Determinants and Consequences of Nutritional Status in Patients with Chronic Kidney Disease

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Scientific environment

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Helene Dahl

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List of abbreviations

ALM	Appendicular lean mass
ALMI	Appendicular lean mass index
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CKD	Chronic kidney disease
CNI	Calcineurin inhibitor
CVD	Cardiovascular disease
DEXA	Dual-energy x-ray absorptiometry
ESKD	End-stage kidney disease
EPO	Erythropoietin
ESPEN	European Society for Clinical Nutrition and Metabolism
EWGSOP	European Working Group on Sarcopenia in Older People
eGFR	estimated glomerular filtration rate
HD	Haemodialysis
HGS	Handgrip strength
HRQOL	Health-related quality of life
ISRNM	International Society of Renal Nutrition and Metabolism
KDIGO	Kidney disease – Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative

MUAC	Mid-upper arm circumference
MUAMA	Mid-upper arm muscle area
NODAT	New-onset diabetes after transplantation
NRS2002	Nutritional risk screening 2002
PD	Peritoneal dialysis
PEW	Protein-energy wasting
PTH	Parathyroid hormone
RAAS	Renin-angiotensin-aldosterone system
RRT	Renal replacement therapy
WHO	World Health Organization

Abstract

Background: Patients with chronic kidney disease (CKD) face numerous challenges regarding their nutritional status due to their reduced kidney function, consequently change in metabolism, frequent comorbidities, and concomitant polypharmacy. Nutritional status may be assessed by measurements of anthropometry, body composition, dietary intake and biochemical markers. However, the determinants and consequences of nutritional status in the continuum of chronic kidney disease are not well described.

Aims: The overall aim of this PhD project was to study nutritional status and the indicators of nutritional status in patients at different stages and treatment modalities of CKD and to investigate possible determinants and consequences of impaired nutritional status.

The specific aims were 1) to assess nutritional status comprehensively, 2) to describe the medication prescription and investigate the association with nutritional status, and 3) to investigate whether indicators of nutritional status are associated with mortality risk in patients along the continuum of CKD.

Methods: Patients with pre-dialysis CKD stages 3-5, end-stage kidney disease treated with haemodialysis and kidney transplanted patients were included in this PhD project, consisting of two cross-sectional studies and one longitudinal study. Nutritional status was thoroughly assessed at inclusion by measurements of anthropometry, muscle strength and body composition, assessment of dietary intake by a 24-hour dietary recall, and biochemical measurements. We identified patients with sarcopenia (European Working Group of Sarcopenia in Older People 2 criteria), at risk of undernutrition (Nutritional Risk Screening 2002), and central obesity (WHO criteria). Further, we collected information about prescribed medications and structured the medications according to the common or very common side effects of nausea and xerostomia. Finally, we collected information about mortality two years after inclusion.

Results: We identified a high prevalence of overweight and obesity, as well as central obesity and sarcopenia. There was a low overall prevalence of undernutrition in patients along the continuum of CKD, while more prevalent in patients receiving haemodialysis.

Furthermore, we observed a high prevalence of polypharmacy and excessive polypharmacy in the study population. The number of prescribed medications was inversely associated with markers of nutritional status such as mid-upper arm circumference, skinfold triceps, handgrip strength, serum albumin and haemoglobin in linear regression models adjusted for age, sex and kidney function. Prescribed medications with nausea as a side effect showed similar associations while medications with xerostomia as a side effect were associated with lower handgrip strength.

Finally, we investigated the two-year mortality risk associated with indicators of nutritional status in CKD patients. Sarcopenia was associated with mortality risk in Cox regression analyses adjusted for age and kidney function, while central obesity was not associated with mortality risk. Other markers of nutritional status, especially those related to muscle mass and strength, were associated with mortality risk, including handgrip strength, phase angle, and mid-upper arm circumference.

Conclusion: Our findings indicate that patients with CKD have several challenges related to nutritional status, including overweight, obesity, central obesity, and sarcopenia. Patients with CKD were prescribed a high number of medications, and CKD patients with long medication lists may be at risk of impaired nutritional status. We observed an increased mortality risk in patients with sarcopenia, but mortality was not associated with waist circumference or BMI. More research on the underlying causes of impaired nutritional status in CKD is required, such as sarcopenia, and the molecular mechanisms involved. The challenges of nutritional status observed in this project would not have been captured by the measurement of height and weight alone, and thus a more comprehensive nutritional assessment in regular patient care to identify the patients at risk of a suboptimal nutritional status is warranted.

Sammendrag

Bakgrunn: Pasienter med kronisk nyresykdom møter mangfoldige utfordringer vedrørende deres ernæringsstatus, relatert til redusert nyrefunksjon, påfølgende metabolske forandringer, mangfoldige komorbiditeter og polyfarmasi. Ernæringsstatus kan vurderes ved hjelp av antropometriske målinger, kroppssammensetning, kosthold og biokjemiske markører. Faktorer som er avgjørende for og konsekvenser av ernæringsstatus i et kontinuum av kronisk nyresykdom er ikke godt beskrevet.

Mål: Det overordnete målet var å studere markører og indikatorer for ernæringsstatus hos pasienter i ulike stadier og behandlingsmodaliteter av kronisk nyresykdom, samt undersøke mulige avgjørende faktorer og konsekvenser av ernæringsstatus.

De spesifikke målene var 1) Å gjøre en omfattende vurdering av ernæringsstatus, 2) å beskrive ordinering av medikamenter, samt sammenhengen mellom medikamenter og ernæringsstatus, 3) og å undersøke hvorvidt indikatorer for ernæringsstatus er assosiert med dødelighet hos pasienter med kronisk nyresykdom.

Metode: Pasienter med pre-dialytisk kronisk nyresykdom stadium 3-5, nyresvikt behandlet med hemodialyse og nyretransplanterte pasienter ble inkludert i dette prosjektet, bestående av to tverrsnittstudier og en oppfølgingsstudie. En omfattende vurdering av ernæringsstatus ble gjennomført ved inklusjon, ved hjelp av antropometriske målinger, kroppssammensetning, muskelstyrke, 24-timers kostintervju og biokjemi. Vi identifiserte også pasienter med sarkopeni (European Working Group of Sarcopenia in Older People 2-kriterier), i risiko for underernæring (Nutritional Risk Screening 2002) og med sentral fedme (WHO-kriterier). Videre samlet vi inn informasjon om ordinerte medikamenter og strukturerte disse etter hvorvidt de hadde kvalme eller munntørrhet som vanlig eller svært vanlig bivirkning. Til slutt samlet vi inn informasjon om dødelighet to år etter inklusjon.

Resultater: Vi fant en høy prevalens av overvekt og fedme, i tillegg til en høy prevalens av sentral fedme og sarkopeni hos pasienter med kronisk nyresykdom. I den

totale populasjonen fant vi en lav prevalens av risiko for underernæring, mens i pasienter behandlet med hemodialyse var dette et mer vanlig funn.

Vi observerte en høy prevalens av polyfarmasi og overdreven polyfarmasi i studiepopulasjonen. Antall ordinerte medikamenter var inverst assosiert med markører for ernæringsstatus, slik som overarmsomkrets, triceps hudfoldtykkelse, gripestyrke, serum albumin og hemoglomin i lineære regresjonsmodeller justert for alder, kjønn og nyrefunksjon. For ordinerte medikamenter med kvalme som bivirkning observerte vi liknende sammenhenger, mens for medikamenter med munntørrhet som bivirkning fant vi en sammenheng med gripestyrke.

Sarkopeni var assosiert med økt risiko for død etter to år, mens sentral fedme var ikke assoisert med økt risiko i Cox regresjonsanalyser justert for alder og nyrefunksjon. Andre markører for ernæringsstatus, spesielt de relatert til muskelmasse og -styrke var assoisert med dødelighet, inkludert gripestyrke, phase angle og overarmsomkrets.

Konklusjon: Våre funn indikerer at pasienter med kronisk nyresykdom har flere utfordringer relatert til ernæringsstatus, inkludert overvekt, fedme, sentral fedme og sarkopeni. Pasienter med kronisk nyresykdom er ordinert et høyt antall medikamenter, og pasienter med lange medikamentlister kan ha økt risiko for redusert ernæringsstatus. Vi har observert økt risiko for død i pasienter med sarkopeni, men fant ikke en sammenheng mellom sentral fedme og dødelighet, eller BMI og dødelighet. Mer forskning på underliggende årsaker for redusert ernæringsstatus i pasienter med kronisk nyresykdom er er nødvendig, slik som sarkopeni og relaterte molekylære mekanismer. Utfordringene relatert til ernæringsstatus som er observert i dette prosjektet ville ikke ha vært fanget opp ved målinger av vekt og høyde alene. En mer omfattende vurdering av ernæringsstatus trengs for å avdekke slike utfordringer i klinisk praksis.

List of Publications

Dierkes J, Dahl H, Welland NL, Sandnes K, Saele K, Sekse I, H.P. Marti. (2018) *High rates of central obesity and sarcopenia in CKD irrespective of renal replacement therapy – an observational cross-sectional study.* BMC Nephrol. Doi: 10.1186/s12882-018-1055-6.

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Related papers – not included in the thesis

Dahl H, Warz SI, Welland NL, Arnesen I, Marti HP, Dierkes J. (2021) *Factors associated with nutritional risk in patients receiving haemodialysis assessed by Nutritional Risk Screening 2002 (NRS2002).* J Ren Care. Doi: 10.1111/jorc.12374

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1. Introduction

1.1 Chronic kidney disease

The kidneys are involved in several vital processes in the body, including the production of urine, excretion of waste products from circulation, and homeostasis of acid-base, electrolytes, and blood pressure. Additionally, the kidneys are involved in the final hydroxylation of vitamin D and the production of erythropoietin (EPO) (1). A reduced kidney function will cause all the functions mentioned above to diminish, which will have great implications for metabolism and overall health.

Kidney disease – Improving Global Outcomes (KDIGO) has defined kidney disease as "*an abnormality of kidney structure or function with implications for the health of an individual, which can occur abruptly, and either resolve or become chronic*" (2). Reduced kidney function is classified as either acute kidney injury or chronic kidney disease (CKD). CKD is diagnosed when an impairment of kidney function is present for at least three months and measured twice. CKD can be defined by a decreased estimated glomerular filtration rate (eGFR) (< 60 ml/min/1.73 m^2) or as abnormalities of kidney structure or function, despite normal eGFR (2).

The glomerular filtration rate (GFR), the rate at which fluid is filtrated through the kidneys, is considered an overall measure of kidney function. As GFR is not easy to measure directly, equations based on age, sex, race, and serum levels of creatinine and/or cystatin C are applied to calculate eGFR. Creatinine is a non-enzymatic breakdown product from creatine phosphate in muscle mass that is unchanged and excreted through the kidneys. Serum creatinine has therefore been applied as a marker of kidney function for decades. However, serum creatinine may be influenced by other factors, such as dietary protein intake, physical activity, and muscle mass, and thus not a predictor of the true kidney function (3,4). Cystatin C is a small protein and protease inhibitor that is produced by all nucleated cells at a constant rate and freely filtrated in the renal glomeruli with no reabsorption. The effect of non-renal determinants is reported to be smaller on cystatin C than on serum creatinine (4). Thus, cystatin C has

been suggested as a more precise marker for kidney function, but analyses of cystatin C are not widely performed as a routine in clinical settings. Several equations for eGFR based on either creatinine, cystatin c or both exist, and today the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) based on creatinine measures from 2009 is most commonly used for the calculation of eGFR (5–7).

Another marker for kidney function, in addition to eGFR, is the excretion of proteins, which is absent or present in minimal concentrations in healthy kidneys. In kidney disease, the appearance of albumin or other proteins in urine is common, thus, albuminuria or the albumin to creatinine ratio in urine are used as diagnostic criteria (see Section 1.1.3).

1.1.1 Epidemiology of chronic kidney disease

The global burden of CKD has been increasing in recent decades, and it is predicted that the impact of CKD will continue to grow in the years to come (8,9). In 2017, it was estimated that globally, 1.2 million people died from CKD, which is an increase of 41.5 % since 1990. The estimated global prevalence of CKD was 9.1 % in 2017, which comprises approximately 700 million individuals. Since 1990, there has been an increase of approximately 30 % in CKD prevalence. In Norway, the prevalence of CKD has been stable at 11 % in the last decade (10). Still, CKD is under-recognised by many patients and clinicians (11).

In the general population, renal function generally decreases with age, and consequently, the prevalence of CKD increases with age, which is also evident in the Norwegian population (10,12,13). The prevalence of CKD is estimated to increase in the future due to the ageing population, as well as the growing prevalence of life-style related conditions such as diabetes, hypertension and obesity, which are well-established risk factors for CKD (see Section 1.1.2) (8,14–16).

CKD is a progressive disease and may eventually end up as end-stage kidney disease (ESKD) requiring renal replacement therapy (RRT), which can either be given as dialysis or kidney transplantation. Worldwide, more than 2.5 million people with ESKD were treated with renal replacement therapy (RRT) in 2010, and estimates

predict that 5.4 million people will be in need of RRT in 2030. A shortage of RRT services is already present in many countries, especially in low-income regions in Asia and Africa. It is estimated that 1 in 1000 Europeans receive RRT (17). According to the annual report published by the Norwegian Renal Registry, there were 5,450 individuals in Norway who received RRT by the end of 2020, equivalent to 1,015 patients per 1 million inhabitants (18). There is an annual increase of approximately 100 patients receiving RRT per year, and the mean age of patients receiving RRT was 62.2 years, ranging from 1.9 to 89.8 years, where 67.8 % of the patients were male. An elaboration on ESKD and RRT will be given in Section 1.1.3.

Altogether, the burden of CKD is significant, both on society and the patient, and this calls for further development concerning the prevention and treatment of CKD.

1.1.2 Primary causes of chronic kidney disease

CKD is a heterogeneous group of diseases, and the classification according to eGFR gives no immediate information about the underlying diagnosis. The primary causes of CKD vary globally, both geographically and according to socioeconomic status. Overall, diabetes and hypertension are considered major causes of CKD, especially in high- and middle-income countries, but also in low-income countries (1). In Asia, India and sub-Saharan Africa, glomerulonephritis is a common primary cause, as well as CKD with unknown aetiology. Infection with the human immunodeficiency virus (HIV) also represents a common cause of CKD, especially in sub-Saharan Africa. CKD may also be caused by genetic conditions, such as congenital abnormalities or autosomal dominant polycystic kidney disease; however, these represent a low percentage of the total population with CKD (1).

In Norway, there are no systematic data available on primary causes of CKD in the milder stages of the disease, but the annual report from the Norwegian Renal Registry provides information about primary kidney disease at the start of RRT. In 2020, vascular/hypertensive diseases were the most common causes (32 %), followed by glomerulonephritis (18%), and diabetic nephropathy (17%) (18).

Hypertension has been recognised as one of the major primary causes of CKD, and the increasing prevalence of hypertension in the general population may partly explain the increase in the prevalence of CKD (19). From 1990 to 2019, the disease burden of CKD due to hypertension has increased by 125.2 % according to disability-adjusted life years (DALYs), while the age-standardised DALY was quite stable, an indication of an ageing population (20). Hypertension may also be a consequence of CKD, which will further be elaborated in Section 1.1.4. Hypertension increases the risk of vascular disease in the renal arteries and glomerular arterioles; glomerulosclerosis; interstitial fibrosis and tubular atrophy, all factors increasing the risk of CKD (1).

Another major primary cause of CKD is diabetes. The global prevalence of diabetes has increased since 1980 (15). In 2021, the International Diabetes Federation estimated a global diabetes prevalence of 10.5 % in adults aged 20-79 years, and it is projected that the prevalence will increase to 12.2 % by 2045 (21). The estimated risks of developing diabetic nephropathy with type 1 and 2 diabetes are 25-40 % and 5-40 %, respectively (22). However, type 2 diabetes accounts for the vast majority of diabetes (90 %), and consequently it will be more prevalent as a primary cause of CKD (23–26). The mechanisms connecting diabetes and CKD are complex, and several pathways are involved. The presence of hyperglycaemia plays a role through the production of advanced glycation end-products (AGEs) and reactive oxygen species; and the insulin resistance and hyperinsulinemia may also play significant roles. The activation of renin-angiotensin-aldosterone system (RAAS) is also involved, as well as glomerular lesions, similar to the consequence of hypertensive nephropathy may be observed (27).

According to World Health Organization (WHO), the worldwide prevalence of obesity has tripled since 1975. In 2016, more than 650 million adults were considered obese and 1.9 billion overweight (28). WHO also reports that today, more people die of causes related to overweight and obesity than causes related to underweight, and there are more obese than underweight people in the world (28). These numbers emphasise the gravity of the epidemic of overweight and obesity, which is considered one of today's major health challenges. Overweight and obesity are related to both

hypertension and diabetes type 2, but obesity has also been described as an individual risk factor for CKD (29–31). The mechanisms behind the direct association between overweight, obesity and CKD remain unclear, but hyperfiltration may be pivotal. Proposed mechanisms are mediated through the production of adiponectin, leptin and resistin, among others, which are involved in inflammation, oxidative stress abnormal lipid metabolism, activation of RAAS, and increased production of insulin and insulin resistance (30).

1.1.3 Progression of chronic kidney disease

CKD is a progressive disease that can be categorised in stages by either eGFR (**Table 1**) or eGFR in combination with albuminuria (urinary albumin excretion of < 30 mg/d, 30-300 mg/d, > 300 mg/d, classified as A1, A2, A3, respectively) (2).

Table1: Classification of stages of chronic kidney disease by estimated glomerular filtration rate (2)

Stage	eGFR, ml/min/1.73 m^2	Description of kidney function
1	≥ 90	Normal or high
2	60-89	Mildly decreased
3a	45-59	Mildly to moderately decreased
3b	30-44	Moderately to severely decreased
4	15-29	Severely decreased
5	< 15	Kidney failure/ESKD

eGFR indicates estimated glomerular filtration rate; ESKD, end-stage kidney disease. In stages 1-2, kidney damage must be present to fulfil diagnostic criteria of chronic kidney disease, such as albuminuria, abnormalities in urine (e.g., haematuria, red cell casts etc.), abnormalities in electrolyte levels due to tubular disorders, abnormalities detected by histology or imaging, or a history of transplantation.

In the early stages of CKD, many patients are asymptomatic and often unaware of their decreased kidney function (32). As kidney function declines, the implications of health caused by CKD will be more evident, and symptoms presented in the Section 1.1.4 will arise. In the early stages, the treatment goal is to manage the symptoms of the kidney

disease and the following comorbidities, as well as slow the progression of CKD by also treating the underlying disease.

If CKD progresses to CKD stage 5, also called kidney failure or ESKD, kidney function is so diminished that long term prospects of survival are dependent on RRT. The progression rate of kidney disease will depend on the primary cause of CKD, as well as other exposures and treatment, and it can take months or even decades to progress to ESKD. Not all patients progress to ESKD, and studies have shown that patients with CKD are at greater risk of death than those progressing to ESKD (33,34). Nevertheless, a substantial proportion of patients rely on RRT, which consists of either treatment by dialysis or kidney transplantation. If neither dialysis nor kidney transplantation is possible, treatment options that increase survival or quality of life, such as conservative treatment, may be an alternative (35).

Despite kidney transplantation being considered the gold standard for RRT, most patients with ESKD are treated with dialysis (17). Globally in 2017, it was estimated that 280 per one million people were treated with dialysis, compared to the prevalence of 65 per one million people who were kidney transplanted (1). Not all patients are suited for transplantation, and a proportion of patients may also require dialysis treatment while waiting for kidney transplantation.

Dialysis treatment is divided into two main groups: haemodialysis (HD) and peritoneal dialysis (PD). In-centre HD is the most common RRT for CKD patients and involves treatment two-four times a week (36). The principle of dialysis treatment is common for both HD and PD: excess fluid and electrolytes are removed, as well as urea and other compounds in the circulation such as by-products of protein metabolism, and body buffers are restored (37). In HD, the patients are connected to a dialysis apparatus, where the blood is transported through the capillaries surrounded by a dialysis solution within the dialysis filter. The semipermeable membrane in the dialysis filter allows compounds to cross according to the principles of diffusion, osmosis and ultrafiltration (38). The process is regulated by blood/dialysate flow rates, duration of dialysis and composition of dialysis solution. The principle for PD is similar to HD, except for the

blood being filtered through the membrane of the peritoneal cavity instead of the dialysis apparatus. Additionally, the dialysate contains an osmotic agent, most often a high concentration of glucose to effect ultrafiltration (39). However, newer solutions without glucose functioning as osmotic agents exist. These include, either icodextrin or amino acids, which enable PD treatment for patients with, e.g, diabetes (40). Dialysis treatment in general cannot replace complete kidney function, but it can sufficiently function to sustain life.

Kidney transplantation is the treatment of choice for patients who require RRT. Kidney transplant recipients have a better life expectancy and quality of life compared to age-matched patients on dialysis (41,42). In addition, the risk of death in the long-term for kidney transplant patients is considered less than half the risk among patients receiving dialysis treatment (43,44). From an economic perspective, kidney transplantation is more cost-effective compared to dialysis treatment (45–47). In Norway, it was estimated in 2014 that dialysis patients cost society at least half a million NOK each year, while transplanted patients cost 25 % of this sum the first year after transplantation (48).

However, as not all patients are suitable for kidney transplantation, eligibility should be carefully evaluated. Common exclusion criteria include major comorbidities that may disqualify major surgery or chronic immunosuppression after transplantation; addiction to alcohol or other substances; and possibly a cognitive status that precludes regular use of prescribed medication (49). Exessive weight may also be a contraindication (50). There are several factors affecting the outcome of the transplantation. Good matching of the human leucocyte antigens (HLA) between the transplant recipient and the donor is shown to be an advantage for graft survival. Patients with a delayed graft function after transplantation might require a certain period of dialysis, which is associated with reduced one-year graft survival. Survival prospects are also associated with the age of the patient, with increased estimated survival for patients aged 15 to 55 years (51).

Kidney transplantation can be done by donation from living or deceased donors. Living donors offer huge advantages for the patient and transplant survival as it is possible to plan the transplantation and even avoid dialysis (17,48). It also offers the advantage compared to transplants with long cold ischemia time. In Europe, 29 % of kidney transplantations in 2019 were from living donors, and similar numbers are reported in Norway (17,18). For deceased donors, Scandiatransplant facilitates organ exchange within the Scandinavian countries; nevertheless, more than 90 % of Norwegian recipients receive kidneys from within Norway (48,52). All solid organ transplantations in Norway are performed at one hospital, Oslo Universitetssykehus, Rikshospitalet.

1.1.4 Implications of health and treatment

Early detection is key in preventing the progression of CKD. However, CKD is also a silent disease at its early stages, which makes it challenging to detect, both for the patient and the physician. Screening, in terms of measurement of blood pressure and creatinine/proteinuria measurements and registries, would be beneficial for early detection (53). Early detection also enables the gradual adaptation of the patient's diet and nutritional education, making it possible to take one step at a time (20).

As CKD progresses, the condition will implicate health in multiple ways. Changes in metabolism occur and comorbidities are common (54). Additionally, the course of CKD and any following symptoms and comorbidities usually require multiple prescribed medications, associated with several side effects. Due to the nature of the disease and following comorbidities, CKD has been considered a model of accelerated ageing (55). In the following sections, the different aspects of health implications related to CKD will be presented. An overview of the presented implications is given in **Figure 1**.

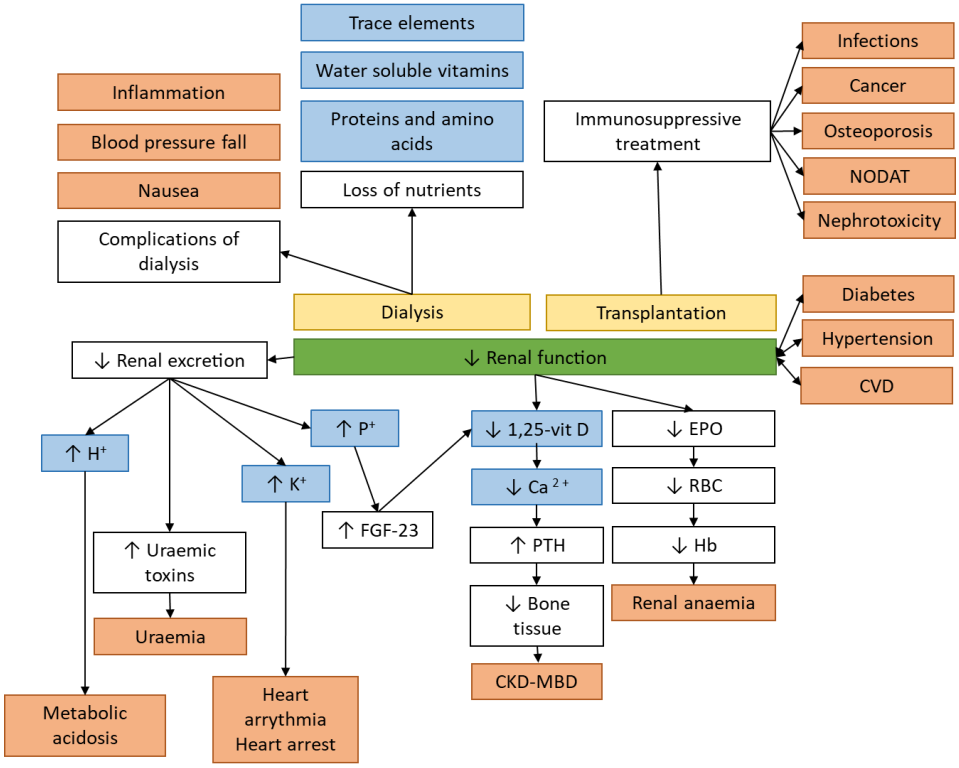

Figure 1: Overview of health implications related to decreased renal function.

Note that this is a simplified overview. Blue boxes represent nutrients and components; orange, health implications; yellow, treatment modalities of CKD; white, intermediate steps to health implications. 1,25-vit D indicates 1,25dihydroxyvitamin D; CKD-MBD, chronic kidney disease mineral bone disorder; CVD, cardiovascular disease; EPO, erythropoietin; FGF-23, fibroblast growth factor 23; Hb, haemoglobin, NODAT, new-onset diabetes after transplantation; PTH, parathyroid hormone; and RBC, red blood cells.

Uraemia

When the waste products of protein degradation are not effectively removed from circulation by the kidneys an accumulation of waste products and uraemic toxins will occur in the circulation. This condition is known as uraemia and is associated with systemic inflammation, oxidative stress, immune dysfunction, vascular disease, alteration in the gut microbiota, as well as the progression of CKD (1,56). The symptoms are diffuse and may be a challenge to identify as connected to impaired kidney function. Common symptoms are nausea, itching of the skin, and taste changes

(57). Restriction of the dietary intake of proteins may ameliorate/prevent uraemic symptoms for a while in patients with advanced kidney failure (58).

Metabolic acidosis

The maintenance of arterial blood pH and bicarbonate levels have a narrow range of normal values. A measure of serum bicarbonate < 22 mmol/L is defined as metabolic acidosis in patients with normal pulmonary function and is commonly observed in patients with CKD, with increasing prevalence as CKD advances (59,60). The kidneys in moderate/advanced renal failure cannot regulate pH homeostasis sufficiently by the excretion of acid through the kidneys. If not treated, metabolic acidosis may contribute to reduced bone density and muscle function (61). Metabolic acidosis may also accelerate the progression of CKD if not treated, as it is associated with increased systemic and kidney inflammation, insulin resistance, decreased albumin synthesis and increased risk of cardiovascular disease (CVD). Treatment with oral bicarbonate is often necessary in CKD. Additionally, studies on dietary interventions with higher intakes of fruits and vegetables have shown promising results (62).

Renal anaemia

In CKD, the production of EPO is reduced, which stimulates the production of red blood cells in the bone marrow and regulates the homeostasis of haemoglobin. Levels of hepcidin are increased in CKD, a peptide hormone involved in iron metabolism, which is stimulated by increased iron uptake and an inflammatory state (63). Thus, the uptake of iron from the gut and release from iron stores may be reduced at the same time as the production of red blood cells is reduced, resulting in renal anaemia. Concurrent uraemia may shorten red blood cell survival, thus worsening the state of anaemia, with increasing significance as kidney function declines (11,64). Renal anaemia is associated with CVD, more frequent hospital admission, cognitive impairment, reduced quality of life, and mortality (65,66). Other clinical manifestations of renal anaemia are fatigue, decreased exercise tolerance, dysphagia, depression, increased incidence of infections and restless legs syndrome. Treatment with oral or intravenous iron supplementation, as well as erythropoiesis-stimulating agents (ESAs), is commonly used to treat renal anaemia (1).

Hyperkalaemia

Potassium is the most potent intracellular electrolyte, and small changes in serum levels may cause muscle weakness, unwellness and disturbances in the cardiac system (67,68). Both hypo- and hyperkalaemia are associated with increased risk of mortality, CVD risk and progression to ESKD. As eGFR decreases, the requirement for the dietary restriction of potassium to strive for normal serum levels becomes more prevalent (58). However, there are several non-dietary causes of hyperkalaemia in CKD including interactions with glucose metabolism, acidosis, medication interactions, catabolism or breakdown of tissue, gastrointestinal symptoms or other diseases that may cause hyperkalaemia (69,70).

Mineral bone disorder/Osteoporosis

Reduced kidney function affects the ability to excrete excess phosphate, as well as the ability to produce 1,25-dihydroxy vitamin D. Consequently, serum levels of phosphate will increase, which will cause an increase in fibroblast growth factor 23 (FGF-23), which will lead to a further decreased hydroxylation of 25-hydroxyvitamin D in the kidneys (1). The reduction of 1,25-dihydroxy vitamin D will cause reduced uptake of both phosphate and calcium in the intestines, which will give a reduced level of calcium in serum. This will stimulate the increased release of parathyroid hormone (PTH), which will increase bone osteoclast activity and thus the breakdown of bone tissue to maintain calcium homeostasis in serum. Clinical manifestations in terms of osteoporosis are most evident in patients with ESKD, but it is also observed in earlier stages of CKD (31,71). The associated fracture risk with osteoporosis is also increased in patients with CKD compared to the general population, especially hip fracture risk with an increased fracture risk as eGFR decreases (72). Supplementation of vitamin D and restriction of dietary phosphate intake are common strategies for preventing mineral bone disorder in CKD (25).

Hypertension

Due to hypertensive nephropathy being one of the most common causes of CKD, and the increased risk of hypertension when CKD is established, a large proportion of patients with CKD are identified with hypertension. It is estimated that 70-85 % of

patients with CKD have hypertension (54,73). Hypertension and CKD are closely linked in pathophysiology, and the conditions may amplify each other if not treated (74). Several aspects of the pathophysiology of CKD may contribute to an increased risk of hypertension, such as sodium retention/overhydration, increased activity of the RAAS system, secondary hyperparathyroidism, and uraemia (32). Additionally, treatment with EPO may have a side effect of increased blood pressure (75). Other conditions related to CKD may also increase the risk and severity of hypertension, such as obesity and diabetes. Treatment of hypertension is essential to the management of CKD, and may consist of weight management, dietary restriction of salt intake, prescription of RAAS blockers, and blood pressure-lowering medications (32).

Cardiovascular disease (CVD)

Among patients with CKD, the most prevalent cause of death is CVD (32). In patients with mild to moderate CKD, the risk of progressing to kidney failure is lower than the risk of cardiovascular mortality (76). In patients with CKD, decreased eGFR and presence of albuminuria are associated with an increased risk of CVD of two to four times, even after adjustment for traditional risk factors such as hypertension, hypercholesterolemia and lifestyle-related risk factors (76,77). After kidney transplantation, CVD is also the leading cause of late renal allograft loss (78).

The pathophysiological mechanisms linking CKD and CVD are complex and not fully understood. The associated risk in CKD may be related to the primary causality of CKD, such as diabetes, obesity, and hypertension. However, studies suggest that CKD propose a higher CVD risk, overshadowing the risk associated with diabetes and hypertension. There are also common risk factors for both CKD and CVD, such as dyslipidaemia, smoking, inflammation, and genetic risk factors. Added consequences following the course of decreased kidney function in terms of damage on glomeruli or interstitial damage such as disturbances in electrolyte balance and oedema will further increase the risk of CVD. The presence of chronic, low-grade inflammation is one of the main hallmarks in the development, progression and complication of CKD, as it can lead cause tissue damage and fibrosis (79). If CKD reaches severe stages and fibrosis arises, hormonal imbalances, anaemia and vascular calcification are common

(80). In addition, electrolyte disturbances can be more severe, and increased activity of PTH and the sympathic nerve system may further contribute to increased CVD risk. Atherosclerosis (vascular calcification), coronary artery disease, valvular disease, left-ventricular hypertrophy, decreased coronary perfusion, heart failure, arrhythmias and sudden cardiac death are common conditions for patients with CKD (76).

Dialysis treatment

In patients who are treated with dialysis, the implications mentioned above are applicable, but additional complications due to the dialysis treatment arise. Patients treated with dialysis are at risk of uraemic symptoms causing confusion, coma and eventually death, if not treated (81). The purpose of the dialysis treatment is to remove excess fluid and waste products from circulation, but nutrients may also be lost in the dialysis process. This applies mainly to water-soluble vitamins, amino acids, and proteins, and it increases the risk of a negative nitrogen balance (82,83). Indeed, studies have shown a loss of up to 12 g of amino acids during a single HD session (84). Other challenges related to dialysis are the fall in blood pressure directly after dialysis, low-grade inflammation, as well as symptoms of nausea, loss of appetite, and a decreased sense of smell and taste, leading to decreased dietary intake (83).

In dialysis, residual urine production is present in a proportion of the patients, often facilitated by the prescription of diuretics (85). The continuous fluid removal facilitates the regulation of fluid and electrolytes to some extent. Continued urine production in dialysis has been associated with beneficial outcomes, such as better nutritional status and increased survival (85–89).

Kidney transplantation and immunosuppressive treatment

After a successful kidney transplantation, renal function will improve and many of the consequences of decreased kidney function will diminish. However, some consequences and comorbidities will remain, and new ones will arise, mainly because of the immunosuppressive treatment following kidney transplantation.

Receiving a kidney transplant requires lifelong suppression of the recipient's immune system to avoid rejection of the organ (90). It is recommended to start with

immunosuppressive medications before, or at the time of, the kidney transplantation (44). Such induction therapy should be with a biologic agent, either a lymphocyte-depleting agent or an interleukin 2 receptor antagonist (IL2-RA). This should be followed by a Calcineurin inhibitor (CNI), Corticosteroid, and antiproliferative agent (44,48).

Table 2: Common medications applied in the immunosuppressive treatment regimen after kidney transplantation and associated side effects

Name (Commercial name)	Generic name	Associated side effects
Tacrolimus (Prograf) Cyclosporin (Sandimmun)	Calcineurin inhibitor	Nephrotoxicity, hypertension, ischemic cardiovascular disease, hyperglycaemia, NODAT, hyperlipidaemia, GI symptoms, inflammation, electrolyte disruption
Prednisone	Corticosteroid	Increased appetite, weight gain, glucose intolerance, sodium retention, hyperlipidaemia, hypertension, increased protein catabolism, osteoporosis, masking of infections,
Mycophenolate/Axathioprine (CellCept, Myfortic)	Antiproliferative agent	Leukopenia, thrombocytopenia, diarrhoea, nausea, vomiting

GI indicates gastrointestinal; and NODAT, new-onset diabetes after transplantation

These medications are necessary to prevent graft rejection; however, they also increase the risk of several side effects. Potential side effects include weight gain, hypertension, dyslipidaemia, and increased risk of virus infections (91,92). An increased risk of several other conditions is also associated with immunosuppressive treatment, such as osteoporosis, new-onset diabetes after transplantation (NODAT), CVD, and malignancies, especially skin cancer and lymphoma (1,93). Due to the suppressed immune system, patients are also at risk of food borne diseases. An overview of the common immunosuppressive treatment regimen and associated side effects can be found in **Table 2**. In addition, kidney transplanted patients are at increased risk of

reduced kidney function. This is partly due to the treatment with CNIs, but also due to high pressure on the one functioning kidney and the present risk of allograft rejection (94).

Polypharmacy

Due to the impaired kidney function and the frequent comorbidities, patients with CKD are at risk of being concurrently prescribed a high number of medications, known as polypharmacy (95,96). Historically, polypharmacy has been associated with negative connotations and considered inappropriate for the patient's overall health. Today, the term polypharmacy is used as a guide to identifying patients who require medical attention; however, polypharmacy has been associated with an increased risk of mortality, especially in individuals being prescribed >10 medications concurrently (97–99). Currently, there is no consensus definition of polypharmacy, and in a systematic review by Masnoon et al., 138 different definitions were found in the 110 included studies (97). The most common definition of polypharmacy was ≥ 5 concurrent medications, while excessive polypharmacy has most commonly been defined as ≥ concurrent 10 medications. Polypharmacy has also been associated with adverse outcomes for frailty, disability, falls and mortality (100).

Other implications

Patients with CKD have a decreased health-related quality of life (HRQOL), especially patients receiving dialysis (101). Common problems perceived are fatigue, frequent hospitalisation, surgery and time-consuming treatment, polypharmacy, immune deficiency, anaemia, altered physical appearance and uncertainty about the future (102). In dialysis patients, factors such as being eligible for transplantation or not, and the burden of comorbidities may influence the HRQOL (103,104). Kidney transplanted patients generally have an increased HRQOL, compared to patients on dialysis and CKD patients not on dialysis, although not improved to the level of the general population (105). Strategies that prevent the incidence of CKD and patients progressing to ESKD are beneficial from a socioeconomic perspective due to the shortage of RRT and patient strain. Thus, prevention and treatment of nutritional challenges related to

increased risk of CKD, such as overweight, obesity, hyperglycaemia, and hypertension would also be beneficial for prevention of CKD (106).

It is also observed that patients with CKD have reduced participation in society (107). Unemployment is frequent among CKD patients, especially in ESKD, but also after kidney transplantation. In a Swiss study, unemployment rates as high as 75 % were reported (108).

Mortality

Patients with CKD have an increased risk of mortality compared to age-matched peers without CKD (109). The reduced life expectancy is associated with kidney function, also after adjustments for diagnosis of diabetes or hypertension (109–111). It is estimated that patients with eGFR < 60 mL/min/1.73 m^2 have a 57 % higher cardiovascular mortality compared to the general population, and the risk is 63 % higher in patients with micro-albuminuria.

In 2017, 1.2 million people died as a consequence of CKD (1,8). The burden of CKD is increasing, which is also mirrored in the risk of mortality which increased by 41.5 % from 1990 to 2017. According to the review of the global burden of disease numbers from 2017, CKD is particularly important to address and treat to reach the UN goal of a one-third decrease in deaths caused by non-communicable diseases by 2030 (8). According to estimates from the Global Burden of Disease study, CKD was the 12th leading cause of death in 2017, compared to being the 17th leading cause of death in 1990 (8). In 2040, it is estimated to be the 5th leading cause of death (9).

1.2 Nutritional status in chronic kidney disease

Nutritional status is a comprehensive term, and several methods are are applied to assess nutritional status. According to the European Society of Clinical Nutrition and Metabolism (ESPEN), the assessment of nutritional status should include data on body weight, height, body mass index (BMI), body composition and biochemical indices (112). This assessment is often carried out by a dietitian. Disturbances in nutritional status can occur as either over- or undernutrition, or the abnormal metabolism of nutrients (113,114). Methods for assessing nutritional status are further described in the following sections.

1.2.1 Assessment of nutritional status

Anthropometry and body composition

Anthropometric measurements were defined by Jelliffe in 1966 as "*measurements of the variations of the physical dimensions and the gross composition of the human body at different age levels and degree of nutrition*" (115). Anthropometric measurements do not necessarily require advanced and expensive equipment and are easy to perform in a clinical setting, including in low-income countries. Today, anthropometric measurements are used to assess nutritional status, both on individual and population levels. The methods can be subdivided into two groups: The first group which provides information about body size, and the second group which provides information about body composition (116). Measurements and indicators of nutritional status used in this thesis are height, weight, BMI, waist circumference, mid-upper arm circumference (MUAC), skinfold triceps, skinfold biceps, mid-upper arm muscle circumference (MUAMC), mid-upper arm muscle area (MUAMA), bioelectrical impedance analysis (BIA), appendicular lean mass (ALM), and appendicular lean mass index (ALMI).

The measurement of MUAC is a measure of the subcutaneous fat and muscle in the arm, and a reduction in this measure indicates a reduction in either one of these components or both. By adding the measure of skinfold triceps, an estimate of the subcutaneous fat can be made, and these two measurements can then be combined to calculate MUAMC and MUAMA. Estimates of MUAC have been correlated with

nutritional status and are a widely used measure in emergencies, crisis, and famines. skinfold triceps has been proposed to reflect the proportion of total body fat, and estimations for total body fat can be done from the measurements of skinfold triceps (116).

The principle of BIA is that the conductivity of each tissue in the body is specifically based on the content of water and electrolytes in the tissue (117). Fat-free mass will lead electricity better than fat mass, which has an insulating function in the body. Body impedance is measured by the detection of electrical current, often of 800 μA and 50 kHz (Ω), sent through the body between two electrodes, e.g., on the ankle and wrist of an individual (116). Resistance, reactance, and phase angle are measured, and these measurements can be applied to calculate the proportion of fat-free mass, ALM and further ALMI. Such equations have been validated against dual-energy x-ray absorptiometry (DEXA), the golden standard for assessing body composition, also in patients with CKD (118–120). The phase angle is calculated from the arctangent of the resistance and reactance and is considered a measure of cell membrane integrity and vitality (121). Phase angle has been associated with nutritional status, and low phase angle has been associated with several adverse outcomes, such as morbidity and mortality both in CKD and the general population (122–124).

Physical function

Functional measurements with the purpose of measuring muscle strength and function can be useful when assessing nutritional status. Functional measurements can also be used to identify sarcopenia. An example of such measurement is handgrip strength (HGS), which measures muscle strength (116). Although strength in lower limbs may be of more importance concerning physical function, HGS is well correlated with relevant outcomes of physical function, and low HGS has been associated with increased mortality risk in the general population (125,126).

Dietary intake

In a clinical setting, the purpose of collecting information about dietary intake is to assess the actual dietary intake, and further to be able to give relevant advice to the

patient to improve the diet and thereby also their prognosis and health outcome. In a research setting, dietary assessment in a population can give information about challenges concerning diet in, e.g., an age or disease group. Dietary intake can be assessed using several different methods with different purposes, strengths, and limitations. Examples of such methods are food frequency questionnaires, food records and double portions. In this project, the method of 24-hour dietary recall is applied.

A 24-hour dietary recall collects information about dietary intake over the preceding 24 hours and is thus a retrospective method of collecting information about dietary intake. A 24-hour dietary recall is an inexpensive, easy, and quick method that does not demand much of the participant, except for remembering the dietary intake the day before. However, a single 24-hour dietary recall does not account for variance in the diet, e.g., day-to-day, through the week, or seasonal variance. To capture such variance, at least two, but preferably multiple, 24-hour dietary recalls should be conducted (127).

Biochemical markers

Biomarkers can be useful for assessing and monitoring nutritional status. It is, however, important to have in mind that several biomarkers can change rapidly, others slowly, and they may also be influenced by non-nutritional factors, such as age, sex, inflammation, and state of disease (112). One example is albumin, which can be used as an overall marker of protein intake over time. However, albumin will among others be affected by age, inflammation, and hydration status. Thus, careful interpretation of albumin is essential. Another biomarker associated with nutritional status is haemoglobin, and measures of both albumin and haemoglobin have been associated with mortality (128). On the other hand, some micronutrient deficiencies, such as vitamin D, vitamin B12 and iodine, are diagnosed by biochemical measurements alone.

1.2.2 Diagnoses of nutritional status

Malnutrition and/or undernutrition

Malnutrition or undernutrition can be defined as a compromised intake of nutrients, but as acknowledged by the Global Leadership Initiative on Malnutrition (GLIM),

malnutrition may also be caused by disease-related inflammation or other mechanisms related to disease (129).

Patients at nutritional risk include those who are already undernourished and those who are at risk of undernutrition in the near future. Nutritional risk may be due to insufficient energy and nutrient intake and/or due to increased requirements because of disease or metabolic stress (130). It is well established that a considerable proportion of patients in hospitals are undernourished (130,131). A study on inpatients at Haukeland University Hospital revealed a prevalence of nutritional risk to be 29 %, including a prevalence of 12 % among patients with BMI > 25 kg/m^2 (132). Patients at nutritional risk or already undernourished are at increased risk of longer hospital stays, rehospitalisation, reduced quality of life, and mortality, in addition to the economic burden on society (133,134).

The purpose of nutritional screening tools is to identify patients who are in need of nutritional care, and who would have a better clinical outcome given that they receive nutritional care. To assess the nutritional risk, several screening tools have been developed, and in this thesis, Nutritional Risk Screening 2002 has been used, which is recommended by ESPEN and the Norwegian Department of Health (130,135).

NRS 2002 was developed in Denmark and is a screening tool for hospitalised patients. The screening tool consists of an introductory screening and main screening. It consists of questions about food intake, body weight, weight loss, degree of morbidity and age (131). Other screening tools exist, such as the Malnutrition Universal Screening Tool (MUST) and Mini Nutritional Assessment (MNA), recommended by ESPEN for use in primary health care and for the elderly, respectively (130).

Sarcopenia

The term ‘sarcopenia’ (sarx from flesh and penia from loss) was proposed for the first time in 1989 by Irwin Rosenberg as a description of the decrease in muscle mass related to age (136,137). In 2010, the European Working Group of Sarcopenia in Older People (EWGSOP1) presented a definition of sarcopenia as *a syndrome characterised by generalised and progressive loss of muscle mass and muscle strength and is primarily*

associated with ageing (125). This definition was widely accepted, and this is considered a major milestone in the recognition of sarcopenia as an independent diagnosis. Another major milestone was the inclusion of sarcopenia with an International Classification of Diseases-10 (ICD-10) code in 2016 (138). A revised consensus by EWGSOP was published in 2018 (EWGSOP2), with the aim of including new scientific and clinical evidence built up over the past decade. In this definition, sarcopenia was also associated with other factors such as malnutrition and chronic diseases, in addition to ageing, leading to the terms primary (age-related) and secondary (disease-related) sarcopenia (139). In many individuals, especially the elderly, the condition will be a combination of these two and difficult to distinguish in clinical practice.

Other definitions of sarcopenia also exist, such as those by The Foundation of the National Institutes of Health (FINH), The International Working Group on Sarcopenia, and Society of Sarcopenia, Cachexia and Wasting Disorders (SSCWD), and The Asian Working Group for Sarcopenia (AWGS). Nevertheless, the EWGSOP definition is the most cited and widely accepted definition (140–143). In addition to these definitions, SARC-F has been developed as a screening tool for sarcopenia (144). The variation of diagnostic criteria and lack of procedures for the measurement of sarcopenia in the clinic remains a challenge for the incorporation of sarcopenia as a diagnosis to consider in a clinical setting, and there is also a low prevalence of coding for sarcopenia (145,146).

Patients with chronic diseases, such as CKD are at increased risk of sarcopenia (55). In CKD patients, a higher prevalence of sarcopenia has been observed at a younger age compared to the general population, and overall, the prevalence is estimated to be twice as high as in the general population (146–148).

The pathophysiology of sarcopenia in general, and sarcopenia in CKD, is complex and not fully understood, however, several pathways are suggested. A brief overview of the proposed mechanisms of sarcopenia in CKD is presented in **Figure 2**. Metabolic acidosis and vitamin D deficiency, common conditions in CKD, are associated with

increased catabolism and reduced protein synthesis, as well as hormonal alterations, such as insulin resistance, growth hormone (GH) resistance and reduced levels of insulin growth factor type 1 (IGF-1) and testosterone. Insulin resistance contributes to muscle fibre atrophy and mitochondrial dysfunction, which will impair muscle function. CKD related changes in the anabolic hormones testosterone, IGF-1, and GH, may cause decreased skeletal muscle turnover, and thus decreased muscle mass and muscle strength (149). It has also been suggested that sarcopenia is an inflammatory state where proinflammatory cytokines and oxidative stress may impair protein synthesis in skeletal muscle tissue (150). Recently, there has been proposed an association between the observed inflammation in CKD and an altered gut microbiota caused by the uraemic toxins related to CKD. P-cresol sulfate and indoxyl sulfate are considered uraemic toxins in this context and are metabolites generated in the gut from tyrosine and tryptophane, respectively (151). Inadequate intakes of energy and protein or malabsorption due to reduced appetite and dietary restrictions, losses of amino acids in dialysis treatment, and physical inactivity may also lead to sarcopenia.

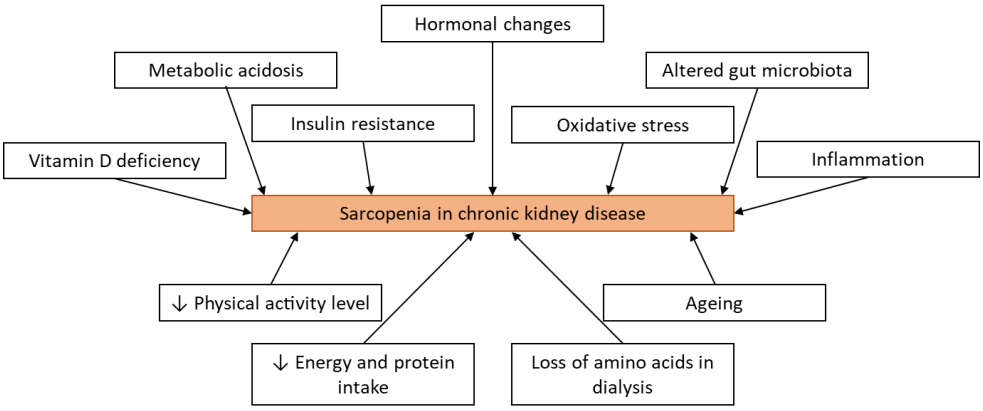

Figure 2: Proposed aetiology of sarcopenia in chronic kidney disease

The mechanisms of sarcopenia in chronic kidney disease is complex and not completely understood. This is a simplified overview, and several of the mechanisms will also interact with each other, such as vitamin D deficiency, metabolic acidosis and inflammation being associated with insulin resistance. Hormonal changes include reduced testosterone and insulin growth factor type 1, as well as growth hormone resistance. Hormonal changes and ageing are associated with reduced dietary intake, and the dietary restrictions following the course of chronic kidney disease may also contribute to reduced dietary intake.

Sarcopenia has been associated with adverse outcomes such as the increased risk of falls, reduced quality of life, functional capacity, frailty, and increased mortality risk in the general population. For the CKD population, sarcopenia has been associated with depression, fracture risk, cardiovascular complications, and in kidney transplanted patients, graft failure and post-operative complications (55,143).

Traditionally, sarcopenia has been associated with leanness, but it can also be present in individuals with obesity, known as sarcopenic obesity. Sarcopenic obesity is a condition where body mass increases concurrently with a reduction of lean body mass, which indicate that loss of muscle mass and muscle strength may happen independently of body mass. Obesity and sarcopenia have several common pathophysiological mechanisms, such as hormonal changes, insulin resistance, the elevation of pro-inflammatory cytokines and oxidative stress (149). These similarities may be an explanation for sarcopenic obesity. Weakness among the elderly has for a long time been associated with loss of muscle mass. However, it seems like fat infiltration into the muscle tissue also has an impact on muscle weakness as it implicates muscle quality and work capacity (125,139). As many of the pathophysiological mechanisms are common for sarcopenia and obesity, the consequences are also similar. These include increased risk for dyslipidaemia, diabetes type 2, CVD, hypertension, frailty, and mortality (149,152,153). A meta-analysis from 2016 demonstrated an association between sarcopenic obesity and all-cause mortality 24 % higher compared to patients without sarcopenic obesity, especially among men (153). There is, however, no clear definition of sarcopenic obesity.

There are other conditions concerning muscle wasting with similarities to sarcopenia, but also with distinct differences in the underlying mechanisms (154). The term *wasting* was introduced in 1983 by WHO as a definition of involuntary weight loss of more than 10 % (155). Cachexia is a condition of severe muscle wasting associated with diseases, such as cancer and ESKD (125). Protein-energy wasting is a CKD specific condition of malnutrition and wasting which will be further elaborated in the

next section. Since the introduction of these terms, wasting and cachexia have been used inconsequently and the conditions also overlap in CKD.

Protein-Energy Wasting

In 2008, The International Society of Renal Nutrition and Metabolism (ISRNM) proposed protein-energy wasting (PEW) as a new terminology for describing the syndrome of muscle wasting, malnutrition and inflammation in patients with kidney disease, and ISRNM recommend PEW as a tool to identify undernutrition in CKD (156). PEW is defined as a state of disordered catabolism in patients with CKD, identified as biochemical criteria (low serum albumin, prealbumin, or cholesterol), low body weight, reduced body fat or weight loss, decreased muscle mass, and low dietary intake of energy or protein. Causality is believed to be multifactorial, which is also reflected in the complexity of the diagnostic criteria of PEW.

Patients with PEW, especially patients with severe PEW expressed as frailty, are at increased risk of premature death, caused by cardiovascular or infectious complications. It is hypothesised that the infectious risk is associated with compromised immunity in patients with PEW following altered myokine physiology, decreased thermogenesis and fatigue of muscle respiration in stressed conditions, e.g., sepsis or pneumonia (157).

The prevalence of PEW has been estimated to increase in line with decreasing eGFR; <2 % in CKD stages 1-2, 11-54 % in CKD stages 3-5, and 28-70 % among dialysis patients (155,158). Dialysis patients are at increased risk of muscle wasting due to the loss of amino acids during the dialysis session.

Overweight and obesity

As mentioned previously, there is an overall increase in the prevalence of overweight and obesity in patients with CKD. Consequently, there has also been an increase in patients with CKD and obesity. In patients with pre-dialysis CKD and kidney transplanted patients, obesity is considered an independent risk factor for adverse outcomes, independent of diabetes (159). However, in pre-dialysis CKD and dialysis patients, a higher BMI is associated with increased survival. This is known as the

obesity paradox in CKD or reversed epidemiology (160–162). In addition to the generally increased prevalence of overweight and obesity, transplanted patients are more prone to gain weight due to immunosuppression, as mentioned in Section 1.1.4. A few studies have investigated the association between waist circumference and outcomes in CKD, however; the results are contradictory (163–165).

1.2.3 Nutritional care in chronic kidney disease

Nutritional care plays a key role in the management of CKD due to the change in metabolism following the progression of CKD and the frequent comorbidities (166). Nutritional care is defined by ESPEN as "*an overarching term to describe the form of nutrition, nutrient delivery and the system of education that is required for meal service or to treat any nutritional-related condition in both preventive nutrition and clinical nutrition*" (112). Several international guidelines for nutritional care in CKD are available, and these include guides on nutritional status assessment, medical nutrition therapy, dietary requirements, and dietary supplements (2,58,167–169). The most recently published guideline for nutrition in CKD is the Kidney disease outcome quality initiative (KDOQI) clinical practice guideline published by the National Kidney Foundation (NKF) in 2020 (58). The whole range of CKD was included, not just for ESKD, which was the case for the previous KDOQI guideline published in 2000 (170). To date, no Norwegian guideline exists for patients with CKD. Overall, there is an agreement in the existing guidelines for patients with CKD. A summary of recommendations according to CKD modalities will follow below.

In the early stages of CKD, medical nutritional management consists of restrictions of salt intake and control of protein intake. A controlled intake of salt will be favourable for blood pressure, which is often elevated in patients with CKD or at risk of becoming elevated. The effect of dietary protein intake in pre-dialysis CKD has been a field of interest for decades, as low protein intake has been proposed to slow the progression of CKD, as well as reduce blood pressure and proteinuria (32). However, the benefits of protein restriction must be balanced against the potential risk of PEW and sarcopenia. A protein intake of 0.55-0.60 g/kg body weight/day is recommended for patients with CKD not on dialysis, or 0.28-0.43 g/kg body weight/day with

supplementation of keto acid/amino acid analogues (58). The protein restriction should be under close supervision to ensure sufficient intake. The energy requirement is similar to the general population.

Blood samples will be decisive when the restriction of phosphate and potassium is necessary. If CKD progresses and ESKD is approaching, restriction of fluid intake is often also necessary. Dietary supplements, e.g., vitamin D are initiated, and requirements for dietary energy intakes are similar to that of the general population.

In dialysis, an increased protein intake is required to make up for the loss in the dialysate fluid. The recommended protein intake is 1.0-1.2 g/kg body weight/day, which is double the protein intake of pre-dialysis CKD patients (58). Other restrictions from pre-dialysis may be necessary to keep. Dietary supplements of multivitamins may also be required, and intravenous iron supplementation is often given during HD.

The recommendations for kidney transplanted patients are more similar to the general population, as long as kidney function improves sufficiently after transplantation (171). The exception is the consideration of increased risk concerning food borne infections caused by bacteria, viruses, and parasites. Foods at risk include raw meat, fish or seafood, and unpasteurised milk and dairy, as well as a violation of hygiene when handling food (172). Other foods might interact with the medication regimen, such as grapefruit which may inhibit the metabolism of cyclosporine through the inhibition of cytochrome P450 enzymes in the gut and liver (173).

2. Rationale for this thesis

As the estimated life expectancy will continue to increase globally, it is estimated that the burden of CKD will increase in the years to come, as will the prevalence of the major CKD causes. Patients with CKD will also live longer while treated. CKD entails changes in metabolism and nutritional status, but there is a lack of understanding of the relation and mediators between nutritional status and kidney disease. Clinical practice guidelines for nutrition in CKD do already exist; nevertheless, these guidelines underscore that there is still a scarcity of research available on nutritional status and CKD. To provide more specific evidence-based nutritional guidelines for these patients, more research is required. Additionally, CKD is a costly condition, both for society and the individual patient. We, therefore, wanted to conduct a project that included a wide assessment of nutritional status along the continuum of CKD and investigate the determinants and consequences of different challenges of nutritional status.

3. Objectives

Main objective and hypothesis

The ***overall aim*** of this PhD project is to assess nutritional status in patients at different stages and treatment modalities of CKD, and investigate possible determinants and consequences of nutritional status.

We ***hypothesised*** that patients with CKD have several challenges associated with nutritional status and that a wide assessment of nutritional status is necessary to identify the whole range of challenges. Further, we hypothesised that impaired nutritional status is associated with the degree/modality of chronic kidney disease, comorbidities, polypharmacy, and mortality.

Specific objectives

Paper I: To assess nutritional status at different CKD stages and with different CKD modalities.

Paper II: To describe the medication prescription in a population of patients with CKD and investigate the association between nutritional status and medication prescription.

Paper III: To assess the association between nutritional status and mortality in patients at different stages of CKD and with different CKD modalities.

4. Patients and methods

4.1 Study design and population

In this project, the study population consists of patients at different stages of CKD treated at Haukeland University Hospital, Bergen, Norway. The patients were included in the three papers, of which **Paper I-II** are cross-sectional studies, while **Paper III** is a cohort study with a two-year follow-up. **Table 3** summarises the key characteristics of the papers included in the thesis.

Table 3: Key characteristics of the included papers from the CKD population

	Paper I	**Paper II**	**Paper III**
Study design	Cross-sectional	Cross-sectional	Cohort
Sample size	208	217	170
Population	CKD n = 112 HD n = 24 KTR n = 72	CKD n = 112 HD n = 33 KTR n = 72	CKD n = 82 HD n = 42 KTR n = 46
Duration	-	-	2 years
Exposure	-	Prescribed medication	Indicators of nutritional status
Outcome	Description of nutritional status	Measures of nutritional status	Mortality

CKD indicates pre-dialysis chronic kidney disease stage 3-5; HD, end-stage kidney disease patients treated with haemodialysis; and KTR, kidney transplant recipients.

The papers include patients from different stages of CKD, consisting of pre-dialysis CKD patients at stages 3-5, ESKD patients receiving HD, and kidney transplant recipients. In total, 235 patients participated in the project, of which 112 patients were CKD, 51 were ESKD patients receiving HD and 72 were kidney transplant recipients. An overview of the inclusion of patients and belonging papers can be found in **Figure 3**.

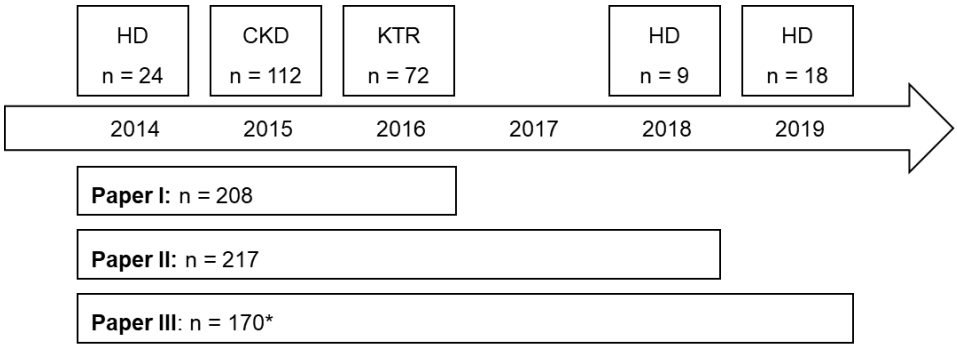

Figure 3: Overview of the inclusion process of study participants and patients included in the different papers

CKD indicates pre-dialysis chronic kidney disease stages 3-5; HD, haemodialysis patients; and KTR, kidney transplant recipients. *Patients still alive without an updated consent were excluded from Paper III (n = 65).

In **Paper III**, an updated consent was required from the patients in the study population still alive by 31.12.21. A review of the medical records showed that 66 patients were deceased by the end of 2021. Then, the 169 patients who were still alive by the end of 2021 were asked whether they would agree to continue their participation, and 104 gave written consent to participate in the follow-up study, resulting in a total of 170 patients included in **Paper III** (**Figure 4**).

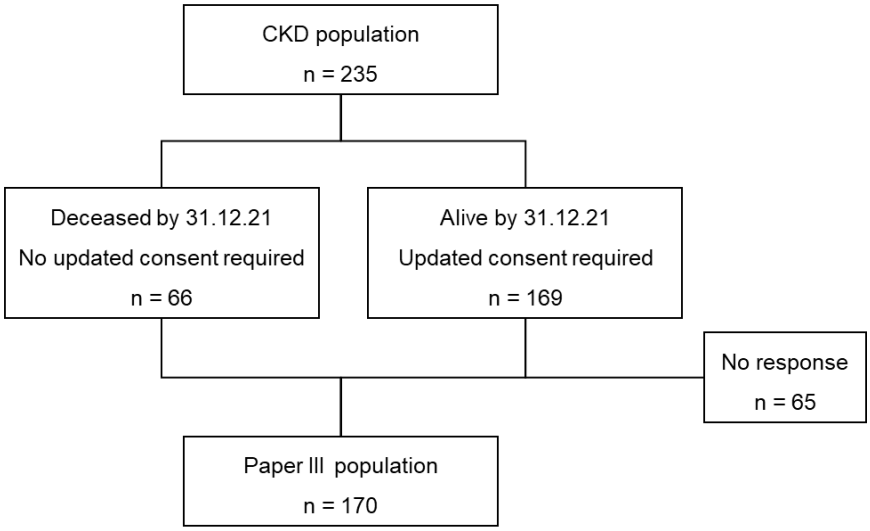

Figure 4: Overview of the inclusion process of study participants in Paper III.
CKD indicates chronic kidney disease

No formal power calculation was performed for this project, as the aim was to include as many patients as possible for each of the rounds of data collection. Eligible patients were adult patients (> 18 years) that were able to speak and understand Norwegian or English. All rounds of data collection were done as part of a master's thesis in clinical nutrition, with the exception of data collection in 2018, which was an additional data collection round of HD patients. All patients that accepted participation in the study gave written consent in advance of participation.

4.2 Data collection

Participation in the project consisted of a structured interview about medical history, lifestyle habits, and dietary intake. Measurements of anthropometry, body composition, and muscle strength were performed. Additional information on blood pressure, clinical-chemical measurements and disease history was registered from the patients' electronic journals (DIPS) after the interview. Samples of blood and urine (if possible) were collected and stored in a biobank for further analyses not performed routinely at the hospital. Within each round of data collection, all data collection was performed by the same interviewer, and the former data collector was responsible to train the next one.

Anthropometric and functional measurements

Anthropometric measurements included measurements of height, body weight, MUAC, skinfold triceps, skinfold biceps and waist circumference. These measurements were used to calculate BMI, MUAMC, and MUAMA, and to identify central obesity.

Height

The patient's height was measured with a free-standing stadiometer (Seca model 217, Seca Hamburg, Germany). The measurement was conducted with the patient wearing light clothing and no shoes. The patient was asked to stand straight with their heels and knees together and arms hanging loosely along the body. They were asked to look straight ahead, and the measurer ensured that their head was kept in the Frankfurt plane. The measurement was taken once to the nearest 0.5 cm.

Body weight

To measure the patients' weight a portable electronic scale was used (Seca, model 877, Seca Hamburg, Germany). Patients were measured with the patient wearing light clothing and no shoes. The measurement was taken once to the nearest 0.1 kg.

Body mass index (BMI)

BMI was calculated as weight (kilograms) divided by height (metres) squared, and categories from WHO were applied (174): Underweight (BMI < 18.5 kg/m^2), normal

weight (BMI 18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (BMI > 30 kg/m^2).

Mid-upper arm circumference (MUAC)

The patient was asked to remove any clothing from their non-dominant arm. The midpoint between the acromion process on the shoulder blade and the olecranon process of the ulna was marked. A flexible non-stretch tape was wrapped firmly around this point to measure the circumference of the upper arm while the patient had their arm hanging loosely by their side without flexing any muscles. The measurement was taken once to the nearest 0.5 cm.

Mid upper arm muscle circumference (MUAMC) and mid-upper arm muscle area (MUAMA)

A formula was used to calculate the MUAMC of the non-dominant arm, by using the mean measurements from the MUAC and skinfold thickness triceps. MUAMC was used to calculate MUAMA:

$$\text{MUAMC (mm)} = \text{MUAC (mm)} - (\pi \times \text{TSF (mm)})$$

$$\text{MUAMA (mm}^2\text{)} = \text{MUAMC (mm)}^2 / 4\pi$$

Waist circumference

Waist circumference was measured on bare skin at the midpoint between the lower costal arch and the iliac crest. Patients were asked to breathe normally, and the measurement was taken on the out-breath to the nearest 0.5 cm. The measurement was repeated three times, and the mean value was noted. Cut-off values for increased waist circumference, indicating central obesity, were set to 102 cm for men and 88 cm for women, as suggested by the WHO and National guidelines on the primary prevention, investigation, and treatment of overweight and obesity from the Norwegian Directory of Health (175,176).

Skinfold triceps

Skinfold triceps was taken at the same point as the MUAC on the non-dominant arm, at the midpoint between the acromion process and the olecranon process using a Lange

skinfold calliper (Quick Medical, Issaquah, USA). The investigator grasped the skinfold approximately two centimetres over the marked point on the dorsal side of the arm. The measurement was taken three times to the nearest 0.01 cm, and the mean value was applied.

Skinfold biceps

Skinfold biceps was taken with the same method as skinfold triceps, except that this measurement was performed on the frontal side of the arm. The measurement was taken three times to the nearest 0.01 cm, and the mean value was applied.

Handgrip strength (HGS)

A JAMAR hydraulic hand dynamometer (Sammons Preston, Bolingbrook, IL, USA) was used to measure HGS. The patients were asked to sit down on a chair without armrests, keep their elbow flexed to 90 degrees, their wrist straight, and grasp as hard as they managed around the device. The dynamometer could be adjusted according to hand size. The investigator tried to encourage the patient to get as good results as possible. The results were measured in kilograms to the nearest 0.1 kg. This was repeated three times on each side, with alterations between the arms at each measurement. The mean and maximum measure, irrespective of hand dominance, were noted.

Knee extension

To measure the strength in the muscles of the legs a hand-held digital force gauge (Chatillion-Ametek DFE Series II) was used. This measurement was taken on the non-dominant side, without shoes. The patients sat on a chair with their knees flexed to 90 degrees. The examiner, kneeling, placed the device just below the patient's knee. The patient then led their non-dominant foot along the floor while the investigator used their body weight and muscle strength to resist the movement of the patient. The measurement was repeated three times and the results were measured in newton, N.

Bioelectrical impedance analysis (BIA)

A single frequency tetrapolar BIA 101 Anniversary Sport Edition (AKERN) was used for measuring body composition by BIA. The measurement was conducted on the non-

dominant side with the patient in a supine position at an examination table with their limbs abducted from the body and each other. Watches, jewellery, and belts were removed, but the patients were not fasting, asked to have their skin cleaned or systematically prompted to empty their bladder in advance of the examination as a routine.

The current electrodes were placed on bare skin on the dorsal side of the hand and foot, proximal to the phalangeal-metacarpal joint and the metatarsal phalangeal joint, respectively. The voltage detection electrodes were placed on the pisiform prominence of the wrist and between the medial and lateral malleoli of the ankle. Contraindications to this measurement are implanted pacemakers and pregnancy, and in these cases, the measurement was not carried out.

Appendicular lean mass (ALM) was calculated with an equation by MacDonald et al., as this has been validated to predict muscle mass in patients with CKD (119):

$$ALM = -11.626 + (0.292 \times height^2 / resistance) + (0.06983 \times reactance) + (0.08553 \times height) + (-2.092 \times sex) + (-0.05 \times age)$$

Parameters in the equation: height (cm); resistance and reactance at 50 kHz (Ω); sex, 0 = male, 1 = female; age (years).

ALMI was calculated as ALM/height^2.

The measurements of BIA were also used to calculate total fat mass (kg and %) facilitated by the equation for total fat free mass (FFM) of Deurenberg et al. (177):

$$FFM = 0.652 \times 10^4 \times height^2/resistance + 3.8\ sex + 10.9$$

Parameters in the equation: height (m); resistance (Ω); sex, male = 1, female = 0.

Nutritional risk of undernutrition

Nutritional risk screening 2002 (NRS2002) was applied as a screening tool to identify patients at nutritional risk of undernutrition in the study population. NRS2002 consists

of an initial screening section and a main screening section. The initial screening section consists of four questions:

1. Is BMI < 20.5 kg/m^2?
2. Has the patient lost weight within the last three months?
3. Has the patient had a reduced dietary intake in the last week?
4. Is the patient severely ill? (e.g., in an intensive care unit)

If the answer to at least one of these questions is yes, the screening continues to the main screening section. In this section, there are two categories, one regarding the nutritional status and one regarding the severity of disease. Points from 0 to 3 are given in each category, depending on the severity of the impairment in each category. The points of the two categories are added together and an extra point is given if the patient is aged 70 years or older. If the total score from the main screening section is three or higher the patient is considered at nutritional risk of undernutrition.

Sarcopenia

In **Paper I**, the EWGSOP1 citeria was applied to identify patients with sarcopenia, while the EWGSOP2 criteria was applied in **Paper III** (125,139). The measures and associated cut-offs for sarcopenia concerning the respective definitions are presented in **Table 4**.

Table 4: Diagnostic criteria for sarcopenia

Consensus	Measure	Male	Female
EWGSOP1	HGS	< 30 kg	< 20 kg
	SM/HT^2	≤ 8.87 kg/m^2	≤ 6.42 kg/m^2
EWGSOP2*	HGS	< 27 kg	< 16 kg
	ASM/ALM	< 20 kg	< 15 kg

ALM indicates appendicular lean mass; ASM, appendicular skeletal muscle mass; EWGSOP, European working group on sarcopenia in older people; HGS, handgrip strength; HT^2, height squared; and SM, skeletal muscle mass by BIA

*Physical performance tests may be conducted to assess the severity of sarcopenia if sarcopenia is confirmed. Such tests include gait speed, short physical performance battery, time up and go, and a 400 m walking test.

Dietary intake

Information about dietary intake was collected by a 24-hour dietary recall. The patient was asked to report the food and fluid intake the day before the interview in a 24-hour dietary recall. Details about brand and amounts in household measures were inquired of, as were snacking and drinking between meals. The information about the dietary intake was registered in Kostholdsplanleggeren, a diet tool developed by the Norwegian Directorate of Health and the Norwegian Food Safety Authority using dietary data from the Norwegian Dietary Database (178).

Information from patient records

Blood pressure was registered from the electronic patient record. Blood pressure measurements from two weeks in advance and one week after the inclusion were accepted. If the blood pressure was noted as a range, the mean value was registered in the dataset.

The patients' electronic journal was used to obtain information about major clinical-chemical variables. In ESKD patients treated with HD, these were from the same day as the long interval of dialysis and obtained before dialysis. In pre-dialysis CKD stage 3-5 patients and kidney transplant recipients, these variables were usually analysed in a blood sample obtained the same day as the patient's physician appointment, but some patients had their blood drawn in advance of the appointment. Samples taken up to two weeks prior to the study day were accepted.

Table 5: Analysis retrieved from routine blood and urine samples

Whole blood	Serum	Urine analysis
Haemoglobin	Albumin	Creatinine
HbA1c	Glucose	Albumin (mg/mmol creatinine)
	CRP	Protein (mg/mmol creatinine)
	Creatinine	
	eGFR*	
	Urea	

**Calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. CRP indicates C-reactive protein; and eGFR, estimated glomerular filtration rate.*

An overview of the analyses performed in routine blood and urine samples collected from the patients' electronic journals is shown in **Table 5**. Samples taken more than two weeks in advance of or two weeks after the interview were not included. Samples were analysed at the Department of Medical Biochemistry and Pharmacology at Haukeland University Hospital, using standard methods. More information about the coefficient of variation and the methods used can be found on www.analyseoversikten.no.

Medicine prescription

In **Paper II**, information about prescribed medications was collected from patient records and categorised according to the Anatomical Therapeutic Chemical (ATC) Classification system (first, second and fifth level) by a dietitian and a final year master's student in pharmacy in collaboration. Prescriptions of five or more medications at the same time were identified as polypharmacy and prescriptions of ten or more medications at the same time were identified as excessive polypharmacy. Medications were also grouped according to side effects. A medication was included in a side-effect of either nausea or xerostomia if it was listed as a common or very common side-effect of that specific medication according to the Norwegian Pharmaceutical Product Compendium ("Felleskatalogen") or "Norsk Legemiddelhåndbok" (179). The medications included in the categories of common or very common side-effects of nausea or xerostomia are shown in **Table 6**.

Table 6: Medications, presented as an ATC-number and active substance, with nausea or xerostomia as a common or very common side-effect

Nausea		
A07E C01 Sulfasalazine	A07E C02 Mesalazine	A10B A02 Metformin
A10B J02 Liraglutide	B03A A01 Ferrous glycine sulfate	B03A A07 Ferrous sulfate
C01B D01 Amiodarone	H05B X01 Cinacalcet	H05B X02 Paricalcitol
L04A A06 Mycophenolic acid	L04A A10 Sirolimus	L04A D01 Ciclosporin
L04A D02 Tacrolimus	L04A X03 Methotrexate	M04A C01 Colchicine
N02A A01 Morphine	N02A B03 Fentanyl	N02A E01 Buprenorphine
N02A X02 Tramadol	N03A X09 Lamotrigine	N03A X12 Gabapentin
N03A X14 Levetiracetam	N03A X16 Pregabalin	N05A D01 Haloperidol
N05A N01 Lithium	N05B B01 Hydroxyzine	N05C F02 Zolpidem
N06A B04 Citalopram	N06A B06 Sertraline	N06A B10 Escitalopram
N06A X11 Mirtazapine	N06A X16 Venlafaxine	N06D A02 Donepezil
V03A E01 Polystyrene sulfonate	V03A E02 Sevelamer	V03A E03 Lanthanum carbonate
Xerostomia		
N02A X02 Tramadol	G04B D07 Tolterodine	N02A E01 Buprenorphine
N05A D01 Haloperidol	N02A B03 Fentanyl	N03A X16 Pregabalin
N06A B05 Paroxetine	N03A X12 Gabapentin	N05A H04 Quetiapine
N06A X11 Mirtazapine	N05A H03 Olanzapine	N05C F01 Zopiclone
R06A X22 Ebastine	N05B B01 Hydroxyzine	N06A B04 Citalopram
N06A X16 Venlafaxine	N06A A09 Amitriptyline	N06A B10 Escitalopram
N06A B06 Sertraline	R06A E07 Cetirizine	R06A X27 Desloratadine

Medicines associated with a nutrition-related side-effect are defined according to information on common (>1/100 - <1/10) and very common (>1/10) side-effects of medicines from the Norwegian Pharmaceutical Product Compendium (*Felleskatalogen*), *Norsk legemiddelhåndbok* (22) and *ATC/DDD Index 2019* by WHO Collaborating Centre for Drug Statistics Methodology. ATC indicates anatomical therapeutical (ATC).

Comorbidities

In **Paper III**, measures of nutritional status and the diagnoses of sarcopenia and central obesity were assessed as risk factors for mortality in the study population. The associated risks were adjusted for the comorbidities of diabetes or cardiovascular disease, as well as present HD treatment and serum albumin. An overview of diagnostic criteria applied is presented in **Table 7**.

Table 7: Diagnosis and the respective diagnosis criteria applied in the study

Diagnosis	Criteria
Diabetes mellitus	Written in patient record *or* Diagnosis: E10-14 *or* HbA1c ≥ 48 mmol/L *or* Prescription of antidiabetic medications: A10A-B
Cardiovascular disease	Diagnosis of coronary heart disease I20-25 *or* Diagnosis of atrial fibrillation I48 *or* Diagnosis of heart failure I50 *or* Diagnosis of total stroke I60-61, 63-64 except I63.6

Diagnoses are classified according to International Classification of Diseases.

4.3 Statistical analyses

The statistical analysis of **Paper I** were performed in IBM SPSS Statistics version 25 (IBM, NY, USA). Each CKD modality was analysed separately. For continuous variables, independent samples t-tests were used to compare two groups with approximately normal distribution, and the non-parametric Mann Whitney-U test was applied when there was a lack of normal distribution. For categorical variables, the Chi-squared, or Fisher's exact test were applied. For assessment of differences between treatment modalities, analysis of variance or a Kruskal-Wallis test was applied, while associations between continuous variables were investigated by Spearman's rho correlation analysis. To explore factors associated with central obesity and sarcopenia, we used multivariate logistic regression.

In **Paper II**, the study population was grouped in three different ways. First, according to CKD modality (pre-dialysis, dialysis, or transplant), and second according to their CKD stage. Third, patients were grouped according to the prescription of medications with nutrition-related side effects xerostomia and nausea. The characteristics for each CKD modality and the total population were presented with means and standard deviations. For differences between the CKD modalities, unadjusted regression analyses were performed. The association between the number of prescribed

medications and the different measurements of nutritional status were investigated by linear regression analysis adjusted for age, sex and eGFR. Differences in measurements of nutritional status were also estimated according to the prescription of medications with nutrition-related side effects, followed by a linear regression analysis with adjustment for sex, age, eGFR, and the total number of prescribed medications. The analyses in **Paper II** were performed in R software version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria), and the packages within "*Tidyverse*" (180); "*dplyr*" (181), "*tidyr*" (182), "*broom*" (183), and "*ggplot2*" (184) were applied.

In **Paper III**, patient characteristics were presented according to whether they were alive or deceased after two years. The groups are presented with means and standard deviations or counts and percentages. The association between nutritional status and mortality was investigated by the Kaplan Meier curve and Cox regression models for the diagnosis of sarcopenia and central obesity. Cox regression hazard ratios were also estimated for a one-unit change in HGS, ALM, ALMI, waist circumference, skinfold triceps, MUAC, and MUAMC. For phase angle, the Cox regression hazard ratios were estimated for 0.1-unit change. The Cox regression models were adjusted for age and eGFR for all markers and additionally adjusted for sex for the continuous markers. Additional models were created, where adjustments for albumin, diabetes mellitus, cardiovascular disease or dialysis treatment were added one by one to the original model. Generalised additive models were plotted for the association between markers of nutritional status as continuous variables and mortality risk to explore non-linear relationships. The analyses in **Paper III** were performed in R software version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). The packages applied in the analyses of this paper were the packages within the "*Tidyverse*" (180); "*dplyr*" (181), "*tidyr"* (182), "*ggplot2*" (184), and "*lubridate*" (185). In addition, the packages "*Survival*" (186) and "*Survminer*" (187), and the function "*plotHR*"(188) were applied.

4.4 Ethics

The patients that participated in the project were exposed to low risk and the workload for the patients was small. As a routine, the patients were interviewed on the same day as their routine appointment with their nephrologist at Haukeland University Hospital, since they were already present at the hospital. The interview and examination together lasted for about 45 minutes. In addition, the kidney transplant recipients were asked to answer some questions by telephone about a week later. This phone call usually took 5-10 minutes.

The patients were also asked to give blood samples and urine samples to a biobank for future analysis. These samples were, if possible, collected at the same time as their routine samples, which did not lead to extra time spent waiting or the extra distress of retaking the blood samples. As a routine, many of the outpatients had their blood samples taken in advance of their appointment with the nephrologist, which made it impossible to coordinate the samples. If this was the case, the patients were asked if they were comfortable with taking a new round of blood samples and there was no enforcement from the examiner's side. The urine samples for the biobank were delivered directly to the examiner.

The studies included in this thesis were approved by the Regional Committee for Medical and Health Research (REK Vest, No 2014/1790 and 10155) and conducted following the principles of the Helsinki Declaration. Written and informed consent was collected before study participation, and for the patients participating in the study for **Paper III**, a renewed consent was obtained. All patients participating in the study were offered to receive information about their personal results from the examination as well as access to the respective master’s thesis.

5. Results

5.1 Paper I: Assessment of nutritional status

The aim of **Paper I** was to assess nutritional status in a population of CKD patients at different stages, including patients with pre-dialysis CKD stage 3-5, ESKD patients treated with HD, and kidney transplant recipients. Nutritional status was assessed widely including several anthropometric measures, as well as functional measures, data on dietary intake and biochemical measures. The collected data material was used to assess the nutritional risk of undernutrition, sarcopenia, and central obesity.

Adult patients with chronic kidney disease followed at Haukeland University Hospital were eligible for participation in this cross-sectional study. The data collection took place from 2014 to 2017, and we included 24 patients treated with HD, 112 patients with CKD stages 3-5, and 72 kidney transplant recipients.

Among the 208 patients included in **Paper I**, we observed a low prevalence of patients at nutritional risk as well as patients with underweight. The exception was patients treated with HD, who showed a prevalence of 33 % concerning the nutritional risk of undernutrition. In the total population, a large proportion of the patients were overweight (37 %) or obese (26 %). Additionally, a high prevalence of both sarcopenia (36 %) and central obesity (49 %) was observed. Among the patients with central obesity, 49 % were either overweight or normal weight according to the BMI-classification.

We identified that challenges regarding nutritional status are common in patients with CKD, especially sarcopenia and central obesity. Such conditions would not have been revealed by measuring body weight or BMI, and measurements of body composition and body shape are warranted to facilitate a comprehensive assessment of nutritional status.

5.2 Paper II: Medicine prescription and nutritional status

In **Paper II**, we aimed to investigate the association of medication prescription with nutritional status in patients with CKD. Information about medication prescriptions was collected from the patients' electronic records, and an assessment of nutritional status was performed by anthropometric and functional measurements. We evaluated the total number of prescribed medications, as well as the number of prescribed medications with the common or very common side effects of nausea or xerostomia.

In this study, patients from pre-dialysis CKD stages 3-5 (n = 112), ESKD patients treated with HD (n = 33) and kidney transplanted patients (n = 72) were included, in a total 217 patients. On average, patients were prescribed nine medicines, with a higher mean number in dialysis patients (15 prescribed medications) and a lower number among patients with pre-dialysis CKD stages 3-5 (8 prescribed medications). Of the study population, 84 % was identified with polypharmacy and 37 % with excessive polypharmacy. The number of prescribed medications was inversely associated with MUAC, skinfold triceps, HGS, serum albumin, and haemoglobin in linear regression analyses with adjustments for age, sex and eGFR. The prescription of medications with nausea as a side effect was associated with lower MUAC, skinfold triceps, albumin, and haemoglobin, while medications with xerostomia were associated with lower HGS.

5.3 Paper III: Nutritional status and mortality risk

In **Paper III**, the aim was to investigate the association between measures of nutritional status and mortality risk after a two-year follow-up. We measured nutritional status at baseline and collected information about mortality state at the end of 2021 from the patients' records. If applicable, the cause of death was also collected.

Out of the 170 patients included in this study, 31 patients (18 %) were dead after two years. The mortality rate was higher among the patients treated with HD compared to the patients with pre-dialysis CKD stages 3-5 and kidney transplanted patients, which had a similar mortality rate. The patients that were deceased were older, had lower mean serum albumin and eGFR, and had a higher prevalence of diabetes, CVD, and

sarcopenia. In Cox regression models adjusted for age and eGFR, sarcopenia was associated with mortality (hazard ratio 2.92, [95 % confidence interval 1.24, 6,89]), while central obesity was not associated with mortality risk (1.05, [0.51, 2.15]). For the continuous markers assessed, the Cox regression models were adjusted for age, eGFR and sex. We observed no association between mortality risk and the markers of BMI and waist circumference, while an inverse association was observed for the markers of ALM, HGS, MUAC, phase angle, and triceps skinfold. Additional adjustment for albumin, diabetes, CVD, or dialysis treatment in the Cox regression models did not change the estimates substantially. The Cox regression models for the continuous markers were also assessed in generalised additive models to assess non-linear relationships. Measures of BMI showed no relationship to mortality risk, apart from BMI < 22 kg/m^2. For the markers of waist circumference and MUAMC, we observed a U-shaped relationship, with increased mortality risk at extreme values measured. For the remaining markers, we observed a negative linear relationship with mortality risk.

The results from this study suggest that markers of nutritional status may be predictive of mortality risk in patients with CKD, however, the most frequently applied measure in the clinic, BMI, was not a predictive marker in this study. Our results suggest that the inclusion of measurements other than BMI may be of value in clinical practice to identify patients at risk.

6. Discussion

6.1 Methodological considerations

6.1.1 Study design

The studies of **Paper I** and **II** included in this thesis are of cross-sectional design. A cross-sectional study is designed to give a snapshot of the characteristics of a specific population at a one-time point, with descriptive statistics, allowing for assumptions about concurrent characteristics. In the hierarchy of research designs, cross-sectional studies are ranked lower than longitudinal observational studies and intervention studies. However, studies with a cross-sectional design offer many advantages that more sophisticated study designs do not offer. The aim of the study is also important to consider when choosing a study design, in terms of the balance of benefits and harm in medical research (189). In a cross-sectional study design, there is no loss to follow-up and such studies are quite quick and cheap to conduct. For the purpose of investigating prevalences and characteristics, a cross-sectional study design would be a suitable choice of study design, and it also enables the possibility of studying several characteristics at the same time. Additionally, cross-sectional studies are also suitable as hypothesis-generating for future investigations (190).

The limitations of a cross-sectional design include no ability to measure incidence, nor the ability to make a causal inference, and interpretation of the results from a cross-sectional study should be done according to these limitations. Thus, we can conclude that there are high prevalences of central obesity and sarcopenia in **Paper I**, but we cannot distinguish whether there is an associative or causal relationship between these conditions and CKD. In the case of the latter, we do not have any information about the direction of the causality, whether the identified conditions of nutritional status cause CKD or vice versa. In **Paper II**, we were cautious about drawing any conclusions about the associations we observed between prescribed medications and nutritional status, and these should be further investigated in studies with a longitudinal study design.

In **Paper III**, a longitudinal study design, or cohort study design, was applied. Longitudinal studies offer the advantage of investigating the association of baseline characteristics with endpoint measures over time, such as mortality. It is also possible to study incidence in cohort studies, and multiple endpoints can be studied in the same study. In such a study design, it is possible to calculate the risk of an outcome, e.g., mortality. However, conclusions about causality cannot be drawn from a cohort study design. Nevertheless, the results from a cohort study design are useful as a starting point for further investigation of causal associations. As in any study design, there are disadvantages that require consideration, such as loss to follow-up and incomplete assessment of endpoint measures (191). In our study, we experienced loss to follow-up due to the requirement of an updated consent to participate in the study, but the assessment of outcome (e.g., mortality) was regarded as complete. Our study only included measurements at baseline (one time) and associated the measurements to mortality status after two years. We did not include any information about the progression of CKD during the two years of follow-up in our analyses, nor information on whether the patients had changed their CKD modality (from pre-dialysis to dialysis, dialysis to transplantation, transplantation to second transplantation, etc). These may have been important confounding factors to include, especially for the patients at less severe stages of CKD at baseline, and this will be the next step forward after this PhD project.

The challenges of confounding and bias are important to consider in the context of all observational studies. A confounder is defined as a factor that is associated with both the exposure and outcome studied without it being the causal pathway between the two (190). As an example from **Paper II**, we are not able to separate the number of prescribed medications from the morbidity of the patients, and thus the number of prescribed medications may be a confounder of the association observed. Stratification, restriction and matching are methods to prevent or control confounding, as well as adjustment in analyses. We attempted to handle the challenge of confounding by adjusting for assumed confounding factors in our analyses, such as age, sex and kidney function, in **Papers II** and **III**. In these papers, we also stratified by sex for markers of nutritional status where differences due to sex are well-established.

Bias is considered, as any systematic error in a study, either in data collection or study participant selection, to preclude the true effect of an expose on the outcome or the general application of the results (190). Standardisation of measurements and pre-defined inclusion criteria for the study are thus important strategies to reduce the influence of bias; this notwithstanding, some bias will always be present.

6.1.2 Study population and data collection

As presented in the introduction, the primary cause of CKD may be of importance when assessing nutritional status and consequences such as mortality. In the data collection for the studies included in the thesis, we included patients with all primary causes of kidney disease along the continuum of CKD. We did not specify the vintage of HD or time since transplantation for the HD or kidney transplanted patients in the inclusion criteria. This wide acceptance of patients to the studies introduces heterogeneity to the study population. On the other hand, such wide acceptance of patients was necessary to include as many patients as possible. The population also ranged in age, from 21-89 years at inclusion, which is of importance when interpreting both dietary intake and anthropometric measures of nutritional status. While such heterogeneity may be considered a disadvantage, it also enables the advantage of assessing nutritional status at different modalities of CKD.

A sample size calculation was not done at the start of the project due to the exploratory and observational nature of the project, and the goal was to include as many patients as possible within each subproject. The sample size was based on a convenience sample in a single centre, and even though the data collection was done at a tertiary hospital with wide geographic coverage, the sample size was modest. This did not allow further subgroup analyses of the population, both regarding CKD stage, CKD modality and cause of disease, which would all have been interesting to investigate further, especially in **Papers II** and **III**. At the same time, the heterogenous study population allowed us to investigate nutritional status widely in terms of the inclusion of several markers of nutritional status and a wide range of the CKD spectra. As CKD is a progressive disease, this might also be a strength of the studies. Compared to the available patients in each modality, the sample size reflected the mean age of all

patients approached. Nevertheless, the prevalence of males recruited was higher than the overall prevalence (data not shown).

In this project, all data on nutritional measures were measured directly, not using a proxy. Within the same round of data collection (see **Figure 3**), all measurements were performed by the same investigator, and the investigator collecting the data in the prior data collection round was responsible for training the next in the standardised measurement methods. Thus, bias was reduced to a minimum. All investigators were either master's students in clinical nutrition in their final year or a dietitian. The data collection of medication prescriptions was done in collaboration with a final year master's student in pharmacy and supervised by an associate professor in pharmacy, ensuring the quality of the data collection.

6.1.3 Assessment of nutritional status

In this project, we have assessed nutritional status widely and applied several assessment methods for that purpose. While many of these measurements are easy to conduct, there are still methodological aspects to consider. In the following sections, the methodological aspects of different categories of assessment of nutritional status will be elaborated.

Dietary data

In the current project, dietary intake was assessed by one 24-hour dietary recall. The respondent is asked to give as many details about their dietary intake as possible regarding food preparation methods, ingredients, brand names, and estimates of amounts according to household measures (192). A 24-hour dietary recall is quick and easy to conduct, both for the interviewer and the participant, as it asks about the dietary intake of the previous day. Due to the retrospective methodology of a 24-hour dietary recall, there is also less probability that the dietary intake of the patient will be influenced by the dietary assessment. However, there are limitations to this method of dietary intake assessment: it is dependent on the patients remembering their dietary intake, both what they ate and in what amounts. This can be a challenge, especially in the ageing population, which was a major proportion of our study population. This also

makes the method exposed to underreporting, which also may have been a challenge in the present project (193).

Another limitation to a single 24-hour dietary recall is that it is not sufficient to capture day to day differences in dietary intake, nor variances during the week or seasons. This may be of importance in patients with chronic diseases, and an especially important factor in dialysis patients, where differences in dietary intake have been observed depending on whether the dietary assessment was from a dialysis day or non-dialysis day (194). The day-to-day variability of dietary intake is regarded as requiring at least two, but preferably even more 24-hour dietary recalls to acquire a reasonable estimate of habitual dietary intake. By adding at least one more 24-hour dietary recall the quality of the dietary data would have improved significantly (195). We did an additional 24-hour dietary recall in subgroups of the study population, however not in a sufficient proportion so that this could be included in the analyses of dietary intake. On the other hand, one can argue that the use of a 24-hour dietary recall may be appropriate for the assessment, as this is used as a basis in the nutritional assessment and treatment in clinical practice (112). However, we decided not to include dietary data in **Papers II** and **III** due to the uncertainty of the data as well as the limited sample size, as earlier described.

Nutritional risk of undernutrition

In this project, we applied NRS 2002 as a screening tool for undernutrition. NRS 2002 has been recommended by ESPEN (112,130). A screening tool should be quick and fairly easy to apply and should be able to identify the patients that are at risk of adverse outcomes and that will benefit from nutrition therapy. In studies with patients with CKD, NRS 2002 has been reported to adequately identify patients that are considered undernourished, as well as be able to predict adverse outcomes. It may thus be appropriate to apply it to patients with CKD (196,197). However, these are studies conducted with hospitalised patients, and the patients in our project are outpatients, thus the results may be different in such patient groups. It also remains to compare the reliability of NRS 2002 to other screening tools in the CKD population (169).

Further, NRS 2002 has also been incorporated in clinical practice in Norway, as this has been the recommended screening tool for hospitalised patients (135). Of note, from March 2022, the revised National Guidelines for prevention and treatment of undernutrition were updated, and Malnutrition Screening Tool (MST) was proposed as the recommended screening tool for the whole health care system in Norway (198).

Diagnosis of sarcopenia

In **Paper I** and **III**, sarcopenia was identified in the study population as a deviation from normal nutritional status. Sarcopenia was first described in 1989 by Irvin Rosenberg, and numerous definitions for diagnosis are in place, usually based on the measurement of muscle mass and strength. In **Paper I**, we used the EWGSOP1 definition, which uses muscle mass and strength. In 2018, this definition was updated with new cut-offs and extended with functionality for an assessment of the severity of sarcopenia (EWGSOP2). The application of EWGSOP2 lead to a lower prevalence of sarcopenia, compared to the old definition (125,139). For the purpose of comparability, this is a challenge, not only with the papers included in this thesis but the overall comparability of the identification of sarcopenia in the literature.

There are several studies where sarcopenia is defined by low HGS alone, but the cut-offs applied may vary according to the consensus followed (146,199). Other studies only included the measure of muscle mass as a criterion for the diagnosis of sarcopenia (200). Today, the current definitions have different cut-offs for males and females but do not differentiate in patient demographic or origin of the potential muscle weakness. Whether cut-offs should also be disease-specific remains to be investigated, but this has been proposed in the literature (201). The lack of a common definition of the diagnosis of sarcopenia also causes differences in reported prevalence in the literature (146,200). Additionally, the methodology for the measurement of muscle strength and muscle mass is not very detailed in the consensus by EWGSOP, which will be further discussed in the following sections (202,203).

Handgrip strength (HGS)

Even though cut-offs for HGS exist for the diagnosis of sarcopenia, there is a large variation in the measurement procedure, e.g., how many repetitions, whether the

dominant or non-dominant hand should be used, and whether the mean, median, or maximum value should be used (203). This is not stated by EWGSOP or any of the other consensuses for sarcopenia. Protocols exist for the measurement of HGS, such as the protocol of the American Society of Hand Therapists (ASHT) and the Southampton protocol, but these are rarely applied or referred to in studies, and we did not either refer to such protocol. However, our methodology is similar to the Southampton protocol (204,205). The biggest difference between the two protocols is whether the maximum or mean measure of HGS should be applied. In a recently published study, the maximum and mean HGS was validated against physical performance in the diagnosis of sarcopenia, and the use of max HGS was found most predictive, which is in line with the Southampton Protocol (206).

Body composition

In the current thesis, muscle mass was assessed by measurements of BIA. The advantages of BIA are that it is cheap and easy to use compared to DEXA, and the results are easy to reproduce. Additionally, the conduction of the procedure is considered easy and non-invasive for the patient (120,207). One of the limitations of BIA, compared to DEXA, is that BIA measurements can be affected by hydration status (208). The presence of oedema is common in CKD patients, especially in HD patients. To minimise the influence of overhydration in patients treated with HD, BIA measurements were done after dialysis. However, overhydration may also be present in other CKD patients. In our study population, the kidney transplanted patients were assessed for oedema, and indeed approximately 10 % of the patients were identified with pitting oedema or visible oedema. Thus, the results of body composition by BIA should therefore be interpreted with some uncertainty.

Physical function and physical activity

In the EWGSOP2 definition, it is recommended to assess the severity of sarcopenia by physical function (139). In the current thesis, we aimed to assess nutritional status thoroughly; however, physical function was not well assessed. In parts of the study, the data collection involved assessment of both physical function and estimation of physical activity level, but this was not done for a sufficient proportion of the study

population. It was therefore not possible to assess the severity of sarcopenia in the current project, nor give an estimate of energy expenditure (139,209).

6.1.4 Medication prescription

In **Paper II**, we investigated the association between prescribed medications and nutritional status. We described the number and type of medications according to ATC level 1 for the CKD patients, in addition to categorising medications according to the side effects of nausea or xerostomia. To our knowledge, this way of structuring medications has not been done before, and this structure was the result of a close collaboration between the fields of medicine, pharmacy and nutrition. The work was driven by the heterogeneity in medications prescribed for the patients (216 different medications prescribed in different combinations for 217 patients), which made the further analyses of the type of prescribed medication complex without any structure of the prescribed medication. By structuring medications according to the side effects, we were able to create a quite simple system for the overwhelming number of prescribed medications.

There are also some limitations to the methodology applied in **Paper II** regarding the prescribed medications. The heterogeneity in the lists of prescribed medications precluded analyses of dosages of specific medications, and thus the dosages and frequencies of medications are not taken into account. Also, we did not check for compliance, nor include over the counter substances in our analyses. Regarding the side effects studied, we did not collect any data to confirm whether the prescription of such medications was associated with the relevant side effect.

In the analyses of the number of prescribed medications, linear regression models were conducted, where the effect of each additional medication was studied. In such analyses, the effect of each medication may be more than just additive, due to the interactions between medications. The interactions between medications in patients with CKD were studied in a Spanish study, and the study revealed interactions in 91 % of the patients (210). Also, it is difficult to distinguish between the effect of prescribed medications in themselves and the medications as a marker for morbidity.

The investigation of the effect of medication on nutritional status is complex. This complexity may explain why there is a general scarcity of research on the prescription of medications and nutritional status, let alone the prescription of medications and nutritional status in patients with CKD.

6.1.5 Continuous variables, categorisation and classification

The categorisation of continuous variables is common practice in medicine as it identifies patients with and without disease and risk of disease, and it also recurs in this thesis. Examples are the staging of CKD according to eGFR, the classification of sarcopenia according to cut-offs of HGS and ALM, and the assessment of dietary intake according to dietary requirements. Such classifications are useful and necessary for the health care system to be efficient and able to capture patients at risk or with a disease. However, it is important not to be blinded by such classification systems. A patient with an HGS barely exceeding the cut-off for sarcopenia will not be identified as a patient with sarcopenia, even though muscle strength may still be diminished and metabolism not abruptly altered at the set cut-offs. Another example is the assessment of dietary intake, where pre-set cut-offs may be decisive for whether a patient is given medical nutrition therapy. A patient barely exceeding the cut-off will not receive such treatment; however, during the following days, the patient may be below the cut-off.

The application of the categorisation of continuous variables also requires careful measurement of the variables included, as even small measurement errors may entail the wrong classification of a patient. When the variables are applied as continuous variables, this may not entail large consequences, but when a patient is either identified as with or without sarcopenia, this demands even more specific data collection.

6.2 Discussion of the results

This thesis had the aim to assess the determinants and the importance of nutritional status along the continuum of CKD, applying a wide range of measures of nutritional status. We investigated the association between nutritional status and prescribed

medications, as well as mortality risk. The aims of the thesis are investigated in two cross-sectional studies and one longitudinal observational study.

We found a high prevalence of sarcopenia, overweight and obesity, and central obesity in our combined CKD population. In the patients with ESKD treated with HD, we observed a high prevalence of patients at nutritional risk of undernutrition, while in pre-dialysis CKD and kidney transplantation, the prevalence was low.

When investigating the association with prescribed medications, we found an association between several markers of impaired nutritional status and the number of prescribed medications. Even though the number of prescribed medications increased with the severity of CKD, polypharmacy was present even in patients with mild to moderate CKD. Prescribed medications with nausea as a common or very common side effect were associated with several markers of nutritional status, while medications with xerostomia as a common or very common side effect were inversely associated with hand grip strength.

The overall two-year mortality was 18 %, and sarcopenia was associated with mortality risk. The continuous indicators of nutritional status such as HGS and MUAC were inversely associated with mortality risk, while for the more commonly measured markers such as BMI and waist circumference, we did not observe a linear association with mortality.

6.2.1 Sarcopenia

In this thesis, we have observed a high prevalence of sarcopenia, 36 % and 18 % with EWGSOP1 and EWGSOP2, respectively. Other studies have observed sarcopenia in CKD with prevalences between 4 and 49 %, and the large variation can be explained by the population studied (age, advancement in CKD, CKD modality) and the definition of sarcopenia applied, as elaborated in Section 6.1.3 (55,145,211,212).

In a large scale study from the UK, the prevalence of sarcopenia in CKD patients was estimated to be twice the prevalence in the general population, and in a Turkish study of community-dwelling elderly (mean age 79.4), the observed prevalence of sarcopenia

according to EWGSOP1 was 0.8 %, indicating a lower prevalence in the general population than in the CKD population (146,213). This may be explained by CKD being more prevalent with age, and thus the concordance of the conditions may be partly driven by ageing (primary sarcopenia) (139). However, the nature of CKD may also contribute to the deterioration of muscle mass and strength (secondary sarcopenia). The accumulation of uraemic toxins, low-grade inflammation, oxidative stress, insulin resistance, a decrease of the anabolic hormones such as IGF-1, and testosterone, deficiency of vitamin D, metabolic acidosis, as well as low dietary intake of energy and protein may altogether cause a net negative protein balance, and thus the breakdown of muscle mass (55,214). Additionally, low physical activity level which is prevalent in CKD may preclude the maintenance of muscle strength, and consequently further increase the risk of sarcopenia.

Sarcopenia has become a focus in recent years, as many studies in non-CKD ageing populations and ESKD showed that the condition is related to adverse outcomes as well as increased health costs (143). In CKD, sarcopenia has been associated with lower quality of life, as it impairs the ability to perform activities of daily living, contributing further to the burden of CKD (213,215,216). Sarcopenia has also been associated with the risk of mortality, both in our study and in other studies (211). This will be further elaborated in the following section on mortality (Section 6.2.5).

Assessment of sarcopenia is not an established routine in the hospital setting, which challenges both prevention and treatment. First, our results suggest that screening for the diagnosis must become a part of the routine in clinical practice, but this identification of sarcopenia is not sufficient to combat the implications of health that sarcopenia entails. Further, prevention of sarcopenia will be easier than the treatment of an already established sarcopenia diagnosis, thus early diagnosis seems to have better treatment results, even though more research is required.

6.2.2 Overweight, obesity and central obesity

In **Paper I**, we assessed nutritional status in the population, and we discovered both under and overnutrition among CKD patients, in terms of a high prevalence of HD

patients at nutritional risk of undernutrition, while the overall prevalence of overweight and obesity was high. The prevalence of overweight and obesity in our study is comparable to the prevalence in the general population of Norway (217). In **Paper III**, BMI and waist circumference were not related to mortality risk, which will be further elaborated in Section 6.2.5.

The obesity paradox in pre-dialysis CKD and dialysis patients is established, where increased BMI has been observed as related to decreased mortality risk, as elaborated in the introduction (160). However, increased BMI is also considered a risk factor for onset CKD and progression to ESKD, which makes it important to treat. Reducing or managing a high BMI has been proposed to slow down the progression of CKD in its early stages, as well as enable patients to be assigned to the waiting list for transplantation. In a recently published Cochrane review, interventions for weight loss in CKD were studied (218). The weight loss of six included studies was calculated to a weight loss of 3.69 kg compared to the control group, however, the uncertainty was high (95 % CI 5.82 kg). The effect on eGFR was uncertain, and the effect on CVD and death was not included in any of the studies. More research is thus needed to investigate the effects of weight loss in CKD.

6.2.3 Dietary intake

Assessment of dietary intake in patients with CKD is a difficult task, especially in advanced kidney disease where dietary restrictions are in place, and dietary intake may also be affected by dialysis treatment. There is a lack of studies that include a thorough dietary assessment in patients with CKD, including our studies, where dietary intake assessment was based on one 24-hour dietary recall. This precludes strong conclusions on dietary intake and is the reason why we only include an analysis of dietary intake in **Paper I**. In this paper, we also limited the analysis to energy and protein intakes, and we observed similar intakes of protein in all three CKD modalities (mean intake of 0.95-1.00 g/kg body weight/day in the three groups), despite the recommended intake being different between the groups (58). For the pre-dialysis CKD patients, the protein intake was too high compared to the recommended intake, while for the HD patients, the intake was too low. Other studies have observed similar protein intakes in HD

patients (219). The protein intake of the kidney transplanted patients was in line with the dietary recommendations for the general population, which is recommended for this group of CKD patients (171). The reported energy intakes were low in all groups compared to the recommended intake.

The patients included were also asked whether they had received dietary advice from a dietitian, and a proportion of the CKD population had never received dietary advice from a dietitian. The patients that had received advice from a dietitian had most often attended “The kidney school”, a 12-hour course offered to patients with CKD, where the dietitian had a one hour lecture about nutrition in CKD. A proportion of the patients had received dietary advice from other health care professionals. In other hospitals, positive effects of individual nutrition support have been observed (220). Moreover, in this study of the general hospitalised population at nutritional risk, the patients with CKD had a pronounced beneficial effect of nutritional support. However, these findings have to be further investigated in studies focusing on patients with CKD.

Due to the lack of dietary intake studies in CKD, nutritional guidelines on CKD consequently do often not include high graded evidence for specific dietary advice. This is specifically evident for kidney transplant recipients (221) as seen in the most recently published nutritional guideline from KDOQI, where 27 of 34 guidelines concerning kidney transplantation were graded as OPINION, while the remaining seven were graded from 1A-2D (58).

6.2.4 Medication prescription

In **Paper II**, we observed a high prevalence of polypharmacy (84 %) and excessive polypharmacy (37 %) in the study population, and medicine prescription was associated with severity of disease and treatment modality. Our results are similar to other studies on prescribed medications in patients with CKD (96). We also found associations with number of medications and markers of nutritional status, which to our knowledge have not been investigated before in a CKD. In a Spanish study, the interactions between medications were investigated in patients with CKD, and a large proportion of the patients (91 %) were identified with prescribed medications with

potential interactions (210). The severity of the interactions was graded, and in the majority of the patients (77 %) the potential interaction between medications was estimated as moderately severe. Other studies have reported that a high number of prescribed medications is associated with lower HRQOL, which also adds to the burden of chronic kidney disease and dialysis treatment (95).

In our study, the nutrition-related side effects of nausea and xerostomia were associated with nutritional markers, which indicates that the burden of side effects of prescribed medications may be high. Nausea has been related to other adverse outcomes of nutritional status, as well as reduced quality of life in other patient groups (222–224).

We did not confirm the presence of the side effects in the patients; however, there have been observed high prevalences of xerostomia and nausea in a population of ESKD patients. In this study, nausea and xerostomia were related to taste changes, and taste changes were associated with malnutrition (225). However, several other side effects related to nutrition are of interest to be investigated with longitudinal studies in the future. This includes the side effects of weight gain and hyperglycaemia, which would be of particular interest in kidney transplanted patients.

It is important to highlight that we are not opting for leaving out necessary medication prescriptions. We are in fact opting for a regular critical review of prescriptions and careful assessment of nutritional status in patients with CKD and long medication lists, and suggesting that nutritional care should be given accordingly.

6.2.5 Mortality

In **Paper III**, we investigated the association between indicators of nutritional status and mortality risk after two years of follow-up. Sarcopenia was associated with an increased risk of mortality, while central obesity was not associated with mortality. Regarding the continuous markers of nutritional status, an inverse association with mortality was observed for HGS, ALM, phase angle, and MUAC. There was no obvious mortality risk associated with BMI, ALMI, MUAMC, and waist circumference. When investigating non-linear relationships, we found a U-shaped

association between mortality risk and MUAMC and waist circumference, while BMI was associated with increased risk at BMI < 22 kg/m^2.

Our findings regarding BMI and mortality are in line with other studies (163). In a systematic review and meta-analysis on obesity and mortality risk, differences in mortality risk were observed according to treatment modality; in pre-dialysis CKD, the mortality risk was increased by 1 % per additional BMI unit, while for patients treated with HD, each additional BMI unit decreased the mortality risk by 3 %. For the kidney transplanted patients, no estimated association was found. As we did not investigate the association between BMI and mortality stratified by CKD modalities in our study, due to the limited sample size, we were not able to investigate such differences. Our general findings of the association between BMI and mortality risk highlight the importance of low BMI in the population with chronic disease, which is also proposed in the PEW diagnosis (156). Indeed, in the general population, a J-shaped association between BMI and mortality has been estimated, with the lowest all-cause mortality risk at BMI 22-25 kg/m^2 (226,227). However, in the presence of disease, the energy storage of fat may be of importance for survival (228).

Although in the general population waist circumference is strongly associated to mortality risk, we did not observe such an observation in our population (176,229). However, in the non-linear investigation, a U-shaped relationship was observed, but the uncertainty was high. Other studies investigating the mortality risk associated with waist circumference in CKD have shown contradictory results (163). Similar to the results of BMI, we did not conduct stratified analyses for waist circumference and mortality risk according to CKD modality, which would be of interest in a larger-scale study.

In CKD, sarcopenia may be of age-related origin (primary sarcopenia) but exacerbated by the nature of CKD (secondary sarcopenia) (55). In the general population, sarcopenia is associated with increased mortality risk, and studies of the CKD population show similar indications (143,211). The determinants of CKD proposed to be involved in sarcopenia, such as the accumulation of uraemic toxins, systemic

inflammation, oxidative stress, and insulin resistance are associated with increased mortality risk, and it remains to investigate whether the association between mortality and sarcopenia in CKD is purely associative or wether it also exists as a causal relationship.

7. Conclusion

Overall, the findings from this thesis indicate that a thorough assessment by a variety of measurements is necessary to capture nutritional status in patients with CKD. Patients with long medication lists, especially medications with nausea as a common or very common side effect, may be more likely at risk of reduced nutritional status.

On the other hand, indicators of impaired nutritional status such as sarcopenia, and its components of low HGS and muscle mass, may be associated with increased mortality risk in patients with CKD. Even if obesity is more prevalent than undernutrition, our results suggest that undernutrition and sarcopenia is associated with mortality, rather than measures of obesity.

Our results call, on the scientific side, for more research on the underlying causes and consequences of sarcopenia in CKD, and the molecular mechanisms involved in the impairment of skeletal muscle mass and strength. On the clinical side, our results urge the inclusion of a comprehensive nutritional assessment in regular patient care to capture the patients at risk of a suboptimal nutritional status.

8. Further perspectives

We have investigated the prevalence and consequences of impaired nutritional status in patients with CKD. Our results emphasise the high prevalence of nutritional disturbances and their detrimental consequences in these patients. The next step would be to investigate both underlying causes and mechanisms of disturbances of nutritional status, such as sarcopenia, as well as treatment options and the effects of treatment on clinical outcomes.

There is a lack of data on early stages of CKD, which is evident both in the current thesis and in the literature review of the recently published KDOQI guideline (58). This underlines the need for more research in the earlier stages. If CKD patients could be identified at an early stage, the potential to prevent further progression could be even better. An early implementation of nutritional care would be interesting to investigate further, both the compliance and the potential of slowing the progression of the kidney disease.

Future studies should investigate the effect of the prevention and treatment of nutritional related conditions in CKD, such as sarcopenia. The effect of physical activity in patients with CKD has been investigated with convincing results, and the intervention was also found extremely cost-effective (8,45,230,231). Future studies should combine the interventions of physical activity and nutritional care, as suggested by Hendriks et al., with the following cost-analysis (232).

In the current thesis, we have observed several challenges in nutritional status, both related to the CKD, the prescribed medications and mortality risk. The presence of sarcopenia, low muscle strength and mass, measures of MUAC and skinfold triceps, as well as central obesity were only captured by extensive assessment of nutritional status. In today's clinical practice, the assessment of nutritional status is focused on BMI, a measure that is not able to capture body composition or body shape. We have also observed that diagnoses of malnutrition can also occur in patients with a high BMI which has also been demonstrated in other studies (160,233).

Implementation of a wider range of measurements would enable the identification of patients with diagnoses of sarcopenia, central obesity, and patients at risk of such conditions. Even though the identification of such nutritional impairments is important, the true value is if we can go further to find a way to treat such challenges. The wide variety of impairments of nutritional status demands different treatment strategies and thus individualised nutritional care is important to study. Intervention studies with the aim to improve nutritional status in patients with CKD would be the way forward.

9. References

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RESEARCH ARTICLE Open Access

High rates of central obesity and sarcopenia in CKD irrespective of renal replacement therapy – an observational cross-sectional study

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Abstract

Background: Poor nutritional status of patients with renal disease has been associated with worsening of renal function and poor health outcomes. Simply measuring weight and height for calculation of the body mass index does however not capture the true picture of nutritional status in these patients. Therefore, we measured nutritional status by BMI, body composition, waist circumference, dietary intake and nutritional screening in three groups of renal patients.

Methods: Patients with chronic kidney disease not on renal replacement therapy (CKD stages 3–5, $n = 112$), after renal transplantation ($n = 72$) and patients treated with hemodialysis ($n = 24$) were recruited in a tertiary hospital in Bergen, Norway in a cross-sectional observational study. Dietary intake was assessed by a single 24 h recall. All patients underwent nutritional screening, anthropometric measurements, body composition measurement andfunctional measurements (hand grip strength). The prevalence of overweight and obesity, central obesity, sarcopenia, sarcopenic obesity and nutritional risk was calculated.

Results: Central obesity and sarcopenia were present in 49% and 35% of patients, respectively. 49% of patients with central obesity were normal weight or overweight according to their BMI. Factors associated with central obesity were a diagnosis of diabetes and increased fat mass, while factors associated with sarcopenia were age, female gender, number of medications. An increase in the BMI was associated with lower risk for sarcopenia.

Conclusion: Central obesity and sarcopenia were present in renal patients at all disease stages. More attention to these unfavorable nutritional states is warranted in these patients.

Keywords: ESRD, Renal disease, Nutritional status, Sarcopenia

Background

Worldwide, the prevalence of patients treated for chronic kidney disease is increasing. Improvements in therapy have improved the outcomes of chronic kidney disease and renal replacement therapy, such as hemodialysis and transplantation, leading to higher numbers of patients who represent with increased number of comorbidities [1]. Diet and nutritional status play a major role in chronic renal disease, as loss of renal function has a major impact on nutritional metabolism and its regulation, as the progression of disease can be modified by diet and nutritional status, and dietary measures can reduce the burden of comorbidities such as hypertension, diabetes mellitus, and risk of cardiovascular disease [2].

Nutritional status can be affected by both over- and undernutrition. Obesity and especially diabetes mellitus are strong risk factors to develop renal disease [3]. Overweight and obesity are common features of diabetes mellitus, and especially central obesity, with increased visceral fat accumulation and waist circumference, is associated with

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unfavorable metabolic changes and increased risk of diabetes mellitus and cardiovascular disease [4, 5].

On the other hand, during dialysis, the risk to develop malnutrition or protein-energy wasting (PEW), due to insufficient energy and protein intake or increased losses, is increased and poses an important risk factor for increased morbidity and mortality. Patients on hemodialysis often suffer from lack of appetite and increased catabolism, which can lead to undernutrition if not adequately diagnosed and treated [6].

As chronic kidney disease and end-stage renal disease are especially common among older subjects, common age related changes in metabolism and body composition are also observed in patients with kidney disease. Changes in body composition associated with aging affect an increase of fat mass and a decrease of lean body mass. Skeletal muscles are especially affected and aging is associated with a decrease of muscle mass and strength, also called sarcopenia. Sarcopenia has been identified as a major risk factor for frailty, which itself is a risk factor for mortality in dialysis patients [7], falls and other unfavorable health outcomes. As it affects skeletal muscles, it can also occur in obese patients ('sarcopenic obesity'). Estimates of body composition and sarcopenia can be made either with DEXA or with bioelectrical impedance assessment (BIA) methods [8]. BIA has the advantage of being transportable, easy to use and cheap, and studies have shown that BIA estimates are comparable to DEXA estimates of lean body mass [9, 10]. Muscle strength can be measured by functional measurements and the measurement of hand grip strength with handheld dynamometers has been widely used [11, 12].

Patients in hospitals are a vulnerable group for developing undernutrition. It has been estimated that about every third patient admitted to hospitals in Western countries is undernourished or at risk of undernutrition as assessed by screening tools [13]. Nutritional screening usually focuses on body mass, recent weight losses, loss of appetite and disease-related conditions [14]. In many Norwegian hospitals, the screening tool NRS2002 is used. This tool can also be used in patients attending outpatient clinics such as CKD and patients with a kidney transplant.

Thus, nutritional status can be measured in different dimensions: over- and undernutrition, the distribution of fat mass, changes in body composition associated with aging and disease (loss of muscle mass, sarcopenia) or nutritional risk. However, in clinical praxis, nutritional status is often defined by body mass index only which is based on weight and height measurements but does not take into account body composition (skeletal muscle mass) and fat distribution. We propose that a single measurement will not be able to capture these different dimensions of nutritional status. In addition, renal patients require dietary advice and treatment that is adapted to the patients' stage of renal disease and that changes during the course of the disease. Therefore, the aim of the current study was to investigate the feasibility and meaning of different dimensions of nutritional status assessment by anthropometry, body composition measurement, dietary assessment, functional measurements of muscle strength and nutritional screening in patients with renal disease ranging from CKD stage 3 to pre-dialysis, hemodialysis and renal transplant patients.

Methods

Patients, consent and ethics

This is a cross-sectional, single center observational study conducted at the Haukeland University Hospital, Bergen Norway. Adult patients with renal disease were eligible for inclusion into the study, which was conducted at the dialysis unit and the outpatient clinic of the Section of Nephrology at the Department of Medicine. During 2014–2017, outpatients from the Section of Nephrology were recruited to the study after signing informed consent (November 2014 to February 2015: $n = 24$ patients with hemodialysis (selected by consent from $n = 74$ patients), August to December 2015: $n = 112$ patients with chronic kidney disease stage 3 to 5 (selected by consent from $n = 183$ CKD patients without renal replacement therapy), and September 2016 to January 2017: $n = 72$ patients with a renal transplant (selected by consent from $n = 249$ patients)) Included patients were compared regarding age and sex to the total patient group, and in dialysis patients, regarding time on dialysis and dialysis treatments and no significant deviations were found (data not shown).

The study was conducted in accordance with principles of the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics at the University of Bergen (REK Vest, No. 2014/1790).

Study procedures

For renal transplant patients and CKD patients, all patients were informed about the study by mail prior to their regular outpatient visit. During the visit, they were asked whether they were interested to participate in a study on dietary habits, nutritional status and health. Eligible patients were patients providing informed consent, 18 years or older, and able to communicate either in Norwegian or English. Reasons for exclusion were refusal of informed consent, language problems or cognitive decline. After informed consent, these patients filled in a questionnaire about lifestyle habits and disease history, underwent a single 24 h dietary recall, measurement of hand grip strength, anthropometric measurements (weight, height, skinfolds, waist and upper arm circumference), body composition

measurement by bioelectrical impedance, and donated an extra blood and urine sample for later analyses.

Patients treated with hemodialysis were asked during dialysis whether they wanted to participate in the study. After providing informed consent, a new appointment for the data collection was scheduled with the routine blood sampling. Identical questionnaires and procedures were used as for renal transplant patients and CKD patients. All functional, body composition and anthropometric measurements were made after dialysis.

All measurements were conducted by clinical dieticians trained in anthropometric measurements and dietary recall. Information about disease history including comorbidities, medication and blood pressure were obtained from the patients' records.

Bioelectrical impedance analysis (BIA)

Body composition was measured by a single frequency (50 KHz) tetrapolar BIA 101 Aniversary Sport Edition (AKERN). The measurements were usually performed on the non-dominant side of the body, unless the patients had a fistula on this side of the body. All jewelry, clocks and belts were removed. Patients were usually non-fasting. The current–injector electrode was placed on the dorsum of the hand, just above the phalangeal-metacarpal joint and on the ventral side of the foot just below the transverse arch. Detector electrodes were placed on the dorsal side of the wrist, midline and in line with the pisiform bone, and across the ankle in line with the medial malleolus. Patients with a pacemaker or an implantable cardioverter-defibrillator were not investigated by BIA. In this way, resistance and reactance values were obtained in Ohms, and in addition the phase angle. The total fat free mass (FFM) in kg and fat mass (FM, in kg and in % of body weight) were calculated using a formula of Deurenberg 1989 [15].

$$FFM = 6.520 \times 100 \times height^2/resistance + 3.8\,x\,gender + 10.9$$

(height in m, resistance at 50 kHz in Ω, gender with male = 1 and female = 0).

For the calculation of appendicular lean mass (ALM), the following formula (Macdonald 2006) was used (ALM):

$$ALM_{BIA} = -11.626 + (0.292 \times height^2/resistance) + (0.06983 \times reactance) + (0.08553 \times height) + (-2.092 \times gender) + (-0.05 \times age)$$

(height in cm; resistance and reactance at 50 kHz (Ω); gender, 0 = male, 1 = female; age in years).

The obtained ALM was used for the calculation of the skeletal muscle index (ALM/Ht^2). Cut-off values in men of ≤8.87 kg/m^2 and in women of ≤6.42 kg/m^2 were applied (in addition to low hand grip strength) for the definition of sarcopenia [8].

Hand grip strength was measured using a hand held dynamometer (JAMAR, Sammons Preston, Bolingbrook, IL, USA) in triplicate. Both average and maximum hand grip strength was recorded. For the definition of sarcopenia, a cut off of 30 kg in men and 20 kg in women was applied [16].

Diagnosis of sarcopenia was made when the patient fulfilled the definition for both ALM/ht^2 and HGS.

Weight (while wearing light clothing and no shoes) and height (without shoes) was measured using the same type of scales and stadiometer (Seca model 877, and model 217, Seca, Hamburg, Germany). The body mass index (BMI) was then calculated, and the patients were classified as either underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.99 kg/m^2), overweight (BMI 25.0–29.99 kg/m^2), or obese (BMI ≥ 30 kg/m^2). In addition, a patient was identified as having central obesity when the waist circumference was > 102 cm in males and > 88 cm in females, regardless of the patient's BMI.

Nutritional screening was performed using NRS2002 which is an established tool for patients in hospitals and used routinely in Haukeland University Hospital [13]. The screening is based on 4 initial questions (BMI < 20.5 kg/m^2, weight loss during the last three months, reduced food intake during the last week, presence of severe illness?). If any question was answered with yes, the interviewer continued to the main screening with questions regarding both nutritional status and disease status. Both sections are graded with a score from 0 to 3, with increasing scores in relation to severity of disease and deterioration of nutritional status. Patients aged 70 years or older received an extra score. A score ≥ 3 identifies patients at nutritional risk for malnutrition [17].

Dietary intake was assessed by a single 24 h dietary recall. The patients were asked about food and drink intake the day before the appointment and the interviewer went through all meals and possible consumption between meals, using a standardized interview guideline [18]. Portion size was estimated using a booklet with four different portion sizes demonstrated or in household measurements or no. of items consumed. Data were entered in the online dietary tool 'Kostholdsplanleggeren.no' which is based on the official Norwegian food composition table and edited by the Norwegian Food Safety authority and the Norwegian directorate of health.

Patients were also asked whether they followed dietary restrictions and if so, they were asked to specify them. In addition, the number of prescribed medications was noted.

Laboratory data were taken from the patients' routine blood samples which were usually taken the same day as the appointment. Laboratory variables were analyzed in

the central laboratory of the Haukeland University hospital which is ISO 15189 certified. Variables of interest were hemoglobin, albumin, C-reactive protein, creatinine in serum, and urinary albumin excretion rate (in spot urine, per mmol creatinine). The estimated glomerular filtration rate (eGFR) was calculated using the CKD-Epi equation [19].

Statistical analysis

Each group of patients was analyzed separately. Differences between continuous variables were tested with either the t-test or the Mann Whitney U test, and between categorical variables were tested by the Chi squared or the Fisher's exact test. Differences between the patients' groups were tested with analysis of variance or Kruskal-Wallis test. Associations between continuous variables were investigated by Spearman's rho correlation analysis.

Logistic regression was used to explore factors associated with central obesity and sarcopenia. SPSS (version 25) was used for the statistical calculations. A p-value of 0.05 was regarded as significant.

Results

Age and sex distribution of the selected patients were similar to the patient cohort of kidney patients treated at the Hospital.

Patient characteristics are depicted in Table 1. In brief, patients with CKD were older than ESRD-HD and renal transplant patients, and the distribution of men and women was similar in the three patient groups. Renal function was best in the renal transplant group, with higher eGFR and lower albumin excretion than in the CKD patients. Patients in the ESRD-HD group were at median 2 years on dialysis (reflecting the short waiting time for a kidney transplant in Norway of less than one year), and in renal transplant patients, at median almost 9 years were gone after transplantation. The prevalence of hypertension and diabetes was highest in the ESRD-HD group and lowest in the renal transplant group, with highly significant differences. Albumin concentrations were lowest in the ESRD-HD group, but only five of 24 patients in this group showed low albumin levels (< 38 g/L).

The average BMI was highest in the CKD group, followed by the renal transplant and the ESRD-HD group.

Table 1 Characteristics of the patients with different stages of renal disease (CKD chronic kidney disease; ESRD-HD end-stage renal disease treated with hemodialysis; renal transplant: recipients of a renal transplant)

	CKD *N* = 112	ESRD-HD *N* = 24	Renal transplant *N* = 72	*P* (ANOVA) Kruskal Wallis test
Age	66 (51, 76)	63 (50, 76)	60 (49, 67)	0.04
Sex (m/f)	79/33 (71%/29%)	17/7 (71%/29%)	51/21 (71%/29%)	0.999
Body mass index (kg/m^2)	27.4 (23.9, 31.0)	24.7 (21.8, 27.5)	26.0 (24.0, 29.3)	0.02
Hypertension n (%)	82 (92%)	23 (96%)	28 (39%)	< 0.001
Diabetes mellitus n (%)	33 (30%)	11 (46%)	11 (15%)	< 0.001
Current smoking n (%)	17 (15%)	3 (12%)	8 (11%)	0.104
No. of prescribed medication[a]	7 (4, 9)	14 (12, 17)	9 (7, 11)	< 0.001
eGFR[b] (ml/min/1.73m^2)	28 (18, 38)	6 (5, 8)	53 (38, 73)	< 0.001
CKD stages n (1–3/4/5)	44/52/16	0/0/24	59/11/1	
Systolic blood pressure (mmHg)	134 (125, 145)	159 (142, 175)[c]	130 (120, 140)	< 0.001
Diastolic blood pressure (mmHg)	80 (70, 82)	67 (61, 77)[c]	80 (71, 82)	< 0.001
Years on dialysis	–	2 (1–4)	–	
Years since renal transplant	–	–	8.9 (5.9, 15.5)	
Serum creatinine (μmol/L)	209 (159, 278)	656 (560, 844)	114 (96, 164)	< 0.001
Serum urea (mmol/L)	16 (11.2, 20.0)	23 (19, 28)	9.3 (6.7, 13.8)	< 0.001
Hemoglobin (g/L)	12.9 ± 1.6	11.9 ± 1.6	13.6 ± 1.9	< 0.001
Serum albumin (g/L)	44 (41, 45)	40.5 (38, 43)	43 (41, 45)	0.001
Serum C-reactive protein (mg/L)	3 (1, 6)	3 (1, 16)	2 (1, 4)	0.08
HbA1c (%)	5.8 (5.5, 6.3)	5.8 ± 1.2	5.7 (5.5, 6.1)	0.12
Urinary albumin (mg/mmol Crea)	30 (5, 104)	–	2.7 (0.9, 17.0)	< 0.001

[a]Medication and supplements described in The Norwegian Pharmaceutical Product Compendium (Felleskatalogen AS)
[b]eGFR was calculated using CKD-Epi equation [18]
[c]pre dialysis, median (IQR)

CKD patients also showed the highest prevalence of obesity (BMI > 30 kg/m^2, 33%) and central obesity (increased waist circumference, 53%), followed by the renal transplant group (22% and 50%, respectively) and the ESRD-HD group (4% and 39%, respectively). In the renal transplant group, there were 3 patients (all female) who were underweight with a BMI < 18.5 kg/m^2 (Fig. 1a). Applying higher BMI cut-offs for underweight as suggested in patients with renal disease [20], resulted in higher numbers: BMI < 23 kg/m^2 was observed in 21 (19%) of the CKD patients, 13 (18%) of the transplant group and 9 (37.5%) of the ESRD-HD group.

Nutritional and functional data are shown in Table 2. Nutritional risk and sarcopenia were most prevalent in the ESRD-HD group with 33% being at nutritional risk by NRS2002 screening and 42% diagnosed as having sarcopenia (low skeletal muscle index plus low hand grip strength). Nutritional risk was rare in the CKD and renal transplant group (3% and 7%, respectively). Patients at nutritional risk were either underweight ($n = 2$), normal weight ($n = 9$) or overweight ($n = 5$). In CKD and renal transplant patients, sarcopenia was almost as prevalent as in the ESRD-HD group. Overall, only 29% of patients in the CKD group, 39% in the ESRD-HD group and 31% of patients in the renal transplant group had neither sarcopenia nor central obesity (Fig. 1b).

Dietary intake was assessed by a single 24 h dietary recall (Table 2). Neither dietary energy nor protein intakes were significantly different across patient groups. On average, protein intake exceeded 0.8 g/kg BW, the recommended amount of protein in the CKD and renal transplant patients [21], respectively, and was lower than recommended (1.2 g/kg body weight) in the ESRD-HD group [22]. In addition, the energy intake was on average lower than the expected dietary energy requirement, and even if underreporting of dietary intake was considered, the dietary intake was well below the recommended dietary intake (30–35 kcal/kg/d) [22, 23].

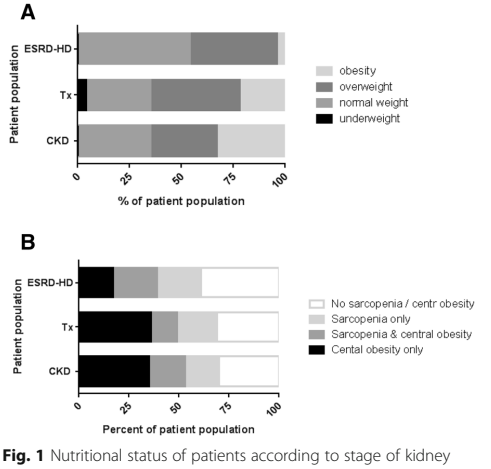

Fig. 1 Nutritional status of patients according to stage of kidney disease (CKD chronic kidney disease; ESRD-HD end-stage renal disease treated with hemodialysis; Tx: recipients of a renal transplant) and established BMI cut-offs (**a**) and according to sarcopenia, central obesity and sarcopenic obesity (**b**). Sarcopenia was defined by low skeletal muscle index and low hand grip strength, central obesity according to waist circumference and sarcopenic obesity as presence of sarcopenia and central obesity

About half of the patients mentioned that they were following dietary restrictions ($n = 107$, 74 men and 33 women). While most patients from the ESRD-HD group had restrictions ($n = 19$, 79%), CKD and renal transplant patients had less often dietary restrictions ($n = 55$, 49%, and $n = 27$, 38%, respectively). Most restrictions were on salt and fluid ($n = 35$), or phosphate/potassium intake ($n = 20$), or patients followed multiple (protein, salt, potassium, phosphate, fluid) restrictions ($n = 40$). Restrictions on energy intake were only mentioned by two patients specifically. Overall, dietary restrictions had little effect on dietary intake (data not shown).

Sarcopenia was significantly associated with higher age, lower mean upper arm circumference, lower phase angle by BIA, lower serum levels of creatinine and hemoglobin, higher CRP, but not with differences in serum albumin, BMI or waist circumference. While absolute protein intake was lower in sarcopenic patients, there were no differences in g protein intake per kg body weight or in energy intake (data not shown). There was no difference in patient group, or presence of central obesity (Table 2 and Fig. 1b).

In a multivariate logistic regression model, age, female gender, and number of prescribed medications were significantly associated with a higher risk for sarcopenia and higher fat mass or body mass index were associated with lower risk, while type of renal disease, comorbidities like diabetes mellitus or hypertension were not significantly associated with risk for sarcopenia (Table 3).

Central obesity, as defined by increased waist circumference, was observed in 102 patients. Remarkably, 50 patients (49%) with increased waist circumference had a BMI either in the normal range or in the overweight category and would therefore not be classified as obese by BMI only. In the multivariate logistic regression model, higher fat mass and diabetes mellitus were associated with central obesity. (Table 4). In CKD patients and renal transplant patients, urinary albumin excretion rate was also significantly associated with central obesity (data not shown).

Sarcopenia and obesity defined by a BMI exceeding 30 kg/m^2 was only observed in 12 CKD patients and one renal transplant patient, but sarcopenia with concurrent increased waist circumference was frequent and affected

Table 2 Nutritional data and functional data of patients with renal disease according to stage of renal disease (CKD chronic kidney disease; ESRD-HD end-stage renal disease treated with hemodialysis; renal transplant: recipients of a renal transplant)

	CKD $N = 112$	ESRD-HD $N = 24$	Renal transplant $N = 72$	*P* (ANOVA) Kruskal Wallis test
Weight (kg)	82.1 ± 18.6	72.5 ± 12.4	79.0 ± 15.0	0.04
BMI (kg/m^2)	27.8 ± 5.1	24.7 ± 3.7	26.7 ± 4.5	0.02
Resistance (Ω)	475 ± 80	509 ± 67	487 ± 86	0.104
Reactance (Ω)	48 ± 11	45 ± 14	50 ± 13	0.215
Phase angle (°)	5.76 ± 1.19	5.0 ± 1.4	5.86 ± 1.03	0.027
Appendicular lean mass (kg)[a]	21.3 ± 5.2	19.6 ± 5.3	21.4 ± 4.8	0.274
Skeletal muscle index (ALM/Ht^2, kg/m^2)[b]	7.1 (6.3, 7.6)	6.6 (5.7, 7.6)	7.6 (6.2, 8.0)	0.077
Fat mass (kg)	27.4 (19.8, 35.1)	22.4 (13.9, 27.1)	25.2 (15.9, 34.8)	0.102
Fat mass (% of weight)	33.6 (27.4, 39.1)	29.0 (21.4, 34.5)	32.9 (23.4, 41.1)	0.256
Fat free mass (kg)	53.3 (45.8, 61.6)	49.5 (44.9, 54.8)	55.2 (43.3, 59.9)	0.385
Waist circumference (cm)	99.2 ± 14.4	95.9 ± 13.6[c]	98.0 ± 14.3	0.47
Mid upper arm circumference (cm)	32.6 ± 4.8	29.0 ± 3.6	30.5 ± 3.4	< 0.001
Biceps skinfold (mm)	15 (10, 21)	8 (4, 11)	7 (5, 12)	< 0.001
Triceps skinfold (mm)	23 (17, 30)	14 (10, 19)	18 (12, 26)	< 0.001
Dietary intake (Kcal/d)	1730 (1380, 2120)	1700 (1230, 1927)	1794 (1303, 2087)	0.635
Dietary intake (Kcal/kg bw/d)	22 (16, 29)	23 (17, 30)	21 (18, 28)	0.875
Dietary protein (g/d)	76 (56, 96)	71 (60, 80)	78 (59, 103)	0.238
Dietary protein (g/kg bw/d)	0.95 (0.73, 1.23)	1.00 (0.77, 1.23)	0.96 (0.79, 1.38)	0.493
Handgrip strength average (kg)	30 ± 12	28 ± 12	30 ± 11	0.66
Handgrip strength maximum (kg)	32 ± 13	31 ± 13	32 ± 11	0.75
Knee extension average (*N*)	173 ± 52	–	183 ± 37	0.234
Knee extension maximum (*N*)	184 ± 54	–	195 ± 39	0.235
Nutritonal risk (NRS2002)	3 (3%)	8 (33%)	5 (7%)	< 0.001
Sarcopenia[d]	41 (37%)	10 (42%)	23 (32%)	0.642
Central obesity	58 (53%)	9 (39%)[c]	35 (50%)	0.490

Data are shown as median with interquartile range or as mean with standard deviation
[a]appendicular lean mass was calculated according to MacDonald et al. [10]
[b]Skeletal mass index calculated from appendicular lean mass divided by height squared
[c]$n = 23$
[d]BIA measurements were performed in 101 CKD patients, 23 ESRD-HD patients and 69 renal transplant patients due to contraindications present. In patients with missing BIA measurements, sarcopenia was defined by low hand grip strength only

20 CKD patients (18%), 5 ESRD-HD patients (22%) and 9 renal transplant patients (13%) (Fig. 1B).

Discussion

This study aimed to investigate nutritional status of patients with renal disease at different stages. There was a particular interest in the concurrent occurrence of low muscle mass and accumulation of fat mass, as has been described to be typical for patients with kidney disease but which is less obvious from routine weight measurements.

The main findings were that 1) Obesity was frequent in CKD and renal transplant patients. Increased waist circumference, indicating central obesity affected almost half of all patients in all patient groups, 2) A substantial proportion of patients on hemodialysis was found to be at nutritional risk, while the proportion of patients at nutritional risk was low in CKD and renal transplant patients, 3) Sarcopenia was present in about one third of the patients. Low skeletal mass index and low appendicular lean muscle mass were present in almost all patients with ESRD and in ¾ of CKD patients, while low hand grip strength was present in more than a third of all patients across renal disease stages, 4) Sarcopenic obesity, defined as the concurrence of central obesity with increased waist circumference and sarcopenia was frequent. Sarcopenic obesity with BMI > 30 kg/m^2 was less frequently observed, and not at all in the ESRD-HD patients.

Thus, the study revealed a number of nutritional problems in patients with kidney disease, spanning over- and undernutrition and nutritional quality. These problems need to be carefully addressed during treatment as they

Table 3 New

Odds ratio (95% confidence interval)	
Multivariate logistic regression with Sarcopenia as dependent variable	
CKD patients (reference)	
ESRD-HD	0.31 (0.08, 1.25)
Renal transplant	0.80 (0.35, 1.83)
Gender (female =1)	2.87 (1.27, 6.48)
Age (per year increase)	1.10 (1.06, 1.14)
Prescribed medications (per no. increase)	1.19 (1.07. 1.32)
BMI (per unit increase)	0.92 (0.85, 0.99)

may affect disease progression, metabolic control, and quality of life.

The high rate of high BMI but also of central obesity in the CKD and renal transplant patients reflects both the overall high prevalence of overweight and obesity in the general population and disease-specific reasons [24]. Diabetes mellitus type 2, which is usually associated with overweight and obesity, was frequent especially in the CKD patients (30%). It has been shown that obesity itself is a risk factor for the development of CKD and the progression of the disease [3, 25]. Overweight and obesity in renal transplant patients is a known problem due to weight gain after transplantation [26, 27].

Other studies have also reported high prevalence of overweight and obesity in patients with CKD [28, 29]. Similar to data of the present study, the British patients with central obesity had higher prevalence of cardiovascular risk factors.

The concurrent finding of low ALM and overweight/obesity puts a challenge on all approaches of weight reduction in these patients. Body weight reduction is the sum of reductions in fat mass and in fat-free mass, which usually outweigh about 20% of lost weight [30]. Although reduction of fat mass is warranted in overweight and obese CKD and renal transplant patients for improvement of metabolic control, especially in patients with diabetes mellitus, any diet would also compromise the maintenance of muscle mass. Protein-rich diets have been recommended in weight loss studies due to their effects on satiety and maintenance of muscle mass [31, 32], however, CKD patients are advised not to increase their protein intake [22, 33]. Thus, approaches involving increase of physical activity and targeted muscle training are warranted in combination with weight reduction diets.

Table 4 New

Odds ratio (95% confidence interval)	
Multivariate logistic regression with 'central obesity' as dependent variable	
CKD patients (reference)	
ESRD-HD	2.12 (0.55, 8.18)
Renal transplant	2.00 (0.71, 5.62)
Diagnosis of diabetes mellitus	3.10 (1.20, 8.03)
Fat mass (increase in 1 kg)	1.29 (1.20, 1.39)

In the present study, we did not observe differences in dietary intake between the patient groups. A careful evaluation of the 24 h recalls revealed underreporting especially in the obese patients, who had lower energy intakes than lean or overweight patients. This is a known phenomenon [34, 35] that should be acknowledged in the evaluation of dietary intake [36]. As obesity (and thus underreporting) was much more prevalent in CKD and renal transplant patients than in the ESRD-HD patients, it can be argued that probably the true energy intake was lower in ESRD-HD than in CKD and renal transplant. A sensitivity analysis, where all patients with BMI > 30 kg/m^2 were removed showed that average energy intake increased in CKD and renal transplant, but there were still no significant differences between the patient groups (data not shown).

The high prevalence of sarcopenia can both be attributed to the age of the patients which was on average over 60, and the kidney disease in conjunction with the common comorbidities in these patients. We did not assess physical activity in the patients, but it can be assumed that many of them had a sedentary lifestyle as reported by others [37] and which is also associated with low muscle muss and muscle strength. As sarcopenia is associated with lower quality of life [38, 39], more attention should be awarded to the condition and lifestyle changes to slow down the process should be encouraged [40].

Protein intake is a major concern in renal disease. While CKD patients are advised to limit their protein intake, ESRD-HD patients should have a high protein intake of 1.2 g/kg body weight. Protein intake was similar in the three patient groups, indicating on average high protein intake in CKD patients and low protein intake in ESRD-HD. A protein intake of less than 0.8 g/kg BW was reported in 26% of the patients with ESRD, and was associated with nutritional risk in this group of patients. Protein intake of less than 0.6 g/kg BW was reported in 20% of CKD patients. More focus on nutritional education including dietary protein at all stages of renal disease would probable enable more patients to follow a diet adequate in protein.

The study had several advantages and limitations. Advantages of the present study were that the study patients represent typical and well-documented patients with renal disease of a tertiary hospital, the comprehensive assessment of nutritional status, including nutritional screening, anthropometric measurements, body composition measurement and clinical variables combined with dietary assessment. Three different groups of patients suffering from kidney diseases with or without renal

replacement therapy were included which allows to mirror the development of nutritional status during the course of the disease. All analyses have been made in a highly standardized way.

Among the limitations, it has to be mentioned that the study lacked an assessment of physical activity, that underreporting limited the use of the dietary data, and that future studies should also include a follow up to investigate the importance of nutritional status on the course of the disease. The number of patients on hemodialysis is rather low and this makes it difficult to draw more general conclusions. Also, we did not include patients on peritoneal dialysis. Other limitations that apply include that we did not have a non-CKD, age-matched control group, and no 24-h urine samples due to logistic reasons e.g. to assess normalised protein catabolic rate (nPCR) as a more objective marker for protein intake. Another limitation is the single 24-h recall, which is less accurate than two or more 24-h recalls. The cut-off values for sarcopenia were derived from a population without kidney disease, and the applicability to renal patients may be questioned.

In conclusion, the study showed that nutritional problems are highly prevalent at all stages of renal disease, with sarcopenia and obesity being the most prevalent conditions in CKD and renal transplant patients, while ESRD-HD patients also show a high prevalence of nutritional risk. The high prevalence of central obesity and sarcopenic obesity warrants attention.

Future studies should focus on treatment of obesity in renal disease with concurrent focus on maintenance of muscle mass. Most urgently, all CKD patients with stages ≥3 should strongly be advised to increase their physical activity in formalized programs especially for reduction of central obesity and sarcopenia.

Conclusion

The present study shows that nutritional disturbances are common in patients with chronic kidney disease, with a predominance of sarcopenia and central obesity. These cannot easily measured by weight and height, but need determination of body composition and waist circumference. As both are associated with unfavorable health outcomes, these additional measurements are strongly recommended in patients with chronic kidney disease regardless of renal replacement therapy.

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Availability of data and materials
The dataset used and analysed during the current study is available from the corresponding author on reasonable request.

Authors' contributions
JD and HPM designed the study, HD, NLW, KS1, KS2, IS contributed to data collection and analysis, JD, HD, NLW and KS1 performed the statistical analysis, and the primary manuscript preparation. All authors contributed to the writing process and reviewed the manuscript. JD has the primary responsibility for the final content. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was conducted in accordance with principles of the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics (REK Vest, (regionale komiteer for medisinik og helsefaglig forskningsetikk, University of Bergen, No. 2014/1790). All patients signed an informed consent prior to participation.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests. The results presented in this paper have not been published elsewhere in whole or in part, except in abstract form.

Publisher's Note

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II

ORIGINAL RESEARCH

Medication Prescription, Common Side-effects, and Nutritional Status are Associated in Patients With Chronic Kidney Disease

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Objective: Chronic kidney disease (CKD) is associated with metabolic, nutritional, and extra-renal changes, as well as a high rate of comorbidities, which necessitates the prescription of numerous medications. Patients with CKD often experience poor nutritional status related to disease severity and prescribed medication; however, this association has not been investigated in depth. Therefore, this study aimed at investigating the association between prescribed medication and nutritional status in patients with CKD.

Methods: Assessment of nutritional status was performed using anthropometric and functional measurements and by biochemical measures. Patient history and the number and type of currently prescribed medications were collected from patients' records. We evaluated the total number and the number of specific medicines with common or very common side-effects of nausea or xerostomia.

Results: Two hundred seventeen patients with CKD were included in this cross-sectional study (n = 112 with pre-dialysis CKD stages 3-5, n = 33 with hemodialysis, and n = 72 with kidney transplant). On average, patients were prescribed nine medications concurrently. The number of prescribed medications was inversely associated with mid-upper arm circumference, skinfold thickness triceps, handgrip strength, serum albumin, and hemoglobin after adjustment for age, sex, and kidney function. Prescription of medications with nausea as a side-effect showed similar associations, whereas prescription of medications with xerostomia as a side-effect was associated with lower handgrip strength.

Conclusion: Medication prescription was associated with poor nutritional status in patients with CKD, and monitoring of nutritional status in patients with CKD with long medication lists is warranted to identify and treat patients with poor nutritional status.

Keywords: nutritional status; chronic kidney disease; pharmacotherapy; medication prescription; polypharmacy; xerostomia; nausea; hemodialysis; kidney transplantation

Introduction

DISEASE PROGRESSION IN chronic kidney disease (CKD) is associated with major metabolic, nutritional, and extra-renal changes, all associated with increased use of pharmacotherapy. In addition, the treatment of end-stage kidney disease (ESKD), either by dialysis or transplantation, requires specific medication to be successful, adding to the list of prescribed medications and subsequently polypharmacy in these patients.[1,2]

As the kidney function declines, dietary intake and metabolism of nutrients will be affected, increasing the occurrence and severity of poor nutritional status.[3,4] These may include both obesity and undernutrition, as well as changes in nutrient metabolism.[5,6] Therefore, a thorough assessment of nutritional status is required, including anthropometric measurements, functional tests, and biomarkers such as albumin and hemoglobin.[7-9] Several anthropometric measurements have been

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associated with long-term outcomes among hospitalized or elderly populations in general.[8,10] A poor nutritional status in patients with CKD has been associated with increased morbidity and mortality underscoring the importance of identification and treatment of this condition.[10-12]

Prescription of medications may expose the patient to side-effects, which are usually distinguished as per severity and occurrence. When investigating the association of medication prescription and nutritional status, it may be useful to classify medications as per side-effects which may affect nutritional status. Such side-effects include nausea and xerostomia that may have implications on nutritional status by directly affecting appetite, the ability to chew and swallow, and dietary intake.[13,14]

Nausea is a common side-effect of numerous medications. Specifically, chemotherapy-induced nausea has been associated with malnutrition.[15] However, the association between nausea as a side-effect of medications and nutritional status is not fully understood. Xerostomia is listed as a side-effect of more than 500 medications, including anticholinergic (tricyclic antidepressants, diuretics, antihistamines) and sympathomimetic medicines (antihypertensives, antidepressants). The association between xerostomia and malnutrition has been investigated mainly in the elderly; however, studies show contradicting results.[16-18]

To our knowledge, the association between nutritional status and the number of prescribed medications or their nutritional-related side-effects has not yet been investigated in patients with CKD. The study aimed to describe the prescribed medications in patients at different stages of treatment of CKD and to investigate the association of prescribed medications and nutritional status. We hypothesize that an increasing number of prescribed medications is associated with poor nutritional status. In addition, we hypothesize that the prescribed medications with nutrition-related side-effects may be specifically associated with poor nutritional status.

Patients and Methods

Adult, predominantly Caucasian, patients at different stages of CKD were included in this cross-sectional observational study. The patients were recruited from November 2014 until July 2018. Because of the limited research in this field with a lack of knowledge on variability among subjects and effect size, no formal power calculation was performed. Instead, we aimed to include as many patients as possible. The study was approved by the Regional Committee for Medical and Health Research and conducted following the principles of the Helsinki Declaration.

Eligible patients had an established CKD stage 3-5 or were patients with ESKD treated with either hemodialysis or kidney transplantation. The patients had to be aged >16 years and be able to speak and understand Norwegian or English. Patients with a life expectancy under 6 months were not considered for participation in the study. Written and informed consent was collected before study participation. Requirements for predialysis patients were CKD stage 3-5 without dialysis; for hemodialysis patients, the requirement was current hemodialysis treatment in a steady state, and the transplanted patients had to have a successful kidney transplant with stable graft function. Kidney function was determined by the estimated glomerular filtration rate (eGFR) calculated by the CKD-Epi equation based on creatinine measures.[19] CKD stages were classified by the eGFR in accordance with Kidney Disease–Improving Global Outcomes.[20]

Information on prescribed medication was obtained from electronic patients' records. Medications were classified as per the Anatomical Therapeutic Chemical classification system into the first and fifth levels, which divide medications as per the organ or system on which they act and the medication's chemical structure.[21] Polypharmacy was defined as the prescription of five or more medications simultaneously, and excessive polypharmacy was defined as the prescription of ten or more medications at the same time.[2]

Considering the high number of different medications prescribed, medications were grouped as per their nutrition-related side-effects xerostomia and nausea. A nutrition-related side-effect was noted when it was described as common (>1/100- < 10/1) or very common (>1/10) in the Norwegian Pharmaceutical Product Compendium ("Felleskatalogen") or "Norsk legemiddelhåndbok".[22] A complete list of medications prescribed to the study population as per the relevant side-effects is presented in Table S1.

Nutritional status was determined using anthropometric measurements of height, weight, body mass index (BMI), mid-upper arm circumference (MUAC), skinfold thickness triceps (SFT triceps), and waist circumference (WC). MUAC was measured with a nonflexible measure tape at the midpoint between the olecranon and acromion on the nondominant arm in a relaxed position. SFT triceps was measured at the same midpoint, with a Lange skinfold caliper (Quick Medical, Issaquah, USA), and the mean value of three measures was used. WC was measured with a nonflexible measure tape at the midpoint between the superior border of the iliac crest and the lower rib bones. BMI and central obesity were classified by using World Health Organization's cutoffs.[23,24] Muscle strength was estimated by handgrip strength (HGS) which was measured with a Jamar hydraulic hand dynamometer (Sammons Preston, Bolingbrook, IL, USA) with the patient sitting on a chair without an armrest bending the arm at a 90-degree angle at the elbow. The highest measure of three measurements of the dominant side was applied. Nonfasting blood samples were obtained (before hemodialysis in patients receiving hemodialysis) and analyzed with standard methods. An overview of missing measurements for each measure is provided in Table S2.

Data Analysis

Patients were grouped in three different ways: first, as per the current treatment of CKD (predialysis, dialysis, or transplant) and second, as per their CKD stage defined by the eGFR.[20] Third, patients were grouped as per the prescribed medications with nutrition-related side-effects xerostomia and nausea. The groups are presented with means, standard deviations, and *P*-values from unadjusted regression analysis for the different characteristics. The association between the number of prescribed medications and the different measurements of nutritional status was investigated by linear regression analysis adjusted for age, sex, and eGFR. Differences in measurements of nutritional status were also estimated as per the prescriptions of medications with nutrition-related side-effects, followed by linear regression analysis with adjustment for sex, age, eGFR, and the total number of prescribed medications. Statistical analyses were performed using R software, version 3.4.3, (The R Foundation for Statistical Computing, Vienna, Austria) and the packages within the "Tidyverse".[25]

Results

Study Population

A total of 217 patients with CKD were included in this study; of those, 112 patients were with predialysis CKD stages 3-5, 33 patients were with ESKD receiving hemodialysis, and 72 patients were kidney transplanted patients. Characteristics of the study population as per the treatment group are given in Table 1, whereas Table S3 shows characteristics as per the CKD stage. Most of the participants were male (71%), and the mean age was 60 years (standard deviation 25.8), ranging from 21 to 89 years. The kidney transplanted patients had the highest mean eGFR and were also the treatment group with the lowest mean age. Nephropathy caused by diabetes or hypertension was the most common primary kidney disease in the study population (28%), followed by glomerular disease (25%) and polycystic or unspecified cystic kidney disease (14%).

Prescribed Medications

An overview of the number of prescribed medications in the study population is given in Figure 1. On average, patients were prescribed approximately nine medications, and in total, 216 different medications were prescribed for the total study population. Polypharmacy was present in 84% of the patients, and excessive polypharmacy was present in 37%.

An overview of the prescribed medications in the study population as per Anatomical Therapeutic Chemical classification system level 1 is given in Figure S1. Most patients had prescriptions from group C—cardiovascular system (94%)—and from group A—alimentary tract and metabolism (84%). For the most frequently prescribed medications, their modal dose per application and the percentage of patients per group receiving the specific medications are presented in Table S4.

When grouping the medications as per nutrition-related side-effects, 143 (66%) of the patients were prescribed at least one medication with nausea as a side-

Table 1. Characteristics of the Study Population As Per Treatment Groups

Variable	Total	CKD 3-5	ESKD-HD	ESKD-TX	
n	217	112	33	72	*P*-value
Male patients	154 (71)	79 (70.5)	24 (72.7)	51 (70.8)	.807
Age, years	60.4 (15.8)	62.6 (16.4)	59.5 (17.9)	57.4 (13.4)	.091
Number of medicines	8.8 (4.6)	6.8 (3.7)	15.1 (4.3)	9.1 (3.1)	<.001
BMI, kg/m^2	26.9 (4.8)	27.8 (5.1)	24.3 (3.6)	26.6 (4.5)	.001
eGFR, mL/min/1.73 m^2	33.3 (22)	27.9 (11.6)	6.97 (3.51)	53.8 (21.7)	<.001
Systolic BP, mmHg	137 (19)	135 (17)	154 (25)	132 (14)	<.001
Diastolic BP, mmHg	76 (10)	77 (10)	72 (14)	78 (8)	.042
Albumin, g/L	42.8 (3.4)	43.1 (3.2)	40.9 (4)	43.1 (3)	.002
Hemoglobin, g/dL	12.9 (1.9)	12.9 (1.6)	11.4 (1.6)	13.7 (2)	<.001
Creatinine, mg/dL	3.19 (2.70)	2.66 (1.28)	8.45 (2.58)	1.58 (0.72)	<.001
Urea, mmol/L	15.9 (7.8)	16.8 (6.9)	22.9 (7.6)	11.4 (6.3)	<.001
CRP, mg/L	6.0 (13.9)	6.5 (12.6)	10.5 (25.6)	3.4 (4.2)	.046
Glucose, mg/dL*	117.1 (48.6)	112.1 (45.0)	132.4 (68.5)	114.4 (37.8)	.102
HbA1c, mmol/L	41.8 (10.7)	42.5 (10.9)	39.5 (13.3)	41.7 (9.2)	.459
Kt/V	n.a.	n.a.	1.14 (0.36)	n.a.	n.a.
Years on dialysis	n.a.	n.a.	2.5 (1.9)	n.a.	n.a.
Years since transplantation	n.a.	n.a.	n.a.	11.5 (8.5)	n.a.

BMI, body mass index; BP, blood pressure; CKD 3-5, predialysis chronic kidney disease stage 3-5; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESKD-HD, end-stage kidney disease–hemodialysis; ESKD-TX, end-stage renal disease–kidney transplanted; HbA1c, glycated hemoglobin; n.a., not applicable.

Continuous variables are presented as means (SD), and categorical variables are reported as counts (%). Treatment groups are compared by mean linear (continuous variables) or logistic (categorical variables) regression.

*Nonfasting blood samples.

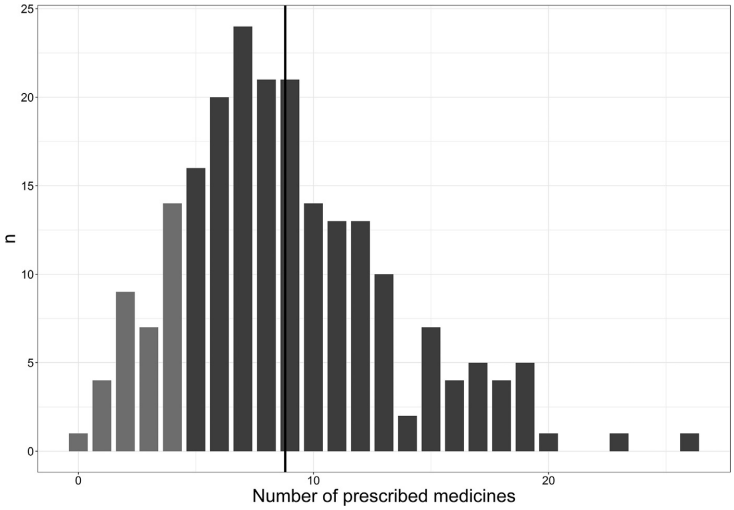

Figure 1. Overview of number of prescribed medicines in the study population. The average number of prescribed medicines was 8.8, shown as the black line, and 84% of the patients were prescribed ≥5 medicines, indicating polypharmacy, shown in dark gray bars.

effect (36 different medications) and 51 (24%) with xerostomia as a side-effect (21 different medications) (Figure S2). Characteristics of patients as per the medication prescriptions with nutrition-related side-effects are presented in Table S5a-b. There was a positive association between the number of prescribed medications with either nausea or xerostomia as a side-effect and the total number of prescribed medications and a negative association between these medications and eGFR.

Nutritional Status

An overview of measurements of nutritional status as per treatment groups is presented in Table 2. Description of nutritional status as per the CKD stage is presented in Table S6. In total, 133 patients (62%) were either overweight or obese (BMI >25 kg/m^2), and 104 patients (48%) had central obesity (WC > 102 cm for men and 88 cm for women). A higher proportion of female patients (62%) was identified with central obesity compared with

Table 2. Measurements of Nutritional Status As Per Treatment Groups

Variable	Total	CKD 3-5	ESKD-HD	ESKD-TX	
n	217	112	33	72	*P*-value
BMI, kg/m^2	26.9 (4.8)	27.8 (5.1)	24.3 (3.6)	26.6 (4.5)	.001
Waist circumference, cm					
Male	100 (14)	102 (14)	93 (13)	101 (13)	.028
Female	93 (14)	93 (14)	94 (14)	90 (14)	.690
Central obesity, n*	104 (47.9)	58 (51.8)	10 (30.3)	36 (50)	.026
MUAC, cm					
Male	31.6 (4.3)	32.7 (4.8)	28.7 (3.4)	31.2 (3.0)	<.001
Female	30.5 (4.7)	32.1 (4.8)	28.7 (4.7)	28.8 (3.7)	.018
SFT triceps, mm					
Male	18.9 (7.9)	21.5 (7.5)	12.9 (5.9)	17.7 (7.7)	<.001
Female	25.9 (9.7)	29.0 (9.2)	22.2 (10.6)	22.7 (8.7)	.028
Handgrip strength, kg					
Male	35.5 (7.9)	35.1 (11.9)	34.2 (11.6)	36.6 (9.7)	.632
Female	22 (8.2)	22.9 (10.1)	21.0 (7.0)	21.0 (5.0)	.611

CKD 3-5, pre-dialysis chronic kidney disease stage 3-5; ESKD-HD, end-stage kidney disease–hemodialysis; ESKD-TX, end-stage kidney disease–renal transplanted; MUAC, mid-upper arm circumference; SFT, skinfold thickness.

Continuous variables are presented as mean (SD), and categorical variables are reported as counts (%). Treatment groups are compared by mean linear (continuous variables) or logistic (categorical variables) regression.

*Identified as waist circumference exceeding cutoff values of 102 cm for men and 88 cm for women, as suggested by the World Health Organization.[23]

male patients (42%). Eighty (37%) patients were normal weight (BMI 18.5-24.9 kg/m^2), and 3 patients were underweight (BMI <18.5 kg/m^2).

Number of Prescribed Medications and Nutritional Status

A linear regression analysis was conducted to investigate the association between the number of prescribed medications and different measures of nutritional status. All analyses were adjusted for age, sex, and eGFR. The association of the ß-estimates of one additional medication on the change of a respective marker of nutritional status is presented in Figure 2. Inverse associations were observed between the number of medications and MUAC, SFT triceps, HGS, hemoglobin, and serum albumin.

Type of Prescribed Medications and Nutritional Status

Prescribed medications with xerostomia or nausea as a side-effect were further investigated in a linear regression analysis, with adjustment for sex, age, eGFR, and the total number of prescribed medications. Medications with nausea as a side-effect were associated with lower MUAC, SFT triceps, albumin, and hemoglobin (Fig. 3), whereas medications with xerostomia as a side-effect were associated with lower HGS (Fig. 4).

Discussion

In this study, we have described the number and type of medications prescribed and the nutritional status of patients with CKD, including patients with predialysis CKD stage 3-5, patients receiving hemodialysis, and kidney transplanted patients. The main findings are a high prevalence of polypharmacy and excessive polypharmacy (84% and 37%, respectively), a high prevalence of overweight and obesity (62%), but a low prevalence of underweight (1.4%). When nutritional status was described with additional measures (MUAC, SFT triceps, HGS, albumin, and hemoglobin), we observed an association between an increased number of prescribed medications and poorer outcomes of these measures. We also observed associations of medications with nutritional-related side-effects of nausea and xerostomia with measurements of nutritional status.

The number of prescribed medications or the prevalence of polypharmacy tends to increase with age and varies profoundly among countries.[26] However, the literature on the association between polypharmacy and nutritional status is scarce.[27,28] Indeed, we did not identify a single study investigating this in a population with CKD. Reasons for this may include the heterogeneous nature of the patient group and disease progression which is also reflected in the high number of different medications prescribed in our study population. The number of prescribed medications was

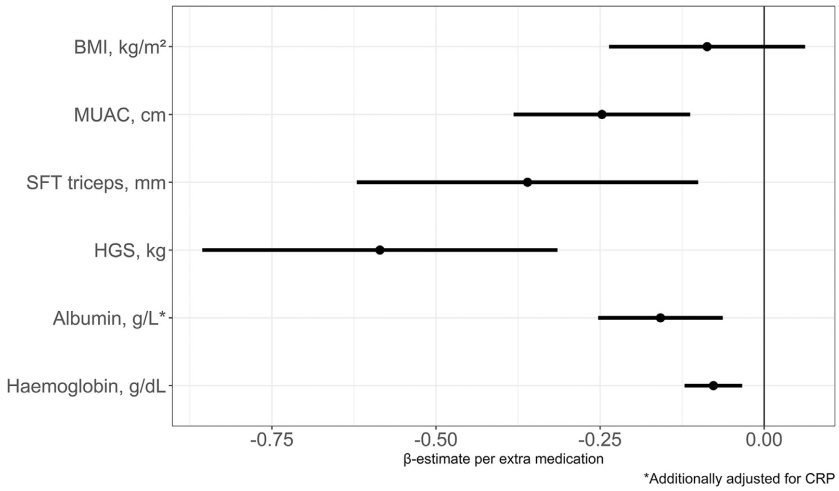

Figure 2. Association of the number of medicines and nutritional status. Linear regression analysis is adjusted for age, sex, and eGFR. BMI, body mass index; CRP, C-reactive protein; HGS, hand-grip strength; MUAC, mid-upper arm circumference; SFT, skinfold thickness.

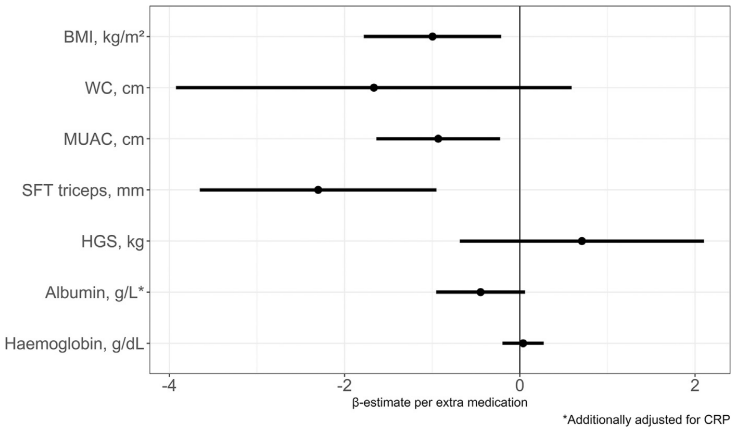

Figure 3. Association between medicines with nausea as a side-effect and markers of nutritional status. Nausea was noted as a side-effect of medicines when the side-effect was described as a common (>1/100- < 10/1) or very common (>1/10) side-effect in the Norwegian Pharmaceutical Product Compendium ("Felleskatalogen") or "Norsk legemiddelhåndbok".[22] Linear regression analysis is adjusted for age, sex, eGFR, and total number of prescribed medicines. BMI, body mass index; CRP, C-reactive protein; HGS, hand-grip strength; MUAC, mid-upper arm circumference; SFT, skinfold thickness; WC, waist circumference.

highest among those with the most advanced kidney failure, the patients receiving hemodialysis. Among patients receiving hemodialysis or those with a kidney transplant, almost every patient was prescribed heparin or prednisone, respectively. Among patients with predialysis CKD, there was much more variation in the medication prescriptions (Table S4). This heterogeneity in medication prescription as well as differences in group size of the treatment groups precluded more specific analysis of treatment groups.

The findings from our study suggest that patients with CKD with an increasing number of prescribed medications are at risk of reduced nutritional status, also after adjustment for age and kidney function. We included several markers of nutritional status, which allowed us to cover both under-

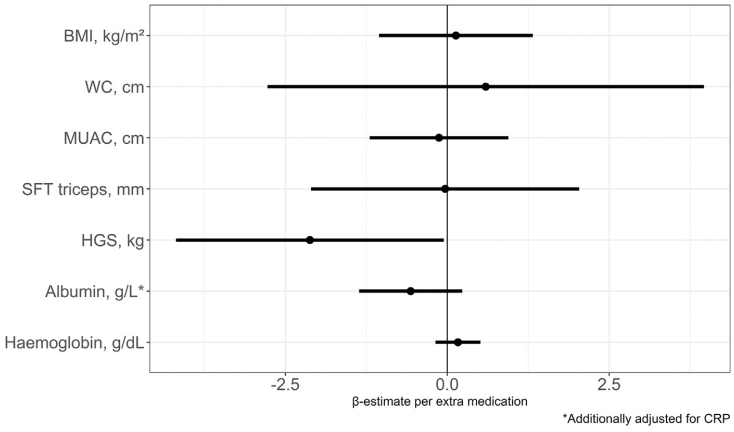

Figure 4. Association between medicines with xerostomia as a side-effect and markers of nutritional status. Xerostomia was noted as a side-effect of medicines when the side-effect was described as a common (>1/100- < 10/1) or very common (>1/10) side-effect in the Norwegian Pharmaceutical Product Compendium ("Felleskatalogen") or "Norsk legemiddelhåndbok".[22] Linear regression analysis is adjusted for age, sex, eGFR, and the total number of prescribed medicines. BMI, body mass index; CRP, C-reactive protein; HGS, hand-grip strength; MUAC, mid-upper arm circumference; SFT, skinfold thickness; WC, waist circumference.

and over-nutrition, biomarkers of nutritional status as well as body composition and muscle function. To date, no specific biomarker of nutritional status has been established, although biochemical measures such as hemoglobin and serum albumin are already widely used in the assessment of nutritional status. However, hemoglobin is influenced by treatment of CKD, medications, gastrointestinal bleedings, diet, and others and therefore an unspecific marker of nutritional status. In addition, albumin is an unspecific marker, as it is mainly influenced by inflammation.[29] These results should, however, not be interpreted as a suggestion to remove prescribed medications but rather to raise awareness of the possible implications of long medication lists and the importance of both assessment and monitoring nutritional status in patients with CKD.

The huge number of different medications prevented the further investigation of single medications, and therefore, we grouped and analyzed medications as per their nutritional-related side-effects. This has, to our knowledge, not been applied as a method before. Although we did not control the occurrence of these side-effects, we observed that medications with nausea as a side-effect were associated with lower BMI, MUAC, and SFT triceps, whereas medications with xerostomia as a side-effect were associated with lower HGS. This may be of importance as lower MUAC, SFT triceps, and HGS may be an indication of reduced muscle status and, thus, a sign of malnutrition.[30–32] Muscle status has also been associated with an increased risk of morbidity and mortality in patients with CKD.[33]

To our knowledge, the association of nausea as a side-effect of prescribed medications and nutritional status has not been investigated in patients with CKD before; however, a recently published study has identified a high prevalence of nausea in a population of patients with ESKD.[34] In this study, taste changes were associated with both nausea and malnutrition. In other conditions, it is known that nausea is associated with malnutrition, e.g., in cancer, liver disease, and pregnancy.[35–37] In our study, 216 different medications were prescribed to the study population, and of these medications, 17% had nausea as a common (>1/100->1/10) or very common (>1/10) side-effect. Prescription of at least one such medication was present in two-thirds of our patients, and 14% of the patients had three or more of such medications prescribed. Therefore, the findings of our study suggest that nutritional status should be closely monitored in patients receiving medications with nausea as a common or very common side-effect.

The recently published guidelines on nutrition in CKD by The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative recommend both regular and comprehensive assessment of nutritional status, by a registered dietitian nutritionist or international equivalent.[7] Our findings support that assessment of nutritional status in patients with CKD is complex and that the simple measurement of weight and height followed by calculation of BMI is not sufficient.

We observed a profound lack of literature on medication prescription or use and nutritional status in patients with CKD. Even though this field is complex, our study may highlight possible associations between medication prescriptions and poor nutritional status in patients with CKD which potentially could be identified and treated. In the present study, data collection and interpretation of the results required close collaboration between different specialties and professions, including physicians, nurses, pharmacists, and dietitians. It has been earlier documented that such collaboration is urgently needed and is associated with improved results of interdisciplinary research.[38]

The study has several limitations. As this is a cross-sectional study, we cannot derive causal relationships. In addition, the analysis of polypharmacy did not follow a prespecified hypothesis but was rather driven by the overwhelming number of medications observed and the lack of available literature. In addition, the data on prescribed medications were collected from patients' records, and we do not know to which degree this reflects their actual intake. This may reduce the generalization of the study findings. In addition, we did not account for over-the-counter medicines. We did not analyze the dosage of the different medications or the total spectra of comorbidities or side-effects. In addition, side-effects were not verified in the individual patients. We did not apply clinical tests, e.g. oral dryness, (hyposalivation, chewing problems) nor did we assess the occurrence of nausea. In addition, we did not assess physical activity.

As there are no previous studies investigating polypharmacy and nutritional status in patients with CKD, this study contributes to fill in a knowledge gap. Further strengths of the study include our comprehensive assessment of nutritional status. The collaboration of different groups of health professionals made these analyses possible and facilitated the design of a new approach for structuring prescribed medications. Larger longitudinal studies are warranted to confirm our findings based on this new method of categorizing medications and to further map the effect of specific medications on nutritional status.

Conclusion

In this study, medication prescriptions were associated with poor nutritional status in patients with CKD. Monitoring of nutritional status in patients with CKD with long medication lists is warranted to identify and treat patients with poor nutritional status. The methodology in our study offers a new approach to categorize medications, and larger longitudinal studies should be conducted to confirm our findings. Future studies should also focus on the mechanisms behind the observed associations between prescribed medications and nutritional status and offer a

more comprehensive analysis of both side-effects and specific medications for patients with CKD.

Practical Application

In this study, patients with a high number of prescribed medications were at risk of a poor nutritional status. The association was especially evident by a comprehensive assessment, including factors beyond height, weight, and BMI. In particular, nutritional status was poor in patients who had been prescribed medications with common or very common side-effects of nausea, accounting for 66% of patients in our population. These findings suggest that special attention should be paid to the nutritional status of patients with CKD with long medication lists. A wider assessment of nutritional status including measurements such as MUAC, SFT triceps, and HGS should be conducted regularly to identify potential challenges of nutritional status and address these accordingly in patients with CKD.

Credit Authorship Contribution Statement

Helene Dahl: Investigation, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. **Silje R.T. Sandblost:** Investigation, Data curation, Formal analysis, Writing – review & editing. **Natasha L. Welland:** Investigation, Writing – review & editing. **Kristina Sandnes:** Investigation, Resources. **Ingegjerd Sekse:** Resources, Writing – review & editing. **Hans-Peter Marti:** Supervision, Writing – review & editing. **Lone Holst:** Conceptualization, Methodology, Writing – review & editing. **Jutta Dierkes:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1053/j.jrn.2021.10.008.

Data Sharing Statement

The data underlying this article cannot be shared publicly because of the privacy of individuals who participated in the study. The data will be shared at reasonable request to the corresponding author.

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Table S1: Active substances with nutrition-related side-effects

Xerostomia

N02A X02 Tramadol	G04B D07 Tolterodine	N02A E01 Buprenorphine
N05A D01 Haloperidol	N02A B03 Fentanyl	N03A X16 Pregabalin
N06A B05 Paroxetine	N03A X12 Gabapentin	N05A H04 Quetiapine
N06A X11 Mirtazapine	N05A H03 Olanzapine	N05C F01 Zopiclone
R06A X22 Ebastine	N05B B01 Hydroxyzine	N06A B04 Citalopram
N06A X16 Venlafaxine	N06A A09 Amitriptyline	N06A B10 Escitalopram
N06A B06 Sertraline	R06A E07 Cetirizine	R06A X27 Desloratadine

Nausea

A07E C01 Sulfasalazine	A07E C02 Mesalazine	A10B A02 Metformin
A10B J02 Liraglutide	B03A A01 Ferrous glycine sulfate	B03A A07 Ferrous sulfate
C01B D01 Amiodarone	H05B X01 Cinacalcet	H05B X02 Paricalcitol
L04A A06 Mycophenolic acid	L04A A10 Sirolimus	L04A D01 Ciclosporin
L04A D02 Tacrolimus	L04A X03 Methotrexate	M04A C01 Colchicine
N02A A01 Morphine	N02A B03 Fentanyl	N02A E01 Buprenorphine
N02A X02 Tramadol	N03A X09 Lamotrigine	N03A X12 Gabapentin
N03A X14 Levetiracetam	N03A X16 Pregabalin	N05A D01 Haloperidol
N05A N01 Lithium	N05B B01 Hydroxyzine	N05C F02 Zolpidem
N06A B04 Citalopram	N06A B06 Sertraline	N06A B10 Escitalopram
N06A X11 Mirtazapine	N06A X16 Venlafaxine	N06D A02 Donepezil
V03A E01 Polystyrene sulfonate	V03A E02 Sevelamer	V03A E03 Lanthanum carbonate

Medicines associated with a nutrition-related side-effect are defined according to information on common (>1/100 - <1/10) and very common (>1/10) side-effects of medicines from the Norwegian Pharmaceutical Product Compendium (*Felleskatalogen*), *Norsk legemiddelhåndbok* (22) and *ATC/DDD Index 2019* by WHO Collaborating Centre for Drug Statistics Methodology.

Table S2: Missing measurements according to treatment group

	Total population n = 217	CKD 3-5 n = 112	ESRD-HD n = 31	ESRD-TX n = 72
BMI	1	1	0	0
Systolic BP	4	2	2	0
Diastolic BP	5	2	2	1
Albumin	9	6	0	3
Hemoglobin	5	3	0	2
Creatinine	3	3	0	0
Urea	4	4	0	0
CRP	7	6	0	1
Glucose	15	8	0	7
HbA1c	41	16	9	16
WC	3	2	0	1
MUAC	1	0	0	1
SFT triceps	1	0	0	1
HGS	2	1	1	0

All values presented as counts. BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; HGS, handgrip strength; MUAC, mid-upper arm circumference; SFT, skinfold thickness; WC, waist circumference.

Table S3: Characteristics of the study population according to CKD stage

Variable	Total	CKD stage					p-value
		1+2	3a	3b	4	5	
n	217	31	27	46	64	49	
Female patients	63 (29)	9 (29)	6 (22.2)	12 (26.1)	20 (31.2)	16 (32.7)	0.556
Age, years	60.4 (15.8)	54.9 (14.3)	58.4 (12.5)	58 (15.1)	62.3 (16.4)	64.8 (17.3)	0.039
Number of medicines	8.8 (4.6)	7.9 (2.4)	8.4 (4.3)	6.5 (3.6)	7.9 (3.9)	13 (4.9)	<0.001
BMI, kg/m2	26.9 (4.8)	27.5 (5.0)	28.6 (5.6)	27.3 (4.6)	26.5 (4.7)	25.6 (4.5)	0.079
eGFR, ml/min/1.73m2	33.3 (22.0)	74.6 (10.0)	49.8 (4.1)	37.3 (4.3)	22.7 (3.9)	8.1 (3.3)	<0.001
Systolic BP, mmHg	137 (19)	130 (12)	133 (15)	132 (17)	136 (19)	149 (23)	<0.001
Diastolic BP, mmHg	76 (10)	77 (8)	78 (9)	78 (9)	77 (11)	73 (12)	0.226
Albumin, g/L	42.8 (3.4)	43.9 (2.5)	42.7 (3.8)	43.5 (2.8)	42.7 (3.2)	41.4 (3.9)	0.008
Hemoglobin, g/dL	12.9 (1.9)	14.7 (1.8)	13.9 (1.5)	13.1 (1.6)	12.8 (1.3)	11.4 (1.5)	<0.001
Creatinine, mg/dL	3.19 (2.70)	1.05 (0.15)	1.43 (0.14)	1.82 (0.27)	2.75 (0.60)	7.32 (2.79)	<0.001
Urea, mmol/L	15.9 (7.8)	6.8 (1.7)	9.8 (2.9)	13.3 (4.1)	18.7 (6.6)	23.7 (6.6)	<0.001
CRP, mg/L	6.0 (13.9)	3.0 (3.5)	3.9 (4.5)	4.7 (6.3)	5.1 (6.7)	11.4 (26.2)	0.036
Glucose, mg/dL*	117.1 (48.6)	120.7 (36.0)	118.9 (46.8)	106.3 (27.0)	106.3 (32.4)	135.1 (75.7)	0.013
HbA1c, mmol/L	41.8 (10.7)	40.5 (8.2)	42 (10.6)	42.3 (10.5)	41.1 (8.8)	43.3 (14.9)	0.861
Years on dialysis	2.5 (1.9)	n.a.	n.a.	n.a.	5.3 (n.a.)	2.36 (1.9)	n.a.
Years since transplantation	11.5 (8.5)	10.1 (8.8)	9.93 (6.44)	15.4 (10.6)	12.4 (6.5)	10.4 (NA)	n.a.

Continuous variables are presented as mean (SD) and categorical variables are reported as counts (%). CKD stages compared by mean linear (continuous variables) or logistic (categorical variables) regression. CKD stages are classified according to estimated glomerular filtration rate, as suggested by Kidney Disease Improving Global Outcomes (20).

*Non-fasting blood samples.

BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; n.a., not applicable.

Table S4: Most frequent medicines and modal dosages prescribed by treatment groups

Group	Medicine		Modal dosage	Prevalence within group
CKD 3-5	A11C C03	Alfacalcidol	0.25 µg	45 %
	B01A C06	Acetylsalicylic acid	75 mg	32 %
	C10A A01	Simvastatin	40 mg	30 %
ESRD-HD	B01A B04	Dalteparin	1429 IU	97 %
	A11C C03	Alfacalcidol	0.25 µg	78 %
	B03A C-	Iron (parenteral)	14 mg	73 %
ESRD-TX	H02A B06	Prednisolone	5 mg	97 %
	L04A A06	Mycophenolic acid	1500 mg	76 %
	C10A A04	Fluvastatin	80 mg	63 %

CKD 3-5, Pre-dialysis chronic kidney disease stage 3-5; ESRD-HD, End-stage renal disease – hemodialysis; ESRD-TX, End-stage renal disease – renal transplanted; IU, international units.

Table S5a: Description of the study population according to prescription of medicines with nausea as a side-effect

Variable	Total	0	1	2	>3	p-value
n	217	74	49	63	31	
BMI, kg/m2	26.9 (4.8)	27.6 (5.3)	27.3 (4.5)	26.7 (4.7)	24.8 (4)	0.0429
MUAC, cm	31.3 (4.4)	32.6 (4.6)	31.5 (4.9)	30.8 (3.9)	28.8 (3.1)	<0.001
SFT triceps, mm	21 (9)	23.4 (8.9)	21.7 (9)	20.1 (8.8)	15.9 (7.7)	<0.001
HGS, kg	29.6 (11.6)	29.8 (11.2)	29 (11.9)	31 (11.2)	27.3 (12.7)	0.5306
Albumin, g/L	42.8 (3.4)	43.5 (2.6)	42.4 (3.5)	42.8 (3.5)	41.4 (4.2)	0.0292
Hemoglobin, g/dl	12.9 (1.9)	13.2 (1.4)	12.7 (2)	13.1 (2.3)	12.4 (1.6)	0.1626
Female patients	63 (29 %)	20 (27 %)	18 (36.7 %)	17 (27 %)	8 (25.8 %)	0.2555
Age, years	60.4 (15.8)	63.7 (16.4)	59.1 (15.1)	57.1 (14.4)	61.4 (17.4)	0.0924
Number of medicines	8.8 (4.6)	5.8 (3.0)	7.8 (3.3)	10.5 (4.0)	14.1 (4.4)	<0.001
eGFR, ml/min/1.73m2	33.3 (22)	29.6 (12.1)	30.8 (19.2)	43.6 (27.2)	25.1 (26.1)	<0.001

Medicines associated with a nausea as a side-effect are defined according to information on common (>1/100 - <1/10) and very common (>1/10) side-effects of medicines from the Norwegian Pharmaceutical Product Compendium (*Felleskatalogen*), *Norsk legemiddelhåndbok* (22) and *ATC/DDD Index 2019* by WHO Collaborating Centre for Drug Statistics Methodology. Continuous variables are presented as mean (SD) and categorical variables are reported as counts (%). BMI, body mass index; MUAC, mid-upper arm circumference; SFT, skinfold thickness; HGS, handgrip strength; eGFR, estimated glomerular filtration rate.

Table S5b: Description of the study population according to prescription of medicines with xerostomia as a side-effect

Variable	Total	0	1	>2	p-value
n	217	166	35	16	
BMI, kg/m2	26.9 (4.8)	27 (4.9)	26.9 (4.7)	25.7 (4.4)	0.6015
MUAC, cm	31.3 (4.4)	31.6 (4.4)	30.6 (4.3)	29.3 (4.6)	0.085
SFT triceps, mm	21 (9)	21.6 (8.9)	19 (9.3)	18.4 (9.3)	0.1478
HGS, kg	29.6 (11.6)	30.8 (11.4)	27.7 (11.5)	21.2 (9.2)	0.0043
Albumin, g/L	42.8 (3.4)	43 (3.1)	42.7 (3.5)	40.1 (5.1)	0.0064
Hemoglobin, g/dl	12.9 (1.9)	13.2 (1.8)	12.3 (2)	12.3 (1.5)	0.0184
Female patients	63 (29 %)	50 (30.1 %)	8 (22.9 %)	5 (31.2 %)	0.3907
Age, years	60.4 (15.8)	59.5 (15.8)	60.9 (16.1)	68.6 (14.6)	0.0911
Number of medicines	8.8 (4.6)	7.5 (3.5)	12.1 (4.7)	15.1 (6)	<0.001
eGFR, ml/min/1.73m2	33.3 (22.0)	36.9 (22.1)	22.3 (18.2)	20.3 (16.0)	<0.001

Medicines associated with a xerostomia as a side-effect are defined according to information on common (>1/100 - <1/10) and very common (>1/10) side-effects of medicines from the Norwegian Pharmaceutical Product Compendium (*Felleskatalogen*), *Norsk legemiddelhåndbok* (22) and *ATC/DDD Index 2019* by WHO Collaborating Centre for Drug Statistics Methodology. Continuous variables are presented as mean (SD) and categorical variables are reported as counts (%). BMI, body mass index; MUAC, mid-upper arm circumference; SFT, skinfold thickness; HGS, handgrip strength; eGFR, estimated glomerular filtration rate.

Table S6: Description of nutritional status according to CKD stage

	Total	CKD stage 1+2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5	p-value
n	217	31	27	46	64	49	
BMI, kg/m2	26.9 (4.8)	27.5 (5.0)	28.6 (5.6)	27.3 (4.6)	26.5 (4.7)	25.6 (4.5)	0.079
WC, cm							
Male	100 (14)	104 (15)	105 (15)	101 (13)	98 (13)	96 (13)	0.062
Female	93 (14)	90 (13)	94 (11)	91 (11)	94 (16)	94 (15)	0.921
CO*	104 (47.9)	17 (54.8)	17 (63)	23 (50)	28 (43.8)	19 (38.8)	0.531
MUAC, cm							
Male	31.6 (4.3)	32.5 (3.0)	32.6 (5.4)	32.5 (4.4)	31.4 (4.4)	29.7 (3.7)	0.038
Female	30.5 (4.7)	27.8 (4.0)	30.6 (3.9)	32.6 (4.8)	30.6 (4.6)	30.4 (5.1)	0.259
SFT triceps, mm							
Male	18.9 (7.9)	19.9 (8.2)	19.8 (7.8)	21.4 (7.7)	19.2 (8.2)	14.9 (6.4)	0.012
Female	25.9 (9.7)	22.5 (7.5)	26.1 (7.4)	28.2 (10.9)	26.0 (10.4)	25.9 (10.1)	0.785
HGS, kg							
Male	35.5 (11.1)	38.9 (8.3)	38.6 (11.8)	37.9 (11.7)	32.5 (11.1)	32.6 (10.7)	0.029
Female	22.0 (8.2)	20.2 (5.5.)	24.8 (9.2)	23.9 (5.6)	24.4 (9.4)	16.7 (7.6)	0.047

Continuous variables are presented as mean (SD) and categorical variables are reported as counts (%). CKD stages compared by mean linear (continuous variables) or logistic (categorical varables) regression. CKD stages are classified according to estimated glomerular filtration rate, as suggested by Kidney Disease Improving Global Outcomes (20).

*Identified as waist circumference exceeding cut-off values of 102 cm for men and 88 cm for women, as suggested by the World Health Organization (23).

BMI, body mass index; CKD, chronic kidney disease; CO, central obesity; HGS, handgrip strength; MUAC, mid-upper arm circumference; SFT, skinfold thickness; WC, waist circumference.

III

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