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THERAPEUTICS ADVANCES

Fluid overload as a major target in management of cardiorenal syndrome: Implications for the practice of peritoneal dialysis

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Abstract

Congestion is an integral component of cardiorenal syndrome and portends an adverse impact on the outcomes. Recent studies suggest that congestion has the ability of modulating the interactions between the kidney and the heart in this setting. Peritoneal dialysis (PD) is a home-based therapeutic modality that is not only offered to patients with end-stage renal disease to provide solute clearance and ultrafiltration, but it has also been used in patients with refractory heart failure and fluid overload to help optimize volume status. Several uncontrolled studies and case series have so far evaluated the role of PD in management of hypervolemia for patients with heart failure. They have generally reported favorable results in this setting. However, the data on the outcomes of patients with end-stage renal disease and concomitant heart failure is mixed, and the proposed theoretical advantages of PD might not translate into improved clinical endpoints. Congestion is prevalent in this patient population and has a significant effect on their survival. As studies suggest that a significant subset of patients with end-stage renal disease who receive PD therapy are hypervolemic, suboptimal management of congestion could at least in part explain these conflicting results. PD is a highly flexible therapeutic modality and the choice of techniques, regimens, and solutions can affect its ability for optimization of fluid status. This article provides an overview of the currently available data on the role and clinical relevance of congestion in patients with cardiorenal syndrome and reviews potential options to enhance decongestion in these patients.

Key words: Heart failure; Peritoneal dialysis; Congestion; Cardiorenal syndrome

Core tip: Congestion has been recognized as a dynamic state capable of modulating the interactions between the heart and the kidney in patients with cardiorenal syndrome. Optimization of volume status could significantly affect the outcomes of patients treated with peritoneal dialysis (PD) patients for end-stage renal disease and

pre-existing heart failure. Since PD is a highly modifiable therapeutic modality, it is conceivable that a regimen customized to the clinical characteristics and needs of the patients could improve their outcomes through efficient decongestion and optimization of volume status.

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INTRODUCTION

Heart failure (HF) is a public health problem due to its increasing prevalence, associated morbidity, high mortality, and a remarkable financial burden on the healthcare system. Prevalence of HF increases with age; it is currently one of the most common chronic conditions with a lifetime prevalence reaching 20%-33% in the United States[1]. Despite advancements in diagnosis and treatment, the HF population is expected to expand to more than 8 million by 2030 due to the increase in the proportion of aging population as well as the improving number of patients surviving ischemic events[2].

Congestion is the hallmark of HF, is the primary reason for hospitalization of these patients, and can contribute to HF progression[3]. Renal dysfunction is a prevalent clinical finding in HF and portends an untoward impact on potential management options, course, and outcome. The population of patients presenting with both heart failure and chronic kidney disease [*i.e.,* cardiorenal syndrome (CRS)] is large and steadily growing[3,4]. The pathophysiology of HF is complex as there exist a multitude of mechanisms by which the heart and the kidneys interact in the setting of cardiac dysfunction. Congestion can directly affect the interactions between the kidney and the heart in CRS[4]. Indeed, several studies have so far highlighted the clinical significance of congestion, rather than renal dysfunction, as the primary driver of the adverse outcomes in patients with CRS. For example, in a study on 594 patients with acute HF, patients with concomitant congestion and deterioration in renal function had the worst outcomes while worsening kidney function alone (without lingering congestion) showed no adverse impact[5]. Similarly, in a study on HF patients who were admitted to the hospital for congestion, those with hemoconcentration (proxy for decongestion) presented more often with deterioration in renal function but their outcome (*i.e.,* time to death) was still significantly improved compared to those who did not experience hemoconcentration during their hospitalization[6].

FLUID OVERLOAD IN CRS

In chronic CRS, the maladaptive mechanisms involved in HF, whether in the form of low forward flow or high backward pressure, could ultimately result in diminished water and sodium excretion, lingering venous congestion, endothelial cell activation, systemic inflammation, and progressive deterioration in renal function to the point of renal failure and end-stage renal disease (ESRD)[7]. In a subset of patients with HF, reduced cardiac output and fluid redistribution result in decreased renal perfusion. The aberrant compensatory mechanisms such as activation of the sympathetic nervous system, renin-angiotensin-aldosterone axis, and arginine vasopressin lead to enhanced renal water and sodium absorption in an effort to preserve renal perfusion, transglomerular pressure, and glomerular filtration rate. However, at long term, these mechanisms could induce deleterious effects on the heart and the kidney by promoting fibrosis, apoptosis, oxidative stress, activation of inflammatory mechanisms, and ventricular remodeling[8,9]. A number of studies have also found an association between high venous pressures and deterioration in renal function that could be even stronger than the impact of arterial blood pressure or cardiac index on renal function[10,11]. Increased pressure along renal veins is thought to reduce the net pressure gradient across the glomerulus leading to a decrease in glomerular filtration rate, diminished renal excretion of water and sodium, and progressively worsening congestion[10].

Hence, systemic congestion is a key target in management of these patients, and its relief is considered a treatment success. Control of congestion not only is associated with improvement in clinical outcomes and reduction in the rate of hospitalization, but could also prevent progression of kidney disease associated with renal venous congestion[12].

While high dose intravenous diuretics remain the cornerstone of decongestive therapy in patients with acute HF and acute CRS, extracorporeal ultrafiltration has recently re-emerged as a potential alternative in this setting with a number of proposed advantages such as effective and predictable fluid removal, efficient sodium extraction, and reduction in the rate of re-hospitalization[13,14]. In the setting of chronic CRS, the studies have mainly focused on improving cardiac function, whether through medications or devices. The currently available pharmacologic options for decongestion are limited to diuretics that have been in use for several decades as well as the newly marketed neprilysin inhibitors[15]. However, the use of diuretics in HF remains largely empirical, with potential disadvantages and untoward effects such as variable dose-response rate and diuretic resistance[16]. Moreover, a number of practical aspects of their use such as concomitant administration of loop and distal diuretics

remain elusive, and an association between high doses of loop diuretics and adverse outcomes has also been proposed by observational studies[17].

Peritoneal dialysis (PD) represents an intriguing home-based therapeutic option that provides the possibility of continuous, gentle, and customized removal of excess fluid and sodium in patients with HF who commonly present with various degrees of renal dysfunction. Herein, we explore the studies on the role of PD in management of CRS in two subsets of CRS patients separately; those non-ESRD patients with concomitant HF and chronic kidney disease (CKD) in whom PD is primarily used as an ultrafiltration modality for relief of refractory congestion rather than solute clearance, and those patients with HF and concomitant ESRD who have selected PD as a modality for chronic renal replacement therapy.

CKD and HF

Several studies so far have evaluated the role of PD in patients with chronic CRS and refractory volume overload in whom renal dysfunction is not severe enough to necessitate dialysis therapy for clearance of solutes. These trials have in general reported favorable outcomes. In a prospective single-center study including 118 patients with severe HF [New York Heart Association (NYHA) class Ⅲ and Ⅳ], Koch *et al*[18] evaluated the impact of intermittent automated PD (APD) therapy performed at least three times per week for 12 h per session. Mean baseline creatinine clearance was 19.2 mL/min and the patients were followed for slightly more than a year. The clinical symptoms of HF improved after starting PD as evidenced by improvement in the NYHA class at 6 mo, and fluid overload was also significantly reduced as shown by reduction in body weight from 78.7 to 74.7 kg (P < 0.001). In another prospective study, PD therapy was used for management of 25 patients with HF (NYHA class Ⅲ/Ⅳ), CKD, persistent fluid overload, and at least two previous hospitalizations for acute HF[19]. The mean daily peritoneal ultrafiltration was 679 mL; PD was associated with significant improvement in the Minnesota Living With Heart Failure Questionnaire and NYHA class at 6 and 24 wk. An 84% reduction in the number of hospitalized days for acute HF was also observed. Later, Courivaud *et al*[20] published the largest study to-date in this field that included 126 patients with refractory HF. The mean estimated glomerular filtration rate was 33.5 mL/min per 1.73 m^2 and the mean duration on PD was 16 mo. During the first year of PD therapy, left ventricular ejection fraction improved significantly (38% at baseline *vs* 42% at 1 year, P = 0.001). The striking observation of the study was that PD therapy was associated with a 90% reduction in the duration of HF-related hospitalization (3.3 d/patient-month before PD *vs* 0.3 d/patient-month after PD, P < 0.0001). Recently, a meta-analysis of the studies on the use of PD in refractory HF reported that PD was associated with a significant decline in hospitalization days and improvement in cardiac function defined by left ventricular ejection fraction and NYHA class[21]. Since congestion is the primary reason for hospitalization of patients with HF, the improvement in the hospitalization of these patients implies better management of fluid overload by PD. It can also have an important impact on the cost related to inpatient care of these patients. Overall, the currently available data suggest that PD is a clinically-relevant therapeutic option for removal of fluid in patients with chronic CRS who present with persistent congestion despite optimal medical therapy. Finally, it is notable that the favorable results of these studies are evident despite typical use of PD as the "last resort" for patients refractory to conventional therapies.

The studies on the role of PD in chronic CRS have three major limitations: Lack of a reasonably matched control group, relatively short follow-up periods, and the possibility of a publication bias. A major concern regarding the use of PD in this patient population has long been that its morbidity might replace that of HF. In modern practice, with an acceptably low incidence of PD-related complications, this concern appears to be less relevant. Moreover, those studies that assessed the quality of life of the patients reported significant improvement after initiation of PD[22]. Concerning the impact on survival, there is no conclusive evidence to this date to suggest that PD could indeed alter the natural course of the disease state although there have been reports of improvement in cardiac function[20].

ESRD and HF

For those CRS patients in whom renal dysfunction progresses to ESRD, fluid removal can be achieved through either hemodialysis (extracorporeal ultrafiltration) or PD (intracorporeal ultrafiltration). A number of advantages have been proposed for PD in this setting such as gentle and continuous fluid and solute removal being less likely to exacerbate neurohormonal activation as well as better preservation of residual renal function[23-25]. Importantly, it has been shown that patients undergoing fluid removal by hemodialysis experience myocardial stunning (*i.e.,* persistent left ventricular dysfunction due to repeated transient demand myocardial ischemia) even in the absence of angiographically significant coronary artery disease[26]. Myocardial stunning at long run can lead to progression of HF *via* development of fixed systolic dysfunction[27]. It has been shown that PD is not associated with myocardial stunning and hence would be less likely to lead to progression of HF in ESRD patients[28].

Despite theoretical advantages of PD therapy in patients with ESRD and HF, studies have so far yielded conflicting results. Panday *et al*[29] retrospectively compared the outcomes of 139 ESRD patients with concomitant HF, and reported no difference in 2-year mortality, cardiac outcomes, or hospitalization between PD and hemodialysis. Two large registry-based studies on ESRD population (one from United States and one from France) found that PD can be associated

with an even increased risk of mortality compared to hemodialysis in HF patients while these two modalities are associated with similar outcomes in ESRD patients without HF[30,31]. Similarly, in a study on National Health Insurance Research Database in Taiwan including more than 35000 patients, Wang *et al*[32] reported that PD was associated with inferior survival in ESRD patients with concomitant HF. It is not clear whether these findings are related to unexplored underlying mechanisms, the interplay of a number of well-known factors [*e.g.,* difficulty in management of volume status in ESRD patients with reduced residual renal function (RRF)], or could possibly reflect the inherent limitations of the registry-based data analysis (*e.g.,* treatment-by-indication bias). On the other hand, in a registry study from Lombardy in Italy, Locatelli et al. reported that the risk of *de novo* cardiovascular disease (HF and coronary artery disease) was similar between hemodialysis and PD[33]. More recently, a study based on Taiwanese national registry including more than 45000 patients with ESRD found that the risk of *de novo* HF in patients receiving hemodialysis is 29% higher than those undergoing PD therapy (CI: 1.13-1.47, $P < 0.001$) although the advantage seemed to disappear over time[34,35].

Despite the fact that the data is mixed, altogether they imply that the impact of PD as a dialysis modality on the outcomes of ESRD patients with "pre-existing HF" might be different from those without HF.

VOLUME STATUS IN ESRD - FOCUS ON PD

Fluid overload is a prevalent finding in patients with renal dysfunction and is associated with adverse cardiovascular outcomes[36,37]. Recently, a multicenter study on more than 1000 incident PD patients revealed that fluid overload is present already at baseline when they start PD therapy[38]. Using bioimpedance spectroscopy, the investigators found that the median fluid overload was 2 L, and less than half of the patients (38.7%) were indeed euvolemic; 25.1% of the patient population also had HF. Unfortunately, initiation of PD therapy does not seem to markedly improve fluid overload in patients with ESRD; congestion appears to remain a prevalent problem in a subset of PD population. For example, in the multicenter cross sectional European Body Composition Monitoring (EuroBCM) study that included 639 patients receiving PD therapy (mean time on PD 32.6 mo), only 40% were found to be euvolemic[39]. Extracellular fluid volume expansion in PD patients has been shown to be directly associated with increase in inflammatory markers, an established underlying mechanism for deterioration in cardiac function[40,41]. This could in part explain the unexpected outcomes of ESRD patients with pre-existing HF who choose PD for renal replacement therapy.

In recent years, there has been a renewed interest in the concept of optimization of fluid status in patients receiving renal replacement therapy due to the recognition of its significant impact on survival[42,43]. Overhydration is associated with hypertension, left ventricular hypertrophy, and increased mortality in PD patients[44]. Moreover, high serum levels of pro-B type natriuretic peptide (BNP), a surrogate for fluid overload, is an independent predictor of mortality in these patients[45]. To examine whether fluid overload *per se* is associated with poor outcomes in PD population or it merely reflects potential untoward effects of other comorbidities such as HF, Jotterand Drepper *et al*[46] studied 54 prevalent PD patients and found that overhydration was a strong and independent predictor of mortality after adjustment for cardiac function (relative hazard of 7.8). Similarly, in a study on 529 PD patients, O'Lone *et al*[47] found that overhydration measured by bioimpedance spectroscopy is an independent predictor of mortality.

HYDRATION STATUS AND RESIDUAL RENAL FUNCTION

Since RRF has been reported to be associated with reduced mortality in PD patients, preservation of RRF has become one of the major goals in management of patients receiving PD therapy[48]. The apparent importance of RRF is likely a proxy for adequate volume control in these patients. Since intravascular volume depletion could lead to a loss of RRF, it has been suggested that PD patients should avoid intravascular volume depletion and preferably be maintained hypervolemic to help preserve RRF. However, in an interesting study on 237 ESRD patients, McCafferty *et al*[49] showed that extracellular volume expansion measured by bioimpedance did not have any association with preservation of RRF. Moreover, correction of severe overhydration does not seem to result in a significant drop in RRF[50]. Therefore, based on currently available data, overhydration in the setting of PD therapy could increase the risk of cardiac dysfunction and adverse outcomes without an apparent beneficial impact on preservation of RRF.

VOLUME STATUS *VS* SOLUTE CLEARANCE

The clinical relevance of fluid overload and its impact on the outcomes in the setting of PD is to the point that euvolemia is likely to be even more important than small solute clearance as a marker of dialysis adequacy because fluid overload, but not small solute clearance, could predict outcomes[45,51]. In the landmark Canada-United States study that included 601 PD patients, urine volume superseded renal small solute clearance as a predictor of mortality; every 250 mL increment in urine

volume was associated with a 36% reduction in the risk of death[48]. In an interesting study on 125 PD patients, Ateş *et al*[52] showed that total sodium and fluid removal were independent factors affecting survival while Kt/V_{urea} and total creatinine clearance were not. Similarly, in the European Automated Peritoneal Dialysis Outcome Study, the survival of 177 anuric patients who were treated with PD was associated with baseline ultrafiltration, but not with clearance of creatinine or membrane permeability status[53].

DECONGESTION: SODIUM *VS* WATER

The common pathway for several maladaptive mechanisms involved in the development of HF is aberrancy in renal excretion of sodium with resultant extracellular fluid expansion. Since sodium is the main determinant of extracellular fluid volume, any therapeutic modality with greater ability for extraction of sodium will be advantageous in the setting of HF and volume overload. In a landmark study on vasopressin antagonists, addition of a vasopressin receptor antagonist to standard therapy of HF (with subsequent enhanced sodium-free water excretion) failed to reduce all-cause mortality, cardiovascular death, or re-hospitalization despite significant decongestion, highlighting the paramount role of sodium removal in this setting[54]. When applying therapeutic modalities for management of fluid overload, this distinction should be taken into consideration. In the PD therapy, during the first 60-90 min of the intraperitoneal dwell of the dextrose-containing PD solution, rapid transport of solute-free water takes place across the aquaporins while the remaining solute-rich water moves much more slowly through the small pores of the peritoneal membrane. Hence, the initial dissociation between the rate of water and sodium transport into the peritoneal cavity results in an early drop in the concentration of dialysate sodium, called sodium sieving. The slow diffusive movement of sodium continues and, if the dwell is long enough, the concentration of sodium in the dialysate will eventually approach that of serum. These mechanistic considerations should be accounted for when PD therapy is offered to ESRD patients with HF as there seem to be significant variations in the ability of this therapy for fluid and sodium removal based on the techniques as well as the regimens that are selected.

DECONGESTION: CAPD *VS* APD

The concept of sodium sieving is clinically relevant in that shorter dwells, such as those typically achieved with APD, might not provide enough time for adequate extraction of sodium; they could mainly result in removal of sodium-free water and lead to reduced net sodium removal and progressive congestion at long run. Longer dwells, such as those typically provided by continuous ambulatory peritoneal dialysis (CAPD), might be advantageous in the setting where sodium removal is the primary target (*i.e.,* patients with HF and volume overload). In a study on 141 PD patients, sodium removal was found to be significantly greater in those receiving CAPD compared to APD group, and switching techniques from CAPD to APD led to significant reduction in sodium removal[55]. In another study, BNP (a surrogate for volume status) and left ventricular mass were reported to be significantly higher in the APD patients compared with CAPD[56]. It should however be noted that several other factors such as the PD solutions and the regimens as well as the clinical characteristics and dietary habits of the patients can affect these results. For example, in a study on 158 prevalent PD patients (90 CAPD, 68 APD), Davison *et al*[57] used bioimpedance spectroscopy to assess and compare the hydration status of the patients. They reported no difference between APD and CAPD with regard to the ratio of extracellular fluid volume to total body water. Mean total daily removal of sodium was 109 mmol for patients on CAPD and 130 mmol for APD (P = 0.23). Among CAPD patients, 41% had a sodium removal of less than 100 mmol/d compared to 33.8% in the APD group (P = 0.36). Blood pressure was also similar in the two groups. The results of this study can be in part explained by the fact that nearly 80% of the APD patients were on icodextrin for their long daytime dwell (hence improving fluid management), and also the number of nocturnal exchanges were decreased (*i.e.,* allowing for longer dwells and less sodium sieving).

ENHANCING SODIUM REMOVAL

Since sodium concentration of most conventional PD solutions (*i.e.,* 132 mmol/L) is close to that of serum, sodium removal is mainly convective; diffusion does not typically play an important role in this setting. In an attempt to improve sodium extraction through increased diffusion gradient, a number of studies have evaluated the impact of low-sodium PD solutions on various endpoints. For example, in a recent randomized controlled trial on 108 patients, Rutkowski *et al*[58] used PD solution containing 125 mmol/L of sodium and compared it with the control group. They found that low-sodium solution could significantly increase sodium removal (by 1.1 g/d, P < 0.001) and improve blood pressure control. Although low-sodium solutions can prove helpful in specific settings and select patients (*i.e.,* those with HF), their widespread use is hindered by a number of factors such as reduced osmolality of the solution and consequent decrease in ultrafiltration thus offsetting their benefit.

APD, once used mainly for patients who were rapid transporters, has become the modality of choice by many patients and physicians in the developed countries due to it being not only convenient and adaptable to the lifestyle of patients but also modifiable to fit a wide range of clinical characteristics and needs. In the United States, more than 70% of patients are treated with this technique[59]. As previously mentioned,

there is concern with regard to the ability of APD to adequately extract sodium and to address congestion in these patients. There are a number of strategies that are based on the mechanisms of water and solute transport in PD and can potentially improve fluid and sodium extraction by APD. This could be of special importance in specific clinical settings such as HF where decongestion, rather than clearance, is the primary target of this therapy. Decreasing the number of nocturnal cycles could increase the dwell time hence reducing sodium sieving. This is likely to improve sodium removal and, if the patient is on low sodium diet, could provide negative or even sodium balance especially through concomitant use of loop diuretics for those with significant RRF. Adding an exchange in the evening for select APD patients (*i.e.,* those with slow peritoneal transport characteristics) could also ensure adequate small solute clearance while further increasing sodium removal. Use of icodextrin, a high molecular weight glucose polymer developed specifically for use as an alternative osmotic agent to dextrose during the once-daily long-dwell exchange, allows for sustained fluid removal and optimization of volume status due to reduced back diffusion[60]. Icodextrin has the advantage that it does not activate aquaporins; all the ultrafiltration takes place at the intercellular small pores where sodium fluxes with water (*i.e.,* no sodium sieving). This process allows for more efficient sodium removal compared to an equal volume of ultrafiltration with a dextrose-based solution. Therefore, icodextrin could prove helpful in clinical settings such as HF where enhanced sodium removal is of particular importance. In a multicenter randomized controlled trial on 50 PD patients with urine volume of less than 750 mL/d and high solute transport, Davies *et al*[61] reported an average increase of 61.7 mmol in daily sodium removal and an average increase of 399 mL in ultrafiltration in patients receiving icodextrin instead of a glucose-based solution. Basile *et al*[62] reported their experience with the use of icodextrin (1 to 2 exchanges a night) in patients with end-stage HF and severe volume overload over a follow up period of 2 years. After starting PD, the patients experienced a significant decrease in their mean weight by 11.3 kg ($P < 0.007$), an increase in urine output (from 587 to 1700 mL/d, $P < 0.003$), and significant reduction in the number of days hospitalized for HF (from 4.4 to 0.7 d/mo, $P < 0.04$). Therefore, the initial results with the use of icodextrin seem to be promising. A combination of the above-mentioned strategies (simultaneous or successive) could be used to enhance effective sodium removal by APD and help further improve patients' volume status. Whether these approaches would translate to better outcomes is to be determined by future studies.

CONCLUSION

While lingering congestion remains an unresolved issue in a significant subset of patients with CRS, PD therapy has been offered as a clinically-relevant alternative to conventional therapies for optimization of volume. In those patients who present with ESRD and pre-existing HF, there is mixed data with regard to the role of PD therapy and its impact on survival. Whether this is related to suboptimal management of overhydration or other factors remains elusive. Optimization of volume status appears to be at least as important as providing clearance in patients receiving PD therapy, and sodium removal plays an integral role in this regard especially in those with concomitant HF. Clinicians could take advantage of the known strategies to enhance extraction of sodium-rich effluent in these patients. Future studies are needed to assess whether these methods would indeed lead to improvement of the outcomes.

REFERENCES

1 **Lloyd-Jones DM**, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D; Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002; **106**: 3068-3072 [PMID: 12473553 DOI: 10.1161/01.CIR.0000039105.49749.6F]

2 **Heidenreich PA**, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogdon JG; American Heart Association Advocacy Coordinating Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013; **6**: 606-619 [PMID: 23616602 DOI: 10.1161/HHF.0b013e318291329a]

3 **Gheorghiade M**, Zannad F, Sopko G, Klein L, Piña IL, Konstam MA, Massie BM, Roland E, Targum S, Collins SP, Filippatos G, Tavazzi L; International Working Group on Acute Heart Failure Syndromes. Acute heart failure syndromes: current state and framework for future research. *Circulation* 2005; **112**: 3958-3968 [PMID: 16365214 DOI: 10.1161/CIRCULATIONAHA.105.590091]

4 **Kazory A**, Elkayam U. Cardiorenal interactions in acute decompensated heart failure: contemporary concepts facing emerging controversies. *J Card Fail* 2014; **20**: 1004-1011 [PMID: 25230240 DOI: 10.1016/j.cardfail.2014.09.005]

5 **Metra M**, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B, Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail* 2012; **5**: 54-62 [PMID: 22167320 DOI: 10.1161/CIRCHEARTFAILURE.111.963413]

6 **Testani JM**, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation* 2010; **122**: 265-272 [PMID: 20606118 DOI: 10.1161/CIRCULATIONAHA.109.933275]

7 **Ronco C**, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; **52**: 1527-1539 [PMID: 19007588 DOI: 10.1016/j.jacc.2008.07.051]

8 **Metra M**, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. The role of the kidney in heart failure. *Eur Heart J* 2012; **33**: 2135-2142 [PMID: 22888113 DOI: 10.1093/eurheartj/ehs205]

9 **Bock JS**, Gottlieb SS. Cardiorenal syndrome: new perspectives. *Circulation* 2010; **121**: 2592-2600 [PMID: 20547939 DOI: 10.1161/CIRCULATIONAHA.109.886473]

10 **Mullens W**, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for

worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 2009; **53**: 589-596 [PMID: 19215833 DOI: 10.1016/j.jacc.2008.05.068]
11 **Damman K**, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* 2009; **53**: 582-588 [PMID: 19215832 DOI: 10.1016/j.jacc.2008.08.080]
12 **Kazory A**. Cardiorenal syndrome: ultrafiltration therapy for heart failure--trials and tribulations. *Clin J Am Soc Nephrol* 2013; **8**: 1816-1828 [PMID: 23723339 DOI: 10.2215/CJN.02910313]
13 **Jain A**, Agrawal N, Kazory A. Defining the role of ultrafiltration therapy in acute heart failure: a systematic review and meta-analysis. *Heart Fail Rev* 2016; **21**: 611-619 [PMID: 27154520 DOI: 10.1007/s10741-016-9559-2]
14 **Kazory A**. Ultrafiltration Therapy for Heart Failure: Balancing Likely Benefits against Possible Risks. *Clin J Am Soc Nephrol* 2016; **11**: 1463-1471 [PMID: 27034400 DOI: 10.2215/CJN.13461215]
15 **Farmakis D**, Bistola V, Karavidas A, Parissis J. Practical considerations on the introduction of sacubitril/valsartan in clinical practice: Current evidence and early experience. *Int J Cardiol* 2016; **223**: 781-784 [PMID: 27573608 DOI: 10.1016/j.ijcard.2016.08.323]
16 **Mentz RJ**, Kjeldsen K, Rossi GP, Voors AA, Cleland JG, Anker SD, Gheorghiade M, Fiuzat M, Rossignol P, Zannad F, Pitt B, O'Connor C, Felker GM. Decongestion in acute heart failure. *Eur J Heart Fail* 2014; **16**: 471-482 [PMID: 24599738 DOI: 10.1002/ejhf.74]
17 **Hasselblad V**, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF Jr. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail* 2007; **9**: 1064-1069 [PMID: 17719273 DOI: 10.1016/j.ejheart.2007.07.011]
18 **Koch M**, Haastert B, Kohnle M, Rump LC, Kelm M, Trapp R, Aker S. Peritoneal dialysis relieves clinical symptoms and is well tolerated in patients with refractory heart failure and chronic kidney disease. *Eur J Heart Fail* 2012; **14**: 530-539 [PMID: 22447950 DOI: 10.1093/eurjhf/hfs035]
19 **Núñez J**, González M, Miñana G, Garcia-Ramón R, Sanchis J, Bodí V, Núñez E, Puchades MJ, Palau P, Merlos P, Llàcer A, Miguel A. Continuous ambulatory peritoneal dialysis as a therapeutic alternative in patients with advanced congestive heart failure. *Eur J Heart Fail* 2012; **14**: 540-548 [PMID: 22327061 DOI: 10.1093/eurjhf/hfs013]
20 **Courivaud C**, Kazory A, Crépin T, Azar R, Bresson-Vautrin C, Chalopin JM, Ducloux D. Peritoneal dialysis reduces the number of hospitalization days in heart failure patients refractory to diuretics. *Perit Dial Int* 2014; **34**: 100-108 [PMID: 23994842 DOI: 10.3747/pdi.2012.00149]
21 **Lu R**, Muciño-Bermejo MJ, Ribeiro LC, Tonini E, Estremadoyro C, Samoni S, Sharma A, Zaragoza Galván Jde J, Crepaldi C, Brendolan A, Ni Z, Rosner MH, Ronco C. Peritoneal dialysis in patients with refractory congestive heart failure: a systematic review. *Cardiorenal Med* 2015; **5**: 145-156 [PMID: 25999963 DOI: 10.1159/000380915]
22 **Courivaud C**, Kazory A. Can we treat fluid overload with fluid? Role of peritoneal dialysis in management of heart failure. *Eur J Heart Fail* 2012; **14**: 461-463 [PMID: 22510421 DOI: 10.1093/eurjhf/hfs053]
23 **Lang SM**, Bergner A, Töpfer M, Schiffl H. Preservation of residual renal function in dialysis patients: effects of dialysis-technique-related factors. *Perit Dial Int* 2001; **21**: 52-57 [PMID: 11280496]
24 **Misra M**, Vonesh E, Van Stone JC, Moore HL, Prowant B, Nolph KD. Effect of cause and time of dropout on the residual GFR: a comparative analysis of the decline of GFR on dialysis. *Kidney Int* 2001; **59**: 754-763 [PMID: 11168959 DOI: 10.1046/j.1523-1755.2001.059002754.x]
25 **Moist LM**, Port FK, Orzol SM, Young EW, Ostbye T, Wolfe RA, Hulbert-Shearon T, Jones CA, Bloembergen WE. Predictors of loss of residual renal function among new dialysis patients. *J Am Soc Nephrol* 2000; **11**: 556-564 [PMID: 10703680]
26 **McIntyre CW**, Burton JO, Selby NM, Leccisotti L, Korsheed S, Baker CS, Camici PG. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol* 2008; **3**: 19-26 [PMID: 18003765 DOI: 10.2215/CJN.03170707]
27 **Burton JO**, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol* 2009; **4**: 1925-1931 [PMID: 19808220 DOI: 10.2215/CJN.04470709]
28 **Selby NM**, McIntyre CW. Peritoneal dialysis is not associated with myocardial stunning. *Perit Dial Int* 2011; **31**: 27-33 [PMID: 20522673 DOI: 10.3747/pdi.2010.00007]
29 **Panday VB**, Tong ZP, Ng PL, Lee EJ, Lau T, Teo BW, Chua HR. Dialysis modality and 2-year outcomes in patients with ischemic cardiomyopathy and end-stage renal disease. *Int J Cardiol* 2014; **176**: 1097-1099 [PMID: 25175518 DOI: 10.1016/j.ijcard.2014.07.120]
30 **Stack AG**, Molony DA, Rahman NS, Dosekun A, Murthy B. Impact of dialysis modality on survival of new ESRD patients with congestive heart failure in the United States. *Kidney Int* 2003; **64**: 1071-1079 [PMID: 12911559 DOI: 10.1046/j.1523-1755.2003.00165.x]
31 **Sens F**, Schott-Pethelaz AM, Labeeuw M, Colin C, Villar E; REIN Registry. Survival advantage of hemodialysis relative to peritoneal dialysis in patients with end-stage renal disease and congestive heart failure. *Kidney Int* 2011; **80**: 970-977 [PMID: 21775972 DOI: 10.1038/ki.2011.233]
32 **Wang IK**, Kung PT, Kuo WY, Tsai WC, Chang YC, Liang CC, Chang CT, Yeh HC, Wang SM, Chuang FR, Wang KY, Lin CY, Huang CC. Impact of dialysis modality on the survival of end-stage renal disease patients with or without cardiovascular disease. *J Nephrol* 2013; **26**: 331-341 [PMID: 22476965 DOI: 10.5301/jn.5000149]
33 **Locatelli F**, Marcelli D, Conte F, D'Amico M, Del Vecchio L, Limido A, Malberti F, Spotti D. Survival and development of cardiovascular disease by modality of treatment in patients with end-stage renal disease. *J Am Soc Nephrol* 2001; **12**: 2411-2417 [PMID: 11675417]
34 **Wang IK**, Lu CY, Lin CL, Liang CC, Yen TH, Liu YL, Sung FC. Comparison of the risk of de novo cardiovascular disease between hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Int J Cardiol* 2016; **218**: 219-224 [PMID: 27236118 DOI: 10.1016/j.ijcard.2016.05.036]
35 **Kazory A**. The lower risk of de novo heart failure associated with peritoneal dialysis; the timing does matter. *Int J Cardiol* 2017; **229**: 122 [PMID: 27825729 DOI: 10.1016/j.ijcard.2016.10.094]
36 **Bellizzi V**, Scalfi L, Terracciano V, De Nicola L, Minutolo R, Marra M, Guida B, Cianciaruso B, Conte G, Di Iorio BR. Early changes in bioelectrical estimates of body composition in chronic kidney disease. *J Am Soc Nephrol* 2006; **17**: 1481-1487 [PMID: 16611719 DOI: 10.1681/ASN.2005070756]
37 **Essig M**, Escoubet B, de Zuttere D, Blanchet F, Arnoult F, Dupuis E, Michel C, Mignon F, Mentre F, Clerici C, Vrtovsnik F. Cardiovascular remodelling and extracellular fluid excess in early stages of chronic kidney disease. *Nephrol Dial Transplant* 2008; **23**: 239-248 [PMID: 17704109 DOI: 10.1093/ndt/gfm542]
38 **Ronco C**, Verger C, Crepaldi C, Pham J, De Los Ríos T, Gauly A, Wabel P, Van Biesen W; IPOD-PD Study Group. Baseline hydration status in incident peritoneal dialysis patients: the initiative of patient outcomes in dialysis (IPOD-PD study). *Nephrol Dial Transplant* 2015; **30**: 849-858 [PMID: 25762355 DOI: 10.1093/ndt/gfv013]
39 **Van Biesen W**, Williams JD, Covic AC, Fan S, Claes K, Lichodziejewska-Niemierko M, Verger C, Steiger J, Schoder V, Wabel P, Gauly A, Himmele R; EuroBCM Study Group. Fluid status in peritoneal dialysis patients: the European Body Composition Monitoring (EuroBCM) study cohort. *PLoS One* 2011; **6**: e17148 [PMID: 21390320 DOI: 10.1371/journal.pone.0017148]
40 **Vicenté-Martínez M**, Martínez-Ramírez L, Muñoz R, Avila M, Ventura MD, Rodríguez E, Amato D, Paniagua R. Inflammation in patients on peritoneal dialysis is associated with increased extracellular fluid volume. *Arch Med Res* 2004; **35**: 220-224 [PMID: 15163463 DOI: 10.1016/j.arcmed.2004.01.003]
41 **Avila-Díaz M**, Ventura MD, Valle D, Vicenté-Martínez M, García-González Z, Cisneros A, Furlong MD, Gómez AM, Prado-Uribe MD, Amato D, Paniagua R. Inflammation and extracellular volume expansion are related to sodium and water removal in patients on peritoneal dialysis. *Perit Dial Int* 2006; **26**: 574-580 [PMID: 16973513]
42 **Van Biesen W**, Verbeke F, Devolder I, Vanholder R. The relation

between salt, volume, and hypertension: clinical evidence for forgotten but still valid basic physiology. *Perit Dial Int* 2008; **28**: 596-600 [PMID: 18981387]

43 **Konings CJ**, Kooman JP, Schonck M, Dammers R, Cheriex E, Palmans Meulemans AP, Hoeks AP, van Kreel B, Gladziwa U, van der Sande FM, Leunissen KM. Fluid status, blood pressure, and cardiovascular abnormalities in patients on peritoneal dialysis. *Perit Dial Int* 2002; **22**: 477-487 [PMID: 12322819]

44 **Chen W**, Guo LJ, Wang T. Extracellular water/intracellular water is a strong predictor of patient survival in incident peritoneal dialysis patients. *Blood Purif* 2007; **25**: 260-266 [PMID: 17429200 DOI: 10.1159/000101699]

45 **Paniagua R**, Ventura MD, Avila-Díaz M, Hinojosa-Heredia H, Méndez-Durán A, Cueto-Manzano A, Cisneros A, Ramos A, Madonia-Juseino C, Belio-Caro F, García-Contreras F, Trinidad-Ramos P, Vázquez R, Ilabaca B, Alcántara G, Amato D. NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. *Nephrol Dial Transplant* 2010; **25**: 551-557 [PMID: 19679559 DOI: 10.1093/ndt/gfp395]

46 **Jotterand Drepper V**, Kihm LP, Kälble F, Diekmann C, Seckinger J, Sommerer C, Zeier M, Schwenger V. Overhydration Is a Strong Predictor of Mortality in Peritoneal Dialysis Patients - Independently of Cardiac Failure. *PLoS One* 2016; **11**: e0158741 [PMID: 27415758 DOI: 10.1371/journal.pone.0158741]

47 **O'Lone EL**, Visser A, Finney H, Fan SL. Clinical significance of multi-frequency bioimpedance spectroscopy in peritoneal dialysis patients: independent predictor of patient survival. *Nephrol Dial Transplant* 2014; **29**: 1430-1437 [PMID: 24598280 DOI: 10.1093/ndt/gfu049]

48 **Bargman JM**, Thorpe KE, Churchill DN; CANUSA Peritoneal Dialysis Study Group. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J Am Soc Nephrol* 2001; **12**: 2158-2162 [PMID: 11562415]

49 **McCafferty K**, Fan S, Davenport A. Extracellular volume expansion, measured by multifrequency bioimpedance, does not help preserve residual renal function in peritoneal dialysis patients. *Kidney Int* 2014; **85**: 151-157 [PMID: 23884340 DOI: 10.1038/ki.2013.273]

50 **Burke SE**, Fan SL. Clinical experience using bioimpedance to optimize blood pressure control. *Perit Dial Int* 2013; **33**: 205-208 [PMID: 23478373 DOI: 10.3747/pdi.2011.00197]

51 **Paniagua R**, Amato D, Correa-Rotter R, Ramos A, Vonesh EF, Mujais SK. Correlation between peritoneal equilibration test and dialysis adequacy and transport test, for peritoneal transport type characterization. Mexican Nephrology Collaborative Study Group. *Perit Dial Int* 2000; **20**: 53-59 [PMID: 10716584]

52 **Ateş K**, Nergizoğlu G, Keven K, Sen A, Kutlay S, Ertürk S, Duman N, Karatan O, Ertuğ AE. Effect of fluid and sodium removal on mortality in peritoneal dialysis patients. *Kidney Int* 2001; **60**: 767-776 [PMID: 11473661 DOI: 10.1046/j.1523-1755.2001.060002767.x]

53 **Brown EA**, Davies SJ, Rutherford P, Meeus F, Borras M, Riegel W, Divino Filho JC, Vonesh E, van Bree M; EAPOS Group. Survival of functionally anuric patients on automated peritoneal dialysis: the European APD Outcome Study. *J Am Soc Nephrol* 2003; **14**: 2948-2957 [PMID: 14569106 DOI: 10.1097/01.ASN.0000092146.67909.E2]

54 **Konstam MA**, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007; **297**: 1319-1331 [PMID: 17384437 DOI: 10.1001/jama.297.12.1319]

55 **Rodríguez-Carmona A**, Fontán MP. Sodium removal in patients undergoing CAPD and automated peritoneal dialysis. *Perit Dial Int* 2002; **22**: 705-713 [PMID: 12556073]

56 **Bavbek N**, Akay H, Altay M, Uz E, Turgut F, Uyar ME, Karanfil A, Selcoki Y, Akcay A, Duranay M. Serum BNP concentration and left ventricular mass in CAPD and automated peritoneal dialysis patients. *Perit Dial Int* 2007; **27**: 663-668 [PMID: 17984428]

57 **Davison SN**, Jhangri GS, Jindal K, Pannu N. Comparison of volume overload with cycler-assisted versus continuous ambulatory peritoneal dialysis. *Clin J Am Soc Nephrol* 2009; **4**: 1044-1050 [PMID: 19406971 DOI: 10.2215/CJN.00020109]

58 **Rutkowski B**, Tam P, van der Sande FM, Vychytil A, Schwenger V, Himmele R, Gauly A; Low Sodium Balance Study Group. Low-Sodium Versus Standard-Sodium Peritoneal Dialysis Solution in Hypertensive Patients: A Randomized Controlled Trial. *Am J Kidney Dis* 2016; **67**: 753-761 [PMID: 26388284 DOI: 10.1053/j.ajkd.2015.07.031]

59 **Bieber SD**, Burkart J, Golper TA, Teitelbaum I, Mehrotra R. Comparative outcomes between continuous ambulatory and automated peritoneal dialysis: a narrative review. *Am J Kidney Dis* 2014; **63**: 1027-1037 [PMID: 24423779 DOI: 10.1053/j.ajkd.2013.11.025]

60 **Frampton JE**, Plosker GL. Icodextrin: a review of its use in peritoneal dialysis. *Drugs* 2003; **63**: 2079-2105 [PMID: 12962523 DOI: 10.2165/00003495-200363190-00011]

61 **Davies SJ**, Woodrow G, Donovan K, Plum J, Williams P, Johansson AC, Bosselmann HP, Heimbürger O, Simonsen O, Davenport A, Tranaeus A, Divino Filho JC. Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. *J Am Soc Nephrol* 2003; **14**: 2338-2344 [PMID: 12937311 DOI: 10.1097/01.ASN.0000083904.12234.27]

62 **Basile C**, Chimienti D, Bruno A, Cocola S, Libutti P, Teutonico A, Cazzato F. Efficacy of peritoneal dialysis with icodextrin in the long-term treatment of refractory congestive heart failure. *Perit Dial Int* 2009; **29**: 116-118 [PMID: 19164263]

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MINIREVIEWS

Causal relationship between hypoalbuminemia and acute kidney injury

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Abstract

Our meta-analysis published in 2010 provided evidence that low levels of serum albumin (hypoalbuminemia) are a significant independent predictor of acute kidney injury (AKI) and death following AKI. Since then, a large volume of additional data from observational clinical studies has been published further evaluating the relationship between serum albumin and AKI occurrence. This is an updated review of the literature to re-evaluate the hypothesis that hypoalbuminemia is independently associated with increased AKI risk. Eligible studies published from September 2009 to December 2016 were sought in PubMed (MEDLINE) and forty-three were retained, the great majority being retrospective observational cohort studies. These included a total of about 68000 subjects across a diverse range of settings, predominantly cardiac surgery and acute coronary interventions, infectious diseases, transplant surgery, and cancer. Appraisal of this latest data set served to conclusively corroborate and confirm our earlier hypothesis that lower serum albumin is an independent predictor both of AKI and death after AKI, across a range of clinical scenarios. The body of evidence indicates that hypoalbuminemia may causally contribute to development of AKI. Furthermore, administration of human albumin solution has the potential to prevent AKI; a randomized, controlled study provides evidence that correcting hypoalbuminemia may be renal-protective. Therefore, measurement of serum albumin to diagnose hypoalbuminemia may help identify high-risk patients who may benefit from treatment with exogenous human albumin. Multi-center, prospective, randomized, interventional studies are warranted, along with basic research to define the mechanisms through

which albumin affords nephroprotection.

Key words: Acute kidney injury; Acute renal failure; Hypoalbuminemia; Mortality; Prevention

Core tip: The relationship between hypoalbuminemia and acute kidney injury (AKI)-related morbidity/mortality is now confirmed. This association is consistently evident in a wealth of observational studies conducted across a wide range of clinical settings, and suggests a causal link. Prospective studies adequately powered to assess severe AKI, mortality and causality are needed, as is evaluation of the trigger and appropriate target serum levels and albumin dose necessary to confer renal protection. Basic research is also warranted to define the mechanisms through which albumin affords nephroprotection. Serum albumin should be measured to identify patients with increased AKI risk who may benefit from treatment correcting underlying hypoalbuminemia.

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INTRODUCTION

Acute kidney injury (AKI), formerly referred to as acute renal failure (ARF), is a syndrome in which kidney function deteriorates rapidly over a period of hours or days. It is characterized by increased serum creatinine level (of $\geqslant$ 0.3 mg/dL in 48 h and/or 1.5-fold within 7 d) and decreased urine output. The staging system for AKI has evolved from the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria, to the acute kidney injury network (AKIN) scheme, and most recently to the Kidney Disease Improving Global Outcomes (KDIGO) score (for a review of AKI diagnosis, see[1]).

AKI is an acute systemic disease with major consequences for other organs besides the kidney, and is associated with significant short-term effects (*e.g.*, fluid, electrolyte, and acid-base abnormalities, uremic toxin accumulation, cytokine elevation, systemic inflammation) and long-term adverse outcomes (*e.g.*, myocardial infarction, chronic kidney disease, end-stage renal disease, mortality)[2,3]. Need for dialysis and transplantation are increased, as is length of hospital stay[4,5].

AKI is recognized as a major global health problem, with increasing incidence in both high- and low-income nations, and high associated healthcare costs[6,7]. It is a common disorder encountered in multiple settings, occurring in 21% of hospital admissions worldwide and in more than 13 million people each year[5], especially critically ill patients[1], where incidence rates well above 50% were reported in the recent prospective AKI-EPI study[8]. The International Society of Nephrology's 0by25 initiative sets out a framework to eradicate preventable death from AKI by 2025 based on the 5 Rs: Risk, Recognition, Response, Renal Support, and Rehabilitation[5].

The etiology of AKI includes community-acquired causes (common in developing countries), such as infections (malaria, dengue, gastroenteritis, pneumonia), acute glomerular disease, underlying chronic disease (kidney, cardiac, diabetes), and trauma, as well as hospital-acquired causes (especially in industrialized nations), such as surgery, hemorrhage, infection, septic shock, drug toxicity, and underlying chronic disease (reviewed in[7]). The pathogenesis of AKI is multifactorial and several risk factors have been identified, both modifiable (*e.g.*, dehydration, intravascular volume depletion, hypotension, anemia, hypoxia, body mass index) and non-modifiable (*e.g.*, age, sex, prior invasive procedures, high-risk surgery, and comorbid disorders such as cancer and lung, liver or gastrointestinal disease)[5,9].

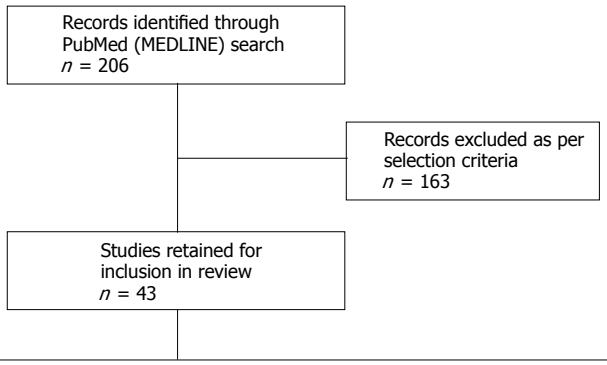
Hypoalbuminemia, or low levels of serum albumin (often defined as < 3.5-4.0 g/dL or $\leqslant$ 3.5 mmol/L), is a well-established risk factor for increased morbidity and mortality[10] and has also been associated with an increased risk of AKI occurrence; it is modifiable by infusion of human albumin solution. Our systematic review and meta-analysis published in 2010 found evidence, from observational studies in surgical and ICU patients, that low serum albumin is a significant independent predictor of AKI [pooled odds ratio (OR) = 2.34, 95%CI: 1.74-3.14] and of death following AKI (pooled OR = 2.47, 95%CI: 1.51-4.05)[9].

Since then, a large volume of additional clinical data has been published on hypoalbuminemia and AKI, across an expanded range of settings. Therefore, we performed an updated review of the literature to define the role of hypoalbuminemia and albumin administration in the development and prevention of AKI. Detailed discussion of the potential nephroprotective mechanisms of albumin is beyond the scope of the present review but was the subject of a separate review[11].

RESEARCH

Literature was sourced by conducting a systematic search of the PubMed (MEDLINE) database using phrases and synonyms for "kidney injury", "albumin", "hypoalbuminemia" and "mortality" (Table 1). The search was limited to articles published from September 2009 to December 2016 (inclusive), *i.e.*, since the end of the search period used in our 2010 systematic review[9].

Only studies meeting the following selection criteria



	Cardiac	Infection	Transplant	Cancer	Other	Total
No. of studies	8	8	6	6	15	43
PRO, INT	1	-	-	-	-	1
PRO, OBS	2	1	1	1	-	5
RET, OBS	5	7	5	5	15	37
Total studies	4344	5623	5032	7028	46235	68262

Figure 1 Flow diagram summarizing the literature screening and the designs and settings of the included studies. The numbers presented for the sizes of the data sets include control populations and do not represent only patients with acute kidney injury/acute renal failure and/or hypoalbuminemia. OBS: Observational; INT: Interventional; PRO: Prospective; RET: Retrospective.

Table 1 PubMed (MEDLINE) search strategy

1 Search: "acute kidney injury" OR AKI OR "acute renal failure" OR ARF
2 Search: mortality OR survival OR death
3 Search: "serum albumin" OR hypoalbuminemia* OR hypoalbuminaemia*
4 Filter: Publication date from 2009/09/01 to 2016/12/31
5 Search: #1 AND #2 AND #3 AND #4

The search was conducted without applying restrictions to language or publication type.

were retained for inclusion in the present review: Reported original data on associations between serum albumin levels (absolute levels, variously defined by authors as < 3.5 or < 3.0 or < 2.5 g/dL, or percentage prevalence of hypoalbuminemia) and the development of AKI (during the different observation periods, depending on the indication), or on mortality in patients with both AKI and hypoalbuminemia.

From included studies, data were extracted on clinical setting/population, study design and size, assessment of albumin levels/hypoalbuminemia, AKI occurrence/risk, and mortality (Tables 2-5).

INCLUDED STUDIES

Our search retrieved a total of 206 entries on PubMed (MEDLINE). The titles and abstracts of all hits were screened and research articles that did not report relevant data as stated in the selection criteria were discarded, along with any review/opinion articles. A total of 43 research articles were retained for inclusion in the present review (Figure 1). The great majority of these were retrospective in nature (37 of 43 studies), except for a single interventional randomized controlled trial (RCT), conducted in off-pump coronary artery bypass (OPCAB) surgery, and five prospective observational studies: Two in cardiac settings, one in HIV-infected patients, one in liver transplant recipients, and one in patients with hepatocellular carcinoma (HCC) with ascites. In total, the data set comprises approximately 68000 patients across a range of clinical settings, as described and discussed below.

CARDIAC SURGERY AND ACUTE CORONARY INTERVENTIONS

AKI is a common complication following cardiac surgery, and is associated with significant morbidity, mortality, and hospital costs (reviewed in[12]). We identified eight studies, involving more than 4000 subjects, which explored the role of albumin in AKI occurring after cardiac surgery or coronary intervention (Table 2).

In the only interventional drug study among the 43 retained articles, Lee *et al*[13] recently performed a single-center, randomized, parallel-arm, double-blind trial which evaluated the effects of exogenous 20% human albumin solution *vs* saline on the incidence of postoperative AKI in adult patients with hypoalbuminemia (< 4.0 g/dL) undergoing off-pump coronary artery bypass (OPCAB) surgery. Dose was 100, 200, or 300 mL immediately before surgery, stratified according to preoperative serum albumin level of 3.5-3.9, 3.0-3.4, or < 3.0 g/dL, respectively. In the saline group, rate of postoperative AKI (KDIGO-criteria patients) appeared to increase as postoperative serum albumin level decreased (29.5%, 31.1%, 41.7% for 3.5-3.9, 3.0-3.4, < 3.0 g/dL, respectively). The incidence of postoperative AKI (KDIGO criteria) was

Table 2 Included studies on cardiac surgery and acute coronary interventions

Ref.	Population/ setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Lee *et al*[13]	OPCAB surgery	Prospective RCT	220	Postoperative albumin 3.5-3.9 *vs* < 3.0 g/dL	Increased rate: 29.5% *vs* 41.7%. AKI rate lower with albumin *vs* control (13.7% *vs* 25.7%; P = 0.048)	ND
Grodin *et al*[20]	Acute heart failure	Prospective, observational	456	Admission albumin level (continuous and stratified by median ⩾ 3.5 g/dL)	NS	NS
Moguel-González *et al*[16]	Cardiac surgery	Prospective, observational, longitudinal	164	Preoperative albumin < 4.0 g/dL	Increased risk: OR = 3.852 (95%CI: 1.101-13.473; P = 0.063)	ND
Lee *et al*[14]	OPCAB surgery	Retrospective, observational, propensity score matching	1182 (incl. 323 matched pairs)	Preoperative albumin < 4.0 g/dL	Increased risk: OR = 1.83 (95%CI: 1.27-2.64); P = 0.001; propensity analysis: OR = 1.62, (95%CI: 1.12-2.35); P = 0.011	ND
Murat *et al*[21]	ACS and PCI	Retrospective, observational	890	Albumin level at hospitalization	Low albumin (3.52 g/dL *vs* 3.94 g/dL) predictive of CI-AKI: OR = 0.177 (95%CI: 0.080-0.392; P < 0.001)	ND
Kim *et al*[17]	Thoracic aorta repair with CPB	Retrospective, observational, propensity score matching	702 (incl. 183 matched pairs)	Preoperative albumin < 4.0 g/dL	Increased risk: OR = 2.50 (95%CI: 1.39-4.50; P = 0.002)	ND
Findik *et al*[15]	CAB surgery	Retrospective, observational	530	Preoperative albumin < 3.5 g/dL	Increased rate: OR = 1.661 (95%CI: 1.037-2.661); P = 0.035	ND
Go *et al*[19]	LVAD implantation	Retrospective, observational	200	< 2.5 g/dL (low) *vs* 2.5-3.5 g/dL (mid-range) *vs* > 3.5 g/dL (normal)	Increased ARF: 42.9% *vs* 16.5% *vs* 17.3%; P = 0.05	NS

ACS: Acute coronary syndromes; AKI: Acute kidney injury; ARF: Acute renal failure; CI-AKI: Contrast-induced acute kidney injury; CPB: Cardiopulmonary bypass; LVAD: Left ventricular assist device; ND: Not disclosed; NS: Not significant; OPCAB: Off-pump coronary artery bypass; OR: Odds ratio; PCS: Percutaneous coronary intervention; RCT: Randomized, controlled trial.

Table 3 Included studies on infectious diseases

Ref.	Population/ setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Prakash *et al*[22]	HIV	Prospective, observational	3540	Albumin level at hospitalization	ND	2.14 g/dL in patients who died *vs* 3.2 g/dL in survivors; P < 0.001
Vannaphan *et al*[34]	Severe falciparum malaria	Retrospective, observational	915	Albumin < 3.5 g/dL	Associated with ARF (P < 0.001)	ND
Lee *et al*[39]	Acute viral hepatitis A	Retrospective, observational	391	Albumin < 3.0 g/dL	OR = 8.24 (95%CI: 2.53-26.86; P < 0.0001)	ND
Lee *et al*[35]	Scrub typhus	Retrospective, observational	246	Admission albumin < 3.0 g/dL *vs* ⩾ 3.0 g/dL	Increased rate of non-oliguric ARF (40.4% *vs* 11.1%; P < 0.001)	ND
Mehra *et al*[40]	Dengue fever	Retrospective, observational	223	Admission Albumin level	Lower albumin (2.65 g/dL) in patients with *vs* without AKI (3.09 g/dL; P < 0.001)	ND
Vikrant *et al*[36]	Scrub typhus	Retrospective, observational	174	Admission albumin level	ND	2.4 g/dL in patients who died *vs* 2.9 g/dL in survivors; P < 0.001
Ceylan *et al*[41]	Antibiotic therapy	Retrospective, observational	112	Albumin level at start of colistin therapy	Lower albumin (2.4 g/dL *vs* 2.7 g/dL) predicts colistin-induced AKI: OR = 0.643 (95%CI: 0.415-0.994; P = 0.047)	ND
Trimarchi *et al*[37]	H1N1 pneumonia	Retrospective, observational	22	Albumin level at study inclusion	NS	ARF in 10 of 12 deaths: 1.82 g/dL in patients who died *vs* 2.61 g/dL in survivors; P < 0.01

AKI: Acute kidney injury; ARF: Acute renal failure; ND: Not disclosed; OR: Odds ratio; NS: Not significant.

lower in the albumin group compared with the saline group (17.6% *vs* 31.7%; P = 0.031). Multivariate

Table 4 Included studies on transplant surgery

Ref.	Population/ setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Tinti *et al*[45]	Liver transplantation	Prospective, observational	24	Preoperative albumin level	Lower albumin (3.1 g/dL *vs* 3.7 g/dL) predictive of ARF (P = 0.02)	ND
Moore *et al*[48]	Renal transplantation	Retrospective, observational	2763	Albumin < 4.0 g/dL	Predictive of transplant failure: HR = 1.71 (95%CI: 1.18-2.49; P < 0.001)	ND
Sang *et al*[46]	LDLT	Retrospective, observational, propensity score matching	998 (incl. 249 matched pairs)	Albumin < 3.0 g/dL *vs* ≥ 3.0 g/dL before surgery	Albumin < 3.0 g/dL associated with increased AKI: OR = 0.42 (95%CI: 0.28-0.64; P < 0.001)	Survival rate lower with postoperative albumin < 3.0 g/dL (P = 0.02)
Park *et al*[47]	LDLT	Retrospective, observational	538	Preoperative albumin level	Albumin < 3.5 g/dL: OR = 1.76 (95%CI: 1.05-2.94; P = 0.032)	ND
Yang *et al*[49]	Renal transplantation	Retrospective, observational	375	Preoperative albumin < 3.5 g/dL *vs* 3.5-3.9 g/dL *vs* 4.0-4.4 g/dL *vs* ≥ 4.5 g/dL	Lowest risk of graft failure with ≥ 4.5 g/dL: HR = 0.536 (P = 0.029) *vs* < 3.5 g/dL	ND
Chen *et al*[44]	Liver transplantation	Retrospective, observational, matching	334 (incl. 118 matched pairs)	Preoperative albumin ≤ 3.5 g/dL	OR = 2.785 (95%CI: 1.427-5.434; P = 0.003); risk factor for posttransplantation AKI or ARF	ND

AKI: Acute kidney injury; ARF: Acute renal failure; HR: Hazard ratio; LDLT: Living donor liver transplantation; ND: Not disclosed; OR: Odds ratio.

Table 5 Included studies on cancer

Ref.	Population/ setting	Study design	Overall study size	Albumin measurement	Hypoalbuminemia-related outcomes	
					AKI/ARF	Mortality
Hsu *et al*[51]	HCC with ascites	Prospective, observational	591	Albumin < 3.3 g/dL	Independently associated with ARF: OR = 7.3 (95%CI: 1.47-35.7; P = 0.009)	ND
Kim *et al*[50]	Gastric cancer surgery	Retrospective, observational	4718	Preoperative albumin < 4.0 g/dL	Independent predictor of AKI: OR = 1.40 (95%CI: 1.11-1.77; P = 0.005)	ND
Mizuno *et al*[55]	Chemotherapy-induced hypotension	Retrospective, observational	972	Hypoalbuminemia defined as ≤ 3.5 g/dL	Associated with low BP: OR = 1.497 (95%CI: 1.070-2.095; P = 0.019). Low BP associated with AKI	ND
Lahoti *et al*[56]	AML or HR-MDS	Retrospective, observational	537	Albumin level at baseline (median 3.3 g/dL)	Hypoalbuminemia predictive of AKI: OR = 0.7 (95%CI: 0.5-0.99; P = 0.049)	ND
Haynes *et al*[57]	Multiple myeloma	Retrospective, observational	107	Albumin ≥ 3.5 g/dL *vs* < 3.5 g/dL	ND	Higher albumin predictive of survival: HR = 0.56 (95%CI: 0.35-0.91; P = 0.02)
Fischler *et al*[59]	Cancer	Retrospective, observational	103	Albumin level at start of CVVHDF	ND	Low albumin (median 2.5 g/dL *vs* 3.05 g/dL) associated with mortality: OR = 3.341 (95%CI: 1.229-9.077); P = 0.02

AKI: Acute kidney injury; AML: Acute myelogenous leukemia; ARF: Acute renal failure; BP: Blood pressure; CVVHDF: Continuous venovenous hemodiafiltration; HCC: Hepatocellular carcinoma; HR: Hazard ratio; HR-MDS: High-risk myelodysplastic syndrome; ND: Not disclosed; OR: Odds ratio.

logistic regression revealed a renal-protective effect of albumin therapy (OR = 0.42, 95%CI: 0.21-0.83; P = 0.012). Administration of albumin increased urine output during surgery (median 550 mL *vs* 370 mL; P = 0.006). No differences were observed between the two groups in the incidence of severe AKI, need for renal replacement therapy (RRT), or mortality.

These findings are interesting for a number of reasons. First, the inverse relationship apparent between serum albumin level and postoperative AKI rate, in the setting of a randomized double-blind trial, provides the highest-quality and most compelling evidence yet that serum albumin level is an independent driver of AKI risk. This corroborates an earlier retrospective analysis in 1182 consecutive adult patients undergoing OPCAB, conducted by the same group[14]. Moreover, the data from Lee *et al*[13] further underline the importance of the relationship between albumin level and renal health, as correction of hypoalbuminemia by exogenous albumin supplementation resulted in smaller increases in serum creatinine and conferred a degree of protection against AKI occurrence. That no significant treatment effect on severe AKI was observed (≥ KDIGO stage 2) might reflect an underpowered analysis due to the relatively

low sample size/event rate. Alternatively, either albumin supplementation is beneficial only in milder AKI, or the dosing regimen was insufficient.

Lee *et al*[13] did not investigate the mechanism(s) underlying the renal-protective effect they observed with albumin administration but speculated whether this might be attributable to augmentation of intravascular volume over correction of hypoalbuminemia. Indeed, both hemodynamic and pharmacodynamic mechanisms may contribute to the beneficial renal effects of albumin, supporting a possible causal link. Pharmacodynamic properties of human albumin with renal-protective potential include mitigation of nephrotoxicity of medications, restoration of balanced net fluid balance, protection against loss of glycocalyx, and maintenance of glomerular filtration (reviewed in[11]). Further studies are needed to ascertain in which clinical indications such properties might be beneficial. In addition, data from large-scale RCTs are needed to define trigger and target levels and dosing for pre-emptive albumin therapy as a strategy for protecting against postoperative renal morbidity and mortality.

Whereas in the RCT performed by Lee *et al*[13] no differences were evident between the albumin and saline treatment groups with respect to subsequent need for RRT or mortality, precedent does exist for the impact of albumin level on both of these outcomes. Findik *et al*[15] recently performed a retrospective review of data collected prospectively from 530 adults with normal renal function who underwent isolated CAB surgery. Their analysis divided the patient population based on preoperative serum albumin level and found that RRT (P = 0.018) and death within 30 d (6.8% *vs* 2.4%; P = 0.037) after surgery were more frequent in the group with albumin < 3.5 g/dL. Mean duration of ventilatory support (7.9 h *vs* 11.4 h; P = 0.001), ICU stay (66.0 h *vs* 59.0 h; P = 0.026), and hospital stay (7.7 d *vs* 7.1 d; P = 0.022) were also greater in the lower albumin group.

Beyond CAB surgery, a prospective, observational, longitudinal study of 164 adult patients undergoing any type of elective cardiac surgery used univariate logistic regression analysis to identify low serum albumin (< 4 g/dL), among other variables [high preoperative blood urea nitrogen (BUN), creatinine, and uric acid], as a major risk factor for postoperative development of AKI[16]. Similarly, Kim *et al*[17] also identified preoperative albumin level < 4.0 g/dL as an independent risk factor for AKI in 183 patients who underwent surgery on the thoracic aorta with cardiopulmonary bypass (CPB) and subsequently developed AKI, matched by propensity score with controls without AKI. The authors suggested that correction of preoperative hypoalbuminemia might protect against AKI in the studied population. However, when patients converted to CPB were included in the randomized analysis performed by Lee *et al*[13], the effect of albumin treatment was unclear. Further research is needed to evaluate the effects of exogenous albumin treatment in patients undergoing cardiac surgery with CPB, though such studies will be complicated by the fact that CPB itself is associated with AKI and contributes to its pathogenesis (reviewed in[18]).

In a single-center, retrospective review, Go *et al*[19] aimed to establish the impact of different serum albumin strata (< 2.5 g/dL, low; 2.5-3.5 g/dL, mid-range; > 3.5 g/dL, normal) on outcomes after left ventricular assist device (LVAD) implantation in 200 patients. Consistent with findings in cardiac surgery patients, lower albumin was associated with significantly increased rates of postoperative ARF (Table 2) and prolonged hospitalization (median 28.5 d *vs* 16 d *vs* 15.5 d; P = 0.008). Survival at 6 mo, 1 year, and 5 years appeared to reflect albumin levels (79%, 79%, 49% with low; 84%, 78%, 51% with mid-range; 94%, 88%, 60% with normal), though this trend was not statistically significant (P = 0.22). The authors concluded that hypoalbuminemia (in this case defined as < 2.5 g/dL) should not be considered a contraindication to LVAD candidacy, and called for more data on the utility of albumin levels for predicting morbidity and mortality after LVAD implantation.

Two studies reported data on albumin levels in patients undergoing acute coronary interventions. In a prospective, observational study of 456 acute heart failure patients undergoing decongestive therapy, no significant associations were found between serum albumin levels at admission and clinical outcomes, either short-term (worsening renal function, worsening heart failure, clinical decongestion by 72 h) or longer-term (60-d mortality, re-hospitalization, unscheduled emergency room visits)[20]. The authors concluded that serum albumin levels might not be relevant in guiding decongestion strategies. They also acknowledged that their post-hoc analysis used a carefully selected cohort drawn from the DOSE-AHF and ROSE-AHF trials that were inadequately powered to detect clinical end points according to baseline albumin, and that their findings may not be generalizable. A separate study, by Murat *et al*[21], retrospectively looked at the impact of serum albumin levels on AKI occurrence in a cohort of 890 patients with acute coronary syndromes (ACS) treated with percutaneous coronary intervention (PCI). Serum albumin was inversely associated with AKI risk and, along with a number of other variables [age, female gender, creatinine kinase-myocardial band, and glomerular filtration rate (GFR)], was independently predictive of AKI occurrence. This was the first such report in ACS patients receiving PCI and requires confirmation by prospective, randomized trial. Nonetheless, these preliminary findings suggest that measurement of serum albumin, widely available and relatively inexpensive, should be included in the risk stratification of ACS patients before undergoing PCI.

INFECTIOUS DISEASES

Our review identified eight studies conducted across a total of more than 5500 subjects with infections and

data on albumin levels and renal injury (Table 3). The only prospective study was an observational analysis of AKI in HIV-seropositive adults[22]. AKI was noted in 138/3540 (3.9%) patients and in most cases was AKIN stage Ⅱ (42.1%) or Ⅲ (48.5%). Mean serum albumin at baseline was 2.92 g/dL. Low serum albumin was one of few variables found to be significantly associated with death of HIV-infected patients following AKI. Prerenal factors (*e.g.*, clinical/laboratory evidence of volume depletion or reduced renal blood flow), ischemic acute tubular necrosis (ATN), and sepsis were among the most frequent causes of AKI in this population. These observations are consistent with clinical trials suggesting efficacy and mortality benefit of albumin therapy for volume resuscitation in sepsis patients[23-30], as well as mechanistic data indicating a role for albumin in preservation of renal tubular cells[31-33].

The largest study on AKI occurrence in an infectious disease setting to be published during the review period was a 10-year retrospective analysis of AKI occurrence in 915 severe falciparum malaria patients[34]. AKI is a major contributor to morbidity and mortality in severe malaria infection, and hypalbuminemia (< 3.5 g/dL) was significantly more prevalent in patients with AKI (135/195; 69%) *vs* those without AKI (308/720; 43%). The authors concluded that although causality could not be deduced, correction of ARF risk factors such as hypoalbuminemia should be incorporated into the management of patients with severe malaria.

Two retrospective studies reported associations between serum albumin level and AKI outcomes in scrub typhus infection. Lee *et al*[35] divided a population of 246 adults with scrub typhus into two groups based on serum albumin level. Their analysis revealed that serum albumin < 3.0 g/dL was closely related to AKI occurrence as well as various other complications (*e.g.*, confusion, pulmonary edema, pleural effusion, arrhythmia), leading to longer mean hospital stay (additional 5.5 d) and higher direct hospital costs (additional United States $1222). Whereas this study found no difference in mortality with lower *vs* higher albumin (overall deaths 9/246; 3.7%), a subsequent study by Vikrant *et al*[36] did detect a difference. This later study was smaller overall than that conducted by Lee *et al*[35] but provided a larger cohort of scrub typhus patients with AKI and substantially more deaths occurred (28/174; 16.1%), providing greater power to assess mortality. Mean serum albumin was 2.8 g/dL and hypoalbuminemia, again defined as < 3.0 g/dL, was present in 56.9% of study subjects. Serum albumin was significantly higher in survivors *vs* non-survivors (mean 2.9 g/dL *vs* 2.4 g/dL; $P = 0.001$).

An association between lower serum albumin and mortality has also been observed in critically compromised patients with H1N1 pneumonia. In a 2-mo, retrospective, ICU study, both hypoalbuminemia and AKI were significantly associated with death ($P < 0.01$), and serum albumin appeared to be lower in those with *vs* without AKI (1.95 g/dL *vs* 2.59 g/dL), though this difference did not reach statistical significance in this small cohort ($n = 22$)[37]. Larger, multivariate analysis is required to confirm these results. The authors suggested that rhabdomyolysis (life-threatening muscle disintegration) is likely to be the main pathophysiologic mechanism of renal dysfunction in this setting, and a separate study subsequently linked hypoalbuminemia with AKI in patients with severe rhabdomyolysis[38].

Other reports on low serum albumin as a predictive factor for AKI include a chart review and multivariate analysis of data from 391 patients with acute viral hepatitis A[39]. AKI was present in 45 (11.5%) patients, and the AKI group had significantly decreased albumin levels compared with the non-AKI group at presentation (mean 3.3 g/dL *vs* 3.8 g/dL; $P < 0.0001$) and at peak during illness (mean 2.7 g/dL *vs* 3.4 g/dL; $P < 0.0001$). Among 223 patients with dengue fever, AKI developed in 24 (10.8%) and was associated with lower serum albumin (2.65 g/dL *vs* 3.09 g/dL; $P < 0.001$)[40]. Low serum albumin (median 2.4 g/dL *vs* 2.7 g/dL) has also been shown to be independently predictive of acute renal injury in patients receiving antibiotic therapy with colistin ($n = 112$)[41], consistent with previous observations[42,43].

TRANSPLANT SURGERY

Hypoalbuminemia is common before and after liver transplantation, especially in patients with cirrhosis[44], and there is a growing body of research exploring the implications of this. Our searches retrieved six relevant studies (including > 5000 subjects) published since September 2009 that reported albumin levels in relation to AKI occurrence after transplantation (Table 4). Four of these were in the setting of liver transplantation (approximately 2000 subjects), while 2 studies focused on renal transplant recipients. All six studies were non-interventional and all except one were conducted retrospectively.

In the only prospective study, data on 24 patients were collected from health records before, during and after deceased donor orthotopic liver transplantation (OLT)[45]. Reduced pre-OLT serum albumin level was found to be associated with ARF (RIFLE classification), whereas no other pre-OLT parameters (*e.g.*, creatinine, GFR, serum sodium, serum bilirubin) were. Interestingly though, higher Model for End-Stage Liver Disease (MELD) score (mean 22 *vs* 18; $P = 0.02$) was also associated with AKI, leading the authors to speculate that the significance of hypoalbuminemia and higher MELD score as risk factors in this population might reflect the close relationship between renal and hepatic function in cirrhosis.

The largest of the three retrospective, observational studies assessing hypoalbuminemia in liver transplantation was a propensity score analysis of 998 consecutive living donor liver transplantation (LDLT) patients in a single center[46]. This analysis aimed to ascertain the influence of early postoperative serum

albumin level on subsequent development of AKI. Serum albumin < 3.0 g/dL within 48 h postoperatively was identified by multivariate analysis as an independent risk factor for AKI (AKIN or RIFLE classification; Table 4), the first such report in the setting of LDLT. Furthermore, ICU (P = 0.006) and hospital (P < 0.001) stays were prolonged in the low albumin group and overall mortality was also higher (P = 0.02), making this one of the few studies retained from our literature review to report data associating serum albumin level with mortality. The findings of Sang *et al*[46] are consistent with an earlier, smaller retrospective study by Chen *et al*[44] in which multivariable analysis of 118 matched pairs of liver transplantation patients with/without postoperative renal injury demonstrated that preoperative hypoalbuminemia (≤ 3.5 g/dL) was strongly predictive of AKI within the first week after surgery. Similarly, Park *et al*[47] also identified by multivariate analysis that preoperative serum albumin < 3.5 g/dL was an independent, modifiable risk factor for AKI (RIFLE classification) in patients (n = 538) undergoing LDLT. Interestingly, the authors also identified MELD score > 20 as a significant risk factor for post-LDLT AKI (OR = 2.01, 95%CI: 1.17-3.44; P = 0.011), as in the study by Tinti *et al*[45], providing further evidence of renal-hepatic interactions in patients undergoing liver transplantation.

Notwithstanding the inherent limitations of retrospective, observational analysis, Sang *et al*[46] postulated that, when considering their results together with evidence accruing from other studies, hypoalbuminemia may be one of the major contributors to AKI development. Park *et al*[47] noted the reported nephroprotective capacity of albumin, through enhanced renal perfusion and reduced apoptosis/increased proliferation of renal tubular cells[31-33]. However, they questioned whether exogenous augmentation of serum albumin could modify renal dysfunction within a short timeframe and reduce the risk of postoperative AKI. Sufficiently powered, prospective, interventional, randomized trials will be required to answer this question. Additional research will also be needed to further elucidate the mechanism(s) by which albumin can positively influence renal function, in LDLT surgery and other settings.

Fewer studies provide evidence on albumin levels in renal transplantation; however, these studies enrolled more subjects than those discussed above in the setting of liver transplantation. One large retrospective study, by Moore *et al*[48], analyzed data from 2763 adult kidney transplant recipients who were enrolled into the Long Term Efficacy and Safety Surveillance study and survived for ≥ 12 mo post transplantation. Multiple regression analysis revealed that hypoalbuminemia in the preceding 6 mo was independently associated with renal transplant failure, both in the death-censored analysis [< 3.5 g/dL, hazard ratio (HR) = 2.19, 95%CI: 1.58-3.05; P < 0.001] and overall (Table 4). Yang *et al*[49] also found a relationship between serum albumin level and likelihood of renal graft failure. In their single-center study of 375 renal transplant recipients, the relative risk of graft failure was lowest in the group with highest serum albumin (≥ 4.5 g/dL) before transplantation. Chronic rejection (36.2%) and delayed graft function (12.8%) were most frequent in patients with albumin < 3.5 g/dL, though these results were not statistically significant. The authors concluded that hypoalbuminemia before kidney transplantation is associated with more serious complications and worse short- and long-term graft outcomes.

CANCER

An association between hypoalbuminemia and AKI morbidity/mortality has also been noted in cancer studies. We identified six relevant studies published during the search period, involving a total of more than 7000 patients, the majority of whom had gastric cancer[50] (Table 5).

One of these studies was prospective (n = 591) and included data on incidence and risk factors of AKI in a subset of 87 patients with HCC with ascites undergoing transarterial chemoembolization (TACE) at a single center[51]. Lower serum albumin was more common in HCC patients with *vs* without ascites (mean 3.2 g/dL *vs* 3.8 g/dL; P < 0.001). Furthermore, hypoalbuminemia (< 3.3 g/dL) occurred in 82% *vs* 38% of ascitic HCC patients who did (n = 11) *vs* did not (n = 76) develop AKI after TACE (P = 0.009). Logistic regression analysis among HCC patients with ascites found that hypoalbuminemia was the only risk factor independently predictive of post-TACE AKI. Based on earlier reports, the authors speculated whether nephroprotection by albumin might result from increased renal blood flow and GFR[52], decreased changes in electrolyte and serum creatinine levels[52], or plasma expansion[53,54].

The largest retained study in cancer patients was a retrospective analysis of AKI occurrence after partial or total gastrectomy for gastric cancer (n = 4718)[50]. Multivariate analysis identified hypoalbuminemia (< 4 g/dL), along with male gender, hypertension, chronic obstructive pulmonary disease, use of diuretics, vasopressors, or contrast agents, and packed red blood cell transfusions, as an independent predictor of postoperative AKI (Table 5). Prevalence of hypoalbuminemia tended to increase with severity of AKI (KDIGO staging). The authors acknowledged that the mechanisms through which hypoalbuminemia causes AKI are not fully understood, but noted that albumin plays a critical role in maintaining the integrity and function of renal tubular cells[32,33].

Smaller retrospective studies also found significant associations between serum albumin level and AKI development in cancer settings. Mizuno *et al*[55] demonstrated significantly lower serum albumin in patients receiving cisplatin as first-line chemotherapy who had low (n = 229) *vs* normal (n = 743) blood pressure (mean 3.73 g/dL *vs* 3.87 g/dL; P = 0.001), suggesting that hypoalbuminemia associates with low blood pressure,

leading to renal hypoperfusion and thereby promoting ischemic AKI. Hypoalbuminemia was similarly associated with AKI in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome undergoing induction chemotherapy (n = 537; 187 with AKI)[56]. In a 20-year, single-center, retrospective study of patients with multiple myeloma and acute severe renal failure (n = 107), serum albumin ⩾ 3.5 g/dL was one of three factors (along with use of chemotherapy, and dialysis independence) found to be independently associated with survival[57], though serum albumin is already incorporated into the International Staging System for multiple myeloma[58]. A recent multivariate analysis of 103 consecutive ICU patients with cancer (any type) and AKI revealed low albumin level to be statistically associated with in-hospital mortality, leading to the conclusion that hypoalbuminemia (and presumably correction thereof) must be considered before initiating RRT in cancer patients[59].

OTHER INDICATIONS

The majority of the recent studies generating data on hypoalbuminemia and AKI occurrence were conducted in the settings of cardiac/coronary interventions, infectious diseases, transplantation, or cancer, as described above. However, a further fifteen studies, all retrospective and observational in nature and involving a total of more than 46000 patients, also reported data on albumin levels and kidney outcomes, across numerous other patient populations.

By far the largest albumin data set among all of the literature retained for this review was a retrospective analysis of 37143 patients in the American College of Surgeons National Surgical Quality Improvement Program who underwent primary total knee arthroplasty (TKA) and had serum albumin data available[60]. Mortality was higher in patients with albumin < 3.5 g/dL *vs* ⩾ 3.5 g/dL (0.64% *vs* 0.15%; OR = 3.17, 95%CI: 1.58-6.35; P = 0.001), as were AKI (0.32% *vs* 0.06%, OR = 5.19, 95%CI: 1.96-13.73; P = 0.001) and a range of other major perioperative complications. The authors drew encouragement from these findings since hypoalbuminemia may be more easily modifiable than other risk factors (*e.g.*, morbid obesity). Results from two subsequent studies also involving thousands of patients undergoing TKA (primary[61] or revision[62]) were consistent with these findings.

In a recent analysis of 408 patients with amyloidosis, serum albumin < 2.5 g/dL at admission was highly associated with requirement for RRT within 30 d of autologous stem cell transplantation (P < 0.001)[63]. A smaller study in amyloidosis patients receiving high-dose melphalan with stem cell transplantation yielded similar results[64]. Recent evidence in other clinical scenarios comes from isolated studies involving a total of more than 2500 patients. Hypoalbuminemia has been associated with AKI-related morbidity/mortality in patients with severe rhabdomyolysis[38], pyogenic liver abscess[65], contrast-induced nephropathy[66], hospital-acquired AKI[67,68], and in critically ill patients requiring continuous RRT[69], geriatric patients[70-72], and those undergoing open ventral hernia repair[73].

Taken together, the recent evidence discussed herein clearly demonstrates that hypoalbuminemia is an important consideration for AKI risk in a broad range of patients. However, each clinical scenario is multifactorial and presents its own complexities, and comorbidities that might also impact the development of AKI and thus be confounders in assessing the relative importance/contribution of serum albumin level in AKI. In diverse clinical settings there is a need for controlled, interventional studies to evaluate exogenous albumin therapy aimed at correcting hypoalbuminemia and reducing the risk of subsequent AKI, mortality, and other adverse outcomes. Also required will be mechanistic studies to define the pathways involved in nephroprotection by albumin.

LIMITATIONS

Limitations of this review include the fact that most of the included studies were observational with patient populations in the various clinical settings that are still quite heterogeneous. In addition definitions of AKI were often creatinine-dependent and based on different classification systems for AKI including RIFLE, AKIN, and KDIGO. As the systematic search of the literature was restricted to PubMed (MEDLINE), additional studies may be missing.

CONCLUSION

The association between hypoalbuminemia and development of AKI and subsequent morbidity/mortality can be regarded as confirmed. This robust association is consistently evident in a wealth of observational studies conducted across a wide range of clinical settings and involving tens of thousands of patients, and may be interpreted as an indication of a causal link.

Furthermore, a prospective RCT conducted in cardiac surgery patients, demonstrated for the first time that correction of low albumin level is associated with lower increase in creatinine, suggesting improved renal function with human albumin therapy and also supporting a causal link. These observations justify further interventional studies with albumin therapy, in cardiac surgery (including CPB) and other settings, such as transplantation other than liver or renal. Multicenter, prospective studies adequately powered to assess severe AKI, mortality and causality would be valuable, as would evaluation of the appropriate trigger and target serum levels and albumin dose necessary to confer renal protection. Basic research is also warranted to define the mechanisms through which albumin affords protection from renal injury. Moreover, because the development of AKI in high-risk patients is multifactorial, modification of a single risk factor might

not be sufficient for prevention. Therefore, further research is needed to advance our understanding of the combinatorial nature of AKI pathogenesis.

In the meantime, the large volume of data already available underscores the need to be alert to risk factors for AKI. Serum albumin level should be monitored to aid early identification of patients who may be at increased risk and who may stand to benefit from treatment to correct hypoalbuminemia.

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REFERENCES

1 **Ostermann M**, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. *Crit Care* 2016; **20**: 299 [PMID: 27670788 DOI: 10.1186/s13054-016-1478-z]

2 **Coca SG**, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009; **53**: 961-973 [PMID: 19346042 DOI: 10.1053/j.ajkd.2008.11.034]

3 **Singbartl K**, Joannidis M. Short-term Effects of Acute Kidney Injury. *Crit Care Clin* 2015; **31**: 751-762 [PMID: 26410142 DOI: 10.1016/j.ccc.2015.06.010]

4 **Chertow GM**, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; **16**: 3365-3370 [PMID: 16177006 DOI: 10.1681/ASN.2004090740]

5 **Mehta RL**, Cerdá J, Burdmann EA, Tonelli M, García-García G, Jha V, Susantitaphong P, Rocco M, Vanholder R, Sever MS, Cruz D, Jaber B, Lameire NH, Lombardi R, Lewington A, Feehally J, Finkelstein F, Levin N, Pannu N, Thomas B, Aronoff-Spencer E, Remuzzi G. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet* 2015; **385**: 2616-2643 [PMID: 25777661 DOI: 10.1016/S0140-6736(15)60126-X]

6 **Lameire NH**, Bagga A, Cruz D, De Maeseneer J, Endre Z, Kellum JA, Liu KD, Mehta RL, Pannu N, Van Biesen W, Vanholder R. Acute kidney injury: an increasing global concern. *Lancet* 2013; **382**: 170-179 [PMID: 23727171 DOI: 10.1016/S0140-6736(13)60647-9]

7 **Ponce D**, Balbi A. Acute kidney injury: risk factors and management challenges in developing countries. *Int J Nephrol Renovasc Dis* 2016; **9**: 193-200 [PMID: 27578995 DOI: 10.2147/IJNRD.S104209]

8 **Hoste EA**, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honoré PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015; **41**: 1411-1423 [PMID: 26162677 DOI: 10.1007/s00134-015-3934-7]

9 **Wiedermann CJ**, Wiedermann W, Joannidis M. Hypoalbuminemia and acute kidney injury: a meta-analysis of observational clinical studies. *Intensive Care Med* 2010; **36**: 1657-1665 [PMID: 20517593 DOI: 10.1007/s00134-010-1928-z]

10 **Vincent JL**, Dubois MJ, Navickis RJ, Wilkes MM. Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. *Ann Surg* 2003; **237**: 319-334 [PMID: 12616115 DOI: 10.1097/01.SLA.0000055547.93484.87]

11 **Wiedermann CJ**, Joannidis M. Nephroprotective Potential of Human Albumin Infusion: A Narrative Review. *Gastroenterol Res Pract* 2015; **2015**: 912839 [PMID: 26136776 DOI: 10.1155/2015/912839]

12 **Mao H**, Katz N, Ariyanon W, Blanca-Martos L, Adýbelli Z, Giuliani A, Danesi TH, Kim JC, Nayak A, Neri M, Virzi GM, Brocca A, Scalzotto E, Salvador L, Ronco C. Cardiac surgery-associated acute kidney injury. *Cardiorenal Med* 2013; **3**: 178-199 [PMID: 24454314 DOI: 10.1159/000353134]

13 **Lee EH**, Kim WJ, Kim JY, Chin JH, Choi DK, Sim JY, Choo SJ, Chung CH, Lee JW, Choi IC. Effect of Exogenous Albumin on the Incidence of Postoperative Acute Kidney Injury in Patients Undergoing Off-pump Coronary Artery Bypass Surgery with a Preoperative Albumin Level of Less Than 4.0 g/dl. *Anesthesiology* 2016; **124**: 1001-1011 [PMID: 26891150 DOI: 10.1097/ALN.0000000000001051]

14 **Lee EH**, Baek SH, Chin JH, Choi DK, Son HJ, Kim WJ, Hahm KD, Sim JY, Choi IC. Preoperative hypoalbuminemia is a major risk factor for acute kidney injury following off-pump coronary artery bypass surgery. *Intensive Care Med* 2012; **38**: 1478-1486 [PMID: 22618092 DOI: 10.1007/s00134-012-2599-8]

15 **Findik O**, Aydin U, Baris O, Parlar H, Alagoz GA, Ata Y, Turk T, Kunt AT. Preoperative Low Serum Albumin Levels Increase the Requirement of Renal Replacement Therapy after Cardiac Surgery. *Heart Surg Forum* 2016; **19**: E123-E127 [PMID: 27355147 DOI: 10.1532/hsf.1577]

16 **Moguel-González B**, Wasung-de-Lay M, Tella-Vega P, Riquelme-Mc-Loughlin C, Villa AR, Madero M, Gamba G. Acute kidney injury in cardiac surgery. *Rev Invest Clin* 2013; **65**: 467-475 [PMID: 24687353]

17 **Kim WH**, Park MH, Kim HJ, Lim HY, Shim HS, Sohn JT, Kim CS, Lee SM. Potentially modifiable risk factors for acute kidney injury after surgery on the thoracic aorta: a propensity score matched case-control study. *Medicine* (Baltimore) 2015; **94**: e273 [PMID: 25590836 DOI: 10.1097/MD.0000000000000273]

18 **Kumar AB**, Suneja M. Cardiopulmonary bypass-associated acute kidney injury. *Anesthesiology* 2011; **114**: 964-970 [PMID: 21394005 DOI: 10.1097/ALN.0b013e318210f86a]

19 **Go PH**, Hodari A, Nemeh HW, Borgi J, Lanfear DE, Williams CT, Paone G, Morgan JA. Effect of Preoperative Albumin Levels on Outcomes in Patients Undergoing Left Ventricular Device Implantation. *ASAIO J* 2015; **61**: 734-737 [PMID: 26262585 DOI: 10.1097/MAT.0000000000000272]

20 **Grodin JL**, Lala A, Stevens SR, DeVore AD, Cooper LB, Abou Ezzeddine OF, Mentz RJ, Groarke JD, Joyce E, Rosenthal JL, Vader JM, Tang WH. Clinical Implications of Serum Albumin Levels in Acute Heart Failure: Insights From DOSE-AHF and ROSE-AHF. *J Card Fail* 2016; **22**: 884-890 [PMID: 26844764 DOI: 10.1016/j.cardfail.2016.01.015]

21 **Murat SN**, Kurtul A, Yarlioglues M. Impact of Serum Albumin Levels on Contrast-Induced Acute Kidney Injury in Patients With Acute Coronary Syndromes Treated With Percutaneous Coronary Intervention. *Angiology* 2015; **66**: 732-737 [PMID: 25260710 DOI: 10.1177/0003319714551979]

22 **Prakash J**, Gupta T, Prakash S, Rathore SS, Usha S. Acute kidney injury in patients with human immunodeficiency virus infection. *Indian J Nephrol* 2015; **25**: 86-90 [PMID: 25838645 DOI: 10.4103/0971-4065.138696]

23 **Caironi P**, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R, Gattinoni L; ALBIOS Study Investigators. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014; **370**: 1412-1421 [PMID: 24635772 DOI: 10.1056/NEJMoa1305727]

24 **Charpentier J,** Mira JP. Efficacy and tolerance of hyperoncotic albumin administration in septic shock patients: the EARSS study. *Intensive Care Med* 2011; **37**(Suppl 1): S115

25 **Delaney AP**, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med* 2011; **39**: 386-391 [PMID: 21248514 DOI: 10.1097/CCM.0b013e3181ffe217]

26 **Finfer S**, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med* 2011; **37**: 86-96 [PMID: 20924555 DOI: 10.1007/s00134-010-2039-6]

27 **Rhodes A**, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ,

Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017; **43**: 304-377 [PMID: 28101605 DOI: 10.1007/s00134-017-4683-6]

28 **Salerno F**, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. *Clin Gastroenterol Hepatol* 2013; **11**: 123-130.e1 [PMID: 23178229 DOI: 10.1016/j.cgh.2012.11.007]

29 **Vincent JL**, De Backer D, Wiedermann CJ. Fluid management in sepsis: The potential beneficial effects of albumin. *J Crit Care* 2016; **35**: 161-167 [PMID: 27481753 DOI: 10.1016/j.jcrc. 2016.04.019]

30 **Wiedermann CJ**, Joannidis M. Albumin replacement in severe sepsis or septic shock. *N Engl J Med* 2014; **371**: 83 [PMID: 24988572 DOI: 10.1056/NEJMc1405675#SA1]

31 **Dixon R**, Brunskill NJ. Activation of mitogenic pathways by albumin in kidney proximal tubule epithelial cells: implications for the pathophysiology of proteinuric states. *J Am Soc Nephrol* 1999; **10**: 1487-1497 [PMID: 10405204]

32 **Iglesias J**, Abernethy VE, Wang Z, Lieberthal W, Koh JS, Levine JS. Albumin is a major serum survival factor for renal tubular cells and macrophages through scavenging of ROS. *Am J Physiol* 1999; **277**: F711-F722 [PMID: 10564234]

33 **Kaufmann MA**, Castelli I, Pargger H, Drop LJ. Nitric oxide dose-response study in the isolated perfused rat kidney after inhibition of endothelium-derived relaxing factor synthesis: the role of serum albumin. *J Pharmacol Exp Ther* 1995; **273**: 855-862 [PMID: 7752090]

34 **Vannaphan S**, Walters N, Saengnedsawang T, Tangpukdee N, Kham-In P, Klubprasit M, Wilairatana P, Looareesuwan S. Factors associated with acute renal failure in severe falciparum [corrected] malaria patients. *Southeast Asian J Trop Med Public Health* 2010; **41**: 1042-1047 [PMID: 21073023]

35 **Lee CS**, Min IS, Hwang JH, Kwon KS, Lee HB. Clinical significance of hypoalbuminemia in outcome of patients with scrub typhus. *BMC Infect Dis* 2010; **10**: 216 [PMID: 20646323 DOI: 10.1186/1471-2334-10-216]

36 **Vikrant S**, Dheer SK, Parashar A, Gupta D, Thakur S, Sharma A, Kaushal SS, Kanga A. Scrub typhus associated acute kidney injury--a study from a tertiary care hospital from western Himalayan State of India. *Ren Fail* 2013; **35**: 1338-1343 [PMID: 23952649 DOI: 10.3109/0886022X.2013.828257]

37 **Trimarchi H**, Greloni G, Campolo-Girard V, Giannasi S, Pomeranz V, San-Roman E, Lombi F, Barcan L, Forrester M, Algranati S, Iriarte R, Rosa-Diez G. H1N1 infection and the kidney in critically ill patients. *J Nephrol* 2010; **23**: 725-731 [PMID: 20349409]

38 **Rodríguez E**, Soler MJ, Rap O, Barrios C, Orfila MA, Pascual J. Risk factors for acute kidney injury in severe rhabdomyolysis. *PLoS One* 2013; **8**: e82992 [PMID: 24367578 DOI: 10.1371/journal.pone.0082992]

39 **Lee JH**, Choi MS, Gwak GY, Lee JH, Koh KC, Paik SW, Yoo BC. [Clinical features and predictive factors of acute hepatitis A complicated with acute kidney injury]. *Korean J Gastroenterol* 2010; **56**: 359-364 [PMID: 21173559]

40 **Mehra N**, Patel A, Abraham G, Reddy YN, Reddy YN. Acute kidney injury in dengue fever using Acute Kidney Injury Network criteria: incidence and risk factors. *Trop Doct* 2012; **42**: 160-162 [PMID: 22472317 DOI: 10.1258/td.2012.120023]

41 **Ceylan B**, Taniş M, Akkoyunlu ME, Çınar A, Kurt AR, Akkoyunlu Y, Ozkan D, Ozcelik HK, Aslan T, Fincancı M, Vatansever Ş, İdin K, Guler E, Uysal H. Variables determining the development of colistin-associated renal impairment. *Wien Klin Wochenschr* 2016; **128**: 614-619 [PMID: 25917365 DOI: 10.1007/s00508-015-0773-z]

42 **Kim J**, Lee KH, Yoo S, Pai H. Clinical characteristics and risk factors of colistin-induced nephrotoxicity. *Int J Antimicrob Agents* 2009; **34**: 434-438 [PMID: 19726164 DOI: 10.1016/j.ijantimicag.2009.06.028]

43 **Kwon JA**, Lee JE, Huh W, Peck KR, Kim YG, Kim DJ, Oh HY. Predictors of acute kidney injury associated with intravenous colistin treatment. *Int J Antimicrob Agents* 2010; **35**: 473-477 [PMID: 20089383 DOI: 10.1016/j.ijantimicag.2009.12.002]

44 **Chen J**, Singhapricha T, Hu KQ, Hong JC, Steadman RH, Busuttil RW, Xia VW. Postliver transplant acute renal injury and failure by the RIFLE criteria in patients with normal pretransplant serum creatinine concentrations: a matched study. *Transplantation* 2011; **91**: 348-353 [PMID: 21127462 DOI: 10.1097/TP.0b013 e31820437da]

45 **Tinti F**, Umbro I, Meçule A, Rossi M, Merli M, Nofroni I, Corradini SG, Poli L, Pugliese F, Ruberto F, Berloco PB, Mitterhofer AP. RIFLE criteria and hepatic function in the assessment of acute renal failure in liver transplantation. *Transplant Proc* 2010; **42**: 1233-1236 [PMID: 20534269 DOI: 10.1016/j.transproceed.2010.03.128]

46 **Sang BH**, Bang JY, Song JG, Hwang GS. Hypoalbuminemia Within Two Postoperative Days Is an Independent Risk Factor for Acute Kidney Injury Following Living Donor Liver Transplantation: A Propensity Score Analysis of 998 Consecutive Patients. *Crit Care Med* 2015; **43**: 2552-2561 [PMID: 26308436 DOI: 10.1097/CCM.0000000000001279]

47 **Park MH**, Shim HS, Kim WH, Kim HJ, Kim DJ, Lee SH, Kim CS, Gwak MS, Kim GS. Clinical Risk Scoring Models for Prediction of Acute Kidney Injury after Living Donor Liver Transplantation: A Retrospective Observational Study. *PLoS One* 2015; **10**: e0136230 [PMID: 26302370 DOI: 10.1371/journal.pone.0136230]

48 **Moore J**, He X, Shabir S, Hanvesakul R, Benavente D, Cockwell P, Little MA, Ball S, Inston N, Johnston A, Borrows R. Development and evaluation of a composite risk score to predict kidney transplant failure. *Am J Kidney Dis* 2011; **57**: 744-751 [PMID: 21349620 DOI: 10.1053/j.ajkd.2010.12.017]

49 **Yang SW**, Choi JY, Kwon OJ. The impact of pretransplantation serum albumin levels on long-term renal graft outcomes. *Transplant Proc* 2013; **45**: 1379-1382 [PMID: 23726577 DOI: 10.1016/j.transproceed.2012.10.063]

50 **Kim CS**, Oak CY, Kim HY, Kang YU, Choi JS, Bae EH, Ma SK, Kweon SS, Kim SW. Incidence, predictive factors, and clinical outcomes of acute kidney injury after gastric surgery for gastric cancer. *PLoS One* 2013; **8**: e82289 [PMID: 24349249 DOI: 10.1371/journal.pone.0082289]

51 **Hsu CY**, Huang YH, Su CW, Lin HC, Chiang JH, Lee PC, Lee FY, Huo TI, Lee SD. Renal failure in patients with hepatocellular carcinoma and ascites undergoing transarterial chemoembolization. *Liver Int* 2010; **30**: 77-84 [PMID: 19818004 DOI: 10.1111/j.1478-3231.2009.02128.x]

52 **Wong PY**, Carroll RE, Lipinski TL, Capone RR. Studies on the renin-angiotensin-aldosterone system in patients with cirrhosis and ascites: effect of saline and albumin infusion. *Gastroenterology* 1979; **77**: 1171-1176 [PMID: 499705]

53 **Ginès P**, Titó L, Arroyo V, Planas R, Panés J, Viver J, Torres M, Humbert P, Rimola A, Llach J. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology* 1988; **94**: 1493-1502 [PMID: 3360270]

54 **Luca A**, García-Pagán JC, Bosch J, Feu F, Jiménez W, Ginés A, Fernández M, Escorsell A, Arroyo V, Rodés J. Beneficial effects of intravenous albumin infusion on the hemodynamic and humoral changes after total paracentesis. *Hepatology* 1995; **22**: 753-758 [PMID: 7657279]

55 **Mizuno T**, Hayashi T, Shimabukuro Y, Murase M, Hayashi H, Ishikawa K, Takahashi K, Yuzawa Y, Yamada S, Nagamatsu T. Lower Blood Pressure-Induced Renal Hypoperfusion Promotes Cisplatin-Induced Nephrotoxicity. *Oncology* 2016; **90**: 313-320 [PMID: 27225867 DOI: 10.1159/000446371]

56 **Lahoti A**, Kantarjian H, Salahudeen AK, Ravandi F, Cortes JE, Faderl S, O'Brien S, Wierda W, Mattiuzzi GN. Predictors and outcome of acute kidney injury in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome. *Cancer* 2010; **116**: 4063-4068 [PMID: 20564156 DOI: 10.1002/cncr.25306]

57 **Haynes RJ**, Read S, Collins GP, Darby SC, Winearls CG. Presentation and survival of patients with severe acute kidney injury and multiple myeloma: a 20-year experience from a single centre. *Nephrol Dial Transplant* 2010; **25**: 419-426 [PMID: 19767634 DOI: 10.1093/ndt/gfp488]

58 **Greipp PR**, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, Boccadoro M, Child JA, Avet-Loiseau H, Kyle RA, Lahuerta JJ, Ludwig H, Morgan G, Powles R, Shimizu K, Shustik C, Sonneveld P, Tosi P, Turesson I, Westin J. International staging system for multiple myeloma. *J Clin Oncol* 2005; **23**: 3412-3420 [PMID: 15809451 DOI: 10.1200/JCO.2005.04.242]

59 **Fischler R**, Meert AP, Sculier JP, Berghmans T. Continuous Renal Replacement Therapy for Acute Renal Failure in Patients with Cancer: A Well-Tolerated Adjunct Treatment. *Front Med* (Lausanne) 2016; **3**: 33 [PMID: 27536658 DOI: 10.3389/fmed. 2016.00033]

60 **Nelson CL**, Elkassabany NM, Kamath AF, Liu J. Low Albumin Levels, More Than Morbid Obesity, Are Associated With Complications After TKA. *Clin Orthop Relat Res* 2015; **473**: 3163-3172 [PMID: 25995174 DOI: 10.1007/s11999-015-4333-7]

61 **Kim HJ**, Koh WU, Kim SG, Park HS, Song JG, Ro YJ, Yang HS. Early postoperative albumin level following total knee arthroplasty is associated with acute kidney injury: A retrospective analysis of 1309 consecutive patients based on kidney disease improving global outcomes criteria. *Medicine* (Baltimore) 2016; **95**: e4489 [PMID: 27495094 DOI: 10.1097/MD.0000000000004489]

62 **Kamath AF**, Nelson CL, Elkassabany N, Guo Z, Liu J. Low Albumin Is a Risk Factor for Complications after Revision Total Knee Arthroplasty. *J Knee Surg* 2017; **30**: 269-275 [PMID: 27362927 DOI: 10.1055/s-0036-1584575]

63 **Leung N**, Kumar SK, Glavey SV, Dispenzieri A, Lacy MQ, Buadi FK, Hayman SR, Dingli D, Kapoor P, Zeldenrust SR, Russell SJ, Lust JA, Hogan WJ, Rajkumar SV, Gastineau DA, Kourelis TV, Lin Y, Gonsalves WI, Go RS, Gertz MA. The impact of dialysis on the survival of patients with immunoglobulin light chain (AL) amyloidosis undergoing autologous stem cell transplantation. *Nephrol Dial Transplant* 2016; **31**: 1284-1289 [PMID: 26627634 DOI: 10.1093/ndt/gfv328]

64 **Lee SY**, Meehan RS, Seldin DC, Sloan JM, Quillen K, Shelton A, Brauneis D, Sanchorawala V. Effect of severe hypoalbuminemia on toxicity of high-dose melphalan and autologous stem cell transplantation in patients with AL amyloidosis. *Bone Marrow Transplant* 2016; **51**: 1318-1322 [PMID: 27183092 DOI: 10.1038/bmt.2016.132]

65 **Yun SE**, Jeon DH, Kim MJ, Bae EJ, Cho HS, Chang SH, Park DJ. The incidence, risk factors, and outcomes of acute kidney injury in patients with pyogenic liver abscesses. *Clin Exp Nephrol* 2015; **19**: 458-464 [PMID: 25091457 DOI: 10.1007/s10157-014-1016-8]

66 **Banda J**, Duarte R, Dickens C, Dix-Peek T, Muteba M, Paget G, Mngomezulu V, Manga P, Naicker S. Risk factors and outcomes of contrast-induced nephropathy in hospitalised South Africans. *S Afr Med J* 2016; **106**: 699-703 [PMID: 27384365 DOI: 10.7196/SAMJ.2016.v106i7.10429]

67 **Qian J**, Fang J, Zhu Q, Ma S, Wang W, Zheng Y, Hao G, Deng B, Zhao X, Ding F. Serum Protein Thiol Levels in Patients with Hospital-Acquired Acute Kidney Injury. *Kidney Blood Press Res* 2015; **40**: 623-629 [PMID: 26672792 DOI: 10.1159/000368538]

68 **Xie Q**, Zhou Y, Xu Z, Yang Y, Kuang D, You H, Ma S, Hao C, Gu Y, Lin S, Ding F. The ratio of CRP to prealbumin levels predict mortality in patients with hospital-acquired acute kidney injury. *BMC Nephrol* 2011; **12**: 30 [PMID: 21714897 DOI: 10.1186/1471-2369-12-30]

69 **Kritmetapak K**, Peerapornratana S, Srisawat N, Somlaw N, Lakananurak N, Dissayabutra T, Phonork C, Leelahavanichkul A, Tiranathanagul K, Susantithapong P, Loaveeravat P, Suwachittanont N, Wirotwan TO, Praditpornsilpa K, Tungsanga K, Eiam-Ong S, Kittiskulnam P. The Impact of Macro-and Micronutrients on Predicting Outcomes of Critically Ill Patients Requiring Continuous Renal Replacement Therapy. *PLoS One* 2016; **11**: e0156634 [PMID: 27352307 DOI: 10.1371/journal.pone.0156634]

70 **Hu W**, He W, Liu W, Fang X, Wu Y, Yu F, Hao W. Risk Factors and Prognosis of Cardiorenal Syndrome Type 1 in Elderly Chinese Patients: A Retrospective Observational Cohort Study. *Kidney Blood Press Res* 2016; **41**: 672-679 [PMID: 27676190 DOI: 10.1159/000447936]

71 **Li QL**, Cheng QL, Ma Q, Wang XD, Ao QG, Zhao JH, Du J, Liu S, Zhang XY. [Risk factors and short-term prognosis of acute kidney injury in elderly patients]. *Zhonghua Yixue Zazhi* 2013; **93**: 2715-2718 [PMID: 24360104]

72 **Shin MJ**, Rhee H, Kim IY, Song SH, Lee DW, Lee SB, Kwak IS, Seong EY. RIFLE classification in geriatric patients with acute kidney injury in the intensive care unit. *Clin Exp Nephrol* 2016; **20**: 402-410 [PMID: 26354675 DOI: 10.1007/s10157-015-1165-4]

73 **Chung CU**, Nelson JA, Fischer JP, Wink JD, Serletti JM, Kovach SJ. Acute kidney injury after open ventral hernia repair: an analysis of the 2005-2012 ACS-NSQIP datasets. *Hernia* 2016; **20**: 131-138 [PMID: 26099501 DOI: 10.1007/s10029-015-1395-0]

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ORIGINAL ARTICLE

Basic Study

Tesevatinib ameliorates progression of polycystic kidney disease in rodent models of autosomal recessive polycystic kidney disease

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Abstract

AIM

To investigate the therapeutic potential of tesevatinib (TSV), a unique multi-kinase inhibitor currently in Phase Ⅱ clinical trials for autosomal dominant polycystic kidney disease (ADPKD), in well-defined rodent models of autosomal recessive polycystic kidney disease (ARPKD).

METHODS

We administered TSV in daily doses of 7.5 and 15 mg/kg per day by I.P. to the well characterized bpk model of polycystic kidney disease starting at postnatal day

(PN) 4 through PN21 to assess efficacy and toxicity in neonatal mice during postnatal development and still undergoing renal maturation. We administered TSV by oral gavage in the same doses to the orthologous PCK model (from PN30 to PN90) to assess efficacy and toxicity in animals where developmental processes are complete. The following parameters were assessed: Body weight, total kidney weight; kidney weight to body weight ratios; and morphometric determination of a cystic index and a measure of hepatic disease. Renal function was assessed by: Serum BUN; creatinine; and a 12 h urinary concentrating ability. Validation of reported targets including the level of angiogenesis and inhibition of angiogenesis (active VEGFR2/KDR) was assessed by Western analysis.

RESULTS

This study demonstrates that: (1) *in vivo* pharmacological inhibition of multiple kinase cascades with TSV reduced phosphorylation of key mediators of cystogenesis: EGFR, ErbB2, c-Src and KDR; and (2) this reduction of kinase activity resulted in significant reduction of renal and biliary disease in both bpk and PCK models of ARPKD. The amelioration of disease by TSV was not associated with any apparent toxicity.

CONCLUSION

The data supports the hypothesis that this multi-kinase inhibitor TSV may provide an effective clinical therapy for human ARPKD.

Key words: Autosomal recessive; Autosomal dominant; Polycystic kidney disease; Therapy; Kinase inhibition; Multi-kinase inhibitor; Phosphorylation; Renal cysts; Biliary; G-protein coupled receptor

Core tip: This study examined the effect of a multi-kinase inhibitor, tesevatinib (TSV) on cyst development and growth in rodent models of autosomal recessive polycystic kidney disease (ARPKD). Tesevatinib which targets epidermal growth factor receptors, Src and KDR is currently in clinical trials for autosomal dominant polycystic kidney disease (ADPKD) and given the molecular and cellular interactions of the ADPKD and ARPKD genes and proteins we sought to determine if TSV would ameliorate ARPKD TSV was tested in two well described models of ARPKD, the BPK a phenocopy, and an orthologous rat model of ARPKD, the PCK. Of particular interest was the effect of TSV's inhibition of VEGFR2 or KDR during early post-natal development and renal maturation.

Sweeney WE, Frost P, Avner ED. Tesevatinib ameliorates progression of polycystic kidney disease in rodent models of autosomal recessive polycystic kidney disease. *World J Nephrol* 2017; 6(4): 188-200 Available from: URL: http://www.wjgnet.com/2220-6124/full/v6/i4/188.htm DOI: http://dx.doi.org/10.5527/wjn.v6.i4.188

INTRODUCTION

Renal cystic diseases encompass a broad group of disorders with variable phenotypic expression. The term polycystic kidney disease (PKD) explicitly refers to two genetically defined renal cystic diseases: Autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD).

ARPKD (OMIM 263200) belongs to a group of congenital hepatorenal fibrocystic diseases characterized by dual renal and hepatic involvement[1-5]. ARPKD has an incidence estimated at 1/20000 to 1/40000 with a wide spectrum of phenotypic expression[2,4-6]. ARPKD occurs as the result of a mutations in a single gene, polycystic kidney and hepatic disease 1 (*PKHD1*)[7,8]; encodes a protein called fibrocystin or polyductin (FPC)[9,10]; and is commonly diagnosed *in utero* through early childhood[2,3,5].

ADPKD is generally an adult-onset multisystem disorder, characterized by bilateral renal cysts, vascular abnormalities including intracranial aneurysms, and cysts in other organs including the liver. ADPKD is increasingly diagnosed in childhood and adolescents[2,11]. Substantial variability in the severity of renal disease and other extrarenal manifestations occurs even within the same family. ADPKD is more common than ARPKD with an incidence of estimated at 1 in 600 and 1 in 1000 live births[12]. ADPKD is a heterogenetic disorder caused by mutations in either the *PKD1* gene (85%) (OMIM173900) encoding the protein polycystin 1 (PC1), or in the *PKD2* gene (15%) (OMIM173910), encoding polycystin 2 (PC2). The recent report of a third ADPKD gene has been reported but it represents a very small number of ADPKD patients that did not map to PKD1 or PKD2 locus[13]. ADPKD is characterized by the progressive development and expansion of fluid-filled cysts derived from renal tubule epithelia and typically leads to ESRD by late middle age[14,15].

Clinically, a significant overlap of symptoms between ARPKD and ADPKD has been observed in children. Recent investigations at the cellular and molecular level provide compelling rationale for this clinical observation as ARPKD and ADPKD share many common pathophysiological features[2,5,16]. Such studies reveal: (1) PKHD1, PKD1 and PKD2 proteins are expressed in multimeric "cystoprotein" complexes at specific locations within epithelial cells[5,17-19]; (2) complex interactions between all three genes and their protein products occur at a molecular and cellular level[15,20-23]; (3) cyst formation not only requires a PKD mutation but also requires simultaneous cell proliferation; (4) cyst development in both ARPKD and ADPKD begins *in utero*[24-26]; and (5) clinical manifestations of both disorders are seen in newborns, children, and adolescents[3,5,27-30]. These findings suggest that therapeutic interventions at an early stage of disease may provide the best opportunity for beneficial long-term clinical outcomes for patients with PKD[3,5,31].

Cyst initiation and expansion are complex pheno-

mena comprised of multiple interacting processes. The precise mechanisms leading to enlarged cystic kidneys and liver abnormalities are unclear. However, various cellular defects have been identified that are common to cystic renal epithelia in both ARPKD and ADPKD. These include: (1) abnormalities of expression, function and polarity of one or more members of the epidermal growth factor (EGF) family of receptors and ligands [the (EGFR)-axis]; (2) abnormal activity of c-Src (pp60c-Src); decreased intracellular calcium leading to aberrant intracellular cAMP signaling; (3) abnormal structure and/or function of the primary cilia; (4) alterations in cell-cell, and cell-matrix interactions; and (5) activation of interstitial macrophages leading to progressive fibrosis.

Tesevatinib (TSV, previously been known as XL7647, XL647, PRIM-001 and KD-019) is a unique multi-kinase inhibitor that is being utilized in a phase II clinical trial for treatment of ADPKD (https//ClinicalTrials.gov/ADPKD: NCT01559363)[32,33]. The basis of this therapeutic approach is that the use of a multi-kinase inhibitor provides "combination therapy" targeting multiple abnormal signal transduction events in PKD. TSV is a particularly appealing candidate for therapy due to its inhibition profile of c-Src (pp60c-Src) which decreases activity of both the EGFR axis and cAMP pathways[34] as well as its inhibition of KDR that will target abnormal angiogenesis necessary for cyst growth.

MATERIALS AND METHODS

Animal models

All animal experiments were conducted in accordance with policies of the NIH Guide for the Care and Use of Laboratory Animals and the Institutional Animal Care and Use Committee of the Medical College of Wisconsin.

The BALB/c-$^{(Bicc1/Bicc1)}$ model

The BALB/c-$^{(Bicc1/Bicc1)}$ (BPK) model, a murine phenocopy of ARPKD, has been extensively characterized[35-37]. Affected animals die at postnatal day (PN) 23 (average) with a range of PN-21 to PN-25. Extrarenal manifestations include biliary ductal ectasia (BDE). BPK animals were identified utilizing a PCR based genotyping method that has been described in detail[38]. BALB/c wildtype (WT) controls were utilized in all experiments.

Both WT and cystic (bpk) male mice were administered the HCL salt of TSV, by intraperitoneal (IP) injections at 7.5 and 15 mg/kg per day starting at PN4. Kidney and liver (left lobe) tissues were harvested at PN-21, 2 h following the last dose, and assessed for the following: Body weight; total kidney weight (TKW); kidney weight to body weight (KW/BW) ratios; morphometric determination of a cystic index (CI); target validation was confirmed by western analysis; and renal function was assessed by determining serum BUN; creatinine (CR); and urinary concentrating ability (UCA).

A colony of bpk animals have been inbred in the Avner laboratory since 1991 without significant phenotypic drift.

PCK rat model

The PCK rat is an orthologous model of human ARPKD characterized by slowly progressing renal cyst formation, impairment of renal function and development of congenital hepatic fibrosis. The PCK arose from a spontaneous mutation in the rat homolog of human PKHD1 in a Sprague Dawley colony in Japan at the Education and Research Center of Animal Models for Human Diseases of Fujita Health University and subsequently transferred to Charles River United States[10,39].

Similar to human disease, previous reports in PCK rats have demonstrated an increased renal expression of active ErbB2 (pY1221/1222)[34], active c-Src (pY418)[34,40] and hepatic sensitivity to EGFR inhibition[41]. Therefore, the PCK is a valuable orthologous model for testing therapeutic intervention in ARPKD.

Male PCK and Sprague Dawley controls were administered TSV daily by oral gavage, from PN30 to PN90 (61 doses). Similar to the bpk, PCK and SD kidney and liver (left lobe) tissues were harvested two hours following the final dose and assessed for the following parameters: Body weight; total kidney weight (TKW); KW/BW ratios; morphometric determination of a CI; target validation by western analysis; and renal function was assessed by determining serum BUN; CR; and UCA.

A colony of PCK and SD animals has been maintained at the Medical College of Wisconsin 2004 without significant phenotypic drift.

TSV

TSV (formerly named XL7647, XL647, PRIM-001 and KD-019) is an orally bioavailable compound with a MW of 663.59 g/mole. TSV is a 4-anilinoquinazoline bearing an octahydro-cyclopentapyrrol substituted methoxy group at the C-7 position. It is a mono-*p*-toluenesulfonic acid salt with a MW of 663.59 g/m. Data from pharmacodynamics *in vivo* experiments show that inhibition spectrum of TSV includes key tyrosine kinases (EGFR, HER2/ErbB2, c-Src) that promote epithelial cell proliferation and VEGFR2/KDR which promotes angiogenesis and/or neovascularization[32,33].

TSV preparation and administration

Compound solutions EtOH:PEG 400:distilled water (5:45:50) were prepared under sterile conditions at concentrations of 5 mg/mL (for 7.5 mg/kg per day dose) or 10 mg/mL (for 15 mg/kg per day dose) to keep injection volumes equivalent despite the different dosing levels. Solutions were prepared in vehicle and stored at 4 ℃ for 3 d. Solutions were made fresh every 4 d.

BPK (cystic) and BALB/c (wild-type control) litter-

mates received TSV at 7.5 or 15 mg/kg per day by intraperitoneal (*i.p.*) injections. This dosage was based on company supplied pharmacologic and pharmacokinetic data of TSV treatment in mice and preliminary dose-response studies (data not shown). Animals were treated from PN4 to PN21 (18 doses). Kidney and liver were routinely harvested at P21 (2 h post last injection) and heart, spleen, pancreas, stomach, and thymus were periodically harvested at PN21 to evaluate possible toxicity of vehicle or TSV. Both BALB/c and bpk animals were divided into four groups each for testing and analysis. These groups included: (1) untreated or sham wildtype control; (2) wildtype treated with vehicle only; (3) wildtype treated with TSV at 7.5 mg/kg per day; (4) wildtype treated with TSV at 15 mg/kg per day; (5) untreated or sham cystic (bpk); (6) vehicle treated bpk; (7) TSV treated bpk at 7.5 mg/kg per day beginning at PN4 to PN21; and (8) bpk treated with TSV at 15 mg/kg per day beginning at PN4 to PN21.

PCK treatment

SD and PCK males were administered TSV by oral gavage from PN30 to PN90. SD sham, vehicle treated and TSV treated at 7.5 and 15 mg/kg per day along with the same groups of PCK animals were examined. Two hours following the last dose, renal and the left lobe of the liver were routinely harvested at P90 (2 h post last substitute dose for injection). Heart, spleen, pancreas, stomach, and thymus were periodically harvested at PN90 to evaluate possible toxicity of vehicle or TSV. The same parameters evaluated in bpk were assessed in the PCK. First urine samples were collected in metabolic cages after 88 d to assess UCA after 12 h without water. TSV treatment of PCK animals resulted in significant improvement of all assessed parameters compared to untreated PCK without evidence of toxicity or detrimental effects of KDR inhibition.

Western analysis

Control and cystic kidneys were first chopped in RIPA buffer supplemented with protease and phosphatase inhibitors (RIPA$^+$), to minimize the contribution of cyst fluid protein to the total cellular protein. Tissue lysates were then extracted in fresh RIPA$^+$ as previously described[34] and were adjusted to an equal amount of protein (1.5 mg) (determined by BCA assay, Pierce, Rockford, IL, United States) per milliliter based on the least concentrated sample.

For Western analysis, 30 μg of the original tissue lysate (after volume adjustment), were denatured with 5 × sample buffer; and subjected to SDS-PAGE on 4% to 20% gradient gels, and were transferred onto membrane by Western blotting. The levels of total protein and active (phosphorylated) proteins were determined using specific primary antibodies, followed by peroxidase-conjugated appropriate secondary antibody and visualized by ECL (GE Healthcare Bio-Sciences Corp, Piscataway, NJ, United States). Transfer efficiency and molecular weight determinations were performed with Rainbow® MW markers (GE Healthcare Bio-Sciences Corp, Piscataway, NJ, United States). Bands were semi-quantitatively compared using NIH Image 1.62. The densitometry value of wildtype untreated control was arbitrarily set at 1 and the densitometry of the other bands was compared to this value. Both Westerns and respective densitometry data shown are representative of three independent experiments with reproducible findings.

Antibodies

Rabbit polyclonal antibody to pan Src (#2108), p-Src (#2101), EGFR (#4267), p-EGFR (pY1068) (#3777), ERK1/2 (#4695), p-ERK1/2 (#4376), KDR (#9698, #2472), p-KDR (#3770), and β-actin (#3700) were purchased from Cell Signaling Technology (Beverly, MA, United States). Mouse anti-rat (#550300) and rat anti-mouse (#553708) CD-31 (PECAM1) (#550300) was purchased from BD Biosciences (San Jose CA, United States) and anti-mouse CD-31 (ab28364), ErbB2 (ab16901), and p-ErbB2 (ab131102) was purchased from Abcam Inc. (Cambridge, MA, United States) and used to probe Western blots. A rabbit polyclonal to β-actin (ab8227) was used to monitor protein loading of Westerns.

Histology, immunohistology, and determination of segmental nephron cyst localization

All kidney and liver tissues were fixed in 4.0% paraformaldehyde in phosphate buffer (pH = 7.4) for 30 min at 4 ℃, dehydrated and embedded in paraffin. Segmental nephron cyst localization and collecting tubule (CT) CI were quantitated in each experimental group by combining morphometric analysis with light microscopy and immunohistology as previously described[34,35,37,42].

Kidney weight/body weight ratio and renal CI

At P21, or PN90 control and cystic, treated and untreated animals were given the last dose weight, as were both excised kidneys. Total kidney weights to body weight ratios were calculated. The degree of CT cyst formation was quantitatively assessed by segment specific morphometric analysis as previously described[34,37,42] and expressed as the CI (see below). Cyst localization was determined by segment-specific lectin binding using Dolichos biflorus agglutinin (DBA) as a marker for CTs and Lotus tetragonolobus agglutinin (LTA) as a marker for proximal tubules[34,37,42]. For each treatment group, a CT CI was determined on 5 to 6 affected pups.

The CI is a model specific means to assess the degree of disease burden or progression based on the natural progression of the renal disease and hepatic disease (BDE in bpk) and (LW/BW in PCK) In the bpk, the CI and BDE index are on a scale of 1 to 5 based on the disease burden normally present at PN0, 5, 10, 15,

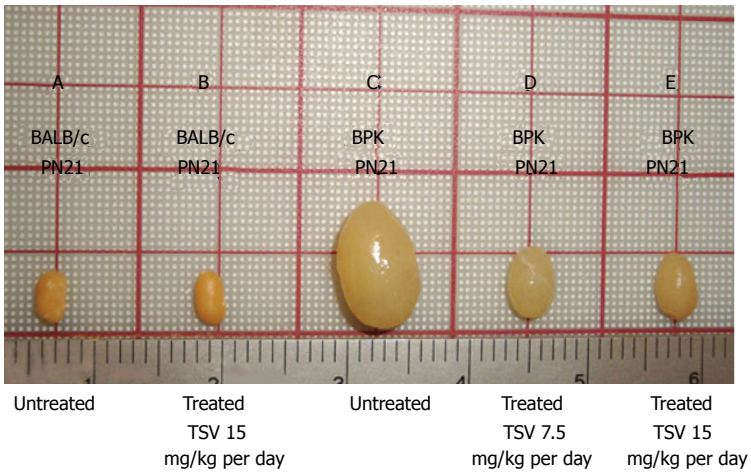

Figure 1 Tesevatinib treatment in the BPK model of autosomal recessive polycystic kidney disease. Compared to wild-type BALB/c control kidneys (A) at PN21, BPK cystic kidneys (C) are extremely enlarged by PN21. TSV treatment resulted in a dose-dependent reduction in the overall kidney size at doses of 7.5 mg/kg per day (C) and 15 mg/kg per day (D) when compared to PN21 BPK untreated cystic kidneys (C). Treatment of wildtype BALB/c with 15 mg/kg per day (B) did not result in significant reduction of overall kidney size when compared to untreated BALB/c kidneys (A). This correlates directly with the total kidney weight (TKW) of each group listed in Table 1. Further, the morphology of wildtype TVS treated kidneys seen in Figure 2A shows no obvious signs of toxicity (Treatment interval: PN4-PN21). TSV: Tesevatinib.

and 20. The renal index in bpk measures the number and size of PT and CT cysts and the BDE (also a 1-5 scale) is based on the number of abnormal portal triads in the left lobe of the liver that is seen during the natural progression in the bpk.

The PCK CI is on a scale of 1 to 10 based on the number and size of cystic lesions seen at 15 d intervals beginning at PN15 and ending at PN150. Since all cysts occur in CT segments the number and size of these lesions are evaluated. The hepatic lesions in the PCK are biliary cysts and all are affected to varying degrees so we use a simple LW/BW ratio to assess hepatic disease progression.

The kidney and left lobe of the liver in bpk and kidney in PCK is embedded medulla side down and a minimum of 3, 4 μmol/L thick sections at depths 100 μMs apart (25 sections) are evaluated as previously described[34,37,42].

Analysis of renal function and UCA

Animals were deprived of water for 12 h prior to collection of urine samples for determination of UCA. Urinary concentrating was determined by freeze point using a freezing point osmometer (Multi-Osmette; Model 2430, Precision Instruments Inc.

Blood samples were obtained by cardiac puncture for serum BUN and CR measurements. Serum BUN and CR was determined on an automated clinical chemistry analyzer as previously described[37].

Statistical analysis

The significance of differences between experimental groups was determined by a one-way analysis of variance. Results are expressed as means ± SD.

RESULTS

BPK

The *in vivo* activity of TSV was evaluated in the bpk mouse, a phenocopy of ARPKD based on the dual organ abnormalities seen in this model. It is a rapidly progressing model that results in ESRD and death by PN 24. The rapid progression simulates the clinical course of severe ARPKD presenting in newborns. The bpk model provides a relatively rapid means of assessing the *in vivo* efficacy of a potential therapeutic compound. Given the reported activity of TSV against the vascular endothelial growth factor receptor 2 (VEGFR2 or KDR), the bpk model is also a good model to evaluate the inhibition of angiogenesis inhibition during postnatal cystic kidney development.

Both wildtype (WT) (BALB/c$^{(Bicc+/Bicc+)}$) and cystic (bpk) (bpk$^{(Bicc-/Bicc-)}$) mice were administered the HCL salt of TSV, by intraperitoneal (IP) injections at 7.5 and 15 mg/kg per day starting at PN4. At PN21 the animals were weighted for the last time and kidney and liver tissues were harvested 2 h following the last injection of TSV. The following parameters were assessed: body weight, total kidney weight (TKW); KW/BW ratios; and morphometric determination of a CI. Renal function was assessed by: Serum BUN; CR; and a 12 h UCA. Validation of reported targets including the level of angiogenesis and inhibition of angiogenesis (active VEGFR2/KDR) was assessed by Western analysis. TSV treatment of bpk mice resulted in significant improvement of all assessed parameters compared to untreated or vehicle treated cystic animals without significant changes in body weight, evidence of toxicity or detrimental effects of the inhibition of KDR (Table 1).

Figure 1 reveals that TSV administration to bpk animals from PN4 to PN21 (18 doses) results in a dose dependent reduction in whole kidney size when compared to untreated bpk cystic kidneys. The change in whole kidney size is also reflected in the dose dependent significant decrease in TKW from 2.03 ± 0.28 g in untreated bpk (column E, Table 1) to 1.59 ± 0.19 (P < 0.001) and 1.21 ± 0.10 g (P < 0.001) with TSV at 7.5 mg/kg per day (column G, Table 1) and 15 mg/kg per day (column H, Table 1) respectively.

The reduction in whole kidney size and TKW for bpk kidneys is associated with markedly improved renal morphology as shown in Figure 2. Accordingly, the CI was significantly reduced by treatment as seen in Table 1.

The CI index was reduced by 25% in bpk mice from

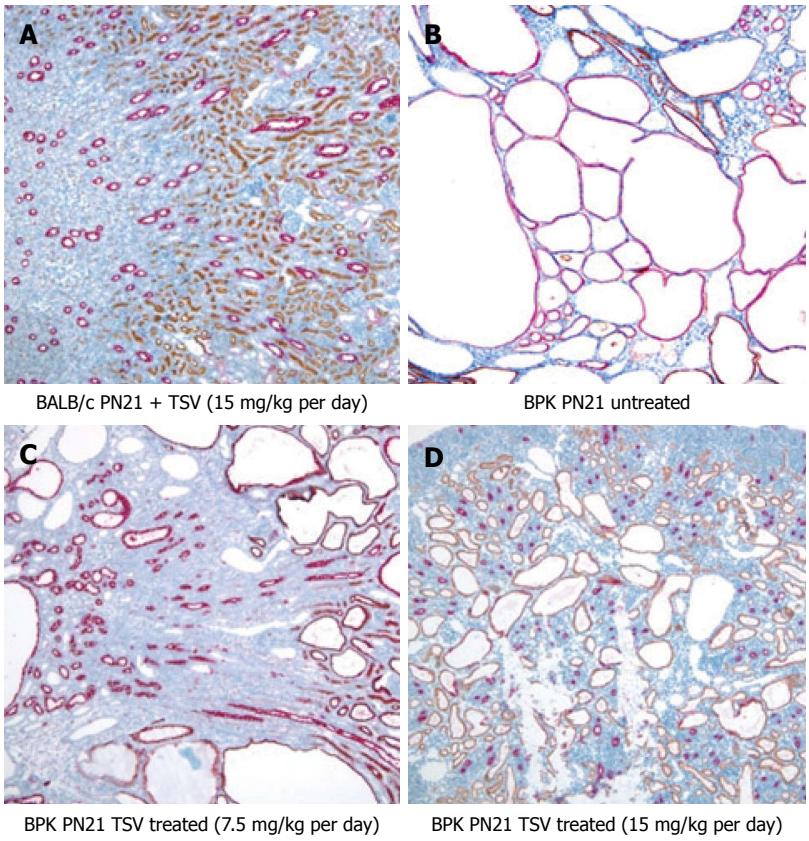

Figure 2 Renal morphology of tesevatinib-treated BPK kidneys. Immuno-histological analysis of BPK kidneys reveals a marked decrease in the size and number of collecting tubule cysts (stained red) following treatment with TSV at 7.5 mg/kg per day (C) and 15 mg/kg per day (D) when compared to the untreated cystic kidneys (B). Treatment of control BALB/c kidneys with TSV at 15 mg/kg per day (A) demonstrated no obvious histological abnormalities (Nephron segment-specific lectin binding of lotus tetragonolabus agglutin shows proximal tubules in brown, and binding of dolichus biflorus agglutin shows collecting tubules in red). TSV: Tesevatinib.

Table 1 BPK summary data

	WT PN-21 Sham n = 22	WT PN-21 VEH n = 10	WT PN-21 TSV 7.5 n = 10	WT PN-21 TSV 15 n = 10	BPK PN-21 Sham n = 17	BPK PN-21 VEH n = 12	BPK PN-21 TSV 7.5 n = 10	BPK PN-21 TSV 15 n = 14
BW (g)	10.31 ± 0.55	10.76 ± 0.72	10.57 ± 0.80	10.10 ± 0.29	10.46 ± 0.60	10.29 ± 0.45	10.50 ± 0.96	10.11 ± 0.50
TKW (g)	0.15 ± 0.01	0.16 ± 0.02	0.141 ± 0.02	0.13 ± 0.01	2.03 ± 0.28	2.01 ± 0.22	1.59 ± 0.19^{e}	1.21 ± 0.09^{f,e}
KW/BW (%)	1.41 ± 0.10	1.50 ± 0.12	1.33 ± 0.08	1.25 ± 0.09	19.32 ± 1.71	19.57 ± 1.62	15.12 ± 1.1^{e}	11.96 ± 1.22^{f,e}
CI	NA	NA	NA	NA	4.7 ± 0.50	4.8 ± 0.42	3.6 ± 0.52^{e}	2.50 ± 0.35^{f,e}
BUN (mg/dL)	19.25 ± 1.14	21.20 ± 1.99	18.60 ± 2.07	19.40 ± 1.5	108.3 ± 17.8	112 ± 23.3	63.6 ± 20.3^{e}	40.9 ± 13.7^{d,e}
Cr (mg/dL)	0.24 ± 0.05	0.29 ± 0.06	0.24 ± 0.05	0.28 ± 0.06	0.55 ± 0.14	0.58 ± 0.10	0.41 ± 0.1^{b}	0.28 ± 0.07^{c,e}
12 h UCA	1043 ± 35	1065 ± 52	1026 ± 39	1024 ± 27	465 ± 83	460 ± 92	581 ± 67^{a}	786 ± 185.2^{d,e}
BDE	NA	NA	NA	NA	4.8 ± 0.4	4.5 ± 0.5	3.70 ± 0.4^{b}	2.8 ± 0.4^{d,e}

$^{a}P < 0.05$, $^{b}P < 0.01$, $^{e}P < 0.001$ *vs* untreated (Sham) BPK; $^{c}P < 0.05$, $^{d}P < 0.01$, $^{f}P < 0.001$ *vs* BPK TSV treatment at 7.5. CI: Cystic index; UCA: Urinary concentration ability at 12 h; BDE: Biliary ductal ectasia; KW/BW: Kidney weight to body weight; NA: Not applicable; TKW: Total kidney weight.

4.80 ± 0.4 to 3.60 ± 0.52 ($P < 0.001$) treated with TSV at 7.5 mg/kg per day and by 48% (2.5 ± 0.5, $P < 0.001$) in BPK mice treated with TSV at 15 mg/kg per day compared to untreated bpk kidneys (Table 1).

The morphology of bpk kidney and liver shown in Figures 2 and 3 respectively, demonstrates a dose dependent reduction in the progression of disease in both kidney and liver respectively. The red labelled CTs cysts in PN21 untreated bpk animals (Figure 2B) are very large with little normal parenchyma in between. TSV treatment reduces the number and size of the CT cysts in kidneys treated with TSV at 7.5 mg/kg per day (Figure 2C) and 15 mg/kg per day (Figure 2D). Kidneys shown in Figure 2C and D reveal LTA labelled proximal tubule cysts (brown) that are indicative of a "younger" PKD disease course as previously described[34,35,43]. The improved morphology with TSV treatment correlates with the reduced whole kidney size (Figure 1) as well as with the reduced TKW, CI and BDE index in Table 1.

All morphometric measures of renal disease and liver abnormalities associated with ARPKD, as well as all renal functional parameters improved in a dose dependent manner in bpk with TSV administration. In the bpk, at PN21 this included an improvement in: BUN of 41% ($P < 0.001$) and 62% ($P < 0.001$); serum CR improved 25.5% ($P < 0.01$) and 49% ($P < 0.001$); and the UCA improved by 25% ($P < 0.05$) and 69.4% ($P < 0.001$) with 7.5 and 15 mg/kg per day respectively as seen in Table 1.

There was also a marked change in biliary ductal ectasia (BDE) with TSV treatment as assessed by histological evaluation of hepatic morphology in the bpk

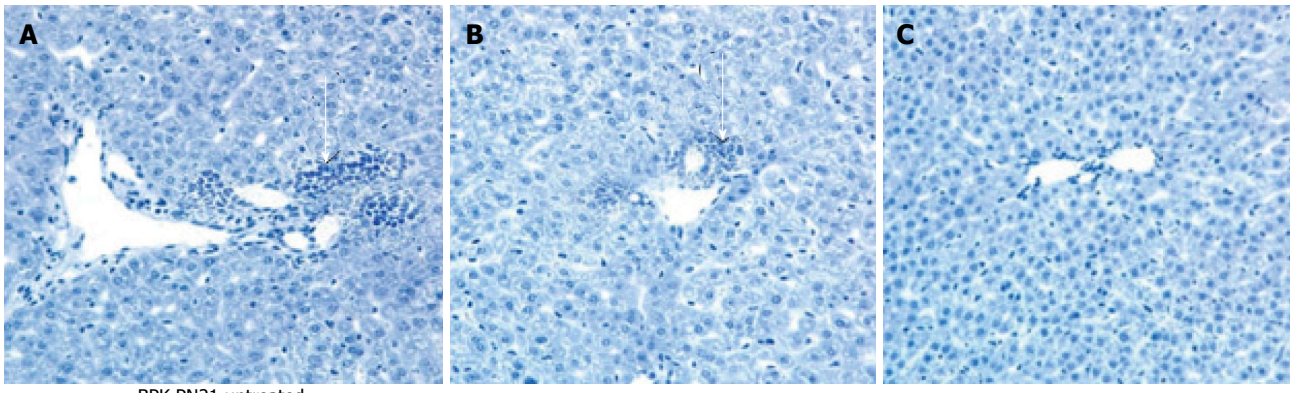

Figure 3 Liver morphology of tesevatinib-treated BPK mice. Histological analysis of hematoxylin stained BPK livers reveals a marked decrease in the biliary ductal ectasia (arrow) following treatment with TSV at 7.5 mg/kg per day (B) (arrow) and 15 mg/kg per day (C) when compared to untreated BPK livers (A) (Treatment interval: PN4-PN21).

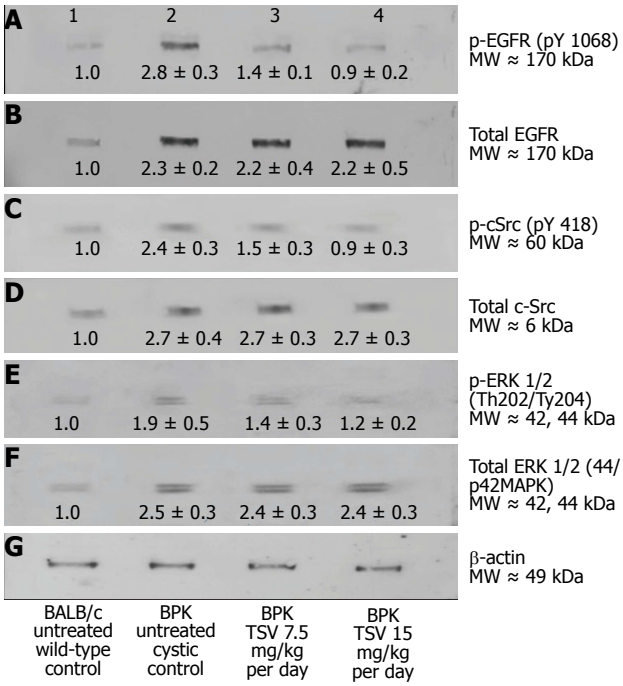

Figure 4 Target validation in BPK. Western analysis of the MAPK pathway activity of EGFR (p-EGFR), cSrc (pSrc), and ERK1/2 (p-ERK ½) reveals that BPK cystic kidneys have significantly increased levels of active or phosphorylated p-EGFR (A2), pSrc (C2) and ERK1/2 (E2) compared to wild-type BALB/c control levels in lanes (A1, C1 and E1) respectively. TSV treatment at 7.5 or 15 mg/kg per day resulted in a dose dependent reduction in the phosphorylation or activity of p-EGFR (A3 and A4), and p-Src (C3 and C4) that correlated directly to a reduction in the activity of ERK1/2 (p-ERK1/2: E3 and E4).The reduced level of phosphorylated proteins occurred without changes in the level of total EGFR (B2, B3 and B4), total Src (D2, D3 and D4) or total ERK1/2 (F2, F3 and F4). The numbers below the band in each lane represents the average ± SD (n = 3) of the relative density of each band when normalized to the wildtype BALB/c control value arbitrarily set at 1.

(Figure 3 and Table 1). BDE at PN21 of TSV treated cystic mice (Table 1) was significantly reduced by 25% from 4.80 ± 0.50 to 3.70 ± 0.40 (P < 0.01) with 7.5 mg/kg per day and was furthered reduced by 42% to 2.80 ± 0.40 (P < 0.001) with TSV treatment at 15 mg/kg per day.

Treatment of BALB/c wildtype control animals showed no statistical difference in any assessed parameters including renal function at 7.5 or 15 mg/kg per day dose when compared to untreated wildtype animals. The morphology of both the kidney (Figure 2A) and liver (Figure 3A) at the 15 mg/kg per day dose and the lack of change in renal function (Table 1) at either dose indicated no obvious signs of toxicity with TSV administration.

Kinase target validation was assessed in the bpk kidneys treated with TSV. As seen in the Western blots of Figure 4, TSV targeted the kinases previously shown to play a role in proliferation and cystic disease in renal epithelia. The use of TSV resulted in a significantly reduced phosphorylation level of EGFR (Figure 4A3, and 4A4), c-Src (Figure 4C3 and 4C4) and ERK1/2 (Figure 4E3 and 4E4). For these key kinases, TSV treatment of 15 mg/kg per day resulted in phosphorylation levels similar to untreated control kidneys (Figure 4, lanes A4, C4 and E4 compared to wildtype control levels as seen in Figure 4 lane 1 of panel A, C and E).

An obvious consideration with the potential use of TSV in pediatric patients is deleterious side effects due to disruption of developmentally critical proteins. A particular concern is the effect of TSV on angiogenesis. The inhibition of KDR or VEGFR2 ideally would not cause a reduction in activity of the receptor much below wildtype levels where inhibition of angiogenesis would likely have significant detrimental effects on normal kidney development. The rapidly progressive bpk was used to evaluate the inhibitory effect of KDR during postnatal development.

To investigate the level of angiogenesis inhibition we measured the change in VEGFR2 (KDR) activity in bpk (Figure 5). As Figure 5 shows, the amount of active p-KDR in TSV-treated kidneys at 15 mg/kg per day is not significantly different from the level of untreated wild type controls. The expression data of CD-31 or PECAM-1, an endothelial cell protein reveal a decreased expression in TSV treated bpk cystic kidneys. These data demonstrate

Table 2 PCK summary data

	SD PN-90 Sham n = 12	SD PN-90 VEH n = 10	SD PN-90 7.5 mg/kg per day n = 8	SD PN-90 15 mg/kg per day n = 8	PCK PN-90 Sham n = 10	PCK PN-90 VEH n = 12	PCK PN-90 7.5 mg/kg per day n = 10	PCK PN-90 15 mg/kg per day n = 12
BW (g)	375.9 ± 12.1	380 ± 19.46	375 ± 23.23	377 ± 13.31	434 ± 16.6	417.8 ± 21.0	413.4 ± 18.7	406.0 ± 18.5
TKW (g)	3.63 ± 0.46	3.70 ± 0.22	3.71 ± 0.16	3.85 ± 0.32	8.02 ± 0.32	7.54 ± 0.52	6.21 ± 0.44[e]	5.06 ± 0.43[e,f]
KW/BW (%)	0.96 ± 0.10	0.97 ± 0.04	0.99.± 0.6	0.91 ± 0.33	1.84 ± 0.09	1.81 ± 0.05	1.50 ± 0.11[b]	1.18 ± 0.1[c,e]
CI	NA	NA	NA	NA	7.44 ± 0.8	7.0 ± 0.6	5.3 ± 1.0[e]	3.8 ± 0.9[d,e]
BUN (mg/dL)	21.17 ± 1.2	22.40 ± 1.6	23.50 ± 1.7	23.6 ± 1.9	49.2 ± 12.7	48.88 ± 15.3	36.40 ± 4.4[b]	24.17 ± 8.7[c,e]
Cr (mg/d)	0.33 ± 0.08	0.34 ± 0.12	0.36 ± 0.05	0.34 ± 0.08	0.67 ± 0.1	0.66 ± 0.12	0.51 ± 0.08[b]	0.38 ± 0.07[c,e]
UCA 12 h	2778 ± 159	2983 ± 421	2749 ± 63.1	2712 ± 113	1390 ± 221.9	1448 ± 236	2196 ± 169[e]	2630 ± 214[d,e]
LW/BW (%)	4.3 ± 0.47	4.2 ± 0.7	4.13 ± 0.57	4.00 ± 0.65	6.02 ± 0.35	6.08 ± 0.42	5.40 ± 0.21[b]	4.92 ± 0.27[c,e]

[a]P < 0.05, [b]P < 0.01, [e]P < 0.001 *vs* untreated (Sham) PCK; [c]P < 0.05, [d]P < 0.01; [f]P < 0.001 *vs* TSV treatment at 7.5. CI: Cystic index; UCA: Urinary concentration ability at 12 h; LW/BW: Measure of cyst burden; KW/BW: Kidney weight to body weight; TKW: Total kidney weight.

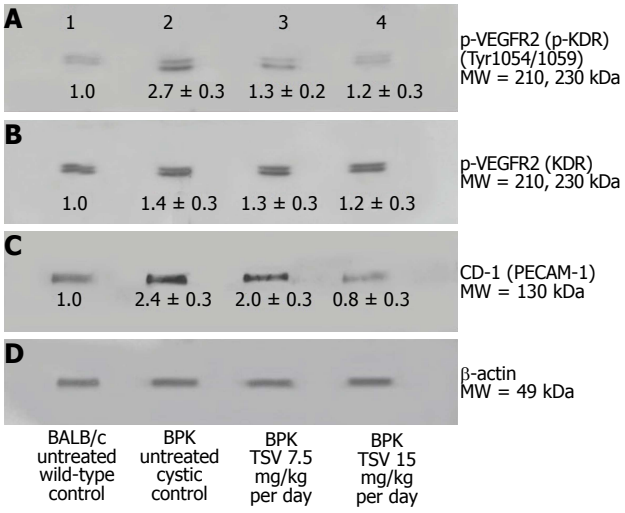

Figure 5 VEGFR2 (KDR) and CD-31 expression in BPK. Western analysis of the renal expression of VEGF2 (KDR) in BPK (B), and active (p-KDR) in BPK kidneys (A) demonstrate an increased phosphorylation of KDR in untreated cystic kidneys (2) compared to BALB/c untreated wildtype controls (A1). TSV treatment of BPK at 7.5 (A3) and 15 mg/kg per day (A4) respectively, reduced the level of p-KDR in a dose dependent manner to near normal (wildtype) levels. This reduced p-KDR correlated directly with expression levels of CD-31 shown in (C) which was also reduced in a dose dependent manner with TSV treatment. The numbers below the band in each lane represents the average ± SD of the relative density of each band when normalized to the wildtype BALB/c control value arbitrarily set at 1. D is the loading control. Each average represents a minimum of n = 3 individual westerns. These data are confirmed by the morphology of CD-1 stained BPK kidneys shown in Figure 6.

that inhibition of angiogenesis as assessed by p-KDR translated into a reduced expression of CD-31. As seen in Figure 6, the level of CD-31, is increased around cystic CT (6B) when compared to age-matched BALB/c animals (6A). It appears that TSV treatment eliminates abnormal peritubular CD-31 expression but still permits the robust expression of CD-31 in glomeruli (6C) of TSV treated bpk kidneys.

PCK

The orthologue of human ARPKD, the PCK, and Sprague Dawley wildtype controls were administered TSV by oral gavage from PN30 to PN90 and the same parameters assessed following TSV administration as in the bpk.

Figure 7 reveals that TSV administration to PCK animals from PN30 to PN90 (61 doses) results in a dose dependent reduction in whole kidney size when compared to untreated PCK. The change in whole kidney size is also reflected in the dose dependent significant decrease in TKW from 8.02 ± 0.32 g in untreated PCK to 6.21 ± 0.44 (P < 0.001) and 5.06 ± 0.43 g (P < 0.001) with TSV at 7.5 and 15 mg/kg per day respectively as shown in Table 2. The reduction in whole kidney size and TKW is associated with markedly improved renal morphology shown in Figure 8. Accordingly, the CI was significantly reduced by treatment as seen in Table 2. The improved renal morphology was mirrored by a dose dependant improvement in hepatic morphology as seen in Figure 9 which was reflected in a reduced LW/BW ratio listed in Table 2.

Results summarized in Table 2, demonstrate th-at compared to untreated PCK animals (n = 10), cystic animals treated with TSV showed an 18%, (P < 0.01) and 36% (P < 0.001) reduction in KW/BW ratio, reductions in CI of 29%, (P < 0.001) and 49%, (P < 0.001) and a 10% (P < 0.05) and 18% (P < 0.001) reduction in LW/BW ratios. There was a dose dependent improvement in KW/BW of 26% and CI of 28% with increased dosage from 7.5 to 15 mg/kg per day. Compared to untreated PCK animals, renal function parameters also demonstrated significant dose dependent improvement with TSV treatment. BUN levels decreased by 26% (P < 0.01), and 49% (P < 0.001), CR levels decreased by 24% (P < 0.01) and 43% (P < 0.001) while UCA improved by 36% (P < 0.001) and 47% (P < 0.001) following TSV treatment with 7.5 and 15 mg/kg per day respectively. Treatment of SD controls shows no significant differences in assessed parameters at either TSV dose.

The improvement in morphology and renal function correlates with target verification shown in Figure 10. The activity (phosphorylation) of ErbB2 (Figure 10A3 and A4) Src (Figure 10C3 and 10C4) ERK1/2 (Figure 10E3 and 10E4) are reduced in a dose dependent manner with treatment with TSV at 7.5 and 15 mg/kg per day respectively. Figure 11 demonstrates that TSV reduces pKDR levels which correlates with a reduced

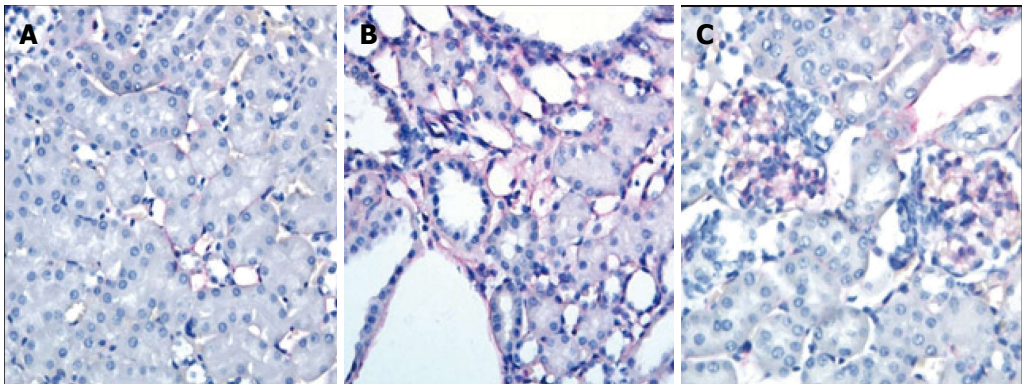

Figure 6 Immuno-histological analysis of CD-31 expression in tesevatinib-treated BPK kidneys. Expression of CD-31 (PECAM1) (red), a marker of endothelium, in PN21 wild-type BALB/c kidneys (A) reveals fine thin lines of endothelial elements that run along the nephrons. Untreated BPK kidneys (B) demonstrate prominent expression of CD-31 along the tubules and pronounced expression surrounding cystic lesions. TSV-treated cystic kidneys at 15 mg/kg per day (C) reveal a marked reduction in CD31 expression along the tubules to near normal levels but maintain robust glomerular staining of CD-31.

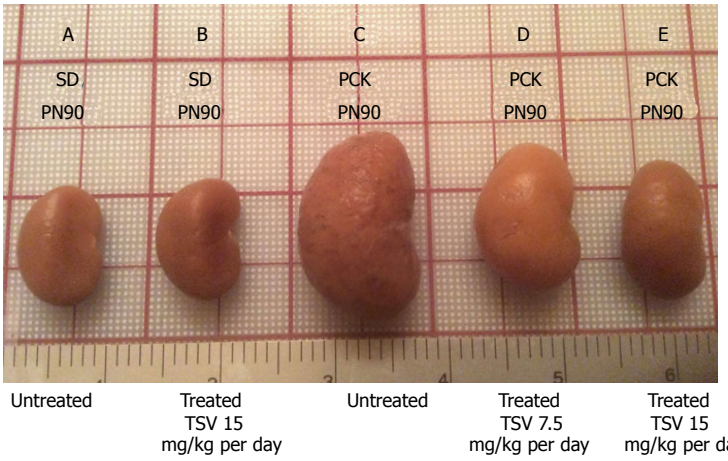

Figure 7 Tesevatinib treatment in the PCK model of autosomal recessive polycystic kidney disease. Compared to wild-type SD control kidneys (A) at PN90, PCK cystic kidneys (C) are significantly enlarged by PN90. TSV treatment results in a dose-dependent reduction in the overall kidney size at doses of 7.5 mg/kg per day (D) and 15 mg/kg per day (E) when compared to untreated PCK cystic kidneys at PN90 (C). Treatment of wildtype SD with 15 mg/kg per day did not result in significant reduction of overall kidney size (B) compared to untreated wildtype SD animals. This correlates directly with the total kidney weight (TKW) of each group listed in Table 2 (Treatment interval: PN30-PN90). TSV: Tesevatinib.

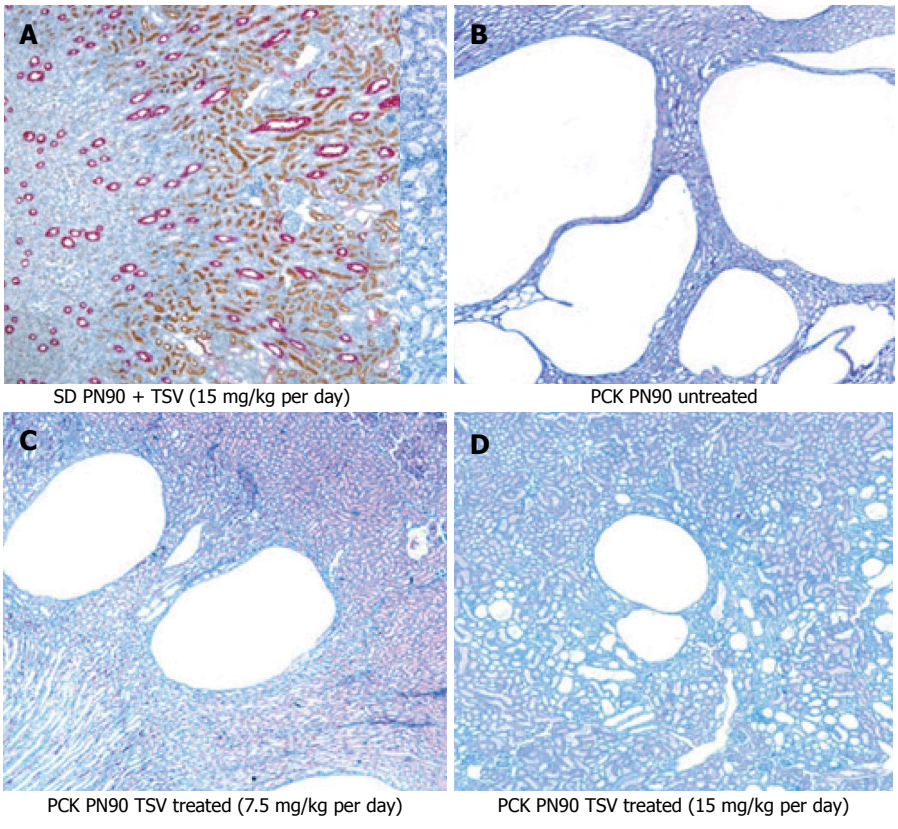

Figure 8 Renal morphology of tesevatinib-treated PCK kidneys. Histological analysis of HE stained PCK kidneys reveals a marked decrease in the size and number of collecting tubule cysts following treatment with TSV at 7.5 mg/kg per day (C) and 15 mg/kg per day (D) when compared to untreated cystic kidneys (B). Treatment of control Sprague Dawley kidneys at 15 mg/kg per day (A) revealed no histological abnormalities (Treatment Interval: PN30-PN90). TSV: Tesevatinib.

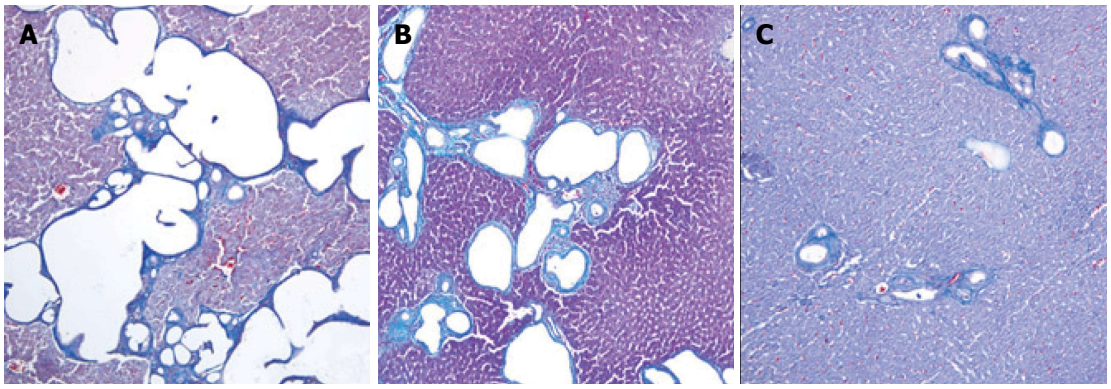

Figure 9 Liver morphology of tesevatinib-treated PCK mice. Histological analysis of PCK livers reveals a marked decrease in the size and number of biliary ductal cysts following treatment with tesevatinib at 7.5 mg/kg per day (B) and 15 mg/kg per day (C) when compared to untreated PCK livers (A) (Treatment interval: PN30-PN90).

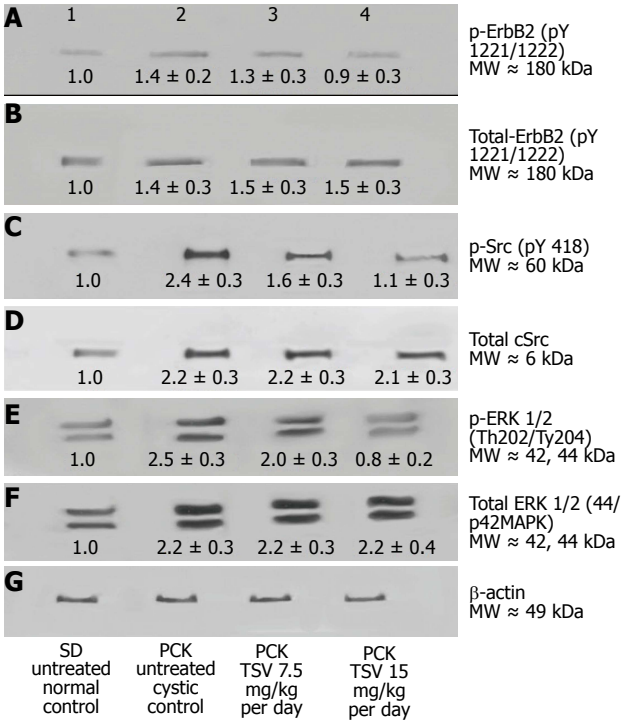

Figure 10 Target validation in BPK. Western analysis of the MAPK pathway activity of EGFR (p-EGFR), cSrc (pSrc), and ERK1/2 (p-ERK ½) reveals that BPK cystic kidneys have significantly increased levels of active or phosphorylated p-EGFR (A2), pSrc (C2) and ERK1/2 (E2) compared to wild-type BALB/c control levels in lanes (A1, C1 and E1) respectively. TSV treatment at 7.5 or 15 mg/kg per day resulted in a dose dependent reduction in the phosphorylation or activity of p-EGFR (A3 and A4), and p-Src (C3 and C4) that correlated directly to a reduction in the activity of ERK1/2 (p-ERK1/2: E3 and E4).The reduced level of phosphorylated proteins occurred without changes in the level of total EGFR (B2, B3 and B4), total Src (D2, D3 and D4) or total ERK1/2 (F2, F3 and F4). The numbers below the band in each lane represents the average ± SD (n = 3) of the relative density of each band when normalized to the wildtype BALB/c control value arbitrarily set at 1.

CD-31 level with TSV therapy.

Toxicology

Treatment of bpk mice and PCK rats with TSV demonstrated no apparent morphological evidence of renal or hepatic toxicity, no compound-related deaths, and no microscopic changes in heart, spleen, stomach, pancreas or thymus with 7.5 mg/kg per day or 15 mg/kg per day dosing.

In sum, the use of TSV at 7.5 or 15 mg/kg per day results in a significant improvement in all assessed parameters compared to untreated or vehicle treated cystic animals in both bpk and PCK animals without obvious evidence of toxicity or detrimental effect of KDR inhibition.

DISCUSSION

A long-recognized clinical observation is the overlap of phenotypic features that at times leads to difficulty delineating ARPKD from ADPKD in pediatric patients[3,5,16]. Data now reveal that the pathophysiology of the two diseases have significant overlap. Recent evidence revealed a complex set of interactions between PKHD1, PKD1 and PKD2 that occur both at the molecular and cellular level[5,15,20-23]. Despite the identification of the causative genes responsible for ARPKD and ADPKD, the precise function of these genes and their protein products is still unclear.

This complexity, in part, is due in part to many novel attributes of the genes including: (1) the complexity of their protein structures; (2) the large size of *PKHD1* and *PKD1*; (3) the multiple transcripts produced by these genes; (4) the interaction of the PKD proteins; (5) the multiple intracellular sites of PKD protein localization; and (6) the participation of these proteins in a number of multimeric protein complexes[5,17-19,44]. The lack of functional PC1, PC2 or fibrocystin is embryonically lethal, indicating and PKD begins *in utero*[25]. ARPKD and ADPKD share common phenotypic abnormalities and intersecting signaling pathways whose disruption leads to cyst formation[3,5,16,23,34]. Despite this rudimentary understanding, emerging molecular and cellular insights into the pathophysiology of PKD is beginning to translate into unique disease-specific, targeted therapies.

Previous work in our laboratory demonstrated that

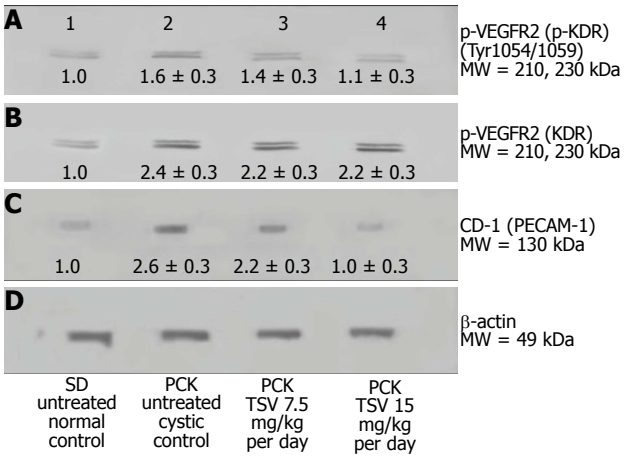

Figure 11 VEGFR2 (KDR) and CD-31 expression in PCK. Western analysis of the renal expression of VEGF2 (KDR) in PCK (B), and active (p-KDR) in PCK kidneys (A) demonstrate an increased phosphorylation of KDR in untreated cystic PCK kidneys (A2) compared to SD untreated wildtype controls (A1). TSV treatment of PCK at 7.5 (A3) and 15 mg/kg per day (A4) respectively, reduced the level of p-KDR in a dose dependent manner to near normal (wildtype) levels. This reduced p-KDR correlated directly with expression levels of CD-31 shown in C, which was also reduced in a dose dependent manner with TSV treatment. The numbers below the band in each lane represents the average ± SD of the relative density of each band when normalized to the wildtype SD control value arbitrarily set at 1. D is the loading control. Each average represents a minimum of n = 3 individual westerns.

the combination of therapies that inhibit both the epidermal growth factor receptor (EGFR) autophosphorylation and EGFR ligand availability provide a novel example of effective combination therapy in murine PKD[37]. Extending this concept, we reasoned that identification of signaling intermediates which: (1) regulate multiple steps in a single pathophysiological pathway; in addition to acting as; and (2) an integration point for multiple signaling cascades may provide even greater benefit than EGFR combination therapy noted above. Key integration points for targeting to prevent disease progression include the activation of the EGFR axis, c-Src, and VEGFR2 by specific kinases[3,34,40,45-50] and cAMP signaling[51-53]. This led us to examine the potential of a novel multi-kinase inhibitor, TSV, in preventing progression of ARPKD.

Given the differences in route of administration, the speed of disease development and the fact that the measure of the disease burden in the kidney and liver are model specific make direct comparison of the results in bpk and PCK unreliable. It is also difficult to compare these results to other interventional therapies we have attempted in these models because we tested two doses only on the basis of recommendations from Kadmon. Never the less the current study demonstrates that TSV ameliorates the progression of renal cystic disease in two well characterized rodent models of ARPKD. Further, TSV's inhibition of the phosphorylation of c-Src, EGFR and ErbB2 led to significant reduction of MAPK activity (ERK 1/2 phosphorylation), and resultant cellular proliferation. In addition to amelioration of renal cystic disease, TSV also led to significant reduction in the biliary ductal abnormalities characteristic of ARPKD in BPK and in the LW/BW ratios of PCK. The results of the current study also indicate that the use of a multi-kinase inhibitor that targets angiogenesis driven by KDR or VEGFR2 can be an effective and safe therapy during postnatal renal maturation and development.

Preliminary data from the ongoing phase Ⅱ clinical trial of TSV (KD-019) for treatment of ADPKD (https//ClinicalTrials.gov/ADPKD: NCT01559363) presented at the American Society of Nephrology 2015 annual meeting reported: (1) QTc prolongation to ⩾ 485 ms was seen in 2/8 pts treated with 100 mg/d; (2) The half-life in adults allowed for intermittent dosing which improved tolerability; (3) The most common AEs were those associated with EGFR kinase inhibition: Diarrhea; nausea; and acneiform rash; and (4) 50 mg/d appeared to be safe and well tolerated and additional patients were being enrolled at this dose to confirm the safety profile[54].

On balance, these data suggest that TSV may be a safe and effective therapy for childhood ARPKD.

COMMENTS

Background

The study detailed here was designed to ascertain if a multi-kinase inhibitor "tesevatinib" would effectively slow the growth of renal cysts and reduce the loss of renal function in two well characterized models of autosomal recessive polycystic kidney disease (ARPKD). This compound targets the EGFR axis, cSrc and it inhibits angiogenesis by preventing phosphorylation of VEGFR2 (also called KDR). The bpk mouse was chosen to examine the effect of KDR inhibition on post-natal development and the orthologous PCK was chosen to examine the effect of oral dosing on inhibition of the target signaling pathways. Tesevatinib inhibit renal cyst growth in both models without overt signs of toxicity.

Research frontiers

This study demonstrated that there is indeed considerable overlap in the aberrant signaling cascades in ARPKD and autosomal dominant polycystic kidney disease (ADPKD). This raises the hope that the lessons learned from therapeutic interventions in ADPKD can be adapted for ARPKD patients.

Innovations and breakthroughs

The most exciting result of this study is that inhibition of angiogenesis, an important component of cyst growth, can now be added to arsenal to slow cyst growth when activity (phosphorylation) is cautiously reduced to normal or wildtype levels. This inhibition with tesevatinib contributed to the amelioration of cyst growth without overt signs of toxicity even in early post-natal development.

Applications

The value of these results is that effective therapies developed and tested for ADPKD patients can be for use in ARPKD patients. A multi-kinase drug with multiple targets theoretically would reduce the amount of compound necessary to achieve equivalent results compared to amounts needed with single target drugs. This effectively reduces the exposure to the compounds and would result in reduced toxicity and potentially allow long term use of the therapeutic compound. This should accelerate the use of therapeutic compounds in clinical trials of ARPKD patients.

Terminology

The activity of a kinase refers to the phosphorylation state of the molecule. It generally means the target molecule becomes phosphorylated and this results in increased activity until it is de-phosphorylated by another molecule. A multi-kinase inhibitor is a compound that targets multiple signaling components simultaneously and can prevent phosphate from binding to and activating the signaling components thus rendering the molecule useless. This occurs

simultaneously and provides a means hitting two or more targets with a single compound.

Peer-review

This paper was well-written.

REFERENCES

1 **Gunay-Aygun M**, Font-Montgomery E, Lukose L, Tuchman Gerstein M, Piwnica-Worms K, Choyke P, Daryanani KT, Turkbey B, Fischer R, Bernardini I, Sincan M, Zhao X, Sandler NG, Roque A, Douek DC, Graf J, Huizing M, Bryant JC, Mohan P, Gahl WA, Heller T. Characteristics of congenital hepatic fibrosis in a large cohort of patients with autosomal recessive polycystic kidney disease. *Gastroenterology* 2013; **144**: 112-121.e2 [PMID: 23041322]

2 **Sweeney W**, Avner ED. Polycystic Kidney Disease, Autosomal Recessive. In: Pagon RA, Adam MP, Ardinger HH, editors. Gene Reviews [Internet]. Seattle (WA): University of Washington, 2001 [updated 2016]. Available from: URL: http://www.ncbi.clm.nih.gov/books/NBK1326

3 **Sweeney WE**, Avner ED. Pathophysiology of childhood polycystic kidney diseases: new insights into disease-specific therapy. *Pediatr Res* 2014; **75**: 148-157 [PMID: 24336431]

4 **Cramer MT**, Guay-Woodford LM. Cystic kidney disease: a primer. *Adv Chronic Kidney Dis* 2015; **22**: 297-305 [PMID: 26088074 DOI: 10.1053/j.ackd.2015.04.001]

5 **Sweeney WE**, Gunay-Aygun M, Patil A, Avner ED. Childhood Polycystic Kidney Disease. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein S, editors. *Pediatr Nephrol* 2016; **31**: 1-58

6 **Gunay-Aygun M**, Tuchman M, Font-Montgomery E, Lukose L, Edwards H, Garcia A, Ausavarat S, Ziegler SG, Piwnica-Worms K, Bryant J, Bernardini I, Fischer R, Huizing M, Guay-Woodford L, Gahl WA. PKHD1 sequence variations in 78 children and adults with autosomal recessive polycystic kidney disease and congenital hepatic fibrosis. *Mol Genet Metab* 2010; **99**: 160-173 [PMID: 19914852]

7 **Guay-Woodford LM**, Muecher G, Hopkins SD, Avner ED, Germino GG, Guillot AP, Herrin J, Holleman R, Irons DA, Primack W, P.D. T, Waldo FB, Lunt PW, Zerres K. The severe perinatal form of autosomal recessive polycystic kidney disease maps to chromosome 6p21.1-p12: Implications for genetic counseling. *Am J Hum Genet* 1995; **56**: 1101-1107

8 **Zerres K**, Rudnik-Schoneborn S, Steinkamm C, Becker J, Mucher G. Autosomal recessive polycystic kidney disease. *J Mol Med* 1998; **76**: 303-309

9 **Onuchic LF**, Furu L, Nagasawa Y, Hou X, Eggermann T, Ren Z, Bergmann C, Senderek J, Esquivel E, Zeltner R, Rudnik-Schoneborn S, Mrug M, Sweeney W, Avner ED, Zerres K, Guay-Woodford LM, Somlo S, Germino GG. PKHD1, the polycystic kidney and hepatic disease 1 gene, encodes a novel large protein containing multiple immunoglobulin-like plexin-transcription-factor domains and parallel beta-helix 1 repeats. *Am J Hum Genet* 2002; **70**: 1305-1317

10 **Ward CJ**, Hogan MC, Rossetti S, Walker D, Sneddon T, Wang X, Kubly V, Cunningham JM, Bacallao R, Ishibashi M, Milliner DS, Torres VE, Harris PC. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. *Nat Genet* 2002; **30**: 259-269

11 **Cadnapaphornchai MA**, McFann K, Strain JD, Masoumi A, Schrier RW. Prospective change in renal volume and function in children with ADPKD. *Clin J Am Soc Nephrol* 2009; **4**: 820-829 [PMID: 19346430]

12 **Ong AC**, Harris PC. Molecular pathogenesis of ADPKD: the polycystin complex gets complex. *Kidney Int* 2005; **67**: 1234-1247 [PMID: 15780076]

13 **Streets AJ**, Magayr TA, Huang L, Vergoz L, Rossetti S, Simms RJ, Harris PC, Peters DJ, Ong AC. Parallel microarray profiling identifies ErbB4 as a determinant of cyst growth in ADPKD and a prognostic biomarker for disease progression. *Am J Physiol Renal Physiol* 2017; **312**: F577-F588 [PMID: 28077374 DOI: 10.1152/ajprenal.00607.2016]

14 **Harris PC**, Torres VE. Polycystic kidney disease. *Annu Rev Med* 2009; **60**: 321-337 [PMID: 18947299]

15 **Harris PC**, Torres VE. Genetic mechanisms and signaling pathways in autosomal dominant polycystic kidney disease. *J Clin Invest* 2014; **124**: 2315-2324 [PMID: 24892705 DOI: 10.1172/JCI72272]

16 **Sweeney WE**, Avner ED. Diagnosis and management of childhood polycystic kidney disease. *Pediatr Nephrol* 2011; **26**: 675-692 [PMID: 21046169]

17 **Wilson PD**. Polycystic kidney disease: new understanding in the pathogenesis. *Int J Biochem Cell Biol* 2004; **36**: 1868-1873 [PMID: 15203099]

18 **Zhang MZ**, Mai W, Li C, Cho SY, Hao C, Moeckel G, Zhao R, Kim I, Wang J, Xiong H, Wang H, Sato Y, Wu Y, Nakanuma Y, Lilova M, Pei Y, Harris RC, Li S, Coffey RJ, Sun L, Wu D, Chen XZ, Breyer MD, Zhao ZJ, McKanna JA, Wu G. PKHD1 protein encoded by the gene for autosomal recessive polycystic kidney disease associates with basal bodies and primary cilia in renal epithelial cells. *Proc Natl Acad Sci USA* 2004; **101**: 2311-2316 [PMID: 14983006]

19 **Wu Y**, Dai XQ, Li Q, Chen CX, Mai W, Hussain Z, Long W, Montalbetti N, Li G, Glynne R, Wang S, Cantiello HF, Wu G, Chen XZ. Kinesin-2 mediates physical and functional interactions between polycystin-2 and fibrocystin. *Hum Mol Genet* 2006; **15**: 3280-3292 [PMID: 17008358]

20 **Lantinga-van Leeuwen IS**, Dauwerse JG, Baelde HJ, Leonhard WN, van de Wal A, Ward CJ, Verbeek S, Deruiter MC, Breuning MH, de Heer E, Peters DJ. Lowering of Pkd1 expression is sufficient to cause polycystic kidney disease. *Hum Mol Genet* 2004; **13**: 3069-3077 [PMID: 15496422]

21 **Gallagher AR**, Germino GG, Somlo S. Molecular advances in autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis* 2010; **17**: 118-130 [PMID: 20219615 DOI: 10.1053/j.ackd.2010.01.002]

22 **Hopp K**, Ward CJ, Hommerding CJ, Nasr SH, Tuan HF, Gainullin VG, Rossetti S, Torres VE, Harris PC. Functional polycystin-1 dosage governs autosomal dominant polycystic kidney disease severity. *J Clin Invest* 2012; **122**: 4257-4273 [PMID: 23064367 DOI: 10.1172/JCI64313]

23 **Fedeles SV**, Gallagher AR, Somlo S. Polycystin-1: a master regulator of intersecting cystic pathways. *Trends Mol Med* 2014; **20**: 251-260 [PMID: 24491980 DOI: 10.1016/j.molmed.2014.01.004]

24 **Harris PC**, Bae KT, Rossetti S, Torres VE, Grantham JJ, Chapman AB, Guay-Woodford LM, King BF, Wetzel LH, Baumgarten DA, Kenney PJ, Consugar M, Klahr S, Bennett WM, Meyers CM, Zhang QJ, Thompson PA, Zhu F, Miller JP. Cyst number but not the rate of cystic growth is associated with the mutated gene in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2006; **17**: 3013-3019 [PMID: 17035604]

25 **Orskov B**, Christensen KB, Feldt-Rasmussen B, Strandgaard S. Low birth weight is associated with earlier onset of end-stage renal disease in Danish patients with autosomal dominant polycystic kidney disease. *Kidney Int* 2012; **81**: 919-924 [PMID: 22297678 DOI: 10.1038/ki.2011.459]

26 **Chapman AB**. The fetal environment: a critical phase that determines future renal outcomes in autosomal dominant polycystic kidney disease. *Kidney Int* 2012; **81**: 814-815 [PMID: 22499140]

27 **Cadnapaphornchai MA**. Hypertension in children with autosomal dominant polycystic kidney disease (ADPKD). *Curr Hypertens Rev* 2013; **9**: 21-26 [PMID: 23971640]

28 **Selistre L**, de Souza V, Ranchin B, Hadj-Aissa A, Cochat P, Dubourg L. Early renal abnormalities in children with postnatally diagnosed autosomal dominant polycystic kidney disease. *Pediatr Nephrol* 2012; **27**: 1589-1593 [PMID: 22689086]

29 **Hartung EA**, Guay-Woodford LM. Autosomal recessive polycystic kidney disease: a hepatorenal fibrocystic disorder with pleiotropic effects. *Pediatrics* 2014; **134**: e833-e845 [PMID: 25113295 DOI: 10.1542/peds.2013-3646]

30 **Hoyer PF**. Clinical manifestations of autosomal recessive polycystic kidney disease. *Curr Opin Pediatr* 2015; **27**: 186-192 [PMID: 25689455 DOI: 10.1097/MOP.0000000000000196]

31 **Grantham JJ**. Rationale for early treatment of polycystic kidney disease. *Pediatr Nephrol* 2015; **30**: 1053-1062 [PMID: 25022529

DOI: 10.1007/s00467-014-2882-8]
32 **Trowe T**, Boukouvala S, Calkins K, Cutler RE, Fong R, Funke R, Gendreau SB, Kim YD, Miller N, Woolfrey JR, Vysotskaia V, Yang JP, Gerritsen ME, Matthews DJ, Lamb P, Heuer TS. EXEL-7647 inhibits mutant forms of ErbB2 associated with lapatinib resistance and neoplastic transformation. *Clin Cancer Res* 2008; **14**: 2465-2475 [PMID: 18413839 DOI: 10.1158/1078-0432.CCR-07-4367]
33 **Gendreau SB**, Ventura R, Keast P, Laird AD, Yakes FM, Zhang W, Bentzien F, Cancilla B, Lutman J, Chu F, Jackman L, Shi Y, Yu P, Wang J, Aftab DT, Jaeger CT, Meyer SM, De Costa A, Engell K, Chen J, Martini JF, Joly AH. Inhibition of the T790M gatekeeper mutant of the epidermal growth factor receptor by EXEL-7647. *Clin Cancer Res* 2007; **13**: 3713-3723 [PMID: 17575237 DOI: 10.1158/1078-0432.CCR-06-2590]
34 **Sweeney WE**, von Vigier RO, Frost P, Avner ED. Src inhibition ameliorates polycystic kidney disease. *J Am Soc Nephrol* 2008; **19**: 1331-1341 [PMID: 18385429]
35 **Nauta J**, Ozawa Y, Sweeney WE, Jr., Rutledge JC, Avner ED. Renal and biliary abnormalities in a new murine model of autosomal recessive polycystic kidney disease. *Pediatr Nephrol* 1993; **7**: 163-172
36 **Nauta J**, Sweeney WE, Rutledge JC, Avner ED. Biliary epithelial cells from mice with congenital polycystic kidney disease are hyperresponsive to epidermal growth factor. *Pediatr Res* 1995; **37**: 755-763
37 **Sweeney WE**, Hamahira K, Sweeney J, Garcia-Gatrell M, Frost P, Avner ED. Combination treatment of PKD utilizing dual inhibition of EGF-receptor activity and ligand bioavailability. *Kidney Int* 2003; **64**: 1310-1319
38 **Nemo R**, Murcia N, Dell KM. Transforming growth factor alpha (TGF-alpha) and other targets of tumor necrosis factor-alpha converting enzyme (TACE) in murine polycystic kidney disease. *Pediatr Res* 2005; **57**: 732-737 [PMID: 15774823]
39 **Katsuyama M**, Masuyama T, Komura I, Hibino T, Takahashi H. Characterization of a novel polycystic kidney rat model with accompanying polycystic liver. *Exp Anim* 2000; **49**: 51-55 [PMID: 10803363]
40 **Talbot JJ**, Song X, Wang X, Rinschen MM, Doerr N, LaRiviere WB, Schermer B, Pei YP, Torres VE, Weimbs T. The cleaved cytoplasmic tail of polycystin-1 regulates Src-dependent STAT3 activation. *J Am Soc Nephrol* 2014; **25**: 1737-1748 [PMID: 24578126]
41 **Sato Y**, Harada K, Kizawa K, Sanzen T, Furubo S, Yasoshima M, Ozaki S, Ishibashi M, Nakanuma Y. Activation of the MEK5/ERK5 cascade is responsible for biliary dysgenesis in a rat model of Caroli's disease. *Am J Pathol* 2005; **166**: 49-60 [PMID: 15631999]
42 **Sweeney WE**, Chen Y, Nakanishi K, Frost P, Avner ED. Treatment of polycystic kidney disease with a novel tyrosine kinase inhibitor. *Kidney Int* 2000; **57**: 33-40
43 **Nakanishi K**, Sweeney WE, Jr, Zerres K, Guay-Woodford LM, Avner ED. Proximal tubular cysts in fetal human autosomal recessive polycystic kidney disease. *J Am Soc Nephrol* 2000; **11**: 760-763
44 **Wilson PD**. Polycystic kidney disease. *N Engl J Med* 2004; **350**: 151-164 [PMID: 14711914]
45 **Bello-Reuss E**, Holubec K, Rajaraman S. Angiogenesis in autosomal-dominant polycystic kidney disease. *Kidney Int* 2001; **60**: 37-45
46 **Yamaguchi T**, Nagao S, Wallace DP, Belibi FA, Cowley BD, Pelling JC, Grantham JJ. Cyclic AMP activates B-Raf and ERK in cyst epithelial cells from autosomal-dominant polycystic kidneys. *Kidney Int* 2003; **63**: 1983-1994 [PMID: 12753285]
47 **Yamaguchi T**, Wallace DP, Magenheimer BS, Hempson SJ, Grantham JJ, Calvet JP. Calcium restriction allows cAMP activation of the B-Raf/ERK pathway, switching cells to a cAMP-dependent growth-stimulated phenotype. *J Biol Chem* 2004; **279**: 40419-40430 [PMID: 15263001]
48 **Belibi FA**, Reif G, Wallace DP, Yamaguchi T, Olsen L, Li H, Helmkamp GM, Grantham JJ. Cyclic AMP promotes growth and secretion in human polycystic kidney epithelial cells. *Kidney Int* 2004; **66**: 964-973 [PMID: 15327388]
49 **Huang JL**, Woolf AS, Long DA. Angiogenesis and autosomal dominant polycystic kidney disease. *Pediatr Nephrol* 2013; **28**: 1749-1755 [PMID: 22990303]
50 **Martins DP**, Souza MA, Baitello ME, Nogueira V, Oliveira CI, Pinhel MA, Caldas HC, Filho MA, Souza DR. Vascular endothelial growth factor as an angiogenesis biomarker for the progression of autosomal dominant polycystic kidney disease. *Genet Mol Res* 2016; **15**: [PMID: 26909926 DOI: 10.4238/gmr.15017623]
51 **Gattone VH**, Wang X, Harris PC, Torres VE. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. *Nat Med* 2003; **9**: 1323-1326 [PMID: 14502283]
52 **Wallace DP**. Cyclic AMP-mediated cyst expansion. *Biochim Biophys Acta* 2011; **1812**: 1291-1300 [PMID: 21118718]
53 **Torres VE**, Harris PC. Strategies targeting cAMP signaling in the treatment of polycystic kidney disease. *J Am Soc Nephrol* 2014; **25**: 18-32 [PMID: 24335972 DOI: 10.1681/ASN.2013040398]
54 **Rastogi A,** Rosner MH, Barash I, Steinman TI, El-Zoghby ZM, Nurko S, Goldberg S, El-Meanawy A, El Ters M, Roche M, Berger MS. Tyrosine Kinase Inhibitor Tesevatinib for Patients with Autosomal Dominant Polycystic Kidney Disease. J *Am Soc Nephrol* 2015: 830A

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ORIGINAL ARTICLE

Retrospective Study

Reproducibility of serial creatinine excretion measurements in peritoneal dialysis

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Author contributions: Xu Z composed the largest part of the first draft of this report; Murata GH was responsible for part of the statistical analysis and made critical changes in the report; Sun Y assisted in the data collection and made critical changes in this report; Glew RH made critical changes in the manuscript; Qualls C was responsible for part of the statistical analysis; Vigil D made important changes in this report; Servilla KS assisted in the data collection and made important changes in the manuscript; Golper TA conceived the study and made critical changes in the report; Tzamaloukas AH designed the study, assisted in the collection of data and wrote parts of the report.

Institutional review board statement: This study was reviewed and approved by the Human Research Committee of the Raymond G. Murphy VA Medical Center.

Informed consent statement: Patients were not required to give informed consent to this retrospective study because the study used anonymous clinical data obtained to evaluate adequacy of dialytic treatment. Each patient has agreed to the dialytic treatment and the collection of the data used in the study. The institutional Human Research Committee approved the use of these data for this study without a signed informed consent.

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Abstract

AIM

To test whether muscle mass evaluated by creatinine excretion (EX_{Cr}) is maintained in patients with end-stage kidney disease (ESKD) treated by peritoneal dialysis (PD), we evaluated repeated measurements of EX_{Cr} in a PD population.

METHODS

One hundred and sixty-six PD patients (94 male, 72 female) receiving the same PD dose for the duration of the study (up to approximately 2.5 years) had repeated determinations of total (in urine plus spent dialysate) 24-h EX_{Cr} (EX_{Cr} T) to assess the adequacy of PD by creatinine clearance. All 166 patients had two EX_{Cr} T determinations, 84 of the 166 patients had three EX_{Cr} T determinations and 44 of the 166 patients had four EX_{Cr} T measurements. EX_{Cr} T values were compared using the paired *t* test in the patients who had two studies and by repeated measures ANOVA in those who were studied three or four times.

RESULTS

In patients who were studied twice, with the first and second EX_{Cr} T measurements performed at 9.2 ± 15.2 mo and 17.4 ± 15.8 mo after onset of PD, respectively, EX_{Cr} T did not differ between the first and second study. In patients studied three times and whose final assessment occurred 24.7 ± 16.3 mo after initiating PD, EX_{Cr} T did not differ between the first and second study, but was significantly lower in the third study compared to the first study. In patients who were studied four times and whose fourth measurement was taken 31.9 ± 16.8 mo after onset of PD, EX_{Cr} T did not differ between any of the studies. The average EX_{Cr} T value did not change significantly, with the exception of the third study in the patients studied thrice. However, repeated determinations of EX_{Cr} T in individuals showed substantial variability, with approximately 50% of the repeated determinations being higher or lower than the first determination by 15% or more.

CONCLUSION

The average value of EX_{Cr} T remains relatively constant for up to 2.5 years of follow-up in PD patients who adhere to the same PD schedule. However, repeated individual EX_{Cr} T values vary considerably in a large proportion of the patients. Further studies are needed to evaluate the clinical significance of varying EX_{Cr} T values and the stability of EX_{Cr} T beyond 2.5 years of PD follow-up.

Key words: Creatinine excretion; Peritoneal dialysis; Lean body mass; Muscle mass

Core tip: Total creatinine excretion (EX_{Cr}) in urine and in the used peritoneal dialysis (PD) fluid is correlated with muscle mass and has been shown to predict survival and morbidity of patients on PD. This retrospective study evaluated the long-term constancy of 24-h excretion of creatinine in urine and spent peritoneal dialysate from patients with end-stage kidney disease treated by PD. Over a period of 2.5 years, the average value of total EX_{Cr} in the study population did not change significantly. However, in individuals there was a substantial variation of repeated measurements of total EX_{Cr} above or below its initial value. Approximately half of those studied repeatedly exhibited total EX_{Cr} above or below its initial value. Further studies are needed to evaluate changes, both increase and decrease, of EX_{Cr} in PD patients and the constancy of EX_{Cr} in patients on PD for more than 2.5 years.

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INTRODUCTION

An elevated serum creatinine concentration ($[Cr]_S$) is a predictor of prolonged survival in patients undergoing chronic peritoneal dialysis (PD)[1]. $[Cr]_S$ is largely a function of muscle mass and is widely regarded as a reliable indicator of somatic nutrition. Exercising muscles secrete a variety of myokines with beneficial effects on various organ systems, including anti-inflammatory effects[2]. Physical inactivity leads to altered pattern of myocyte secretion promoting obesity and atherogenesis[2]. Inactivity is prominent among patients treated by chronic dialysis. McIntyre *et al*[3] reported a tendency to muscle mass depletion in this patient group. However, a significant limitation of $[Cr]_S$ as an indicator of somatic nutrition is reliance on this parameter as the sole determinant of muscle mass. In the steady state, which is defined as equal rates of creatinine production and elimination, $[Cr]_S$ has two physiological determinants, the rate of production of creatinine (P_{Cr}) which is a function of muscle mass, and the rate of removal of creatinine from body fluids, which is expressed as creatinine clearance (C_{Cr}). This relation is expressed as $[Cr]_S = P_{Cr}/C_{Cr}$. Consequently, variations in C_{Cr} in patients on PD can result in variations in $[Cr]_S$ that are unrelated to muscle mass[4].

In the steady state, the total amount of creatinine excreted in spent PD dialysate plus urine over a certain time period (EX_{Cr} T) is in general a better index of muscle mass than $[Cr]_S$. Conditions in which EX_{Cr} T does not reflect muscle mass are addressed in the Discussion section of this report. EX_{Cr} T over 24 h was been proposed by Walser[5] as an index of somatic nutrition in the general adult population and has been evaluated in PD populations. Whereas high EX_{Cr} T values are

associated with favorable outcomes, including survival and continued success of PD[6,7], low values of EX_{Cr} T are associated with a high risk of peritonitis and PD catheter-related infections[8].

The lean body mass formula from creatinine production (LBM_{Cr}) in PD patients[9] takes into account EX_{Cr} T and creatinine eliminated though metabolic creatinine degradation (MCD), the second variable at a clearance of 0.038 L/kg[10]. MCD per 24-h is calculated as 0.038 × $[Cr]_S$ (mg/mL) × 10 × weight (kg). EX_{Cr} T is invariably the larger of the two determinants of LBM_{Cr}. For example, in a 53-year old PD patient who weighs 70 kg and has a $[Cr]_S$ value of 9.5 mg/dL, estimated MCD rate will be 253 mg/24-h. Applying a PD population-specific formula predicting EX_{Cr} T[11] to this illustrative example, average estimates of EX_{Cr} T, in mg/24-h, are 1062 if the patient is male and non-diabetic, 1023 if the patient is male and diabetic, 892 if the patient is female and non-diabetic and 852 if the patient is female and diabetic. High LBM_{Cr} values predict long survival of PD patients[12-14].

The short-term reproducibility of EX_{Cr} T in PD was studied by Lo and coauthors, who obtained two to four 24-h collections of urine and spent dialysate over a one-week interval from five patients undergoing PD[15]. These authors reported maximal variations of EX_{Cr} T from the mean ranging between 0.32% and 19.88%. The purpose of the present study was to investigate the reproducibility of EX_{Cr} T in patients on long-term PD. Changes in renal function or peritoneal transport characteristics will change the amount of creatinine removed through each route. However, regardless of such changes steady state long-term constancy of EX_{Cr} T is consistent with preservation of muscle mass in PD patients. In contrast, a progressive decrease in EX_{Cr} T during PD would indicate progressive loss of muscle mass and deterioration of somatic nutrition.

MATERIALS AND METHODS

We analyzed creatinine excretion data collected during routine clearance measurements for assessment of the adequacy of PD. Patients included in this study were followed in Albuquerque during the years 1992 to 2002. Only patients in whom the prescribed dose of PD did not change during the observation period were included in the study. Approximately 40% of the patients were receiving continuous ambulatory peritoneal dialysis (CAPD) with four or five daily exchanges and 2.0-L or 2.5-L fill volume. The remaining patients received nocturnal automatic PD with 8-10 L fill volume plus one or two daytime PD exchanges with 2.0 L fill volume. Serum ($[Cr]_S$) at the study differed from the preceding or following monthly value by < 0.30 mg/dL in all patients. None of the patients were receiving drugs causing increased creatinine production (*e.g.*, fenofibrate).

The focus of the study was on detecting a statistically significant decline in EX_{Cr} T. The minimal number of patients required to detect a 15% reduction in EX_{Cr} T over time was calculated by power analysis. For a simple power analysis, we considered repeated measurements at two points in time and assumed a correlation of 0.7 between these two samples and a standard deviation of EX_{Cr} T equal to 450 mg/24-h (see Tables in Results). The power and α value of the study were set at 80% and 0.05 respectively.

Between the sequential clearance studies we compared the following variables: Urine volume (V_U), drain volume (V_D), weekly Kt/V urea, weekly C_{Cr}, serum urea nitrogen level (SUN), $[Cr]_S$, EX_{Cr} in urine (EX_{Cr} U), EX_{Cr} in dialysate (EX_{Cr} D),and total creatinine excretion in urine plus dialysate (EX_{Cr} T).

Statistical analysis

Results are reported as mean ± SD. Statistical comparisons were carried out using the two-tailed paired *t* test for patients with two clearance studies and the repeated measures ANOVA for patients who had three or four clearance studies. Statistical analysis was performed using SAS version 9.4.

RESULTS

Power analysis computed a minimal sample size of 37 patients for detecting a 15% decline in EX_{Cr} T. A total of 166 PD patients who had been subjected to at least two clearance studies comprised the initial study group. Among these patients, 84 patients had three clearance studies and 44 patients had four clearance studies. Small number of patients, eight or less, underwent five or more studies. Consequently, this study includes patients who had two, three and four clearance studies.

Table 1 summarizes relevant features of the patients included in the report. There were no significant differences between the three subgroups in terms of the age of patients at the onset of PD, percent of males and females or percent of patients with end-stage renal disease secondary to diabetic nephropathy.

Table 2 compares variables related to creatinine excretion in patients with two clearance studies. Between the first and second clearance study V_U, total Kt/V urea, total C_{Cr}, and EX_{Cr} U decreased, $[Cr]_S$ and EX_{Cr} D increased, while V_D, SUN and EX_{Cr} T did not change significantly. Peritoneal C_{Cr} did not change while renal C_{Cr} decreased from the first to the second study. Average peritoneal (C_{Cr} P) and renal (C_{Cr} R) weekly C_{Cr}, expressed in L/1.73 m^2 throughout this report, values were as follows: C_{Cr} P 48.7 in the first and 49.5 in the second study; C_{Cr} R 29.1 in the first and 18.4 in the second study.

Table 3 compares variables in patients who were studied three times. V_U, total Kt/V urea, total C_{Cr} and EX_{Cr} U decreased progressively from the first to the third measurement, while EX_{Cr} T was significantly lower in the third study than in the first study. V_D and SUN did not change, while $[Cr]_S$ increased; however, the increasing trend in EX_{Cr} D did not reach statistical significance. Peritoneal C_{Cr} did not change while renal

Table 1 Patient characteristics *n* (%)

	Two clearance studies	Three clearance studies	Four clearance studies
Patient number	166	84	44
Age at onset of peritoneal dialysis, yr	52 ± 15	51 ± 16	51 ± 18
Male	94 (56.6)	46 (54.8)	26 (59.1)
Female	72 (43.4)	38 (45.2)	18 (40.9)
Diabetic nephropathy	73 (44.0)	36 (42.9)	17 (38.6)

Table 2 Creatinine excretion in patients with two studies

Variable	1st clearance study	2nd clearance study	*P* value
PD duration, mo	9.2 ± 15.2	17.4 ± 15.8	
VU, L/24-h	0.54 ± 0.63	0.40 ± 0.53	< 0.001
VD, L/24-h	11.3 ± 3.2	12.1 ± 3.6	NS
Kt/V urea, weekly	2.30 ± 0.62	2.12 ± 0.03	0.003
C_{Cr}, L/1.73 m^2, weekly	77.9 ± 32.1	67.9 ± 18.2	0.002
SUN, mg/dL	49.7 ± 15.1	49.4 ± 16.2	NS
$[Cr]_S$, mg/dL	9.1 ± 3.3	10.1 ± 3.4	0.001
EX_{Cr} U, mg/24-h	406 ± 337	286 ± 350	0.003
EX_{Cr} D, mg/24-h	680 ± 337	769 ± 390	< 0.001
EX_{Cr} T, mg/24-h	1087 ± 470	1055 ± 421	NS

PD: Peritoneal dialysis; NS: Not significant; VU: Urine volume; VD: Drained volume of spent dialysate; Kt/V urea: Fractional urea clearance, weekly; C_{Cr}: Weekly renal plus peritoneal creatinine clearance; SUN: Serum urea nitrogen; $[Cr]_S$: Serum creatinine concentration; EX_{Cr} D: Creatinine excretion in spent dialysate; EX_{Cr} U: Creatinine excretion in urine; EX_{Cr} T: Total creatinine excretion in urine plus dialysate.

C_{Cr} decreased progressively from the first to the third study. Average weekly C_{Cr} P and C_{Cr} R values were as follows: C_{Cr} P 50.5 in the first, 48.2 in the second and 49.7 in the third study; C_{Cr} R 28.8 in the first, 23.2 in the second and 18.3 L/1.73 m^2 in the thirst study.

Table 4 compares clearances and creatinine excretion parameters in patients who had four clearance studies. V_U, total Kt/V urea and total C_{Cr} decreased progressively from the first to the fourth determination. EX_{Cr} U decreased significantly between the first and third studies, but reached a stable mean between the third and fourth studies. $[Cr]_S$ increased progressively from the first to the third study; however, the mean values were not different between in the third and fourth studies. V_D and SUN were essentially the same in the four studies. EX_{Cr} D increased progressively from the first to the fourth study, whereas EX_{Cr} T did not change significantly throughout the study. Peritoneal C_{Cr} did not change while renal C_{Cr} decreased progressively from the first to the fourth study. Average weekly C_{Cr} P and C_{Cr} R values were as follows: C_{Cr} P 50.2 in the first, 47.4 in the second, 51.2 in the third and 49.7 in the fourth study; C_{Cr} R 27.3 in the first, 23.0 in the second, 17.3 in the thirst and 16.4 L/1.73 m^2 in the fourth study.

Table 5 shows the results (number and percent) of the second, third and fourth studies where EX_{Cr} T differed from the EX_{Cr} T of the first study by less than 15%. The same table also shows the number and percent of studies with EX_{Cr} T higher or lower than the EX_{Cr} T of the first study by 15% or more. In approximately half of the second, third and fourth studies EX_{Cr} T differed from the first study by less than 15%. In 25.0%-33.3% of the patients, EX_{Cr} T values in subsequent studies were higher than the EX_{Cr} T value found in the first study by more than 15%. In 19.1%-21.1% of the patients, EX_{Cr} T in subsequent studies was lower than the EX_{Cr} T in the first study by more than 15%.

Table 3 Creatinine excretion in patients with three studies

Variable	1st clearance study	2nd clearance study	3rd clearance study	*P* value
PD duration, mo	8.6 ± 7.8	16.8 ± 11.6	24.7 ± 16.3	
VU, L/24-h	0.58 ± 0.66	0.45 ± 0.59	0.38 ± 0.50	0.0001
VD, L/24-h	11.5 ± 4.0	11.8 ± 3.7	12.4 ± 3.7	NS
Kt/V urea, weekly	2.28 ± 0.65	2.14 ± 0.58	2.12 ± 0.63	0.0245
C_{Cr}, L/1.73 m^2, weekly	79.3 ± 35.6	71.4 ± 27.8	68.0 ± 26.9	0.0335
SUN, mg/dL	50.4 ± 18.5	49.5 ± 17.9	49.2 ± 19.2	NS
$[Cr]_S$, mg/dL	9.5 ± 3.5	9.8 ± 3.4	10.1 ± 3.3	0.0066
EX_{Cr} U, mg/24-h	418 ± 404	370 ± 425	286 ± 362	< 0.0001
EX_{Cr} D, mg/24-h	731 ± 379	767 ± 396	779 ± 382	NS[1]
EX_{Cr} T, mg/24-h	1149 ± 416	1137 ± 454	1065 ± 442	0.0087

[1]Statistical trend (P = 0.0895). PD: Peritoneal dialysis; NS: Not significant; VU: Urine volume; VD: Drained volume of spent dialysate; Kt/V urea: Fractional urea clearance, weekly; C_{Cr}: Weekly renal plus peritoneal creatinine clearance; SUN: Serum urea nitrogen; $[Cr]_S$: Serum creatinine concentration; EX_{Cr} D: Creatinine excretion in spent dialysate; EX_{Cr} U: Creatinine excretion in urine; EX_{Cr} T: Total creatinine excretion in urine plus dialysate.

DISCUSSION

This study had two important findings: First the mean EX_{Cr} T value did not change significantly in 2.5 years of follow-up of patients who were on the same PD schedule for the duration of the study, with the exception of a lower mean EX_{Cr} T in the third study than in the first study in EX_{Cr} data analyzed thrice. The constancy of the mean EX_{Cr} T was maintained despite a progressive decrease in urinary volume, urinary C_{Cr} and urinary EX_{Cr}. Increases in peritoneal EX_{Cr} associated with parallel rises in $[Cr]_S$ offset the declines in renal EX_{Cr}. Second, in about half of the patients, individual values of EX_{Cr} T varied substantially in clearance studies following the initial study. These findings have important clinical implications.

The finding of unchanged EX_{Cr} T suggests that the muscle mass of the average patient who remains on PD for 2.5 years is preserved. This observation points to stable creatinine production, and preserved muscle mass, as favorable predictors of outcomes of PD; however, this issue will require further investigation. The finding of great variation of individual EX_{Cr} T values on repeated measurements should prompt investigation of the factors affecting EX_{Cr} T in PD in addition to changes

Table 4 Creatinine excretion in patients with four clearance studies

Variable	1st clearance study	2nd clearance study	3rd clearance study	4th clearance study	*P* value
PD duration, mo	8.1 ± 12.6	16.5 ± 4.4	24.5 ± 16.3	31.9 ± 16.8	
VU, L/24-h	0.54 ± 0.55	0.41 ± 0.49	0.33 ± 0.40	0.29 ± 0.42	< 0.0001
VD, L/24-h	11.8 ± 3.9	12.2 ± 3.6	12.2 ± 3.5	12.5 ± 3.2	NS
Kt/V urea, weekly	2.27 ± 0.65	2.15 ± 0.56	2.13 ± 0.54	2.10 ± 0.55	0.0356
C_{Cr}, L/1.73 m^2, weekly	77.5 ± 29.7	70.4 ± 28.5	68.5 ± 25.7	66.1 ± 22.1	0.0238
SUN, mg/dL	49.8 ± 16.7	49.5 ± 15.4	49.2 ± 15.3	49.0 ± 13.5	NS
$[Cr]_S$, mg/dL	9.8 ± 3.6	10.2 ± 3.7	10.8 ± 3.8	10.8 ± 3.6	0.0009
EX_{Cr} U, mg/24-h	411 ± 438	382 ± 460	272 ± 345	282 ± 481	0.0011
EX_{Cr} D, mg/24-h	755 ± 406	788 ± 424	808 ± 438	853 ± 398	0.0021
EX_{Cr} T, mg/24-h	1166 ± 440	1170 ± 495	1080 ± 455	1135 ± 521	NS

PD: Peritoneal dialysis; NS: Not significant; VU: Urine volume; VD: Drained volume of spent dialysate; Kt/V urea: Fractional urea clearance, weekly; C_{Cr}: Weekly renal plus peritoneal creatinine clearance; SUN: Serum urea nitrogen; $[Cr]_S$: Serum creatinine concentration; EX_{Cr} D: Creatinine excretion in spent dialysate; EX_{Cr} U: Creatinine excretion in urine; EX_{Cr} T: Total creatinine excretion in urine plus dialysate.

Table 5 Number (percent) of studies with creatinine excretion deviating from baseline by < 15% and ≥ 15%

Study	< 15% from the 1st study	≥ 15% above the 1st study	≥ 15% below the 1st study
Second	90 (54.2%)	41 (24.7%)	35 (21.1%)
Third	40 (47.6%)	28 (33.3%)	16 (19.1%)
Fourth	24 (54.5%)	11 (25.0%)	9 (20.5%)

in the muscle mass.

One factor that can affect EX_{Cr} T is a change in total C_{Cr}. Mitch and Walser computed a "metabolic" C_{Cr} equal to 0.038 L/kg per 24-h in patients with renal failure mediated primarily by creatinine elimination through the gastrointestinal tract[16]. As $[Cr]_S$ levels increase progressively in advancing renal failure, the amount of creatinine removed through the metabolic-route increases progressively with a concomitant decrease in the measured renal EX_{Cr}[16].

Large increases in total C_{Cr} in PD patients lead in the steady state to drop in $[Cr]_S$ and in creatinine removal by the "metabolic" route and increase in Ex_{Cr} T. In a previous study, we noted an increase in EX_{Cr} T in PD patients whose measured total (peritoneal plus renal) C_{Cr} was increased, with proportional decrease in $[Cr]_S$, following prescribed increases in the PD dose[17]. This was the reason for including in the present study only patients with unchanged PD schedules. No effect of the decrease in total C_{Cr} through loss of renal function on EX_{Cr} T was seen in this study even when total C_{Cr} decreased by 11.4 L/1.73 m^2 weekly, on the average, between the first and fourth measurements (Table 4). We suggest that the increase in the amount of creatinine removed by the metabolic route due to the rise in $[Cr]_S$ between these two measurements was too small to be detected by our statistical analysis. On average, $[Cr]_S$ rose by 1.0 mg/dL between the first and fourth clearance study (Table 4). With this degree of increase in $[Cr]_S$, the rise in the amount of creatinine removed through the metabolic route at a C_{Cr} of 0.038 L/kg per 24-h would be only 26.6 mg/24-h in an individual weighing 70 kg.

Creatinine is formed by non-enzymatic breakdown of creatine-phosphate. Variations in the rate of creatine-phosphate conversion to creatinine may cause changes in EX_{Cr} T that are independent of changes in muscle mass. Neuromuscular diseases[18] and the stage of recovery from protein malnutrition[19] are examples of conditions characterized by abnormal creatine metabolism which leads to dissociation between creatinine production and muscle mass. In addition, neuromuscular diseases affect creatinine production and excretion through their effect on muscle mass homeostasis. The loss of muscle mass secondary to chronic neuromuscular disease is one of the major causes of decreases in creatinine production and EX_{Cr} T. Acute muscular disease, (*e.g.*, rhabdomyolysis) however, increases creatinine production. Rhabdomyolysis can result from disease, poisons and medications exemplified by lipid-lowering agents[20]. Other conditions causing increases in creatinine production and EX_{Cr} T include pregnancy[21], consumption of meat and intense exercise[22].

Circumstances that raise EX_{Cr} T without affecting creatinine production include errors in the collection of urine and spent dialysate and the presence of a non-steady state. Non-steady state following a rapid rise in C_{Cr} will increase EX_{Cr} T and decrease $[Cr]_S$. A hemodialysis session represents such a non-steady state condition. PD patients, who are non-compliant with their PD prescription and resume the prescribed PD schedule on the day of a clearance study will manifest a similar non-steady state. A high value of measured EX_{Cr} T over the EX_{Cr} T predicted by the Cockroft-Gault formula[23] (M/P_{Cr}) was proposed as a means of identifying non-compliance in PD[24]. Although some

studies supported the use of the M/P_{Cr} ratio as a means of detecting PD non-compliance[25,26], several reports confirmed that the sensitivity of this test is poor[27-32]. Nevertheless, noncompliance will invariably increase EX_{Cr} T on the first day of resumption of the prescribed PD schedule[28] and can be an important cause of the variation of EX_{Cr} T.

Conditions that can potentially lead to low EX_{Cr} T values include decreased production of creatinine, urine and dialysate collection errors, and intercurrent acute illnesses. This last category has not been studied adequately in PD patients. In acute illness, creatinine production could be temporally increased because of muscle disease or decreased because of loss of muscle mass. In one study, PD-associated peritonitis with routine course resulted in a 2.3% drop in body weight and 7.8% drop in $[Cr]_S$, while peritonitis with a protracted course resulted in a 7.2% drop in body weight and 25.0% drop in $[Cr]_S$[33]. These findings suggest a loss of muscle mass proportional to the duration of peritonitis. However, an increase in peritoneal C_{Cr} secondary to peritoneal membrane inflammation could also cause a drop in $[Cr]_S$. EX_{Cr} data, which would allow differentiation between a rise in C_{Cr} and a loss of muscle mass as the cause of the decrease in $[Cr]_S$ were not provided in this study. The effects of acute illness on EX_{Cr} in PD will need further studies.

A final consequence of all the aforementioned influences on EX_{Cr} T is their effect on the estimation of LBM_{Cr}. Two studies reported agreement between LBM_{Cr} and estimation of lean body mass by research methodologies[34,35]. Another study suggested that determination of lean body mass as LBM_{Cr} has advantages over its determination by bioimpedance or dual energy X-ray absorptiometry in overhydrated PD patients[36]. However, several studies have reported substantial differences between LBM_{Cr} and other methods used to assess muscle mass and between LBM_{Cr} and other indices of nutrition in PD patients[35,37-42]. Nevertheless, one of these studies did support the monitoring of EX_{Cr} T as a means of assessing changes in muscle mass[37].

Our study has limitations: First, selection bias could have led to the finding of stable creatinine excretion with stable patients remaining on PD for longer time. Related to this limitation, clinical information and data on other indices of nutrition associated with the observed changes in EX_{Cr} T were not available for analysis. Second, the data available to us do not allow us to address whether any of the known determinants of creatinine excretion in patients treated by PD (body weight, age, gender, and diabetic status) can predict a decrease or increase in their EX_{Cr} T. Finally, monitoring of EX_{Cr} T beyond 2.5 years after initiation of PD was not performed because of the small number of such subjects. Future studies should address these limitations.

In conclusion, average EX_{Cr} T remains stable for up to 2.5 years in patients who are maintained on the same PD schedule, despite a progressive loss of residual renal function which causes a progressive decline in urinary flow rate, C_{Cr} and EX_{Cr}. This finding suggests that the muscle mass of the average patient who remains on PD during this same time period is preserved. However, many patients exhibit substantial variability of EX_{Cr} T in sequential measurements. Both increases and decreases in EX_{Cr} T of individual patients managed by PD call for a systematic search for the conditions responsible for these changes. Further studies are also needed to evaluate the stability of EX_{Cr} T beyond 2.5 years of PD and the potential associations of changes in EX_{Cr} T with clinical outcomes and other indices of nutrition.

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COMMENTS

Background

In the steady state, defined as equal rates of production and removal, creatinine excretion reflects muscle mass. Loss of muscle mass has adverse effects on the outcomes of patients with chronic diseases, including patients with end-stage kidney disease treated by peritoneal dialysis (PD). High levels of creatinine excretion are associated with favorable outcomes in this patient population. The prevalence of adverse influences (*e.g.*, inactivity, chronic inflammatory state) in PD populations suggests loss of muscle mass in long-term PD. Repeated measurement of creatinine excretion in patients on long-term PD, which represents a steady state, provide a means of monitoring muscle mass.

Research frontiers

Muscle mass can be evaluated by several research methods. These methods require expenses and added expertise of the research personnel and, therefore, are not suitable for routine monitoring of PD populations.

Innovations and breakthroughs

Repeated measuring of total excretion of creatinine in spent peritoneal dialysate and urine offers a way of monitoring muscle mass in PD patients. Creatinine excretion measurements have been performed as part of monitoring adequacy of azotemic indices removal in PD. Comparison of subsequent creatinine excretion measurements to the first measurement, as used in this study, is simple and does not require added expenses.

Applications

The methodology explored in this report is appropriate for monitoring patients on long-term PD and for evaluating interventions (*e.g.*, exercise, diet) directed towards preserving or improving muscle mass in these patients.

Terminology

The following abbreviations express the technique for monitoring creatinine excretion in PD: Ex_{Cr} U = urinary creatinine excretion, mg/24-h; Ex_{Cr} D = creatinine excretion in spent peritoneal dialysate, mg/24h; Ex_{Cr} T = Ex_{Cr} U + Ex_{Cr} D.

Peer-review

In this manuscript, the authors describe the reproducibility of serial creatinine excretion measurements in PD patients. They concluded that the average total creatinine excretion in urine plus dialysate (EX_{Cr} T) remains stable for up to 2.5

years in patients who are maintained on the same PD schedule, despite the progressive loss of residual renal function which causes a progressive decline in the urinary flow rate, renal plus peritoneal creatinine clearance (Ccr), and creatinine excretion (EXcr). They also suggested that the muscle mass was preserved in the average patient who remained on PD during this time period. This paper is clinically interesting.

REFERENCES

1 **Park J**, Mehrotra R, Rhee CM, Molnar MZ, Lukowsky LR, Patel SS, Nissenson AR, Kopple JD, Kovesdy CP, Kalantar-Zadeh K. Serum creatinine level, a surrogate of muscle mass, predicts mortality in peritoneal dialysis patients. *Nephrol Dial Transplant* 2013; **28**: 2146-2155 [PMID: 23743018 DOI: 10.1093/ndt/gft213]

2 **Pedersen BK**, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol* 2012; **8**: 457-465 [PMID: 22473333 DOI: 10.1038/nrendo.2012.49]

3 **McIntyre CW**, Selby NM, Sigrist M, Pearce LE, Mercer TH, Naish PF. Patients receiving maintenance dialysis have more severe functionally significant skeletal muscle wasting than patients with dialysis-independent chronic kidney disease. *Nephrol Dial Transplant* 2006; **21**: 2210-2216 [PMID: 16504974 DOI: 10.1093/ndt/gfl064]

4 **Tzamaloukas AH**, Murata GH, Piraino B, Rao P, Bernardini J, Malhotra D, Oreopoulos DG. Peritoneal urea and creatinine clearances in continuous peritoneal dialysis patients with different types of peritoneal solute transport. *Kidney Int* 1998; **53**: 1405-1411 [PMID: 9573559 DOI: 10.1046/j.1523-1755.1998.00896.x]

5 **Walser M**. Creatinine excretion as a measure of protein nutrition in adults of varying age. *JPEN J Parenter Enteral Nutr* 1987; **11**: 73S-78S [PMID: 3312696 DOI: 10.1177/014860718701100510]

6 **Jager KJ**, Merkus MP, Dekker FW, Boeschoten EW, Tijssen JG, Stevens P, Bos WJ, Krediet RT. Mortality and technique failure in patients starting chronic peritoneal dialysis: results of The Netherlands Cooperative Study on the Adequacy of Dialysis. NECOSAD Study Group. *Kidney Int* 1999; **55**: 1476-1485 [PMID: 10201013 DOI: 10.1046/j.1523-1755.1999.00353.x]

7 **Perez RA**, Blake PG, Spanner E, Patel M, McMurray S, Heidenheim P, Lindsay RM. High creatinine excretion ratio predicts a good outcome in peritoneal dialysis patients. *Am J Kidney Dis* 2000; **36**: 362-367 [PMID: 10922315 DOI: 10.053/ajkd.2000.8987]

8 **Wu CH**, Huang CC, Wu MS, Yang CW, Huang JY, Fang JT, Leu ML. Total creatinine appearance as indicator of risk of infectious complication in peritoneal dialysis. *Adv Perit Dial* 2000; **16**: 219-222 [PMID: 11045298]

9 **Keshaviah PR**, Nolph KD, Moore HL, Prowant B, Emerson PF, Meyer M, Twardowski ZJ, Khanna R, Ponferrada L, Collins A. Lean body mass estimation by creatinine kinetics. *J Am Soc Nephrol* 1994; **4**: 1475-1485 [PMID: 8161729]

10 **Mitch WE**, Collier VU, Walser M. Creatinine metabolism in chronic renal failure. *Clin Sci* (Lond) 1980; **58**: 327-335 [PMID: 7379458 DOI: 10.1042/cs0580327]

11 **Tzamaloukas AH**, Murata GH. A population-specific formula predicting creatinine excretion in continuous peritoneal dialysis. *Perit Dial Int* 2002; **22**: 67-72 [PMID: 11929147]

12 **Chung SH**, Lindholm B, Lee HB. Influence of initial nutritional status on continuous ambulatory peritoneal dialysis patient survival. *Perit Dial Int* 2000; **20**: 19-26 [PMID: 10716579]

13 **Dong J**, Li YJ, Lu XH, Gan HP, Zuo L, Wang HY. Correlations of lean body mass with nutritional indicators and mortality in patients on peritoneal dialysis. *Kidney Int* 2008; **73**: 334-340 [PMID: 18033246 DOI: 10.1038/sj.ki.5002644]

14 **Huang JW**, Lien YC, Wu HY, Yen CJ, Pan CC, Hung TW, Su CT, Chiang CK, Cheng HT, Hung KY. Lean body mass predicts long-term survival in Chinese patients on peritoneal dialysis. *PLoS One* 2013; **8**: e54976 [PMID: 23372806 DOI: 10.1371/journal.pone.0054976]

15 **Lo WK**, Prowant BF, Gamboa SB, Moore HL, Nolph KD. How reproducible is daily creatinine recovery in chronic peritoneal dialysis? *Perit Dial Int* 1994; **14**: 286-288

16 **Mitch WE**, Walser M. A proposed mechanism for reduced creatinine excretion in severe chronic renal failure. *Nephron* 1978; **21**: 248-254 [PMID: 714198 DOI: 10.1159/000181400]

17 **Tzamaloukas AH**, Braun M, Malhotra D, Murata GH. Estimated versus predicted creatinine generation as an indicator of compliance with the prescribed dose of continuous peritoneal dialysis. *Int J Artif Organs* 1996; **19**: 151-155 [PMID: 8675358]

18 **Fitch CD**, Sinton DW. A study of creatine metabolism in diseases causing muscle wasting. *J Clin Invest* 1964; **43**: 444-452 [PMID: 14135495 DOI: 10.1172/JCI104929]

19 **Picou D**, Reeds PJ, Jackson A, Poulter N. The measurement of muscle mass in children using [15N]creatine. *Pediatr Res* 1976; **10**: 184-188 [PMID: 765941 DOI: 10.1203/00006450-197603000-00008]

20 **Xu Z**, Gabaldon D, Wiggins B, Rondon-Berrios H, VanderJagt DJ, Tzamaloukas AH. Increase in serum creatinine in a patient on continuous peritoneal dialysis: potential mechanisms and management. *Adv Perit Dial* 2012; **28**: 32-36 [PMID: 23311210]

21 **Lew SQ**, Watson JA. Urea and creatinine generation and removal in a pregnant patient receiving peritoneal dialysis. *Adv Perit Dial* 1992; **8**: 131-135 [PMID: 1361769]

22 **Bleiler RE**, Schedl HP. Creatinine excretion: variability and relationships to diet and body size. *J Lab Clin Med* 1962; **59**: 945-955 [PMID: 13869979]

23 **Cockcroft DW**, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31-41 [PMID: 1244564 DOI: 10.1159/000180580]

24 **Keen M**, Lipps B, Gotch F. The measured creatinine generation rate in CAPD suggests only 78% of prescribed dialysis is delivered. *Adv Perit Dial* 1993; **9**: 73-75 [PMID: 8105967]

25 **Warren PJ**, Brandes JC. Compliance with the peritoneal dialysis prescription is poor. *J Am Soc Nephrol* 1994; **4**: 1627-1629 [PMID: 8025237]

26 **Nolph KD**, Twardowski ZJ, Khanna R, Moore HL, Prowant BF. Predicted and measured daily creatinine production in CAPD: identifying noncompliance. *Perit Dial Int* 1995; **15**: 22-25 [PMID: 7734556]

27 **Fischer A**, Bock A, Brunner FP. Three consecutive day collection of dialysate and urine to identify non-compliance in CAPD patients. *Nephrol Dial Transplant* 1997; **12**: 570-573 [PMID: 9075143 DOI: 10.1093/ndt/12.3.570]

28 **Tzamaloukas AH**. Pharmacokinetic analysis of creatinine generation discrepancy as an index of noncompliance in CAPD. *Adv Perit Dial* 1996; **12**: 61-65 [PMID: 8865875]

29 **Blake PG**, Spanner E, McMurray S, Lindsay RM, Ferguson E. Comparison of measured and predicted creatinine excretion is an unreliable index of compliance in PD patients. *Perit Dial Int* 1996; **16**: 147-153 [PMID: 9147548]

30 **Burkart JM**, Bleyer AJ, Jordan JR, Zeigler NC. An elevated ratio of measured to predicted creatinine production in CAPD patients is not a sensitive predictor of noncompliance with the dialysis prescription. *Perit Dial Int* 1996; **16**: 142-146 [PMID: 9147547]

31 **Bernardini J**, Piraino B. Measuring compliance with prescribed exchanges in CAPD and CCPD patients. *Perit Dial Int* 1997; **17**: 338-342 [PMID: 9284459]

32 **Szeto CC**, Lai KN, Wong TY, Law MC, Li PK. Measured-to-predicted creatinine generation ratio increases with time and decline in residual renal function in continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 1999; **34**: 235-241 [PMID: 10430968 DOI: 10.1016/S0272-6386(99)70349-5]

33 **Fox L**, Tzamaloukas AH, Murata GH. Metabolic differences between persistent and routine peritonitis in CAPD. *Adv Perit Dial* 1992; **8**: 346-350 [PMID: 1361820]

34 **Lo WK**, Prowant BF, Moore HL, Gamboa SB, Nolph KD, Flynn MA, Londeree B, Keshaviah P, Emerson P. Comparison of different measurements of lean body mass in normal individuals and in chronic peritoneal dialysis patients. *Am J Kidney Dis* 1994; **23**: 74-85 [PMID: 8285201 DOI: 10.1016/S0272-6386(12)80815-8]

35 **Negri AL**, Veron D, Fraga A, Arrizurieta E, Zucchini A, Zanchetta JR. Lean body mass estimation by densitometry and creatinine kinetics in chronic peritoneal dialysis patients. *Perit Dial Int* 2000; **20**: 575-576 [PMID: 11117251]

36 **Bhatla B**, Moore H, Emerson P, Keshaviah P, Prowant B, Nolph KD, Singh A. Lean body mass estimation by creatinine kinetics, bioimpedance, and dual energy x-ray absorptiometry in patients

on continuous ambulatory peritoneal dialysis. *ASAIO J* 1995; **41**: M442-M446 [PMID: 8573842 DOI: 10.1097/00002480-199507000-00048]

37 **Nielsen PK**, Ladefoged J, Olgaard K. Lean body mass by Dual Energy X-ray Absorptiometry (DEXA) and by urine and dialysate creatinine recovery in CAPD and pre-dialysis patients compared to normal subjects. *Adv Perit Dial* 1994; **10**: 99-103 [PMID: 7999874]

38 **de Fijter WM**, de Fijter CW, Oe PL, ter Wee PM, Donker AJ. Assessment of total body water and lean body mass from anthropometry, Watson formula, creatinine kinetics, and body electrical impedance compared with antipyrine kinetics in peritoneal dialysis patients. *Nephrol Dial Transplant* 1997; **12**: 151-156 [PMID: 9027791 DOI: 10.1093/ndt/12.1.151]

39 **Johansson AC**, Attman PO, Haraldsson B. Creatinine generation rate and lean body mass: a critical analysis in peritoneal dialysis patients. *Kidney Int* 1997; **51**: 855-859 [PMID: 9067921 DOI: 10.1038/ki.1997.120]

40 **Szeto CC**, Kong J, Wu AK, Wong TY, Wang AY, Li PK. The role of lean body mass as a nutritional index in Chinese peritoneal dialysis patients--comparison of creatinine kinetics method and anthropometric method. *Perit Dial Int* 2000; **20**: 708-714 [PMID: 11216564]

41 **Tzamaloukas AH**, Murata GH. Lean body mass calculation by creatinine kinetics in CAPD. Is it only a measure of somatic nutrition? *Perit Dial Int* 2000; **20**: 351-352 [PMID: 10898059]

42 **Negri AL**, Barone R, Veron D, Fraga A, Arrizurieta E, Zucchini A, Zanchetta JR. Lean mass estimation by creatinine kinetics and dual-energy x-ray absorptiometry in peritoneal dialysis. *Nephron Clin Pract* 2003; **95**: c9-c14 [PMID: 14520016 DOI: 10.1159/000073013]

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ORIGINAL ARTICLE

Observational Study

Exercise-induced albuminuria and circadian blood pressure abnormalities in type 2 diabetes

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Abstract

AIM

To investigate the relationship between circadian variations in blood pressure (BP) and albuminuria at rest, and during exercise in non-hypertensive type 2 diabetes (T2D) patients.

METHODS

We conducted a cross-sectional study in well controlled T2D patients, non-hypertensive, without clinical proteinuria and normal creatinine clearance. In each participant, we recorded the BP using ambulatory blood

pressure monitoring (ABPM) for 24-h, and albuminuria at rest and after a standardized treadmill exercise.

RESULTS

We enrolled 27 type 2 patients with a median age of 52; and a mean duration of diabetes and HbA1c of 3.6 ± 0.8 years and 6.3% ± 0.5% respectively. Using a 24-h ABPM, we recorded a mean diurnal systolic blood pressure (SBP) of 128 ± 17 mmHg *vs* nocturnal of 123 ± 19 mmHg (P = 0.004), and mean diurnal diastolic blood pressure (DBP) of 83 ± 11 mmHg *vs* nocturnal 78 ± 14 mmHg (P = 0.002). There was a significant difference between albuminuria at rest [median = 23 mg, interquartile range (IQR) = 10-51] and after exercise (median = 35 mg, IQR = 23-80, P < 0.001). Patients with exercise induced albuminuria had an increase in nocturnal BP values on all three components (128 mmHg *vs* 110 mmHg, P = 0.03 for SBP; 83 mmHg *vs* 66 mmHg, P = 0.04; 106 *vs* 83, P = 0.02 for mean arterial pressure), as well as albuminuric patients at rest. Moreover, exercise induced albuminuria detect a less increase in nocturnal DBP (83 *vs* 86, P = 0.03) than resting albuminuria.

CONCLUSION

Exercise induced albuminuria is associated with an increase in nocturnal BP values in T2D patients.

Key words: Albuminuria; Ambulatory measurement of blood pressure; Exercise; Type 2 diabetes mellitus

Core tip: Many studies have reported association between abnormalities in ambulatory blood pressure monitoring (ABPM) and albuminuria at rest, or the link between exercise induced albuminuria and future development of microalbuminuria. However, the relationship between exercise-induced albuminuria and nocturnal abnormalities of BP on ABPM have not been investigate. The current study aimed to investigate the potential relationship between exercise-induced albuminuria and circadian variations in BP in a sub-Saharan type 2 diabetes population. We found that exercise-induced albuminuria is associated with less important nocturnal abnormalities of BP than resting albuminuria suggesting that exercise-induced albuminuria be used to detect early abnormalities of nighttime BP.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the leading cause of chronic kidney disease (CKD) worldwide[1,2]. It represents with hypertension - the most common cause of end-stage renal disease (ESRD); affecting at least one-third of patients starting chronic dialysis worldwide, and represents the main cause of mortality in diabetes patients[3]. Early detection and intervention in diabetic nephropathy can help to slow loss in renal function, prevent complications, and decrease cardiovascular events; thereby improving survival and quality of life in T2DM patients[3]. As the global incidence of T2D continues to rise, controlling diabetic nephropathy is becoming a health priority. Fifty years ago, the development of assays for detection of microalbuminuria (MA) revolutionized diabetes management. Microalbuminuria, also called moderate albuminuria (urinary albumin excretion ⩾ 30 mg/24 h but less than 300 mg/24 h), measured at rest became the earliest marker of diabetic nephropathy, and was thought to predict overt diabetic nephropathy in 80% of patients[4]. However, recent evidence have shown that only 30% of patients with microalbuminuria will develop overt diabetic nephropathy[5]. Moreover, screening with albumin excretion rate alone would miss 20% of progressive disease[6]. These evidences suggest that a need for methods for early detection of diabetic nephropathy. Physiologically, it is well known that patients with subclinical nocturnal blood pressure (BP) abnormalities are prone to renal insult and hence at risk of developing microalbuminuria[7]. So, non-dipping nocturnal BP pattern defined as a less than 10% decrease in nocturnal BP, increase the risk of organ damage such as microalbuminuria[7]. In the other hand, exercise-induced albuminuria has been proposed as a long term predictive factor of overt diabetic nephropathy, but there is still a dearth of evidence on its usefulness in routine screening[8]. We sought to explore a possible relationship between resting and exercise-induced albuminuria, and circadian variations in BP levels on 24-h ambulatory blood pressure monitoring (ABPM).

MATERIALS AND METHODS

Setting and study population

This study was carried out at the National Obesity Center of the Yaoundé Central Hospital, a reference diabetes center in this area. Eligible participants were: Type 2 diabetics, according to the WHO definition[9]; without clinical proteinuria (⩽ 30 mg/dL), with clinical BP less than 140/90 mmHg, HbA1c less than 7%, an estimated glomerular filtration rate (eGFR) ⩾ 60 mL/min per square meter using the MDRD formula which was found to be the most accurate formula for sub-Saharan African diabetic patients[10]. We excluded patients working during the night, those receiving drugs for hypertension or any other drugs able to modify albuminuria, patients with contraindication to exercise or presenting signs of urinary tract infection. Patients having a fever and pregnant women were also

excluded. All patient included were on oral anti-diabetic treatment.

Study design and duration: This was a cross sectional study conducted from February to June 2015 a period of five months.

Procedure and investigations

This study was conducted to investigate the relationship between exercise-induced albuminuria and early diabetic nephropathy assessed by nocturnal elevation of ABPM. To this end, albuminuria was measured at rest for microalbuminuria, and after a moderate and standardized exercise for exercise induced albuminuria. Then comparison between patients were planned to shows that exercise induced albuminuria is similar or even higher to microalbuminuria at rest for the detection of abnormal nocturnal BP patterns.

All the patients attending the clinic were assessed, and eligible patients were invited to participate to the study. The procedure was comprised of an inclusion visit and three exploratory visits. Within the two weeks following an information visit, a careful clinical exam including BP measurement, urinary dipstick exam, and resting electrocardiogram were performed on eligible patients. The sample size was estimated using Withley *et al*[11] formula: $n = (2/d^2) \times Cp$, *power.*

The primary outcome was a significant difference of at least 10 mmHg of SBP and/or DBP in patients having exercise induced albuminuria. The standardized difference for BP in T2DM patients used was set at 10 mmHg (UKPDS). Considering α = 5% and β = 10%, with a statistical power of 90%, the minimal size was 11 patients.

The standardized difference, d = (expected difference)/(standard deviation): D = 10/10 = 1.

$N = (2/d^2) \times Cp$, power where Cp, power is a constant defined by the chosen value of the statistical power and the value p. This constant is available in statistical tables[11] $C_{0.05}$, 90% = 10.5.

Thus the minimum size of the sample is: $n = 2/(1^2) \times 10.5$.

n = 10.5 rounded to 11 subjects.

To improve statistical power, we increased the study sample at 30 patients. Patients were screened clinically for eligibility with three clinical BP measurements, a urinary dipstick, resting electrocardiogram and a blood sample for creatinine estimation and creatinine clearance calculation. Of the 30 eligible patients invited, 3 were excluded because they had signs of urinary tract infection on dipstick.

Participants were invited to arrive at the hospital between 8:00 and 10:00 am for all exploratory visits. On arrival, participants were maintained in a sitting position for at least five minutes before BP measurement. Three serial BP measurements taken in the sitting position were obtained from non-dominant arm placed at the level of the heart, using adults cuffs (32-42 cm) adapted to an automated sphygmomanometer Omron HEM-705 CP (Omron Corporation, Tokyo, Japan). The average of the three measurements was used for all analyses. Weight was measured in light clothed subjects to the nearest 0.5 kg with a mechanical scale, while height was measured in an upright position to the nearest 0.5 cm. The body mass index (BMI in kg/m²) was calculated as weight (kg)/[height (m) × height (m)]. Waist circumference was measured horizontally, midway between the lower rib margin and the iliac crest with a measuring tape. Macro or clinical albuminuria was assessed by dipstick of spot urine, and considered positive for at least 1+ (< 30 mg/dL). Electrocardiography was done with the CardiMax FX-7302 electrocardiograph (Fukuda Den Shi, Tokyo, Japan).

Twenty-four hours BP measurement

Twenty-four hour BP was measured by a portable, light weight monitor device i-mapa CE 004 1.1 TM (High-tech Medical St Louis, Paris). The purpose of the examination and practical modalities including: the measurement procedure and related constraints were explained to the participants. The device was then connected to an adult cuff, tested and calibrated. The practical procedure consisted of two major steps.

Programming the measurement over 24 h with patient information: For this purpose, demographic information and anthropometric measurements were entered into the i-mapa software, and then the medical history was recorded, allowing us to have an electronic medical record of the patient. Then a measurement protocol was selected from those proposed by the software and a 24-h measurement cycle was activated.

Installation of the measurement monitor on the patient: Then, the standard cuff was placed around the patient's arm 2.5 cm above the antecubital dimple in direct contact with the skin and the case fixed at the level of the waist. The patient performs some movements to ensure comfort. After the patient had put on his clothes, a manual measurement was made, which enabled the selected measurement protocol to start and ensure functionality of the device. Thereafter, the patient returned to his daily activities with instructions concerning the handling of the device, and a paper where he/her was thought to notice all particular activity during the day such as medication taken with the hour, any important emotional or physical changing (diary) and the appointment was made the next day at the same time. The patient brought us back the monitor 24 h later. Once arrived, the device was turned off and unplugged. The measurements made were then transferred to a computer using a Bluetooth key enabling communication between the software and the monitor.

Reading the 24-h measurement: Readings were obtained automatically at 15-mn intervals during the

day time define from 07:00 to 22:00 and twice an hour from 22:00 to 07:00. This interval was set using a fix clock time but control with a personal diary for each patient.

The protocol used for physical exertion was set up by our research team. It consisted of a simple step at a constant speed of 1 m/s for 30 min with a slope set at 5% with the aim of achieving a sub-maximal physical effort, resulting in a rise in the heart rate to 50%-70% of the patient's maximum HR. For each participant, a complete emptying of the bladder was performed 10 min prior to exercise. In the preceding days, he was recommended to continue to carry out his usual activities, avoid moderate to vigorous physical activity 48 h before the start of each phase of investigations, namely: Jogging, rapid walking for 1 h, and also avoid taking medications that may modify the evaluated parameters such as angiotensin converting enzyme inhibitors.

The exercise was carried out under medical supervision. For this phase, the volunteer was invited to the exploration room of our research laboratory to the National Obesity Center of the Yaoundé central hospital between 08:00 and 10:00 in the morning. Upon arrival, blood glucose was performed; the data sheet was revisited and updated. The patient was driven and installed in the exercise room. The treadmill was then switched on with accessories such as the heart rate monitor. A urine and blood sample was collected at rest and preserved before the beginning of the exercise. The patient was then placed on the treadmill after having installed the heart rate monitor on the chest, the electrodes of the heart being in direct contact with the skin and safety belt installation. Continuous heart rate (HR) recording allowed us to ensure that the patient remained within the limits set for our study 50%-70% of maximal HR. At the end of the exercise, the patient was placed in an armchair to recover and received water for rehydration and to promote diuresis.

Urinary albumin excretion was calculate using albumin to creatinine ratio to reduce effect of urinary concentration after exercise on albuminuria and expressed in mg/g. First void urine collection was used for rest albuminuria and a random sample urine was collected within the 30 mn following physical exercise to measure exercise-induced albuminuria. Retinopathy was assessed by fundoscopy and creatinine measured using modified Jaffe kinetic reaction with colorimetric methods. Albuminuria was measured by turbidimetry and others biochemical parameters using an automatic spectrophotometer.

Statistical analysis

Data acquisition was done by Epi-data3.1 software and statistical analysis was performed using Statistical Package for Social Science (SPSS) version 21.0 for Windows (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp.) and Stata 12.0 software. Continuous variables are expressed as median (interquartile range = IQR) or mean ± SD where appropriate, and categorical variables as count (percentage). The Spearman rank coefficient was used to test correlations. The χ^2 test, Mann-Whitney rank sum test were used to test associations between qualitative variables and difference between two respectively. A P value < 0.05 was considered statistically significant.

RESULTS

General characteristics

We included 27 patients (18 males) with a median age of 52 (IQR = 36-56) years, a mean duration of diabetes of 3.6 ± 0.8 years and a mean HbA1c of 6.3% ± 0.5%. Twenty four hours ABPM recorded a mean diurnal systolic blood pressure (SBP) of 128 ± 17 mmHg *vs* nocturnal of 123 ± 19 mmHg (P = 0.004), and mean diurnal diastolic blood pressure (DBP) of 83 ± 11 mmHg *vs* nocturnal DBP 78 ± 14 mmHg (P = 0.002) for a mean day *vs* night difference of 05 mmHg for SBP and 05 mmHg for DBP. Four/Twenty-seven of patients had diabetic retinopathy.

BP profile in groups with different albuminuria

Our population study was divided three times in two subgroups, according to albuminuria before and after exercise, these groups were subsequently compared pairs. These comparisons are illustrated in Tables 1, 2 and 3. They included clinical and ABPM findings in order to compare possible differences on BP profile associate with albuminuria.

The first two groups compared were patients with albuminuria at rest *vs* patients without resting albuminuria (Table 1). We found that patients with albuminuria at rest had more elevated DBP on clinical measure than non-albuminuric patients at rest (89 mmHg *vs* 77 mmHg, P = 0.04). Using ABPM, there was a marked increase in all component of nocturnal BP (130 mmHg *vs* 115 mmHg, P = 0.06 for SBP; 86 mmHg *vs* 72 mmHg for DBP, P = 0.02; and 107 *vs* 90, P = 0.03 for mean arterial BP).

The 2nd comparison concerned patients presenting with exercise-induced albuminuria and those without albuminuria after exercise (Table 2). This revealed that patients with exercise-induced albuminuria had an increase in nocturnal BP values on all three components [128 mmHg *vs* 110 mmHg, P = 0.03 for SBP; 83 mmHg *vs* 66 mmHg, P = 0.04; 106 *vs* 83, P = 0.02 for mean arterial pressure (MAP)].

The last comparison was made between patients presenting albuminuria only after exercise and those with albuminuria at rest (Table 3). Since patients with exercise-induced albuminuria had elevated night time BP values compared to those with albuminuria at rest, we sought to determine if exercise induced albuminuria is associated with a particular abnormality in BP profile. We found that patients with exercise induced albuminuria had slightly lower BP values

Table 1 Comparison between non albuminuric patients at rest and albuminuric patients at rest

Variables	Normoalb0	Microalb0	*P* value
Frequencies	19	8	/
Age	52 (40-56)	48 (34-56)	0.56
BMI (kg/m²)	25.4 (23.1-28.5)	26.1 (24-31.6)	0.62
Waist circumference	92 (87-96)	93 (84-97)	0.99
SBP (mmHg)	122 (112-133)	137 (122-142)	0.68
DBP (mmHg)	77 (73-87)	89 (79-99)	0.04
HbA1c (%)	6.6 (5.9-7.0)	6.2 (6-7)	0.99
eGFR (mL/min)	93 (77-104)	89 (70-104)	0.52
ACR at rest	13.5 (8.6-21.9)	75.3 (46-94.1)	0.0001
Exercise induced ACR	29.2 (20.5-33.3)	92.3 (56.3-128.7)	0.0001

ACR: Albumin to creatinin ratio; BMI: Body mass index; eGFR: Estimated glomerular filtration rate; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; Normoalb0: Patients without microalbuminuria at rest; Microalb0: Patients with microalbuminuria at rest.

Table 2 Comparison non-albuminuric patients after exercise and exercise induced albuminuric patients

Variables	Normoalb30	Microalb30	*P* value
Frequencies	11	16	/
Diurnal SBP	117 (112-133)	132 (125-136)	0.71
Nocturnal SBP	110 (98-125)	128 (122-138)	0.03
24 h SBP	116 (109-131)	132 (124-136)	0.05
Diurnal DBP	78 (76-85)	85 (80-92)	0.19
Nocturnal DBP	66 (59-82)	83 (74-89)	0.044
24 h DBP	76 (72-84)	85 (78-89)	0.11
Diurnal MAP	93 (89-107)	107 (102-112)	0.05
Nocturnal MAP	83 (77-102)	106 (99-110)	0.02
24 h MAP	89 (85-105)	108 (99-112)	0.03

DBP: Diastolic blood pressure; MAP: Mean arterial blood pressure; SBP: Systolic blood pressure; Normoalb30: Patients without microalbuminuria after 30 min of exercise; Microalb30: Patients with microalbuminuria after 30 min of exercise.

on clinical measure (130/87 mmHg *vs* 137/89 mmHg, $P = 0.08$). However, on ABPM, exercise induced albuminuria was associated with a slight and significant decrease in nocturnal DBP (83 mmHg *vs* 86 mmHg, $P = 0.03$) and a rise of percentage of abnormal SBP value ($P = 0.01$). Apart from the aforementioned abnormalities, both groups were similar in other parameters. Nevertheless, both groups had an increase in BP value compare to the rest of population.

BP profile with ABPM

Using ABPM, the mean BP of our population study was 128 ± 17 mmHg *vs* 124 ± 19 mmHg and 127 ± 17 mmHg (*P* day *vs* night = 0.004) for systolic day time, night time and 24 h values respectively; and 84 ± 11 mmHg *vs* 79 ± 14 mmHg and 83 ± 12 mmHg for diastolic component.

ABPM vs resting albuminuria and ABPM vs exercise-induced albuminuria

Correlation done between albuminuria and different components of BP on a sample population showed that albuminuria at rest is weakly correlated with 24 h MAP ($r^2 = 0.11$, $P = 0.09$; Figure 1A), 24 h DBP ($r^2 = 0.13$, $P = 0.08$; Figure 1B) and nocturnal DBP ($r^2 = 0.13$, $P = 0.08$; Figure 1C). On the other hand, exercise induced albuminuria correlated better with 24-h mean arterial blood pressure (MAP) ($r^2 = 0.13$, $P = 0.07$; Figure 2A), night time DBP ($r^2 = 0.12$, $P = 0.09$; Figure 2B) and nocturnal MAP ($r^2 = 0.12$, $P = 0.09$; Figure 2C).

Table 3 Comparison between albuminuric patients at rest and exercise-induced albuminuric patients

Variables	Microalb0	Microalb30	*P* value
Frequencies	8	8	
Diurnal SBP	131 (126-136)	132 (125-136)	0.95
Nocturnal SBP	130 (126-138)	128 (122-138)	0.38
24 h SBP	133 (126-135)	132 (124-136)	0.60
Diurnal DBP	85 (83-93)	85 (80-92)	0.22
Nocturnal DBP	86 (80-92)	83 (74-89)	0.03
24 h DBP	86 (83-93)	85 (78-89)	0.11
Diurnal MAP	107 (104-111)	107 (102-112)	0.77
Nocturnal MAP	107 (102-112)	106 (99-110)	0.14
24 h MAP	107 (104-110)	108 (99-112)	0.68

MAP: Mean arterial blood pressure; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; Microalb0: Patients with microalbuminuria at rest; Microalb30: Patients with microalbuminuria only after 30 min of exercise.

DISCUSSION

This study was carried out to investigate a relationship between urinary albumin excretion during exercise and circadian variations in BP. We found an average drop of 3.1% during the night with a high proportion of non-dippers (20/27 or 74%) in our study population, with a blunted nighttime BP. The proportion of non-dippers is higher than those of others study on type 2 diabetic population[12]. The increase of non-dippers in our study could be due to the tendency of having elevated nocturnal BP in black subject as described by Hebert *et al*[13] in 1996. So, the non-dipper profile could be more common in black populations. On the other hand, the high frequency of non-dipper status found in our study may reflect an incipient nephropathy in our population of diabetic patients without proteinuria. Since the reduction of nighttime dipping BP is consider as an earlier sign of diabetic nephropathy in diabetic patients with normal BP.

Patients were subsequently separated according to their urinary albumin excretion at rest and during exercise. Firstly, we compared albuminuric and non albuminuric patients at rest, and found that patients with albuminuria at rest exhibited more BP abnormalities compared to those without albuminuria. This include an elevated clinical DBP on clinical measure suggesting that albuminuria at rest is consistent with a slight elevation of clinical BP more marked on the diastolic component. Using ABPM, there was an increase in all diastolic components of BP (diurnal, nocturnal and mean arterial) as well as nocturnal SBP and nocturnal mean MAP in

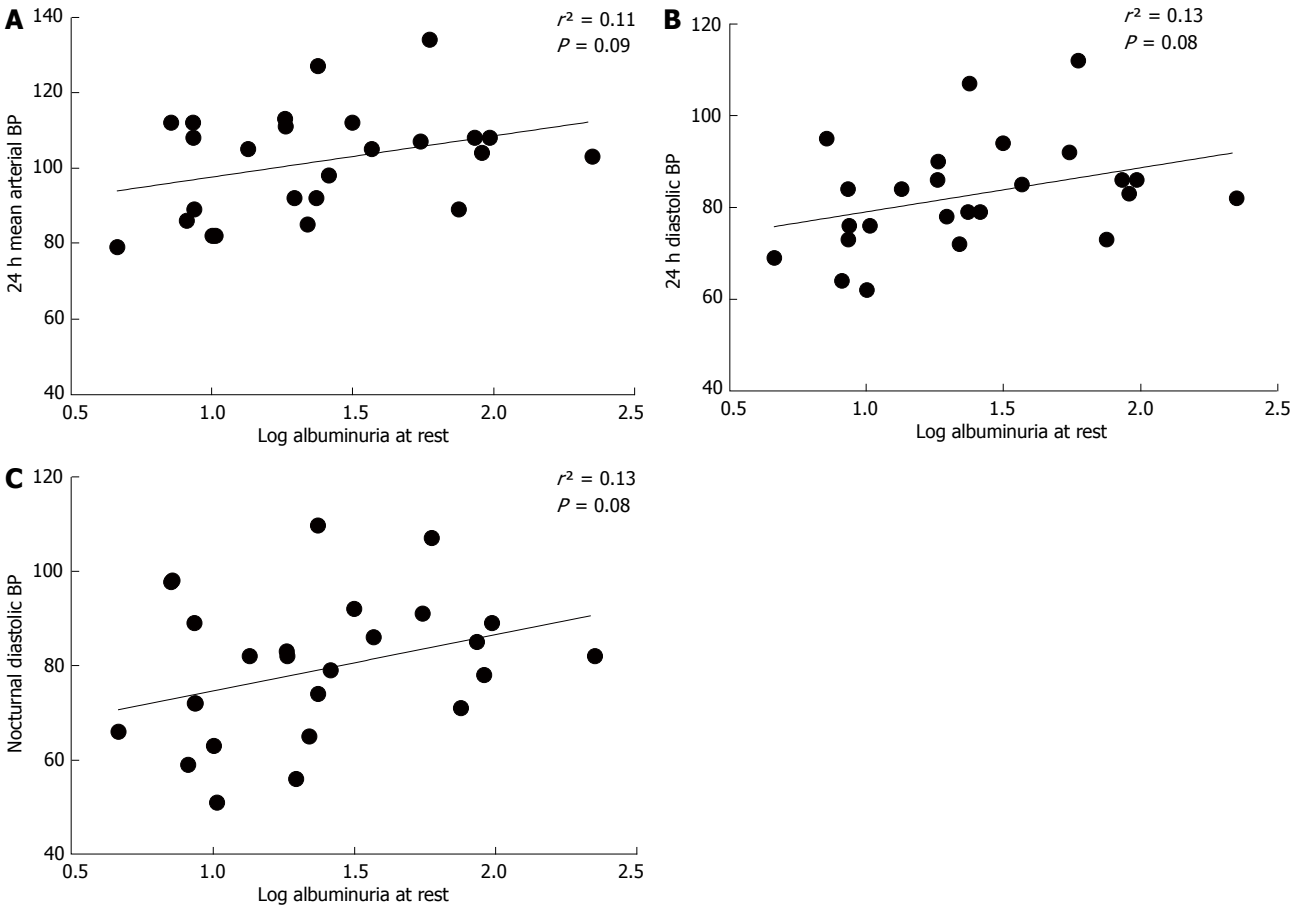

Figure 1 Correlation between albuminuria at rest and diastolic blood pressure. A: Correlation between albuminuria at rest and 24 h MAP; B: Correlation between albuminuria at rest and 24 h diastolic BP; C: Correlation between albuminuria at rest and nocturnal diastolic BP. MAP: Mean arterial blood pressure; BP: Blood pressure.

albuminuric patients at rest. These data are consistent with those found in literature where albuminuria at rest is associated with abnormal patterns of nocturnal BP[13-15]. However, our study highlights the fact that this increase in nocturnal BP is more marked on diastolic component of BP. Therefore, clinical and nocturnal DBP must be checked and managed meticulously in T2D patients to detect even a slight elevation or a moderate rise in baseline DBP comparing with precedent measures. This is to ensure early detection of these patients, thereby improve their management to prevent diabetic nephropathy.

Secondly, we compared the BP of patients exhibiting exercise induced albuminuria at rest and during exercise with those without this abnormality on clinical measure and using ABPM. We found that, though there was no difference in SBP and DBP on clinical measure, but ABPM detected an increase in nocturnal BP including night time SBP, DBP as well as nocturnal MAP. This important finding supports and confirms our research hypothesis stipulating that exercise induced albuminuria is associated with abnormal circadian BP profile particularly abnormalities in night time BP pattern.

Finally, we compared patients exhibiting exercise induced albuminuria without resting albuminuria to those having albuminuria at rest in order to check if there is a difference between BP profiles of these two groups of patients. Comparing with non-albuminuric patients, these two groups had elevated BP values. However, patients with moderate resting albuminuria tend to have a higher BP values than those presenting only exercise-induced albuminuria. This association could be of importance since mild variations in nocturnal BP has been associated with renal injuries in T2D patients. Our findings are consistent with the fact that exercise induced albuminuria is associated with the same abnormalities in BP profile as albuminuria at rest, and therefore could be useful in management of T2D patients to detect the same patients with blunted nighttime BP. Nevertheless, there is an urgent need for longitudinal studies to verify this hypothesis. Moreover, exercise induced albuminuria could be associated with very subtle variations in circadian BP.

Albuminuria at rest had a positive but weak correlation with nighttime DBP and 24 h BP, sustaining the fact that an increase in 24 h BP is associated with an elevation in albuminuria at rest which could be a marker of renal deterioration[16]. Therefore, an increase in nighttime DBP and/or 24 h DBP could be associated with greater kidney damage in diabetic patients without hypertension. These results corroborate with those Rossing in 1993[17]. Similarly, exercise induced

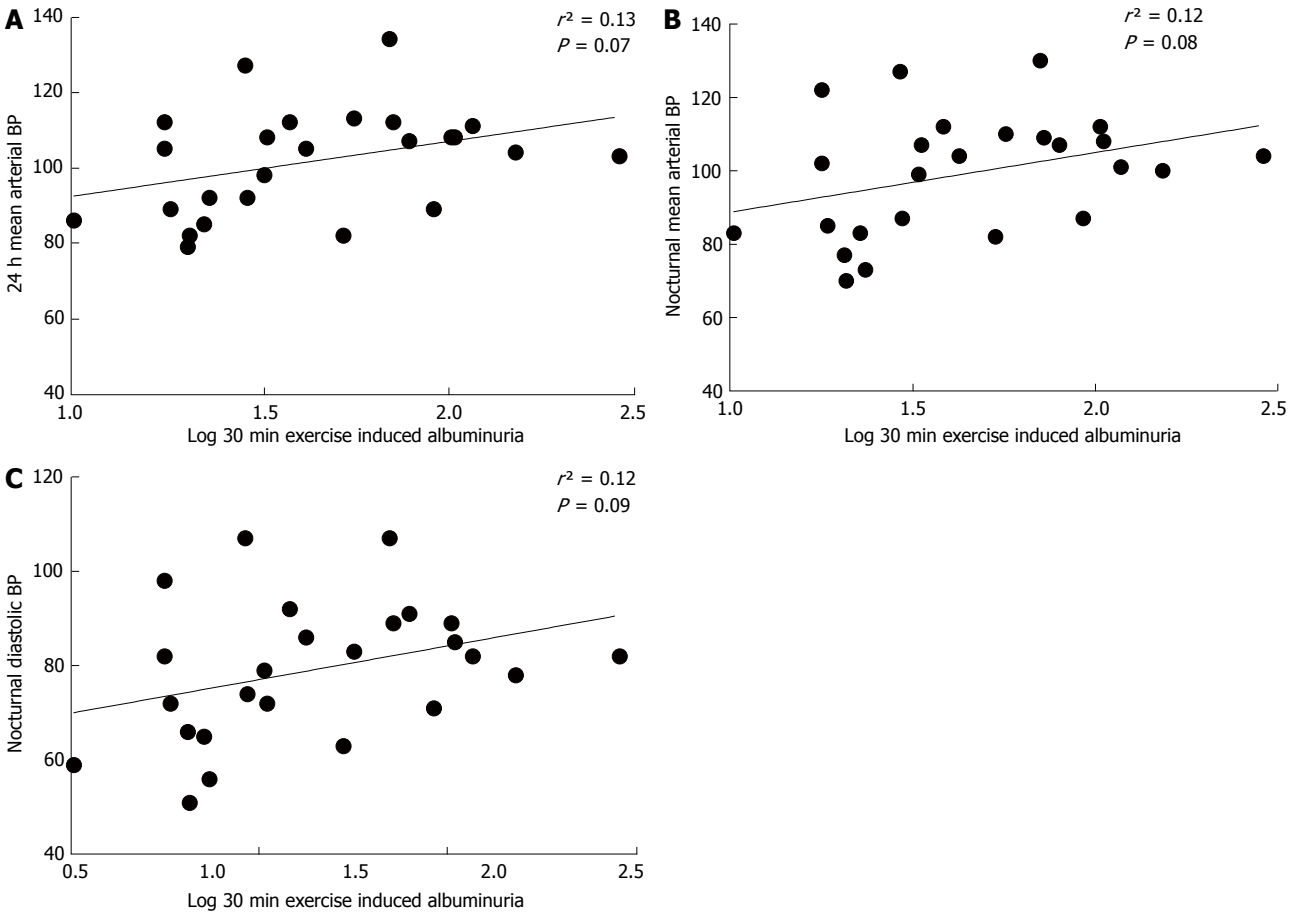

Figure 2 Correlation between exercise-induced albuminuria and diastolic blood pressure. A: Correlation between exercise induced albuminuria and 24 h MAP; B: Correlation between exercise induced albuminuria; C: Correlation between exercise albuminuria. MAP: Mean arterial blood pressure; BP: Blood pressure.

albuminuria correlated better, and positively, with night DBP and 24 h MAP. Thus, exercise induced albuminuria is correlated with the same characteristics as albuminuria at rest.

There was a strong positive correlation between albuminuria at rest and during exercise albuminuria (r = 0.7 and $P < 0.001$). This suggests that patients with a greater resting albuminuria therefore tend to have a higher albuminuria after exercise. Considering the fact that albuminuria at rest is a marker of incipient diabetic nephropathy, this suggests that exercise induced albuminuria would be greater in case of pre-existing renal impairment[18]. This hypothesis is supported by physiology, since it is known that subclinical lesions can be unmasked even by moderate physical exercise[8]. The results obtained in this study shows a significant proportion of abnormal circadian BP profile in patients with T2D, considered normotensive on clinic-based measurements.

Study strengths and limitations

This study presents some limitations related to the study design. Since this is a cross-sectional study, the predictive value of these abnormalities needs to be evaluated with prospective studies. This could bring more evidence and basic arguments to recommend management of T2D patients presenting exercise-induced albuminuria. This study depicts the importance of ABPM in the management of diabetic patients, due to its efficacy in detecting abnormalities in BP values, which is a better predictor of renal damage compared with clinic-based BP measurements. We also found that exercise induced albuminuria discriminate the same patients as resting albuminuria stressing the need to revisit importance of exercise-induced albuminuria in the earlier diagnosis and management of T2D patients. This will require prospective studies in order to evaluate the predictive capacity of exercise induced albuminuria on nighttime BP abnormalities what have not been done yet to date.

Conclusion

Exercise-induced albuminuria is associated with nocturnal blood pressure abnormalities in T2D patients and could discriminate patients with more precocious increase of nighttime blood pressure than albuminuria at rest.

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COMMENTS

Background

Exercise induced albuminuria has long been proposed as early marker of diabetes nephropathy but was not approved due to lack of evidence and clinical importance. Nocturnal blood pressure abnormalities and represent an early marker diabetes kidney disease.

Research frontiers

A relation between nocturnal blood pressure abnormalities detected by ambulatory blood pressure monitoring (ABPM) and exercise-induced albuminuria would be of great importance since this will suggest that the latter can serve as earlier marker of diabetes nephropathy.

Innovations and breakthroughs

Most of studies conducted to determine the clinical importance of exercise-induced albuminuria have been done in type 1 diabetes individuals and has compared it only to albuminuria at rest. This study shows an association between nocturnal blood pressure abnormalities and exercise-induced albuminuria suggesting that it could be useful to discriminate type 2 diabetes (T2D) individuals with early renal diabetes kidney disease. As the best of our knowledge, this study is the first reporting this association in T2D patients who represent more than 90% of diabetes patients worldwide.

Applications

Economically, the separate or combined use of ABPM, and exercise induced albuminuria in assessing diabetic patients clinically normotensive, for the detection of subclinical diabetic nephropathy lesions could represent a significant gain in health spending by its low cost compared to new markers currently in test and would significantly reduce health care spending. Indeed, by allowing very early detection of subclinical renal damage, they would allow a more prompt and early treatment, increasing the chances of controlling the disease and slow its progression to end-stage renal disease (ESRD) and chronic kidney disease. This would be a significant reduction in costs for health systems today face a real inflation of the prevalence of ESRD and dialysis diabetes-related admissions.

Terminology

Albuminuria: Presence of albuminuria in urine which is a marker of renal damage; Microalbuminuria or moderate albuminuria: Urinary albumin excretion $\geqslant$ 30 mg/24 h or 30 mg/g with albumin to creatinin ratio; Exercise-induced albuminuria: Increase or presence of urinary albumin excretion after an exercise.

Peer-review

Well done important information supporting the view that patients regarded as not afflicted with diabetic nephropathy may indeed be progressing towards renal damage that is preventable if treated before diabetic nephropathy progresses to a 24 h disorder.

REFERENCES

1 **Sheen YJ**, Sheu WH. Risks of rapid decline renal function in patients with type 2 diabetes. *World J Diabetes* 2014; **5**: 835-846 [PMID: 25512785 DOI: 10.4239/wjd.v5.i6.835]

2 **Sobngwi E**, Enoru S, Ashuntantang G, Azabji-Kenfack M, Dehayem M, Onana A, Biwole D, Kaze F, Gautier JF, Mbanya JC. Day-to-day variation of insulin requirements of patients with type 2 diabetes and end-stage renal disease undergoing maintenance hemodialysis. *Diabetes Care* 2010; **33**: 1409-1412 [PMID: 20215452 DOI: 10.2337/dc09-2176]

3 **Kim SS**, Kim JH, Kim IJ. Current Challenges in Diabetic Nephropathy: Early Diagnosis and Ways to Improve Outcomes. *Endocrinol Metab* (Seoul) 2016; **31**: 245-253 [PMID: 27246284 DOI: 10.3803/EnM.2016.31.2.245]

4 **Currie G**, McKay G, Delles C. Biomarkers in diabetic nephropathy: Present and future. *World J Diabetes* 2014; **5**: 763-776 [PMID: 25512779 DOI: 10.4239/wjd.v5.i6.763]

5 **Rossing P**, Hougaard P, Parving HH. Progression of microalbuminuria in type 1 diabetes: ten-year prospective observational study. *Kidney Int* 2005; **68**: 1446-1450 [PMID: 16164620 DOI: 10.1111/j.1523-1755.2005.00556.x]

6 **American Diabetes Association**. Standards of medical care in diabetes--2014. *Diabetes Care* 2014; **37** Suppl 1: S14-S80 [PMID: 24357209 DOI: 10.2337/dc14-S014]

7 **Shalaby NM**, Shalaby NM. Study of ambulatory blood pressure in diabetic children: prediction of early renal insult. *Ther Clin Risk Manag* 2015; **11**: 1531-1537 [PMID: 26491340 DOI: 10.2147/TCRM.S87751]

8 **O'Brien SF**, Watts GF, Powrie JK, Shaw KM. Exercise testing as a long-term predictor of the development of microalbuminuria in normoalbuminuric IDDM patients. *Diabetes Care* 1995; **18**: 1602-1605 [PMID: 8722059 DOI: 10.2337/diacare.18.12.1602]

9 **WHO**. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia [Internet]. WHO. [cited 2017 Jan 14]. Available from: URL: http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/

10 **Agoons DD**, Balti EV, Kaze FF, Azabji-Kenfack M, Ashuntantang G, Kengne AP, Sobngwi E, Mbanya JC. Performance of three glomerular filtration rate estimation equations in a population of sub-Saharan Africans with Type 2 diabetes. *Diabet Med* 2016; **33**: 1291-1298 [PMID: 26482216 DOI: 10.1111/dme.12996]

11 **Whitley E**, Ball J. Statistics review 4: sample size calculations. *Crit Care* 2002; **6**: 335-341 [PMID: 12225610 DOI: 10.1186/cc1521]

12 **Cuspidi C**, Sala C, Valerio C, Negri F, Mancia G. Nocturnal hypertension and organ damage in dippers and nondippers. *Am J Hypertens* 2012; **25**: 869-875 [PMID: 22573011 DOI: 10.1038/ajh.2012.49]

13 **Hebert LA**, Agarwal G, Ladson-Wofford SE, Reif M, Hiremath L, Carlton SG, Nahman NS, Falkenhain ME, Agarwal A. Nocturnal blood pressure in treated hypertensive African Americans Compared to treated hypertensive European Americans. *J Am Soc Nephrol* 1996; **7**: 2130-2134 [PMID: 8915972]

14 **Xu H**, Huang X, Risérus U, Cederholm T, Sjögren P, Lindholm B, Ärnlöv J, Carrero JJ. Albuminuria, renal dysfunction and circadian blood pressure rhythm in older men: a population-based longitudinal cohort study. *Clin Kidney J* 2015; **8**: 560-566 [PMID: 26413281 DOI: 10.1093/ckj/sfv068]

15 **Poulsen PL**, Hansen KW, Mogensen CE. Ambulatory blood pressure in the transition from normo- to microalbuminuria. A longitudinal study in IDDM patients. *Diabetes* 1994; **43**: 1248-1253 [PMID: 7926296 DOI: 10.2337/diab.43.10.1248]

16 **Rosenstock J**, Raskin P. Early diabetic nephropathy: assessment and potential therapeutic interventions. *Diabetes Care* 1986; **9**: 529-545 [PMID: 3533477 DOI: 10.2337/diacare.9.5.529]

17 **Rossing P**, Hommel E, Smidt UM, Parving HH. Impact of arterial blood pressure and albuminuria on the progression of diabetic nephropathy in IDDM patients. *Diabetes* 1993; **42**: 715-719 [PMID: 8482428 DOI: 10.2337/diab.42.5.715]

18 **Mogensen CE**, Vittinghus E. Urinary albumin excretion during exercise in juvenile diabetes. A provocation test for early abnormalities. *Scand J Clin Lab Invest* 1975; **35**: 295-300 [PMID: 1188285 DOI: 10.1080/00365517509095743]

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CASE REPORT

Severe cyclophosphamide-related hyponatremia in a patient with acute glomerulonephritis

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Abstract

Cyclophosphamide is frequently used to treat cancer, autoimmune and renal diseases, such as rapidly progressive glomerulonephritis. Its side effects are well-known, including bone marrow depression, infections, alopecia, sterility, bladder malignancy and hemorrhagic cystitis. Moreover, in some cases cyclophosphamide use has been related to the onset of hyponatremia, by development of a syndrome of inappropriate antidiuresis. Indeed, severe hyponatremia has been previously reported in patients treated with high-dose or moderate-dose of intravenous cyclophosphamide, while only few cases have been reported in patients treated with low dose. Here, we discuss a case of a syndrome of inappropriate antidiuresis followed to a single low-dose of intravenous cyclophosphamide in a patient with a histological diagnosis of acute glomerulonephritis, presenting as acute kidney injury. After cyclophosphamide administration (500 mg IV), while renal function gradually improved, the patient developed confusion and headache. Laboratory examinations showed serum sodium concentration dropped to 122 mmol per liter associated with an elevated urinary osmolality of 199 mOsm/kg, while common causes of acute hyponatremia were excluded. He was successfully treated with water restriction and hypertonic saline solution infusion with the resolution of the electrolyte disorder. This case, together with the previous ones already reported, highlights that electrolyte profile should be strictly monitored in patients undergoing cyclophosphamide therapy in order to early recognize the potentially life-threatening complications of acute water retention.

Key words: Hyponatremia; Cyclophosphamide; Syndrome

of inappropriate antidiuresis; Glomerulonephritis; Hypertonic solutions; Antidiuretic hormone; Urine osmolality

Core tip: The syndrome of inappropriate antidiuresis (SIAD) is a disorder of sodium and water balance characterized by hypotonic hyponatremia and impaired urinary dilution in the absence of renal disease or any non-osmotic stimulus known to release anti-diuretic hormone. It may be caused by several conditions including infections, neoplasms and use of some medications, such as antipsychotics, antidepressant and immunosuppressive drugs. Here, we report the clinical course of a case of SIAD attributed to administration of a single low-dose of intravenous cyclophosphamide in a patient with an acute glomerulonephritis.

Esposito P, Domenech MV, Serpieri N, Calatroni M, Massa I, Avella A, La Porta E, Estienne L, Caramella E, Rampino T. Severe cyclophosphamide-related hyponatremia in a patient with acute glomerulonephritis. *World J Nephrol* 2017; 6(4): 217-220 Available from: URL: http://www.wjgnet.com/2220-6124/full/v6/i4/217.htm DOI: http://dx.doi.org/10.5527/wjn.v6.i4.217

INTRODUCTION

Hyponatremia is the most frequent electrolyte disorder, being potentially a marker of different underlying diseases or a cause of morbidity itself.

Clinical manifestations vary from asymptomatic forms to severe neurological alterations, in dependence of hyponatremia severity, progression rate and intra- to extracellular osmotic gradient entity. Differential diagnosis is often challenging, since it includes diseases, which, in view of similar clinical pictures, have very different pathophysiological bases, such as syndrome of inappropriate antidiuresis (SIAD), cerebral/renal salt wasting syndrome (C/RSWS) and endocrine syndromes[1].

SIAD is a disorder of sodium and water balance characterized by hypotonic hyponatremia and impaired urinary dilution in the absence of renal disease or any identifiable non-osmotic stimulus known to release antidiuretic hormone (ADH). SIAD may be itself caused by different conditions, including infections, neoplasms and use of several medications, such as antipsychotics, antidepressant[2] and immunosuppressive drugs[3].

Here, we report the clinical course of a rare case of SIAD attributed to cyclophosphamide (CYC) administration in a patient with a proliferative glomerulonephritis.

CASE REPORT

A 56-year-old man was referred to our Nephrology Department for rapidly decline of glomerular filtration rate (GFR), proteinuria and haematuria.

He presented a history of hypertension, chronic kidney disease (with a stable serum creatinine of 158 mmol/L, estimated GFR 40 mL/min per 1.73 mq CKD-EPI), Crohn disease, psychiatric disorder in treatment with selective serotonin reuptake inhibitors (SSRIs) and normal pressure hydrocephalus with ventriculo-peritoneal shunt.

At the admission, the patient presented a well-controlled blood pressure (17.3/10 kPa) and significant peripheral oedema. Laboratory examinations showed: serum creatinine 290 mmol/L (corresponding to an estimated GFR of 19 mL/min per 1.73 mq), urea 47 mmol/L, sodium 137 mmol/L, potassium 3.69 mmol/L, serum albumin 30 g/L, cholesterol 3.93 mmol/L and triglycerides 2.19 mmol/L.

Urinalysis showed microhematuria, while quantitative proteinuria was 2.26 g/24 h. Autoimmunity evaluation, which included ANA, ENA, ANCA, C3 and C4, resulted negative.

So, in order to better elucidate the causes of renal disorder, we performed a percutaneous renal biopsy. Histological examination showed glomeruli with mesangial expansion and endocapillary hypercellularity due mostly by neutrophils infiltration with some karyorrhectic bodies, fibrinoid necrosis of small arterioles, and fibrocellular crescents (Figure 1). There was also moderate tubular atrophy within massive protein droplets, and moderate interstitial fibrosis. Immunofluorescence analysis did not show immune deposits, while electronic microscopy was not performed. So, considering clinical and histological findings our final diagnosis was rapidly progressive glomerulonephritis secondary to ANCA-negative pauci-immune crescentic glomerulonephritis.

At the time of biopsy pharmacological treatments included intravenous diuretics (furosemide 125 mg/d), antihypertensive drugs and SSRI. After the renal biopsy, also in consideration of the further deterioration of renal function (serum creatinine till 343 mmol/L), intravenous methylprednisolone was administered at the dose of 500 mg for three days followed by oral steroid at the initial dose of 1 mg/kg per day. In addition, the induction therapy was completed with a single dose of 500 mg of intravenous CYC (8 mg/kg). To minimize the risk of haemorrhagic cystitis, saline solution was infused 2 h before the cyclophosphamide administration. In the following days, while renal function gradually improved, patient clinical conditions worsened with development of confusion and headache. Laboratory examinations showed serum sodium 122 mmol/L, serum osmolality 261 mOsm/kg, urinary osmolality 199 mOsm/kg, and serum creatinine 202 mmol/L. Symptomatic hypotonic hyponatremia was further confirmed in the subsequent controls, so that fluid restriction and hypertonic saline solution (at initial concentration of 3%) treatment were initiated, while SSRIs were gradually withdrawn. In the following days, serum sodium progressively improved and we were able to reduce infusive therapy, also to

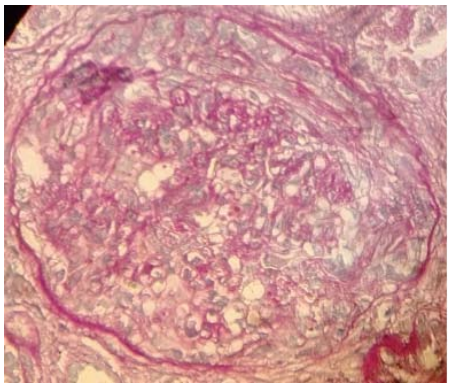

Figure 1 Histological examination showed glomeruli with mesangial expansion and endocapillary hypercellularity with some karyorrhectic bodies, fibrinoid necrosis of small arterioles, and fibrocellular crescents (as shown in the figure-PAS, x 400).

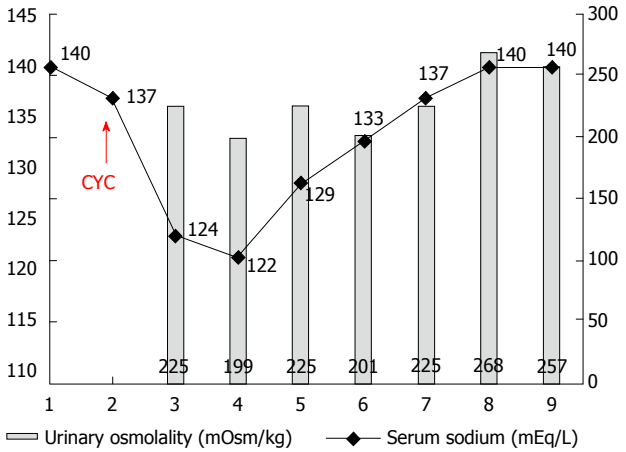

Figure 2 Time trend of serum sodium concentration and urinary osmolality following cyclophosphamide administration. During days 3 and 4 the urinary osmolality was inappropriately high considering the hyponatremia. In days 5 to 9 the urinary dilution capacity was re-established.

prevent the increase of oedema (Figure 2).

To establish the pathogenesis of the acute hyponatremia we investigated thyroid and adrenal functions, which resulted normal and performed a whole-body CT scan that ruled out pulmonary or cerebral complications. Therefore, in absence of further evidence and considering the temporal relationship between CYC infusion and onset of hyponatremia, the fact that diuretic and psychiatric therapy were unchanged and the presence of hypotonic hyponatremia with impaired urinary dilution we established a diagnosis of CYC-related syndrome of inappropriate anti-diuresis (SIAD)[3]. So, in order to prevent other hyponatremia episodes further cyclophosphamide administration was avoided.

DISCUSSION

Cyclophosphamide is an alkylating agent used in the treatment of malignant and autoimmune diseases. Its well-known side effects include bone marrow depression, infections, alopecia, sterility, bladder malignancy and haemorrhagic cystitis. Hyponatremia due to SIAD has been infrequently described and it is considered a rare adverse effect related to CYC use. Indeed, until now severe hyponatremia has been reported only in few patients treated with high-dose (30-40 mg/kg)[4,5] and moderate-dose (20-30 mg/kg) of intravenous cyclophosphamide, while even less were the cases of hyponatremia occurred in patients treated with low dose[6-8]. Different underlying mechanisms have been proposed to explain the onset of water retention and SIAD after CYC administration. They can act either stimulating ADH release or accentuating its renal effects, finally causing hyponatremia[9]. Harlow *et al*[10] demonstrated in a patient who received high dose of cyclophosphamide, the loss of Herrings bodies and degranulation of various hypothalamic neurosecretory organelles, leading to the inappropriate secretion of ADH. It has been also demonstrated a direct effect of an alkylating metabolite of CYC on the kidney resulting in enhanced permeability of the distal tubules to water[11]. Moreover, CYC might cause hyponatremia by up-regulating expression of the ADH receptor V2R and aquaporin 2 (AQ2) through the suppression of interleukin-1 and tumor necrosis factor-α, which generally act as negative regulators of VR2 expression[12]. In addition, recently Kim *et al*[13] demonstrated in experimental models (rat and inner medullary collecting cell cultures) that CYC could also induce V2R activation and AQP2 expression in the absence of ADH stimulation.

Actually, in our case the patient presented several predisposing factors that could have caused water retention, such as renal failure, the continuative use of SSRI and the normal pressure hydrocephalus; but the temporal association with the administration of CYC makes plausible its role in the development of the severe hyponatremia, also considering that prior to CYC treatment, he had normal serum electrolytes and did not present nausea or vomiting. Moreover, our case has common features with other reports in which hyponatremia was induced by intravenous cyclophosphamide. Hyponatremia usually occurs 12-48 h after the administration of cyclophosphamide, and returns to normal in few days.

In conclusion, we think that our case, together with the previous ones already reported, underlined the need to be aware of the potentially life-threatening complications of water intoxication when intravenous pulse cyclophosphamide is applied, especially in patients with other concomitant risk factors. Therefore, we strongly suggest checking electrolytes before and after CYC administration.

COMMENTS

Case characteristics

A patient with an acute glomerulonephritis who developed an acute symptomatic

hyponatremia after treatment with cyclophosphamide.

Clinical diagnosis
Acute Hyponatremia secondary to development of syndrome of inappropriate antidiuresis related to the administration of cyclophosphamide.

Differential diagnosis
Other causes of acute hyponatremia: Cancers, infections, hypovolemia, use of diuretics.

Laboratory diagnosis
Hypotonic hyponatremia associated with impaired urinary dilution.

Imaging diagnosis
CT to exclude cerebral or pulmonary disorders.

Pathological diagnosis
Renal biopsy proving the presence of an acute ANCA-negative pauci-immune crescentic glomerulonephritis.

Treatment
Water restriction, hypertonic saline solution infusion.

Related reports
Previous cases of hyponatremia in patients treated with different doses of intravenous cyclophosphamide.

Experiences and lessons
It is necessary to carefully monitor electrolyte and water balance before and after cyclophosphamide administration.

Peer-review
This case report is well-written and has interesting information.

REFERENCES

1 **Ellison DH**, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; **356**: 2064-2072 [PMID: 17507705 DOI: 10.1056/NEJMcp066837]

2 **Jacob S**, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. *Ann Pharmacother* 2006; **40**: 1618-1622 [PMID: 16896026 DOI: 10.1345/aph.1G293]

3 **Esposito P**, Piotti G, Bianzina S, Malul Y, Dal Canton A. The syndrome of inappropriate antidiuresis: pathophysiology, clinical management and new therapeutic options. *Nephron Clin Pract* 2011; **119**: c62-c73; discussion c73 [PMID: 21677440 DOI: 10.1159/000324653]

4 **Abe T**, Takaue Y, Okamoto Y, Yamaue T, Nakagawa R, Makimoto A, Sato J, Kawano Y, Kuroda Y. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in children undergoing high-dose chemotherapy and autologous peripheral blood stem cell transplantation. *Pediatr Hematol Oncol* 1995; **12**: 363-369 [PMID: 7577388]

5 **Lazarevic V**, Hägg E, Wahlin A. Hiccups and severe hyponatremia associated with high-dose cyclophosphamide in conditioning regimen for allogeneic stem cell transplantation. *Am J Hematol* 2007; **82**: 88 [PMID: 16917917 DOI: 10.1002/ajh.20706]

6 **Koo TY**, Bae SC, Park JS, Lee CH, Park MH, Kang CM, Kim GH. Water intoxication following low-dose intravenous cyclophosphamide. *Electrolyte Blood Press* 2007; **5**: 50-54 [PMID: 24459501 DOI: 10.5049/EBP.2007.5.1.50]

7 **Lee YC**, Park JS, Lee CH, Bae SC, Kim IS, Kang CM, Kim GH. Hyponatraemia induced by low-dose intravenous pulse cyclophosphamide. *Nephrol Dial Transplant* 2010; **25**: 1520-1524 [PMID: 20007128 DOI: 10.1093/ndt/gfp657]

8 **Gilbar PJ**, Richmond J, Wood J, Sullivan A. Syndrome of inappropriate antidiuretic hormone secretion induced by a single dose of oral cyclophosphamide. *Ann Pharmacother* 2012; **46**: e23 [PMID: 22911342 DOI: 10.1345/aph.1R296]

9 **Campbell DM**, Atkinson A, Gillis D, Sochett EB. Cyclophosphamide and water retention: mechanism revisited. *J Pediatr Endocrinol Metab* 2000; **13**: 673-675 [PMID: 10905395]

10 **Harlow PJ**, DeClerck YA, Shore NA, Ortega JA, Carranza A, Heuser E. A fatal case of inappropriate ADH secretion induced by cyclophosphamide therapy. *Cancer* 1979; **44**: 896-898 [PMID: 476599]

11 **DeFronzo RA**, Braine H, Colvin M, Davis PJ. Water intoxication in man after cyclophosphamide therapy. Time course and relation to drug activation. *Ann Intern Med* 1973; **78**: 861-869 [PMID: 4713567]

12 **Park SJ**, Kim JH, Shin JI. Insight on mechanism of hyponatraemia induced by low-dose intravenous pulse cyclophosphamide. *Nephrol Dial Transplant* 2010; **25**: 3453; author reply 3453-3454 [PMID: 20650905 DOI: 10.1093/ndt/gfq429]

13 **Kim S**, Choi HJ, Jo CH, Park JS, Kwon TH, Kim GH. Cyclophosphamide-induced vasopressin-independent activation of aquaporin-2 in the rat kidney. *Am J Physiol Renal Physiol* 2015; **309**: F474-F483 [PMID: 26109089 DOI: 10.1152/ajprenal.00477.2014]

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