Kantonsspital St.Gallen

Endokrinologie Diabetologie

Universität Zürich[UZH]

Epidemiology of Hemoglobin A1c Use in Screening and Diagnosis

20th Post ADA-/Endocrine-Symposium

16. September 2021

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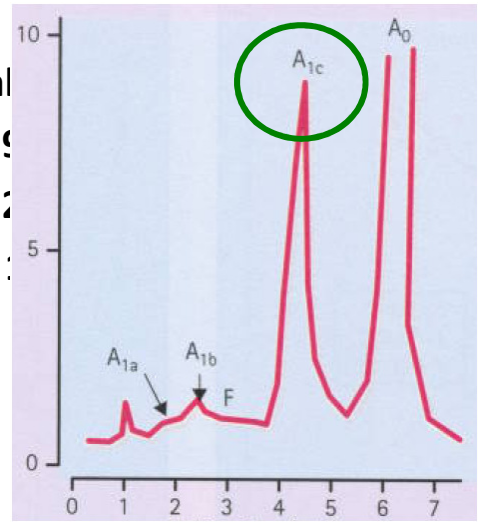
Chefarzt Allgemeine Innere Medizin/Hausarztmedizin, KSSG

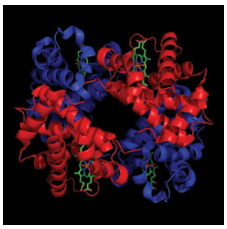
Agenda

- **Introduction**
  - HbA1c – what's that?
- **HbA1c and longterm outcomes**
- **Use of HbA1c for diagnosis of diabetes**
- **Comparison of CGMS and HbA1c**

HbA1c – Measurement

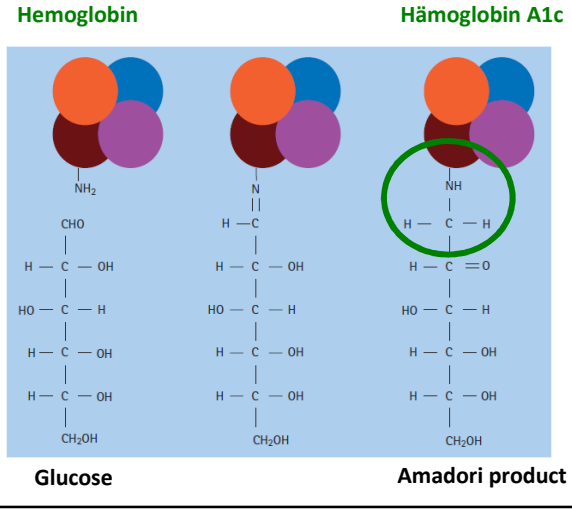
Normal
HbA1: 9
HbA2: 2
HbF: 1





HbA1c – Measurement

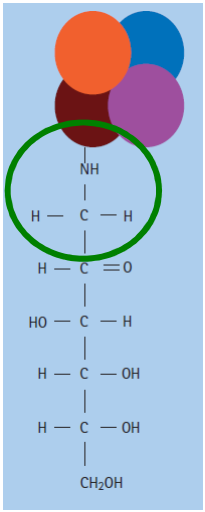
Non-enzymatic glycation of hemoglobin



HbA1c – Measurement

Non-enzymatic glycation of hemoglobin

- HbA1c-level dependent on
  - Life span of erythrocytes
  - Blood glucose concentrations
- Retrospective indicator of the average glucose concentration over the previous 6 – 8 (10) weeks
- Different methods to measure
  - Differentiation between glycated and non-glycated hemoglobin (e.g. HPLC)
  - Structural differences (e.g. Immunoassay)
- National Glycohemoglobin Standardization Program (NGSAP)
- IFFC Standardization (mmol/mol)



Point-of-Care HbA1c

- Methods NGSP-certified and standardized to the DCCT assay
- An increasing number of POC-HbA1c are available
- POC-A1C assays may be more generally applied for assessment of glycemic control in the clinic.
- However, only those point-of-care A1C assays that are also cleared by the FDA for use in the diagnosis of diabetes should be used for this purpose.

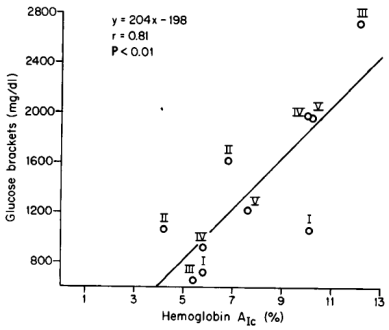
Diabetes Care 2021;44(Suppl. 1):S15–S33

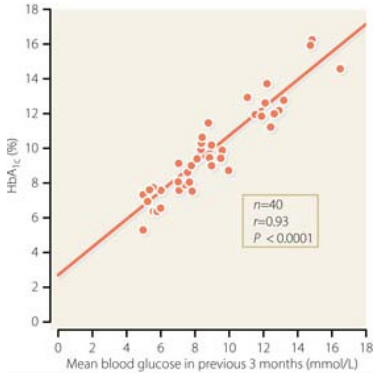
HbA1c as monitor glucose control

Vol. 295 No. 8 GLUCOSE REGULATION AND Hb A_{Ic} IN DIABETES — KOENIG ET AL. 417

CORRELATION OF GLUCOSE REGULATION AND HEMOGLOBIN A_{Ic} IN DIABETES MELLITUS

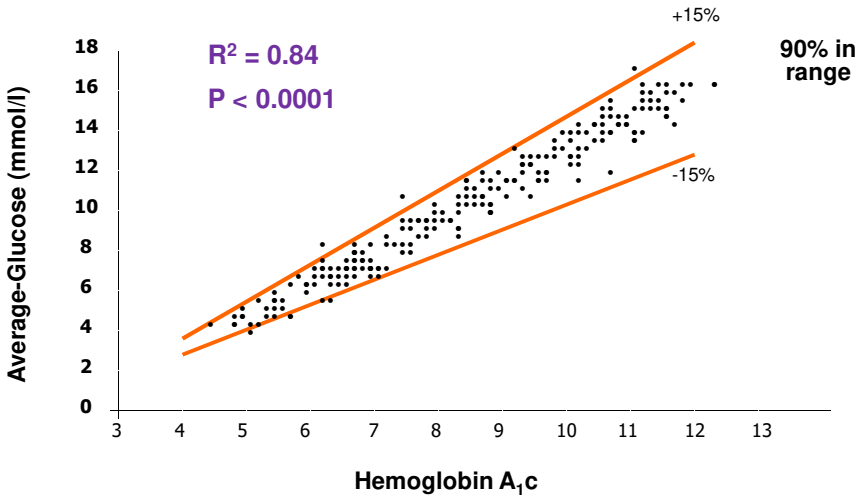
RONALD J. KOENIG, B.S., CHARLES M. PETERSON, M.D., ROBERT L. JONES, M.D., CHRISTOPHER SAUDEK, M.D., MARK LEHRMAN, M.D., AND ANTHONY CERAMI, PH.D.





Koenig R.J et al. ***N Engl J Med.*** 1976; 295:417-420
Paisey et al. ***Diabetelogia*** 1980; 19:31-34

Correlation average glucose and HbA1c



Nathan D.M. et al. ***Diabetes Care*** 2008; 31:1473–1478

NGSP and IFCC HbA1c and e-Average Glucose (mmol/L & mg/dL)

NGSP HbA1c (%)	IFCC HbA1c (mmol/mol)	eAG (mg/dL)	eAG (mmol/l)
5.0	31	97	5.4
6.0	42	126	7.0
7.0	53	154	8.6
8.0	64	183	10.2
9.0	75	212	11.8
10.0	86	240	13.4
11.0	97	269	14.9
12.0	108	298	16.5

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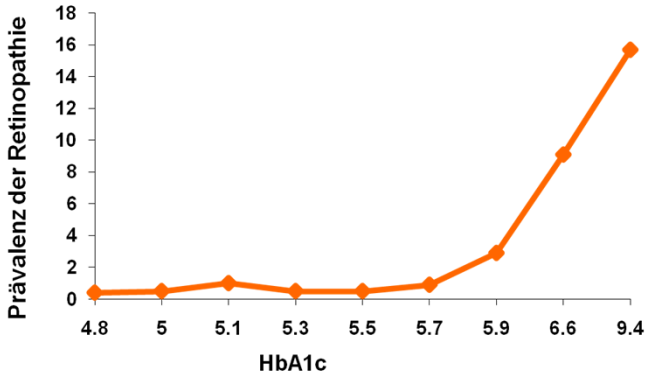
HbA1c and longterm outcomes

Retinopathie in Abhängigkeit vom HbA1c



McCance et al. ***BMJ*** 308:1323-1328; 1994.

HbA1c and cardiovascular outcomes in persons without a prior diagnosis of diabetes

Atherosclerosis Risk in Communities – ARIC Study

Fifteen years of follow-up for:

- **Incident diagnosed diabetes**
- **Coronary heart disease, Ischemic stroke, All-cause mortality**

The NEW ENGLAND JOURNAL of MEDICINE

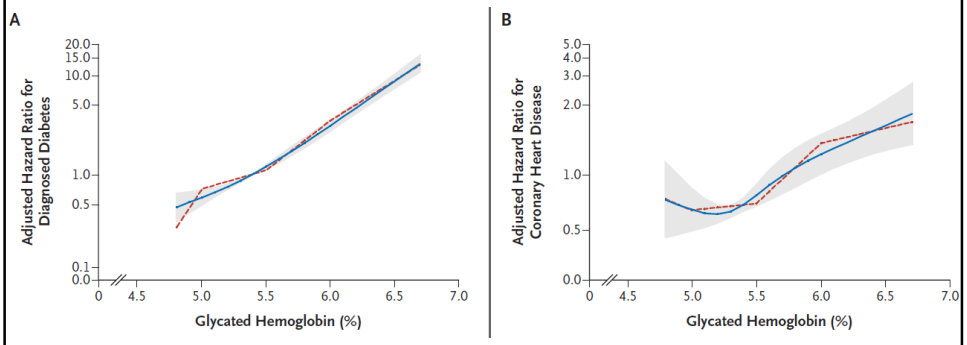
ORIGINAL ARTICLE

Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults

Elizabeth Selvin, Ph.D., M.P.H., Michael W. Steffes, M.D., Ph.D., Hong Zhu, B.S., Kunihiro Matsushita, M.D., Ph.D., Lynne Wagenknecht, Dr.P.H., James Pankow, Ph.D., M.P.H., Josef Coresh, M.D., Ph.D., and Frederick L. Brancati, M.D., M.H.S.

HbA1c and cardiovascular outcomes in persons without a prior diagnosis of diabetes

ARIC



Selvin E. et al. ***N Engl J Med.*** 2010;362:800-11

HbA1c and cardiovascular outcomes in persons without a prior diagnosis of diabetes

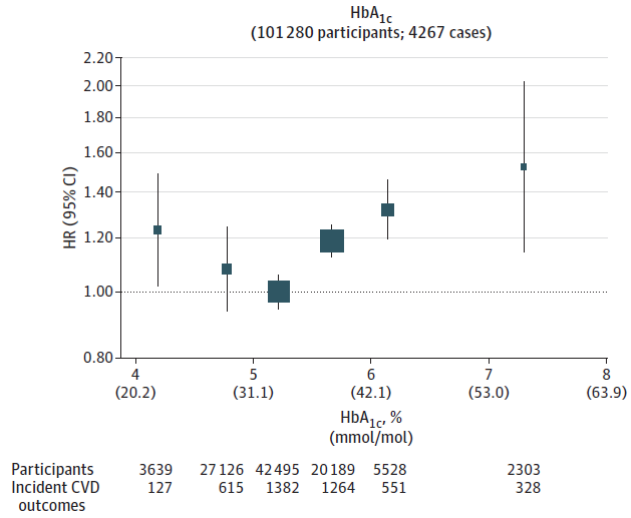
ARIC

Results and Implications

- Persons with HbA1c > 6% are at high risk for the development of diabetes, cardiovascular outcomes and death
- HbA1c is superior to fasting glucose for assessment of long-term prognosis
- Established the link between HbA1c and future vascular risk in an initally non-diabetic population

Selvin E. et al. ***N Engl J Med.*** 2010;362:800-11

HbA1c measurement and CVD Prediction

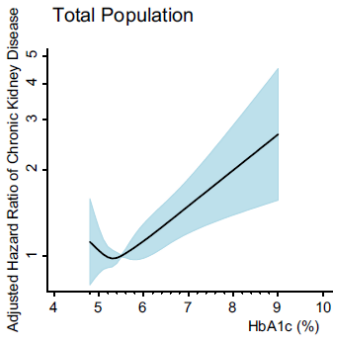


The Emerging Risk Factors Collaboration. ***JAMA.*** 2014;311(12):1225-1233

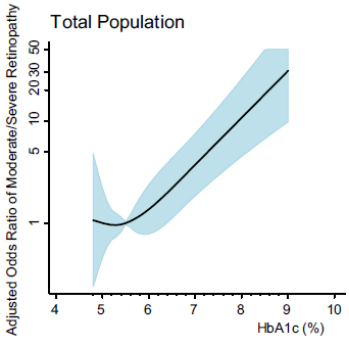
HbA1c and the Risk of Kidney Disease and Retinopathy in Adults with and without Diabetes

ARIC

Kidney Disease



Retinopathy



ARIC study results provide evidence supporting the use of HbA1c as a diagnostic test

Selvin E. et al. ***Diabetes*** 2011;60:800-11

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Use of HbA1c for diagnosis of diabetes

Advantages of HbA1c for Diagnosis of Diabetes

- **Much less biologic variability** (vs fasting or 2-hr glucose)
- **Better index of overall glycemic exposure**
- **Better or as well-standardized as glucose**
- **No need for fasting or timed samples**
- **Relatively unaffected by acute factors**
- **Already used to guide and adjust treatment**
- **Associated with major clinical outcomes incl. death; with stronger associations than fasting glucose**

2010 – Criteria for the Diagnosis of Diabetes

HbA1c and Glucose recommended for Diagnosis

Timepoint	Glucose-Cutoff
Fasting*	≥ 7.0 mmol/l
2 h glucose during an OGTT (75g Glucose p.o.)*	≥ 11.1 mmol/l
Random plasma glucose in a patient with classic symptoms of hyperglycemia	≥ 11.1 mmol/l
Regardless of a specific timepoint	**HbA1c - Cutoff**
HbA1c*	≥ 6.5%**

* In the absence of unequivocal hyperglycemia, measures should be confirmed by repeat testing.
** Methods NGSP-certified and standardized to the DCCT assay.

Diagnosis and classification of diabetes mellitus. ***Diabetes Care*** 2010;33 Suppl 1:S62-69.

«Caveats» in the use of HbA1c for diagnosis

- **Assay interferences**
  - **Some Hb traits interfere with interpretation of HbA1c assys, but not true for the majority of Hb variants**
- **Some conditions interfere with HbA1c test results**
  - **Altered red cell turnover (e.g. hemolytic anemia, iron deficiency)**
- **Expense and availability in some areas**
- **Higher levels of HbA1c in blacks and other ethnicities**
- **Low sensitivity for diabetes diagnosis**
  - **More than 50% of diabetes diagnosis might be missed**

Herman WH et al. Teaching an old dog new tricks, ***Ann Intern Med*** 2010;152:815-817

«Controversy» of racial differences in HbA1c

- **The small, systematic difference in HbA1c in blacks vs whites means that, at current cut-points, HbA1c is a slightly more sensitive test (consistent with higher risk of complications)**
- **The strong link between HbA1c and complications in both blacks and whites ➡ critical clinical importance for use of HbA1c**
- **Race is not a precise construct; it is more a different genetic background that influence the glycation of HbA1c.**

Selvin E, ***Diabetes Care 2016;*** 39 (8): 1462-1467

HbA1c show a low sensitivity for diabetes diagnosis compared to glucose measurements

Sensitivität und Spezifität des HbA1c für die Diagno… basierend auf Nüchternglucosewerten
(Daten aus NHANES 1999-2004)

HbA1c	Sensiti…	…zifität (%)
5.6%		80.3
6.1%		98.0
6.5%	**…4.3**	**99.6**
	25.3	99.9

Diagnostik mit Plasma-Glucose-Bestimmung ergänzen!

*Saudek CD, Herman WH et al., **J Clin Endocrinol Metab** 2008;93: 2447-2453*

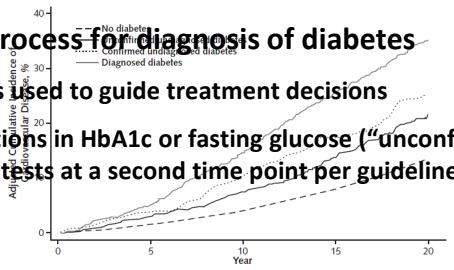
HbA1c *and* Fasting Glucose together for diagnosis

Single-Sample Confirmatory Definition of Diabetes based on HbA1c and Glucose

- **Until 2019, repeat testing of the *same* test in a new blood sample at a *second time point***
  - **Reduce the possibility of a false-positive diagnosis**
  - **But requires a second visit and a second blood draw**
- **It is common two different tests to be measured in the same blood sample (e.g. HbA1c and fasting glucose)**
- **Unclear if a combination of HbA1c & fasting glucose at a single time point provides adequate confirmation for diagnosis DM.**

Single-sample confirmatory testing for undiagnosed diabetes

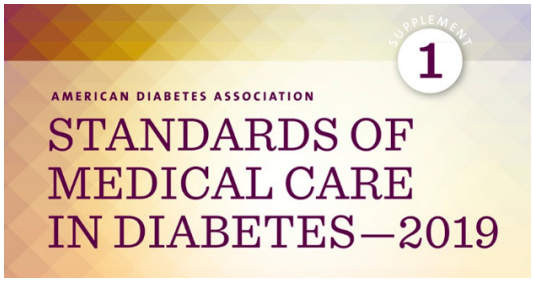
- **Two tests (HbA1c and fasting glucose) from the same blood sample provide adequate confirmation for diagnosis (39%)**
  - **High positive predictive value for future diagnosis of diabetes**
  - **Strongly associated with complications (heart & kidney disease, death)**
- **Streamlined process for diagnosis of diabetes**
  - **HbA1c test is used to guide treatment decisions**
  - **Single elevations in HbA1c or fasting glucose ("unconfirmed cases") should have tests at a second time point per guidelines**



At risk, *n*					
No diabetes	10 466	9995	9306	8331	7073
Unconfirmed undiagnosed diabetes	515	483	422	356	269
Confirmed undiagnosed diabetes	347	314	272	224	164
Diagnosed diabetes	839	742	594	428	305

Selvin E, ***Ann Int Med 2018;*** 169:156-164

HbA1c *and* Fasting Glucose



American Diabetes Association

- **Unless there is a clear diagnosis (e.g. hyperglycemic crisis), diagnosis requires two abnormal test results.**
- ***HbA1c and fasting glucose measured in a single blood sample provide adequate confirmation for diagnosis of diabetes***
  - **i.e. HbA1c ≥6.5% (≥48 mmol/mol) and fasting glucose (≥ 7mmol/l) in a single blood sample**

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Continuous Glucose Monitoring and HbA1c

- **Calls to "move beyond HbA1c" with CGM**
  - **The "Beyond A1c" movement claims that we should be using CGM to overcome certain limitations of HbA1c.**
  - **There have been calls for CGM to replace HbA1c.**
  - **The aspects of glycemia that are captured by CGM are different than those captured by HbA1c.**

Selvin E, ***Diabetes Care 2016;*** 39 (8): 1462-1467

From those in favor of «moving beyond A1c»

"Numerous studies have shown that there are a wide range of possible mean glucose levels [from CGM] for a given A1C level, meaning that for some patients, A1C may not be a reliable indicator of glucose control."
- J Diabetes Sci Technol. 2019 Jul; 13(4): 614–626.

"… Continuous glucose monitoring (CGM) is a tool which helps clinicians and people with diabetes to overcome the limitations of HbA1c in diabetes management." - Diabetes Ther. 2019 Jun; 10(3): 853–863.

"…ultimately HbA1c will become less important than the glucometrics generated by CGM…" - Journal of Diabetes 11 (2019), 23–31

CGM Mean Glucose not perfectly correlated with HbA1c

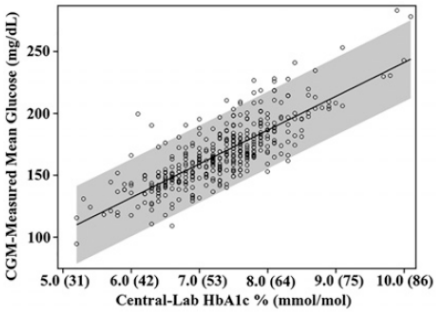
The Fallacy of Average: How Using HbA_{1c} Alone to Assess Glycemic Control Can Be Misleading

Diabetes Care 2017;40:994–999 | https://doi.org/10.2337/dc17-0636

Plot of CGM-mean glucose and HbA1c

Shaded area; 95% prediction interval:

….demonstrating the wide range of mean glucose concentration values that are possible for any HbA1c value.



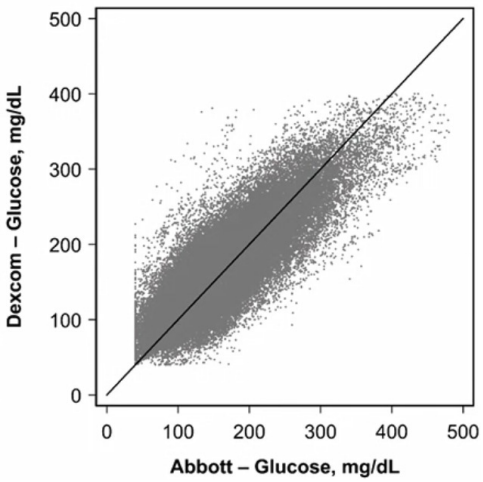
Beck RW, ***Diabetes Care 2017;*** 40: 994-999

Strengths and Limitations of CGM

- **Strengths of CGM**
  - **Latest generation of devices are factory-calibrated** (no fingerstick)
  - **Measurements of interstitial glucose every minute or every few minutes**
  - **Can be used to detect short-term patterns in glucose (hypoglycemia, variability, time in range etc.)**
  - **Particularly useful in type 1 diabetes to keep glucose "in range"**
- **Limitations of CGM**
  - **Expensive**
  - **Concordance with venous (lab) glucose is only moderate** (κ~ 0.55)
  - **Poor accuracy at low glucose values**
  - **Variability within and across sensors**
  - **Not linked to long-term outcomes**
  - **Can be "too much information" for some patients**

CGM Glucose Measures NOT perfectly correlated across leading devices (paired within 5 min)

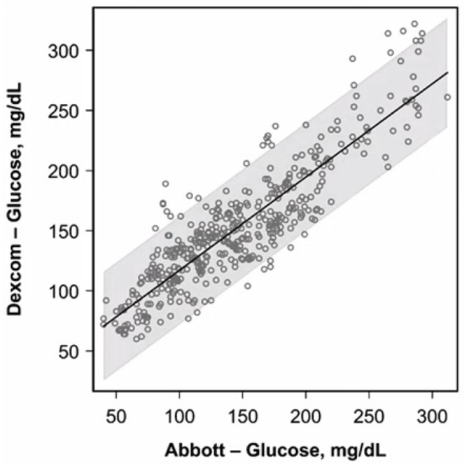
- N=155 adults with DM 2
- Participants wore two CGMs
- 2-week average
- All paired data within ± 5-min time difference (142'812 pairs)
- Mean difference in time of reading 1.4 min, SD 1.0 min



Selvin E, ***unpublishde data***

CGM Glucose Measures NOT perfectly correlated across leading devices (exactly same time)

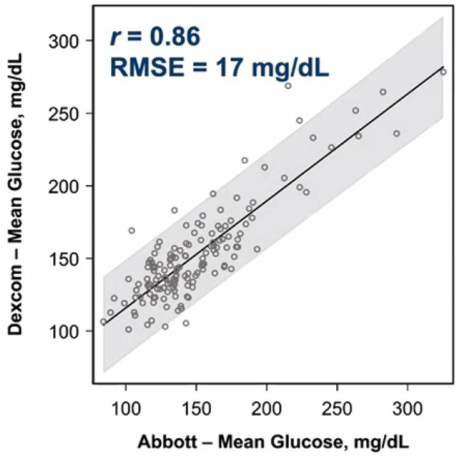
- Matched pairs, glucose readings at exact the same time, n=441 pairs from 19 participants
- 2-weeks of data
- 95% prediction interval (ignores correlation data)



Selvin E, ***unpublishde data***

CGM *Mean Glucose* NOT perfectly correlated across leading devices

- N=149 adults with DM 2
- Mean glucose from two different CGM sensors
- ~1344 Abbott readings /pers
- ~4032 Dexcom reading /pers
- 2-weeks of data
- 95% prediction interval



Selvin E, ***unpublishde data***

The «Beyond A1c Movement» is a false Dichotomy

- HbA1c is central to management and diagnosis of DM
- HbA1c has clear clinical utility and is *strongly* linked to clinical outcomes

- CGM is an expensive and emerging technology
- CGM is not linked to hard clinical outcomes
- CGM data in type 2 diabetes are sparse
- CGM (interstitial glucose) has high variability

CGM and HbA1c: Complementary Tests!

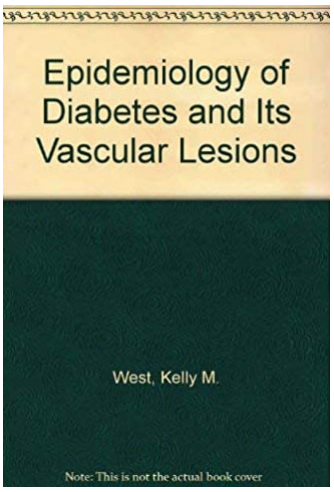
- **Motivating the use of CGM with the limitations of HbA1c is not useful**
- **We don't need to choose between a critically important biomarker and a promising new technology**
- **HbA1c is central to management and diagnosis**
  - **CGM captures different aspects of glycemia**
  - **Neither HbA1c or CGM are perfect**
  - **Stronger if used together, need to be used in synergistic ways**
- **CGM should not replace HbA1c**
  - **Understood strengths and limitations**
  - **CGM should stand on its own merits**

Summary and implications

- **Epidemiologic analyses were used to establish:**
  - **The link between HbA1c and future risk of major complications in an initially non-diabetic population, informing the use of HbA1c for diagnosis (ADA-guidelines 2010)**
  - **No compelling evidence for race-specific thresholds for diagnosis of diabetes**
  - **That two tests (HbA1c and fasting glucose) from *the same blood sample* provide adequate confirmation for diagnosis of diabetes (ADA-guidelines 2019)**
  - **However, pay attention to any discordance (FPG / HbA1c)**

Importance of Epidemiology in Informing Medical Practice

- **HbA1c is strongly linked to outcomes and is one of the most important clinical biomarkers in the practice of medicine.**
- **CGM is a useful new tool but should not replace HbA1c.**
- **Approaches to diagnosis, screening, and management of diabetes should be informed by rigorous epidemiologic studies and sound epidemiologiy thinking.**



.....Thank you!