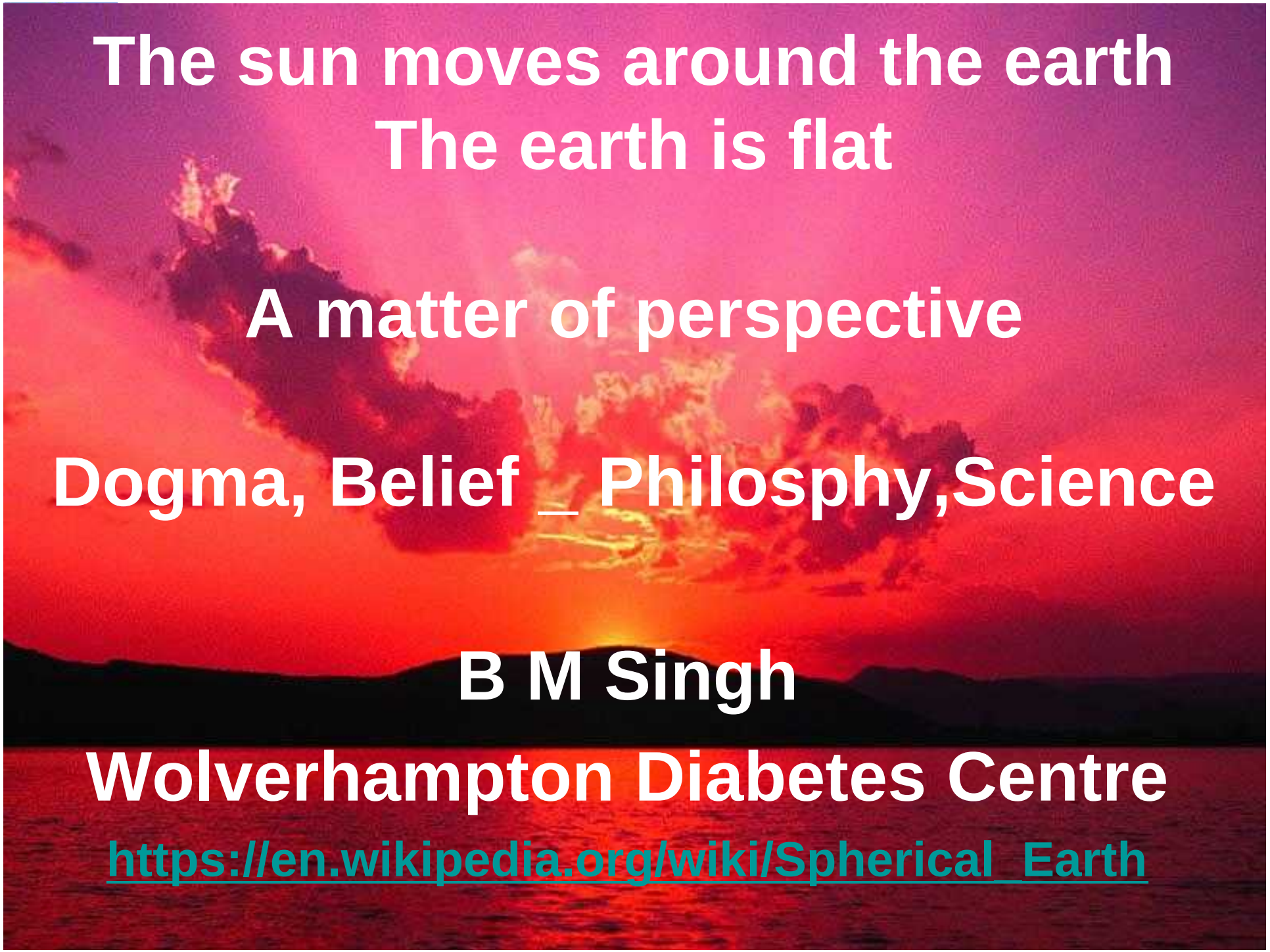
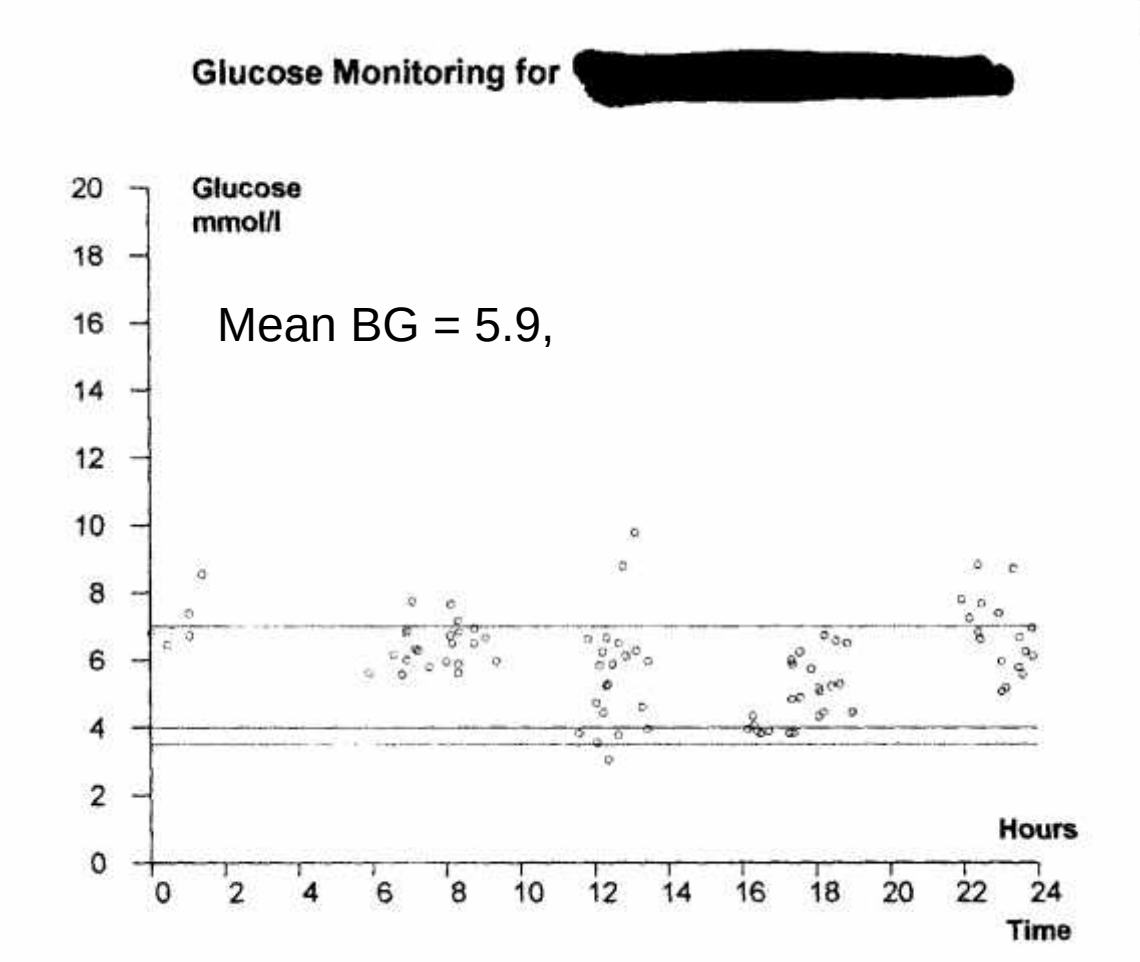

The sun moves around the earth
The earth is flat
A matter of perspective
Dogma, Belief _ Philosphy,Science
B M Singh
Wolverhampton Diabetes Centre
https://en.wikipedia.org/wiki/Spherical_Earth


The Wolverhampton Diabetes Centre

Mrs CG's SMBG


Glucose Monitoring for [redacted]
Glucose
mmol/l
Mean BG = 5.9,
20
18
16
14
12
10
8
6
4
2
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Hours
Time

Of Greeks (and Indians)

- The earth is flat (DOGMA)
- 6th C BC Pythagoras, Aristotle
- 3rd C BC Eratosthenes (276–194 BC) to <5% accuracy.
- 16th C AD Magellan
- The earth is round (TRUE)
- (but everyone knew it was true really)

- Belief system change
- **20 centuries**

- HbA1c is the gold standard measure of glycaemia (DOGMA)
- Increasingly believed (with known caveats) e.g. diabetes diagnosis , IFCC, treatment targets.
- Deviation of HbA1c from prevailing glycaemia is common and very, very, very important (TRUE)
- (but no one believes it)

- Belief system change
- **20 minutes**

Mrs CG's HbA1c

T2DM Insulin Rx

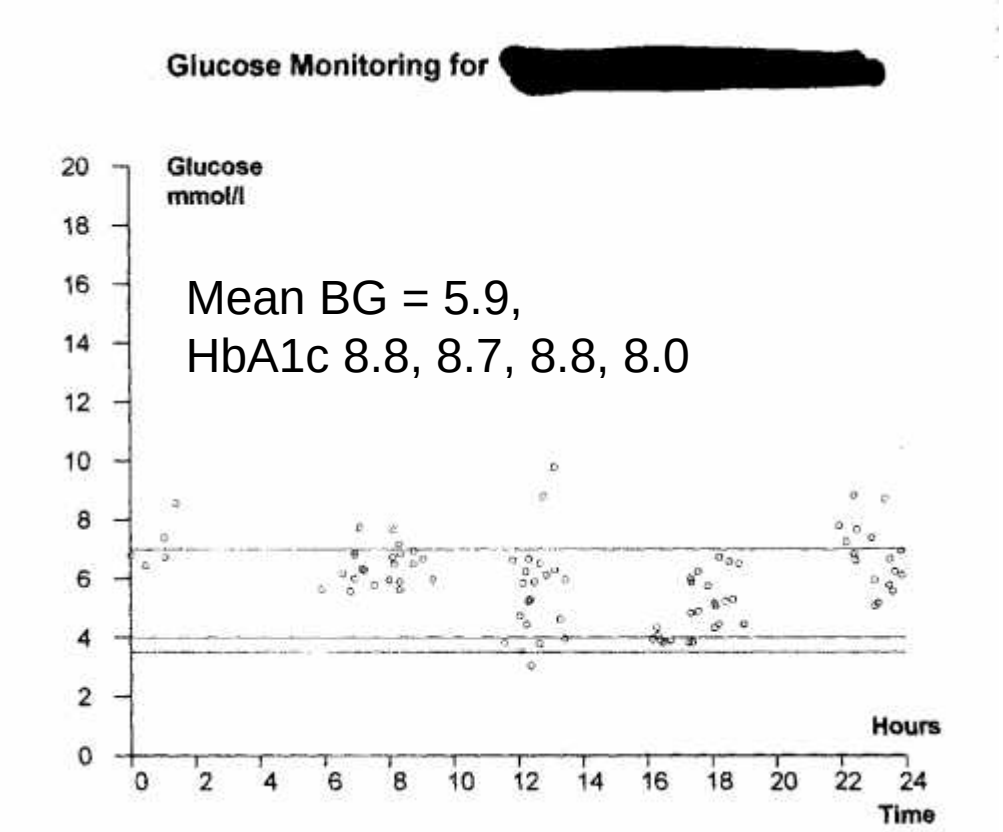
25 consultations with DSN's in 3 years

"?Poor control?"

GP confused

Patient frustrated

"EWTT"



Mrs CG's real glycaemic control ?

HbA1c	8.8, 8.7,8.8,8.0 %
Mean BG	5.9 mmol/l
Fructosamine	287, 280, 240 umol/l

(Fructo / ULN Fructo)*ULN HbA1c (Mickey Mouse)

HbA1c equivalent (rough) = 6.4% (F_HbA1c)

Glycation Gap = HbA1c – F_HbA1c = positive 2.3 HbA1c%

Not just Mrs CG who has the GGap

Ann Clin Biochem 2008; 45: 421–425.

N = 1744 paired results, differences ranged between - 6.9% and + 5.5% HbA1c, 1139 (65%) <1% 438 (25%), 1–2%, 130 (10%) >2–3%

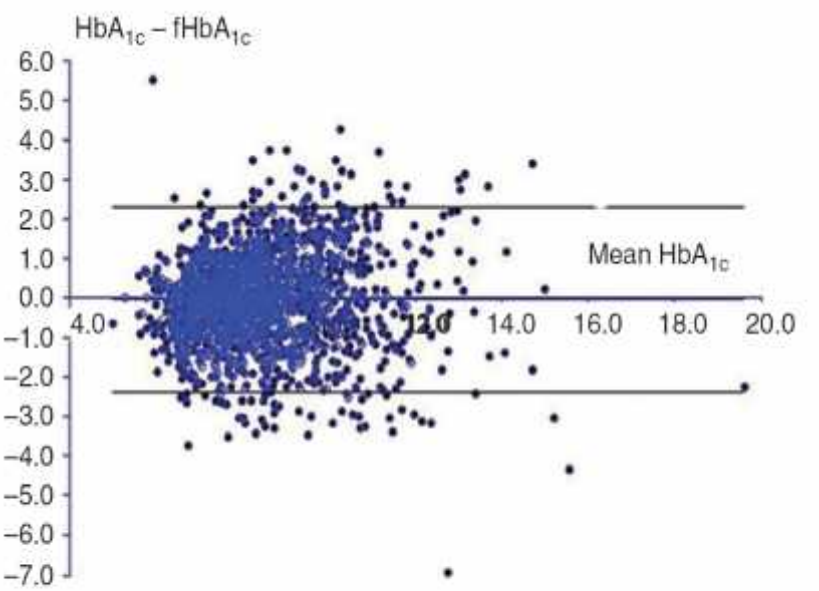
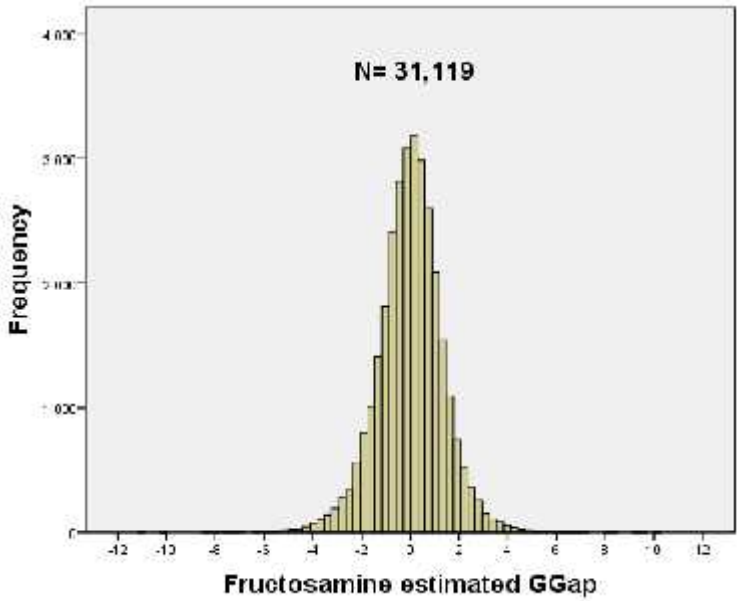


Figure 1 An Altman-Bland plot (with 95% confidence intervals) of percent glycated HbA_{1c} against the difference between it and the equivalent fructosamine-derived HbA_{1c} estimate



GGap clinical error is a real

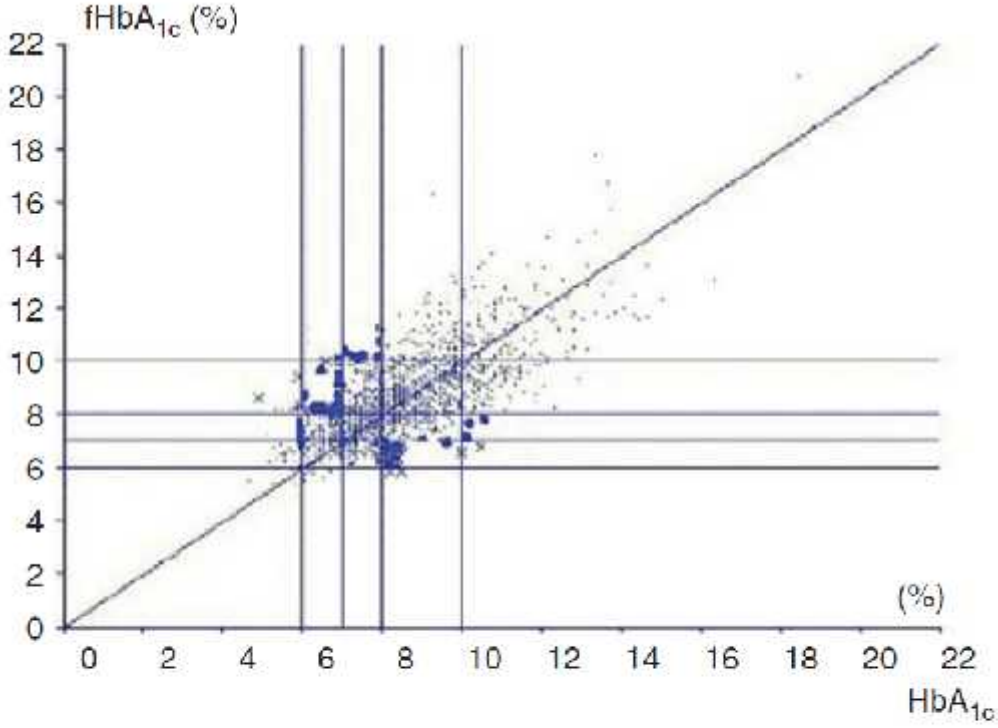


Figure 2 Clinical error grid analysis of the percent glycated HbA_{1c} against the equivalent fructosamine-derived HbA_{1c} estimate. The grid lines are placed to define blocks of excellent, good, average, poor and very poor glycaemic control. The bold dots indicated those values that are two blocks discordant

GGap clinical error is a real

The discordance between HbA1c and the fructosamine derived HbA1c

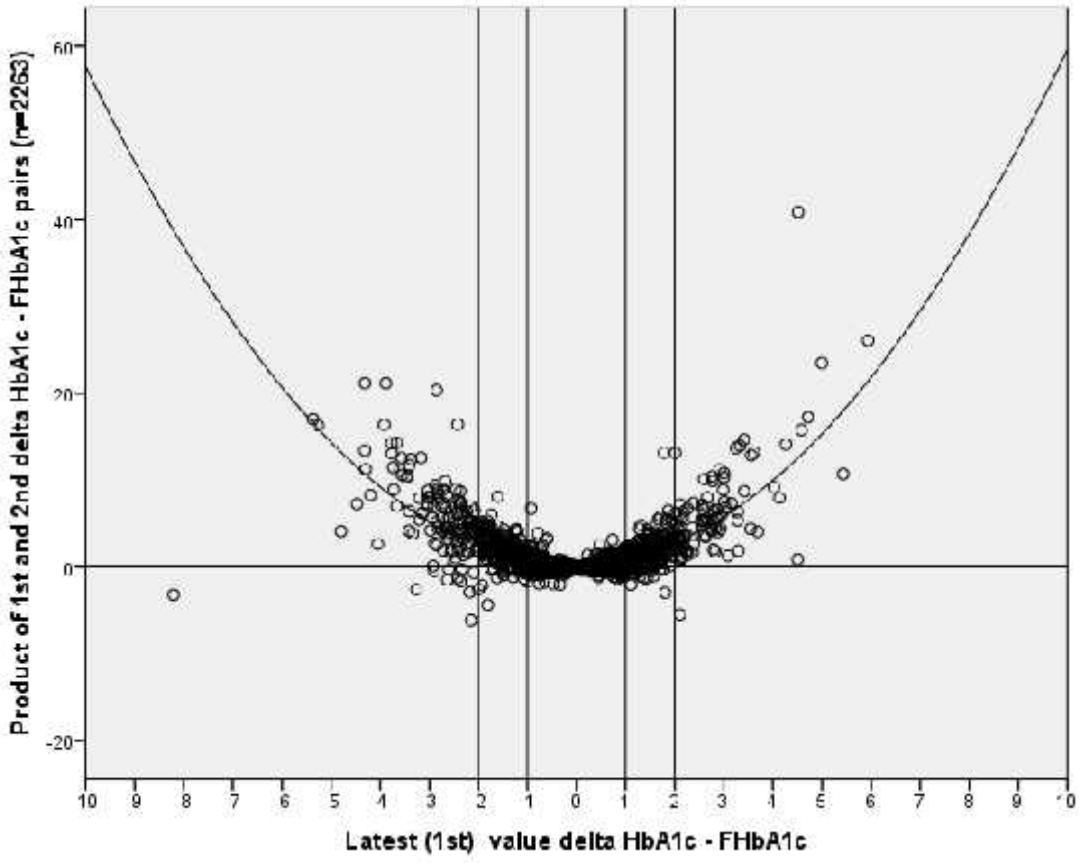
HbA1c	Fructosamine derived HbA1c				
	E	G	A	P	VP
E	11	31	15	19	1
G	24	79	66	50	6
A	18	59	132	113	22
P	9	44	121	208	66
VP	2	17	20	53	57

The GGap is Consistent

The direction of the G-gap is consistent over time

Diabetes Care 34:1712–1716, 2011

Negative G-gap **Positive G-gap**



GGap demographic differences

Diabetes Care 36:3247–3253, 2013

	Positive G-gap	Negative G-gap	Positive vs negative G-gap
Number	416	356	
Age (years)	61.1 ± 12.1	55.9 ± 17.1	Older*
Gender (% Male)	181 (46.1%)	212 (53.9%)	Less male*
Ethnicity (% White, Asian, Black)	63, 32, 5	70, 13, 17	Different ethnic mix*
Smoker (% never, ex, current)	52, 32, 16	64, 29, 7	More current smokers*
Type Diabetes (% T2 DM)	92	56	More T2 DM*
On Insulin (%)	66	70	ns
Duration Diabetes (years)	13.4 ± 7.8	17.1 ±11.3	Shorter duration*
Body Mass Index (kg / m^2)	36.1 ± 7.3	28.4 ± 5.7	Heavier*
Height (m)	1.65 ± 0.09	1.69 ± 0.09	Shorter*
Weight (kg)	98.1 ± 22.9	81.8 ± 18.9	Heavier*
Blood Pressure (mmHg)	135/73 ±22/13	134/74 ±21/12	ns

*p<0.001

GGap complication differences

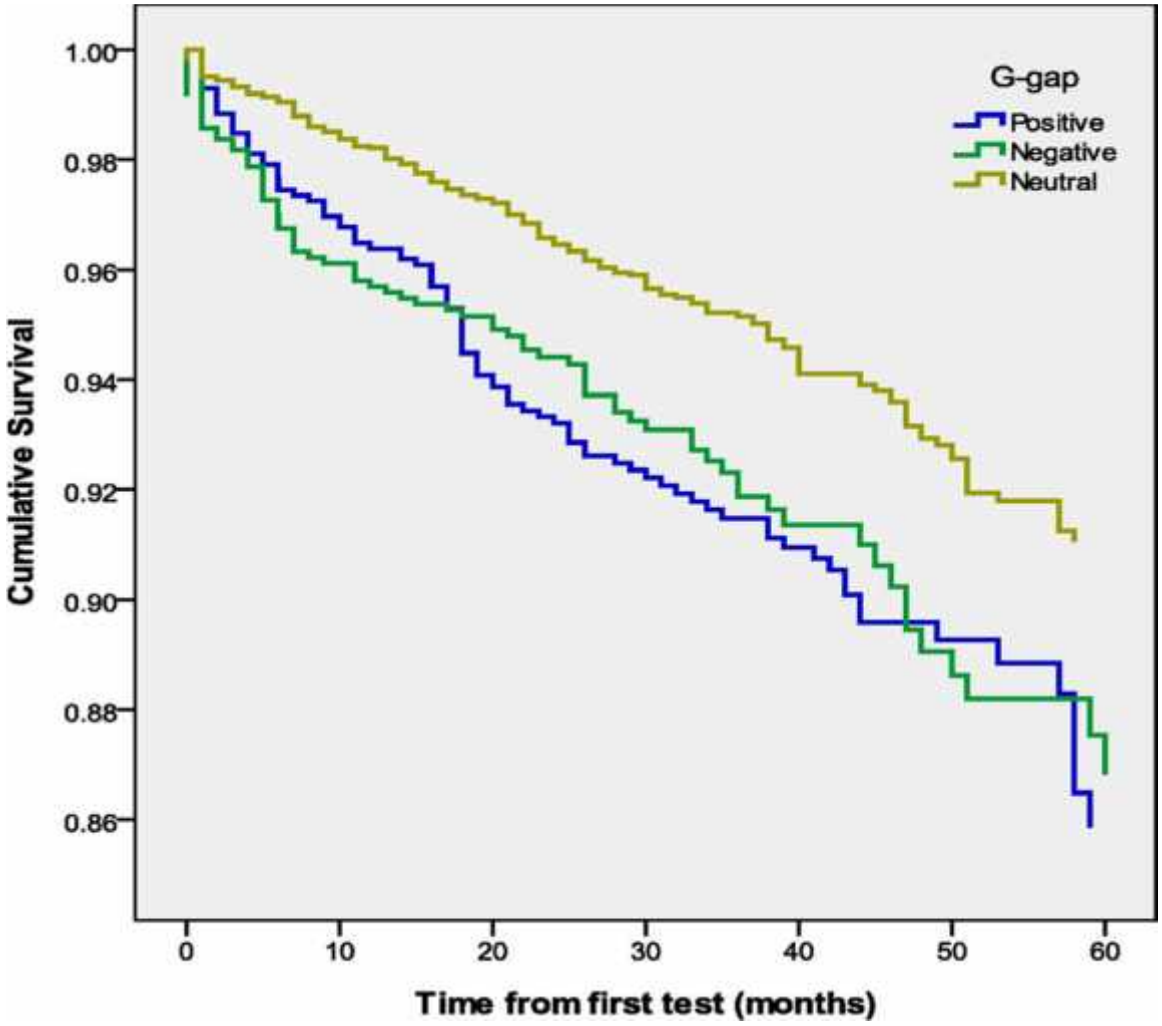
Diabetes Care 36:3247–3253, 2013

	Positive G-gap	Negative G-gap	Positive vs Negative G-gap
Retinopathy Any	**66%**	**62%**	**More***
Urine ACR (mmol/µmol)	**22 ± 70**	**10 ± 56**	**Higher****
Macrovascular risk (% established)	**33**	**17**	**Higher****
% 10-year-CHD risk (primary risk group only)	**12.6 ± 7.4**	**8.5 ± 7.8**	**Higher****
Established Macrovascular Disease	**33%**	**24%**	**More****
Mortality (% died)	**16**	**15**	**???!**

*p<0.05, ** p<0.001

GGap mortality differences

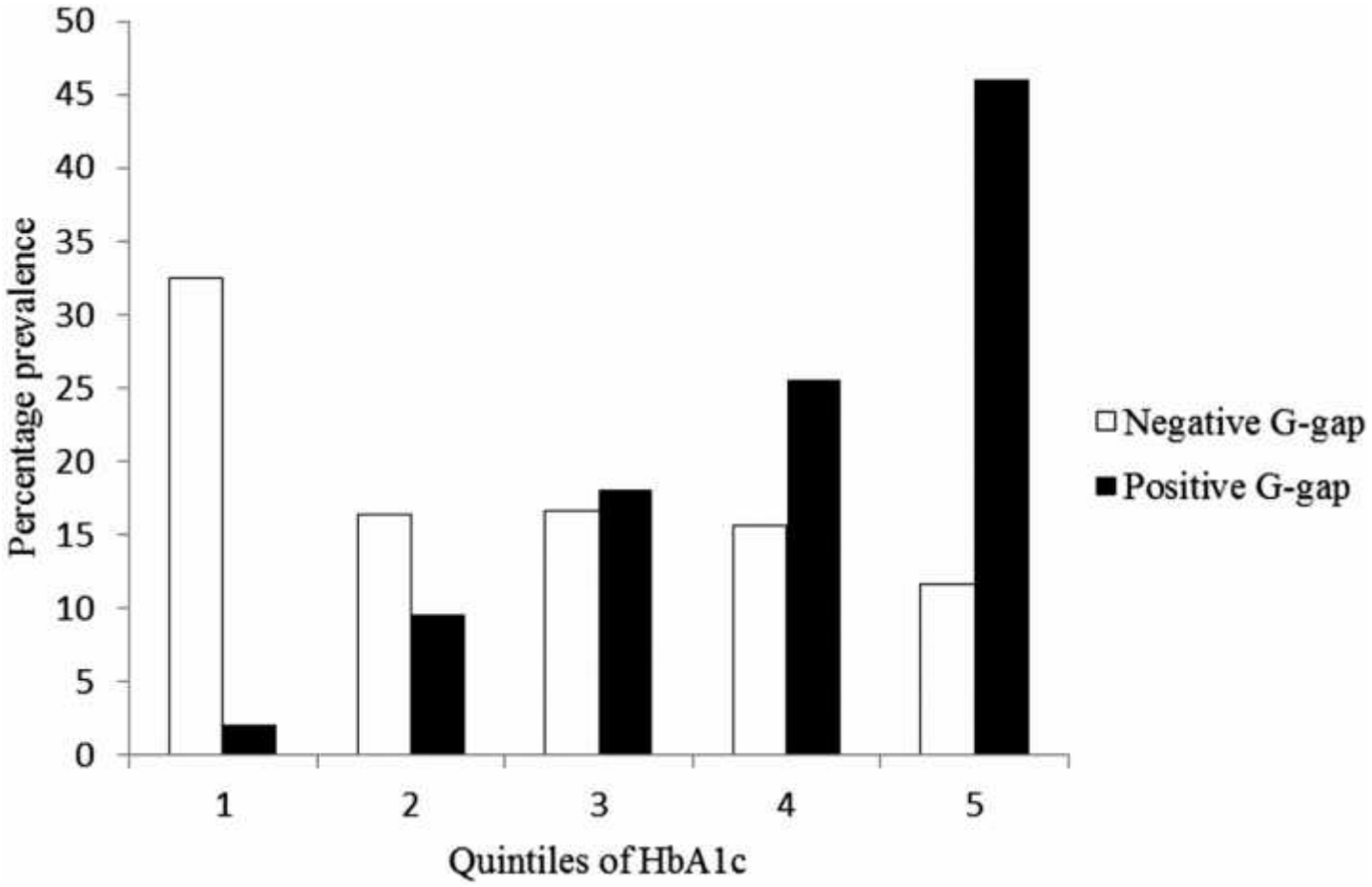
Diabetes Care 36:3247–3253, 2013



GGap mortality differences

Negative GGap preponderance at low HbA1c

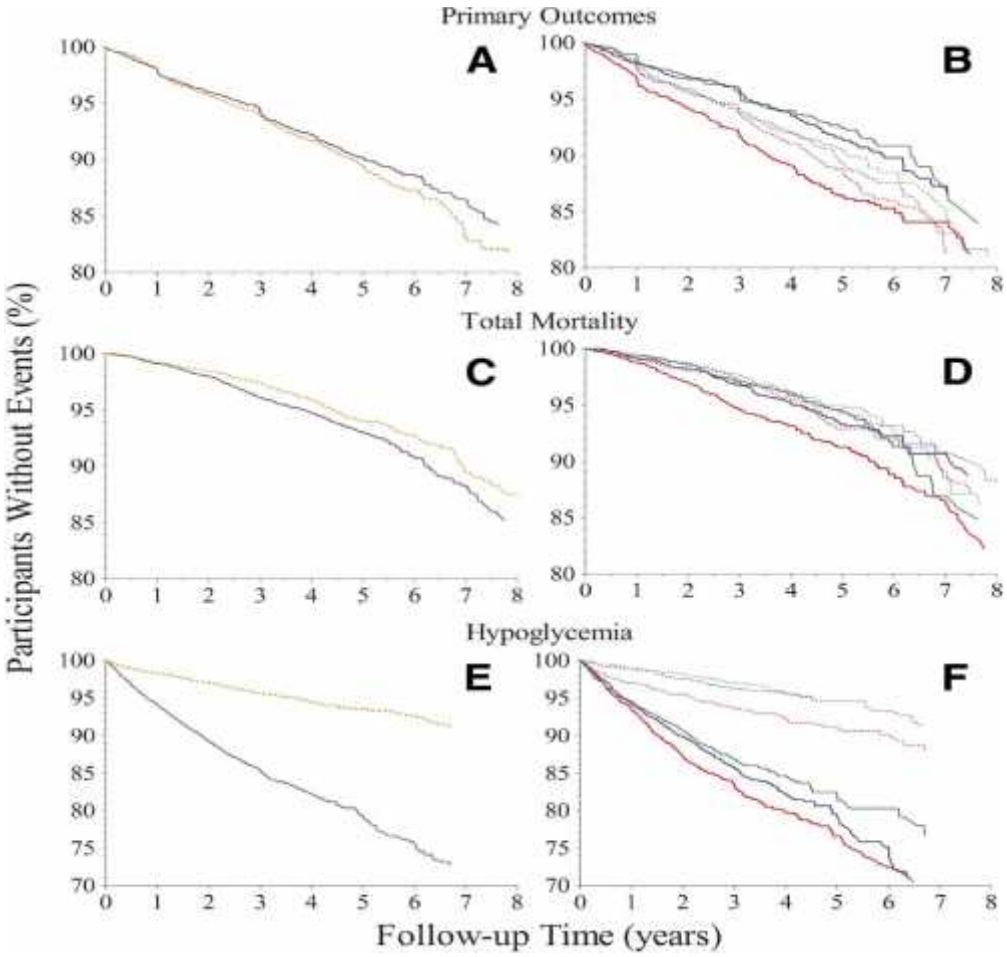
Diabetes Care 36:3247–3253, 2013



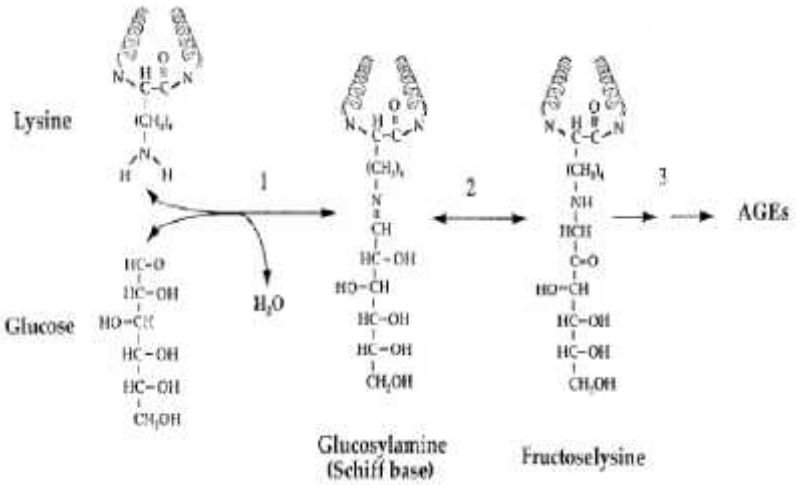
5.9 7.1 8.0 9.0 11.1

GGap (HGI), ACCORD, Mortality

James M. Hempe et al. Diabetes Care 2015;38:1067-1074



But why - Protein Glycation

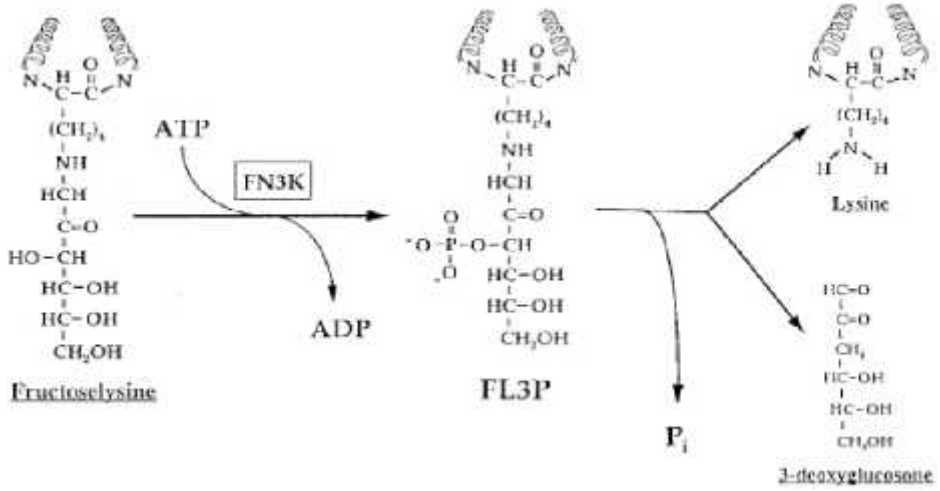


- Glucose reacts spontaneously with amino-groups in proteins such as haemoglobin – especially the amino-terminal valine in the beta chain and intra-chain lysines
- Reversible reactions produce Schiff bases and Amadori products
- Slowly and irreversibly convert to reactive dicarbonyl compounds such as gloxal , methylglyoxal & 3-deoxyglucosone
- Produce a variety of advanced glycated endproducts (AGE) eg pentosidine, N-carboxymethyl-lysine

But why - **Protein Deglycation**

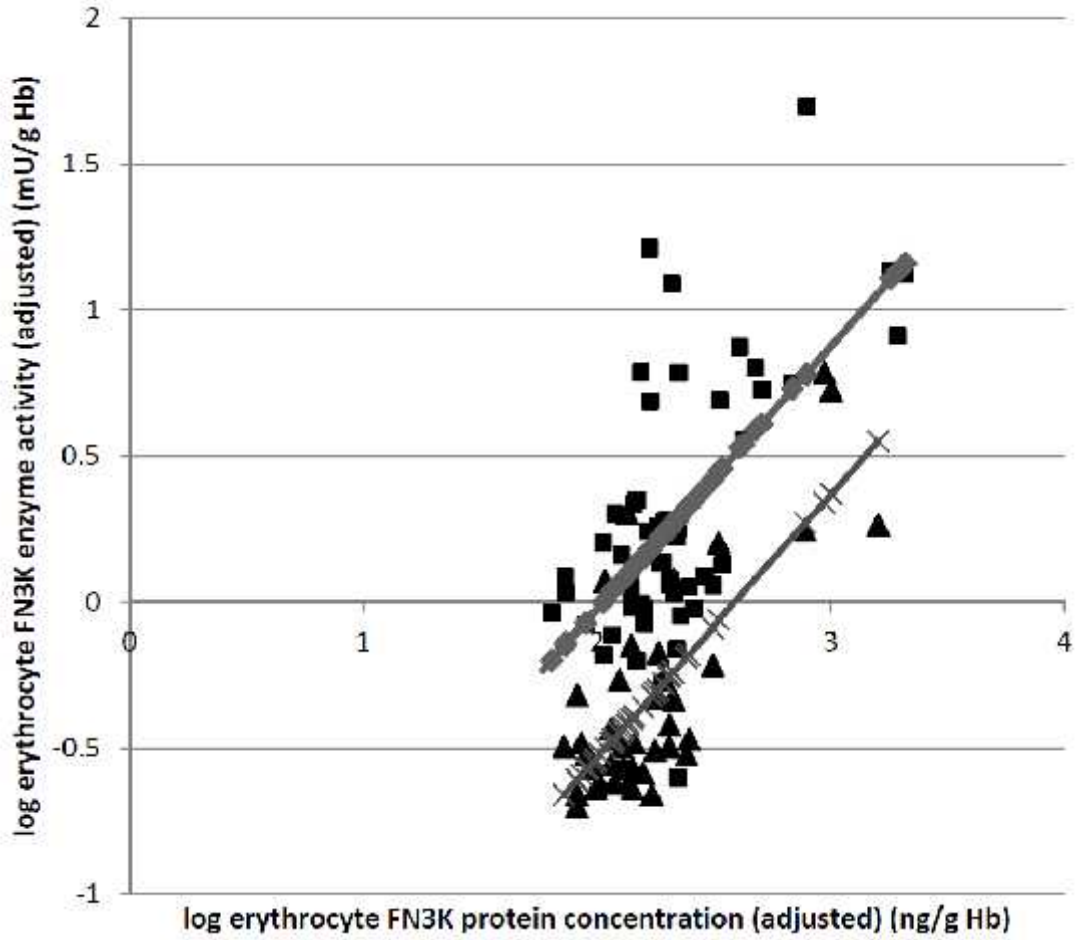
Fructosamine-3-kinase (FN3K) and the deglycation of glycated proteins

- One possible explanation for the glycation gap is the existence of an enzyme-catalyzed deglycation pathway.
- The key enzyme in this pathway is fructosamine-3-kinase.
- It is an intracellular enzyme.
- It will thus deglycate HbA1c, not Fructosamine



The GGap and FN3k

Diabetes 2017 Oct; db170441. https://doi.org/10.2337/db17-0441



GGap – Phenotype to Genotype

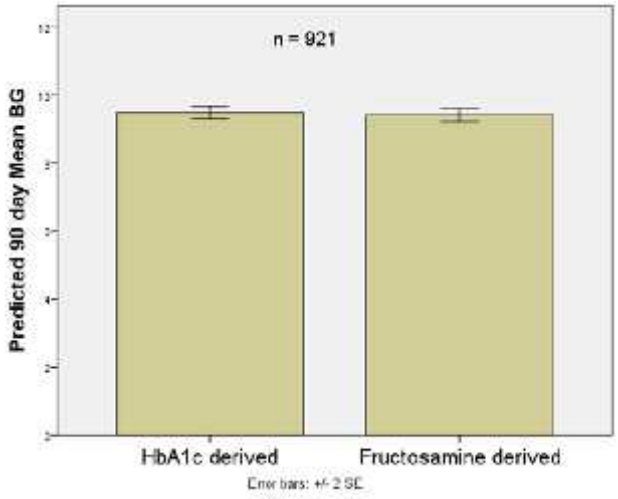
- The GGap can be measured (note HGI)
- It is consistent over time
- It is associated with a demographic
- It is associated with vasculopathy
- It is associated with mortality but oddly so.
- It has a biochemical explanation
- Is this not a **phenotype?**
- Is there a **genotype?**

- SNPs - rs3848403
- Epigenetics – telomere length (shortening) and DNA methylation
- **Splice variants** and **Transcriptome Analysis** and big data with the big boys

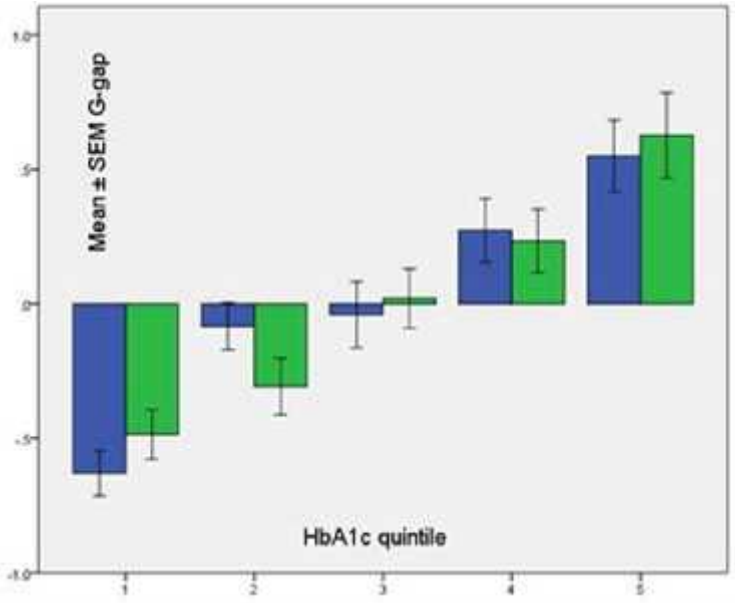
Before Q&A - Fructosamine

Fructosamine just as good as HbA1c as a refection of blood glucose

Blood glucose (HGI) and Fructosamine derived GGaps vary from HbA1c identically.

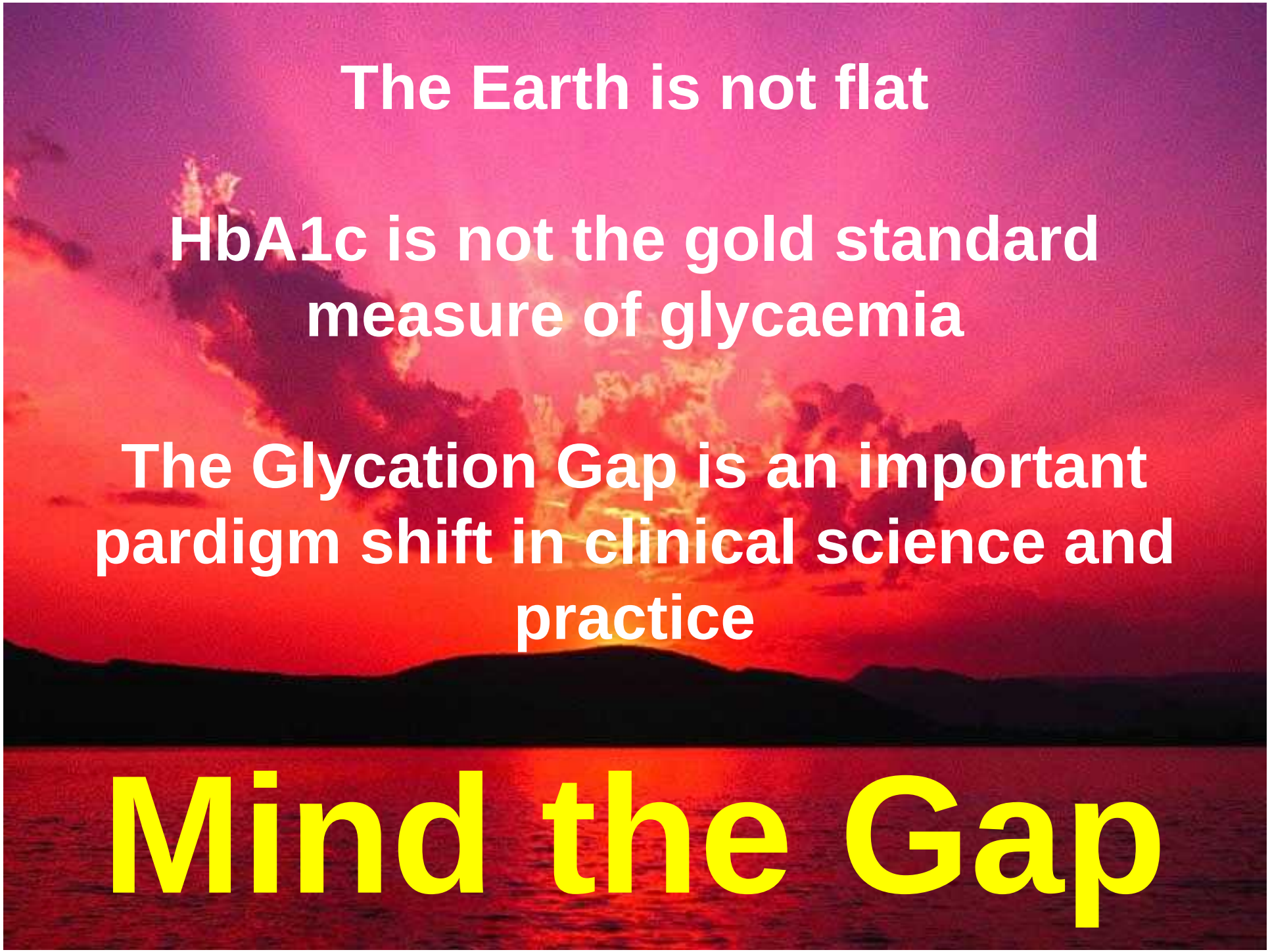


	N	Mean	Std. Deviation
HBA1c derived MBG 90	921	9.4828	2.72428
Fructosamine derived MBG 90	921	9.4168	2.79446



GGap and clinical implications

- Look out for HbA1c deviation (cross check and triangulate, SMBG, AGP, Fructosamine)
- Take care in setting targets in those with an identified GGap of >1 (-ve or +ve)
- Get Fructosamine assays up and running
- A new predictor of complications?
- A new predictor of mortality?
- A potential screening tool?
- A new target for intervention?
- A rapidly expanding research field, so be aware and watch this space.


The Earth is not flat
HbA1c is not the gold standard measure of glycaemia
The Glycation Gap is an important pardigm shift in clinical science and practice
Mind the Gap