

HbA1c

“It is difficult to overestimate the contribution made by glycated haemoglobin measurement ... to the management of patients with diabetes mellitus....”

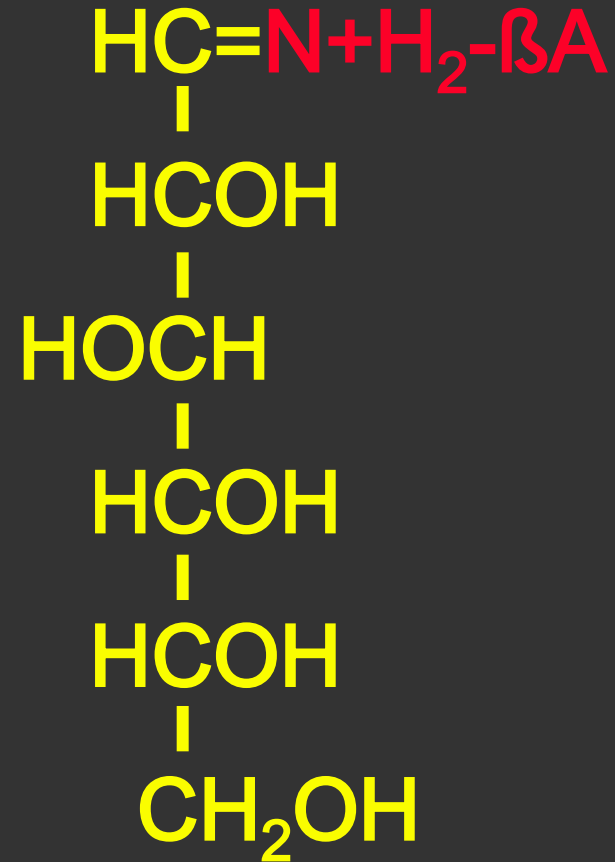
ES Kilpatrick J Clin Path 2004

**"HbA1c is not a sufficiently reliable
marker of glycaemic control in
diabetes care"**

glucose



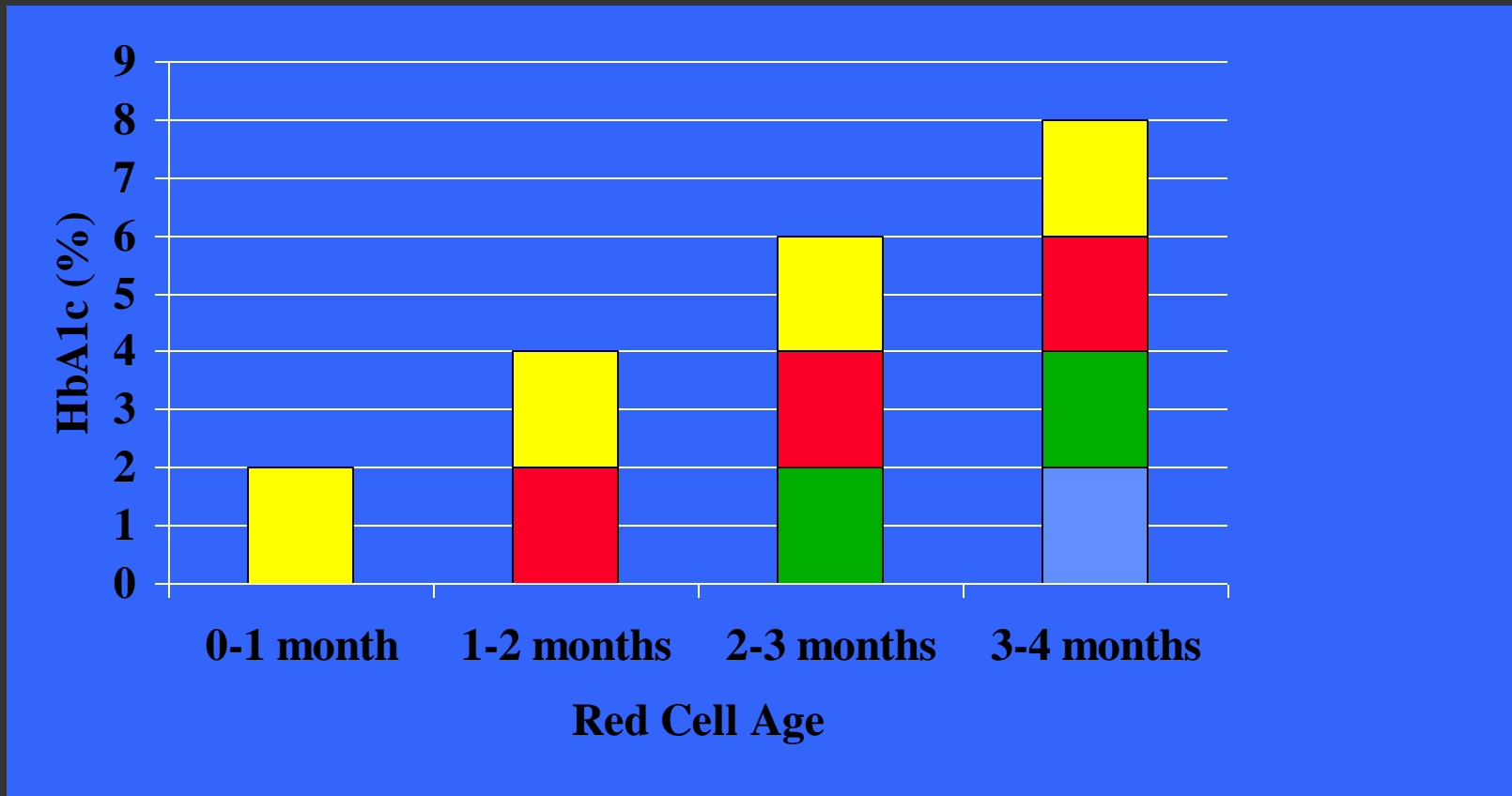
Glycated Haemoglobin



Glycated Haemoglobin

HbA	none	95.0%
HbA _{1a1}	fructose 1,6 diphosphate	0.2%
HbA _{1a2}	glucose-6-phosphate	0.2%
HbA _{1b}	?	0.5%
HbA _{1c}	glucose	4.0%

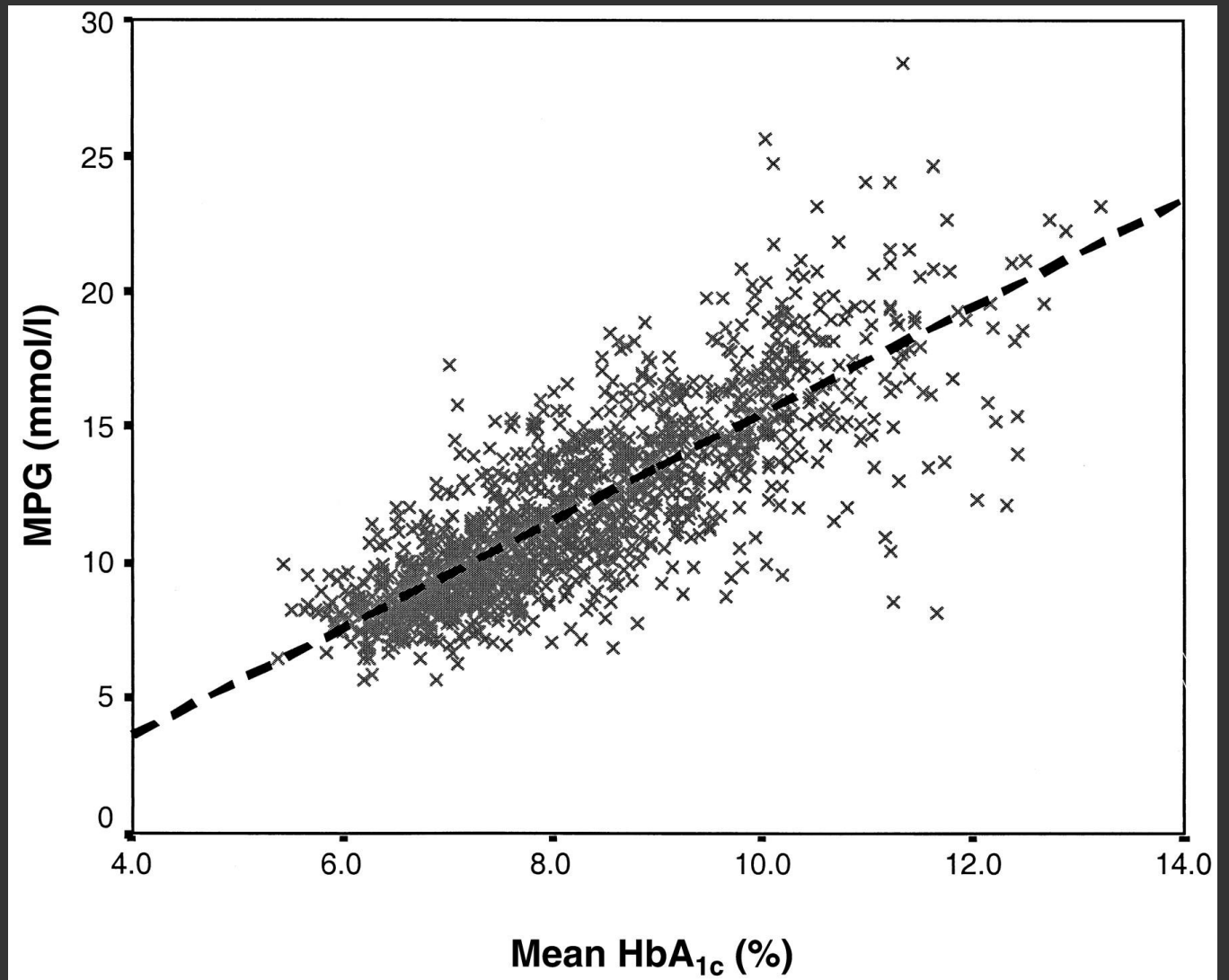
Model of Glycated Haemoglobin Formation



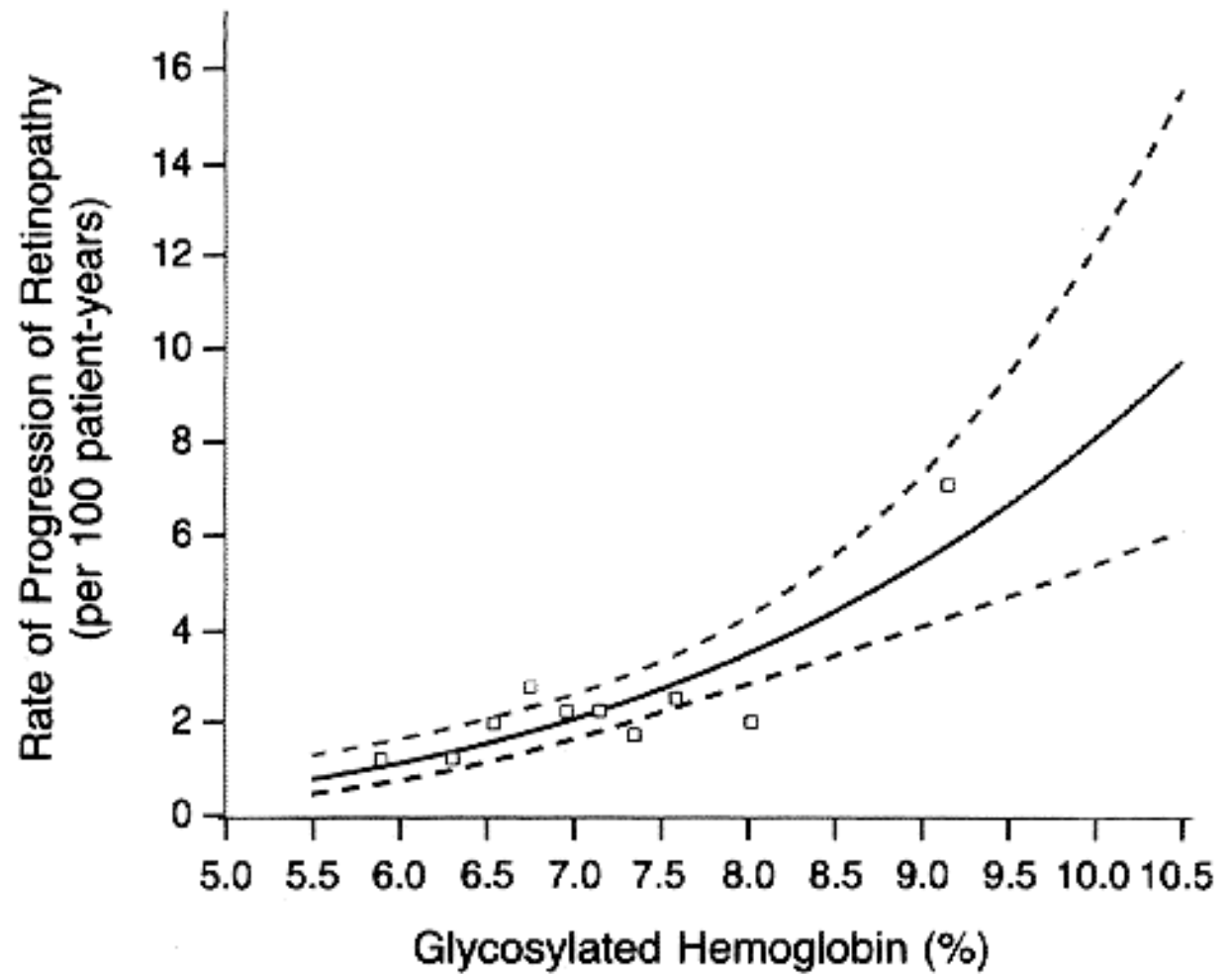
Mean plasma glucose and HbA1c

$r=0.82$

*CL Rohlving et al
Diab Care 2002*



DCCT:

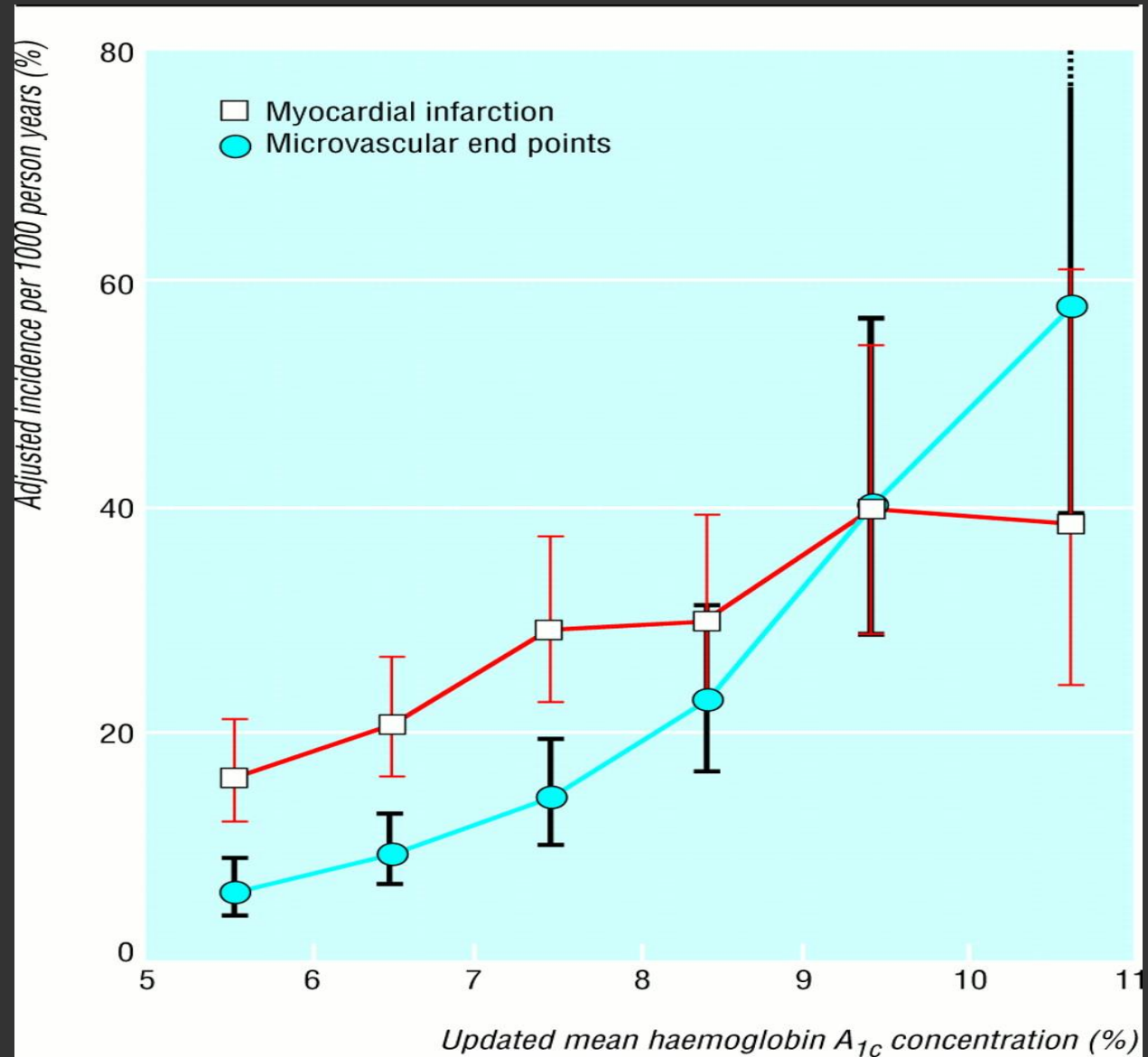


*DCCT Group
NEJM 1993*

A

UKPDS:

*IM Stratton et al
BMJ 2000*



**How standardised is the
“Gold Standard” ?**

HbA_{1c} assays: harmonisation or standardisation ?

DCCT and UKPDS both used the same HPLC method (BioRex 70)

NGSP (“DCCT alignment”) is a mathematical adjustment applied to other methods to produce similar results

HbA_{1c} assays: harmonisation or standardisation ?

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IFCC hexapeptide standard

(non-diabetic reference range 2.9-3.8)

$$\text{DCCT} = 0.927 \times \text{IFCC} + 2.144$$

HbA1c

- **Close correlation with mean blood glucose in populations**
- **Close correlation with microvascular (and macrovascular) endpoints**
- **But it is not standardised**

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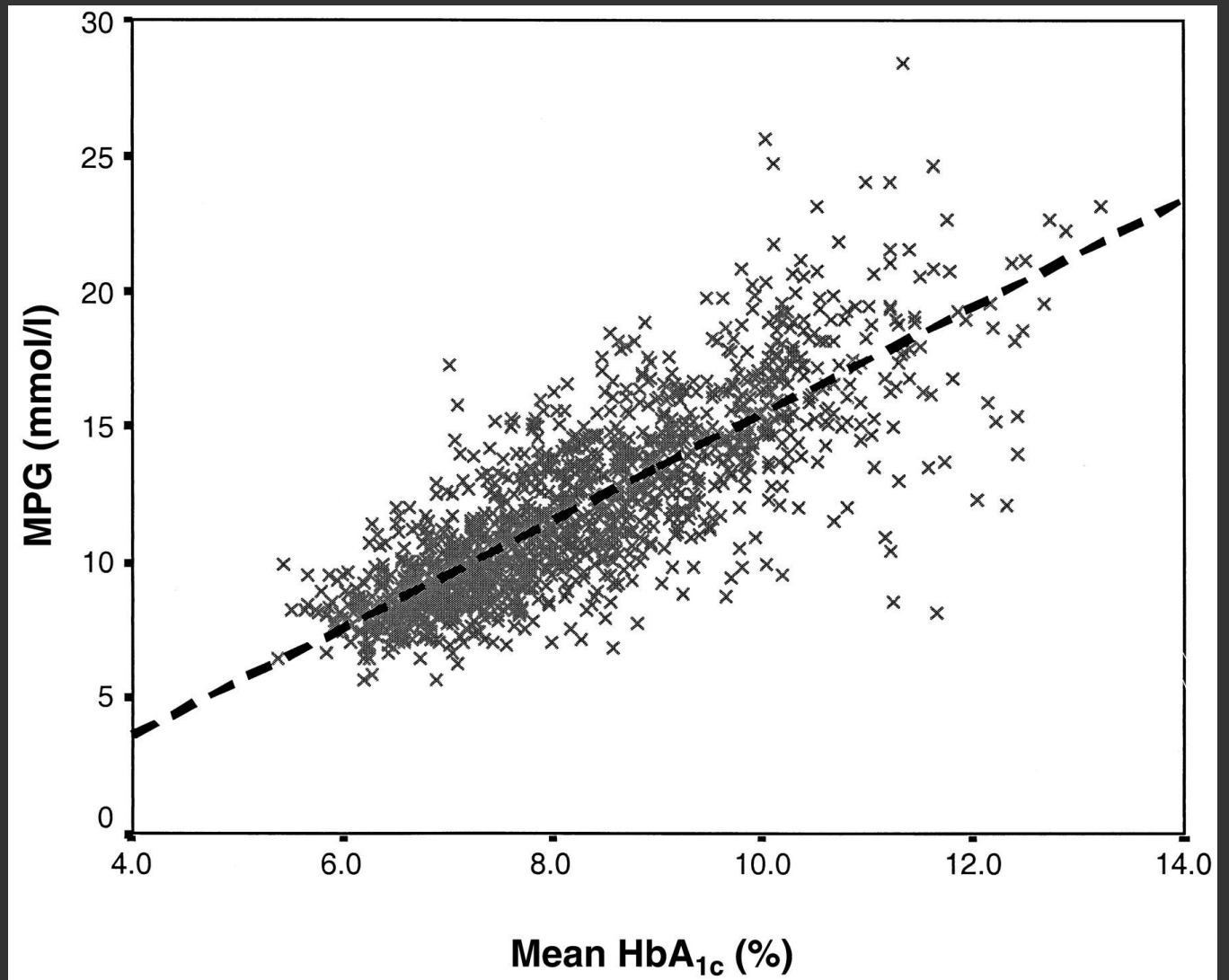
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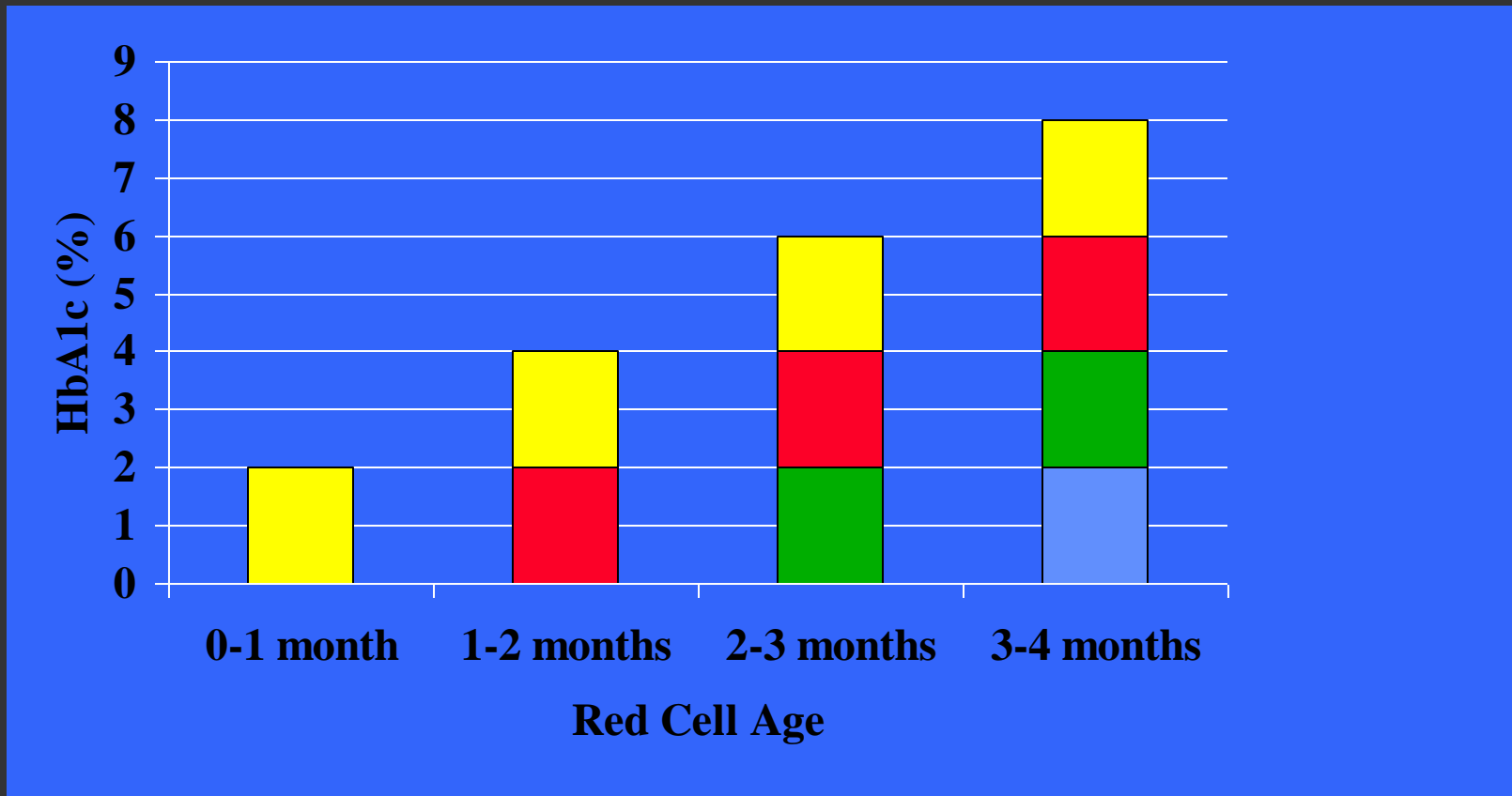
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**What determines the relationship
between mean plasma glucose and
HbA1c in any one person with
diabetes ?**

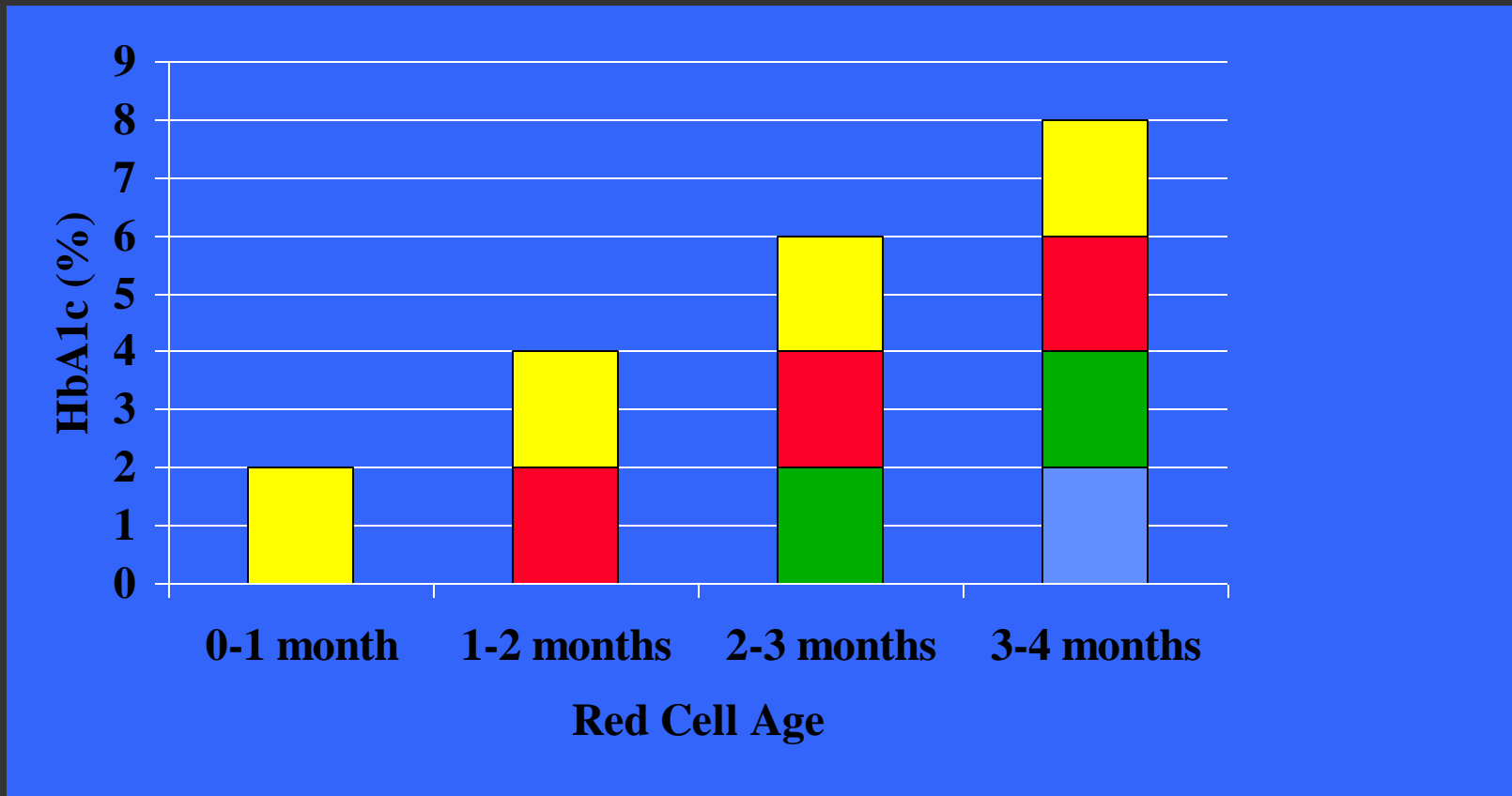
- 1. Haemoglobinopathies**
- 2. Fe deficiency anaemia**
- 3. High red cell turnover**

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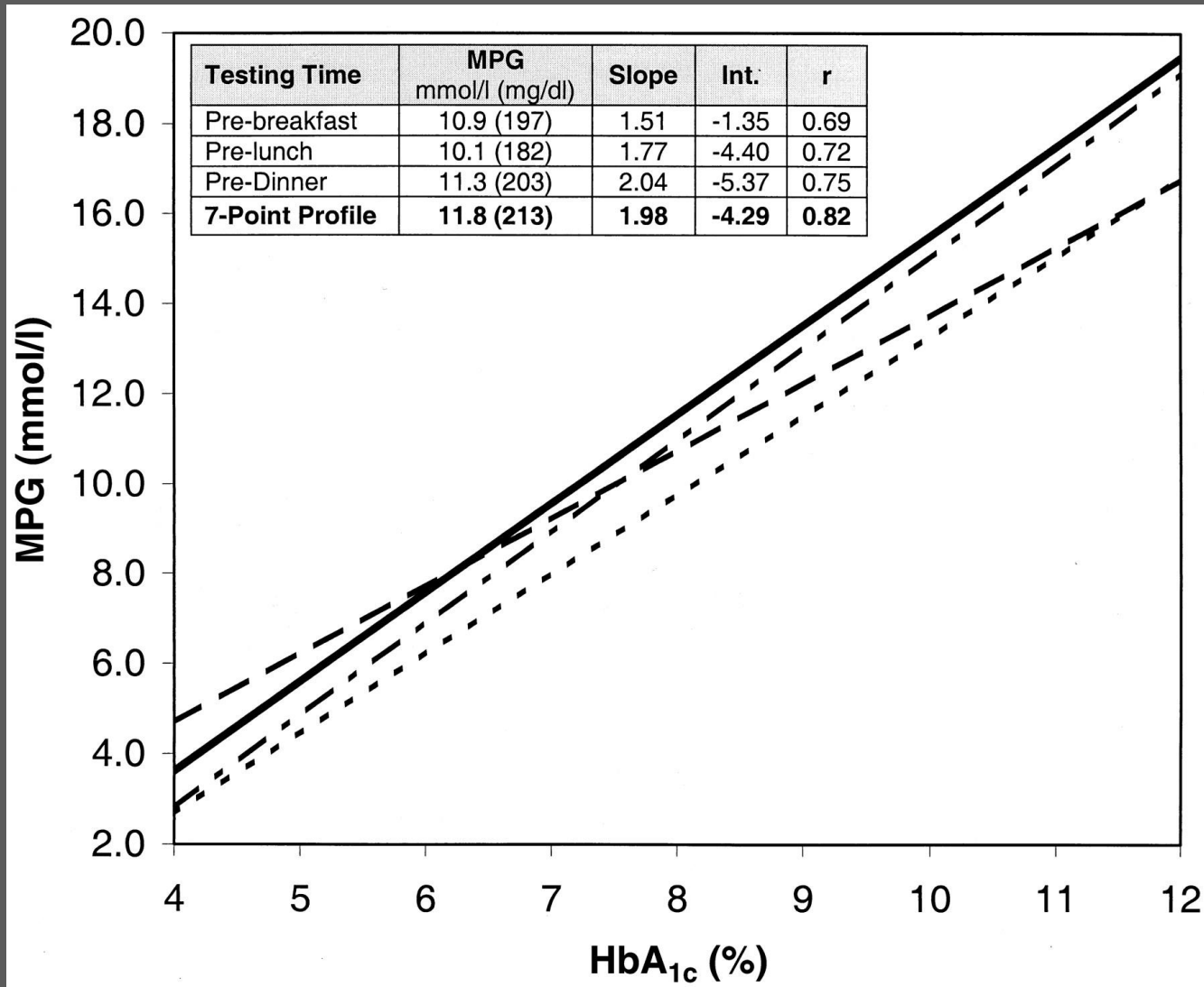
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*Rohlfing
Diab Care 2002*



1. Haemoglobinopathies
2. Fe deficiency anaemia
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4. Recent phase of higher (or lower) blood glucose
5. Circadian patterns of blood glucose
6. Glucose excursions

7. Age

8. Individual variation in the rate of protein glycation

9. Treatment

Relationship between age and HbA_{1c}

232 without diabetes

correlⁿ between age and HbA_{1c}: $r=0.49$

126 without diabetes

correlⁿ between age and HbA_{1c}: $r=0.48$,

but none between age and either FBG
or fructosamine

Kilpatrick Quart J Med 1996

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Interindividual variation in HbA_{1c}

- 10 patients with Type 1 seven point profiles for 12 weeks; weekly HbA_{1c}
- Interindividual variation in relationship between MBG and HbA_{1c}: glycation index

Hudson Ann Clin Biochem 1999

Interindividual variation in HbA_{1c}

- 12 people without diabetes
HbA_{1c} measured
each two weeks x 10
- Very high “index of individuality”
suggesting individuals may have up
to 2% difference in HbA_{1c} for a given
level of glucose control

Interindividual variation in HBA_{1c}

High glycaters have a:

- higher concentration of glucose in RBCs (relative to plasma)
- higher concentration of 2,3-diphosphoglycerate

Gould et al Clin Chim Acta 1997

Interindividual variation in HbA_{1c}

- DCCT data
Haemoglobin glycation index (HGI)
- Interindividual variation in HbA_{1c} results could not be explained by MBG
- Interindividual variation in HbA_{1c} was itself a strong predictor of complications

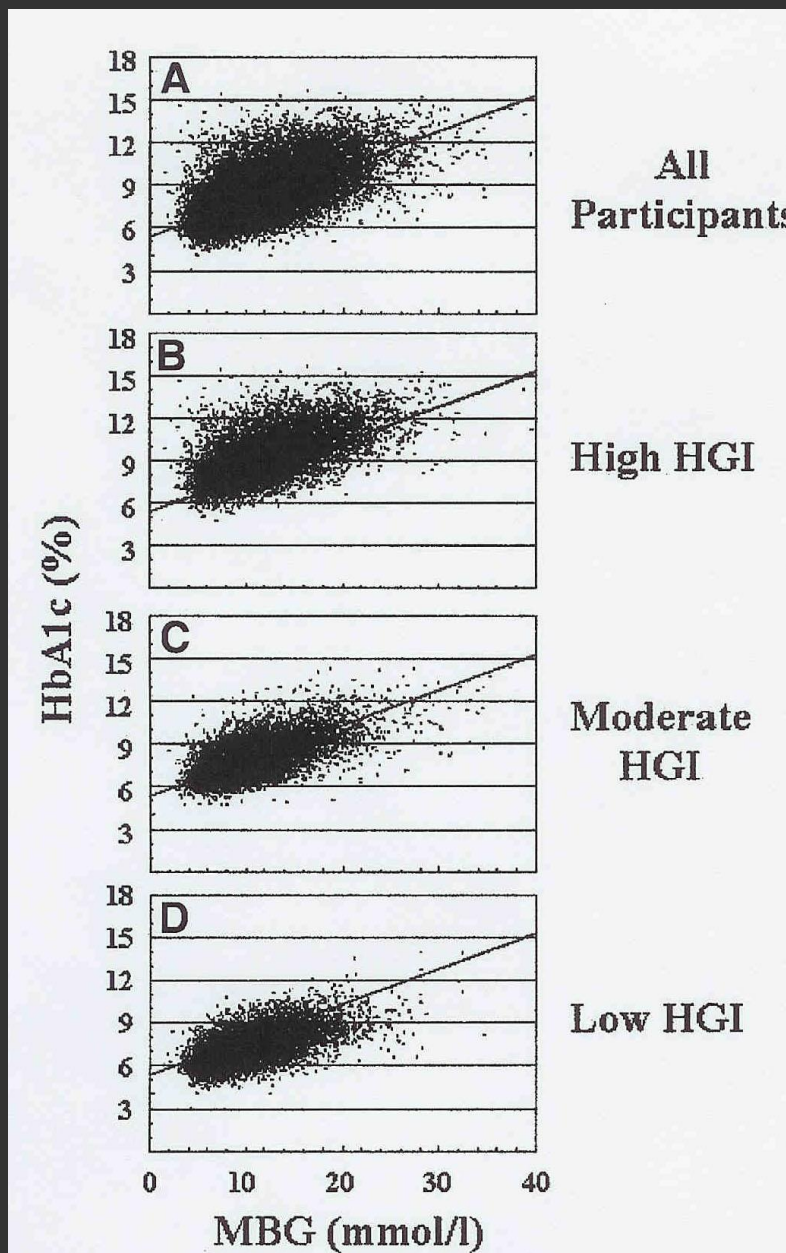
McCarter Diab Care 2004

High HbA1c for MBG →

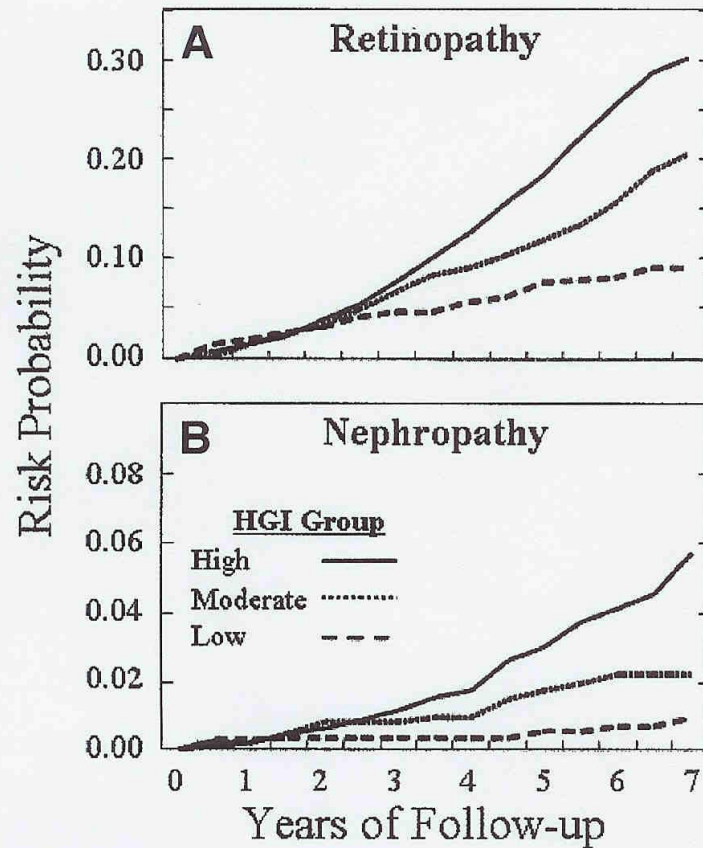
Medium HbA1c for MBG →

Low HbA1c for MBG →

McCarter Diab Care 2004



HGI and risk of complications

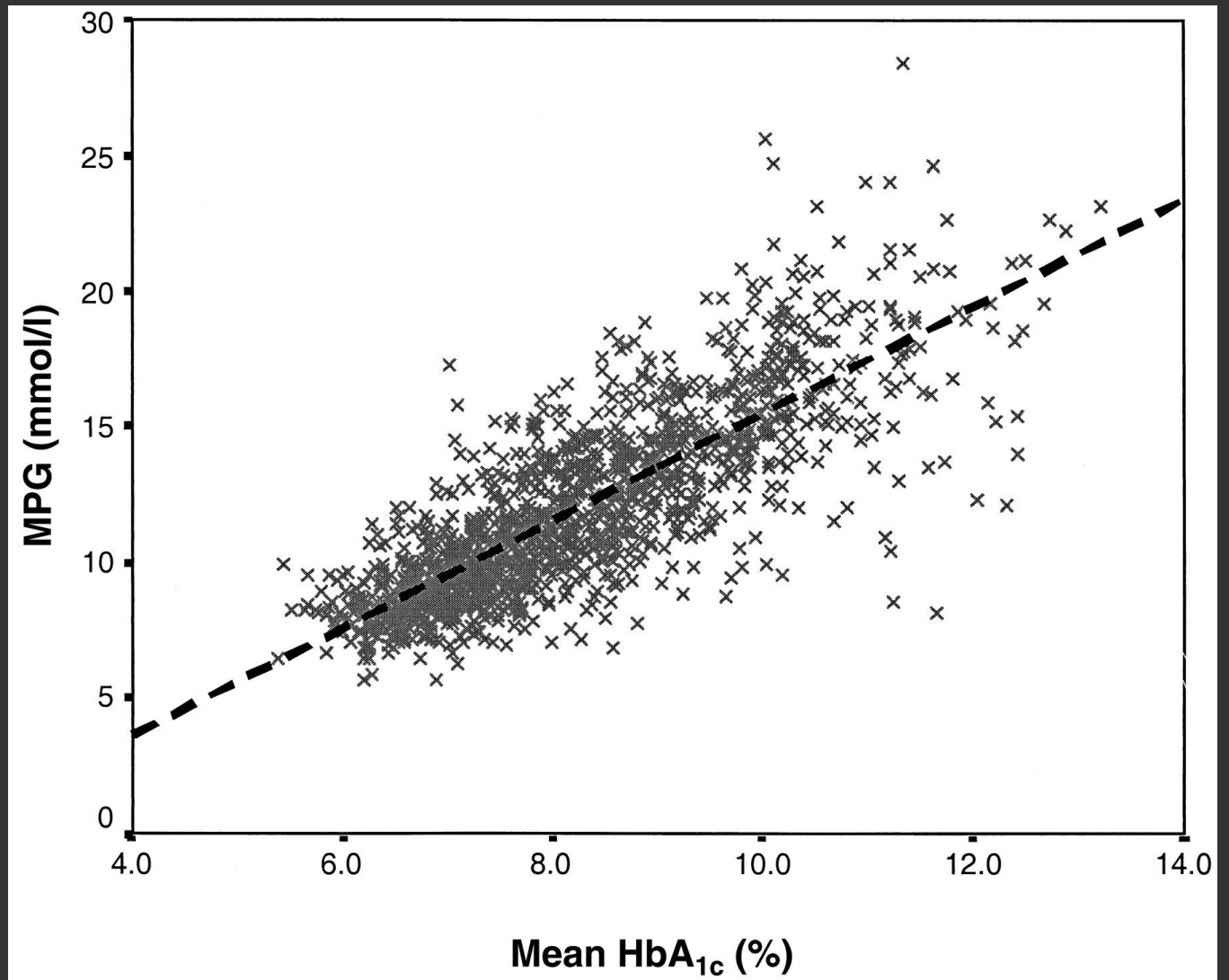


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Effect of biguanides on glycation

- Data (N=921) from two 24 week studies: metformin vs placebo and metformin vs glibenclamide vs both
- Evidence that for an equivalent effect on blood glucose, metformin was associated with a fall of 0.4-0.7% in HbA_{1c}

Innerfield Abstract 1153 EASD 2005

Effect of biguanides on glycation

- Guanide derivatives (eg aminoguanidine) well known to inhibit glycation
- Potent inhibition of formation of AGEs *in vitro* by both metformin and buformin

Kiho Clin Chim Acta 2005

Wide variation in the relationship between HbA1c and MBG from person to person

- Factors related to blood glucose changes: **the extent and timing of glucose excursion**
- **Factors related to individual: haemoglobin rate of glycation (including age)**
- **Factors related to treatment**

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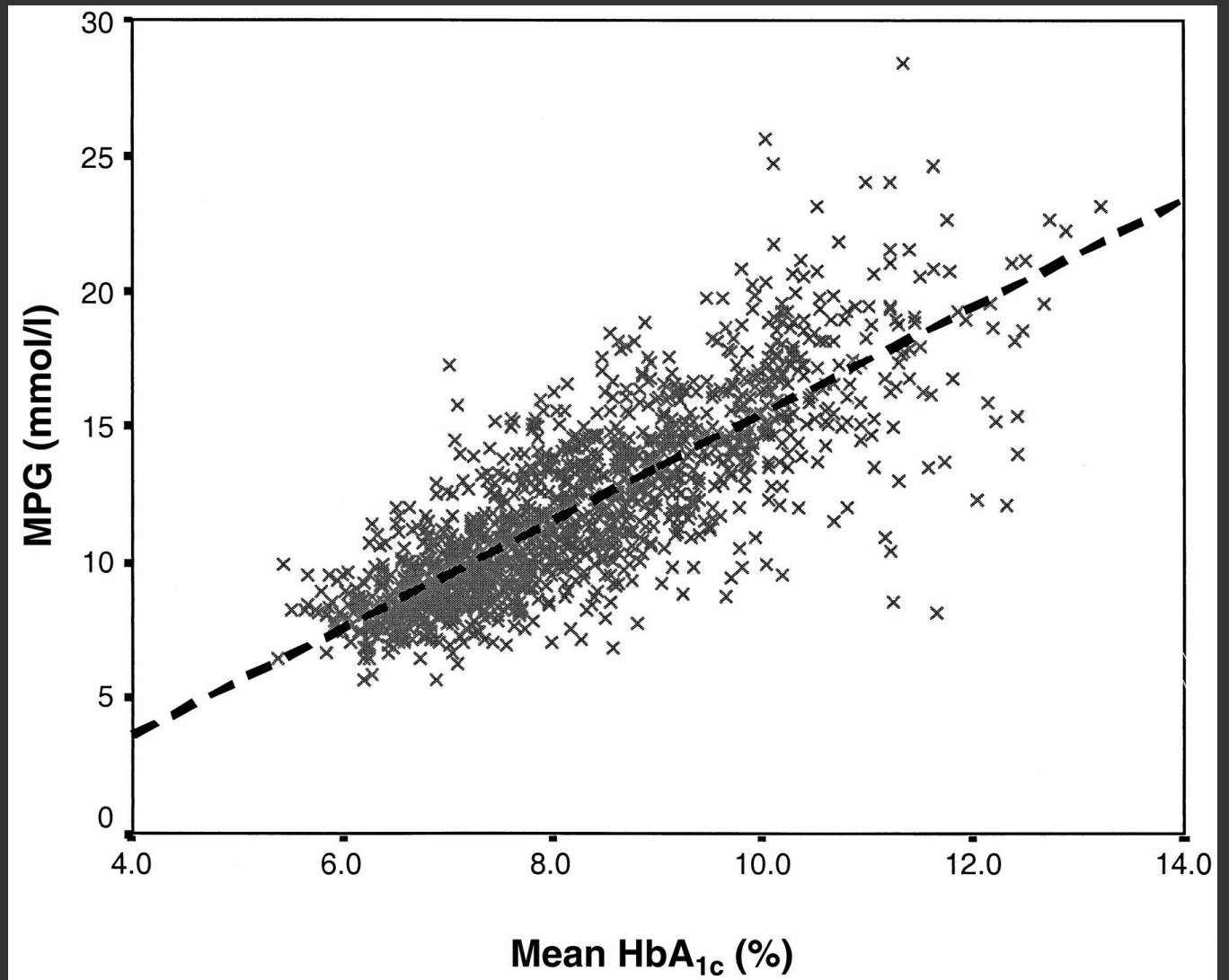
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**GP: “I wonder if I could ask you
about a case...”**

52 year school caretaker with type 2 diabetes

On metformin 1g bd; HbA1c 7.9%

**GP added gliclazide 80 mg daily in order to
lower HbA1c**

Patient has tonic-clonic convulsion at work

HbA1c measurement

1. **Not standardised**
2. A reasonable measure of glycaemic control in populations
3. A good measure of liability to chronic (microvascular) complications
4. An inconsistent marker of good control – glycaemic or otherwise – in the individual
5. Inappropriate reliance on HbA_{1c} results can lead to imperfect assessment of the quality of disease management.

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