Diabetes, Moving beyond HbA1c

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Disclosure Information
Disclosure slide:
• No financial relationships to disclose

I will discuss the following off label use and/or investigational use in my presentation
• Use of CGMS in research

Learning Objectives
• Upon completion of the activity
  – Participants should be better able to describe the development, significance and limitations of HbA1c
  – Understand the limitations of fructosamine and glycosylated albumin
  – Understand and apply continuous glucose monitoring systems to their practice
A typical clinical scenario

- Pt with T1DM or T2DM on insulin
- Check HbA1c
- Give/adjust insulin
- Recheck HbA1c

Outline

- What is HbA1c?
  Quick Quiz
- Alternative measures to HbA1c
  Quick Quiz
- Role of continuous glucose monitoring systems (CGMS)
  Quick Quiz

What is HbA1c?

- HbA is the predominant hemoglobin (97%)
  - HbA2 (2.5%)
  - HbF (0.5%)
- When hemoglobin is separated in a cation exchange resin, minor peaks are eluted before the main peak (HbA1a, HbA1b, HbA1c)
What is HbA1c and its limitations

- HbA1c - adding glucose (glycosylation) to HbA
- Normal HbA1c levels are 4-6%
- Reported that HbA1c is higher in people with type 1 diabetes (1960s-1970s) (~8-12%)
- Glucose is attached to HbA by nonenzymatic, posttranslational process which is continuous over RBC lifespan

Bunn F Biochemical and Biophysical Research Communications, 1975

What is Hba1c?

- RBC are freely permeable to glucose – more glucose, more transmission to the hemoglobin
- Glycated hemoglobin includes HbA1 and other hemoglobin-carbohydrate adducts
- HbA1c is a specific form of glycated Hb
- HbA1c reflects the 120 day lifespan of the RBC, but correlates best with average glucose over 8-12 wks

Development of HbA1c assay

- Originally, "glycated hemoglobin" was used
  - Glycated vs nonglycated hemoglobin could be separated several ways (i.e charge, structure) therefore high variability in results
  - T1DM: DCCT (Diabetes Control and Complications Trial) completed in 1993 – showed that complications related to glycated hemoglobin
  - T2DM: UKPDS (United Kingdom Prospective Diabetes Study) – completed in 1998 – showed that complications are related to glycated hemoglobin used in DCCT
The National Glycohemoglobin Standardization Program (NGSP) started to standardize the process relative to DCCT standards (1993)
- HbA1c measured today is equivalent to the HbA1c from DCCT or UKPDS
- Reported in %

A1c Derived Average Glucose study (ADAG)
- Correlate average glucose with HbA1c
- Wide spectrum of Type 1, Type 2 and normal population across USA, Europe, Africa, Asia
- 507 subjects (268 type 1, 159 type 2, and 80 nondiabetic)
  - Diabetes: Stable control (HbA1c within 1% over 6 months)
- Assessed average glucose by CGMS (2-3 days at baseline, then every 4 weeks, measures glucose q5 min) and regular self-monitoring (8 times per day) * 12 weeks
  - Each participant with 2700 glucose measurements

\[ \text{Hba1c} \times 20 = \text{glucose} \]
When is HbA1c and average glucose discrepant?

- Lower RBC turnover - increase HbA1c
- Rapid RBC turnover - decrease HbA1c
- Hemolysis
- Anemia
- Iron treatment
- EPO treatment
- Blood transfusion

Relevance of HbA1c

- DCCT study
  - N=1441, 726 with no retinopathy, 715 with mild retinopathy
  - Insulin treated diabetes (Age ~27)
  - Intensive (3+ injections/day or pump) vs conventional insulin therapy (1-2 injections/day)
  - Intensive vs conventional treatment for 6.5 years
    - Development of microvascular complications
    - HbA1c measured at a central site

DCCT NEJM 1993
Relevance of HbA1c

Retinopathy
• Primary prevention: Intensive therapy reduced risk for retinopathy by 76%
• Secondary prevention: Intensive therapy slowed progression by 54%, reduced development of severe disease by 47%
• An inverse relationship between the A1C value and the incidence of developing diabetic retinopathy
• Continuous benefit, although reduction in absolute risk was low below HbA1c of 7.0

DCCT NEJM 1993

Relevance of HbA1c

Nephropathy
• Primary prevention: Intensive therapy reduced risk for microalbuminuria by 34%
• Secondary prevention: Intensive therapy reduced risk for microalbuminuria by 43% and albuminuria by 56%

Neuropathy
• Primary prevention: Intensive therapy reduced risk for by 69%
• Secondary prevention: Intensive therapy reduced risk by 57%

DCCT NEJM 1993

Relevance of HbA1c

DCCT intervention versus DCCT observation for microalbuminuria.
- Intensive therapy reduced risk for microalbuminuria by 34%.
- Secondary prevention reduced risk for microalbuminuria by 43% and albuminuria by 56%.

Nathan DM Diabetes Care 2014
Relevance of HbA1c

UKPDS study

• Newly diagnosed patients with T2DM (median age 54, n=4209, enrolled in 1977-1991)
• 2927 with intensive therapy (sulfonylurea+insulin), 1138 with diet therapy, 342 with metformin
• Intensive blood glucose control (fasting glucose < 108 mg/dL) vs conventional treatment (add medication if symptoms or blood sugar >270 mg/dL)
• 10 year study: Ended in 1997

UKPDS Lancet 1998

Relevance of HbA1c

UKPDS

• Intensive group: Mean HbA1c 7.0%
• Metformin group: Mean HbA1c of 7.4%
• Conventional group: Mean HbA1c was 7.9%
• Intervention group closed in 1997
• Microvascular and macrovascular outcomes
  Intensive treatment: 25% reduction in microvascular endpoints (95% CI of 7-40, p=0.0099).
  No significant reduction in macrovascular endpoints
  MI: 16% decline, p=0.052
  Metformin only group:
  No reduction in microvascular endpoints
  Reduction of 39% in risk for MI
  Reduction of 36% in risk for death

UKPDS 33 Lancet 1998
UKPDS 34 Lancet 1998

Relevance of HbA1c

• UKPDS – 10 year follow up

UKPDS Lancet 1998
**Relevance of HbA1c**

- Supported by 2 large prospective, interventional clinical trials in Type 1 and Type 2 diabetes
- Small changes in HbA1c
  - Large reduction in diabetes complications
  - Legacy effect
- HbA1c measurement is standardized and accurate

**Ethnic Effects on HbA1c**

- Review of 11 studies of HbA1c between African Americans compared to Whites with T2DM. African Americans have higher HbA1c than whites (0.2 to 2.0 percentage points, average ~0.65)
- Initial reaction – attributed to health disparities
- Further evaluation
  - Multiple studies have shown persistence after adjusting for access to care, quality of care, psychosocial issues
Differences in A1C by Race and Ethnicity Among Patients With Impaired Glucose Tolerance in the Diabetes Prevention Program

- 3819 individuals with impaired glucose tolerance from the Diabetes Prevention Program
- Demographics (mean±SD: Age 50.7±10.6, BMI 33.9±6.7)
- No difference in fasting glucose across groups (106±9 mg/dL) or postload glucose levels (164±16 mg/dL)

Herman WH Diabetes Care 2007

Ethnic Effects on HbA1c

Average HbA1c
- White: 5.8±0.44 (n=2117)
- Black: 6.19±0.59 (n=752)
- Hispanic: 5.89±0.46 (n=609)
- American Indian: 5.96±0.46 (n=174)
- Asian: 5.96±0.45 (n=167)
- Persisted even after covariate adjustments

Herman WH Diabetes Care 2007

Ethnic Effects on HbA1c

CGMS and HbA1c
- Patients with Type 1 diabetes (n=104 black, n=104 white, T1DM for at least 2 years, HbA1c 6.0-12.0%)
- CGMS for 12 weeks

Key message:
- For same HbA1c, glucose levels lower in blacks than whites
- For same glucose level, higher in HbA1c in blacks than whites

Bergenstal R Annals Internal Medicine 2017
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Quick Quiz

• You have a 42 year old female patient with Type 2 diabetes, a history of fibroids and Hgb of 5.0 and ferritin of 5 ng/mL (low)
• Her HbA1c is 10%
• What do you think her “true” HbA1c might be?
  A. HbA1c is 12% (ie greater than 10%)
  B. HbA1c is 8% (ie less than 10%)

Quick Quiz

B. HbA1c is 8% (ie less than 10%)
• The patient has longstanding iron deficiency
• Turnover of RBC is low
• HbA1c has longer glycosylation – more sugars attached
• HbA1c is artificially higher than expected
Quick Quiz

If you treat her with IV iron and do not change her diabetes program, what would you expect?

A. HbA1c is 10% (ie unchanged)
B. HbA1c is 8% (ie lower)

Relevance of HbA1c

- Average glucose for a given HbA1c can vary
- HbA1c is an indirect measure of glycemia, which can be influenced by multiple factors.
- Lowering HbA1c lowers microvascular complications, CV disease

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Alternative measures to HbA1c

Glycation is the process of adding glucose to proteins

- Fructosamine
  - Measures total concentration of glycated serum proteins, including glycated albumin
  - More variable than HbA1c
  - Heavily influenced by serum albumin
  - Lower values if albumin loss (protein-losing enteropathy or nephrotic syndrome)

- Glycated albumin
  - Glucose added to albumin
  - Turnover of serum albumin is 28 days
  - Reflects glucose over 7-14 days

Alternative measures to HbA1c

Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study

- Observation Cohort (ARIC study)
- 11348 adults without diabetes, 958 adults with diabetes (Type 1 and Type 2) in 1990-1992
- Measured glycated albumin (novel method), fructosamine, HbA1c at baseline
- Examined rates of incident diabetes & chronic kidney disease over 20 years

Selvin E Lancet Diabetes and Endocrinology 2015

Alternative measures to HbA1c

- Glycated albumin and fructosamine predicted incident diabetes and cognitive decline even when adjusting for HbA1c
- May add some predictive value beyond HbA1c, especially if values are ≥95th percentile
- HbA1c better predictor than either glycated albumin and fructosamine

Selvin E Lancet Diabetes and Endocrinology 2015
Alternative measures to HbA1c

- ARIC study: Baseline levels
- Higher levels of HbA1c, fructosamine, glycated albumin in blacks than whites
- Similar relationship of HbA1c, fructosamine, and glycated albumin on microvascular outcomes – race independent

Quick Quiz

When might you order a serum fructosamine?

A. When you are concerned about HbA1c accuracy
B. When you are interested in short term glycemic measures
C. Intellectual curiosity
D. A and B (and maybe C).
Alternative measures to HbA1c

Relevance of fructosamine/glycated albumin
• Fructosamine – readily available – glycated albumin, less so
• No long-term clinical trials examining relationship between fructosamine/ glycated albumin vs diabetes related complications
• Uncertainty of reason to follow-up blood glucose every 1-2 weeks – especially with CGMS results
• HbA1c test : Well standardized , validated

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CGMS
Continuous glucose monitoring systems
• Monitors the interstitial glucose every 5 to 15 minutes.
• Initially approved by FDA in 1999 ->adjunct to self monitoring of blood glucose
• August 2015: FDA approval of Dexcom G5 – send to mobile device – diabetes management without SMBG. Fingerstick calibration twice daily required.
• September 2017 : FDA approval of Freestyle libre – no fingerstick calibration
• March 2018 : FDA approval of Dexcom G6 – no fingerstick calibration and send to mobile device
NO fingerstick calibration needed!

Video of CGMS application
CGMS

- Utility of CGMS
  - Measure hypoglycemia (especially overnight)
  - Identify glucose patterns
  - Measure glycemic variability: At minimum, this affects quality of life

- Glycemic variability
  - Coefficient of variation
  - Mean Amplitude of Glycemic Excursions (MAGE)
  - Standard Deviation

CGMS – Ambulatory Glucose Profile (AGP)

Features
- Average glucose
- GMI – HbA1c estimate – avoid confusion by designating as GMI
- CV: NL is <20%
- Time in range – 70180 mg/dL
- Very low: Glucose ≤ 54 mg/dL

www.agpreport.org
CGMS

Advantages
• Can wear long term * 10-14 days
• Can wear blinded (good for research purposes)
• Validated against capillary blood glucose testing and venous blood glucose testing

CGMS

Freestyle libre:
• 72 patients with either T1DM or T2DM
• Sensor worn for 14 days.
• Sensor results were compared with:
  – Capillary blood glucose testing (8 times per day for 14 days)
  – Venous glucose results - in clinic measurement, every 15 minutes for 8 hours, 3 times over the 14 day sensor period

• The mean absolute relative difference between the sensor and capillary glucose was 11.4%.
• The mean absolute relative difference between the sensor and venous testing reference was 12%.
Over the 14 days of sensor life, 86.7% of sensor results were within 20% of capillary blood glucose reference values.

Critical component of the closed-loop “artificial pancreas”

Population
- N=158 Type 1, 158 Type 2
- All MDI
- HbA1c 7.5-9.9%

Intervention:
- Dexcom G4 - calibrate twice daily
- SMBG – monitor at least 4 times per day

Outcomes: Follow-up at 12 weeks and 24 weeks
- HbA1c
- CGMS use * 7 days for all participants
Type 1: Baseline HbA1c 8.6%

Beck RW JAMA 2017

Type 2: Baseline HbA1c 8.5%

Beck RW Annals Internal Medicine 2017

Future directions

- Clinical significance of Time in Range –
  - DCCT – every 10% less TIR, increased retinopathy by 64% and increased nephropathy by 40%

- Clinical significance of glycemic variability
  (association with cardiac arrhythmia/microvascular complications)

- Use of CGMS in clinical trials of diabetes treatment

Glargine U300 vs U100

- Lower variability,
- Less hypoglycemia

Comparison of bedtime Glargine 300 Units vs. 100 Units in Adult T2DM: Continuous Glucose Monitoring (CGM) and Trandderapeutic Glucose Monitoring in Treating Hyperglycemia

Beck RW JAMA 2017
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Quick Quiz

What is not true about CGMS?

A. CGMS measures blood sugar
B. CGMS is helpful to reduce hypoglycemia frequency
C. Treatment decisions can be made using CGMS results rather than fingerstick confirmation

Diabetes Care 2019
Standards of Care in Diabetes

Quick Quiz

What is not true about CGMS?

A. CGMS measures blood sugar
B. CGMS is helpful to reduce hypoglycemia frequency
C. Treatment decisions can be made using CGMS results rather than fingerstick confirmation

CGMS measures interstitial glucose which parallels capillary glucose levels

Diabetes Care 2019
Standards of Care in Diabetes
Chance for a Beanie

- If you have a Black patient and a White patient with the same HbA1c — who will have the lower average glucose level?

The black patient will have a lower average glucose level than the white patient given the same HbA1c.

A typical clinical scenario

- Pt with T1DM or T2DM on insulin
- Check HbA1c: Decide if HbA1c is appropriate given glucose levels/context
- Give/adjust insulin
  Consider use of CGMS (diagnostic/personal use)
- Recheck HbA1c
Learning Objectives

• Upon completion of the activity
  – Participants should be better able to describe the development, significance and limitations of HbA1c
  – Understand the limitations of fructosamine and glycosylated albumin
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Summary

• What is HbA1c
  – Indirect measure of average glycemia by quantifying the glycation on hemoglobin. Clinical significance established. Ethnic differences exist.

Summary

• Alternative measures to HbA1c
  – Look at glycated proteins, primarily albumin.
  – Measures glucose over 7-14 days.
  – Clinical significance uncertain and now replaced by CGMS
Summary

- Role of continuous glucose monitoring systems (CGMS)
  - Transforming diabetes care.
  - No need for fingersticks.
  - Clinical impact is promising.
  - Added value of describing short term glycemic variability on a large scale

Thank you!