2018 糖尿病臨床照護指引

DAROC Clinical Practice Guidelines for Diabetes Care 2018

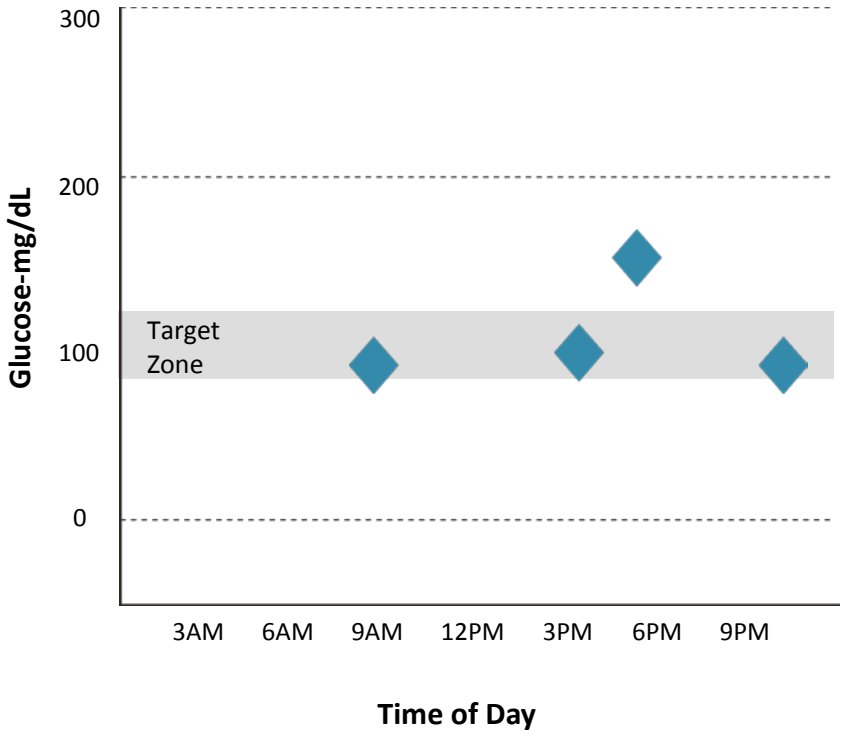
血糖監測的新工具

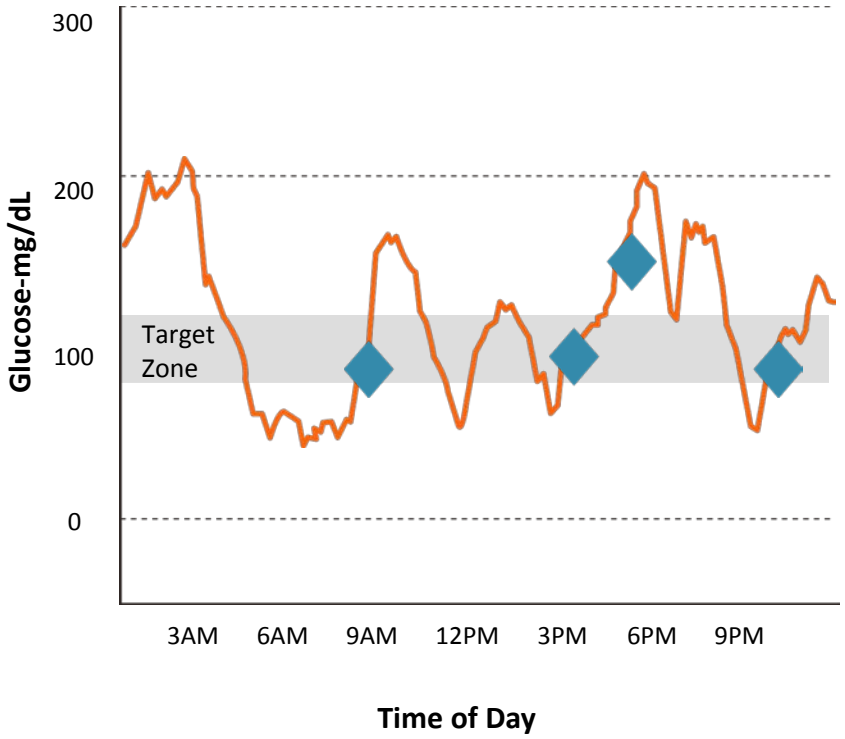
社團法人中華民國糖尿病學會 編著

連續葡萄糖監測

Continuous glucose monitoring (CGM)

How CGM works ?





2 Main Categories of CGM

Professional CGM

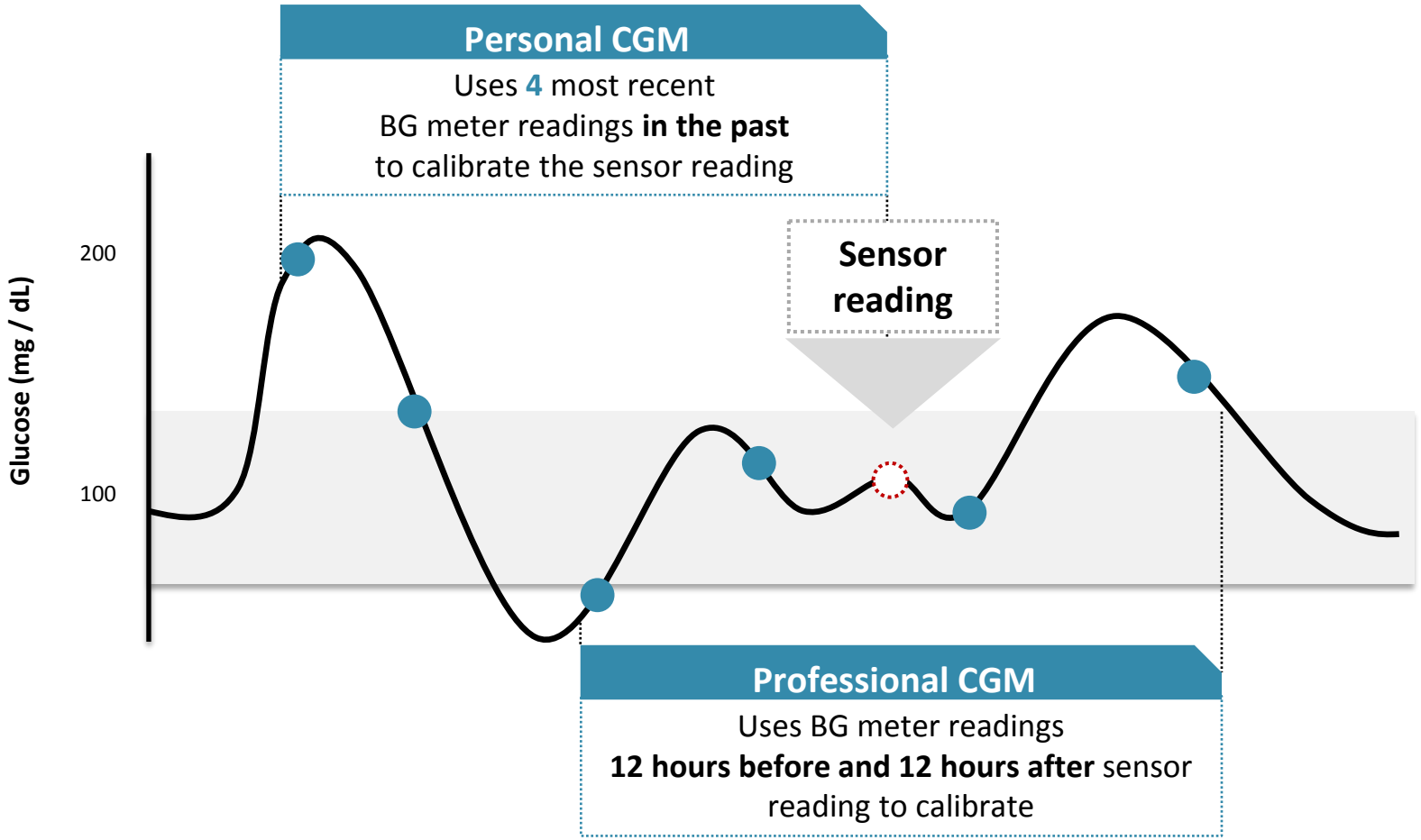
- Owned by clinicians, offices, hospitals
- Episodic, intermittent use (3 days)
- “Blinded” or “masked” evaluation
- Retrospective review by providers
- Minimal training and set-up time

Personal CGM

- Owned by patients
- On-going use by patients
- Displays glucose values and alarms that allow for immediate therapeutic adjustments
- Continuous review of data by patients
- Requires patient education

AACE CGM Task Force. “Statement by the American Association of Clinical Endocrinologists Consensus Panel on Continuous Glucose Monitoring.” Endocrine Practice. 2010; 16(5):730 – 744.

CGM Calculation Algorithm



專業性連續式血糖監測系統

可 **24 小時**瞭解
血糖波動的趨勢

可**彌補於一般自我血糖監測不足之處**，如：

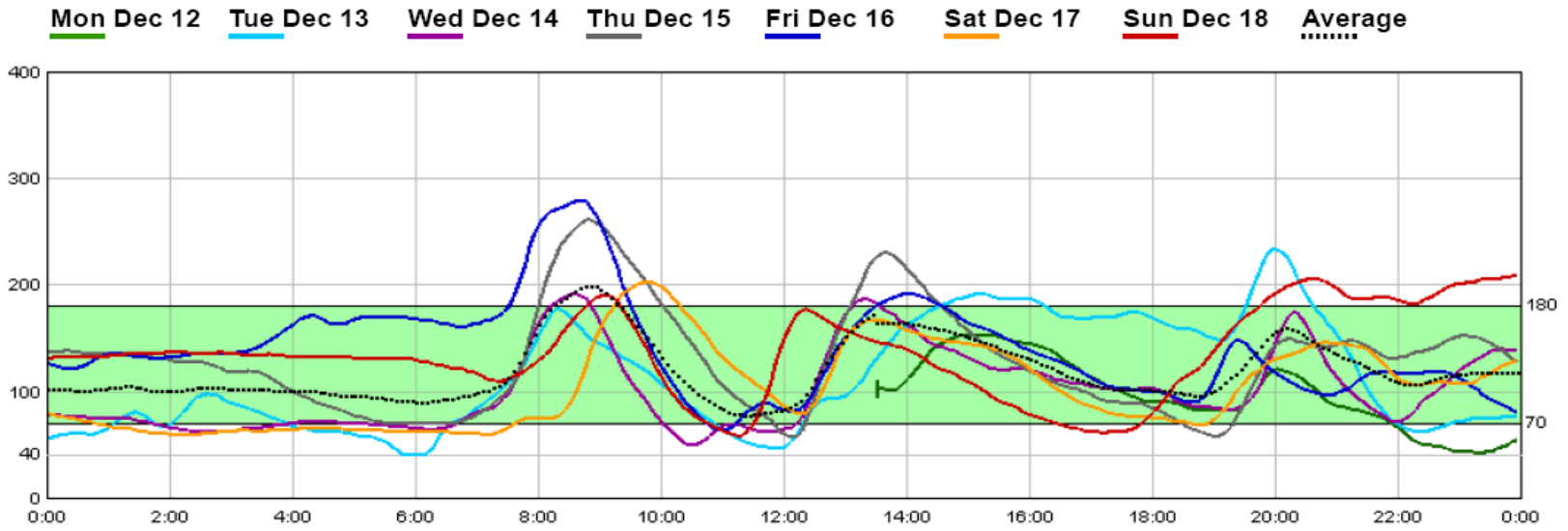
- 不自覺低血糖
- 血糖的波動
- 高血糖
- 夜間低血糖

以下族群可做**短期的回溯性分析**評估**糖尿病用藥及飲食生活型態的調整**：

- 半夜低血糖
- 黎明現象
- 餐後高血糖
- 不自覺的低血糖發作
- 糖尿病治療處方有重大改變者

43 y/o woman, type 1 DM 5 years, on CSII, BMI 20, A1c 8.0

Sensor Data (mg/dL)



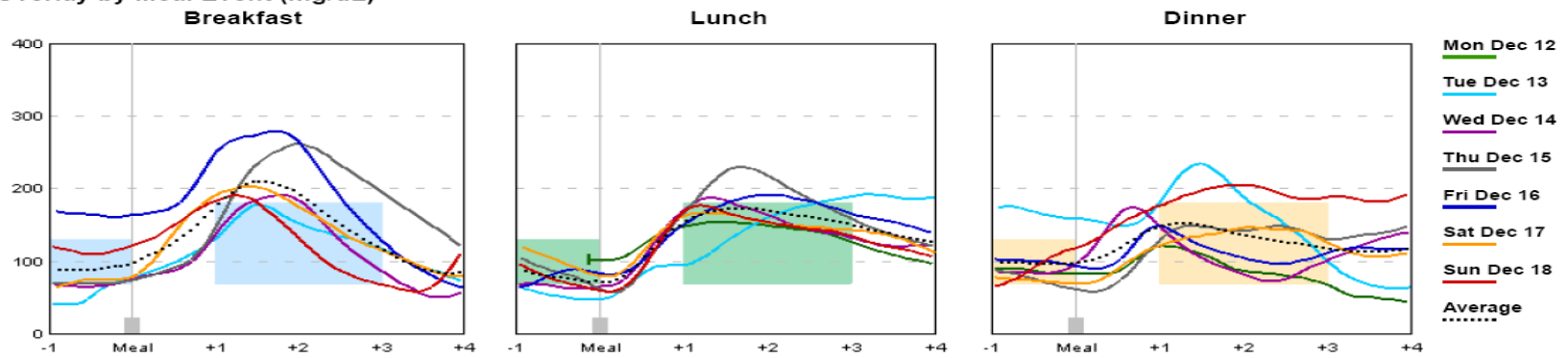
	Mon Dec 12	Tue Dec 13	Wed Dec 14	Thu Dec 15	Fri Dec 16	Sat Dec 17	Sun Dec 18	Average / Total
# Sensor Values	126	288	288	288	288	288	288	1,854
Highest	153	234	191	261	279	203	208	279
Lowest	42	40	50	57	64	59	58	40
Average	99	113	102	129	140	104	136	119
Standard Dev.	33	51	37	48	45	40	40	46
MAD %	14.8	15.2	4.8	7.9	4.7	8.4	7.3	8.9
Correlation	N/A	N/A	N/A	N/A	N/A	N/A	1.00	0.96
# Valid Calibrations	3	4	4	4	3	5	4	27
Designation								

X: Use Clinical Judgment S: No Sensor Data C: No Calibration BG's

Excursion Summary (mg/dL/day)

	Mon Dec 12	Tue Dec 13	Wed Dec 14	Thu Dec 15	Fri Dec 16	Sat Dec 17	Sun Dec 18	Average / Total
# Excursions	1	6	5	4	3	3	4	26
# High Excursions	0	2	2	2	2	1	2	11
# Low Excursions	**1**	**4**	**3**	**2**	**1**	**2**	**2**	15
AUC Above Limit	0.0	2.0	0.3	6.0	5.7	0.7	2.9	2.7
AUC Below Limit	4.1	3.1	1.3	0.4	0.1	2.0	0.5	1.4

Overlay by Meal Event (mg/dL)



	Sleeping 3:00 - 5:00	Before Breakfast	After Breakfast	Before Lunch	After Lunch	Before Dinner	After Dinner	Evening 23:00 - 3:00	All Time Periods
Range	70 - 150	70 - 130	70 - 180	70 - 130	70 - 180	70 - 130	70 - 180	70 - 150	
Highest	171	168	279	119	230	175	234	231	279
Lowest	60	40	70	47	97	62	69	42	40
Average	99	91	177	77	164	97	137	118	126
Standard Dev.	36	38	52	18	24	31	42	51	51
# of Readings	144	72	144	74	168	84	168	336	1,190

Daily Average by Meal Event (mg/dL)

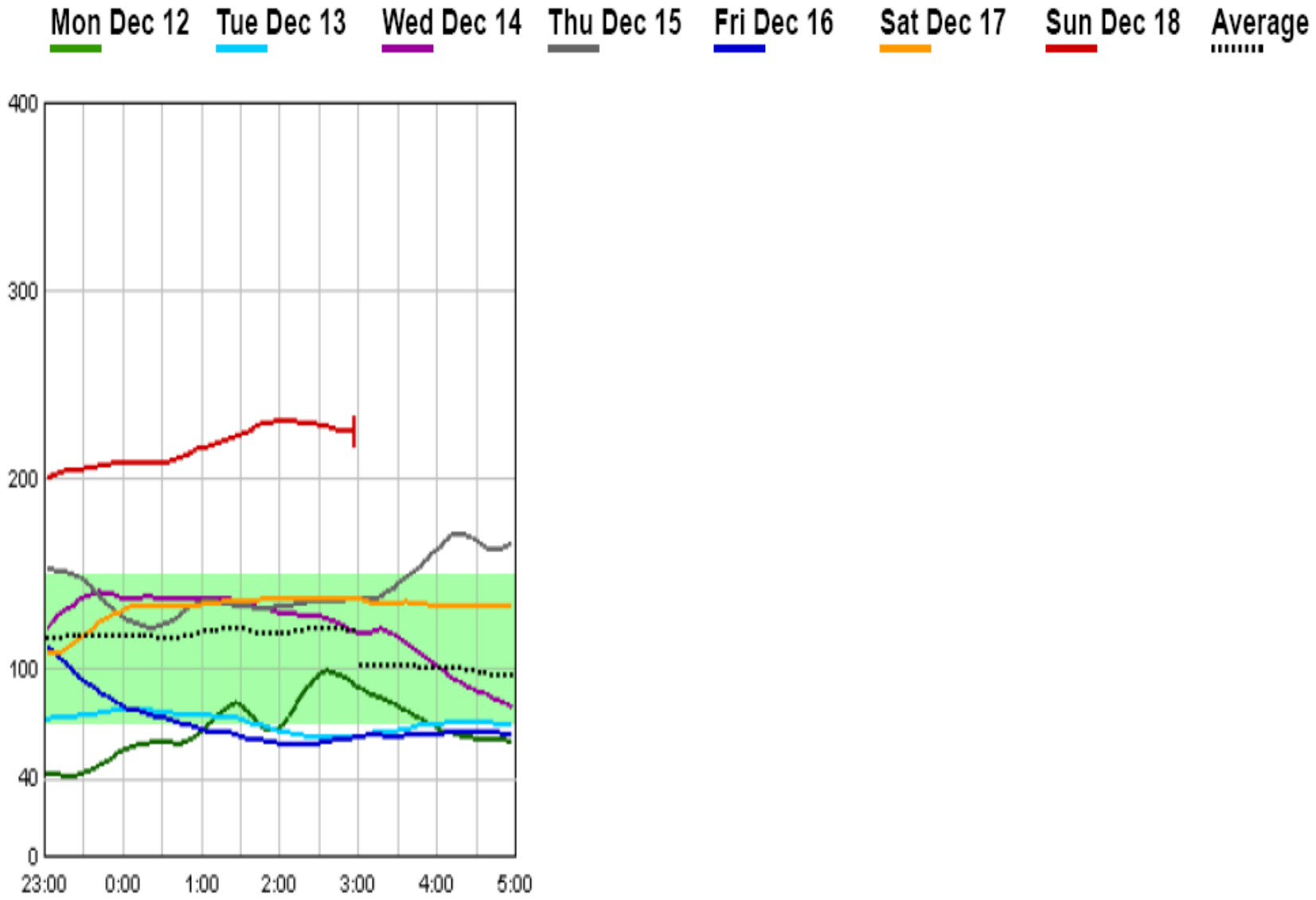
Below Target Range Above Target Range

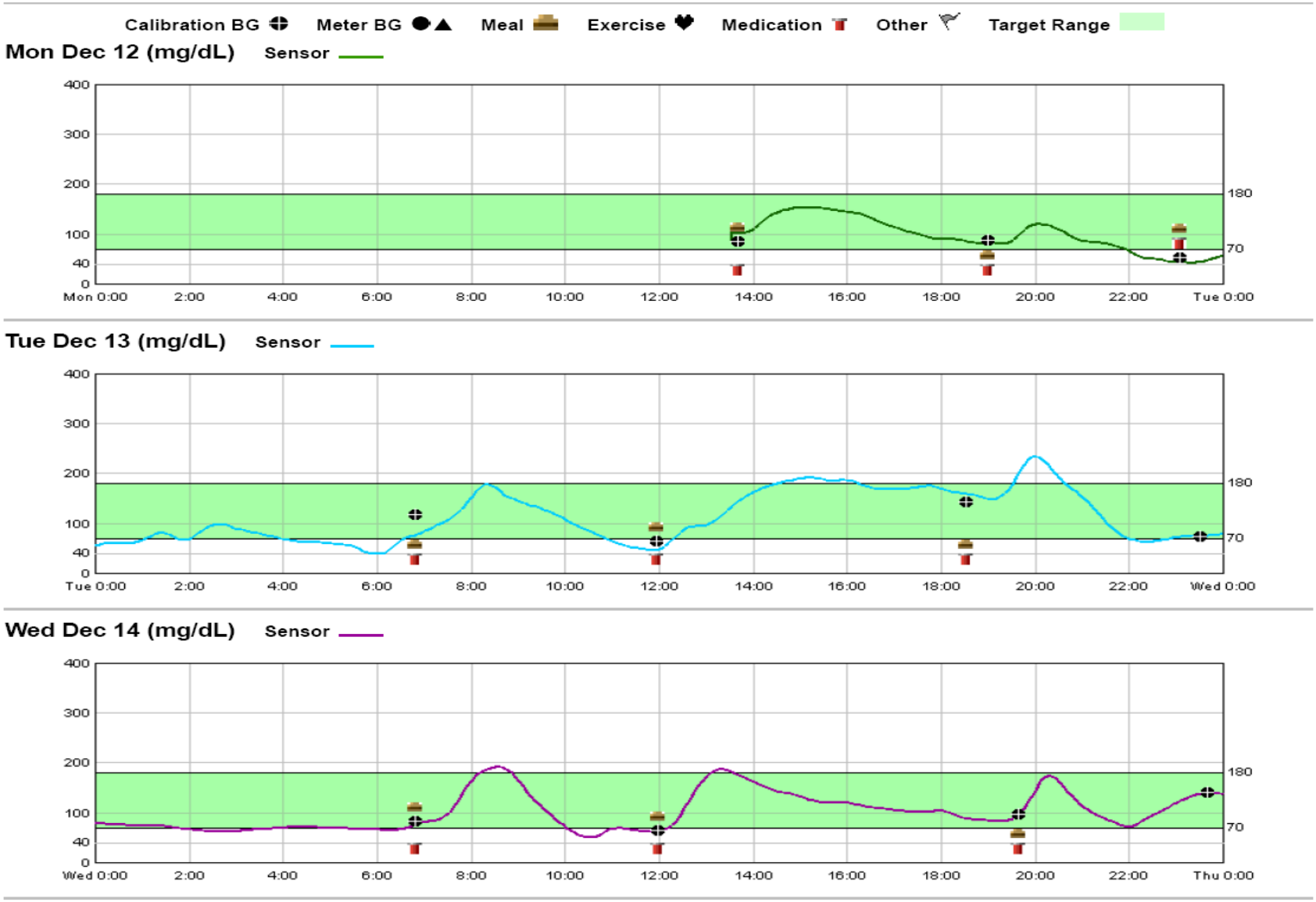
	Sleeping	Before Breakfast	After Breakfast	Before Lunch	After Lunch	Before Dinner	After Dinner	Evening	All Time Periods
Mon Dec 12				102	146	86	93	67	93
Tue Dec 13	71	54	148	52	153	167	180	72	111
Wed Dec 14	69	67	155	66	162	86	95	133	114
Thu Dec 15	101	70	227	84	199	75	143	134	141
Fri Dec 16	156	164	230	80	179	100	113	73	133
Sat Dec 17	64	73	168	99	155	73	138	130	121
Sun Dec 18	133	114	133	75	156	91	194	217	159
Dec 12 - Dec 18	99	91	177	77	164	97	137	118	126

Duration Distribution (hh:mm)

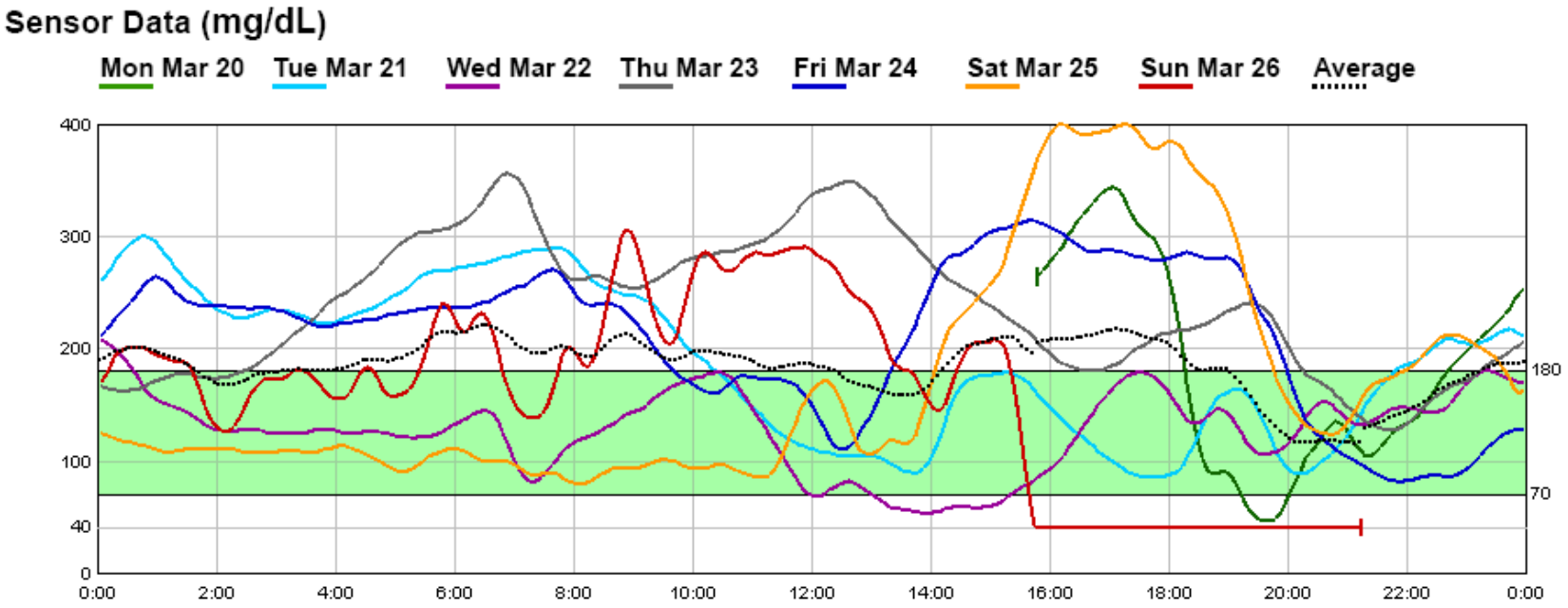
	Sleeping	Before Breakfast	After Breakfast	Before Lunch	After Lunch	Before Dinner	After Dinner	Evening
Above	1:20 11%	1:00 17%	5:20 44%	0:00 0%	3:25 24%	1:00 14%	3:00 21%	4:20 15%
In Range	6:40 56%	3:15 54%	6:40 56%	3:25 55%	10:35 76%	5:25 78%	10:55 78%	17:55 64%
Below	4:00 33%	1:45 29%	0:00 0%	2:45 45%	0:00 0%	0:35 8%	0:05 1%	5:45 21%

Night Time Sensor Data (mg/dL)




Calibration BG
Meter BG
Meal
Exercise
Medication
Other
Target Range
Mon Dec 12 (mg/dL)
Sensor
400
300
200
100
40
0
180
70
Mon 0:00
2:00
4:00
6:00
8:00
10:00
12:00
14:00
16:00
18:00
20:00
22:00
Tue 0:00
Tue Dec 13 (mg/dL)
Sensor
Wed 0:00
Wed Dec 14 (mg/dL)
Sensor
Thu 0:00

25 y/o woman, type 1 DM for 20 years, on CSII, BMI 19, A1C 7.2 %



	Mon Mar 20	Tue Mar 21	Wed Mar 22	Thu Mar 23	Fri Mar 24	Sat Mar 25	Sun Mar 26	Average / Total
# Sensor Values	99	288	288	288	288	288	255	1,794
Highest	344	300	208	357	314	400	306	400
Lowest	46	85	53	127	81	80	40	40
Average	183	189	127	237	213	171	161	183
Standard Dev.	92	66	36	61	65	98	84	80
MAD %	18.1	9.3	5.0	4.6	7.7	19.7	25.5	10.6
Correlation	0.98	0.99	0.99	1.00	0.98	0.95	N/A	0.96
# Valid Calibrations	3	6	4	4	4	3	1	25
Designation							X	

X: Use Clinical Judgment S: No Sensor Data C: No Calibration BG's

Avg SG: **185 mg/dL**

previous avg SG 135 mg/dL on Oct 13, 2015

Estimated A1C[1]: **8.1%** calculated from SG values

Time in range: **44% Above 180 mg/dL**

54% in target range

2% Below 70 mg/dL

OBSERVED PATTERNS & SOME POSSIBLE CAUSES[2]

1 — High SG
Pre-breakfast 5:00 - 10:00

4 out of 7 days excursions observed:
- 1 day(s) 130 - 250 mg/dL
- 3 day(s) > 250 mg/dL

- Oral medication(s) missed, too low, or incorrectly timed?
- Basal insulin injection in evening(s) too low?
- Rebound hyperglycemia after nocturnal hypoglycemia?
- High calorie or high fat foods in prior evening(s)?
- Late evening snack?

2 — High SG
Overnight 23:00 - 5:00

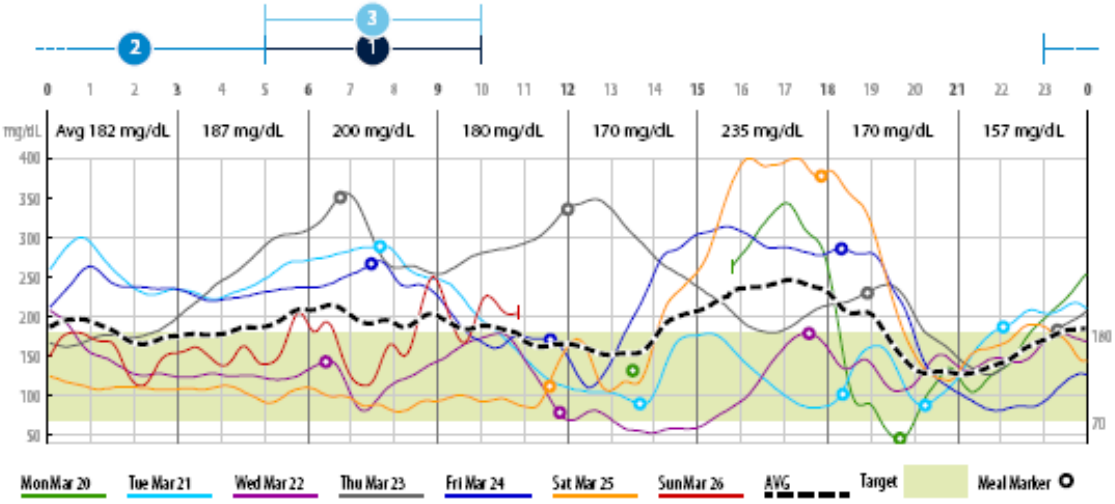
5 out of 7 days excursions observed:
- 2 day(s) 150 - 250 mg/dL
- 3 day(s) > 250 mg/dL

- Oral medication(s) missed, too low, or incorrectly timed?
- Basal insulin injection in evening(s) too low?
- Insulin to carbohydrate ratio not optimal in prior evening(s)?
- High calorie or high fat foods in prior evening(s)?
- Late evening snack?

3 — High SG
Post-breakfast 5:00 - 10:00

3 out of 7 days excursions observed:
- 2 day(s) 180 - 250 mg/dL
- 1 day(s) > 250 mg/dL

- Oral medication(s) missed, too low, or incorrectly timed?
- Pre-breakfast insulin incorrectly timed, too low, or missed?
- Insulin to carbohydrate ratio not optimal for pre-breakfast insulin?
- High calorie or high carbohydrate foods?



Avg SG: **185 mg/dL**

previous avg SG 135 mg/dL on Oct 13, 2015

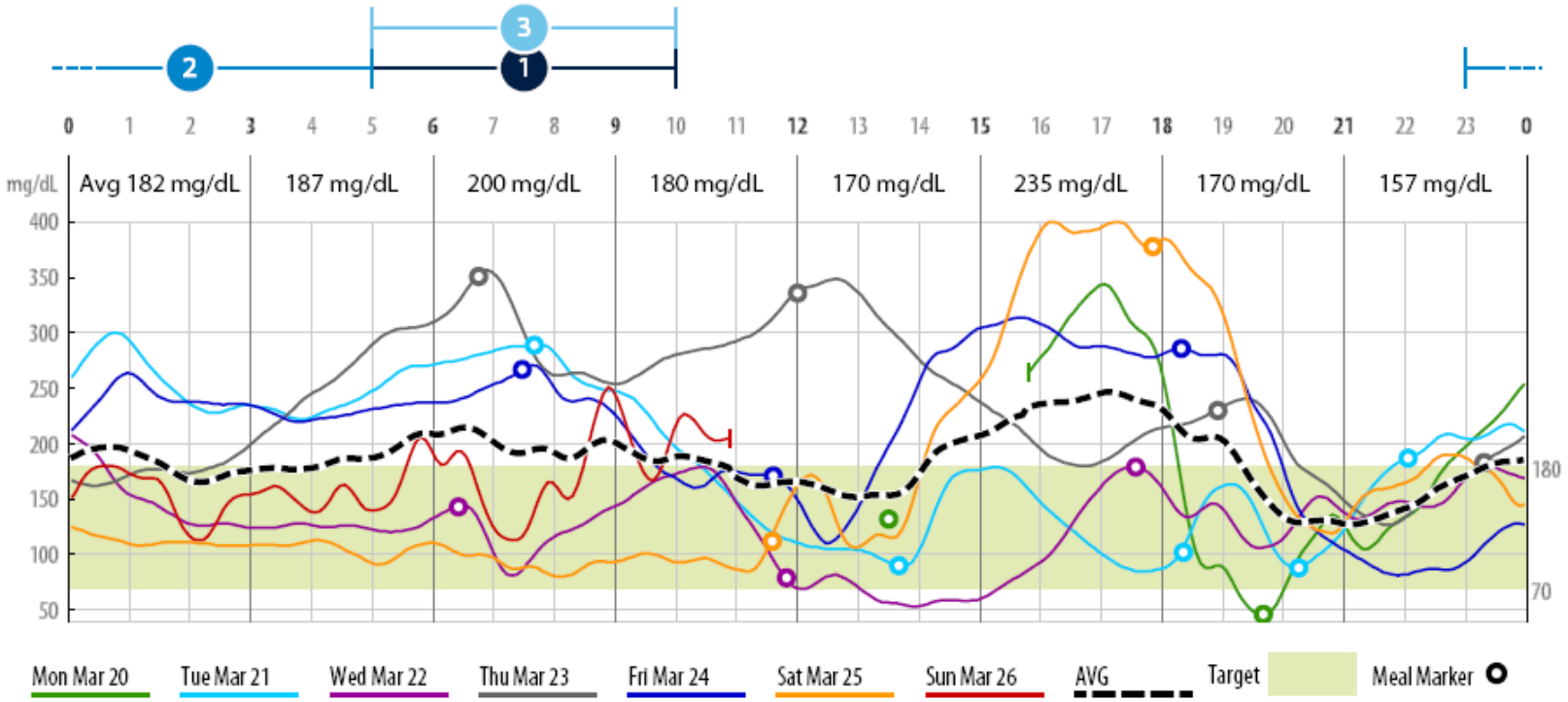
Estimated A1C[1]: **8.1%** calculated from SG values

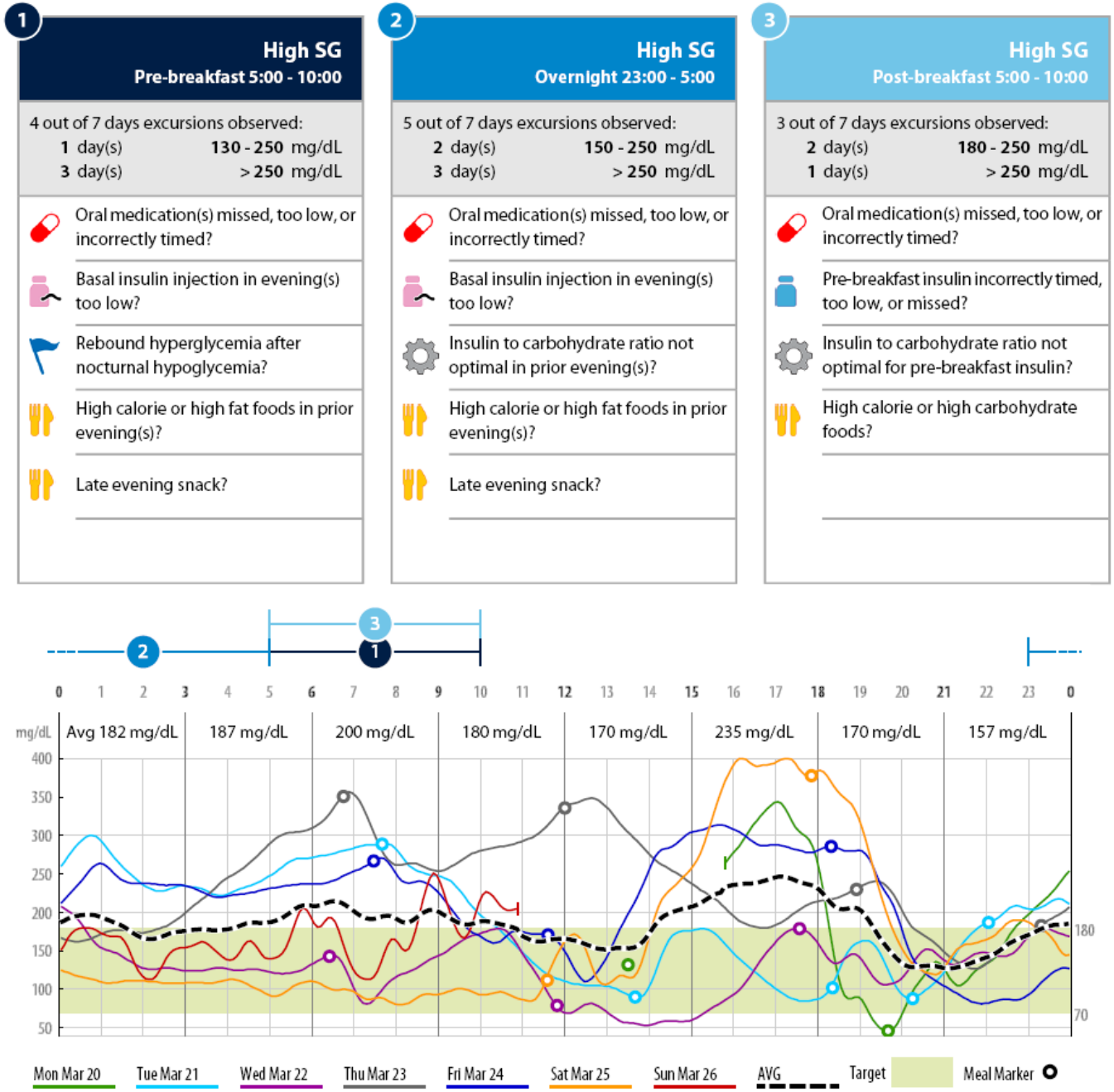
OBSERVED PATTERNS & SOME POSSIBLE CAUSES[2]

Time in range: **44% Above 180 mg/dL**

54% in target range

2% Below 70 mg/dL




1
High SG
Pre-breakfast 5:00 - 10:00
4 out of 7 days excursions observed:
1 day(s) 130 - 250 mg/dL
3 day(s) > 250 mg/dL
Oral medication(s) missed, too low, or incorrectly timed?
Basal insulin injection in evening(s) too low?
Rebound hyperglycemia after nocturnal hypoglycemia?
High calorie or high fat foods in prior evening(s)?
Late evening snack?
2
High SG
Overnight 23:00 - 5:00
5 out of 7 days excursions observed:
2 day(s) 150 - 250 mg/dL
3 day(s) > 250 mg/dL
Oral medication(s) missed, too low, or incorrectly timed?
Basal insulin injection in evening(s) too low?
Insulin to carbohydrate ratio not optimal in prior evening(s)?
High calorie or high fat foods in prior evening(s)?
Late evening snack?
3
High SG
Post-breakfast 5:00 - 10:00
3 out of 7 days excursions observed:
2 day(s) 180 - 250 mg/dL
1 day(s) > 250 mg/dL
Oral medication(s) missed, too low, or incorrectly timed?
Pre-breakfast insulin incorrectly timed, too low, or missed?
Insulin to carbohydrate ratio not optimal for pre-breakfast insulin?
High calorie or high carbohydrate foods?
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 0
mg/dL
Avg 182 mg/dL
187 mg/dL
200 mg/dL
180 mg/dL
170 mg/dL
235 mg/dL
170 mg/dL
157 mg/dL
400
350
300
250
200
150
100
50
180
70
Mon Mar 20
Tue Mar 21
Wed Mar 22
Thu Mar 23
Fri Mar 24
Sat Mar 25
Sun Mar 26
AVG
Target
Meal Marker

即時性連續血糖監測系統

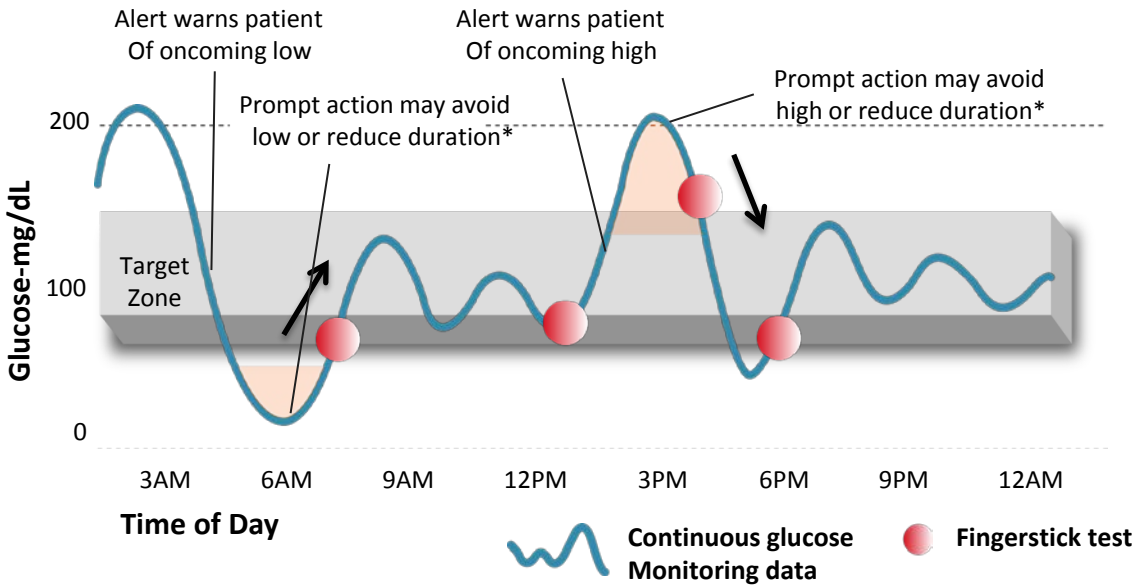
是一種**立即**提供血糖數據高血糖與低血糖警示，
協助病人立即進行**藥物的調整或生活型態的調整**

與專業性 (回溯性) 連續式血糖監測相比，
即時性連續血糖監測運用在
第 1 型糖尿病和第 2 型糖尿病血糖控制上，
皆可**降低糖化血色素及減少低血糖發生頻率成效**

Real-time continuous glucose monitoring (RT-CGM)

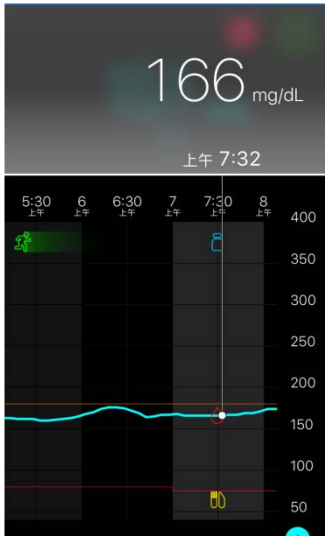
過去的 20 分鐘內血糖**上升**在 **20~40** mg/dl 之內

過去的 20 分鐘內血糖**下降**在 **20~40** mg/dl 之內



*A confirmatory fingerstick is required prior to taking action.

App. in smart phone



臨床證據

- **積極胰島素治療之：**
  - **第 1 型糖尿病 (≥ 25 歲)**
  - **第 2 型糖尿病人**
- **妊娠糖尿病及糖尿病且懷孕者**

→ 在血糖監測策略，適當結合專業性連續式血糖監測系統可**降低糖化血色素**

- **糖化血色素已獲良好控制的第 1 型糖尿病人**

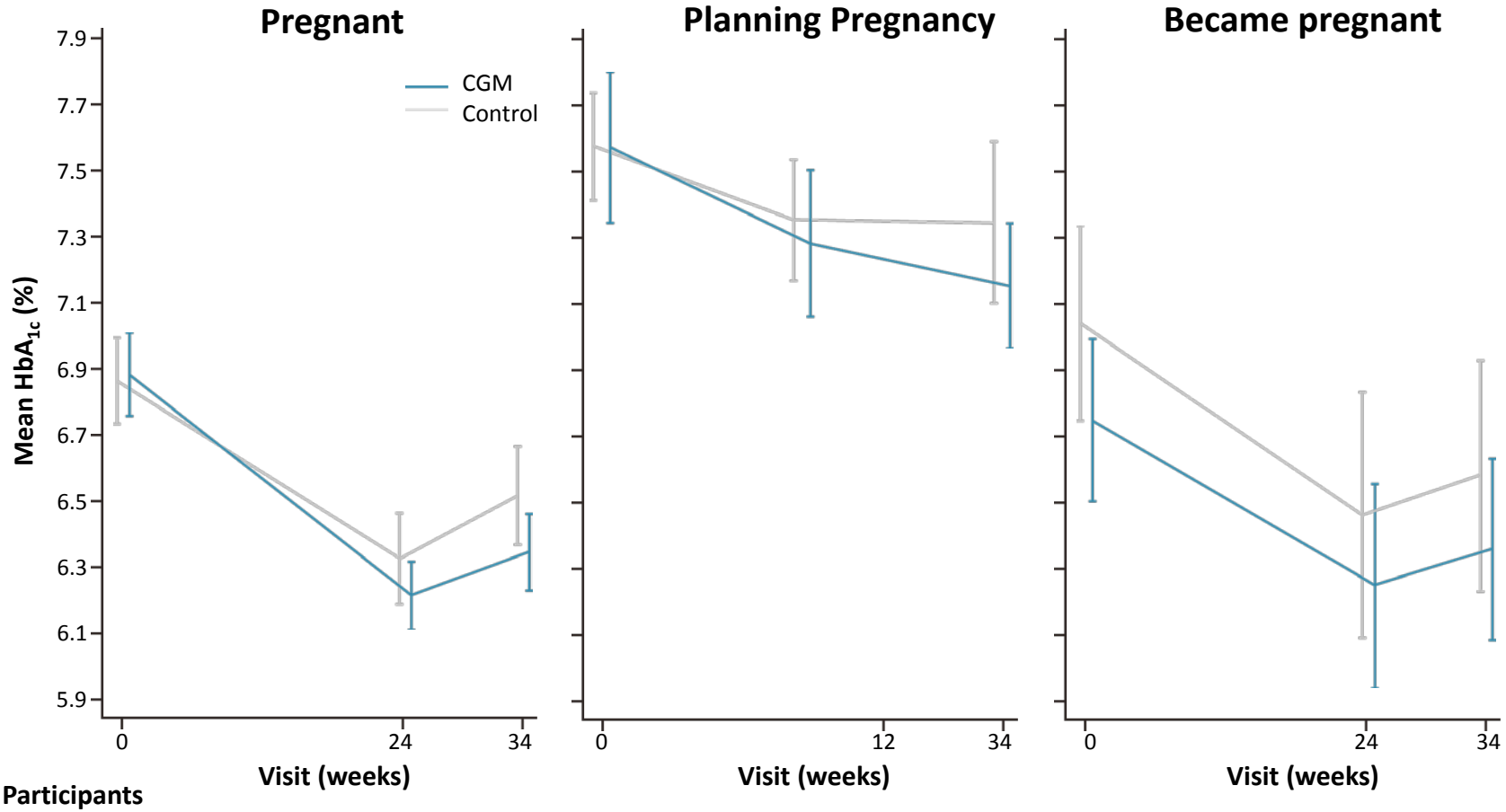
→ 能進一步有益**維持血糖的穩定**

- **年紀較輕的成人、青少年與兒童**

→ 證據雖較低，但**可能也有助益**

Standards of medical care in diabetes--2017. *Diabetes Care*, 2017. 40(Supplement 1): p. S48-S56.

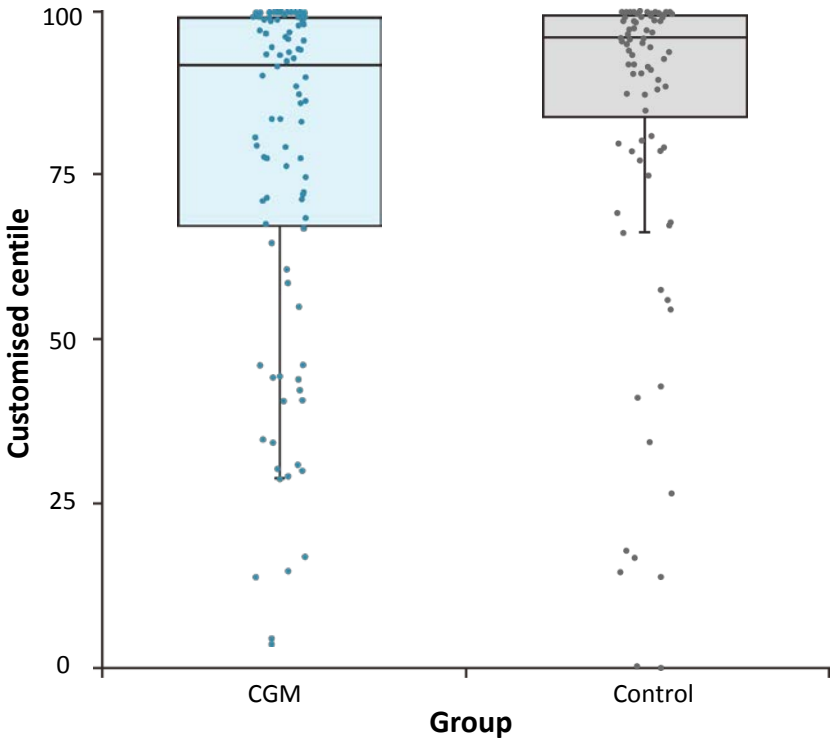
Glycaemic outcome by CGM use according to pregnancy status



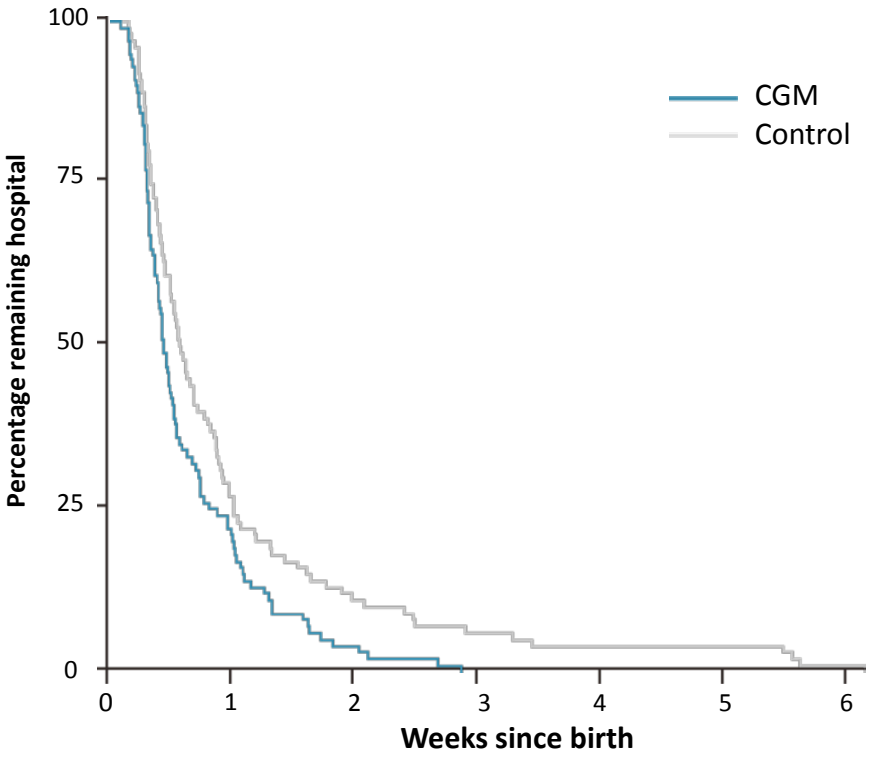
Lancet 2017; 390: 2347–59

Neonatal outcomes of pregnancy by CGM use

Neonatal birthweight



Infants' length of hospital stay from delivery



Lancet 2017; 390: 2347–59

建議以下情形使用連續血糖監測系統

曾發生
嚴重低血糖

不自覺
低血糖者

夜間低血糖

需要頻繁
血糖監測者

血糖水平
波動幅度大

血糖控制不佳，
糖化血色素超過
標準範圍

維持血糖目標
糖化血色素 <7%，
同時減少低血糖發生的風險

妊娠糖尿病患者
或**糖尿病人且**
懷孕中

Real-time CGM in Networking Care for Patients with Diabetes

A better connection to diabetes care

CGM reports

Patient

Care partner

GST

Linked glucose meter

Glucose Sensor

CareLink Personal

Data Display

SMS

CareLink Connect

SMS alerts

Mobile website for remote monitoring

第 1 型糖尿病連續血糖監測健保給付規範

適應症

第一型糖尿病 (領有重大傷病證明)、**新生兒糖尿病**，或因 **Near-total pancreatectomy 所致糖尿病**等個案，且須符合下列任一條件：

(1) 血糖**過度起伏**且最近**六個月兩次**糖化血色數值都**大於 (含) 8%**

(2) **低血糖無感症**

(3) 常有**嚴重低血糖**，須他人協助治療，最近**三個月**有因低血糖曾**至急診診治或住院**

(4) **懷孕**

支付規範

(1) **門診使用**，若為住院使用應事前審查

(2) 一年至多執行**兩次**，且間隔**三個月以上**。若一年執行超過兩次者，須事前審查

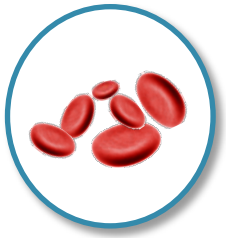
(3) 限**糖尿病共同照護網醫療機構**申報，執行檢查人員和判讀醫師、營養師、衛教師必須參加過有關連續血糖監測之**訓練課程**

糖化白蛋白

Glycated albumin (GA)

Glycated Albumin (GA)

A **ketoamine** formed via non-enzymatic glycation reaction of serum albumin



Not affected by changes in lifespan of **erythrocytes**

Furusyo N et al., Biochim Biophys Acta 2013;
Koga M et al., Endocr J 2010; Zheng CM et al., CCA 2012

糖化白蛋白 Glycated Albumin (GA)
使用時機

在紅血球或血紅蛋白有一些變化或疾病

- 溶血或剛接受過輸血的人
- 有缺鐵性貧血的人
- 鐮刀型貧血帶原者 (sickle cell trait)
- 血色素 HbF 比例比較高的人

慢性腎病變與洗腎病人

由於紅血球的壽命減短，
加上血中的 carbamylated hemoglobin 的干擾、
使用紅血球生成素 EPO 等狀況

懷孕

因為相對性的缺鐵性貧血與血量增加 (volume expansion) 等狀況

Measurement of GA

Step 1

Glycated amino acid elimination reaction

Glycated amino acid —(Ketoamine oxidase)→ Glucosone + amino acid

Step 2

Glycated amino acid assay for glycated albumin

Glycated albumin —(Peroxidase)→ Glycated amino acid

Glycated amino acid + H_2O —(Ketoamine oxidase)→ Glucosone + amino acid

O_2 + H_2O_2 + Chromogens —(Peroxidase)→ Color + H_2O

Step 3

Albumin assay

Albumin + Bromoclezolpurple → color

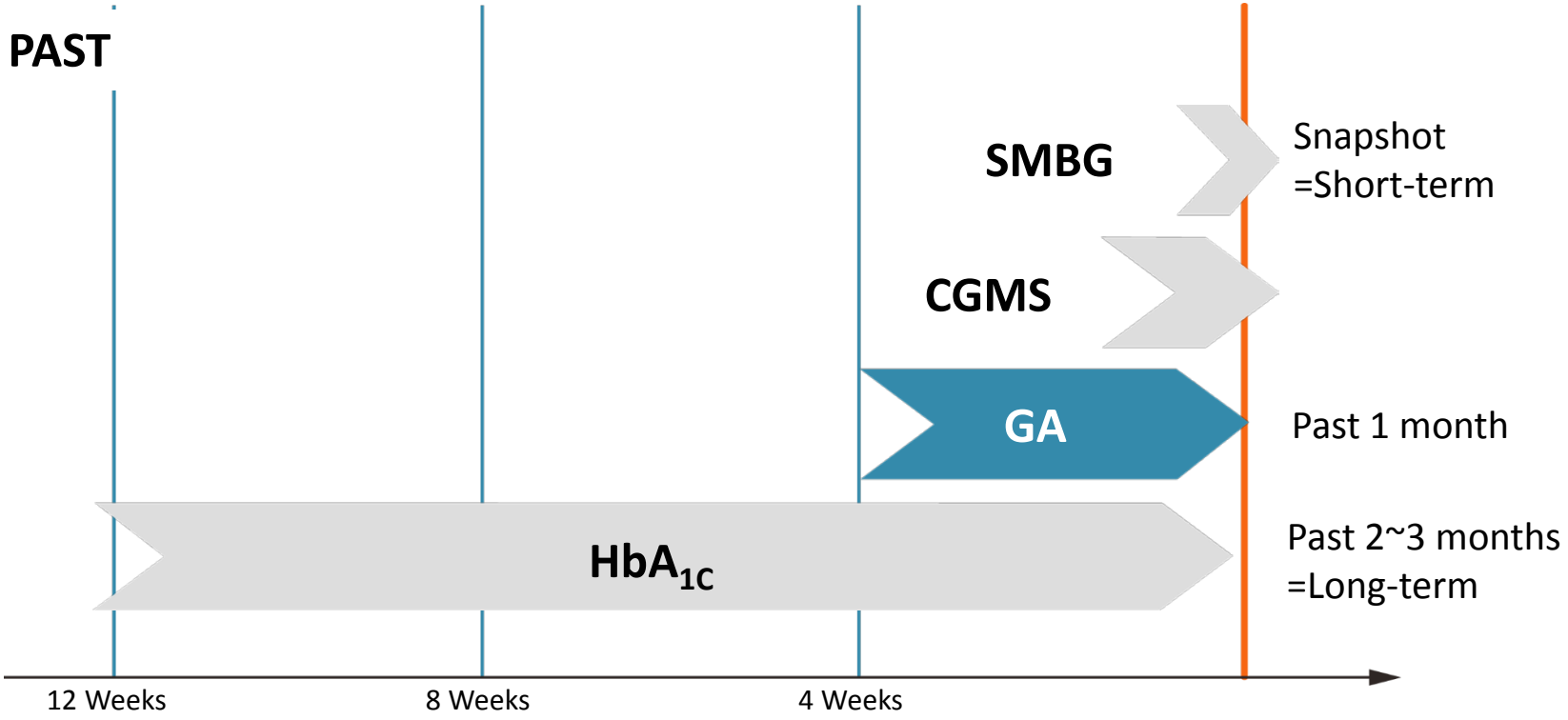
Step 4

Calculation of percentage of glycated albumin in total albumin

GA value:
GA concentration/albumin concentration x 100

Kouzauma T et al., Clin Chim Acta 2004
Asahi Kasei, TUNYEN

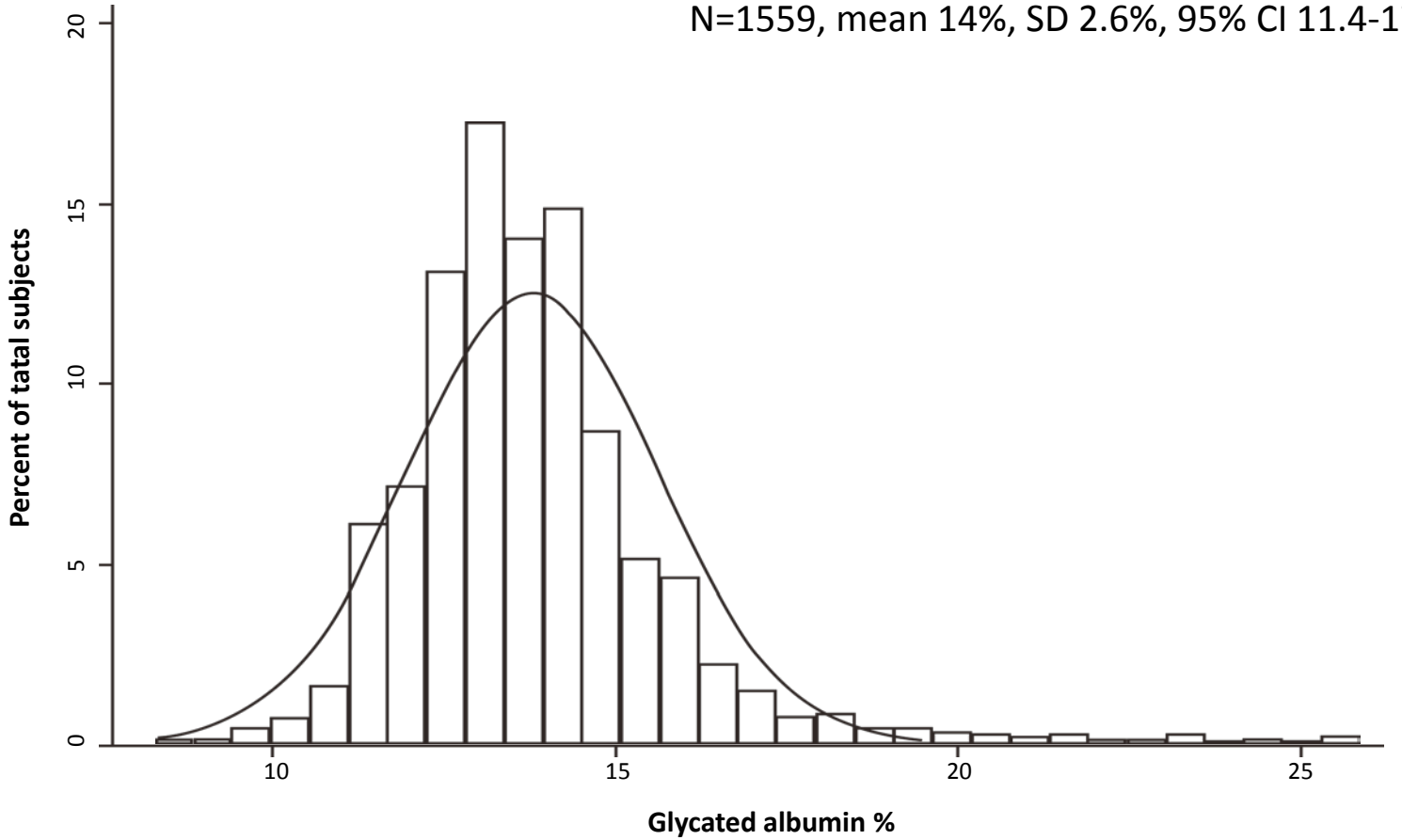
GA, HbA_{1C} and blood glucose



GA Reflects mean glycemic levels over 2-3 weeks.
GA can fill the time gap between SMBG and A1C at approximately 1 month.

Serum GA Distributed Normally

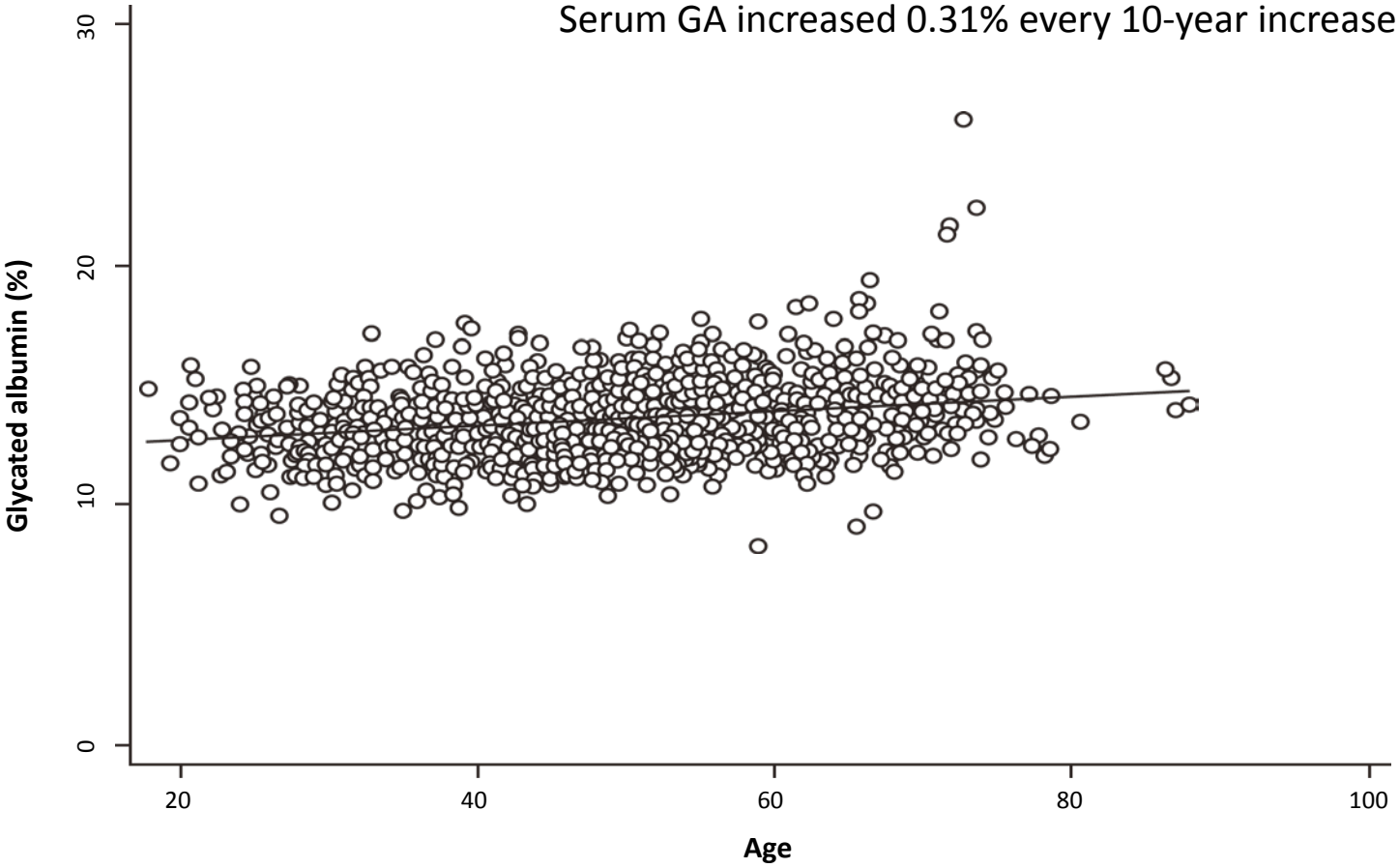
N=1559, mean 14%, SD 2.6%, 95% CI 11.4-17.1%



WC Wu & HY Li et al., PLOS One 2016

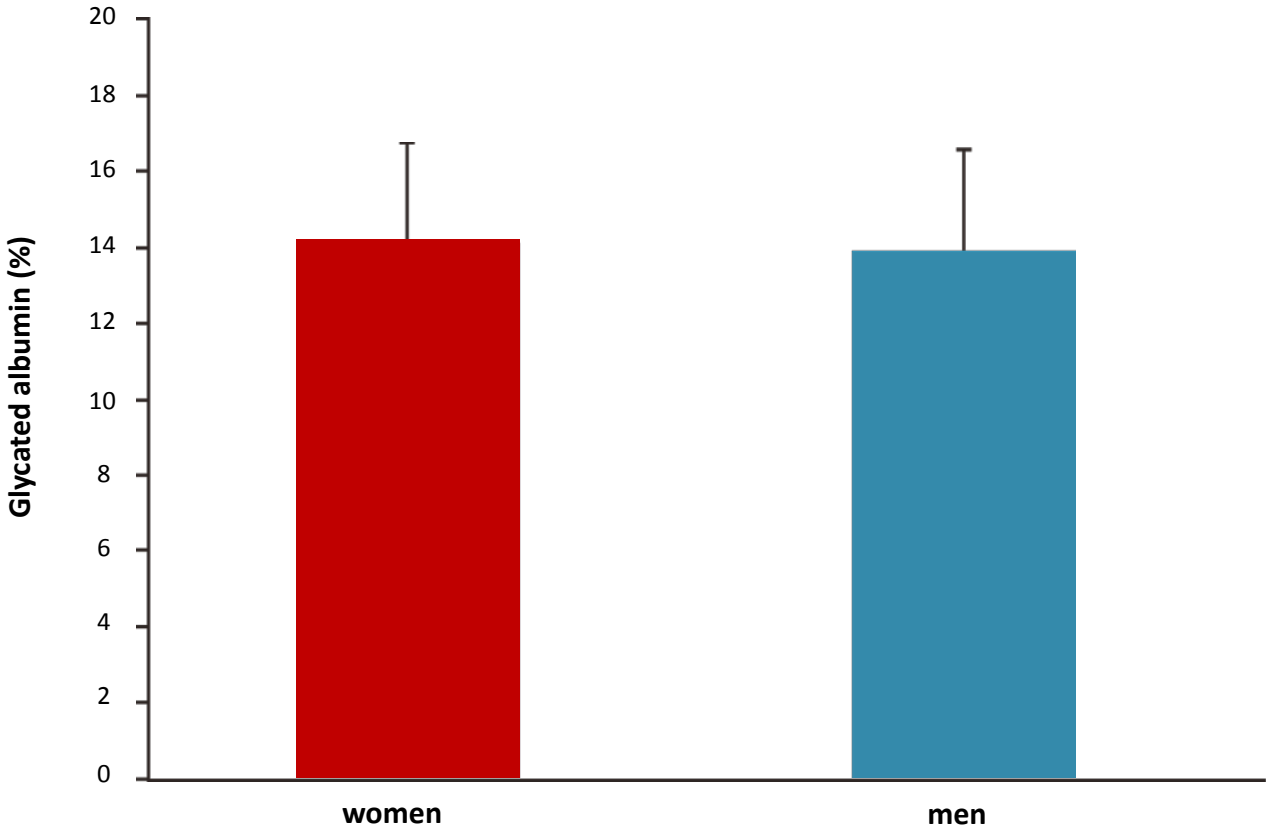
Serum GA Increased by Age in Subjects without Diabetes

Serum GA increased 0.31% every 10-year increase in age.



WC Wu & HY Li et al., PLOS One 2016

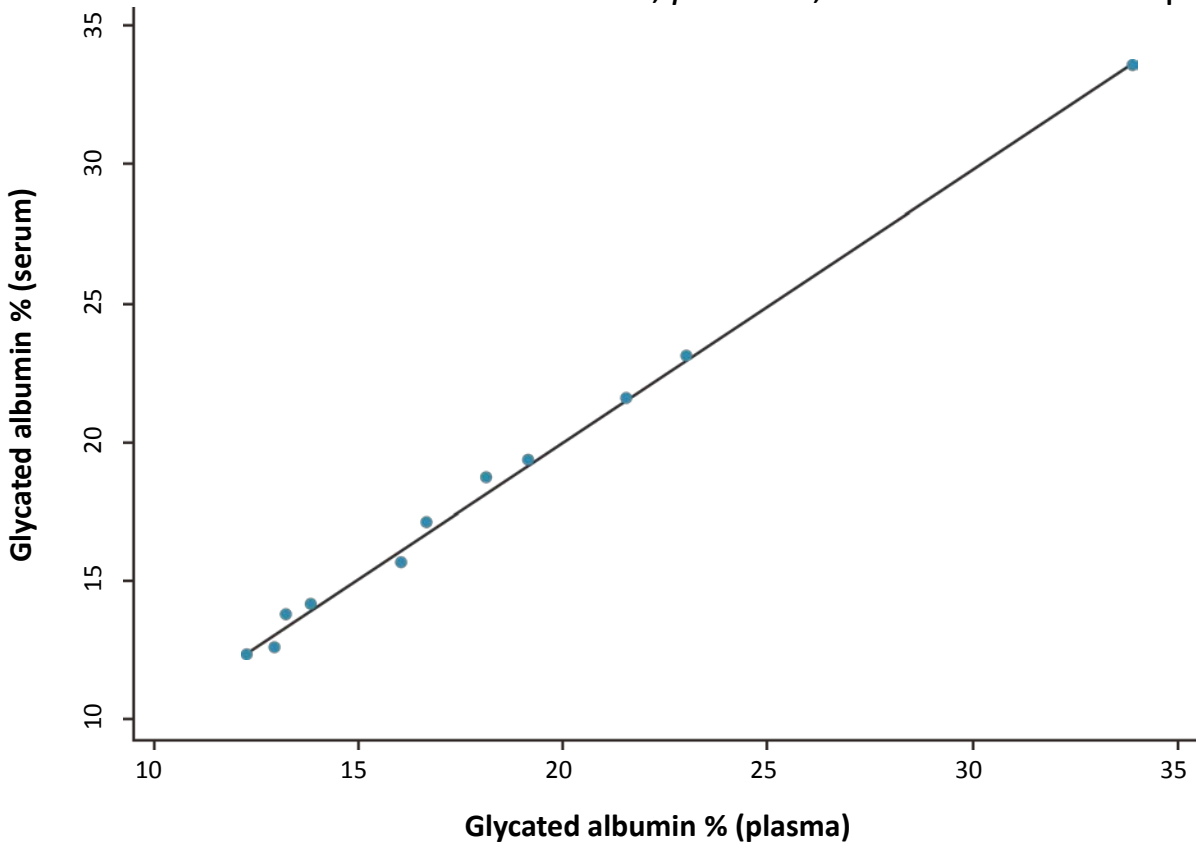
Serum GA is Similar in Both Genders



WC Wu & HY Li et al., PLOS One 2016

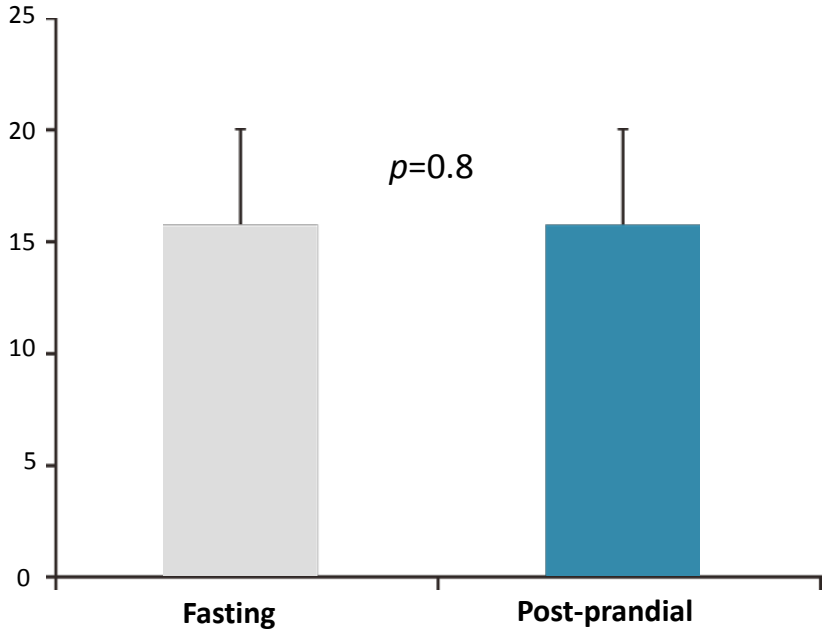
Ways of Sample Collection Did not Affect GA Value

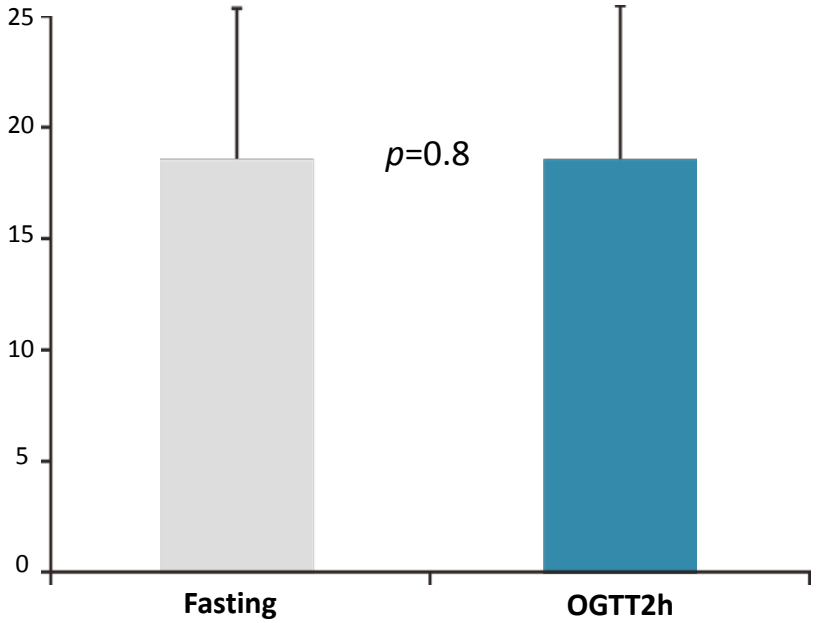
r=0.9987, p<0.001, Serum GA = 0.98 * plasma GA + 0.29



WC Wu & HY Li et al., PLOS One 2016

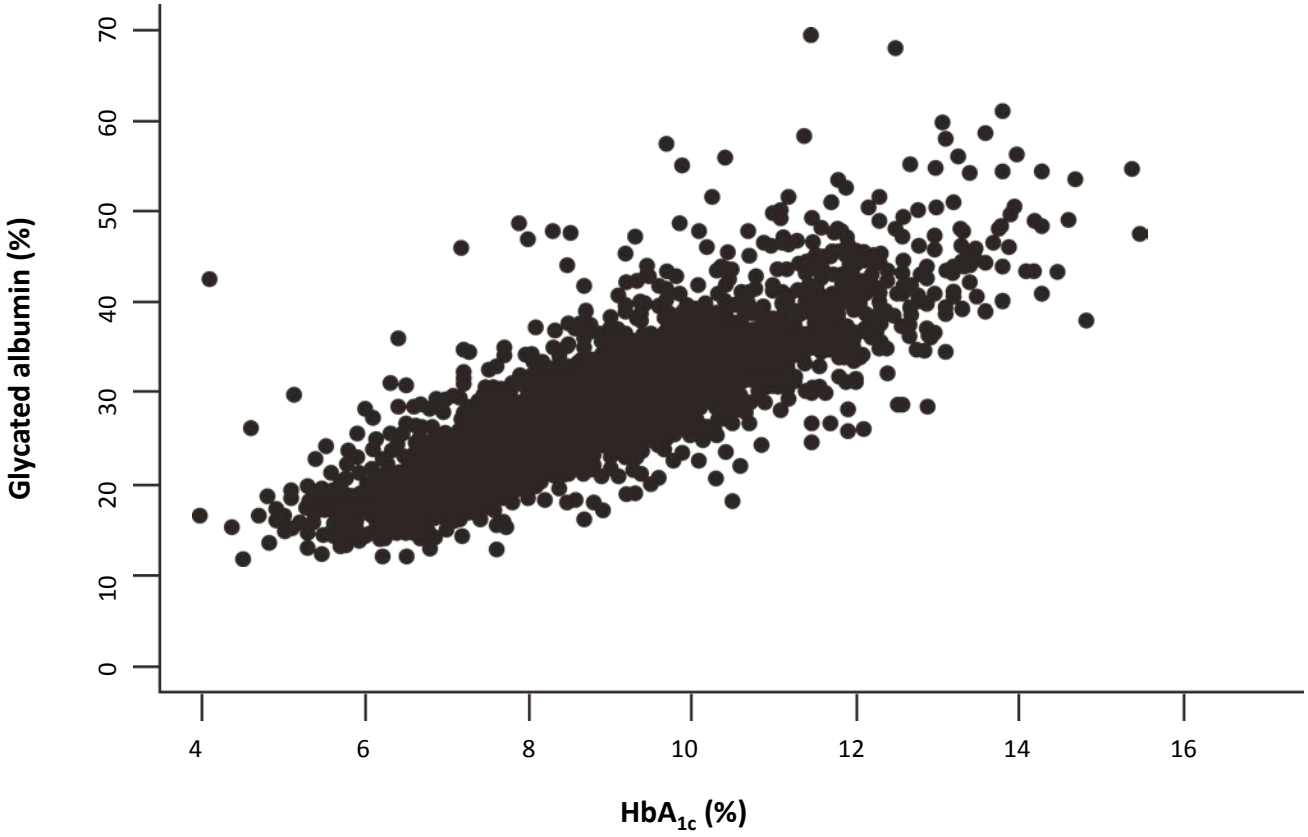
Food or Glucose Intake Did not Affect Serum GA Value





WC Wu & HY Li et al., PLOS One 2016

In DM Patients with Stable Glycemia



Nathan D et al., Diabetes 2014

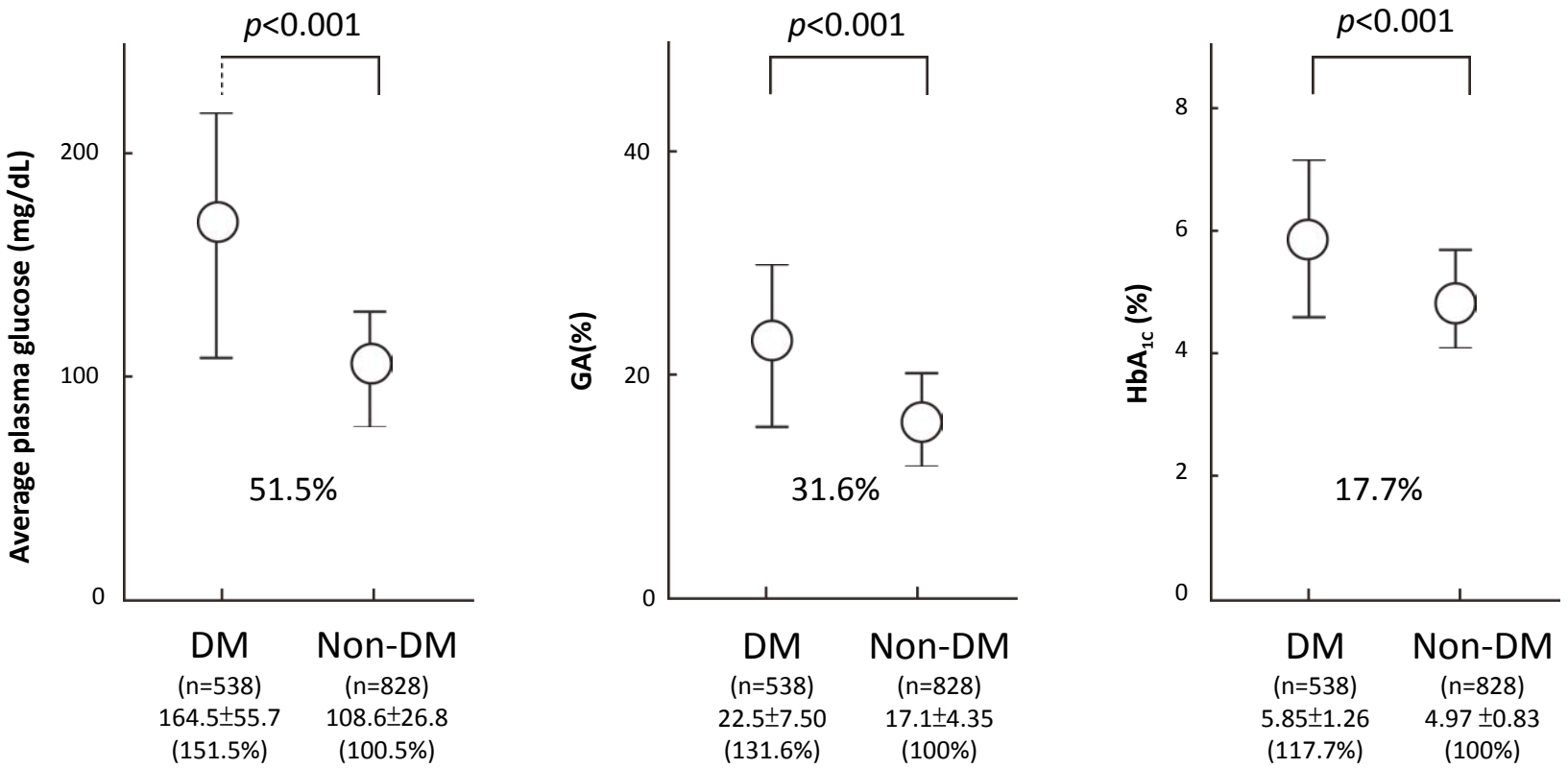
GA 的臨床應用

$$\text{糖化白蛋白 GA} = (\text{糖化血色素 } HbA_{1c} - 2.015) \times 4$$

糖化血色素 (HbA_{1c})		糖化白蛋白 (GA)
7%	=	20%

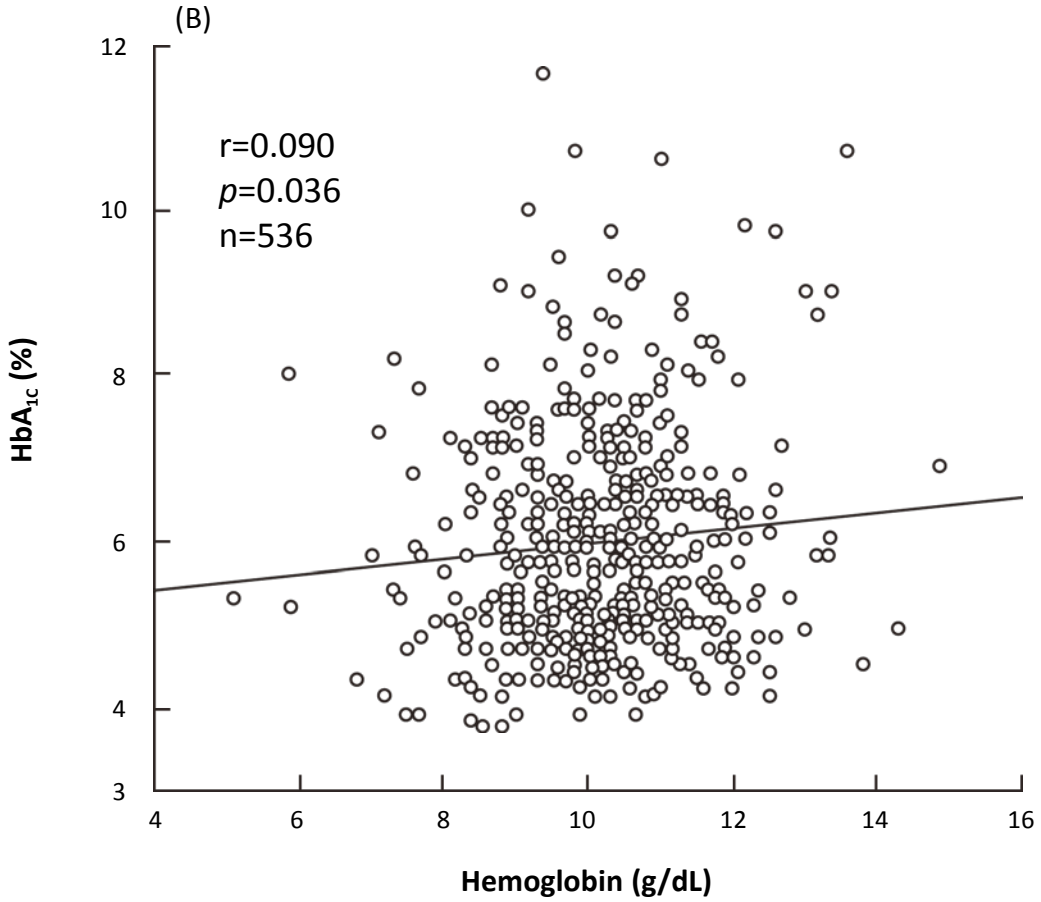
1. Tahara, Y., Analysis of the method for conversion between levels of HbA1c and glycated albumin by linear regression analysis using a measurement error model. *Diabetes Res Clin Pract*, 2009. 84(3): p. 224-9. 149.
2. Kashiwagi, A., et al., International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. *J Diabetes Investig*, 2012. 3(1): p. 39-40.

Larger Difference Shown by GA than HbA1c in Hemodialysis Patients



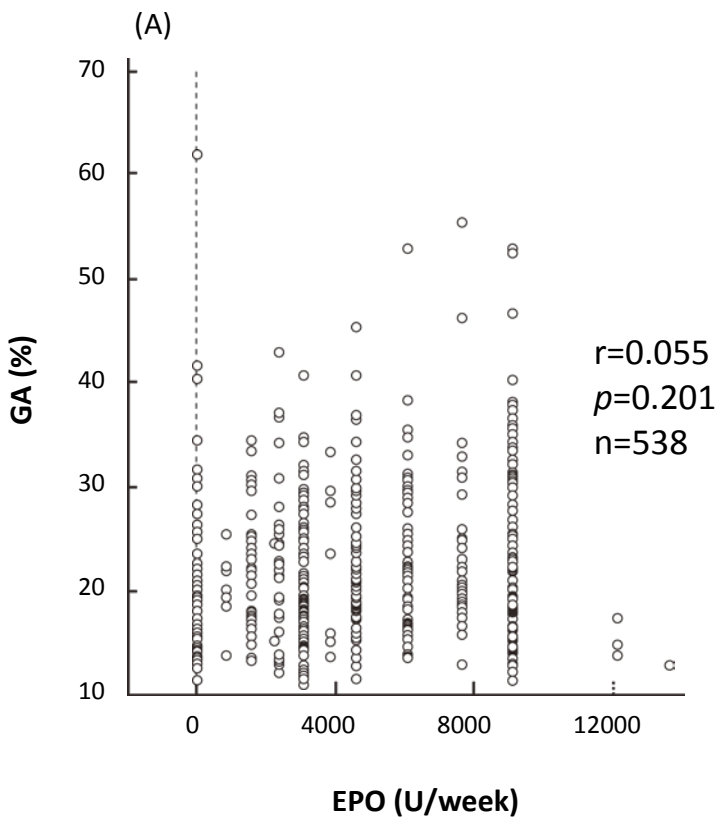
J Am Soc Nephrol 2007

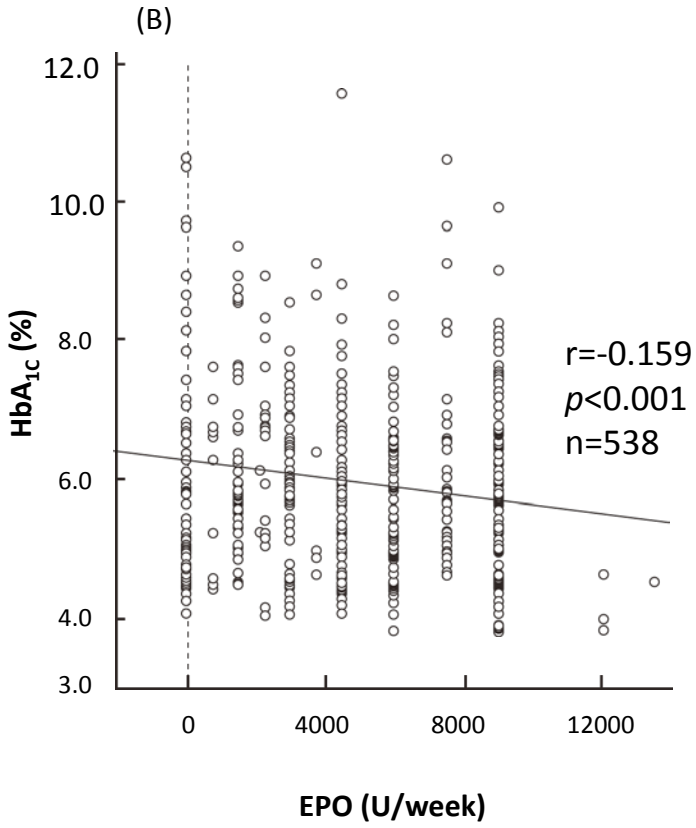
GA is Not Affected by Hemoglobin



J Am Soc Nephrol 2007

GA is Not Affected by EPO



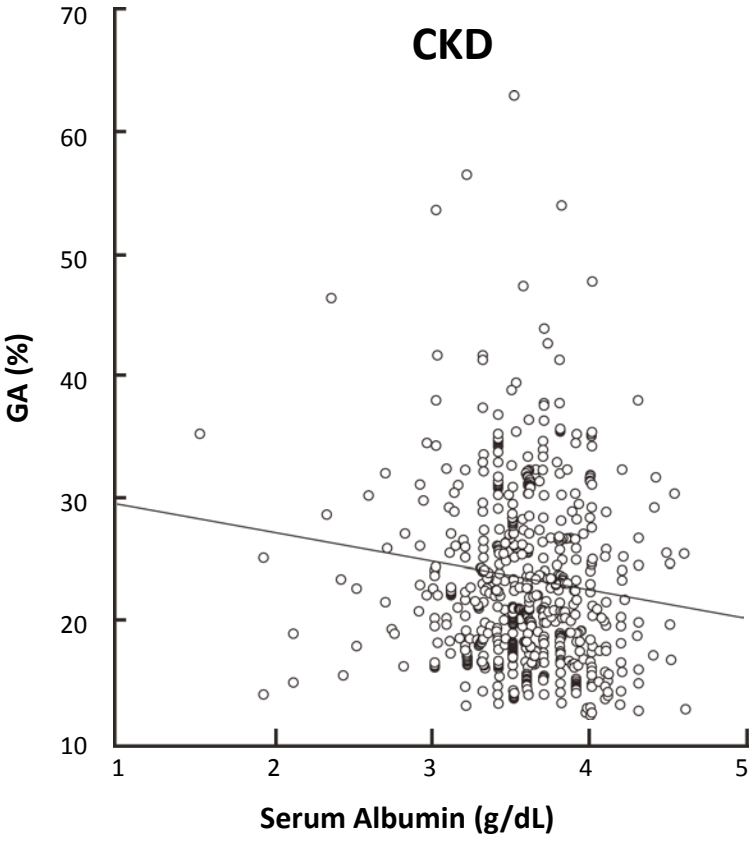


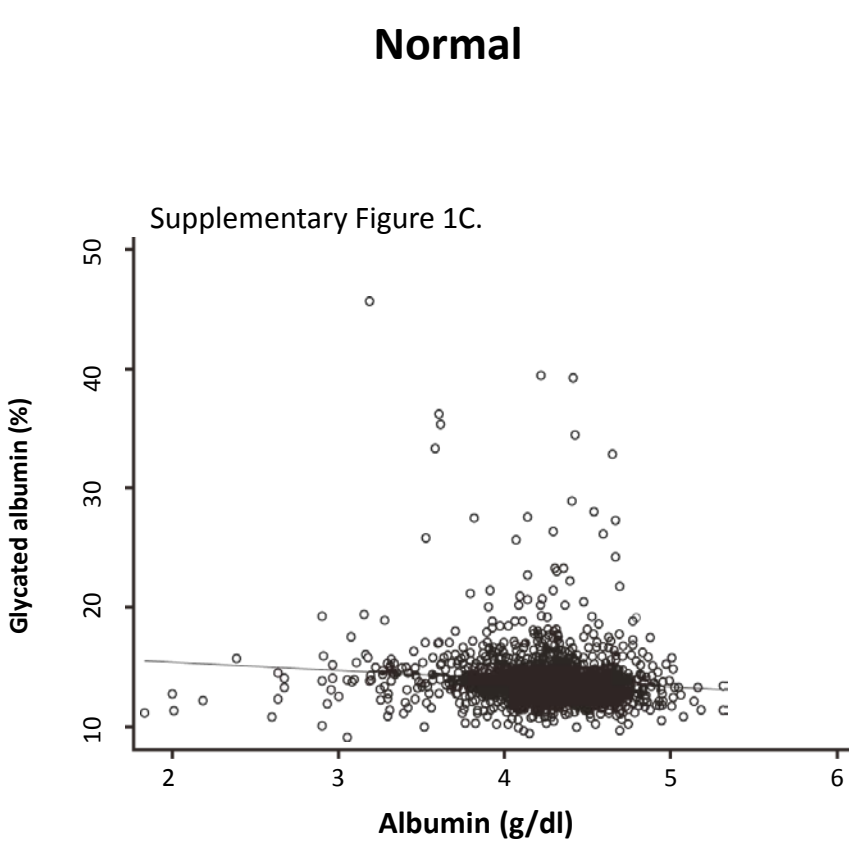
J Am Soc Nephrol 2007

GA is Associated with Serum Albumin

Serum GA decreased 0.32% every 1 g/dl increase in serum albumin.

(A)





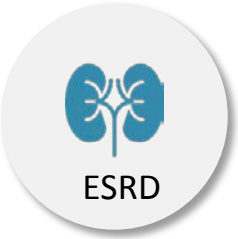
J Am Soc Nephrol 2007
WC Wu & HY Li et al., PLOS One 2016

GA 的臨床應用

1

HbA_{1c} 不準時，
取代 HbA_{1c} 成為中期的血糖指標

例如：



2

用於 monitor glycemic control

A Decrease in GA is Associated with Reduced Retinopathy in DCCT/EDIC

Association of measures of glycemia individually and in combination with the risk of **sustained three-step progression of retinopathy** among 145 case vs. 186 control subjects in weighted Cox proportional hazards models*

Model covariate(s)	% change in risk for a 10% higher value (95% CI)	*p*	Model χ^2 (df)
Model 1: HbA_{1c}	67.8 (48.9-89.0)	< 0.0001	129.2 (2)
Model 2: GA	**49.1 (35.8-63.7)**	**< 0.0001**	**128.5 (2)**
Model 3: MBG	26.3 (18.0-35.2)	< 0.0001	87.1 (2)

Nathan D et al., Diabetes 2014

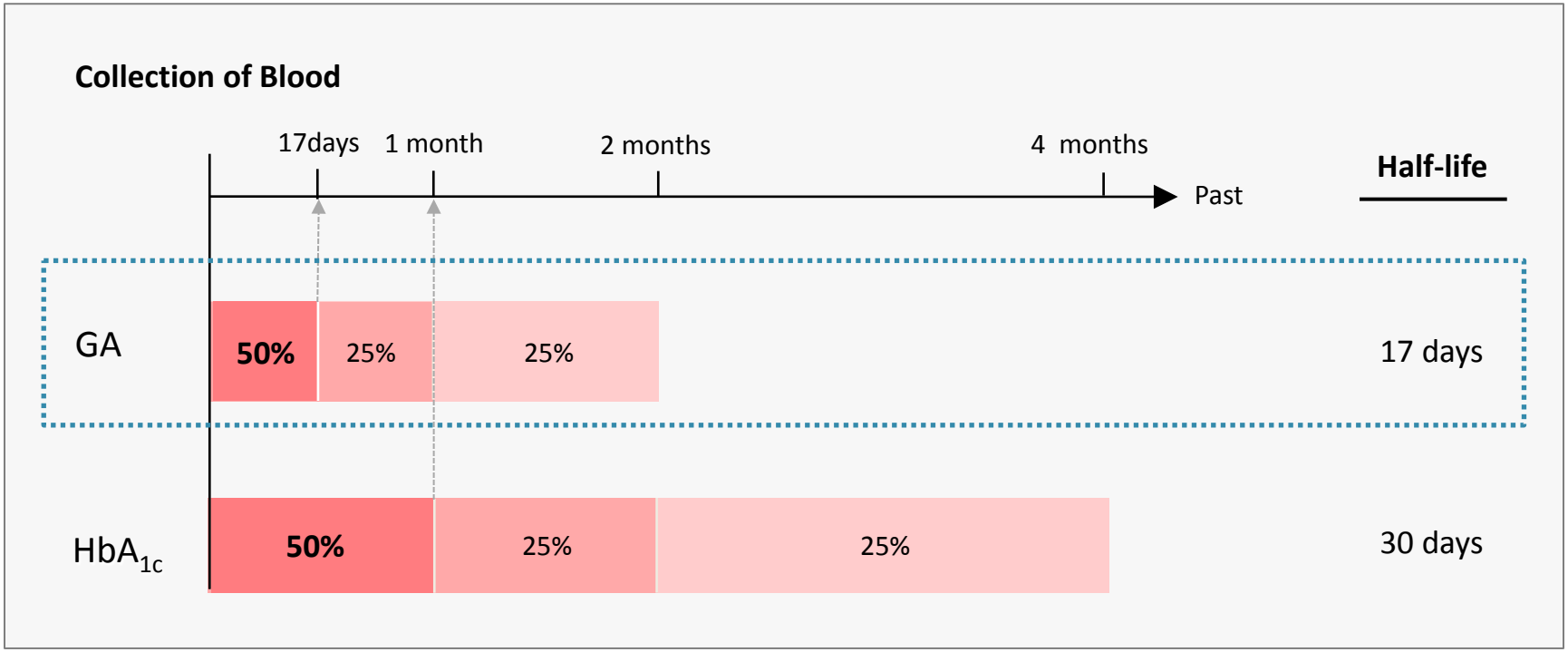
A Decrease in GA is Associated with Reduced Nephropathy in DCCT/EDIC

Association of measures of glycemia individually and in combination with the risk of **microalbuminuria (AER ≥ 40 mg/24 h) or worse** among 145 case vs. 184 control subjects in weighted Cox proportional hazards models*

Model covariate(s)	% change in risk for a 10% higher value (95% CI)	*p*	Model χ^2 (df)
Model 1: HbA_{1c}	15.7 (4.0-28.8)	< 0.0076	17.8 (2)
Model 2: GA	**13.5 (4.7-23.1)**	**< 0.0021**	**20.8 (2)**
Model 3: MBG	7.6 (1.7-13.9)	< 0.0116	15.3 (2)

Nathan D et al., Diabetes 2014

Contribution of Past Blood Glucose to GA Values and HbA_{1c} Values



GA values reflect a more recent "picture" of blood glucose status than HbA_{1c} values.

K. Shima, The Univ. of Tokushima School of Medicine

Drawbacks of GA

影響蛋白質代謝的疾病

腎病症候群

甲狀腺疾病

肝硬化

影響

糖化白蛋白**無法準確反應 2-4 週**的平均血糖值

Dozio E et al., Endocrine 2016

健保給付糖化白蛋白的測定

適應症

糖尿病合併**慢性腎病變**

因**血液疾病**導致 HbA_{1c} 無法反映血糖控制者

懷孕糖尿病患及**妊娠糖尿病**

血糖數值顯示控制不良，但 **HbA_{1c} 數值仍於良好範圍**者

禁忌症

血中白蛋白濃度 < 3g/dL

支付規範

不得同時申報編號09006C

一年限申報**四次**

懷孕糖尿病患及妊娠糖尿病患，一年限申報**六次**

結論

24 連續血糖監測 (CGM)

CGM 用於糖尿病的診斷與治療

即時性 CGM 用於血糖控制，可

- 降低**糖化血色素**
- 減少**低血糖**發生頻率

糖化白蛋白 (GA)

代表 2-4 週內的血糖值

GA 在HbA_{1c}不準時 ，取代其角色，例如：

- 洗腎患者
- 孕婦
- 血液疾病

GA 與 glucose、 HbA_{1c}一起運用，
作為 2-4 週內血糖控制的指標，例如

- 新診斷病人
- 住院病人

中華民國糖尿病學會