PATHOLOGIES RARES
DE L'INSULINO-SÉCRÉTION
ET DE L'INSULINO-SENSIBILITÉ
PRISIS

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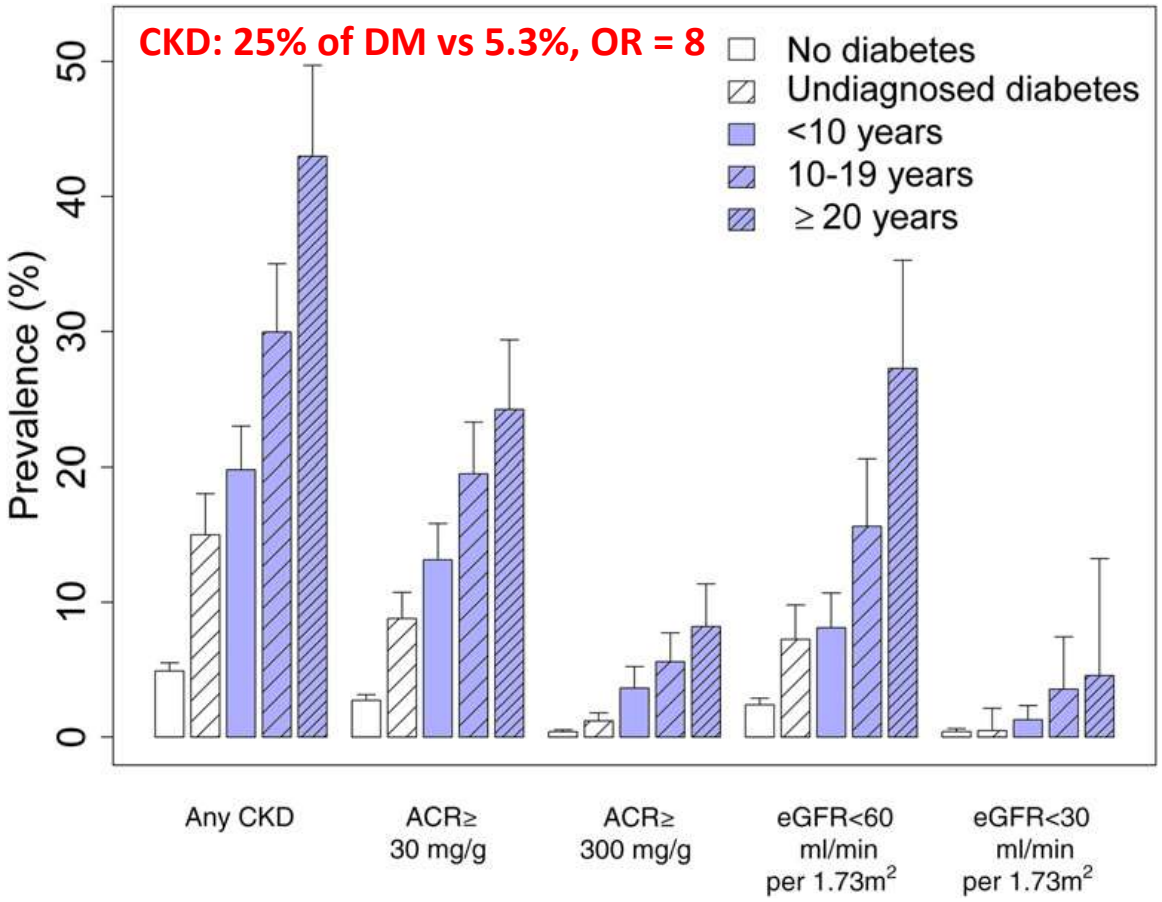
Diagnosis of diabetes and glucose monitoring in CKD

Danièle Dubois-Laforgue

Hôpital COCHIN

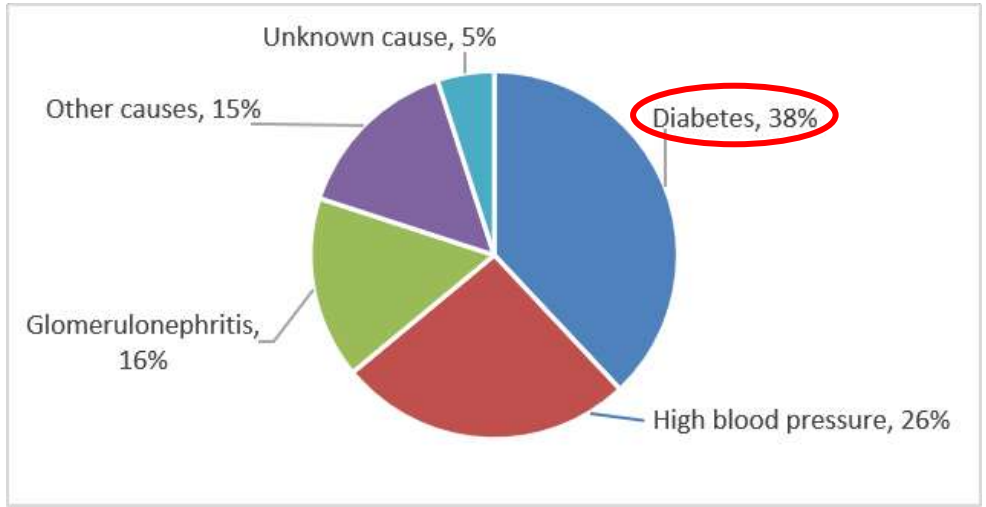
Prevalence of diabetes in CKD



DM-CKD: 30% of CKD

Zelnik CJASN 2017

NHANES cohort (US, aged > 20 yrs), 2009-2014
15675 S, 2279 DM (HbA1c > 6.5% or treatment)

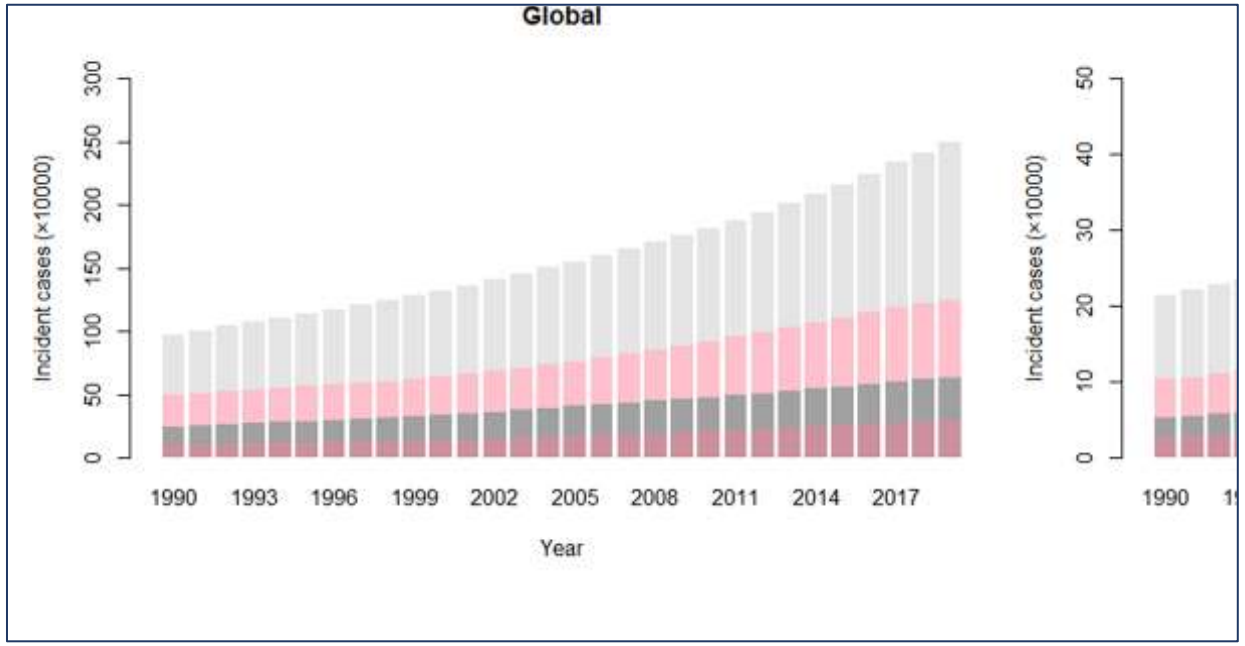


Centers for Disease Control and Prevention, Atlanta 2019

Incidence of T2D-CKD over 30 years

	Incident case (M)			Prevalent case (M)		
	1990	**2019**		**1990**	**2019**	
Global	0.975	2.50	+156%	66.5	129.6	+95%
Europe	0.25	0.47	+88%	1.24	1.71	+38%

Global burden of disease study 2019

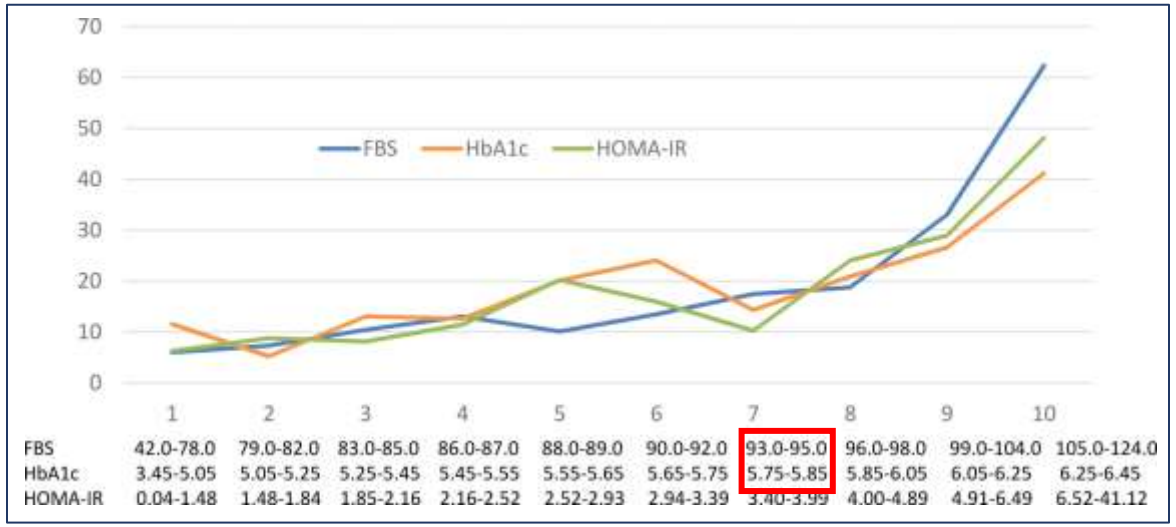


Deng, Front Endocrinol 2021

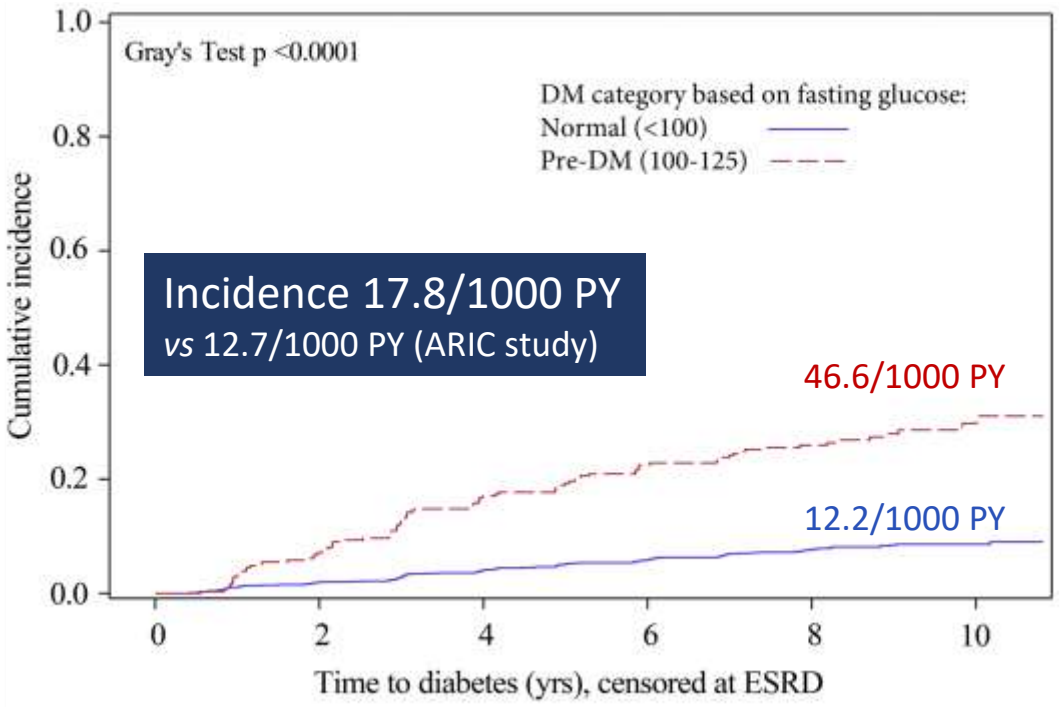
Incidence of diabetes in CKD

Chronic Renal Insufficiency Cohort (CRIC) Study (*Jepson, Am J Kid Dis 2019*)

3939 CKD, 2064 DM = 52%
1713 patients, 312 pre-DM (18%), follow-up 7.7 years



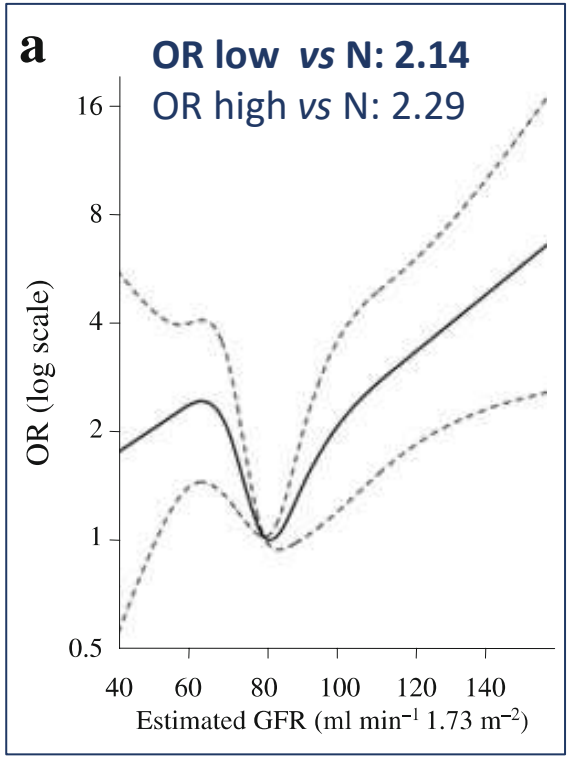
Incidence of db by decile of FBG and HbA1c at baseline



Taiwan: 16000 CKD , 66 000 non CKD, FU 2000-2010
DM incidence: 19.9/1000 PA in CKD *vs* 11.2 in non-CKD, OR 1.30 after adjustment (*Wang, Int Urol Nephrol 2019*)

Incidence of diabetes according to eGFR

IRAS study: 864 non DM subjects, 32.7% IGT at baseline
at 5.2 years : DM 141/864 = 16.3%



Characteristic	Low GFR **< 60 ml/min**	Normal/near-to-normal GFR	High GFR **>123 ml/min**	Low vs normal/ near-to-normal *p* value	High vs normal/ near-to-normal *p* value
n	66	724	74	–	–
Age (years)[a]	60.0±1.0	54.5±0.3	52.6±1.0	<0.001	0.071
BMI (kg/m^2)	28.4±0.7	28.4±0.2	27.8±0.6	0.982	0.321
Waist circumference (cm)	89.5±1.5	90.3±0.4	90.3±1.4	0.633	0.947
Antihypertensive medications (%)	33.5 (22.6–46.5)	19.2 (16.4–22.4)	20.2 (12.5–31.0)	0.011	0.799
GFR (ml min^{-1} 1.73 m^{-2})[a]	55.4±1.4	80.3±0.4	121.3±1.4	<0.001	<0.001

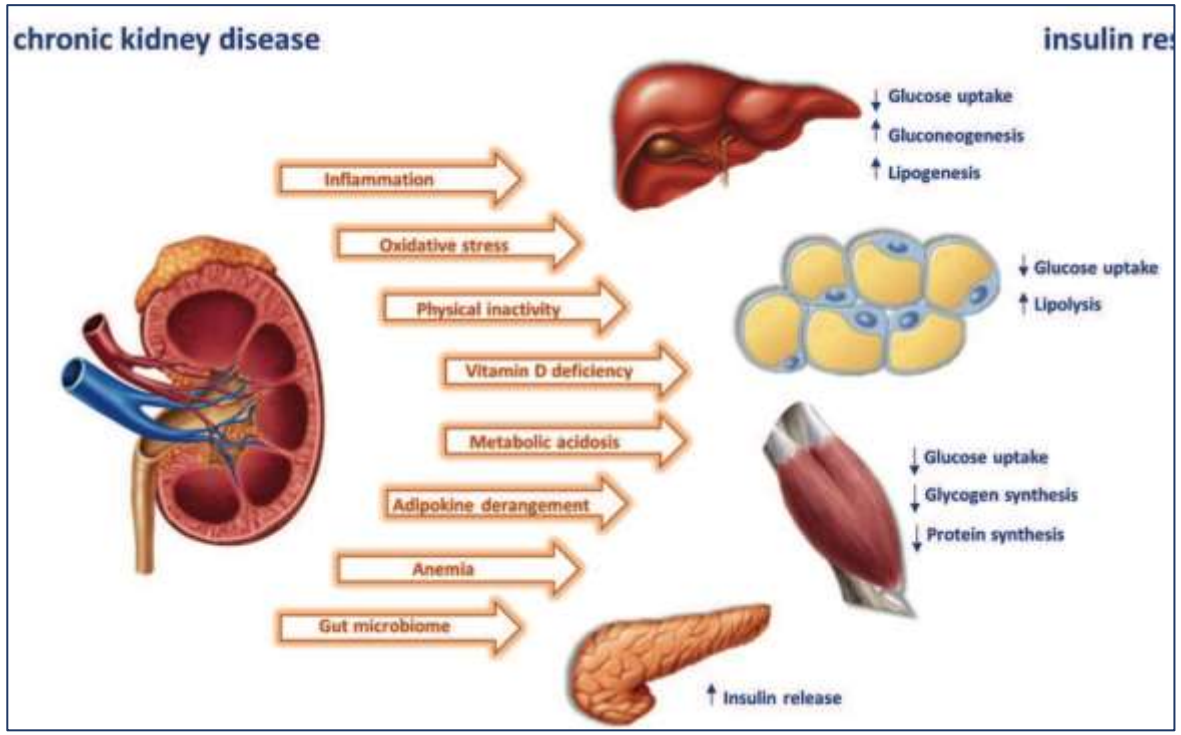
Table 3 Adjusted OR for predicting a 5.2 year incidence of diabetes associated with quintiles of GFR

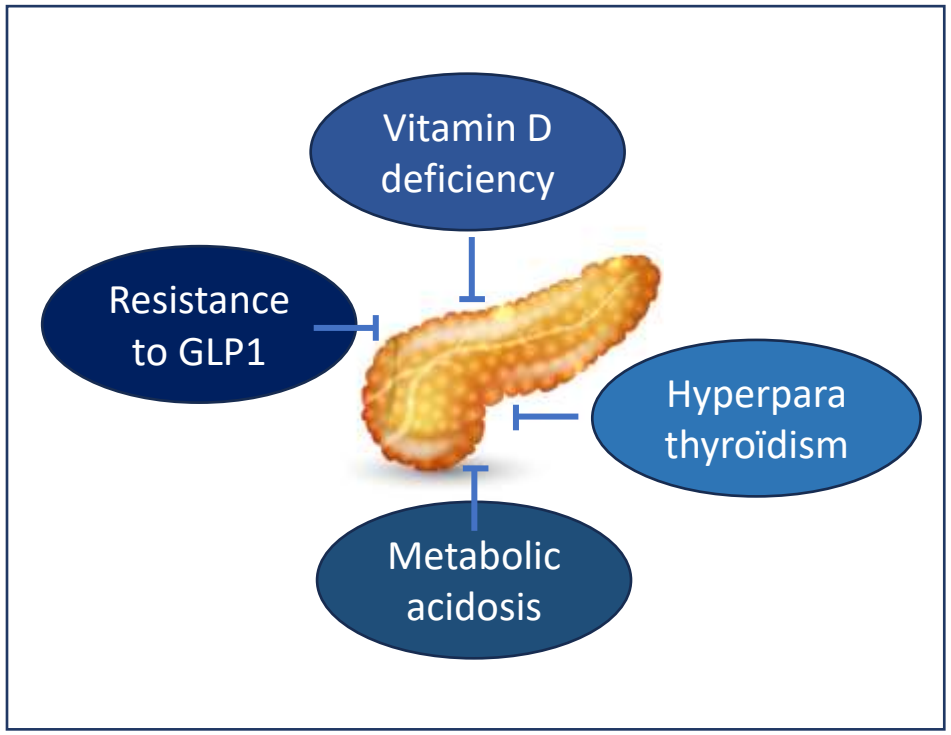
Model	1st quintile (*n*=172)[a]	2nd quintile (*n*=173)[b]	3rd quintile (*n*=173)[c]	4th quintile (*n*=173)[d] 84-93 ml/min	5th quintile (*n*=173)[e]
Model 1	1.95 (1.08–3.55)	1.48 (0.80–2.74)	1.11 (0.58–2.13)	Reference	2.01 (1.11–3.64)
Model 2	1.69 (0.90–3.15)	1.46 (0.78–2.74)	1.12 (0.58–2.15)	Reference	2.34 (1.27–4.32)
Model 3	2.35 (1.08–5.12)	1.74 (0.79–3.84)	1.19 (0.53–2.69)	Reference	2.59 (1.19–5.64)
Model 4	2.32 (1.06–5.05)	1.76 (0.80–3.88)	1.26 (0.56–2.84)	Reference	2.59 (1.18–5.65)

a 39.9–67.5; b 67.6–75.2; c 75.3–83.9; d 84.0–92.9; e 93.0–239.1

Lorenzo, Diabetologia 2009

CKD and glucose metabolism – 1

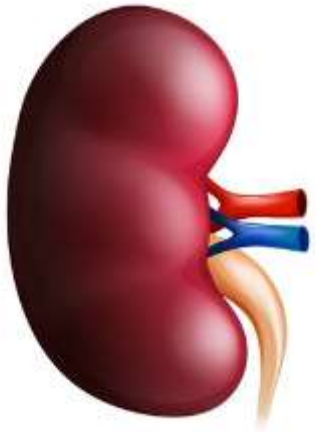




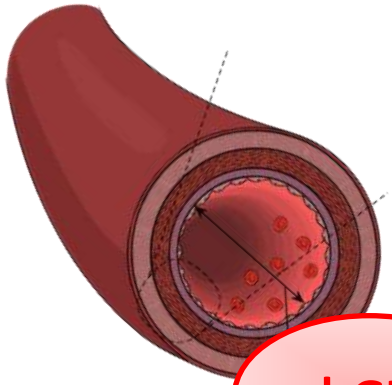
1. Increased insulin resistance

2. Decreased insulin secretion

CKD and glucose metabolism – 2

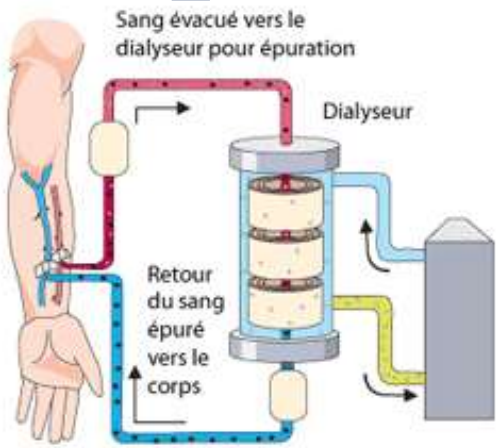


↓ neoglucogenesis
↓ insuline clearance



↓GLC

anorexia
↓ glycogen

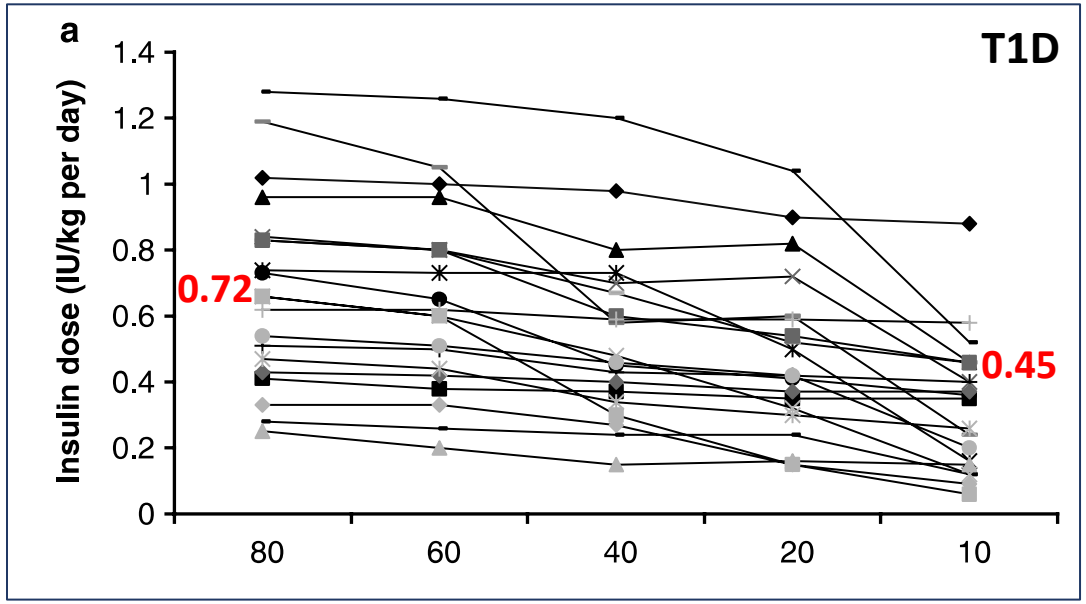


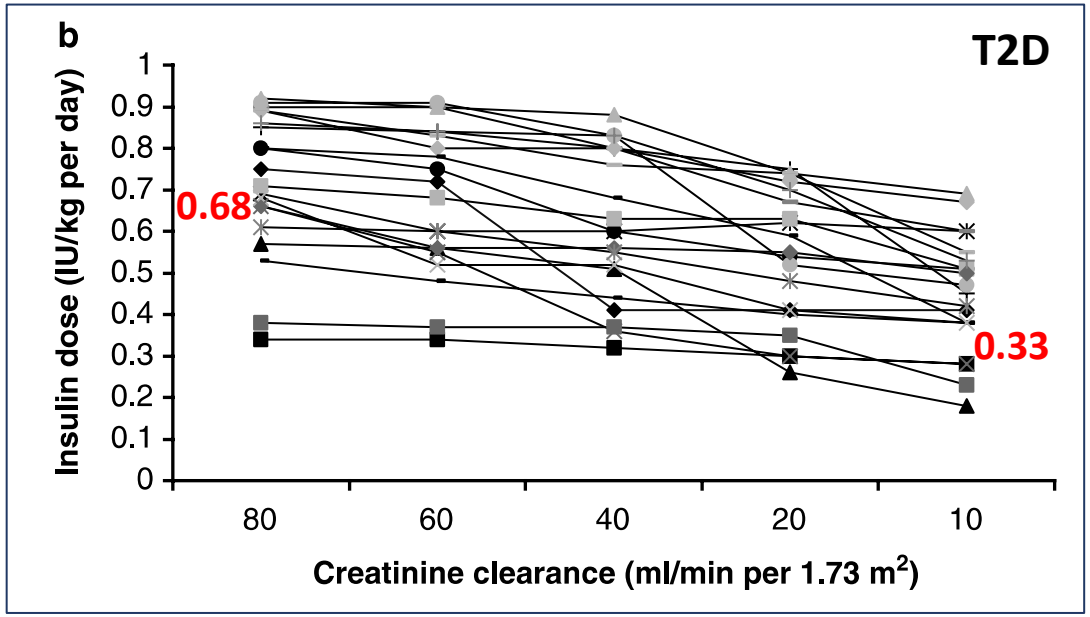
dialysate
↓ conter regulatory H

Review in Rahhal, JCEM 2019

Insulin requirements and DKD

20 T1D (HbA1c 8.1%), 20 T2D (HbA1c 7.6%) with DKD: GFR_{in} > 80 ml/min, PU > 0.5 g/24h
Follow-up until GFR < 10 ml/min



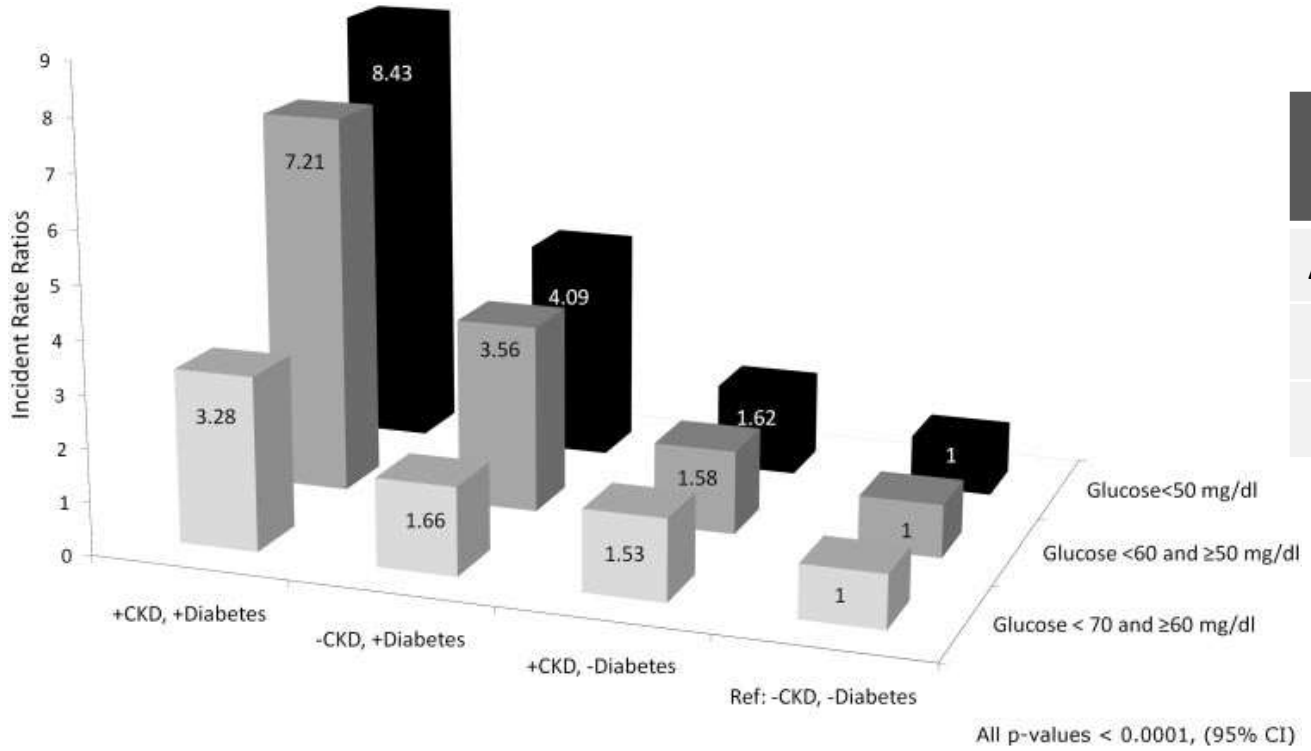


« Burn-out diabetes » : 20-30% of ESRD

Biesenbach, Diab Med 2003

CKD and risk of hypoglycemia

243222 subjects, Veteran Health Administration, follow-up 1 year
2 040 206 blood glucose measurements, hypo: < 0.70 g/l



	70168 CKD (81% stage 3)	173053 N (GFR > 60)
Age	73	61
DM	50.5%	32.7%
Hypo (in DM)	10.72 /100 PM	5.33 /100 PM

Moen, CJASN 2009

T1D with CKD, incidence of severe hypoglycemia: 1.28 PY *vs* 0.25 if GFR N *(Mulhauser D Care 1991)*

HD and blood glucose levels /insulin needs

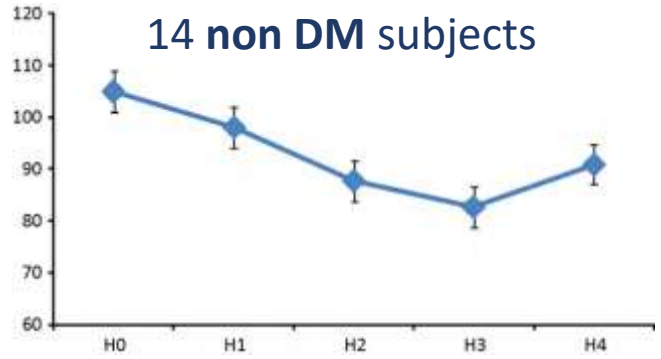


Fig. 1 – Hourly capillary blood glucose variations during haemodialysis session in mg/dl.

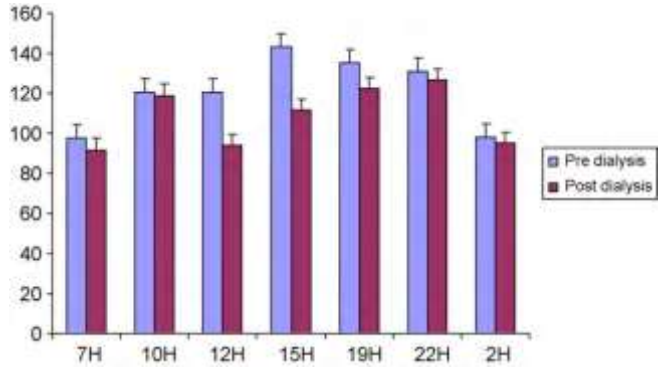


Fig. 2 – circulating glucose profile after versus before haemodialysis in mg/dl.

Sobngwi, Diab Clin res 2010

10 T2D patients on HD for 2 years
euglycemic clamp before/after HD

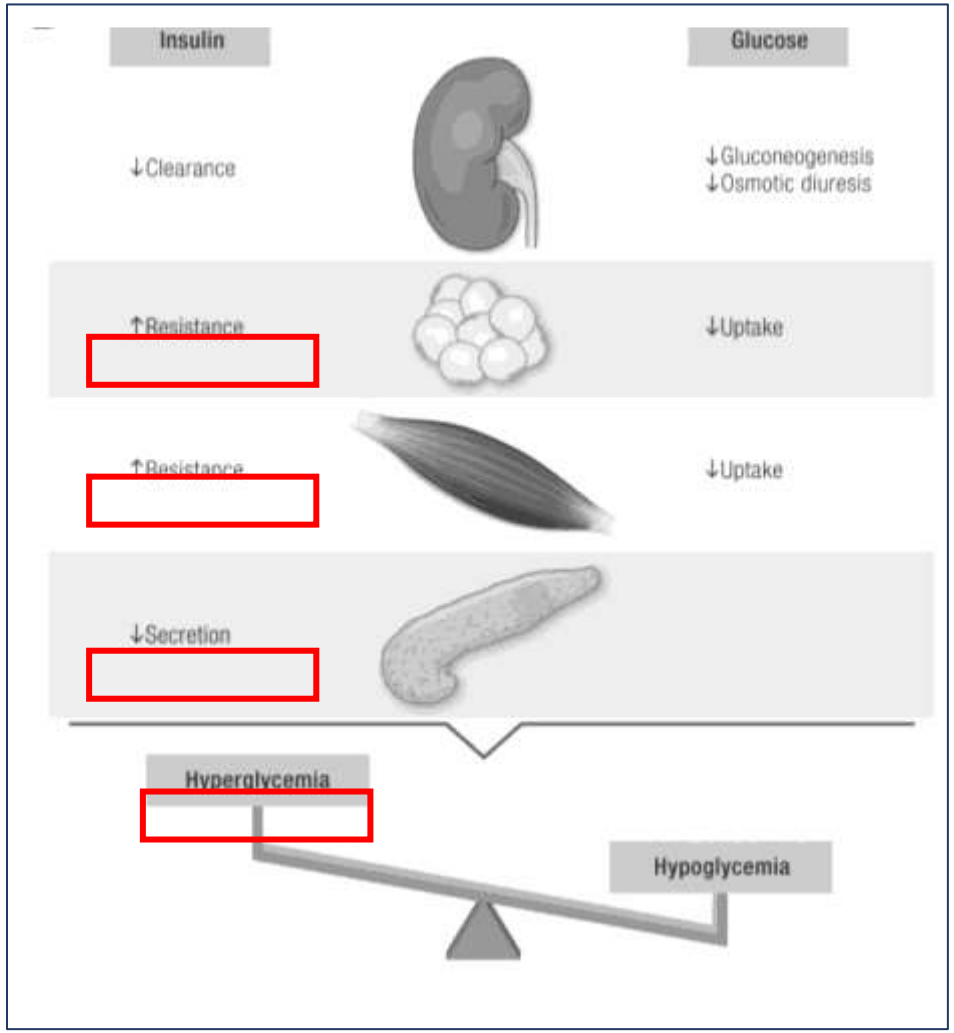
Table 1—*Circadian variation of insulin requirements in the participants*

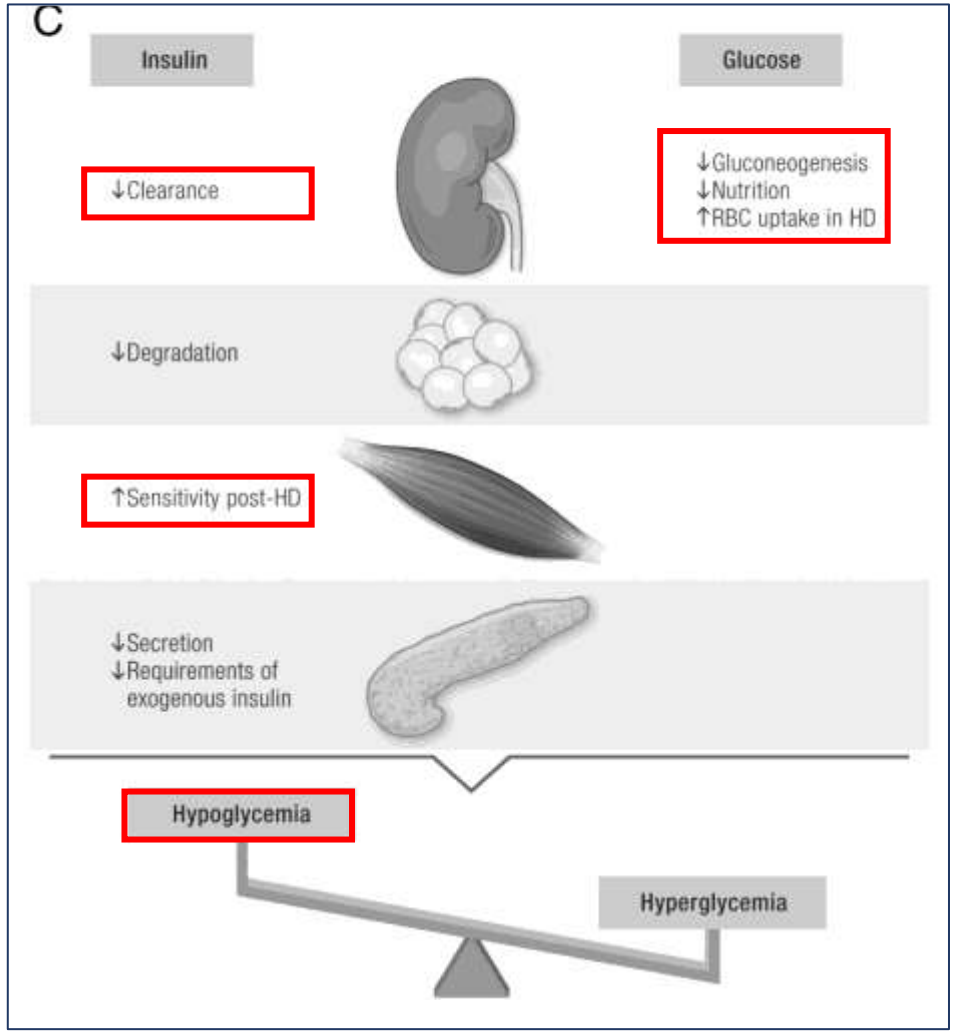
	0600–1200 h	1200–1800 h	1800–2400 h	2400–0600 h
Before dialysis	6.61 ± 2.45	6.82 ± 2.47	6.98 ± 2.71	3.18 ± 1.57
After dialysis	5.87 ± 1.29	5.19 ± 1.98	6.41 ± 1.43	2.49 ± 1.25
P (*t* test)*	0.30	0.048	0.43	0.22

reduction of insulin requirement by 25% after HD

Sobngwi, Diab Care 2010

Changes in glucose metabolism with CKD progression





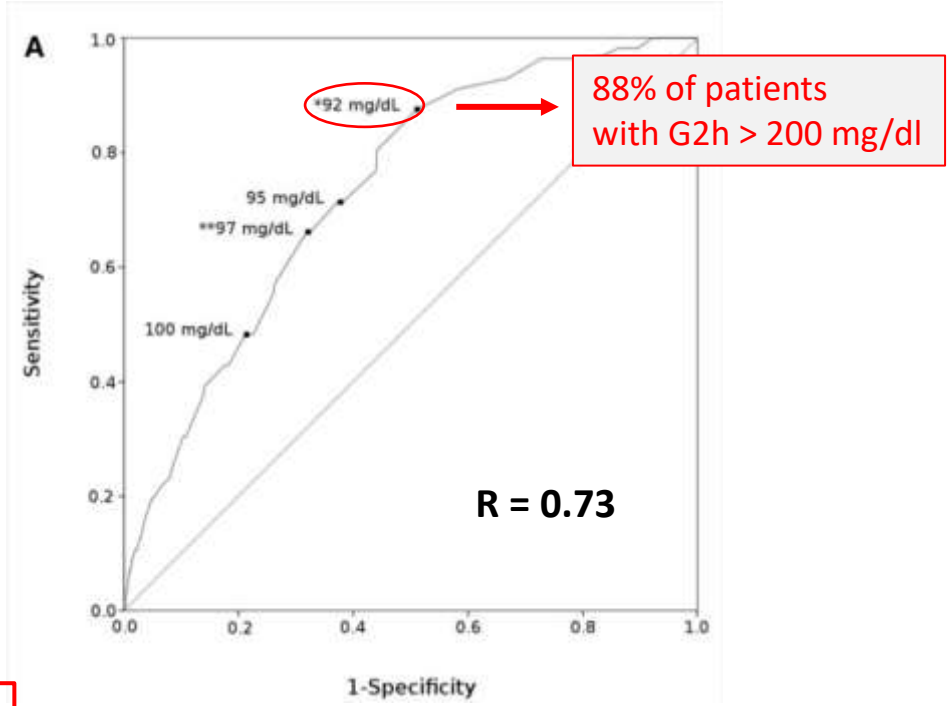
Galindo Endocrin Rev 2020

Diabetes diagnosis in CKD - FPG

889 patients pre-KTR, 33% on HD, no known diabetes: **OGTT** -> **45% with dysglycemia**: DM 8%, IFG 11%, ITG 26%

FPG	2h-PG (*n* [%])		
	Normal (<140)	IGT (140 to 199)	Diabetes (≥200)
WHO			
normal (<110)	563 (70)	203 (25)	44 (5)
IFG (110 to 125)	24 (38)	27 (43)	12 (19)
diabetes (≥126)	3 (19)	2 (12)	11 (69)

Only 22% of diabetic patients had FPG > 126 mg/dl



FPG <-> G2h > 200 mg/dl

Bergrem, CSAJN 2010

Diabetes diagnosis in CKD - FPG

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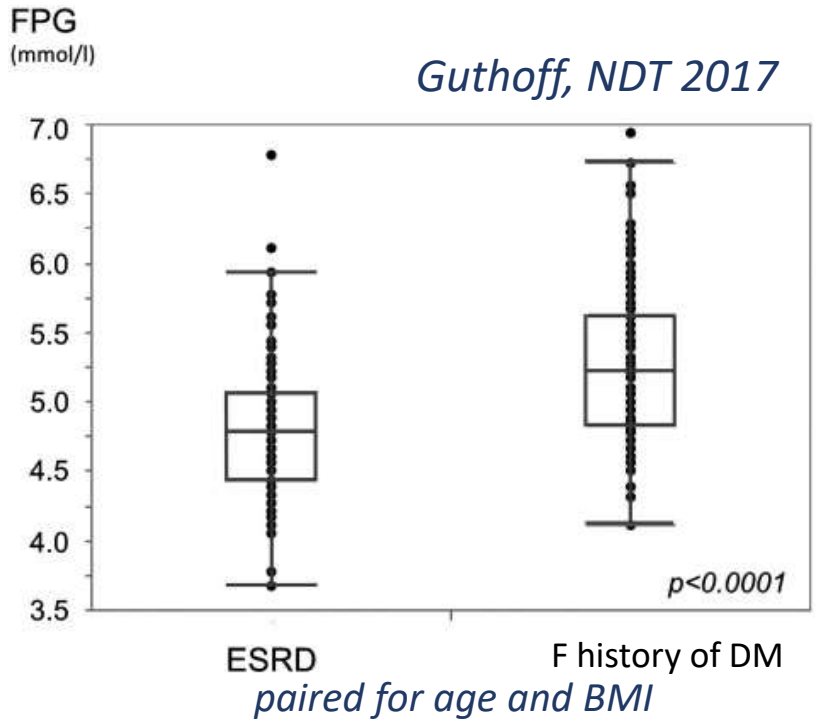
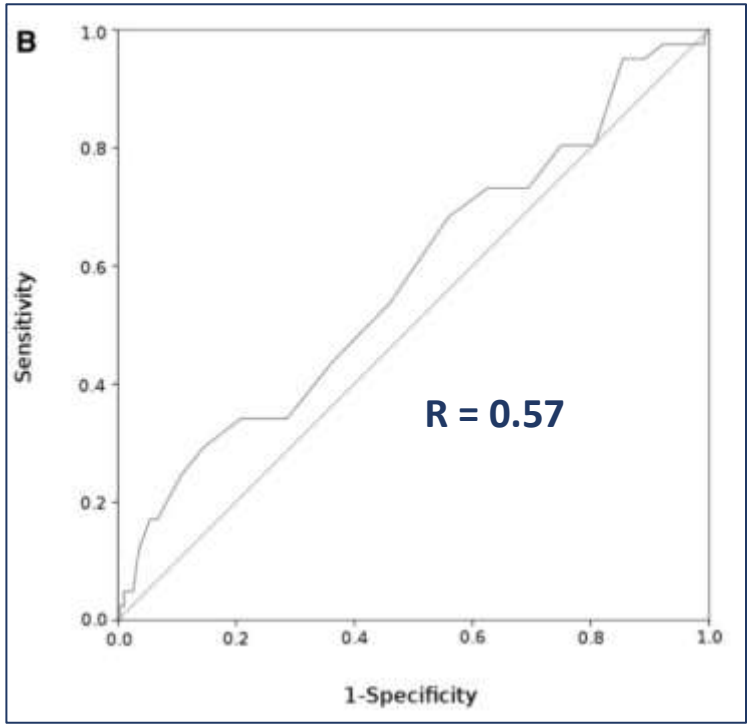


Guthoff, NDT 2017

paired for age and BMI

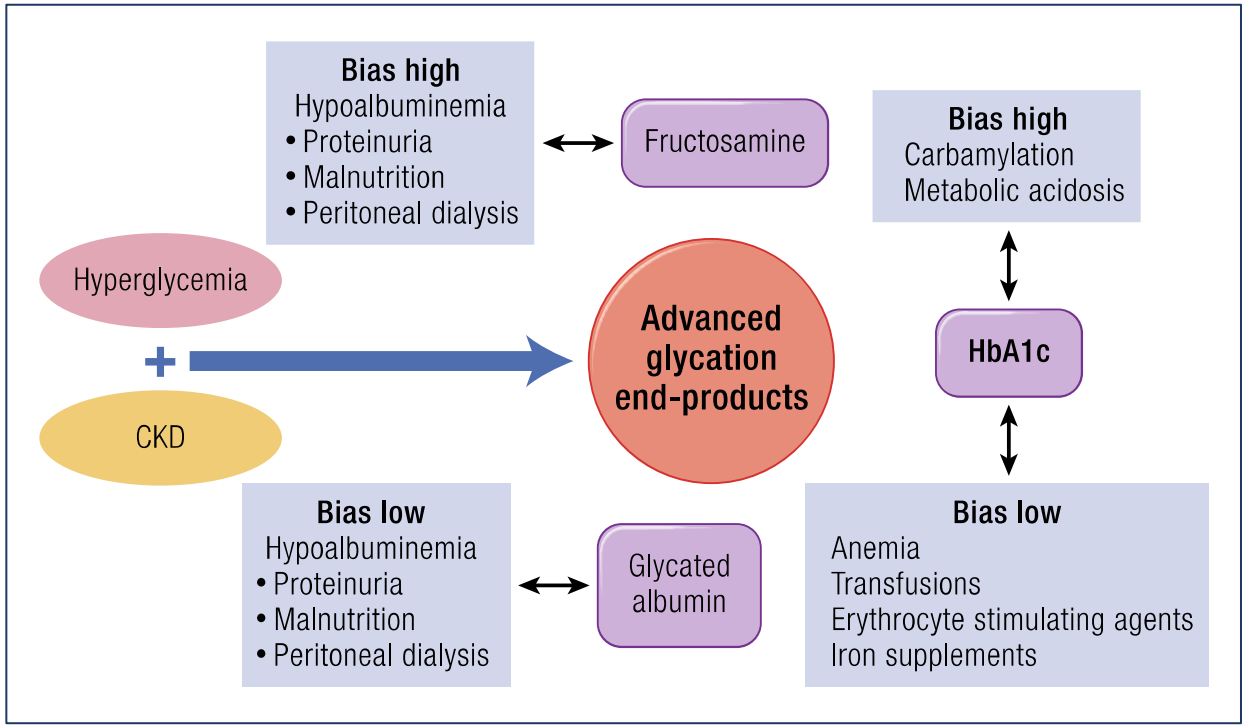
OGTT must be preferred to FPG to assess diabetes diagnosis in CKD

Diabetes diagnosis in CKD - HbA1c



HbA1c <-> G2h > 200 mg/dl

Bergem CJASN 2010



HbA1c is a poor metabolic indicator in CKD

Galindo Endocrin Rev 2020

New developments for glucose monitoring: CGM

Glucometer

All patients
On AOD: 200 strips/yr

CGM: continuous glucose monitoring
First prescription by a diabetologist

≥ 1inj/d

≥ 3 inj/d

T1D, A1c > 8%
or severe hypoglycemia

Freestyle Libre 2

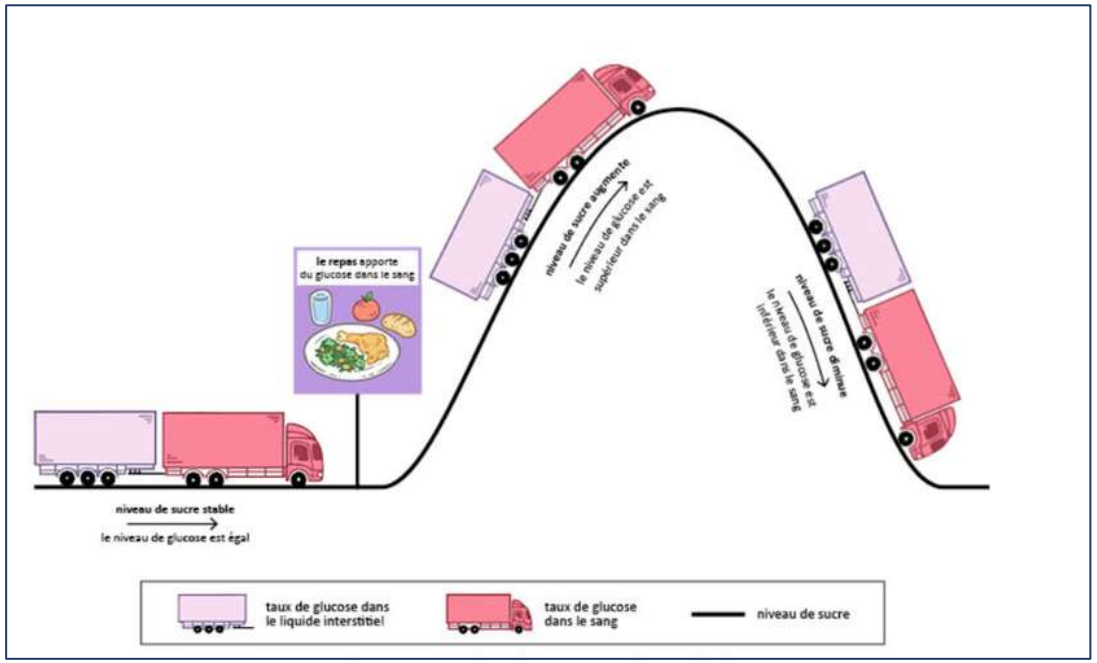
Actual level

Glucose history

Glycemic goals

Tendency

Alerts
- hypoglycemia
- hyperglycemia



Snapshot

Rapport AGP (Ambulatory Glucose Profile)

20 octobre 2022 - 16 novembre 2022 (28 Jours)

LibreView

STATISTIQUES ET CIBLES DE GLYCÉMIE

20 octobre 2022 - 16 novembre 2022	**28 Jours**
% de temps où le capteur est actif	**97%**

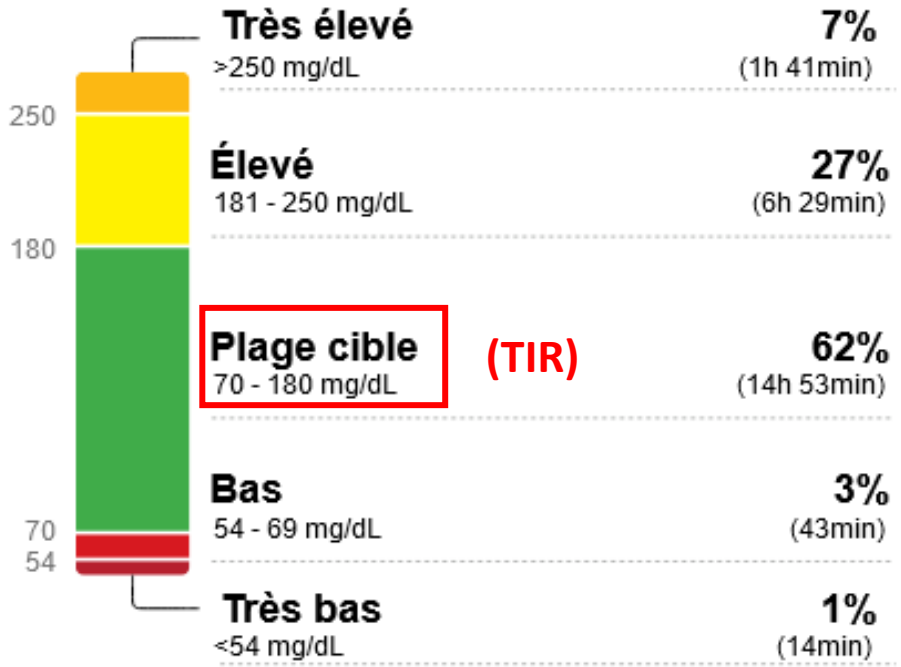
Plages et cibles pour	Diabète de type 1 ou de type 2
Plages de glycémie	**Cibles** % de lectures (heure/jour)
Plage cible 70-180 mg/dL	Supérieur à 70% (16h 48min)
En dessous de 70 mg/dL	Inférieur à 4% (58min)
En dessous de 54 mg/dL	Inférieur à 1% (14min)
Au-dessus de 180 mg/dL	Inférieur à 25% (6h)
Au-dessus de 250 mg/dL	Inférieur à 5% (1h 12min)

Chaque augmentation de 5 % du temps dans la plage (70-180 mg/dL) est bénéfique sur le plan clinique.

Taux de glucose moyen	**162** mg/dL
Indicateur de gestion de la glycémie (GMI)	**7,2% ou 55 mmol/mol**
Variabilité de la glycémie	**35,9%**

Défini en pourcentage du coefficient de variation (%CV)

TEMPS DANS LES PLAGES



GMI: Glucose Management Indicator

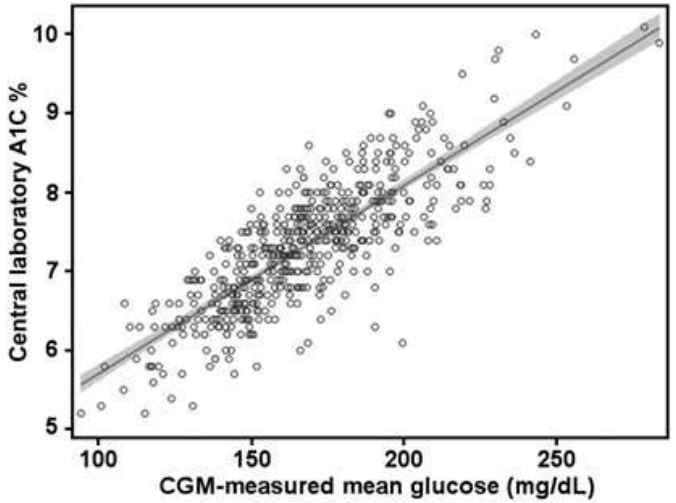


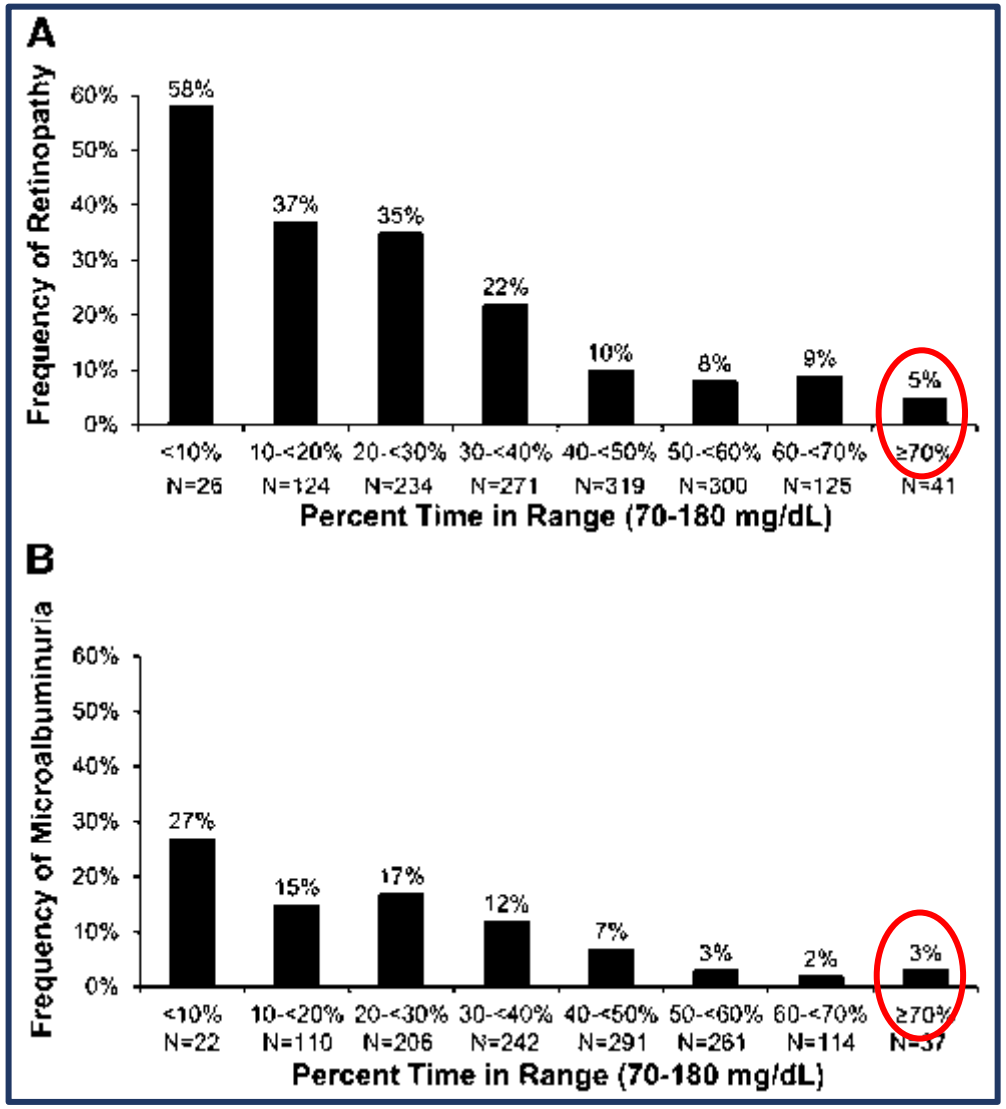
Figure 1—Plot of CGM-measured mean glucose concentration vs. central laboratory–measured A1C used to compute the formula to estimate GMI, combining data from four randomized trials using the Dexcom G4 sensor with 505 software (N = 528) described in the Supplementary Data. The shaded area represents the 95% CI of the regression line. The regression equation to compute GMI (%) = 3.31 + 0.02392 × [mean glucose in mg/dL] or

Table 1—GMI calculated for various CGM-derived mean glucose concentrations

CGM-derived mean glucose (mg/dL)	GMI (%)*
100	5.7
125	6.3
150	6.9
175	7.5
200	8.1
225	8.7
250	9.3
275	9.9
300	10.5
350	11.7

Bergenstal D Care 2018

TIR (Time in Range) - microangiopathy

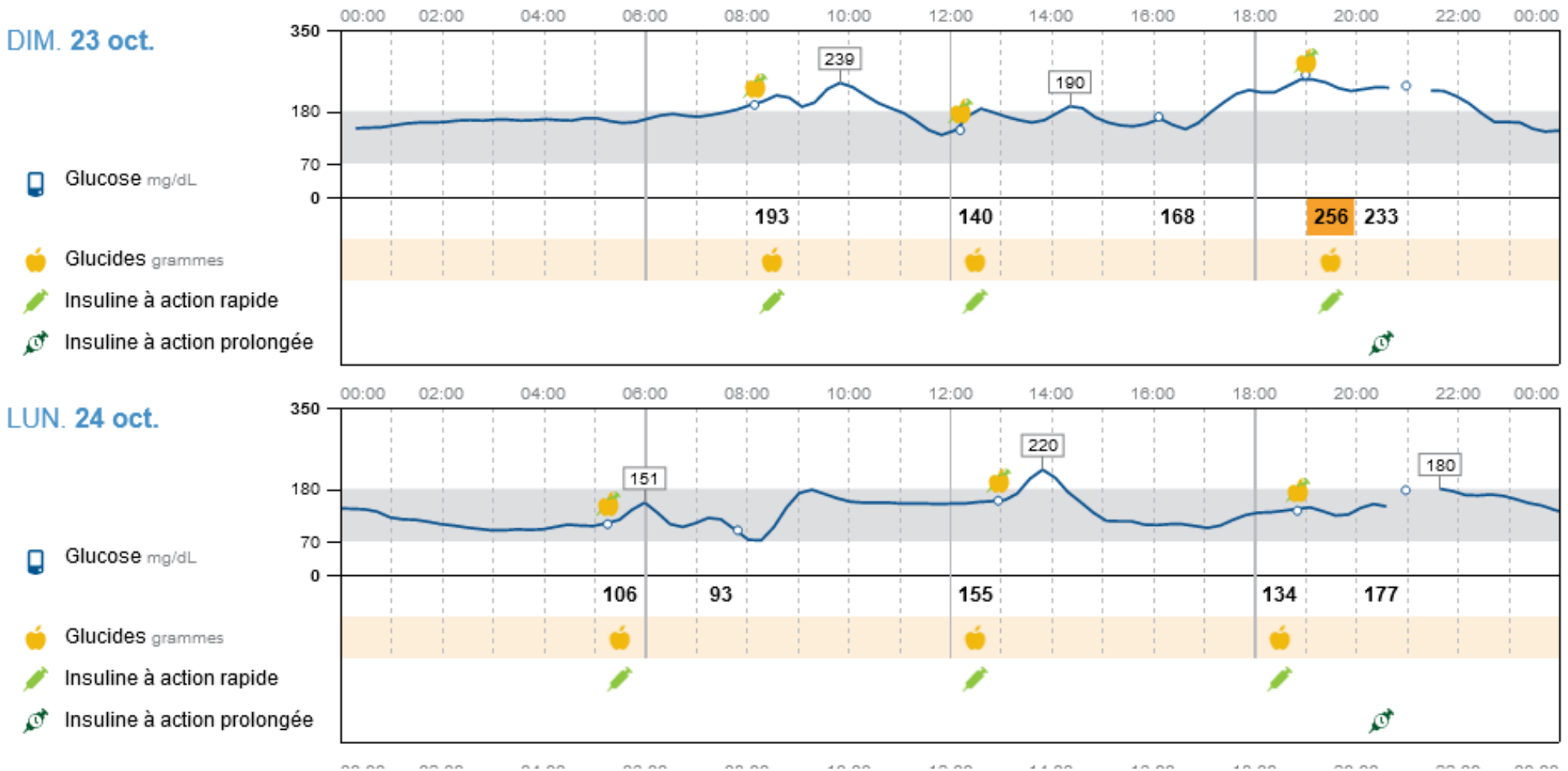


DCCT Study 1983-1993, 1440 T1D
7-points profile /3 months (*vs* 288/d with CGM)

Mean TIR of seven-point profiles for the 1,440 participants was 41 ± 16%. The hazard rate of development of retinopathy progression was increased by 64% (95% CI 51–78), and development of the microalbuminuria outcome was increased by 40% (95% CI 25–56), for each 10 percentage points lower TIR ($P < 0.001$ for each).

Beck, D Care 2019

Daily profile



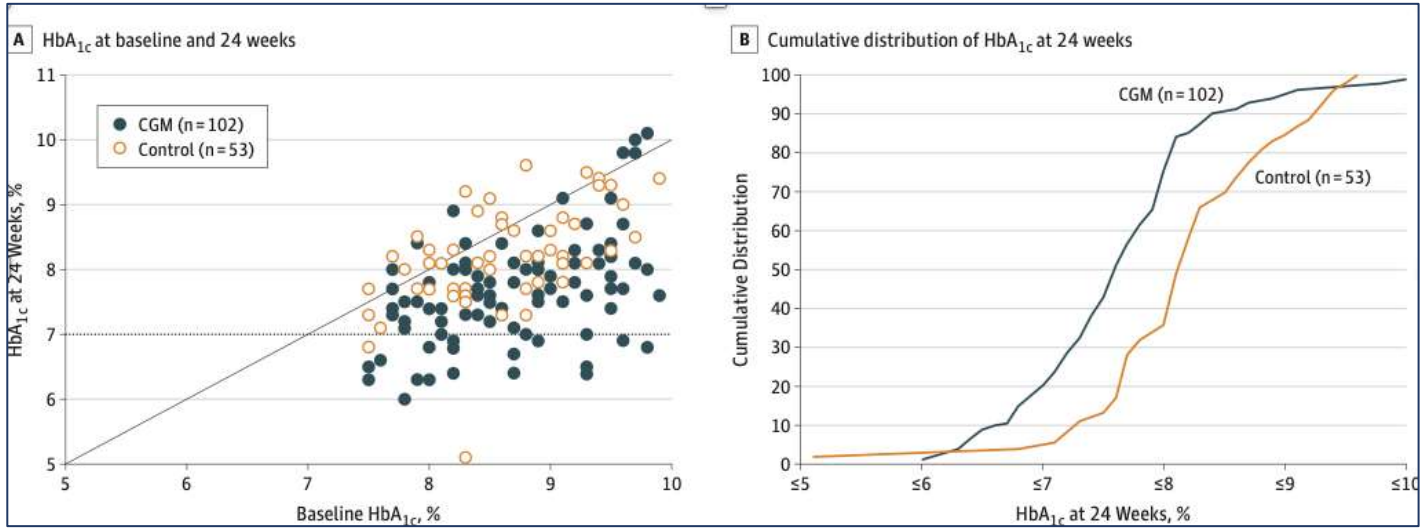
Therapeutic education
Telemonitoring via platforms: Libreview, My Diabby…

Benefice of CGM on HbA1c – T1D

Table 1. Baseline Participant Characteristics

	Group, No. (%)	
	CGM (n = 105)	Control (n = 53)
Age, y		
25-<45	53 (50)	16 (30)
45-<60	32 (30)	23 (43)
≥60	20 (19)	14 (26)
Mean (SD) [range]	46 (14) [26-72]	51 (11) [26-73]
Diabetes duration, median (IQR), y	19 (9-29)	19 (11-35)
Female sex	47 (45)	23 (43)
Highest education[a]		
<Bachelor's degree	47 (47)	22 (43)
Bachelor's degree	43 (43)	19 (37)
Graduate degree	10 (10)	10 (20)
BMI, mean (SD)	28 (6)	27 (5)
Weight, mean (SD), kg	84 (20)	81 (18)
HbA_{1c}, %		
7.5-<8.5	47 (45)	24 (45)
8.5-≤9.9	58 (55)	29 (55)
Mean (SD) [range]	8.6 (0.7) [7.5-9.9]	8.6 (0.6) [7.5-9.9]

at week 24: HbA1c -1% *vs* -0.4%



Beck, JAMA 2017

Meta-analyses in T1D and T2D on multi injections: HbA1c: - 0.55%

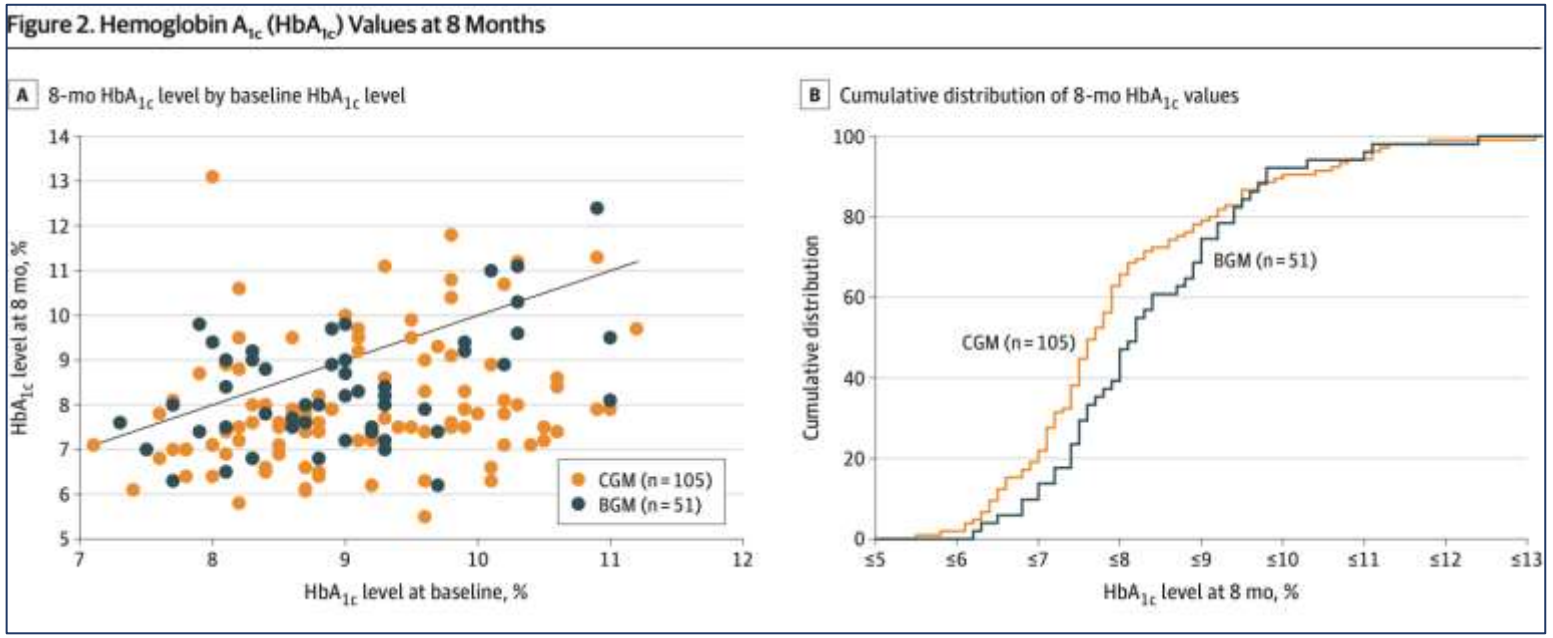
Evans, Diab Ther 2020

Benefice of CGM on HbA1c – T2D on basal insulin

Table 1. Baseline Demographics, Medical History, and Insulin Therapies

	No. (%)	
	Continuous glucose monitoring (n = 116)	Blood glucose meter monitoring (n = 59)
Age, mean (SD), y	56 (9)	59 (9)
≥60	43 (37)	28 (47)
Sex		
Female	61 (53)	27 (46)
Male	55 (47)	32 (54)
Diabetes duration, mean (SD), y	14 (9)	15 (10)
Self-reported blood glucose meter monitoring, checks per day		
≤1	61 (53)	23 (39)
2-3	54 (47)	36 (61)
≥4	1 (<1)	0
Median (IQR)	1 (1, 2)	2 (1, 2)
HbA_{1c} level, %		
At screening, mean (SD)[d]	9.2 (1.0)	9.0 (0.9)
At randomization[d]		
Mean (SD) [No.]	9.1 (1.0) [115]	9.0 (0.9) [58]
<8.5%	31 (27)	17 (29)
8.5%-<10.0%	58 (50)	32 (55)
≥10.0%	26 (23)	9 (16)

At month 8: HbA1c -1.6 vs -0.8%



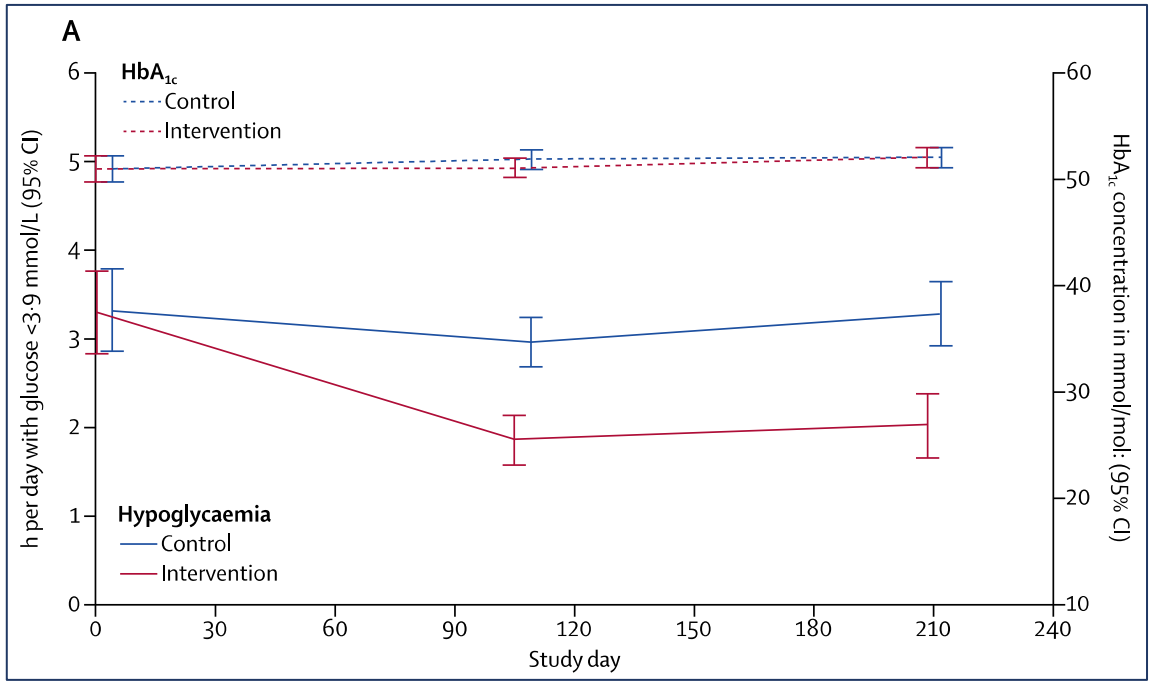
Martens, JAMA 2021

Benefice of CGM on hypoglycemia rate – T1D

	Intervention (n=119)	Control (n=120)
Men	77 (65%)*	59 (49%)*
Women	42 (35%)	61 (51%)
Race		
White	119 (100%)	119 (99%)
Black	0	1 (1%)
Age (years)	42 (33–51)	45 (33–57)
BMI (kg/m²)	25·2 (3·6)	24·8 (3·5)
Duration of diabetes (years)	20 (13–27)	20 (12–32)
Screening HbA_{1c} (%; mmol/mol)	6·7 (0·5); 50·1 (5·7)	6·7(0·6); 50·2 (6·5)
Self-reported blood glucose frequency per day	5·4 (2·0)	5·6 (2·3)

FSL vs SMBG during 6 months

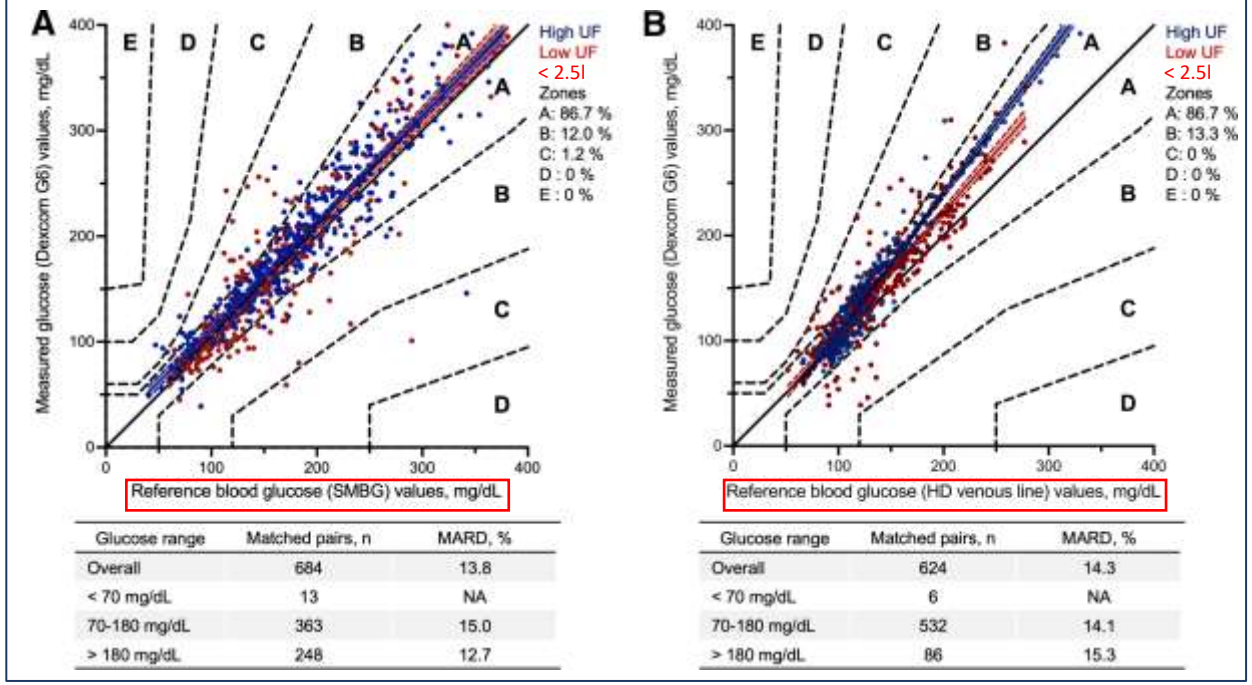
Time spent in hypoglycemia (h/d)					
	Int J0	**C J0**	**Int M6**	**C M6**	**diff**
< 0.70 g/l	3.38	3.44	2.03	3.27	**- 38%**
< 0.54 g/l	1.59	1.77	0.80	1.65	**- 50%**
< 0.40 g/l	0.59	0.75	0.26	0.73	**- 65%**



Bolinder, Lancet 2016

Reliability of CGM in CKD

HemoDialysis (Parks error grid)



Glucose range	Matched pairs, n	MARD, %
Overall	684	13.8
< 70 mg/dL	13	NA
70-180 mg/dL	363	15.0
> 180 mg/dL	248	12.7

Glucose range	Matched pairs, n	MARD, %
Overall	624	14.3
< 70 mg/dL	6	NA
70-180 mg/dL	532	14.1
> 180 mg/dL	86	15.3

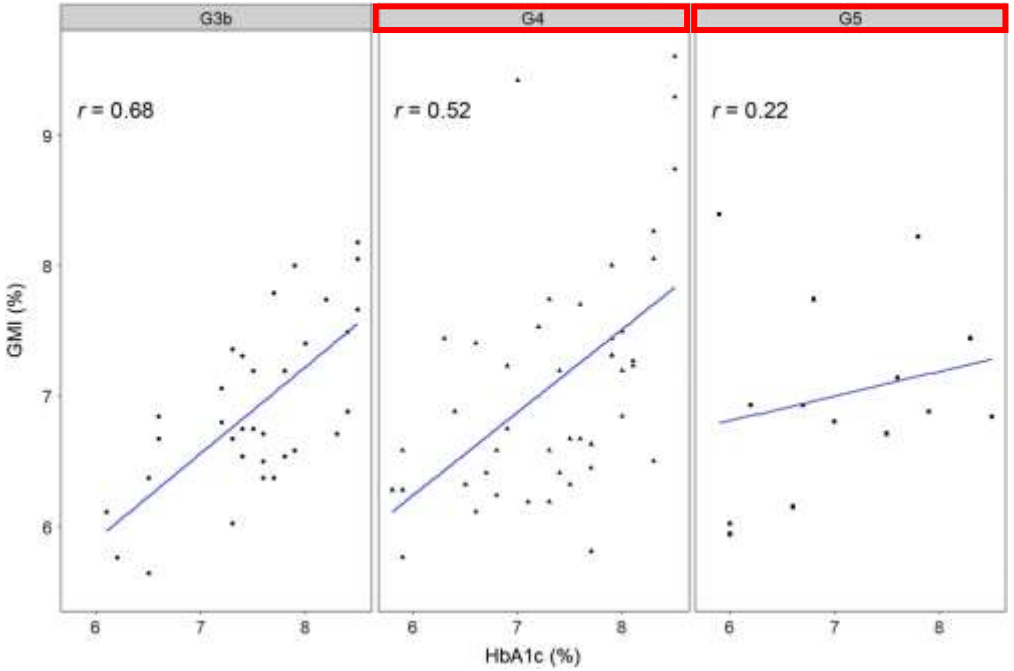
Villard, D Care 2022

Peritoneal Dialysis

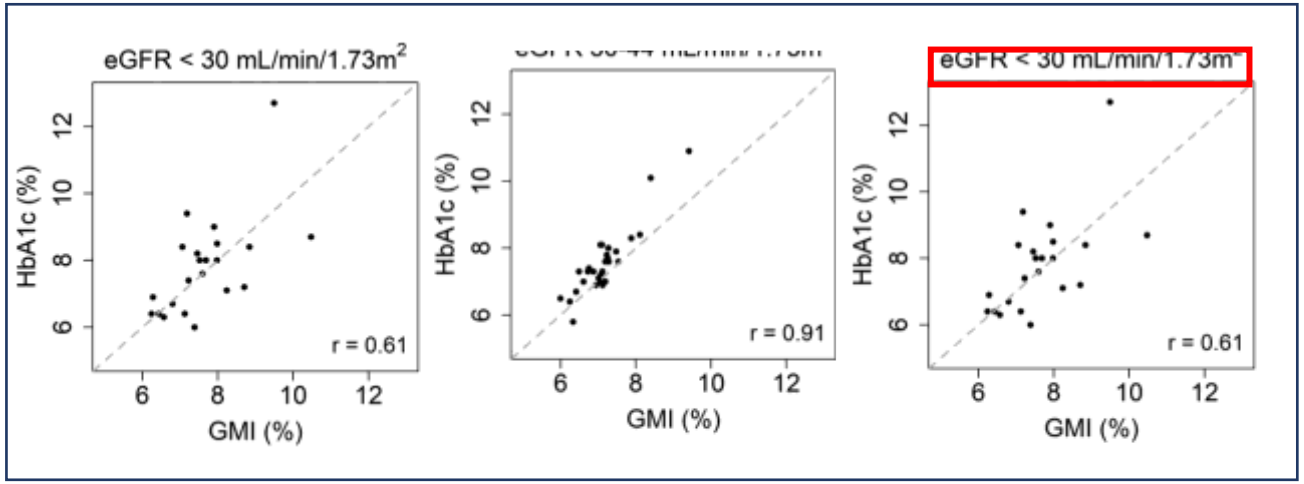
MARD (mean absolute relative difference) was 10.4%
There were no correlations between BMI, extracellular water, relative hydration index, and lean or fat mass with MARD. No correlations were observed between MARD and Hb ($r = 0.016$, $P > 0.05$). In summary, this real-time CGM demonstrated good accuracy in CAPD with minimal influence from body composition and anemia.

Ling, Diab Tech Ther 2024

CGM and evaluation of HbA1c in CKD



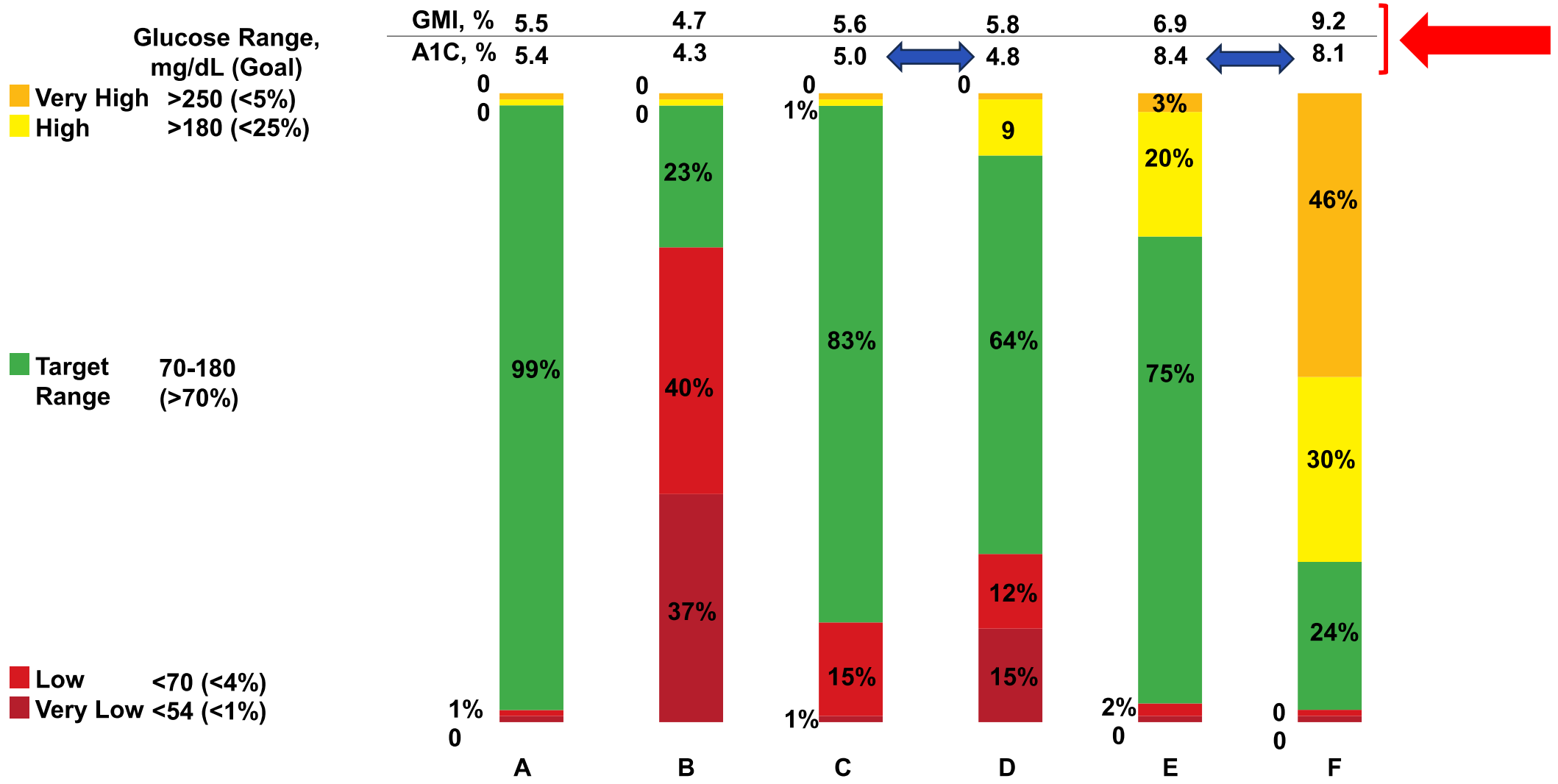
Ling, Ki reports 2022



Zelnik, D Care 2020

estimation of global glycemic control (HbA1c) in advanced CKD

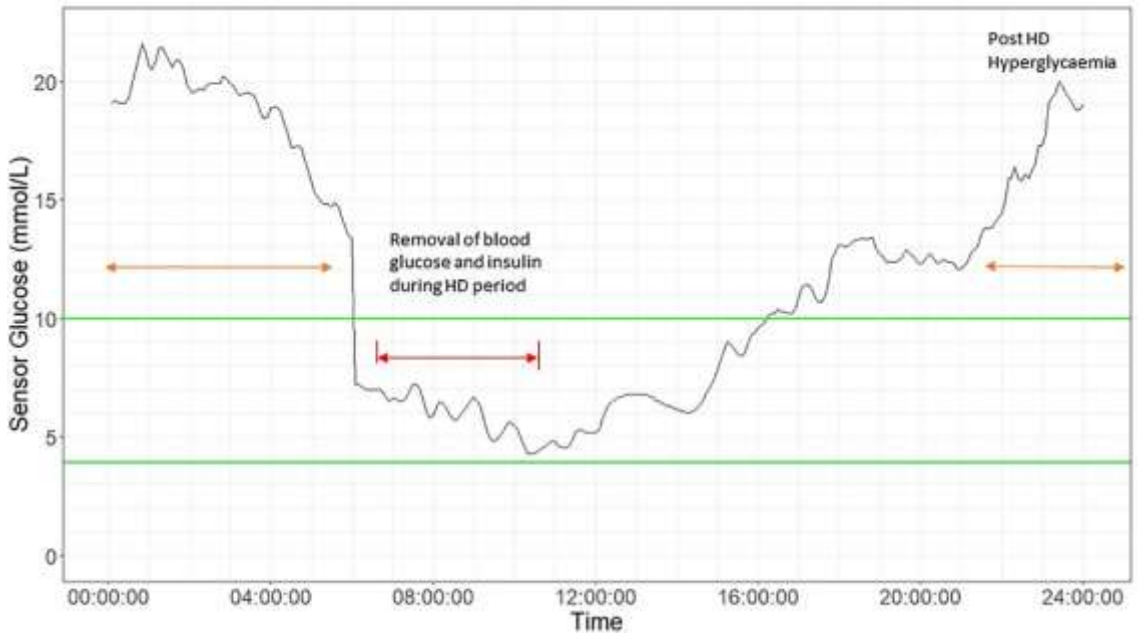
CGM and indicators of diabetes control in HD



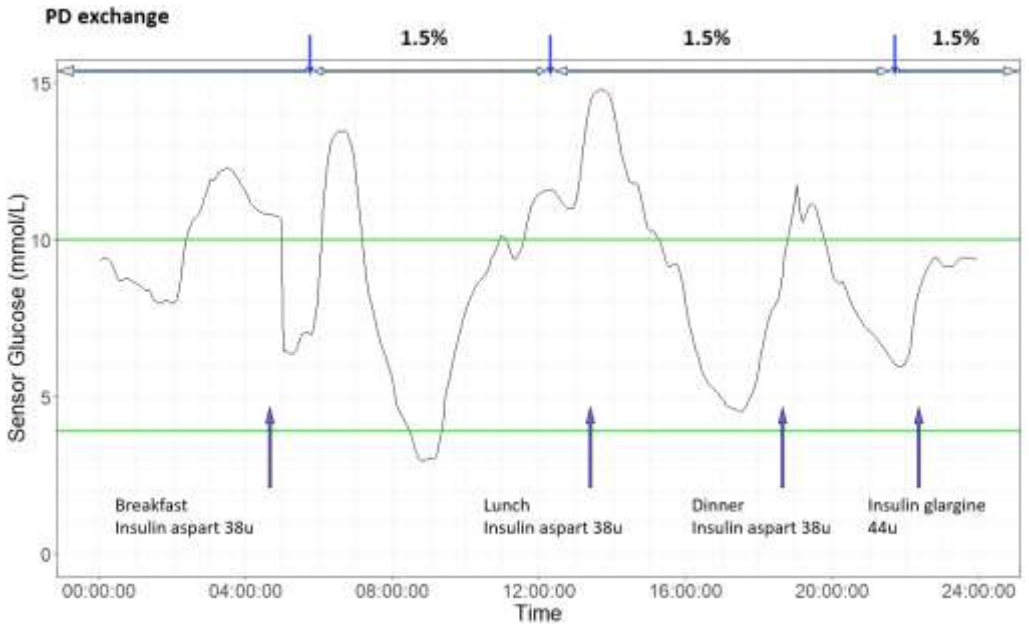
No DM

Hassanein, BMC Med 2022

CGM: glycemic profiles in HD and PD



T2D on Glargine 24 U 8:00, HbA1c 8.2%

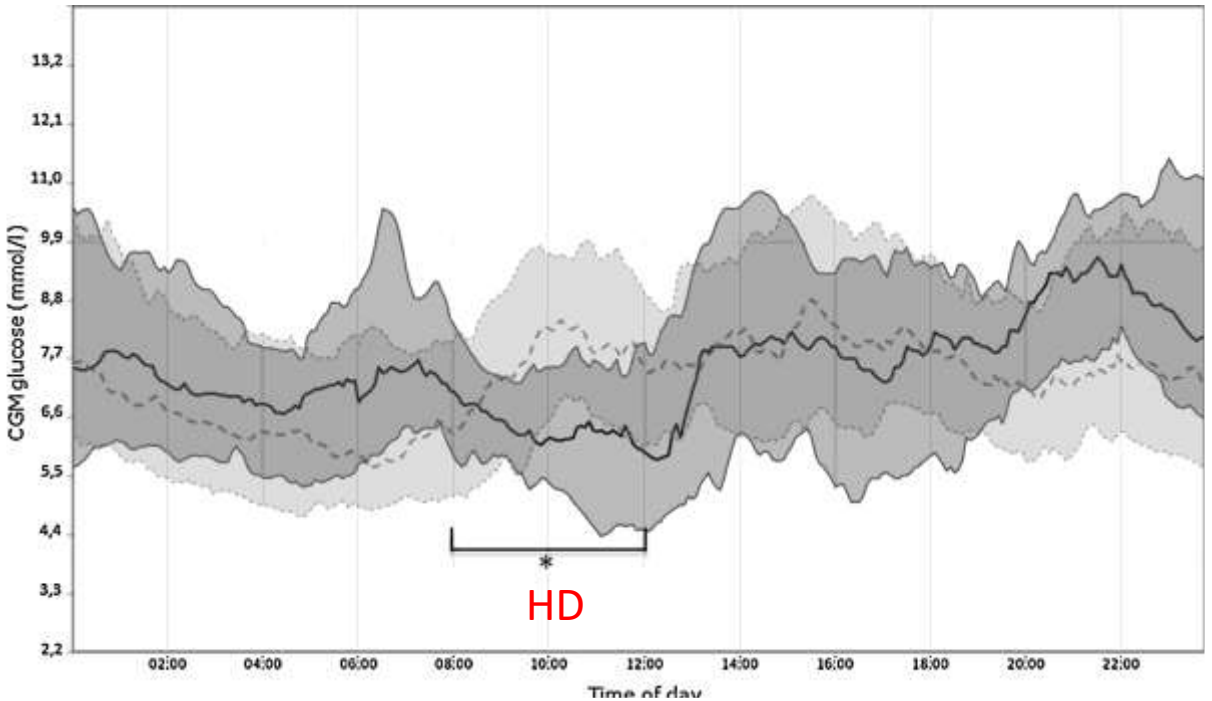


T2D on BB regimen , HbA1c 7.5%, GMI 6.9%

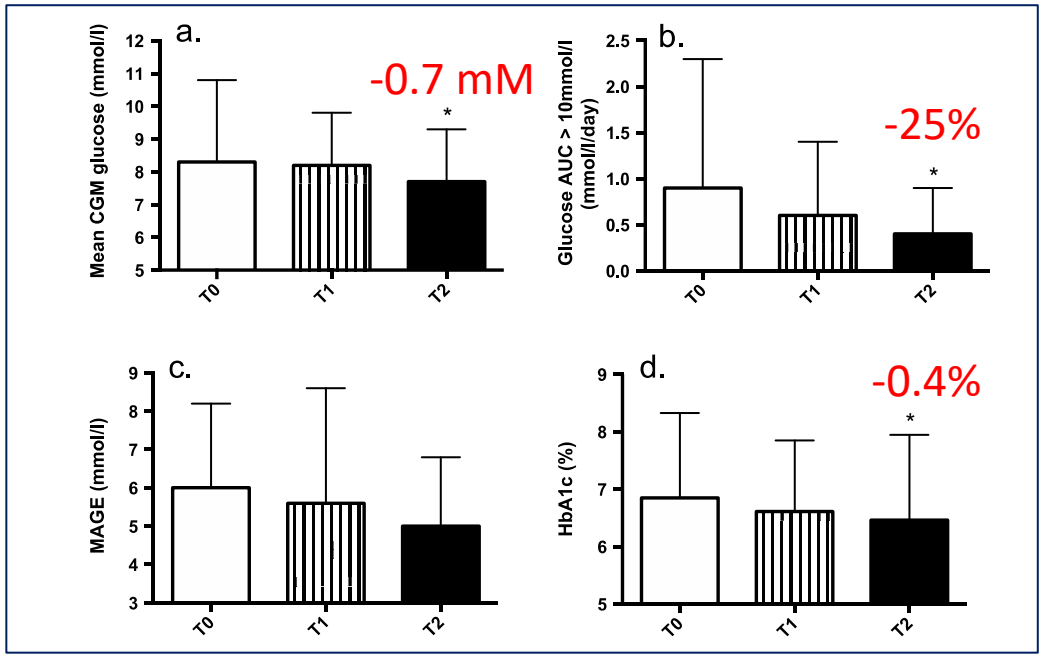
Ling, Front Endocrinol 2022

CGM: benefice in diabetes control - HD

15 T2D; T1: SMBG 6 weeks (3-6/d); T2: CGM 6 weeks

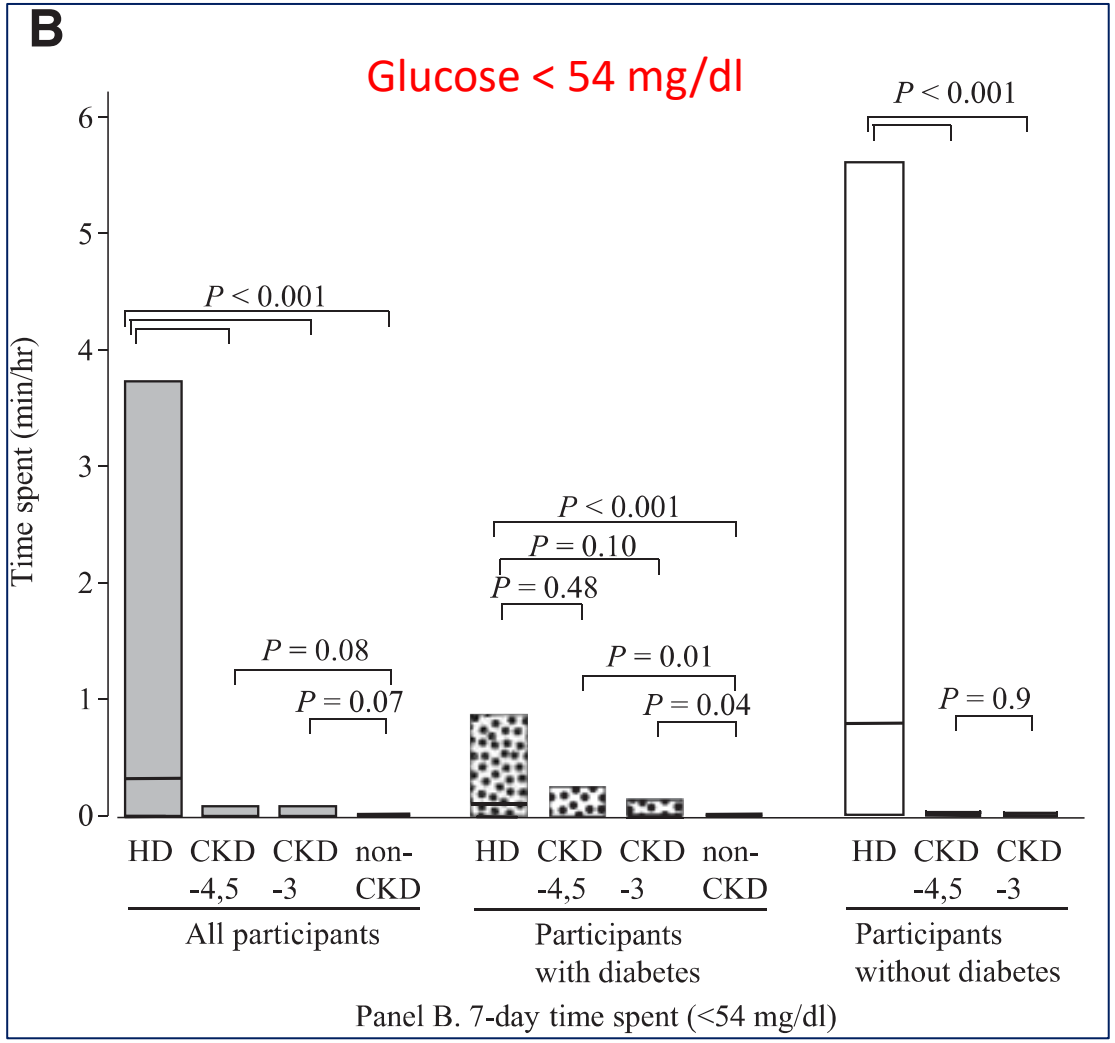


Joubert, Diab Res clin Pract 2015

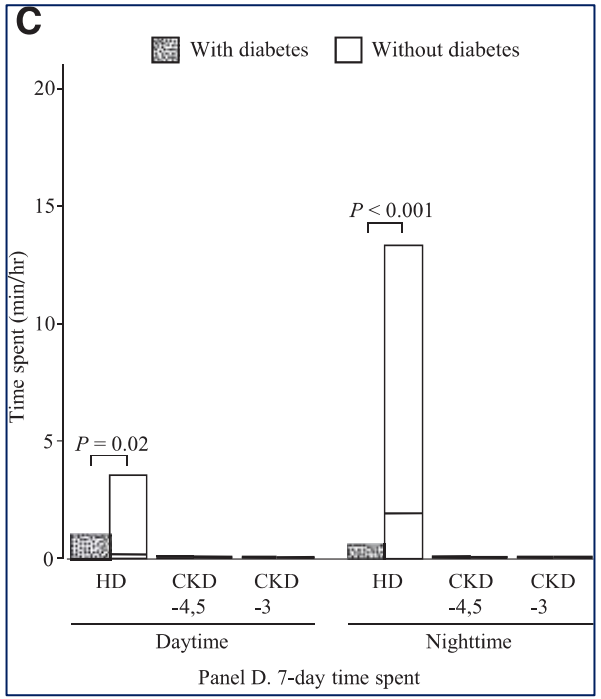


Idem *Kepenekian, Clin Nephrol 2014*
↓ mean PG of 1 mM, HbA1c of 0.8%, TAR of 10%

CGM – hypoglycemia detection in CKD



Glucose < 54 mg/dl
DM + CKD: 48%
CKD no DB: 41%
DM no CKD: 14%
nocturnal in HD



Ushiogi, CJASN 2023

Clinical case -1

GLUCOSE STATISTICS AND TARGETS

September 20, 2019–October 4, 2019	15 days
% Time CGM is active	100%

Ranges and targets for Type 1 or type 2 diabetes

Glucose ranges **Targets** [% of readings (time/day)]

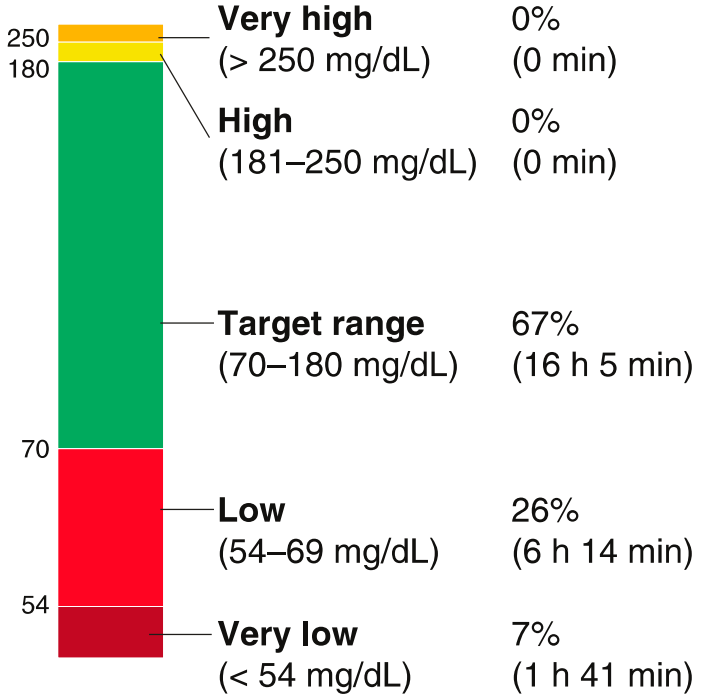
Target range 70–180 mg/dL...Greater than 70% (16 h 48 min)
Below 70 mg/dL.....Less than 4% (58 min)
Below 54 mg/dL.....Less than 1% (14 min)
Above 180 mg/dL.....Less than 25% (6 h)
Above 250 mg/dL.....Less than 5% (1 h 12 min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average glucose	83 mg/dL
Glucose Management Indicator (GMI)	5.3%
Glucose Variability	29.2%

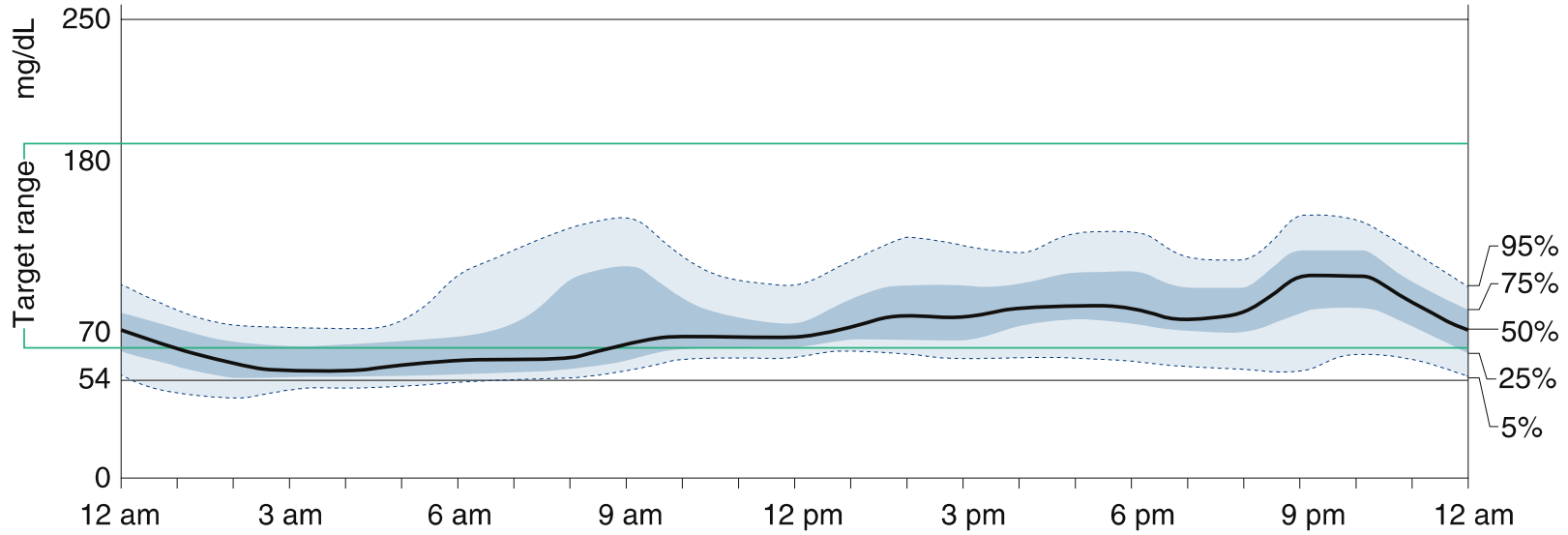
Defined as percent coefficient of variation (%CV); target ≤ 36%

TIME IN RANGES



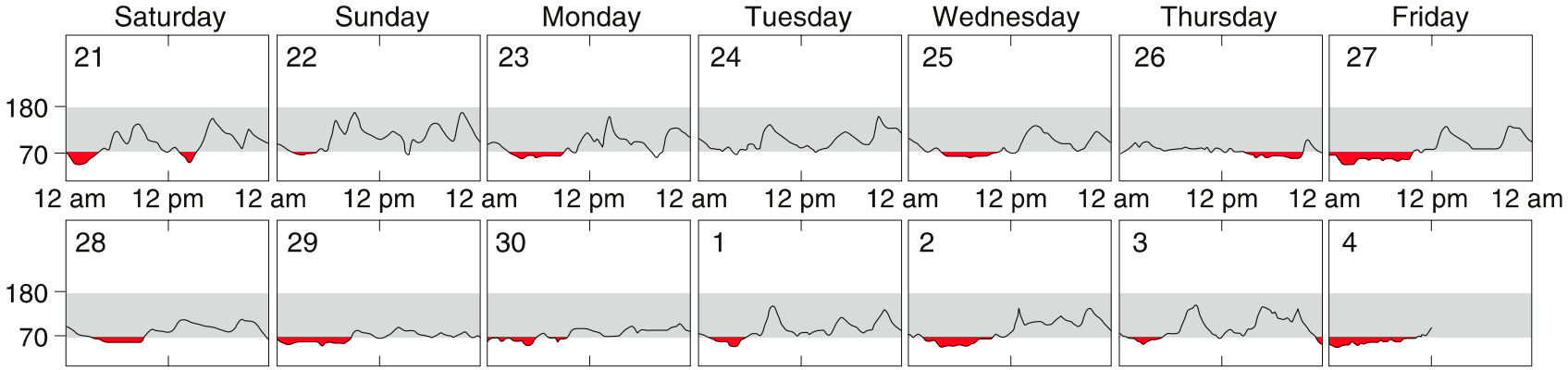
T2D patient on BB regimen, HD

Clinical Case-1



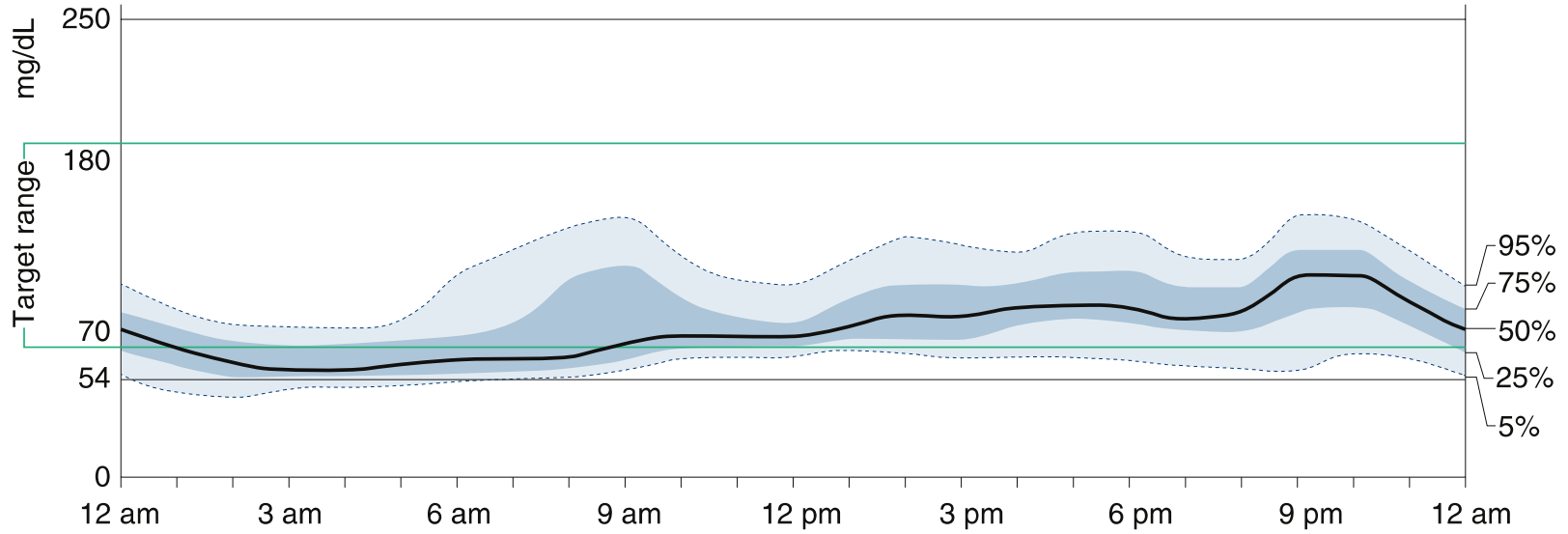
DAILY GLUCOSE PROFILES **Most recent 14 days. See Weekly Summary report for more days.**

Each daily profile represents a midnight to midnight period with the date displayed in the upper right corner.



AGP report derived from a Libre CGM.

Clinical Case-1



Stop rapid insulin
Basal insulin at 8:00
Introduction GLP1RA

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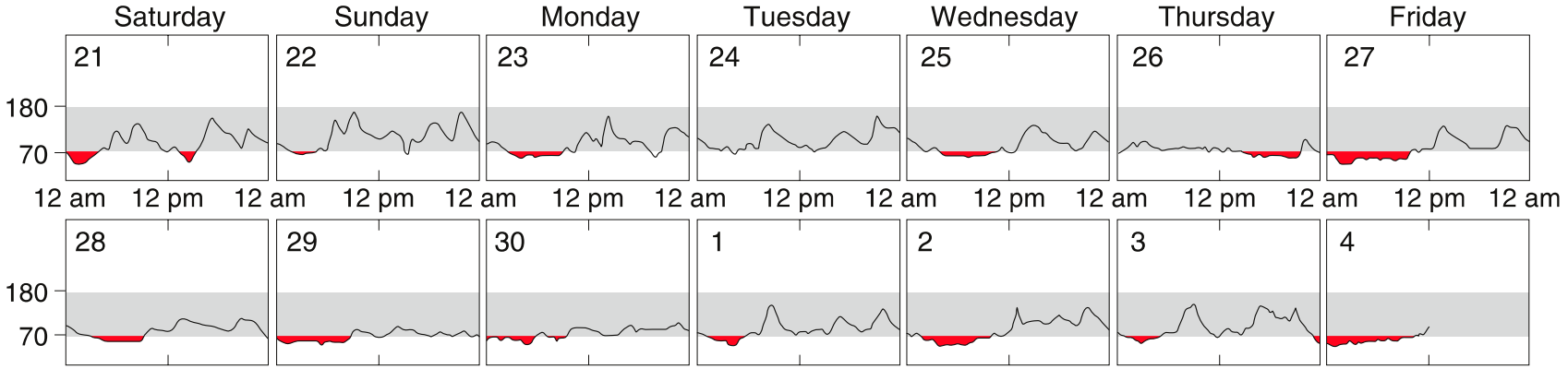


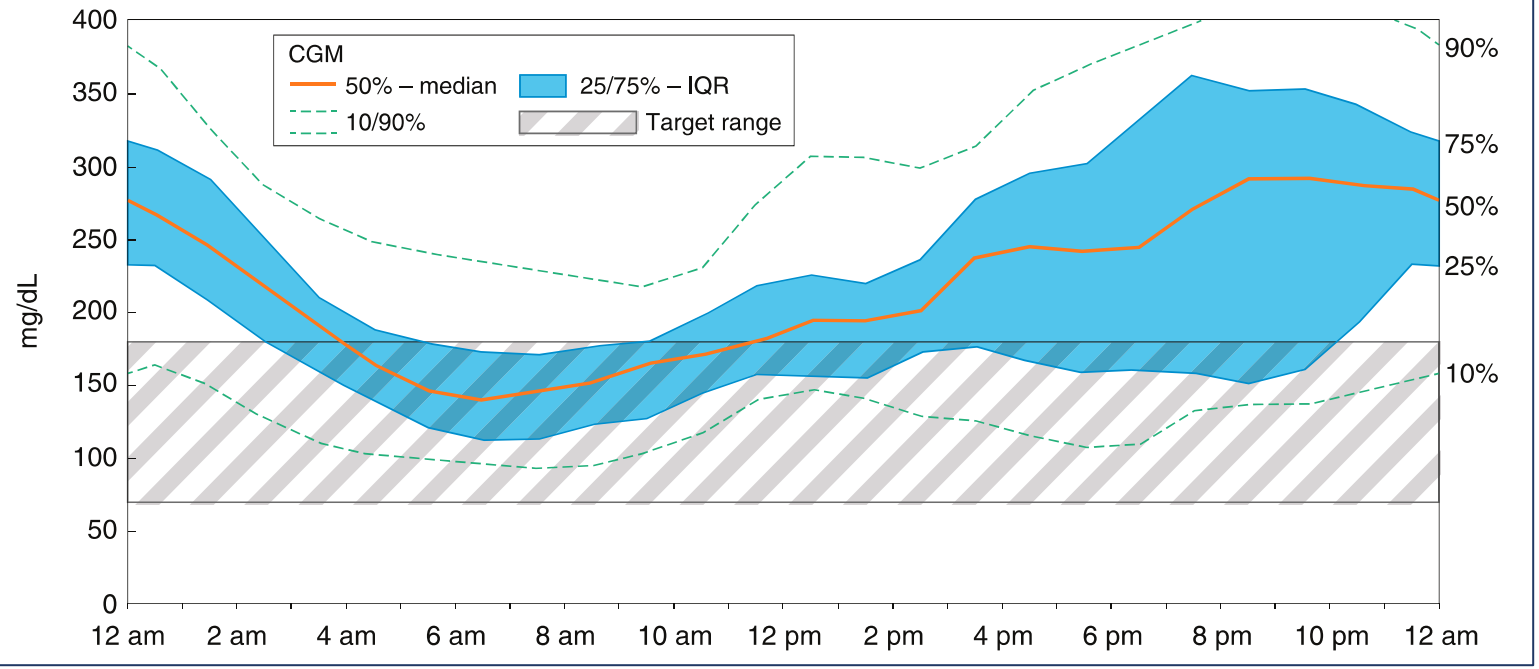
AGP report derived from a Libre CGM.

Clinical Case -2

Glucose statistics

Average glucose mg/dL	Very low	Low	In target range	High	Very high	Coefficient of variation	SD mg/dL	% Time CGM active
	< 54 mg/dL	< 70 mg/dL	70–180 mg/dL	> 180 mg/dL	> 250 mg/dL			
214	0.0%	0.0%	44.0%	56.0%	30.8%	38.1%	81	99.7%
Glucose exposure	Glucose ranges					Glucose variability		Data sufficiency

Ambulatory glucose profile



T2D patient, 79 yr old
HD for 5 years
HbA1c 5.8%
SMBG: 1.26; 1.46
Glargine 10 UI , 20:00

Clinical Case -2

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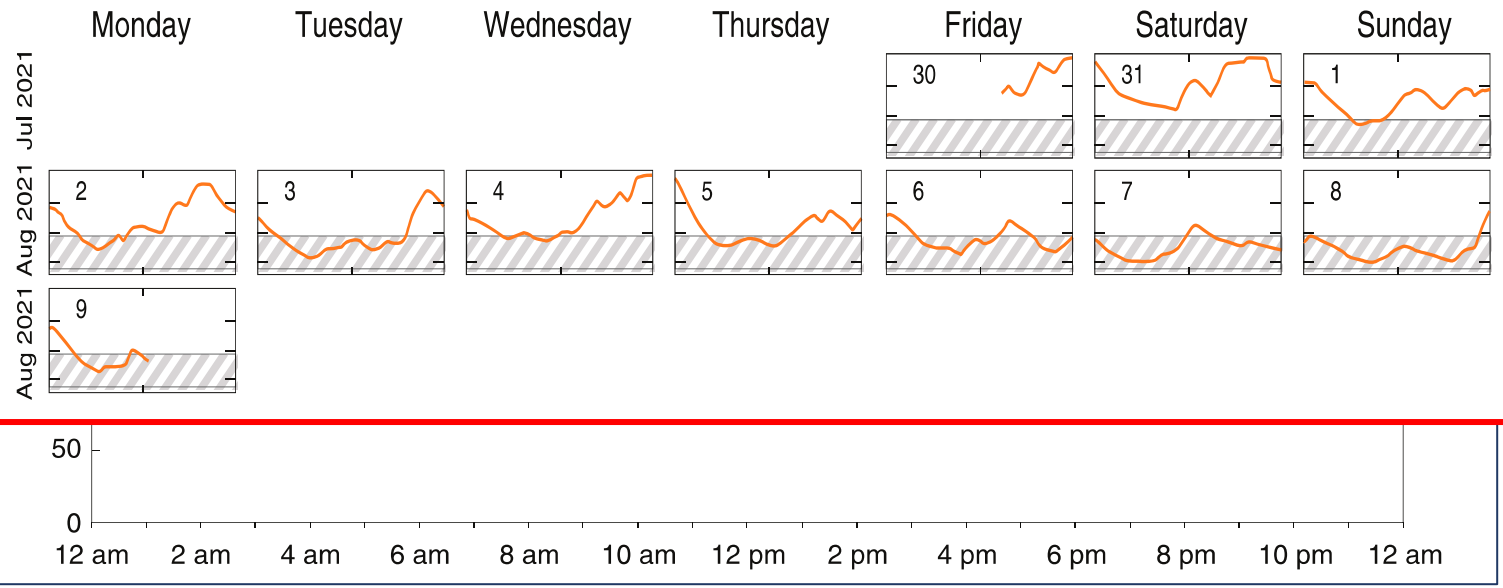
Ambulatory glucose profile

Daily glucose profile



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Ambulatory glucose profile

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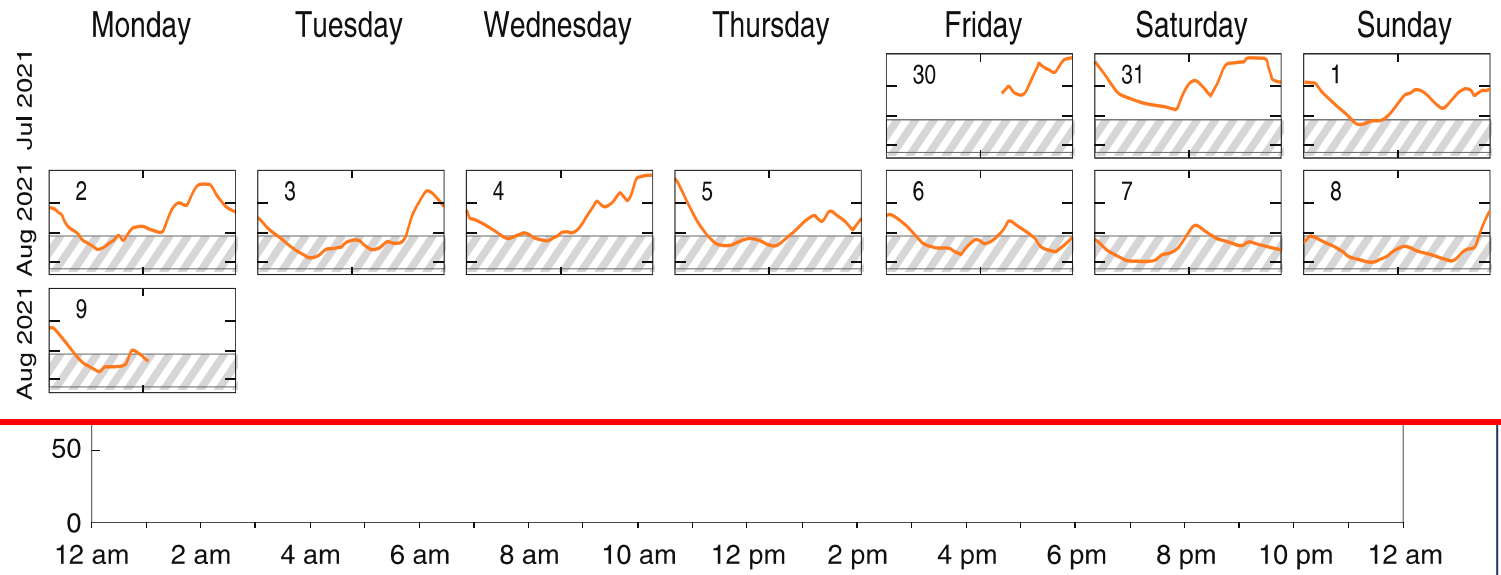

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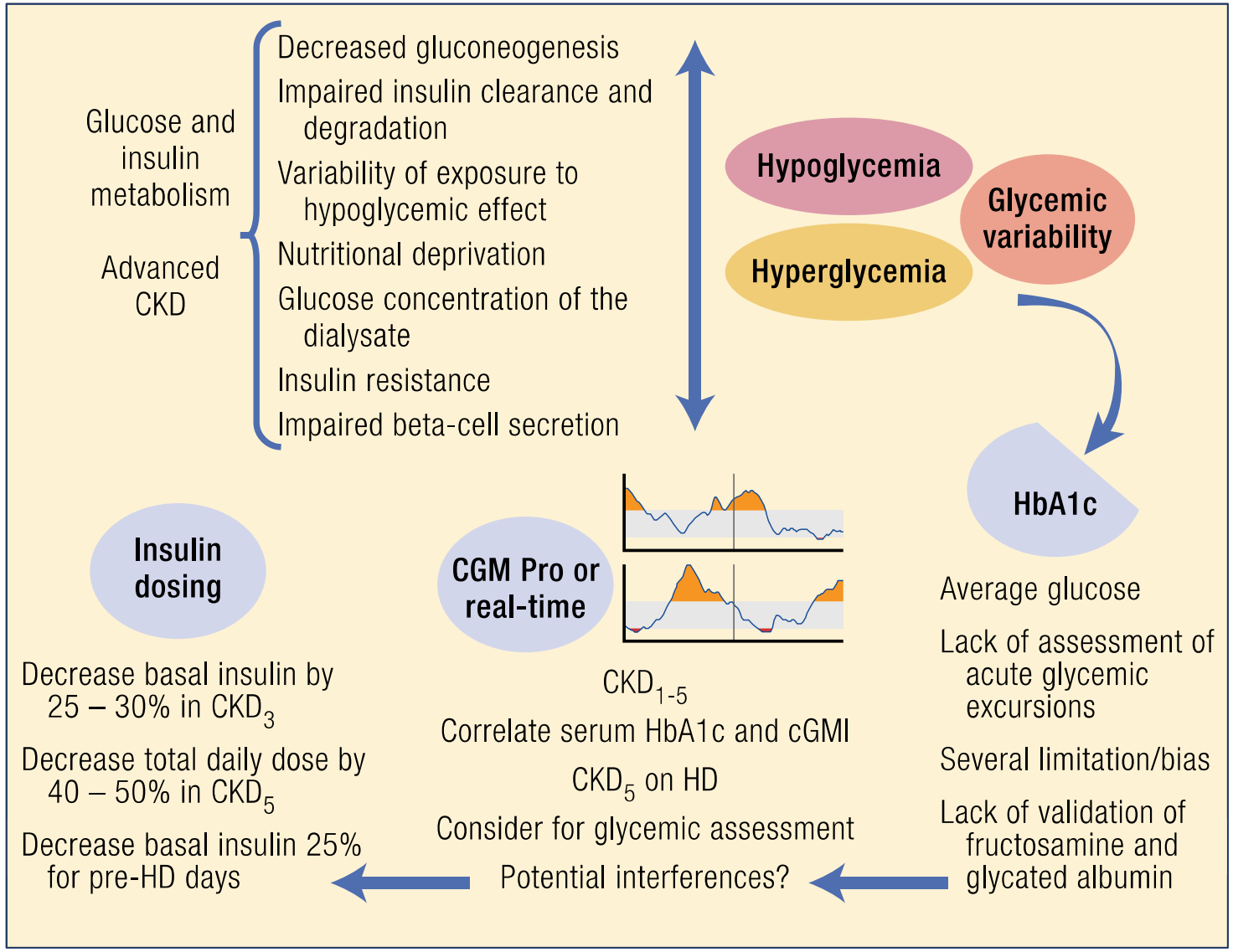
HbA1c 5.8%
SMBG: 1.26; 1.46
Glargine 10 UI , 20:00

-> rapid analog
at diner

-> Glargine at 8:00

In conclusion



Galindo Endocrin Rev 2020