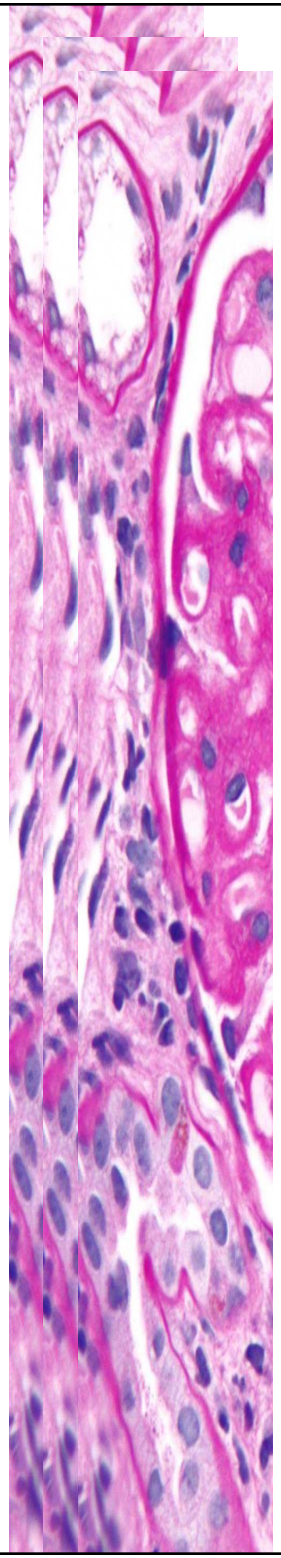

Management of Diabetes in People with ESRD and Dialysis

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Disclosures

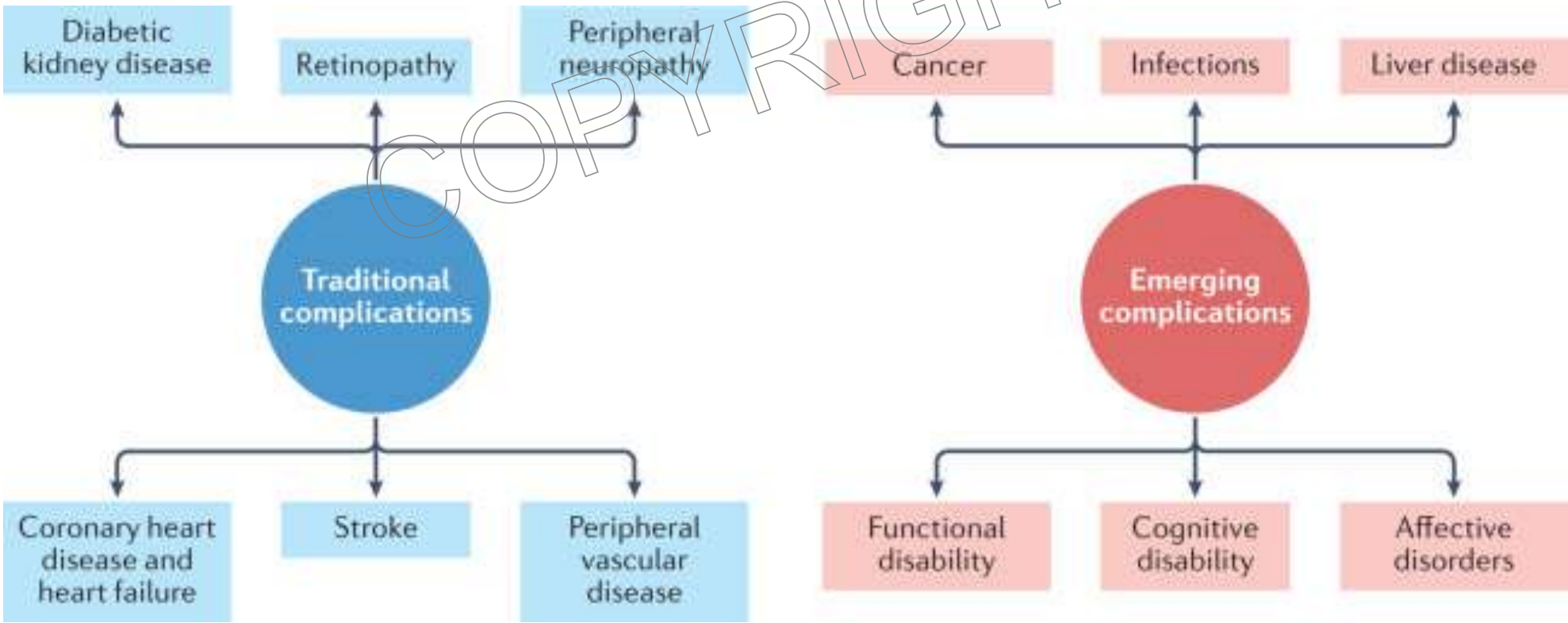
- I have no relevant disclosures

Introduction

- The worldwide prevalence of diabetes will increase by 50 % from 2013 to 2035, especially in under-developed countries
- The largest increase in prevalence of diabetes will occur in sub-Saharan Africa
- Over 40 million persons with diabetes in Africa by 2035
- The majority may remain undiagnosed
- Related to urbanization, obesity, sedentary lifestyle, poverty, social inequity, low medical expenditures
- Health burden in Africa: HIV/AIDS, malaria, and diabetes
- Risk factor for end-stage kidney disease

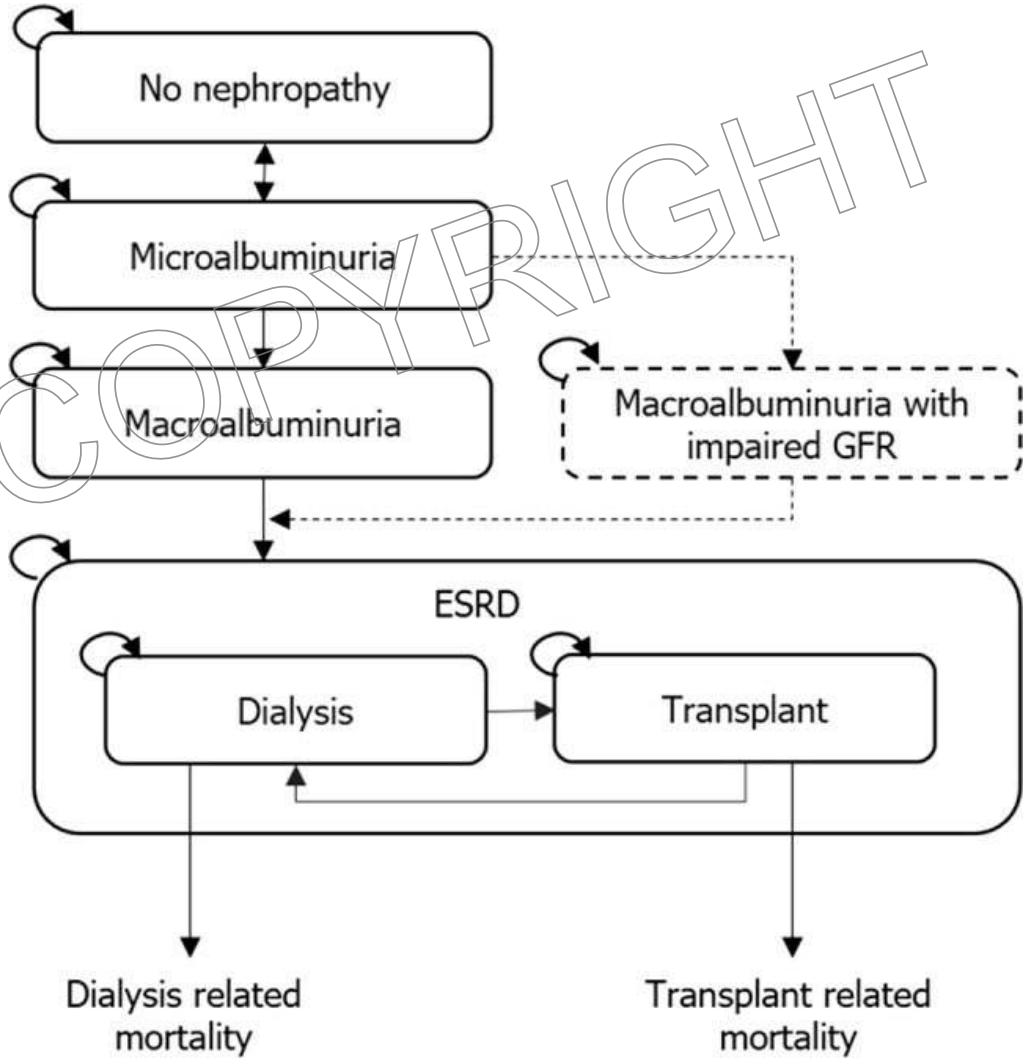
Burden and Risks of Complications of Diabetes Mellitus

(Tomic Nat Rev Endocrin 2022; 18: 525)



Model of diabetic CKD

Sugrue Pharmacoeconomics 2019; 37: 1451



End-Stage Renal Disease Problems for the Patient with Diabetes

Problem	Evaluation
Vascular access	Preservation of vasculature and early assessment for native fistula
Glycemic control	Hemoglobin A1c, home glucose monitoring
Angina, myocardial infarction	Exercise tolerance test, P-thallium, echocardiogram, catheterization
Visual impairment	Ophthalmology evaluation
Foot ulcers	Podiatry evaluation
Peripheral vascular disease, limb amputation	Doppler flow studies
Gastroparesis	Gastric emptying study
Neuropathic problems	Electromyography, neurologist
Malnutrition	Serum albumin, dietary counseling, PE

Care Gap in Diabetic ESKD

(Clemens et al Kidney360)

Table 2. - Two-year diabetes care gaps in 4173 patients using chronic, in-center hemodialysis in Ontario, Canada as of January 1, 2018

Diabetes Care Gap	Number (%)
No evidence of at least annual HbA1c	1410 (34)
>8 HbA1c tests	1278 (31)
No evidence of retinopathy screening	2201 (53)
No electrocardiogram or cardiac stress test	308 (7)
Hospitalization for hyperglycemia[a]	18 (0.4)
Hospitalization for hypoglycemia[a]	182 (4)
Hospitalization for hypertension[a]	217 (5)
Age ≥67 with no evidence of annual test strip prescription (*n*=2334)[b]	1115 (48)

HbA1c, hemoglobin A1c.
aRecorded as main diagnosis.
bOnly patients aged ≥67 were included to facilitate a 2-yr look-back period for use of medications.

“In order to be a competent nephrologist, one has to be a knowledgeable diabetologist.”

Dr. Eli Friedman

Why glycemic control is difficult to achieve in ESRD:

- Confounding effects of uremia and dialysis therapy
- Accurate assessment of glycemia
- Effect of ESKD on management
- Uncertain target for control

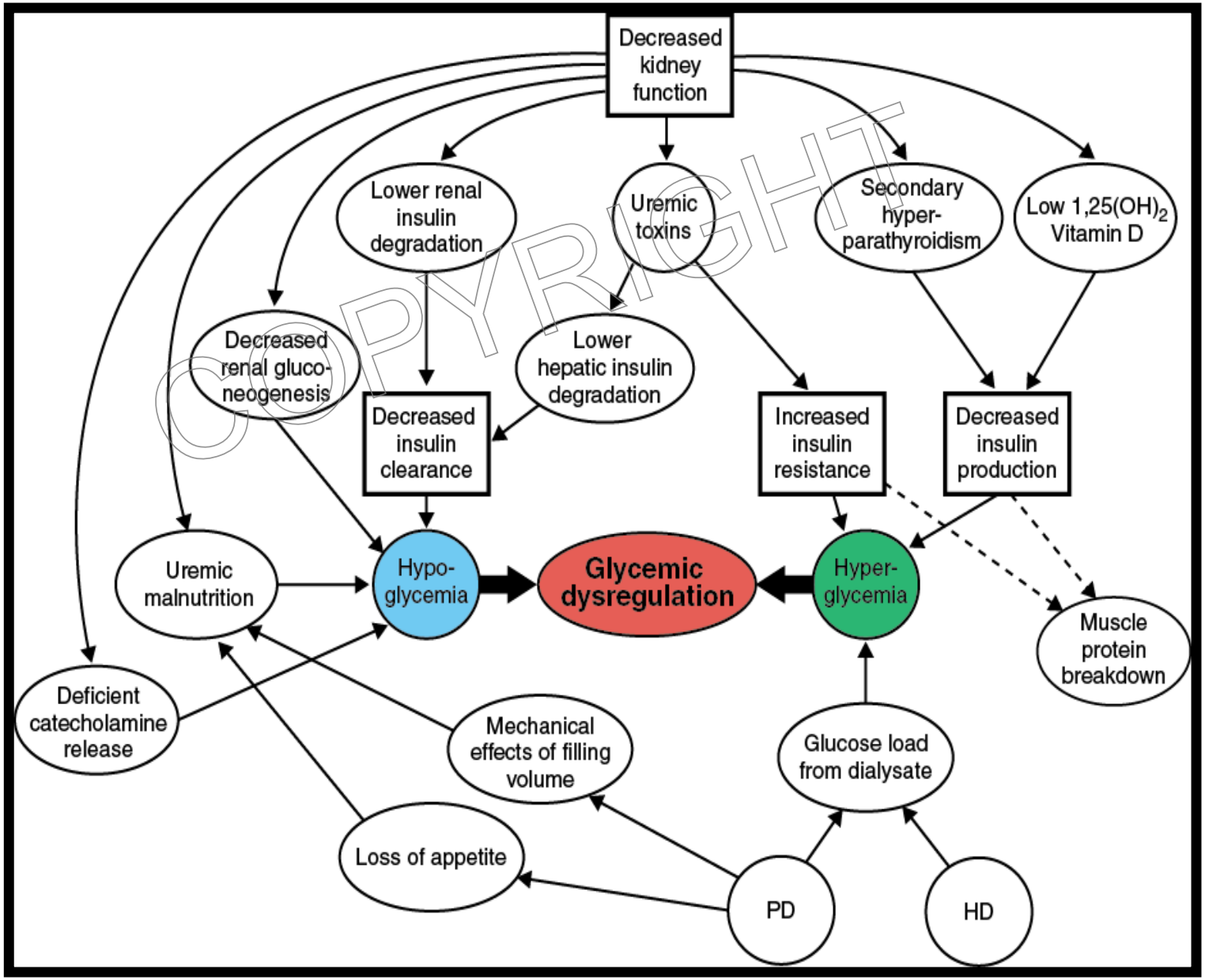
Effects of Uremia and Dialysis Therapy

Glucose and Insulin Homeostasis

Major Factors Contributing to Glucose Metabolism in Uremia

- Insulin resistance
- Impaired insulin secretion
- Reduced clearance of insulin

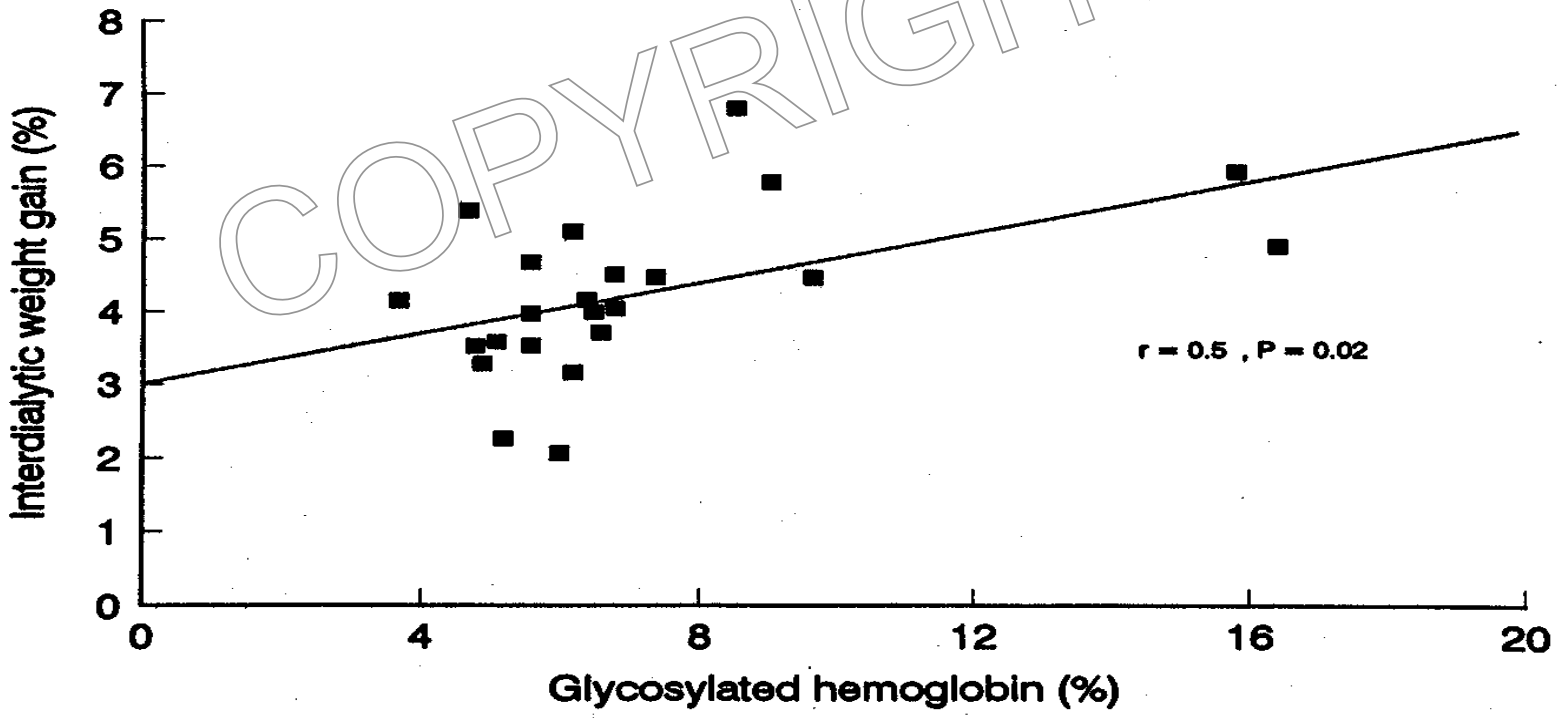
Glycemic Dysregulation in ESKD



Consequences of Hyperglycemia in Patients with Diabetes and End Stage Renal Disease

- Thirst, excessive fluid intake, weight gains between dialysis, hypertension
- Pulmonary edema, increased weight gains
- Severe hyperkalemia
- Diabetic ketoacidois
- Shifts in serum osmolality
- Anorexia, nausea, vomiting, weakness
- Increased risk of infection
- Gastroparesis
- Malnutrition
- Cardiovascular disease

Glycemic Control and Intradialytic Weight Gain in HD Patients



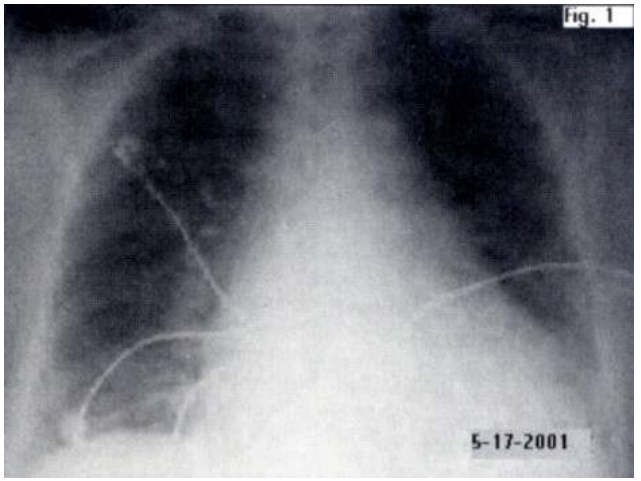
- Ifdu Am J Kidney Dis 23:686, 1994

ESKD Patient #1: Severe Hyperglycemia

- 53 yo female ESRD diabetes c/o SOB. Off insulin for a week. BP 180/80. HR 120. Weight up 4 kg. JVD, rales.

Table I. Initial laboratory workup.

Parameter	Value
plasma sodium (mEq/L)	116
potassium (mEq/L)	4.0
chloride (mEq/L)	79
CO_2 (mEq/L)	18.9
glucose (mg/dl)	1,135
BUN (mg/dl)	49
plasma creatinine (mg/dl)	6.5
plasma osmolality (mOsm/kg water)	315
creatinine phosphokinase (IU/L)	120
troponin-I (ng/ml)	< 0.1



Glycemic Control and Gastroparesis in ESRD

(Eisenberg, Nephron, 1995)

Table 3. Glycemic control indices

Variable	DGP group	Control group	p value
Adequate control, %	24	83	<0.001
Mean glucose			
mmol/l	12.4±4.1	8.9±2.4	<0.001
mg/dl	223±73	161±43	
Euglcycemia, %	39.8±21-0	74.2±22.6	<0.001
Hyperglycemia, %	50.4±24.3	23.4±22.0	<0.001
Hypoglycemia, %	9.8±11.9	2.4±4.6	<0.001
Glycohemoglobin, %	12.4±3.1	8.0±1.6	<0.001
Daily insulin, units	35±22	17±17	<0.001

ESKD Patient #2: Hypoglycemia

56 year old male with brittle Type 1 diabetes mellitus complicated by ESKD, on hemodialysis. Frequent admissions to another hospital with hypoglycemia. Recently left AMA from the other facility, after admission for wildly fluctuating glucose levels. He had fallen out of bed with a nocturnal hypoglycemic episode, was found by his nephew, fingerstick glucose was in the 30s. He received IV dextrose in the ED and was admitted.

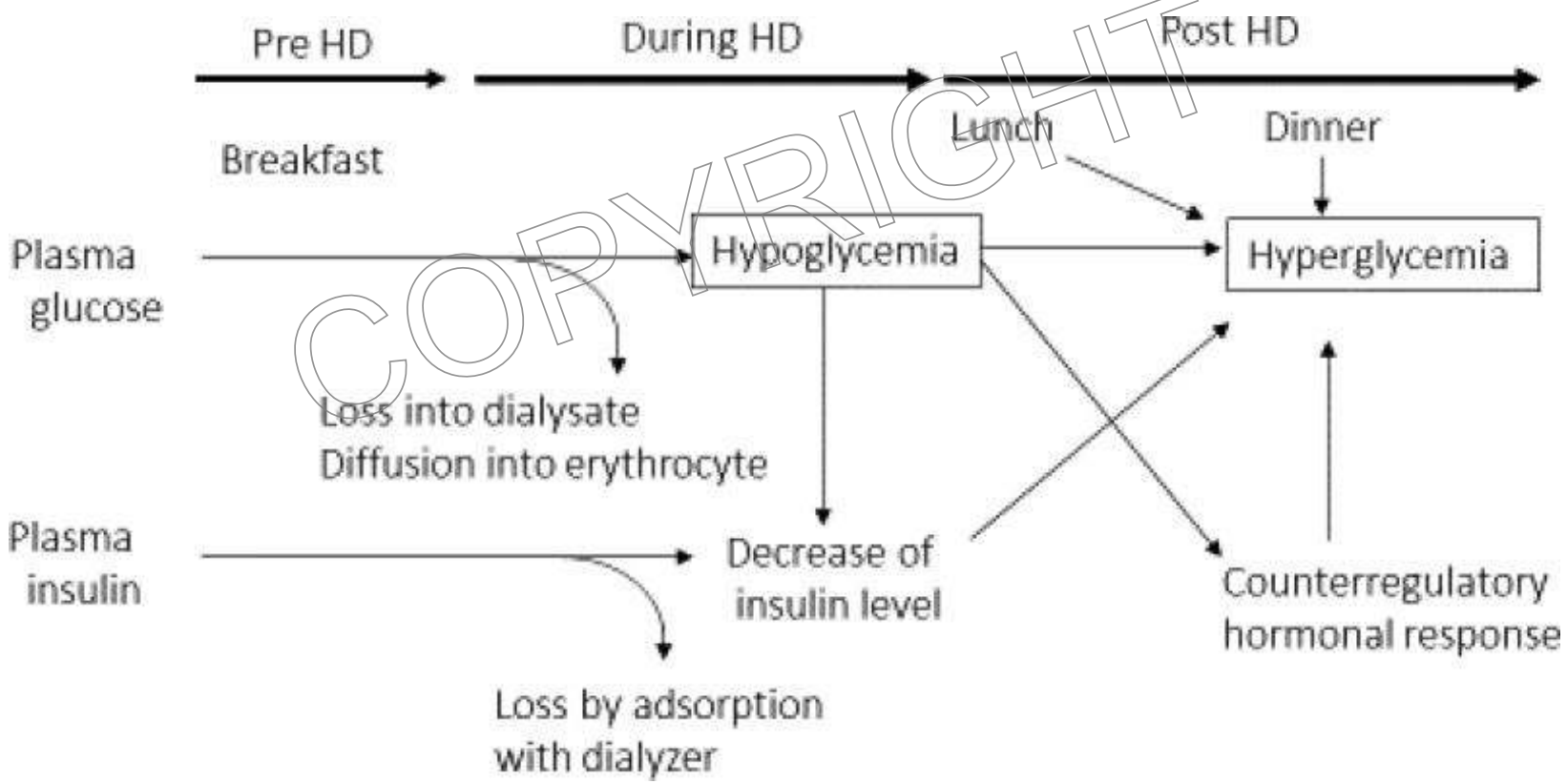
In the current admission, he had a morning hemodialysis session, where random venous glucose level was 157 early in his treatment. An hour after the treatment, he was found at home on the ground and unresponsive. EMS reported he was minimally responsive to sternal rub on arrival, and had a blood glucose of 20. He was given half an amp of D50 en route to the hospital. He had not eaten lunch. His dialysate dextrose bath was 100mg%.

Risk Factors for Hypoglycemia in End-stage Renal Disease

- Oral hypoglycemic agents
- Reduced intake
- Malnutrition
- Liver disease
- Alcohol ingestion
- Longer-duration diabetes
- Other drugs

Glycemic Variability in HD: Hypoglycemia/Hyperglycemia Paradigm

(Abe Nat Rev Nephrol 2015 11: 302)



Effect of Hemodialysis Treatment on Blood Glucose Levels

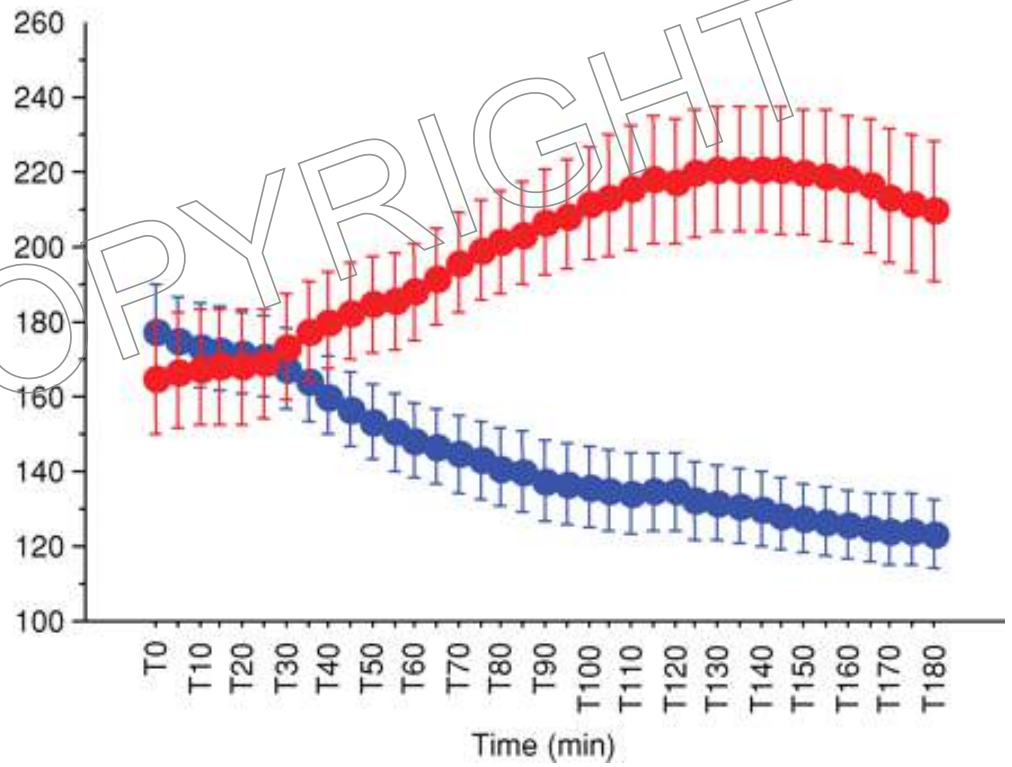


Fig. 4 Glucose concentration in the first 3 h of the dialysis session (blue circles) or equivalent time of the ...

Nephrol Dial Transplant, Volume 24, Issue 9, 2009, Pages 2866–2871, https://doi.org/10.1093/ndt/gfp181

ESKD Patient #3: Glycemic Variability

- 75 y.o. female type 2 diabetes mellitus on HD
- Speaks minimal English
- Insulin administered 3 days/week by VNA
- Treated with Insulin 3 days at adult daycare center; no insulin on Sundays
- No family involvement in diabetes management
- 11:30 a.m. dialysis 3 days per week, may be treated for low or high bs's there by staff
- SMBG's at hemodialysis 40-400mg/dl
- A1C's 10-12%

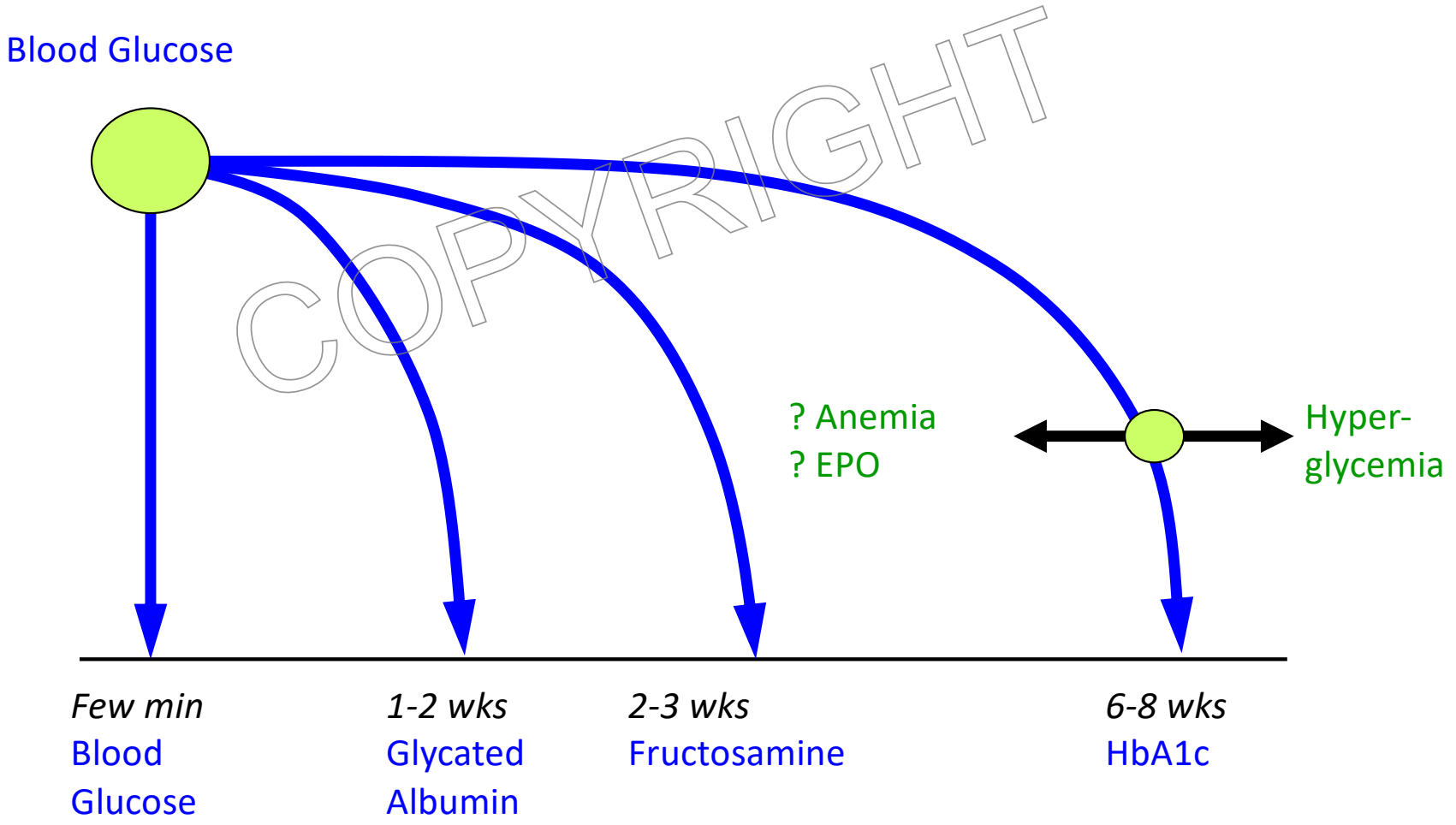
Accurate Assessment of Glycemic Control

Pitfalls of Hemoglobin A1c

Ideal Measure of Glycemic Control

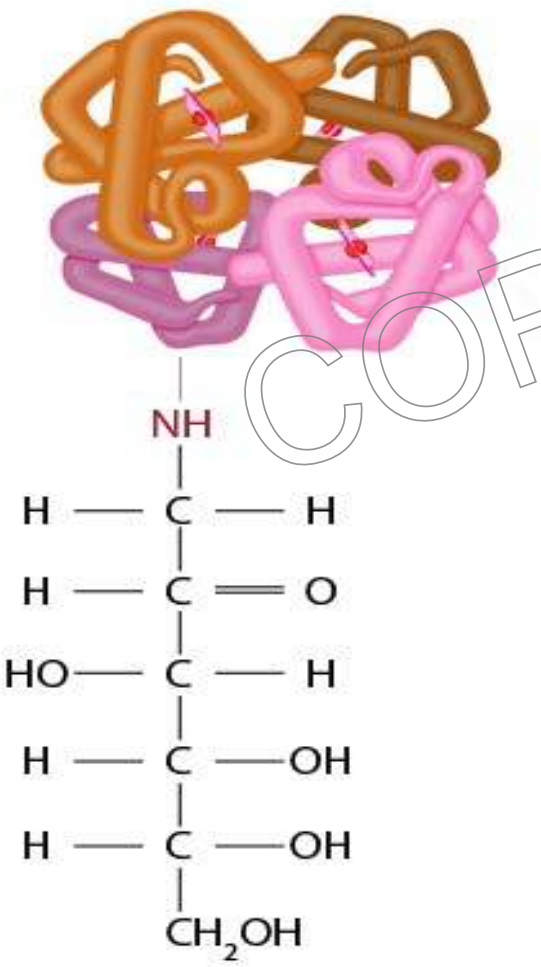
- Accurately reflects recent serum glucose concentrations
- Precise measurement of chronic glycemia
- Correlation with diabetic complications
- Predicts hypoglycemia risk

Assessing Glycemic Control in Diabetic ESRD



Measures of Glycemic Management:

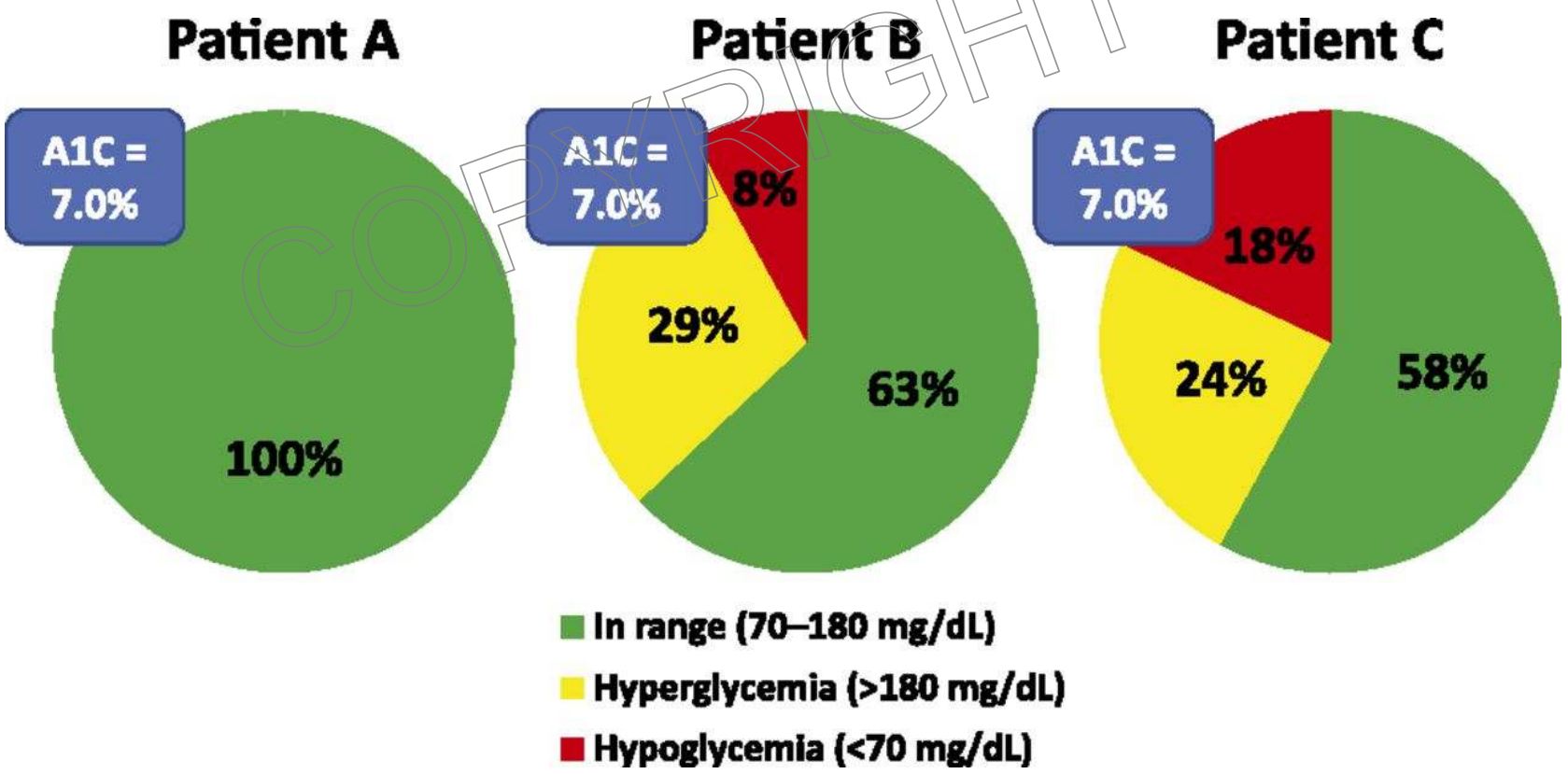
Hemoglobin A1c



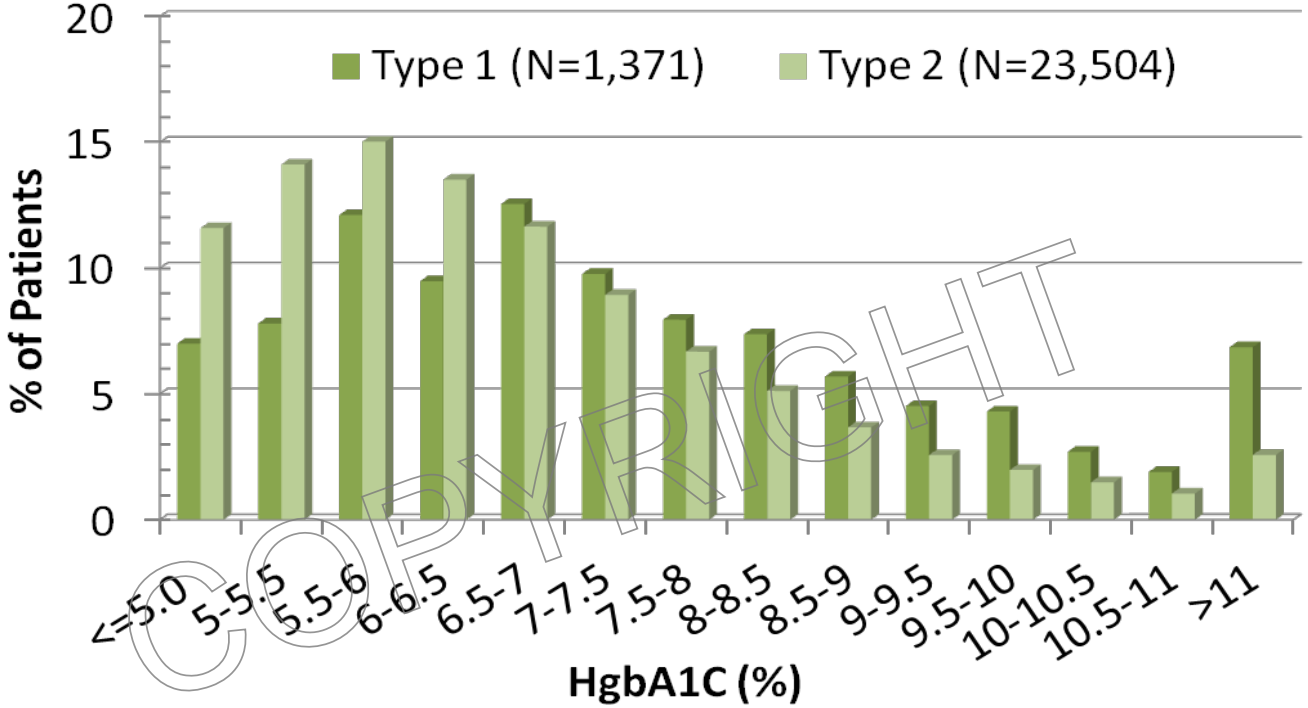
- Per cent of circulating hemoglobin that has nonenzymatically reacted with glucose
- Formed by binding of glucose to N terminal of b chain of hemoglobin
- Continuously formed
- The only index which significantly predicts diabetes-related outcomes

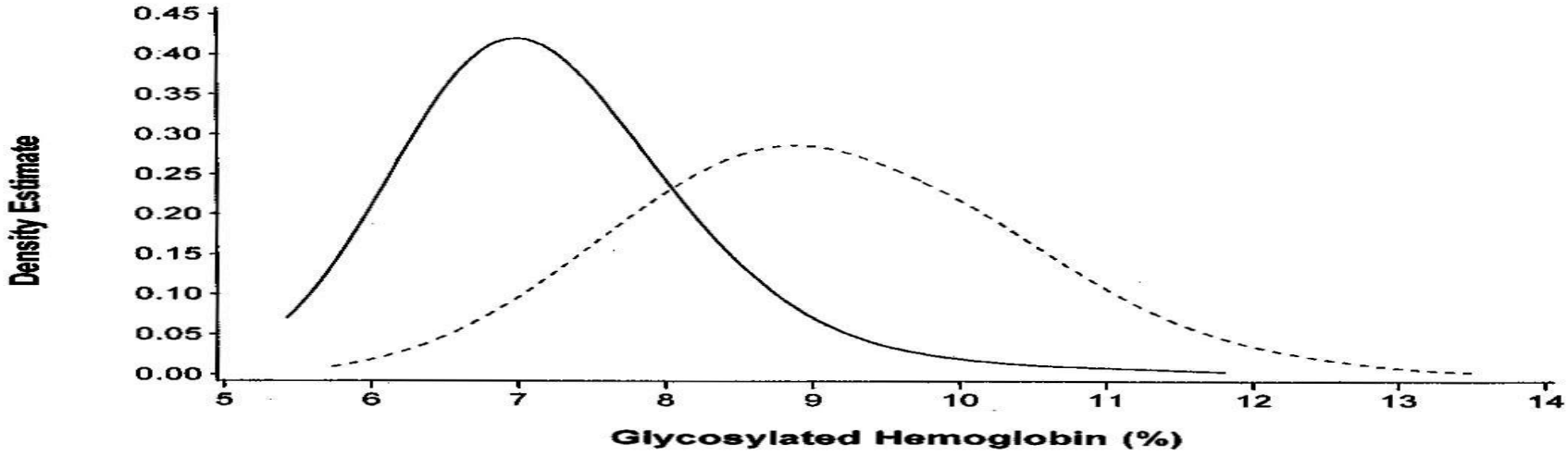
Fallability of Hgb A1c

(Kushner et al Clin Diabetes 2020 38:348)



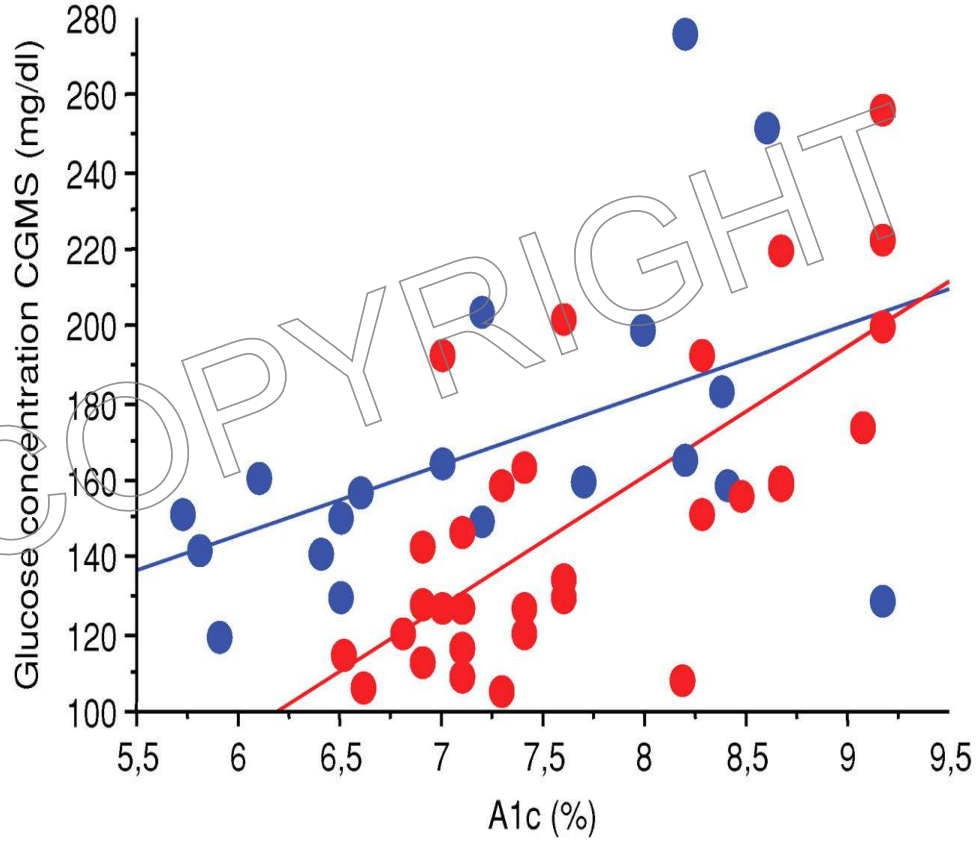
HbA1c Values in Diabetic HD Patients





Spline-smoothed estimates of the distribution of the mean HbA_{1c} level for each subject during the DCCT

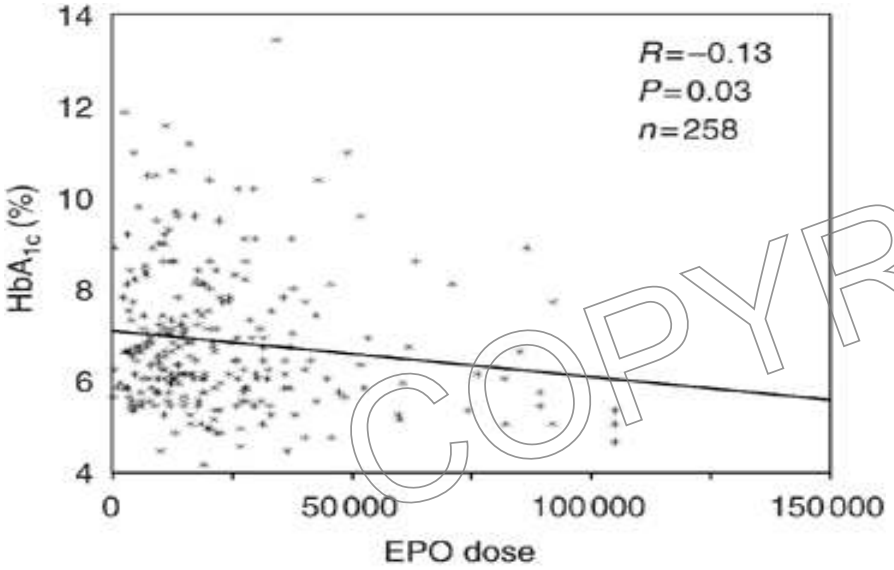
Hemoglobin A1c in Hemodialysis Patients

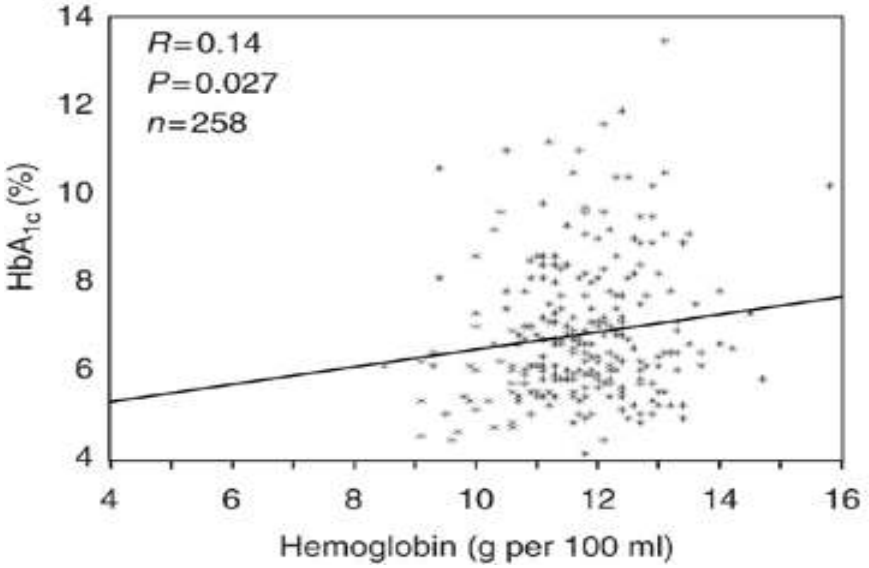


Riveline, J.-P. et al. Nephrol. Dial. Transplant. 2009 24:2866-2871; doi:10.1093/ndt/gfp181

- HD (blue circles; n=19) and nonHD (red circles; n=39)

Impact of Hemoglobin Concentration and EPO dose on HbA1c in ESRD





- Peacock; Kidney Int 2008; 73: 1062
- EPO dose and A1c negatively associated
- Hgb and A1c positively associated
- Contrary to effect of iron deficiency anemia

Glycated Albumin

-Time-averaged index of the state of glycemic control over 1-2 weeks

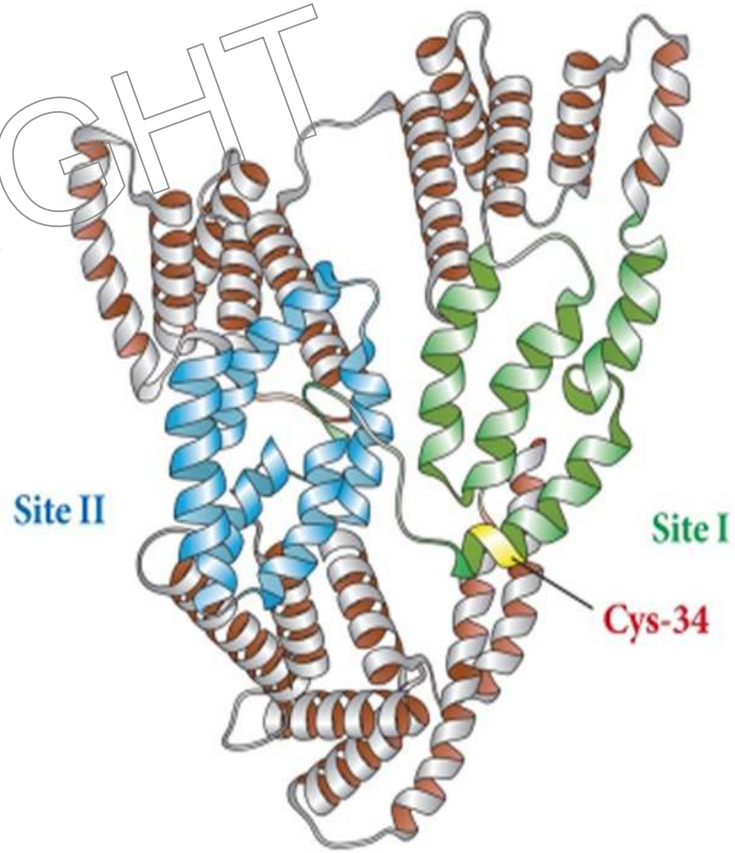
-Marker of short-term variations in glycemic control during treatment

-Early Amadori-type nonenzymatic glycation product

-Reference range 11.9-15.8%

-Analysis adjusted for serum albumin level

-Assay not approved in U.S.



SERUM FRUCTOSAMINE

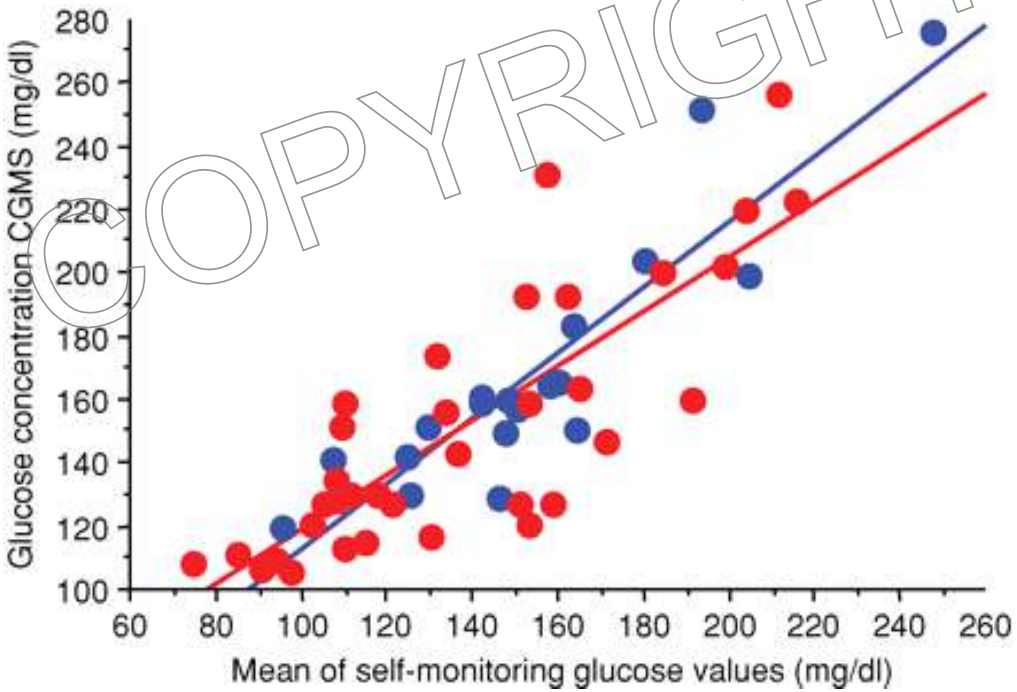
- Spontaneous, nonenzymatic glycation of proteins
- Colorimetric assay
- Recent (1-3 weeks) glycemic control
- No effect of red cell turnover
- Need to be corrected for serum albumin level

Glucose Sensor

(Cavallari G J Clin Med 2022 11: 1521)

- Applied to arm
- Subcutaneous needle
- Interstitial glucose
- Measurements viewed on a receiver unit

CGM: Correlation between mean glucose obtained through CGMS and glucose meters in HD T2 (blue circles) and non-HD Patients

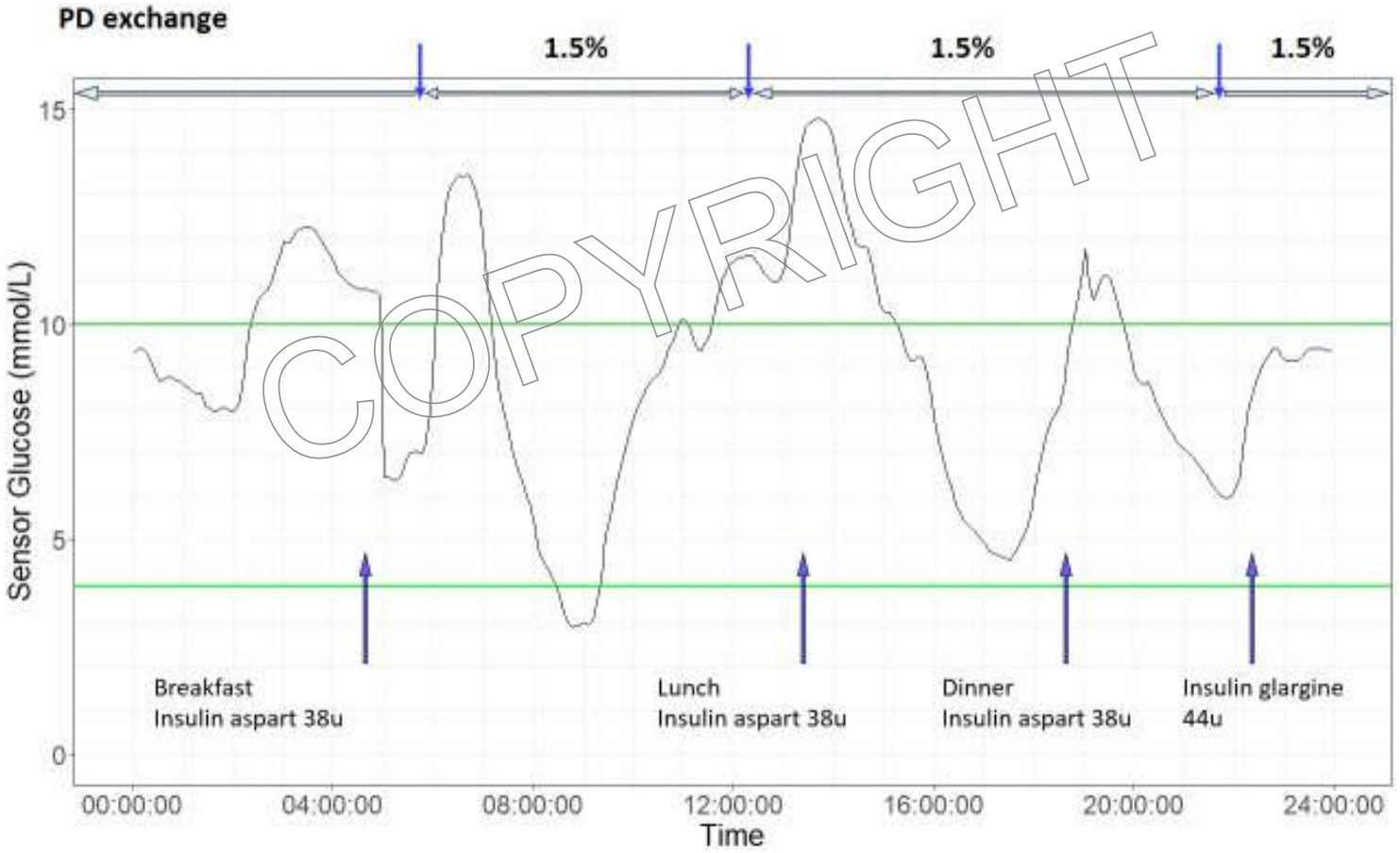


Nephrol Dial Transplant, Volume 24, Issue 9, September 2009, Pages 2866–2871, https://doi.org/10.1093/ndt/gfp181

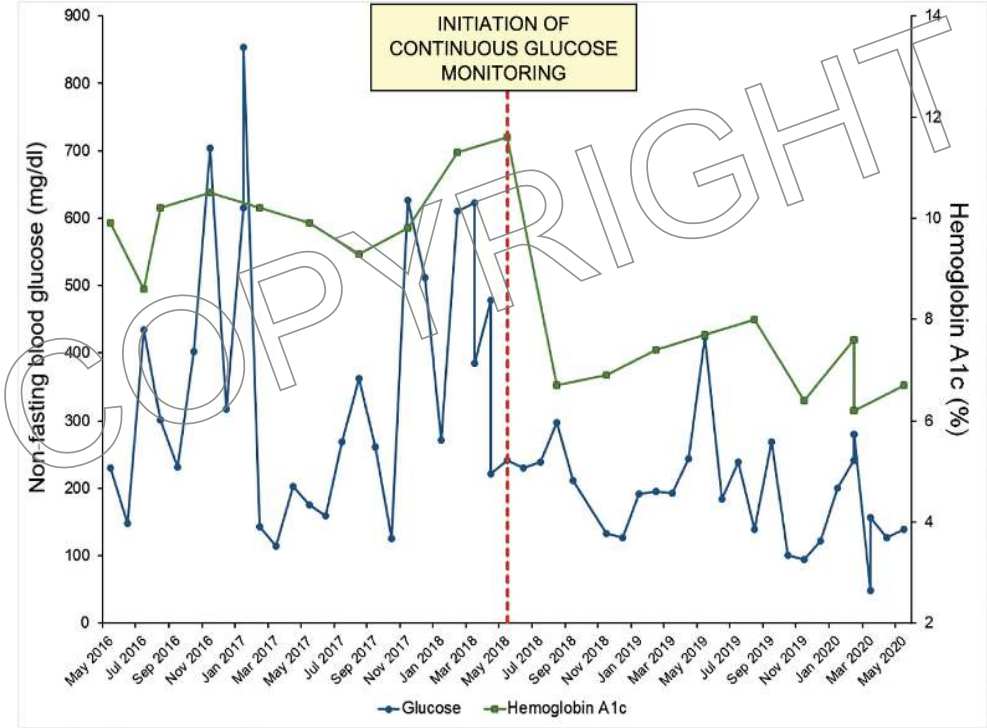
Glucose Variability Related to Hemodialysis Procedure (Ling J Front Endocrin (Lausanne) 2022; 13: 869899)

Glucose Profile in Peritoneal Dialysis

(Ling J Front Endocrin Lausanne)



Continuous glucose monitoring in an end-stage renal disease patient with diabetes receiving hemodialysis



Seminars in Dialysis, Volume: 34, Issue: 5, Pages: 388-393, First published: 10 August 2021, DOI: (10.1111/sdi.13009)

Fully closed-loop insulin delivery Improves glucose control of inpatients with type 2 diabetes receiving hemodialysis.

Patient population

17 patients
- Inpatient
- >18years old
- Insulin-treated type 2 diabetes
- End stage renal disease requiring haemodialysis

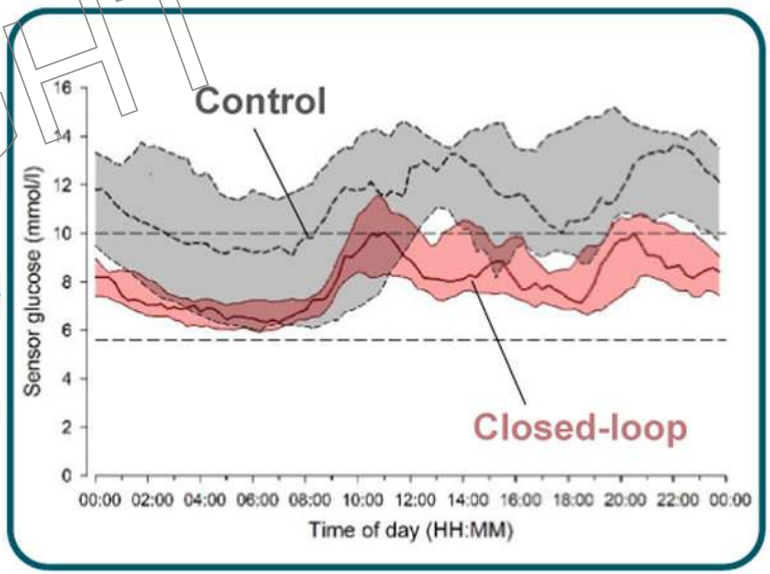
Randomise

Closed-loop insulin delivery (n=9)

Conventional s.c. insulin therapy (n=8)

Up to 15 days

Results



CONCLUSION:

Closed-loop insulin delivery provides a novel approach to improve glucose control without increasing the risk of hypoglycaemia in patients receiving haemodialysis

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Bally et al, 2019

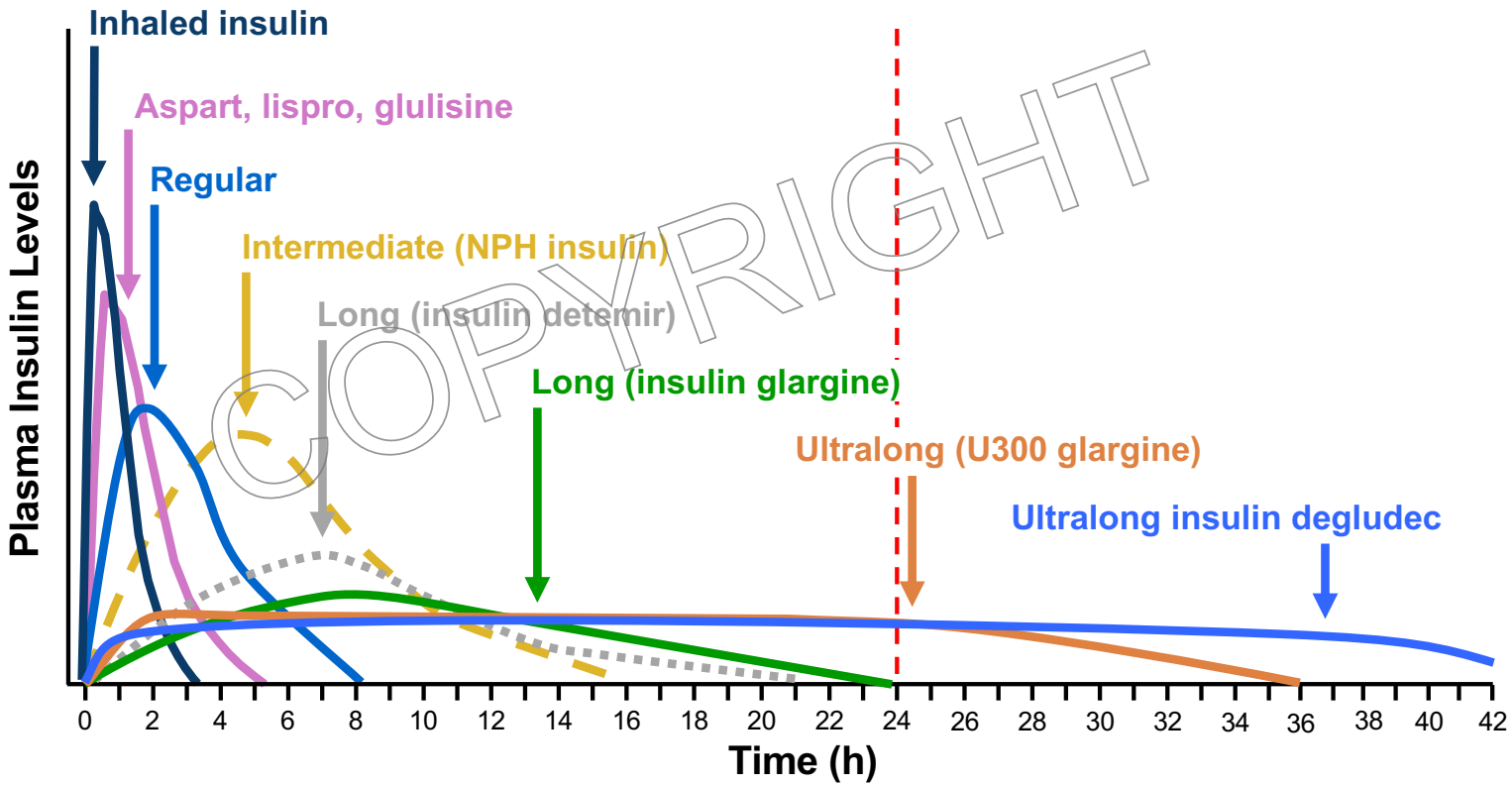
Diabetes Treatment

Effects of ESRD on Management

Evolution of Diabetes Treatment in ESRD Patients

- Reduced insulin requirements (Type I and II)
- From insulin to oral hypoglycemic agents (Type II)
- Reduced oral hypoglycemic agents
- Off oral hypoglycemic agents (type II)
- Off insulin (Type II)

Pharmacokinetics Profiles of Current Insulins



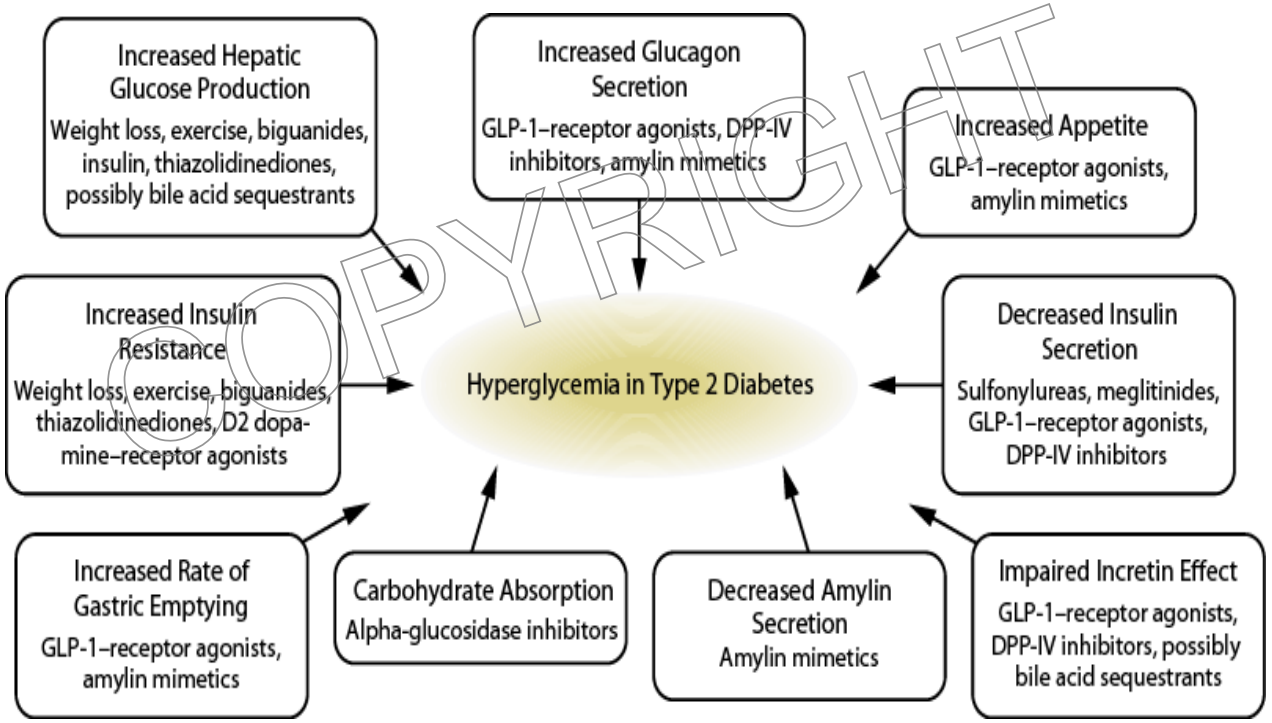
PK = pharmacokinetic; NPH = neutral protamine Hagedorn.

Adapted from Hirsch IB. *NEJM*. 2005;352:174-183. Flood TM. *J Fam Pract*. 2007;56(suppl 1):S1-S12. Becker RH, et al. *Diabetes Care*. 2015;38:637-643. http://www.pdr.net/full-prescribing-information/afrezza?druglabelid=3540. Accessed April 5, 2015. Hompesch M, et al. *Clin Ther.* 2014;36(4):507-515.

Insulin

- More prolonged action in ESRD
- Stopping insulin in type 1 DM leaves risk of DKA
- Use in:
  - Most type I patients
  - Type II DM patients
    - Not controlled with oral agents alone
    - Contra-indication to oral agents
- Consider changing treatment on diaysis days

Specific Oral Treatments of Hyperglycemia in Type 2 Diabetes



- Ismail-Beigi NEJM 2012; 366: 1319

Hypoglycemic Agents and ESRD

- Avoid Metformin – Lactic Acidosis (data inconclusive)
- Glipizide the preferred oral sulfonylurea
- No dose adjustment for Repaglinide
- No dose adjustment for Pioglitazone or Roziglitazone
- Need decreased dose of Sitagliptin (DPPR I) (Januvia); use linagliptin
- SGLT2 inhibitors not recommended
- No dose adjustment semaglutide (Ozempic) or tirzepatide (Mounjaro) or exenatide (Byetta)

Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

Kidney International (2022) 102, 974–989

Preserving Residual Renal Function

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High

Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

Kidney International (2022) 102, 974–989

- A sodium–glucose cotransporter-2 inhibitor (SGLT2i) with proven kidney or cardiovascular benefit is recommended for patients with T2D, CKD, and eGFR ≥20 ml/min/1.73 m^2. Once initiated, the SGLT2i can be continued at lower levels of eGFR.

- CANAGLIFLOZIN – INITIATION NOT RECOMMENDED EGFR <30 BUT CAN CONTINUE A LOW DOSE

- DAPAGLIFOZIN – INITIATION NOT RECOMMENDED IF EGFR <25 BUT CAN CONTINUE

- EMPAGLIFLOZIN – HF/CKD- TRIALS REQUIRED INITIAL EGFR<20

- RISK OF EUGLYCEMIC DIABETIC KETOACIDOSIS

- STOP BEFORE SURGERY, PROLONGED FASTING, SERIOUS ACUTE MEDICAL ILLNESS

- ESKD/DIALYSIS – NO DATA FOR ANY SGLT2 INHIBITORS

GLP-1 Receptor Agonists

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
GLP-1 receptor agonists§			
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
Dulaglutide	No dose adjustment required		
Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide	No dose adjustment required		

8.6 Renal Impairment

No dose adjustment of OZEMPIC® is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed *[see Clinical Pharmacology (12.3)]*.

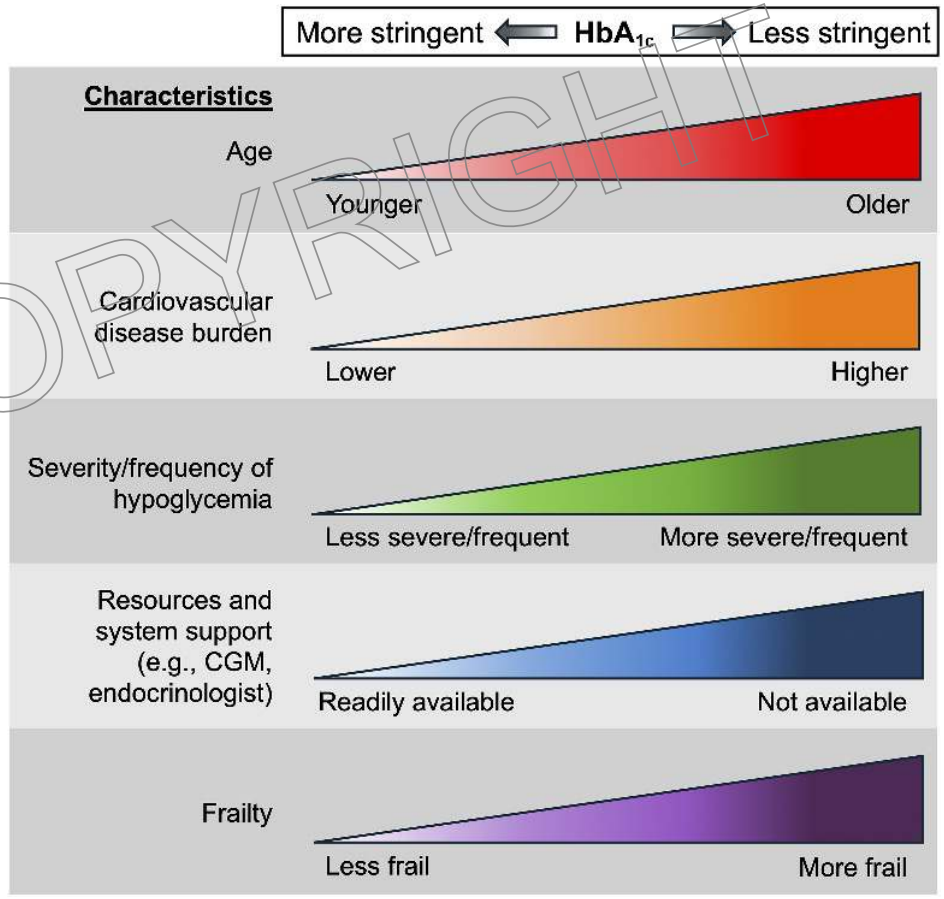
8.7 Hepatic Impairment

Glycemic Targets

Effects of ESRD

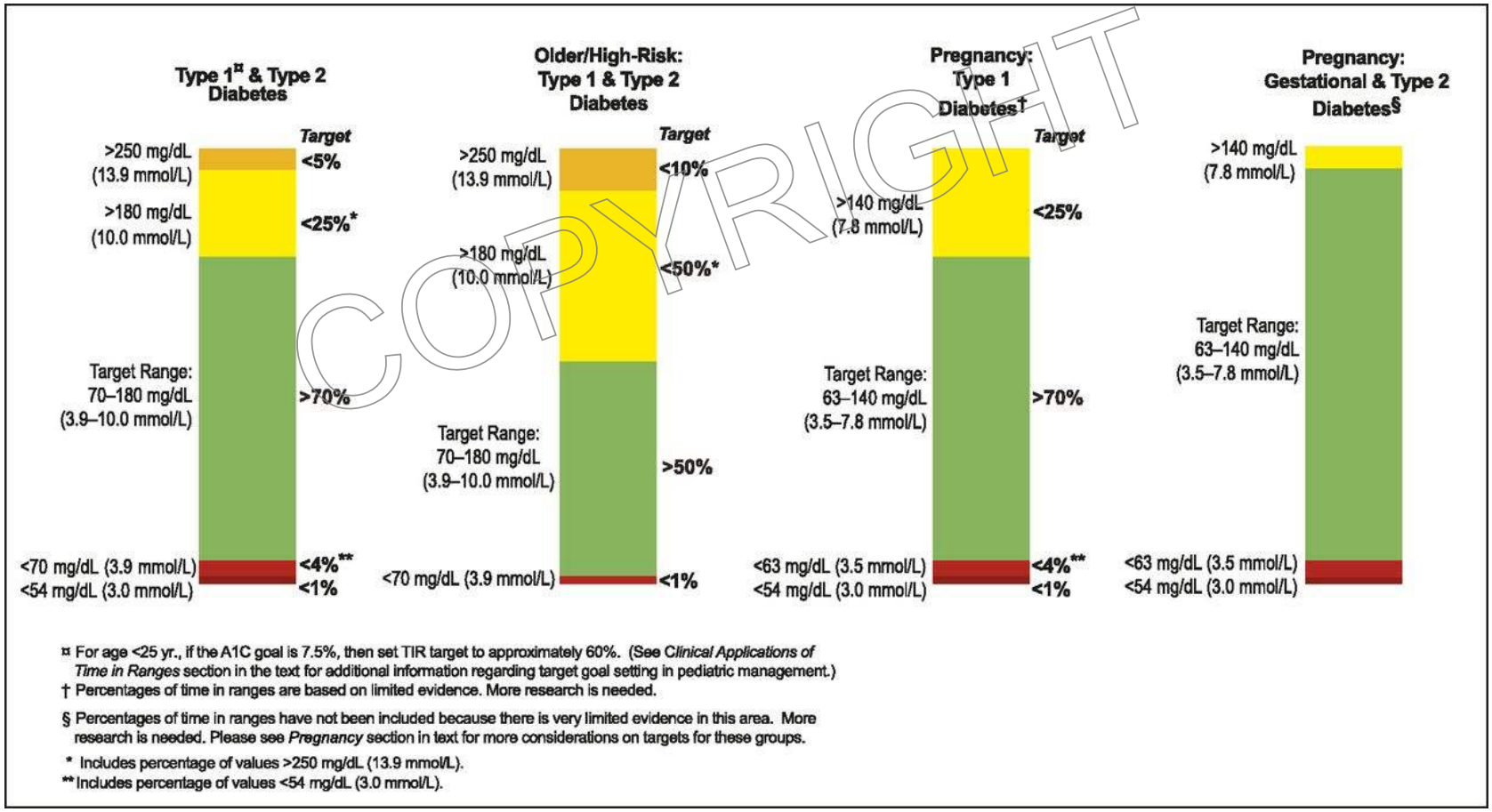
Individualized Glycemic Management in the Dialysis Population

Diabetes Care. 2024;48(2):164-176. doi:10.2337/dci24-0081



Characteristics on the left may justify more stringent targets, and characteristics on the right may justify less stringent HbA_{1c} targets

CGM-based Targets for Different Diabetes Populations



¤ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)

† Percentages of time in ranges are based on limited evidence. More research is needed.

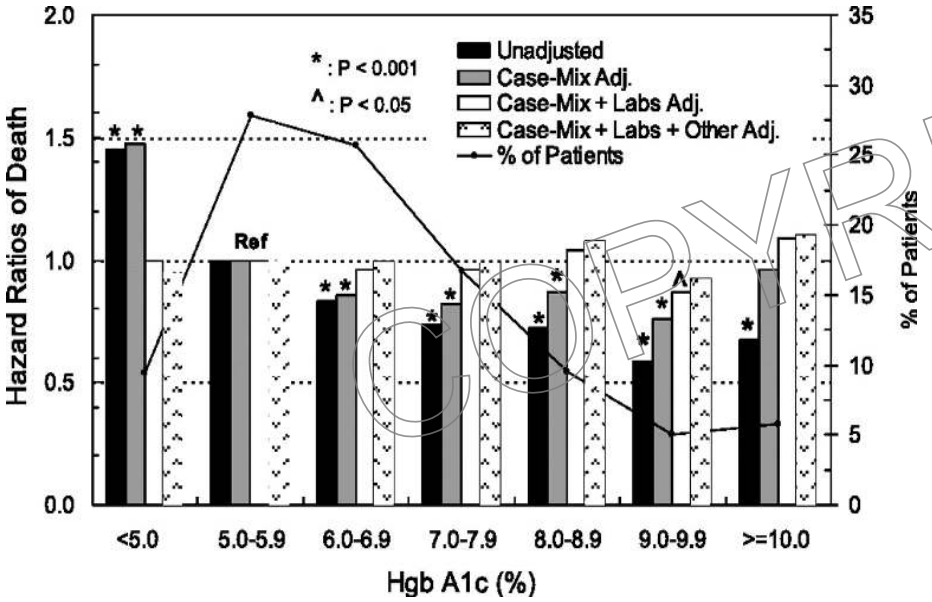
§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.

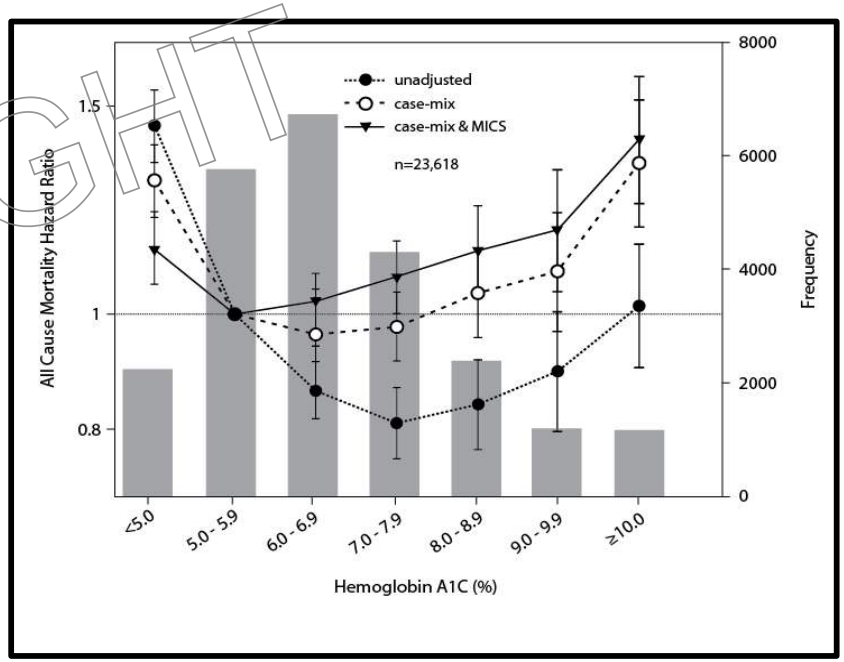
* Includes percentage of values >250 mg/dL (13.9 mmol/L).

** Includes percentage of values <54 mg/dL (3.0 mmol/L).

Tadej Battelino et al. Diab Care 2019;42:1593-1603

Glycemic Control and ESRD Outcomes: Comparison of Two Studies





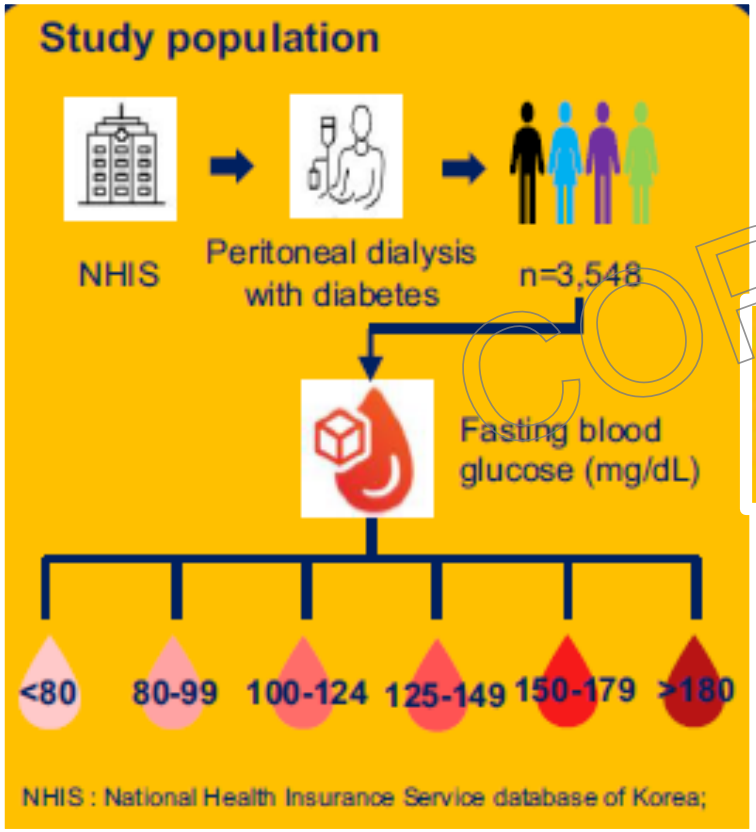
- Williams CJASN Care 2010; 5: 1595

Kalantar-Zadeh Diabetes 2007; 20: 1049

Recent Studies in ESRD Clinical Outcomes and Glycemic Control

Study	Type	Sample Size	Follow-up	Results
Williams et al., 2006	HD	N= 24,875 HD pts	1yr	No difference in survival across A1C increments.
Kalantar-Zadeh et al., 2007	HD	N= 26,187 HD pts	3yrs	Incremental increase in death risk across A1C increments in adjusted model. Paradoxical associations in naive models.
Williams et al., 2009	HD	N= 23,829 HD pts	1yr	High (>11%) and low (<5%) A1C levels were associated with higher hospitalization risk.
Drechsler et al., 2009	HD	N= 1,255 HD pts	4yrs	With each 1% increase in A1C, the risk of sudden death rose by 18%; similarly with each CV event mortality rose by 8%.
Williams et al., 2012	HD	N= 24,875 HD pts	3yrs	In adjusted time-dependent Cox models, extremes of glycemia were associated with poor survival.
Shurraw et al., 2010	HD	N= 1,484 HD pts	8yrs	No association between glycemic control and survival.
Duong et al., 2011	PD	N= 2,798 PD pts	6yrs	Higher (>8%) A1C was associated with increased all-cause and CV death. Similar association trewnds with BG.
Ricks et al., 2012	HD	N= 54,757 HD pts	6yrs	Higher (>8%) and lower (<6%) A1C was associated with increased all-cause and CV death. Similar association trends with BG.
Ramirez, SP, et al.,	HD	N= 9,201 HD pts	4yrs	High and low A1C levels predicted mortality.
Friedman et al. 2011	ESRD	N= 444 pts	2.3yrs	Glycated Albumin predicted outcome

Fasting blood glucose level and risk of all-cause and cause-specific mortality in peritoneal dialysis patients



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- There was a linear increase in the risk of all-cause mortality as FBG levels exceeded 125 mg/dL
- The risk of cardiovascular death showed a strong correlation with FBG levels

DM Outcomes Data: Survival

- Survival still much worse than nondiabetic patients
- Improved 5-year survival both HD and PD
- Higher risk of death with PD in earlier studies attenuated
- PD patients to be younger with less comorbidity
- HD/PD randomized comparisons have proven impossible
- Observational studies are next best design for survival comparisons
- Findings have not been consistent
- Increased risk in elderly diabetic pts.-USRDS
- CAPD and APD provide identical outcomes

Key Take-Home Points

- Glycemic control is difficult to achieve in ESKD/dialysis patients
- Glucose/insulin homeostasis is affected by chronic kidney failure and dialysis treatment
- Accurate assessment of glycemic control may be difficult
- ESKD affects management approach
- The benefits of tight glycemic control are variable