2016). Adipoossuse mõju VK-le on aktuaalne teema, mis aitaks hinnata võimaliku adipoossuse paradoksi kehtivust erinevates staadiumides KNH korral. Samas on oluline uurida võimalikke seoseid luukoe mineraalse tiheduse ja VK vahel KNH-ga patsientidel, et aidata nende teadmiste igapäevases kliinilises praktikas rakendamisel kaasa vaskulaarsete tüsistuste õigeaegsele diagnoosimisele ning varajasele sekkumisele, mis parandaks ravi kaugtulemusi.

Uuringu eesmärgid

Uurimistöö üldine eesmärk oli selgitada välja seosed vaskulaarse kaltsifitseerumise ja kehakoostise vahel KNH patsientidel.

Täpsemad eesmärgid olid järgmised:

1. Võrrelda vaskulaarset kaltsifitseerumist adipoossetel ja mitteadipoossetel KNH-ga patsientidel erinevate raskuskategooriate korral (artikkel I).
2. Uurida adipoossuse mõju vaskulaarsele kaltsifitseerumisele KNH-ga patsientidel (artikkel I).
3. Selgitada välja seosed vaskulaarse kaltsifitseerumise ja luukoe tiheduse vahel KNH-ga patsientidel (artikkel II).
4. Hinnata kõhuaordi kaltsifitseerumise ja perifeerse arteriaalse haiguse prognostilist mõju kardiovaskulaarsetele tüsistustele ja üldsuremusele peritoneaaldialüüsravil olevatel KNH-ga patsientidel (artikkel III).
5. Hinnata vaskulaarse kaltsifitseerumise prognostilist väärtust pikaajalises ravitulemis adipoossetel ja mitteadipoossetel KNH-ga patsientidel (artikkel IV).

Uuritavad ja meetodid

Uuringu põhikohort koosnes 168 järjestikusest KNH erinevate raskuskategooriatega patsiendist, kes olid nefroloogide jälgimisel. Patsiendid kaasati uuringusse aastatel 2012–2019. Kõik patsiendid said ravi parimate rahvusvaheliste ravijuhiste kohaselt.

Uuring I: Prospektiivne läbilõikeuuring viidi läbi Tartu Ülikooli Kliinikumi Sisekliinikus ning hõlmas kogu kohorti (n = 168). Uuringus võrreldi VK-d adipoossetel ja mitteadipoossetel KNH-ga haigetel, et hinnata adipoossuse mõju VK-le.

Uuring II: Prospektiivsesse läbilõikeuuringusse VK ja MLH seoste kohta kaasati 90 patsienti põhikohordist (168 patsienti), kellele oli tehtud kogu keha luudensitomeetriline uuring (ingl *dual-energy X-ray absorptiometry,* DEXA) uuring ja kelle puhul olid uuringu tulemused kättesaadavad.

Uuring III: Prospektiivses vaatlusuuringus, mille jälgimisperiood oli 1–61 kuud (mediaan 46 kuud), hinnati aordi kaltsifitseerumise ja perifeerse arteriaalse haiguse prognostilist rolli suremuse ja kardiovaskulaarsete sündmuste puhul KNH-ga patsientidel, kes olid peritoneaaldialüüsravil. Tegemist oli rahvusvahelise koostööprojektiga, kus patsientide andmeid koguti Rootsist, Soomest, Taanist, Lätist ja Eestist (kokku n = 249). Meie patsientide põhikohordist kaasati uuringusse 20 peritoneaaldialüüsravi saavat patsienti.

Uuring IV: Prospektiivsesse vaatlusuuringusse kaasati 150 patsienti põhikohordist, et hinnata 11,2-aastase jälgimisperioodi jooksul VK prognostilist väärtust adipoossetel ja mitteadipoossetel patsientidel.

Osalemine oli vabatahtlik ja kõik osalejad andsid kirjaliku nõusoleku. Uuring koosnes ühest külastusest, uuringupäeval viidi läbi meditsiiniline intervjuu ning täideti küsimustikud. Teostati füüsiline läbivaatus, võeti vere- ja uriiniproovid. Kehamassiindeks (ingl *body mass index*, BMI) arvutati standardvalemi järgi: BMI (kg/m^2) = kehakaal (kg) / kehapikkus (m^2). Maailma Terviseorganisatsiooni kriteeriumide järgi on alakaalulisus BMI < 18,5 kg/m^2, normaalne kaal BMI < 25 kg/m^2, ülekaalulisus BMI 25–29,9 kg/m^2 ja rasvumine BMI ≥ 30 kg/m^2 (WHO, 2010). Kõhuaordi kaltsifitseerumise (ingl *abdominal aortic calcification*, AAC) hindamiseks kasutati nimmepiirkonna külgprojektsioonis röntgenülesvõtteid, mida hinnati Kauppila skoori järgi (Kauppila *et al*, 1997). Perifeersete veresoonte hindamiseks kasutati hüppeliigese-õlavarre indeksit (ingl *ankle-brachial index*, ABI), kus ABI väärtused ≥ 1,3 on seotud peamiselt veresoonte kaltsifitseerumisega ning < 0.9 perifeerse vaskulaarse haigusega. Südameklappide kaltsifikaatide ja vasaku vatsakese hüpertroofia (VVH) tuvastamiseks kasutati ehhokardiograafiat ning luukoe tiheduse uurimiseks DEXA uuringut.

Peamised tulemused

Adipoossuse mõju vaskulaarsele kaltsifitseerumisele KNH-ga patsientidel

Kõhuaordi kaltsifitseerumist kajastav skoor oli võrdne adipoossete (BMI ≥ 30 kg/m^2) ja mitteadipoossete (BMI < 30 kg/m^2) haigete rühmades. Skoor oli kõrgem adipoossete haigete langenud neerufunktsiooniga (eGFR < 45 ml/min) alarühmas võrreldes nendega, kelle neerufunktsioon oli säilinud (eGFR ≥ 45 ml/min). Võrreldes adipoosseid ja mitteadipoosseid langenud neerufunktsiooniga (eGFR < 45 ml/min) patsiente, leidsime, et adipoossetel esines AAC-d rohkem.

Kõrge ABI (≥ 1,3) esines nii adipoossetel kui ka mitteadipoossetel patsientidel ilma olulise statistilise erinevuseta. Langenud neerufunktsiooniga (eGFR< 45 ml/min) adipoossetel haigetel oli kõrge ABI sagedasem leid võrreldes nendega, kelle neerufunktsioon oli säilinud (eGFR ≥ 45 ml/min).

Südameklappide kaltsinoosi ja fibroosi esinemissagedus oli kõrge nii adipoossete kui ka mitteadipoossete rühmas.

VVH leid oli sage mõlemas rühmas ilma statistiliselt olulise erinevuseta. VVH esinemissagedus oli kõrgem kehvema neerufunktsiooniga patsientidel olenemata kehamassi indeksist.

Seosed vaskulaarse kaltsifitseerumise ja luukoe mineraalse tiheduse vahel KNH-ga patsientidel

Kõhuaordi kaltsifitseerumine oli pöördvõrdelises seoses reieluukaela ja kogu lülisamba luutihedusega. Normist kõrgem või madalam ABI oli samuti pöördvõrdeliselt seotud reieluukaela, lülisamba L1–L4 ja roiete luutihedusega. Reieluu, reieluukaela ja kogu keha luutihedus oli seotud südameklappide kahjustustega. Lisaks leidsime seoseid südameklappide kahjustuste ja kõrge ABI vahel.

Kõhuaordi kaltsifitseerumise ja perifeersete arterite haiguse prognostiline roll lõppstaadiumis KNH-ga patsientidel

Kõrgem iga, raske kõhuaordi kaltsifitseerumine (Kauppila skoor ≥ 7), normist kõrgem või madalam ABI, diabeet, perifeersete arterite haiguse anamnees ja madal seerumi albumiini tase olid seotud üldsuremusega peritoneaaldialüüsil olevatel KNH-ga haigetel. Mõõdukas kuni raske kõhuaordi kaltsifitseerumine, normist kõrgem või madalam ABI, diabeet, perifeersete arterite haiguse anamnees ja madal seerumi albumiini tase olid seotud uute VK tüsistuste esinemisega.

Raske kõhuaordi kaltsifitseerumine oli suremuse tugev ennustaja.

Madala ja kõrge ABI ning raske kõhuaordi kaltsifitseerumisega patsientide suremus oli kõrgem võrreldes nendega, kellel esines kõhuaordi kaltsifitseerumine, aga ABI oli normis.

Vaskulaarse kaltsifitseerumise prognostiline väärtus pikaajalistele tulemustele adipoossetel ja mitteadipoossetel KNH-ga patsientidel

Adipoossete patsientide rühmas oli VVH ainus oluline VK tüsistuste ja suremuse ennustaja. Mitteadipoossete haigete seas (BMI < 30 kg/m^2) olid VK tüsistuste ja suremuse ennustajad ABI, VVH (ainult VK tüsistuste puhul) ja südameklappide kahjustus.

VK parameetrites ei esinenud erinevusi kahe rühma vahel ning tüsistuste ja suremuse esinemissagedus oli sarnane.

Järeldused

1. Vaskulaarne kaltsifitseerumine oli kõige enam väljendunud adipoossetel, langenud neerufunktsiooniga patsientidel.
2. Adipoossusel ei olnud kaitsvat efekti vaskulaarsele kaltsifitseerumisele KNH-ga patsientidel. Siinse uurimistöö tulemused ei toetanud nn adipoossuse paradoksi ei kogu rühmas ega ka erinevate KNH raskuskategooriaga alarühmades.

3. Kõhuaordi, perifeerse vaskulaarse kaltsifitseerumise ning luukoe mineraalse tiheduse vahel oli pöördvõrdeline suhe. Lisaks esines perifeerse vaskulaarse kaltsifitseerumise seos südameklappide kahjustusega.
4. Reieluu, reieluukaela ja kogu keha luu mineraalne tihedus oli seotud südameklappide kahjustusega. Kõhuaordi ja lülisamba kõhrkoe kaltsifikaatide tõttu on kogu keha DEXA uuringu kasutamine KNH-ga haigete puhul luu mineraalse tiheduse hindamiseks sobivaim meetod.
5. Väljendunud kõhuaordi kaltsifitseerumine oli KNH-ga patsientidel oluline üldsuremuse ja südame-veresoonkonna tüsistuste prognostiline marker. Perifeersel vaskulaarsel haigusel ei olnud prognostilist mõju ei uutele kardiovaskulaarsetele tüsistustele ega ka üldsuremusele.

Vaskulaarne kaltsifitseerumine oli ebasoodne prognostiline marker, mis suurendas südame-versoonkonna tüsistuste riski ja halvendas kroonilise neeruhaiguse kulgu.

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15. PUBLICATIONS

16. CURRICULUM VITAE

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Education and professional employment:

1988–1996	Narva 1st School
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2000–2006	University of Tartu, Faculty of Medicine, Medicine
2006–2008	University of Tartu, Faculty of Medicine, Residency of family medicine
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2012–2025	University of Tartu, Faculty of Medicine, PhD student
2012–2016	Specialist, Institute of Clinical Medicine, University of Tartu
2014–…	Nephrologist, Department of Internal Medicine, Tartu University Hospital
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List of publications in international peer-reviewed journals:

1. Uhlinova J., Kuudeberg, A., Denissova, A., Ilves, P., Lember, M., Ots-Rosenberg, M. (2022). Impact of obesity on vascular calcification in patients with chronic kidney disease. *Clinical nephrology*, *97*(1): 10–17. https://doi.org/10.5414/CN110523
2. Uhlinova, J., Kuudeberg, A., Metsküla, K., Lember, M., Ots-Rosenberg, M. (2022). Significant associations between bone mineral density and vascular calcification in patients with different stages of chronic kidney disease. *BMC nephrology*, *23*(1): 327. https://doi.org/10.1186/s12882-022-02955-9
3. Mäkelä, S., Asola, M., Hadimeri, H., Heaf, J., Heiro, M., Kauppila, L., Ljungman, S., Ots-Rosenberg, M., Povlsen, J. V., Rogland, B., Roessel, P.,

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6. Uhlinova, J., Pechter, U., Kermes, K., & Ots-Rosenberg, M. (2011). Peritoneal Dialysis Penetration and Peritonitis Rate at a Single Centre during Last Decade. *International journal of nephrology*, *2011*, 470426. https://doi.org/10.4061/2011/470426

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2006–2008	Tartu Ülikool, Arsteteaduskond, residentuur peremeditsiini erialal
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2014–...	Nefroloog, Ida-Viru Keskhaigla
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Liikmelisus erialaseltsides

Eesti nefroloogide Selts
Eesti Arstide Liit

Teadustöö suunad

Krooniline neeruhaigus, kehakoostis, luukoe mineraalne tihedus, adipoossus, vaskulaarne kaltsifitseerumine

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3. Mäkelä, S., Asola, M., Hadimeri, H., Heaf, J., Heiro, M., Kauppila, L., Ljungman, S., Ots-Rosenberg, M., Povlsen, J. V., Rogland, B., Roessel, P., Uhlinova, J., Vainiotalo, M., Svensson, M. K., Huhtala, H., Saha, H. (2018). Abdominal aortic calcifications predict survival in peritoneal dialysis patients. *Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis*, *38*(5): 366–373. https://doi.org/10.3747/pdi.2017.00043
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