Improving treatment and Imaging in ADPKD
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Chapter 1

Introduction
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Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease with a prevalence of 3 to 4 patients per 10,000 of the general population. The disease is characterized by cyst formation in both kidneys. Extra-renal symptoms include cardiac valve abnormalities and intracranial aneurysms, as well as cyst development in other organs, predominantly the liver with a prevalence of 94% in patients older than 35 years. Cyst formation is characterized by proliferation of tubular epithelial cells and excessive fluid secretion. This cyst formation leads to expansion of kidney size, and leads to end-stage renal disease (ESRD) requiring renal replacement therapy in the majority of patients. As shown in the magnetic resonance image (MRI) in Figure 1, kidney (and liver) growth can vary among patients, even within one family (patients C and D). Kidney volumes in healthy individuals are 202 ± 36 ml per kidney for men and 154 ± 33 ml per kidney for women.

ADPKD is most commonly caused by a mutation in the PKD1 and PKD2 gene, responsible for approximately 85% and 15% of detected mutations. They encode for polycystin-1 (PC1) and polycystin-2 (PC2) respectively. The type of mutation is associated with prognosis. Patients with a mutation in the PKD1 gene generally have an earlier expression of disease and reach ESRD at a younger age than those with a mutation in the PKD2 gene, with median ages of onset of ESRD of 58.1 and 79.7 years, respectively. A truncating mutation in the PKD1 gene causes a 12-year earlier onset of ESRD compared to patients with a non-truncating PKD1 mutation, with median ages of onset of ESRD of 55.6 versus 67.9 years, respectively.

VASOPRESSIN AND ADPKD

The vasopressin pathway plays a pivotal role in the pathophysiology of ADPKD. Vasopressin is commonly known for its antidiuretic effects. This hormone binds to the vasopressin V2 receptor located in the kidney at the basolateral side of the principal cells in the collecting duct cells, leading to adenylyl cyclase 6 activation. This results in cyclic AMP-dependent protein kinase A activation that in turn phosphorylates aquaporin-2 (AQP2). Increased trafficking of AQP2 into the apical membrane results in water reabsorption in the kidney.

Vasopressin, measured by its surrogate marker copeptin, has shown to be associated with disease severity and progression in ADPKD. Treatment with a vasopressin V2 receptor antagonist slowed disease progression in various animal models orthologous to human cystic diseases. In addition, the vasopressin V2-antagonist tolvaptan was shown in the TEMPO 3:4 trial, which included 1,445 patients with ADPKD, to ameliorate the rate of disease progression. Tolvaptan lowered annual TKV growth from 5.5% to
2.8% and decreased the estimated GFR slope from −3.70 to −2.72 mL/min/1.73m² compared to placebo, and is now approved by, among others, the European Medicines Agency as first drug that ameliorates the rate of disease progression in ADPKD.

During the TEMPO 3:4 trial aquaretic side-effects, like thirst (55.3%), polyuria (38.3%) and nocturia (29.1%) were more common in the tolvaptan treated group. These aquaretic side-effects led to treatment discontinuation in 8.3% of tolvaptan treated patients during this trial.

**Figure 1. Variability of the disease progression.** Patient A is a 26-year old male with a total kidney volume (TKV) of 7374 mL, total liver volume (TLV) of 1744 mL and an eGFR of 60 mL/min/1.73m², patient B is 36-year old female, with a TKV of 844 mL, TLV of 7660 mL and an eGFR of 49 mL/min/1.73m². Patient C and D show the variability within one family. These two sisters are 27 (C) and 33 (D) years of age, with a TKV of 1495 and 703 mL, TLV of 3171 mL and 2204 mL, and an eGFR of 117 and 118 mL/min/1.73m², respectively.
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The finding that tolvaptan ameliorated the rate of disease progression in ADPKD has confirmed that the vasopressin pathway is detrimental in ADPKD. Given this line of evidence, it is of interest to study whether lowering vasopressin activity can also be achieved via lifestyle measures instead of tolvaptan, as this would imply that such lifestyle measures could potentially ameliorate the rate of disease progression in ADPKD. Furthermore, increasing tolerability of tolvaptan treatment by lowering its aquaretic side-effects as well as improvement of its treatment efficacy have become of interest now tolvaptan is marketed. Theoretically, lifestyle or drug interventions that lower the circulating vasopressin concentration could decrease tolvaptans aquaretic side-effects and potentially improve its efficacy. Other potential treatment modalities that could lower aquaretic side-effects of tolvaptan use are treatment options that have been proven to be effective in nephrogenic diabetes insipidus, where the vasopressin V2 receptor is dysfunctional, resulting in increased urine production as well.

RISK PREDICTION OF DISEASE PROGRESSION IN ADPKD

Biomarkers that can identify patients with rapid disease progression in an early phase of the disease course have become increasingly important, especially now drug interventions that can ameliorate the rate of disease progression in ADPKD are available. This will enable selection of patients that have a rapid disease progression, and thus are most likely to benefit from drug intervention. Simultaneously, such markers may be of help to prevent unnecessary treatment of patients that will never reach ESRD in their life.

As ADPKD leads to renal function decline, measurement of the glomerular filtration rate (GFR) appears to be a logical biomarker to assess disease severity and progression in ADPKD. However, measurements of GFR can be misleading to assess disease severity in ADPKD (Figure 2) as remaining glomeruli have a remarkable capacity to compensate for the loss of functioning nephrons, a phenomenon called hyperfiltration. Another candidate biomarker would be total kidney volume (TKV). Cyst formation already starts in utero and continues throughout life. Importantly, TKV is already markedly increased by the time the GFR decline becomes apparent\(^1\). A classification based on TKV adjusted for height and age to predict the rate of disease progression has been introduced, and works reasonably well to select patients with a high likelihood of rapidly progressive disease.

Measurement of TKV is recognized by the American Food and Drug Administration and European Medicines Agency as an official biomarker for risk prediction in ADPKD. TKV measurement is most reliably done by manual tracing using magnetic resonance imaging (MRI).
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Historically, gadolinium enhanced T1 weighted images were used for the measurement of TKV because of the short scanning time, low variations in image quality and higher contrast of the renal structures against the surrounding tissues compared to T1 weighted images without gadolinium. When not using gadolinium contrast, T2 weighted images might be preferred for the measurement of the TKV, because this technique shows high kidney tissue-contrast and hyperintense renal cysts in T2 weighted images and would help to better delineate the kidney boundaries against background tissue. MRI techniques have developed over the last decades, and the single-shot turbo spin-echo technique was developed, being potentially more feasible to use for TKV assessment. This technique has a shorter examination time, fewer motion artifacts and ensures that all images are obtained from the same anatomic position regardless of the patients' ability to hold their breath, making this technique potentially more feasible for manual TKV measurement in ADPKD.

Figure 2. Natural history of PKD. A. Shows the natural growth of total kidney volume. B. Total kidney volume (red line) exhibits exponential growth at an average rate of 5% per year, presumably due to cyst epithelial cell proliferation and fluid secretion, although this rate can vary widely from patient to patient.
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Still, manual tracing of the kidneys is very laborious, limiting its applicability in clinical care. In case kidney volume could be estimated with sufficient accuracy and reliability, it would alleviate the time consuming process of kidney volume measurement. Recently, two kidney volume estimation methods have been developed: the mid-slice method by the CRISP consortium \(^{18}\) and the ellipsoid method by the Mayo Clinic \(^{17}\). For both methods, measured and estimated kidney volumes appeared to be well correlated, but other groups have yet not validated these methods.

AIMS AND OUTLINE OF THIS THESIS

This thesis consists of two parts. In the first part of this thesis, the aim is to investigate whether the prognosis of ADPKD can be improved via lifestyle interventions that lower vasopressin concentration and via optimization of vasopressin antagonism. In the second part of this thesis the aim is to optimize total kidney and liver volume measurement in ADPKD to improve feasibility of this procedure in clinical practice.

Part I. Treating ADPKD by influencing the vasopressin pathway

Vasopressin plays a pivotal role in development and progression of ADPKD. Chapter 2 provides a comprehensive overview on the pathophysiological relation of vasopressin with ADPKD, as well as an overview of potential treatment options, by either antagonizing the vasopressin V2 receptor using tolvaptan or lowering circulating vasopressin concentration by changing lifestyle factors that are known to physiologically influence vasopressin, like fluid and salt intake, but also other lifestyle factors.

Identification of modifiable factors that are associated with vasopressin concentration opens potential to treat patients with ADPKD by means of lifestyle changes. In Chapter 3 it is investigated which lifestyle factors are associated with vasopressin in a large general population cohort. Physiological stimuli of vasopressin release are factors that influence plasma osmolality \(^{20}\). Water and dietary sodium intake are the main determinants of plasma osmolality \(^{20}\). It was therefore hypothesized that these two lifestyle factors would be associated with vasopressin concentration. Vasopressin was assessed using its surrogate copeptin.

To verify whether these lifestyle factors also are associated with copeptin concentration in ADPKD patients, and to see whether there may be ADPKD specific associations of lifestyle factors with vasopressin, a similar study is performed specifically in this patient group in Chapter 4.

The TEMPO 3:4 trial has shown that tolvaptan, a vasopressin V2 receptor antagonist,
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ameliorates the rate of disease progression in ADPKD\(^\text{13}\). In \textit{Chapter 5} it was investigated whether plasma copeptin levels, as marker of plasma vasopressin, are associated with disease progression, and whether pre-treatment copeptin and treatment-induced change in copeptin are associated with tolvaptan treatment efficacy.

Exploring new treatment modalities for ADPKD and optimizing tolvaptan treatment are the scope of Chapters 6 and 7. \textit{Chapter 6} investigates whether lowering sodium intake, as main stimulus for systemic vasopressin release\(^\text{20}\), could lower plasma vasopressin concentration in two experimental models, of which one performed in the Mayo Clinic (Rochester, MN, USA). This would be of interest because a decrease in vasopressin concentration could hypothetically ameliorate the rate of disease progression in ADPKD, as an increased vasopressin concentration is associated with disease severity and progression\(^\text{7-9}\). Furthermore, it can be hypothesized that lowering the agonist (vasopressin) may increase the treatment efficacy of its antagonist, i.e. the vasopressin V2 receptor antagonist. In addition, a lower sodium intake (i.e. less osmolar intake) will lead to a lower plasma osmolality and consequently less thirst, leading to less fluid intake and thus less urine production. This may be of benefit for patients, as the excessive urine production during tolvaptan use is for most patients the most debilitating side-effect of this drug. The third hypothesis therefore is that combining a vasopressin V2 receptor antagonist with a low sodium diet will reduce aquaretic side-effects.

Blockade of the vasopressin V2 receptor physiologically resembles a situation in which the vasopressin V2 receptor is not functioning, such as in patients with nephrogenic diabetes insipidus (NDI). In such patients hydrochlorothiazide (HCT) is known to reduce polyuria by up to 50\%\(^\text{21}\). \textit{Chapter 7} reports a patient that concomitantly used tolvaptan and HCT in a patient with ADPKD. From this report interesting conclusions can be drawn with respect to the effectivity of CHT to lower tolvaptan induced polyuria, and whether this co-medication may have influence on the rate of eGFR decline.

Part II. Assessing ADPKD severity by MR imaging

TKV is an important parameter that enables detection of disease progression in ADPKD, even before GFR declines. New magnetic resonance imaging (MRI) techniques have been developed, leading to new imaging techniques with fewer artifacts that require less scanning time. The newer T2-single shot fast spin echo-technique has previously been suggested to be the preferred sequence for TKV assessment in ADPKD, as this technique shows high kidney tissue-contrast and hyperintense renal cysts, which may help to better delineate the kidney boundaries against background tissue\(^\text{16}\). In \textit{Chapter 8} the hypothesis is studied that this new technique is preferable over the historically used T1-3D spoiled gradient echo-technique.
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The gold standard for TKV measurement is manual segmentation of the whole kidney. Thus far, there is no validated alternative that performs equally to this laborious method. This limits the feasibility of TKV measurement in clinical care. Recently, two techniques have been developed to estimate TKV in ADPKD patients\textsuperscript{17-18}. In Chapter 9 these methods are validated, hypothesizing that these techniques provide reasonably adequate TKV measurements that will not affect the risk prediction of disease progression in these patients.

However, there is still need for a more accurate methodology to assess TKV, especially for use in clinical trials. In Chapter 10, a validation study is described, that investigates the validity of the artificial deep neural network that was developed for fully automated assessment of TKV.
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REFERENCES

Chapter 1


PART I

Lowering vasopressin concentration and optimization of vasopressin antagonism in polycystic kidney disease treatment