Introduction
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Kidney transplantation is considered the preferred treatment for patients with end-stage kidney disease, offering better quality and life and survival compared to dialysis treatment, while at the same time being more cost-effective. Consequently, over the last 15 years, the population of kidney transplant recipients has increased by more than 2 fold to more than 10,000 patients in the Netherlands, accounting for more than 60% of all patients receiving renal replacement therapy.

In 1954, the first successful human kidney transplantation was performed in Boston with a donor kidney obtained from the patient’s identical twin. By using the kidney from an identical twin, the barrier of allograft rejection was overcome but it would take another decade of experimenting with radiation therapy, 6-mercaptopurine and its derivative azathioprine before the implementation of Starzl’s immunosuppressive regimen of azathioprine combined with prednisolone that allowed for successful kidney transplantation with kidneys from genotypically nonidentical donors. In the decades following this discovery, the utilization of organs of brain-death donors, advances in organ preservation, histocompatibility typing, use of T-cell antibodies and the discovery of more potent immunosuppressive drugs, including calcineurin-inhibitors and mycophenolic acid all have led to further improvement of patient and graft survival in kidney transplant recipients. Moreover, the development of living kidney donor exchange programs and strategies to increase living kidney donation have increased the pool of living kidney donors, offering donor kidneys with superior graft and patient survival compared to deceased donor organs.

Unfortunately, life expectancy of kidney transplant recipients remains considerably lower compared to the general population and the advances in the field of transplantation have mainly benefitted short term outcomes but not led to improvements of similar magnitude on long term outcomes. Inevitably, graft failure also further strains the existing worldwide donor organ shortage since nowadays 1 in 5 patients being waitlisted for a kidney transplant is consequence of a previously failed donor kidney. Identifying actionable factors that explain long-term outcome in kidney transplant recipients is imperative to improve patient and graft survival of kidney transplant recipients and to alleviate the donor kidney shortage.
Nutrition is increasingly being recognized as a potential modifiable risk factor for the prevention and management of chronic diseases\textsuperscript{14-17}. Traditionally, the importance of nutrition in the treatment for patients with chronic kidney disease has been well-recognized and dietary management in patients with chronic kidney disease is often characterized by sodium restrictions to prevent hypertension and avoiding high protein intake to prevent glomerular hyperfiltration\textsuperscript{18}. Moreover, as kidney disease progresses, additionally restrictions of phosphate, potassium and protein intake are recommended to prevent the development of hypophosphatemia, hyperkalemia and excessive urea generation. Such dietary restrictions are often warranted due to the inability of the kidney to excrete metabolic waste products. However, these dietary restrictions also increase risk for malnutrition and poor diet quality by limiting protein intake and intake of otherwise considered healthy foods, such as fruit and vegetables. After transplantation, kidney function is restored in most patients, alleviating the need to limit phosphate, potassium and protein intake. Nevertheless, adequate dietary management remains a major concern after transplantation as many kidney transplant recipients experience substantial weight gain post-transplantation and are prone to develop cardio-metabolic disorders, including hypertension, dyslipidemia and post-transplant diabetes, contributing to a high cardiovascular risk in kidney transplant recipients\textsuperscript{19-21}.

Although the importance of a healthy diet is acknowledged in the management of kidney transplant recipients\textsuperscript{22}, nutritional research in kidney transplant recipients has predominantly focused on the prevention of post-transplant obesity and little
is known to what extent nutritional factors could serve as potential modifiable risk factors to improve long-term outcome of kidney transplant recipients. In the general population, a healthy diet is already considered as being the cornerstone of cardiovascular disease prevention due to its effect on established risk factors such as cholesterol, blood pressure, body weight and diabetes, and through direct effects independent of these risk factors. This is all the more relevant for kidney transplant recipients considering that most of the established cardiovascular risk factors are adversely affected by the immunosuppressive drugs used to prevent and treat graft rejection and the leading cause of death in kidney transplant recipients is cardiovascular disease. Moreover, evidence arising from longitudinal studies in the field of nephrology also stress the importance of a healthy diet in the prevention of chronic kidney disease and prevention of progressive kidney function loss as well as its cardiovascular complications.

By studying the complete diet, as well as its individual food components and nutrients, a better understanding of the impact of nutrition on health can be obtained and help determine the optimal composition of a healthy diet to prevent disease development and progression. For the prevention of cardiovascular disease, marine derived omega-3 fatty acids have received much attention. Evidence from both epidemiological and interventional studies indicate that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may exert beneficial effects on all-cause and cardiovascular mortality in patients with pre-existing cardiovascular disease and in the general population. Moreover, recently it was shown that also in kidney transplant recipients higher plasma phospholipid concentrations of marine-derived omega-3 fatty acids were associated with better long-term survival. In addition, another nutritional factor that could favorably affect health is the consumption of fruits and vegetables, which are rich sources of antioxidant compounds, polyphenols, carotenoids, flavonoids, fibers and minerals. In the general population, diets characterized by higher intake of fruits and vegetables have been linked to a lower risk of diabetes and many studies consistently confirmed the substantial role of adequate consumption of fruits and vegetable on cardiovascular prognosis.

Next to the potential of individual contributions of nutrients and food groups to improving health, increasing interest is directed to the study of dietary patterns, which allows for complex interactions and intercorrelations among nutrients to
be taken into account and encompass the full health potential of a diet\textsuperscript{62,63}. The Mediterranean diet and the Dietary Approach to Stop Hypertension (DASH) diet are two of the most well-studied dietary patterns that both have been attributed to benefit cardiovascular health\textsuperscript{64-67}. The Mediterranean Diet is a dietary pattern traditionally consumed by inhabitants of Mediterranean regions and features a high intake of fish, fruit, vegetables, legumes, nuts and olive oil, together with low intake of meat and dairy products. The Mediterranean diet has the potential to significantly reduce cardiovascular risk as demonstrated by large interventional studies aimed at primary and secondary cardiovascular prevention\textsuperscript{64,65} and has also been associated with a lower risk of diabetes, all-cause mortality, and cardiovascular mortality in meta-analyses\textsuperscript{68,69}. Moreover, epidemiological studies indicate that the Mediterranean diet might also benefit kidney function preservation\textsuperscript{31,36,70,71}. In contrast to the Mediterranean diet, the DASH diet does not originate from a specific population, but was designed specifically to prevent and control hypertension\textsuperscript{66}. The DASH diet emphasizes a high intake of fruits, vegetables, legumes, nuts, whole grains, low-fat dairy products and low intake of sodium, red and processed meat and sugar-sweetened beverages. In addition to its blood pressure lowering effect, the DASH diet also reduces total cholesterol concentrations and consequently reportedly reduces 10-year cardiovascular risk by 13\%\textsuperscript{67}.

Despite increasing evidence demonstrating the contribution of nutritional factors to cardiovascular and kidney health in multiple subgroups of the general population, studies investigating nutritional factors and diet quality in kidney transplant recipients are scarce and warranted. Importantly, a poor diet can also lead to a state of malnutrition, a well-recognized problem in other subgroups of patients with chronic kidney disease leading to poor patient outcomes\textsuperscript{72,73}, that has, however, been insufficiently explored in kidney transplant recipients. The cause of malnutrition in chronic kidney disease is multifactorial and include anorexia, increased protein catabolism, decreased anabolism, chronic inflammation, metabolic acidosis and hormonal imbalances\textsuperscript{74,75}. In both non-dialysis dependent and dialysis-dependent patients with chronic kidney disease, malnutrition is known to be an important contributor to low quality of life and high morbidity and mortality risk\textsuperscript{76}. Although transplantation may alleviate some of these factors, transplantation-related factors including adverse drug effects from immunosuppressive drug use such as steroid induced muscle wasting\textsuperscript{77},
renal tubular acidosis leading to metabolic acidosis\textsuperscript{78} and diarrhea\textsuperscript{79}, may further contribute to development of malnutrition in kidney transplant recipients. Previously, malnutrition prior to kidney transplantation has been linked to poor transplant outcomes\textsuperscript{80–82}, but little is yet known about the prevalence and consequences of malnutrition in stable outpatient kidney transplant recipients\textsuperscript{83}.

It may now be clear that nutrition plays a significant role in maintaining and optimizing health and could be an actionable factor to improve long term outcome after kidney transplantation. It should however also be noted that kidney transplant recipients constitute a specific population and differ from the general population and other populations of patients with chronic kidney disease, which does not allow for simple extrapolating of findings in those populations to kidney transplant recipients. Nevertheless, dietary recommendations for kidney transplant recipients are often based on recommendations from high risk groups in the general population and other subgroups of patients with chronic kidney disease, as a result of insufficient data in kidney transplant recipients\textsuperscript{18}. Hence, patient-specific nutritional studies and development of research platforms that allow for such studies are warranted to provide empirical, high-quality data to determine the optimal diet composition for kidney transplant recipients.

**GENERAL OVERVIEW OF THESIS**

In this thesis, we pursue to strengthen the empirical basis for dietary recommendations in kidney transplant recipients. To this purpose, we aimed to explore whether nutritional factors could serve as potential modifiable risk factors to improve long term outcome after kidney transplantation. In Chapter 2 the intake of marine-derived omega-3 fatty acids EPA and DHA in stable kidney transplant recipients and its association with mortality is investigated. In Chapter 3, the focus is on potential health benefits of fruit and vegetable consumption on cardiovascular mortality and all-cause mortality and in Chapter 4 the potential benefit of fruit and vegetable intake on development of post-transplant diabetes mellitus (PTDM) in stable kidney transplant recipients is investigated. In Chapter 5, we investigate the role of dietary patterns and investigate the association of adherence to the DASH diet with kidney function decline and the association of adherence to the DASH diet with mortality in kidney transplant recipients. The role of the Mediterranean diet on development of graft failure, kidney function decline
and graft loss is subsequently investigated in Chapter 6. In Chapter 7, we studied the prevalence of malnutrition in kidney transplant recipients and the association between malnutrition with quality of life and mortality risk and in Chapter 8 the design and rationale for the TransplantLines Study is described which will allow for future nutritional research in the field of transplantation.
REFERENCES


