Is exosome analysis a potentially useful tool for physiological studies? We have demonstrated that all of the predominant apical Na^+ transporters expressed along the renal tubule are detectable in urine via exosome isolation [11]. Furthermore, the water channel aquaporin-2 is likewise detectable [12]. Do the rates of excretion of these transporters provide a measure of the rate of their production in the kidney? Probably not, since the rate of excretion of a given protein is the difference between the rate of its production and the rate of its degradation in the cell. Unless we know the rate of degradation, we cannot draw conclusions about production rate.

Like any new tool, exosome analysis has advantages and disadvantages that need to be explored prior to any exosome analysis project. However, given the non-invasive nature of the sample collection procedure and the large amount of information potentially available from such studies, it seems likely that exosome analysis will play a role in nephrology research in the future. With this possibility in mind, we have created internet sites to provide technical protocols (http://intramural.niddk.nih.gov/research/uroprot/) and listings of proteins already found in exosomes (http://dir.nhlbi.nih.gov/papers/lkem/exosome/index.htm) for use by researchers.

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Residual renal function: the delicate balance between benefits and risks

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Keywords: chronic kidney disease; dialysis adequacy; fluid volume overload; haemodialysis; peritoneal dialysis

Introduction

Residual renal function (RRF) facilitates the achievement of dialysis adequacy in stage 5 chronic kidney disease (CKD-5) patients [1]. It facilitates patients' acceptance of renal replacement therapy (RRT) in minimizing dietary and fluid restriction. RRF has been confirmed recently to be a significant determinant of morbidity and mortality in dialysis patients [2]. In addition, the preservation of RRF is also highly suitable in CKD-5 patients to enhance removal or degradation of middle and large uraemic toxins implicated

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in long-term complications of CKD patients. Preserving RRF in incident CKD-5 patients is an old holistic dream that still remains to date a source of debate among the nephrologists [3].

The aim of this editorial is to analyse benefits and risks of maintaining RRF in dialysis patients. In this scope we explore four aspects: What are the positive effects of maintaining RRF in dialysis patients? What are the negative effects of maintaining RRF in dialysis patients? What are the factors implicated in the loss of RRF in dialysis patients? What is the meaning of RRF persistence in dialysis patients?

What are the positive effects of maintaining RRF in dialysis patients?

RRF may play a significant role in the treatment adequacy and outcomes of dialysis patients [4]. Several recent prospective observational and interventional studies have shown that the presence of RRF was associated with an improved outcome and a reduced mortality in CKD patients on RRT. Interestingly, this beneficial effect of RRF has now been reported both in peritoneal dialysis (PD) or haemodialysis (HD) patients. In PD, a reanalysis of the CANUSA study (prospective cohort of 601 incident patients) has clearly established that patient survival was linked to the importance of RRF and urine volume [5]. For each 5 l/week per 1.73 m^2 increment in RRF, there was a 12% decrease in the relative risk (RR) of death, and no association was found with the peritoneal creatinine clearance [6]. Simultaneously, for each 250-ml increment of urine volume, a 36% decrease in the RR of death was noted. In the ADEMEX study, a prospective randomized trial exploring the effects of increased peritoneal small solutes clearances in 965 prevalent patients, no survival advantage for patients was obtained with increases of peritoneal clearances, even when patients were stratified for age, nutritional and comorbid factors [7]. Such contrasting results may be explained in part by the fact that the RRF declines more significantly in the interventional group (−0.99 ml/min, 64%) than in the control group (−85 ml/min, 51%). It is worth noting that for each 10 l/week per 1.73 m^2 increment in RRF, there was an 11% decrease of RR of death and no association was found with the creatinine peritoneal clearance. In HD patients, the effects of RRF and urine volume on patient survival were less explored until recently. Two recent prospective cohort studies have addressed this issue. The NECOSAD study has evaluated the contribution of treatment adequacy and RRF to patient survival after 3 and 6 months of treatment in a large incident HD population (740 patients) [8]. As expected, both components of dialysis adequacy, peritoneal clearance (dKt/V) and renal function (rKt/V) were positively associated with survival, but RRF was a stronger predictor of patient survival than peritoneal clearance. For each increase of 1 l/week, there was a 56% decrease of RR of death associated with RRF as compared to 24% with peritoneal clearance. The international prospective observational DOPPS study has also recently reported that the diuretic use and presence of RRF was associated with a better patient survival in prevalent HD patients. Diuretic use varied substantially among patients (0–83%) and decreased sharply after the start of dialysis (9.2% in Europe versus 21.3% in the United States). Patients with RRF on diuretics had almost twice the odds of retaining RRF after 1 year compared to patients not receiving diuretics. Patients receiving diuretics and maintaining RRF had a 7% lower all-cause mortality risk and 14% lower cardiac-specific mortality risk versus those not administered diuretics [9]. Loop diuretic use was associated with lower interdialytic weight gain and lower hyperkalaemic risk. RRF contributes to the adequacy of RRT in adding a native kidney component that seems to be physiologically more important than the dialysis dose established on small molecules. RRF enhances the removal of middle molecule solutes while reducing their circulating levels (e.g. ß2-microglobulin); this appears beneficial from a recent study [10]. Urine production is also beneficial to reduce interdialytic weight gain and extracellular fluid volume control. RRF is also associated with a better anaemia correction and reduced erythropoietic-stimulating agent consumption, improved nutritional status and quality of life and enhanced metabolic profiles [11].

What are the negative effects of maintaining RRF in dialysis patients?

On the dark side, maintenance of RRF in dialysis patients should make the clinician suspicious of maintaining dialysis patient in subclinical chronic fluid overload. This assumption is well illustrated in recent studies by direct and indirect arguments. Gunal *et al*. showed in a prospective interventional study, in a group of 47 prevalent hypertensive PD patients, that by means of a strong dietary salt restriction and intensified ultrafiltration, they were able to reduce dry weight by 2.8 kg, to normalize blood pressure with minimal use of antihypertensive medications and to reduce cardiothoracic index [12]. Meanwhile they observed a 50% reduction of the 24-h urine output with a significant reduction of the weekly dialysis dose delivered (1.85 versus 2.06). Gunal *et al*. showed in a prospective study involving now 19 incident CKD-5 patients treated by HD that a strict volume control (5-kg reduction of dry weight) was accompanied by a significant reduction of the blood pressure, a marked decrease of the left ventricular mass and a major reduction of residual urine production in virtually all patients [13]. Wang *et al*. exploring the relationship between fluid volume status (bioimpedance assessment) and blood pressure control in 100 prevalent CAPD patients showed clearly that hypertensive patients had significantly higher normalized extracellular fluid volume than normotensive patients with a residual daily urine production which was almost triple (996 versus 369 ml/24 h) in this group [14]. Meanwhile, a higher total sodium removal (dialysate and urine) was noted in the hypertensive group meaning that these patients had higher dietary salt intake. Interestingly, this phenomenon was more marked in the male group. Jones *et al*. also reported an interesting prospective study exploring the relationship between low serum albumin and overhydration in 21 PD patients [15]. By intensifying daily ultrafiltration over a 4-week period, dry weight and extracellular volume (bioimpedance assessment) were reduced by 1–1.5%, blood pressure was normalized, serum albumin

was significantly increased (35.9 versus 34.6 g/l), while 24-h urine output and RRF were reduced by almost 21%. These findings are by nature confirmatory of the previous observations made by the group of Tassin, indicating that tight control of extracellular fluid volume was associated with a better control of the blood pressure but a dramatic reduction of 24-h urine production [16,17]. More recently, using bio-markers of extracellular fluid expansion and left ventricular dysfunction (natriuretic peptides, BNP, NT-pro-BNP), it has been shown that both prevalent PD and HD patients were exposed to extracellular fluid overload and cardiovascular events [18,19]. Due to the cross-sectional design of these studies, no direct relationship could be established with RRF. Indeed, to evaluate the potential significance of these sensitive biomarkers and their relationship with the RRF, it is necessary to conduct a prospective controlled study in incident CKD-5 patients. Correction of fluid volume excess by combining dietary salt restriction and gentle ultrafiltration to achieve dry weight is a simple and effective means to control hypertension and to reverse left ventricular hypertrophy [20,21]. Fluid status equilibrium in PD patients is more critical than in HD patients since it relies strongly on the maintenance of RRF and peritoneal transfer capacities [22,23].

What are the factors implicated in the loss of RRF in dialysis patients?

Decline of RRF is commonly observed in CKD-5 dialysis patients. It is an unavoidable phenomenon caused by the degenerative and fibrosis process of CKD. However, the rate of RRF loss is not homogeneous among patients and may be affected by other factors such as treatment modalities and practice patterns [24].

Determinants of RRF decline in dialysis patients are multifactorial. Patient-related factors include age, causal nephropathy and comorbid conditions. It has been shown that decline of RRF was age dependent [25]. It is known from daily practice that chronic interstitial nephritis will preserve urine production longer. On the opposite, what is not really known is the impact of the comorbid state at the start of RRT on the persistence of RRF over time. One can speculate that late referral of CKD-5 patient or CKD case-mixed patients presenting with severe pathologies (diabetes, congestive heart failure, vascular disease, etc.) requiring aggressive fluid volume control by ultrafiltration will quickly lose RRF. Intercurrent events such as recurrent blood pressure drop during HD, cardiac events and sepsis may precipitate loss of RRF. Renal transplant patients lose their RRF very rapidly [26].

Medical practice-related factors including intensity and aggressiveness in achieving dry weight are important factors affecting the decline of RRF. This is the paradigm Tassin's approach that privileges rapid and tight arterial pressure control rather than preserving RRF [27]. As mentioned above, the extended use of loop diuretics in dialysis patients may help to prolong diuresis and preserve RRF. Although controversial, several factors known for their nephrotoxicity (aminoglycosides, contrast media) should be avoided or administered with caution [28,29].

Dialysis-related factors should be clearly identified. PD therapies have long been considered to preserve 24-h urinary output and RRF longer than HD therapies [30]. Recent controlled studies, best reflecting contemporary conditions of HD therapy using a high-flux synthetic membrane [31], ultrapure bicarbonate buffered dialysis fluid [32] and ultrafiltration controlled preventing intradialytic hypotensive events, have shown that RRF decline was virtually identical in PD and HD patients. In addition, several studies in PD-treated patients have shown that intensification of treatment efficacy based on daily automated PD (APD) was responsible for a steeper decline of RRF when compared to continuous ambulatory PD (CAPD) [33,34]. By reducing chronic microinflammation in PD patients, it has been assumed that the use of new biocompatible PD solutions had the potential of best preserving RRF. Unfortunately, a quite recent prospective randomised controlled trial failed to prove this positive impact [35]. Further studies in incident CKD-5 patients are needed to test this hypothesis.

Nowadays, the superiority of PD over HD in preserving RRF should be discussed taking into consideration a state-of-the-art technique both in HD and PD therapies. As far as the preservation of RRF is concerned, several protective measures have been identified. In PD patients, maintenance of RRF requires that fluid volume depletion is prevented, biocompatible and smoother ultrafiltration profile offered by icodextrin-based dialysis fluid solutions [36] are used, nephrotoxic medications are avoided, use of angiotensin receptor blocker is privileged [37,38] and peritoneal permeability capacity is preserved. In HD patients, preservation of RRF may be achieved by preventing intradialytic hypotensive episodes and by developing a highly biocompatible HD system including a synthetic membrane and ultrapure dialysis fluid.

What is the meaning of RRF persistence in dialysis patients?

Indeed, preservation of RRF must be considered as a permanent trade-off between patient comfort with relative diet freedom and the risk of fluid volume overload with its deleterious cardiac and nutritional consequences. Fluid volume control is an essential target for dialysis adequacy that should be regularly reassessed. Poor or inadequate control of the extracellular fluid volume in PD requires an evaluation of the urine volume production, the peritoneal membrane performances and a diet survey. When both peritoneal and renal function fail, a rapid transfer to HD is indicated to improve patient outcomes [39]. Inadequate control of fluid volume in HD patient requires intensifying ultrafiltration and dietary sodium restriction in order to correct hypertension and left ventricular dysfunction. Accordingly, it would be helpful for nephrologists to have tools facilitating appraisal of extracellular fluid volume of dialysis patient in order to achieve the ideal 'dry weight'. Bioimpedance assessment and sensitive biomarkers such as natriuretic peptides appear quite appealing options for guiding and supporting clinical assessment.

Another interpretation would be to consider that the persistence of RRF is a surrogate marker of relatively good

health in CKD patients with a timely referral and early start of RRT. In this case, RRF preservation would be an independent factor from the dialysis modality. However, this is a purely speculative hypothesis that deserves to be evaluated in a prospective study.

In conclusion, the preservation of RRF should not be considered as a primary goal but rather as a means for facilitating optimal RRT and improving patient survival. The tight control of the fluid volume should remain a prominent priority in the dialysis adequacy quest. Maintenance of RRF at the expense of chronic fluid overload is not suitable or acceptable for patients who are already at high risk for cardiovascular events. Preservation of RRF should remain a clinical concern for dialysis patients who express the delicate balance between benefits and risks.

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Sunscreens in organ transplant patients

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Introduction

Non-melanoma skin cancer, specifically basal cell carcinoma and squamous cell carcinoma, is the most frequent type of cancers diagnosed in fair-skinned populations. Their respective incidence is increasing worldwide by 3–5% per year [1].

Ultraviolet radiation is a major environmental cause. Both the total cumulative lifetime exposure to UV radiation and sporadic patterns of sun exposure (i.e. chronic, during work versus intermittent, during leisure time) are determinants for the individual risk of skin cancer. Increased cumulative lifetime sun exposure is associated with an increased risk of squamous cell carcinoma and actinic keratosis, the latter representing possible precursors of invasive squamous cell carcinoma [2].

Epidemiology in organ transplant recipients

Organ transplant recipients have particularly high rates of squamous cell carcinoma with a relative risk ∼100-fold higher than that in the immunocompetent population [3].

In an Irish study of renal transplant recipients, 93.5% of all squamous cell carcinomas occurred on the traditional 'sunny terraces' of the body, mainly head, neck, dorsum of the hands and forearms (Figure 1) [4]. Basal cell carcinoma is increased 'only' by a factor of 10 in organ transplant recipients. The reason for this is that the preferential sites of basal cell carcinoma are infrequently exposed to UV radiation, which could explain their occurrence on areas like the trunk that are less frequently exposed to the sun [5]. While basal cell carcinomas are believed to develop *de novo*, the development of cutaneous squamous cell carcinomas is viewed as a multi-step process that is initiated by p53 mutations of single cells leading to p53-mutated clusters and patches in clinically nonsuspicious skin and gradually progressing via different stages of actinic keratosis to invasive squamous cell carcinoma. Whereas, in immunocompetent patients, only ∼10% of individual lesions of actinic keratosis advance to invasive squamous cell carcinoma during a 5- to 10-year time frame, in organ transplant recipients the rate of progression of actinic keratosis is apparently accelerated (months) and the incidence of progression higher (>20–30%) [6]. Unfortunately, standardized data on the progression of actinic keratosis in organ transplant recipients are still missing.

The role of immune suppression

Apart from the direct effect of UV radiation causing DNA damage in keratinocytes, increasing evidence supports the hypothesis that UV radiation has also a negative effect on

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