How to Cope with the Surge of Diabetes in PD?

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Topics

- Should diabetic patients be offered PD?
- What is the target for blood glucose control?
- How they can control blood glucose?

Mortality in matched hemodialysis and peritoneal dialysis patients

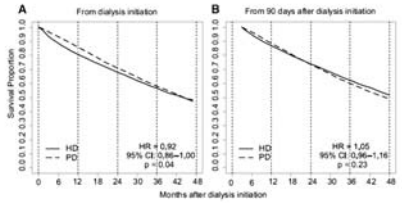


Figure 1. Intention-to-treat in the matched cohort showed lower death risk in PD when follow up began at initiation of dialysis. Risks were similar when follow-up began at day 90. HD, hemodialysis; PD, peritoneal dialysis.

The cohort consisted of adult patients who initiated dialysis in the United States in 2003. Follow-up continued until the earliest occurrence of death, kidney transplant, loss to follow-up, or December 31, 2006.

Weinhandl ED. J Am Soc Nephrol. 2010

Mortality in matched hemodialysis and peritoneal dialysis patients

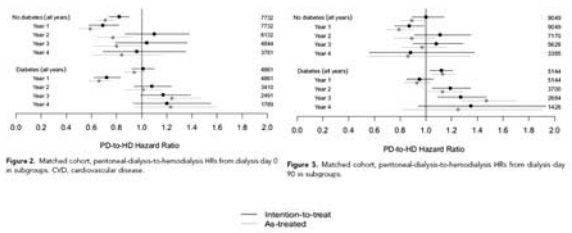
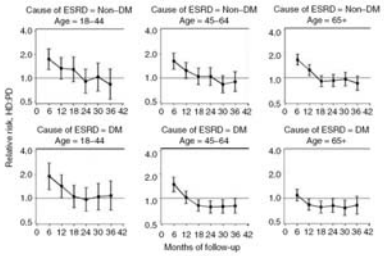


Figure 2. Matched cohort, peritoneal-dialysis-to-hemodialysis HRs from dialysis day 0 in subgroups. CVD, cardiovascular disease.

Figure 3. Matched cohort, peritoneal-dialysis-to-hemodialysis HRs from dialysis day 90 in subgroups.

Weinhandl ED. J Am Soc Nephrol. 2010

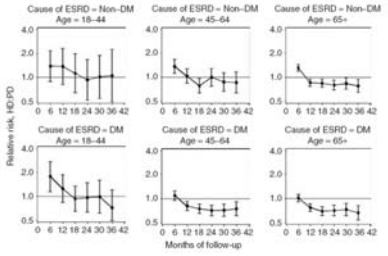
The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis.



Relative risk of death, RR(HD:PD), among patients with no reported comorbidity at baseline. RRs are adjusted for age, gender, race, and cause of ESRD, and baseline values of GFR, albumin, hemoglobin, and BMI.

Vonesh EF. Kidney Int. 2004

The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis.



Relative risk of death, RR(HD:PD), among patients with one or more reported comorbid conditions at baseline. RRs are adjusted for age, gender, race, and cause of ESRD, and baseline values of GFR, albumin, hemoglobin, and BMI.

Vonesh EF. Kidney Int. 2004

Comparing mortality rates on CAPD/CCPD and hemodialysis:Canadian experience

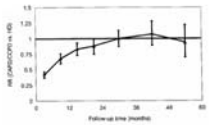


Figure 1 — Mortality rate ratios (RRs, CAPD/CCPD relative to hemodialysis (HD)) by follow-up interval adjusted for age, primary renal diagnosis, and comorbid conditions, and estimated using Poisson regression. Follow-up time on each of HD and CAPD/CCPD was computed for each patient within each follow-up interval. Deaths were allocated to the modality the patient was receiving at the time of death. Each RR is plotted against the midpoint of the follow-up interval to which it pertains.

TABLE 1
Mortality Rate Ratios: CAPD/CCPD Relative to Hemodialysis End-Stage Renal Disease Patients Initiating Therapy During 1990 to 1995 in Canada

Patients	"As-treated" analysis[a] RR[b]	(95% CI)	"Intent-to-treat" analysis[c] HR[d]	(95% CI)
All patients	0.73	(0.69, 0.77)	0.93	(0.87, 0.99)
Nondiabetics ≤64 yr	0.53	(0.46, 0.60)	0.84	(0.73, 0.96)
Nondiabetics ≥65 yr	0.75	(0.65, 0.86)	0.95	(0.86, 1.05)
Diabetics ≤64 yr	0.76	(0.65, 0.83)	0.90	(0.82, 1.10)
Diabetics ≥ 65 yr	0.88	(0.75, 1.04)	1.04	(0.87, 1.24)

Schaubel DE. Perit Dial Int. 1998

Dialysis outcomes in Colombia study: A comparison of patient survival on peritoneal dialysis vs hemodialysis

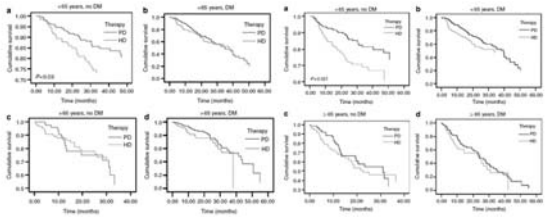


Figure 3 | Survival analysis by intention-to-treat adjusted for age and DM. (a-d)

Figure 5 | Survival analysis, as-treated, adjusted for age and DM. (a-d)

Sanabria M. Kidney Int. 2008

Hemodialysis and Peritoneal Dialysis: Comparison of adjusted mortality rates according to the duration of dialysis: Analysis of the Netherlands Cooperative Study

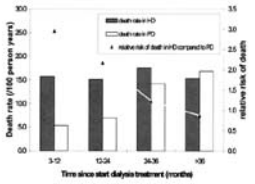


Figure 1. Unadjusted death rates and relative risk of death for hemodialysis (HD), compared with peritoneal dialysis (PD), according to time since the initiation of dialysis treatment (as-treated censoring).

Termorshuizen F. J Am Soc Nephrol. 2004

Hemodialysis and Peritoneal Dialysis: Comparison of adjusted mortality rates according to the duration of dialysis: Analysis of the Netherlands Cooperative Study

Table 3. Multivariate Cox proportional-hazards model for death, with RR (and 95% CI) for HD patients, compared with PD patients, adjusted for age, gender, comorbidity, primary kidney disease, SOA score, hemoglobin concentration, serum albumin level, and renal Kt/V_{urea} at baseline, according to time since the initiation of dialysis, subgroup determined on the basis of age and the presence of diabetes mellitus, and censoring strategy

	AT Censoring[a]		ITT Censoring[b]	
	Adjusted RR	95% CI	Adjusted RR	95% CI
Age <60 yr/no diabetes mellitus				
3 to 24 mo (n = 488)	0.60	0.25 to 1.42	0.77	0.34 to 1.73
24 to 48 mo (n = 223)	1.15	0.35 to 3.81	0.77	0.31 to 1.94
Age <60 yr/diabetes mellitus				
3 to 24 mo (n = 108)	9.99	1.29 to 77.29	6.35	1.42 to 28.36
24 to 48 mo (n = 50)	0.60	0.13 to 2.72	0.41	0.13 to 1.32
Age ≥60 yr/no diabetes mellitus				
3 to 24 mo (n = 479)	1.28	0.71 to 2.30	1.03	0.62 to 1.72
24 to 48 mo (n = 250)	0.30	0.18 to 0.51	0.41	0.25 to 0.67
Age ≥60 yr/diabetes mellitus				
3 to 24 mo (n = 147)	1.45	0.67 to 3.14	1.28	0.65 to 2.52
24 to 48 mo (n = 50)	0.45	0.18 to 1.17	0.66	0.30 to 1.49

[a] Overall test for interaction of modality and time and subgroup. Wald χ^2 = 8.1917, df = 3, P = 0.0422.
[b] Overall test for interaction of modality and time and subgroup. Wald χ^2 = 5.9493, df = 3, P = 0.1141.

Termorshuizen F. J Am Soc Nephrol. 2004

Initial survival advantage of PD relative to HD. Danish Register

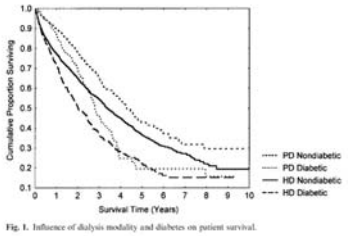


Fig. 1. Influence of dialysis modality and diabetes on patient survival.

Heaf JG. Nephrol Dial Transplant. 2002

Peritoneal dialysis in Romania: analysis of differences in mortality by dialysis modality and influence of risk factors in a national cohort

TABLE 5
Crude Death Rates (DR) per 100 Patients-Years with Unadjusted and Adjusted Relative Risks (HD:PD), Stratified by Comorbidity, Cause of End-Stage Renal Disease (ESRD), and Age

Comorbid conditions	Patient stratum Cause of ESRD	Age	HD Deaths	HD DR	PD Deaths	PD DR	RR (HD:PD) Crude DR	RR (HD:PD) Adjusted RR (95% CI)
None	Non-DM	18–65	71	6.14	9	5.43	1.13	1.59 (1.20–2.10)*
		>65	3	10.51	1	9.48	1.1	1.24 (0.47–3.26)
	DM	18–65	4	8.84	2	8.4	1.05	1.75 (0.71–4.29)
		>65	1	25.03	0	—	—	—
One or more	Non-DM	18–65	202	11.81	34	12.27	0.96	1.50 (1.19–1.89)*
		>65	37	21.52	12	23.75	0.81	1.39 (0.83–2.33)
	DM	18–65	38	21.52	23	22.18	0.97	0.96 (0.57–1.61)
		>65	11	38.12	5	28.83	1.32	1.25 (0.43–3.63)

HD = hemodialysis; PD = peritoneal dialysis; DM = diabetes mellitus; RR = relative risk.
* $p < 0.05$.

Mircescu G. Perit Dial Int. 2006

Survival analysis:Comparing peritoneal dialysis and hemodialysis in Taiwan

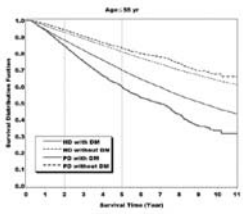


Figure 3 — Kaplan–Meier survival estimates, using the Cox proportional hazards model, for patients 55 years of age or younger, grouped by age and diabetes status. The tests for "equality of survival" between hemodialysis (HD) and peritoneal dialysis (PD) patients yielded a p value of less than 0.001 for the group with diabetes and 0.378 for the group without diabetes.

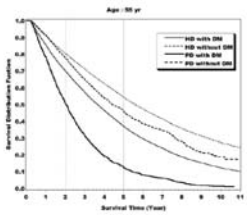


Figure 4 — Kaplan–Meier survival estimates, using the Cox proportional hazards model, for patients more than 55 years of age, grouped by age and diabetes status. The tests for "equality of survival" between hemodialysis (HD) and peritoneal dialysis (PD) patients yielded p values of less than 0.001 for the patients both with and without diabetes.

Huang CC. Perit Dial Int. 2008

우리나라 신대체 요법의 현황

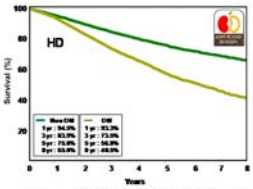


Fig. 8-4 . Diabetic & non diabetic hemodialysis patient survival since 2001 (Non DM : n=11,898, DM : n=11,401).

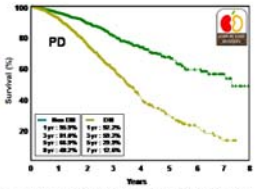


Fig. 8-5. Diabetic & non diabetic peritoneal dialysis patient survival since 2001 (Non DM : n=3,703, DM : n=2,742).

Probably significant portion of hemodialysis patients' death report was not submitted during patient transfer to another hospital (censored data) which could result hemodialysis patient survival is much higher than peritoneal dialysis patient survival.

대한신장학회 등록위원회

Target for blood glucose control

- Target HbA_{1c} for people with diabetes should be < 7.0%, irrespective of the presence or absence of CKD. (A)
- The patient on long-term dialysis therapy no longer needs to achieve good glycemic control to prevent deterioration of kidney function. However, good control may still prevent or slow the progression of retinopathy, neuropathy, and possibly macrovascular disease. Survival improves with better glycemic control in patients on peritoneal dialysis and hemodialysis therapy.

K/DOQI 2007

Predialysis glycemic control is an independent predictor of clinical outcome in type II diabetics on continuous ambulatory peritoneal dialysis.

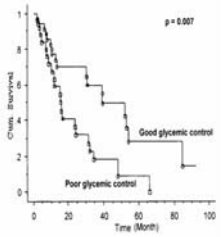


Figure 1 — Cumulative survival curves of patients with good and poor glycemic control were plotted by the Kaplan-Meier method and compared by Cox-Mantel log rank test. The patients with good glycemic control had significantly better survival ($p < 0.01$).

In group good glycemic control, more than 50% of blood glucose determinations were within 3.3-11 mmol/L and HbA1C level was within 5-10% at all times.

In group poor glycemic control, fewer than 50% of blood glucose determinations were within 3.3-11 mmol/L or HbA1C level was above 10% at least once during the follow-up duration.

YU CC. Perit Dial Int. 1997

Patients with decreased kidney function have increased risks for hypoglycemia.

(1) decreased clearance of insulin and some of the oral agents used to treat diabetes, and (2) impaired kidney gluconeogenesis.

With reduced kidney mass, the amount of gluconeogenesis carried out by the kidney is decreased. This reduction in gluconeogenesis may reduce the ability of a patient who is becoming hypoglycemic as the result of excessive insulin/oral agent dosage or lack of food intake to defend against hypoglycemia. About one third of insulin degradation is carried out by the kidney, and impaired kidney function is associated with a prolonged half-life of insulin. Thus, patients with type 1 diabetes receiving insulin who had significant creatinine elevations (mean, 2.2 mg/dL) had a 5-fold increase in the frequency of severe hypoglycemia. Therefore, it is imperative that patients being treated intensively monitor their glucose levels closely and reduce doses of medicines (insulin and oral agents) as needed to avoid hypoglycemia.

K/DOQI 2007

Insulin preparations in diabetes and CKD

Table 23. Insulin Preparations Categorized by Duration of Effect

Duration of Effect	Insulin Preparation
Rapid-acting	Regular insulin
	Lispro insulin solution
	Insulin aspartate solution
	Insulin glulisine
Intermediate-acting	Isophane insulin suspension (NPH)
Long-acting	Insulin glargine
	Insulin detemir

Doses are not specified by level of kidney function, but should be adjusted based on frequent monitoring to balance goals of glycemic control with avoiding hypoglycemia.

K/DOQI 2007

Oral hypoglycemic agents in diabetes and CKD

Table 22. Dosing Adjustments by CKD Stage for Drugs Used to Treat Hyperglycemia

Class	Drug	Dosing Recommendation CKD Stages 3, 4, or Kidney Transplant	Dosing Recommendation Dialysis
First-generation sulfonylureas	Acetohexamide	Avoid	Avoid
	Chlorpropamide	Reduce dose by 50% when GFR <70 and ≥50 mL/min/1.73 ml Avoid when GFR <50 mL/min/1.73 ml	Avoid
	Tolazamide	Avoid	Avoid
	Tolbutamide	Avoid	Avoid
Second-generation sulfonylureas	Glipizide	Preferred sulfonylurea No dose adjustment necessary	Preferred sulfonylurea No dose adjustment necessary
	Glyburide	Preferred sulfonylurea No dose adjustment necessary Not available in US	Preferred sulfonylurea No dose adjustment necessary Not available in US
	Glyburide	Avoid	Avoid
	Glimepiride	Initiate at low dose, 1 mg/day	Avoid
Alpha-glucosidase inhibitors	Acarbose	Not recommended in patients with SCr >2 mg/dL	Avoid
	Miglitol	Not recommended in patients with SCr >2 mg/dL	Avoid
Biguanides	Metformin	Contraindicate with kidney dysfunction defined as SCr ≥1.5 mg/dL in men or ≥1.4 mg/dL in women	Avoid
Meglitinides	Repaglinide	No dose adjustment necessary	No dose adjustment necessary
	Nateglinide	Initiate at low dose, 60 mg before each meal	Avoid
Thiazolidinediones	Pioglitazone	No dose adjustment necessary	No dose adjustment necessary
	Rosiglitazone	No dose adjustment necessary	No dose adjustment necessary
Incretin mimetic	Exenatide	No dose adjustment necessary	No dose adjustment necessary
Amylin analog	Pramlintide	No dose adjustment necessary for GFR 20-50 mL/min/1.73 ml	No data available
DPP-4 inhibitor	Sitagliptin	Reduce dose by 50% (50 mg/day) when GFR = 50 and ≥ 30 mL/min/1.73 ml and by 75% (25 mg/day) when GFR < 30 mL/min/1.73 ml	Reduce dose by 75% (25 mg/day)

K/DOQI 2007

Glucose absorption in peritoneal dialysis

- Glucose is a very successful osmotic agent in peritoneal dialysis.
- Does systemically absorbed glucose contribute to increased mortalilty especially in elderly diabetic patients? (Vonesh EF. Kidney Int. 2004)
- Excessive glucose absorption may play an important role in many of the metabolic imbalances, such as the dyslipidemia, hyperinsulinemia, insulin resistance, oxidative stress, inflammation, and altered adipokine levels. (Burkart J. Semin Dial. 2004)

Glucose sparing in peritoneal dialysis

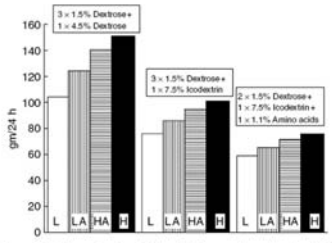


Figure 1 | Mathematical modeling of glucose absorption in CAPD patients with various membrane transport characteristics. The model assumes three shorts dwells of 5 h and a long dwell of 9 h. Legend: L = low (MTAC 5.96 ml/min); LA = low-average (MTAC 8.35 ml/min); HA = high-average (MTAC 11.7 ml/min); H = high (MTAC 16.3 ml/min).

Holmes C. Kidney Int. 2006

Glucose sparing in peritoneal dialysis

Table 3 | Comparison of icodextrin and 2.5% dextrose during the long dwell in CAPD patients

	Dwell time (h)	Net UF (ml)	CHO absorbed (g)	UF efficiency (ml/g)
2.5% Dextrose	10.1 ± 0.16	271 ± 42	39.3 ± 0.7	7.9 ± 1.3
Icodextrin	10.6 ± 0.16	599 ± 33	34.6 ± 2.0	27.8 ± 3.3
P-value	0.001	<0.0001	< 0.05	< 0.0001

CAPD, continuous ambulatory peritoneal dialysis; CHO, carbohydrate; UF, ultrafiltration.
Values are mean ± s.e.

Table 4 | Comparison of icodextrin and 4.25% dextrose during the long dwell in APD patients

	Dwell time (h)	Net UF (ml)	CHO absorbed (g)	UF efficiency (ml/g)
4.25% Dextrose	14.2 ± 0.1	220 ± 86	77.7 ± 1.4	3.1 ± 1.1
Icodextrin	14.1 ± 0.1	540 ± 46	56.2 ± 2.4	10.9 ± 1.1
P-value	0.64	<0.001	<0.001	<0.001

APD, automated peritoneal dialysis; CHO, carbohydrate; UF, ultrafiltration.
Values are mean ± s.e.

UF efficiency defined as the amount of net UF obtained for every gram of carbohydrate absorbed.

Holmes C. Kidney Int. 2006

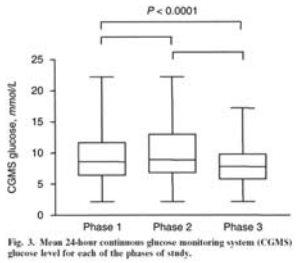
Glucose sparing in peritoneal dialysis

Table 6 | Strategies for implementation of glucose sparing

1. Reduction for the need for peritoneal ultrafiltration
   (a) Dietary salt and water restriction
   (b) Use of diuretics
2. Optimization of peritoneal ultrafiltration with minimization of glucose use
   (a) Appropriate design of prescription
   (b) Use of icodextrin for the long dwell
   (c) Use of amino-acids-based solution in short dwells

Holmes C. Kidney Int. 2006

Glycemic control in diabetic CAPD patients assessed by continuous glucose monitoring system



Phase I: lactate/bicarbonate-buffered solutions 1.36% x 3 and 3.86% x 1
Phase 2: lactate-buffered solutions 1.36% x 3 and 3.86% x 1
Phase 3: lactate/bicarbonate-buffered solutions 1.36% x 2, 1.1% amino acids solution x 1, icodextrin solution x 1

Fig. 3. Mean 24-hour continuous glucose monitoring system (CGMS) glucose level for each of the phases of study.

Marshall J. Kidney Int. 2003

Summary

- Diabetic patients with younger age, and less comorbid conditions may have survival advantage from PD compared to HD especially in early period of dialysis (~2 years)
- Target HbA_{1c} for CKD patients with diabetes should be < 7.0%.
- Be alert to the increased frequency of severe hypoglycemia in CKD patients with diabetes.
- Glucose sparing strategies in PD should be considered.