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REVIEW

Choice of dialysis modality prior to kidney transplantation: Does it matter?

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Abstract

The population of patients with end stage renal disease (ESRD) is increasing, lengthening waiting lists for kidney transplantation. Majority of the patients are not able to receive a kidney transplant in timely manner even though it is well established that patient survival and quality of life after kidney transplantation is far better when compared to being on dialysis. A large number of patients who desire a kidney transplant ultimately end up needing some form of dialysis therapy. Most of incident ESRD patients choose hemodialysis (HD) over peritoneal dialysis (PD) as the modality of choice in the United States, even though studies have favored PD as a better choice of pre-transplant dialysis modality than HD. PD is largely underutilized in the United States due to variety of reasons. As a part of the decision making process, patients are often educated how the choice regarding modality of dialysis would fit into their life but it is not clear and not usually discussed, how it can affect eventual kidney transplantation in the future. In this article we would like to discuss ESRD demographics and outcomes, modality of dialysis and kidney transplant related events. We have summarized the data comparing PD and HD as the modality of dialysis and its impact on allograft and recipient outcomes after kidney transplantation.

Key words: Dialysis; Kidney transplant; Outcomes; Peritoneal dialysis; Health literacy

Core tip: Patients with end stage renal failure need some form of dialysis therapy as a bridge while they wait for kidney transplantation. In this paper we discuss if dialysis modality pre transplantation has any impact on transplant related outcomes.

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INTRODUCTION

Kidney transplantation is the ideal form of renal replacement therapy (RRT) in patients with end stage renal disease (ESRD). Preemptive kidney transplantation is ideal for many, as it is associated with lower rates of acute rejection, increased allograft and patient survival[1]. However, a preemptive kidney transplant (17% overall) is not always possible for many reasons which were explored by Jay *et al*[2], which included disparities in health insurance, race/ethnicity, patient education level, socioeconomic status, access to healthcare, diabetes status and regional variations. It is also well established that patient survival and quality of life after kidney transplantation is far better when compared to being on dialysis[3].

According to statistics, close to 10% of the population are diagnosed with chronic kidney disease around the world. Also only appropriate 10% of this patient population receives some treatment in the form of dialysis or transplant to stay alive. There were 30869 adults patients newly added to the waiting list and 33291 patients were removed from the list according to annual report from SRTR registry released in 2016. Unfortunately, a quarter of those patients were removed due to death or decline in medical condition[4]. Patients waiting for kidney transplant are also gradually getting older (median wait for a newly listed 2010 candidates was 3.9 years[5]), thereby the burden of kidney disease is rising in the elderly population. There has been some improvement in the dialysis related mortality overall but the organ shortage and continued increasing list of patients waiting for a transplant is still haunting the nephrology community. The average time on the waitlist for a deceased donor can be quite variable depending on age, blood group, panel reacting antibodies, history of prior transplantation, race/ethnicity and regional factors[4]. Hence, patients end up needing some form of RRT while they wait for transplantation.

Peritoneal dialysis (PD) leads to minimal disruption of the patient's life, thereby allowing the patient to continue to work or school or other usual activities, along with encouraging patient empowerment in self-management. Hence, for the patients who plan on receiving a transplant after starting dialysis, it can be a better bridge therapy to kidney transplantation, especially, when a lot of patients initiating hemodialysis (HD) *via* catheters are associated with adverse outcomes[6]. As a part of the decision making process, the education generally includes how the choice of therapy would fit into the patient's life however it is not clear and hence not discussed, how a dialysis modality may affect eventual kidney transplantation in the future. A number of studies have addressed the outcome of kidney transplantation after PD versus in-center HD, reporting mixed results. A meta-analysis by Tang *et al*[7] in 2016 concluded that PD was a better choice of pre-transplant dialysis modality than HD. Another study by Jones *et al*[7] in 2018 found PD as a viable bridge therapy for patients waiting for simultaneous liver-kidney transplantation. In another Cohort of 92884 patients, HD as a choice of RRT was associated with an increased risk for graft failure and recipient death[9]. On the other hand, study by Resende *et al*[10] and Dipalma *et al*[11] did not find any impact of dialysis modality on graft function or patient's survival after transplantation.

Our goal of this discussion is to review the current evidence in regards to choice of RRT and impact on kidney transplantation outcomes. We have organized the review into two categories: short-term outcomes, including delayed graft function (DGF), and allograft thrombosis; and long-term outcomes, including mortality. At first, we would like to review the demographics and outcomes of ESRD in the United States, as this crucial decision regarding modality choice can have large impact on choices of significant number of ESRD patients.

ESRD DEMOGRAPHICS

As per the United Network for Organ Sharing, in 2017, there were 94897 patients on the waiting list for kidney transplantation. Among those, majority were aged 50+ years (43% of patients were between 50-64 years of age and 23% of patients were 65+

years of age). Only, 19849 patients (40% of patients were age 50-64 years and 18% of patients were 65+ years of age) received kidney transplantation alone in the United States of America (USA) in the year of 2017[12].

Unites States Renal Data System (USRDS) is the most robust national database in the USA on all patients with ESRD covered by Medicare and Medicaid. At the end of 2015, there were 207810 patients living with a functioning kidney transplant and 83978 dialysis patients (17% of all prevalent dialysis patient population) were on waiting list for kidney transplantation[5]. In the USA, there were 124114 incident ESRD patients in the year 2015 with an unadjusted incident rate of 378 per million population, which is increasing steadily since 2012[13]. Unfortunately, approximately one third (36%) of those patients did not receive significant pre-ESRD care and 80% of patients initiated HD with a catheter as opposed to preferred arteriovenous access[6,13]. Majority of incident ESRD patients chose HD (87.8%) over PD (9.6%) as the modality of choice in the USA[13]. As per the latest data, there were 703243 prevalent ESRD patients in the USA (on December 2015) with an unadjusted prevalence rate of 2128 per million populations, which is also steadily increasing by adding about 20000 patients each year[13]. Among all prevalent ESRD patients, 63.2% of patients were on HD, 29.6% had a functioning kidney transplant and only 7% of patients were utilizing PD. In-center HD accounts for almost all of HD (98%) modality and only a very small percentage of patients perform home HD (2%)[13].

It is in stark contrast to countries like Hong Kong (70%), the Jalisco region of Mexico (51%), New Zealand (30%), Thailand (29%), Qatar (27%), Colombia (27%), Australia (20%) and Canada (20%), where much higher proportion of patients utilize PD as compared to the patients in the USA[14]. PD is an acceptable and could be a preferred form of RRT owing to flexibility, autonomy, care satisfaction[15], better preservation of residual renal function[16], better hypertension control[17], lower intra-dialytic hypotension episodes[18], lower risk of dementia, slower cognitive decline[19,20], better anemia management with lower doses of erythropoietin stimulating agents (ESA) and lower proportions of patients needing ESAs[21]. It is largely underutilized in the USA due to variety of reasons which have been explored by many researchers and found causes to be multifactorial which were physician specific (lack of experience, inadequate training, comfort with HD); patient specific (lack of adequate PD education, health literacy, burden of therapy, age, comorbidities); modality specific (concerns for mortality, solute clearance, peritonitis, treatment failure, regulatory issues on PD fluid, easy availability of HD); and financial incentives for HD units[22-24].

ESRD OUTCOMES

In recent times, success of PD technique has improved and risk of peritonitis had dwindled[22,23]. Review of the data also suggests that as per the USRDS[25], in 2015, adjusted mortality rate for patients on HD was slightly higher than patients on PD (169 per 1000 patients years *vs* 159 per 1000 patients years; respectively) and much higher than patients who received kidney transplantation (29 per 1000 patients years). A very interesting trend of mortality with age and time on dialysis has been noted.

Among those patients who started RRT with HD in 2015, mortality rates in patients < 65 years of age decreased from 200 deaths per 1000 patient-years in month 2 to 134 deaths per 1000 patient-years in month 12. Mortality rates in patients aged ≥ 65 years were much higher as compared to patients with < 65 years but also noted to decrease similarly (615 deaths per 1000 patient-years in month 2 to 278 deaths per 1000 patient-years in month 12).

In contrast, among patients who started RRT with PD[25], mortality increased in both patients < 65 years of age (28 deaths/1000 patient-years in month 1 to 64 deaths/1000 patient-years in month 12) and ≥ 65 years of age (124 deaths per 1000 patient-years in month 1 to 223 deaths per 1000 patient-years in month 12). This study showed two important findings, mortality rates for PD patients were much lower as compared to HD and secondly elderly patients tend to do better on PD versus HD. However, one concern from this mortality data arises that whether it is PD or HD, elderly patients age ≥ 65 years suffer from far more increased risk of mortality as compared to patients < 65 years of age. As the ESRD patient population is aging and dying waiting for a transplant, it will be imperative to increase utilization of kidney transplantation at the earliest and offer a better RRT modality.

In-fact, overall adjusted survival probability of incident patients on PD is much better at the end of 3 years than patients on HD (68% *vs* 57%). Expenditure of PD is also better than HD (75140 $ per patient per year *vs* 88750 $ per patient per year) but much higher than cost for transplant patients (34084 $ per patient per year)[26]. HD and PD patients have similar hospitalizations rate (1.7 per patient year) but almost double

of patients with kidney transplantation (0.8 per patient year). Patients on HD gradually has lower hospitalization rates as time goes on but patients on PD tends to have slightly higher hospitalization rates with time (1.4 PPY in 2013 but increased to 1.6 PPY at end of 3rd year) but still remained lower than HD cohort (1.7 PPY)[27]. This data suggests that PD is a more cost effective modality with somewhat lower risk of mortality as compared to HD in pre-transplant period.

While on the waitlist for a kidney transplant, mortality for PD and in-center HD patients was found to be similar by Inrig *et al*[28]. This prospective observational study used a cohort of patients placed on the transplant list who initiated dialysis (n = 12568) between May 1, 1995 and October 31, 1998. Two-year mortality was 6.6% among PD patients and 6.9% among HD patients, with no significant differences [hazard ratio (HR) 1.01; 95% confidence interval (CI) 0.82 to 1.23] when controlled for baseline characteristics, comorbidities, and laboratory variables. This study used the modality the patient was on at 90 d of dialysis as the treatment group, and excluded those who died in the first 90 d. Of note, in this study 24% of the patients were on PD, indicating that PD patients are much more likely to be listed for a kidney transplant early since the percentage of PD utilization nationally is much lower.

Delayed graft function for kidney transplant

DGF defined as need of dialysis within seven days of kidney transplantation, occurred in 21.3% of patients transplanted in 2008 in the USA[29].

Numerous studies as mentioned in Table 1 have investigated DGF rates and have found mostly similar to lower rates of DGF in PD versus HD patients[29-39]. Some of the earlier studies were performed in an era when different immunosuppressive regimens were used[31-34]. A large study by Snyder *et al*[38] investigated this question in 2002 using USRDS data with over 22000 patients; also found a lower incidence of DGF among PD patients (RR = 0.74, 95%CI: 0.67-0.81, P < 0.0001) after adjustment of multiple clinical covariates. They also noted that PD patients were 1.39 times more likely to get transplanted as compared to HD patients (95%CI: 1.35-1.43, P < 0.0001). In a more recent study by Molnar *et al*[39] of 14508 dialysis patients who underwent kidney transplantation for the first time, the case-mix-adjusted risk of DGF was 34% lower for patients on PD *vs* HD (HR = 0.66 with 95%CI of 0.55-0.79, P < 0.001). However, once adjusted for malnutrition inflammation complex syndrome and donor characteristics, PD was no longer an independent predictor for decreased DGF (HR = 0.82 with 95%CI of 0.60-1.13, P = 0.23)[31]. But, PD was found to be protective against DGF in a subgroup of patients with hemoglobin between 12 and 13 gram/dL. A meta-analysis by Tang *et al*[7] found significantly lower risk of DGF in PD patients as compared to HD patients (OR 0.67, 95%CI: 0.62-0.72, P = 0.024). Lin *et al*[41] also postulated higher risk of DGF in HD patients based upon the observation that there more dialysis events were noted in HD group (1.59 in HD *vs* 0.71 in PD, P < 0.05).

In a retrospective observation study of patients with DGF requiring HD or PD, Thomson *et al*[42] found an increased risk of wound infection/leakage (PD 5/14 *vs* HD 6/63, P = 0.024), shorter length of hospitalization (PD 13.7 d *vs* HD 18.7 d, P = 0.009) and lesser time requiring dialysis post-operatively (PD 6.5 d *vs* HD 11.0 d, P = 0.043) with use of PD however no differences in readmission to hospital within 6 mo, graft loss or acute rejection episodes at one year. GFR also did not differ between the PD and HD groups at one month, six months or at one year[42].

Reasons for better outcome in terms of DGF in PD patients are not entirely clear. PD patients have better preservation of residual renal function[37,38]. There may be lead time bias as well because, generally PD patients may be more motivated and hence may have increased transplant access. Few other reasons like difference in immune function, cytokine production, and different response to ischemic kidneys among PD *vs* HD patients have been proposed as well[37]. In fact, maintenance dialysis prior to transplantation is noted to be a major contributor to DGF[29]. Since, PD is performed daily and patients are less likely to be hyperkalemic, hence are less likely to require additional treatments just prior to kidney transplantation. PD patients are not likely to be volume depleted either; this will also ensure adequate perfusion of the allograft. HD prior to transplant may be associated with volume removal, which in turn may result in eventual decreased perfusion of the transplanted organ and some tubular necrosis[43]. In addition, intra-op aggressive hydration has been proved to be effective in reducing DGF[29,43], which may have been countered against by pre-transplant HD.

Thrombosis of the allograft: Comparing prior HD to PD

In contrast to DGF, thrombosis of the graft may be surprisingly higher in the PD patients (Table 2) as compared to their HD counterparts[38,44-46].

In Snyder *et al*'s[38] subgroup analysis of allografts surviving < 3 mo, patients on PD prior to the transplant had higher adjusted risk for both allograft failure (RR 1.23, 95%CI: 1.09-1.39, P < 0.001) and death-censored allograft failure (RR 1.33, 95%CI: 1.16-

Table 1 Pre-transplant dialysis modality and delayed graft function

Study Period	Authors	Study Design	Study Participants	DGF Incidence	Favors
1983-2006	Caliskan *et al*[30]	Retrospective observational	44 PD and 44 HD patients	No difference in DGF incidence	None
1983-1989	Cacciarelli *et al*[31]	Retrospective observational	cohort of 662 patients	26% of PD and 36% of HD patients	PD
1984-1988	Triolo *et al*[32]	Retrospective observational	18 PD and 18 HD patients	27% patients on PD and 27% patients on HD	None
1988-1995	Fontan *et al*[33]	Retrospective observational	92 PD and 587 HD patients	22.5% in PD and 39.5% of HD patients	PD
1989	Cardella *et al*[34]	Retrospective observational	31 PD and 37 HD patients	35% in PD and 35% in HD patients	None
1990s	Vanholder *et al*[35]	Case-control	117 PD and 117 HD patients	23.1% in PD and 50.4% in HD	PD
1993-2014	Song *et al*[36]	Retrospective observational	97 PD and 178 HD patients	19.6% in PD and 32% in HD	PD
1994- 1995	Bleyer *et al*[37]	Retrospective observational	Cohort of 9291 patients	20% of PD and 28.6% of HD patients	PD
1995-1998	Snyder *et al*[38]	Retrospective observational	5621 PD and 17155 HD patients	12% in PD and 16% in HD	PD
2001-2006	Molnar *et al*[39]	Retrospective observational	2092 PD and 12,416 HD patients	15% in PD and 21% in HD	PD
2002-2011	Prasad *et al*[40]	Retrospective observational	45 PD and 45 HD patients	8.8% in PD and 11.1% in HD	None

DGF: Delayed graft function; PD: Peritoneal dialysis; HD: Hemodialysis.

1.53, $P < 0.0001$) than HD patients[38]. Forty one percent of those on prior PD, who had allograft failure in the first 3 mo, had thrombosis *vs* 30% of those on prior HD (OR 1.59, 95%CI: 1.08-2.36, $P = 0.02$). All other early causes of allograft loss were similar between the two groups. In another study of 84513 renal transplant recipients between 1990-1996, Ojo *et al*[48] found much higher odds of renal vein thrombosis (RVT) in PD patients as compared to HD patients (OR = 1.87, $P = 0.001$). Change in pre-transplant dialysis modality was also predictive of RVT among patients who switched from HD to PD (OR = 3.59, $P < 0.001$) as compared to HD patients who never switched and among patients who switched from PD to HD as compared to HD patients who never switched (OR = 1.62, $P = 0.047$)[48]. In another study of 119 HD and 39 PD patients who underwent simultaneous kidney-pancreas transplantation, renal allograft loss due to thrombosis was much more common in PD patients as compared to HD patients (5.1% *vs* 0%, $P = 0.058$)[50].

Since most patients on PD do not have an arteriovenous access, underlying thrombotic tendencies may be masked, and only uncovered at the time of transplantation. In addition, some PD patients may have been driven to switch after repeated thrombosis of the HD access. Moreover, PD patients are noted to have increased pro-coagulant factors such as apolipoprotein A, factors II, VII, VIII, IX, X, XI and factor XII, and hemo-concentration as compared to HD patients which can predispose them at higher risk of allograft thrombosis[46,48]. The reasons behind increase in such factors are likely due to moderate non-specific inflammatory cell harvesting when the peritoneal membrane gets exposed to dialysis solutions. This leads to macrophage activation and increased presence of thromboplastin and plasminogen activator in the peritoneal cavity.

On the contrary, a study by Pérez Fontán *et al*[47] on 827 patients (127 PD and 700 HD patients), who received deceased donor kidney transplantation between 1988 and 1997, there were similar incidence of primary allograft thrombosis between PD and HD patients (4.7% *vs* 6.1%, P = NS). Arterial and venous thrombosis was also similar in both groups[47]. Studies by Lin *et al*[41] and Escuin *et al*[49] also reported similar results whereby they found no difference in incidence of graft thrombosis among PD versus HD patients.

Risk of infection and diabetes mellitus after transplantation

Patients receive multiple immunosuppressive medications in post-transplant period which increases the risk of infections. Infectious complications related with PD catheter after transplantation remain a concern[42,50]. In a study by Rizzi *et al*[51] on 313 PD patients who underwent transplantation between 2000 to 2015, authors found that 8.9% patients had post-transplant peritonitis especially among those who had DGF requiring dialysis. In addition, PD catheter was associated with an increased risk of exit-site infection and peritonitis even if it's not used[52]. There is also a report of increased conversion from PD to HD after transplant due to leakage of dialysate fluid from surgical incision[52]. Hence, authors had suggested low threshold for PD catheter removal at time of transplantation in patients with low risk of DGF. In patients with an increased risk of DGF, PD catheter could be left in place but to be removed at the

Table 2 Pre-transplant dialysis modality and allograft thrombosis

Study Period	Authors	Study Design	Study Participants	Thrombosis Incidence	Odds Ratio (OR)
1980s-1990s	Van der Vliet *et al*[44]	Retrospective observational	303 PD and 612 HD patients	7.3% in PD and 3.6% in HD patients	$P < 0.02$
1988-1997	Pérez Fontán *et al*[47]	Retrospective observational	127 PD and 700 HD patients	4.7% in PD and 6.1% in HD patients	P = NS[b]
1989-1992	Murphy *et al*[45]	Retrospective observational	202 renal transplant procedures	9 PD versus 0 HD patients	Chi-squared = 9.63; $P < 0.01$
1990-1996	Ojo *et al*[48]	Retrospective Case-control match	63 PD and 161 HD patients	30.7% in PD and 18.9% in HD	OR = 1.87, 95%CI[c] 1.28-2.72, $P < 0.001$
1990-1994	Escuin *et al*[49]	Retrospective observational	138 PD and 892 HD patients	2.17% in PD and 3.47% in HD	P = NS
1992-1996	Vats *et al*[46]	Retrospective observational	1090 PD and 780 HD children	20% in PD and 10% in HD[a]	$P = 0.04$
1995-1998	Snyder *et al*[38]	Retrospective observational	156 PD and 349 HD patients	41% in PD and 30% in HD	OR 1.59, 95%CI 1.08-2.36, $P = 0.02$
1998-2011	Lin *et al*[41]	Retrospective cohort	603 PD and 1209 HD patients	Not available	P = NS

[a]:vascular thrombosis as cause of graft failure;
[b]:non-significant;
[c]:Confidence Interval. PD: Peritoneal dialysis; HD: Hemodialysis.

earliest once no longer needed. Also, incidence of post-operative infections after transplantation was found to be increased in PD patients as compared to HD patients (67.5% *vs* 25.9%, $P < 0.00001$) with an increased median length of hospital stay[53]. Lin *et al*[41] also found higher risks of peritonitis and urinary tract infection in PD patients after transplantation. But, authors reported higher risk of new onset tuberculosis and chronic hepatitis C in patients after 90 d of kidney transplantation treated with prior HD[41].

Risk factors for post-transplant diabetes mellitus (PTDM) was evaluated by Courivaud *et al*[54] among 137 patients and did not find any impact of dialysis modality on development of PTDM. On the contrary, in a cohort of 72 patients, Madziarska *et al*[55] found that PD was associated with an increased risk of PTDM ($P = 0.007$) in the multivariate analysis. In another study of 121 non-diabetic patients by Seifi *et al*[56], authors found when used as pre-transplant modality, PD was associated with an increased risk for PTDM in univariate analysis, but not in multivariate analysis. The factors associated with new onset of diabetes after transplantation are multiple and variable, but not limited to presence of pre diabetes, immunosuppressive medication regimen, improved appetite and weight gain post-transplant among other.

Long-term outcome: Comparing those on prior HD vs PD

Preemptive kidney transplant without dialysis was associated with excellent patient survival compared to HD prior to transplant (HR 0.81 with 95%CI of 0.73-0.89, $P < 0.001$)[9]. Data on long-term graft survival after PD and HD is mixed from most studies. Goldfarb *et al*[9] analyzed 92844 patients who underwent kidney or kidney-pancreas transplants in 1990-1999. They reported better graft outcomes in patients previously treated predominantly with PD as compared to HD patients (HR 0.97 with 95%CI of 0.94-1.0, $P < 0.05$), after controlling for multiple variables. Lin *et al*[41] also reported higher risk of death censored graft failure in a multivariate analysis in HD patients as compared to PD patients after 10 years of follow up (HR 1.31, 95%CI 1.03-1.84, $P = 0.031$). Although, Tang *et al*[7] did not found 5 years graft survival rate to be different with pre-transplant PD as compared to HD technique in their meta-analysis (HR 0.92, 95%CI: 0.84-1.01, $P = 0.08$). Ten year graft survival was reported to be similar between a cohort of 80 HD and 80 PD patients[11]. In another study of 11664 PD and 45561 HD patient, a similar death-censored graft survival was reported ($P = 0.39$)[57]. Discrepancies in these results were evaluated by Kramer *et al*[58] in a cohort of 29088 patients who received kidney transplantation between 1999 and 2008 and found that statistically significant association of PD with better allograft and patient survival in a multivariable cox regression analysis disappeared when used instrumental variable method that used the case-mix adjusted center percentage of PD as predictor variable.

Patient survival may also be better after kidney transplantation in those on preceding PD as compared to HD. The Goldfarb *et al*[9] study also revealed that predominate PD prior to transplant was independently associated with better recipient survival compared to patients on preceding HD (HR 0.96 with 95%CI of 0.92-0.99, $P < 0.05$). Authors also looked at various RRT combinations and outcomes. They found that patient survival was significantly better in those on prior PD only when compared to those whose prior treatment consisted of solely HD (HR 0.90 with CI of 0.86 to 0.94, $P < 0.001$)[9]. In another study by López-Oliva *et al*[59], authors looked at a cohort of 236 patients and reported that long term patient survival was higher for the PD group than the HD group ($P = 0.04$). Interestingly the combination of prior PD and HD had a worse survival than those on HD alone (HR 1.10, with 95%CI of 1.06 to 1.15, $P < 0.001$).

Similarly, a European center in 2006 reported that prior-PD patients fare better and have lower post-transplant mortality than those on preceding HD. The same authors had postulated that exposure to the HD dialyzer membrane could be immunogenic and lead to an increased risk of graft loss. They found that despite using the biocompatible membranes, patient survival on pre-transplant PD was still superior to the HD counterparts[60].

Mortality benefits in PD patients were again seen in the results reported by Molnar *et al*[39] from 2012. They reported that patients who had been on PD before receiving a kidney transplant have an adjusted 43% lower death risk compared to those on prior HD (HR 0.57 with CI of 0.38-0.87). Using propensity matching, those with a high likelihood of being on PD ($n = 4836$) when adjusted for many variables including transplant donor variables had a HR of 0.56 (0.31-0.99, $P = 0.04$) of all-cause death in comparison to previous HD[39]. Cardiovascular mortality in recipients who were on prior PD was lower compared to those on prior HD, controlling for many variables (HR 0.94)[39]. In an another study, superior survival of PD patients after transplantation was reported to be due to lower risk of cardiovascular death in a cohort of 60008 patients[57]. Still, there are many studies reported whereby authors didn't found survival benefit of PD over HD after transplantation[10,11,58]. Reasons for these mixed results is that even though most of the studies looked at standard variables like time and duration of dialysis, comorbidity index, it still does not take into account many other factors which may determine the long term survival benefits post transplantation. The choice of dialysis modality for any patient also leads to selection bias which may confound the end results like patient or graft survival post transplantation.

Mehrotra *et al*[61] looked at the USRDS database to compare the impact of dialysis modality on survival. They reported no significant difference in the risk of death for PD and HD patients during the 5-year follow-up period. Earlier studies from other countries reported to have shown a marked early survival advantage for PD compared to in-center HD[62-64]. The reasons for this are, may be due to better planning before starting PD, as opposed to HD. PD patients are better prepared and more motivated which might to increased access to transplantation care both pre and post. In addition, this could be explained by the better preservation of residual kidney function on PD, which has been repeatedly shown to enhance survival[65,66].

CONCLUSIONS

Incidence and prevalence of ESRDs in the USA is rising; adding to already a large number of patients on dialysis despite the knowledge that kidney transplantation is ideal and associated with far superior clinical outcomes for patients with ESRD than being on dialysis. Majority of patients in the USA choose HD over PD and initiate dialysis with catheters as opposed to preferred arteriovenous access. Current evidence favors PD over HD as modality of choice as it is associated with lower risk of hospitalizations, healthcare expenditures and mortality. Although, conflicting data exists on mortality benefit of PD versus HD; as mortality for PD and in-center HD patients was found to be similar while on the waitlist[28]. In regards to kidney transplantation outcomes, PD was associated with lower risk of DGF and cardiovascular mortality as compared to HD but with higher risk of infectious complications. Reports on allograft thrombosis, 5 years and 10 years graft survival and patient survival showed mixed results.

Overall, we believe that the choice of dialysis modality prior to kidney transplantation matters. While it is difficult to do a large numbered randomized controlled trial in an attempt to answer this extremely question, education regarding pre-transplant dialysis modality choices needs to be multi-faceted and should include all considerations including impact on kidney transplantation; its short term and long

term outcomes along with the impact on lifestyle[67-69]. This education should not biased on health literacy levels, and no matter what modality patients choose, the education and training must be patient centered, using universal approach. PD is an underutilized modality in the USA and can be a therapy of choice with a potential to be associated with improved outcome for transplantation. Further research and attention from nephrologist and transplantation community is needed in this regard.

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REVIEW

Insulin receptors in the kidneys in health and disease

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Abstract

Insulin is an important hormone that affects various metabolic processes, including kidney function. Impairment in insulin's action leads to insulin resistance in the target tissue. Besides defects in post-receptor insulin signaling, impairment at the receptor level could significantly affect insulin sensitivity of the target tissue. The kidney is a known target of insulin; however, whether the kidney develops "insulin resistance" is debatable. Regulation of the insulin receptor (IR) expression and its function is very well studied in major metabolic tissues like liver, skeletal muscles, and adipose tissue. The physiological relevance of IRs in the kidney has recently begun to be clarified. The credit goes to studies that showed a wide distribution of IR throughout the nephron segments and their reduced expression in the insulin resistance state. Moreover, altered renal and systemic metabolism observed in mice with targeted deletion of the IR from various epithelial cells of the kidney has strengthened this proposition. In this review, we recapitulate the crucial findings from literature that have expanded our knowledge regarding the significance of the renal IR in normal- and insulin-resistance states.

Key words: Insulin receptor; Insulin resistance; Kidney disease; Renal sodium reabsorption; Gluconeogenesis; Proteinuria; Systemic blood pressure

Core tip: Dysregulation of the renal insulin receptor (IR) not only affects local renal metabolism, but also disturbs the systemic glucose homeostasis and blood pressure, leading to metabolic abnormalities. The objective of this review is to highlight the pathophysiological stature of renal IRs in the kidney function, as well as, overall metabolism.

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INTRODUCTION

The incidence of insulin resistance is increasing worldwide in parallel with the rate of obesity. Insulin resistance, *per se*, is often subclinical, and defined by inefficient insulin receptor (IR) signaling in major metabolic tissues, including liver, muscle, and adipose, resulting in impaired cellular glucose uptake. The function and role of reduced IR signaling has been extensively studied in these metabolic tissues. In addition to downstream signaling, alterations in the expression, binding, and phosphorylation of the IR itself may affect target cell sensitivity to insulin[1-3]. The kidney expresses IRs[4,5]; however, it is still debatable whether kidney develops classic "resistance" in the same manner as the liver, muscle, and adipose tissues. Reduced expression of IR and its phosphorylated form, the first step in IR signaling, have been demonstrated in renal epithelial cells of diabetic and insulin-resistant rat models[6,7]. Nevertheless, presence of these receptors throughout the nephron segments suggests an important role in renal metabolism. Insulin could undoubtedly regulate several vital kidney functions through its receptors. However, it has been a mere decade since the role of renal epithelial IR in kidney physiology and pathology began to be illuminated. In this review, we bring together the findings from published literatures that have contributed to our understanding in the area. For easy reading we will use the phrase "renal IR" in place of "IR in renal epithelial cells".

INSULIN RECEPTORS AND INSULIN SIGNALING

Insulin, secreted by pancreatic β-cells, is a peptide hormone with pleiotropic actions and plays an indispensable role in human metabolism. Biological effects of insulin are exerted by binding to IRs. IRs belong to the receptor tyrosine kinases and the IR subfamily, which consists of the IR, the insulin-like growth factor (IGF-I/-II) receptors, and the IR-related receptor[8]. The IR is a transmembrane protein that is composed of two α- and two β-subunits forming a heterotetramer α2β2 (Figure 1), with disulfide bonds between the α-subunits and between the α- and β-subunits[9]. The human IR cDNA was isolated and cloned in the 1980s[10,11]. These studies demonstrated that the α- and β-subunits are derived from proteolytic cleavage of a common precursor. Later, Seino *et al*[12] reported that the IR gene (*INSR*) is encoded by 22 exons and 21 introns. Alternative splicing of exon 11 results in two isoforms, A and B with differential insulin affinity, with isoform B having higher affinity.

Insulin binding to extracellular α-subunits confers conformational changes within the molecule, leading to autophosphorylation of specific tyrosine residues in intracellular domains[13]. Upon activation, various adaptors and signaling proteins (IRS, SHC, GRB, *etc*.) are recruited to the receptor to initiate the intracellular signaling cascade and regulate different biological functions[8,13] (Figure 2).

LOCALIZATION OF THE IR IN THE KIDNEY

The attempts to examine the expression pattern of IRs in the kidney had started about four decades ago; however, their physiological role in the kidney has recently come to light[4,14-16]. Renal localization of IRs was first studied by ^{125}I-labeled insulin binding in microdissected rat glomeruli and tubules in 1988. The results showed high affinity binding sites in the proximal and distal convoluted tubules (PCT and DCT), and to a lesser extent in the cortical and outer medullary collecting duct (CD) and thick ascending limb (TAL)[15]. Later, Sechi *et al*[4] exploited an *in situ* autoradiographic technique to observe insulin binding in glomeruli, renal cortex, outer and inner renal medulla. Findings from their studies revealed the highest IR density in the inner portion of the medulla, which also exhibits the maximal insulin activity in the renal tubule. The localization of IR in the proximal tubule (PT), TAL, DCT, and CD have also been shown by immunofluorescence using polyclonal antibodies against the α- and β-subunits of IR[16]. This approach illustrated an exclusive localization pattern of IR as these antibodies did not overlap with IGF-1 receptor and the IR-related receptor in kidney[17,18]. The significance of IR expression in different segments of the nephron

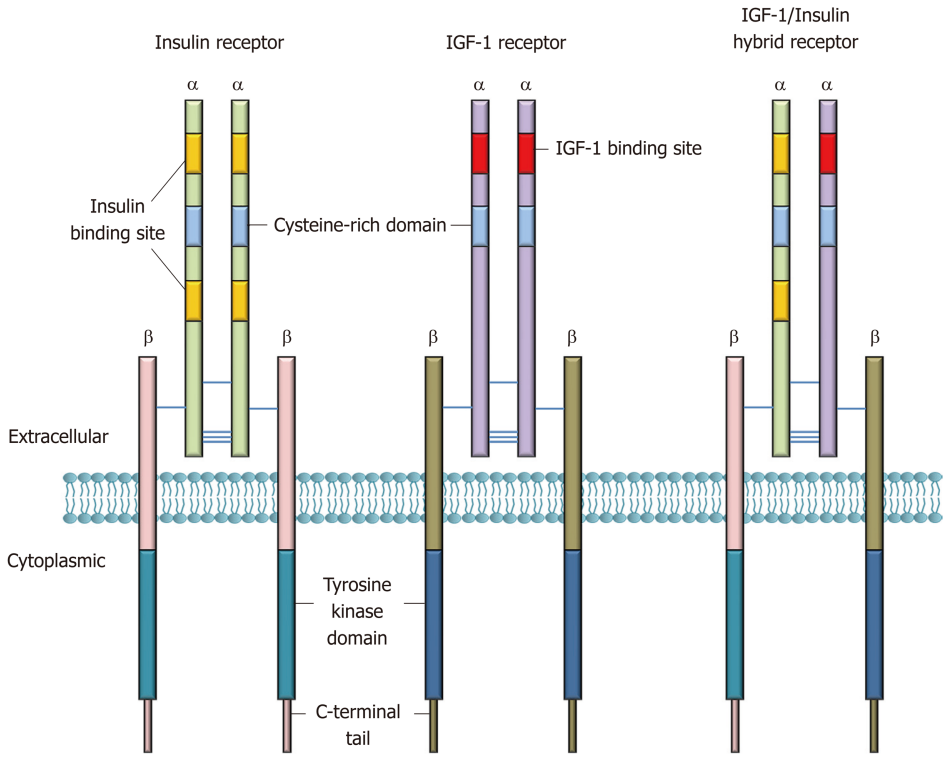

Figure 1 Architecture of insulin and insulin-like growth factor-1 receptors. Insulin and IGF-1 receptors consist of two extracellular α-chains and two transmembrane β-chains. The α-subunits have binding sites for insulin and IGF-1, whereas the cytoplasmic kinase domain comprises major sites for tyrosine autophosphorylation that are crucial for receptor activation. The α- and β-subunits are connected together *via* disulfide linkages (Figure is adapted from reference[9]). IGF: Insulin-like growth factor.

was later confirmed by targeted deletion of IR from these segments[19,20].

RENAL IR IN CARDIOVASCULAR PHYSIOLOGY

Renal regulation of sodium reabsorption is crucial for maintaining homeostasis, fluid balance, and systemic blood pressure. Excessive intake of dietary sodium and/or impaired salt excretion augments the incidences of hypertension[21]. There is substantial evidence suggesting restriction of dietary sodium could decrease cardiovascular risk and reduce blood pressure in normotensive and hypertensive individuals[22,23]. In kidney, sodium reabsorption occurs throughout the tubular segments of nephron including the PT, TAL, DT, and CD[24-26].

Insulin is reported to have antinatriuretic properties and has been shown to increase sodium absorption by regulating the activities of different renal sodium channels including the Na^+/H^+ exchanger type 3, the sodium-bicarbonate cotransporter, and the Na-K-ATPase in PT, the sodium-potassium-chloride cotransporter type 2 and the Na-K-ATPase in TAL, and the sodium-chloride cotransporter and the epithelial sodium channel in DCT and CD[27].

To elucidate the sodium-insulin interaction in the kidney, Sechi *et al*[28], examined renal IR binding and mRNA levels of IRs in rats fed on different salt concentration. They reported an inverse relationship between dietary salt (NaCl) intake and renal IR density. In concordance with this study, Catena *et al*[29] also reported a decrement in IR number and mRNA levels in control rats fed on a high-salt diet. However, IR densities were reported comparable in fructose-fed rats maintained on high- or low-salt diet. Further, a reduced antinatriuretic effect of insulin in high-salt-fed control rats was not observed in fructose-fed rats, implying that the fructose-fed animals lacked the feedback mechanism that limits insulin-induced sodium retention during high salt intake, which may contribute to fructose-induced hypertension[29].

Nevertheless, the expression pattern of IR in the PT, TAL, and CD implies the involvement of IRs in insulin-mediated renal sodium retention[15,30-32]. Therefore, investigating the correlation between IRs and renal sodium reabsorption has been a major focus of researchers to understand the connection between insulin resistance and hypertension. Hypertension is one of the most common cardiovascular complications worldwide. High blood pressure and associated complications lay a

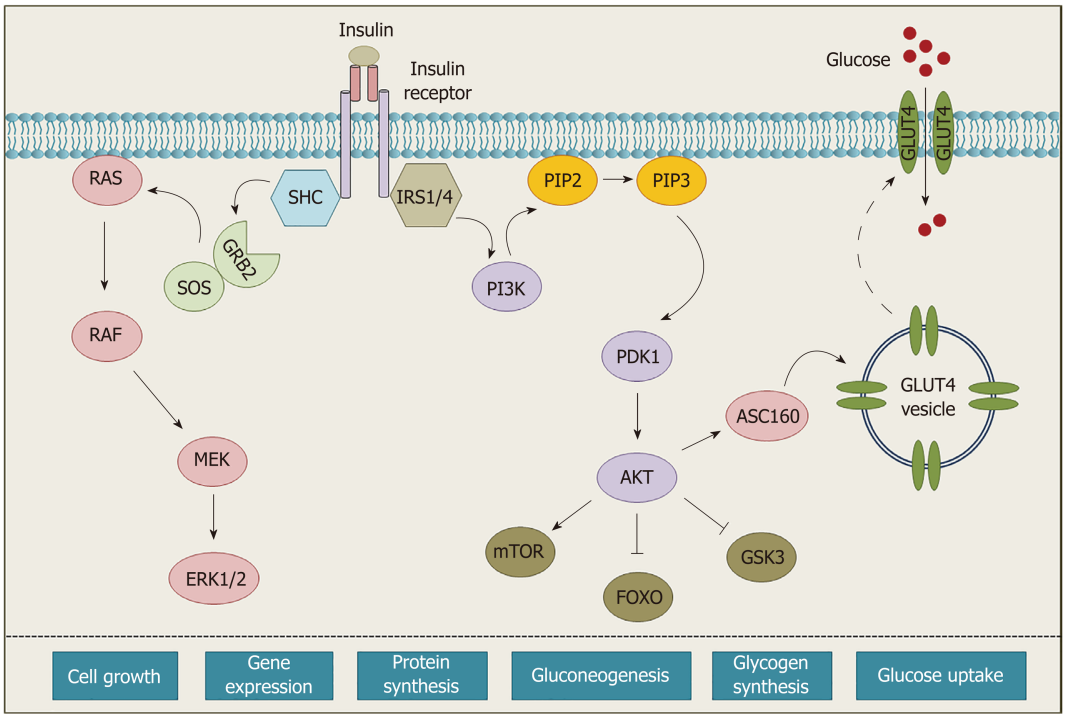

Figure 2 Schematics of the insulin receptor signaling. Binding of insulin to its receptor causes autophosphorylation of specific tyrosine residues. Upon activation IR recruits different adaptor proteins and initiates a cascade of phosphorylation events. These signaling events ultimately lead to activation or repression of an array of proteins, which regulate various biological functions (Figure is adapted from reference[8]).

grave burden on patients. Among various determinants of hypertension, insulin resistance is considered to be a major determinant. Although the precise role of insulin resistance is debatable in the development of hypertension, activation of the sympathetic nervous system, insulin-regulated sodium retention, and activation of the renin-angiotensin system (RAS) are considered as plausible mechanisms[33-35]. The interrelation between insulin resistance and hypertension could either be a non-causal association (two independent processes) or a cause-and-effect relationship, where insulin resistance acts as a cause of hypertension[36].

Interestingly, we observed that specific knockout of renal epithelial cell IR caused elevated systolic blood pressure in mice. Our study has shown that targeted deletion of IRs from renal epithelial cells significantly increased systolic blood pressure and impaired sodium excretion in response to saline load as compared to wild-type (WT). Moreover, intraperitoneal administration of insulin caused a significant drop in blood pressure in WT, but not in IR-knockout (KO) mice. Urinary excretion of nitrates and nitrites (UNOx) was also reduced in KO mice relative to WT mice (Figure 3). These observations suggested that renal IRs could play a key part in the maintenance of normal blood pressure and volume-expansion-associated natriuresis[19]. A study from Bhalla's lab also has shown that renal tubule-specific knockout of IR decreased NCC-mediated sodium reabsorption in high fat-fed mice[37]. However, further investigation is required to comprehensively understand the IR-dependent regulation of sodium retention and associated hypertension during insulin resistance.

Insulin has a complex role in the maintenance of blood pressure. On one hand, insulin-induced sodium retention and increased sympathetic activity is a root cause of hypertension, at the same time, insulin itself has a vasodilatory effect, which is associated with nitric oxide (NO) production[38]. In kidney, hyperinsulinemia affects renal blood flow in a NO-dependent manner[39] and insulin resistance impedes this effect[40,41]. Moreover, experimental diabetes in rats has resulted in reduced renal NO production[42]. Local renal production of NO production has also been implicated in impaired renal blood flow during congestive heart failure[43]. Apart from its vasodilatory effects, NO is also reported to reduce sodium reabsorption in renal tubules[44,45]. Specific deletion of IR from renal epithelial cells has been reported to impair sodium and NO excretion and elevate systemic blood pressure in mice, suggesting a possible role of impaired renal NO production in blood pressure regulation[19]. Moreover, reduced renal expression of the IR in TAL has been linked to salt sensitivity of blood pressure *via* blunted production of NO[46]. These IR-knockout mice also exhibited low protein levels of nitric oxide synthase isoform, NOS1, which is expressed in macula densa cells, TAL, and in CD[46]. Together, these studies support a

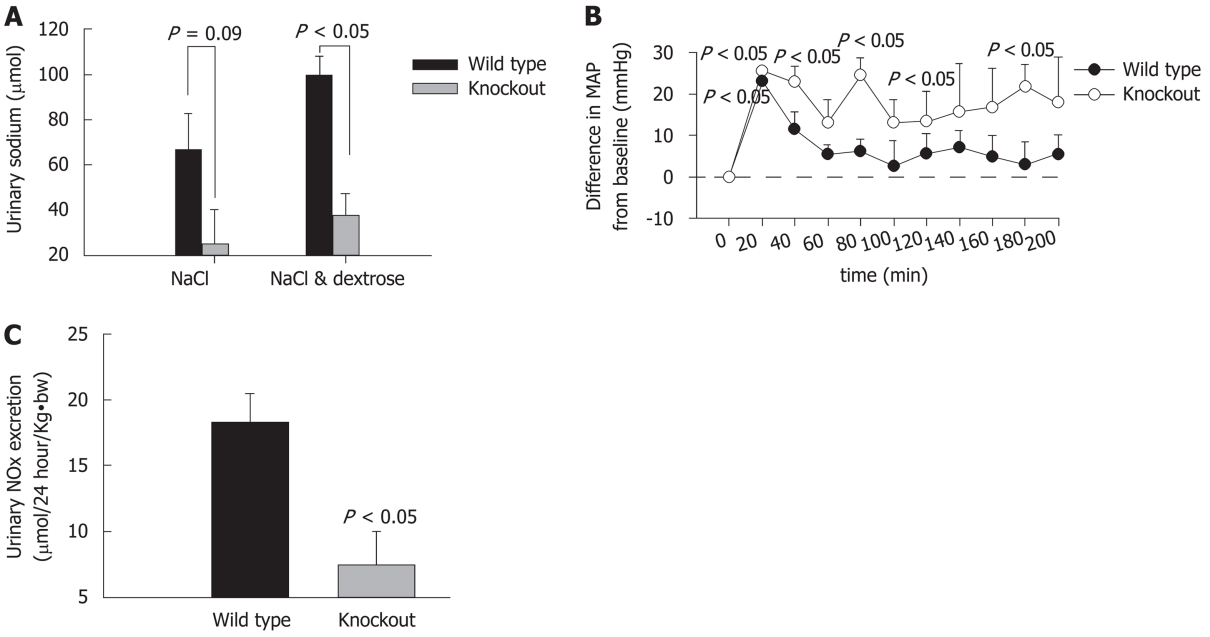

Figure 3 Altered natriuresis and impaired nitric oxide metabolism in insulin receptor-knockout mice. A: Urinary sodium excretion after oral administration of saline with and without dextrose in 4 h; B: Mean arterial blood pressure (ΔMAP) after NaCl and dextrose administration in mice; C: Urinary nitrate and nitrite excretion in wild-type and insulin receptor-knockout mice after 24 h. (Figure is a modification of figures published in reference[19] and taken with permission).

crucial role of renal NO in blood pressure regulation by its autocrine and paracrine actions, particularly in the medullary TAL and CD[47-49].

A fairly recent report from our group showed for the first time that insulin induces eNOS activation and NO generation in the renal inner medullary collecting duct (IMCD) cells[50]. We observed a time- and dose-dependent increase in NO and its metabolite NOx in insulin-stimulated mouse IMCD cells. Moreover, chronic insulin infusion in C57BL/6J mice led to increased expression of endothelial NOS (eNOS) and elevated NO levels in the inner medulla. However, treatment of cells with wortmannin (PI3K inhibitor) and IR-knockdown abolished these effects of insulin *in vitro*, implying the involvement of the IR/PI3K pathway in insulin-stimulated NO generation. Further, targeted deletion of IR from renal tubule epithelial cells resulted in significant downregulation of eNOS in inner medulla with concomitant rise in blood pressure in KO mice. These observations implied that IR signaling in the IMCD could contribute to hypertension in the insulin-resistant state.

The renal RAS is another imperative pathway that regulates systemic blood pressure and maintains water and electrolyte homeostasis. Typically, angiotensin II (Ang II) produced in the RAS pathway interacts with angiotensin type 1 receptors (AT_1R) to exert its biological effects in various tissues including the kidney, the heart, adipocytes, adrenal tissues[51], *etc*. The classical RAS pathway induces sodium reabsorption, vasoconstriction, and blood pressure. Moreover, Ang II has been established to inhibit insulin-mediated PI3K activation and is involved in the pathogenesis of insulin resistance[52]. An interrelation between insulin resistance and the RAS pathway has been reported in hypertensive patients. Although precise mechanism of insulin resistance and RAS is not well established, these two pathways interact at multiple levels to regulate cellular metabolism[53]. Previously, it has been demonstrated that Ang II induces phosphorylation of IRS1 (a key substrate of IR) at Ser616 and Ser312, which is responsible for its inactivation and inhibition of insulin/PI3K signaling cascade[54]. A direct link between renal IRs, RAS, and cardiovascular complications has not been reported and warrants further investigation.

RENAL IR IN SYSTEMIC GLUCOSE HOMEOSTASIS

IR signaling has been reported to maintain blood glucose levels in the liver and other metabolic tissues[55-57], however, there is limited knowledge regarding this action in the kidney. Recent studies have highlighted that renal IR signaling is an equally important contributor and regulator of systemic glucose levels[19,58-60]. The first evidence on kidney's involvement in glucose metabolism came in 1938, where

Bergman *et al* observed that removal of kidneys in hepatectomized rabbits doubled the sugar utilization rate as compared to the hepatectomized animals only[61]. Following which a number of studies substantiated the glucose production activity of the kidney[62,63] and provided evidence that kidney, in addition to acidosis or prolonged starvation, also releases considerable amounts of glucose in normal post-absorptive conditions[64]. Moreover, accumulating evidence predicts that the kidneys impart a critical role in regulating overall glucose homeostasis by various mechanisms, such as reabsorption of glucose from the glomerular ultrafiltrate specifically in the renal epithelial cells, glucose uptake and utilization for meeting the body's energy demands, and gluconeogenesis, *i.e.*, endogenous glucose production from non-carbohydrate sources[55,56].

Similar to liver tissue, renal gluconeogenesis and metabolism were found to be dysregulated in diabetes and the insulin-resistant state[6,7]. There are studies which suggest that renal epithelial cells double their glucose uptake in response to insulin stimulation *via* translocation of GLUT (GLUT1 and GLUT4) to the plasma membrane, which accentuates the effect of insulin on renal gluconeogenesis and on systemic blood glucose levels[65]. Moreover, hyperinsulinemia is reported to inhibit glucose production and stimulate glucose uptake by the renal epithelial cells[60,66]. Both experimental and clinical studies have documented the insulin-mediated regulation of uptake and release of glucose. A hyperinsulinemic clamp study in humans showed a 61% decrease in renal glucose output and approximately a 72% decrease in renal glutamine gluconeogenesis [much higher than liver (25%)] in subjects treated with insulin[67]. Insulin has also been reported to affect the transport of gluconeogenic substrates in the kidney[68]. These studies highlighted the significance and magnitude of renal glucose production, and also revealed higher sensitivity of renal glucose release towards insulin as compared to liver. Moreover, enhanced renal gluconeogenesis in the post-absorptive conditions has been suggested to contribute towards hyperglycemia in Type 2 diabetes in the insulin-resistant state. This is supported by the increased intrinsic gluconeogenesis with simultaneous decrease in IR levels reported in the kidney cortex of Zucker diabetic fatty rats[69]. In addition, a marked decrease in IR expression has been observed in the renal cortex of high-fat diet-fed rats as well as in Type 2 diabetic patients[6,7,69,70].

The role of insulin/IR signaling in regulation of gluconeogenesis transcriptional modulation of gluconeogenic genes, *i.e.*, PCK1 and G6PC is well known in liver[71-73]. However, studies on the role of the IR in renal gluconeogenesis regulation are limited. In 2012, a study from the DeFronzo lab elucidated that insulin negatively regulates gluconeogenesis *via* downregulating the expression of key gluconeogenic genes in the kidney[74]. Around the same time, our group demonstrated that targeted deletion of the IR from the PT resulted in hyperglycemia despite normal whole body insulin sensitivity[20]. More so, an increased activity and elevated mRNA expression of glucose-6-phosphatase (G6Pase, a rate-limiting enzyme in gluconeogenesis) was observed in the PT-specific IRKO mice, signifying the involvement of the IR in regulating the expression of key gluconeogenic genes. Further, reduced IR expression and early IR signaling along with a significant increase in phosphoenolpyruvate carboxykinase (PEPCK) levels were found in kidney cortex of high-fat diet-fed mice[75], providing a clue to the possible mechanism of insulin involving transcriptional regulation of PEPCK, also a rate-limiting gene in gluconeogenesis. In liver, insulin has been shown to suppress the expression of gluconeogenic genes, G6Pase and PEPCK[76]. *In vitro* studies performed in primary PT cells from human kidney (hPT) showed an inhibitory role of insulin on cAMP/DEXA-induced gluconeogenesis, and silencing of IR attenuated this inhibitory effect of insulin on PT-gluconeogenesis in hPT[77]. All these findings clearly state that reduced IR expression/signaling might have a causal function in gluconeogenic gene upregulation and gluconeogenesis.

In vitro studies from our group has demonstrated that loss of IR in human proximal tubule cells attenuated the inhibitory effect of insulin on PEPCK expression in hPT cells[77]. These studies, suggest that impaired insulin sensitivity of PT may affect whole body glucose homeostasis by elevating gluconeogenesis *via* transcriptional induction of gluconeogenic enzymes in the kidney. However, the mechanism by which IR signaling targets gluconeogenic genes in PT needs to be further elucidated. A recent study from Yáñez lab demonstrated downregulation of IR levels, which was accompanied by increased expression and activity of PEPCK in the kidney of both Type 2 diabetic patients (Figure 4) and in a Type 1 diabetic rat model. Moreover, they also observed an apical redistribution of gluconeogenic genes in both the models, implying that insulin signaling may regulate gluconeogenesis through luminal substrate uptake[6]. Recently, Horita *et al*[78], put forward a concept of "selective insulin resistance" in kidney. The state of selective insulin resistance has been recognized in the case of liver, where inhibition of gluconeogenesis by the insulin receptor substrate (IRS) 2 is hindered, whereas IRS1-regulated lipogenesis is not altered. On the

contrary, in kidney, IRS1-dependent inhibition of gluconeogenesis is impaired in the proximal tubule leading to hyperglycemia, while IRS2-dependent signaling is preserved[78-81]. Sasaki *et al*[82] have also reported the role of insulin signaling in maintaining systemic glucose homeostasis in IRS1/IRS2 double KO mice. This study emphasized dual regulation of gluconeogenesis by insulin signaling and glucose reabsorption. This is in consonance with previous studies suggesting impaired glucose levels in diabetic human PT because of enhanced glucose reabsorption and insulin-dependent inhibition of gluconeogenesis[74,83,84], ultimately leading to more glucose release by the kidney as compared to the liver[58]. In the light of these findings, regulation of renal gluconeogenesis is still a matter of debate because both suppression and elevation of gluconeogenic gene expression has been reported in experimental rodent models of diabetes[6,85]. These observations open a whole new avenue for investigating the role of IRs in renal glucose homeostasis.

Together, it can be implied that impaired renal insulin signaling (especially IR signaling) may increase gluconeogenesis, and in the setting of insulin resistance, these impairments can further contribute to other deleterious effects. Therefore, more conclusive studies are warranted to understand the pathophysiological association of renal insulin signaling and glucose metabolism.

RENAL IR IN PROTEINURIA

The presence of proteins especially albumin in urine, aka proteinuria is an important hallmark of renal disease, including diabetic nephropathy. Although glomerular dysfunction is an established cause of proteinuria[86,87], impaired tubular function also contributes to albuminuria in diabetic nephropathy[88,89]. Normally, albumin is reabsorbed by the PT cells through receptor-mediated and fluid phase endocytosis[90]. In the proximal tubules, receptor-mediated reabsorption of albumin is executed by endocytic receptors, megalin and cubilin that are highly expressed in the apical membrane of the PT cells[91]. Existing evidences suggest that besides other factors, insulin could have a potential role in albumin uptake by the PT cells in diabetic and non-diabetic conditions. Retrieval of albumin from ultrafiltrate by the PT cells is crucial for kidney homeostasis. A cohort study on non-diabetic individuals (Relationship between Insulin Sensitivity and Cardiovascular Disease; RISC) proposed a causal relationship between insulin resistance and albuminuria[92]. The RISC study demonstrated that reduced insulin sensitivity, measured by a hyperinsulinemic-euglycemic clamp, is linked to increased risk of albuminuria in a healthy cohort.

Intriguingly, various studies have reported that insulin could also have a potential role in albumin uptake by the PT cells in diabetes. In the STZ-induced diabetic mice model, downregulation of pSer473-Akt expression in the proximal tubule epithelial cells was accompanied by decreased expression of megalin and cubilin establishing the link between insulin signaling and albumin uptake[93]. Recently, Zeng *et al*[94], showed that the ORAI (calcium release-activated calcium channels) are also accountable for the internalization of albumin in proximal tubular epithelial cells *via* clathrin-mediated endocytosis and expression of these channels is insulin-dependent. In concordance with previous studies, Mottl *et al*[95] showed that the urinary ACR was positively associated with insulin-resistant young Type 2 diabetic subjects. Moreover, insulin treatment under high-glucose conditions increased megalin expression and albumin internalization in OK cells[96]. Insulin treatment has attenuated urine albumin excretion in Akita mice also[97]. These reports establish a causal role of PT-specific insulin resistance in the pathogenesis of albuminuria; however, exact mechanism of insulin-dependent albumin uptake needs to be elucidated.

Recent data from our laboratory showed that targeted deletion of IRs from the proximal tubule impairs tubular albumin uptake and results in albuminuria in mice (unpublished data). We have also established circulating insulin levels as a determinant of tubular albumin uptake. Moreover, down-regulation of IR and early IR signaling in the kidney has been reported in Type 2 diabetes and models of insulin resistance[7] , which can contribute to elevated albuminuria. These recent findings support a direct physiological role of PT-specific insulin action on albumin uptake and albuminuria.

CONCLUSION

The physiological relevance of IRs in renal epithelial cells has gained more attention in recent years. Studies based on targeted deletion of IR have now provided sufficient

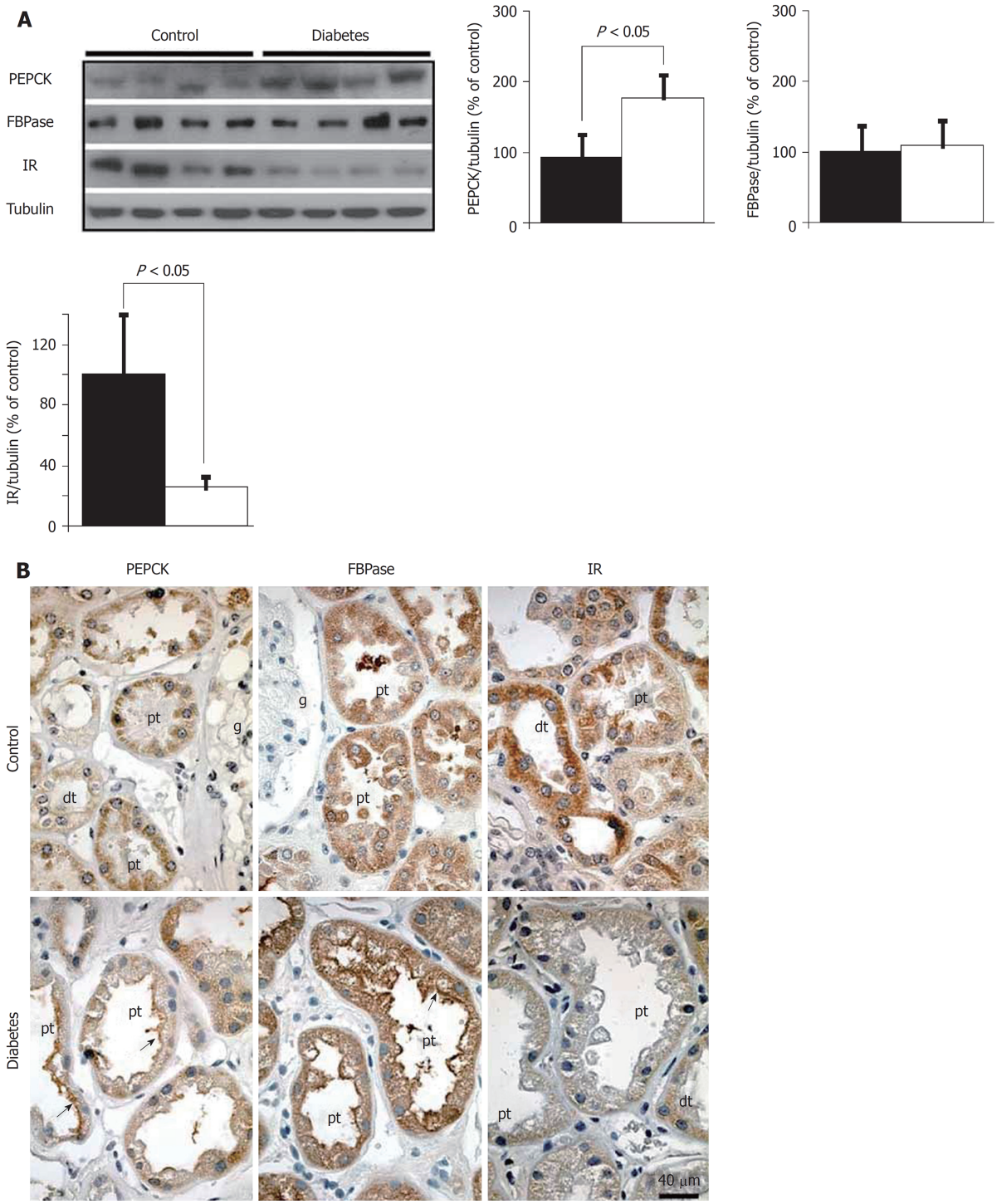

Figure 4 Expression patterns of insulin receptor and gluconeogenic enzymes in normal and diabetic human kidney. A: Expression of FBPase, PEPCK, IR, and tubulin in renal cortex biopsies of control and Type 2 diabetic individuals analyzed by western blotting; B: Immunohistochemical analysis of FBPase, PEPCK, and IR in renal cortex biopsies of control and Type 2 diabetic individuals (Figure is taken from reference number[6] with permission). PEPCK: Phosphoenolpyruvate carboxykinase; IR: Insulin receptor.

evidence to suggest the significance of the renal IR in kidney physiology and pathology. In addition, these studies have enhanced our understanding surrounding the contribution of reduced renal IR observed in the insulin-resistance state. Overall, it can be suggested that modulation of insulin signaling at the receptor level could significantly affect kidney function, which thereby may result in systemic effects. However, more mechanistic studies are warranted to understand the causal role of reduced renal IR in the regulation of blood pressure, systemic glucose levels, and proteinuria.

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MINIREVIEWS

Dehydration and volume depletion: How to handle the misconceptions

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Abstract

Dehydration and volume depletion describe two distinct body fluid deficit disorders with differing pathophysiology, clinical manifestations and treatment approaches. However, the two are often confused or equated with each other. Here, we address a number of commonly encountered misconceptions about body-fluid deficit disorders, analyse their origins and propose approaches to overcome them.

Key words: Body fluids; Dehydration; Volume depletion; Misconceptions

Core tip: The conceptual error of using the term "dehydration" as a non-specific generic term to represent any type of fluid deficit affecting any fluid compartment, or even worse, to imply extracellular fluid volume depletion remains disturbingly prevalent among medical students and doctors. Careless and casual use of the term "dehydration" for patients who, in fact, have intravascular "volume depletion" contaminates the medical language, creates misleading impressions and unfortunately, in some cases, leads to inappropriate management. We propose a multi-faceted approach that supplements real life clinical scenarios with reflective activities through active participation of students and helps remove these robust misconceptions and instigate conceptual restructuring.

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INTRODUCTION

Students often confuse concepts related to sodium and water balance. One concept that has received considerable attention in recent medical teaching is the notion that disorders of water balance are manifested as hyponatraemia or hypernatraemia, whilst disorders of sodium balance are manifested as disruption of extracellular fluid (ECF) volume. In this review, we focus on another key concept regarding dehydration and volume depletion, and how the two are completely different clinical syndromes with distinct pathophysiological mechanisms, clinical features, biochemical characteristics, and management strategies.

Assessment of body fluid status is an integral component of the physician's evaluation of most hospitalized patients. A competent fluid assessment requires sound knowledge of the dynamic interaction between body fluid compartments, as well as a skilful examination and careful biochemical analysis of serum and urine. In addition, a command of medical language and terminology is essential to precisely describe and categorize body-fluid status. Mange *et al*[1] highlighted the importance of recognizing dehydration and volume depletion as two completely different clinical entities. However, the conceptual error of using the term "dehydration" as a non-specific, generic term to represent any type of fluid deficit affecting any fluid compartment, or even worse, to imply ECF volume depletion, remains disturbingly prevalent among medical students and doctors. Careless and casual use of the term "dehydration" for patients who, in fact, have intravascular "volume depletion" contaminates the medical language, creates misleading impressions and unfortunately, in some cases, leads to inappropriate management. Considering the magnitude of the problem, in 2004 the International Classification of Diseases coordination and maintenance Committee made recommendations to modify the coding for body fluid disorders to uniquely identify dehydration and volume depletion[2]. For the sake of this review, we will use the term "students" to refer to medical students as well as to junior physicians who fall prey to the dehydration/volume depletion misconceptions.

Body fluid compartments – basic facts

Total body water (TBW) is estimated to be 50%-60% of body weight, varying with age, gender and race, and resides in three main fluid compartments of body (Figure 1)[3,4]. The bulk of the TBW (67%) is confined intracellularly; the remaining 33% is distributed between the two sub-compartments of the extracellular space: interstitial and intravascular (25% and 8% respectively)[5]. Hence, in a 70 kg man, TBW is approximately 42 L, out of which 28 L, 10.5 L and 3.5 L are distributed in the intracellular, interstitial and intravascular compartments, respectively. Another subcategory of ECF, albeit small, is transcellular fluid (not shown in the figure) that resides in pleural, pericardial, peritoneal, synovial, ocular and cerebrospinal spaces, although in some cases, its chemical composition and physical properties may differ from that of intravascular or interstitial fluid[6]. Fluid input and output from the body proceeds *via* the intravascular compartment.

Intravascular and interstitial compartments are separated solely by highly permeable capillary membranes. Hence, their ionic composition is almost identical; the major cation is sodium (Na^+) and the major anions are chloride and bicarbonate. In contrast, the major cation in the intracellular fluid (ICF) is potassium (K^+) and the major anions are inorganic phosphates. Sodium chloride is typically confined to the ECF compartment by virtue of the Na-K-ATPase pumps, anchored in the cell membranes, which pump Na^+ out and K^+ into the cells. This constant active transport of Na^+ and K^+ across the cell membrane makes the ECF rich in Na^+ and the ICF rich in K^+. Consequently, the osmolality of the ECF is largely dependent on sodium and chloride whereas the osmolality of the ICF is derived from potassium along with other intracellular osmoles. Water moves freely between all fluid compartments through highly water permeable cell membranes; therefore, the osmolality of the plasma is equal to the osmolality of other compartments.

Of the total plasma volume, 85% is in venous circulation and 15% is in arterial circulation. It is this small arterial volume (approximately 700 mL) that constitutes the effective circulating volume, which is responsible for tissue perfusion and regulation

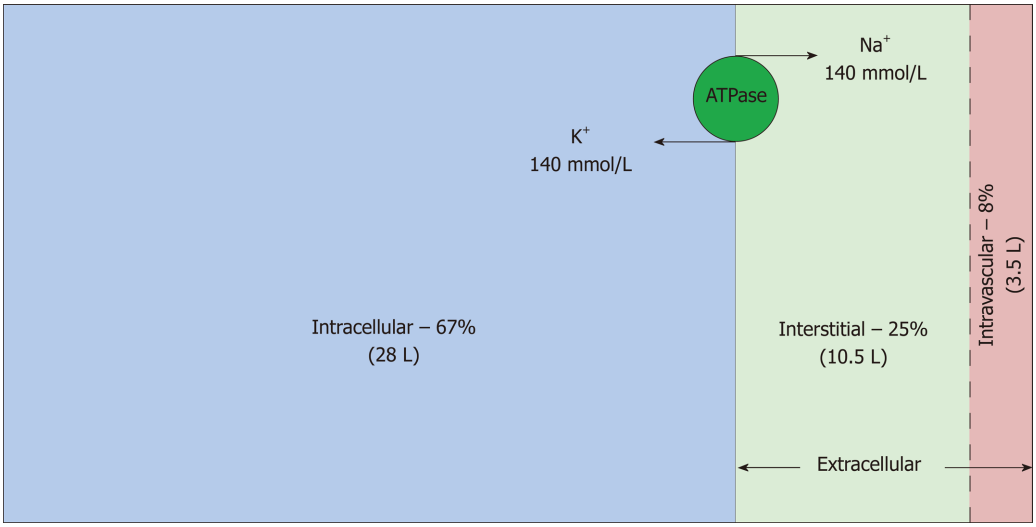

Figure 1 Distribution of total body water in various fluid compartments of a 70 kg man (see text for explanation).

of the body's salt and water balance[7,8].

Considering the differing permeability of the membranes that separate fluid compartments in the body, administration of different IV fluids will result in differing distribution amongst these compartments. Since water flows freely between all three compartments, infusion of one litre of 5% dextrose water (D5W) will lead to an increase in the volume of the intracellular compartment of approximately 670 mL (67% of one litre), that of the interstitial compartment of 250 mL (25% of one litre) and that of intravascular compartment of 80 mL (8% of one litre). On the other hand, infusion of one litre of normal saline (0.9% NS) will add approximately 750 mL to the interstitial space and 250 mL to the intravascular space due to the inhibition of Na+ entry into the cell by the aforementioned Na/K/ATPase pumps located in the cell membranes. Though the water content of both D5W and 0.9% NS solutions is equal (1000 mL), much more fluid will reside in the intravascular space if given in the form of 0.9% NS (as none enters the intracellular space). Hence, 0.9% NS is preferred over D5W if the aim is to correct intravascular volume depletion. Conversely, if the aim is to correct dehydration (pure water loss) then a fluid that flows to all the compartments, such as D5W is the preferred solution. Giving D5W is equivalent to giving free water because glucose is rapidly metabolized.

TBW and volume of each fluid compartment can be accurately measured by radionuclide and "indicator-dilution" methods or by bioelectrical impedance[9-11].

Dehydration and volume depletion – two distinct entities

As indicated by Mange *et al*[1], two distinct clinical syndromes can develop secondary to excessive body fluid losses: (1) Dehydration, which means pure water loss ("Hydro" originates from the ancient Greek word "hudōr", meaning "water"; to dehydrate means removing water). Loss of water reduces the distribution space of Na^+, thereby disturbing the Na^+ and water ratio, leading to hypernatremia and hypertonicity. Because cell membranes are freely permeable to water, this results in osmotic movement of water from the larger intracellular compartment to the extracellular compartment. There is a contraction of all body water compartments proportional to their share of TBW[12]. Since the intracellular compartment is the largest reservoir of body water, it suffers the largest water deficit. For instance, for each litre of water lost from the body, the intracellular compartment contributes 670 mL. In contrast, the intravascular compartment suffers a loss of only 80 mL; hence pure water loss rarely compromises the effective circulating volume or haemodynamic stability. Pure water loss results in hypernatremia and hypertonicity because Na^+ is a membrane-impermeant solute. This induces shrinkage of osmoreceptor cells in the anterior hypothalamus, stimulating the release of antidiuretic hormone (ADH) from the posterior pituitary gland. ADH promotes incorporation of water channels (aquaporin 2) in the distal nephron segments allowing increased water reabsorption. At the same time, the thirst mechanism is triggered leading to increased water ingestion. Renal conservation of water along with increased water intake act to reverse the osmolal changes brought about by the initial water loss by restoring normonatremia (Figure 2); (2) Volume depletion, which implies an ECF volume deficit secondary to the loss of both sodium and water.

Sodium is confined into the extracellular compartment by the Na-K-ATPase pumps in the cell membranes, which helps to hold water extracellularly[13]. Sodium and water loss lead to a reduction in the effective circulating volume. The human body orchestrates a number of homeostatic responses to combat hypovolemia that include activation of the renin-angiotensin-aldosterone system (receptors in renal afferent arterioles), stimulation of the sympathetic nervous system (aortic arch and carotid sinus receptors), suppression of ANP (atrial receptors) and stimulation of ADH release. All these lead to renal conservation of both salt and water, thereby restoring normovolemia. It is noteworthy that ADH release is stimulated in both dehydration (due to hypertonicity), and ECF volume depletion (due to decreased effective circulating volume).

ORIGINS OF MISCONCEPTIONS

Insufficient knowledge/faulty mental models of body fluid compartments and fluid assessment:

Though uncommon, some physicians have insufficient knowledge of body fluids due to a lack of factual information about body fluid compartments and differences in their composition. Most are aware that a patient with haemorrhagic shock has a depleted intravascular compartment, but only a few recognize which compartment suffers the most in a dehydrated patient with a serum sodium of 170 μmol/L. Suppose an elderly patient is admitted with community-acquired pneumonia. He has been rather drowsy for two days before admission with poor oral intake. He is tachypneic and pyrexial, but his blood pressure is normal with no postural change. Initial laboratory tests reveal a serum sodium of 170 μmol/L. He is receiving antibiotics and D5W infusion. When asked "What condition are you treating with D5W infusion?", most students reply "hypernatremia" rather than "dehydration", *i.e.*, they mention the biochemical derangement rather than the condition that produced it. Further probing reveals that some students do not recognize that hypernatremia in most instances represents loss of water in relation to Na^+ (not an excess of sodium) and is a manifestation of dehydration (hence we calculate the free water deficit to assess the amount of water replacement needed to correct hypernatremia). In other words, it is the water intake/excretion (rather than Na^+ handling) that regulates the ECF sodium concentration. It also appears that although some students have knowledge of the different fluid compartments, they fail to apply their knowledge to real life cases.

A number of students have a skewed understanding of body fluid compartments and harbour various misconceptions, the most common of which is erroneously referring to "ECF volume depletion" or "intravascular volume depletion" as "dehydration". The vast majority of doctors appreciate that patients who present with profuse diarrhoea and vomiting and are consequently hypotensive and tachycardic are intravascularly depleted. They also very appropriately resuscitate these patients with 0.9% NS rather than D5W infusion. However, when presenting such a case during the ward round, they say "this patient was severely dehydrated and resuscitated with 0.9% NS". So, although they correctly identify and treat the clinical syndrome of intravascular volume depletion, they use imprecise terminology.

Another common misbelief among students is that dehydration can be reliably diagnosed by physical signs such as sunken eyes, decreased skin turgor and dry mucous membranes. Contrarily, the predictive value of these individual clinical signs in diagnosing dehydration is limited in adult populations. Studies endorsing these physical signs were mostly carried out on paediatric and elderly patient populations[14-18]. Many of these patients in fact had ECF volume depletion rather than dehydration, as evidenced by haemodynamic compromise and normal serum sodium levels.

The term "sunken eyes" (enophthalmos) implies posterior displacement of the eyeballs within the orbits due to a decrease in volume of orbital soft tissues. However, exophthalmometry, the standard objective technique for measuring enophthalmos, is not used in general medicine leaving substantial variation in inter-observer agreement for this physical sign. Furthermore, normal anatomical variation amongst individuals and age-related changes (lipodystrophy of orbital fat with increasing age) make "sunken eyes" an unreliable physical sign of dehydration.

Reduced skin turgor means reduced elastic recoil of the skin to its normal contour after being pinched in a fold. As pointed out by Laron *et al*[19], it reflects contraction of the interstitial and intravascular space (both are subcategories of the extracellular compartment) rather than the loss of intracellular water. Skin turgor also correlates directly with the elastin content of the skin, which decreases significantly with

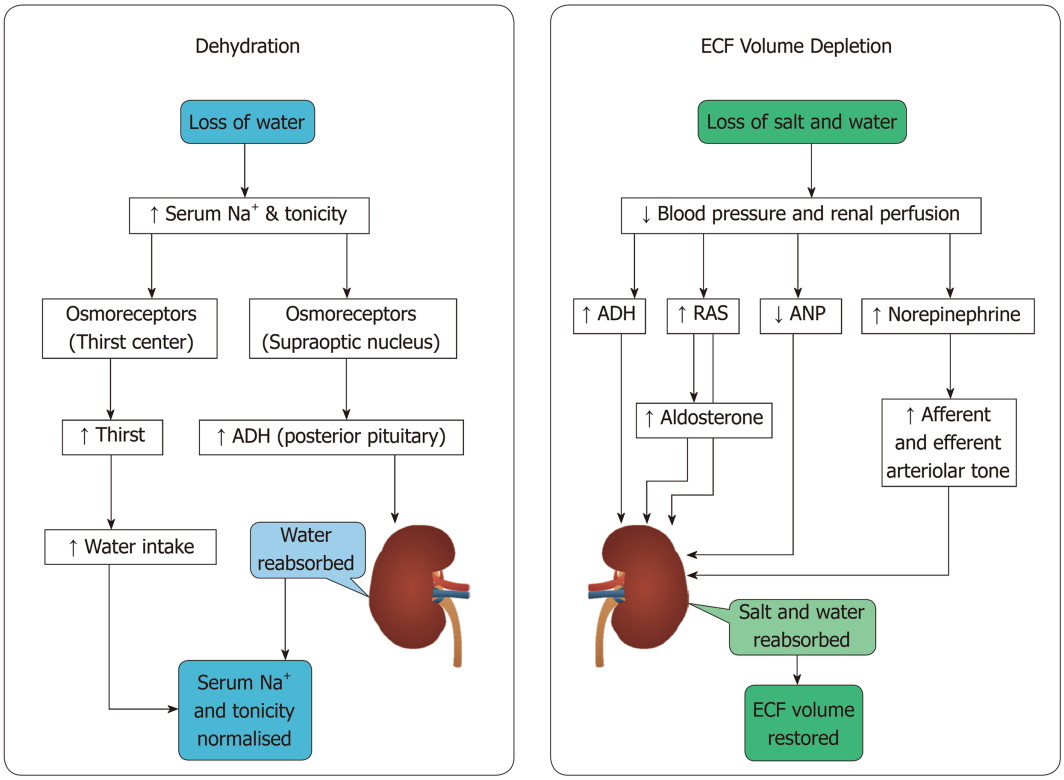

Figure 2 Compensatory responses to dehydration and extracellular fluid volume depletion. The kidneys retain what is lost from the body – water conserved in dehydration; salt and water are reabsorbed in extracellular fluid volume depletion. ADH: Antidiuretic hormone; ANP: Atrial natriuretic peptide; ECF: Extracellular fluid; RAS: Renin angiotensin system.

ageing[16,20].

"Isonatraemic, hyponatraemic, and hypernatraemic dehydration" – ancient concepts prevailing in modern doctors

Though it had long been known that primary loss or deprivation of water produces biological disturbances (thirst) dissimilar to those seen in primary loss or deprivation of salt (circulatory instability), both types of deficits were considered to be subcategories of dehydration in the early 20th century[21,22]. These ancient concepts have managed to exercise a strong pull on some modern doctors, who have persevered in using the term "dehydration" to refer to both intracellular water loss and ECF volume loss and to sub-classify dehydration into isonatraemic, hyponatraemic and hypernatraemic forms[23-27].

In fact, it is *volume depletion* that has isonatraemic, hyponatraemic and hypernatraemic subtypes determined by the tonicity of the fluid lost and the type of fluid ingested[28-31]. If the losses are isotonic, *i.e.*, proportionate quantities of water and sodium are lost (*e.g.*, blood loss), then serum sodium and tonicity will remain unchanged resulting in isonatraemic volume depletion. However, if more sodium relative to water is lost (or the patient takes plenty of salt-free fluids, for example tap water), hyponatraemic volume depletion ensues. Finally, if less sodium is lost relative to water (or if the patient does not drink water, or takes hypertonic soup), hypernatraemic volume depletion follows. In contrast to volume depletion, dehydration is always hypernatraemic (due to loss of pure water); the categories "hyponatraemic" and "isonatraemic" do not apply in dehydration.

Co-existence of dehydration and intravascular volume depletion in some patients

Some patients can present with features of both dehydration and intravascular volume depletion. The co-existence of these two different entities is partly responsible for some physicians misjudging them as a single disorder. Indeed, many patients in paediatric clinical studies with diarrhoeal illnesses were both dehydrated and ECF volume depleted[14,32]. This complex pathophysiological state was oversimplified as "dehydration" and the severity of body fluid losses categorized according to percentage of body weight loss. The "dehydration" assessment scales included the physical signs and laboratory parameters of both intracellular water loss and ECF volume depletion[14,32].

Clinically, it is not possible to establish whether hypernatremia in an intravascularly depleted patient is secondary to hypernatraemic intravascular depletion (water loss greater than sodium loss), severe dehydration (profuse water loss alone), or a combination of the two. This differentiation requires marker/tracer studies[9-11]. In clinical situations, there is hardly any need for this differentiation. As a first step, intravascular volume depletion is treated with 0.9% NS to support organ function. Once adequate haemodynamic stability is achieved, hyperosmolality is corrected with D5W.

Potential of dehydration to cause intravascular volume depletion

Usually, dehydration does not lead to intravascular volume depletion as the intravascular space contributes only a small percentage to the TBW loss; the major bulk is lost from the intracellular space, the largest reservoir of body water. As discussed earlier, a loss of 1 L from TBW removes only 80 ml from the intravascular space (2.3% of intravascular volume); consequently, no appreciable deleterious effects on haemodynamics are seen. Development of signs and symptoms of intravascular volume depletion usually require more than 0.5 L of intravascular volume deficit. For this intravascular volume deficit to develop in a 70 kg person with dehydration, a TBW deficit of more than 6 litres (more than 15% of TBW) will be required. By this time severe hypernatremia (serum Na^+ > 170 mmol/L) would have developed[12].

Oversimplification of medical terminology

Albert Einstein said, "everything should be made as simple as possible, but not simpler". When discussing a patient's condition, physicians commonly use shortened forms of legitimate medical words and phrases as a time-saving measure. The drawback of this is that these brief forms can lead to varied interpretations and thus confound medical personnel. The term "volume depletion" is used as a brief (though obscure) form for ECF volume depletion or intravascular volume depletion but might not adequately convey the intended meaning. It neither clarifies whether the loss of fluid is from intracellular or extracellular space, nor indicates the type of fluid lost (hypotonic or isotonic). Hence, for some it may imply depletion of TBW (*i.e.*, dehydration), while for others, depletion of the intravascular fluid alone (*i.e.*, isotonic fluid loss).

STRATEGIES TO OVERCOME MISCONCEPTIONS

An organized approach is imperative in correcting robust misconceptions related to body fluid deficit disorders. First, it is crucial that all faculty members develop a critical understanding of the body-fluids, as misconceptions acquired from faculty members and textbooks are very difficult to eliminate from the minds of young doctors later in their professional lives.

In the following section we present our approach to overcoming misconceptions in a manner that will create a lasting effect on students and prevent them from reverting to their preconceptions.

Identify misconceptions in the students

Although misconceptions about body fluids disorders are widespread, students are generally unaware that the knowledge they possess is faulty. Mere use of medical terminology is not sufficient evidence of students' knowledge; it needs to be ensured that these terms are used with accurate meaning in the context of body fluid compartments. We actively bring up the subject when encountering patients with body fluid deficits in order to probe students for the presence of misconceptions.

Tackle the misconceptions

Once identified, we try to make students discontent with their misconceptions. This provides a strong stimulus for refinement or replacement of the flawed concepts with intelligible and plausible ones. Utmost care is given to maintain a favourable learning environment where the students are not ridiculed for holding incorrect preconceptions.

We split teaching into short modules, each with a clear framework and objectives. Most of the modules remain "learner-centred" where students are engaged in meaningful activities which promote thought. Multiple teaching techniques are employed to cater to the diverse learning styles of the students and rekindle students' interest and participation.

Introductory presentation: We start with a 10-min introductory presentation using visual aids such as a white-board or PowerPoint presentation to orient the students to

body fluid compartments. Classifying the body fluid deficit disorder based on the nature of the fluid deficit (water alone *vs* water with salt) and the main body fluid compartment affected (intracellular *vs* extracellular) in each disorder generates uneasiness in the minds of those students who misconceive dehydration and volume depletion as one entity. This serves as an important turning point in the students' learning as they start feeling dissatisfied with their pre-conceptions.

We make a conscious effort to avoid ambiguous linguistic expressions. We use the term "dehydration" to specifically refer to a body-fluid disorder resulting from pure water depletion with consequent hypernatremia, rather than using it as a blanket term for any type of fluid deficit. Furthermore, since the term "volume depletion" gives rise to referential ambiguity (because it does not specify the referent body fluid compartment), we disambiguate this term by adding an adjective, for example, "ECF" or "Intravascular" to indicate the depleted body-fluid compartment. This also encourages students to abandon the habit of using misleading abbreviations.

Clinical encounter: The newly implanted concepts must be supplemented with real life applications within a patient care context ensuring the students do not merely learn the new rote information. Utilizing the "think-pair-share" technique, we invite students to form either pairs or small groups. One group evaluates a pre-selected patient with dehydration while the other group assesses a patient with ECF volume depletion.

Debriefing session 1: After seeing their respective patients, the two groups return to the "classroom". They are given a 2 min "reflection time" for formulation of ideas after which each group interacts with the other to compare the clinical, laboratory and therapeutic details of their patients. The instructor facilitates the learning process and highlights the contrasting features of the two patients. This session also provides an opportunity for the instructor to point out any common conceptual errors and offer constructive suggestions.

Instead of beginning with the presenting illness, which is the generally considered "norm", a unique way to provoke curiosity in the minds of the students is to start the discussion with the management of the two patients. This disrupts the students' expectations, captures their attention and makes them think and reflect retrospectively. An example of this could be asking: "Both the patients are receiving IV fluids because they have body fluid deficits; why is one patient being treated with slow infusion of D5W and the other with rapid administration of 0.9% NS or blood?" or "What factors have influenced the choice of fluid and the rate of infusion?" These queries will encourage the students to talk about the body fluid compartment from which the fluid has been lost in each condition and the concept of replacing "like with like" by choosing appropriate fluids for each condition. These questions also help cement the fact that dehydration and volume depletion are different disorders and hence necessitate different treatments. At this juncture, schematic illustrations of fluid compartments to demonstrate the effect of the addition of different types of fluids (blood, albumin, 0.9% NS, NaHCO3, D5W, *etc*.) on each body fluid compartment are utilized. Students are interested to note how each type of fluid initially expands the intravascular space but then distributes distinctively through different fluid compartments. This also helps them with the application of theoretical knowledge into direct patient care. The ECF volume maintains blood pressure and perfusion of organs, hence a fluid that is more likely to stay in the ECF compartment (0.9% NS) is administered as a rapid infusion in a volume depleted patient to ensure haemodynamic stability. Conversely, a fluid that predominantly restores the ICF compartment (D5W) is administered to a dehydrated patient in a controlled fashion to prevent the development of cerebral oedema. Again, throughout the session, the terms "ECF volume depletion" and "intravascular volume depletion" are used to dispel referential ambiguity.

Analysis of the laboratory values: After the debriefing session, we focus on the laboratory investigation results of the two patients. This is done either at the computer station on the ward or in the classroom where lab values from electronic medical records are projected on to the screen. It is important to emphasize the dissimilarity between the urinary and serum biochemical values of the two patients. In the ECF volume depleted patient, the urine becomes concentrated and contains very little Na^+ consequent to renal conservation of salt and water. In the dehydrated patient, although urine is concentrated (due to water absorption in the distal tubule), urinary Na^+ is not decreased. In fact, hypernatremia in a dehydrated patient can augment renal natriuresis by mechanisms that appear to be independent of changes in atrial natriuretic peptide[33]. In ECF volume depletion, BUN/creatinine ratio rises due to renal hypo-perfusion with variable effects on serum sodium (depending upon the

type of fluid loss). In contrast, there is no significant increase in serum urea or creatinine in dehydration; the gold standard is hypernatremia and consequent hypertonicity[1,34].

Back to the patients: After going through the laboratory results, students go back to the patients to demonstrate physical signs. If the physical signs have resolved consequent to the treatment, then students review the medical file to note the physical findings at time of presentation. Important findings include orthostatic hypotension, tachycardia, prolonged capillary refill time and decreased skin turgor. These are defined to students as signs of ECF volume depletion, as dehydration cannot be reliably determined by use of clinical examination. Finally, to complete the chain of events in reverse chronological order, we focus on the modes of presentation of the two patients by reviewing their medical records. ECF volume depleted patients usually present with a history of blood-loss or gastrointestinal fluid loss, conditions that cause third-spacing (*e.g.*, ileus or pancreatitis) or sepsis (vasodilatation induced relative hypovolemia). On the other hand, since intracellular hydration influences cellular function, severely dehydrated patients may present with altered cognitive and neuromuscular function. It is noteworthy that altered mentation can be both a cause (by affecting the patient's ability to access water) and a consequence (due to the resultant deranged neuro-cellular function) of dehydration. Critically ill patients in the ICU are prone to develop dehydration because they are unconscious, sedated or ventilated and are hence unable to voluntarily control their free water intake.

After going through all the aspects of care for their respective patients, the two groups switch and examine the other patient using the same system. This session is usually shorter as it simply affirms the pre-discussed differences between the two clinical conditions, cementing the newly acquired knowledge in the students' minds. We find that by the end of this session, most students can appreciate the key differences between dehydration and volume depletion and the clinical implications of each.

Home assignment: The above stated clinical and biochemical differences invariably prompt analysis of different homeostatic mechanisms that operate in ECF volume depletion and dehydration. We direct students to carry out further reading to explore pathophysiological differences between the two disorders (Figure 2). We also provide them with additional learning resources that allow them to adequately explore the whole subject at their own comfortable pace to build up their new conceptual frameworks.

Debriefing session 2: On the following day, the pathophysiology of dehydration and volume depletion are addressed in the final session. Representatives from both student groups are invited to draw simple diagrams on a white board illustrating the homeostatic mechanisms. As they do this, it highlights to the audience that the sensors and effectors of both conditions are different (Figure 2); in dehydration, the osmoregulatory mechanisms are activated whereas in volume depletion the ECF volume regulatory pathways are stimulated to restore a normal physiologic environment. Students should then be able to link up the pathophysiological changes to the symptoms, signs and treatment of dehydration and volume depletion. They appreciate that the therapeutic manoeuvres mimic the response of normal kidneys to these conditions – kidneys retain water in dehydration, so we treat dehydration with water administration; kidneys retain salt and water in volume depletion, hence we infuse 0.9% NS to combat volume depletion.

In the second half of this session, students may share their perspectives on the whole topic. They also reflect on how the new concepts will resolve the problems that previously led to dissatisfaction in the management of such patients, and how their new understanding will benefit them in their future clinical experiences.

Create opportunities for the students to apply the new knowledge into routine clinical practice

New concepts that are not reflected upon often fade away rapidly. Therefore, opportunities are tactfully created for the students to continuously apply the new knowledge into clinical practice; acute medical admissions' wards are good places to see patients with ECF volume depletion whereas ICUs are good avenues to evaluate intubated and ventilated patients who are prone to dehydration. Multiple encounters with volume depleted and dehydrated patients allow the students to revise new concepts and train them to identify and treat these two contrasting conditions appropriately.

Another effective strategy is to have the advanced students in the team (fellows or senior residents who has successfully demonstrated proficiency in the subject) teach

the subject to the junior residents or interns. During this process, the senior students invest more personal effort into learning and thus consolidate deeper understandings. The faculty member acts as a facilitator who designs and supervises the learning environment as well as provides on-the-spot advice when required.

Preventing relapse

Dehydration/volume depletion misconceptions are prone to relapse. We regularly revisit these misconceptions through lectures, case discussions, publications and board review programmes. In our training programme, most residents from general medical teams rotate to nephrology. This opportunity is used to advance-train these residents in the field of fluid balance so that they may act as surrogate teachers to complement professional teaching by faculty. Finally, questions on our in-house exams are crafted to carefully test the conceptual framework of students rather than their ability to memorize facts.

CONCLUSION

The terms dehydration and volume depletion represent two fundamentally different clinical disorders. Erroneous concepts about these body fluid disorders are worryingly prevalent among medical students and physicians. A multi-pronged approach is required to wipe out these robust misconceptions. We strongly believe that the most effective strategy to instigate conceptual restructuring is by supplementing real life clinical experiences with reflective activities through active participation of students. We recommend that dehydration/volume depletion misconceptions be included in medical school curricula and textbooks so that medical students become aware of the common pitfalls of fluid status evaluation.

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