Blood glucose variations and cardiovascular risk in patients with diabetes

Thessaloniki 13 November 2009

Oliver Schnell, Executive Member of the Managing Board Diabetes Research Institute, Munich

UKPDS Follow-up: Reduction of diabetes-related endpoints and myocardial infarction



Holman R et al. New Engl J Med 2008;359, epub 10 September 2008

UKPDS Follow-up: microvascular disease and death from any cause



Holman R et al. New Engl J Med 2008;359, epub 10 September 2008

Multifactorial intervention in type 2 diabetes The Steno 2 study

Composite endpoint

CV-death, MI or stroke, CABG or PCI, limb amputation or vascular surgery



(Gaede et al N Engl J Med 2008;358:580-91)

European guidelines: diabetes and cardiovascular disease



Severe hypoglycemic episodes in ACCORD, VADT, ADVANCE



Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment

	Intensive treatment/ standard treatment		Weight of	Odds ratio	Odds ratio		
	Participants	Events	- study size	(95% CI)	(95% CI)		
UKPDS	3071/1549	221/141	21.8%		0.78 (0.62-0.98)		
PROactive	2605/2633	119/144	18.0%		0.83 (0.64-1.06)		
ADVANCE	5571/5569	153/156	21.9%		0.98 (0.78-1.23)		
VADT	892/899	64/78	9.4%		0.81 (0.58-1.15)		
ACCORD	5128/5123	186/235	28.9%	i	0.78 (0.64-0.93)		
Overall	17267/15773	743/754	100%		0.83 (0.75-0.93)		
				0.6 0.8 1.0 1	.2 1.4 1.6		
			Intensiv	e treatment S	Standard treatment		

Probability of events of coronary heart disease with intensive glucose-lowering versus standard treatment



*Included non-fatal myocardial infarction and death from all-cardiac mortality

SMBG testing is associated with better glycemic control independent of diabetes type or therapy



Karter AJ et al. Am J Med. 2001;111:1-9

ORIGINAL ARTICLE

Longitudinal Study of New and Prevalent Use of Self-Monitoring of Blood Glucose

ANDREW J. KARTER, PHD¹ Melissa M. Parker, ms¹ Howard H. Moffet, mph¹ Michele M. Spence, phd² James Chan, pharmd, phd² Susan L. Ettner, phd³ Joe V. Selby, md¹

DIABETES CARE, VOLUME 29, NUMBER 8, AUGUST 2006

All

Self monitoring and glycemic control at Kaiser
 Permanente
 Northern California – an integrated health care system

Longitudinal study of

New user cohort (patients starting SMBG) – 16,091
Ongoing user cohort (prevalent users) – 15,347

models were stratified by therapy (no medications, oral agents only, or insulin) and adjusted for baseline A1C, sociodemographics, insulin injection frequency, comorbidity index, medication adherence, smoking status, health care use, and provider specialty.



Initiation of strips/day

Karter A et al. (2006), Diabetes Care

ROSSO: Combined Non-fatal Endpoints in diabetic patients with and without SMBG



ROSSO: Fatal Endpoints in diabetic patients with and without SMBG



Feedback of SMBG measurements to HCPs is important for maximising SMBG benefits

SMBG plus feedback reduced HbA_{1c} levels 0.6% more than SMBG without feedback



Jansen J. Curr Med Res Opin 2006;22:671-81.

HbA1c: Change from baseline (DINAMIC 1 study)



SMBG is a key component of diabetes management programmes

All persons with diabetes using insulin and/or oral antidiabetes drugs can benefit from SMBG use"

American Association of Diabetes Educators¹

"SMBG empowers patients to take greater responsibility for glycaemic control, improving self-awareness, self-management and self-confidence"

American Diabetes Association²

"SMBG should be available for all newly diagnosed people with T2DM, as an integral part of self-management education"

International Diabetes Federation³

AADE. The Diabetes Educator 2006;32(6):835–46.
 ADA. Diabetes Care 1996;19(Suppl 1):S62–6.
 IDF. <u>http://www.idf.org/home/index.cfm?unode=B7462CCB-3A4C-472C-80E4-710074D74AD3</u>

Postprandial state



Monnier L. Eur J Clin Invest 2000;30(Suppl. 2):3–11.

Relationship between postprandial blood glucose peaks and CHD mortality

The evidence:



- 1. Nakagami T, et al. Diabetologia 2004;47:385-94.
- 2. DECODE. Diabetes Care 2003;26:688-96.
- 3. Shaw J, et al. Diabetologia 1999;42:1050-54.
- 4. Tominaga M, et al. Diabetes Care 1999;22;920-24.
- 5. Balkau B, et al. Diabetes Care 1998;21:360-67.
- 6. Barrett-Connor E, et al. Diabetes Care 1998;21:1236-39.
- 7. Hanefeld M, et al. Diabetologia 1996;39:1577-83.
- 8. Donahue R. Diabetes 1987;36:689-92.

DECODA: Diabetes Epidemiology, Collaborative Analysis of Diagnostic Criteria in Asia DECODE: Diabetes Epidemiology, Collaborative Analysis of Diagnostic Criteria in Europe

Postprandial hyperglycaemia is associated with an increased risk of mortality

DECODA (n=6,817)



Nakagami T, et al. Diabetologia 2004;47:385–94.



Conclusions Glucose fluctuations during postprandial periods and, more generally, during glucose swings exhibited a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia. The present data suggest that interventional trials in type 2 diabetes should target not only hemoglobin A_{1c} and mean glucose concentrations but also acute glucose swings.

Variability of glucose in type 1 diabetes



Variability of glucose: A new independent risk factor for hospital mortality in the ICU



Krinsley JS, Crit Care Med 2008; 36:3008-3013

Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture.

Risso A, Mercuri F, Quagliaro L, Damante G, Ceriello A.

Am J Physiol, 2001



Normal glucose (5mM)

High glucose (20mM)



Alternating glucose (5/20mM)

→ 14 days

Cell death of HUVECs cultured with different concentrations of glucose









A = normal glucose (5 mM)
B = high glucose (20mM)
C = alternating
 low / high glucose (5/20 mM)

Endothelial dysfunction and hyperglycemia



NGT = normal glucose tolerance; IGT = impaired glucose tolerance; DM = diabetes mellitus

Kawano H et al. J Am Coll Cardiol 1999

Oxidative stress and postprandial hyerglycemia



Kawano H et al. J Am Coll Cardiol 1999;34:146–54

Oxidative Stress and Glucose variability



MAGE = Mean Amplitude of Glycemic Excursions

Monnier, L, et al, JAMA, 295, 1681-1687, 2006

Traditional biomarkers of glycemia are not associated with oxidative stress

Glycemic Control Markers

HbA_{1C} Mean Post-meal MAGE Glucose glucose

8-Isoprostanes 0.06 0.22 0.55* 0.86* Pearson Correlation coefficients

*p<0.05

Monnier, L, et al, JAMA, 295, 1681-1687, 2006

Increase in postprandial blood glucose preceeds preprandial blood glucose elevation



HbA1c: blue < 6,5 %, red 6,5 – 7 %, green 7,1 – 8 %, orange 8,1 – 9%, brown 9,1 % and higher

Monnier L et al, Diabetes Care 2007 (30) 263-269

Contribution of pre- and postprandial blood glucose to HbA_{1c}



a: pre- and postprandial BG significantly different b: significant os. other quintiles (ANOVA) c: significant vs. quintile V (ANOVA)

Monnier et al. Diabetes Care 2003; 26: 881-885

EASD

European Association for the Study of Diabetes

New ESC/EASD Guidelines

On hyperglycemia



Eur Heart J (2007) 28, 88-136

ESC & EASD GUIDELINES Executive summary		
Recommendation	Class	Leve
Information on post-load glucose provides better information about future risk for CV disease than fasting glucose, and elevated post-load glucose also predicts increased CV risk in subjects with normal fasting glucose		A
Improved control of post-prandial glycemia may lower CV risk and mortality	llb	С
The relationship between hyperglycemia and CV diseases should be seen as a continuum	I	А

Lindgren (Sweden); Qing Qiao (Finland).

Is postmeal hyperglycaemia harmful?

MAJOR EVIDENCE STATEMENT

 Postmeal and postchallenge hyperglycaemia are independent risk factors for macrovascular disease. [Level 1+]

OTHER EVIDENCE STATEMENTS

- Postmeal hyperglycaemia is associated with increased risk of retinopathy. [Level 2+]
- Postmeal hyperglycaemia is associated with increased carotid intima-media thickness (IMT). [Level 2+]
- Postmeal hyperglycaemia causes oxidative stress, inflammation and endothelial dysfunction. [Level 2+]
- Postmeal hyperglycaemia is associated with decreased myocardial blood volume and myocardial blood flow. [Level 2+]
- Postmeal hyperglycaemia is associated with increased risk of cancer. [Level 2+]
- Postmeal hyperglycaemia is associated with impaired cognitive function in elderly people with type 2 diabetes. [Level 2+]

RECOMMENDATION

Postmeal hyperglycaemia is harmful and should be addressed.



What are the targets for postmeal glycaemic control and how should they be assessed?

EVIDENCE STATEMENTS

- Postmeal plasma glucose levels seldom rise above 7.8 mmol/l (140 mg/dl) in people with normal glucose tolerance and typically return to basal levels two to three hours after food ingestion. [Level 2++]
- IDF and other organizations define normal glucose tolerance as <7.8 mmol/l (140 mg/dl) two hours following ingestion of a 75-g glucose load. [Level 4]
- The two-hour timeframe for measurement of plasma glucose concentrations is recommended because it conforms to guidelines published by most of the leading diabetes organizations and medical associations. [Level 4]
- Self-monitoring of blood glucose (SMBG) is currently the optimal method for assessing plasma glucose levels. [Level 1++]
- It is generally recommended that people treated with insulin perform SMBG at least three times per day; SMBG frequency for people who are not treated with insulin should be individualized to each person's treatment regimen and level of control. [Level 4]

RECOMMENDATIONS

- Two-hour postmeal plasma glucose should not exceed 7.8 mmol/l (140 mg/dl) as long as hypoglycaemia is avoided.
- Self-monitoring of blood glucose (SMBG) should be considered because it is currently the most practical method for monitoring postmeal glycaemia.
- Efficacy of treatment regimens should be monitored as frequently as needed to guide therapy towards achieving postmeal plasma glucose target.

Guideline

Self-Monitoring

of Blood Glucose in Non-Insulin Treated Type 2 Diabetes





International Diabetes Federation

5-point profile

	Pre- Breakfast	Post- Breakfast	Pre- Lunch	Post- Lunch	Pre- Supper	Post- Supper	Bedtime
Monday							
Tuesday							
Wednesday	x	x		x	x	x	
Thursday	x	x		x	x	x	
Friday	x	x		x	x	x	
Saturday							
Sunday							

7-point profile

	Pre- Breakfast	Post- Breakfast	Pre- Lunch	Post- Lunch	Pre- Supper	Post- Supper	Bedtime
Monday			-				
Tuesday	x	x	x	x	x	x	х
Wednesday	x	x	x	x	x	x	x
Thursday	х	х	x	х	х	х	x
Friday							
Saturday						_	
Sunday							
Consensus Statement on Self-Monitoring of Blood Glucose in Diabetes mellitus – a European perspective

Schnell O, Alawi A, Battelino T, Ceriello A, Diem P, Felton A, Grzeszczak W, Harno K, Kempler P, Satman I, Verges B.

Consensus Statement on Self-Monitoring of Blood Glucose in Diabetes. Diabetes, Stoffwechsel und Herz (Diab Metabol Heart) 2009; 18: 285-289

Consensus Statement on SMBG: Intensified insulin treatment

- 4-8 tests every day
- SMBG should be performed primarily preprandially and at bedtime
- Postprandial testing 7-10 times per week
- Nocturnal testing once a week

Consensus Statement on SMBG: Conventional insulin treatment

- 2-4 tests every day
- SMBG should be performed primarily preprandially
- Postprandial testing 1-2 times per week
- Nocturnal testing once a week or once every two weeks

Consensus Statement on SMBG: Oral glucose-lowering treatment

- 6-8 tests per week with an equal amount of preprandial and postprandial tests
- In people who are not on insulin or do not test frequently couplets (pre- and postprandial) are recommended

Self-monitoring of blood glucose: Individual situations

- Diabetic patients on oral glucose lowering agents:
 - To provide informations on hypoglycemia
 - To assess glucose excursions
 - To assess medication and live style changes
 - To monitor during intercurrent illness

SMBG values need to make a difference !

- meal and activity plans
- type and dose of oral agents
- regimen and dose of insulin
- interaction between physician and patient
- empowerment of the patient

Self-monitoring of blood glucose in type 2 diabetes mellitus: Summary

- Improvement of metabolic control reduces micro- and macrovascular complications in diabetes
- Pre- and postprandial glucose and glycemic variability matter, they can be visualized by SMBG
- SMBG is increasingly recommended in guidelines (e.g. IDF, European Consensus), potential for more elaborate recommendations
- Implementation at the national levels needs to be enforced
- SMBG needs to be individually tailored to the patient
- SMBG is a key element of an optimized diabetes management

Consensus Report of the Coalition for Clinical Research— Self-Monitoring of Blood Glucose

David C. Klonoff, MD, FACP **Richard Bergenstal, MD** Lawrence Blonde, MD, FACP, FACE Suzanne Austin Boren, PhD, MHA Timothy Church, MD, MPH, PhD Jenifer Gaffaney, MS, RD, CDE Lois Jovanovič, MD David Kendall, MD Craig Kollman, PhD Boris Kovatchev, PhD Claudia Leippert, Diabetesberaterin DDG David Owens, MD, CBE William H. Polonsky, PhD, CDE Gerard Reach, MD Eric Renard, MD, PhD Michael Riddell, PhD Richard R. Rubin, PhD Oliver Schnell, MD Linda M. Siminiero, RN, PhD, CDE COL MC Robert A. Vigersky, MD; Darrell M. Wilson, MD Alison Okada Wollitzer, PhD

Consensus Report: <u>Skills of caregivers</u> needed to interpret and act upon SMBG information appropriately

- Interpret SMBG results relative to appropriate target levels
- Possess the knowledge to make therapeutic adjustments in therapy
- Create a simple action plan for the patient
- Adress fasting, postprandial, and post-meal excursion glucose levels
- Act to prevent hypoglycemia

Consensus report: <u>Skills of the patient</u> in order to appropriately perform, interpret and act upon SMBG information

- Understand appropriate timing and testing sites for monitoring
- Interpret SMBG results relative to pretermined target levels
- Know how to modify diet, exercise, stress, and medication dosing to modify level of glycemia
- Possess the knowledge to make therapeutic adjustments in therapy
- Accurately record SMBG test results on paper or electronically

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RECOMMENDATION

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SMBG: Future directions

- Agreement on patterns of SMBG (e.g. pre- and postprandial BG), individual recommendations for patients
- Emphasis on education
- Standardisation of display and communication of SMBG data
- Trials (RCT or observational) to reinforce that SMBG has value in type 2 diabetes
 - Clinical Outcomes, Glucose control (level and variability), Hypoglycemia, QOL

QUESTION 1

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RECOMMENDATION

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QUESTION 2

Is treatment of postmeal hyperglycaemia beneficial?

EVIDENCE STATEMENTS

- Treatment with agents that target postmeal plasma glucose reduces vascular events. [Level 1-]
- Targeting both postmeal and fasting plasma glucose is an important strategy for achieving optimal glycaemic control. [Level 2+]

RECOMMENDATION

Implement treatment strategies to lower postmeal plasma glucose in people with postmeal hyperglycaemia.

'Staggered' SMBG regimen

	Pre- Breakfast	Post- Breakfast	Pre- Lunch	Post- Lunch	Pre- Supper	Post- Supper	Bedtime
Monday	x	x					
Tuesday			x	x			
Wednesday				1	x	x	
Thursday	x	x					
Friday			x	x			
Saturday					x	x	
Sunday	x	x					

Intensive or 'focused' SMBG protocols use 'pattern analysis', a systematic approach to creating glucose profiles that can identify daily glycaemic patterns and then take appropriate action based upon those results. These profiles can be generated by performing 5 to 7 measurements per day over 1 to 3 days, or through 'staggered' testing, in which the individual performs pre- and postprandial testing for alternating meals over the course of a week.

Meal-based testing

	Pre- Breakfast	Post- Breakfast	Pre- Lunch	Post- Lunch	Pre- Supper	Post- Supper	Bedtime
Monday	x	x					
Tuesday]			
Wednesday			x	x			
Thursday	1			9	0		
Friday							
Saturday					x	x	
Sunday							

Meal-based SMBG (before and after selected meals) helps individuals with diabetes understand the effects of their treatment on blood glucose concentrations and assists clinicians in identifying postprandial hyperglycaemia, guides therapeutic adjustments and provides more timely feedback regarding medication changes ⁽⁷²⁾.

A more comprehensive approach, which has been used in early education programmes with good results (84), is to perform 3 tests per day (2 times per week – one weekday and one weekend day) – fasting and preprandial/postprandial at the largest meal (often supper) for a few weeks. Monitor fasting glucose to track trends in glucose control. Monitor preprandial/postprandial (largest meal first) during week and weekend for a few weeks and then change diet and exercise to optimize the result. Then monitor preprandial/postprandial glucose at another meal and repeat it.

HbA1c am Ende von DCCT und während EDIC



Nathan DM et al, DCCT/ EDIC Study Research Group, N Engl J Med (2005) 353: 2643 - 2653

Intensivierte Insulintherapie reduziert langfristig das Auftreten kardiovaskulärer Komplikationen bei Typ 1 Diabetes



Häufigkeit des ersten Auftretens eines vordefinierten kardiovaskulären Endpunkts

Häufigkeit des ersten Auftretens eines nicht-tödlichen Herzinfarkts, Schlaganfalls oder Todes aufgrund einer kardiovaskulären Erkrankung

> DCCT/ EDIC Study Research Group N Engl J Med 2005;353:2643-2653

Multifactorial intervention in type 2 diabetes The Steno 2 study

Cumulative Incidence of All Cause Mortality



1

(Gaeue et al N Engl J Meu 2008;358:580-91)

ACCORD: Primary Endpoints

No. of No. of Hazard Ratio P Value Subgroup Patients Events 10,251 Total 723 Previous cardiovascular event 0.04 No 6.643 330 3,608 393 Yes Sex 0.74 Female 3,952 212 Male 6,299 511 Age at baseline 0.65 <65 yr 6,779 383 ≥65 yr 3,472 340 ┛┤ Glycated hemoglobin at baseline 0.03 <8.0% 4,868 284 >8.0% 5,360 438 0.29 Race Nonwhite 3.647 222 White 6,604 501 0.6 1.0 1.4 Intensive Standard

Evidence of benefit for

A Primary Outcome

Patients without preexisting cardiovascular events

Patients with baseline HbA1c<8%

The Action to Control Cardiovascular Risk in Diabetes Study Group*, N Engl J Med 2008;358:2545-59

Therapy

Better

Therapy

Better

BMJ Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial

Andrew Farmer, Alisha Wade, Elizabeth Goyder, Patricia Yudkin, David French, Anthea Craven, Rury Holman, Ann-Louise Kinmonth, Andrew Neil and Diabetes Glycaemic Education and Monitoring Trial Group

BMJ published online 25 Jun 2007; doi:10.1136/bmj.39247.447431.BE

- Three arm, open, parallel group randomized trial
- 435 patients with Dm and no insulin
- 3 groups: no SMBG, SMBG and no instructions, SMBG and training to enhance motivation and adherence to a healthy livestyle
- At 12 months no statistical differences differences in HbA1c between the two groups

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- No statistical differences in HbA1c between the groups
- 435 patients with Dm and no insulin
- 3 groups: no SMBG, SMBG and no advise, SMBG and training to enhance motivation and adherence to a healthy livestyle

DIGEM: considerations

- The mean HbA1c ranged from 7.41 to 7.53 %: this might have attenuated the need for a modification or intensification of treatment within any of the three groups
- The usage of oral antidiabetic agents (OADs) was increased only in less than one third of the patients (29 and 32% vs 30%)
- The difference in the number of SMBG measurements per week was small between the group with intensive SMBG vs. standard SMBG (7 times vs. 5 times)

DIGEM - considerations

• The use of self-monitoring of glucose was somehow blurred:

Nearly one third of the patients had performed self monitoring of blood glucose prior to inclusion into the study: 31.6 % in the control group

In the less and more intensive self monitoring groups: 26.7% and 32.5 %

Recommended frequency and timing of <u>SMBG</u>

 $\mathbf{\Phi} \rightarrow$ It depends on the type of diabetes,

- the treatment approach and
- the educational level

Gestational Diabetes

• High frequency testing: 4-8 tests per day or more

• Postprandial testing 1-hour post-meal

Recommended targets for Preprandial Blood Glucose

< 6 mmol/l for the most patients
Children:
→ 0-6 years: 5-8 mmol/l
→ ≥ 7 years: 4-8 mmol/l
→ Patients with CAD: 5-7 mmol/l
→ Pregnant women: 3,3-5 mmol/l

Recommended Target for Postprandial Blood Glucose • <7,8 mmol/l 2-h-postprandial</p> Pregnant woman: \rightarrow <7,8 mmol/l 1-h-postprandial \rightarrow <6,6 mmol/l 2-h-postprandial

Accu-Chek 360° View

Paper-Based – No software or computer required

Simple Concept – Patient tests 7 times per day over 3 day period; Record results on easily-understood form

Comprehensive – Allows recording of BG, meal size, "feel-good" score and more



Enhances Patient / HCP Interaction

INCA 2 Munich Case reports



Postprandial state



Monnier L. Eur J Clin Invest 2000;30(Suppl. 2):3–11.

INCA: Intelligent Controll Assistent for Diabetes



Smart assistant



Data transfer

INCA : HbA1c

Group 1: INCA period followed by control period

Group 2: Control period followed by INCA period



HbA1c Group 2

