English Summary

This PhD thesis is based on three original manuscripts. The clinical studies were performed at the Department of Nephrology, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark.

Chronic kidney disease (CKD) is associated with a significantly increased risk of cardiovascular disease (CVD) and even discrete degrees of proteinuria and/or reduced glomerular filtration rate is associated with cardiovascular morbidity and mortality. CVD in CKD is related to traditional risk factors such as hypertension and dyslipidemia, but other CKD-specific disturbances, especially changes in mineral metabolism, may have even greater impact on cardiovascular health.

As glomerular filtration rate decreases, CKD patients develop hyperphosphatemia which secondarily increases plasma levels of fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) leading to increased morbidity, mortality and renal bone disease. The standard treatment options for hyperphosphatemia are dietary reductions of phosphorus intake often in combination with oral phosphate binders, medications that reduce the absorption of phosphate from the gut. However, phosphate binders may have adverse effects and strict dietary rules are unbearable for the patients. Thus, there is an unmet need for safe and sustainable interventions to reduce the phosphorus load in CKD patients to prevent vascular calcifications and CVD.

The purpose of this PhD thesis was two-fold: first to develop a diet with a reduced phosphorus content tailored to a Danish CKD cohort and secondly, to evaluate the diet's impact on phosphorus homeostasis in patients with CKD, within a randomized controlled cross-over study.

A recent Danish initiative to develop palatable, healthy and sustainable dietary recommendations based on foods produced in the Nordic region - termed the New Nordic Diet (NND) - has been tested in different populations with promising results regarding cardiovascular risk profile, and the Nordic Diet has been recognized by WHO to represent a healthy alternative to the Mediterranean Diet(1).

In *study I* we compared the impact of this NND versus an Average Danish Diet (ADD) regarding the dietary phosphorus intake. The NND is based on recommendations of the intake of local, organic and less processed food including large amounts of fruit, vegetables, wholegrain and fish. The hypothesis was that less phosphorus-containing food additives, less animal protein and more plant-based proteins could have a positive effect on phosphorus parameters.

In a post hoc analysis of data acquired from a 26-week controlled trial, phosphorus and creatinine were measured in plasma and urine at baseline, and at 12 and 26 weeks accordingly in 132 centrally obese subjects with normal renal function. We applied the urinary fractional phosphorus excretion as a marker of phosphorus absorption. The study showed that NND, contrary to our expectations, had high phosphorus content and did not decrease the fractional phosphorus excretion compared with ADD, hence modifications to suit the requirements for the CKD population was needed.

Study II was designed to clarify the real world phosphorus intake in Danish CKD patients and to evaluate 24-h urine collection as a monitoring-tool of phosphorus absorption.
Accordingly, we investigated the daily dietary intake of phosphorus in a Danish CKD population, and the reproducibility of the phosphorus excretion in urine in 20 patients with CKD stage 3-4. We found that the daily phosphorus intake was almost 50% above international recommendations. 24-h urinary excretion of phosphorus was reproducible and our data indicate that a single 24-h urine collection is sufficient to estimate the individual phosphorus excretion.

Based on the results of study I and II we refined and adjusted the NND and termed this the New Nordic Renal Diet (NNRD). By reducing the content of the most phosphorus containing food-items like dairy products, nuts, rye bread and meat we achieved a phosphorus content in accordance with the international recommendations of 800-1000 mg/day verified by inductively coupled plasma mass spectrometry.

This NNRD was tested in *Study III*.
A group of 18 patients with CKD stage 3-4 was put on the NNRD for 7 days and were monitored with blood tests and 24-h urinary phosphorus excretion for alterations of phosphorus homeostasis. All meals were handed out as packaged meals. Dietary compliance and satisfaction were investigated by self-reporting questionnaire. This was compared to 7 days on their habitual diet.
We found that NNRD for 7 days reduced 24-h urinary phosphorus excretion with almost 40%, and p-FGF23 with 18% as compared to a habitual diet. There was no significant difference in plasma phosphate between the dietary periods. The participants were satiated during the intervention and the dietary compliance and satisfaction was high.

In conclusion, we showed that real life dietary phosphorus intake in a small cohort of Danish CKD stage 3-4 patients was above international recommendations. We therefore designed a dietary intervention to optimize phosphorus intake and homeostasis in CKD patients in a feasible and effective manner. We demonstrated that phosphorus specific modifications of an accepted dietary concept reduced the phosphorus content from 1500 to 850 mg/day and improved phosphorus homeostasis while dietary compliance and satisfaction was high. This regionally founded, non-restrictive diet can be used to further explore the impact of phosphorus control in patients with moderate CKD.

Now prospective long-term dietary intervention studies are possible and will elucidate the potentially positive effects of lowering dietary phosphorus intake on hard endpoints like cardiovascular morbidity and mortality in CKD patients.