PD in Diabetics

Yong-Lim Kim
Kyungpook National University Hospital, Daegu, Korea
Epidemiology
Prevalence of DM is increasing in US
1980-2010 data from CDC

Percentage of US Population with Diagnose DM (18~79 yrs old)

Polonsky KD, NEJM 2012; National Diabetics Statistics Report (CDC), 2017
Prevalence of Diabetes among ≥20 yr old is high in China

National study from 2007 to 2008, 46,239

Yang W, NEJM, 2010; IDF Report

10.9% (2017)

9.7%

15.5%
Percentage of incident diabetic ESRD patients, 2015

Data source: Special analyses, USRDS ESRD Database. Data presented only for countries from which relevant information were available. United Kingdom: England, Wales, Northern Ireland (Scotland data reported separately). Data for France exclude Martinique. Data for Indonesia represent the West Java region. Data for Italy includes five regions. Data for Canada excludes Quebec. Data for Latvia represents 80% of the country’s population. Abbreviations: ESRD, end-stage renal disease; sp., speaking. NOTE: Data collection methods vary across countries, suggesting caution in making direct comparisons.
Trends in the incidence rate of diabetic ESRD (per mil/year), 2002-2015

Data source: Special analyses, USRDS ESRD Database. Ten countries having the highest percentage rise in 2014/15 versus that in 2002/03, plus the U.S. Data presented only for countries from which relevant information were available. Abbreviation: ESRD, end-stage renal disease. NOTE: Data collection methods vary across countries, suggesting caution in making direct comparisons.
Advantages and Disadvantages of PD/HD in Diabetic CKD stage 5
Dialysis modality-dependent changes in serum metabolites

A

Control

B

HD

C

PD

PCA Score Plot

These long-time different pattern of metabolites will make different metabolic consequences.

1 D 1H-NMR Spectroscopy Spectra

Choi JY & Kim YL et al. NDT 2011
PD: Potential Advantages in Diabetic Patients

- No need for vascular access
- No need for systemic anticoagulant
- Continuous therapy
- Gradual UF
- Fewer episode of hypotension
- Better preservation of renal function
- Better BP control
- Better control of anemia
- More liberal diet
- IP insulin administration
- Lifestyle advantages

Passadakis PS & Oreopoulois, Seminar Dial 2010
PD: Potential Disadvantages in Diabetic Patients

- Glucose PDF: Glucotoxicity & GDP toxicity
- Fluid balance: more difficult
- In poorly controlled diabetics:
  Glucose PDF → induce hyperglycemia → thirsty & fluid overload → using more hypertonic glucose PDF
- Visceral Fat a/w PD:
  - Negative impact on insulin sensitivity
  - Source of adipokines and proinflammatory cytokines

Laecke SV, PD Int 2007
IP glucose may have negative systemic and local impacts

Kim YL, J Renal Nutri 2013
Estimated Cal of absorbed glucose in PD

Burkart J, Seminar in Dial 2004
IP glucose extends period of hyperglycemia rather than oral glucose

* $P<0.05$ vs oral glucose
+ $P<0.01$ vs oral glucose

Delarue, KI, 1994
Glucose levels are lower on dialysis days in HD. The risk of asymptomatic hypoglycemia is highest within 24 h of dialysis.

19 HD T2D

Equivalent time of following day without HD

Glucose con. in the 1st 3 hr of HD session
Long interdialytic interval a/w mortality among HD patients.

32,065 HD

HD1, the day of the 1st HD session of week, HD1+1, the day after 1st session, HD2, the day of the 2nd session; HD2+1, the day after 2nd session, HD3, the day of the 3rd session; HD3+1, the day after 3rd session, HD3+2, the 2nd day after 3rd session

Foley RN, NEJM 2011
Difference of death rate between interdialytic period is greater in DM

32,065 HD

- Events on the day after the long (2-day) interdialytic interval
- Events on other days

Annualized Mortality Rate

<table>
<thead>
<tr>
<th>Diabetes</th>
<th>Non-DM</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVD admission

<table>
<thead>
<tr>
<th>CVD admission</th>
<th>Non-DM</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rate per 100 person-Yr

Foley RN, NEJM 2011
There is no variation in mortality risk by day of the week among PD patients
N=8855, Canadian Organ Replacement Register from 2001 to 2010

Perl J, Arch Intern Med, 2012
Should patients with diabetic CKD stage 5 start with PD or HD as a 1st modality?

Mortality Rate

QOL
Mortality studies comparing PD and HD
early cohort before year 2000

Risk Ratio (95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Compared to HD</th>
<th>Risk Ratio 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schaubel PDI 1998</td>
<td>All Pt</td>
<td>0.93 [0.87-0.99]*</td>
</tr>
<tr>
<td>Canada</td>
<td>DM≥65 y</td>
<td>1.04 [0.87-1.24]NS</td>
</tr>
<tr>
<td>Heaf NDT 2002</td>
<td>All Pt</td>
<td>0.86 [0.78-0.95]**</td>
</tr>
<tr>
<td>Denmark</td>
<td>DM≥55 y</td>
<td>1.04 [0.75-1.43]NS</td>
</tr>
<tr>
<td>Vonesh KI 2004</td>
<td>All Pt</td>
<td>1.04 [1.03-1.06]***</td>
</tr>
<tr>
<td>US Medicare</td>
<td>DM≥65 y</td>
<td>1.22 [1.16-1.27]***</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001
Increased risk among elderly female patients with diabetes on PD compared to HD

US Medicare, 99,046 HD and 18,110 PD, 1994-1996 cohort

Collins AJ, AJKD 1999
Increased risk among elderly patients with diabetes on PD compared to HD

Canadian Organ Replacement Register, 32,531 HD and 14,308, 1991-2004 cohort

RR of PD vs HD

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>18-64</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>NS</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Female</td>
<td>NS</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

RR 1.27

Yeates K, NDT 2012
Dutch, RENINE Registry, n=16,643, 1987-2002 cohort

Age 50 years, DM

Age 60 years, DM

Age 70 years, DM

Liem YS, KI, 2007
ANZDATA n=27,015, 1991-2005 cohort

McDonald SP, JASN 2009
Dialysis Modality and Mortality of Diabetic subgroup in Elderly: A Meta-Analysis *aged ≥ 65 years

Taken together, in elderly diabetic patients, PD mortality seems to be higher compared to HD mortality in early cohorts.
Survival Improvement in both modalities after year 2000
Adjusted survival probabilities

HD patients

PD patients
Improving PD outcomes in US
2003-2006 cohort, CMS from US, HD=92187, PD=6688
6337 propensity-matched

CMS, centers for medicare & medicaid

No diabetes (all years)
- Year 1
- Year 2
- Year 3
- Year 4

Diabetes (all years)
- Year 1
- Year 2
- Year 3
- Year 4

PD-to-HD Hazard Ratio
PD to HD HRs from dialysis day 0 in Propensity-Matched cohort

Weinhandl ED, JASN 2010
Survival Improvement in both modalities after year 2000
Canadian Organ Replacement Register, 32,531 HD and 14,308, 1991-2004 cohort

Adjusted Patient Survival by Cohort Period

Cohort Period = Overall

Adjusted Median Life Expectancy:
- HD: 50.9 months
- PD: 45.8 months
|Δ|: 5.1 months

Cohort Period = 1991-1995

Adjusted Median Life Expectancy:
- HD: 48.3 months
- PD: 43.8 months
|Δ|: 4.5 months

Cohort Period = 1996-2000

Adjusted Median Life Expectancy:
- HD: 52.2 months
- PD: 44.2 months
|Δ|: 8.0 months

Cohort Period = 2001-2004

Adjusted Median Life Expectancy:
- HD: 51.7 months
- PD: 50.8 months
|Δ|: 0.9 months

Yeates K, NDT 2012
Survival Improvement in PD
DM, 37~49%

PD versus HD survival over time in A/NZ

HD: 23% improvement in mortality 1998-2012
PD: 29% improvement in mortality 1998-2012

Adjusted for demographics and an extensive range of co-morbidity

Marshall M et al. AJKD 2015
Survival Improvement in PD

 adjusted for demographics and an extensive range of co-morbidity

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0090119
Survival Improvement in Diabetic PD

**DM**
- HR 0.85 (0.75-0.97)

**Elderly DM >=65**
- HR 0.85 (0.71-1.01)

Adjusted for demographics and an extensive range of co-morbidity

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0090119
Survival Improvement in PD 2004~2015 cohort population based study

HAZARD RATIO FOR MORTALITY (PD VS. HD)

PD vs HD

Lee SW et al. Sci Reports 2019
Survival Improvement in Diabetic PD
2004~2015 cohort, population based study

HR for Mortality (PD vs HD)

2004-2007
2008-2011
2012-2015

HR 1.06 (0.96-1.18)

Lee SW et al. Sci Reports 2019
Survival Advantage of PD relative to HD in the Early Period of Incident Dialysis Patients

**Propensity score matching: Nationwide Prospective Cohort**

Survival probability from day 90: 2009 to 2011 cohorts

![Survival probability graph](image)

**HR 0.49, 95% CI 0.25-0.97**

<table>
<thead>
<tr>
<th></th>
<th>12 m</th>
<th>24 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>94.1</td>
<td>87.6</td>
</tr>
<tr>
<td>PD</td>
<td>96.9</td>
<td>94.3</td>
</tr>
<tr>
<td>P value</td>
<td>0.152</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Cumulative survival (%)

Number of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 m</td>
<td>278</td>
<td>278</td>
</tr>
<tr>
<td>24 m</td>
<td>273</td>
<td>263</td>
</tr>
<tr>
<td></td>
<td>203</td>
<td>184</td>
</tr>
<tr>
<td>3 m</td>
<td>203</td>
<td>184</td>
</tr>
<tr>
<td>3 m</td>
<td>132</td>
<td>121</td>
</tr>
<tr>
<td>3 m</td>
<td>63</td>
<td>52</td>
</tr>
<tr>
<td>3 m</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

Choi JH & Kim YL, PLoS One Dec 2013
Survival probability from day 90 by dialysis modality Propensity-score matched (n=1,348)

The period that survival benefit for PD disappears was analyzed by cumulative hazard ratio

Cho JH et al, Paper Preparing
Survival Advantage of PD relative to HD in the Early Period of Incident Dialysis Patients

Survival probability from day 90 in Propensity score matched Diabetic Patients

Recent PD cohorts have shown remarkable improvement in patient survival, including diabetics.

> 65 years old
< 65 years old

Choi JH, PLoS One Dec 2013
Quality-adjusted Life Expectancy of HD & PD

National cohort with 14 yr FU and Propensity score matched Taiwan, 4285 pairs

QALE, Quality-adjusted Life Expectancy, including both the quality and the quantity of life lived

Average life time health cost
HD 237,795 vs PD 204,442

P=0.072
## The Impact of Dialysis Modality on QOL: Systematic Review

**Boateng EA, J Renal Care 2011**

<table>
<thead>
<tr>
<th>Study</th>
<th>S/P</th>
<th>EKD</th>
<th>BKD</th>
<th>CF</th>
<th>WS</th>
<th>SF</th>
<th>QSI</th>
<th>SL</th>
<th>SS</th>
<th>DSE</th>
<th>PS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molsted et al. (2007)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>74.4 ± 15.2</td>
<td>64.1 ± 18.6</td>
<td>38.4 ± 28.9</td>
<td>84.4 ± 19.3</td>
<td>17.9 ± 31.9</td>
<td>73.6 ± 29.0</td>
<td>85.1 ± 18.7</td>
<td>66.6 ± 25.8</td>
<td>74.5 ± 31.4</td>
<td>78.5 ± 22.0</td>
<td>81.7 ± 19.9</td>
</tr>
<tr>
<td>PD</td>
<td>74.0 ± 15.5</td>
<td>71.1 ± 16.2</td>
<td>44.7 ± 29.0</td>
<td>82.9 ± 18.4</td>
<td>33.6 ± 43.3</td>
<td>65.2 ± 35.1</td>
<td>83.4 ± 20.1</td>
<td>65.3 ± 22.8</td>
<td>81.6 ± 23.5</td>
<td>87.7 ± 14.9</td>
<td>89.0 ± 15.3</td>
</tr>
<tr>
<td><strong>Frimat et al. (2006)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>66.9</td>
<td>55.9</td>
<td>38.8</td>
<td>65.8</td>
<td>11.0</td>
<td>49.1</td>
<td>78.4</td>
<td>54.3</td>
<td>67.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PD</td>
<td>75.0</td>
<td>64.0</td>
<td>51.0</td>
<td>71.7</td>
<td>17.3</td>
<td>70.8</td>
<td>80.2</td>
<td>60.3</td>
<td>66.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Manns et al. (2003)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>73.1 ± 1.5</td>
<td>59.4 ± 2.0</td>
<td>40.3 ± 2.4</td>
<td>78.3 ± 1.7</td>
<td>29.2 ± 3.3</td>
<td>76.3 ± 9.2</td>
<td>77.7 ± 1.5</td>
<td>55.9 ± 1.9</td>
<td>72.6 ± 2.4</td>
<td>81.6 ± 2.0</td>
<td>77.2 ± 1.9</td>
</tr>
<tr>
<td>PD</td>
<td>73.5 ± 3.2</td>
<td>66.7 ± 2.9</td>
<td>51.8 ± 5.2</td>
<td>81.1 ± 3.2</td>
<td>29.2 ± 7.9</td>
<td>70.9 ± 12.1</td>
<td>75.6 ± 2.9</td>
<td>53.7 ± 2.7</td>
<td>72.2 ± 5.0</td>
<td>87.0 ± 3.1</td>
<td>77.1 ± 3.7</td>
</tr>
<tr>
<td><strong>Carmichael et al. (2000)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>69.9 ± 20.7</td>
<td>42.8 ± 17.3</td>
<td>79.3 ± 20.2</td>
<td>40.6 ± 35.8</td>
<td>-</td>
<td>-</td>
<td>72.5 ± 21.4</td>
<td>53.7 ± 24.4</td>
<td>78.8 ± 17.7</td>
<td>-</td>
<td>82.8 ± 16</td>
</tr>
<tr>
<td>PD</td>
<td>79.9 ± 11.8</td>
<td>76.3 ± 15</td>
<td>54.4 ± 22.8</td>
<td>81.0 ± 16</td>
<td>-</td>
<td>-</td>
<td>50.8 ± 39.7</td>
<td>79.6 ± 18.3</td>
<td>50.9 ± 22.8</td>
<td>-</td>
<td>94.3 ± 13.3</td>
</tr>
<tr>
<td><strong>Kutner et al. (2000)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>-</td>
<td>-</td>
<td>47.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>70.8</td>
<td>70.3</td>
</tr>
<tr>
<td>PD</td>
<td>-</td>
<td>-</td>
<td>57.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>89.4</td>
<td>82.9</td>
</tr>
</tbody>
</table>

S/P, symptoms or problems; EKD, effect of kidney disease on daily life; BKD, burden of kidney disease; CF, cognitive function; WS, work status; SF, sexual function; QSI, quality of social interaction; SL, sleep; SS, social support; DSE, dialysis staff encouragement; PS, patient satisfaction

In general, QOL of PD patients are better than that of HD except the physical dimensions over time.
PD patients had better QOL in Incident elderly patients
prospective cohort study in Korea, N=807 (315HD+492PD), KDQOL-36

* P value in elderly HD vs. PD < 0.05
** P value in elderly HD vs. PD = 0.001

How to improve the outcomes in Diabetic PD?

Referral Time
Dialysis Initiation Time
Planned Dialysis
Patient-centered Intervention
Factors affecting the Referral Time to Nephrologist

CRC for ESRD in Korea, prospective multicenter cohort, n=1744 CKD

<table>
<thead>
<tr>
<th>Risk Ratio for Late Referral</th>
<th>Risk Ratio 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>1.507 [1.057, 2.148]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.995 [1.305, 3.051]</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>2.152 [1.543, 3.0]</td>
</tr>
<tr>
<td>Walk with Assistance</td>
<td>2.072 [1.381, 3.111]</td>
</tr>
</tbody>
</table>

Patients with DM are referred later than those with GN to Nephrologist.

Early Referral to a Nephrologist improved Patient Survival

**HR difference between ER and LR**
Relationship btw log Relative Hazard for Mortality and Age according to the timing of referral, Prospective Cohort n=1028

**Total Patients**

A.

**DM**

B.

Adjusted for age, gender, modified CCI, BMI, eGFR, Hgb, Calcium, iPTH, uric acid, TG, total cholesterol and LDL-cholesterol

Early referral, meeting with a nephrologist more than a year before dialysis

Kim DH & Kim YL et al, PLoS One 2013
Early Referral to a Nephrologist improved Patient Survival

K-M Survival Curve in **Diabetic Patients** by the timing of referral

HR 4.74 (1.73-13.0)

Early referral, meeting with a nephrologist more than a year before dialysis

Adjusted for age, gender, modified CCI, BMI, eGFR, Hgb, Calcium, iPTH, uric acid, TG, total cholesterol and LDL-cholesterol

Kim DH et al, PLoS One 2013
# IDEAL: Effect of the Dialysis Initiation Timing in Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Early Start</th>
<th>Late Start</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GFR C–G</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12.5 ml/min/1.73 m²</td>
<td>56/139 (40)</td>
<td>56/137 (41)</td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>≥12.5 ml/min/1.73 m²</td>
<td>96/265 (36)</td>
<td>99/287 (34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GFR MDRD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9.5 ml/min/1.73 m²</td>
<td>58/195 (30)</td>
<td>57/203 (28)</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>≥9.5 ml/min/1.73 m²</td>
<td>94/209 (45)</td>
<td>98/221 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 yr</td>
<td>39/180 (22)</td>
<td>38/194 (20)</td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>≥60 yr</td>
<td>113/224 (50)</td>
<td>117/230 (51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>55/143 (38)</td>
<td>58/143 (41)</td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Male</td>
<td>97/261 (37)</td>
<td>97/281 (35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>65/232 (28)</td>
<td>63/241 (26)</td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>Yes</td>
<td>87/172 (51)</td>
<td>92/183 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body-mass index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25.0</td>
<td>40/102 (39)</td>
<td>46/126 (37)</td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>53/143 (37)</td>
<td>52/146 (36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30.0</td>
<td>59/159 (37)</td>
<td>57/152 (38)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effect of Dialysis Initiation Timing
n=1691, classified into early or late-start group according to the mean eGFR, 7.37 mL/min/1.73m², prospective cohort study in Korea

<table>
<thead>
<tr>
<th></th>
<th>Late-start</th>
<th>Early-start</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal dialysis</td>
<td>129</td>
<td>123</td>
<td>1.728 (0.563-5.309)</td>
<td>0.339</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>298</td>
<td>304</td>
<td>1.623 (0.859-3.065)</td>
<td>0.136</td>
</tr>
<tr>
<td>Diabetes</td>
<td>253</td>
<td>263</td>
<td>2.024 (1.025-3.996)</td>
<td>0.042</td>
</tr>
<tr>
<td>Non diabetes</td>
<td>174</td>
<td>164</td>
<td>1.315 (0.498-3.473)</td>
<td>0.580</td>
</tr>
<tr>
<td>Female</td>
<td>163</td>
<td>155</td>
<td>1.866 (0.734-4.740)</td>
<td>0.190</td>
</tr>
<tr>
<td>Male</td>
<td>264</td>
<td>272</td>
<td>1.542 (0.776-3.064)</td>
<td>0.216</td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td>143</td>
<td>157</td>
<td>2.268 (0.946-5.440)</td>
<td>0.066</td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>284</td>
<td>270</td>
<td>1.226 (0.589-2.552)</td>
<td>0.585</td>
</tr>
<tr>
<td>All</td>
<td>427</td>
<td>427</td>
<td>1.665 (0.958-2.894)</td>
<td>0.071</td>
</tr>
</tbody>
</table>

Lee J & Kim YL et al. PLOS ONE 2014
DM: Risk Factor for Burnout in dialysis patients

Burnout Cycle includes Withdrawal & Depression

Uncontrolled Diabetes? HbA1c > 8%
- HbA1c 9-<10% 5%
- HbA1c ≥ 10% 3%
- HbA1c < 5% 11%

HbA1c 8-<9% 9%

Target HbA1c for Dialysis Patients?
- HbA1c 6-<7% 27%
- HbA1c 5-<6% 29%

Burnt-Out Diabetes? (HbA1c < 6%)

N=56,000

Hypoglycemia referred to as ‘Burn-Out Diabetes’ in Dialysis

Rhee CM Semin Dial 2014 data based on Ricks et al Diabetes 2012

Independent of treatment
Risk Factors for Dialysis Withdrawal in the 1st year
ANZDATA 1999-2008 cohort, n=24,884, multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 y)</td>
<td>1.70</td>
<td>1.59-1.83</td>
</tr>
<tr>
<td>Gender (ref fem) Male</td>
<td>0.75</td>
<td>0.65-0.86</td>
</tr>
<tr>
<td>Race (ref white) indigenous</td>
<td>0.74</td>
<td>0.58-0.95</td>
</tr>
<tr>
<td>Modality (ref HD) PD</td>
<td>0.59</td>
<td>0.49-0.72</td>
</tr>
<tr>
<td>Comorbidity (per 1 add co-morbidity)</td>
<td>1.33</td>
<td>1.25-1.41</td>
</tr>
<tr>
<td>Late referral</td>
<td>1.83</td>
<td>1.59-2.11</td>
</tr>
</tbody>
</table>

Chan HW, CJASN 2012
Planned dialysis improves QOL and depression in Incident patients
prospective cohort study in Korea, N=643 (HD+PD), KDQOL-36 or BDI scores

Planned Dialysis, defined as dialysis therapy initiated with a permanent access (PD catheter or AVF/AVG)

Park JI & Kim YL, PLoS One 2015
Patient-centered intervention involving nurse improves glycemic control & depression
n=214, RCT, poorly controlled DM, coronary heart ds, depression

SCL-20 score

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted Estimate</th>
<th>Estimated Between-Group Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention Group (N=105)</td>
<td>Usual-Care Group (N=106)</td>
<td>Four-Outcome Composite</td>
</tr>
<tr>
<td>SCL-20 score</td>
<td>change</td>
<td>change</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.74±0.59</td>
<td>0.91</td>
<td>1.65±0.60</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.84±0.68</td>
<td></td>
<td>1.26±0.72</td>
</tr>
<tr>
<td>12 mo</td>
<td>0.83±0.68</td>
<td>1.14±0.66</td>
<td></td>
</tr>
</tbody>
</table>

Glycated hemoglobin — %

| Baseline | 8.14±2.03 | 0.81 | 8.04±1.87 | 0.23 | -0.56 (-0.85 to -0.27) | <0.001 |        |
| 6 mo     | 7.42±1.32 |         | 7.87±1.93 |       |                       |        |        |
| 12 mo    | 7.33±1.21 | 7.81±1.90 |         |       |                       |        |        |

SCL-20, Symptom Checklist-20 Depression Outcomes

Patients worked collaboratively with nurses and primary care physicians to establish individualized clinical and self-care goals every 2 to 3 weeks.

Katon WJ, et al. NEJM 2010
PD had the benefit in BDI in Incident elderly patients
prospective cohort study in Korea, N=807 (315HD+492PD), BDI scores

Should we aim to lower HbA1C level by tighter glycemic control & control BP intensively?
Hyperglycemia and mortality

ARIC study, n=11,092, Selvin E NEJM 2010 Atherosclerosis Risk in Communities study
Intensive Glycemic Control does not improve overall survival rate:
10 years FU, RCT, n=1791

Hazard ratio, 1.05 (95% CI, 0.89–1.25)
P=0.54

VADT Investigators, NEJM 2015
Intensive glucose control does not reduce death from renal disease in T2D: systematic review and meta-analysis

7 trials, n=28065

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight, %</th>
<th>Risk Ratio M-H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE$^{12}$</td>
<td>79.3</td>
<td>0.84 (0.43-1.64)</td>
</tr>
<tr>
<td>UKPDS 33$^{16}$</td>
<td>14.6</td>
<td>1.67 (0.35-7.85)</td>
</tr>
<tr>
<td>UKPDS 34$^{17}$</td>
<td>6.1</td>
<td>2.40 (0.22-26.39)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0</td>
<td>0.99 (0.55-1.79)</td>
</tr>
</tbody>
</table>

Coca SG, Arch Intern Med 2012
UK Renal Registry 1997-2006 cohort
n=3157 diabetics (HD 70%), excluded those who had died within 6 months

Poor glycemic control is a/w mortality in T2D HD

1255 HD T2D from 4 D Study, median FU 4 years

All-cause mortality

Data from 4D study
(German Diabetes Dialysis Study)

Logrank test, p=0.015

Drechsler C, Circulation 2009
Better Glycemic Control a/w Better Survival in Diabetic PD

N=2,798, Contemporary cohort of diabetic PD in DaVita dialysis clinic

Duong U, CJASN 2011
Better Glycemic Control a/w Better Survival in Diabetic PD

N=140, Prospective observational

Divided into tertiles according to the means of quarterly HbA1c levels during 1st year

- Mean HbA1c 6.3%
- Mean HbA1c 7.1%
- Mean HbA1c 8.5%

p=0.005

Yoo DE, PLoS One 2012
Glycemic Control and Mortality in Diabetic Patients
N=1,239, prevalent, Nationwide Prospective Cohort

Hgb A1c ≥8.0% adjusted HR 2.23 (1.27-3.93, p=0.006)

Log-rank P = 0.081

Log-rank P = 0.006

Time (month)
Higher Mortality a/w Poor Glycemic Control in Younger Diabetic PD Patients

N=1,239, prevalent, Nationwide Prospective Cohort

Hemodialysis

Age <55 (N = 254), ≥8%

Age 55-64 (N = 266), ≥8%

Age ≥65 (N = 353), ≥8%

Peritoneal dialysis

Age <55 (N = 153), ≥8%

Age 55-64 (N = 113), ≥8%

Age ≥65 (N = 100), ≥8%
Glycemic Control modifies Mortality Risk btw HD and PD in Diabetic Patients
N=902, incident, Nationwide Prospective Cohort

Kaplan-Meier Analysis in Propensity Score Matched Group

Taken together, vigilant (rather than intensive) glycemic control in diabetic dialysis patients is needed, particularly in PD patients, for improving Survival.

Median FU 28 mo
### Active BP control reduces CV events in dialysis patients: meta-analysis of RCTs - 8 RCTs, n=1679

<table>
<thead>
<tr>
<th>Study</th>
<th>Numbers of events/patients</th>
<th>SBP/DBP difference (mm Hg)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al (2003)</td>
<td>5/30</td>
<td>+0.7/-3.5</td>
<td>1.00 (0.34–2.92)</td>
</tr>
<tr>
<td>Takahashi et al (2006)</td>
<td>7/43</td>
<td>+3.0/0.0</td>
<td>0.43 (0.21–0.89)</td>
</tr>
<tr>
<td>Tepel et al (2008)</td>
<td>19/123</td>
<td>-9.0/NA</td>
<td>0.60 (0.36–0.99)</td>
</tr>
<tr>
<td>Cice et al (2003)</td>
<td>17/58</td>
<td>-10.5/-7.0</td>
<td>0.42 (0.27–0.65)</td>
</tr>
<tr>
<td>Suzuki et al (2008)</td>
<td>34/183</td>
<td>-2.3/-0.5</td>
<td>0.58 (0.40–0.83)</td>
</tr>
<tr>
<td>Nakao et al (2007)</td>
<td>NA/57</td>
<td>-7.3/-6.3</td>
<td>0.97 (0.67–1.34)</td>
</tr>
<tr>
<td>Zannad et al (2006)</td>
<td>67/196</td>
<td>-3.9/-1.7</td>
<td>1.12 (0.84–1.49)</td>
</tr>
<tr>
<td>Cice et al (2006)</td>
<td>59/151</td>
<td>NA</td>
<td>0.79 (0.61–1.02)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>208/841</strong></td>
<td><strong>-4.5/-2.3</strong></td>
<td><strong>0.71 (0.55–0.92)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2=67.5\%$, $Q=21.5$, $p=0.003$

**Excluding unpublished studies**

Test for heterogeneity: $I^2=73.7\%$, $Q=19.0$, $p=0.002$

Heerspink L, Lancet 2009
Intensive BP control does not reduce mortality and CV events in DM
4733 T2DM, RCT, SBP < 120 mmHg vs < 140 mmHg, mean FU 4.7 years

A Primary Outcome

Primary outcome: Nonfatal MI, nonfatal stroke, death from cardiovascular causes

No. at Risk
Intensive 2362 2273 2182 2117 1770 1080 298 175 80
Standard 2371 2274 2196 2120 1793 1127 358 195 108

The ACCORD Study Group, NEJM, 2010
Optimal BP target in Dialysis Patients with DM
n=2299, HD (60%), DM (32%), Nationwide Prospective Cohort

Jhee JH & Kim YL et al Scientific Report 2018
Are there better alternatives than HbA1C to estimate glycemic control? Is any oral drug superior to another?
Measure of glycemic control

<table>
<thead>
<tr>
<th>Measure</th>
<th>Represents glycaemic control over:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting serum glucose</td>
<td>Days</td>
</tr>
<tr>
<td>Fructosamine</td>
<td>2–3 weeks</td>
</tr>
<tr>
<td>Glycated albumin</td>
<td>2–3 weeks</td>
</tr>
<tr>
<td>HbA1c</td>
<td>2–3 months</td>
</tr>
<tr>
<td>Skin AGE</td>
<td>Long term</td>
</tr>
</tbody>
</table>

- HbA1c is the standard measure of glycaemic control in diabetic patients and is the most widely used in diabetic dialysis patients

- In diabetic dialysis patients, fructosamine and glycated albumin may more accurately reflect glycaemic control compared with HbA1c\(^1\)\(^2\) as they are not affected by changes in red cell mass or lifespan

HgbA1c levels in Dialysis

• Lower than expected HgbA1c
  – Decreased RBC survival
  – Increased RBC formation (Use of Iron or EPO)

• Higher than expected HgbA1c
  – Accumulation of Uremic toxin

  * Analytic interference from carbamylated Hgb in Agar gel EP

* Glycated albumin
  – shorter-term glycemic control (2-3 wks)
  – a/w markers of vascular injury
  – May not reliable in patients with proteinuria or PD
The most important concern is to avoid episodes of hypoglycemia in CKD stage 5 with DM

ERBP Clinical Practice Guideline, Patients with DM and CKD stage 3b or higher, 2015
# Drug-specific factors to consider when selecting antihyperglycemic treatment

<table>
<thead>
<tr>
<th>Class</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight change</th>
<th>In Patients on Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>No</td>
<td>Neutral (potential for modest loss)</td>
<td>Avoid</td>
</tr>
<tr>
<td>SGLT2-i</td>
<td>Intermediate</td>
<td>No</td>
<td>Loss</td>
<td>Avoid</td>
</tr>
<tr>
<td>GLP1-RA</td>
<td>High</td>
<td>No</td>
<td>Loss</td>
<td></td>
</tr>
<tr>
<td>DPP4-i</td>
<td>Intermediate</td>
<td>No</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>TZD</td>
<td>High</td>
<td>No</td>
<td>Gain</td>
<td>Avoid</td>
</tr>
<tr>
<td>SU</td>
<td>High</td>
<td>Yes</td>
<td>Gain</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>Highest</td>
<td>Yes</td>
<td>Gain</td>
<td></td>
</tr>
</tbody>
</table>

SGLT2, sodium-glucose transport protein 2; GLP1-RA, GLP1-receptor agonist; TZD, thiazolidinediones; SU, sulfonylurea
Drug-specific factors to consider when selecting antihyperglycemic treatment

<table>
<thead>
<tr>
<th>Class</th>
<th>CV effects</th>
<th>Renal effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASCVD</td>
<td>CHF</td>
</tr>
<tr>
<td>Metformin</td>
<td>Potential benefit</td>
<td>Neutral</td>
</tr>
<tr>
<td>SGLT2-I</td>
<td>Benefit: Empagliflozin &gt; Canagliflozin</td>
<td>Benefit: Empagliflozin Canagliflozin Dapagliflozin</td>
</tr>
<tr>
<td>GLP1-RA</td>
<td>Neutral: Lixisenatide/Exenatide ER</td>
<td>Neutral</td>
</tr>
<tr>
<td>DPP4-I</td>
<td>Neutral</td>
<td>Potential risk: Saxagliptin, Alogliptin</td>
</tr>
<tr>
<td>TZD</td>
<td>Potential benefit: Pioglitazone</td>
<td>Increased risk</td>
</tr>
<tr>
<td>SU</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Insulin</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

ASCVD, Atherosclerotic Cardiovascular Disease
## Dose Adaptation in Advanced CKD

<table>
<thead>
<tr>
<th>Class</th>
<th>Avoid</th>
<th>Need dose adaptation</th>
<th>No dose adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>Exenatide, Lixisenatide</td>
<td></td>
<td>Liraglutide, Albiglutide, Dulaglutide, Semaglutide</td>
</tr>
<tr>
<td>DPP4-i</td>
<td></td>
<td>Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin</td>
<td>Linagliptin</td>
</tr>
<tr>
<td>SU</td>
<td>Chlorpropamide, Acetohexamide, Tolazamide, Tolbutamide, Glyburide, Glimepiride</td>
<td></td>
<td>Glipizide, Gliquidone</td>
</tr>
</tbody>
</table>

Limited experience with GLP1-RA & DPP4-i
GLP1-RA, delayed gastric emptying or GI discomfort; DPP4-i, risk of hospitalization for heart failure in combination with another oral drug

Diabetes Care 2019;42(Suppl. 1):S90–S102
IP Insulin can be used

• Most peritoneal dialysis patients require insulin to maintain good glycemic control.

• Most nephrologists, do not use intraperitoneal insulin, since it often does not adequately control blood sugars.

• Disadvantages:
  ▪ the required insulin regimen is very complex
  ▪ the risk of bacterial contamination of dialysate
  ▪ the risk of peritoneal fibroblastic proliferation
  ▪ the risk of hepatic subcapsular steatosis
  ▪ lower HDL cholesterol levels and higher TG levels
  ▪ requirement for a higher total insulin dose due to losses into spent dialysate and to binding to the plastics in bags and tubing
IMPENDIA/EDEN Primary outcome: HbA1c*

n=251, Diabetic PD, RCT

Mean change in HbA1c from baseline (%)

Non-glucose sparing (Dianeal)  Glucose sparing (P-E-N or D-E-N)

Mean HbA1c ± SE (%)

Time (months)

No change from baseline in non-glucose sparing group

Difference between groups in mean change in HbA1c profile:
0.5% (95% CI 0.1 – 0.8, p=0.006)

ANZDATA on BMI and Mortality Risk in PD

Patient mortality

Univariate

Hazard ratio

BMI (kg/m²)

Multivariate

Hazard ratio

BMI ≥30 kg/m²
Adjusted HR 1.36
(1.20-1.54, p<0.001)
Ref. BMI 20-24

Stephen P. McDonald et al. JASN 2003;14:2894-2901

©2003 by American Society of Nephrology
Weight loss and improved fitness slowed the decline in mobility in overweight T2DM
4 years FU, RCT, n=5145

The intensive LSI was aimed at achieving and maintaining weight loss of at least 7% by focusing on reduced calorie intake and increased physical activity.

Look AHEAD Research Group, NEJM 2012
**DM: risk factor of volume overload**

Stepwise Multivariate Linear Regression Model  
N=338, stage 3-5 CKD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard error</th>
<th>Beta coefficient</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dl)</td>
<td>1.059</td>
<td>-0.304</td>
<td>-5.756</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM</td>
<td>0.831</td>
<td>0.213</td>
<td>4.429</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>0.023</td>
<td>0.169</td>
<td>3.665</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.822</td>
<td>0.156</td>
<td>3.508</td>
<td>0.001</td>
</tr>
<tr>
<td>ln TNF-α (pg/ml)</td>
<td>0.650</td>
<td>0.114</td>
<td>2.375</td>
<td>0.018</td>
</tr>
<tr>
<td>ln UPCR (g/g)</td>
<td>0.357</td>
<td>0.131</td>
<td>2.346</td>
<td>0.020</td>
</tr>
<tr>
<td>CVD</td>
<td>0.909</td>
<td>0.094</td>
<td>2.117</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Hung SC, et al. KI, 2014
Modifiable and nonmodifiable factors for fluid status in PD patients

Modifiable:
- Non-compliance with Salt & Fluid Restriction
- Lower BMI
- Malnutrition
- Protein-energy wasting
- Hypoalbuminemia
- ↑ Blood Pressure
- Systemic Inflammation
- Atherosclerosis
- Arterial Stiffness
- Endothelial dysfunction

Non-Modifiable:
- Older Age
- Male Gender
- Diabetes
- Fast Peritoneal Transport
- ↓ RRF
- ↓ Urine volume
- Co-morbidity

Fluid Overload

Kim YL & Biesen WV, Semin Nephrol 2017
Diabetic PD patients have greater ECW compared to non-diabetics, n=386

Real time monitoring of UF volume and bidirectional remote connectivity between patients and HCP are possible. This system may improve the volume status.
Recent PD cohorts have shown remarkable improvement in patient survival including diabetics. In diabetic patients, PD survival is generally equal to HD survival including elderly diabetics.

PD patients mostly enjoy a better QOL compared to HD patients.

Early referral to nephrologist, planned dialysis, patient-centered intervention involving nurse may improves the outcomes. Vigilant (rather than intensive) glycemic and BP control in diabetic dialysis patients is needed for improving Survival.

It may also need to find the diabetic patients who are expected to have good outcomes on PD.
Thank you for your attention !!