ADPKD
Beyond Growth and Decline

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Contents

Chapter 1

General introduction

General background

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, with a prevalence of approximately 3-4 per 10.000 in the general population, and is characterized by progressive cyst formation in both kidneys and renal function loss (1). It is the fourth most common cause of end-stage renal disease (ESRD) for which renal replacement therapy has to be started (2). Up to 2015 there was no treatment option available to slow disease progression, but recently a vasopressin V2 receptor antagonist (tolvaptan) has been approved for this indication by the European Medicines Agency (3). Beyond decline of renal function and renal cyst growth, patients may experience other symptoms such as pain, gastrointestinal discomfort and polyuria (4). Although these symptoms are common in ADPKD patients, they attain little attention and their consequences may be underestimated by physicians.

Renal and liver anatomy and sensory innervation

The kidneys are retroperitoneal structures that are located at the level of the transverse processes of vertebrae thoracic 12 to lumbar 3, with the left kidney being positioned somewhat higher than the right. The kidney is surrounded by dense fibrous tissue, the renal capsule, which itself is surrounded by perirenal fat. This perinephric fat is encapsulated by a thin connective tissue sheath, known as Gerota's fascia. A normal kidney has a length of approximately 10–14 cm and a volume of 150 mL (5). In ADPKD, however, the kidneys can be extremely enlarged due to cyst formation, with a single kidney volume increasing up to 6,000 mL (6) (Figure 1). In this latter case the kidney reaches into the pelvic cavity. The majority of patients develop cysts in the liver as well. On radiological imaging liver cysts were found in 94% of ADPKD patients older than 35 years (7). Most patients do not experience symptoms of their liver cysts, but liver enlargement and increased renal volume add both to a high intra-abdominal volume, that can lead to gastrointestinal symptoms as regurgitation, nausea and early satiety (8). Patients show a considerable variability in liver volume from 1,500 mL up to 14,000 mL (Figure 1).

In general, sensory innervation of internal organs travels by sympathetic and parasympathetic fibers. Nociceptive information from the thoracic, abdominal and pelvic organs reaches the spinal cord via sympathetic pathways, whereas those structures that bypass the pelvic floor convey the nociceptive impulses via parasympathetic pathways. As a consequence, sympathetically and parasympathetically conveyed nociception ends in the spinal cord segments C8-L1 and S2-4, respectively (5). In this

way, the levels of segmental sensory innervation determine to which dermatomal areas visceral pain is referred.

Pain originating from the upper abdominal organs, including the liver, reaches the spinal cord (levels T5 – T9), via the celiac plexus, the major splanchnic nerves and the sympathetic trunk, respectively (9, 10). Pain originating from the kidneys reaches the spinal cord (levels T10-L1) via the nerve plexus surrounding the renal artery, the aorticorenal plexus, the lesser and least splanchnic nerve and the sympathetic trunk, respectively (10). Small nerve connections between the renal plexus and celiac plexus have been reported, indicating that the sensory nerve supply is complex and can overlap.

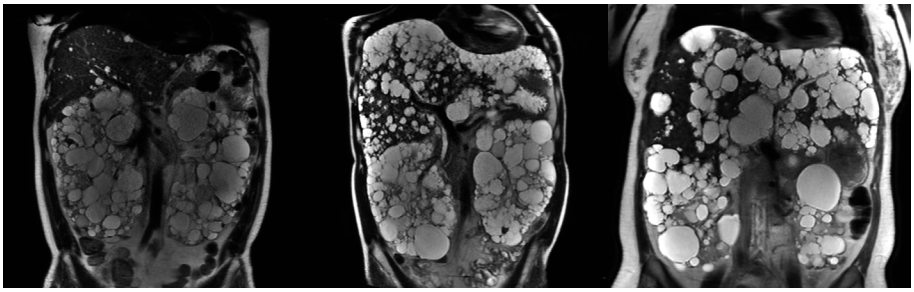

Figure 1. In ADPKD the kidneys and liver can be extremely enlarged due to cyst formation, with a single kidney volume increasing up to 6,000 mL and a liver volume up to 14,000 mL.

Natural course of ADPKD

Mutations in the PKD-1 and PKD-2 genes, that encode for the proteins polycystin-1 and polycystin-2 respectively, account for most ADPKD cases (11, 12). Mutations in the PKD-1 gene (located on chromosome 16p13.3) account for 85% and mutations in the PKD-2 gene (located on chromosome 4q21) for 15% of the ADPKD cases where a mutation has been found (11, 12). At present, no mutation can be identified in approximately 10% of patients. Mutations can be distinguished in truncating (frameshift, nonsense, splice mutations and large rearrangements) and non-truncating mutations (in frame and missense mutations). The PKD-1 gene is adjacent to a disease gene for tuberous sclerosis (TSC-2), a disorder that is characterized primarily by renal angiomyolipomas and renal cysts. Deletions of both the PKD-1 and TSC-2 genes are rare, but cause a severe form of ADPKD (13). Mutation penetrance in ADPKD is 100%. A child of an affected ADPKD patient has therefore a 50% risk to inherit and develop ADPKD. In 5-10% of the cases, there is no family history of ADPKD, and in such cases the disease is assumed to be caused by a spontaneous mutation.

Cyst formation leads to massively enlargement of both kidneys and distortion of the renal architecture. By glomerular hyperfiltration the kidneys compensates for the progressive loss of glomeruli, but after sometimes considerable length of time renal function starts to decline, and ultimately approximately 70% of the patients reaches end-stage renal disease between the age of 40-70 years (7). Peritoneal dialysis is not contraindicated in ADPKD patients, unless the kidneys are extremely enlarged (14). Sometimes nephrectomy of the native polycystic kidney is needed to assure enough space in the iliac fossa for a renal allograft (15).

The natural course of the disease with respect to loss of kidney function has a substantial variability within and between affected families (16). Factors positively associated with disease severity are PKD1 mutations (particularly truncating mutations), male sex, and early onset of hypertension and urological symptoms, such as macroscopic hematuria, recurrent urinary tract infections and renal stones (17). High total kidney volume, greater than expected for a given age, also signifies rapid disease progression (18-20). Laboratory markers that are associated with worse prognosis include overt proteinuria, macroalbuminuria, and elevated plasma copeptin levels (21, 22). All these markers may help to identify ADPKD patients who are most likely to have rapid disease progression and thus may benefit most from early disease modifying interventions.

Diagnosis and screening

At present the diagnosis of ADPKD can easily be made by radiological imaging. The implications of a positive diagnosis should be discussed before testing. The diagnosis ADPKD could for instance lead to an increase in insurance costs and some patients experience a negative psychological impact. Typical findings on radiological imaging include large kidneys and extensive cysts scattered throughout both kidneys. Because of costs and safety, ultrasound is the method of first choice. At the moment the Ravine criteria adjusted by Pei are used to diagnose ADPKD by imaging (23). The criteria for diagnosis varies, based upon age and whether family history is ADPKD positive. MR imaging is commonly used for monitoring disease progression, since MR imaging is more sensitive than ultrasound. Although genetic testing is rarely performed in routine clinical practice, it may be helpful in cases of atypical renal imaging findings or renal failure without significant kidney enlargement (20).

Symptoms

Clinical manifestations are often directly related to the degree of enlargement of the polycystic kidneys. Cyst growth often starts already in utero. Data from the Consortium

of Radiologic Imaging Studies to assess the Progression of Polycystic Kidney Disease (CRISP) showed that the annual increase in total kidney volume is on average 5 to 6% per year (18, 24). Most patients maintain their renal function until the fourth to sixth decade, despite of cyst growth. The kidneys are often significantly enlarged by the time renal function starts to decline. When renal function starts to drop, the average rate of eGFR decline is 1.6 to 5.0 mL/min/year (18).

Another early renal manifestation is hypertension that has a prevalence of 50% of patients aged 20-34 years and up to 100% in patients with ESRD (25). Factors proposed to contribute to hypertension in ADPKD are activation of the renin angiotensin system, increased sympathetic nerve activity and plasma endothelin-1 concentration (26). Since hypertension could lead to renal function decline and predisposes to cardiovascular disease, adequate therapy is indicated. First line treatment is blockade of the Renin-Angiotensin System, because of the alleged activation of this system in ADPKD. However, superiority of RAS blockers over other blood pressure lowering agents has never formally been tested. Furthermore ADPKD patients may have other complications associated with the disease e.g. cyst infections, cyst bleedings, renal stones, cardiac valve abnormalities, abdominal wall herniations and intracranial aneurysms. Cysts can also be formed extra-renal, with a high prevalence in the liver (up to 94%) (7), and in rare cases in the pancreas, seminal vesicles and the brain (4).

The majority of patients also experience pain and polyuria, both symptoms that are not always recognized by clinicians. Pain in ADPKD can be classified as acute or chronic. Acute severe pain is relatively uncommon. Data from the TEMPO 3:4 trial suggest an average incidence of clinically significant acute pain episodes of 7 per 100 person years in untreated patients (27, 28). In contrast, chronic pain is very common in patients with ADPKD with an estimated prevalence of 60% (29, 30). A subanalysis of the HALT trial showed that chronic pain even in ADPKD patients with retained renal function is often severe and leads to use of analgesic drugs in 28.0%, sleep disturbances in 16.8% and impacts physical activity and relationships with others in 20.8% (30). Thus, chronic pain has a major effect on physical and social functioning in many patients with ADPKD.

Another under-recognized symptom is polyuria, that is caused by an impaired urinary concentrating capacity. The mechanism behind this concentrating defect is not fully understood, although probably abnormalities in the renal medullary architecture, due to cyst formation and expansion, play an important role. In a previous study from our group, it was found that already in early stage disease this impaired maximal urine concentrating capacity results in increased plasma osmolality and vasopressin levels during water deprivation, in comparison with healthy controls (31). Vasopressin is secreted from the pituitary gland when, amongst other stimuli, plasma osmolality

increases. Vasopressin subsequently binds to the V2 receptor of the collecting ducts, which stimulates water reabsorption by migration of aquaporin-2 to the apical cell membrane (32). In addition, vasopressin has deleterious effects in ADPKD as it increases intracellular cAMP, which promotes cell proliferation and cyst formation (33). Indeed, animal models and a large randomized controlled trial showed that blocking the vasopressin V2 receptor reduces the rate of cyst growth and renal function loss (22, 27, 34, 35).

Finally, for patients, the diagnosis ADPKD could also have a strong physical and psychological impact (36-38). Patients are monitored in hospitals during their lifetime and deal with the uncertainty about the eventual need to become dependent of renal replacement therapy. Furthermore in case of family planning, difficult decisions have to be made about testing in case subjects with a positive family history have not been screened yet, and there may be concerns about the consequences of possible genetic transmission to children. Managing this burden can be emotionally challenging. Indeed, a recent study showed that ADPKD patients experience considerable distress, frustration and confusion, especially when they perceive that physicians do not deal appropriately with the impact of ADPKD on their daily life (36). Patients report also feelings of shame and guilt because of their physical limitations, inability to work and the invisibility of pain (37). ADPKD-related pain can be described as invalidating insofar that it affects their daily living, whilst the lack of effective pain therapies can increase their frustrations. These psychological aspects can lead to depression and anxiety and there is evidence that in ADPKD patients, indeed, depression and anxiety are more common than in the general population (38). Early identification of these problems is indicated to induce adequate management and to improve quality of life in ADPKD patients.

Symptomatic therapies

Over the past two decades, various, general renoprotective treatment options have been investigated in randomized controlled clinical trials, unfortunately without success. In these trials neither the assignment to a low protein diet, nor strict blood pressure control or double RAS inhibition reduced the rate of renal function decline in ADPKD patients (21, 39-42). Therefore treatment of ADPKD is as yet symptomatic. When patients experience pain, it is important to regard it within a biopsychosocial model. Careful assessment by obtaining a detailed history, physical examination and imaging techniques are necessary to identify the cause of pain, and interventions should be directed towards these causes. Various conservative and pharmacological options are available (43). In case analgesics do not achieve sufficient pain relief, several

minimal invasive procedures, such as cyst aspiration, cyst fenestration or nerve blocks can be performed. Surgical nephrectomy is the last option, because it is a difficult decision to remove a functioning kidney in subjects with a disease that is known to be progressive and can lead to ESRD.

Disease modifying therapies

Several disease specific therapies have been investigated in ADPKD. Since animal experiments with mTOR-inhibitors were encouraging, three studies, of which one large RCT, investigated the effect of mTOR-inhibitors in ADPKD patients (44-46). In all studies, mTOR-inhibitors had no effect on the rate of decline in renal function. Therefore it is concluded that this therapy is not useful in ADPKD patients to slow disease progression.

Another promising treatment option is inhibition of the enzyme adenylyl cyclase by stimulation of the somatostatin SSR2 receptor. In animal studies as well as in human studies, stimulation of the somatostatin receptor led to reduced cyst growth (47-49). In a smaller randomized controlled trial of 12 months duration, the efficacy of Octreotide, a somatostatin analogue, was investigated in 24 ADPKD patients and 8 polycystic liver disease patients (48). In this study, mean liver volume decreased compared to baseline with Octreotide, whereas it increased slightly in the placebo group (-4.95% vs. +0.92%, p=0.048). Total kidney volume was stable on Octreotide, but increased in the placebo group (+0.25% vs. +8.61%, p=0.045). Renal function decreased in both treatment groups (-3.5 vs. -5.1 mL/min/1.73m^2, p=1.0). Although these data are encouraging, firm conclusions regarding efficacy cannot be drawn because of the short duration of the trial and the relatively small population that was included. A larger, yet still relatively small randomized control trial was performed, including 75 ADPKD patients with preserved renal function, the ALADIN trial (49). This study suggested that somatostatin analogues may act renoprotective. A significant difference in change in total kidney volume was found at 1 year, but after 3 years of treatment the effect was no longer significant. Change in renal function from baseline to 3 years of treatment was also not significantly different between Octreotide and placebo treated patients, but the difference in change in renal function between year 1 and 3 was highly significant between both treatment groups, favoring Octreotide. It is known from literature that somatostatin analogues cause an acute decrease in eGFR, because an increase in somatostatin levels leads to vasoconstriction of the afferent artery (50). This may be explain why the investigators of the ALADIN trial found a significant difference in change in renal function on treatment (year 1 and 3) between both treatment groups, whereas they did not find a difference in change renal function between baseline and

year 3. Additionally, in the ALADIN trial, there were clinically relevant differences in baseline characteristics between both treatment group favoring the somatostatin analogue. Therefore, the results of this study are difficult to interpret.

Administration of somatostatin analogues is generally well tolerated. These agents play a role in bile release and patients can experience gastro-intestinal side effects, e.g. diarrhea, flatulence, abdominal pain and hypoglycaemia. These symptoms are often experienced only after the first injections caused by a direct increase in somatostatin levels, and are in most patients not a problem because after 3-4 injections patients will have reached a steady state concentration of somatostatin levels (48, 49).

Since the data of the ALADIN study are difficult to interpret, there is a need for a large RCT to investigate whether somatostatin analogues are effective to reduce the rate of disease progression in ADPKD. For this aim our research group designed the DIPAK-1 study to examine the efficacy of the somatostatin analogue Lanreotide to preserve kidney function in 300 ADPKD patients (51). It is the first large scale randomized clinical trial that will investigate the efficacy of a somatostatin analogue for renoprotection in ADPKD. It is expected that at the end of 2017 the results will become available.

Another therapeutic treatment option is inhibition of the enzyme adenylyl cyclase by blockade of the vasopressin V2 receptor. The TEMPO 3:4 trial publication showed for the first time in ADPKD patients in a randomized controlled clinical trial setting renoprotective effects of an intervention (27). The TEMPO 3:4 trial was a prospective, blinded, randomized, controlled trial in 1445 ADPKD patients with a total kidney volume >750 mL and preserved renal function. During 3 years of follow-up the vasopressin V2 receptor antagonist tolvaptan decreased the rate of growth in total kidney volume with 49% and the rate of eGFR loss with 26%. The major side effect was that, due to its aquaretic effect, tolvaptan causes polyuria that sometimes can be severe (up to 6-8 liters per day). Based on these data tolvaptan has recently been approved in Japan, Canada and Europe for the indication of slowing disease progressing in ADPKD patients, whereas the Food and Drug Authorization in the United States had requested additional clinical evidence.

Outline of the thesis

ADPKD patients may suffer from other symptoms beyond growth in renal volume and decline in renal function. The majority of patients also experience two other clinical manifestations, i.e. pain and polyuria, which often receive too little attention from

clinicians. It is important to adequately respond to ADPKD patients who experience pain and polyuria, because these symptoms can have a negative impact on a patient's quality of life. It should also be noted that polyuria will become a more prominent manifestation in ADPKD patients, since tolvaptan, that has recently been approved for the indication to slow disease progression by the European Medicines Agency, leads to polyuria up to 6-8 liters per day because of its aquaretic effect. Because pain and polyuria are often neglected, this thesis aims to investigate and discuss these symptoms in more detail. The goal of the first part of this thesis (Chapters 2-7) is to analyze pain in ADPKD patients, which, when under-treated, can lead to distress and frustration, especially when the patients perceive that physicians do not deal appropriately with the impact of their pain complaints. In addition, it includes a comprehensive overview of potential new pain therapies in ADPKD. In part II (Chapters 8-10) polyuria caused by impaired urinary concentrating capacity is evaluated and discussed. At the moment, many clinicians are not aware of the impact of this condition which may have a role in the pathophysiology of disease progression.

I. Pain in ADPKD

During lifetime kidney and liver volume increase, leading to distension of the renal and hepatic capsules, and compression of adjacent organs (52). Consequently, a substantial proportion of ADPKD patients suffer from pain and gastrointestinal symptoms, such as abdominal fullness and early satiety (20, 30, 43, 53). There is an ongoing debate if and how kidney and liver volume are associated with pain and gastrointestinal symptoms patients (30, 54-57). Another factor that potentially affects symptom burden is gender. To our knowledge, it has not been investigated whether higher symptom burden in females with ADPKD is caused by differences in reporting by sex in general, or by differences in kidney and/or liver size between both sexes. Given these considerations, it is investigated in a large cohort of ADPKD patients whether combined kidney and liver volume is more strongly associated with ADPKD-related pain and gastrointestinal symptoms than kidney or liver volume alone, and secondly whether there is a differences in the strength of this association between males and females (**Chapter 2**).

Symptom burden in ADPKD is multifactorial and other factors, in addition to organ volume, may contribute (55). Potential other determinants may include comorbidity, such as a history of urinary tract infection, renal cyst infection, liver cyst infection and macroscopic hematuria. In case an ADPKD patient experiences acute pain and fever, the diagnosis cyst infection should be considered. Cyst infections in ADPKD are often difficult to treat and may lead to hospitalization and even mortality (58, 59). At this moment, there is no evidence-based treatment to guide clinicians in the management

of renal cyst infection in ADPKD patients (20). **Chapter 3** tries to resolve this gap in knowledge, by performing a systematic review identifying all reports describing renal cyst infections in individual ADPKD patients. Based on these data, treatment preferences and potential factors that could affect treatment outcome are identified.

Pain in ADPKD is arbitrarily classified as acute or chronic. Recently the vasopressin V2 receptor antagonist tolvaptan has been approved in Europe for the indication to slow disease progression in ADPKD. The authors of the original paper suggested that tolvaptan use may be associated with a reduction in clinical progression as assessed by its key secondary composite endpoint through a reduction of ADPKD-related clinical events (27). This outcome was driven by two components of the composite, time to decline in kidney function and time to clinically significant renal pain events. In **Chapter 4** this last finding is explored more closely. The association of ADPKD clinical characteristics (such as history of renal pain, infection, renal stones or hematuria at baseline) with the incidence of acute renal pain events during the 3-year trial is investigated. Furthermore, the effect of tolvaptan use on incidence of renal pain events is analyzed and the possible mechanisms by which tolvaptan reduced their incidence are explored.

In contrast to acute pain, chronic pain is very common in patients with ADPKD with an estimated prevalence of 60% (29, 30). Chronic pain in ADPKD can have various causes and may be difficult to manage. Several algorithms for pain management in ADPKD have been published and indicated that as a last resort, nephrectomy can be performed for pain relief in patients with refractory renal pain (60-62). This is a difficult decision, removing a functioning kidney in patients with a disease that often leads to end-stage renal disease. Therefore there is a need for effective and less invasive therapies for chronic pain in ADPKD. **Chapter 5** reports a potential new treatment option, i.e. catheter based renal denervation, for chronic pain in ADPKD. Renal denervation has already been performed by laparoscopic and thoracoscopic procedures with satisfactory results in ADPKD patients with chronic pain, but these invasive techniques are difficult to perform. Recently a catheter-based percutaneous transluminal method has been introduced to ablate efferent and afferent renal sympathetic nerve fibres. This procedure may be a simple and effective alternative.

In **Chapter 6** an overview of pathophysiological mechanisms that can lead to pain and the sensory innervation of abdominal organs (including the kidneys and the liver) is provided. Based on pathophysiological considerations and evidence derived from literature an argumentative stepwise multidisciplinary approach for the effective management of chronic pain in ADPKD is proposed. In this approach the potential role for minimal invasive nerve blocks is discussed. From a theoretical point of view a celiac

plexus block, a block of the splanchnic nerves and catheter-based renal denervation are attractive options in selected cases, but further research is needed to determine the efficacy and their exact role in the management of refractory chronic pain in ADPKD patients. So, this stepwise multidisciplinary approach was applied in a large series of patients with refractory chronic ADPKD-related pain (**Chapter 7**).

II. Polyuria in ADPKD

At the moment, little attention is paid to polyuria in ADPKD patients. Impaired urine concentrating capacity resulting in polyuria deserves more attention, since it may have potentially negative consequences in the pathophysiology of disease progression (63, 64). The mechanism leading to decreased urine concentrating capacity is not fully understood, although probably abnormalities in the renal medullary architecture, due to cyst formation and expansion, play an important role. Impaired urine concentrating capacity is accompanied by increased plasma osmolality and vasopressin levels. In ADPKD vasopressin has deleterious effects as it increases intracellular cAMP, which promotes cell proliferation and cyst formation (33). In addition to blocking of the vasopressin V2 receptor, drinking a sufficient volume of water can also reduce vasopressin concentration. Increasing water intake could therefore be an alternative to medical treatment with a V2 receptor antagonist to ameliorate disease progression in ADPKD.

In a previous study in ADPKD patients, it was found that already in the early stages of disease there is an impaired maximal urine concentrating capacity in comparison to healthy controls, which is accompanied by increased plasma osmolality and vasopressin levels during water deprivation (31). It is hypothesized that in later stage of ADPKD, patients have a more severely impaired urine concentrating capacity in comparison to other patients with chronic kidney disease at a similar level of kidney function, with consequently an enhanced vasopressin response to water deprivation with higher circulating vasopressin concentrations (65, 66). To test this hypothesis, a water deprivation test was performed in ADPKD and non-ADPKD patients with impaired kidney function (**Chapter 8**).

In **Chapter 9** the clinical implications of an impaired urinary concentrating capacity are discussed. As mentioned earlier, an increased water intake could be an alternative to medical treatment with a V2 receptor antagonist to ameliorate disease progression in ADPKD. For clinicians, the question arises which ADPKD patients they should advise to increase their water intake, and what volume of fluid they should drink. In this respect, measuring urine osmolality could be of help (67-70). It is generally assumed that a urine osmolality below 285 mOsmol/kg, i.e., a urine osmolality lower

than plasma osmolality, reflects adequate suppression of vasopressin (68, 69). This chapter describes whether urine and plasma osmolality can be used to identify ADPKD patients with a high vasopressin concentration that are at risk for a more rapid rate of kidney function decline during follow-up (52).

Due to its aquaretic effect tolvaptan, a V2 receptor antagonist, causes polyuria that sometimes can be severe. In every patient with polyuria (e.g. a patient with diabetes insipidus or psychogenic polydipsia) infrequent voiding can lead to an increase in bladder volume, high bladder pressure, ureter dilatation and reflux, with consequently renal function loss (71-73). These patients are, therefore, usually advised to void frequently to prevent these potential negative consequences (71). ADPKD patients using tolvaptan have potentially a risk to develop similar problems. In a series of ADPKD patients that was started on tolvaptan or placebo in a trial setting, MR imaging was performed routinely for total kidney volume assessment. These MR images were used in **Chapter 10** to investigate the effect of tolvaptan induced polyuria on ureter diameter.

Finally, in the General discussion (**Chapter 11**) the main findings of the individual chapters are summarized and their potential consequences for daily practice are discussed. Furthermore, future perspectives are described.

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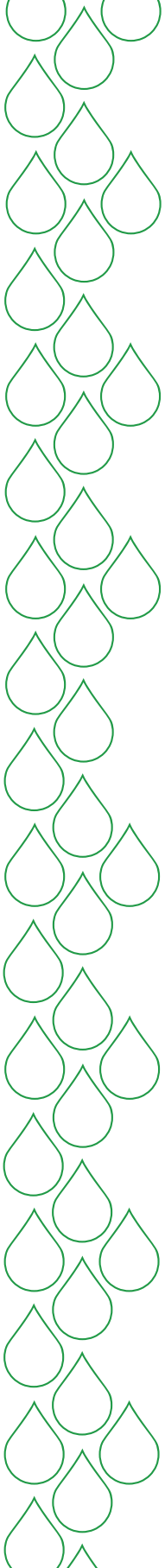

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Pain in ADPKD

Chapter 2

The association of combined total kidney and liver volume with pain and gastrointestinal symptoms in patients with later stage ADPKD

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Abstract

Background: There is an ongoing debate if and how kidney and liver volume are associated with pain and gastrointestinal symptoms in ADPKD patients. Since both volumes could interact, we investigated whether combined total kidney and liver volume had stronger associations with ADPKD-related pain and gastrointestinal (GI) symptoms than the volumes of the organs separately.

Methods: We used baseline data from the DIPAK-1 study which included ADPKD patients with an eGFR between 30-60 mL/min/1.73m^2. MR imaging was performed to measure height adjusted total kidney volume (hTKV), total liver volume (hTLV) and the combination of both (hTKLV).

Results: 309 ADPKD patients were included with a mean age of 48±7 years, 53% female, eGFR of 50±11 mL/min/1.73m^2 and median hTKV, hTLV and hTKLV of 1095 [758-1669], 1173 [994-1523] and 2496 [1972-3352] mL/m, respectively. ADPKD-related pain and GI symptoms were present in respectively 27.5% and 61.2% of patients. Sex was no effect modifier in the association between kidney and/or liver volume, and symptom burden, indicating that all models could be tested in the overall study population. hTKLV and hTLV were significantly associated with pain and GI symptoms, whereas hTKV was not. Model testing revealed that the associations of pain and GI symptoms with hTKLV were significantly stronger than with hTKV (p=0.04 and p=0.04, respectively), but not when compared to hTLV (p=0.2 and p=0.5, respectively).

Conclusions: This study indicates that combined kidney and liver volume was associated with the presence and severity of pain and GI symptoms in ADPKD, with a more prominent role for hTLV than for hTKV.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive renal cyst formation and the majority of patients also have liver cysts (>94%) (1). During lifetime kidney and liver volume increase, leading to distension of the renal and hepatic capsules, and compression of adjacent organs (2). Consequently, a substantial proportion of ADPKD patients suffers from pain and gastrointestinal symptoms, such as abdominal fullness and early satiety (3-6).

There is an ongoing debate if and how kidney and liver volume are associated with pain and gastrointestinal symptoms. A number of studies have investigated symptom burden in ADPKD patients (5, 7-9). The largest of these studies did not find an association between kidney volume and pain, except in a small subgroup with very large kidneys (5). Another study concluded that quality of life was not different between patients with a total kidney volume (TKV) larger or smaller than 1000 mL, but the effect of liver volume was not assessed (8). Two studies that analyzed the effect of liver volume on quality of life, showed conflicting results, with one study finding no relation and the other a significant, but weak association between liver volume and symptom burden (10, 11). Of note, all aforementioned studies varied in the use of height or non-height adjusted kidney and liver volumes (5, 7-10). In terms of disease progression height adjusted total kidney volume (hTKV) has been shown to be more closely related to the rate of disease progression than non-height adjusted TKV (12). The question arises whether the conflicting data in literature may be explained by the fact that sometimes height and sometimes non-height adjusted volumes were used to test correlations with symptom burden.

Another factor that potentially affects symptom burden is a difference in sex. In literature females are overrepresented among cohorts of patients with symptomatic ADPKD (13, 14). This is usually attributed to the presence of a more severe liver phenotype in females (15). On the other hand, pain sensitivity has been suggested to be greater among females, and females are more likely to report gastrointestinal symptoms when compared to males (16-18). To our knowledge, it has not been investigated whether higher symptom burden in females with ADPKD is caused by differences in reporting by sex in general, or by differences in kidney and/or liver size between both sexes.

Since both kidney and liver volume drive intra-abdominal volume, it is reasonable to assess the association of combined kidney and liver volume with ADPKD-related pain and gastrointestinal symptoms (19). Therefore, we investigated in a large cohort of ADPKD patients whether combined kidney and liver volume is more strongly

associated with ADPKD-related pain and gastrointestinal symptoms than kidney or liver volume alone, secondly whether there is a difference in the strength of this association between males and females, and thirdly whether height adjusted volumes are more strongly associated with pain and gastrointestinal symptoms than non-height adjusted volumes.

Methods

Patients and study design

Baseline data were used from the DIPAK-1 study, an investigator driven, multi-center, randomized, controlled clinical trial that included ADPKD patients with an estimated glomerular filtration rate (eGFR) between 30-60 mL/min/1.73m^2 and age 18-60 years. Patients were enrolled at 4 University Medical Centers in the Netherlands (Groningen, Leiden, Nijmegen and Rotterdam) between June 2012 and March 2015. ADPKD diagnosis was based on the modified Ravine criteria (20). Exclusion criteria were among others, concomitant illnesses likely to confound the natural decline of renal function in ADPKD, for example diabetes mellitus. Details of the study protocol have been published elsewhere (21). The Medical Ethics Committee of the University Medical Center Groningen approved the protocol of the DIPAK-1 study that was conducted in accordance with the International Conference of Harmonization Good Clinical Practice Guidelines and in adherence to the ethics principles that have their origin in the Declaration of Helsinki (METc2012/060). All patients gave written informed consent.

Data collection, measurements and definitions

Evaluations were performed in all patients at baseline including standardized interviews, physical examination, collection of blood samples and MR imaging. During the interviews information was gathered about demographics, medical history, pain and gastrointestinal symptoms. Renal pain was defined as pain or discomfort located in the flank, the lower back or abdomen. Liver pain was defined as pain or discomfort located in the right upper abdomen, behind or below the rib cage. The severity of renal and/or liver pain during the last 4 weeks was assessed on a 1-10 scale (1=no pain, 10=worst possible pain), and presence of renal or liver pain was defined as a score >2. Since it is difficult to distinguish between renal and liver pain, we used a composite score for ADPKD-related pain. Presence of ADPKD-related pain was defined as a composite score of >2 on either renal or liver pain. For severity of ADPKD-related pain the highest score on either renal or liver pain was used. The presence of gastrointestinal symptoms

over the last 4 weeks was recorded via the gastrointestinal symptoms questionnaire (22). This questionnaire contains 11 items including: lower and upper abdominal pain, heartburn, regurgitation, nausea, vomiting, loss of appetite, early satiety, dyspnea, increase of abdominal waist and involuntary weight loss. All symptoms were assessed using a 7-point Likert scale, ranging from 1 ("none") to 7 ("severe"). Symptom severity sum score was calculated by summing all scores and converting it to a score from 0 to 100 (22). Presence of gastrointestinal symptoms was defined as a score of >2 on at least one of 11 gastrointestinal symptoms.

Serum creatinine was reported and used to estimate GFR (applying the CKD-EPI equation) (23). All patients underwent a MRI to assess kidney and liver volumes by the manually tracing method using the commercially available software Analyze Direct 11.0 (Analyze Direct, Inc., Overland Park, KS, USA). Kidney and liver volumes were calculated from the set of contiguous images by summing the products of the area measurements within the kidney or liver boundaries and slice thickness. Details of the imaging protocol have been reported previously (21). hTKV, height adjusted total liver volume (hTLV) and combined total kidney liver volume (hTKLV) were calculated as total organ volume in mL divided by height in meters.

Statistical analyses

We performed a cross-sectional analysis of the baseline data of the DIPAK-1 study. Baseline characteristics were calculated for the overall population and stratified for patients experiencing ADPKD-related pain, experiencing gastrointestinal symptoms and sex. Parametric variables are expressed as mean ± standard deviation (SD), non-parametric variables as median ± interquartile range [IQR]. Differences in baseline characteristics between groups were calculated with a Chi-square test for categorical data, and for continuous data with Student's t-test or a Mann-Whitney U test in case of non-parametric data.

To investigate whether organ volume correlated with ADPKD-related pain and gastrointestinal symptoms, univariate and multivariate linear regression analyses were performed. hTKV, hTLV and hTKLV were logarithmic transformed to fulfill the requirement of normal distribution of the residuals for regression analysis. The multivariate linear analyses were subsequently adjusted for age and eGFR to correct for disease severity. To investigate differences between males and females the variable sex was added to the regression analysis. To explore whether associations between organ volume (i.e. hTKV, hTLV and hTKLV) and symptom burden (i.e. ADPKD-related pain and gastrointestinal symptoms) were different between males and females, interaction was tested by adding product terms (sex times volume) as independent variable to the models.

We used bootstrapping (2000 times) to investigate whether the association of hTKLV with ADPKD-related pain and gastrointestinal symptoms was stronger than the associations between either hTKV or hTLV, and ADPKD-related pain and gastrointestinal symptoms. In all models we corrected for disease severity by adjustment for sex, age and eGFR. As sensitivity analysis, we restricted the analysis of the associations between organ volume and symptom burden to patients with extremely enlarged kidney volumes (hTKV >1000 mL/m), as defined previously in literature (5). Lastly, bootstrapping was performed to analyze whether height adjusted volume models were more strongly associated with pain and gastrointestinal symptoms than non-height adjusted volume models. All analyses were performed using SPSS (software version 22.0, Chicago, IL, USA) and STATA (Version 14 StataCorp SE) statistical software, and a two-sided $p<0.05$ was considered to indicate statistical significance.

Results

Patient characteristics

We enrolled 309 ADPKD patients in our study, of which 53% were female with a mean age of 48±7 years. Following our inclusion criteria all patients had an impaired renal function, with a mean eGFR of 50±11 mL/min/1.73m^2. Blood pressure was on average well controlled and almost all patients used antihypertensive medication (91.2%). Median height adjusted total kidney volume (hTKV), total liver volume (hTLV) and combined total kidney liver volume (hTKLV) were respectively 1095 [758-1669] mL/m, 1173 [994-1523] mL/m and 2496 [1972-3352] mL/m. Liver cysts were present in the large majority of patients (93.2%).

ADPKD-related pain and gastrointestinal symptoms

ADPKD-related pain was reported by 27.5% of the study population (renal pain: 24.9% and liver pain: 11.3%) (Table 1). Pain was more common in females than in males. Age and eGFR did not differ between patients with and without pain, while a history of renal pain, liver pain, urinary tract infection, renal cyst infection, liver cyst infection and macroscopic hematuria were more common in those who reported pain. Liver cysts were also more common in patients experiencing ADPKD-related pain. Larger hTLV and hTKLV were associated with pain, whereas hTKV was not.

Table 1. Baseline characteristics of DIPAK study participants stratified according to presence or absence of ADPKD-related pain and gastrointestinal symptoms.

	Presence of ADPKD-related pain			Presence of gastrointestinal symptoms		
	Yes	No	P-val.	Yes	No	P-val.
N	85 (27.5)	224 (72.5)	-	189 (61.2)	117 (37.9)	-
Female sex (%)	56 (65.9)	106 (48.8)	0.006	111 (58.7)	52 (44.4)	0.02
Age (yrs)	48±7	48±7	0.6	48±8	48±7	1.0
Height (m)	1.75±0.1	1.77±0.1	0.05	1.75±0.1	1.79±0.1	0.001
Weight (kg)	82±16	85±17	0.3	84±18	85±15	0.6
BMI (kg/m^2)	26.9±4.4	27.0±4.8	1.0	27.2±4.7	26.5±4.5	0.2
History of						
- Renal pain (%)	70 (82.4)	75 (34.2)	<0.001	105 (55.6)	40 (34.2)	<0.001
- Liver pain (%)	27 (31.8)	10 (4.6)	<0.001	35 (18.5)	2 (1.7)	<0.001
- UTI (%)	52 (61.2)	93 (42.5)	0.003	100 (52.9)	46 (39.3)	0.02
- Renal cyst infection (%)	14 (16.5)	14 (6.4)	0.006	23 (12.1)	5 (4.2)	0.02
- Liver cyst infection (%)	2 (2.4)	0 (-)	0.02	2 (1.1)	0 (-)	0.3
- Macroscopic hematuria (%)	40 (47.1)	60 (26.9)	0.001	64 (33.9)	36 (30.8)	0.6
- Renal surgery >1 year (%)	1 (1.2)	2 (0.9)	0.8	0 (-)	3 (2.6)	0.03
- Liver surgery >1 year (%)	3 (3.5)	1 (0.5)	0.04	3 (1.6)	1 (0.9)	0.6
SBP (mmHg)	134±13	132±14	0.4	133±14	131±13	0.3
DBP (mmHg)	85±10	81±10	0.01	82±9	82±10	0.5
Use of BPLD (%)	82 (96.5)	195 (89.4)	0.05	173 (92.0)	105 (89.7)	0.5
Presence of hypertension (%)	80 (94.1)	189 (86.3)	0.1	169 (89.4)	102 (87.2)	0.6
Presence of liver cysts (%)	84 (100)	199 (92.6)	0.01	180 (97.3)	105 (90.5)	0.01
eGFR (mL/min/1.73m^2)	49±11	50±11	0.4	49±11	50±10	0.5
TKV (mL)	2054 [1423-3319]	1910 [1256-2868]	0.4	2119 [1380-3185]	1809 [1246-2668]	0.05
hTKV (mL/m)	1193 [809-1869]	1056 [719-1646]	0.3	1221 [784-1796]	982 [684-1489]	0.02
TLV (mL)	2300 [1908-4334]	2031 [1744-2556]	0.001	2148 [1803-3075]	2010 [1717-2474]	0.02
hTLV (mL/m)	1345 [1080-2435]	1149 [986-1418]	<0.001	1219 [1023-1699]	1144 [955-1367]	0.003
TKLV (mL)	5366 [3954-6955]	4182 [3402-5500]	<0.001	4645 [3698-6491]	4002 [32925091]	<0.001
hTKLV (mL/m)	2979 [2186-3921]	2392 [1931-3030]	<0.001	2661 [2135-3617]	2216 [1873-2854]	<0.001

Abbreviations are: BMI, body mass index; UTI, urinary tract infection; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPLD, blood pressure lowering drug; eGFR, estimated glomerular filtration rate; TKV, total kidney volume; hTKV, height adjusted total kidney volume; TLV, total liver volume; hTLV, height adjusted total liver volume; TKLV, total kidney liver volume; hTKLV, height adjusted total kidney liver volume. Data are shown as number (%), mean± standard deviation or median [interquartile range]

Table 2. Prevalence and severity of ADPKD-related pain and gastrointestinal symptoms overall and stratified for sex.

	Overall % or median ± IQR	Males % or median ± IQR	Females % or median ± IQR	P-val.
History of pain				
- *Renal related pain*	47.6%	43.2%	51.5%	0.14
- *Liver related pain*	12.0%	2.1%	20.9%	<0.001
- *Renal or liver related pain*	50.8%	45.2%	55.8%	0.06
Presence of pain				
- *Renal related pain*	24.9%	19.2%	30.1%	0.04
- *Liver related pain*	11.3%	4.1%	17.8%	<0.001
- *Renal or liver related pain*	27.5%	19.9%	34.4%	0.006
Severity of present pain				
- *Renal related pain*	4 [3-6]	4 [3-6]	5 [3-5]	0.3
- *Liver related pain*	5 [4-7]	4 [4-5]	6 [4-7]	0.1
- *Renal or liver related pain*	4 [3-7]	4 [3-6]	5 [3-7]	0.2
Gastrointestinal symptoms				
- *Lower abdominal pain*	14.9%	9.6%	19.6%	0.02
- *Upper abdominal pain*	17.8%	9.6%	25.2%	<0.001
- *Heartburn*	22.7%	22.6%	22.7%	0.9
- *Regurgitation*	18.4%	17.8%	19.0%	0.9
- *Nausea*	13.6%	6.8%	19.6%	0.001
- *Vomiting*	3.2%	2.1%	4.3%	0.3
- *Loss of appetite*	16.2%	10.3%	21.5%	0.01
- *Early satiety*	32.0%	19.9%	42.9%	<0.001
- *Dyspnea*	24.6%	19.2%	29.4%	0.05
- *Increasing abdominal volume*	25.2%	16.4%	33.1%	0.001
- *Involuntary weight loss*	2.9%	1.4%	4.3%	0.1
Severity of present GI symptoms				
- *GI- sum score*	12.0 [8.0-21.0]	9.0 [4.5-16.7]	17.6 [15.2-23.1]	<0.001

Abbreviations are: GI, gastrointestinal. Denominators depend on the number of patients who provided an answer for a specific question in the questionnaire. Renal and liver pain measured on scale 1-10 (1= no pain); GI-sum score ranging from 0-100. (0 = no symptoms).

A total of 61.2% of the ADPKD patients experienced gastrointestinal symptoms, with females being overrepresented in patients reporting these symptoms (Table 1). Age and eGFR were not different between patients with or without gastrointestinal symptoms. Presence of gastrointestinal symptoms was associated with a history of renal pain, liver pain, urinary tract infection, renal cyst infection and renal surgery. Out of the 11 gastrointestinal symptoms that were assessed, the most frequently reported symptom was early satiety (32.0%), followed by increased abdominal volume (25.2%), dyspnea (24.6%), heartburn (22.7%) and regurgitation (18.4%) (Table 2).

Association of kidney and liver volume with pain and gastrointestinal symptoms

To investigate whether associations between volumes (hTKV, hTLV and hTKLV) and symptom burden (ADPKD-related pain and gastrointestinal symptoms) were sex dependent, we tested the interaction between these characteristics. No significant interaction with sex was found, indicating that all associations could be tested across the complete study population and that stratification by sex was not necessary. hTKV was not associated with severity of ADPKD-related pain in the overall population ($R=0.05$, $p=0.44$) (Figure 1). In contrast, hTLV and hTKLV were both correlated with ADPKD-related pain ($R=0.20$, $p<0.001$ and $R=0.23$, $p<0.001$). After adjustment for disease severity, by correction for age, sex and eGFR, these associations remained significant ($R=0.23$, $p<0.001$ and $R=0.20$, $p<0.001$, respectively). The hTKLV model was also more strongly associated with pain than the hTKV model ($p=0.04$), whereas this was not the case for the hTLV model ($p=0.2$).

We then tested whether kidney and liver volume were associated with gastrointestinal sum score. No association was found for hTKV ($R=0.10$, $p=0.09$), whereas hTLV and hTKLV were both associated with the gastrointestinal sum score ($R=0.23$, $p<0.001$ and $R=0.23$, $p<0.001$, respectively) (Figure 2). Again, the association with gastrointestinal symptoms was significantly stronger for the model containing hTKLV compared with the model containing hTKV ($p=0.04$), but not compared with the model with hTLV ($p=0.5$).

Of note, we performed a sensitivity analysis to test whether these associations were different in patients with larger kidneys (hTKV >1000 mL/m). Essentially the same results were found as in the initial analysis; hTLV and hTKLV were, and hTKV was not associated with ADPKD-related pain and gastrointestinal symptoms.

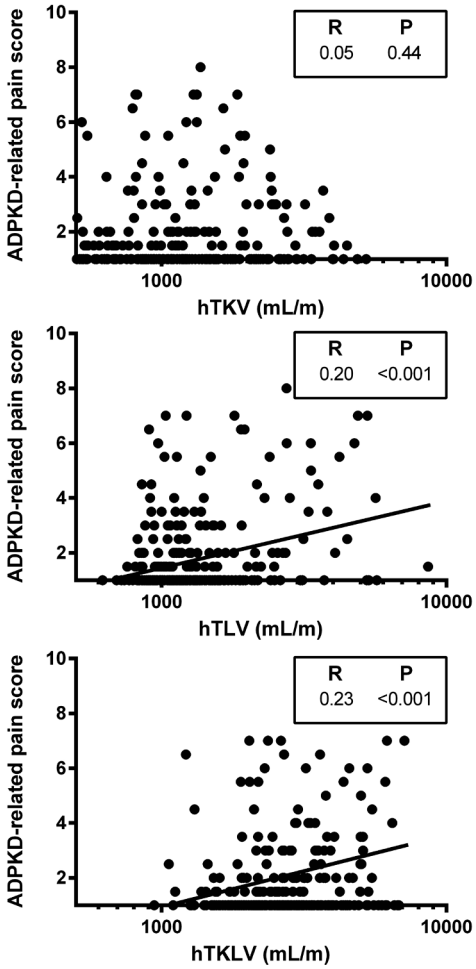

Figure 1. Associations of height adjusted Total Kidney Volume (hTKV), Total Liver Volume (hTLV) and combined Total Kidney Liver Volume (hTKLV) with ADPKD-related Pain Score (1-10).

Differences in symptom burden between males and females

Renal and liver pain were present in 30.1% and 17.8% of females while this only accounted for 19.2% and 4.1% in males ($p=0.04$ and $p<0.001$, respectively). In case a patient experienced renal or liver pain, the severity of pain was similar among males and females. Gastrointestinal symptoms were more prevalent among females. The following symptoms were reported more frequently by females: abdominal pain, nausea, early satiety and an increased abdominal volume, compared to males (Table 2). Gastrointestinal symptoms as expressed in the gastrointestinal sum score were more severe in females than in males (17.6 vs. 9.0, $p<0.001$).

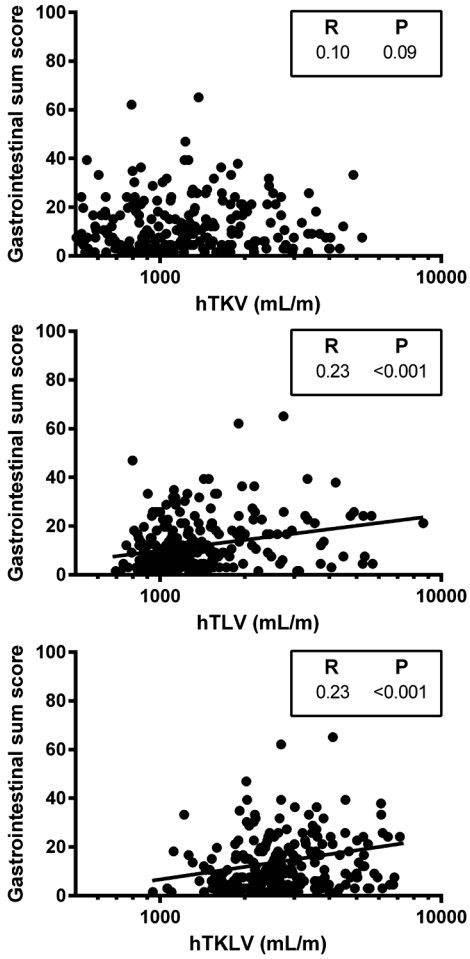

Figure 2. Associations of height adjusted Total Kidney Volume (hTKV), Total Liver Volume (hTLV) and combined Total Kidney Liver Volume (hTKLV) with gastrointestinal sum score (0-100).

Females had larger hTLV and smaller hTKV than males (hTLV: 1249 [1034-1901] vs. 1130 [967-1336] mL/m, p<0.001 and hTKV: 923 [604-1330] vs. 1314 [935-2145] mL/m, p<0.001). hTKLV did not differ between both sexes (females: 2424 [1939-3213] mL/m, males 2537 [2065-3547] mL/m, p=0.2). Female sex was positively associated with symptom burden in ADPKD patients, but after adjustment for hTLV, this association lost significance.

Height adjusted versus non-height adjusted models

No difference was observed in the association with symptoms between the models with either hTKV or TKV (p=1.0), whereas the models with hTLV and hTKLV had

stronger associations with pain than the models with TLV and TKLV (p=0.02 and p=0.01, respectively). For gastrointestinal sum score, similar results were found. hTLV and hTKLV models were more strongly associated with gastrointestinal symptoms than non-height adjusted models (p=0.01 and p=0.01, respectively), which did not account for the hTKV model (p=1.0). Of note, the results of correlation analyses of ADPKD-related pain and gastrointestinal symptoms with non-height adjusted TKV, TLV and TKLV, were essentially similar to the results of the primary analyses with hTKV, hTLV and hTKLV (Table 3 and Supplementary Table 1). The relations between organ volume and symptom burden still existed, but were less strong compared to the height adjusted models (Table 3).

Table 3. Associations of height adjusted kidney and liver volumes with pain and gastrointestinal symptoms.

	hTKV		hTLV		hTKLV	
	R	P-val.	R	P-val.	R	P-val.
History of pain						
- Renal related pain	0.10	0.1	**0.15**	0.01	**0.22**	<0.001
- Liver related pain	-0.06	0.3	**0.30**	<0.001	**0.20**	0.001
- Renal or liver related pain	0.12	0.1	**0.21**	<0.001	**0.27**	<0.001
Presence of pain						
- Renal related pain	0.07	0.2	**0.16**	0.01	**0.21**	<0.001
- Liver related pain	0.01	0.8	**0.25**	<0.001	**0.21**	<0.001
- Renal or liver related pain	0.06	0.3	**0.21**	<0.001	**0.24**	<0.001
Severity of present pain						
- Renal related pain	0.04	0.5	**0.14**	0.02	**0.17**	0.003
- Liver related pain	0.04	0.5	**0.27**	<0.001	**0.26**	<0.001
- Renal or liver related pain	0.02	0.8	**0.20**	<0.001	**0.22**	<0.001
Gastrointestinal symptoms						
- Lower abdominal pain	0.06	0.3	0.10	0.1	0.09	0.1
- Upper abdominal pain	0.03	0.6	**0.22**	<0.001	**0.19**	0.001
- Heartburn	**0.15**	0.01	0.05	0.4	**0.13**	0.03
- Regurgitation	**0.12**	0.03	**0.14**	0.02	**0.15**	0.01
- Nausea	-0.04	0.5	**0.22**	<0.001	**0.11**	0.05
- Vomiting	-0.02	0.8	**0.13**	0.03	0.09	0.1
- Loss of appetite	0.01	0.8	**0.18**	0.002	**0.16**	0.01
- Early satiety	0.06	0.3	**0.21**	<0.001	**0.21**	<0.001
- Dyspnea	0.06	0.3	**0.14**	0.02	0.11	0.1
- Increasing abdominal volume	**0.12**	0.03	**0.15**	0.01	**0.22**	<0.001
- Involuntary weight loss	-0.02	0.7	0.08	0.2	0.00	1.0
Severity present gastrointestinal symptoms						
- GI- sum score	0.10	0.1	**0.23**	<0.001	**0.23**	<0.001

Abbreviations are: hTKV, height adjusted total kidney volume; hTLV, height adjusted total liver volume; hTKLV, height adjusted total kidney liver volume; GI, gastrointestinal. hTKV, hTLV and hTKLV were log transformed. Denominators depend on the number of patients who provided an answer for a specific question in the questionnaire. Renal and liver pain measured on scale 1-10 (1= no pain); GI-sum score ranging from 0-100. (0 = no symptoms).

Discussion

This study showed that both hTKLV and hTLV were moderately associated with pain and gastrointestinal symptoms in patients with later stage ADPKD, while hTKV was not. Other patient related characteristics, such as a history of urinary tract infection, renal cyst infection, liver cyst infection and macroscopic hematuria, were also associated with symptom burden. We found that females more frequently suffered from symptoms than males. However, sex was not an effect modifier in the relation between organ volume and symptoms and the higher symptom burden in women seems to be explained by their larger hTLV. In addition, the models containing height adjusted organ volumes were more strongly associated with pain and gastrointestinal symptoms compared to non-height adjusted models.

The general assumption is that a large kidney volume in ADPKD plays a role in causing pain (2). Interestingly, two studies that investigated the association between kidney volume and pain, did not confirm this assumption (5, 8). The authors found that total kidney volume did not differ between those patients taking or not taking analgesics (8). Only at the extreme of renal volumes in ADPKD (hTKV >1000 mL/m), an association between kidney volume and pain was found (5). In our study no association was found between hTKV and pain in the overall study population, nor in patients with very large kidneys. The present data add therefore to the evidence that the link between hTKV and pain is weak or even absent.

Previous studies found inconsistent results regarding the relation between liver volume and symptom burden. One study by Hogan et al, that included patients with early stage ADPKD (eGFR >60 mL/min/1.73m^2), found an association between liver volume and reduced quality of life (10). However, another study found no such relation in 92 patients with polycystic liver disease, of whom 67% had ADPKD (11). Of note, this latter study included only patients with symptomatic polycystic liver disease, which makes finding associations between symptoms and liver volume population difficult. Our results suggest, in accordance with the results of Hogan et al, that liver volume in ADPKD contributes significantly to symptom burden, as both hTLV and hTKLV were associated with pain and gastrointestinal symptoms. The reason why liver volume seems to play a more important role in causing symptoms than kidney volume cannot be concluded from the present data. However, we hypothesize that organ location might be important. The liver has a position more closely to other intra-abdominal organs than the kidneys, that are located retroperitoneal. An increase in liver volume may consequently lead to more compression of adjacent tissues (i.e. stomach, intestines and lungs) than an increase in kidney volume, causing symptoms such as dyspepsia, early satiety, dyspnea and pain (4).

Only one previous study has investigated the role of combined total kidney liver volume on patient reported outcome measures and found no association with health related quality of life (7). Of note, kidney and liver volumes were available in only 31 out of 219 included patients (of which 21 were on dialysis) and the lack of significant associations may be due to the small sample size. In contrast, we found significant association between hTKLV, hTLV and symptoms. It should be noted, however, that the strength of these associations was moderate. This suggests that symptom burden is multifactorial and that other factors may contribute (7). Potential other determinants may include coping mechanisms and comorbidity, such as a history of urinary tract infection, renal cyst infection, liver cyst infection and macroscopic hematuria, which according to our results, were also related to current ADPKD-related symptom burden. Adequate management of these events may be indicated to reduce the presence of symptom burden in ADPKD.

Our data indicate a gender disbalance in prevalence and severity of ADPKD-related pain and gastrointestinal symptoms. This is in accordance with earlier studies that found that females more frequently reported pain, used analgesics and were more impaired in their physical activities compared to males (5). The same observation is true for the general population, where females report pain and gastrointestinal symptoms more frequently (16-18). Surprisingly, sex was no effect modifier in the relation between volumes and symptom burden in our study. As expected, females had larger hTLV compared to males, and when adjusted for hTLV, variations in symptom burden between males and females disappeared. Based on these data we hypothesize that the higher symptom burden in women could be explained by their larger hTLV, though it might be that women experience more pain in general, compared to men. Despite these findings, physicians have to realize that symptomatic polycystic liver disease will mainly be present in females, as estrogens stimulate liver cyst growth (24, 25). Therefore the use of estrogens, such as in oral contraceptives, should be discouraged in symptomatic female ADPKD patients.

In symptomatic ADPKD patients, therapies are indicated that can slow cyst growth in both kidneys and liver. The TEMPO 3:4 trial demonstrated that tolvaptan, a vasopressin V2 receptor antagonist, decreased the rate of growth in total kidney volume (26). This study also suggested that tolvaptan had a positive effect on acute renal pain events (26). In contrast to the beneficial effect on renal cyst growth, tolvaptan presumably has no effect on liver cyst growth because the V2 receptor is not expressed in liver tissue. Our results suggest that in order to effectively reduce ADPKD-related symptom burden, therapy should also target liver cysts. Somatostatin analogues have been shown to reduce liver growth rate and symptoms in ADPKD patients with severe

polycystic liver disease (13, 14, 27). These agents also hold promise to reduce the rate of growth of total kidney volume (13, 28) and the rate of renal function decline in ADPKD patients (29). Somatostatin analogue therapy may therefore become a treatment option in ADPKD patients who suffer from pain and gastrointestinal symptoms, but this issue needs additional study before somatostatin analogues can be prescribed in clinical practice. Two randomized controlled trials are ongoing to test the efficacy of somatostatin analogues to delay disease progression and reduce symptom burden in ADPKD (21, 30).

A limitation of our study is that it is performed in the setting of a randomized controlled trial with specific inclusion criteria for age (18-60 years) and renal function (eGFR 30-60 mL/min/1.73m^2). This may make extrapolation of our findings to the general ADPKD population difficult. However, we observed that neither ADPKD-related pain, nor gastrointestinal symptoms were associated with renal function, suggesting that our results may be valid for the general ADPKD population. The main strength of our study is the systematic and prospective nature of data collection, that resulted in a well-phenotyped population.

In conclusion, we found that combined kidney and liver volume is associated with pain and gastrointestinal symptoms in ADPKD, with a more prominent role for liver volume than for kidney volume. It should be noted, however, that other determinants, such as a history of urinary tract infection, renal cyst infection, liver cyst infection and macroscopic hematuria, also seem to be of importance in determining symptom burden in ADPKD. Height adjusted organ volumes were more strongly associated with symptom burden compared to the non-height adjusted organ volumes, emphasizing the relevance of height adjustment to assess associations with symptom burden. Female ADPKD patients more often experienced pain and gastrointestinal symptoms than males. This sex difference could be explained by larger liver volumes in females compared to males. Lastly, our results implicate that physicians should be aware of the role of liver volume in symptomatic ADPKD and that efforts to reduce symptom burden should target especially liver volume.

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DIPAK Consortium

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Disclosure

The authors have no potential conflicts of interest relevant to the content of this article.

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Supplementary Table 1. Associations of kidney and liver volumes with pain and gastrointestinal symptoms (not height-adjusted).

	TKV		TLV		TKLV	
	R	P-val.	R	P-val.	R	P-val.
History of pain						
- Renal related pain	0.10	0.2	**0.16**	0.006	**0.21**	<0.001
- Liver related pain	-0.08	0.2	**0.28**	<0.001	**0.16**	0.006
- Renal or liver related pain	0.11	0.1	**0.20**	<0.001	**0.26**	<0.001
Presence of pain						
- Renal related pain	0.06	0.3	**0.15**	0.008	**0.19**	0.001
- Liver related pain	0.00	1.0	**0.23**	<0.001	**0.19**	0.001
- Renal or liver related pain	0.05	0.4	**0.20**	<0.001	**0.22**	<0.001
Severity of present pain						
- Renal related pain	0.03	0.6	**0.13**	0.03	**0.16**	0.01
- Liver related pain	0.02	0.8	**0.25**	<0.001	**0.23**	<0.001
- Renal or liver related pain	0.02	0.8	**0.19**	0.001	**0.20**	0.001
Gastrointestinal symptoms						
- Lower abdominal pain	0.04	0.5	0.07	0.2	0.07	0.2
- Upper abdominal pain	0.02	0.8	**0.20**	0.001	**0.17**	0.004
- Heartburn	**0.1**	0.01	0.05	0.4	**0.12**	0.03
- Regurgitation	0.11	0.05	**0.13**	0.03	**0.14**	0.01
- Nausea	-0.06	0.3	**0.19**	0.001	0.08	0.2
- Vomiting	-0.02	0.7	**0.12**	0.04	0.07	0.2
- Loss of appetite	0.00	1.0	**0.16**	0.006	**0.13**	0.02
- Early satiety	0.04	0.5	**0.18**	0.002	**0.17**	0.003
- Dyspnea	0.04	0.5	**0.11**	0.05	0.08	0.2
- Increasing abdominal volume	0.10	0.1	**0.12**	0.03	**0.20**	0.001
- Involuntary weight loss	-0.03	0.6	0.07	0.2	-0.01	0.9
Severity present gastrointestinal symptoms						
- GI- sum score	0.07	0.2	**0.20**	0.001	**0.20**	0.001

Abbreviations are: TKV, total kidney volume; TLV, total liver volume; TKLV, total kidney liver volume; GI, gastrointestinal. TKV, TLV and TKLV were log transformed. Denominators depend on the number of patients who provided an answer for a specific question in the questionnaire. Renal and liver pain measured on scale 1-10 (1= no pain); GI-sum score ranging from 0-100. (0 = no symptoms).

Chapter 3

Management of renal cyst infection in patients with ADPKD: a systematic review

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Abstract

Background: Renal cyst infection is one of the complications patients with autosomal dominant polycystic kidney disease (ADPKD) face. Cyst infection is often difficult to treat and potentially leads to sepsis and death. No evidence-based treatment strategy exists. We therefore performed a systematic review to develop an effective approach for the management of renal cyst infection in ADPKD patients based on the literature.

Methods: A systematic search was performed in PubMed (1948 – February 2014), EMBASE (1974 – February 2014) and the Cochrane Library (until February 2014) according to the PRISMA guidelines.

Results: We identified 60 manuscripts that included 85 ADPKD patients with renal cyst infection (aged 52±12 years, 45% male, 27% on dialysis, 13% history of renal transplantation and 6% diabetes mellitus). Included patients received a total of 160 treatments of which 92 antimicrobial, 29 percutaneous and 39 surgical. Initial management often consisted of antimicrobials (79%), quinolone-based regimens were favored (34%). Overall, 61% of patients failed initial treatment, but treatment failure has decreased over time (< 2000: 75%; ≥ 2000: 51%, p=0.03). Post-renal obstruction, urolithiasis, atypical or resistant pathogens, short duration of antimicrobial treatment and renal function impairment were documented in patients failing treatment.

Conclusions: First-line treatment of renal cyst infection in ADPKD consists of antimicrobials and is associated with a high rate of failure, but treatment success has increased over the last years. A large-scale unbiased registry is needed to define the optimal strategy for renal cyst infection management in ADPKD.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common renal hereditary disorder, often leading to end-stage renal disease between the fourth and seventh decade of life (1). Other symptoms that ADPKD patients may encounter include pain, urolithiasis and cyst haemorrhage (2). In addition, renal cyst infection may complicate ADPKD, a complication that is often difficult to treat and may lead to mortality (3, 4). Renal cyst infection should be considered in an ADPKD patient who presents with acute abdominal pain and fever. Cyst infection may be the result of an ascending urinary tract infection (5). However, as pyuria is frequently absent, it is hypothesized that hematogenous spread is an alternative mechanism for infection (6).

At this moment, there is no evidence-based treatment to guide clinicians in the management of renal cyst infection in ADPKD patients (7). To fill this gap in knowledge, we performed a systematic review identifying all reports describing renal cyst infections in individual ADPKD patients. Based on these data, we identified treatment preferences and potential factors that could affect treatment outcome.

Methods

Data sources and searches

For this literature review, we applied a systematic search strategy using an extensive set of search queries (Supplementary Table 1). The electronic databases of PubMed (January 1948 to February 2014), EMBASE (January 1974 to February 2014) and the Cochrane Library (until February 2014) were used. Reference lists of retrieved articles were manually searched for additional publications. Figure 1 provides a comprehensive overview of our literature search. This systematic review is reported in accordance with the PRISMA guidelines (Supplementary Table 2) (8).

Study selection

Publications were identified using predefined selection criteria. We focused on ADPKD patients (≥18 years) who received renal cyst infection treatment. We used a citation management program (EndNote, version X5.0.1. Thomson Reuters (Scientific) LLC, New York, NY, USA) to export our search results. ML and AG independently reviewed titles and abstracts. English, Dutch, French or German publications of any design were included. Articles that met the selection criteria and could be retrieved for full text evaluation were independently assessed by ML and AG. We excluded studies when

treatment could not be traced back to the individual patient, a malignant cyst was suspected or cyst intervention preceded cyst infection. Disagreement between ML and AG was resolved by discussion.

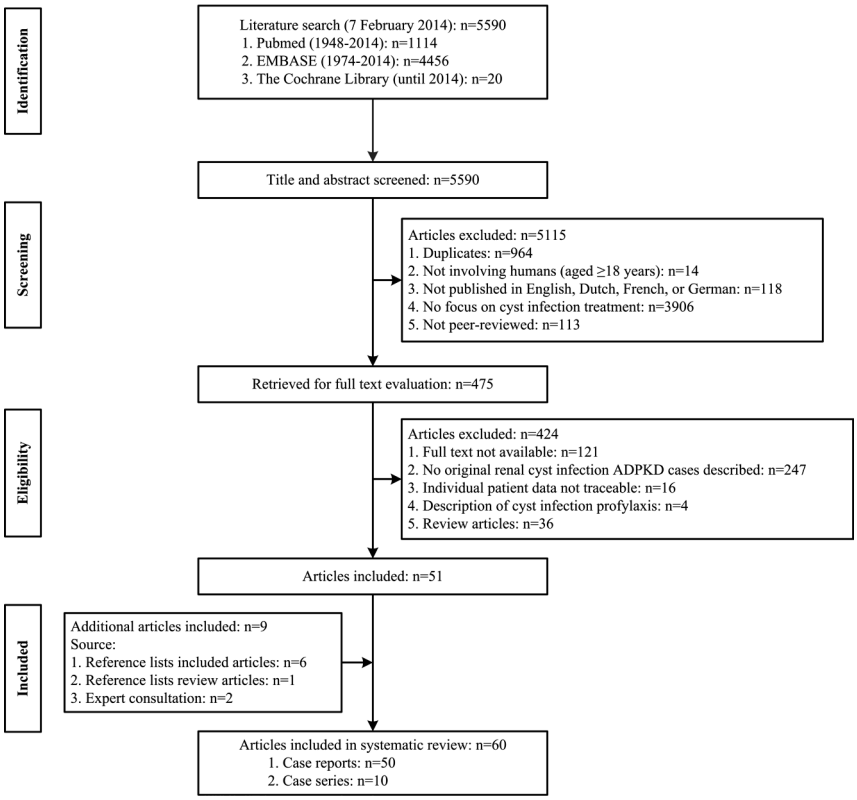

Figure 1. Search strategy and article selection.
Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; n, number.

Data extraction and quality assessment

We collected variables on study design, patient characteristics, diagnosis and treatment. ML, NC and AG extracted data. ML and NC independently reviewed data for completeness and accuracy. We assessed initial antimicrobial regimen duration and timing of invasive treatment following antimicrobial treatment. We defined antimicrobial regimens as therapies consisting of mono- or combination antimicrobial therapy. Percutaneous and invasive treatments were defined as procedures with a known therapeutic effect even if the procedure was performed for diagnostic purposes (3).

Treatment failure was defined as any treatment modification independent of reported outcome, such as switching or adding antimicrobial therapy or switching between treatment modalities. We defined recurrent cyst infection as re-occurrence of symptoms and restart of treatment after a treatment as well as symptom free interval of >1 week. Deaths were considered contributable to cyst infection in case the authors of the original article stated so. We did not contact study authors for additional information.

For sensitivity analyses, we compared our results with two case series without individual patient data available. This allowed us to investigate the presence of selection bias, since the most severe renal cyst infection cases are more likely to be discussed separately in literature. In addition, we reviewed their definitions for diagnosis, treatment and recurrence.

Data synthesis and analysis

Definite cyst infection was defined as the isolation of a pathogen from cyst aspirate (9). As there are no uniform criteria for the diagnosis of probable cyst infection, we included all remaining cases under the diagnosis of probable infection (9). We considered pathogens to be antimicrobial-resistant and ^{18}F-FDG PET/CT imaging results positive for cyst infection, when the original study authors stated so.

Parametric variables were expressed as mean with standard deviation (± SD), non-parametric variables as median with interquartile range [IQR]. Data analysis was performed by categorizing the sample into two time periods in relation to the availability of ^{18}F-FDG PET/CT imaging (10): period 1, < 2000 (not available); period 2, ≥ 2000 (available). Differences in characteristics between time periods were calculated with Chi-square test for categorical data, with Student's t-test for continuous parametric data or with Mann-Whitney U test in case of non-parametric data. Statistical analyses were performed by ML and NC using SPSS 20 (SPSS Statistics, Inc., Chicago, IL, U.S.A.). A p-value of <0.05 was considered significant and all statistical tests were 2-tailed.

Results

Study selection

The literature search identified 5590 citations (Figure 1). We evaluated 475 full texts of which 424 did not meet our inclusion criteria. Manual searching of references revealed nine additional studies. In total, we included 60 studies describing 85 ADPKD patients with a renal cyst infection. Detailed information of the individual cases is shown in Supplementary Table 3 and Supplementary Table 4.

Patient characteristics

We identified 85 ADPKD patients with a definite or probable renal cyst infection (Table 1). Patients were 52±12 years old and predominantly female (55%). A positive cyst aspirate culture (i.e. definite cyst infection) was reported in 49% of patients. *Escherichia coli* (*E.coli*) grew in 50% of cyst aspirates (Supplementary Table 5). Impaired renal function was frequent, 79% of the patients had an eGFR <60 ml/min/1.73m^2 of which 27% were on dialysis and 13% had a renal transplantation. Furthermore, Table 1 shows patient and microbiological characteristics categorized by time period. No significant differences were found between patients treated before and after the year 2000.

Treatment options

Overall 160 treatments were performed: 92 antimicrobial, 29 percutaneous and 39 surgical (Table 2). Details on treatment regimen were available in 77% of antimicrobial treated patients. Overall, quinolone-based regimens were favored (34%). Prior to the year 2000, significantly more patients were treated with a penicillin (31% vs. 21%, p=0.02), whereas after 2000 almost half of the antimicrobial regimens contained a quinolone (45%). Median duration of antimicrobial treatment was 14 days [IQR 6-28], and significantly longer (p=0.006) after the year 2000. In addition, median time until invasive treatment was significantly longer after 2000 (20 vs. 28 days, p=0.04).

Overall, 29 percutaneous treatments were performed. Percutaneous treatment consisted of cyst puncture, drainage and cyst aspiration. Regardless of the point in time after the diagnosis of infection, the majority of percutaneous treatments was combined with antimicrobials (overall: 83%; <2000: 86% and ≥2000: 82% respectively). Percutaneous therapy was significantly more often performed after the year 2000 (10% vs. 25%, p=0.04).

Surgical treatment included cyst drainage, cyst fenestration, cyst decortication, cyst resection and nephrectomy. Overall, nephrectomy was the most frequently reported procedure, accounting for 79% of surgeries (Table 2). In recent years, significantly less nephrectomies were performed (25% vs. 15%, p=0.03).

Therapy strategy and treatment failure

Table 3 provides an overview of therapies that were instituted and success rates of initial therapy. Initial management predominantly consisted of antimicrobials (79%). Before 2000, initial therapy failed in 75% of the cases, compared to 51% after 2000 (p=0.03). Overall, antimicrobials were the final therapy in 28% of cases. After 2000, significantly more percutaneous therapies (p=0.001) and significantly less surgical procedures (p=0.002) were performed.

Table 1. Characteristics of included ADPKD patients with renal cyst infection.

Characteristics		Therapies initiated in patients		
	Total (n=85)	< 2000 (n=36)	≥ 2000 (n=49)	P-value
Cyst infection diagnosis				
- Probable, n (%)	43 (51)	18 (50)	25 (51)	0.9
- Suspected on ^{18}F-FDG PET/CT, n (%)	12 (28)	-	12 (48)	-
- Definite, n (%)	42 (49)	18 (50)	24 (49)	0.9
Age, years (mean ± SD)	52 ± 12	50 ± 11	53 ± 13	0.3
Male sex, n (%)	38 (45)	14 (39)	24 (49)	0.4
eGFR stage, n (%)				
- eGFR stage I-II	4 (5)	2 (6)	2 (4)	0.8
- eGFR stage III-IV	19 (22)	9 (25)	10 (20)	0.6
- eGFR stage V	14 (16)	8 (22)	6 (12)	0.2
- eGFR stage V_d	23 (27)	10 (28)	13 (27)	0.9
- eGFR stage V_t	11 (13)	3 (8)	8 (16)	0.3
- eGFR not available	14 (16)	4 (11)	10 (20)	-
Diabetes mellitus documented, n (%)	5 (6)	3 (8)	2 (4)	0.1
Presence of urolithiasis reported, n (%)	4 (5)	2 (6)	2 (4)	0.8
Post-renal obstruction documented, n (%)	1 (1)	1 (3)	-	-
Cyst diameter reported, n (%)	27 (32)	8 (22)	19 (39)	0.2
- < 5 cm, n	4	2	2	0.8
- ≥ 5 cm, n	23	6	17	0.07
Microbiological characteristics reported				
- Failure to culture a pathogen, n (%)	10 (12)	4 (11)	6 (12)	0.8
- Other than *E.coli* cultured reported, n (%)	34 (40)	14 (39)	20 (41)	0.7
- Antimicrobial-resistant pathogen reported, n (%)	9 (11)	4 (11)	5 (10)	0.9

Parametric variables are expressed as mean ± SD. Percentages may not add up to 100 due to rounding. *Abbreviations:* n, number; SD, standard deviation; ^{18}F-FDG PET/CT, ^{18}Fluorodeoxyglucose positron-emission computed tomography; eGFR; estimated glomerular filtration rate; stage I-II, eGFR ≥ 60 ml/min/1.73m^2; stage III-IV, eGFR 15-59 ml/min/1.73m^2; stage V, eGFR < 15 ml/min/1.73m^2; stage V_d, receiving dialysis; stage V_t, renal transplantation; *E.coli*, *Escherichia coli*.

Table 2. Therapies initiated in ADPKD patients with renal cyst infection (n=85).

Treatment category[a]	Total	Therapies initiated in patients		P-value
		< 2000	≥ 2000	
Antimicrobial regimens				
Regimens in total, n	92	43	49	0.4
- Regimen not specified, n (%)	21 (23)	14 (33)	7 (14)	0.4
- Regimen specified, n (%)	71 (77)	29 (67)	42 (86)	0.4
- Regimen containing[b], n (%)				
- Aminoglycoside	14 (20)	9 (31)	5 (12)	0.1
- Cephalosporin	20 (28)	9 (31)	11 (26)	0.8
- Penicillin	18 (25)	9 (31)	9 (21)	0.02
- Quinolone	24 (34)	5 (17)	19 (45)	0.2
Duration of antimicrobial regimens				
Duration of initial regimen reported, n (%)	37	16	21	
- Duration, days (median [IQR])	14 [6-28]	7 [4-14]	15 [7-36]	0.006
Time until invasive treatment reported, n (%)	36	14	22	
- Timing, days (median [IQR])	26 [14-30]	20 [12-28]	28 [14-46]	0.04
Percutaneous treatments				
Treatments in total, n	29	7	22	0.04
- Combined with antimicrobials, n (%)	24 (83)	6 (86)	18 (82)	0.1
Surgical procedures				
Procedures in total, n	39	23	16	0.004
- Surgical drainage, n (%)	7 (18)	4 (17)	3 (19)	0.4
- Combined with antimicrobials, n (%)	5 (71)	3 (75)	2 (67)	0.8
- Partial resection, n (%)	1 (3)	1 (4)	-	-
- Combined with antimicrobials, n (%)	1 (100)	1 (100)	-	-
- Total resection[c], n (%)	31 (79)	18 (78)	13 (81)	0.03
- Combined with antimicrobials, n (%)	6 (19)	2 (11)	4 (31)	0.2

Non-parametric variables are expressed as median [IQR]. Percentages may not add up to 100 due to rounding. *Abbreviations:* n, number; IQR, interquartile range.

[a] Patients could receive more than one treatment during a cyst infection episode.

[b] Antimicrobial regimens could contain multiple antibiotic classes.

[c] Nephrectomy was the only procedure that was classified as a total resection.

Table 3. Treatment strategy and success rates for renal cyst infection, overall and according to time periods.

Initial and final therapy		Therapies initiated in patients		
	All therapies	< 2000	≥ 2000	P-value
Initial therapy, n (%)	85	36	49	
- Antimicrobial	67 (79)	31 (86)	36 (74)	0.2
- Percutaneous	6 (7)	1 (3)	5 (10)	0.2
- Surgical	12 (14)	4 (11)	8 (16)	0.5
Initial therapy, n (%)				
- Success	33 (39)	9 (25)	24 (49)	0.03
- Failure	52 (61)	27 (75)	25 (51)	0.03
Final therapy, n (%)				
- Antimicrobial	24 (28)	10 (28)	14 (29)	0.9
- Percutaneous	23 (27)	3(8)	20 (41)	0.001
- Surgical	38 (45)	23 (64)	15 (31)	0.002

Percentages may not add up to 100 due to rounding. *Abbreviations:* n, number.

Only in 39% of patients, initial therapy led to effective management of cyst infection (Table 4). In patients with initial treatment failure (n=52) impaired function of the native kidneys was common (77% had an eGFR < 60 ml/min/1.73m^2, of which 33% received dialysis, and 13% had a renal transplantation. Urolithiasis (6%) or large cysts (diameter ≥ 5 cm, 27%) were frequently reported in patients with initial treatment failure. In such patients, the median duration of initial antimicrobial treatment was only 7 days, despite antimicrobial resistance that was seen in 13%. Atypical pathogens (i.e. other than *E. coli*) were cultured in 54% of patients failing initial treatment.

In patients initially receiving antimicrobials (n=67), surgery was the final therapy in 37% (n=25) (Table 3 and Supplementary Table 6). If initial treatment consisted of percutaneous treatment (n=6), 17% (n=1) required additional invasive treatment.

Recurrence and cyst infection related death

Six patients developed recurrent renal cyst infection (7%), of which four patients received dialysis (67%, Table 5). Except for one patient, these patients had initially been treated with antimicrobials. The median time of recurrence was two weeks [IQR 2–9 weeks]. Ultimately, six patients died because of renal cyst infection-related complications, three of them were on dialysis (50%). Three patients who ultimately developed septic shock, multi organ failure or bowel perforation received antimicrobials as first line therapy. The remaining three cases died as a result of surgical complications.

Table 4. Treatment success versus treatment failure.

	Initial treatment outcome		
Baseline characteristics	**Success (n=33)**	**Failure (n=52)**	**P-value**
Age, years (mean ± SD)	57 ± 13	49 ± 11	0.001
Male sex, n (%)	14 (42)	24 (46)	0.7
eGFR stage, n (%)			
- eGFR stage I-II	1 (3)	3 (6)	0.6
- eGFR stage III-IV	6 (18)	13 (25)	0.5
- eGFR stage V	5 (15)	9 (17)	0.8
- eGFR stage V_d	10 (30)	13 (25)	0.6
- eGFR stage V_t	6 (18)	5 (10)	0.3
- eGFR not available	5 (15)	9 (17)	-
Diabetes mellitus, n (%)	-	5 (10)	-
Presence of urolithiasis, n (%)	1 (3)	3 (6)	0.6
Post-renal obstruction, n (%)	-	1 (2)	-
Cyst diameter ≥ 5 cm, n (%)	9 (27)	14 (27)	0.6
Duration of initial antimicrobial regimen, days (median [IQR])	28 [21-44]	7 [5-14]	< 0.001
Failure to culture a pathogen, n (%)	5 (15)	5 (10)	0.3
Other than *E.coli* cultured, n (%)	6 (18)	28 (54)	0.001
Antimicrobial-resistant pathogen, n (%)	2 (6)	7 (13)	0.4

Parametric variables are expressed as mean ± SD, non-parametric variables as median [IQR]. Percentages may not add up to 100 due to rounding. *Abbreviations:* n, number; SD, standard deviation; IQR, interquartile range; eGFR; estimated glomerular filtration rate; stage I-II, eGFR ≥ 60 ml/min/1.73m^2; stage III-IV, eGFR 15-59 ml/min/1.73m^2; stage V, eGFR < 15 ml/min/1.73m^2; stage V_d, receiving dialysis; stage V_t, renal transplantation; *E.coli*, *Escherichia coli*.

Table 5. Follow-up of ADPKD patients with renal cyst infection (n=85).

Characteristics	Renal cyst infection cases
Recurrence	
Total of recurrences, n (%)	6 (7)
Weeks until recurrence, median [IQR]	2 [2-9]
Baseline characteristics	
- Age, years (median [IQR])	49 [36-65]
- Male sex, n (%)	4 (67)
- eGFR stage V_d reported, n (%)	4 (67)
- eGFR stage V_t reported, n (%)	-
- Diabetes mellitus reported, n (%)	-
Initial therapy of previous cyst infection, n (%)	
- Antimicrobial	5 (83)
- Percutaneous	-
- Surgical	1 (17)
Cyst infection related deaths	
Total of cyst infection related deaths, n (%)	6 (7)
Baseline characteristics	
- Age, years (median [IQR])	58 [45-68]
- Male sex, n (%)	4 (67)
- eGFR stage V_d reported, n (%)	3 (50)
- eGFR stage V_t reported, n (%)	-
Initial therapy of previous cyst infection, n (%)	
- Antimicrobial	3 (50)
- Percutaneous	-
- Surgical	3 (50)

Non-parametric variables are expressed as median [IQR]. Percentages may not add up to 100 due to rounding. *Abbreviations:* IQR, interquartile range; n, number; eGFR, estimated glomerular filtration rate; stage V_d, receiving dialysis; stage V_t, renal transplantation.

Sensitivity analysis

As a sensitivity analysis, we compared our study results with two case series with ≥10 ADPKD patients which did not report individual patient data as needed for our systematic review (3, 11). One study reported 15 cases of renal cyst infection (11), the other documented 31 cases (3). We compared the pooled data of these studies (n=46) to our cases (n=85) (Supplementary Table 7). Despite the fact that our series of cases contained significantly more definite cyst infections (49% vs. 22%, p=0.002), initial treatment failure rates did not differ significantly between our series and the pooled data (61% vs. 52%, p=0.2). Our cases more frequently received percutaneous treatment (p=0.005) and surgery (p<0.001) as final treatment at the cost of antimicrobial therapies (p<0.001). This indicates that in the present review patients with a relatively severe renal cyst infection are included, which are potentially more prone to fail initial treatment.

Lastly, we compared our definitions for diagnosis, treatment and recurrence of renal cyst infection with those of the two case series (Table 6). This table shows that there is heterogeneity between diagnostic and treatment outcome criteria, which limits the ability to pool data from these series with our individual ADPKD cases. Both papers did not include a definition for renal cyst infection recurrence.

Table 6. Definitions of diagnosis, treatment and recurrence of renal cyst infection.

Definitions	Individual ADPKD cases (this systematic review)	Schwab et al. (1987)	Sallée et al. (2009)
Diagnosis			
- Probable	All patients without a positive cyst aspirate culture were categorized as probable cyst infection in line with the authors of the original articles.	Presence of all of the following features: fever (>38.5°C); positive urine or blood culture; clinical signs referable to the kidney with other infection sources excluded; refractoriness to conventional antibiotic therapy (intravenous ampicillin and an aminoglycoside) despite favorable in vitro sensitivities of the isolated organism.	Presence of all of the following features: fever (temperature >38.5°C for three days); abdominal pain (particularly renal or liver tenderness); increased CRP (> 50 mg/L); absence of any significant recent intracystic bleeding on CT (intracystic content <50 Hounsfield units) or other causes of fever.
- Definite	Cyst aspirate culture leading to pathogen isolation		Presence of cyst aspiration showing evidence of infection (neutrophils debris and/or microorganism).
Treatment			
- Treatment outcome assessment	Treatment failure: Modification of therapy (i.e. switching or adding antimicrobials, or switching between treatment categories antimicrobial, percutaneous or surgical therapy), independent of reported treatment outcome, was classified as treatment failure.	Treatment failure: Patient did not show clinical improvement	Treatment success: Disappearance of fever, normalization of CRP levels, and at least two negative blood and/or urine cultures.
Recurrence	Re-appearance of symptoms and restart of treatment after a treatment as well as symptom free interval of at least one week.	Not reported	Not reported

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CRP, C-reactive protein; CT, computed tomography.

Discussion

This systematic review shows that ADPKD patients with renal cyst infection present with a range of comorbid conditions, causative pathogens and other clinical factors. These differences in clinical presentation likely merit different initial treatment strategies. Antimicrobial therapy was the first step in 79% of cases and was associated with a high rate of failure (75%), eventually leading to either percutaneous intervention (27%) or surgery (37%). We found that treatment success rates increased significantly over time (25% vs. 49%, p=0.03). Notwithstanding, recurrence and even cyst infection-related mortality still occurred in a number of cases in the most recent period studied.

We identified several factors that could have potentially affected antimicrobial treatment outcome in our series. First, we detected a high rate of renal impairment (eGFR-stage III-V) amongst those failing initial treatment (42%). In patients with chronic renal insufficiency, inadequate arterial perfusion of the renal parenchyma could result in insufficient drug concentrations in both parenchyma and urine (12). The efficacy of some antimicrobials, such as trimethoprim-sulfamethoxazole, an antimicrobial that is recommended for renal cyst infection (7), is decreased in patients with impaired renal function (12). Therefore, we suggest to take renal function into consideration when choosing an antimicrobial for initial treatment. Second, the duration of antimicrobial treatment was significantly shorter in patients with treatment failure and success rates were higher in recent published cases. One possible explanation is the longer duration of treatment in cases published after 2000 (7 vs. 15 days). Third, we found that urolithiasis, post-renal obstruction or a cyst diameter ≥ 5 cm were reported in patients with initial treatment failure. Larger cysts might affect antimicrobial efficacy because of low intracystic concentrations (3, 13, 14). As a result, this could potentially increase the risk of treatment failure. Presence of urolithiasis and post-renal obstruction are known as potential risk factors for developing cyst infection (15). In patients without ADPKD, urolithiasis and post-renal obstruction complicate treatment due to an increased risk of antimicrobial resistance (16). It is hypothesized that urolithiasis and post-renal obstruction lead to the development of a pathogen reservoir, potentiating the risk of antimicrobial failure. Indeed, we found that urolithiasis (6%) and post-renal obstruction (2%) were present in some cases. Lastly, it is clinical experience that urine and blood cultures in renal cyst infection often remain sterile, even in patients with a positive cyst aspirate (3). This leads to an antimicrobial regimen that cannot be adapted according to the resistance pattern of cultured pathogens. In our series, we found that only in 12% of patients microbiological cultures failed to identify the causative pathogen, without a difference between patients who failed treatment or not. Thus, inability to culture the causative pathogen has no important effect on outcome of initial therapy.

This study comes with strengths and limitations. Strength of this study is its systematic character, identifying 85 published ADPKD patients with renal cyst infection on an individual patient level, and its comprehensive overview of treatment strategies. A limitation is that our search result was limited to case series and case reports. This may have introduced outcome reporting bias. However, in a sensitivity analysis we did not detect a significant difference in the rate of treatment failure between our case series and the pooled data of two case series without individual patient level data (61% vs. 52%, p=0.2). We therefore consider our data as an adequate representation of renal cyst infection in ADPKD. Moreover, our data set did not allow to investigate the effect of immunosuppressive drugs and other factors affecting immune status (e.g. age, nutritional status, dialysis duration, activities of daily living, kidney volume) on treatment outcome. Lastly, we applied our own criteria to assess treatment failure. This could have resulted in over- or underestimation of failure rate. However, to facilitate equal evaluation, we chose to assess each case using predefined uniform definitions (Table 6).

By performing this systematic review, we tried to identify gaps in knowledge and provide an evidence-based treatment advice for the management of renal cyst infection in ADPKD patients (7). Based on the available data, we identified factors that could potentially contribute to treatment failure. Unfortunately, there is limited evidence to support a specific algorithm for treatment. Such an algorithm may aid clinicians when confronted with a clinical suspicion of renal cyst infection in a patient with ADPKD. Since renal cyst infection is often difficult to treat and may result in death (3, 4), we do suggest to manage renal cyst infection in a hospitalized setting, if these resources are available. When antimicrobial treatment does not lead to improvement, and alternative diagnoses and potential risk factors for treatment failure are ruled out, we suggest contacting a polycystic kidney disease (PKD) expertise center for advice or admitting the patient for further treatment, i.e. a medical center with special interest and experience in invasive treatment options for the multidisciplinary management of cyst infection in ADPKD. To optimize the treatment of renal cyst infections, a large prospective multicenter registry is needed. A registry study offers the opportunity to fill in gaps in knowledge through an international collaboration (17). Such a registry, in which all cases with presumed cyst infection are included in an unbiased manner, will allow development of the optimal evidence-based treatment strategy for this condition.

In conclusion, antimicrobial treatment for renal cyst infection in ADPKD is associated with a high rate of failure. The available evidence limits the identification of risk factors for treatment failure. To develop an algorithm for renal cyst infection treatment, a large clinical registry is needed.

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Transparency declarations
None to declare.

Supplementary data
Supplementary Table 1: Search Queries
Supplementary Table 2: PRISMA Checklist
Supplementary Table 3: Individual case data – baseline characteristics.
Supplementary Table 4: Individual case data – treatment and follow-up.
Supplementary Table 5: Pathogens isolated from renal cyst aspirate.
Supplementary Table 6: Treatment strategy in renal cyst infection.
Supplementary Table 7: Treatment outcome of identified cyst infection cases vs. case series reporting cyst infection cases without individual patient data.

The supplementary material for this article is available at: http://ndt.oxfordjournals.org/content/early/2016/01/29/ndt.gfv452/suppl/DC1

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Chapter 4

Tolvaptan and kidney pain in patients with ADPKD: secondary analysis from a randomized controlled trial

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Abstract

Background: Kidney pain is a common complication in patients with ADPKD, and data from the TEMPO 3:4 trial suggested that tolvaptan, a vasopressin V2 receptor antagonist, may have a positive effect on kidney pain in this patient group. Because pain is difficult to measure, the incidence of kidney pain leading to objective medical interventions was used in the present study to assess pain.

Methods: Kidney pain events were recorded during the 3-year TEMPO 3:4 trial and independently adjudicated. Incidence of a first kidney pain event was assessed overall as well as categorized in 5 subgroups according to severity. Total kidney volume (TKV) was measured by MRI and GFR was estimated with the CKD EPI equation.

Results: Of 1445 participating patients (48.4% women, age 39±7 year, mean eGFR 81±22 mL/min/1.73m^2, median total kidney volume (TKV) 1692 (750 – 7555) mL), 50.9% reported a history of kidney pain at baseline. History of urinary tract infections, kidney stones or hematuria (all $p<0.001$) and female sex ($p<0.001$) were significantly associated with a history of kidney pain. Tolvaptan use resulted in a significantly lower incidence of kidney pain events when compared to placebo: 10.1% versus 16.8% ($p<0.001$), with a risk reduction of 36% (HR = 0.64; 95% CI: 0.48-0.86). The reduction in pain event incidence by tolvaptan was found in all groups irrespective of pain severity and was independent of predisposing factors (p for interaction >0.05). The effect of tolvaptan was at least in part explained by a decrease in incidence of urinary tract infections, kidney stones and hematuria, when compared to placebo.

Conclusions: Tolvaptan decreased the incidence of kidney pain events independent of patient characteristics predisposing for kidney pain and possibly in part due to reductions in ADPKD-related complications.

Introduction

Pain is a common complication in patients with autosomal dominant polycystic kidney disease (ADPKD). It is a symptom that is often reported early in the disease course and that sometimes can be severe, difficult to manage, and adversely affect a patient's quality of life (1-3). Acute pain in ADPKD patients can be caused by cyst hemorrhage, infection and kidney stones, which are often accompanied by hematuria. When pain is present during a period longer than 4 to 6 weeks it is typically classified as chronic pain, which has a reported prevalence as high as 60% (4).

The TEMPO 3:4 trial demonstrated the renoprotective effects of tolvaptan treatment in a randomized controlled clinical trial setting (5). During 3 years' follow-up, tolvaptan, a vasopressin V2 receptor antagonist, reduced the annual rate of growth in total kidney volume (TKV) from 5.5 to 2.8% ($p<0.001$) and the annual rate of eGFR decline from -3.70 to -2.72 mL/min/1.73m^2 ($p<0.001$) compared to placebo (5). This trial also demonstrated a reduction in clinical progression as assessed by its key secondary composite endpoint through a reduction of ADPKD-related clinical events. This outcome was driven by two components of the composite, time to decline in kidney function and time to clinically significant kidney pain events (5).

In the present study, we explored this last finding more closely. We characterized what constituted a "clinically significant kidney pain event" by objectively examining the intensity of medical interventions used to define them. We also investigated the association of ADPKD clinical characteristics (such as history of kidney pain, infection, kidney stones or hematuria at baseline) with the incidence of acute kidney pain events during the 3-year trial. Furthermore, we analyzed the effect of tolvaptan use on incidence of kidney pain events and explored if new pain events were associated with baseline patient characteristics and explored the possible mechanisms by which tolvaptan reduced their incidence.

Methods

Study design and patients

The present study was performed as a post-hoc exploratory analysis of the TEMPO 3:4 trial, a prospective, blinded, randomized, placebo-controlled trial in patients with diagnosed ADPKD (ClinicalTrials.gov identifier: NCT00428948). Patients were enrolled at 129 sites worldwide during January 2007 to January 2009. Inclusion criteria were age 18-50 year, with a diagnose of ADPKD, TKV measured by magnetic resonance imaging

(MRI) ≥750 mL and creatinine clearance estimated by the Cockcroft-Gault formula (eCrCl) ≥60 mL/min. Exclusion criteria included, among others, concomitant illnesses likely to confound end point assessments, such as diabetes mellitus, and prior kidney surgery. The Institutional Review Board or Ethics Committee at each site approved the protocol. Written informed consent was obtained from all participants. Details of the study protocol (6) and the primary study results (5) have been published previously. This manuscript has been prepared in accordance with the CONSORT 2010 Statement (7).

Study Treatment

Patients were randomly assigned to receive tolvaptan or placebo (2:1). Tolvaptan dosing was started at 45 mg am/15 mg pm (daily split-dose) and increased weekly to 60/30 mg and 90/30 mg if tolerated. Patients remained on the highest tolerated dose for 36 months.

Study assessments and definitions

Evaluations were performed at baseline, every 4 months during treatment, and twice for 2-6 weeks after completion of treatment at 36 months and included interviews, examinations, vital sign measurements, and blood and trough spot morning urine samples. TKV was assessed using standardized kidney MRIs at baseline and at months 12, 24, and 36 or at early withdrawal. In addition, height adjusted TKV (hTKV) was calculated as TKV in mL divided by height in meters. Serum creatinine was reported to two decimal points and used to estimate GFR (applying the CKD-EPI equation) (8).

At baseline a standardized interview was performed to gather information about demographic characteristics and medical history, including information for prior kidney pain. Incidence of acute kidney pain during follow-up was a component of the composite secondary efficacy end point, which assessed kidney pain events requiring medical intervention and that required documentation of clinical signs and symptoms that pain was kidney related (i.e., flank tenderness or evidence of cystic expansion or hemorrhage). The Investigator's clinical judgment was required to arbitrate whether the level of pain met the definition of end point, which required clinically significant kidney pain necessitating pharmacologic treatment or invasive intervention. Pain was a priori categorized according to the intensity of intervention into 5 groups; mild: prescription of acetaminophen; moderate: prescription of other non-narcotic analgesics; moderately severe: prescription of non-narcotic analgesic and limitation in physical activity; severe: prescription of narcotic analgesics; most severe: need for hospitalization and/or invasive intervention. Events were assessed by an independent

adjudication committee blinded for treatment allocation. Finally, the incidence of urinary tract infection, kidney stones and hematuria was assessed as a composite score and separately. Of note, the initial TEMPO 3:4 trial publication provided data on these events only when reported as (serious) adverse events, whereas in the present study all clinically significant pain related adverse events are taken into account.

Study outcomes

The primary end point in this study was the effect of tolvaptan use on incidence of acute kidney pain events compared to placebo. Second, we investigated: (1) the association of ADPKD clinical characteristics (such as history of kidney pain, infection, kidney stones or hematuria at baseline) with the incidence of acute kidney pain events during the 3-year trial; (2) whether new acute kidney pain events were associated with baseline patient characteristics; (3) the possible mechanisms by which tolvaptan reduced their incidence.

Statistical analyses

Baseline characteristics were calculated for participants with and without a history of kidney pain separately. Normally distributed variables are expressed as mean±SD, whereas non-normally distributed variables are given as median (IQR). Differences in baseline characteristics between patients with and without a history of kidney pain were calculated with a Chi-square test for categorical data, and for continuous data with Student's t-test or a Mann-Whitney U test in case of non-normally distributed data. To investigate whether baseline patient characteristics correlated with a history of kidney pain, univariate and multivariate logistic regression analyses were performed. The multivariate logistic analyses were subsequently adjusted for sex, age, hTKV and eGFR to investigate the impact of patient characteristics that predispose for kidney pain events that are not associated with disease severity. TKV, hTKV and albumin creatinine ratio (ACR) were log2 transformed to fulfill the requirement of normal distribution of the residuals for regression analysis.

In the placebo and tolvaptan groups, the overall incidence of a first acute kidney pain event during the 3-year trial was assessed in the intention-to-treat population, and the incidence of acute kidney pain events was subdivided in 5 categories named by pain severity and defined by the medical intervention used to treat the event. Cox proportional hazards regression analyses were performed to investigate whether baseline characteristics associated with the first acute kidney pain event during the trial, with censoring of patients lost to follow-up or stopping study medication. First unadjusted Hazard Ratios (HRs) with 95% Confidence Interval (95% CI) were calculated.

Second, we calculated multivariate-adjusted HRs, which were adjusted for sex, age, hTKV and eGFR to investigate the impact of patient characteristics that predispose for acute kidney pain events that are not associated with disease severity. The number needed to treat (NNT) to prevent 1 acute kidney pain event were calculated based on the cumulative event proportions. In addition, we investigated the effect of tolvaptan on incidence of acute kidney pain events in the overall TEMPO 3:4 trial population, as well as in subgroups according to baseline characteristics and p-value for interaction by subgroup was calculated. Last, the effect of tolvaptan on renal complications known to cause pain was investigated.

Two sensitivity analyses were performed. First, the effect of tolvaptan on incidence of acute kidney pain events was investigated as time to first occurrence of each specific category of intervention/pain severity instead of as cumulative incidence. Second, the effect of tolvaptan was investigated including multiple acute kidney pain events per patient. All analyses were performed with SAS 9.2 (SAS Institute, Cary, North Carolina, USA) statistical software, and a two-sided $p<0.05$ was considered to indicate statistical significance.

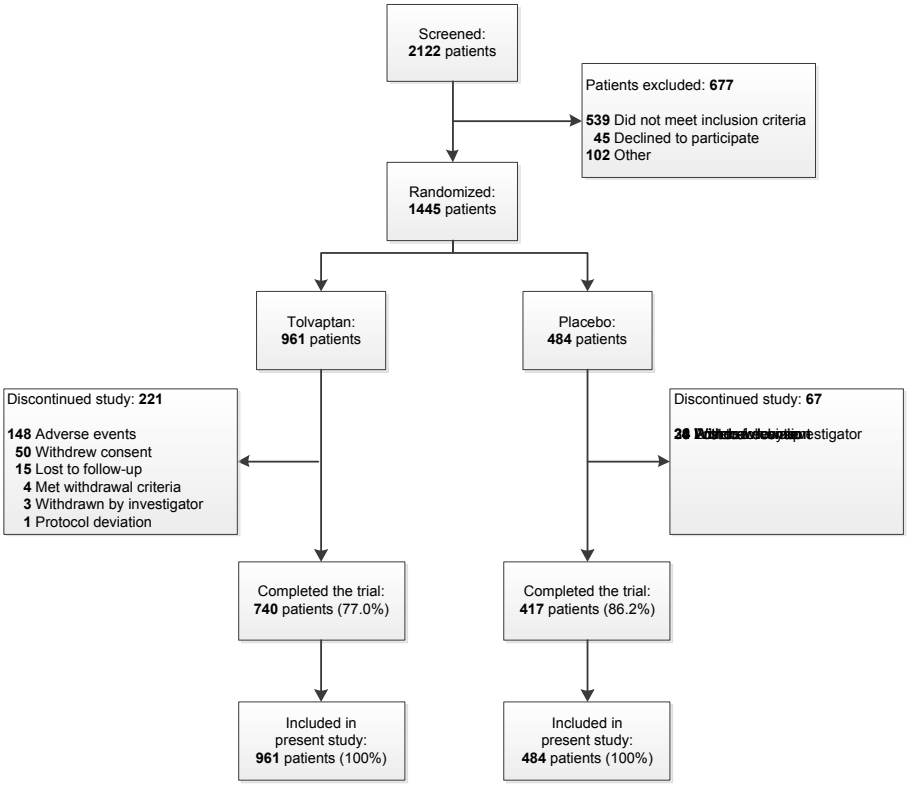

Figure 1. Patient enrollment and outcomes.

Results

Baseline characteristics

A total of 1445 ADPKD patients were enrolled in the TEMPO 3:4 trial (Figure 1). Mean age was 39±7 years and 48.4% were women (Table 1). By protocol, patients had preserved kidney function, with mean eGFR of 81±22 mL/min/1.73m^2 and a median TKV of 1692 (750 – 7555) mL. At baseline, 50.9% of participants reported having a history of kidney pain. Patient characteristics were stratified according to those with or without a history of kidney pain (Table 1). A history of urinary tract infection, kidney stones or hematuria was associated with having a history of kidney pain.

Table 1: Baseline characteristics of TEMPO 3:4 Trial participants stratified according to history of kidney pain.

	History of kidney pain		
	Yes	No	P-value
N	735	710	
Female sex (%)	389 (52.9)	310 (43.7)	<0.001
Age (yrs)	38.8±7.0	38.4±7.2	0.2
Height (cm)	172.9±10.1	174.2±10.1	0.01
Weight (kg)	79.3±18.4	79.0±18.1	1.0
BMI (kg/m^2)	26.4±5.3	25.9±4.8	0.2
History of			
- UTI (%)	307 (41.9)	147 (20.7)	<0.001
- Hematuria (%)	318 (43.3)	185 (26.1)	<0.001
- Kidney stones (%)	196 (26.7)	100 (14.1)	<0.001
- Liver cysts (%)	450 (61.4)	412 (58.0)	0.2
SBP (mmHg)	128.6±13.3	128.5±13.7	1.0
DBP (mmHg)	82.6±9.5	82.4±10.0	1.0
Use of BPLD (%)	529 (72.0)	510 (71.8)	0.9
Presence of hypertension (%)	609 (82.9)	583 (82.1)	0.7
eGFR (mL/min/1.73m^2)	82.4±21.8	80.8±21.4	0.2
TKV (mL)	1694±899	1690±912	0.7
hTKV (mL/m)	976±501	967±508	0.5
Urine osmolality (mOsm/kg)	493.4±175.5	510.4±181.8	0.04
ACR (mg/mmol)	3.1 (1.2 – 8.1)	3.3 (1.1 – 8.8)	0.2

Abbreviations are: BMI, body mass index; UTI, urinary tract infection; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPLD, blood pressure lowering drug; eGFR, estimated glomerular filtration rate; TKV, total kidney volume; hTKV, height adjusted total kidney volume; ACR, albumin creatinine ratio.

Other significant associations included female sex, smaller body size and lower urine osmolality, although for the last two variables the absolute difference between patients with and without a history of kidney pain was small and likely not clinically relevant. Each of these characteristics remained significant when adjusted for sex, age, hTKV

and eGFR (Supplementary Table 1). No associations were found for history of kidney pain and eGFR, TKV or hTKV. Of the 1445 participating patients, 484 were randomly assigned to placebo, and, 961 to tolvaptan, of whom 49.4% and 51.6% had a history of kidney pain, respectively (p=0.4). No significant differences in patient characteristics were observed between treatment groups when comparing participants with or without a history of pain.

Kidney pain events over 3-years in placebo group

In the placebo group 16.8% of patients had an episode of kidney pain during the 3-year trial. A history of urinary tract infection, kidney stones, hematuria or kidney pain, and female sex tended to be associated with incident kidney pain events (Table 2). After adjusting for age, sex, hTKV and eGFR, these factors were significantly associated with kidney pain events during the study, except for a history of urinary tract infection (Table 2). No association was found between baseline TKV, hTKV or eGFR with kidney pain events during follow-up; neither crude analysis nor analysis after multivariate adjustment for covariates.

Effect of tolvaptan on incidence of kidney pain events

In contrast to the 16.8% incidence reported for patients in the placebo group, 10.1% of the tolvaptan group had clinically significant kidney pain during the 3-year trial. Identified risk factors for acute kidney pain events in the placebo group, for example, history of kidney stones, hematuria or kidney pain and female sex, tended also to be associated with incident kidney pain events in the tolvaptan group (Supplementary Table 2).

Table 2: Associations of baseline characteristics with first kidney pain events during 3 years' follow-up in the 484 placebo treated patients in the TEMPO 3:4 Trial.

	Crude		Adjusted for age, sex, hTKV and eGFR	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Female sex (%)	2.01 (1.27-3.20)	0.003	2.15 (1.33-3.45)	0.002
Age (per 5 yrs)	0.97 (0.83-1.13)	0.7	0.99 (0.83-1.18)	0.9
Height (per 5 cm)	0.85 (0.75-0.96)	0.01	0.92 (0.78-1.09)	0.3
Weight (per 5 kg)	0.95 (0.89-1.02)	0.1	0.98 (0.91-1.06)	0.6
BMI (kg/m^2)	1.00 (0.95-1.04)	0.8	1.00 (0.95-1.05)	0.9
History of				
- Kidney pain (%)	2.24 (1.40-3.58)	<0.001	2.15 (1.33-3.48)	0.002
- UTI (%)	2.00 (1.28-3.12)	0.002	1.54 (0.94-2.51)	0.08
- Hematuria (%)	1.55 (0.99-2.43)	0.1	1.75 (1.10-2.79)	0.01
- Kidney stones (%)	1.63 (1.01-2.64)	0.04	1.84 (1.13-3.00)	0.01
SBP (per 5 mmHg)	1.00 (0.92-1.09)	1.0	1.03 (0.95-1.12)	0.5
DBP (per 5 mmHg)	1.08 (0.95-1.21)	0.2	1.12 (0.99-1.26)	0.1
Use of BPLD (%)	0.88 (0.54-1.44)	0.6	0.93 (0.55-1.58)	0.8
Presence of hypertension (%)	1.20 (0.63-2.27)	0.6	1.36 (0.69-2.69)	0.4
eGFR (per 5 mL/min/1.73m^2)	1.00 (0.96-1.06)	0.8	1.00 (0.94-1.06)	1.0
Log TKV (per doubling of TKV (mL))	0.96 (0.67-1.37)	0.8	1.14 (0.76-1.73)	0.3
Log hTKV (per doubling of hTKV (mL/m))	1.02 (0.71-1.45)	0.9	1.17 (0.77-1.75)	0.5
Urine osmolality (per 50 mOsm/kg)	0.98 (0.92-1.04)	0.4	0.98 (0.92-1.04)	0.5
Log ACR (per doubling of ACR (mg/mmol))	1.09 (0.95-1.25)	0.2	1.08 (0.93-1.26)	0.3

Abbreviations are: BMI, body mass index; UTI, urinary tract infection; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPLD, blood pressure lowering drug; eGFR, estimated glomerular filtration rate; TKV, total kidney volume; hTKV, height adjusted total kidney volume; ACR, albumin creatinine ratio. In the multivariate analyses, risks were adjusted for age, sex, hTKV and eGFR. In case the association between eGFR and first acute kidney pain event was investigated, the variable eGFR was not incorporated twice in the model.

Tolvaptan use was associated with a significantly lower incidence of first kidney pain events when compared to placebo ($p<0.001$), with a risk reduction of 36% (HR = 0.64; 95% CI: 0.48-0.86) (Table 3). The difference in cumulative incidence of patients having a kidney pain event between the tolvaptan and placebo groups increased over time (Figure 2). We analyzed the effects of tolvaptan on the incidence of kidney pain events among various subgroups based on specific baseline characteristics (Figure 3). No interactions were found between the effect of tolvaptan on kidney pain and patient characteristics of disease severity, characteristics predisposing for worse renal prognosis, or with characteristics predisposing for kidney pain (p for interaction all nonsignificant). When pain was defined more strictly, similar efficacy of tolvaptan was noted (Table 3). The number needed to treat to prevent one pain event ranged from 35 patients when taking any pain event into account (prescription of acetaminophen or worse) to 384 patients when taking only the most severe pain category into account (hospitalization or invasive intervention) (Table 3).

Last, we investigated whether the mechanism of tolvaptan in reducing kidney pain events could be elucidated. ADPKD patients having an acute kidney pain event had a similar TKV growth rate compared with ADPKD patients who did not have such an event. This was the case for patients in the placebo group and those in the tolvaptan group (Table 4). The significant reduction in number of participants having reported kidney pain was matched by similar reductions in the incidence of renal complications likely to cause such pain in ADPKD, such as urinary tract infections and kidney stones, and, bouts of macroscopic hematuria that can be detected in patients having cyst ruptures and bleeds (infections: 11.1% vs. 15.3%, $p=0.02$; kidney stones 2.2% vs. 3.5%, $p<0.001$; hematuria 8.0% vs. 14.3%, $p<0.001$; any of the three aforementioned: 18.9% vs. 28.7%, $p<0.001$). Irrespective of treatment arm, patients with kidney pain events had a higher incidence of these disease related complications than those not having pain events.

Table 3: Cumulative incidence of patients having a kidney pain event during 3 years' follow-up according to severity of pain as scored by intensity of intervention.

Pain severity	Pain events per 100 person-years of follow-up	Hazard Ratio (95% CI)	NNT	P-value
Mild or worse (overall)				
Tolvaptan	5.09	0.64 (0.48-0.86)	35	<0.001
Placebo	8.09			
Moderate or worse				
Tolvaptan	4.05	0.62 (0.45-0.86)	39	0.01
Placebo	6.74			
Moderately severe or worse				
Tolvaptan	2.94	0.67 (0.45-1.00)	64	0.05
Placebo	4.55			
Severe or worse				
Tolvaptan	2.31	0.74 (0.46-1.18)	94	0.2
Placebo	3.40			
Most severe				
Tolvaptan	0.21	0.22 (0.04-1.14)	384	0.07
Placebo	0.38			

Definitions; mild, prescription of acetaminophen; *moderate,* prescription of non-narcotic analgesics; *moderately severe,* limitation in physical activity; *severe,* prescription of narcotic analgesics; *most severe,* need for hospitalization and/or invasive intervention.
Abbreviations; NNT, number needed to treat

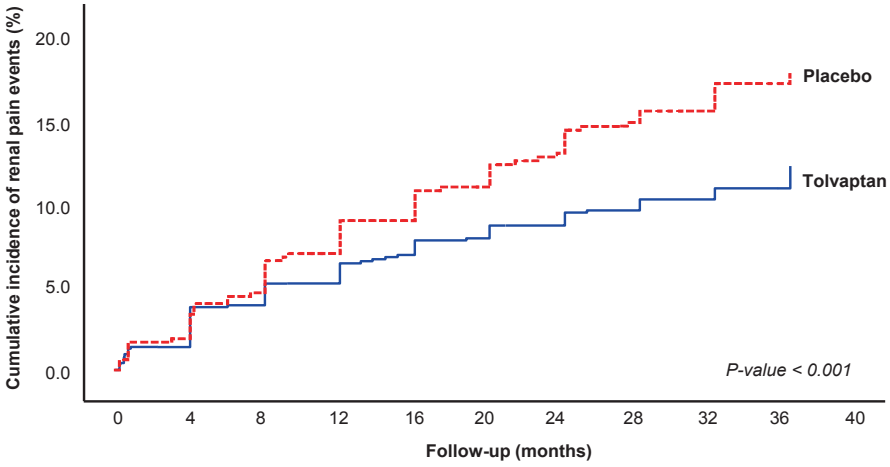

Figure 2. Cumulative incidence of patients having a first kidney pain event in tolvaptan (blue solid line, N=97) and placebo (red dashed line, N=81) treated patients from baseline to month 36. Tolvaptan use was associated with a significantly lower incidence of first kidney pain events when compared to placebo, with a risk reduction of 36% (HR = 0.64; 95% CI: 0.48-0.86) (p<0.001). Assessment of the assumption of proportional hazards indicated that the hazard ratio was constant over time (Supplementary Figure 1).

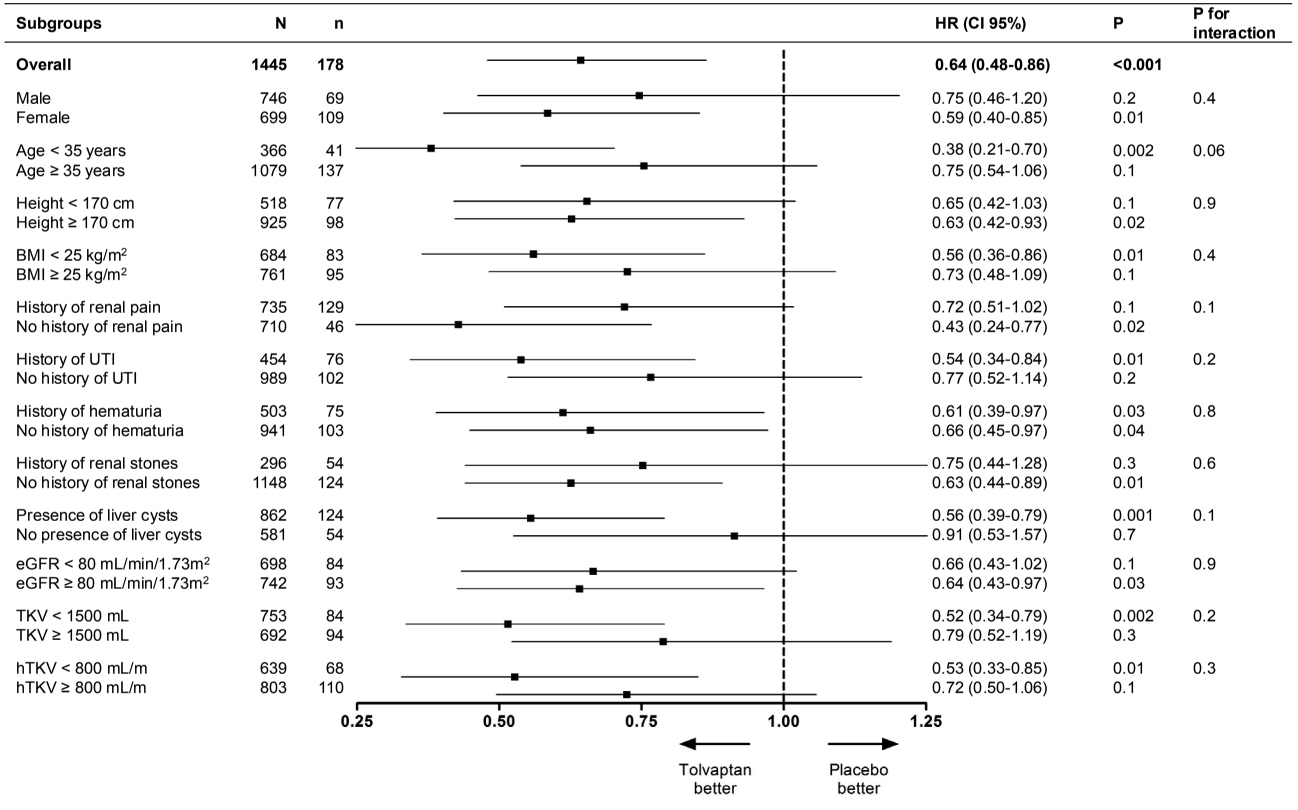

Figure 3. Effect of tolvaptan on first acute kidney pain events versus placebo during 3 years' follow-up in the overall study population and in subgroups according to baseline characteristics. *Abbreviations are:* N, number of subjects; n, number of events; BMI, body mass index; UTI, urinary tract infection; eGFR, estimated glomerular filtration rate; HR, Hazard ratio; TKV, total kidney volume; hTKV, height adjusted total kidney volume.

Table 4: Change in total kidney volume, kidney function and cumulative incidence of renal complications known to be associated with acute pain in placebo and tolvaptan groups during 3 years' follow up. Data are given overall, as well as separately for patients having and patients not having kidney pain events.

	Placebo				Tolvaptan			
	Overall	Pain	No pain	P-value	Overall	Pain	No pain	P-value
N	484	81	403		961	97	864	
Change in TKV (% per year)	5.6 ± 5.3	6.5 ± 6.9	5.4 ± 4.9	0.2	2.8 ± 5.7	2.8 ± 5.0	2.8 ± 5.7	0.9
Change in eGFR (ml/min/1.73m^2 per year)	-3.7 ± 5.8	-3.8 ± 4.8	-3.7 ± 5.9	0.4	-2.3 ± 8.7	-3.1 ± 7.9	-2.2 ± 8.8	0.02
Incidence of								
- UTI (%)	15.3	24.7	13.4	0.02	11.1	16.5	10.5	0.1
- Hematuria (%)	14.3	32.1	10.7	<0.001	8.0	21.7	6.5	<0.001
- Kidney stones (%)	3.5	12.4	1.7	<0.001	2.2	9.3	1.4	<0.001
- Any of the above (%)	28.7	51.2	24.1	<0.001	18.9	41.2	16.4	<0.001

Abbreviations are: N, number; TKV, total kidney volume; eGFR, estimated glomerular filtration rate; UTI, urinary tract infection.

Sensitivity analyses

When pain events were analyzed by subgroup of pain severity instead of as cumulative incidence, risk reduction was observed for tolvaptan across all subgroups. Of note, relative risk reductions did not reach formal statistical significance in all subgroups, likely due to the small number of patients per pain category (Supplementary Table 3). The sensitivity analysis focused on multiple-event analyses yielded essentially the same result as the primary time to first-event analysis (Supplementary Table 4).

Discussion

Our study had a cross-sectional and a longitudinal part. In the cross-sectional analysis of baseline data of the TEMPO 3:4 trial, history of kidney pain was observed in 50.9% of participants. Acute kidney pain events in ADPKD patients are often caused by urological complications such as urinary tract infections, kidney stones, and cyst bleeding and rupture. The latter two are clinically diagnosed by bouts of macroscopic hemorrhage (1, 2, 4, 9). In support of this, we found independent associations between history of kidney pain and history of urinary tract infection, kidney stones, and hematuria. Three prior studies have investigated the prevalence of pain in ADPKD patients in a cross-sectional setting (10-12). The largest of these studies was performed by Miskulin et al. using baseline data from 1,043 ADPKD patients participating in the HALT-PKD studies. The authors described that pain is an early symptom in the course of ADPKD (10). The percentage of participants with a history of pain events in HALT-PKD was similar to the percentage of participants in the TEMPO 3:4 trial (5, 10). Furthermore, they found that pain prevalence was inversely correlated with eGFR, but only in patients at lower eGFR (<45 mL/min/1.73m^2) (10). In our study we did not find such an association, which may be explained because TEMPO 3:4 enrolled patients with relatively preserved kidney function (eCrCl>60 mL/min) (5). In the other two studies (involving 219 and 152 ADPKD patients, respectively), pain was assessed in patients across a broad range of kidney function, including patients on dialysis therapy (11, 12). These studies found that pain was positively correlated with the physical component score of health-related quality-of-life questionnaires, but they did not identify potential risk factors for kidney pain. We found that female sex was significantly associated with history of kidney pain, even when adjusted for height, age and disease severity. To our knowledge, no other study has specifically reported this association. However, the study by Miskulin et al. shows that a history of pain was also reported more by female compared with male ADPKD patients. A history of back pain, for instance, was reported by 56.8% versus 45.1%,

respectively (10). Medical and invasive treatments for pain were also more frequent in female patients. Whether this sex difference is specific for ADPKD is not clear. Several reviews concluded, for instance, that in the general population pain is more frequently reported by women than by men (13, 14). It has been suggested that an interaction of biological (e.g. sex hormones), psychological (e.g. coping strategies) and sociocultural (e.g. femininity) factors may contribute to this sex difference (13).

In the longitudinal part of our study, 16.8% of the patients in the placebo group reported acute kidney pain events during the 3 year trial. This is the first trial to prospectively investigate the incidence of such events in ADPKD. We found that history of kidney pain, kidney stones and hematuria and female sex were associated with incident kidney pain. Therefore our study shows in a cross-sectional and a longitudinal setting that these factors are associated with acute kidney pain.

In ADPKD, it is generally assumed that large kidney volumes play a role in causing pain. Interestingly, in this study, neither TKV nor hTKV associated with acute kidney pain at baseline (Table 1) or during the trial (Table 2). These results are supported by findings in the 539 patients in the study by Miskulin et al. for whom MR images were available. In these patients, no relationship was found between TKV and pain except in patients with very large kidneys (10). The authors proposed that cyst number, size or location may be more important than TKV in causing pain. However, information for these variables was not available in their study and thus needs additional investigation. Others have suggested that the combined volume of the kidneys and liver is the major determinant of ADPKD-related symptoms, including pain (11, 15). However, total liver volumes were not measured in TEMPO 3:4, so we can neither confirm nor reject this hypothesis.

During the trial, 10.1% of the tolvaptan group had events of clinically significant acute kidney pain compared to 16.8% of the placebo group, indicating a relative risk reduction by tolvaptan of 36% (Table 3). This pain incidence-lowering effect was found in all subgroups defined by intervention and was independent of baseline clinical characteristics shown to predispose for kidney pain. We attempted to determine a mechanism for the kidney pain-lowering effect of tolvaptan. It was hypothesized that patients with a lower TKV growth rate would have a lower incidence of kidney pain events because tolvaptan reduced the rate of TKV growth by 49% (5). However, per treatment arm TKV growth rate was similar in patients having and not having a kidney pain event (Table 4). This finding, in combination with the lack of association between TKV and history of kidney pain at baseline (Table 1) and incident pain events during the trial (Table 2), suggests that the effect of tolvaptan on incidence of kidney pain events may not be primarily related to its effect on TKV growth rate.

Another mechanism may be related to a drug-related decrease in the incidence of renal complications that are known to be associated with acute kidney pain events (e.g. a reduction in incidence of urinary tract infections, kidney stones, and cyst hemorrhage and ruptures (assessed as bouts of hematuria)). At baseline and during the trial, associations were found between these disease-related complications and history or incidence of kidney pain. Importantly, tolvaptan lowered the incidence of these complications when compared to placebo: for urinary tract infections by 27% ($p=0.02$), for kidney stones by 37% ($p<0.001$) and for hematuria by 44% ($p<0.001$) (Table 4). In addition, a significantly higher incidence of these complications was observed in patients having versus those not having a kidney pain event, irrespective of treatment arm. Tolvaptan-induced polyuria, which can be up to 4-6 liters per day, might explain the lower incidence of these aforementioned renal complications because increased water intake is associated with lower recurrence of kidney stones and urinary tract infections in the general population (16). It may be that increasing water intake to such an extent without using tolvaptan could have a similar effect on acute kidney pain events. However, this has never been studied, and data in literature suggest that it is questionable whether such high spontaneous water intake is feasible during prolonged periods (17). Our data indicate that the pain-lowering effect of tolvaptan might be mediated at least in part by a reduction in incidence of renal complications known to be associated with kidney pain. Of note, 58.8% of the tolvaptan group who had a kidney pain event did not report one of these complications. This suggests that other yet unidentified mechanisms may play a role. For instance, it might well be that tolvaptan reduces cyst fluid secretion and thereby fluid pressure within cysts, leading to fewer pain events. Another possible additional mechanism may be the reflex increase in vasopressin concentration that is observed when the V2 receptor is blocked by tolvaptan (18, 19). Vasopressin stimulates the secretion of beta-endorphins by the hypothalamus, which could cause a central analgesic effect (20, 21).

The number needed to treat to prevent one acute kidney event is high to prescribe tolvaptan to ADPKD patients with the sole aim of preventing such acute kidney pain events, and should be weighed against the fact that in the TEMPO 3:4 trial, patients who were given tolvaptan had a greater number of adverse events related to aquaresis (i.e. polydipsia, polyuria and nocturia) (5) and that tolvaptan has a potential hepatotoxic effect. The rates of all observed adverse events during the 3-year trial were discussed in more detail in the initial publication (5). Any potential benefit should of course be weighed against these disadvantages. In our opinion, the primary aim of prescribing tolvaptan in ADPKD remains therefore its renoprotective efficacy. However, the present analyses indicate that when prescribed, there is an additional benefit that may

be important, especially for ADPKD patients with recurrent acute pain events. When considering whether to prescribe this drug, healthcare providers should carefully inform patients about potential risks and benefits.

There are limitations to our study worth addressing. First, this study was performed as a post-hoc analysis of an RCT. However, the outcome under study was pre-specified per protocol. Second, the TEMPO 3:4 study had specific inclusion criteria for TKV and eGFR that were defined to enrich the patient population to be included for rapid disease progression. This may make extrapolation of our findings to the general ADPKD population difficult. However, neither the incidence of kidney pain events nor the effect of tolvaptan on kidney pain events was associated with baseline TKV or eGFR, suggesting that our results may be valid in the general ADPKD population. Third, the aquaretic response to tolvaptan causes polyuria. This may have caused unblinding in the study which may have resulted in under- or overestimation of pain reporting. However, we assessed kidney pain events defined by objective criteria (i.e. the need for medical intervention), and moreover, events were adjudicated by an independent committee that was blinded for treatment allocation. Therefore we consider our data to be robust. Last, this study focuses on only acute kidney pain events and did not investigate the effect of tolvaptan on chronic pain in ADPKD, which is beyond the scope of the present study. The main strength of this study is that it was performed in a large population of ADPKD patients in several countries across the world, making it the most comprehensive study available that investigates characteristics predisposing for kidney pain events among ADPKD patients in a cross-sectional setting and the first study addressing this question in a longitudinal setting. Moreover, it describes the effect of tolvaptan as the first disease modifying drug on kidney pain incidence, another important part of the ADPKD phenotype besides TKV growth and eGFR loss.

In conclusion, this study shows that a history of urinary tract infection, kidney stones, or hematuria and female sex were associated with a history of kidney pain at baseline, as well as with incident kidney pain events during the trial. No association was found between total kidney volume and history of pain at baseline, or with incident kidney pain events during the trial, indicating that kidney volume per se did not play a major role in causing pain. Tolvaptan use was associated with a lower incidence of acute kidney pain events in all subgroups defined according to pain severity and independent of factors predisposing to pain. The tolvaptan-induced reduction in incidence of renal complications, such as urinary tract infections, kidney stones and hematuria, may at least in part explain the kidney pain-lowering effect of this drug.

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Contributions
Research area and study design: JDB, ABC, FSC, OD, EH, JO, RDP, VET, RTG; data acquisition: NFC, JDB, FSC JO, RTG; data analysis/interpretation: NFC, JDB, JO, RTG; statistical analysis: NFC, JDB, JO, RTG; supervision or mentorship: ABC, OD, EH, AML, RDP, VET, RTG. Each author contributed important intellectual content during manuscript drafting and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. RTG takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

A full list of the investigators in the TEMPO 3:4 trial is reported in the Supplemental Appendix of the initial TEMPO 3:4 publication (Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012; 367: 2407-2418).

Supplementary data

Supplementary Table 1: Cross-sectional associations of baseline characteristics with history of kidney pain in overall population in TEMPO 3:4 trial.

Supplementary Table 2: Associations of baseline characteristics with first acute kidney pain event during 3 years' follow-up in tolvaptan group.

Supplementary Table 3: Incidence of patients having first acute kidney pain event during 3 years' follow-up.

Supplementary Table 4: Cumulative incidence of all kidney pain events during 3 years' follow-up according to severity of pain.

Supplementary Figure 1: Assessment of assumption of proportional hazards for time to first acute kidney pain event.

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Chapter 5

Chronic kidney pain in ADPKD, a case report of successful treatment by catheter-based renal denervation

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Abstract

Chronic pain is a common concern in patients with autosomal dominant polycystic kidney disease (ADPKD). We report what to our knowledge is the first catheter-based renal denervation procedure in a patient with ADPKD resulting in successful management of chronic pain. The patient was a 43-year-old woman whose chronic pain could not be controlled by pain medication or splanchnic nerve blockade. Transluminal radiofrequency renal denervation was performed as an experimental therapeutic option with an excellent result, indicating that this procedure should be considered for chronic pain management in ADPKD.

Introduction

Up to 60% of all patients with autosomal dominant polycystic kidney disease (ADPKD) experience some pain, which in some individuals can be debilitating enough to lead to decreased psychosocial functioning and limitation in daily activities (1). Chronic pain in ADPKD may be multifactorial, and can be caused by cystic enlargement of the kidneys resulting in distension of the renal capsule; by pressure on adjacent tissues; or may be unrelated to ADPKD. Bajwa et al. introduced a stepwise approach for effective pain management in ADPKD, beginning with non-pharmacological therapies, such as ice pads and psychological behavioral modification, stepping up to non-opioid analgesics, opioids, transcutaneous electrical nerve stimulation, and finally surgical procedures (2). Several surgical procedures, such as cyst aspiration and cyst fenestration, have been tried with success to relieve ADPKD-related pain. However, pain relief is often only temporary, and aspiration and fenestration are associated with a high risk for infection (2). Renal denervation also has been proposed for patients with intractable ADPKD-related pain and was performed by laparoscopic and thoracoscopic procedures with satisfactory results (3, 4). Recently a catheter-based percutaneous transluminal method has been introduced to ablate efferent and afferent renal sympathetic nerve fibres. This procedure now is applied mainly in patients with therapy-resistant hypertension.

We report a case of a patient with ADPKD and chronic pain who underwent catheter-based renal denervation for pain treatment, with an excellent result.

Case report

A 43-year-old woman with ADPKD was referred to our tertiary-care hospital with a history of pain that was difficult to treat since 2008. The diagnosis of APDKD was made based upon the revised Ravine criteria (5).

At presentation in May 2013, the patient reported progressive abdominal pain, in particular on the left side in the epigastric region with a visual analogue scale score ranking 6-8 of 10. The pain was constant and described as stabbing and nagging, with radiation toward the left upper abdomen. On the right side, she also experienced pain, but this was less intense. Because of the pain, she could not sleep on her left side and woke up at least 5 times every night, leading to progressive fatigue. Inspiration increased her pain sensation, suggesting a visceral origin. Defecation and micturition did not influence pain, whereas exercise worsened it. Her symptoms were debilitating, influencing her social life and leading to an inability to work full-time. For blood pressure control, the patient used losartan, 100 mg, once daily; amlodipine, 10 mg,

once daily; and hydrochlorothiazide, 25 mg, once daily, on which her mean daytime blood pressure was 139/95 mm Hg during a 24-hour ambulatory blood pressure measurement.

Previous attempts at pain control using non-pharmacologic therapies or acetaminophen had not been effective. Buprenorphine patches (regulated dose release, 10 µg/h) were tried, but the pain remained and the patient experienced side effects of drowsiness and progressing fatigue that precluded dose increases. Two years earlier, a successful temporary blockade of the left splanchnic nerve had been performed for pain control. Therefore a long-term neurolytic nerve block with phenol was given on both sides with some success. Unfortunately, after 2 months the pain returned with the same intensity as before. A second long-term neurolytic nerve block was attempted with only temporary limited pain relief. In the patient's eyes, the best option was now to remove her left kidney, although this procedure might shorten her time to end-stage renal disease.

Spiral computed tomography was performed and showed the presence of multiple bilateral renal and hepatic cysts, leading to enlargement of kidneys and liver (Figure 1).

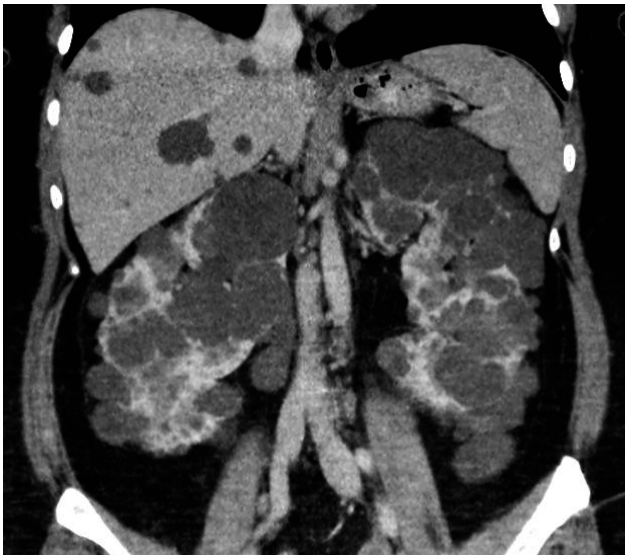

Figure 1. Spiral computed tomography scan.

The patient's right kidney volume was 1142 mL; left kidney volume, 1472 mL; and liver volume, 2004 mL. These images did not show cyst bleeding, cyst infections, kidney stones or extra-renal abnormalities that might cause pain. This scan also showed no signs that her kidneys compressed adjacent tissue, indicating that this theoretical

cause of intractable pain also was less likely. Given her serious situation, we decided to try catheter-based renal denervation of the afferent sensory nerves using the Simplicity Catheter System, a 6F-compatible single-use radio frequency (RF) probe. Before introducing the RF probe, a renal angiogram was performed and showed no contra-indications for the procedure. Subsequently, the system was introduced into the renal artery and the catheter electrode was positioned in contact with the vessel wall at the most distal location possible. The catheter was connected to an automated RF generator, and 5 applications of RF energy in a spiral pattern along the renal artery from distal to proximal and with 5-mm interspaces were performed (Figure 2).

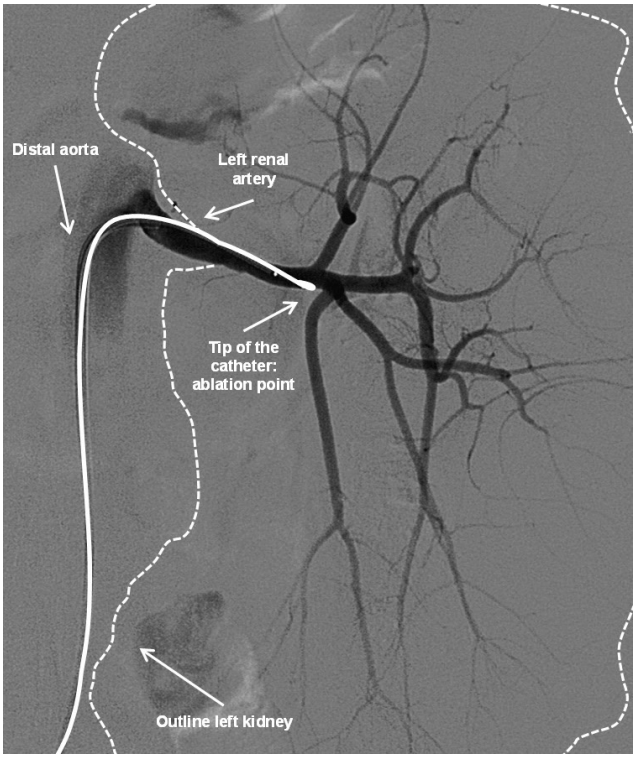

Figure 2. Angiography of the renal denervation procedure. The solid line represents the Simplicity Catheter System (a 6F-compatible, single-use radio frequency probe) that was introduced into the renal artery. The catheter electrode is positioned at the most distal location possible in the renal artery.

Immediately after the procedure, the pain was different and more intense, which was thought to be the result of using too low a dose of fentanyl during the procedure. The patient was discharged without complications on the day after the procedure. In the following days, her pain completely disappeared on the left side and she needed

only half the dosages of her pain medication. Because of this satisfactory result, the patient requested to denervate the right kidney as well. Four months later, a right-sided renal denervation was performed. The procedure was uncomplicated and she was pain free immediately. Moreover, her blood pressure had decreased to 117/79 mm Hg. Therefore, we reduced her antihypertensive medication before discharge the next day.

Four months later, the patient was still pain free, reported a visual analogue scale score of 0 of 10, did not use pain relief medication and had resumed her normal working and social life. Office blood pressure had decreased from a pre-intervention level of 145/96 mm Hg to 120/75 mm Hg, even though her antihypertensive medication had been reduced from 3 to 2 agents. Her eGFR had not changed (76 mL/min/1.73m^2 pre-intervention vs. 78 mL/min/1.73m^2 post-intervention).

Discussion

Chronic abdominal pain in ADPKD can be directly or indirectly related to the cystic enlarged kidneys (2). The renal nerves, which carry both sympathetic efferent and sensory afferent nerve fibers, are distributed circumferentially in the adventitia around the renal artery. Two previous case reports have described the possibility of renal denervation for direct ADPKD-related pain by thoracoscopic or laparoscopic procedures (3, 4). However, these invasive techniques are difficult to perform and require surgical experience, which is difficult to gain because there is only a limited number of patients with intractable ADPKD-related pain. We performed transluminal RF renal denervation as an alternative procedure to surgery with an excellent result.

Recent studies demonstrated the beneficial effect of renal denervation for treating resistant hypertension, heart failure and insulin resistance (6). Catheter-based renal ablation may be effective for pain-related syndromes as well. This procedure has been shown to be successful in a single patient with the loin pain haematuria syndrome (7). One case report suggested that catheter-based renal denervation also might have a beneficial effect on pain in cystic disease (8). However, in this case, the procedure was performed for therapy-resistant hypertension and the patient only had several one-sided renal cysts, rather than ADPKD (8).

The present evidence suggests that this procedure is safe up to 3 years after intervention (9). Another reason aside from pain management to apply renal denervation in patients with ADPKD is to treat hypertension. Hypertension in patients with ADPKD is associated with higher sympathetic activity (10-12). This indicates that

patients with ADPKD could benefit from renal denervation for hypertension treatment. Our patient's blood pressure control improved after the procedure. Contra-indications for this procedure are a history of renal artery stenting, renal artery stenosis > 50%, the presence of multiple arteries, or the renal artery having an average diameter ≤ 4 mm or being < 20 mm long. Because contrast is used during the procedure, local prevailing guidelines to prevent contrast nephropathy should be followed.

In conclusion, this case report suggests that percutaneous catheter-based renal denervation may be a simple and effective procedure for pain relief in selected patients with ADPKD in whom chronic pain is likely to be related directly to the increase in size of the kidneys and for whom oral analgesics did not result in effective pain treatment. Further research will have to be performed to indicate the place that renal denervation could have in the stepwise approach for effective pain management in ADPKD.

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Conflicts of interest
The authors declare that they have no relevant financial interests.

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Chapter 6

A stepwise approach for effective management of chronic pain in ADPKD

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Abstract

Chronic pain, defined as pain existing for more than 4-6 weeks, affects more than 60% of patients with autosomal dominant polycystic kidney disease (ADPKD). It can have various causes, indirectly or directly related to the increase in kidney and liver volume in these patients. Chronic pain in ADPKD patients is often severe, impacting physical activity and social relationships, and frequently difficult to manage. This review provides an overview of pathophysiological mechanisms that can lead to pain and discusses the sensory innervation of the kidneys and the upper abdominal organs, including the liver. In addition, the results of a systematic literature search of ADPKD specific treatment options are presented. Based on pathophysiological knowledge and evidence derived from literature an argumentative stepwise approach for effective management of chronic pain in ADPKD is proposed.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common renal hereditary disorder, with an estimated prevalence of 1 per 1000 subjects in the general population (1). Development of renal function decline is the main threat for patients with ADPKD, often leading to end-stage renal disease between the fourth and seventh decade of life (1). Pain is one of the other debilitating complications (2).

Pain in ADPKD is classified as acute or chronic. Acute severe pain is relatively uncommon. Data from the TEMPO 3:4 trial suggest an average incidence of clinically significant pain episodes of 7 per 100 person years in untreated patients (3, 4). By contrast, chronic pain is very common in patients with ADPKD with an estimated prevalence of 60% (5, 6). A subanalysis of the TEMPO 3:4 trial shows that chronic pain in ADPKD patients with retained renal function is often severe and leads to use of pharmacological agents in 28.0%, sleep disturbances in 16.8% and impacts physical activity and relationships with others in 20.8% (3, 4). Similar findings were observed in the HALT trial (6). Thus, chronic pain has major effect on physical and social functioning in patients with ADPKD.

Chronic pain in ADPKD can have various causes and is often difficult to manage. In this review we give an overview of pathophysiological mechanisms that can lead to pain and discuss the sensory innervation of abdominal organs (including the kidneys and the liver). In addition, we present the results of a systematic literature search of ADPKD specific treatment options. Based on pathophysiological considerations and evidence derived from literature we propose an argumentative stepwise approach for the effective management of chronic pain in ADPKD.

Pathophysiology of pain in ADPKD

Acute pain

Acute pain in ADPKD patients can be ADPKD related, or arise from other sources as in any patient. Specific for ADPKD are among others cyst hemorrhage, cyst rupture, cyst infection and urinary tract stone formation.

Neovascularization within cysts, due to angiogenesis promoted by vascular endothelial growth factor, may be involved in renal and liver cyst hemorrhages (7). Symptomatic episodes probably underestimate the true frequency of cyst hemorrhage. More than 90% of patients with ADPKD have renal cysts with a high signal on MR imaging, indicative for blood or high protein content, whereas only a minority of these

patients had been clearly symptomatic (8). Hematuria is not always a feature of renal cyst hemorrhage. In one study hematuria was only present in 14 of the 24 patients with pain and evidence of a cyst hemorrhage on CT-scan (9). Spontaneous renal cyst ruptures are uncommon, but traumatic and infection related ruptures of renal cysts into the pyelocalyceal system and the retroperitoneum have been reported (10, 11). Acute pain in ADPKD can also be related to liver cysts. A retrospective cohort study in 34 ADPKD patients with polycystic livers showed a prevalence of 11.8% hemorrhages and 11.8% ruptures in liver cysts (12). Typically, these complications occur more frequently in patients with severe hepatomegaly (13). The acute onset of pain in ADPKD patients with cyst hemorrhage is probably caused by stretching of the renal and liver capsule, although evidence for this is formally lacking.

A history of upper urinary tract infections is seen in 60% of all ADPKD patients, with a higher prevalence in women (14). The episodes of isolated cyst infection were more frequent than those of acute or chronic pyelonephritis (14). Liver cyst infections have been described in 5.9% of ADPKD patients (12). In an ADPKD patient with acute abdominal pain and fever, the diagnosis of cyst infection can be made by fluordeoxyglucose position emission tomography (FDG-PET). The greatest advantage of FDG-PET over conventional CT and MR imaging is the good spatial discrimination of FDG-PET, which may guide invasive interventions and the evaluation of adjacent tissue (15). Since discrimination between renal and liver cyst infections is not possible using clinical findings, FDG-PET can assist in establishing the diagnosis by localizing the infection (16).

Patients with ADPKD have an increased risk for kidney stones, with a prevalence of about 8-36% (17-19). The cause of stone formation is multifactorial and may result from structural abnormalities secondary to cyst growth that lead to urinary stasis, but also from concomitant metabolic disorders. Uric acid is usually the main component of these stones followed by oxalate stones (18). In fact, the prevalence of hypercalciuria, hyperuricosuria and hyporcitraturia is lower in ADPKD with stones compared to ADKPD patients without stones (18, 20). Surgical management of renal stones is not affected by the underlying (renal) disorder and medical management will be dictated by stone composition (21).

The management of acute pain in ADPKD patients is beyond the scope of the present review, which focuses on the treatment of chronic pain. However, it should be noted that episodes of acute pain may lead up to the development of chronic pain. The exact mechanism underlying this association is still unknown, but may be due to sensitization (8). Timely and adequate management of acute pain in ADPKD patients is therefore indicated.

Chronic pain

When pain is present during a period longer than 4 to 6 weeks it is classified as chronic pain. In ADPKD chronic pain can have several causes. Non-ADPKD related causes, such as irritable bowel syndrome, inflammatory bowel disease and gynecological pathology in females, must be ruled out, especially in patients with relatively small kidneys and liver. Chronic pain may bear a direct relation with ADPKD or not. Indirect associations between ADPKD and chronic pain are seen especially in patients with a severe increase in renal and liver volume. The increased abdominal mass may cause musculoskeletal pain, for instance low back pain, because subjects develop an aberrant posture similar to pregnant women. Remarkably, a recent sub-analysis from the HALT study showed among patients with an eGFR >60 ml/min*1.73m^2 that total kidney volume corrected for height was not related to the frequency or intensity of back, abdominal, or radicular pain (6). Chronic pain directly related to ADPKD is caused by cyst growth induced distension of renal and hepatic capsules or by compression of adjacent tissue (22).

Pain due to renal cysts is typically located abdominally rather than in the low back area, and described from steady nagging discomfort to a dull aching or severe stabbing pain (4, 22). Lying on bed is often the most comfortable position, whereas standing, walking and sitting for a long period of time can induce pain (22). Usually there is no relationship with defecation or micturition, whereas deep inspiration may induce an increase in pain intensity, suggesting a visceral component.

Hepatic cysts are very common in patients with ADPKD, with an overall prevalence of 83% in the age-group of 18-46 years (23). Most hepatic cyst patients are asymptomatic, but those with more severe liver enlargement may experience abdominal fullness or discomfort, gastrointestinal symptoms and nagging or stabbing pain either by compression of adjacent abdominal and thoracic organs or by distension of the hepatic capsule (2). Furthermore, some of these patients develop chronic shoulder pain due to irritation or tension of the diaphragm. When renal and liver cysts co-exist, the primary source of pain may be difficult to determine.

Chronic pain has also been shown to have negative consequences with respect to anxiety and depression, of which the prevalence is higher in ADPKD patients than in the general population (24). Furthermore, the use of pain medication was negatively associated with physical well being in pre-dialysis ADPKD patients (25). Anxiety, depression and chronic pain may lead to a decrease in quality of life (24). In the management of chronic pain, the presence of anxiety or depression should therefore be investigated, and, when present, adequately treated.

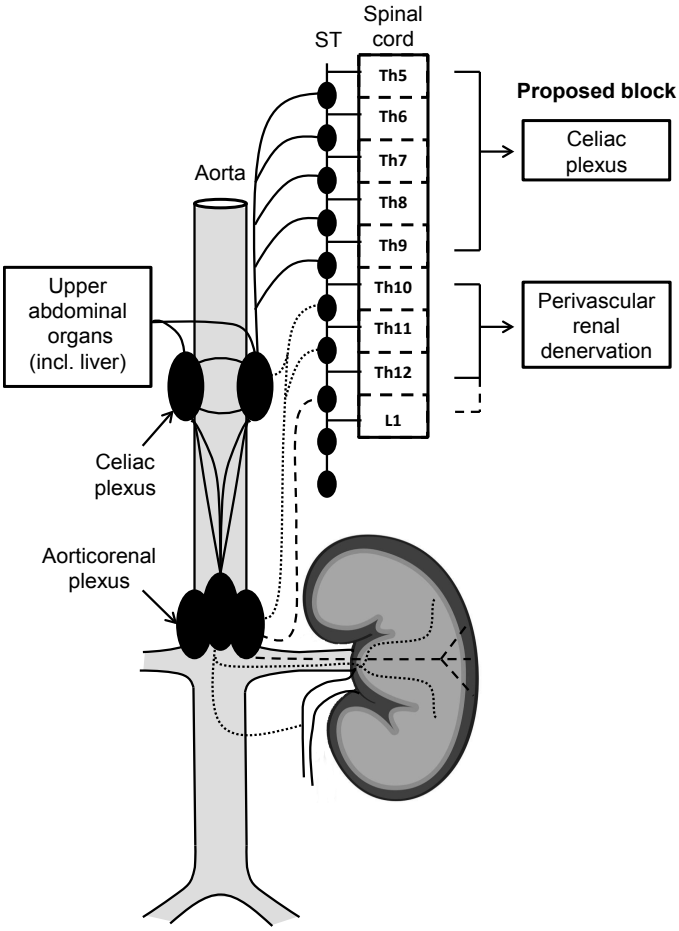

Figure 1. Schematic drawing of the sensory nerve supply of kidneys and upper abdominal organs via sympathetic pathways. Solid line: Major splanchnic nerve providing sensory innervation of the upper abdominal organs, including the liver via the celiac plexus. Dotted line: Lesser splanchnic nerve providing sensory innervation of the renal parenchyma and ureter. Dashed line: Least splanchnic nerve providing sensory innervation of the renal capsule. The perivascular nerve plexus around the renal artery forms the final common pathway to and from the kidney. ST; Sympathetic Trunk.

Sensory innervation of kidneys and upper abdominal organs

Paramount to the understanding of the sensory nerve supply of visceral organs is that visceral afferent fibers travel via visceral efferent pathways. Thus, in general, sensory innervation of internal organs is described in terms of efferent, i.e., sympathetic and parasympathetic fibers. It should be emphasized, however, that all efferent pathways

contain visceral afferents, including nociceptive fibers. Except for nociception from the pelvis floor organs, nociception from all internal organs traverse via sympathetic pathways to the spinal cord and, consequently, end in the spinal cord segments C8-L1 (26). Referral of visceral pain to dermatomal areas depends on the level of segmental innervations. Thus, e.g., pain felt in dermatomal area T10 can derive from any (part of) internal organ that projects its nociceptive impulses to spinal cord segment T10 (26, 27).

The sensory nerve supply of the upper abdominal organs via sympathetic and parasympathetic fibers (26) is schematically depicted in Figure 1. Pain originating from the kidney and upper abdominal organs reaches the lower thoracic spinal cord via the celiac and aorticorenal plexus, the major splanchnic nerve (T5 – T9, upper abdominal organs including liver) (28, 29), the lesser splanchnic nerve (T10-T11, renal parenchyma and ureter) (29), the least splanchnic nerve (T12-L1, renal capsule) (29), and finally the sympathetic trunk.

The major splanchnic nerves terminate in the celiac plexus, formed by the left and right celiac ganglion and interconnecting nerve fibers. Its location and extent make it an effective target for invasive pain therapy by blockade by alcohol or phenol injection. A celiac plexus block has been applied for many years, especially for oncological upper abdominal pain (30). The lesser and least splanchnic nerves travel via the aorticorenal plexus to their target organ. This makes it technically much more difficult to obtain an effective and selective blockade. In contrast, in celiac blocks overflow to the aortico-renal plexus might not be overcome.

Parasympathetic fibers to the kidney originate from the vagus nerve. They traverse through the celiac plexus or pass directly to the aorticorenal plexus (28). They end upon solely to the smooth muscles of the renal pelvis and calyces, but do not supply the renal parenchyma nor the renal capsule. In trying to determine the original source of pain, a practical approach would be to 'follow the dermatome where the pain is felt'. This means, that when pain is referred to dermatomes T5 and T6, the most plausible route is via the celiac plexus and major splanchnic nerve (including all other organs supplied by T5 and T6). When the pain is referred to dermatomes T11-12, consequently the lesser and least splanchnic nerve may be the pathways including, again, all other organs that project to T11 and T12. Given the above, analysis of the dermatomes, where the (visceral) pain is referred to, should be part of the investigation of possible causes of chronic pain in ADPKD, because it may help the decision making process which (invasive) pain therapy to consider.

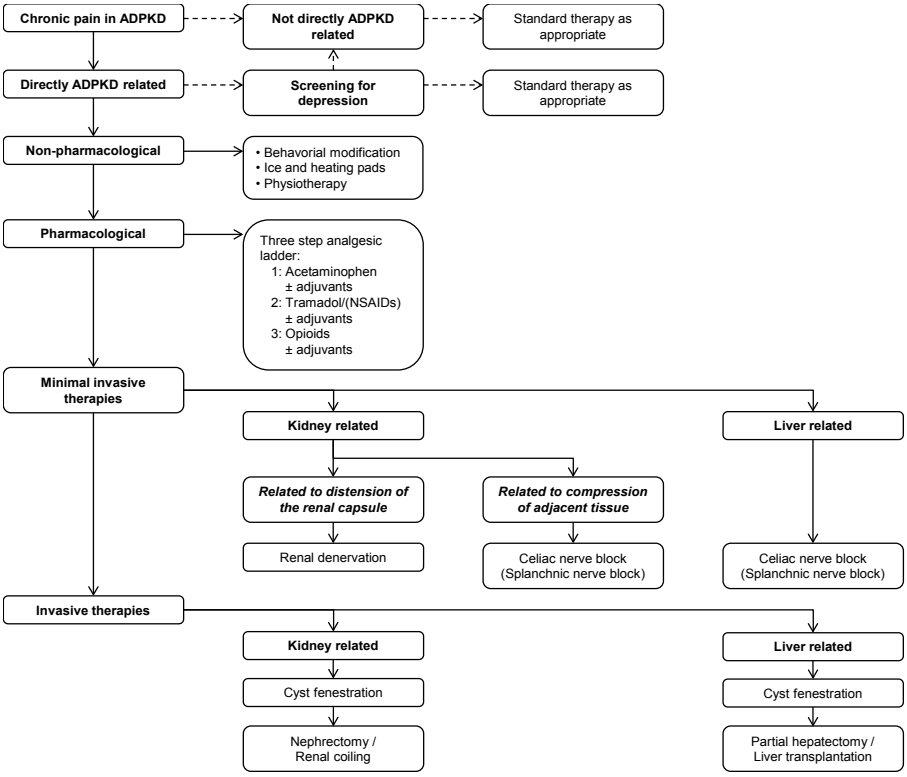

Figure 2. Proposed management algorithm for chronic pain in ADPKD patients, starting with measures that are non-pharmacological, progressing to pharmacological, minimal invasive and ultimately to complex, invasive therapies.

Potential treatment options for chronic pain in ADPKD

Literature search

An electronic literature search was performed up and until December 28, 2013, to obtain a complete overview of treatment options for chronic pain in ADPKD. For this literature review, PubMed was searched using the string: [('ADPKD' OR 'polycystic kidney disease' OR 'polycystic liver disease' OR 'PLD') AND ('pain')]. Obtained manuscripts were searched for cross-references, and experts in the field were consulted to identify all relevant articles. This search yielded a total of 419 articles. Articles that were left after removal of duplicates and title and abstract screening for eligibility, were critically appraised whether interventions were performed for pain as indication. Finally 45 articles (18 kidney and 27 liver related) were included, that are summarized in treatment option tables (Tables 1 through 4). A detailed flowchart of the literature search can be found as Web Appendix Figure 1.

Table 1. Summary of reports describing renal denervation in ADPKD patients for chronic kidney pain related to polycystic disease

Author	Year	Technique	Patient (N)	Location	Pain outcome	Follow-up (months)	Complications
Renal denervation							
Valente	2001	Laparoscopic	1	Bilateral	90% pain free	Unknown	Blood pressure unchanged
Chapuis	2004	Thoracoscopic	1	Unilateral	80% pain free	24	None
Resnick	2006	Laparoscopic	4	Unilateral (one patient bilateral)	100% pain free	6-16	None
Casteleijn	2014	Radio frequency ablation	1	Bilateral	100% pain free	4	Blood pressure decreased

Table 2. Summary of reports describing cyst fenestration, cyst aspiration and sclerotherapy in ADPKD patients for chronic kidney pain related to polycystic disease

Author	Year	Technique	Patient (N)	Location	Pain outcome	Follow-up (months)	Complications
Cyst aspiration and cyst sclerotherapy							
Bennett	1987	Percutaneous cyst aspiration	11	Unilateral	33% had some pain relief	18	None, part of the patients needed open cyst aspiration
Uemasu	1993	Cyst aspiration and sclerotherapy with minocycline hydrochloride	3	Unilateral	66% had some pain relief	8	None
Uemasu	1996	Cyst aspiration and sclerotherapy with minocycline hydrochloride	10	Bilateral	20% had some pain relief	12	Cyst volume did not differ statistically after sclerotherapy
Kim	2003	Cyst ablation with N-butyl cyanoacrylate and iodized oil	21	Unilateral	80% had some pain relief	54	None
Lee	2003	Cyst ablation with absolute ethanol	11	Unilateral. One bilateral	64% had some pain relief	12	4 patients had increased perception of pain
Singh	2006	Cyst ablation with absolute ethanol	15	Unilateral. Two bilateral	Mean pain relief of 66%	7 days	1 patient had worsening pain and 1 patient developed a nephrocutaneous fistula
Kim	2009	Cyst ablation with N-butyl cyanoacrylate and iodized oil	21	Unilateral	76% had some pain relief	36-90	ESRD in 6 patients, 22% of the cysts reappeared
Cyst Fenestration							
Elzinga	1992	Open	30	19 unilateral, 11 bilateral	63% pain free	21	2 patients needed a second procedure
Brown	1996	Laparoscopic	8	Unilateral	80-100% pain reduction	12-28	2 patients had persistent pain
Lifson	1998	Laparoscopic	8	Unilateral	25% pain reduction	36	1 patient had retroperitoneal bleeding, ileus and chemical peritonitis
Dunn	2001	Laparoscopic	15	9 unilateral, 6 bilateral	62% pain reduction	26	3 patients had urinoma, 2 had perforations of collecting system
Lee	2003	Laparoscopic	29	23 unilateral, 6 bilateral	81% had some pain relief	36	3 patients had urinoma
Fryczkowski	2007	Laparoscopic	15	Unilateral, 2 bilateral)	23% pain free	24	Mean hospitalization of 10 days
Haseebuddin	2012	Laparoscopic	18	Unknown	67% pain reduction	130	3 patients needed nephrectomy

Abbreviation: ESRD, end stage renal disease.

Table 3. Summary of reports describing cyst aspiration and sclerotherapy in patients for chronic pain related to hepatic cystic disease

Author	Year	Technique	Patient (N)	Underlying diagnosis	Pain reduction	Follow-up (months)	Complications
Cyst aspiration and cyst sclerotherapy							
Goldstein	1976	AS with pantopaque	1	1 Solitary cyst	100% pain free	16	None
Kairaluoma	1989	AS with ethanol	8	4 Solitary cyst; 3 PLD; 1 ADPKD	100% pain free	12-32	Postoperative pain, elevated temperature, nausea
Furuta	1990	AS with ethanol	6	4 Solitary cyst; 2 PLD	100% pain free	60-68	Fever
Tanis	1994	AS with ethanol	4	2 Solitary cyst; 2 PLD	75% pain free	8-60	None
Tikkakoski	1996	AS with ethanol	25	11 Solitary cyst; 10 PLD; 4 ADPKD	56% pain free; 16% pain reduction	12-84	Pain after procedure, fever, nausea
Okano	2000	AS with ethanol	1	1 Solitary cyst	0% pain reduction	12	Fever
Ferris	2003	AS with ethanol	1	1 PLD	100% pain free	52	Abdominal pain
Larssen	2003	AS with ethanol	7	5 Solitary cyst; 2 PLD	100% pain free	12-47	Pain after procedure
Blonksi	2006	AS with ethanol	1	1 Solitary cyst	100% pain free	4	None
Van Keimpema	2008	AS with ethanol	15	4 Solitary cyst; 11 PLD	53% pain free; 20% pain persistence	3-30	Nausea, pain; 4 PLD patients had worsening pain
Nakaoka	2009	AS with ethanol	11	1 Solitary cyst; 10 PLD/ ADPKD	100% pain free	1-95	Vasovagal collapse, pain, fever
Fabrizzi	2009	AS with tetracycline	1	1 Solitary cyst	100% pain free	12	None
Karam	2011	AS with ethanol	1	1 Solitary cyst	100% pain free	12	None; patient had previous laparoscopic fenestration

Abbreviations: AS, aspiration and sclerotherapy; PLD, isolated polycystic liver disease.

Table 4. Summary of reports describing cyst fenestration in patients for chronic pain related to hepatic cystic disease

Author	Year	Technique	Patient (N)	Underlying diagnosis	Pain outcome	Follow-up (months)	Complications
Cyst fenestration							
Van Erpecum	1987	Open	7	7 PLD/ADPKD	86% pain free	6-132	Ascites
Morino	1994	Laparoscopic (2 conversion)	11	4 Solitary cyst; 7 PLD	64% pain free; 18% pain persistence; 18% pain recurrence	6-21	Ascites, pleural effusion
Farges	1995	Laparoscopic	12	2 PLD; 10 ADPKD	77% pain free; 23% pain recurrence	12-140	Ascites
Kabbej	1996	Laparoscopic	13	13 ADPKD	23% pain free; 15% pain persistence; 62% pain recurrence	3-49	Ascites, pleural effusion
Gigot	1997	8 Open; 2 Laparoscopic (1 conversion)	10	5 PLD; 5 ADPKD	90% pain free; 10% pain recurrence	17-239	Biliary leakage, massive hemorrhage
Kakizaki	1998	Laparoscopic	3	1 Solitary cyst; 2 PLD	100% pain free	46-61	None
Tan	2002	Laparoscopic	10	9 Solitary cyst; 1 PLD	90% pain free; 10% pain recurrence	4-80	PLD patient needed re-surgery
Konstadoulakis	2005	Laparoscopic	9	1 PLD; 8 ADPKD	78% pain free; 22% pain recurrence	20-38	1 death due to hepatorenal syndrome
Hsu	2005	Laparoscopic	2	2 PLD	100% pain free	24-70	Biliary leakage
Neri	2006	Laparoscopic	15	12 Solitary cyst; 1 PLD	100% pain free	3-38	Pneumonia, pleural effusion, ascites
Van Keimpema	2008	Laparoscopic	12	12 PLD	25% pain free; 25% pain reduction; 25% pain persistence; 25% pain worsening	5-25	Biliary leakage, vena cava inferior compression, sepsis, hemorrhage
Faulds	2010	Laparoscopic[a]	5	5 Solitary cysts/ PLD	100% pain free	3-13	Pleural effusion, nausea
Kamphues	2011	Laparoscopic	31	31 Solitary cysts/ PLD	Mean pain relief of 48%	19-97	None
Scheuerlein	2013	Mixed (3 conversion)	33	33 Solitary cysts/ PLD	66% pain free; 33% pain recurrence/ persistence	3-119	Bilioma/biliary leakage

[a] Laparoscopic fenestration was combined with falciform ligament pedicle graft. *Abbreviations: FU, follow up; PLD, isolated polycystic liver disease.*

Non-pharmacological therapies

Since chronic pain is a composite of physical and psychophysical derangements, management should incorporate both aspects to be successful. Non-pharmacological therapies include therefore a wide range of options that may be divided into physical interventions (including physical therapy, massage, and ice and heat pads) and psycho-educational interventions (for example patient education, cognitive-behavioral therapy or psychotherapy). In the general population psycho-educational interventions are the cornerstone for modern pain management practice in patients with chronic pain. These treatment options should also be discussed with ADPKD patients with chronic pain and can often lead to effective pain reduction. However, to our knowledge, the effectiveness of these interventions has never been investigated in specifically ADPKD patients.

The two previous reviews on pain management in ADPKD discussed the Alexander technique (8, 22). This is a non-exercise approach to improve the natural body posture, and patients learn how to move and position their body to reduce pain. This technique may also help ADPKD patients, especially when musculoskeletal pain due to aberrant posture is the main cause of pain, although we are not aware of studies that test the efficacy of the Alexander technique in specifically ADPKD patients.

Pharmacological therapies

Causal treatment

As yet no treatment options are available to modify the course of disease progression in ADPKD. However, there are recent interesting developments. The TEMPO 3:4 trial found that the vasopressin V2 receptor antagonist tolvaptan slowed the increase in total kidney volume and the decline in kidney function over a 3-year period in patients with ADPKD. In addition, tolvaptan use was associated with pain reduction (3, 4), and the frequency of acute pain events was significantly lower in the treatment arm (3). Interestingly, tolvaptan was also associated with a significant lower incidence of reported chronic kidney pain. Somatostatin analogues offer another therapeutic option. Recent clinical trials found that Octreotide and Lanreotide reduced the growth rates of liver as well as kidneys (31-33), with benefits in terms of perception to health to ADPKD patients. The above data suggest a beneficial effect on the incidence and prevalence of pain by agents slowing disease progression in ADPKD. Unfortunately, vasopressin V2 receptor antagonists as well as somatostatin analogues are not available for clinical use in ADPKD subjects yet (3, 4). Current pharmacological treatment options for the management of chronic pain are therefore symptomatic.

Symptomatic treatment

The World Health Organization defined a three-step analgesic ladder to describe its guideline for the use of drugs in the management of pain. It was originally applied to the management of cancer pain, but is now widely used by medical professionals for the management of all types of pain including in renal patients (34). The drugs that may be prescribed are, first, acetaminophen (paracetamol) with or without adjuvant therapy. Adjuvants are used for enhancing the efficacy of pain medication, controlling side effects or managing other symptoms that may be associated with pain. Second, in case pain is insufficiently relieved, non-steroidal anti-inflammatory drugs (NSAIDs) or mild opioids,(e.g. tramadol), both with or without adjuvants, can be tried. Because of their renal hemodynamic effects and nephrotoxicity, NSAIDs are not recommended in ADPKD patients with impaired kidney function. Before opioids are given, combination therapy of acetaminophen with NSAIDS can be tried, which may lead to effective pain therapy and avoid the use of opioids. Thirdly, when combination therapy did not provide sufficient pain relief, strong opioids (e.g. morphine), with or without adjuvants, can be given. Analgesics should be given in a fixed dose schedule, since pain medication is most effective when a steady blood level of pain medication is obtained. The dose of these analgesics varies between patients and is identified as the dosage needed to relieve pain without producing intolerable side effects. Patients should be aware of especially the potential side effects of opioids, such as constipation, nausea, vomiting, sedation and mental changes, as well as that this medication can lead to habituation and addiction. Opioids can be given via several routes, but the best evidence for efficacy applies to the transdermal route (35). Caution is needed when using opioids in patients with GFR < 30 ml/min or end-stage renal disease. Because of retention due to decreased renal clearance of pharmacologically active metabolites, these drugs can result in considerable side-effects. This three-step approach of administering analgesics is inexpensive and in 80 to 90% of patients effective (34).

Of note, sometimes also anti-epileptics (e.g. pregabalin or gabapentin) and antidepressants (e.g. amitryptiline or nortryptiline) are prescribed to ADPKD patients with success, although these medications for neuropathic pain have never been formally investigated for pain related to ADPKD.

Minimal invasive pain therapies

Celiac and splanchnic nerve block

Renal pain related to compression of adjacent tissue can be successfully treated by celiac nerve block. Injecting neurolytic agents like alcohol or phenol destroys nerve fibers within the celiac plexus by which the pain pathway of the upper abdominal organs

including the liver is blocked. A celiac block has been used for chronic intractable abdominal pain related to cancer, in particular pancreatic, gastric and intestinal cancer (36) and in pediatric patients for pain related to compression by neuroblastoma and hepatoblastoma (37, 38). Success rates in cancer vary between 70% and 100% (36, 39).

A temporary celiac block by short acting local anesthetics may help differentiate between pain caused by distension of the renal capsule and compression of adjacent tissue. When a celiac block is effective and results in complete pain relief, the pain is probably caused by compression of adjacent visceral tissue. If no pain relief is observed, it may suggest that the pain is related to distension of the renal capsule (where pain follows another pathway, see Figure 1).

As the liver and liver capsules are supplied by visceral afferent nerves via the celiac plexus, interventions that block this plexus may relieve liver pain in ADPKD (40). Indeed, one case report showed that liver capsule pain after blunt trauma can be managed by a paravertebral block at the T10 level (40). However, in this case more nervous structures are blocked, such as the sympathetic trunk and the lower thoracic spinal nerves. We could not identify studies that describe similar therapies in patients with hepatic cystic disease.

When a celiac nerve block cannot be performed, a splanchnic nerve block can be an alternative treatment option. Traditionally, neurolysis with 10 mLs of absolute alcohol or 6–10% phenol has been performed (41). However, the difficulty in dividing the agent within the anatomical compartment of the splanchnic nerves with a chance of nerve root damage, is considered a disadvantage of this block (42). Radiofrequency thermal coagulation might be a useful alternative method (42).

Although, at present, neurolytic blocks are not often applied in chronic ADPKD related pain, they deserve in our opinion a prominent place in the stepwise approach for chronic pain related to ADPKD.

Renal denervation

The renal nerves, carrying both sympathetic efferent and sensory afferent nerve fibers, are circumferentially distributed in the adventitia around the renal artery. Renal denervation has been proposed for patients with intractable ADPKD related pain that is caused by distension of the renal capsule, and may be a good alternative for the various surgical procedures that are described below. Table 1 shows an overview of studies that investigated renal denervation in patients with ADPKD. Three case reports describe thoracoscopic or laparoscopic procedures, leading to excellent pain control (43-45). However, these invasive techniques are difficult to perform, and require surgical experience, which is difficult to obtain given the limited number of

patients with intractable ADPKD related pain. Recently a catheter-based percutaneous transluminal method has been introduced. By applying high frequency energy, adjacent tissue is coagulated resulting in ablation of efferent and afferent renal nerve fibers. This procedure is now mainly applied for blood pressure control in patients with therapy resistant hypertension. We applied this procedure in an ADPKD patient with intractable pain likely to be related to the large polycystic kidneys and in whom oral analgesics did not result in effective pain treatment (46). Following this procedure, the patient was completely free of pain. Although from a theoretical point of view catheter-based renal ablation of renal sensory nerves is an attractive option in selected cases, additional reports on efficacy are awaited before its exact place in the management of chronic pain in ADPKD patients can be determined.

Transcutaneous electrical nerve stimulation and spinal cord stimulation

For transcutaneous electrical nerve stimulation (TENS) small electrodes are placed on the cutaneous receptive fields of somatic sensory nerve fibers that project to the same spinal cord segments as the involved visceral afferents. By electrical stimulation of giving continuous electrical impulses, the responsiveness of pain fibers is reduced which leads to a decreased stimulus to the dorsal horn cells, resulting in a decrease in pain sensation. At the moment, particularly in patients with low back pain TENS is used. To our knowledge no report has been published on the effectiveness of TENS for ADPKD related chronic pain.

Spinal cord stimulation is an alternative analgesic technique, which has been performed for pain related to cancer (47). It has become fashionable for treatment of chronic intractable pain, especially from neuropathic origin (48). This technique uses electrodes placed in the epidural space to modulate pain pathways. One case report described a patient with uncontrolled severe chronic pain related to renal cysts with complete pain relief after spinal cord stimulation (49).

All aforementioned non-pharmacological pain therapies have been described thus far only in case reports. Elucidating their efficacy and their place within the treatment algorithm for ADPKD related chronic pain should be part of the research agenda.

Invasive therapies for renal and hepatic cysts

Renal cyst aspiration, sclerotherapy and fenestration

Table 2 shows an overview of studies that investigated renal cyst aspiration, sclerotherapy and fenestration as treatment options for ADPKD related pain (50-63).

In 1987 percutaneous renal cyst aspiration was first described in a study of 11 patients (57). Pain improved in most patients, but after 18 months only 33% of the

patients had sufficient pain relief. This may be caused because after aspiration, fluid secretion causes cysts to re-appear. Later studies, mainly from Asia, injected cysts with ethanol, minocycline hydrochloride, N-butyl cyanoacrylate or iodized oil after aspiration are were more effective in preventing cyst re-appearance (58, 60, 64). This seems to be associated with a higher success rate, but unfortunately also comes with limited pain control. Furthermore, percutaneous aspiration may be difficult, because it is often not known which cyst causes pain.

With renal cyst fenestration or marsupialization, cysts can also be drained to prevent their re-appearance. This procedure is invasive and can be performed in case of extremely large cysts, where they have been shown to be effective. The kidney is approached, either laparoscopically or by open procedure, and the renal capsule is opened and cysts are unroofed. Bleeding can occur, but is in general easily controlled by coagulation. Cysts that are drained should not communicate with the peritoneal cavity to avoid infection. The immediate success rate is very high and varies between 85 – 90%, but 1 to 2 years follow up showed a decrease in success rate to around 65% (53, 54) and severe complications have been observed.

Given the uncertain success rate and common complications we advise to be reluctant with performing renal cyst aspiration, sclerotherapy or fenestration for pain management.

Liver cyst aspiration, sclerotherapy and fenestration

Similar as in renal cysts, aspiration with sclerotherapy or cyst fenestration can be performed for relief of liver cyst associated pain (65).

Aspiration-sclerotherapy is the preferential treatment for a dominant cyst > 5 cm that can be reached percutaneously. Table 3 shows an overview of studies that evaluated the effect of cyst aspiration-sclerotherapy on liver-related pain (66-78). Ethanol was the most commonly used sclerosing agent. In contrast to the situation for renal cysts, most studies demonstrated high rates of pain relief after aspiration-sclerotherapy of hepatic cysts. However, outcomes were less favorable in patients with polycystic livers compared to those with solitary cysts (76, 77). Therefore, we do not recommend this therapy for ADPKD patients with severe polycystic livers except in cases where there is a large accessible anterior hepatic segment cyst(s) that appears to correlate with patient symptoms.

Hepatic fenestration involves surgical deroofing of multiple large cysts in order to reduce liver volume and ameliorate symptoms (79). Results on pain relief after hepatic cyst fenestration are shown in Table 4 (79-91). Although immediate pain relief was achieved in almost all patients, pain recurrence occurred in up to 62% of

treated patients (80, 83, 86). Furthermore, the procedure is associated with several complications, including ascites, pleural effusion, arterial or venous bleeding, and biliary leakage although these complications are much more infrequent with adoption of laparoscopic fenestration techniques as opposed to laparotomy (65, 92). Again, patients with severe polycystic livers, characterized by numerous small liver cysts, had worse outcomes than patients with single of multiple large liver cysts. Therefore, hepatic fenestration is only a viable option for patients who are highly symptomatic and have one or more large liver cysts accessible by laparoscopy (91).

Nephrectomy, renal coiling, partial hepatectomy and liver transplantation

Nephrectomy and renal coiling are last resort options. In patients with preserved renal function it is a difficult decision to remove a functioning kidney knowing that ADPKD may lead to renal failure. The options should therefore be reserved for patients that are pre-end stage renal disease or those already receiving renal replacement therapy.

Nephrectomy leads to some or even complete pain relief, but such an intervention is not without risks (93-100). Major complications that have been reported include retroperitoneal hematoma, incisional hernia's and arteriovenous fistula (95, 97-99). In general, the removal of large polycystic kidneys may be safely accomplished via laparoscopy instead of open surgery, but sometimes conversion to open surgery is necessary (101). The benefits of laparoscopic surgery are decreased postoperative pain, less blood loss, shorter hospitalization and a better cosmetic result when compared to the open procedure (101). Hand assisted laparoscopic techniques (unilateral or bilateral) have been shown to be safe, associated with reduced morbidity (100, 102), and facilitates the resection of the massively enlarged polycystic kidney through a smaller incision than traditional simple or radical nephrectomy approaches. Laparoscopic nephrectomy has been performed safely bilateral and even in combination with allograft placement (103) .

Renal artery coiling is indicated especially for patients with severe pain and contraindications to surgical interventions. A steel or platinum coil is placed into the main renal arteries to obstruct blood supply. The effectiveness of coiling is reported to be 53 – 60% for pain relief following this procedure (64, 104). When coiling fails, other techniques as alcohol injection or gelatin sponges can be used. However the experience with these latter interventions is limited (105). Severe complications after renal coiling are possible in situations where for instance adrenal, gonadal, and phrenic branches of the renal arteries exist or when there is incorrect catheter placement.

Partial hepatectomy is performed in patients with severe hepatomegaly with at least one liver segment without liver cysts (92). While 86% of patients experience relief

of symptoms, including pain, this procedure is associated with considerable morbidity (63%) and mortality (3%) (65). Furthermore, adhesions might complicate future liver or kidney transplantation. Therefore, we do not recommend this option for treating liver pain in ADPKD.

Liver transplantation is the last option for liver pain management, only indicated in patients with extremely impaired quality of life due severely disabling symptoms and diffuse cystic disease (65). This option should be weighed carefully in view of the associated morbidity and organ shortage, especially because liver synthetic capacity remains normal even in advanced polycystic liver disease (106).

Suggested approach for evaluation and treatment of chronic pain in ADPKD

In Figure 2 we present our approach to patients with ADPKD and chronic pain. The first step is to exclude non-ADPKD related sources of pain, that should be treated as normal. Treatment of non-ADPKD related somatic pain or neuropathic pain is beyond the scope of this review.

In ADPKD patients the prevalence of symptoms of depression and anxiety is higher than in the general population. In management of chronic pain, the presence of depression should be investigated. When depression is diagnosed, adequate management is necessary with medication (e.g. antidepressants) and/or psychotherapy.

When pain is considered to be related to the cystic kidneys or liver, subacute or prolonged courses of acute kidney pain must be considered, such as cyst hemorrhage, cyst infection and urinary tract stones. Careful anamnesis and physical examination should trigger to these possibilities and additional laboratory tests and imaging should be performed on indication. Imaging studies may be of limited value in this respect because ultrasound, CT and MRI can often not distinguish between infected cysts and asymptomatic or hemorrhaged cysts (15). FDG-PET scan has the best performance in detecting a cyst infection.

The next step is to consider the possibility of aberrant posture or motion, that can lead to pain due to increased or abnormal muscle tension. These subjects are most likely to benefit from physiotherapy (such as the Alexander technique) and should not receive any invasive treatment. Management in cases where there is intractable pain should be based on an interdisciplinary approach consisting of both pain physicians and nephrologists. All subjects with chronic pain should be advised first to try conservative methods for pain reduction, these are behavioral methods (for example cognitive-

behavioral therapy) and try ice/heat pads, before invasive therapies are considered. In many patients these conservative interventions, may lead to effective pain relief.

When these methods are inadequate, pharmacological treatment can be considered, starting with acetaminophen, adding the mild opioid tramadol on indication, and, when not effective enough, replace tramadol for hydrocodone, oxycodone, other opiates such as buprenorphine or fentanyl patch or in some refractory cases, oral or transdermal morphine. Adjuvants may be added when needed, for example a laxative should be added to opioids in order to avoid constipation, which in our experience occurs more often in ADPKD than in non-ADPKD patients.

When conservative and pharmacological strategies are ineffective, more invasive methods can be considered. The most subtle and probably most effective method is to perform a neurolytic block of the sensory nerves that are involved. For this purpose it is important to distinguish between pain deriving from tension of the renal capsule, which is innervated via the least splanchnic nerve, and pain due to compression of adjacent tissue (including the liver), which leads to visceral pain via the celiac plexus. Anamnesis, (including analysis of the dermatomes of referred visceral pain), physical examination and imaging may help to discriminate between these two types of pain. However, often this is not sufficiently possible. In such cases a temporary celiac nerve block can be used as test procedure. Subsequently a long-term plexus block can be given when pain is considered to be due to compression of adjacent tissue. When pain is believed to be caused by distension of the renal capsule we suggest considering renal denervation, which should be effective from a theoretical point of view, although further experience with this technique is awaited. Other experimental interventions that may have a place in management of chronic pain in ADPKD are transcutaneous electrical nerve and spinal cord stimulation (49).

More invasive methods can be considered only as a last step. Due to limited effects in patients with ADPKD we do not recommend cyst aspiration. Cyst fenestration is a method with better long term results and can be considered, especially in settings where preservation of residual renal function is important and when there are a limited number of very large cysts. However, complications are relatively common and pain relief was only achieved in approximately 60% of subjects. Nephrectomy is associated with major complications and obviously any residual renal function will be lost. Therefore, a nephrectomy should be considered as a last resort, and be reserved for especially patients receiving renal replacement therapy. Embolization of the renal artery, with the same disadvantage of losing kidney function, is a technique with variable technical success rate. When successful, promising results with respect pain relief can be obtained, while no major complications have been reported. Laparoscopic

fenestration, partial hepatectomy or liver transplantation can be performed in case of severe, untreatable chronic pain related to liver cysts. Partial hepatectomy is especially indicated in patients, in which the liver cysts are mainly presented in one liver segment. Because of the associated morbidity and mortality liver transplantation is only indicated in patients with extremely impaired quality of life.

Conclusions

Chronic pain in ADPKD is abdominal or loin pain in the kidney or liver region that exists for more than 4-6 weeks. It affects more than 60% of ADPKD patients, and can have serious negative impact on impact on physical and social functioning. Careful assessment by obtaining a detailed history and physical examination along with imaging techniques are necessary to identify the cause of pain, and interventions should be directed towards these causes. A stepwise approach for pain management according to a treatment algorithm as proposed in this review may be of help to achieve successful pain relief in ADPKD patients.

Conflict of interest
All authors stated not to have conflicts of interest.

DIPAK Consortium
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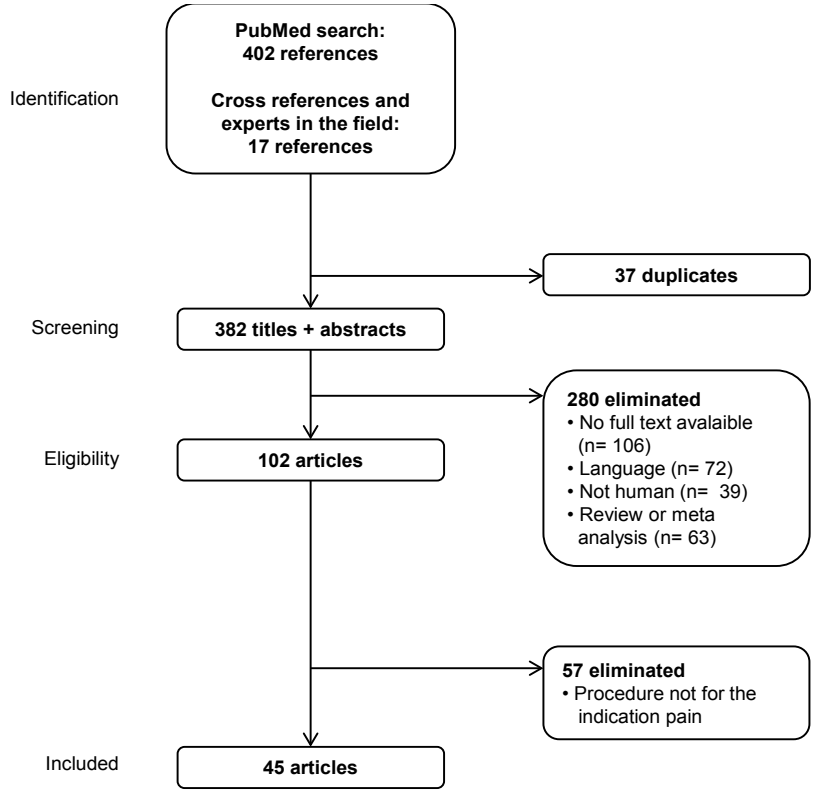

Web Appendix Figure 1: Flow chart representation of the literature search process.

Chapter 7

Results of a novel treatment protocol for invalidating chronic pain in patients with ADPKD

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Abstract

Background: ADPKD patients can suffer from chronic pain, that can be invalidating and may even lead to a wish for nephrectomy. This study aimed to evaluate the effect of a novel, multidisciplinary treatment protocol with sequential nerve blocks on pain relief in ADPKD patients with invalidating chronic pain.

Methods: Patients were eligible if pain was present ≥3 months with a VAS-score of ≥50 out of 100 and a large impact on daily activities and social life, and if they had insufficient response to previous therapy, including chronic opioid treatment. As first step a diagnostic, temporary celiac plexus block with a local anesthetic was performed. In case substantial pain relief was obtained, we assumed that pain was relayed via the celiac plexus and major splanchnic nerves (MSN). When pain recurred, patients were scheduled for an ipsilateral MSN block with radiofrequency ablation. In case no pain relief was obtained, it was assumed that pain was relayed via the aorticorenal plexus, and catheter-based renal denervation was performed.

Results: Sixty patients were referred, of which 44 patients were eligible. In 36 patients (81.8%) the diagnostic celiac plexus block resulted in substantial pain relief (change in VAS pre-post intervention 50/100 [26-68]; $p<0.001$). Of these patients, 23 (52.3%) received a MSN block because pain recurred, with a change in VAS pre-post MSN block of 53/100 [23-65]; $p<0.001$). Out of the 8 patients without pain relief after the diagnostic celiac plexus block, renal denervation was performed in 5 (11.4%), with a change in VAS pre-post intervention 20/100 [0-50]; $p=0.07$). After a follow-up of 12 [8-17] months, 81.8% of the 44 patients experienced a sustained improvement in pain intensity.

Conclusions: These data indicate that our treatment protocol consisting of sequential nerve blocks is effective in obtaining substantial pain relief in ADPKD patients with invalidating chronic pain.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disorder with a prevalence of 4.4 per 10.000 (1). In affected patients numerous cysts are formed in both kidneys and often also in the liver, leading to organ enlargement that can be massive. Renal function decline is the main clinical problem, leading to end-stage renal disease between the fourth and seventh decade of life in most patients (2). Chronic pain is another debilitating complication, with an estimated prevalence of 60%. In a number of cases it can be severe, and have a large impact on physical and social activity (3, 4). In case of pain caused by pressure of the enlarged organs on adjacent tissues or by distension of the hepatic capsule, pain stimuli are considered to be relayed via the celiac plexus and major splanchnic nerves, whereas in pain caused by distension of the renal capsule, the predominant pathway is via the aorticorenal plexus and minor and least splanchnic nerves (5) (Figure 1). Chronic pain can be difficult to manage, and may lead to a need for major analgesic therapy and surgical procedures, such as cyst aspiration, cyst fenestration or even nephrectomy (6, 7). In literature it has been suggested that nerve blocks can be used for pain management before such invasive therapies are explored (6-9). However, no study has been performed to investigate the effect of nerve blocks on pain relief in ADPKD patients.

We recently proposed a novel approach for treatment of invalidating chronic pain in ADPKD that applies sequential nerve blocks (8). When after a multidisciplinary assessment non-ADPKD related causes are ruled out, a diagnostic, temporary celiac plexus block with a local anesthetic agent is performed. In case substantial pain relief is obtained, it is assumed that pain was caused by pressure on adjacent tissues or distension of the hepatic capsule. Consequently, when pain recurs, a long-term block of the major splanchnic nerves by radiofrequency ablation is performed (RF-MSN block). When there is no response to the diagnostic celiac plexus block, pain stimuli are likely to be relayed via the alternative pathway, i.e. the aorticorenal plexus, in which case renal denervation is the preferred option. This intervention is executed via a catheter-based technique, originally developed as treatment for refractory hypertension, and has recently been suggested as an effective treatment of chronic pain in selected ADPKD patients (10, 11). Here we present the results of our multidisciplinary protocol consisting of sequential nerve blocks in ADPKD patients with invalidating chronic pain.

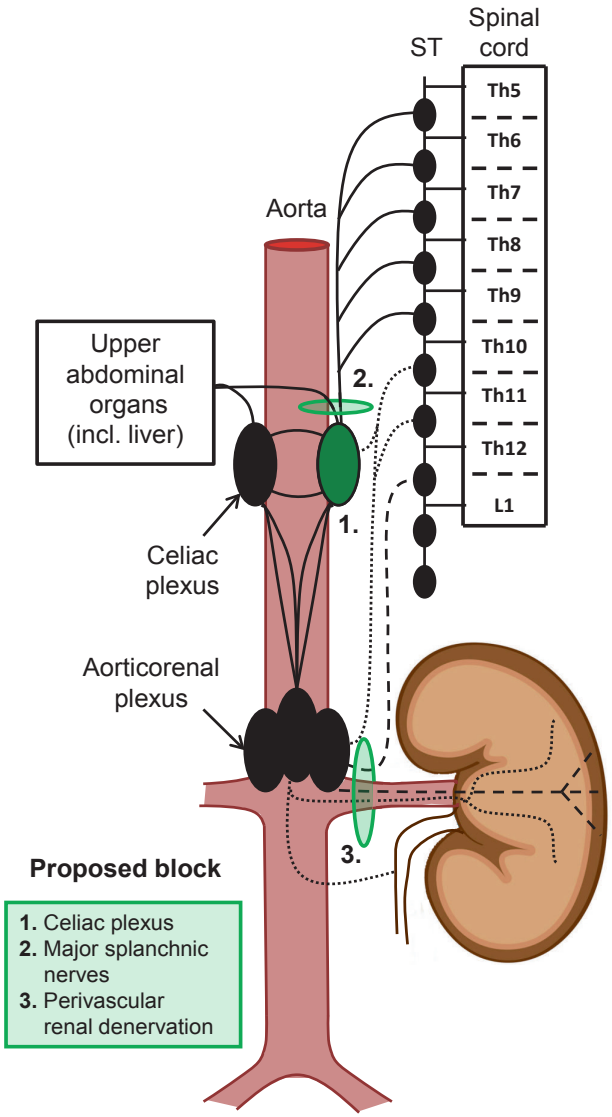

Figure 1. Schematic representation of the sensory nerve supply of the kidneys and upper abdominal organs. Solid line: major splanchnic nerve providing sensory innervation of the upper abdominal organs, including the liver via the celiac plexus. Dotted line: lesser splanchnic nerve providing sensory innervation of the renal parenchyma and ureter. Dashed line: least splanchnic nerve providing sensory innervation of the renal capsule. The perivascular nerve plexus around the renal artery forms the final common pathway to and from the kidney. ST; Sympathetic Trunk. Figure adapted from Bajwa (6).

Materials

Study population

ADPKD patients with invalidating chronic pain were screened for eligibility between August 2013 and May 2016 at our Expertise Center for Polycystic Kidney Diseases of the University Medical Center Groningen, the Netherlands. Patients were referred by their treating nephrologist or were self-referrals from all over the country. Patients were eligible if pain was present ≥3 months, had a severity on a visual analogue scale (VAS)-score of ≥50 out of 100, limited the patient in work, daily activities and social life, and if they had insufficient response to or contraindications for opioid treatment. Patients were excluded when after a multidisciplinary assessment pain was deemed not to be ADPKD-related or when invasive therapies (such as cyst aspiration or nephrectomy) were found to be a better option to achieve pain relief. The institutional research board concluded that this protocol was exempted from IRB approval, because it was considered to be protocolized introduction of novel clinical care (METc 2013.299).

Study assessments

All patients were screened by a nephrologist and a pain specialist. Before intake, all patients filled out a questionnaire to rate their pain intensity by a VAS-score (scale 0-100) and their quality of life by the short form-36 (SF-36). The SF-36 scores were aggregated into a physical component score (PCS) and mental component score (MCS) (12). PCS and MCS were scored from 0 to 100, with a higher score reflecting better quality of life. During an interview information was collected on demographics, medical history, medication use, pain and gastrointestinal symptoms. Renal pain was defined as pain or discomfort located in the flank, the lower back or abdomen. Liver pain was defined as pain or discomfort located in the right upper abdomen, behind or below the rib cage. Blood pressure was assessed during rest in supine position with an automatic device for 5 minutes, of which the last 3 values were averaged to obtain systolic and diastolic blood pressure values. After intake, blood and urine samples were collected for routine laboratory testing. Serum creatinine was used to estimate GFR (applying the CKD-EPI equation) (13). All patients underwent magnetic resonance imaging (MRI) with assessment by a radiologist to exclude other anatomic causes for pain, and for measurement of total kidney volume (TKV) and total liver volume (TLV). In addition, the location of the abdominal aorta and celiac plexus was identified, especially to check for potential displacement by the enlarged kidneys and liver. In case the nephrologist and pain specialist agreed that pain appeared to be related to the cystic disease, patients were planned for a diagnostic celiac plexus block. In case

of doubt, patients were discussed multidisciplinary by a nephrologist, pain specialist, radiologist, urologist, gastro-enterologist and when needed a transplant surgeon and gynecologist.

Study procedures

The diagnostic, temporary celiac plexus block was performed at the side the patient reported the highest level of pain. Prior to the nerve block an intravenous access was obtained and vital signs were monitored throughout the procedure. The patient was placed in a prone position with a pillow under the abdomen to reduce lumbar lordosis. After a time-out procedure, sterile preparation and drape, a 20 gauge 15 cm spinal type needle (Cosman) was advanced from posterior to anterior towards the ventral surface of the L1 vertebral body. Positioning took place under fluoroscopic guidance. After the needle position was confirmed by injection of contrast medium (to be spread direct anteriorly from the L1 vertebral body in lateral fluoroscopic view; and in anterior posterior (AP) view within the bilateral vertebral body borders), 10 mL of bupivacaine (0.5 %) was injected (Figure 2). Patients were observed closely for 2-4 hours post-procedure, including vital signs monitoring.

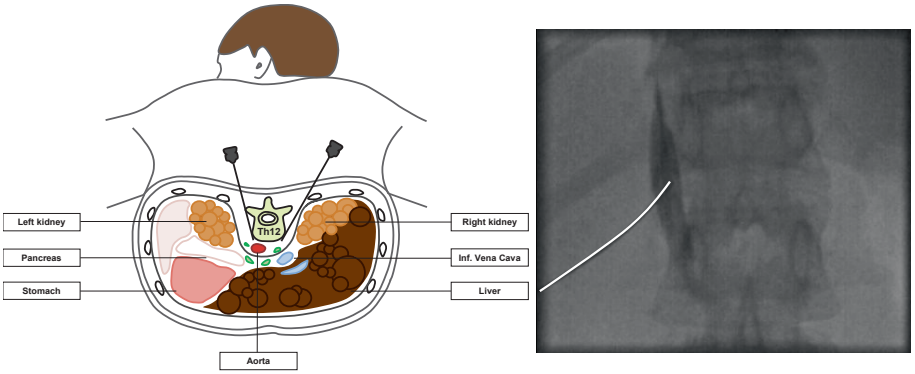

Figure 2. Left panel: Schematic drawing of a diagnostic celiac plexus block. Right Panel: Antero-posterior radiograph showing an example of a diagnostic celiac plexus block near the vertebral column. The solid white line represents the needle.

In case substantial pain relief was observed (i.e. reaching a VAS score ≤30/100), patients were scheduled for a long-term RF-MSN block, when pain recurred with a severity of >50/100. For this procedure, patients were similarly placed in a prone position, with an intravenous access and monitoring of vital signs. After a time-out procedure, sterile preparation and drape, a 20 gauge, 15 cm spinal type needle (Cosman RF) was advanced from posterior to anterior towards the ventral 1/3 surface

of the vertebral body of Th11. Positioning took place under fluoroscopic guidance and was deemed correct when there was bone contact. After the correct needle position was confirmed by injection of contrast medium by direct anterior spread to the Th11 vertebral body in lateral and AP view), 3 applications of radiofrequency energy at 80 degrees Celsius were executed with 3 mm interspatial space between every application in posterior direction, starting on the first most anterior needle tip position. Patients were observed closely for 2-4 hours post-procedure, including vital signs monitoring.

In case no substantial pain relief was observed after the diagnostic celiac plexus block, patients were referred to the University Medical Center Utrecht for catheter-based renal denervation. Renal denervation of afferent sensory nerves was performed using the Simplicity Catheter System, a 6 Fr compatible, single-use RF-probe. Before introduction of the RF–probe, a renal angiogram was performed to exclude contra-indications for the procedure, such as renovascular abnormalities (including renal artery stenosis), and previous renal stent or angioplasty. Subsequently, the system was introduced in the renal artery located at the side of pain and the catheter electrode was positioned in contact with the vessel wall. The catheter was placed at the most distal location possible, since in the distal segment the sensory nerves travel closer to the arterial lumen compared with the proximal and middle segments (Figure 3) (14). The catheter was connected to an automatic RF-generator, and applications of RF energy in a spiral pattern along the renal artery, from distal to proximal and with 5 mm interspaces, were performed. Patients were observed closely for 24 hours post-procedure, including vital signs monitoring.

Two to four weeks after all interventions, VAS-score, defined daily dose (DDD) of analgesic use, quality of life with the Short Form-36 (SF-36), renal function and blood pressure were monitored. Adverse events occurring during the treatment protocol were recorded.

Statistical analyses

Normally distributed variables are expressed as mean ± SD, whereas non-normally distributed variables are given as median [IQR]. Differences in baseline characteristics between eligible and ineligible patients were calculated with a Chi-square test for categorical data, and for continuous data with Student's t-test or a Mann-Whitney U test in case of non-normally distributed data. A paired Student's t-test or Wilcoxon Signed Rank Test for non-normally distributed data was used to compare VAS-score, PCS score, MCS score, blood pressure, DDD analgesics, DDD blood pressure lowering drugs and eGFR before and after intervention. Statistical analyses were performed using SPSS 22 (SPSS Statistics, Inc., Chicago, IL, U.S.A.). A two-tailed p-value <0.05 was considered to indicate statistical significance.

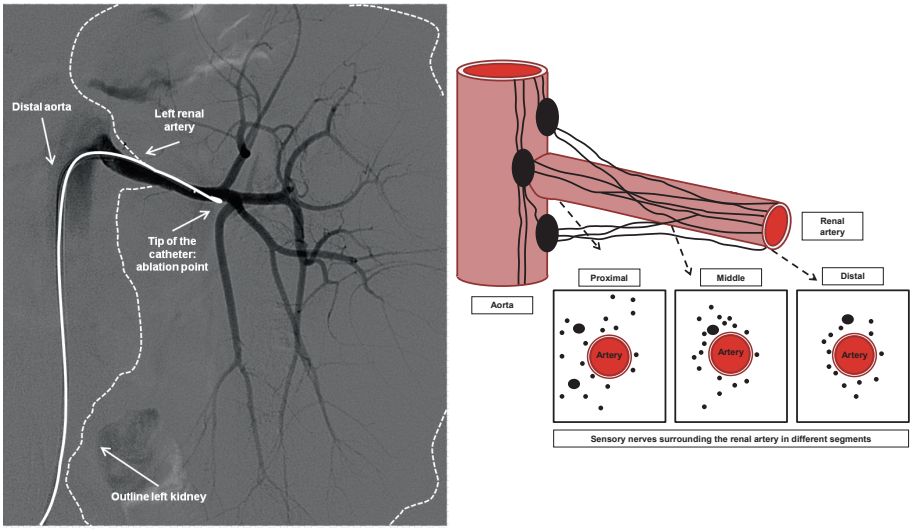

Figure 3. Left panel: Angiography during the renal denervation procedure. The solid white line represents the Simplicity Catheter System. The catheter electrode is positioned at the most distal location possible in the renal artery. The dashed line represents the outer border of the polycystic kidney. Right panel: Schematic drawing of the peri-arterial renal sensory nerves location. In the distal segment, the sensory nerves travel closer to the arterial lumen when compared to the situation in the proximal and middle segments (Adapted from Sakakura (14)).

Results

Patient characteristics

A total of 60 patients visited our Expertise Center for analysis and treatment of invalidating chronic ADPKD-related pain. After assessment of in- and exclusion criteria 44 patients were deemed to be eligible to participate in our treatment protocol (Figure 4). Sixteen patients were ineligible because another treatment option was chosen (such as nephrectomy in patients on renal replacement therapy (RRT) or cyst aspiration in case of a limited number of very large cysts), pain was likely non-ADPKD related, pain could be treated with additional medication, or because patients rejected the treatment protocol. Characteristics of these ineligible patients are given in Suppl. Table 1 and Suppl. Table 2. Mean age of the included patients was 50±9 years and 77.3% were female (Table 1). Three patients were RRT-dependent, and in the non-RRT dependent patients (N=41) mean eGFR was 57±25 mL/min/1.73m^2. Pain was present for a median period of 7 [4-18] years and was experienced as invalidating for 12 [10-24] months. Nearly all patients (95.5%) used daily opioids, except one who had a contra-indication against opioid use, and 18 (40.9%) had previously been treated by invasive therapies,

such as cyst aspiration (N=8), cyst fenestration (N=5) or contralateral nephrectomy (N=5). Pain had an impact on patient's work, daily activities and social life, as indicated by low PCS and MCS scores (34±17 and 50±21 respectively). No associations of TKV, TLV or combined kidney and liver volume (TKLV) with VAS-score were found (p=0.6, p=0.3 and p=0.5 respectively).

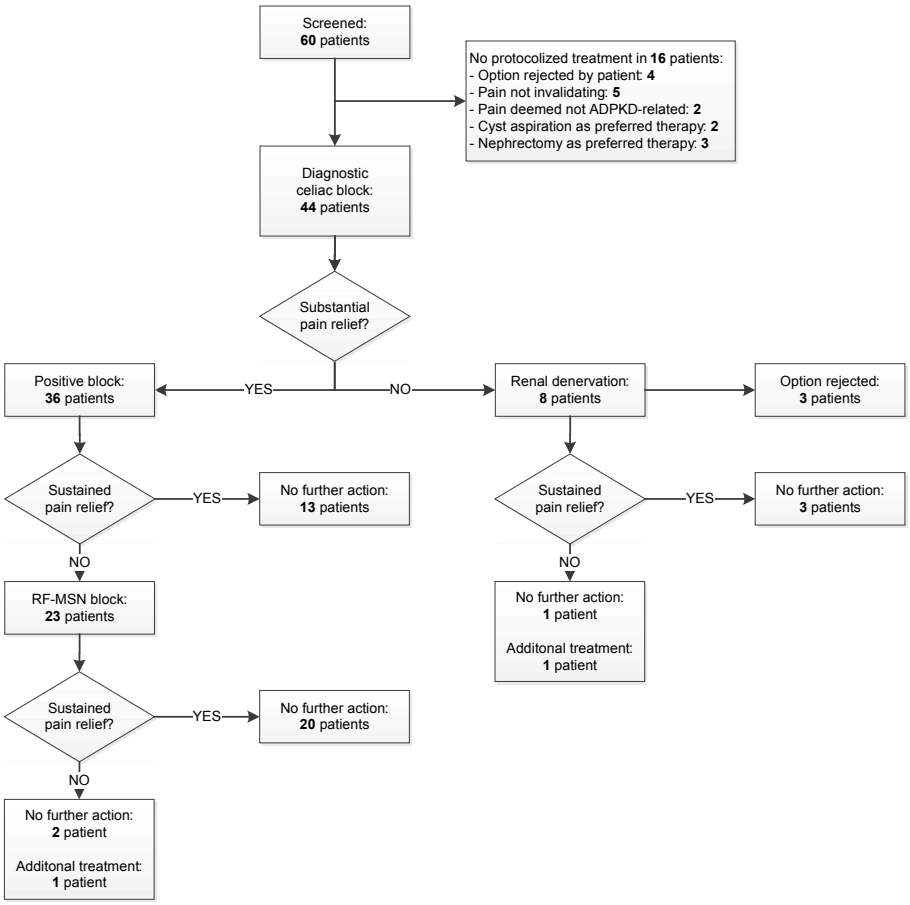

Figure 4. Flowchart of patients screened for treatment according to the multidisciplinary protocol for invalidating chronic pain in ADPKD.

Table 1. Patient characteristics (N=44)

Age (yrs)	50±9
Female sex (%)	77.3
Height (cm)	173±8
Weight (kg)	80±16
Body mass index (kg/m^2)	27±4
History of	
- Urinary tract infection (%)	65.9
- Renal cyst infection (%)	22.7
- Liver cyst infection (%)	6.8
- Bouts of macroscopic hematuria (%)	59.1
- Renal stones (%)	13.6
- Renal surgery (%)	18.2
- Liver surgery (%)	6.8
- Liver cysts (%)	95.3
Systolic blood pressure (mmHg)	132±12
Diastolic blood pressure (mmHg)	84±8
Use of blood pressure lowering drugs (%)	75.0
Non-RRT dependent (%)	93.2
- eGFR (mL/min/1.73m^2)	57±25
Renal transplantation (%)	6.8
- eGFR (mL/min/1.73m^2)	52±14
Short Form-36 Score	
- Physical Component Score (0-100)	34±17
- Mental Component Score (0-100)	50±21
Organ volumes	
- Left kidney (mL)	874 [548-1309]
- Right kidney (mL)	854 [545-1326]
- Total kidney (mL)	1664 [932-2609]
- Liver (mL)	2612 [1944-3327]
- Total kidney and liver (mL)	4446 [3427-5695]

Abbreviations are: RRT, renal replacement therapy; eGFR, estimated glomerular filtration rate.

Table 2. Pain characteristics (N=44)

Duration of	
- Pain (yrs)	7 [4-18]
- Invalidating pain (months)	12 [10-24]
Pain severity last 4 weeks	
- Minimum VAS-score (0-100)	40 [21-60]
- Maximum VAS-score (0-100)	88 [80-90]
- Average VAS-score (0-100)	70 [55-80]
Patient reported location as	
- Left kidney (%)	65.9
- Ventral side	*27.6*
- Dorsal side	*72.4*
- Right kidney (%)	52.2
- Ventral side	*39.1*
- Dorsal side	*60.9*
- Liver (%)	27.2
- Ventral side	*66.7*
- Dorsal side	*33.3*
Management of pain	
- Non-pharmacological therapies (%)	65.9
- Acetominophen (%)	74.4
- NSAID (%)	2.3
- Sleep medication (%)	13.6
- Low dose opioids (%)	45.5
- High dose opioids (%)	50.0
- Previous invasive pain therapies (%)	40.9

Abbreviations are: VAS score, visual analogue scale score; NSAIDs, non-steriodal anti inflammatory drugs.

Sequential blocks

In all 44 patients an ipsilateral, diagnostic, temporary celiac plexus block with 10 mL of bupivacaine 0.5% was performed. In 36 (81.8%) substantial pain relief was obtained (median change in VAS pre-post intervention 50/100 [26-68]; p<0.001) (Figure 4 and Table 3). In 13 (36.1%) patients pain did not recur (i.e. remained below 50/100) after the initial celiac plexus block and no further action was taken (median change in VAS pre-post intervention 60/100 [35-70]; p<0.002) (Table 3). Twelve of these 13 patients were not dependent of daily use opioids anymore and only 5 used daily acetaminophen.

Table 3. Overall results and results of the diagnostic celiac plexus block, RF-MSN block and renal denervation separately. In all patients a diagnostic celiac plexus block was performed (N=44). No further action was taken when pain relief was obtained (N=13). In case pain recurred after the celiac plexus block, a RF-MSN block was performed (N=23). In case no pain relief after the diagnostic celiac plexus block was obtained, renal denervation was performed (N=8). Two to four weeks after the interventions pain score, quality of life, blood pressure and renal function were monitored.

	Intervention		
	Pre	Post	P-value
Overall (N=44)			
Substantial pain relief (%)	X	36 (81.8)	
VAS score (0-100)	70 [55-80]	18 [0-30]	<0.001
Defined Daily Dose non-opioids	0.9±0.6	0.5±0.6	0.003
Defined Daily Dose opioids	0.3±0.4	0.1±0.2	0.06
Physical Component Score (0-100)	34±17	44±19	0.001
Mental Component Score (0-100)	50±21	55±23	0.04
SBP (mmHg)	132±12	128±12	0.1
DBP (mmHg)	84±8	81±8	0.01
Defined Daily Dose BPLD	1.8±0.3	1.8±0.3	0.3
eGFR (mL/min/1.73m^2)	56±24	52±24	0.3
Follow-up (months)	X	12 [8-17]	
Diagnostic celiac plexus block (N=13)			
Substantial pain relief (%)	X	13 (100.0)	
VAS score (0-100)	70 [50-80]	10 [0-28]	0.002
Defined Daily Dose non-opioids	0.9±0.6	0.3±0.6	0.1
Defined Daily Dose opioids	0.3±0.4	0.02±0.01	0.03
Physical Component Score (0-100)	37±20	44±20	0.6
Mental Component Score (0-100)	51±22	59±22	0.3
SBP (mmHg)	131±10	132±17	0.3
DBP (mmHg)	80±8	79±8	0.3
Defined Daily Dose BPLD	1.2±0.5	1.2±0.5	1.0
eGFR (mL/min/1.73m^2)	58±31	53±33	0.3
Follow-up (months)	X	11 [6-15]	
RF-MSN block (N=23)			
Substantial pain relief (%)	X	20 (86.9)	
VAS score (0-100)	70 [60-80]	13 [0-28]	<0.001
Defined Daily Dose non-opioids	0.8±0.7	0.5±0.6	0.02
Defined Daily Dose opioids	0.3±0.4	0.1±0.2	0.1
Physical Component Score (0-100)	33±16	45±20	0.001
Mental Component Score (0-100)	48±21	54±22	0.07
SBP (mmHg)	132±15	127±10	0.2
DBP (mmHg)	81±9	81±9	0.1
Defined Daily Dose BPLD	1.7±0.9	1.7±0.9	1.0
eGFR (mL/min/1.73m^2)	60±20	55±19	0.6
Follow-up (months)	X	11 [7-14]	

Catheter-based renal denervation (N=5)			
Substantial pain relief (%)	X	3 (60.0)	
VAS score (0-100)	60 [50-75]	20 [0-20]	0.07
Defined Daily Dose non-opioids	0.8±0.6	0.5±0.6	0.4
Defined Daily Dose opioids	0.4±0.7	0.2±0.3	0.7
Physical Component Score (0-100)	43±18	44±11	0.8
Mental Component Score (0-100)	53±30	63±33	0.1
SBP (mmHg)	134±6	126±9	0.01
DBP (mmHg)	86±6	83±9	0.2
Defined Daily Dose BPLD	2.1±0.9	2.0±0.9	0.3
eGFR (mL/min/1.73m^2)	40±27	39±28	0.3
Follow-up (months)	X	15 [12-19]	

Abbreviations are: N, numbers; RF-MSN block, radiofrequency ablation block of major splanchnic nerves; VAS score, visual analogue scale score; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPLD, blood pressure lowering drug; eGFR, estimated glomerular filtration rate.

In the remaining 23 (63.9%) patients, pain recurred after a median follow-up of 6 [3-11] weeks, for which reason the patients were scheduled for a long-term RF-MSN block. In 2 patients the ipsilateral RF-MSN block was performed twice, because initial success was moderate, which ultimately resulted in substantial pain relief in both patients. A bilateral RF-MSN block was performed in 5 (13.9%) patients, because they experienced left- as well as right-sided pain. Ultimately, the median change in VAS pre-post RF-MSN was 53/100 [23-65], measured at 2-4 weeks after the final procedure ($p<0.001$). In 20 of the 23 patients (87.0%), a substantial and sustained improvement in pain intensity was observed, leading to cessation of daily opioid use in 16 patients (69.6%) and a decrease in dosage in 4 (17.4%) (Table 3). In the 3 patients without pain relief after the RF-MSN block, additional treatment was given in one. A diagnostic, temporary sympathetic block with local anesthetics was applied at the level of L2 with success, but the subsequent long-term RF-block resulted in a decrease in pain of only 20%.

The 8 (18.2%) patients without a response to the initial celiac plexus block were scheduled for catheter-based renal denervation. This procedure was performed in 5, because 3 patients rejected this option. The median change in VAS pre-post renal denervation was 20/100 [0-50], measured at 2-4 weeks after the procedure ($p=0.07$). In 3 patients a sustained improvement in pain intensity was observed, leading to cessation of daily opioid use. In the remaining 2 patients no pain relief was noticed. Additional treatment (i.e. diagnostic sympathetic block with local anesthetics at the level of L2) was given in one of these two patients with success, but the subsequent long-term RF block did not lead to a decrease in pain.

In the overall group of included patients we observed an increase in quality of life (change in PCS +7 [0-20]; p=0.001, change in MCS +5 [-1-13]; p=0.04). Of note, not in all subgroups a formal statistical significant effect was reached on these quality of life measures, likely due to the small number of patients in some subgroups (e.g. the renal denervation group, Table 3). Characteristics of patients in the various aforementioned subgroups are presented in Supplementary Table 3.

Follow-up

After a follow-up of 12 [8-17] months, 81.8% of the 44 patients that underwent one or more nerve blocks experienced a sustained improvement in pain intensity (median change in VAS pre-post intervention 53 [35-70], p<0.001). Daily opioid use was stopped in 63.6% of the patients. A considerable number of cases continued to have intermittent abdominal discomfort (VAS-score 20 [20-30]), which in general could be managed adequately with on-demand acetaminophen (54.5%). These results were similar in patients with a follow-up longer than 18 months (n=9), with 77.8% reporting a sustained improvement in pain (median change in VAS pre-post intervention 55 [38-73], p<0.001) and only 2 of 9 patients still using daily opioids, but in a lower dose.

Effect on blood pressure and renal function

In patients, who underwent a celiac plexus and/or RF-MSN block, a decrease in blood pressure was observed (median change in systolic blood pressure: -5 [-9 - +2] mmHg, p=0.1; and median change in diastolic blood pressure: -4 [-0 - 0] mmHg, p=0.01) (Table 3). None of these patients had a change in type or dosage of blood pressure lowering drugs. In the renal denervation group, a similar effect on the blood pressure was seen (median change in systolic blood pressure: 0 [-17 - +3] mmHg, p=0.1; median change in diastolic blood pressure: -3 [-7 - 0] mmHg, p=0.01 respectively), but this effect was obtained while in 80.0% patients the dosage of antihypertensive treatment was reduced. The procedures had not influence kidney function (eGFR pre-intervention; 56±24 mL/min/1.73m^2; post-intervention; 52±24 mL/min/1.73m^2, p=0.3).

Adverse events

Two patients experienced orthostatic hypotension immediately after the diagnostic celiac plexus block, which was self-limiting within 4 hours. Another patient reported diarrhea after this intervention, which stopped within 3 days without the need for additional treatment. In one patient blood was aspirated during the diagnostic celiac plexus block procedure, resulting that the procedure was interrupted and repeated after 4 weeks with success. In 3 patients the RF-MSN block was extremely painful,

and the procedure was shortly interrupted, but could be successfully finished. No direct post-intervention complications occurred after the RF-MSN block. One patient developed 2 months after the intervention dyspnea with fever and was admitted to the hospital for one day and diagnosed with hyperventilation. No antibiotic treatment was given. Another patient reported an episode of a cerebrovascular transient ischemic attack 4 weeks after the RF-MSN block, and was hospitalized for 2 days. Both incidents were judged to be not related to the RF-MSN procedure. Renal denervation was technically successful in 4 out 5 patients. In the fifth case spasms in the left renal artery occurred when the catheter was introduced. The procedure was interrupted and successfully repeated after 3 months. No direct or late post-intervention complications occurred after the renal nerve ablation procedure.

Discussion

These data show that our treatment protocol, that applies sequential nerve blocks, results in substantial pain relief in ADPKD patients with invalidating chronic pain. After a follow-up of 12 months, the majority of eligible patients experienced a sustained improvement in pain intensity. Furthermore we observed an increase in quality of life. No procedure related serious adverse events or decrease in eGFR were noticed.

At present, no study has been performed to systematically investigate the effect of nerve blocks on pain in ADPKD patients. Several studies analyzed the effect of cyst aspiration, sclerotherapy and fenestration as treatment options for chronic pain in ADPKD patients when (non)-pharmacological options fail (15-18). The success rates of these interventions were highly variable, i.e. between 20% and 80%. Given the uncertain success rate and risk for complications, such as infection, these treatment options are not widely performed. Other more invasive treatment options include surgical nephrectomy or transcutaneous arterial embolization. According to literature these options can result in adequate pain relief, but both lead inherently to a decrease in renal function (6, 7, 9, 19). Since renal function decline, with ultimately need for renal replacement therapy, is the main clinical problem in ADPKD, there is a need for kidney function sparing techniques. The present data provide evidence that sequential nerve blocks should be considered and tried before more invasive therapies are explored.

Celiac plexus and RF-MSN blocks have proven to be effective in treatment of invalidating chronic abdominal pain related to for instance chronic pancreatitis and pancreatic, gastric and intestinal cancer (20-22). Renal denervation is now mainly applied in patients with therapy resistant hypertension and heart failure (23), but may also be

effective for treatment of chronic pain syndromes. Two older studies described renal denervation for ADPKD-related pain by thoracoscopic and laparoscopic procedures (24, 25). In a recent case report we were the first to describe that also catheter-based renal denervation can be successful to treat pain in patients with ADPKD (10, 26), which is a far less invasive procedure. The present study adds evidence in a relatively large series of patients that this procedure is simple, safe and effective. Catheter-based renal denervation should, however, only be performed in selected patients, because our data indicate that just in a minority of patients chronic pain stimuli are relayed via the aorticorenal plexus. The protocol used in this study may help to select ADPKD patients for catheter-based renal denervation.

It should be noted that we did not perform sequential nerve blocks in all patients that were referred. When pain was not invalidating or not ADPKD-related, we first optimized analgesic use and treated the other causes. In case patients were RRT-dependent, we preferably performed nephrectomy, and in case patients had a limited number of extremely enlarged cysts, cyst aspiration or cyst fenestration was the first-line treatment. These procedures (nephrectomy (N=3)) and cyst aspiration (N=2) led to adequate and sustained pain relief in 4 of the 5 patients in which they were applied.

In a number of cases with a positive response to the diagnostic temporary celiac plexus block, this intervention resulted in a sustained pain relief, even up to 2.5 years. This is surprising, because local anesthetics are only able to interrupt a sensory pathway to a maximum of 24 hours. A possible explanation for this unexpected finding may be an effect on central sensitization caused by longstanding nociceptive stimulation in the past, e.g. from a cyst infection or cyst bleeding. As part of this sensitization process, activation thresholds of sensory neurons decrease and their excitability increases (7, 20). Consequently, minor stimuli will lead to a pain response that normally would not occur. We hypothesize that by applying local anesthetics the continuous excitation of visceral nociceptive neurons is temporarily interrupted, by which the neurons may return to their normal resting potential (20).

In some patients no pain relief was obtained or pain recurred. In two patients the diagnostic celiac plexus block and subsequent renal denervation were both unsuccessful. This may imply that nociceptive stimuli followed a pathway different from the ones that were blocked. It has been suggested that small sensory nerve connections, which do not travel via the renal artery, can exist between the renal plexus and the renal capsule (5). These sensory nerve fibers will not be blocked by catheter-based renal denervation. Another explanation may be that, as technical failure, not all targeted sensory pathways were blocked. For instance, the spiraling ablation technique for renal denervation may not have completely blocked the aorticorenal

pathway. In three patients, pain recurred after a positive diagnostic celiac plexus block and subsequent positive ipsilateral RF-MSN block. In two out of three pain recurred after an acute painful event (cyst bleeding and infection), which suggests that the RF-MSN block may have been incomplete and that remaining sensory nerve fibers relayed the new nociceptive stimuli to the spinal cord.

When considering sequential nerve blocks for treatment of chronic ADPKD-related pain in clinical care, the expected benefits should of course outweigh potential disadvantages. Severe adverse events related to the procedures were not observed, but these interventions could have late negative clinical consequences. A RF-MSN block interrupts the upper abdominal sensory nerve supply that leads to a limited or altered nociceptive sensory function in the upper abdomen. Clinicians and patients should be aware that abdominal diseases may therefore present with a different symptomatology, i.e. an altered pain sensation, which may lead to undesired doctor and patient delay. Of note, we performed this treatment protocol only in patients with ADPKD. However, other patients with chronic, invalidating kidney pain related to a non-malignant and non-infectious cause, such as loin pain hematuria syndrome or symptomatic para-pelvic cysts, may also benefit from our novel approach (10, 26).

This study has limitations, of which the most important is the non-randomized single center design. We chose to perform this study in such setting, because we considered it unethical to perform sham procedures in patients with invalidating chronic pain in line with literature on placebo anesthetic blocks (27). Since not all medical centers have expertise with sequential nerve blocks and treatment of chronic pain in ADPKD patients, and the prevalence of such patients is relatively low, treatment was performed in one center. The main strength of our study is the systematic and prospective nature of data collection, including information on quality of life, that resulted in a well-characterized population.

In conclusion, the present study indicates that our novel multidisciplinary treatment protocol, that applies sequential nerve blocks, is effective in obtaining substantial and sustained pain relief in ADPKD patients with chronic invalidating pain. Patients should be carefully selected for eligibility, and other treatment options should be considered for ineligible patients. We advise therefore that sequential nerve blocks are only be performed in this patient group in a protocolized setting in centers with expertise in treatment of ADPKD-related pain. No serious procedure related adverse events were noted. However, it should be kept in mind that altered pain sensation may lead to a different symptomatology of later abdominal disease.

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DIPAK Consortium

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Contributions

Research area and study design: NFC, PJB, GJG, RTG; data acquisition: NFC, MDAG, PJB, JPHD, RLJ, AML, RS, APW, GJG, RTG; data analysis/interpretation: NFC, MDAG, APW, GJG, RTG; statistical analysis: NFC, MDAG, RTG; supervision or mentorship: PJB, JPHD, AML, GJG, RTG. Each author contributed important intellectual content during manuscript drafting and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. RTG takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Declaration of interest

All authors stated not to have conflicts of interest.

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Supplementary Table 1. Patient characteristics stratified according to eligibility for the multidisciplinary treatment protocol consisting of sequential nerve blocks (N=60).

	Eligible (N=44)	Ineligible (N=16)	P-value
Age (yrs)	50±9	51±11	0.9
Female sex (%)	77.3	56.3	0.1
Height (cm)	173±8	175±12	0.5
Weight (kg)	80±16	81±20	0.8
Body mass index (kg/m^2)	27±4	26±5	0.7
History of			
- Urinary tract infection (%)	65.9	56.3	0.5
- Renal cyst infection (%)	22.7	37.5	0.3
- Liver cyst infection (%)	6.8	6.3	0.9
- Bouts of macroscopic hematuria (%)	59.1	81.3	0.3
- Renal stones (%)	13.6	12.5	0.4
- Renal surgery (%)	18.2	35.7	0.2
- Liver surgery (%)	6.8	7.1	1.0
- Liver cysts (%)	95.3	100.0	0.1
Systolic blood pressure (mmHg)	132±12	134±19	0.7
Diastolic blood pressure (mmHg)	84±8	83±10	0.6
Use of blood pressure lowering drugs (%)	75.0	85.7	0.4
Non-RRT dependent (%)	93.2	37.5	<0.001
- eGFR (mL/min/1.73m^2)	57±25	59±29	0.8
Renal transplantation (%)	6.8	31.2	0.1
- eGFR (mL/min/1.73m^2)	52±14	32±10	0.1
Dialysis dependent	0	31.2	0.1
- residual renal function (mL/min/1.73m^2)	-	4±2	-
Short Form-36 Score			
- Physical Component Score (0-100)	34±17	41±26	0.3
- Mental Component Score (0-100)	50±21	52±23	0.7
Organ volumes			
- Left kidney (mL)	874 [548-1309]	2241 [984-2947]	0.002
- Right kidney (mL)	854 [545-1326]	2163 [879-3010]	0.001
- Total kidney (mL)	1664 [932-2609]	3270 [1605-5821]	0.004
- Liver (mL)	2612 [1944-3327]	2364 [1990-3585]	0.9
- Total kidney and liver (mL)	4446 [3427-5695]	5888 [4404-8261]	0.02

Abbreviations are: RRT, renal replacement therapy; eGFR, estimated glomerular filtration rate.

Supplementary Table 2. Pain characteristics stratified for eligibility in our treatment protocol (N=60).

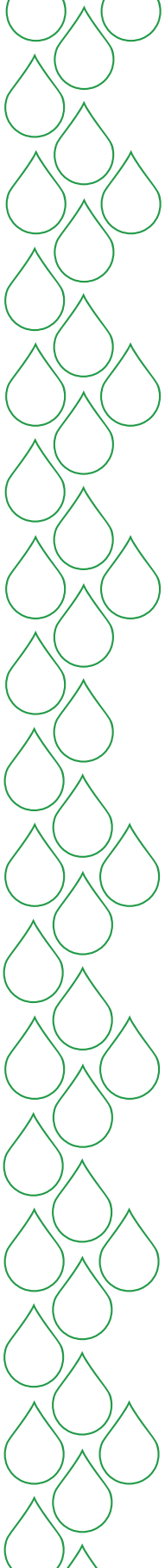
	Eligible (N=44)	Ineligible (N=16)	P-value
Duration of			
- Pain (yrs)	7 [4-18]	6 [2-20]	0.6
- Invalidating pain (months)	12 [10-24]	18 [10-38]	1.0
Pain severity last 4 weeks			
- Minimum VAS-score (0-100)	40 [21-60]	18 [0-40]	0.02
- Maximum VAS-score (0-100)	88 [80-90]	80 [55-96]	0.5
- Average VAS-score (0-100)	70 [55-80]	50 [31-69]	0.02
Patient reported location as			
- Left kidney (%)	65.9	75.0	0.5
- *Ventral side*	*27.6*	*37.5*	0.2
- *Dorsal side*	*72.4*	*62.5*	0.2
- Right kidney (%)	52.2	68.8	0.3
- *Ventral side*	*39.1*	*22.2*	0.6
- *Dorsal side*	*60.9*	*77.8*	0.6
- Liver (%)	27.2	18.8	0.5
- *Ventral side*	*66.7*	*33.3*	0.3
- *Dorsal side*	*33.3*	*66.7*	0.3
Management of pain			
- Non-pharmacological therapies (%)	65.9	42.9	0.1
- Acetominophen (%)	74.4	71.4	0.8
- NSAID (%)	2.3	7.1	0.4
- Sleep medication (%)	13.6	25.0	0.2
- Low dose opioids (%)	45.5	42.9	0.7
- High dose opioids (%)	50.0	28.6	0.3
- Previous invasive pain therapies (%)	40.9	37.5	0.9

Abbreviations are: VAS score, visual analogue scale score; NSAIDs, non-steriodal anti inflammatory drugs.

Supplementary Table 3. Characteristics of patients stratified according to achieved pain relief after the final treatment they received.

	Pain relief after celiac plexus block		Pain relief after renal denervation	No pain relief after all treatments
	No need for Long-term block	Need for Long-term block		
N	13	20	3	8
Age (yrs)	49±5	53±10	40±5	47±7
Female sex, %	84.6	70.0	66.7	87.5
Height (cm)	174±6	173±10	171±10	173±7
Weight (kg)	79±11	83±16	81±10	76±23
Body mass index (kg/m^2)	26±3	28±4	28±2	25±5
History of				
- Urinary tract infection, %	84.6	45.0	66.7	87.5
- Renal cyst infection, %	7.7	35.0	0.0	25.0
- Liver cyst infection, %	0.0	5.0	0.0	25.0
- Bouts of macroscopic hematuria, %	46.2	60.0	66.7	75.0
- Renal stones, %	0.0	15.0	33.3	25.0
- Renal surgery, %	0.0	30.0	0.0	25.0
- Liver surgery, %	15.4	5.0	0.0	v
- Liver cysts, %	100.0	90.0	100.0	100.0
Systolic blood pressure (mmHg)	131±10	131±15	135±8	135±7
Diastolic blood pressure (mmHg)	80±7	87±9	87±8	83±7
Use of blood pressure lowering drugs, %	61.5	85.0	100.0	62.5
Non-RRT dependent, %	92.3	100.0	100.0	75.0
- eGFR (mL/min/1.73m^2)	59±32	59±32	35±15	52±15
Renal transplantation, %	7.7	0.0	0.0	25.0
- eGFR (mL/min/1.73m^2)	44	-	-	57±13
Organ volumes				
- Left kidney (mL)	860 [641-1264]	968 [569-1301]	1301 [1130-1403]	540 [453-1184]
- Right kidney (mL)	854 [545-1383]	718 [507-1428]	1081 [1019-1189]	793 [373-1192]
- Total kidney (mL)	1701 [1193-2424]	1699 [1089-2718]	2382 [2149-2594]	896 [645-1283]
- Liver (mL)	2735 [1635-3333]	2575 [1946-3806]	2004 [2098-2206]	2599 [1756-3305]
- Total kidney and liver (mL)	4489 [3758-5060]	4334 [3437-6286]	4480 [4342-4800]	3644 [2522-5790]

Abbreviations are: RRT, renal replacement therapy; eGFR, estimated glomerular filtration rate.



II

Polyuria in ADPKD

Chapter 8

Urine concentrating capacity, vasopressin and copeptin in ADPKD and IgA nephropathy patients with renal impairment

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Submitted

Abstract

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) patients have an impaired urine concentrating capacity. Increased circulating vasopressin (AVP) concentrations are supposed to play a role in the progression of ADPKD. We hypothesized that ADPKD patients have a more severely impaired urine concentrating capacity in comparison to other patients with chronic kidney disease at a similar level of kidney function, with consequently an enhanced AVP response to water deprivation with higher circulating AVP concentrations.

Methods: 15 ADPKD (eGFR<60) patients and 15 age-, sex- and eGFR-matched controls with IgA nephropathy (IgAN), underwent a water deprivation test to determine maximal urine concentrating capacity. Plasma and urine osmolality, urine aquaporin-2 (AQP2) and plasma AVP and copeptin (a surrogate marker for AVP) were measured at baseline and after water deprivation (average 16 hours). In ADPKD patients, height adjusted total kidney volume (hTKV) was measured by MRI.

Results: Maximal achieved urine concentration was lower in ADPKD compared to IgAN controls (533±138 vs. 642±148 mOsm/kg, p=0.046), with particularly a lower maximal achieved urine urea concentration (223±74 vs. 299±72 mmol/L, p=0.008). After water deprivation, plasma osmolality was similar in both groups although change in plasma osmolality was more profound in ADPKD due to a lower baseline plasma osmolality in comparison to IgAN controls. Copeptin and AVP increased significantly in a similar way in both groups. AVP, copeptin and urine AQP2 were inversely associated with maximal urine concentrating in both groups.

Conclusions: ADPKD patients have a more severely impaired maximal urine concentrating capacity in comparison to IgAN controls with similar endogenous copeptin and AVP responses. This impairment consists of a nephrogenic component with lower urine urea concentrations and possibly a central component with inadequate AVP secretion.

Introduction

One of the first clinical features in autosomal dominant polycystic kidney disease (ADPKD), is an impaired urine concentrating capacity that occurs prior to kidney function decline (1-3). The mechanism leading to decreased urine concentrating capacity is not fully understood. Probably abnormalities in the renal medullary architecture, due to cyst formation and expansion, play an important role. In a previous study, we found that already in the early stages of disease there is an impaired maximal urine concentrating capacity, which is accompanied by increased plasma osmolality and vasopressin (AVP) levels during water deprivation, in comparison to healthy controls (4).

AVP is secreted from the pituitary gland when plasma osmolality increases. AVP subsequently binds to the vasopressin V2 receptor of the collecting ducts which stimulates water reabsorption by migration of aquaporin-2 (AQP2) to the apical cell membrane. Besides being important for water hemostasis, AVP has deleterious effects in ADPKD. AVP has been shown to increase intracellular cAMP, which promotes cell proliferation and cyst formation (5). Indeed, animal models and a large randomized controlled trial in ADPKD patients showed that blocking the vasopressin V2 receptor reduces the rate of cyst growth and renal function loss (6-9).

In the present study, we hypothesized that in advanced stages of ADPKD, the increase in AVP in response to water deprivation is stronger than might be expected from impaired kidney function per se (10, 11). To study urine concentrating capacity and AVP response in ADPKD, we performed water deprivation tests in ADPKD patients with impaired kidney function and in a control group of patients with IgA nephropathy (IgAN), matched for age, sex and eGFR. In addition to AVP, copeptin was measured as a surrogate marker for AVP, since copeptin is more stable than AVP (12-14).

Methods

Study Population

Eligible for this study were patients with ADPKD, as diagnosed using the revised Ravine criteria (15), aged between 18-65 years and with an estimated GFR (eGFR) <60 ml/min/1.73m^2. The control group consisted of IgA nephropathy (IgAN) patients, matched for eGFR, age and sex. The diagnosis of IgAN was based on renal biopsy or clinical history and laboratory values in accordance with clinical practice. IgAN patients were eligible when they were in a stable phase of their disease, as defined by proteinuria <1 g/d and eGFR loss ≤5 ml/min/1.73m^2 in the previous year and without use of

immunosuppressive medication. Exclusion criteria for both patient groups were: use of medications or concomitant diseases that influence urine concentration capacity other than ADPKD or IgAN (e.g., diuretics, lithium and diabetes mellitus), factors that may influence urine concentration capacity (e.g. smoking, menstruation, urinary tract infection, pregnancy, and consumption of ≥4 units of alcohol per day) or active cardiovascular disease (e.g. angina pectoris), which is a contraindication for DDAVP administration. This study was approved by our institutional review board and was performed in adherence to the Declaration of Helsinki. All participants gave written informed consent.

Study Protocol

All patients routinely collected a 24-hour urine sample the day preceding the water deprivation test. Patients underwent a standard prolonged water deprivation test, based on the protocol originally described by Miller *et al.* (16). The day before the water deprivation test and during the test, participants were not allowed to smoke, drink alcohol or consume caffeine-containing products. At the day of the test, a baseline spot urine sample was collected at 5 p.m. and blood was drawn for direct biochemical evaluation. Plasma was separated and stored at -80°C for later assessment of copeptin and AVP. Thereafter, participants received a standardized meal and were not allowed to eat or drink anymore until the end of the water deprivation test. Patients spent the evening and the night at home.

The following day patients returned to the hospital at 8 a.m., after 14 hours of thirsting. Patients spent the day in the hospital, with spot urine samples being collected every hour until two consecutive measurements showed an increase in urine osmolality ≤30 mOsm/kg. After reaching this plateau, participants received an intramuscular injection of 2 mcg DDAVP, a synthetic replacement for AVP. Two hours after injection, blood and urine samples were collected. Urine osmolality that was measured at this time point was used to define maximal urine concentrating capacity. Two hours after injection of DDAVP, participants were allowed to drink and eat ad libitum. To ensure patient safety during the water deprivation test stopping criteria were defined as reaching a body weight reduction >3% or a plasma sodium >150 mmol/L.

Measurements

Standard biochemical evaluation was performed in fresh urine and plasma samples, using a Roche Modular Autoanalyser (Hitachi, Tokyo, Japan). Plasma and urine osmolality were measured directly via determination of freezing point depression using an Osmometer (Arkray, Kyoto, Japan), with an intra-assay coefficient of variation

<1.0%). eGFR was calculated with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation (17).

Blood for AVP and copeptin measurement was drawn into a chilled EDTA tube, and immediately centrifuged at 4°C and stored at −80°C until assay. AVP was measured by RIA after an extraction using ODS-silica (DiaSorin, Stillwater, MN). The lower limit of detection was 0.2 pg/ml and the intra-assay coefficient of variation 3.5%. Copeptin was measured using a sandwich immunoassay (B.R.A.H.M.S. AG, Hennigsdorf/Berlin, Germany), with a lower limit of detection of 0.4 pmol/L and intra-assay coefficient of variation of 4 and 3% for the copeptin concentrations of 15 and 50 pmol/L, respectively. Urine aquaporin-2 (AQP2) concentration was measured by a direct ELISA (18) using rabbit-anti-AQP2 antibody (Santa Cruz Biotechnology, Dallas, TX, USA) with a lower limit of detection of 6.67 ng/mL and intra-assay coefficient of variation of 6.1%. In all ADPKD patients MR imaging was performed, using a standardised abdominal MR imaging protocol without the use of intravenous contrast (19). Total kidney volume (TKV) was assessed using Analyze Direct 8.0 software (AnalyzeDirect, Inc., Overland Park, KS, USA). Total kidney volume was divided by height to calculate the height adjusted total kidney volume (hTKV).

Statistical Analyses

Parametric variables are expressed as mean±SD, non-parametric variables as median (IQR). Differences in baseline characteristics between ADPKD and IgAN patients were calculated with a Chi-square test for categorical data, and for continuous data with a Student's t-test or a Mann-Whitney U test in case of non-parametric data. Percentage change between baseline and maximal urine concentration were tested in the overall population and within study groups using a one sample t-test with 0% change as reference value. Linear regression analyses were performed to test associations between plasma and urine osmolality, AVP, copeptin, AQP2-creatinine ratio, hTKV, albumin-creatinine ratio (ACR) and urine-to-plasma urea ratio (U/P Urea). AVP, copeptin, AQP2-creatinine ratio, hTKV, ACR and U/P Urea were log (ln) transformed to fulfill the requirement of normal distribution of the residuals for regression analysis. To investigate differences between the two study groups the categorical variable 'study group' (ADPKD vs. IgAN) was added to the regression analysis. Furthermore, to investigate whether associations between copeptin and other study variables were different between the study groups, interaction was tested by adding product terms including 'study group' and the independent variable to this model. Univariate (crude) linear regression models are presented with the correlation coefficient whereas for multiple variable models the standardized regression coefficient beta (St. β) is given.

All statistical analyses were performed using SPSS 22 (SPSS Statistics, Inc., Chicago, IL, U.S.A.). A p-value of <0.05 was considered to indicate statistical significance and all statistical tests were 2-tailed.

Results

Before water deprivation at baseline

Baseline characteristics with respect to age, sex and eGFR were similar between ADPKD patients and the IgAN controls, indicating that matching was successful (Table 1). Blood pressure was slightly higher and 24-hour urine volume was particularly higher in ADPKD patients than in IgAN controls. Total solute, urea and creatinine excretion did not differ between the groups, indicating that both groups had similar nutritional intake and muscle mass. Baseline plasma osmolality, copeptin and AVP were similar in both study groups, although plasma osmolality tended to be lower in ADPKD patients than in IgAN controls (Table 2). A spot urine sample collected before start of the water deprivation test, showed less concentrated urine with lower urine osmolality, sodium and urea in ADPKD patients than IgAN controls (Table 3).

After water deprivation at maximal urine concentration

All patients underwent a standard prolonged water deprivation test. None of the patients met the safety stopping criteria during the test. Plasma osmolality increased significantly in ADPKD patients but not in IgAN controls. Upon water deprivation, copeptin and AVP increased significantly in ADPKD patients and IgAN controls in a similar way (Table 2). Urine osmolality increased both in ADPKD patients and IgAN controls (Table 3). However, the maximal achieved urine osmolality was significantly lower in ADPKD patients in comparison to IgAN controls, especially due to a decreased urine urea concentration. AQP2 at maximal urine concentration was similar in both groups and decreased in a similar way during water deprivation. After DDAVP administration, urine osmolality increased in ADPKD patients with an average of +4.7% (p=0.001). However, numerically this increase was small and similar to the increase in the IgAN control group (+4.5%, p=0.01, ADPKD vs. IgAN: p=0.4).

Table 1. Characteristics of the overall population, and of ADPKD and IgA Nephropathy patients separately.

	Overall N=30	ADPKD N=15	IgAN N=15	P-value
Age (y)	49±8	49±7	49±9	0.91
Male (%)	66.7	66.7	66.7	1.00
BMI (kg/m^2)	28±4	27±3	29±4	0.10
BSA (m^2)	2.06±0.20	2.00±0.19	2.13±0.18	0.06
Systolic blood pressure (mmHg)	129±13	134±14	123±8	0.02
Diastolic blood pressure (mmHg)	81±9	85±10	78±6	0.03
Using antihypertensives (%)	93.3	93.3	93.3	1.00
eGFR (mL/min/1.73m^2)	47±14	46±11	48±17	0.38
TKV (L)		1.7 (0.9-2.5)		
hTKV (L/m)		1.0 (0.5-1.3)		
24-hour urine				
Volume (L)	2.3±0.9	2.8±0.9	1.9±0.5	0.002
Osmolality (mOsmol/kg)	422±144	347±133	496±117	0.003
Osmolality excretion (mOsmol/24h)	431±99	441±88	421±111	0.59
Urea (mmol/L)	190±69	146±53	233±55	<0.001
Urea excretion (mmol/24h)	194±54	201±64	187±43	0.50
Creatinine (mmol/L)	6.7±2.8	5.1±1.9	8.4±2.6	0.001
Creatinine excretion (mmol/24h)	6.7±1.3	6.5±1.2	6.9±1.5	0.39
Albumin excretion (mg/24h)	95 (25-360)	47 (16-288)	148 (68-522)	0.045
Albumin/creatinine ratio (mg/mmol)	9 (2-21)	3 (1-19)	11 (6-39)	0.06
AQP2 excretion (ng/24h)	760 (549-2280)	752 (418-2239)	760 (605-3185)	0.62
AQP2/creatinine ratio (µg/mmol)	62 (45-204)	69 (32-206)	58 (45-204)	1.00

ADPKD and IgA Nephropathy patients were matched for age, sex, and eGFR. Data are given as mean±SD for parametric data or median (IQR) for non-parametric data. Significance was tested using a chi-square test, Student's t-test or a Mann-Whitney U test, when appropriate. Osmolality, urea and creatinine excretion were adjusted for BSA. *Abbreviations:* IgAN, IgA Nephropathy; BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; TKV, total kidney volume; hTKV, height adjusted total kidney volume; AQP2, aquaporin-2.

Table 2. Measurements in plasma at baseline (5 p.m.) and at maximal urine concentration during a standard prolonged water deprivation test. Data are presented for the overall population, and for ADPKD and IgA Nephropathy patients separately.

Plasma	Overall N=30	ADPKD N=15	IgAN N=15	P-value
At baseline				
Osmolality (mOsmol/kg)	291±8	289±5	294±10	0.14
Sodium (mmol/L)	140±2.5	141±2.9	140±2.0	0.67
Potassium (mmol/L)	4.3±0.4	4.3±0.4	4.3±0.5	0.97
Urea (mmol/L)	11.2±5.3	10.3±3.7	12.1±6.6	0.35
AVP (pmol/L)	4.4 (1.4-12.0)	2.2 (1.3-14.0)	6.3 (1.4-12.0)	0.49
Copeptin (pmol/L)	11.9 (7.1-28.3)	14.0 (6.1-30.1)	11.9 (7.3-27.7)	0.98
At maximal urine concentration				
Osmolality (mOsmol/kg)	294±8	293±6	295±10	0.51
Sodium (mmol/L)	142±1.9	142±2.4	141±1.0	0.10
Potassium (mmol/L)	4.4±0.5	4.3±0.5	4.5±0.6	0.30
Urea (mmol/L)	11.0±5.3	10.3±3.5	11.7±6.6	0.47
AVP (pmol/L)	9.6 (2.4-12.3)	9.2 (1.4-12.0)	10.0 (2.5-13.0)	0.57
Copeptin (pmol/L)	23.7 (10.6-44.6)	26.6 (12.7-43.0)	20.7 (10.0-48.3)	0.84
Change between baseline and maximal urine concentration				
Osmolality (%)	0.8±1.2*	1.1±1.2*	0.5±1.1	0.09
Sodium (%)	0.8±1.3*	1.0±1.5*	0.7±1.1*	0.32
Potassium (%)	2.2±6.7	0.1±6.5	4.2±6.5*	0.08
Urea (%)	-3.2±11.6	-0.2±7.4	-6.0±14.1	0.14
AVP (%)	86±158*	116±208*	35±61*	0.11
Copeptin (%)	82±89*	94±113*	72±59*	0.51

Data are given as mean±SD for parametric data or as median (IQR) for non-parametric data. Significance between groups was tested using Student's t-test or a Mann-Whitney U test, when appropriate. Percentage change within groups was tested using a one-sample t-test, * $p<0.05$. *Abbreviations:* IgAN, IgA Nephropathy; AVP, vasopressin; AQP2, aquaporin-2.

Table 3. Measurements in spot urine at baseline (5 p.m.) and at maximal urine concentration during a standard prolonged water deprivation test. Data are presented for the overall population, and for ADPKD and IgA Nephropathy patients separately.

Spot urine	Overall N=30	ADPKD N=15	IgAN N=15	P-value
At baseline				
Osmolality (mOsmol/kg)	438±160	378±157	498±144	0.04
Sodium (mmol/L)	66±32	55±29	77±32	0.06
Potassium (mmol/L)	46±21	44±20	49±23	0.46
Urea (mmol/L)	207±81	177±80	237±71	0.04
Creatinine (mmol/L)	7.9±3.8	7.2±4.3	8.7±3.3	0.28
Albumin (mg/L)	98 (38-218)	64 (21-127)	137 (64-476)	0.045
Albumin/creatinine ratio (mg/mmol)	14 (7-29)	9 (3-26)	19 (9-51)	0.10
AQP2 (ng/mL)	986 (283-3396)	584 (171-3297)	1562 (293-3693)	0.54
AQP2/creatinine ratio (µg/mmol)	177 (45-361)	106 (28-532)	189 (50-325)	0.87
At maximal urine concentration				
Osmolality (mOsm/kg)	587±151	533±138	642±148	0.046
Sodium (mmol/L)	77±31	75±24	80±38	0.65
Potassium (mmol/L)	81±35	78±28	84±41	0.61
Urea (mmol/L)	261±81	223±74	299±72	0.008
Creatinine (mmol/L)	12.8±4.7	11.5±4.2	14.1±5.1	0.14
Albumin (mg/L)	92 (57-245)	64 (26-130)	160 (86-554)	0.01
Albumin/creatinine ratio (mg/mmol)	10 (4-49)	7 (-13)	11 (9-6)	0.045
AQP2 (ng/mL)	676 (343-1444)	410 (274-2844)	833 (425-1274)	0.33
AQP/creatinine ratio (µg/mmol)	52 (31-130)	33 (21-290)	56 (39-109)	0.60
Change between baseline and maximal urine concentration				
Osmolality (%)	52±81*	68±107*	36±41*	0.29
Sodium (%)	37±83*	61±93*	12±66	0.11
Potassium (%)	126±266*	171±370	82±73*	0.37
Urea (%)	40±59*	48±73*	33±42*	0.13
Creatinine (%)	98±139*	118±184*	78±75*	0.44
Albumin (%)	122±455	198±641	45±69*	0.09
Albumin/creatinine ratio (%)	-10±60	-7±73	-12±47	0.41
AQP2 (%)	8±98	20±122	-4±68	0.32
AQP/creatinine ratio (%)	-43±44*	-48±22*	-37±59*	0.08

Data are given as mean±SD for parametric data or as median (IQR) for non-parametric data. Significance was tested using Student's t-test or a Mann-Whitney U test, when appropriate. Percentage change within groups was tested using a one-sample t-test, * $p<0.05$. *Abbreviations:* IgAN, IgA Nephropathy; AVP, vasopressin; AQP2, aquaporin-2.

Associations between copeptin, AVP, plasma and urine osmolality and AQP2

At baseline and at maximal urine concentration, copeptin and AVP concentrations were strongly associated (R=0.72 and R=0.78, respectively, both p<0.001). Furthermore, copeptin was associated with plasma osmolality, a stimulus for AVP release, both at baseline and at maximal urine concentration (Supplementary Table 1 and Figure 1). No interactions by study group for the associations between copeptin and plasma osmolality were found (Supplementary Table 1). The aforementioned associations were also tested for AVP instead of copeptin, which rendered essentially similar results, albeit that the associations were less strong (Supplementary Table 1).

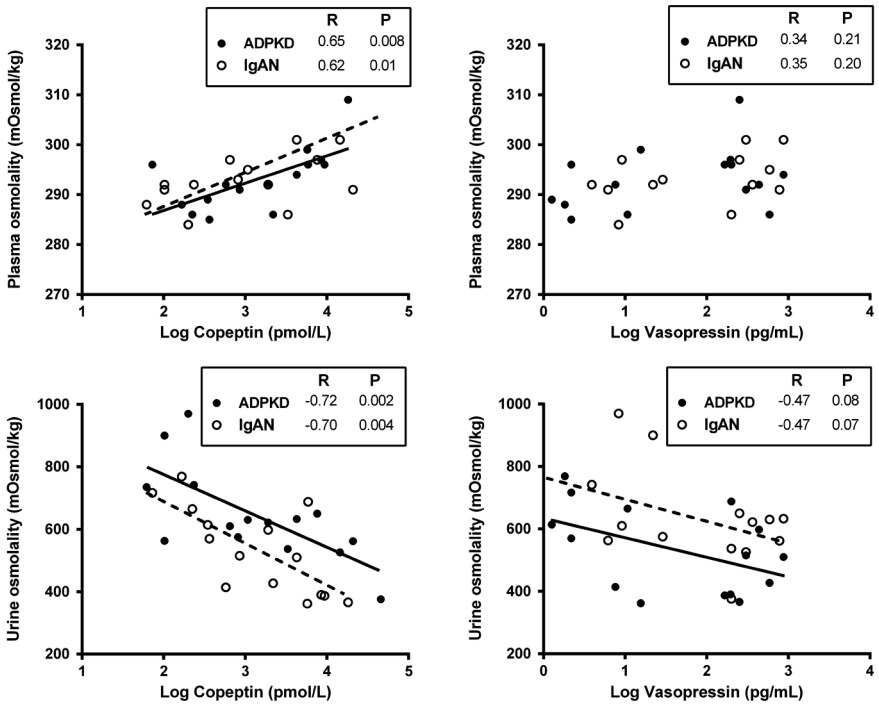

Figure 1. Associations of copeptin and vasopressin concentration with plasma osmolality and urine osmolality in ADPKD patients (solid line) and IgA Nephropathy patients (IgAN, dashed line) at maximal urine concentration.

Urine osmolality was inversely associated with copeptin at maximal urine concentration (Figure 1). Addition of the categorical variable study group to the linear regression model, with maximal urine osmolality as dependent variable, showed that ADPKD patients had a 105 mOsmol/kg lower maximal urine osmolality compared with the control group at a similar copeptin value (St. β=-0.35, p=0.01, Table 4). No

interactions by study group for the association between copeptin and urine osmolality was found. AVP was associated with maximal urine osmolality in a similar way, with a 119 mOsmol/kg lower maximal urine osmolality in ADPKD patients at a similar AVP value (St. β=-0.40, p=0.02, Table 4).

The AQP2 to creatinine ratio at maximal urine concentration was inversely associated with maximal urine osmolality. ADPKD patients had a 110 mOsmol/kg lower maximal urine osmolality in comparison with the control group at a similar AQP2 level (St. β=-0.37, p=0.02, Table 4). No interactions by study group for the association between AQP2 and the maximal urine concentrating capacity was found. Furthermore, AQP2 at maximal urine concentration was positively associated with both copeptin and AVP (Supplementary Table 2). Having ADPKD or IgAN did not affect these associations (i.e., no significant interactions with study group).

Table 4. Linear regression analyses of urine osmolality with plasma copeptin, AVP and urine AQP2/creatinine ratio (all log transformed) at maximal urine concentration, including analyses testing whether study group (i.e. having ADPKD) interacts with these associations.

Urine osmolality	Crude		Model 1		Model 2	
	R	P-value	St. β	P-value	St. β	P-value
Plasma copeptin						
Plasma copeptin	-0.66	<0.001	-0.66	<0.001	-0.61	0.001
Study group (ADPKD vs. IgAN)			-0.35	0.01	-0.13	0.81
Plasma copeptin * Study group					-0.24	0.67
Plasma AVP						
Plasma AVP	-0.41	0.03	-0.44	0.01	-0.47	0.06
Study group (ADPKD vs. IgAN)			-0.40	0.02	-0.45	0.17
Plasma AVP * Study group					0.06	0.87
Urine AQP2/creatinine						
Urine AQP2/creatinine	-0.51	0.004	-0.52	0.002	-0.58	0.06
Study group (ADPKD vs. IgAN)			-0.37	0.02	-0.53	0.44
Urine AQP2/creatinine * Study group					0.17	0.82

Standardized beta coefficients (St. β) and p-values were calculated using linear regression. Dependent variable is urine osmolality, independent variables are plasma copeptin (log transformed), plasma AVP (log transformed), urine AQP2/creatinine (log transformed), the categorical variable study group and the interaction term between plasma copeptin, AVP or urine AQP2/creatinine and study group. *Abbreviations:* IgAN, IgA Nephropathy; AVP, vasopressin; AQP2, aquaporin-2.

Associations between copeptin and kidney damage

Next we investigated whether copeptin was associated with kidney damage. In ADPKD, copeptin at baseline was univariately associated with ACR (R=0.88, p<0.001) and this held also true at maximal urine concentration (R=0.71, p=0.003, Figure 2).

The association remained significant after multivariable adjustment for eGFR and hTKV at baseline (St. β=0.82, p=0.001) and was of borderline significance at maximal urine concentration (St. β=0.58, p=0.06). In the IgAN control group copeptin was not associated with ACR at baseline, neither crude (p=0.2) nor after adjustment for eGFR (p=0.7). At maximal urine concentration copeptin tended to be associated with ACR in IgAN controls (R=0.50, p=0.06), but this association lost significance after adjustment for eGFR (p=0.4). In ADPKD, copeptin was furthermore associated with hTKV (R=0.58, p=0.03). Of note, hTKV was positively associated with plasma osmolality and inversely with urine osmolality at maximal urine concentration (R=0.52, p=0.048, R=-0.54, p=0.04, respectively).

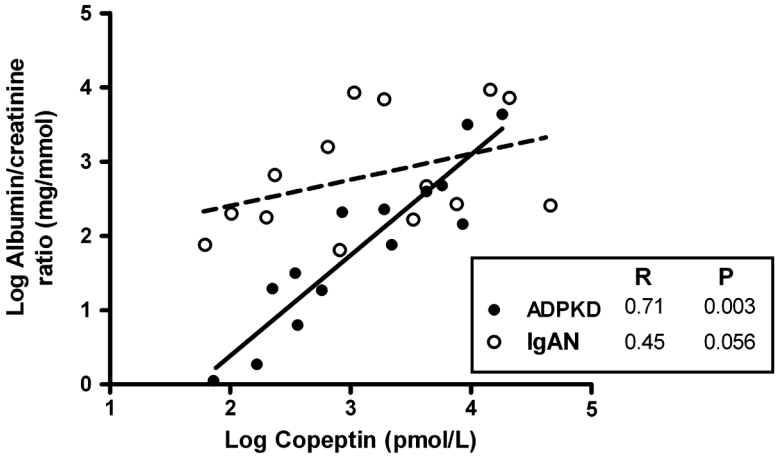

Figure 2. Associations of plasma copeptin concentration with urine albumin to creatinine ratio in ADPKD (solid line) and IgA Nephropathy (IgAN, dashed line) patients at maximal urine concentration.

Baseline U/P Urea as marker for maximal urine concentration capacity

In a previous study, we suggested that the urine-to-plasma urea ratio (U/P Urea), measured routinely in an out-patient clinic setting, may be a marker for maximal urine concentrating capacity (20). We therefore tested in this study also the association between baseline U/P Urea ratio and maximal urine osmolality. In the two study groups combined (R=0.73, p<0.001), as well as in both groups separately, strong associations were found (ADPKD: R=0.67, p=0.006; IgAN control: R=0.75, p=0.001, Figure 3). In the total study group, the association remained significant after adjustment for age, sex and eGFR (St. β=0.62, p=0.003) and showed a trend towards significance in the separate study groups (ADPKD: St. β=0.51, p=0.1 and IgAN control: St. β=0.76,

p=0.054). In addition, we tested whether U/P Urea is a marker for disease severity in ADPKD. Significant associations were found for baseline U/P urea with hTKV (R=-0.53, p=0.04) and eGFR (R=0.60, p=0.02), and with copeptin at maximal urine concentration (R=-0.58, p=0.03).

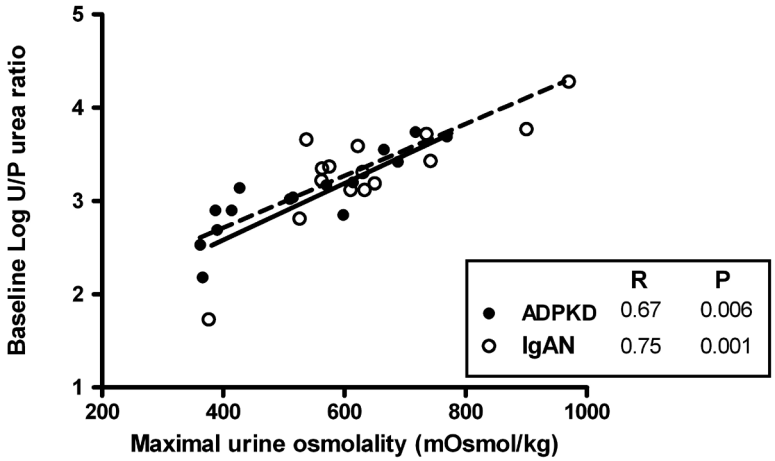

Figure 3. Associations of maximal urine osmolality with baseline urine-to-plasma (U/P) urea ratio in ADPKD patients (solid line) and IgA Nephropathy patients (IgAN, dashed line).

Discussion

In the present study we found a more severely impaired urine concentrating capacity in ADPKD patients with, surprisingly, similar AVP and copeptin responses in comparison with IgAN control patients at similar low kidney function. Furthermore, more severe ADPKD, assessed as a higher total kidney volume, was positively associated with plasma osmolality, copeptin and albuminuria, and with a more severely impaired urine concentrating capacity during water deprivation.

After water deprivation, concentrations of plasma AVP, plasma copeptin and urine AQP2 were similar in both study groups, whereas the maximal urine concentrating capacity was significantly more impaired in ADPKD patients. This shows that the process of urine concentration is complex and comprises more than solely variation in the permeability of collecting duct cells. In addition the medullary osmotic gradient is of great importance. This gradient is determined by a complex mechanism involving intra-renal urea recycling by urea transporters in the renal medulla. The importance of these urea transporters for urine concentration has been confirmed in knock-out

mouse models (21, 22). Mice with a defect in one or multiple urea transporters were still able to concentrate urine, but to a lesser extent than wild-type mice, due to a reduced urea clearance, whereas sodium and other electrolytes were cleared in a similar way. In APDKD signs of such a urea selective concentrating defect can be observed as well. In a previous study we found that ADPKD patients with preserved kidney function had at maximal urine concentration markedly lower urine urea levels compared to healthy controls (280±56 mmol/L vs. 405±110 mmol/L, p=0.001) (4). We hypothesized that in ADPKD patients cyst formation disrupts the medullar osmotic gradient and urea recycling. The present study suggests that this difference in solute clearance seems ADPKD-specific and is not part of kidney damage in general, as urine urea levels at maximal urine concentration were lower in ADPKD patients than in the IgAN control group despite similar level of impaired kidney function. In addition, when comparing urine urea concentrations at the moment of maximal urine concentration in ADPKD with preserved kidney function (23) with findings from the present study, it shows that urine urea concentration decreases when disease progresses (preserved kidney function: 280±56 mmol/L, impaired kidney function: 223±74 mmol/L, p=0.03). The fact that the U/P urea ratio correlates well with maximal urine concentrating capacity shows the importance of urea in the urine concentration process as well.

After water deprivation, the increase in copeptin and AVP was similar in both study groups, even though the maximal urine concentrating capacity was more impaired and the increase in plasma osmolality seemed more profound in ADPKD patients in comparison to the control group. In both groups plasma osmolality was comparable at the end of the water deprivation test, which could be the explanation for similar copeptin and AVP levels at the moment of maximal urine concentration. On the other hand, Ho et al. have described the possibility of a central component causing the impaired urine concentrating capacity in ADPKD. These authors hypothesized that expression of *PKD1* and *PKD2* transcripts in hypothalamic nuclei that synthesize AVP could be involved (24). They found in ADPKD patients a lower maximal urine osmolality in comparison with healthy controls, but no AVP response during water deprivation. They also did not find an association between AVP and plasma osmolality, and suggested that AVP secretion was blunted in ADPKD patients. In our study, a significant response in both copeptin and AVP was seen. Nevertheless, we found no association between plasma osmolality and AVP as well, suggesting that a central component may play a role. However, an association between plasma osmolality and copeptin was present. The latter suggests that copeptin and therefore also AVP secretion responded appropriately to plasma osmolality, which makes a central component less likely. The contradictory results between AVP and copeptin that are seen in our study may be

explained by differences in assay sensitivity, as copeptin is more stable than AVP ex-vivo and therefore probably more reliable to measure (4, 12-14). Based on our results a central component in the impaired maximal urine concentration capacity in ADPKD seems unlikely but cannot be excluded.

In this study ADPKD patients with later stages of disease showed markedly higher AVP and copeptin levels at the end of a water deprivation test compared to levels that were achieved in our previous study that was performed in ADPKD patients with earlier stages of disease (9.2 (1.4-12.0) pmol/L vs. 1.6 (1.13-2.41) pmol/L, p=0.007) (4). It is assumed that AVP has a detrimental role in ADPKD, because it leads to an increase in intracellular cAMP in distal tubular cells, which in turn leads to cell proliferation and increased fluid section, the processes that drive cyst formation and growth (25). When cysts are formed and expand because of a genetic defect, urine concentrating capacity decreases, leading to an increase in AVP and consequently to even more cyst formation and expansion. Thus a vicious circle is created that predisposes for kidney growth and loss of kidney function. To reduce cyst growth, an increase in AVP levels should be avoided. Our study results indicate that thirsting enhances AVP release, also in ADPKD, and suggest that dehydration should be avoided in this patient group.

The major strength of our study is the inclusion of a control group of eGFR-, age- and sex-matched IgAN patients. This allowed us to conclude whether our observations in ADPKD patients are disease specific or due to impaired eGFR, without misinterpreting data due to differences in age and sex distribution. These latter factors have been shown to be associated with maximal urine concentrating capacity (11, 26, 27). In addition, we measured both AVP and copeptin levels. Therefore we were able to confirm outcomes with respect to AVP that showed a trend toward significance, with copeptin values that are more easy and reliable to measure. Using copeptin levels we indeed were able to detect more subtle associations and differences between the two study groups. Limitations are the relatively small sample size. No data on urine concentration capacity of IgAN patients was available from literature to perform a power calculation a priori. Therefore the size of our study population was based on experience obtained in a previous water deprivation test (4). Although differences between the present study groups were less profound compared to the differences between study groups in our previous study, our main findings are clear and well powered (i.e., statistically significant). Furthermore, our study design may not be optimal to detect a central component causing partial diabetes insipidus. We used a standard prolonged water deprivation test, which can distinguish between a complete central or nephrogenic origin of diabetes insipidus, but is less accurate in detecting partial and especially mixed syndromes (16). Lastly, the control group consisted of

IgAN patients. We preferred this option over including patients with a case mix of diseases with uncertain results.

In conclusion, ADPKD patients have a more severely impaired maximal urine concentrating capacity in comparison with IgAN control patients with a similar level of decreased kidney function. This impaired urine concentrating capacity consists of a nephrogenic component, probably due to disruption of the medullary osmotic gradient, and perhaps also a central component with inadequate AVP secretion from the pituitary gland. Nevertheless, AVP secretion as response to water deprivation increases when disease progresses, which can be harmful as AVP is known to enhance cell proliferation and cyst formation. This suggests that water deprivation may be deleterious and should be avoided by ADPKD patients.

Disclosure

The authors have no potential conflicts of interest relevant to the content of this article.

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Supplementary Table 1. Univariate linear regression associations of plasma copeptin and AVP (log transformed) with plasma osmolality and multivariable linear regression analyses testing the effect of having ADPKD on the associations at baseline and at maximal urine concentration.

Plasma copeptin	Crude		Model 1		Model 2	
	R	P-value	St. β	P-value	St. β	P-value
Baseline						
Plasma osmolality	0.60	0.001	0.64	<0.001	0.57	0.004
Study group (ADPKD vs. IgAN)			0.14	0.40	-5.3	0.46
Plasma osmolality * Study group					5.4	0.45
Maximal urine concentration						
Plasma osmolality	0.62	<0.001	0.63	<0.001	0.57	0.004
Study group (ADPKD vs. IgAN)			0.10	0.51	-3.8	0.54
Plasma osmolality * Study group					3.9	0.53
Plasma AVP						
Baseline						
Plasma osmolality	0.32	0.09	0.29	0.14	0.26	0.25
Study group (ADPKD vs. IgAN)			-0.10	0.61	-2.77	0.74
Plasma osmolality * Study group					2.66	0.75
Maximal urine concentration						
Plasma osmolality	0.34	0.06	0.34	0.08	0.29	0.20
Study group (ADPKD vs. IgAN)			-0.03	0.85	-3.35	0.66
Plasma osmolality * Study group					3.31	0.66

Standardized betas (St. β) and p-values were calculated using multivariable linear regression. Dependent variables are plasma copeptin and AVP (log transformed), independent variables are plasma osmolality, the categorical variable study group (1=ADPKD, 0=IgAN) and the interaction term between plasma osmolality and study group. *Abbreviations:* IgAN, IgA nepghropathy; AVP, vasopressin.

Supplementary Table 2. Univariate linear regression associations of the urine AQP2 to creatinine ratio with plasma copeptin or AVP (both log transformed) at maximal urine concentration, and multivariable linear regression analyses testing the effect of having ADPKD on these associations.

Urine AQP2/creatinine	Crude		Model 1		Model 2	
	R	P-value	St. β	P-value	St. β	P-value
Plasma copeptin						
Plasma copeptin	0.49	0.006	0.49	0.006	0.38	0.09
Study group (ADPKD vs. IgAN)			-0.02	0.92	-0.59	0.40
Plasma copeptin * Study group					0.61	0.40
Plasma AVP						
Plasma AVP	0.45	0.01	0.46	0.01	0.33	0.20
Study group (ADPKD vs. IgAN)			0.03	0.87	-0.17	0.63
Plasma AVP * Study group					0.25	0.52

Standardized beta coefficients (St. β) and p-values were calculated using multivariable linear regression. Dependent variable is urine AQP2/creatinine (log transformed), independent variables are plasma copeptin (log transformed), plasma AVP (log transformed), the categorical variable study group (1=ADPKD, 0=IgAN) and the interaction term between plasma copeptin or AVP and study group. *Abbreviations:* AQP2, aquaporin-2; IgAN, IgA Nephropathy; AVP, vasopressin.

Chapter 9

Urine and plasma osmolality in patients with ADPKD: reliable indicators of vasopressin activity and disease prognosis?

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Abstract

Background: Vasopressin plays an essential role in osmoregulation, but has deleterious effects in patients with ADPKD. Increasing water intake to suppress vasopressin activity has been suggested as potential renoprotective strategy. This study investigated whether urine and plasma osmolality can be used as reflection of vasopressin activity in ADPKD patients.

Methods: We measured urine and plasma osmolality, plasma copeptin concentration, total kidney volume (TKV, by MRI) and GFR (^{125}I-iothalamate). In addition, change in estimated GFR (eGFR) during follow-up was assessed.

Results: 94 patients with ADPKD were included (56 males, age 40±10 year, mGFR 77±32 ml/min/1.73m^2, TKV 1.55 (0.99 – 2.40) L. Urine osmolality, plasma osmolality and copeptin concentration were 420±195 mOsmol/l, 289±7 mOsmol/l and 7.3 (3.2 – 14.6) pmol/l, respectively. Plasma osmolality was associated with copeptin concentration ($R=0.54$, $p<0.001$), whereas urine osmolality was not ($p=0.4$). In addition, urine osmolality was not associated with TKV ($p=0.3$), in contrast to plasma osmolality ($R=0.52$, $p<0.001$) and copeptin concentration ($R=0.61$, $p<0.001$). Fifty-five patients were followed for 2.8±0.8 years. Baseline plasma and urine osmolality were not associated with change in eGFR ($p=0.6$ and $p=0.3$, respectively), whereas baseline copeptin concentration did show an association with change in eGFR, in a crude analysis (St. β= -0.41, $p=0.003$) and also after adjustment for age, sex and TKV (St. β= -0.23, $p=0.05$).

Conclusions: These data suggest that neither urine nor plasma osmolality are valid measures to identify ADPKD patients that may benefit from increasing water intake. Copeptin appears a better alternative for this purpose.

Introduction

The antidiuretic hormone arginine vasopressin (AVP) is an essential hormone for osmoregulation. When plasma osmolality increases, AVP is secreted by the pituitary gland, subsequently activating the V2 receptors of renal collecting duct cells (1), which results in translocation of aquaporin 2 to the luminal surface of these cells, making them permeable for water (2).

Besides the physiological stimulation of water reabsorption, AVP appears to have an essential role in the pathophysiology of Autosomal Dominant Polycystic Kidney Disease (ADPKD) (3). Animal models and a large scale phase 3 multicenter randomized controlled trial in patients with ADPKD showed that blocking the AVP V2 receptor with a V2 receptor antagonist, leads to a reduction in the rate of cyst growth and renal function loss (4, 5).

Drinking a sufficient volume of water can also reduce AVP concentration. Increasing water intake could therefore be an alternative to medical treatment with a V2 receptor antagonist to ameliorate disease progression in ADPKD. In a rat PKD model, it was indeed shown that increased water intake attenuated disease progression (6). In ADPKD patients only one small-scale, non-randomized study has been performed, that was not able to show a favorable effect of increasing water intake (7-9). Until other data become available, it is, based on theoretical grounds and convincing animal data, still advised that ADPKD patients should increase their water intake (7-9). For clinicians, the question arises which ADPKD patients should increase their water intake, and what volume of fluid they should be advised to drink. In this respect, measuring urine osmolality could be of help (3, 9-11). It is generally assumed that a urine osmolality below 285 mOsmol/l, or a urine osmolality lower than plasma osmolality, reflects adequate suppression of AVP (9, 11).

ADPKD patients, however, have an impaired urine concentrating capacity, that worsens throughout their disease, presumably because they have an impaired renal medullar osmolar gradient due to cyst formation (12). This lack of renal concentrating capacity is expected to lead to a lower urine osmolality, a higher plasma osmolality and a compensatory high level of AVP. Clinically we observed that in patients with more advanced ADPKD, urine osmolality can indeed be low, whereas AVP is high (13). Given this observation, urine osmolality might not be a good reflection of AVP concentration in ADPKD patients, especially in those with more advanced disease.

The aim of the present study is therefore to cross-sectionally investigate in ADPKD patients whether urine osmolality and plasma osmolality are associated with AVP concentration (measured by the concentration of its surrogate plasma copeptin),

and whether these associations are influenced by disease severity. Furthermore, the associations of urine and plasma osmolality as well as plasma copeptin concentration with the rate of renal function decline during follow-up are investigated.

Methods

ADPKD patients

For this study, all consecutive patients with ADPKD, aged 18-70 years, visiting our out-patient clinic from January 2007 until August 2011 were asked to participate. A diagnosis of APDKD was made based upon the revised Ravine criteria (14). Patients were considered ineligible to participate if they received renal replacement therapy (including renal transplantation), had undergone renal surgery, were unable to undergo magnetic resonance (MR) imaging or had other diseases or conditions potentially affecting renal function (such as diabetes mellitus, pregnancy or lactation).

One hundred forty-six patients met these criteria. Thirteen patients did not give informed consent, leaving 133 patients that were scheduled for a 1-day outpatient clinical evaluation. Thirty six of these patients used diuretics and were excluded from the present analysis, because use of diuretics may influence AVP levels and urine osmolality. Three patients had plasma copeptin concentrations more than 10 times the interquartile range above the third quartile, although their plasma osmolality was within normal limits. These patients were considered outliers and their data were not taken into consideration (15), leaving 94 patients for the cross-sectional analyses. In 55 of these patients at least one year of follow-up was available for longitudinal analyses. This study was performed in adherence to the Declaration of Helsinki, and all patients gave written informed consent.

Measurements

All patients routinely collected a 24-hour urine sample the day preceding renal function measurement. They were advised to refrain from heavy physical exercise during this urine collection. Of note, in the time period of the study (2007-2011) ADPKD patients did not receive advice on water intake. Just before renal function measurement, fasting blood samples were drawn in which creatinine (Roche enzymatic assay), plasma and urine osmolality (by freezing point depression using an Osmometer (Arkray, Kyoto, Japan), with a variation coefficient <1.0%) and copeptin were measured. Effective plasma osmolality (2 x (plasma sodium + plasma potassium) + plasma glucose) was calculated. Measurement of endogenous AVP is problematic, because AVP is unstable

in isolated plasma and the available assays to measure AVP have limited sensitivity (16). Therefore we decided to measure copeptin, a precursor of AVP, that has been shown to be a reliable marker for endogenous AVP and can be measured more reliably (16-18). Plasma samples for copeptin measurement were immediately centrifuged at 4°C and stored at minus 80°C until the samples were thawed and measured using a sandwich immunoluminometric assay in one run on the same day (Thermo Fisher Scientific, U.S.A). The lower limit of detection was 0.4 pmol/L and the functional assay sensitivity (interassay coefficient of variation 0.20%) was 0.1 pmol (19).

At the day of renal function measurement blood pressure was assessed during rest in supine position with an automatic device (Dinamap® G E Medical Systems, Milwaukee, WI, USA) for 15 minutes during renal function measurement, of which the last 5 values were averaged to obtain systolic and diastolic blood pressure values. Furthermore, weight and height were determined. Body mass index was calculated as weight in kilograms (kg) divided by height in square meters. Body surface area (BSA) was calculated according to the DuBois formula (20).

Renal function measurements were performed using the constant infusion method with ^{125}I-iothalamate to measure glomerular filtration rate (mGFR) (21, 22). mGFR was normalized for BSA. After renal function measurement, the patients were followed for at least 12 months to again assess creatinine concentration to calculate the estimated Glomerular Filtration Rate (eGFR) by the Chronic Disease Epidemiology Collaboration (CKD-EPI) equation (23). Change in eGFR during follow-up was calculated using linear regression slopes through all eGFR values (at least 2) that were available in our database.

MR imaging was performed immediately after renal function measurement, using a standardised abdominal magnetic resonance imaging protocol without the use of intravenous contrast (24). Scanning was performed on a 1.5 Tesla MR (Magnetom Avento, Siemens, Erlangen, Germany) and in 9 patients on a 3.0 Tesla MR (Intera, Philips, Best, The Netherlands). Total kidney volume (TKV) was assessed using Analyze Direct 8.0 software (AnalyzeDirect, Inc., Overland Park, KS, USA). Intra- and interreviewer coefficients of variation for TKV measurement were 2.4% and 3.1%, respectively.

Statistical Analysis

Because impaired renal function could affect the study results, baseline characteristics and all other analyses are given for the overall population as well as for participants with an mGFR > 60 ml/min/1.73m^2 and ≤ 60 ml/min/1.73m^2 separately. Parametric variables are expressed as mean ± SD, non parametric variables as median (IQR). Differences in baseline characteristics between the two mGFR subgroups were calculated with a

Chi-square test for categorical data, and for continuous data with Student's t-test or a Mann-Whitney U test in case of non-parametric data.

To investigate whether mGFR and TKV correlated with urine osmolality, plasma osmolality and copeptin concentration, the Pearson correlation coefficient was calculated. Because TKV, copeptin and urine to plasma osmolality (Uosm/Posm) ratio showed a skewed distribution, logarithmic transformation was applied to fulfill the requirement for correlation and regression analysis of normal distribution of the residuals. To visualize the associations, scatterplots were made showing the associations of mGFR and TKV with urine and plasma osmolality and with copeptin concentration. For significant associations the Deming fit regression line is depicted. In these plots patients with a mGFR > 60 ml/min/1.73m^2 and mGFR ≤ 60 ml/min/1.73m^2 are shown separately.

Furthermore univariate and multivariate regression analyses were performed to investigate whether plasma copeptin was correlated with urine osmolality, plasma osmolality, Uosm/Posm ratio, sex, age and TKV. Univariate and multivariate regression analyses were also performed to investigate whether the change in eGFR was associated with these variables. For these analyses interactions of baseline mGFR with baseline urine osmolality, plasma osmolality, Uosm/Posm and copeptin were tested.

Various sensitivity analyses were performed. Because sex influences copeptin concentration and possibly also the rate of renal function decline, interactions of sex with baseline copeptin were investigated, and the analyses were repeated stratified for sex. Analyses were also repeated including outliers of copeptin concentration. Lastly, because plasma urea concentration may rise with progressive worsening kidney function, this could distort the association between measured plasma osmolality and copeptin concentration. Therefore also the association between calculated effective plasma osmolality and copeptin concentration was investigated.

All statistical analyses were performed using SPSS 22 (SPSS Statistics, Inc., Chicago, IL, U.S.A.). A value of $p<0.05$ was considered significant and all statistical tests were 2-tailed.

Results

Patient characteristics are presented in Table 1. A total of 94 patients were included, aged 40 ± 10 years of which 59.6% were male. Most of the patients used antihypertensive medication (75.5%), on average one single class, but per protocol none of the participating patients used diuretics.

Table 1. Baseline patient characteristics

	All	Stratified according to mGFR (ml/min/1.73m²)	
		≤ 60	> 60
N	94	30	64
Age (y)	40 ± 10	47 ± 10	38 ± 9*
Male (%)	59.6	70	54.7
Body mass index (kg/m²)	25.5 ± 3.9	25.7 ± 3.1	25.4 ± 4.2
Body mass surface (m²)	2.05 ± 0.24	2.06 ± 0.25	2.03 ± 0.23
Systolic blood pressure (mmHg)	128 ± 11	130 ± 10	128 ± 12
Diastolic blood pressure (mmHg)	79 ± 9	80 ± 8	79 ± 9
Antihypertensive medication use (%)	75.5	96.7	65.6*
Plasma creatinine (umol/L)	123 ± 82	208 ± 97	82 ± 17*
Plasma osmolality (mOsmol/L)	289 ± 7	292 ± 7	289 ± 7*
Plasma copeptin (pmol/L)	7.3 (3.2 – 14.6)	19.4 (12.0 – 34.6)	4.5 (3.1 – 9.1)*
eGFR (ml/min/1.73m²)	72 ± 27	38 ± 12	90 ± 19*
mGFR (ml/min/1.73m²)	77 ± 32	38 ± 15	95 ± 18*
Urine volume (mL/24h)	2350 (1790 – 2755)	2575 (2056 – 3225)	2150 (1650 – 2650)*
Urine osmolality (mOsmol/L)	420 ± 195	329 ± 79	459 ± 164*
Urine to plasma osmolality ratio	1.4 (1.1 – 1.8)	1.3 (1.0 – 1.3)	1.5 (1.2 – 2.1)
Total kidney volume (L)	1.55 (0.99 – 2.40)	2.20 (1.42 – 3.12)	1.36 (0.08 – 1.84)*

Abbreviations: eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate. *, p<0.05 versus group with mGFR ≤ 60 ml/min/1.73m². Parametric variables are expressed as mean ± SD, whereas non-parametric variables are given as median (interquartile range).

There was a large spread in disease severity, with mGFR ranging from 12 to 138 ml/min/1.73m^2 and TKV from 0.47 to 10.28 L. Table 1 also shows patient characteristics stratified according to mGFR, indicating that patients with lower mGFR, as expected, were older, used more antihypertensives and had a larger total kidney volume. Furthermore, patients with lower mGFR had a lower urine osmolality, a higher plasma osmolality and a higher copeptin concentration compared to patients with mGFR > 60 ml/min/1.73m^2 (all p<0.001). mGFR was strongly correlated with eGFR (*R*=0.9, p<0.001).

Figure 1 presents the associations of urine osmolality and Uosm/Posm ratio with copeptin concentration (upper and middle panel), and shows that a considerable number of patients had a urine osmolality below 285 mOsmol/l (n=14, of which 7 with a mGFR > 60 ml/min/1.73m^2) and a Uosm/Posm ratio below 1 (n=13, of which 8 with a mGFR > 60 ml/min/1.73m^2). Table 2 gives the results of univariate and multivariate analyses with copeptin concentration as dependent variable. There was no association between urine osmolality and copeptin concentration, neither in a crude analysis nor after adjustment for age and sex. This was both the case for patients with mGFR > 60 and for patients with a mGFR ≤ 60 ml/min/1.73m^2. (p=0.2 and p=0.2, respectively). Also when urine osmolality was expressed as ratio to plasma osmolality (Uosm/Posm ratio), no association was found with plasma copeptin concentration. This correlation again was not different in patients with mGFR > 60 compared to patients with mGFR ≤ 60 ml/min/1.73m^2 (*R* =0.19, p=0.2 and *R* = 0.26, p=0.2, respectively). Only after adjustment for mGFR and TKV, the associations between urine osmolality and Uosm/Posm ratio with copeptin concentration reached statistical significance (Table 2). In addition, we investigated the association of 24-hour urine volume with urine osmolality and copeptin concentration. No significant association was found between 24-hour urine volume and copeptin concentration (p=0.7), but 24-hour urine volume was associated with urine osmolality (*R* =-0.66, p<0.001).

The associations of plasma osmolality with copeptin concentration are also presented in Figure 1 (lower panel). Model 1 shows that crude plasma osmolality was positively associated with copeptin concentration in the overall population (*R* =0.54, p<0.001), and in ADPKD patients with mGFR > 60 as well as mGFR ≤ 60 ml/min/1.73m^2 (*R* =0.4, p=0.003 and *R*=0.56, p=0.002, respectively). Model 2 shows that this association remained significant, when adjusted for age and sex. In Model 3, when additionally adjusted for TKV and mGFR, this association remained, although it did not reach formal statistical significance. Of note, urine osmolality and Uosm/Posm ratio were negatively associated with plasma osmolality (*R* =-0.22, p=0.04 and *R* =0.97, p<0.001, respectively).

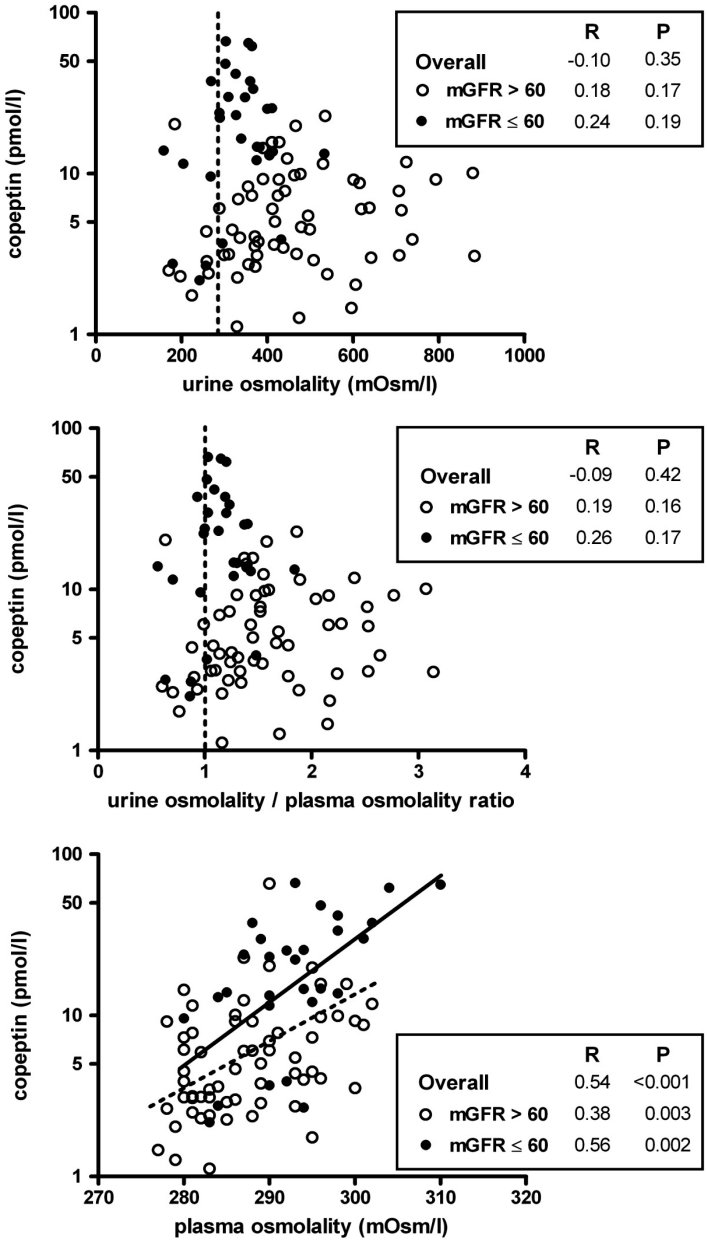

Figure 1. Association of 24-hour urine osmolality, urine to plasma osmolality ratio and plasma osmolality with copeptin concentration in ADPKD patients (overall n=94, mGFR > 60 ml/min/1.73m^2 n=64, and mGFR ≤ 60 ml/min/1.73m^2 n=30). Dashed line in upper panel represents a urine osmolality = 285 mOsmol/l, and the dashed line in the middle panel a urine osmolality equal to plasma osmolality. In the lower panel the association of plasma osmolality with copeptin concentration is shown separately for ADPKD patients with mGFR ≤ 60 ml/min/1.73m^2 (solid line) and > 60 ml/min/1.73m^2 (dashed line).

Table 2. Multivariate linear regression analyses investigating the cross-sectional association of baseline urine osmolality, urine to plasma osmolality ratio and plasma osmolality with baseline copeptin concentration (as dependent variable) in 94 ADPKD patients.

	Model 1*		Model 2**		Model 3***	
	St. β	p-value	St. β	p-value	St. β	p-value
Uosm	-0.10	0.35	-0.02	0.86	+0.22	0.006
Age			+0.26	0.01	-0.12	0.14
Male sex			-0.32	0.001	-0.07	0.33
mGFR					-0.66	<0.001
TKV					+0.33	<0.001
Uosm/Posm ratio	-0.09	0.42	-0.01	0.98	+0.21	0.006
Age			-0.27	0.002	-0.13	0.13
Male sex			-0.31	0.01	-0.08	0.30
mGFR					-0.66	<0.001
TKV					+0.34	<0.001
Posm	+0.54	<0.001	+0.44	<0.001	+0.18	0.07
Age			+0.09	0.36	-0.21	0.03
Male sex			-0.15	0.13	-0.10	0.26
mGFR					-0.46	<0.001
TKV					+0.30	0.004

*Model 1: crude; **Model 2: adjusted for age and sex; ***Model 3 adjusted for age, sex, mGFR and TKV. *Abbreviations*: St. β, standardized beta; Uosm, urine osmolality; mGFR, measured glomerular filtration rate; TKV, total kidney volume; Uosm/Posm ratio, Urine to plasma osmolality ratio; Posm, plasma osmolality.

Figure 2 shows that mGFR was significantly associated with urine osmolality, plasma osmolality and plasma copeptin concentration (all p<0.001). TKV was also significantly associated with plasma osmolality and plasma copeptin concentration (both p<0.001), but not with urine osmolality (*R* = -0.12, p=0.3).

Table 3 presents the associations of baseline urine osmolality, plasma osmolality, Uosm/Posm ratio and copeptin concentration with change in estimated glomerular filtration rate (eGFR) during follow-up. Fifty-five patients were followed for 2.8 ± 0.8 years and their mean change in eGFR was -3.3 ± 2.9 ml/min/1.73m^2 per year. Baseline urine osmolality was not associated with change in eGFR, neither crude, nor after adjustment for age and sex or additional adjustment for TKV. When urine osmolality was expressed as ratio of plasma osmolality, using the Uosm/Posm ratio, similar results were obtained. In contrast, plasma osmolality was significantly associated with decline in eGFR. However after adjustment for age and sex, only a trend was seen, and after further adjustment for TKV, the association was absent. The association of baseline copeptin concentration with change in eGFR was significant (*St.* β = -0.41, p=0.003), also after adjustment for age, sex and TKV (*St.* β = -0.23, p=0.048). In addition, we investigated the association between 24-hour urine volume with change in renal

function and copeptin concentration. No significant associations were found (p=0.6 and p=0.7 respectively). Lastly, urinary sodium excretion was not correlated with change in eGFR (*R*=0.02, p=0.9).

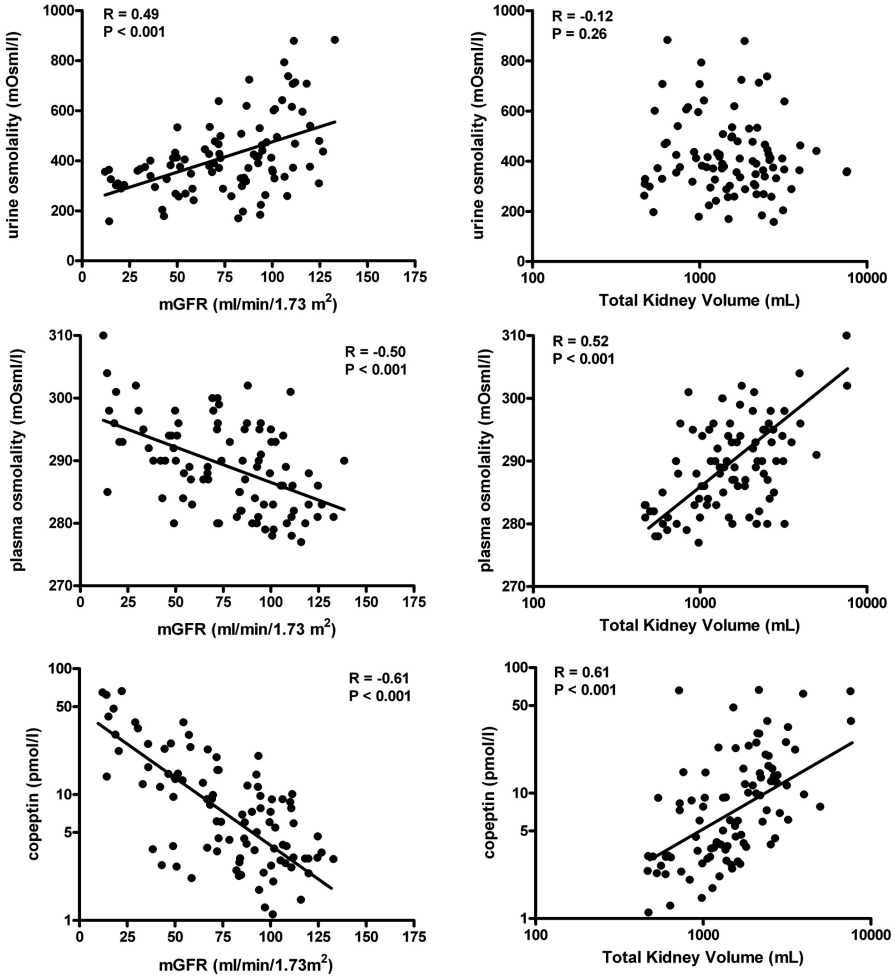

Figure 2. Associations of measured glomerular filtration rate (mGFR) and total kidney volume (log scale) with 24-hour urine osmolality, plasma osmolality and copeptin concentration in 94 ADPKD patients.

Of note, the results of the sensitivity analyses (i.e. analyses stratified for sex and analyses including outliers of copeptin concentration) were essentially similar to the results of the primary analyses. In addition, in the multivariate regression analyses with copeptin concentration as dependent variable, interaction terms of mGFR with

urine osmolality, plasma osmolality and Uosm/Posm ratio were not significant (p=0.3, p=0.2 and p=0.6, respectively). Furthermore, for baseline copeptin concentration the interactions of sex with urine and plasma osmolality and with the Uosm/Posm ratio were not significant (p=0.3, p=0.6 and p=0.1, respectively). In addition, no significant interaction terms of copeptin with sex and mGFR were found in the analyses with change in eGFR as dependent variable (p=0.5 and p=0.4, respectively). Lastly, when calculated effective plasma osmolality was studied instead of measured plasma osmolality, essentially similar results were obtained. Effective plasma osmolality was independently associated with copeptin concentration, but lost significance after adjustment for age, sex, mGFR and TKV (*St.* β = 0.31, p=0.01; *St.* β = 0.17, p=0.1, respectively). Effective plasma osmolality was also independently associated with mGFR and TKV (*R* =-0.43, p=0.004 and *R* =0.36, p=0.002, respectively).

Table 3. Multivariate linear regression analyses investigating the association of baseline urine osmolality, urine to plasma osmolality ratio, plasma osmolality and plasma copeptin concentration with change in eGFR during follow-up (as dependent variable) in 55 ADPKD patients.

	Model 1*		Model 2**		Model 3***	
	St. β	p-value	St. β	p-value	St. β	p-value
Uosm	+0.11	0.43	+0.17	0.30	+0.14	0.34
Age			+0.10	0.54	+0.21	0.18
Male sex			+0.18	0.22	-0.06	0.71
TKV					-0.53	0.001
Uosm/Posm ratio	+0.09	0.53	+0.16	0.37	+0.13	0.40
Age			+0.09	0.59	+0.21	0.20
Male sex			+0.17	0.26	-0.04	0.78
TKV					-0.52	0.002
Posm	-0.29	0.04	-0.32	0.06	-0.11	0.55
Age			+0.11	0.49	+0.18	0.23
Male sex			+0.01	0.93	-0.09	0.56
TKV					-0.48	0.007
Copeptin	-0.41	0.003	-0.43	0.006	-0.23	0.048
Age			-0.34	0.71	+0.14	0.30
Male sex			-0.15	0.83	-0.12	0.41
TKV					-0.41	0.02

*Model 1: crude; **Model 2: adjusted for age and sex; ***Model 3 adjusted for age, sex and TKV. *Abbreviations*: St. β, standardized beta; Uosm, urine osmolality; TKV, total kidney volume; Uosm/Posm ratio, Urine to plasma osmolality ratio; Posm, plasma osmolality.

Discussion

Given the deleterious role of AVP in ADPKD we tried to address in the present study the question how to identify ADPKD patients with high AVP levels. In healthy persons with normal kidney function, it has been shown that AVP concentration correlates positively with urine osmolality (18, 25). In this situation, urine osmolality seems the perfect marker to monitor AVP levels. Consequently it has been suggested that in ADPKD patients a urine osmolality under 285 mOsmol/l or a urine osmolality below plasma osmolality indicates a water intake appropriate to suppress AVP levels (9, 11). However, our findings suggest that in such patients both urine osmolality and urine to plasma osmolality ratio are not appropriate to monitor AVP levels, measured as plasma copeptin concentration. Moreover, we found that urine osmolality was not associated with the rate of renal function decline during follow-up. These observations were similar in patients with impaired, as well as with relatively preserved kidney function.

A possible explanation of the fact that urine osmolality did neither correlate with copeptin levels nor with decline in renal function during follow-up, is that patients with ADPKD, even in a relatively early stage of their disease, can have an impaired urine concentration capacity. In a water deprivation test in which 15 ADPKD patients were included and 15 healthy controls, matched for sex and age, it was found that ADPKD patients had a reduced maximal urine concentration capacity compared to healthy controls, despite the fact that their GFR was still normal (26). Early cyst formation leads to destruction of the renal architecture which, in turn, causes a failure to generate and maintain a hyperosmotic interstitial milieu, resulting in a low urine osmolality independent of vasopressin level (12, 27). The fact that the association between copeptin and urine osmolality reached significance only after correction for TKV supports this hypothesis.

Another marker to monitor activity of the AVP system might be measuring plasma osmolality. It is well known that under normal conditions, secretion of AVP is predominantly driven by an increase in plasma osmolality. In healthy persons with normal kidney function, plasma osmolality correlates therefore well with AVP levels (18). In this study we found that in ADPKD patients plasma osmolality was indeed positively associated with copeptin concentration, although after adjustment for sex, age, TKV and mGFR, this association lost significance.

In addition, in our study plasma osmolality was only weakly associated with change in eGFR during follow-up, and this association was also lost after adjustment for covariates, indicating that measuring plasma osmolality has limited added value to predict prognosis. Again, these observations held true in patients with impaired, as

well as with relatively preserved kidney function. That plasma osmolality had a limited role as marker for disease progression may be caused by the fact that plasma osmolality is usually held within narrow ranges (i.e. between 275 to 290 mOsmol/l) as variations of only 1 to 2 percent initiate feed-back mechanisms to return osmolality to normal. Of note, measured plasma osmolality could theoretically be less reliable in case of impaired kidney function, because increases in urea concentration could influence measured plasma osmolality and thereby disturb the association of plasma osmolality with copeptin concentration. As a sensitivity analysis we therefore also analyzed the association of calculated effective plasma osmolality with copeptin concentration. Essentially similar results were obtained. We therefore consider measured plasma osmolality reliable, and used this parameter as one of our primary outcome measures.

In literature, several cohort studies have shown that TKV and AVP (measured as copeptin) are good predictors for a decline in renal function during follow-up (28-30). Also in the present study TKV was the strongest marker for renal function decline. However, measurement of TKV is labor intensive and therefore difficult to operationalize in clinical care. In that respect measurement of copeptin concentration might be a more feasible alternative. The present study corroborates that higher copeptin is associated with more rapid renal function decline and that this associations persists after correction for age, sex, and even after additional correction for TKV. These data suggest that measurement of copeptin concentration, as alternative for measuring urine or plasma osmolality to reflect AVP activity, may be of help to identify ADPKD patients at risk for rapid disease progression.

Patients with impaired renal function had on average higher copeptin levels. However, it should be noted that copeptin concentration has a broad distribution. Some patients with impaired renal function had lower copeptin levels than the average level in patients with normal kidney function. In patients with preserved renal function the opposite can be found. Therefore, selecting patients based on GFR will not be similar as selecting patients on copeptin concentration.

It should be emphasized that the present study did not investigate the role of increasing water intake on copeptin or AVP concentration, nor on the rate of disease progression. Theoretically, however, an increase in water intake is expected to reduce the rate of disease progression in ADPKD by decreasing AVP activity, as has been shown for AVP V2 receptor blockade by tolvaptan (3). On the other hand, there may be limitations to the efficacy of increasing water intake (7). Medical treatment with tolvaptan leads to a long-term pharmacologic suppression of the AVP pathway. It is unknown whether long-term increases in water intake can also suppress AVP activity sustainably and what volume of fluid would be necessary to achieve this. A cautionary

note should be made, being that clinicians should monitor ADPKD patients with impaired renal function that increase their water intake, because these patients are at risk for overhydration and hyponatremia.

We acknowledge that this study has limitations, the main ones being that this is an observational study and that most associations are based upon cross-sectional data. Our findings should therefore be considered as hypothesis generating. Secondly, a relatively small number of patients was included. That we despite this limitation found a significant association between copeptin concentration and change in kidney function indicates that our data are robust. Of note, this number of patients did also not allow analyses stratified for all CKD stages, and we therefore analyzed our data for participants stratified for mGFR > and ≤ 60 ml/min/1.73m2. Lastly, in the participants with a ≤ 60 ml/min/1.73m2 the majority of patients was male, which potentially could influence the study results. However, our study results did not change essentially in sex stratified analyses, and sex did not appear to be a significant effect modifier. Strengths of our study are that this is the first study that investigates in ADPKD patients the associations between plasma copeptin concentration, plasma and urine osmolality at baseline, and the associations of these variables with change in kidney function during follow-up. Moreover, we investigated whether these associations depend on disease severity in ADPKD. Furthermore, we assessed GFR and TKV at baseline using gold standard measures.

In conclusion, our data suggest that plasma and urine osmolality cannot be used to identify ADPKD patients with a high copeptin (i.e. vasopressin) concentration that are at risk for a more rapid rate of kidney function decline during follow-up. Urine and plasma osmolality seem therefore no valid measures to identify ADPKD patients with a worse prognosis. For this purpose measuring copeptin concentration may be a better alternative.

Sources of support
None.

Disclosures
JS is an employee of ThermoFisher Scientific, the company that manufactures and holds patent rights on the copeptin assay. The other authors declared no competing interests.

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Chapter 10

Polyuria due to vasopressin V2 receptor antagonism is not associated with increased ureter diameter in ADPKD patients

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Abstract

Background: Tolvaptan, a vasopressin V2 receptor antagonist, has been shown to reduce the rates of growth in total kidney volume (TKV) and renal function loss in ADPKD patients, but also leads to polyuria because of its aquaretic effect. Prolonged polyuria can result in ureter dilatation with consequently renal function loss. Therefore, we aimed to investigate the effect of tolvaptan induced polyuria on ureter diameter in ADPKD patients.

Methods: 70 ADPKD patients were included (51 were randomized to tolvaptan and 19 to placebo). At baseline and after 3 years of treatment renal function was measured (mGFR) and MRI was performed to measure TKV and ureter diameter at the levels of renal pelvis and fifth lumbar vertebral body (L5).

Results: In these patients (65.7% male, age 41±9 years, mGFR 74±27 mL/min/1.73m^2 and TKV 1.92 (1.27 – 2.67) L), no differences were found between tolvaptan and placebo treated patients in 24-hour urine volume at baseline (2.5 vs. 2.5 L, p=0.8), nor in ureter diameter at renal pelvis and L5 (4.0 vs. 4.2 mm, p=0.4 and 3.0 vs. 3.1 mm, p=0.3). After 3 years of treatment 24-hour urine volume was higher in tolvaptan treated patients when compared to placebo (4.7 vs. 2.3 L, p<0.001), but no differences were found in ureter diameter between both groups (renal pelvis: 4.2 vs. 4.4 mm, p=0.4 and L5: 3.1 vs. 3.3 mm, p=0.4).

Conclusions: Tolvaptan induced polyuria did not lead to an increase in ureter diameter, suggesting that tolvaptan is a safe therapy from a urological point of view.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) has a diagnosed prevalence of approximately 3-4 per 10.000 in the general population and is characterized by progressive cyst formation in both kidneys and renal function loss (1, 2). It is the fourth most common cause of end-stage renal disease for which renal replacement therapy is the only therapeutic option (3). The TEMPO 3:4 trial publication recently showed renoprotective effects of tolvaptan therapy in a randomized controlled clinical trial setting (4). During 3 years of follow-up the vasopressin V2 receptor antagonist tolvaptan decreased the rate of growth in total kidney volume and the rate of renal function loss compared to placebo. Due to its aquaretic effect tolvaptan causes polyuria that sometimes can be severe. In some ADPKD patients tolvaptan use could result to a urine output up to 8-10 liters per day.

Patients with prolonged polyuria should be used to void more frequently since the maximum bladder capacity is reached earlier. Infrequent and inconstant voiding could easily lead in these patients to an accumulation of urine retention with more often higher intravesical pressure. Consequently this may result to higher pressure in the upper urinary tract which can cause ureter dilatation, hydronephrosis and ultimately renal function loss. This mechanism from polyuria to renal function loss has already been described several times in literature in patients with (nephrogenic) diabetes insipidus and psychogenic polydipsia (5-11). To reduce the risk of these problems, patients with polyuria are therefore advised to void more frequently (5).

ADPKD patients who use tolvaptan potentially have the risk to develop similar problems. Hypothetically, it could be that in some patients the beneficial effect of tolvaptan with respect to kidney function preservation is partially offset due to these urological side effects. The aim of the present study was therefore to investigate the effect of tolvaptan induced polyuria, assessed as 24-hour urine volume, on the ureter diameter in patients with ADPKD.

Methods

Patients and study design

The present study was performed as a post-hoc exploratory analysis of ADPKD patients that were included in the TEMPO 3:4 trial (ClinicalTrials.gov identifier NCT00428948) and 284 trial (NCT01336972) in the University Medical Center Groningen. All participating patients of the TEMPO 3:4 trial were included (n=51) and 19 of the 27

patients from the 284 study, because only 19 patients had used tolvaptan for at least 12 months. Details of both study protocols (12) and the primary study results (4, 13) have been published previously. Patients were included in the TEMPO 3:4 trial if they were 18-50 years old, had a total kidney volume (TKV) measured by magnetic resonance imaging (MRI) ≥750 ml and creatinine clearance estimated (eCrCl) by the Cockcroft-Gault formula ≥60 ml/min. ADPKD patients between 18-70 years were included in the 284 trial and were assigned by estimated GFR (eGFR) in three groups (group 1: eGFR >60; group 2: eGFR 30-60; group 3: eGFR <30 ml/min/1.73m^2). Exclusion criteria for both studies were most importantly concomitant illnesses likely to confound endpoint assessments, such as diabetes mellitus and previous use of tolvaptan.

In the TEMPO 3:4 trial patients were randomized to tolvaptan or placebo (2:1) with stratification by hypertension status, eCrCl and TKV. Tolvaptan dosing was started at 45 mg am/15 mg pm (daily split-dose) and increased weekly to 60/30 mg and 90/30 mg, if tolerated. Patients remained on the highest tolerated dose for 36 months. Patients in the 284 trial used open label tolvaptan, dosing started at 45 mg am/15 mg pm and increased weekly to 60/30 mg and 90/30 mg if tolerated. After completing the TEMPO 3:4 trial and 284 trial, all patients were offered to continue tolvaptan use in the open-label tolvaptan study (TEMPO 4:4 trial, NCT01214421). All studies were performed in adherence to the Declaration of Helsinki, and all patients gave written informed consent.

Data collection and measurements

All patients routinely collected a 24-hour urine sample the day preceding the baseline assessment. Fasting blood samples were drawn for determination of creatinine and estimated GFR (eGFR) was applied by the CKD-EPI equation (14). After blood samples were drawn, renal function measurements were performed using the constant infusion method with ^{125}I-iothalamate to measure glomerular filtration rate (mGFR) (15, 16). MR imaging was performed immediately after renal function measurement (around 5 pm) using a standardised abdominal MR imaging protocol without the use of intravenous contrast (17). Per protocol patients took their afternoon tolvaptan dose at 4 pm, so MR imaging was performed within 1.5 hour after tolvaptan administration. 56 patients were scanned on a 1.5 Tesla MR (Magnetom Avento, Siemens, Erlangen, Germany) and 14 patients on a 3-Tesla research MR scanner (Intera, Philips, Eindhoven, the Netherlands). TKV was assessed using Analyze Direct 8.0 software (AnalyzeDirect, Inc., Overland Park, KS, USA). After 3 years, MR imaging as well as renal function measurements were performed again per protocol in the Tempo 3:4 trial, with patients still being on treatment.

The MR images on baseline and after 3 years of treatment were used to assess anatomy of the urinary tract and to measure ureter diameter. MR imaging is, among others, a valuable and accurate imaging method for evaluating the urinary tract system including the ureter (18-21). Ureter diameter was measured, preferably on the coronal T2-Half Fourier Single Shot Turbo Spin Echo (HASTE) (Figure 1). Ureter diameter was measured at both sides at two places (3 cm distally from the pyelo-ureteral junction as well as at the level of the fifth lumbar vertebral body: L5) as the diameter of the ureter measured perpendicular from ureter wall to ureter wall. Normal diameter of the ureter is 3-5 mm. Ureter dilation was defined as a ureter diameter >7 mm according to the prevailing classification system (22, 23).

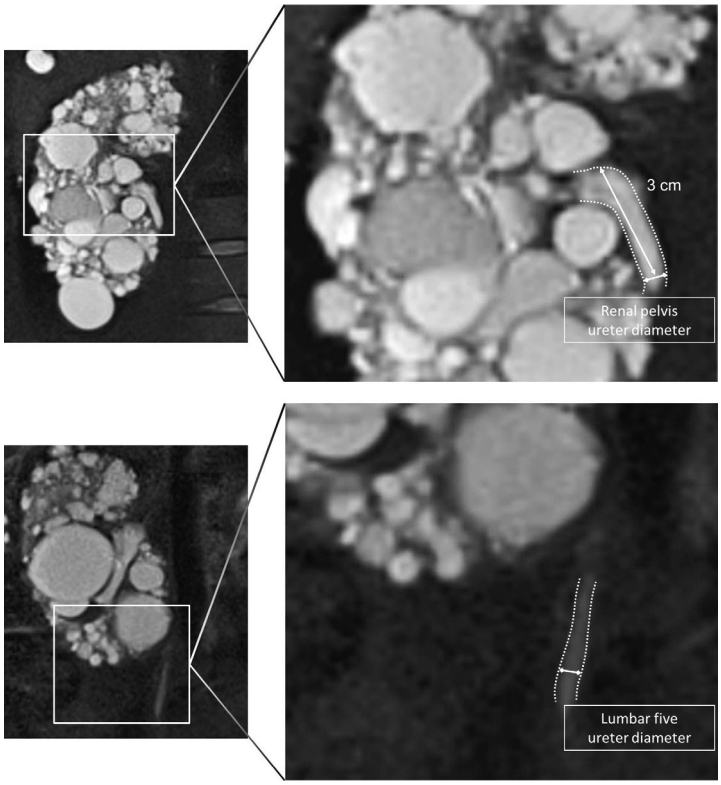

Figure 1. Ureter diameter was measured 3 cm after the pyelo-ureteral junction (upper panel) and on the level of L5 (lower panel), perpendicular from ureter wall to ureter wall, preferably on the coronal T2-Half Fourier Single Shot Turbo Spin Echo (HASTE) sequence. White lines indicate the place of measurement.

Statistical analysis

Baseline characteristics were calculated for the overall population and for both treatment groups separately. Parametric variables are expressed as mean ± SD, non-parametric variables as median (IQR). Differences in baseline characteristics between the two treatment groups were calculated with a Chi-square test for categorical data, and for continuous data with Student's t-test or a Mann-Whitney U test in case of non-parametric data.

To investigate reliability of ureter diameter measurement on MR images, we assessed intra- and inter-observer variability. Two physicians were trained to measure ureter diameter. In a test set of 10 patients, ureter diameter was measured twice at baseline as well as at the end of the study. The physicians were blinded for their previous measurement results. These results were analysed to calculate intra- and inter-observer coefficients of variation (CV). Inter-CV was calculated as the SD of ureter diameter values measured by two observers in the 10 subjects divided by the mean ureter diameter of those subjects multiplied by 100%. The intra-CV was calculated as SD of ureter diameter values measured by a single observer divided by the mean ureter diameter of single observer multiplied by 100%.

Pearson's Chi squared test was used to assess differences in prevalence of a dilated ureter (defined as a ureter with exceeding 7 mm (22, 23)) between the placebo group and the tolvaptan group at baseline and after 3 years of treatment. Paired t-tests were used to compare ureter diameter at baseline and three years of treatment, whereas unpaired t-tests were used to assess any differences in ureter diameter between placebo and tolvaptan treated patients at baseline and after 3 years of treatment.

Furthermore, univariate and multivariate linear regression analyses were performed to investigate which variables were associated with ureter diameter (defined as mean diameter at renal pelvis and L5). Determinants were, among others, patient characteristics (e.g. sex and age), use of tolvaptan and 24-hour urine volume. Determinants with $p<0.1$ in univariate analyses were selected for multivariate analyses. Statistical analyses were performed using SPSS 22 (SPSS Statistics, Inc., Chicago, IL, U.S.A.). A 2-tailed P-value <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics

Patient characteristics are presented in Table 1. A total of 70 patients with ADPKD were included, of which 51 used tolvaptan and 19 patients placebo.

Table 1. Baseline characteristics.

	All	Placebo	Tolvaptan	P-value
N	70	19	51	-
Age (y)	41 ± 9	37 ± 6	42 ± 9	0.03
Male sex (%)	65.7	63.2	66.7	0.8
Length (cm)	181 ± 11	181 ± 11	181 ± 10	0.1
Weight (kg)	86 ± 15	85 ± 14	86 ± 14	0.6
Body mass index (kg/m^2)	26.2 ± 3.5	25.7 ± 3.9	26.3 ± 3.3	0.5
Antihypertensive use (%)	84.3	78.9	86.3	0.5
Systolic blood pressure (mmHg)	132 ± 11	132 ± 11	132 ± 11	0.9
Diastolic blood pressure (mmHg)	82 ± 8	82 ± 7	83 ± 9	0.7
Heart rate (per minute)	68 ± 12	66 ± 11	69 ± 12	0.3
Plasma creatinine (umol/l)	117 ± 57	106 ± 39	121 ± 62	0.3
mGFR (mL/min/1.73m^2)	74 ± 27	80 ± 24	72 ± 28	0.2
eGFR (mL/min/1.73m^2)	69 ± 27	73 ± 21	68 ± 29	0.5
Total kidney volume (L)	1.92 (1.27 – 2.67)	1.68 (1.13 – 2.37)	2.03 (1.31 – 2.67)	0.3

Abbreviations: mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate

Overall, patients were 41±9 years old and 65.7% were male. Table 1 also shows the patient characteristics stratified according to tolvaptan and placebo use. No significant differences in characteristics were observed between these two groups, except for age. Patients in the placebo group were slightly younger (p=0.03).

At baseline, no differences were found between tolvaptan and placebo treated patients in 24-hour urine volume (2.46 (2.08-2.72) vs. 2.50 (1.94-3.08) L, p=0.8) (Table 2). Ureter diameter was measured in all patients except for two, because their ureters were not depicted on MR images. At baseline 2 patients had a dilated ureter, one patient left-sided, and one patient right-sided. No significant difference in ureter diameter was found between tolvaptan and placebo treated patients (renal pelvis: 4.0±0.9 vs. 4.2±1.1 mm, p=0.3 and L5: 3.0±0.5 vs. 3.1±0.4 mm, p=0.2, respectively). Mean baseline ureter diameter was not associated with baseline 24-hour urine volume, neither in a crude analysis nor after adjustment for age, sex, TKV and mGFR (p=0.8 and p=0.4, respectively) (Figure 2). Furthermore, no association was found between baseline ureter diameter and baseline TKV or mGFR.

Ureter assessment during follow-up

After 36 months of treatment, 24-hour urine volume was significantly higher in tolvaptan treated patients (4.74 (3.34-5.68) vs. 2.33 (2.08-2.66) L, p<0.001) (Table 2). One patient had a dilated ureter right-sided. This was a patient from the placebo group and had at baseline a ureter diameter of 5.9 mm and after three years of 8.4 mm at the level of the renal pelvis. No significant differences in ureter diameter were found between baseline and after 3 years in the 51 tolvaptan treated patients for ureter diameter measurements at renal pelvis and L5 right as well as left-sided (Table 2). In addition, no differences were found in ureter diameter between both treatment groups after 3 years (renal pelvis: 4.1±1.0 vs. 4.4±1.2 mm, p=0.4 and L5: 3.1±0.7 vs. 3.3±0.7 mm, p=0.4). No significant association was found between ureter diameter and 24-hour urine volume at year 3, neither in a crude analysis nor in a multivariate model adjusting for age, sex, TKV and mGFR (p=0.9 and p=1.0, respectively) (Figure 2). Ureter diameter at year 3 was also not associated with TKV and mGFR. Tolvaptan use led to a decreased kidney growth, annual change in TKV was significantly lower in the tolvaptan treated patients (2.7% vs. 6.0%, p=0.003). We did not find an association between annual change in TKV and ureter diameter (p=0.2).

Table 2. Ureter diameter subdivided in placebo group (n=19) and tolvaptan group (n=51).

	Baseline	Year 3	Change	P-Value Base vs. Year 3	P-Value P vs. T Year 3
24-hour urine volume (L)					
- *Placebo*	2.50 (2.08 – 2.72)	2.33 (2.08 – 2.16)	0.09 (-0.38 – 0.96)	0.4	<0.001
- *Tolvaptan*	2.46 (1.94 – 3.08)	4.74 (3.34 – 5.68)	2.08 (1.08 – 3.03)	<0.001	
Renal pelvis left (mm)					
- *Placebo*	4.0 ± 1.0	4.1 ± 0.9	0.1 ± 0.5	0.6	0.5
- *Tolvaptan*	3.8 ± 1.0	3.9 ± 1.1	0.1 ± 1.0	0.8	
Renal pelvis right (mm)					
- *Placebo*	4.4 ± 1.2	4.7 ± 1.7	0.2 ± 1.0	0.6	0.5
- *Tolvaptan*	4.1 ± 1.1	4.4 ± 1.2	0.2 ± 1.1	0.2	
Ureter L5 left (mm)					
- *Placebo*	3.1 ± 0.4	3.4 ± 0.8	0.3 ± 0.8	0.2	0.2
- *Tolvaptan*	3.0 ± 0.7	3.1 ± 0.7	0.1 ± 0.7	0.3	
Ureter L5 right (mm)					
- *Placebo*	3.2 ± 0.5	3.2 ± 0.9	0.0 ± 0.9	1.0	0.7
- *Tolvaptan*	2.9 ± 0.5	3.1 ± 1.0	0.2 ± 1.1	0.2	

Abbreviations: Base, baseline; P, placebo; T, tolvaptan.

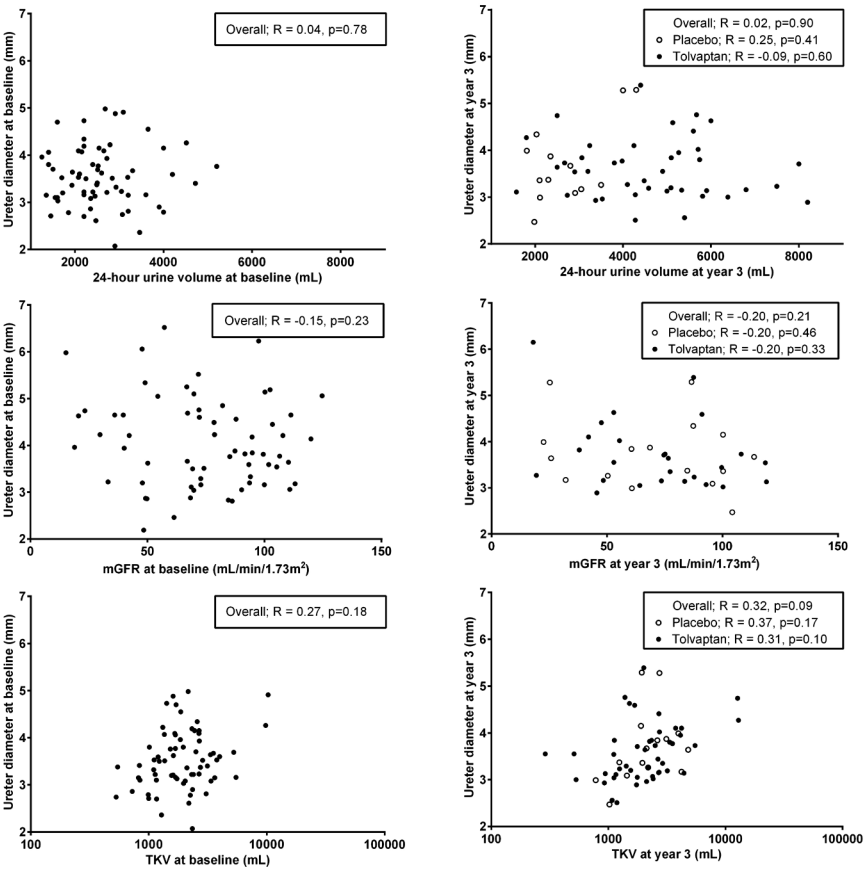

Figure 2. Associations of 24-hour volume (upper panels), measured glomerular filtration rate (middle panels) or total kidney volume (log scale, lower panels) with ureter diameter at baseline (left panels) and at year 3 (right panels).

After 3 years of treatment with study medication in the TEMPO 3:4 trial, we offered our patients to participate in the open-label tolvaptan study (TEMPO 4:4 trial, NCT01214421). From the initial 51 patients, 32 patients used tolvaptan and 19 patients used placebo. From these 32 patients, 22 patients were followed for an average of 3.6±0.8 years and again MR imaging was performed. Their 24-hour urine volume was still significantly higher compared to their baseline volume (2.45 (2.02-2.91) vs. 5.13 (3.24-5.90) L, $p<0.001$). No significant differences in ureter diameter were found between ureter diameter at baseline and at follow-up in these 22 tolvaptan treated patients for ureter diameter measurements at the renal pelvis and L5, right as well as left-sided (renal pelvis left: 3.7±0.9 vs. 3.7±0.7 mm, p=0.7; renal pelvis right: 4.1±1.2 vs. 3.9±0.7 mm, p=0.3; L5 left: 3.1±0.7 vs. 3.1±0.6 mm, p=0.9 and L5 right 3.0±0.6 vs. 3.1±0.8 mm, p=0.4).

Sensitivity analysis

For sensitivity analysis of the ureter measurement, intra- and inter-reviewer coefficients of variation for ureter measurement were 6.4% and 7.2%, respectively, and did not differ when measured on the level of the renal pelvis level or L5, nor between left or right sided ureters. The association between baseline ureter diameter with ureter diameter at the end of the study is shown in Figure 3. As depicted, baseline ureter diameter at the renal pelvis was strongly correlated with ureter diameter at the end of the study in the overall group, as well as in tolvaptan and placebo treated patients (overall R=0.69, p<0.001; tolvaptan R=0.60, p=0.012; placebo R=0.87, p<0.001). At the level of L5 baseline ureter diameter was also associated with ureter diameter at the end of the study (overall R=0.52, p<0.001). This indicated and supported that ureter diameter measurements were reproducible and could be measured adequately on MRIs that were performed for TKV measurement in ADPKD patients.

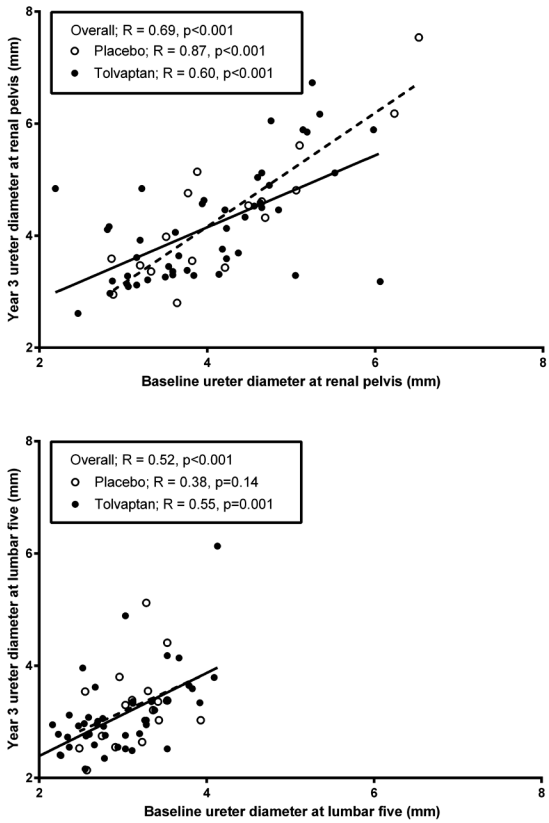

Figure 3. Associations of ureter diameter at baseline with ureter diameter at year 3 in ADPKD patients at the level of the renal pelvis (upper panel) or lumbar 5 (lower panel) (overall n=70, tolvaptan use n=51 (solid line), placebo use n=19 (dashed line)).

Of note, the results of the sensitivity analyses (i.e. analyses stratified for sex) were essentially similar to the results of the primary analyses. When eGFR was studied instead of mGFR, similar results were obtained. Lastly, there were no significant interaction terms of 24-hour urine volume with sex and age in the analyses, with ureter diameter at the end of study as dependent variable (p=0.6 and p=0.8, respectively).

Discussion

The present study shows that tolvaptan induced polyuria did not lead to an increase in ureter diameter after 3 years of tolvaptan treatment, suggesting that tolvaptan did not cause high pressure in the upper urinary tract which can lead to renal function loss.

Up to 2014, no treatment options were available to modify the course of disease progression in ADPKD. In 2007, the first large-scale randomized controlled trial, the TEMPO 3:4 trial, started with a potential therapeutic drug, tolvaptan, in ADPKD patients (4). For the first time, a medical treatment proved to be beneficial with respect to kidney outcomes. In 1445 ADPKD patients with a preserved kidney function, treatment with tolvaptan reduced the rate of growth in TKV by 49% and the rate of eGFR loss by 26% compared with placebo (4). Despite of these promising results, the Food and Drug Administration (FDA) decided against approval of tolvaptan for the indication of slowing disease progression in ADPKD. Whereas the FDA decided not to register tolvaptan, it is recently been approved in Japan, Canada and Europe.

Patients who received tolvaptan had, as expected, a higher frequency of adverse events related to increased aquaresis (thirst, polyuria, nocturia, and polydipsia, as a result of the excretion of electrolyte-free water). The urine output was highly increased, even up to 10 liters per day. In normal conditions, contractions in the ureter wall cause peristaltic waves that transport the urine from the collecting ducts via the renal pelvis and ureter into the bladder. To enter the bladder, the intra-ureteric pressure should be higher than the intravesical pressure. In case of prolonged polyuria and inconstant and infrequent voiding, the intravesical pressure increases by the persistent accumulation of urine in the bladder. In this situation the ureteric pressure is too low for the urine to enter the bladder resulting in decompensation, ureter dilatation and hydronephrosis (8).

Prolonged polyuria as cause of ureter dilatation and bilateral non-obstructive hydronephrosis has been documented in patients with (nephrogenic) diabetes insipidus and psychogenic polydipsia (5-11). This phenomenon has not only been observed in adult diabetes insipidus patients with polyuria since childhood, but also

in adult patients with polyuria for only 3 to 5 years (11, 24). Interestingly, some patients had large bladder volumes and hydronephrosis by radiological investigations, while others did not have an increased bladder volume. However their renal function already declined because of hydronephrosis. This indicated and supported that persistent polyuria itself could cause dilatation of the urinary tract, which could also be a theoretical issue in tolvaptan treated patients.

To our knowledge, no studies have been performed to investigate the effect of polyuria on ureter diameter in ADPKD patients. Our study results are supported by previous studies published in the renal transplant literature. It has been shown that one kidney can process an increased fluid load up to 4 liter per day without developing structural or functional defects in the renal pelvis or ureter as well as progressive kidney function decline (25, 26).

Since tolvaptan is recently approved in Japan, Canada and Europe, we are aware that this theoretical problem of tolvaptan exists and clinicians should therefore inform their ADPKD patients, who use tolvaptan, about the potential urological effects. Patients are instructed to void more frequently than usual. When they feel the urge to void, they should not ignore their voiding tendency. In addition, ADPKD patients on tolvaptan have to avoid drugs that diminish, at least the sense of, bladder contractility like anticholinergic drugs (27). Long-term use of anticholinergic drugs in combination with polyuria could potentially lead to urological problems of bladder distension and hydronephrosis (11). Lastly, patients with known obstructive lower urinary tract symptoms should be informed that the combination of polyuria and these symptoms might lead to an increased risk of renal failure (28).

We acknowledge that this study has limitations. First, a relatively small number of patients was included, which may lead to false negative conclusions. Only patients from our center were included in this study, because this data was readily available to investigate this issue for the first time and our center has the highest number of ADPKD patients on tolvaptan treatment in the world. However, to exclude the risk for ureter dilatation in tolvaptan treated patients, ureter diameter should be assessed in all participating patients in the TEMPO 3:4 trial. Second, ureter diameter depends on ureteral peristalsis, bladder pressure and filling. Ureter diameter varies from time to time, however ureter diameter may be steadily dilated when the physiological peristaltic movement is hampered by prolonged polyuria. Unfortunately, we did not have information about the bladder filling, because the bladder was not depicted on the MR images. Third, the way the ureter was measured is not the gold standard method, which is intravenous pyelography or MR urography. The present study was a post-hoc exploratory analysis of ADPKD patients that were included the TEMPO 3:4

trial and 284 trial. Per protocol only MR imaging was performed for TKV assessment, therefore, no intravenous pyelography or MR urography was performed. However, the way the ureter was measured seems to be a reliable method because we found a strong association between ureter diameter at baseline and after three years tolvaptan use in our population and intra- and inter-observer variability were relatively low. Furthermore, among others, MR imaging is considered as a valuable and accurate imaging tool for evaluating the urinary tract system including the ureter (18-21). Fourth, no data was available about the micturition frequency and volume. Lastly, our negative findings could be caused by a too short follow-up. Patients with diabetes insipidus could have polyuria from childhood. However, our study patients had polyuria only for 3 years, but also patients with a longer follow-up time of more than 6 years (n=22) were investigated with no significant increase in ureter diameter. Furthermore, previous studies reported that short term polyuria could also lead to urological involvement (10, 11, 24, 29).

In conclusion, our data suggest that tolvaptan is safe from a urological point of view. Because of the limited power of our study, a larger scale investigation needs to be performed to exclude that tolvaptan induced polyuria can lead to the development of an increase in ureter diameter in ADPKD. Until such data become available we still advise, when tolvaptan is prescribed as a treatment option in ADPKD, that patients should be instructed to void frequently.

Conflict of interest

The authors have declared that no conflict of interest exists.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number METc2006.285, METc2010.173 and METc2010.187) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Chapter 11

General discussion and future perspectives

General background

The most well-acknowledged clinical problems in ADPKD are cyst growth and renal function loss. However, beyond these, ADPKD patients may experience a number of other symptoms, of which pain and polyuria deserve special attention. In the first part of this thesis a comprehensive overview of pain in ADPKD is given, and several novel pharmacological approaches and minimally invasive therapeutic options are investigated as potential new therapies for ADPKD-related pain. In the second part, the symptom polyuria caused by an impaired urinary concentrating capacity is evaluated and discussed, with special attention for its possible consequence for disease progression.

I. Pain in ADPKD

Due to massive cyst formation in the kidneys and liver, a considerable number of ADPKD patients suffer from pain and gastrointestinal symptoms such as abdominal fullness and early satiety (1-3). There is an on-going debate if and how kidney and liver volume are associated with pain and gastrointestinal symptoms in ADPKD (3-7). Since both kidney and liver volume drive intra-abdominal volume, it is reasonable to assume an association of combined kidney and liver volume with symptom burden in ADPKD. Another factor that potentially affects symptom burden is gender. Higher symptom burden in female ADPKD patients may be caused by differences in reporting between sexes in general, or by differences in relative kidney or liver size between both sexes. In Chapter 2, it was therefore investigated in 309 ADPKD patients whether combined kidney and liver volume is more strongly associated with ADPKD-related pain and gastrointestinal symptoms than kidney or liver volume alone, and secondly whether there is a difference in the strength of this association between males and females. Combined total kidney and liver volume as well as liver volume were positively associated with pain and gastrointestinal symptoms, while total kidney volume was not. Women experienced symptoms more frequently than men. However, sex was not an effect modifier in the relation between organ volume and symptoms and the higher symptom burden in women could be explained by their larger liver volume. The results of Chapter 2 indicate that liver volume plays a prominent role in symptom burden in ADPKD patients, and that therapy to reduce these symptoms should therefore focus especially on the liver.

Symptom burden in ADPKD is multifactorial and other factors than organ volume alone, may contribute (5). Potential other determinants may include clinical events, such as a cyst bleeding, renal stones, urinary tract infection and cyst infection. At this point there is no evidence-based approach for the management of renal cyst infection in ADPKD patients. To fill this gap in knowledge, a systematic review was performed to identify treatment preferences as well as potential factors that could affect treatment outcome in case of a renal cyst infection (**Chapter 3**). Several factors were identified that potentially affect outcome of antimicrobial treatment. Decreased renal function, presence of renal stones, post-renal obstruction, large cyst diameter and a short duration of antimicrobial treatment were detected as potential factors for antibiotic treatment failure. Interestingly, treatment success rates increased significantly over time. Prior to the year 2000, initial therapy succeeded in 25% of the cases, compared to 49% thereafter. One possible explanation for this finding is the longer duration of antimicrobial treatment in cases published after 2000 (7 vs. 15 days). Based on the available data, this systematic review enabled us to design a stepwise approach for the management of renal cyst infection. To optimize the treatment of renal cyst infections in the future, we advocate the construction of a large, prospective multicenter registry, in which all cases with presumed cyst infection are included. Such a registry may be of help to identify the optimal antimicrobial choice and treatment duration for this condition.

Chapter 4 focuses on the effect of tolvaptan, a vasopressin V2 receptor antagonist, on acute renal pain events in ADPKD. Recently tolvaptan has been approved in Europe for the indication to slow disease progression in ADPKD. The authors of the original paper suggested that tolvaptan use may also be associated with a reduction of acute renal pain events (8). In Chapter 4 this finding is explored more closely. This comprehensive study showed that in 1445 ADPKD patients a history of pain-causing-events, such as urinary tract infection, renal stones or hematuria were associated with history of renal pain. These risk factors were associated with a higher incidence of acute renal pain events in the treatment group as well as in the placebo group. Tolvaptan use resulted in a significantly lower incidence of acute renal pain compared to placebo. Pain was a priori categorized according to the intensity of intervention into 5 groups from mild (i.e. prescription of acetaminophen) to most severe (need for hospitalization and/or invasive intervention). The number needed to treat to prevent one pain event ranged from 35 patients when taking any pain event into account (prescription of acetaminophen or worse) to 384 patients when taking only the most severe pain subgroup into account (hospitalization or invasive intervention). We attempted to determine the underlying mechanism for the pain reducing effect

of tolvaptan and found that tolvaptan reduced the incidence of renal complications that are known to be associated with acute kidney pain events, e.g. a reduction in the incidence of urinary tract infections, kidney stones, and cyst hemorrhages. Tolvaptan induced polyuria might explain the lower incidence of these aforementioned renal complications as increased water intake is associated with a lower recurrence of renal stones and urinary tract infections in the general population (9).

Based on these data the question arises whether tolvaptan should be considered as treatment option in ADPKD patients with acute renal pain events. The number of patients needed to treat with tolvaptan to prevent one severe pain related event (i.e. prescription of opioids or worse) in three years was 94, which is quite high to prescribe tolvaptan to ADPKD patients with as sole aim prevention of acute renal pain events. Any potential benefit should of course be weighed against the disadvantage of drug-induced polydipsia, polyuria, nocturia and potential hepatotoxicity. The primary aim to prescribe tolvaptan in ADPKD remains therefore its renoprotective efficacy. These analyses, however, indicate that there is an additional benefit that may be important, especially for those ADPKD patients with recurrent acute renal pain events.

In contrast to acute pain, chronic pain in ADPKD has drawn less attention. However, still 60% of ADPKD patients suffers from some sort of chronic pain, which is, in a number of cases, severe necessitating major analgesic therapy, and have a large impact on physical and social activities (3, 10). Several reviews including algorithms for management of chronic pain in ADPKD have been published (11-13). These reviews emphasize that chronic pain is often difficult to treat, and that nephrectomy is always an option. Since the decision to remove a functioning kidney in patients that invariably will progress to end-stage renal disease is a difficult one, there is a need for effective and kidney function sparing therapies. **Chapter 5** investigates therefore the value of catheter-based renal denervation as new potential treatment for refractory, invalidating, chronic pain in ADPKD. This procedure is now mainly applied in patients with therapy resistant hypertension. After the catheter system is introduced in the renal artery and the catheter electrode is positioned in contact with the vessel wall, applications of radiofrequency energy in a spiral pattern along the renal artery are given to ablate efferent and afferent renal sympathetic nerve fibers. This procedure was performed in a female ADPKD patient with bilateral ADPKD-related refractory chronic pain with a VAS score of 70/100. After left- and right-sided renal denervation, complete pain relief was achieved (VAS score 0/100). Office blood pressure dropped from 145/96 to 120/75 mmHg after the intervention, even while her antihypertensive medication had been reduced from three to two agents. The intervention had no effect on her renal function and no complications occurred, indicating the procedure seems safe. These results

suggest that catheter-based renal denervation may be an effective procedure for pain relief in selected ADPKD patients with refractory invalidating chronic pain.

A stepwise approach for pain management according to a treatment algorithm may be of help to achieve successful pain relief in ADPKD patients. A systematic literature search of ADPKD specific treatment options was therefore conducted to better understand how chronic pain in ADPKD currently is treated (**Chapter 6**). In literature it is suggested that nerve blocks can be used in ADPKD patients to avert the need for more invasive surgical therapies (11-13). However, to our knowledge, no study has been performed to investigate the effect of nerve blocks on pain relief in ADPKD patients. Based on the knowledge and evidence derived from literature a stepwise approach with sequential nerve blocks for the management of chronic pain in ADPKD is proposed. When (non)-pharmacological options fail, minimally invasive nerve blocks may be indicated. In this approach it is important to identify through which sympathetic pathway pain is relayed. In case of pain predominantly attributed to pressure on adjacent tissues or distension of the hepatic capsule, the presumed pathway is the celiac plexus and major splanchnic nerves, whereas in pain attributed to distension of the renal capsule, the pathway is considered to follow the aorticorenal plexus and minor and least splanchnic nerves (14, 15). A celiac plexus block with local anesthetics is used as first diagnostic procedure. When, after the initial diagnostic celiac plexus block, pain relief is obtained and recurred, a consecutive long-term block of the major splanchnic nerves by radiofrequency ablation is scheduled (RF-MSN block). When there is no response to the diagnostic celiac plexus block, the alternative pathway via the aorticorenal plexus is likely, in which case catheter-based renal denervation is planned.

In **Chapter 7** the initial results of our stepwise protocol of sequential nerve blocks are presented. Overall 60 patients were referred, of which 44 were eligible. These patients were generally referred by their treating physician, but also included self-referrals, and they came from all over the Netherlands. In 36 patients the diagnostic celiac plexus block resulted in substantial pain relief (change in VAS pre-post intervention 50/100 [26-68]). Of these patients, 23 received RF-MSN block because pain recurred after diagnostic celiac plexus block (change in VAS pre-post MSN 53/100 [23-65]). Out of the 8 patients without pain relief after the diagnostic celiac plexus block, renal denervation was performed in 5 (change in VAS pre-post intervention 20/100 [0-50]). After a median follow-up of 12 months, 81.8% of the 44 patients experienced a sustaining improvement in pain intensity (i.e. VAS score ≤30/100) and 63.6% of the patients were able to cease their daily use of opioids.

Surprisingly, in a number of cases with a positive response to the diagnostic temporary celiac plexus block, this intervention resulted in a sustained pain relief, even up to 2.5 years. This is unexpectedly, because local anesthetics are only able to interrupt a sensory pathway for a couple of hours with a maximum of 24 hours. It was hypothesized that this finding may be an effect on central sensitization caused by longstanding nociceptive stimulation in the past, e.g. from a cyst infection or cyst bleeding. Consequently, minor stimuli lead to a pain response that normally would not occur (12, 16). By applying local anesthetics the continuous excitation of visceral nociceptive neurons is temporarily interrupted, by which the neurons may return to their normal resting potential (16).

In the stepwise treatment protocol little attention was given to the psychosocial aspect of pain complaints within a biopsychosocial model (17). However, our experience is that the majority of patients, who have been referred to our expertise center regarding their invalidating pain, have a real and clear pain complaint in which the biological physical component seems to prevail above the psychosocial component. It may be so that this group of ADPKD patients is different from other patients with chronic visceral pain, e.g. patients with irritable bowel syndrome or bladder pain syndrome. It appears that in ADPKD patients a causal factor is more evident, for both patients and social environment. The presence of cyst formation and the increase in size of kidneys and liver seem to explain to ADPKD patients why they experience pain, in contrast to the generally negative findings in patients with an irritable bowel syndrome or bladder pain syndrome. Although in ADPKD pain could be explained by an obvious anatomic abnormality, central sensitization may exist. In ADPKD patients with central sensitization, psychosocial factors, such as behavioral, emotional, social and cognitive factors, could negatively impact on their pain experience (18, 19). When such illness-focused coping strategy is diagnosed, adequate management may be necessary with medication (e.g. antidepressants), psychotherapy or cognitive behavioral therapy.

The present data add to the evidence that nerve blocks may be considered and tried before more invasive surgical therapies are used. However, it is important to realize that sensory nerve blocks could also have negative clinical consequences in ADPKD. For instance, a RF-MSN block interrupts the upper abdominal sensory nerve supply that leads to a limited or altered nociceptive sensory function in the upper abdomen. Clinicians should therefore be aware that these patients may have a different presentation of symptoms, resulting in a potential patient and doctor's delay. At this moment there is only limited experience with these interventions in ADPKD patients. Preferably our promising results may be corroborated by other centers. Until these data become available, we advise that sequential nerve blocks are only be performed

in this patient group in a protocolized setting in centers with expertise in treatment of ADPKD-related pain.

II. Polyuria in ADPKD

The last decade it has been proven that vasopressin plays a deleterious role in the pathogenesis of ADPKD by provoking cyst formation and growth (20). Vasopressin levels may be increased in ADPKD patients due to a diminished concentrating capacity, that worsens over time, presumably because patients have an impaired renal medullary osmotic gradient due to cyst formation (21). This deficit in renal concentrating capacity may lead to a high urine output with low urine osmolality, an increase in plasma osmolality and consequently a compensatory rise in vasopressin. In line with this hypothesis, a recent study from our research group described that the maximal urine concentrating capacity was already lower in ADPKD patients with early stage disease compared to healthy controls that had a similar level of kidney function (22).

Non-ADPKD patients with chronic kidney disease also have an impaired urine concentrating capacity related to the degree of tubulointerstitial damage, that precludes a normal medullary urea gradient, that is necessary for water reabsorption (23, 24). We hypothesized that in advanced stages of ADPKD, the increase in vasopressin concentration in response to water deprivation may even be stronger than might be expected from impaired kidney function per se because of the extra component that the numerous (micro)cysts add, that is expected to cause destruction of the renal architecture resulting to a further derangement of the medullary urea gradient (21, 25). To study urine concentrating capacity and vasopressin response in advanced stages of ADPKD, water deprivation tests were performed in ADPKD patients with an eGFR ≤60 ml/min/1.73m^2 and in a control group of patients with IgA nephropathy, matched for age, sex and eGFR (**Chapter 8**). Indeed, ADPKD patients had a lower maximal concentrating capacity compared to the control group, but surprisingly the vasopressin response was similar in both groups.

The results of Chapter 8 show that urea clearance plays a role in the impaired concentrating capacity in ADPKD patients. The medullary osmotic gradient is determined by a complex mechanism involving intra-renal urea recycling by urea transporters in the renal medulla. The importance of these urea transporters for urine concentration has been confirmed in animal studies. Mice with a defect in this urea transporter were still able to concentrate urine, but to a lesser extent compared to

wild type mice (26, 27). Other electrolytes were excreted in a similar way (26, 27). This difference in urea clearance seems to be observed in ADPKD as well. In a previous study of our research group, it was found that ADPKD patients with preserved kidney function had at maximal urine concentration markedly lower urine urea levels compared to healthy controls (280±56 mmol/L vs. 405±110 mmol/L) (22). The results of Chapter 8 confirms these findings, urine urea levels at maximal urine concentration were lower in ADPKD patients than in the control IgA nephropathy patients despite similar levels of impaired kidney function.

Surprisingly, though the maximal urine concentrating capacity was lower and the increase in plasma osmolality seemed more profound in ADPKD patients, the vasopressin response was similar compared to the control group. No association was found between plasma osmolality and vasopressin, indicating that vasopressin did not adequately respond on the plasma osmolality level. This suggests that a central component may be involved in causing this urine concentrating defect. A previous study have already hypothesized that in ADPKD patients the impaired urine concentration capacity is caused by a central component (28). They found that vasopressin secretion was blunted during water deprivation, whereas in our study a significant response in both copeptin and vasopressin was observed.

Lastly, high vasopressin levels are known to stimulate in ADPKD intracellular cAMP, which promotes cell proliferation, and cyst formation, and consequently cause renal function decline (29). To avoid these processes, an increase in vasopressin levels should be avoided. Chapter 8 indicates that thirsting enhances vasopressin release, suggesting that dehydration should be avoided in this patient group. The clinical advice to avoid thirsting in ADPKD does not necessarily mean that ADPKD patients may benefit from an increased water intake to suppress vasopressin levels. However, increasing water intake is nowadays considered as a potential treatment for ADPKD, because theoretically, a consistent and sustained high water intake should suppress vasopressin levels (20, 30). For clinicians, the question arises which ADPKD patients should increase their water intake, and what volume of fluid they should be advised to drink. In healthy persons with normal kidney function, it has been shown that vasopressin concentration correlates positively with urine osmolality (31, 32). In this situation urine osmolality seems the perfect marker to monitor vasopressin levels. In **Chapter 9** it was investigated whether in ADPKD patients urine osmolality is also associated with vasopressin concentration (measured by the plasma concentration of its surrogate copeptin), and whether this association is influenced by disease severity. In 94 patients with a broad range of renal function, urine osmolality was not associated with copeptin concentration, indicating that this marker was not suitable to monitor

vasopressin levels. Moreover, it was found that urine osmolality was not associated with the rate of renal function decline during follow-up. These observations were similar in patients with preserved as well as with impaired renal function. A possible explanation for the fact that urine osmolality is not suitable to monitor vasopressin levels, is that ADPKD patients, even in early stage of their disease, have an impaired urine concentration capacity (22).

The results of Chapter 9 also corroborate that higher copeptin is associated with more rapid renal function decline and that this associations persists after correction for age, sex, and even after additional correction for TKV. Measurement of copeptin concentration has therefore been suggested, as an alternative for measuring urine or plasma osmolality to reflect vasopressin activity, and may be of help to identify ADPKD patients, who are at risk for rapid disease progression. At the moment, serum copeptin concentration was assessed in only three observational ADPKD cohorts to investigate the association between baseline copeptin concentration and disease progression (31, 33, 34). All three studies showed that copeptin concentrations were associated with eGFR and TKV at baseline, but more importantly with an increase in TKV and a decrease in eGFR during follow-up. These are promising findings, but more studies are necessary to confirm the value of copeptin levels to predict disease outcome in ADPKD. These studies should investigate the added value to normal progression risk factors (i.e. total kidney volume and PKD genotype), and sensitivity and specificity of increased copeptin values to predict accelerated renal function loss in ADPKD before copeptin can be adopted in clinical care for risk stratification.

It should be emphasized that **Chapter 9** did not investigate the role of increasing water intake on vasopressin concentration, nor on the rate of disease progression. This was not possible due to the observational study design. Theoretically, an increase in water intake is expected to reduce the rate of disease progression in ADPKD by decreasing vasopressin activity, as has been shown for vasopressin V2 receptor blockade by tolvaptan (20). On the other hand, there may be limitations to the efficacy of increasing water intake (35). Medical treatment with tolvaptan leads to a long-term pharmacologic suppression of the vasopressin pathway. It is uncertain whether long-term increases in water intake can also suppress vasopressin activity sustainably and what volume of fluid would be necessary to achieve this. Only Higashihara et al. have investigated the effects of increased water intake on disease progression in ADPKD (35). Thirty-four ADPKD patients were divided into two groups, a high water intake and a free water intake group. In contrast to the hypothesis that an increase in water intake is expected to reduce the rate of disease progression in ADPKD, no difference in change in kidney volume or kidney function were found between both treatment

groups. It may be so that the study design was not valid to investigate whether a high water intake can reduce disease progression in ADPKD patients. Only a small number of patients was included, and there was a lack of randomization and a relatively short study duration of 12 months. This may have led to false-negative conclusions. Secondly, water intake may have to be higher than was achieved in this study to suppress vasopressin concentration sufficiently. The advised fluid intake (on average approximately 3.15 L/24h) was not achieved, given the measured 24-hour urine volume (2.66 L/24h). This suggests that it may be a challenge to instruct ADPKD patients to increase their water intake up to 3-4 liters per day.

A cautionary note should be made that an increased water intake may also have adverse effects. Although normal kidneys are able to excrete several liters of free water, there are situations in which patients drink more free water than the kidneys can excrete. Especially in patients with an impaired renal function the risk exists that an increased water intake leads to overhydration and hyponatremia, that may lead to medical problems, such as cerebral edema and osmotic demyelination. The risk of hyponatremia during high water intake is further increased in situations of salt depletion, for instance as a result of a low salt diet, gastrointestinal disorders, or overuse of diuretics (30). An additional problem may be that it is not clear whether the urogenital system can deal with a consistent high urine output. In case patients void too infrequent, this will theoretically induce high intravesical pressure, which may lead to ureter dilatation, hydronephrosis and renal function loss. Several case reports have been published that link polyuria to due renal function loss via this mechanism in patients with central or nephrogenic diabetes insipidus (36-38). Since tolvaptan also leads to polyuria, that in some patients can be 6 to 8 liters per day, we studied in **Chapter 10** the effect of tolvaptan induced polyuria on ureter diameter in ADPKD patients. A total of 70 ADPKD patients were included, of which 51 used tolvaptan and 19 placebo. As expected urine output increased in the tolvaptan group, with median 24-hour urine volume being 2.5 [2.1-2.7] L at baseline versus 4.7 [3.3-5.7] L after three years of treatment, which was not the case in the placebo group (2.5 [1.9-3.1] vs. 2.3 [2.1-2.7] L). Tolvaptan induced polyuria did not lead to an increase in ureter diameter after three years of tolvaptan treatment when compared to baseline, nor to a difference in ureter diameter between both study groups. A small number of patients (n=22) used tolvaptan for almost six years and in these patients still no increase in ureter diameter was found. This suggests that tolvaptan use does not cause high pressure in the upper urinary tract. It should be noted that a relatively small number of patients was included, which may lead to false negative conclusions. The present findings should therefore be considered as hypothesis generating. To exclude the risk for ureter dilatation in

tolvaptan treated patients, ureter diameter should be assessed in a larger number of patients, for instance in all patients participating in the TEMPO 3:4 trial. Despite our comforting data, clinicians should be aware that this theoretical problem of tolvaptan induced polyuria on the urogenital system may exist. For safety reasons they should inform their tolvaptan treated ADPKD patients about these potential urological effects and instruct them to urinate frequently and avoid feelings of urge.

Future perspectives

Currently pain is often a neglected symptom in ADPKD. Patients sometimes experience that physicians do not recognize or appreciate the severity of their pain complaints and the impact these complaints can have on quality of life and social functioning (39-41). This is one of the causes that pain management is often inadequate. Persistent and untreatable pain leads to frustration for patients, who often experience that they have little or no input in the decision-making process about pain management. These patients would benefit from detailed discussion about potential causes of pain and therapeutic options.

Results from part one of this thesis suggest that liver volume plays a prominent role in pain related symptom burden in ADPKD, whereas, in contrast to the general assumption, total kidney volume does less. Therapy should therefore focus especially on the liver to reduce symptom burden. Somatostatin analogues, such as Lanreotide and Ocreotide, have been proven in small scale studies to reduce the growth rates of liver as well as kidneys (42-44), with benefits in terms of perception of health in ADPKD patients. It is also suggested that these agents have a beneficial effect on the incidence and prevalence of pain. Despite these promising findings, larger scale studies are necessary to confirm the promising effect of somatostatin analogues on symptom burden in ADPKD. Upcoming results from the ongoing DIPAK-1 study may help in this regard. This multi-center, randomized, controlled clinical trial is designed to investigate in 300 ADPKD patients the effect of the somatostatin analogue Lanreotide on disease progression in ADPKD (45). In addition, in this clinical trial symptom burden and health related quality of life are measured and with these data the question may be answered whether Lanreotide use is associated with a decrease in prevalence and severity of ADPKD-related pain and gastrointestinal symptoms. Until these results become available, somatostatin analogues should only be prescribed in this specific patient group in a clinical trial setting.

Currently, patients with chronic pain often are treated with analgesics. In case pain was not sufficiently relieved by analgesics, tolerating pain seemed to be the only option available to these patients. Some of these patients experienced so much pain, that they were willing to have a kidney removed, notwithstanding the fact that this procedure might shorten their time to reaching end-stage renal disease. In case of invalidating chronic pain, our experience described in Chapter 7 of this thesis indicates that a multidisciplinary stepwise treatment protocol that applies sequential nerve blocks may be of help to obtain substantial pain relief. Since the experience with these techniques is limited, the success and failure rate should be discussed openly with all patients before such treatment is started.

Along with the potential beneficial effects of these interventions for pain relief, we have to realize that these interventions also have side-effects. Patients using somatostatin analogues can experience gastro-intestinal symptoms, e.g. diarrhea, flatulence and abdominal pain, and develop hypoglycaemia and cholelithiasis. Patients who undergo a long-term nerve block, may have an altered nociceptive sensory function in their abdominal cavity afterwards. Clinicians should be aware that these patients may have a different presentation of symptoms, resulting in a potential patient and doctor's delay in case of serious abdominal disease. Since pain is a subjective symptom, the final decision to consider pharmacological or minimal invasive treatment is a decision to be made by the patient. As clinicians, we can advise the patient about the available options and potential side-effects of each option, but ultimately the patient decides whether the benefits outweigh the disadvantages.

Ultimately, when other therapies have not achieved sufficient pain relief, ADPKD patients may benefit from nephrectomy (12). Several studies have suggested that a laparoscopic nephrectomy may be preferred over an open approach in ADPKD patients, because of a shorter duration of hospitalization, less blood loss, and improvement in post-surgery cosmetic aspects (46-48). Despite these apparently promising results it is doubtful whether laparoscopic nephrectomy can be easily performed in the general ADPKD population. In literature the mean weight of the removed kidney is considerably lower than the kidney volume of the removed kidneys in our expertise center for polycystic kidney disease, which suggests that selection bias is likely in these studies (49). It seems that ADPKD patients with relatively large kidneys have not been selected to undergo a laparoscopic procedure in the aforementioned studies. Given these considerations, no definite conclusion can yet be drawn, which approach should be chosen for nephrectomy in ADPKD patients. Radiological imaging before the procedure, with volumetry of the kidney that is to be removed, may help to decide which patients can be selected for a laparoscopic approach. Information on

eligibility criteria and pre-operative kidney volume should also be included in future investigations that compare various operative nephrectomy techniques in ADPKD patients in order to be able to conclude whether size does matter when deciding what the best surgical approach is for a nephrectomy.

In conclusion, in the last couple of years major steps have been taken to improve ADPKD specific patient care. In order to further optimize this care, the establishment of polycystic kidney disease expertise centers may be of help. In a multidisciplinary setting, with involvement of a nephrologist, urologist, gastro-enterologist, radiologist and pain specialist, complex ADPKD-related problems can be discussed, which can lead to better patient care, but also to new insights with respect to pathophysiology. In addition, these expertise centers can inform and update other hospitals how to implement new treatment strategies in ADPKD. For instance, it is now possible to slow disease progression in ADPKD with tolvaptan (8, 50). Expertise centers can take a role in selecting the patients that have a high likelihood of rapid disease progression in whom the benefit to risk ratio of tolvaptan treatment is expected to be higher, informing ADPKD patients what they may expect from tolvaptan use with respect to benefit, risks and side effects, and how to incorporate tolvaptan's aquaretic effect in their daily life. At this moment current research collaborations by these expertise centers mainly focus on developing interventions that can slow cyst growth and decline in renal function. Although pain and polyuria are common in ADPKD patients, the consequences of these symptoms are underestimated, and they attain little attention. Another aspect of clinical care that needs improvement is that the diagnosis of this inherited kidney disease may be an emotional burden, because of the consequences for family and career planning. For these reasons sometimes customized care by physicians or nurses with specific experience in ADPKD is indicated. Also for regular clinicians it is important to recognize and adequately respond to the emotional, social and symptom burden that ADPKD patients can experience, because they can have a negative impact on a patient's quality of life. These aspects are often understudied in medicine, because they are difficult to operationalize in clinical trials. Although there may be methodological difficulties in studying these aspects, they nonetheless are important. As Albert Einstein is cited to have said: 'Not everything that counts can be counted, and not everything that can be counted counts'.

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Nederlandse samenvatting

Algemene achtergrond

Cystenieren, ook wel Autosomaal Dominante Polycysteuze Nierziekte (ADPKD) genoemd, is de meest voorkomende erfelijke nierziekte en komt voor bij 3 tot 4 per 10.000 personen. De ziekte wordt gekarakteriseerd door cystevorming in beide nieren wat resulteert in nierfunctieachteruitgang. Het overgrote merendeel van de patiënten wordt uiteindelijk afhankelijk van nierfunctie vervangende therapie (dialyse of transplantatie) en het is daardoor de op drie na meest voorkomende oorzaak van nierfalen. Tot 2015 waren er geen behandelopties beschikbaar. De vasopressine V2-receptor antagonist, genaamd tolvaptan, is echter recent goedgekeurd in Europa als eerste therapie om ziekteprogressie bij patiënten met ADPKD te remmen.

Door een genetisch defect in het *PKD-1* of *PKD-2* gen ontstaat er cystevorming in de nieren. Deze genen zijn autosomaal dominant overdraagbaar. Dit betekent dat kinderen van wie één van de ouders ADPKD heeft, 50% kans hebben om ADPKD te erven, en dat ook zij gedurende het leven cysten in hun nieren zullen ontwikkelen. Het aantal en de grootte van cysten verschilt van persoon tot persoon. Een gezonde nier heeft ongeveer een volume van 150 ml. In ADPKD-patiënten kan het niervolume zodanig vergroot zijn (tot wel 10 liter), dat de nier tot in het kleine bekken reikt. In de meerderheid van de patiënten is er ook cystevorming in de lever, wat overigens zelden leidt tot leverfalen. Meestal ervaren patiënten geen klachten van cystevorming in de lever, maar soms kan het vergrootte levervolume resulteren in pijn en maag-darmklachten (opgeblazen gevoel, zuurbranden, passagestoornissen).

In de nieren zorgt cystevorming ervoor dat het gezonde nierweefsel wordt verdrukt. De nieren gaan hun functie eerst compenseren door hyperfiltratie, maar uiteindelijk zorgt deze steeds toenemende verdrukking van gezond nierweefsel voor nierfunctieverlies. De gemiddelde leeftijd waarop ADPKD-patiënten nierfunctie vervangende therapie nodig hebben is 58 jaar. In een klein deel van de patiënten moet vanwege de grootte van de cystenieren een nier worden verwijderd voordat een niertransplantatie kan worden uitgevoerd, omdat er anders te weinig ruimte is voor de transplantatienier.

Dit proefschrift gaat over twee andere symptomen die naast nierfunctieachteruitgang en toename in niergrootte kunnen optreden bij ADPKD-patiënten. Het eerst deel van het proefschrift gaat over pijn in ADPKD. We onderzochten welke risicofactoren van belang zijn voor het ontstaan van pijn en analyseerden het effect van verschillende potentiële nieuwe therapieën voor de behandeling van acute en chronische pijn in ADPKD. Het tweede deel richt zich op een ander onderbelicht veelvoorkomend

symptoom in ADPKD: polyurie, wat veel plassen betekent. Polyurie wordt veroorzaakt doordat de nieren minder goed in staat zijn de urine te concentreren en heeft mogelijk een negatieve invloed op de ziekteprogressie in ADPKD.

I. Pijn in ADPKD

Pijn is een veelvoorkomend probleem in ADPKD en kan worden onderverdeeld in acute en chronische pijn. Acute pijn wordt vaak veroorzaakt door een infectie, nierstenen of een cystebloeding. Wanneer pijn langer bestaat dan 4-6 weken spreken we over chronische pijn. Deze pijn kan ontstaan door rek of lokale irritatie van het nier- en leverkapsel als gevolge van de cystegroei of door druk op omliggende organen. Een deel van deze pijnklachten is goed te behandelen, maar een klein deel van de patiënten blijft invaliderende chronische pijnklachten houden ondanks hoge doseringen pijnmedicatie. In dat laatste geval kunnen pijnklachten een groot effect hebben op zowel het fysiek als psychisch functioneren en vormen daarmee een ernstige belemmering in het dagelijks leven van deze patiënten. Indien pijnmedicatie niet voldoende helpt de pijn te onderdrukken, is de volgende stap in de behandeling van chronische pijn bij ADPKD het toepassen van invasieve technieken, zoals cysteaspiratie (leegzuigen van een cyste), cystefenestratie (een "venster" maken in een cyste) of zelfs nefrectomie (het verwijderen van een nier). Deze ingrepen zijn echter niet zonder risico, zijn niet altijd effectief en leiden bovendien tot nierfunctieverlies, waardoor patiënten eerder in dialyse komen.

Risicofactoren voor pijn

Door massale cystevorming in de nieren en de lever lijkt het logisch dat er een verband bestaat tussen nier- en levervolume en pijn en gastro-intestinale (maag-darm)klachten bij ADPKD-patiënten. Er bestaat op dit moment echter onduidelijkheid of nier- dan wel levervolume een rol speelt als oorzaak van klachten. Aangezien de totale grootte van het nier- en levervolume mogelijk een rol speelt bij het ontstaan van symptomen, hebben we onderzocht of het gecombineerde nier- en levervolume geassocieerd is met pijn en gastro-intestinale klachten in ADPKD-patiënten (Hoofdstuk 2). In 309 ADPKD-patiënten bleek niervolume geen relatie te hebben met klachten, maar levervolume en gecombineerd nier- en levervolume wel. Vrouwen hadden meer pijn en gastro-intestinale klachten dan mannen en dit verschil in klachten was te verklaren doordat vrouwen een groter levervolume hadden dan mannen. Uit ons onderzoek bleek dus dat met name levervolume een belangrijke rol heeft in symptoombeleving in ADPKD-patiënten. Potentiële behandelingen om klachten te reduceren moeten zich dan ook concentreren op het verminderen van levervolume.

Naast orgaanvolume zijn er ook andere factoren die kunnen bijdragen aan het ontstaan van pijnklachten bij ADPKD zoals cystebloedingen, nierstenen, urineweginfecties en cyste-infecties. Op dit moment is er geen wetenschappelijk bewezen behandeling voor niercyste-infecties in ADPKD. Wij hebben geprobeerd om met behulp van de bestaande literatuur risicofactoren voor niercyste-infecties te identificeren en een behandelprotocol voor niercyste-infecties in ADPKD te ontwikkelen (Hoofdstuk 3). Een verminderde nierfunctie, nierstenen, een post-renale obstructie (obstructie van de urinewegen), cystegrootte en een korte behandeltijd met antibiotica waren factoren die werden gezien bij patiënten bij wie de initiële behandeling niet aansloeg. We waren helaas niet in staat een stapsgewijs behandelprotocol te ontwerpen voor de behandeling van niercyste-infecties in ADPKD omdat er te weinig wetenschappelijk bewijs is in de literatuur. Het is zeer wenselijk dat er een landelijke of Europese dataregistratie wordt gestart op basis waarvan een optimaal behandelstrategie kan worden ontwikkeld.

Acute pijn

Tot voor kort was er geen behandelmogelijkheid om ziekteprogressie in ADPKD te remmen. Uit recent onderzoek bleek echter dat tolvaptan, een vasopressine V2-receptorantagonist, in staat is om nierfunctieachteruitgang en cystegroei in de nieren te remmen. In de eerste publicatie over de effectiviteit van dit geneesmiddel werd gesuggereerd dat tolvaptan mogelijk ook zorgt voor een afname van acute nierpijnaanvallen. Daarom hebben we in Hoofdstuk 4 in meer detail hebben gekeken naar het effect van tolvaptan op pijn. Tolvaptangebruik leidde tot minder acute nierpijnaanvallen vergeleken met placebobehandeling, onafhankelijk van risicofactoren voor nierpijn. Een mogelijk mechanisme achter de positieve werking van tolvaptan op acute nierpijn is dat tolvaptan zorgt voor een afname van urineweginfecties, nierstenen en cystebloedingen. Het blijft de vraag of tolvaptan geïndiceerd is om ADPKD-patiënten met acute pijn te behandelen. Vierennegentig ADPKD-patiënten moeten met tolvaptan worden behandelend om één ernstig acute nierpijnaanval te voorkomen. Daarom blijft in onze optiek de primaire indicatie voor voorschrijven van tolvaptan remming van ziekteprogressie in ADPKD en niet preventie van acute nierpijnaanvallen.

Chronische pijn

Wanneer pijn langer dan 4-6 weken bestaat spreken we van chronische pijn. Chronische pijn kan door een aantal patiënten als invaliderend worden beschouwd. In dat geval zijn patiënten beperkt in fysiek en sociaal functioneren. In de bestaande

behandelalgoritmes die over dit onderwerp zijn gepubliceerd wordt al kort de mogelijkheid van het uitschakelen van zenuwen die van en naar de nier gaan (renale denervatie) genoemd als behandeloptie voor invaliderende pijn. Deze behandeling is chirurgisch echter erg lastig en wordt zelden uitgevoerd. Recent is er een methode ontwikkeld waarbij deze procedure vanuit de lies via een katheter in de nierslagader wordt uitgevoerd. Deze interventie wordt met name uitgevoerd bij patiënten met een therapieresistente hypertensie. Om te onderzoeken of deze methode ook kan werken voor ADPKD-gerelateerde pijnklachten, hebben we deze ingreep bij een vrouwelijke ADPKD-patiënte met invaliderende chronische pijn in beide flanken (VAS score 70/100) verricht met goed resultaat op de pijnbeleving (Hoofdstuk 5). De VAS score is een cijfer om aan te geven hoeveel pijn er wordt ervaren door de patiënt en heeft een schaal van 0 (geen pijn) tot 100 (ondraaglijke pijn). Doordat de sensorische (pijn) zenuwen van de nier via de zgn. sympathicus lopen - de zenuw die verantwoordelijk is voor de bloeddrukregulatie - is het verwachte neveneffect van deze behandeling dat de bloeddruk daalt. Dit was ook het geval bij deze patiënte.

Om een beter inzicht te krijgen in de exacte plek van zenuwblokkades voor de behandeling van invaliderende chronische pijn in ADPKD, is er eerst een literatuuroverzicht gemaakt om vast te stellen hoe chronische pijn in ADPKD op dit moment wordt behandeld. Er zijn diverse behandelalgoritmes gepubliceerd, waarin wordt aangegeven dat farmacologische behandelingen gestart kunnen worden, wanneer non-farmacologische opties onvoldoende effectief zijn. Dit gebeurt stapsgewijs van eerst zogeheten lichtere pijnstillers, non-opioïde preparaten (paracetamol) naar zwaardere pijnstillers, zoals opiaten (tramadol en morfine). Indien dit niet leidt tot een effectieve pijnverlichting, kan worden overgegaan tot cyste-aspiratie, cystefenestratie of zelfs nefrectomie.

Op basis van de kennis van de zenuwbanen via welke pijn vanuit de nieren en de lever via het ruggenmerg naar de hersenen wordt geleid, is in Hoofdstuk 6 een behandelprotocol met zenuwblokkades opgesteld om invaliderende pijn in ADPKD te behandelen. Wanneer de pijn met name wordt veroorzaakt door druk van de vergrootte nieren of lever op omliggende organen, wordt verondersteld dat de pijn via de zgn. plexus coeliacus en de n. splanchnicus major naar het ruggenmerg wordt geleid. Wanneer de pijn samenhangt met rek van het nierkapsel, is het aannemelijk dat de pijn via de sensorische zenuwen rondom de nierslagader en zgn. aorticorenale plexus naar het ruggenmerg wordt geleid. In het door ons voorgestelde multidisciplinaire protocol is het van belang om onderscheid te maken tussen deze twee verschillende routes. Door middel van een diagnostische coeliacus blokkade kan tijdelijk de plexus coeliacus worden uitgeschakeld met een lokaal verdovingsmiddel. Als de pijn afneemt na dit

tijdelijke blok, wordt aangenomen dat de pijn via de plexus coeliacus wordt geleid. Wanneer de pijn terugkeert, kan een langduriger blok van de n. splanchnicus major worden toegepast door radiofrequente ablatie (met warmte de zenuw beschadigen). Wanneer de pijn niet afneemt bij de tijdelijke coeliacus blokkade, veronderstellen we dat de pijn via de sensorische zenuwen rondom de nierslagader en de aorticorenale plexus wordt geleid en kan renale denervatie worden verricht.

In Hoofdstuk 7 zijn de resultaten van dit multidisciplinaire behandelprotocol beschreven. Patiënten kwamen voor dit protocol in aanmerking wanneer er sprake was van ADPKD-gerelateerde pijn ≥3 maanden, een VAS-score (pijnscore) van ≥50/100 ondanks gebruik van opioïden en een ernstige beperking in het dagelijks functioneren. Zestig patiënten werden verwezen vanuit heel Nederland naar het Expertise Centrum Polycysteuze Nierziekten in Groningen, waarvan 44 patiënten geschikt waren voor ons behandelprotocol. In 36 patiënten resulteerde een diagnostische coeliacus blokkade met lokaal verdovingsmiddel tot pijnafname. In 23 van deze patiënten keerde de pijn terug en werd een langdurige n. splanchnicus major blokkade uitgevoerd. In acht patiënten nam de pijn niet af na de diagnostische coeliacus blokkade en in vijf van deze patiënten werd renale denervatie uitgevoerd. Na een gemiddelde follow-up van 12 maanden was de pijnbeleving in 82% van de 44 patiënten verbeterd. Onze resultaten laten zien dat een multidisciplinair behandelprotocol met zenuwblokkades effectief is in de behandeling van invaliderende chronische pijn in ADPKD-patiënten en moet worden overwogen voordat invasieve chirurgische technieken, zoals het verwijderen van een nier, worden uitgevoerd. Het moet worden benadrukt dat zenuwblokkades niet zonder risico's zijn. Door een verminderde en veranderde pijnbeleving in het geblokkeerde gebied kunnen symptomen zich op een andere manier presenteren. Bijvoorbeeld, het kan zijn dat een ADPKD-patiënt met een niercyste-infectie geen pijnklachten ervaart in de flank. Dit kan leiden tot uitstel van de patiënt om medische hulp te zoeken of onderschatting van de klacht bij de behandelend arts. Daarom is het van belang dat zowel de arts als de patiënt zelf hier goed van op de hoogte zijn. Op dit moment is de ervaring met zenuwblokkades bij ADPKD-patiënten beperkt en zal er meer kennis en ervaring opgedaan moeten worden om onze resultaten te ondersteunen. Zolang deze resultaten nog niet beschikbaar zijn, adviseren we dat deze ingrepen alleen worden uitgevoerd bij ADPKD-patiënten in een gestandaardiseerde setting in een centrum met expertise in de behandeling van ADPKD-gerelateerde pijn.

II. Polyurie in ADPKD

Verminderd concentrerend vermogen

Door cystevorming in de nier wordt de normale bouw van de nier verstoord, waardoor de nier minder goed in staat is vocht vast te houden, met als gevolg dat de urine minder geconcentreerd is. Het resultaat hiervan is dat ADPKD-patiënten een verhoogde urineproductie hebben (ook wel polyurie genoemd). Door dit verminderd urine concentrerend vermogen gaat het lichaam proberen vocht vast te houden met als gevolg dat de concentratie van het antidiuretisch hormoon (vasopressine) omhoog gaat. In ADPKD speelt vasopressine een cruciale rol, doordat vasopressine het cAMP in de cellen verhoogt, wat cystevorming en cystegroei stimuleert. Eerder Gronings onderzoek laat zien dat bij ADPKD-patiënten met een ongestoorde nierfunctie het urine concentrerend vermogen is verminderd in vergelijking met gezonde vrijwilligers wat betekent dat het onvermogen de urine goed te concentreren al vroeg in de ziekte optreedt. Dit resulteerde in een toename in vasopressine- en copeptinconcentraties, een stabiele marker voor vasopressine.

In ADPKD-patiënten met een verminderde nierfunctie is de toename van vasopressine op dorsten mogelijk sterker, doordat een verminderde nierfunctie zelf ook zorgt voor een toename van de vasopressine concentratie. Om dit te onderzoeken is er een dorstproef uitgevoerd bij 15 ADPKD-patiënten met een verminderde nierfunctie (eGFR ≤60 ml/min/1.73m^2) en bij 15 IgA-patiënten, gematcht op leeftijd, geslacht en nierfunctie, om het urine concentrerend vermogen, vasopressine en copeptin te onderzoeken (Hoofdstuk 8). Zoals verwacht bleek dat de ADPKD-patiënten vergeleken met de IgA-patiënten een verminderd urine concentrerend vermogen hebben, maar tot onze verbazing waren vasopressine- en copeptinconcentraties gelijk in beide groepen. Deze resultaten laten zien dat het concentrerend defect zowel een nier-gerelateerde als mogelijk ook een centrale (systemische) component heeft. Door de verandering in renale architectuur vermindert het vermogen om de urine te concentreren (nier-gerelateerde component), maar doordat vasopressine hier niet goed op reageert, is de nier ook niet in staat om maximaal te concentreren (centrale component). Tevens laat deze studie zien dat dorsten slecht is voor ADPKD-patiënten, omdat we zagen dat de vasopressine concentratie steeg. We adviseren dan ook aan ADPKD-patiënten om een dorstgevoel te voorkomen.

Urine en plasma osmolaliteit

Dat dorsten moet worden vermeden in ADPKD-patiënten betekent niet automatisch dat een toename in waterinname een gunstig effect heeft op vasopressine. Het is lastig voor behandelend artsen om vast te stellen welke patiënten hun

waterinname moeten verhogen en hoeveel water deze patiënten moeten drinken. Vasopressineconcentraties zijn erg lastig te meten, omdat deze bepaling onstabiel is. Mogelijk kunnen urine en plasma osmolaliteit (concentratie van bepaalde stoffen in de urine of in het bloed) hierbij helpen, omdat deze twee markers bij gezonde mensen sterk geassocieerd zijn met vasopressineconcentraties. Patiënten zouden dan op basis van hun urine en plasma osmolaliteit kunnen worden geïdentificeerd of hun waterinname voldoende is om zo het ziekteproces te remmen. We onderzochten deze hypothese in 94 ADPKD-patiënten en vonden dat zowel urine als plasma osmolaliteit niet waren geassocieerd met copeptinconcentratie (marker voor vasopressine), noch met snelheid van ziekteprogressie (Hoofdstuk 9). We vermoeden dat het verminderd urine concentrerend vermogen ervoor zorgt dat urine en plasma osmolaliteit niet meer gecorreleerd zijn aan de copeptinconcentraties in het bloed. Hierdoor kunnen deze markers niet worden gebruikt om patiënten te identificeren bij wie de waterinname onvoldoende is.

Ureterdiameter

Tolvaptan, een vasopressine V2-receptorantagonist, is in staat niercystegroei en nierfunctieachteruitgang te remmen. Door de vasopressinereceptor te blokkeren, heeft tolvaptan als bijwerkingen een urineproductie tot wel 5-6 liter per dag (polyurie), en daardoor dorst en een droge mond. Patiënten met langdurige polyurie moeten hun mictiefrequentie (aantal keer dat ze naar het toilet moeten) aanpassen aan hun urineproductie. Infrequente mictie bij patiënten met polyurie kan leiden tot problemen in de urinewegen: urineretentie (het niet leeg kunnen plassen van de blaas), verhoogde blaasdrukken en uiteindelijk ureterdilatatie (verwijding van de urineleider tussen de nier en de blaas), hydronefrose (opzwelling van het urineverzamelsysteem in de nier) en nierschade. Dit proces is meermaals beschreven in patiënten met polyurie door psychogene polydipsie en diabetes insipidus. ADPKD-patiënten die tolvaptan gebruiken lopen in theorie dit risico ook. Mocht dat zo zijn, dan zou het gunstige niersparende effect van tolvaptan teniet worden gedaan door het nierfunctieverlies wat optreedt door dit theoretische probleem. Vandaar dat wij bij alle ADPKD-patiënten in ons centrum de ureterdiameter hebben gemeten om dit te onderzoeken. Hieruit bleek dat gedurende de drie jaar dat zij tolvaptan gebruikten, de ureterdiameter niet toenam ten opzichte van baseline, maar ook niet ten opzichte van de placebogroep. Tolvaptan zorgde dus niet voor een toename van druk in de hogere urinewegen. Een deel van deze groep patiënten hebben we voor meer dan zes jaar gevolgd om het effect van tolvaptan op ureterdiameter te onderzoeken. Ook na zes jaar tolvaptangebruik, wordt er geen effect gezien van de tolvaptan geïnduceerde polyurie op de ureterdiameter.

Met deze resultaten kunnen we het risico van tolvaptan op verhoogde druk in de urinewegen helaas niet volledig uitsluiten. Om dit te kunnen, zal de ureterdiameter in een grotere groep ADPKD-patienten, die tolvaptan gebruiken, moeten worden gemeten; bijvoorbeeld in alle 1445 deelnemers aan de TEMPO 3:4 Trial. Daarom bevelen we op dit moment aan dit (theoretische) probleem te melden aan ADPKD-patiënten en hen actief te blijven instrueren naar het toilet te gaan wanneer ze aandrang voelen tot mictie.

Toekomstperspectief

Resultaten uit dit proefschrift laten zien dat levervolume een prominente rol heeft als oorzaak van pijn en gastro-intestinale klachten. Therapie moet zich dan niet alleen op de nieren, maar ook op de lever focussen. Tolvaptan is in staat om cystegroei te remmen in de nieren, maar niet in de lever. Somatostatine-analogen, zoals Lanreotide en Ocreotide daarentegen kunnen wellicht gebruikt worden als behandeling van symptomatische ADPKD-patiënten, omdat somatostatine-analogen zowel in de nier als in de lever cystegroei remmen. Er wordt gesuggereerd dat deze medicijnen een gunstig effect hebben op pijn en maag-darmklachten. Mogelijk kunnen de resultaten van de DIPAK-1 studie hierover meer duidelijkheid verschaffen. De DIPAK-1 studie is een 2.5 jaar durende multicenter studie bij 309 ADPKD-patiënten om het effect van Lanreotide op ziekteprogressie te onderzoeken. Eind 2017 zullen de resultaten worden gepresenteerd en wordt bekend of Lanreotide effectief is om ziekteprogressie in ADPKD te remmen. Dan kan ook worden geanalyseerd of behandeling met Lanreotide resulteert in symptoomverlichting in ADPKD. Totdat deze resultaten bekend zijn adviseren we om somatostatine-analogen alleen voor te schrijven in een gestandaardiseerde setting.

Voor patiënten met ADPKD-gerelateerde invaliderende chronische pijn, laat de behandeling met zenuwblokkades goede resultaten zien. De vraag is nu of deze behandelstrategie moet worden geïmplementeerd als standaardzorg voor patiënten met invaliderende chronische pijn. Omdat de ervaring met deze blokkades in ADPKD-patiënten op dit moment beperkt is, moeten de kansen op behandelsucces en falen openlijk met de patiënt worden besproken. Tevens moeten patiënten en artsen goed worden ingelicht over de potentiële bijwerkingen en risico's van een verminderde pijnbeleving in de buik. Door een verminderde pijnbeleving kan een aandoening – zoals een niercyste-infectie – niet of in mindere mate geassocieerd zijn met pijn, waardoor de patiënt medische hulp uitstelt of de behandelend arts de klachten onderschat. Het is daarom van belang dat zowel de arts als patiënt op de hoogte zijn van dit risico, waardoor hierop adequaat geanticipeerd kan worden.

De afgelopen jaren zijn er grote stappen gezet om ADPKD-specifieke zorg te verbeteren. Voor het verder optimaliseren van deze zorg kunnen expertisecentra wellicht een coördinerende rol vervullen. In een multidisciplinaire setting kunnen complexe ADPKD-gerelateerde problemen worden bediscussieerd, wat kan leiden tot nieuwe inzichten en behandelstrategieën. Daarnaast kunnen deze expertisecentra andere ziekenhuizen informeren hoe nieuwe behandelopties, zoals onder andere tolvaptan, te implementeren in zorgpaden. Op dit moment focussen samenwerkingsverbanden zich met name op het remmen van de ziekteprogressie in ADPKD en wordt er minder aandacht besteed aan het reduceren van andere symptomen zoals pijn en polyurie. Voor een deel van de patiënten staan juist deze symptomen op de voorgrond in hun dagelijks leven. Behandelend artsen moeten zich dan ook bewust zijn van het bestaan en de impact van deze symptomen op het dagelijks functioneren van de patiënt. We moeten ons bovendien beter realiseren dat het hebben van deze erfelijke ziekte ook een emotionele en sociale impact heeft. Daarom is patiënt specifieke zorg geïndiceerd. Als behandelend arts is het van belang deze fysieke, emotionele en sociale impact te herkennen en hier aandacht aan te schenken, omdat met name deze facetten invloed hebben op de kwaliteit van leven van een patiënt. Helaas zijn deze facetten in de huidige klinische studies vaak onderbelicht, omdat het methodologisch lastig is om deze te meten. Desalniettemin zijn deze aspecten toch belangrijk. Want zoals Albert Einstein mogelijk heeft gezegd: 'Not everything that counts can be counted, and not everything that can be counted counts'.

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Niek

About the author

Niek Frederik Casteleijn was born in Wageningen, the Netherlands, on September 11th in 1989. He received his Gymnasium degree at the Ubbo Emmius in 2007. In the same year he started Medical School at the University of Groningen. In the first 3 years he was actively involved in the student Rowing Club Gyas, and rowed on professional level. As a medical intern, he went to South Africa for an elective of social medicine and urology. In 2013 he graduated from the University of Groningen.

In October 2013, he started his PhD-fellowship at the department of Nephrology of the University Medical Center Groningen with his supervisors prof. dr. Ron Gansevoort, prof. dr. Carlo Gaillard, prof. dr. Gerbrand Groen and dr. Annemarie Leliveld. As part of his PhD research, he conducted and coordinated several multicenter randomized controlled trials and observational studies in ADPKD patients (TEMPO trials, OVERTURE, DIPAK-1 study, EuroCyst studies). His research focused especially on pain in ADPKD and he participated in the nationwide Expertise Center for the management of chronic pain in ADPKD. During his studies he held position in the 'Platform Landelijke Arts-onderzoekers Nefrologie'. On December 1st 2016, he started as ANIOS Urology at the University Medical Center Groningen. On January 11th 2017, Niek will defend this thesis in the Academy building of the University of Groningen.

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N.F. Casteleijn, M.D. van Gastel, P.J. Blankestijn, J.P. Drenth, R.L. de Jager, A.M. Leliveld, R. Stellema, A.P. Wolff, G.J. Groen, R.T. Gansevoort, on behalf of the DIPAK Consortium, Results of a novel treatment protocol for invalidating chronic pain in patients with autosomal dominant polycystic kidney disease, *Submitted*

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