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.

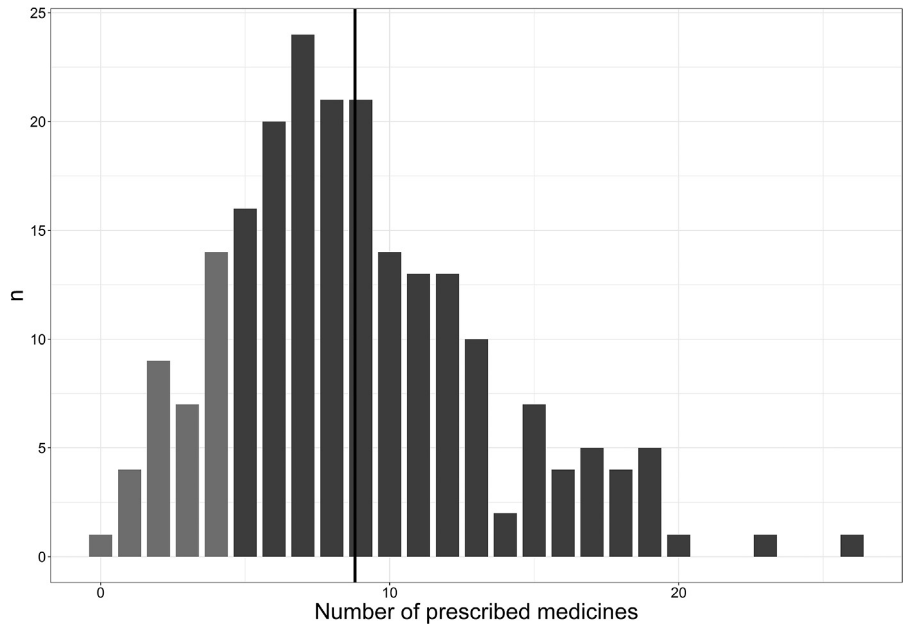

Figure 1. Overview of number of prescribed medicines in the study population. The average number of prescribed medicines was 8.8, shown as the black line, and 84% of the patients were prescribed ≥5 medicines, indicating polypharmacy, shown in dark gray bars.

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 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.

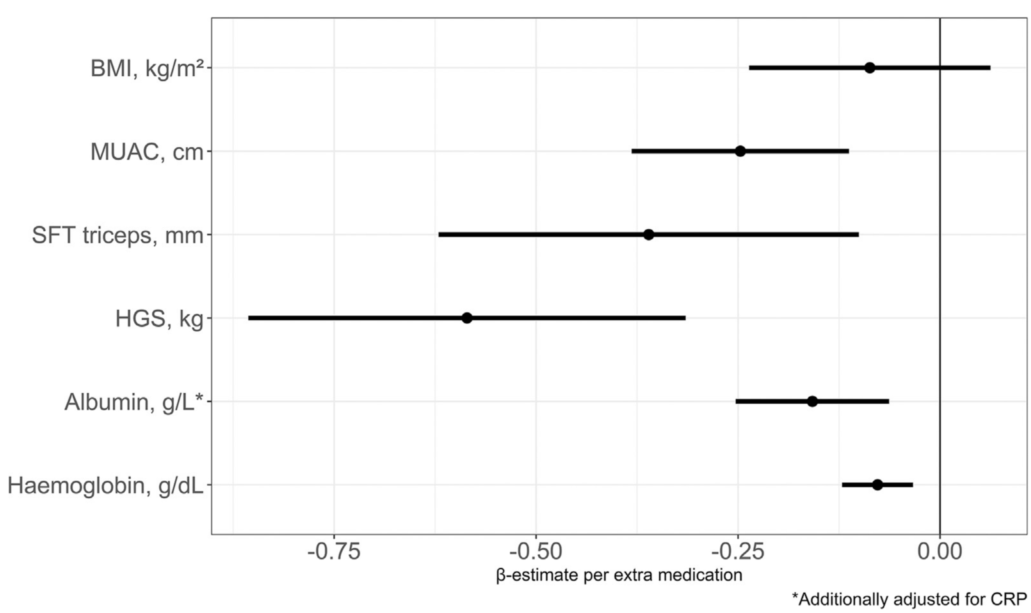

Figure 2. Association of the number of medicines and nutritional status. Linear regression analysis is adjusted for age, sex, and eGFR. BMI, body mass index; CRP, C-reactive protein; HGS, hand-grip strength; MUAC, mid-upper arm circumference; SFT, skinfold thickness.

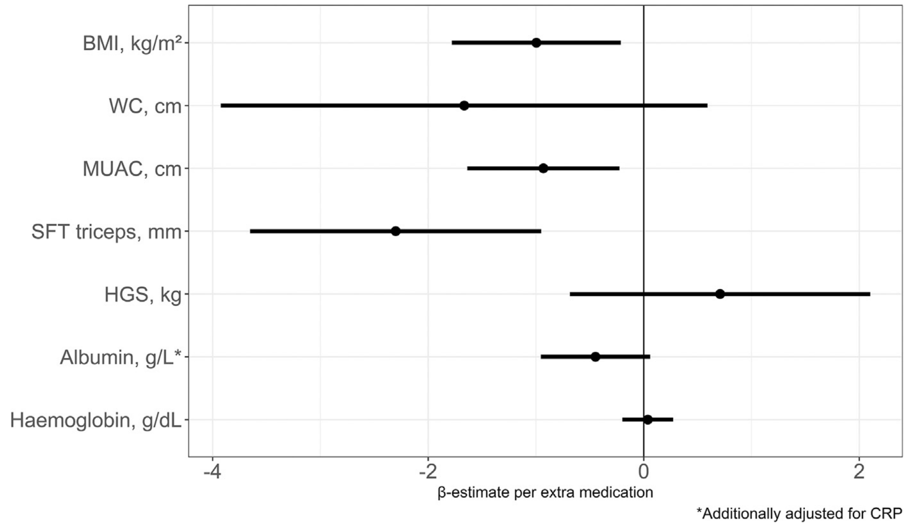

Figure 3. Association between medicines with nausea as a side-effect and markers of nutritional status. Nausea was noted as a side-effect of medicines when the side-effect was described as a common (>1/100- < 10/1) or very common (>1/10) side-effect in the Norwegian Pharmaceutical Product Compendium ("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.

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- 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

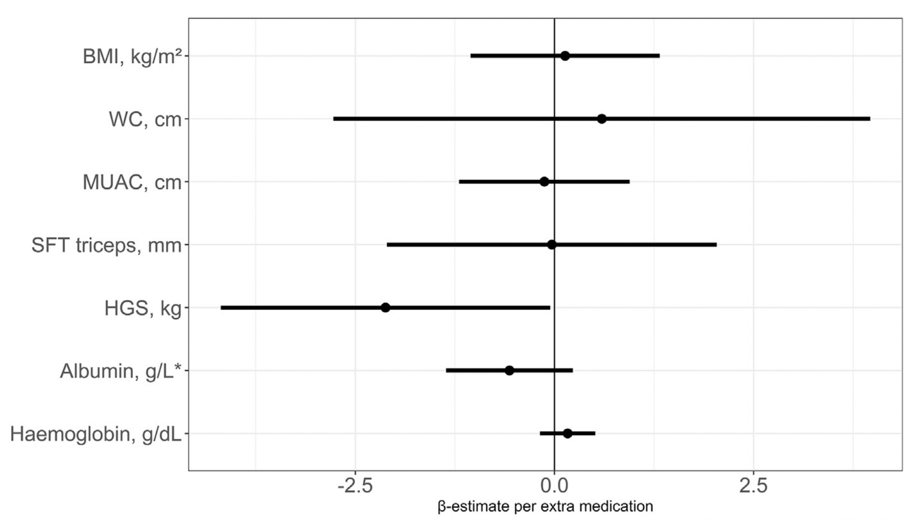

Figure 4. Association between medicines with xerostomia as a side-effect and markers of nutritional status. Xerostomia was noted as a side-effect of medicines when the side-effect was described as a common (>1/100- < 10/1) or very common (>1/10) side-effect in the Norwegian Pharmaceutical Product Compendium ("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.

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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